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Multipolar Technoscience:
Clinical Science Collaborations in a
Changing
World System

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Dissertation Summary:

This dissertation focuses on the formation and governance of international clinical research collaborations in the field of regenerative stem cell medicine, and analyzes these processes against the background of the current transition to a multipolarizing scientific world system. The empirical point of departure of this study is an ethnographic analysis of the establishment of a trans-continental academia-centered clinical trials infrastructure, between researchers based in China, Hong Kong and the USA. Field research was carried out in mainland China and Hong Kong amongst scientists, clinical researchers, medical entrepreneurs, government regulators and patients, between April 2010 and May 2011. The dissertation contributes to debates on the processes and challenges that surround the global distribution of evidence-based medicine clinical research standards, and the study of science and globalization in the context of the emergence of new scientific, economic and geopolitical center regions in the world, with a particular focus on literature that comments on the scientific ascent of the People's Republic of China.

The dissertation reveals that the global diffusion of evidence-based clinical research standards, in regenerative stem cell medicine, is accompanied by the surfacing of vital forms of resistance and the creation of novel transnational spaces of alter-standardization, in which less rigorous, physician-based forms of experimental clinical practice are endorsed, publicized and tried to be legitimized. The dissertation uncovers, furthermore, that the creation of internationally standardized research zones, in the clinical stem cell field, is not necessarily a stable or constant process. The implementation of internationally recognized standards can be highly temporary and depends upon activation in specific situational contexts. Multiple modalities of experimental clinical practices continue to exist side by side to each other.

Another line of theorization in this study focuses on the contemporary dynamics of global scientific multipolarization, and explores the empirical and theoretical implications of this trend for international clinical research collaborations. The dissertation argues that a new mode of clinical research partnerships may gradually be emerging. Processes of collective financiering and joint-innovation are giving rise to changing patterns of labour division, decision-making, benefit sharing, profit sharing and revised forms of ownership regarding inventions and research data. Based on a reflective engagement with postcolonial approaches to the study of science

and technology, the dissertation concludes that new analytical perspectives are required, through which the empirical transformations and impact associated with the move toward a multipolarizing science system, can be captured in a more nuanced, and comprehensive manner.

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Table of Contents

Statement	1
Dissertation Summary	3
Acknowledgements	5
Table of Contents	7
List of Abbreviations	10
 Chapter I: Introduction	 12
Analytical Level 1	15
Analytical Level 2	28
Analytical Level 3	36
Chapter Outline	50
 Chapter 2: Methodology	 52
Methods of Data Collection	52
Investigating Processes of Clinical Translation	56
Investigating Scientific Multipolarization	59
Shortcomings and Limitations of Study	67
Positioning myself in the Field	67
 Chapter 3: Foundation and History of the China SCI Net and Transcontinental Scientific Exchanges	 69
PART I: A brief History of the China SCI Net	70
PART II: New Opportunities through Collaboration	80
Conclusions	86
 Chapter 4: Conducting a Stem Cell-Based Clinical Trial for Spinal Cord Injury	 88
Locating the Trial	89

Logistical Aspects of the Trial	92
Patient Recruitment	94
Origins and Preparation of UCB Mononuclear Cells	102
Surgical and Cell Transplantation Procedure	105
Outcome Measurement	113
Summary	114
 Chapter 5: Situating the Network in the Context of China	 118
PART I: Experimental SC Research and Applications in China	119
PART II: Problematization and Regulation	126
PART III: Medical Innovation and National Experimental Pluralism	133
Conclusions	137
 Chapter 6: Regulatory Approval and Controversies	 140
PART I: Interacting with the Regulatory System	142
PART II: Controversies	155
Among researchers in China	156
Among researchers in the USA	163
Among patients	168
PART III: Conclusions	173
 Chapter 7: Restructuring Local Grounds	 175
PART I: Objectives and Domains of Restructuring	176
PART II: Methods and Techniques of Restructuring	182
PART III: The Global Distribution of Evidence-Based Medicine	192
Conclusions	200
 Chapter 8: Organizational Basis of the China SCI Net	 203
PART I: Funding of the China SCI Net	205
PART II: A new modality of transnational clinical research	215
PART III: Involvement of spinal cord injury patients in decisions about future trials	226
Conclusions	229

Chapter 9: Conclusions	232
Analytical Level 1	234
Analytical Level 2	243
Analytical Level 3	253
 Bibliography	 258

List with abbreviations

ANT	Actor Network Theory
ASIA	American Spinal Injury Association Impairment Scale
ATV	Asia Television, Hong Kong
BRICS	Brazil, Russia, India, China, South Africa
CCTV	Central Chinese State Television
CEO	Chief Executive Officer
China SCI Net	China Spinal Cord Injury Network
CO ₂	Carbon Dioxide
CRO	Contract Research Organization
DoH	Declaration of Helsinki
DOH	Department of Health, Hong Kong
EAE	Experimental Autoimmune Encephalomyelitis
EBM	Evidence Based Medicine
EMA	European Medicines Agency
FDA	Food and Drug Administration, USA
FDIs	Foreign Direct Investments
GCP	Good Clinical Practice Standards
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
hESC	Human Embryonic Stem Cells
IANR	International Association of Neurorestoratology
IPR	Intellectual Property Rights
HIV	Human immunodeficiency virus
HLA	Human Leukocyte Antigens
HK SCI Fund	Hong Kong Spinal Cord Injury Fund
HKU	Hong Kong University
ICH	International Conference on Harmonization
IND	Investigational New Drug Application
IRB	Institutional Review Board
MAS	Modified Ashworth Scale
MDACS	Medical Device Administration Control System, Hong Kong
MOH	Ministry of Health, China

MRI	Magnetic Resonance Imaging Technology
MS	Multiple Sclerosis
MSC	Mesenchymal Stem Cells
NGO	Non Governmental Organization
NIH	National Institute of Health, USA
NSF	National Science Foundation, USA
NYU	New York University
OECD	Organization for Economic Co-operation and Development
PI	Principal Investigator
PRC	People's Republic of China
RCTs	Randomized Controlled Trials
R&D	Research and Development
SC	Stem Cells
SCI	Spinal Cord Injury
SCI Net USA	Spinal Cord Injury Network USA
SCIM	Spinal Cord Independence Measure
SFDA	State Food and Drug Administration, China
SOPs	Standard Operating Procedures
STS	Science and Technology Studies
UCB	Umbilical Cord Blood
UCBM	Umbilical Cord Blood Mononuclear Cells
VAS	Visual Analog Scale
WIRB	Western Institutional Review Board, USA
WISCI	Walking Index for Spinal Cord Injury

Introduction

The emergence of new scientific center regions in the world change the ways in which science and technology is produced at a global scale, and give rise to new opportunities for collaboration and joint innovation. In this thesis I focus on one such collaborative project: the formation of an intercontinental academic clinical research infrastructure that is dedicated to the testing of stem cell-based approaches for the cure of spinal cord injury. This evolving transnational research economy is active across the geographic contexts of mainland China, Hong Kong, Taiwan and the USA. It comprises two interrelated academia-initiated clinical trial networks, namely the China Spinal Cord Injury Network (hereafter known as the China SCI Net) and the Spinal Cord Injury Network USA (hereafter known as the SCI Net USA).

The thesis explores in depth the formation and operation of the China SCI Net. Its activities are analyzed against the background of the wider landscape of clinical stem cell research and application in mainland China. Attention is also given to the synergetic processes and exchanges between the networks in China and the USA, and the wider trans-national linkages and flows between the China network and patient and scientific communities in the USA. My analysis of the China SCI Net is based on ethnographic fieldwork conducted in Hong Kong, mainland China and Taiwan between April 2010 and April 2011, for a period of ten months. The data generated in Taiwan are not included because the main activities of the China SCI Net during the period of fieldwork was in Hong Kong and China.

The China SCI Net is registered in Hong Kong, and was founded in 2005 by a spinal cord injury (SCI) researcher from Rutgers University in New Jersey, USA, in close collaboration with leading researchers from Hong Kong and the Chinese mainland. It operates as an independent academia-driven clinical research infrastructure (set out in Chapter III). Since 2009, the China network has been paralleled by the SCI Net USA, which (at the time of writing) is still in a formative stage, and has not yet conducted clinical trials. The USA network is dedicated to the clinical testing of the same treatment combination that is currently being assessed in

China, which is a combination of umbilical cord blood mononuclear cells (UCBMC), lithium, and methylprednisolone.¹

The China SCI Net is the first intercontinentally operating clinical trial infrastructure in the field of regenerative stem cell research in Asia. Further, it has conducted one of the earliest officially approved multicenter (i.e. multi-hospital) clinical trials of stem cells in China. As I will show in this study, the Network's commitment toward the adoption of internationally acknowledged evidence-based research standards, and systematic multi-country regulatory approval, has required significant alterations of locally evolved clinical research practices in affiliated hospitals. By focusing on the translocal implementation of these changes (against a background of institutional heterogeneity and a non-harmonized regulatory environment for clinical stem cell research), I aim to contribute to a more nuanced understanding of the processes and challenges that arise in the development, organization and governance of large-scale international clinical research collaborations – not only in regenerative stem cell medicine, but also other evolving spheres of experimental medicine. In this thesis I employ three levels of analysis. At the first level, I analyze the China SCI Net as the formation of a trans-national standardized research zone (*cf.* Barry 2008) that is evolving on a background of regulatory, institutional and cultural heterogeneity. There are four issues: (i) the methods and organizational procedures through which standardization is attempted; (ii) the role of transnational forms of scientific self-governance in navigating through a diverse and internationally non-harmonized regulatory environment; (iii) the transformation of local clinical research and innovation practices (in hospitals affiliated to the China network) as a result of the adoption of homogenized evidence-based clinical research standards; and (iv) the ways in which these processes were perceived, facilitated and resisted by local agents in divergent institutional contexts and subject positions.

At the second level, I focus on the implications of the contemporary dynamic of what I call global 'scientific multipolarization', on the organization of international clinical research collaborations. The term 'scientific multipolarization' refers here to the emergence of novel scientific center regions in the world; that is, the increasing availability of scientific capacity, expertise, high-level scientific infrastructures,

¹ This study does not involve a systematic analysis of the SCI Net USA, mainly because the network in the USA, at the time of writing, was still at an initial stage, and no clinical trials had been conducted.

finance and innovation breakthroughs outside of the historically longer-established scientific center regions of Japan, the USA and Europe. A 2011 report of the UK Royal Society on *Knowledge, Networks and Nations* states in this respect:

‘The strength of the traditional centers of scientific excellence and the emergence of new players and leaders point towards an increasingly multipolar scientific world, in which the distribution of scientific activity is concentrated in a number of widely dispersed hubs’ (Royal Society 2011: 5).

My working assumption in exploring this dynamic is that the transition toward a multipolarizing science world can be associated with significant changes in organizational forms and the kinds of exchange that characterize international research partnerships; it can also be associated with changes of the ways in which collaborative projects are initiated, judged and legitimized. In this thesis I examine this hypothesis by restricting myself to academic clinical research partnerships in the field of regenerative stem cell medicine, with a geographic focus on collaborations with China. My analysis of the China SCI Net functions in this respect as a case study, through which the implications of the growing scientific and economic significance of China can be explored. Scientific multipolarization is understood here as a contextual dynamic, whose characteristics and implications must be examined by empirical research on a case-by-case basis. The concept of scientific multipolarization, then, is treated here as a ‘sensitizing concept’ (Blumer 1954). The specific meanings and empirical manifestations of the processes indicated by this term are seen as open and unresolved, in the sense that they refer to (and follow) a dynamic that is itself progressing and which, in many respects, is open-ended and subject to continuing changes (see for further details on the use of this concept pages 36-37).

At a third level, I focus on the theoretical implications of the scientific multipolarization trend. I engage, in particular, in reflective dialogue with post-colonial theory, and post-colonial science and technology studies (STS). This involves a careful examination of the conceptual, ideological and methodological presumptions embedded in post-colonial theory, and an exploration of the possibilities and limitations of post-colonial approaches to the study of science and technology in the context of a multipolarizing science world. It also involves searching for new and complementary analytical strategies, through which the empirical changes and impact

that can be associated with the trend toward scientific multipolarization can be captured in a more nuanced, comprehensive way. With a geographical focal point of my current research on the People's Republic of China (PRC) I explore the theoretical implications of the multipolarization dynamics, especially from the standpoint of China. The PRC is now the world's most rapidly and extensively developing economic and scientific center region outside the more established research economies in the USA, the European Union (EU) and Japan (Bound et al. 2013). This focus on the ascent of China to a global science 'superpower' offers an important opportunity to develop new lines of analysis and theorization, through which to enter debates on and study the emergence of other (scientific) center regions in the world, and to trace the impact of these developments on the production and application of science and technology innovation elsewhere, including the USA and Western Europe.

In this thesis, I examine the theoretical implications of the dynamics of scientific multipolarization with respect to the organizational dimensions of international clinical research collaborations. At the end of the dissertation, however, in the final parts of the *Conclusions*, I expand the analytical scope of this study and develop an analytical framework that allows examination of the transition toward a multipolarizing global science system at a more general level (i.e. beyond the topic of international collaborations). Based on empirical data from my fieldwork, and an extensive review of the literature, I will outline a range of analytical dimensions through which the changes and the local, regional and global impact of the multipolarization dynamics in the sciences can be identified and traced in a comprehensive and methodical way. By developing this 'multipolar technoscience' framework, I intend to open up and elucidate new directions for future research, analysis and theorization, through which the connections between science, globalization and geopolitical diversification can be examined from new angles, and in ways that are not yet conveyed in the current literature on scientific globalization.

In the remainder of this Introduction I will discuss these three analytical levels in relation to relevant literature. I will identify analytical gaps and describe the central lines of investigation in this research in greater detail. In doing so, I will introduce the empirical and theoretical contributions that this dissertation makes.

1. Regenerative Stem Cell Medicine as a Global Collaborative Project

Stem cell research as an object of anthropological inquiry

In recent years, research on human stem cells has become a serious object of analysis in anthropology, STS, and other social science disciplines. While the therapeutic use of stem cells for hematological diseases reaches back to the 1960s (Martin, Brown and Kraft 2008), the trigger point for the rapidly growing interest in stem cell science by social scientists was when the first human embryonic stem cell (hESC) lines were derived by Jamie Thompson in 1998. Prompted by the public controversies surrounding the use of human embryos for hESC research in many countries (Walters 2004; Kaufman and Morgan 2005), this interest developed into a multifaceted field of investigation that has explored how stem cell science reshapes political, economic, social, cultural, legal and ethical forms, categories and practices (Geesink, Prainsack and Franklin 2008; Prainsack, Geesink and Franklin 2008; Rosemann 2011; Sleeboom-Faulkner 2011; Bharadwaj 2012a). These evolving insights had important implications also for social theory. Franklin and Lock (2003), for instance, stressed that the technological ability to alter the human embryo and to redirect its biological potential towards new types of therapeutic and economic projects, gave rise to significant alterations of the meanings and practices that were commonly associated with classical terms of economic analysis, such as labor, exchange, value, production and distribution (Franklin and Lock 2003; Waldby 2002). This line of analysis has been developed further by Waldby and Mitchell (2006) in their analysis of contemporary tissue economies; by Rajan (2006) in his study on the increasing corporatization of life science research; by Cooper (2008b) in her exploration of biological life as 'a surplus' against the background of neoliberal capitalism; and more recently by Kent (2012) in her investigation of the exchange and commodification practices of human tissues in the context of newly evolving stem cell therapies.

A related line of analysis has explored the changing forms and meanings of value, labor, production and reproduction from a feminist perspective. Dickenson (2006), for example, has pointed out that the perceptions, experiences and moral dilemmas of the women and couples who are asked to donate their ova and embryos to scientific research, have for many years been ignored in the ethical debates

surrounding stem cell research. Waldby and Cooper took up this line of criticism; they refer to the arduous process of ‘female reproductive work’ (Waldby and Cooper 2008) in the context of *in vitro* fertilization (IVF), which lies at the center of the ‘embryonic economies’ (Franklin 2006) emerging in the context of hESC and somatic cell nuclear transfer (SCNT) research. Dickenson (2006), Waldby and Cooper (2008, 2010), Cooper (2008b) and more recently Gupta (2011) all point to the danger of exploitation of women, particularly in the context of economic deprivation and substandard medical conditions.

Others have emphasized the ontological and philosophical implications of stem cell research, pointing to the emergence of new forms and narratives of life (Waldby 2002; Waldby and Squier 2003) and the reshaping of boundaries between culturally defined conceptions of the natural and the artificial (Thompson 2005; Franklin 2006a), life and death (Franklin and Lock 2003; Bharadwaj 2005; Rosemann 2009), waste and value (Waldby and Mitchell 2006) and the ethical and the unethical (Franklin 2003; Bender, Hauskeller and Manzai 2005; Geesink, Prainsack and Franklin 2008; Bharadwaj and Glasner 2009; Bharadwaj 2012a; Kato and Sleeboom-Faulkner 2011).

Yet another line of inquiry has focused on the emergence of promissory discourses of therapeutic, scientific and economic hopes and opportunities (Rubin 2008), and the ways in which these representations have been used to mobilize resources such as research funding (Cooper 2008b), political support (Gottweis, Salter and Waldby 2009), new forms of economic revenue (Martin, Brown and Turner 2008), as well as increased levels of legitimacy and public acceptance (Kitzinger and Williams 2005; Kitzinger, Williams and Henderson 2007). Kitzinger explored in this respect the re-negotiation of discourses of hype and hope in the aftermath of the Hwang scandal in South Korea (Kitzinger 2008); while Cooper analyzed the creation of hype in the stem cell field as a manifestation of ‘capitalist delirium’ (Cooper 2008b: 20), whereby the potential value of cells and cellular processes in the future becomes itself an object of capital speculation and profit generation. Brown (2007) has suggested in this regard that the increasing dependence of emerging fields of life science research on expectations of promissory value signifies a shift from ‘regimes of truth’, in which behavior is structured and resources are mobilized on the basis of established evidence, to ‘regimes of hope’, in which speculative and imaginative invocations of future benefits are elevated to a source of authority and to a guiding principle for the organization of economic and scientific action.

In the mid to late 2000s came the realization that the development of clinically and commercially successful applications with human embryonic stem cells were still a long way off. The analytical attention moved gradually away from hESC research and toward the exploration of research with adult stem cells (Prainsack, Geesink and Franklin 2008). In contrast to hESC, stem cells from adult sources (such as bone marrow, nerve tissue, fat tissue and umbilical cord blood) were now seen by many scientists and biotech companies as being more suitable for clinical translation, with the potential to be applied in routine clinical practice more rapidly (Franklin and Kaftantzi 2008). The use of adult stem cells (to be precise: mononuclear cells derived from umbilical cord blood; details will follow in Chapter IV) lies also at the heart of the scientific project that is described and analyzed in this dissertation. While a complete overview of the literature on research with adult stem cells is beyond the purpose of this dissertation project, I will in the following sections survey a range of studies that deal with the translation of stem cell-based therapeutic approaches from the laboratory to the clinic, which – as mentioned above – forms a central analytical theme of this study. The objective of this review is to locate my study within the context of the existing literature on clinical translation processes in the stem cell field, and to highlight analytical niche areas to which this dissertation will make theoretical contributions.

Towards the clinic: Stem cell medicine from bench to bedside

The translation of discoveries in regenerative stem cell medicine from the laboratory to the level of the clinic has received increasing attention over the last years. In broad terms, four central directions of analysis can be observed. A first field of investigation has focused on the processes of preclinical development and the development of research and technology that precedes and legitimizes first-in-human applications with stem cells. This body of work has contributed insights into the decision-making processes behind the types of preclinical inventions that shall be translated to the clinic (Wainwright and Williams 2009). It has also contributed to the construction of ethical positions in stem cell translational research (Cribb et al. 2008), and the formation of ‘communities of expectation’ around promissory stem cell applications (Martin, Brown and Kraft 2008). Insights have also been gained into the difficulties that arise from diverging perspectives and interests of basic scientists and clinical researchers, in the upstream translational process (Wainwright et al. 2006).

A second field of analysis has concentrated on the clinical testing of stem cell-based applications through phase I to III randomized controlled trials (RCTs) in the context of investigational new drug (IND) applications, which are reviewed by national-level drug regulatory agencies. Webster, Haddad and Waldby (2011), for instance, have explored the regulatory, scientific and clinical challenges of stem cell clinical trials that arise with respect to the biological contingencies and the provisionality of stem cell-based interventions in humans. Wilson-Kovacs, Weber and Hauskeller (2010) have, in turn, illustrated that the enactment of regulation for RCTs with stem cells in the UK and Germany is a ‘practical accomplishment’, and is based on complex negotiations and ‘interpretational strategies’ rather than clearcut and top-down following of unequivocally defined rules (2010: 89; Wilson-Kovacs and Hauskeller 2012).

A third field of investigation was concerned with bench to bedside translations outside the methodological format of the RCT, especially in the context of experimental for-profit stem cell therapies. Interestingly, while the studies cited above referred exclusively to the situation in Europe and USA, this third area of analysis has taken a more global perspective, with a particular focus on Asia. This is not surprising. The speed of scientific developments in many Asian societies, in combination with often very lenient regulatory frameworks, have resulted in more rapid and frequently minimally controlled forms of bench to clinic translation in the stem cell field. The availability of unproven, albeit potentially beneficial experimental therapies with stem cells has led to new forms of capitalization, and to the rise of a global stem cell tourism (Wahlberg and Streitfeldner 2008; Sipp 2012). Commenting on the situation in China, Song (2010; 2011) has shown how unclear regulatory conditions and changes in China’s political economy of healthcare have invited the market-driven pursuit of clinical experimentation in the stem cell field. In a study on stem cell research in India, Bharadwaj (2012) has explored how ‘dislocations’ or global locales – hitherto imagined as ‘inconceivable sites for high-tech scientific innovation’ (2012: 305) – have emerged as prolific places of clinical experimentation and commercial development. These evolving sites of human experimentation, Bharadwaj argued, have also given rise to new manifestations of ‘sub-altern ethicality’. By this he means lines of ethical reasoning and legitimization that remain unrecognized in the ‘hegemonic sensible space’ of mainstream science (Bharadwaj 2013: 38). In another article on India, Patra and Sleeboom-Faulkner (2009) look into the complex institutional

networks through which experimental stem cell therapies and related forms of profit making are realized. They point, too, to the ways in which stem cell clinics use their own patients as ‘recruiter–patients’, to enlist new experimental subjects in an increasingly competitive environment (Patra and Sleeboom-Faulkner 2010).

A fourth field of analysis has focused on the transnational flows and exchange chains that surround the development of new therapies in the stem cell field. Such studies have concentrated on cross-border movements of cells, technology, expertise, capital and scientists, and on the role that these exchanges play in generating new types of economic and scientific opportunities. Waldby and Mitchell (2006), for instance, and more recently Kent (2012), have analyzed the global ‘tissue economies’ of stem cells and other engineered tissue products, on which the realization of the therapeutic and economic promise of regenerative medicine is based. These two studies have located the changes in the legal structures that underlie and enable these transnational tissue flows, and the new practices of ownership and dispossession, through which the donation, modification and commoditization of human tissues are rendered possible and legitimate. Transnational flows of cells, technologies, capital and new inventions are often facilitated by the strategic exploitation of regulatory differences across countries and regions. For instance, some of the largest providers of experimental for-profit therapies in the stem cell field are currently located in China, where regulation of clinical stem cell research and their applications is evolving only gradually (Cyranoski 2009, 2012; Zhang 2012; Rosemann 2013a). Chen and Gottweis (2011) have reported in this respect about a Chinese stem cell bank corporation that has links with clinics and subsidiary companies not only in China, but also in other leniently regulated countries in Asia, the Middle East and Eastern Europe. Beside collaborative research and development (R&D) projects, the main function of these partnerships is to push the marketization of this company’s experimental stem cell products to an expanding global community of patients (*ibid.*: 13). These processes of marketization are not subject to the approval and review procedures of national-level drug regulatory authorities, which are mandatory in more stringently regulated countries such as the USA, Taiwan, South Korea and Japan (Song 2011; Sipp 2012). Sleeboom-Faulkner and Patra (2011) have shown, though, that the instrumentalization of regulatory differences is just one of several other forms of geography-bound inequalities through which economic and scientific opportunities are realized in the regenerative medicine field. Using the case study of a medical entrepreneur, the

authors illustrate how an experimental stem cell therapy that was developed (but prohibited) in Japan, was successfully marketized in hospitals in India. In addition to the impact of regulatory differences, the authors explain this situation in terms of the strategic use of socioeconomic differences, cross-regional inequalities in quality and access to health care, and divergent standards of scientific development (2011: 648).

International clinical stem cell trials: A neglected area of research

Taken together, these studies offer important insights into several of the forms and conditions under which promissory therapeutic strategies with stem cells are translated from the laboratory to the clinic and to for-profit applications. An area that has remained unexplored so far, however, is the development of the field of regenerative stem cell medicine through multi-country clinical trial partnerships. The emergence of a global clinical trial landscape has been a key theme in the literature on more conventional forms of biomedical drug research (e.g. research with chemical compounds and small molecules), as organized by the pharmaceutical industry (Petryna 2009; Rajan 2010; Sariolla and Simpson 2011, 2012). To date, however, no study has focused on the formation of international, or intercontinental clinical trials collaborations in regenerative stem cell medicine. As reported above, in contexts other than the USA and Europe, social analysts have focused almost exclusively on the surfacing of unproven for-profit stem cell therapies, rather than the development of more systematic clinical research and clinical trials. This is an important analytical shortcoming for two reasons. First, it overlooks that international clinical trial partnerships have started to play an increasingly important role in the stem cell field in recent years. Clinical trial collaborations have emerged not only between institutes in the USA and Europe,² but also with institutes in Asia, where important advances in stem cell medicine have been made. Various international clinical trial projects have been launched or have already been completed.³

² For instance: a trial of Stem Cell Inc. that is conducted in Switzerland, Canada and the USA. For details see: <http://online.wsj.com/article/PR-CO-20140113-904540.html> (accessed on January 18, 2014).

³ Some examples are:

- (1) A trial on Thalassemia conducted by the US cord blood bank corporation Stemcyte in Taiwan. For details see: <http://www.stemcyte.com/why-save-cord-blood/research-developments> (accessed on January 18, 2014).
- (2) A phase I/II trial for ischemic stroke, which is conducted by the US biotech company Neuralstem Inc. in China; <http://www.neuralstem.com/cell-therapy-for-ischemic-stroke> (accessed on January 18, 2014).

Second, the focus on unproven stem cell therapies has failed to recognize that in many Asian societies the adoption of clinical trial methodology has become increasingly important, also in domestic innovation projects with stem cells. For instance, there has been media hype about the uptake and untimely ending of the first phase I clinical trial with human embryonic stem cells (hESC) by Geron Corporation in the USA, but hardly any attention has been paid to South Korea, where the Korean Food and Drug Administration (KFDA) approved in 2011 three stem cell treatments for routine clinical use; including the world's second stem cell 'batch' product (Sipp 2012). In 2011, the KFDA also approved three hESC based clinical products for clinical trials. Three out of the world's first four hESC products approved for clinical trials were developed in Korea (GAAN 2013). But the uptake of stem cell-based RCTs in the context of IND applications under review by national-level drug regulatory authorities has also been reported from Taiwan, Hong Kong, mainland China (Rosemann 2013a), India and Japan (Sipp 2012).⁴ The currently emerging regulations for clinical stem cell research in these societies consistently define phase I to phase III randomized controlled trials as obligatory passage points for the development of stem cell-based medicinal applications (Sipp 2012). This is also the case in China and India, where clinical experiments with stem cells have been carried out for years in a very permissive regulated environment (Sleeboom-Faulkner and Patra 2011; Rosemann 2013a). The current shift toward more reliable regulation, combined with the evolution of advanced clinical trial infrastructures and experiences in the stem cell field in these countries, make multi-country clinical research collaborations with partners in Asia an increasingly sought-after opportunity.

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- (3) A phase I trial for chronic spinal cord injury, which will be conducted by Neuralstem Inc in South Korea; <http://www.neuralstem.com/cell-therapy-for-sci> (accessed on January 18, 2014).
 - (4) A phase I stem cell trial on autism, conducted by the US-American Sutter Institute in Singapore; <http://www.biospectrumasia.com/biospectrum/regulatory/3134/fda-approves-stem-cell-trial-autism#.UtrsEJg4IPM> (accessed on January 18, 2014).

⁴ Some examples are:

- (1) From Taiwan: http://clinicaltrials.gov/ct2/show/NCT01649687?term=stem+cell&locn=taiwan&rcv_s=01%2F01%2F2006&rcv_e=01%2F18%2F2014&rank=13 (accessed on January 18, 2014).
- (2) From Japan: <http://blogs.nature.com/news/2013/07/japan-to-start-stem-cell-study-on-humans.html> (accessed on January 18, 2014).
- (3) From Hong Kong: <http://clinicaltrials.gov/ct2/show/NCT01046786?term=cn102b+hong+kong&rank=1> (accessed on January 18, 2014).
- (4) From India: <http://www.indiaprwire.com/pressrelease/health-care/2011020476844.htm> (accessed on January 18, 2014).

Multi-country stem cell trials and the challenge of standardization

The empirical focal point in this dissertation, as mentioned above, is the formation of an intercontinental clinical trials infrastructure that is active across the contexts of mainland China, Hong Kong, Taiwan and the USA. The aim of this evolving trans-national research economy is to develop and clinically assess stem cell-based combination therapies for spinal cord injury. (A more detailed description of the Network's clinical studies will follow in Chapter III). From an analytical perspective, the formation of the China SCI Net provides a unique opportunity to gain insights into the processes and challenges involved in the development, organization and governance of large-scale, trans-continental clinical research collaborations in the field of regenerative stem cell medicine. Of particular interest, in this dissertation, are processes of (and challenges to) standardization, and the role of standards as instruments of scientific governance, which in recent years have evolved to an important concern in the social study of science, technology and medicine (Timmermans and Berg 1997; Bowker and Star 1999; Timmermans and Epstein 2010; Zwanenburg, Ely and Smith 2011).

This analytical interest is well demonstrated in the literature on pharmaceutical research and the global pharmaceutical economy. The forging of international standards and of a harmonized regulatory environment for drug research and approval of new medicines has led to increased international trade in pharmaceuticals, and has enabled the commercialization of new drugs in a wider global market, and at reduced costs (Zwanenberg, Ely and Smith 2011). At the heart of this integration process, lies the global distribution of standardized evidence-based clinical research protocols, where the RCT is the widely accepted methodological gold standard (Timmermans and Berg 2003; Will 2007). Indeed, evidence based medicine (EBM) and the distribution of internationally recognized clinical trial standards have evolved into massive standardization projects in the contemporary era, with worldwide implications (Epstein 1996; Mykhalovskij and Weir 2004; Petryna 2009). At a global level, the increasing reliance on RCTs has led to an explosion of clinical trials organized by the pharmaceutical industry in low-income to mid-income countries (Petryna 2009). It has also resulted in extensive changes in clinical research and healthcare systems (Epstein 2008; Petty and Heimer 2011), and given rise to significant clashes with local

perceptions of medicine, medical research and forms of medical entrepreneurship (Keating and Cambrosio 2012).

The formation of international clinical trial collaborations in the stem cell field provides a valuable opportunity to gain insights into these processes, and to understand how the promotion and global distribution of evidence-based clinical research standards and the RCT plays out in an emerging field of medical research. While in the established forms of pharmaceutical research the use of RCTs has now become an essential requirement globally for the marketization of new medicines (Petryna 2009; Keating and Cambrosio 2012), in emerging areas of medical research such as regenerative stem cell medicine, the situation is far more diverse and complex. As regards clinical research in stem cells and their application, there are no internationally binding standards or harmonized global governance frameworks as yet, and widely divergent regulatory conditions exist across (and within) countries. In China, for instance, the experimental clinical use of stem cells was largely unregulated until January 2012, with the result that highly dissimilar types of clinical research and experimental for-profit applications have been initiated since the early 2000s (Chen 2009; Cyranoski 2009; Rosemann 2013a; Song 2010, 2011).⁵ The variety of clinical research methodologies and forms of commercialization observed in medical institutions in China pose a significant challenge to the establishing of international clinical research projects. In order to achieve inter-institutionally shared scientific standards, which are required to make valid comparisons between clinical data from different localities (and thus render them internationally acceptable), important adjustments are necessary of locally evolved clinical research conditions (Wahlberg *et al.* 2013).

Multi-country clinical trial collaborations, such as the China SCI Net, represent the first projects in regenerative stem cell medicine where such processes of cross-border standardization can be observed. The study of such projects allows one to trace the travel and trans-local re-embedding of EBM standards and the RCT format in new institutional contexts and regions, as well as newly emerging spheres of clinical medicine. By focusing on these partnerships, insights can be gained into the negotiations, exchanges and institutional transformations that underlie the formation of newly emerging standardized research zones (*cf.* Barry 2008), and into the rationales,

⁵ A detailed overview of the regulatory situation for clinical stem cell research and applications in China is provided in Chapter V.

interests and regulatory pressures involved. Insights can also be obtained into the ways in which local clinical research and innovation practices in divergent national and institutional contexts, are altered and transformed, and the ways in which these changes are promoted, perceived, facilitated or resisted by local agents in divergent geographical and institutional settings and subject positions. Moreover, an understanding can be reached regarding the underlying economic and scientific drivers and the global power relations through which the trans-local adoption of RCTs in evolving fields of experimental medicine is advocated and pushed ahead.

Standardized trans-national research zones and the role of scientific self-governance

In this dissertation, the China SCI Net will be analyzed as the formation of a standardized transnational research zone, that is evolving against a background of regulatory, institutional and cultural heterogeneity. A central analytical theme in this respect is the role of scientific self-governance. As will become clear, the establishing of standardized clinical research practices in trans-continental stem cell trials is based on extensive forms of self-regulatory activity and capacity building; these are instigated and implemented by the scientists who run and coordinate the projects. Such project-internal forms of self-governance are strategic efforts to navigate through a diverse and internationally non-harmonized regulatory environment. The aim is to create compliance with the divergent requirements of drug regulatory authorities and related processes of peer-review in multiple countries (*cf.* Wahlberg *et al.* 2013). The forms, roles and implications of the self-regulatory activities of scientists in cross-border clinical research projects have been subject to surprisingly little analysis so far. Studies on transnational governance processes in science and technology research have focused primarily on the development and impact of external frameworks, such as state regulation or international governance frameworks (Peel 2010; Zwanenberg, Ely and Smith 2011). In the case of emerging technologies, however, where state regulations are still evolving – and internationally harmonized regulatory frameworks are not yet in place, a focus on the self-governing activities of scientists may yield important insights. An understanding can be gained first of all into international standardization processes, both before and during the creation of fully developed state regulation and the development of internationally harmonized regulatory frameworks. Insights can be gained, in particular, into the ways in which scientists try to balance out regulatory disparities between regions and institutions, compensating regulatory

gaps and creating congruence with the auditing demands of diverging regulatory and political systems. Important analytical insights can be obtained too, into the interplay and conflicts between the divergent values, normative systems and forms of legal authority that underlie the creation of standardized trans-national research zones in contemporary global scientific projects.

To sum up, with regard to the first analytical level of this dissertation (the formation of a transnational standardized research zone), a total of four analytical themes will be addressed. The first explores the methods, techniques and organizational procedures by which standardization is sought in the context of the China SCI Net. The second focuses on the ways in which these transnational forms of scientific self-governance take shape, and how they are used to navigate through a diverse and internationally non-harmonized regulatory environment. The third examines the impact of standardization, namely how the adoption of homogenized evidence-based clinical research standards transforms local clinical research and innovation practices in network-affiliated hospitals. The fourth theme deals with the ways in which these processes (of standardization and local transformation) are perceived, facilitated and resisted by local agents in divergent institutional contexts and subject positions.

Several lines of argument in regard to these themes will be developed in this dissertation. The first is that the creation of standardized research zones in trans-continental clinical research infrastructures is not necessarily a stable or enduring process. The case study of the China SCI Net indicates that in the hospitals taking part in these trans-national infrastructures, the adoption of homogenized, internationally recognized clinical research standards is often temporary and depends on participation in specific projects. Locally evolved and newly adopted (i.e. internationally recognized) forms of clinical experimentation can exist side-by-side with each other in these medical institutions, and they are legitimized on the basis of different perceptions of science and healthcare, as well as divergent approval and review procedures. Researchers switch back and forth between these divergent schemas depending on the purpose of their research, the partners they work with, the geographic scale of their projects, the targeted territory of marketization and the conflicting demands for regulatory review and approval that result from these differences.

A second argument is that the coexistence of diverging methodological forms of clinical experimentation in the hospitals affiliated to international clinical trial infrastructures can create important knowledge opportunities. The China SCI Net illustrates how such opportunities evolve particularly in the context of cooperation between medical institutions in countries where specific forms of clinical research (in this case, stem cell research) are controlled at different levels of regulatory stringency. The widespread availability of clinical experiences with stem cells in China, has facilitated the tapping into and integration of clinical experiences and knowhow which in the USA were still not available at that time. Insights from prior clinical experimentation informed, in particular, the surgical and cell injection procedures that the China SCI Net uses, in its current series of clinical trials. These procedures were developed by researchers in mainland China, who had years of clinical experience in surgery-based experimental (stem) cell interventions, in large numbers of spinal cord injury patients. While these forms of knowledge transfer from little regulated to highly regulated countries reflect the current opportunities for international academic research collaborations (especially in non-harmonized fields of experimental research), they indicate too, the kinds of ethical questions and potential dilemmas that accompany contemporary trajectories of international drug research.

A third argument concerns the emergence of a trans-national politics of resistance that has its roots in China. Based on a case study of the International Association of Neurorestoratology (founded by a member of the China SCI Net), I will show how more flexible ethical and clinical research standards are advocated, as a complementary alternative to the methodological format of the RCT. I suggest in this regard that what is happening in the clinical stem cell field is not only the diversification of ethical and scientific forms at the level of individual institutions, but a gradual movement toward the pluralization of international clinical research standards themselves.

2. International Research Collaborations in a Multipolarizing Science World

The second analytical level in this dissertation concerns the empirical implications of the contemporary dynamics of scientific multipolarization for the organization of international clinical research collaborations. With the concept ‘scientific multipolarization’ I refer to the emergence of novel scientific center regions in the world; a trend that is closely linked to the emergence of new global centers of economic, financial and geopolitical influence that has been taking place since the late 1970s. The development of these new scientific hubs is epitomized by the increasing availability of research capacity, expertise, know-how, high-level technological infrastructures, finance, a well-trained scientific labor force, and inventions and technoscientific breakthroughs. These events give rise to an intensification of global competition and new forms of interdependencies, as well as new opportunities and challenges for international research cooperations. My working assumption is, in this respect, that the transition toward a multipolarizing global science system can be associated with significant changes in organizational forms, kinds of interaction, and types of exchange that characterize international research partnerships. But changes can be expected, too, in the ways in which, and reasons why, collaborative projects are initiated, and with regard to the criteria and mechanisms by which these projects are appraised, judged and legitimized.

In this dissertation, I examine these assumptions by restricting myself to academic international clinical research partnerships in the field of regenerative stem cell medicine, with a geographic focus on collaborations with China. My analysis of the China SCI Net serves in this respect as an empirical case study, through which the implications of the ascent of China to a global scientific center can be explored, in terms of the organization of trans-national, academia-driven clinical research collaborations. As mentioned previously, the characteristics and consequences of the trend toward multipolarization in the sciences, are viewed in this dissertation to be open-ended, gradually evolving, and subject to continuous change. The dynamics of scientific multipolarization is thus not conceived as a radical or abrupt transformation, but as a long-term process that unfolds incrementally, in small steps, and along multiple logics and dimensions, in uneven and sometimes incongruous ways. While

older patterns and institutionalized forms of social life continue to exist, new behavioral patterns, forms of interaction and exchange are gradually emerging. The concrete pathways of change, and the impact that these transformations have on established social, material and organizational forms have yet to be identified; they have to be explored gradually, through empirical research, and on a case-by-case basis. For these reasons, the research in this study is explorative and hypothesis-generating, rather than hypothesis-testing. I do not depart from a clearly specified body of theory that offers firmly established causal relationships, which can then be verified or refined. What I aim to do instead, is to generate a body of nuanced insights through which initial lines of theorization on the forms and characteristics of scientific multipolarization processes can be developed, as well as the ways in which these impact on clinical research collaborations.

In order to achieve this purpose, I set out four analytical dimensions, along which the lines of transformation in international research collaborations that can be associated with the move toward a multipolarizing global science world can be analyzed. Before introducing these dimensions, however, I will substantiate the notion of ‘scientific multipolarization’ with some concrete data and empirical evidence.

Processes of economic and geopolitical multipolarization

Globalization has increasingly become a dynamic that is driven by multiple economic and geopolitical center regions, within an era in which European and American forms of economic and political influence have encountered repeated crises. Let us have a brief look first, at some of the central transformations that characterize the contemporary situation.

The contemporary world is characterized by a gradual move toward a system in which economic, financial and geopolitical power is increasingly distributed between various states and world regions. Brazil, Russia, India, China, South Africa (BRICS) and other ‘rising powers’ are gradually objecting to the unipolar world system that followed the crash of the Soviet Empire in which the USA have been seen to dominate – politically, militarily, economically, and also in the sciences (Herolf 2011: 5). This transition process has been intensified by the recent global economic crisis and the European currency crisis that followed, and has resulted in massive flows of capital from China and other countries to the USA and Europe, and a large

transfer of assets and securities in the other direction (Kurlantzick 2009). Four lines of transformation deserve contemplation in this respect: the intensification of global competition; the redirection of flows of capital and investments; the reconfiguration of trade routes; and the reshaping of identities.

Let me first address the intensification of global economic competition. According to Marc Spelman, from Accenture Management Consulting, the current trend toward economic and geopolitical multipolarization is giving rise to an intensification of competition in ‘five economic battlegrounds’ (Spelman 2009: 3). These are the battlegrounds (a) for talent and human resources, (b) for natural resources, (c) for consumers and markets, (d) for access to capital flows, and (e) for innovation (Scholtissek 2008; Spelman 2009). These challenges, according to Spelman, are currently affecting every state, enterprise and employee in the world. The ways in which these issues are handled will decide upon the success or failure in a multipolarizing world economy (Scholtissek 2008: 27).

The second point concerns the redirection of flows of capital and investments. Until the 1990s, foreign direct investments (FDIs) flowed predominantly from the ‘triad’ of the USA, Western Europe and Japan, to ‘developing’ and threshold countries (Scholtissek 2008). This situation is experiencing significant change. According to the 2012 Forbes Global 2000 Companies List, more than half of the world’s largest corporations are now in countries other than the USA and those in Europe. South Korea, a relatively small country, contributes 68 companies, and China 106, up from 44 in 2007 (DeCarlo 2012). Accordingly, capital streams are now being redirected substantially. FDIs from multinational corporations of emerging economies now flow on a large scale into the acquisition of US–American, European and Japanese companies, including many well-known companies who produce time-honored brands. According to Sauviant *et al.* (2010), outward FDIs from emerging economies have in the last three decades grown by a factor of 40, rising from US\$ 50 billion in 1980 to over US\$ 2.1 trillion in 2007 (*ibid.*: 1).

The reconfiguration of trade routes and the emergence of new structures of dependency and ‘center—periphery’ relationships is the third line of transformation. Increasing exports of companies from the new economic centers means that companies from all over the world compete for market shares. Due to the rapid growth of consumer markets in threshold countries, it is expected that by 2025 more than half of the global turnover of consumer goods will be occurring in these booming regions

(Scholtissek 2008: 50). What can be observed in this regard, is a reconfiguration of global trade routes, characterized by the establishment of new routes between the evolving ‘poles’ (i.e. evolving global political and economic center regions), an intensification of multidirectional flows on established trade routes, the strengthening of exchange relations between the new centers and neighboring societies (National Science Foundation (NSF) 2012: 21), and the forging of strategic linkages between the evolving global poles and resource-rich developing countries, as for instance reflected in China’s engagement in African societies (Shirk 2007: 134). These changes have resulted in new patterns of interdependency (Vasconcelos 2008: 12), and also in a reconfiguration of center—periphery relationships, whereby the new economic and political centers engage in projects of strategic development, supply alliances – and sometimes exploitation (Herolf 2011: 10-15). These transformations result in new geographies of inclusion, responsibility, influence and inequality, that in many respects re-shape the geopolitical and economic order that has been created under Euro–American forms of global hegemony (Geeraerts 2011: 65). These changing global conditions have also given rise to an intensification of economic and increasing numbers of scientific collaborations, particularly between established and evolving center regions (The Royal Society 2011: 5). For the USA and Europe, the forging of international collaborations has become a core strategy through which to mediate global competition and achieve economic sustainability of their own societies (Ozolina *et al.* 2009: 10).

The fourth line of transformation is the reshaping of social and political identities. The trend of global multipolarization goes hand in hand with the emergence of new forms of economic and geopolitical oppositions, leading to novel scenarios of competition and political antagonism, such as that, for instance, between China and India (Van Kemanade 2008). These processes are resulting, in a re-conceptualization of regional and national identities, and new forms of identity politics. Conceptions of ‘self’ and ‘other’ are becoming increasingly defined in relation to conflicts between evolving ‘poles’, rather than to anti-Western sentiment or colonial history alone (Massey 2007: 85).

Scientific Multipolarization

This trend toward global multipolarization is reflected in the fields of science and technology. According to Wagner, what is emerging is a global science system in which the USA and Europe will be single players among many others (Wagner 2011, cited in Swayne and Messer 2011: 1). A 2008 publication of Reinhilde Veugelers entitled *Towards a Multipolar Science World* (2008) reaches similar conclusions. Based on the figures of the 2008 US National Science Foundation's (NSF) science and engineering indicators, Veugelers describes the shift in the status of EU and the Triad countries (USA, EU and Japan) as follows:

The evidence demonstrates that despite the continued dominance of the US and the increasing importance of the EU, the TRIAD is in relative decline. Other geographic sources of science outside the TRIAD are rising, both in quantity, but also, although still to a lesser extent, in quality. Especially China drives this non-TRIAD growth. This catch-up of non-TRIAD countries drives a slow but real process of global convergence (Veugelers 2008: 14).

The NSF indicators for 2012 show the rapid upswing of non-Triad countries over recent years. In terms of expenditure on R&D (research and development), China overtook Japan in 2009, and now lies second behind the USA (National Science Foundation 2012: O-4). Another indicator is the relative output of research articles. NSF figures reveal a decline in the dominance of papers from the EU and US (National Science Foundation 2012), again with China taking second place.

[In 2009] Asia's world-article share had 'expanded from 14% to 24%, driven by China's 16% average annual growth. By 2007, China surpassed Japan's article output and moved into second place behind the United States – up from 14th place in 1995. By 2009, China accounted for about 9% of world-article output. India's output of scientific and technical articles, stagnating through the late 1990s, began to rise after 2000, but India's ranking hardly changed from 12th to 11th place in 2009. Japan's output declined in volume and global share. (National Science Foundation 2012: O-7).

It is important to note that scientific multipolarization does not automatically follow the same pattern as economic multipolarization. The BRICS countries—Brazil, Russia, India, China and South Africa—showed the greatest economic growth over the last two decades, but only two of them – China and, to a lesser extent, India – are

approaching global leadership status in science and technology. In 2012, the other BRICS nations are still outperformed by small non-BRICS countries, especially those in Asia like South Korea, Taiwan, Singapore and Hong Kong, all of which are likely to become global scientific centers (National Science Foundation 2012). A 2011 report by the Royal Society (2011) proposed the following:

...the strength of the traditional centers of scientific excellence and the emergence of new players and leaders point towards an increasingly multipolar scientific world, in which the distribution of scientific activity is concentrated in a number of widely dispersed hubs (2011: 5).

The trend toward scientific multipolarization is increasingly driven by multinational corporations. This is not only reflected by the off-shoring of the R&D laboratories from US and European multinationals to the new scientific center regions (Sholtissek 2008), but progressively by the merging and acquisitions (M&A) of companies in the Triad's regions by non-Triad multinationals. As Sleigh and Lewinski point out, through M&A these corporations gain access to the R&D laboratories of established and high-quality enterprises and brands. In doing so, they at once move to the top of the global value chain, and furthermore, obtain access to established marketing and branding strategies (2006: 50). This is not a trivial process. According to the 2012 *Forbes Global 2000 Companies List*, more than half of the world's largest corporations are now in countries other than the USA and Europe. South Korea, with its relatively small population hosts 68 companies, and China hosts 106—up from 44 in 2007 (DeCarlo 2012).

As a consequence, the flow of capital and investments is being substantially redirected. Large-scale foreign direct investments (FDIs) are being made by multinational corporations of emerging economies for acquisition of US–American, European and Japanese companies, including well-known ones who produce well-established brands. According to Sauviant *et al.* (2010), there has been a forty-fold increase in outward FDIs from emerging economies in the last three decades alone—rising from US\$ 50 billion in 1980 to over US\$ 2.1 trillion in 2007.

Scientific multipolarization and international collaborations: Four analytical dimensions

Considering these developments, it is not surprising that science and technology collaborations are now seen as key assets in the global competition for innovations. In political discourse and the media in the USA and Europe, collaborations with the emerging scientific center regions are now frequently portrayed as a core strategy for the realization of economic sustainability, and for tackling threats such as global competition and economic disintegration (Swayne and Messer 2011: 1; Bound *et al.* 2013). These factors, in addition to the processes outlined above, have given rise to the formation of increasingly complex geographies of joint innovation, collaboration and technoscientific exchange. It is clear that these evolving global networks and assemblages of cooperation and scientific exchange transcend, in some important respects, older forms of research collaboration, from a time when technoscientific expertise was clustered largely in the Triad regions.

But which kinds of collaboration and exchange, and which types of global infrastructures do actually emerge here? In which ways are these processes influenced by the changes in global power relationships and the presence of new centers of scientific and economic influence, that we are currently witnessing? And how can these evolving global forms, and the changes they set in motion, be studied? In this dissertation, I propose four interrelated analytical dimensions along which international research collaborations in the context of a multipolarizing science world can be analyzed. These dimensions are:

- 1) The organizational modalities of trans-national research alliances; in particular the analysis of:
 - a. the forms and practices of labor division between associated stakeholders and partners
 - b. the decision-making processes
 - c. involved types of exchange and transaction, and
 - d. forms of profit and benefit sharing.
- 2) Patterns of research financiering and ownership.
- 3) Patterns of exchange and resource mobilization from within and between the involved center regions (in this dissertation these are China and the USA), including the mobilization of human, biological, technological and infrastructural resources.

4) Emerging forms of sociality and social movement.

My analytical concern in this study, as highlighted above, is restricted to the study of academic international clinical research collaborations in the field of regenerative stem cell medicine. The geographical focus is exclusively on collaborations with institutions in China. My central case study for this purpose is the China SCI Net. In this dissertation, the China SCI Net will be analyzed along each of these four analytical dimensions. The findings from the analysis will then be compared with the existing literature on clinical research collaborations, in order to discern corresponding patterns, new trends and contrasts. The methodological strategies underlying each of these four analytical dimensions will be discussed in the Methodology section (Chapter II). I will continue now with a discussion on the third analytical level in this dissertation.

3. Theoretical implications of the scientific multipolarization trend

At the third analytical level I am concerned with the theoretical implications of the current dynamics of scientific multipolarization. My primary concern here is to explore the theoretical significance and ramifications of the move toward a multipolarizing science world, with regard to the organizational dimensions of international research collaborations. Given that the geographic focus of this research is the People's Republic of China, I explore in this dissertation the theoretical implications of the multipolarization dynamics especially from the vantage point of China. The People's Republic of China has, in recent years, been the world's most rapidly and most extensively expanding region in the world, in both scientific and economic respects (Bound et al. 2013). I suggest that a focus on the transition of China to a global 'science superpower' provides unique opportunities to enter debates and open new lines of analysis and theorization about the emergence of other center regions in the world (*cf.* Pieke 2012). It also facilitates the study of the impact of these developments on the production and application of science and technology innovation at a global level, including the USA and Western Europe.

A central analytical concern of this dissertation is to engage in a reflective dialogue with postcolonial theory, and postcolonial science and technology studies. This will involve the thorough examination of some of the conceptual, ideological and methodological assumptions embedded in postcolonial theory, as well as exploration of the possibilities and limitations of postcolonial approaches to the study of science and technology in the context of a multipolarizing science world. How feasible is the use of a postcolonial analytical framework for studying the interrelationship between science, globalization, and the processes of geopolitical and economic diversification that characterize the contemporary world?

As the previous sections have shown, we cannot understand the production of science and technology in the present day, without taking into account the current dynamic of global geopolitical and economic 'multipolarization', which is reflected also in the sciences. If one looks at the global flows and exchanges in the sciences from this perspective, are the analytical tools offered by postcolonial approaches

precise enough to capture the empirical transformations that are related to these changes?

One argument I will make in this regard is that many of the analytical tools and insights offered by post-colonial science are highly relevant also in the context of a multipolarizing science world. None the less, the conceptual, methodological, political and ideological presumptions embedded in postcolonial theory require careful scrutiny, and other complementary strategies are required to capture the impact of the current multipolarization process in the sciences more completely. This study shows that the increasing availability of funding, expertise, knowledge, technological infrastructures and high-level education in the evolving science centers in the world is resulting in important re-articulations of the organizational forms and types of transactions and subjectivities that characterize processes of science and technology research. Older forms of historically determined and geographically situated hierarchies are gradually transcending, and new practices of socioeconomic and intellectual participation are emerging, with potentially profound implications for the production of science in the historically longer-established scientific centers of the Triad regions.

Before exploring these issues in greater detail, I will orientate this study in the context of the existing literature on science and globalization, and the emergence of new centers of scientific significance outside of the Triad countries, particularly in the context of Asia. Thereafter I will engage in a dialogue with postcolonial theory, and explore the possibilities and limitations of postcolonial approaches to the study of science in a context of multipolar globalization. Then I will explain and define the theoretical relevance of scholarship on the technoscientific expansion of China, in terms of understanding contemporary global transformations and the formation of other scientific center regions in the world.

The study of science in the era of globalization

Studies that depart from the presumption of scientific multipolarization are not new. In recent years, investigations focusing on the emerging geographies and global impact of centers of science and technology production outside the USA and EU have become increasingly popular. Some studies have examined these developments using scientometric and bibliometric data such as R&D expenses, the numbers of publications, registered patents, the number of science and technology graduates, and the size of the profits generated by the sale of scientific products (Salter et al. 2007; Veugelers 2008; The Royal Society 2011; NSF 2012; Bound 2013; Chakma, Sammut, Agrawal 2013; Leydesdorff *et al.* 2013; McMahon and Thorstiansdottir 2013). Others have explored the changing global landscape in the sciences from ethnographic and qualitative methodological perspectives. A fertile field of analysis in this area are studies that have concentrated on contemporary developments in the biosciences and biomedicine, especially in the context of a ‘rising Asia’.

This growing interest in life and health sciences in Asia is demonstrated by an increase in the number of edited books and journal volumes (Gottweis 2009; Ong and Chen 2010; Salter and Waldby 2008; Coopmans, Graham, Gelfert and Clancey 2012; Chen and Clancey 2013; Clancey and Graham 2013; Sleeboom-Faulkner 2004, 2009, 2010, 2011; Sleeboom-Faulkner and Simpson 2013), various monographs (Rajan 2006; Bharadwaj and Glasner 2009; Saini 2011; Bharadwaj 2012b; Zhang 2012), and a growing number of articles in international peer-reviewed journals of anthropology and STS.

These published studies have examined a variety of themes within diverse analytical venues. Ong and Chen (2010) and collaborators, for instance, have pointed to the ways in which situated perceptions of ethics, community, national identity and politics have been reshaped through the deployment of biotechnologies in Asian societies, and how these perceptions are influenced by local life-worlds, the ambitions of nation states, and wider geopolitical and economic developments. Thompson (2010) has referred in this respect to the different ways in which stem cell science is practiced and embedded in society in South Korea and Singapore. She suggests that a comparative exploration of these differences provides vital insights into national and regional differences in innovation strategies, differing patterns of economic development, and the changing roles and structures of state governments.

Strathern, Sleeboom-Faulkner, Simpson, Konrad and collaborators (among which the author of these lines), in the context of the ‘International Science and Bioethics Project’, have been concerned with the conceptual and practical implications of processes of ethical capacity building in international life science collaborations, in the context of several Asian societies. They have referred to the ways in which ethical issues in trans-national knowledge collaborations have given rise to complex international negotiations (Konrad 2007; Sleeboom-Faulkner 2011; Simpson 2013), to new forms of resourcing, review and policing (Konrad 2007, 2012; Simpson 2011; Buergi 2012; Douglas-Jones 2012; Simpson and Sariola 2012; Rosemann 2013a, 2013b; Sariola and Simpson 2011, 2013; Sleeboom 2013), as well as active forms of ‘ethical experimentality’ that aim to ‘reconcile global forms with local forms of customization’ (Sleeboom-Faulkner and Simpson 2013: 5). Attention has also been drawn to the challenges arising from interdisciplinary, intercultural and socioeconomic cleavages, and the ways in which these divides affect processes of ethical governance and capacity building in collaborative life science projects (Strathern 2012; Sleeboom-Faulkner and Patra 2011; Buergi 2012; Konrad 2012; Bharadwaj 2013; Sariola and Simpson 2013; Rosemann 2011).

Clancey, Fisher, Phillips and collaborators conducted another large-scale research program on the life and health sciences in Asia, in the context of the ‘Asian Biopoleis Project’ at the National University of Singapore. They have explored the emergence and impact of new (bio)scientific hubs in Asia from a thematically more open and interdisciplinary perspective. The project has concentrated on the historical origins, local contexts and policy changes that enabled the rise of these new biomedical infrastructures, and on the ways in which local histories influenced domestic research agendas, strategies of translation, and the appropriation of foreign forms, technologies and practices (Coopman, Graham, Gelfart and Clancey 2012; Clancey and Chen 2013). The project has also addressed the emergence of new interregional networks, as well as interdisciplinary spaces, and the ways in which these evolving webs of knowledge production transform contemporary understandings of science, life, nation, ethnicity and citizenship in Singapore and other locales in Asia (Clancey and Graham 2013; Coopman, Graham, Gelfart and Clancey 2012). Another line of investigation has been initiated by Rajan. In a multi-site ethnographic study of biotech companies in the USA and India, Rajan has explored how current

developments in genomics research reshape global capitalist practices and conceptions of the market, as well as corporate strategies and subjectivities (2006, 2012).

Together, these series of studies have generated critical insights into the characteristics, underlying processes and transformations that can be associated with the emergence of new scientific and technological center regions in Asia. However, the shift toward a multipolarizing science world and the empirical and theoretical implications of this trend have never been explored in a coherent or systematized manner. The whole notion of ‘multipolarization’ and its use as an analytic or structuring concept through which to examine the contemporary reconfiguration of resources, flows, capabilities and global influence (and the effects of these changes on processes of international competition and forms of research organization, collaboration, capital extraction, etcetera) has never been articulated or explored in detail in science and technology studies, or in cognate academic disciplines. Therefore, one of the central issues in this dissertation is the careful examination of the analytical and theoretical possibilities, as well as the limitations of the notion of ‘multipolarization’ in the study of the contemporary sciences.

A central aim in this respect, which is in line with the relatively restricted empirical focus of this dissertation, is to explore the theoretical significance and ramifications of the shift toward a multipolarizing science system, with regard to the organization of international research collaborations.

Scientific multipolarization and postcolonial STS

A crucial analytical theme in this dissertation is to engage in a reflective dialogue with postcolonial theory, and to scrutinize the investigative possibilities, limits and potential pitfalls of postcolonial approaches to the study of science and globalization in the context of a multipolarizing science world. These issues will be explored in the following sections, and be taken up again in the Conclusions, where I will reflect on them in the light of my empirical findings.

Postcolonial theory has, in recent years, led to a vital field of inquiry in science and technology studies and the anthropology and history of the sciences. Initially under the heading ‘postcolonial science studies’ (Harding 1994), later under the label ‘postcolonial technoscience’ (Anderson 2002), this evolving analytical program has explored how knowledge, scientific practices and technology ‘travel’ across cultural, socioeconomic and geopolitical borders. Attention has been drawn in particular to the

historical circumstances and politico-economic relations that have enabled and shaped these flows, and to the ways in which these motions have transformed local situations and subjectivities (Prasad 2008). The vantage point of these studies has initially been the residual effects of European colonialism on processes of postcolonial science, state and identity formation. Since the late 1990s, however, postcolonial science studies have also increasingly addressed ‘new forms of exploitative global relations’ (McNeil 2005). Harding has summarized these, as processes of ‘neo-colonization and neo-imperialism’ (2009: 406), which have evolved in relation to more contemporary manifestations of ‘European-American empire’ (Harding 1998: 3).

In a series of recent essays, Anderson (2002, 2009) and Anderson and Adams (2008) proposed more subtle ways of using postcolonial theory for the study of processes of science and globalization. Rather than departing from ‘simple [notions] of dominance and submission’ (Anderson 2009: 392), the authors suggest exploring postcolonial exchanges, flows and forms of relatedness, as processes of complex entanglements, hybridization and heterogeneity. Most noteworthy, Anderson and Adams (2008) have proposed to enlarge the postcolonial agenda in STS beyond the study of postcolonial societies, and to integrate postcolonial analytical tools and perspectives, for the study of science and globalization at a more general level. The authors state that:

Postcolonial analysis [...] offers a flexible and contingent framework for understanding contact zones *of all sorts* [my italics], for tracking the unequal and messy translations and transactions that take place between different cultures and social positions, including between different laboratories and disciplines even within Western Europe and Northern America (2008: 184).

If my interpretation is correct, the clause ‘contact zones of all sorts’ means in this quotation not only a focus on the making of science in ‘postcolonial societies’ and in relation to ‘the West’, but to science *interchanges* between potentially *all* places. Whether or not I am on the right track is touched upon in a statement they make later, in the same text. The authors ask:

If we now recognize complex sites of technoscience outside Europe and North America, what do we know about travel between these places? How do we avoid

default to the old stories of the expansion of Europe, and instead manage to recognize the multiple vectors of technoscience? (2008: 189).

With these questions, it is of my opinion that Anderson and Adams indicate a fundamental alteration of the analytical scope of postcolonial science studies. They take seriously the changing geographies of exchange and collaboration that emerge in relation to (and between) the currently evolving scientific and geopolitical centers outside of Europe and Northern America. If this is so, then the authors would have ‘liberated’ the field from its defining – but single-minded – focus on the transformative global role of ‘the West’ and, at the same time, open up new research pathways for postcolonial studies of technoscience at a time when American—European forms of global hegemony are increasingly under pressure. Postcolonial technoscience would thus evolve into an analytical framework for the study of science and globalization in a very open and general sense.

But how appropriate is the use of a postcolonial analytical framework for studying global scientific flows, and the interrelationship between science, technology and globalization in the contemporary world? Globalization, after all, as indicated above, is increasingly driven by multiple geopolitical and economic force fields and scientific center regions, in an era in which Europe and the USA are dealing with various crises, and have less political and economic influence globally. Is a postcolonial framework sufficient to capture the complex dynamics, the changing forms of partnership and activity, and the redirections of global flows, power, property and infrastructure that are occurring in the evolving multipolar scientific world system? To explore these questions, it is first of all necessary to examine some of the key tenets of postcolonial theory, and the ways these are applied in postcolonial science and technology studies. My departure point, again, is the work of Warwick Anderson, this time in collaboration with Vincanne Adams.

In their essay ‘Pramoedya's chickens: Postcolonial studies of technoscience’, Anderson and Adams (2008) point out the need for a ‘critical spatial consciousness’, which allows the identification of trans-local schemas of connectedness, of forms of asymmetric exchange, of heterogeneous practices, and contestation. As analytical foci, the authors proposed:

A multiplication of the sites of technoscience, revealing and acknowledging hidden geographical notations and power relations, and further study of the mechanisms and forms of travel between sites. It means we have to be sensitive to dislocation, transformation, and resistance; to the proliferation of partially purified and hybrid forms and identities; to the contestation and negotiation of boundaries; and to recognizing that practices of science are always multi-sited (Anderson and Adams 2008: 183–84).

This quotation, and other passages in the text, reveal five interrelated core themes of the study of science and globalization. These analytical themes are: (a) a focus on heterogeneity/multi-perspectiveness; (b) a concern with hybridity and processes of hybridization; (c) the tracking of power asymmetries and related inequalities; (d) a preoccupation with processes of contestation and resistance; and (e) a focus on science as situated practice. It is obvious, that these analytical themes will remain of central importance to a nuanced understanding of the operation of science also in the context of a multipolarising scientific world system. Postcolonial studies have, furthermore, introduced what Rizvi has called the ‘five epistemic virtues’ of postcolonial theory – historicity, reflexivity, relationality, positionality and criticality (2009: 109). These ‘virtues’, no doubt, will remain at the center of nuanced globalization scholarship. Postcolonial studies of science and technology, in sum, offer crucial analytical tools to the study of science, in the context of multi-polar globalization. There are, however, also significant pitfalls, regarding the use of postcolonial analysis. These will be examined now.

The limits of postcolonial science and technology studies in the light of scientific multipolarization

The historical, geographic and political connotations of postcolonial theory: a source of bias?

The central reference point in postcolonial science and technology studies, has been a deep-seated and critical concern with the historical roots of the contemporary sciences, and the ways in which colonial forms work through, or are replicated (in one way or the another) in the present. As Seth puts it: ‘The history of almost all modern science, it has become clear, must be understood as ‘science in a colonial context’ (2009: 374). Most of the empirical situations that the field addresses, thus, have been grounded in the study of the global impact of Euro–American forms of dominance; first in relation

to colonialism, then in connection to other forms of control, such as those embodied in development, neoliberal trade policies, or foreign military interventions. The investigative counterpoint in these studies remains essentially ‘the West’. Hence, the practices, techniques and discourses of domination, and their trans-local responses, which have been the objects of analysis in postcolonial science studies, have grown out of very specific historical, cultural and geopolitical contexts. Moreover, these investigations have been part of a critical and emancipatory political project, that aimed to deconstruct and overcome colonial assumptions, definitions and stereotypes. The analytical repertoire that postcolonial analysis provides, therefore, is far from ‘neutral’. Its application in new historical contexts must be combined with a critical appraisal of its methods and concepts, and the underlying assumptions, values and political agendas on which they are based. Three issues shall be discussed in this respect.

Implicit Assumptions, Encoded Beliefs

The first refers to reified imaginaries of knowledge through fixed geographic categories. Abraham (2006) notes in this respect, that ‘knowledge that is western’ is sometimes conceived as ‘a fixed knowable and dominant entity’, which is ‘counterposed to other [knowledges]’ that are framed as ‘alternative’ or ‘unmodern’, and ‘characteristic of subaltern or marginal sites in a global political economy’ (*ibid.*: 210). A related point Abraham makes is, that such geography-bound forms of knowledge reifications (i.e. claims in which specific forms of knowledge are treated as concrete and clearly separable objects, that are bound to particular territories) frequently go hand in hand with a host of other implicit assumptions in postcolonial science studies. These, his text implies, are often tacitly presupposed, rather than empirically verified (*ibid.*: 210). What Abraham refers to are encoded beliefs on ‘unequal exchanges’, ‘exploitation’ and ‘clashes’ between ‘western’ and ‘alternative’ knowledges, that are frequently presumed – rather – than thoroughly deduced from empirical studies of actual practices and perceptions of people (*ibid.*: 210). In identifying and addressing ‘“local” and incommensurable knowledges that are built around non-western ontologies’, Abraham’s critique continues, postcolonial technoscience studies evoke notions about ‘the invisible knowledge work of subalterns being subsumed into capitalist property relations that will eventually lead to exploitation, expropriation and even extermination’ (*ibid.*: 210). Abraham’s critique

may be overstated, but in the light of the current global transformations, in particular the shift toward scientific multipolarization, Abraham's points are of significance. This will be shown in the next section.

Voluntary Engagement, Changing Geographies of Inequality

In the currently evolving scientific and political global centers, there is a widespread, typically voluntary and strategic engagement with 'Western' knowledge forms, technologies, and scientific methodologies. These processes are usually intensely promoted from within – not imposed from the outside. In this process, newly imported forms are disassembled, locally transformed, merged with other knowledge practices, and developed further. These hybrid forms, and domestic inventions, are utilized for projects of independent innovation, economic development, and national self-strengthening. Indeed, it is difficult to say whether and where concepts of 'foreign' and 'domestic' start and end in light of the complex, trans-local joint production of scientific forms, escalating interdependencies and multi-directional flow of knowledge.

In this complex global field, forms of asymmetric exchanges and the strategic use of various types of differentials will, of course, continue to exist, and must be identified and mapped. Furthermore, a critical engagement with the global role of science and power in the USA and European societies remains in this respect vital. However, the fact that the production of science is now increasingly marked by multiple vectors and geopolitical force fields, and the implications this has, will have to be explored in greater detail. The diversification of geopolitical and economic influence across several global center regions simultaneously, will—aside to manifold opportunities—almost certainly also result in novel forms of subjectification, utilization, and dependencies. There will also be revised patterns of regional peripheralization and exclusion. Many of these processes, however, are likely to occur *not* in relation to manifestations of North American or European power, but in relation to the activities of other emerging spheres of influence.

Intermediary Conclusions

In sum, to push postcolonial studies of technoscience beyond its conventional analytical focal points requires a nuanced awareness of the current historical and geopolitical transformations that drive the formation of global scientific centers

outside of Europe and Northern America. It requires, furthermore, a detailed understanding of the implications of these processes (with respect to forms of global labor organization, competition, interdependencies, changing identities, shifting patterns of ownership, political influence, and so on). If postcolonial technoscience studies really start to take seriously the investigation of the global impact and role of the ‘complex sites of technoscience outside Europe and North America’ (Anderson and Adams 2008: 189), then a mere focus on the ‘travel between these places’, as suggested by Anderson and Adams, will be too narrow. In order to account for the reconfigurations of global exchange routes, forms of collaboration and geographic patterns of dependency that emerge in relation to these evolving scientific center regions, such studies would also need to focus on the exchanges between the evolving global ‘poles’ and economically less advanced regions and countries elsewhere (as reflected, for instance, in China’s engagement in African societies). A further area of interest would be, the ways in which these emerging scientific center regions impact on processes of science and technology invention, production, application and distribution throughout the USA, Europe and Japan. The shift toward scientific multipolarization implies that vital structural changes and social ramifications in these established scientific center regions can be expected; for instance, through the increase of foreign investments in domestic scientific infrastructures, companies and universities (Scholtissek 2008).

While the specific details of these transformations remain to be explored on a case-by-case basis, it is apparent that a very specific vocabulary and set of analytical tools are required to capture these dynamics. An open question is, in this respect, whether such investigations should still be conducted under the label ‘postcolonial science studies’. While the situation of ‘postcoloniality’, i.e. postcolonial dynamics and the residual impact of colonialism continue to play a role in current globalization processes, it is one among various historical and political dynamics that shape the deployment of technology and science in the contemporary world. I will take up this discussion in the Conclusions of this dissertation, where I will reflect on these themes in the light of the findings from my empirical research. The discussion now continues with the theoretical implications of the scientific multipolarization trend, from the analytical vantage point of China.

Theoretical relevance of the scientific multipolarization trend from the perspective of China

The People's Republic of China has recently become the world's most rapidly and most extensively expanding center region in the world, outside the USA and the EU, in both scientific and economic respects. According to a BBC News Report from 14 October 2013, the Chinese government, research foundations and private corporations now spend about 500 million US dollars on research every day, and employ a quarter of the world's R&D workforce (Shukman 2013). The annual R&D expenses for 2012 were 163 billion US dollars, which constitutes an increase of 18% on the previous year, with further increases planned for the coming years (*ibid.*). As recently stated in a report of the UK think-tank Nesta (National Endowment for Science, Technology and the Arts), the shift toward a more innovative economy and the promotion of domestic innovation trajectories is a top priority, as it is for China's new leadership (Bound et al. 2013: 7).

While the impressive growth of the country's innovation and research base continues, this expansion has 'not yet been matched by similar leaps in quality' (*ibid.*: 7). In numerous fields, however, China is reported to be on the frontier of scientific knowledge production (*ibid.*: 4), and the country's strong technological basis is transforming global scientific processes and opportunities. For instance, the People's Republic of China has gone from 1% of the global gene sequencing capacity in 2001 to nearly 50% in 2013 (Shukman 2013). This means that almost half of the world's sequencing capability for DNA is now located in China. Quality, efficiency and improved evaluation, moreover, are actively promoted by the Chinese government, and this shift has been announced to be strengthened further in the country's thirteenth Five-Year Plan, which will be published in 2016 (Bound 2013: 7). According to the Nesta report, what is 'happening to China is challenging to the UK and others. It means tougher competition' (*ibid.*: 4). However, the report continues (predictively), there 'will also be many new opportunities for collaboration' (*ibid.*: 4). To seize these opportunities, and to reduce the potential threat of competition through the initiation of joint projects, the report suggests an extensive strategy of collaboration in a broad array of fields. In this respect, the report states:

China's innovation system is advancing so rapidly in multiple directions that the UK needs to develop a more ambitious and tailored strategy, able to maximise opportunities and minimize risks across the diversity of its innovation links to China. For the UK, the choice is not whether to engage more deeply with the Chinese system, but how (Bound et al. 2013: 6).

Given that the geographical focal point of my current research is the People's Republic of China, I explore in this dissertation the theoretical implications of the multipolarization dynamics specifically from the perspective of China. According to Pieke (2012), the country is now self-consciously seeking a place at the center of the global stage. In doing so, it is developing – partly from its grassroots, partly through its leadership – its very own trajectories of modernity, modernization and civilizational power. These factors are interconnected, but differ in vital respects from western blueprints, concepts and values. According to Pieke:

After the rise of Japan in the previous century, China is the first country that is making the transition from simply a part of the non-western periphery of the world system to being a superpower and core of its own regional and increasingly global system of political, strategic, economic, religious and cultural dominance. For anthropologists this means that they will have to find ways of thinking and writing about a society that is much more than just another culture. As a global power, China not only self-consciously draws upon its remembered civilization to realize the wish to be in charge of its own version of modernity independently from western civilizers. China also does not hesitate to become a civilizer in its own right, imposing its modernity upon others. With it, anthropologists of China will bear ethnographic witness to global processes of domination, expansion and exploitation from the vantage point of a newly emerging center (Pieke 2012: 7).

As will become clear in Chapters V and VII in this dissertation, this deliberate departure from 'western' conceptions of modernity and modernization, is reflected also in the sciences. Moreover, in the realms of science and technology, as in the corporate and political world, China is increasingly becoming a globalizing power, whereby domestic forms become de-territorialized and start to travel around the world, following both historically established and more recently initiated links, pathways and trade connections. According to Pieke, what can be observed now are gradually

evolving forms of ‘Chinese globalization’ that are reflected in processes of trans-national migration, intensive flows of capital and investment, engagement of political leaders and institutions in global decision-making processes, and the cross-border transit of cultural forms ranging from religion and literature, to food and organized crime (Pieke 2012: 7).

Following Pieke’s ideas on the study of the growing global role of China, I suggest that a focus on the ascent of China to the status of an influential global science power presents a valuable opportunity to enter debate, and devise new lines of analysis and theorization regarding the emergence of other evolving scientific center regions in the world. Such an analysis must involve, on the one hand, understanding the rise of these emerging centers as modernizing powers in their own right; and, on the other hand, exploring and acknowledging the ways in which these centers are embedded in a global world system, certain aspects of which are still dominated by the institutions and cultural forms of the Triad regions. Obviously, such a project must also consider the impact of these developments on the production, distribution and application of science and technology innovation elsewhere in the world, including the USA and Western Europe.

Chapter Outline

Each chapter in this dissertation addresses a different aspect of the complex sets of relationships and interdependencies, through which clinical scientific research is organized, and grounded into the social fabric of societies. Chapter II is a methodological reflection, in which I introduce the methods and strategies of data collection. I explain how these have related to the empiric–theoretical themes that are addressed in the dissertation. Thereafter, I will reflect on my location in the field, and speak about the methodological, empirical and theoretical limitations of this dissertation. In Chapter III, I provide a brief historical sketch of the China SCI Net (or ‘the Network’) and I introduce some of the central processes of transcontinental resource mobilization that underlie the operation of the Network. It will become clear that collaboration with partners in China has enabled academic spinal-injury researchers in the context of the USA to overcome some of the central barriers to clinical translation of promising preclinical and laboratory findings. In Chapter IV, I shift the analytical focus to the level of the clinic and the micro-practices involved in clinical research. I introduce the first clinical trial with stem cells which was conducted by the Network. This was clinical trial CN102b, located in Hong Kong. The organizational aspects and clinical procedures of this trial are introduced through four central themes: (i) the recruitment of patients; (ii) the origin and preparation of the cells for transplantation; (iii) the surgery and process of cell transplantation; and (iv) the outcome-measurement procedures. Chapter V is a contextual analysis of the situation regarding clinical stem cell research in China that takes into account developments until early 2012. It traces the institutionalization of experimental clinical stem cell research and clinical applications in China, and describes their stepwise problematization, by scientists, government agencies and the media. It also explains how this field of clinical research metamorphosed into an object of regulatory concern and intervention. The chapter adds perspective to the operations and activities of the Network within the context of wider circumstances and the dynamics prevalent in China. Chapter VI builds on these insights by focusing on the interactions of the Network with the regulatory agencies in China. It describes the challenges that arose during these interactions, and the problems faced when attempting to meet multi-regional requirements and dealing with differences in regulatory matters. The chapter

also draws attention to some of the central controversies that emerged in relation to the clinical trials of the China SCI Net, and explores these from the perspective of (i) affiliated research in China, (ii) spine-injury researchers in the USA, and (iii) people with spinal cord injury. Chapter VII concentrates on the processes of capacity building, education and self-regulation, through which the China SCI Net has worked to restructure local research and innovation infrastructures in associated partner institutes. It elucidates local responses to these trans-local forms of restructuring and explores the motivations for participation. The chapter ends with a debate on the global distribution of evidence-based medicine (EBM) research standards, and on related forms of local response and resistance. Chapter VIII discusses the organizational basis of the Network as compared with the organization of international clinical trials by the pharmaceutical industry. Four differences that exist in more conventional forms of global drug research are pinpointed for discussion: (i) the flattening of hierarchies and the opening up of decision-making processes; (ii) observations on benefit-sharing and ownership of clinical outcomes; (iii) the evolution of a collectivist approach of knowledge production; and (iv) the targeting of indigenous forms of innovation and knowledge production.

In the Conclusion the three analytical levels that have been outlined in this Introduction, will be discussed in relation the empirical findings of this study as well as relevant literature. At the end of these conclusions, I will define a number of analytical dimensions through which the transformations and the local, regional and global impacts of the transition to a multipolar science world can be identified and mapped at a more open and broad level, extending beyond the topic of international collaboration, which has been central to this dissertation. By developing this ‘multipolar technoscience’ framework, I aim to look ahead and identify future lines of research, analysis and theorization. This will allow the connections between science, globalization and geopolitical diversification to be examined from new perspectives.

Chapter II

Methodology

Introduction

In this chapter I will introduce and reflect on the methods of data collection through which this research was conducted, and explain how these methodological strategies relate to the theoretical aims of the dissertation. I will, furthermore, discuss the methodological limitations of the dissertation, and show how they play out in terms of data validity and requirements for future research.

The approach I use in this chapter is to elucidate the relationships between the different empirical levels of my research, and the key theoretical themes that are addressed herein. The methods of data collection that were used will be examined in the context of each of these empiric–theoretical theme complexes. Thereafter, I will speak about the shortcomings and limitations encountered, and position myself in the field.

There are two overarching analytical and theoretical themes of this study. The first is *clinical translation*. The second is *scientific multipolarization* (or, more specifically, the implications of processes of scientific multipolarization on academia-driven clinical research collaboration). Both of these themes will now be briefly discussed in the light of the methodological choices made during this research, and the concrete methodological possibilities that opened up thereafter.

The theme of scientific multipolarization is discussed in relation to the four analytical dimensions defined in the Introduction. First I will provide a brief overview of the methods of data collection that I was able to employ, so that a general idea can be obtained of the kinds of data that underlie this dissertation.

Methods of Data Collection – A Brief Overview

Several different methods of data collection were employed during my fieldwork, and will be discussed in greater detail later in the context of four analytical dimensions.

Fieldwork for this research was conducted for between April 2010 and April 2011, in mainland China, Hong Kong and Taiwan, for a period of ten months. The central case study in this dissertation is the China SCI Net, which has already been mentioned in the Introduction. The network operates not only in East Asia, but also in the USA (in conjunction with its parallel network the SCI Net USA), therefore part of the research has been to explore transnational linkages and flows within the scientific and patient communities and related organizations and biotechnology companies in the USA.

I had developed an interest into the China SCI Net in 2009, when I discovered information on the Network in the newspaper. This was during a research stay in Taiwan, in the context of the *International Science and Bioethics Collaborations Project*, where I focused on hESC policy in Taiwan. In those days the China SCI Net appeared an interesting case study for my PhD research. Almost one year later, when I had almost forgotten about it, I met the founding director of the Network coincidentally in April 2010 during a conference in Taiwan, and was invited to join another conference, organized by the Network one week later in Hualian, also in Taiwan. There I met some of the affiliated staff and clinical researchers of the Network, and was invited for a visit to the headquarters in Hong Kong. In Hong Kong other opportunities emerged, and I was permitted to get in contact with the PIs of in Prince of Wales and Queen Mary Hospitals. Visits with researchers in mainland China, were primarily initiated by myself, through emails, and formal letters.

Overall, the methodological approach of this study can be described as ethnographic field research, which combines a broad range of data from different sources. The primary forms of data on which the research is based stem from open-ended in-depth interviews, documentary research, and participant observation.

Interviews

Open-ended, semi-structured, in-depth interviews were conducted with 70 people. Twenty-eight of them were affiliated to the China SCI Net. They included the two Directors of the Network, its Executive Manager and 25 researchers from the 11 hospitals affiliated to the Network (of which, one in Taiwan, two in Hong Kong, and eight in mainland China). Interviews were also conducted with five patients with spinal cord injury (SCI), three of whom lived in mainland China and two in Hong Kong.

Another 15 of the interviewees were clinical stem cell researchers from China, from ten hospitals and research institutions. These researchers had no affiliations with the China SCI Net, and were interviewed in order to obtain a wider overview of stem cell research in China. In mainland China, an additional eight people were interviewed with some involvement in stem cell policy-making processes; they provided more understanding of the evolving regulatory situation.

Another ten preclinical and clinical stem cell researchers were interviewed in Taiwan, drawn from eight hospitals and research centers. Three of them were involved with the China SCI Net. The data generated in Taiwan are not included in this dissertation, because the main activities of the China SCI Net during the fieldwork lay in Hong Kong and China only. An initial observational (non-interventional) study and a Phase II trial with lithium had before my fieldwork been conducted in Taiwan, but participation in a stem cell-based study is scheduled only for 2013/2014.

A systematic comparison of the ways in which clinical stem cell research and its applications are conducted and approved in Taiwan, Hong Kong and China is of great interest, but it exceeds the scope of this dissertation. For practical reasons, the focus of this dissertation is limited to the situation in mainland China and Hong Kong.

Another group of interviewees was drawn from the staff of various biotechnology companies in mainland China, specifically those supplying laboratory equipment and those involved in stem cell R&D (research and development). These individuals were highly knowledgeable, offering profound insights into the clinical stem cell landscape at that time.

With most interview partners, in particular those from the China SCI Net and the researchers in China, I had repeated meetings and interviews, sometimes lasting four or five hours. The interviews were either audio recorded and later transcribed, or (especially in case of repeated interviews) written notes were taken. Everyday conversations with researchers in China were usually led in Chinese Mandarin. Language of the interviews was predominantly English. Interviews in Chinese were audio recorded, relevant passages transcribed, and subsequently translated. Passages I did not understand were translated with the help of a MA student of English from Beijing.

Participant observation

The research described here does not involve extended or in-depth forms of participant observation. Prolonged forms of participant observation would have been of interest, especially with individuals in the hospitals in which the clinical trials were conducted, but this was not possible for practical reasons. Nonetheless, the first clinical trial with stem cells conducted by the Network in Hong Kong (which coincided with my fieldwork) yielded rich data from many sources, including participant observation at professional meetings.⁶

Participant observation covered various scientific conferences, public lectures and trial investigator meetings. They offered insights into the operation and procedures of the clinical trial in Hong Kong, and the challenges it faced. Participant observation was also conducted in a virtual manner, by virtue of video-recordings of the first international conference of the Network in Hong Kong, 2005. These recordings documented some of the earliest discussions on treatment approaches, and revealed some of the central decision making processes of the Network.

Documentary research

Documentary research constitutes a very important part of this study. Sources I draw upon are policy documents and regulations, scientific journals, newspapers, websites and television programs. Chinese television programs and newspaper articles were recorded from the Internet and used specifically to document public perceptions of the subject and the forms of problematization of experimental clinical stem cell research in China. These sources were first screened for significant information, then the relevant passages were carefully translated from written Chinese to English. The regulatory documents, if not already available in English, were translated by myself from Chinese.

I will explain how these data sources were used in greater detail later, but suffice to say here that the transnational linkages of the China SCI Net were explored through documentary research via the Internet. This provided a wealth of significant information, including video documentation of contributions to conferences on translation of research in the spinal cord injury field into the clinical arena in the USA; North American newspaper reports on the activities of the China SCI Net; and

⁶ This clinical trial will be introduced in greater detail in Chapters III and IV.

exchanges between Dr Wise Young (the Network's Director) and individuals from the American and international spinal cord injury community. These appeared on the *CareCure* community website (founded by Dr Wise Young), which is currently the largest website on this subject in the world.

The content available on *CareCure* covered a broad spectrum of supportive and critical insights on the operation of the China SCI Net and, more recently, on the parallel network, the SCI Net USA. The conversations on this website clarified many of the transnational linkages between the two networks, and gave insights into the formation of a transnational community among people with spinal cord injury in the USA, Hong Kong, China, and other countries. The website was also an important reservoir of information about the complex politics of funding, and the role of patient activism that underlies research in the two networks. The close collaborations between the researchers and patients with spinal cord injuries, in the context of the China and USA SCI networks, resulted in a very high level of transparency, which meant that information on the trial, and any related debates, decisions, developments and backlashes was shared on the Internet in a very open way. This provided some fascinating opportunities to explore the motivations and perceptions related to the trials carried out by the two networks, from the perspective of people with spinal injuries, their families, and the researchers.

Clinical translation

Clinical translation was one of the overarching themes in this study. It is an object of both empirical description and theoretical analysis. The term 'clinical translation' refers to translation of research findings from the laboratory bench to the clinic in the context of therapy development based on experimental interventions in humans. In this dissertation, the focus lay exclusively on clinical translation in the field of stem cell medicine. These transnational processes of clinical translation in the field of stem cell medicine form the central thematic medium through which the processes of scientific multipolarization in international research collaborations are explored. The modalities of clinical translation that lie at the heart of this dissertation are based on complex transnational linkages, and patterns of collaboration and spatial inter-relatedness. Processes of clinical translation are deeply embedded in the institutional and cultural dimensions of societies, and increasingly take place in multiple societies at once.

A broad range of stakeholders is involved, far exceeding the space of the scientific laboratory and hospital. The stakeholder groups, for instance, that are involved in the clinical translation project described in this dissertation encompassed the patients, their families, clinicians, scientists, international patient organizations and advocacy groups, biotech and pharmaceutical companies, state ministries and regulatory agencies, the Chinese military, the Buddhist Tzu Chi Order, independent scientific accreditation bodies, the media and a string of professional fundraisers and celebrities (not least among them, Barcelona's prestigious football team). This multiplicity of stakeholders operated across an extended transnational space, and collaborations (as well as the occasional dispute) took place across cultural, institutional, regional and disciplinary boundaries.

To make sense of this complexity it helps to make a basic distinction between two central analytical levels of clinical translation. First, there is the level of the clinic and clinical labor; second, is the level of non-clinical processes (through which the work in the clinic is enabled). The complex analytical levels regarding non-clinical processes, and the related methodological strategies employed to capture these, will be unraveled in the context of the four central dimensions that are used to study the impact of the 'scientific multipolarization dynamic, on international clinical research collaborations.

For now, the discussion will focus on the methodological strategies at the analytical level of the clinic and clinical labor. The goal is to provide an understanding of types of data on which this study was based, and to make clear what the empirical and analytical limitations of the study were. Specifically, the analytical level of the clinic and the processes of clinical labor relate to the micro-practices in the preparation and execution of a clinical trial – in this case, a trial involving surgery-based injection of stem cells. The use of stem cells and the use of surgery give rise to a very particular set of practices, clinical challenges and risks for both patients and doctors, and capturing these issues presents a specific methodological challenge. The level of the clinic involves the concrete physical and mechanical process of experimental intervention in the bodies of human subjects, as well as a complex range of organizational and long-term observational practices, together with collaboration with other departments (such as the specialists from the cell transplantation laboratory, or rehabilitation department), through which a clinical trial can be carried out and completed.

In the context of this study, I explored these processes by focusing on the first clinical trial to be carried out with stem cells by the China SCI Net. This Phase I/II safety study was conducted in two hospitals in Hong Kong. The organization and execution of the trial was explored from the perspectives of the hospital staff as well as the patients themselves. Data on the organizational and coordinational practices of this study, in the context of the clinic, were generated through interviews with the principal investigators (PIs) of the two Hong Kong hospitals, and the clinical trial coordinator in one of these two hospitals.

Insights into the clinical work were generated through interviews with three neurosurgeons (of which two were the PIs). Insights into the cellular aspects were gained through interviews and documentary data on the process of cell transplantation provided by the head of the stem cell transplantation laboratory in one of the two Hong Kong hospitals. Information on the trial protocol and challenges and risks for patients were provided by information presented at conferences and public lectures. Insights into the progress of the trial were obtained from investigator meetings.

I succeeded in speaking to two people with spinal cord injury in Hong Kong, one who wanted to take part in the trial but did not fully meet the inclusion criteria, and one who did meet the criteria and took part in the study. These yielded important first-hand accounts about the execution of the trial from the perspective of people with SCI, as well as revealing what participation in a trial (or rejection from it) meant from a corporeal and emotional perspective. Speaking with these two persons was a highly interesting and unique experience, especially as it was not possible to speak to more patients from the trial.

Clinical translation and the study of regulation

A concern with processes of clinical translation involves also the study of clinical research regulations, and processes of regulatory harmonization as well as related disputes. This strand of the research involved (i) interviews with scientists; (ii) the study of debates on clinical trial protocols (at conferences and in scientific publications); (3) international scientific commentary on evidence-based medicine, experimental treatments and clinical trials in the media; and (iv) the study of regulations through documentary analysis, interviews with policy makers, and the media (particularly newspapers and TV resources). Diverging perceptions of regulatory systems, evidence-based medicine (EBM) standards and the adoption of

internationally acknowledged clinical trial protocols were investigated among both, researchers affiliated to the China SCI Net (in Hong Kong and mainland China) and among unrelated clinical stem cell researchers in mainland China.

Scientific multipolarization

Scientific multipolarization, at least in this thesis, is seen as a gradually evolving process, whose consequences play out in diverging ways, across regions, institutions, scientific fields and specific projects. Older forms of research organization, in which the central parameters and goals are shaped by the economic political regimes of the established triad regions, continue to exist, and to interfere, in various ways, with the emergence of a multipolarizing scientific world. In this respect, the whole idea of scientific multipolarization requires careful empirical scrutiny and justification. The methodological strategies that underlie each of the four central analytical dimensions, through which the implications and manifestations of the scientific multipolarization dynamic is explored, are now brought up for discussion.

All four dimensions are reviewed in relation to the central case study – the China SCI Network. These four dimensions are: (1) the organizational modalities of transnational research alliances; (2) patterns of research financiering; (3) patterns of exchange and resource mobilization within and between the involved center regions; and (4) emerging forms of sociality and social movement.

1. Organizational modalities of transnational research alliances

The methodological choices on which research into the organizational modalities of the China SCI Net is based were as follows. First, I tried to understand the organizational structure of the Network, in particular the relationship between the leadership level of the Network, its coordination center in Hong Kong, and the PIs and affiliated staff in the hospitals in Hong Kong and mainland China. A particular interest here was in the patterns of communication, the allocation of responsibilities and influence, decision-making processes, and division of labor. This involved primarily interviews with people at distinct organizational levels, as well as the study of websites and other written text sources of related information. Details on decision-making processes, forms of labor organization in the institutions, and organizational levels were determined by analysis of panel discussions and workshop elements from

video-documented meetings, presentations and discussions, some of which I participated in.

Another crucial part of the Network's operation, from an organizational aspect, were education and training, which enabled standardized clinical practices across multiple institutions. The training elements were listed on the Internet and some were documented on videos. The experiences, perceptions and challenges of these sessions, as well as comments on their results, were obtained from interviews.

Benefit-sharing was another important aspect of the research in this thematic cluster. Insights into incentives behind and forms of benefit-sharing of participation in the organization and its trials were primarily gathered through interviews. This was in the early stages of the trials. A complete picture of the benefits and patterns of sharing was not expected to emerge until the outcomes of the trials are known. Accordingly, many remarks of interviewees were still based on expectations. Concrete statements, though, could be made with regard to the sharing of research data, access to publications, possibilities for application and access of the tested treatments in the case of positive outcomes, as well as a number of other benefits that participation in the Network resulted in.

It was also possible to identify exchanges between the leadership and associated hospitals, and between the leadership and other stakeholders (e.g. companies and patient organizations) on the basis of interviews and documentary analysis, in particular via the commentaries on *CareCure*, conference presentations by the corporate sponsor, Stemcyte, and other media sources on the Internet.

2. Patterns of research financing

In order to understand patterns of research financing of the Network, a broad array of people and sources were consulted. In the course of the research it became clear that the financing strategies of the Network was based on various approaches. Different patterns were observed in the networks in the USA and China. Both networks were dedicated to testing the same treatment approach, and the data and experiences from China informed the planned studies in the USA, therefore an understanding of the financing patterns of both of these networks was of interest.

My investigation of the financing pattern in the USA was based exclusively on web analysis, particularly the *CareCure* website and other SCI community

websites. *CareCure* is a forum for exchanges between the spinal cord injury community and advocacy leaders in the US, which also generate income for clinical projects, including the SCI Net USA. *CareCure*, and its members, provide numerous links to other funding organizations and SCI activist groups in the USA and in Canada that can be explored. Financial information on the funds raised for the SCI Net USA trials are publicly available, together with explanations of how the money is used. *CareCure* also provided news on funding and achievements in the China SCI Net. Information on charity funding campaigns in Hong Kong was published here also, and on the gaining of grants in specific hospitals, from provincial governments or the military health agency in China.

CareCure also provided detailed assessments and calculations of the costs involved in the clinical trials in both China and the US, showing how they were calculated on a per patient basis. It should be pointed out that this level of transparency is rarely seen in other international trials and academic clinical trial projects.

Aside from *CareCure*, insights into the financing of the Network were obtained by interviewing with the Head of China SCI Net's Funding Unit in Hong Kong. Details on fund-raising events, voluntary work and various financial achievements were also shared on the website of the China SCI Net. A significant amount of fund-raising occurs at a local level, through associated PIs, therefore interviews were also conducted with people in the leadership level of the organization, such as the PIs and clinical staff within associated hospitals.

3. Patterns of resource mobilization and exchange

Resource Mobilization

Resource mobilization was analyzed with respect to human, biological and technological resources, as well as clinical infrastructure. The latter included the selection and recruitment of suitable hospitals in the three East Asian regions, of which most were positioned in mainland China. This selection and recruitment process was, to some extent, documented on *CareCure*. More concrete details were obtained through interviews at the leadership level of the Network and with the Head of the Funding Unit, who played a crucial role in linking the Director of the Network (Dr Young) to a number of relevant people in Hong Kong and mainland China. Further

information was gleaned from researchers in China who helped in the recruitment process for the Network partners in China.

Human resources, in the context of the trials, relate to the recruited patients. Details for the patient recruitment procedures and strategies were obtained for the Hong Kong trial, where my fieldwork was ongoing. The doctors were open and frank in discussion on several subjects, such as informed consent, communication of risks, and patient reluctance and patient fears, as well as the concrete pathways of communication and the kinds of information used to inform patients about participation (and the responses to it). Patient recruitment in Hong Kong was also discussed with two people with SCI (John and Catherine) who undertook the recruitment process. These interviews provided important and complementary insights on the role of the doctors.

Patient recruitment was discussed further in interviews with Network researchers and three patients in mainland China, as well as with the leaders of the Network, in particular with Dr Young. The patient recruitment process and its challenges were also widely reported on *CareCure*. Together these data sources yielded important data on the recruitment process, and the ethical safeguards and standards on which recruitment procedures are performed. Other important insights were obtained regarding the different situations of patients in China and Hong Kong, where diverse healthcare arrangements and socio-economic parameters were at play, not least because of different cultural attitudes to physical disabilities that present a range of challenges to people with spinal cord injuries; these in turn influence motivation and willingness to partake in clinical trials and other forms of clinical experimentation. Solid statistical analysis and further in-depth interviews were required to make reliable statements on these issues.

The term ‘mobilization of biological resources’ refers to the human cells that were used as a treatment in the trial; they were sponsored by a US–Taiwanese cord-blood-bank corporation. The motivations of and forms of exchanges between this company and the Network were determined by interviewing a staff member of the company, from conference presentations of the company’s Marketing Director, web resources, and interviews with the researchers and leadership of the Network

To find out more about mobilizing technological resources, I relied primarily on interviews. This aspect was not a priority, but it became more significant in the course of the research; virtually all of the involved hospitals offered an advanced

technology platform that could be used by the Network. It is interesting that it is cheaper to use these technologies and equipment in China than in the USA, which offers an additional economic dimension to the issue.

From these findings, an argument emerged that the scientific pole of China offered a substantial and readily available clinical infrastructure and technology platform, and this had a strongly enabling effect for the Network and made operations in China particularly attractive.

Exchanges and flows

The theme of transnational flows and exchanges is closely related to resource mobilization. However, there are several other dimensions of high importance to consider. These are: perceptions of - and identification with - the trials in China among patients as well as researchers in the USA; the flow of SCI specialists between China and the USA (in both directions); the flow of scientific data and clinical experiences between China and the USA (also in both directions); future access to developed cures from successful trials; and the transfer and application of scientific and ethical standards.

First of these was the perception of – and identification with - the trials in China among patients and researchers in the USA. The trial was discussed at great length by patients in the US, and was perceived to be part of a US project since the data from the trials in China was to be used to inform the trials in the USA, and because the developed treatments would be accessible not only in China but also in the USA. Studying these perceptions was an important part of the research, as were the ways in which the trials in China played a role in motivating patients in the USA to engage in fundraising (for the SCI Net USA).

To capture the perceptions of people with SCI, the central sources of data I relied on were the *CareCure* website and another interactive SCI community website called *Apparelyzed*, which were vital sources of opinion, debate and disagreement on the trials in China. With regard to evolving perceptions and debates among the scientific spinal cord injury community in the USA, I reviewed previously published newspaper articles, media interviews with experts, and video-recordings of conference presentations (and panel discussions) in which the China SCI Net was discussed by some of the most renowned experts in the field at that time.

Lines of support and criticisms were also mapped, and scientific debates were followed during international conferences organized by the Network in Hong Kong. These were documented on video (publicly available), and could be followed further through discussions on *CareCure*.

A vital observation was the flow of subject experts from China to the USA and vice versa; as reported in personal narratives in interviews. They could be documented further through (a) studying programs from international conferences organized by the Network in China, Hong Kong and the US; (b) photos of professional and social meetings available on the web; and (c) video documents of conference presentations and debate panels. These researchers, particularly those from the USA to China, were (as I interpreted it) part of a large process of trust and legitimacy formation, through which researchers in the USA spinal cord injury community became aware of the infrastructure and organizational rigor of the Network, and of the interesting research going on in China. Note that such research is not normally reported in American or English-language journals. Clinical trials conducted by the Network in affiliated hospitals in China, on the other hand, were designed to fully conform to international standards that are acceptable to the top international journals and multi-country drug regulatory bodies, such as Food and Drug Administration (FDA) in the USA.

Analyzing the flow of scientific data and clinical experiences between China and the USA was another of my interests in this study. However, this is more difficult to grasp from a methodological perspective. Nevertheless, research via interviews, as well as examining scientific publications and commentaries on *CareCure*, yielded much information on this issue. It became clear that, regarding the intended clinical trials by the SCI Net USA, there is an important flow of data and clinical experiences, from China to the USA.

Access to cures is a theme that can only be understood fully if a successful treatment is developed. The study of the organizational model of the Network revealed that developed therapies were to be made available in all the regions where the trials were conducted. Research into this was based on interviews and the study of regulatory approval procedures of each region, which played a fundamental role in creating access to developed treatments.

Information on the flow with respect to scientific and ethical standards was obtained by discussions with involved clinicians, and through the study of the research protocols posted on (1) the website of the China SCI Network, (2) *ClinicalTrials.Gov*,

the online clinical trials registry of the National Institute of Health in the USA, and (3) discussions on the *CareCure* website.⁷

Information on the standardization process and the implications for scientific protocols was obtained through the study of training sessions (recorded on video) as well as interviews with clinical researchers in China, and the leadership level of the network in Hong Kong.

Further insights on the flow of scientific and ethical standards were gained by studying the state and non-state agencies (institutional, regional, national and transnational) through which the trials of the China SCI Net were audited and approved. These insights are based on oral reports from involved researchers, and textual sources, rather than documentation of actual practice.

4. Emerging forms of sociality and social movement

As to the emerging forms of sociality, I focused on three central levels. First, there were the forms of interaction, community building and collaboration among clinicians associated to the Network. Most of these individuals, from widely dispersed hospitals and spinal injury research units had no, or only limited, interaction or collaboration before the China SCI Net began planning. I examined the processes of the formation of a shared identity, and notions of community, in the context of professional meetings, collective training sessions, and social activities and communal forms of entertainment and consumption. An additional point of focus was on the processes of collective decision-making and patterns of interaction between those at the leadership level, the coordinating center, and the affiliated partners of the Network. Information on these issues was gained through interviews as well as participant observation at conferences and analysis of websites that described professional and social activities. Insights into the processes of community and identity formation among the Network partners, however, were limited and required further in-depth research to be conducted. However, a good understanding was gained about the decision-making

⁷ (1) Website of the China SCI Net: 'Our Studies':

http://www.chinascinet.org/index.php?option=com_content&task=view&id=129&Itemid=173 (last accessed September 22 2012).

(2) Website of the NIH clinical trial registry ClinicalTrials.Gov: <http://clinicaltrials.gov> (last accessed September 22 2012).

(3) The information from *CareCure* was collected from multiple forums of the website. Information from these forums is referenced by footnotes in the text.

processes and to what extent the affiliated Network partners would define the Network as being Chinese, or as being for researchers in China, or as being a transnational organization.

Second, I was concerned with cross-continental forms of sociality formation among researchers and institutions of the Network in mainland China and Hong Kong, and researchers, institutions and companies in the USA. As mentioned in the previous section (on transnational flow), there was a trend for back and forth movement of researchers from China to the USA, and vice versa. This dynamic resulted in the creation of new linkages and pathways for future collaborative research. Once again, only limited insights were possible from interviews, conference videos and a broad range of web documents. This line of analysis did deliver, however, a social network chart. This clearly sketched out the relations of support for and opposition to the China SCI Net, and links between individual researchers and companies who were interested in collaborating in the future and conducting clinical trials in the context of the Network in China.

The third level concerned transnational linkages among patient communities, organizations and charity fundraising organizations in relation to both, the network in China and the USA. A central finding of this study was that the formation of the China SCI Net gave rise to multiple forms of transnational fundraising and patient activism, in which important linkages were formed between activists and charitable organizations and the involved institutions in Hong Kong, China, Taiwan and the USA. This involved holding interviews with the individual in charge of the Network's fundraising activities in Hong Kong, and charting the linkages and inter-related activism and fundraising campaigns with organizations and advocacy groups in Northern America (USA and Canada) and Taiwan (not yet in mainland China). I also analyzed community websites for patients in the USA, and to a lesser extent those in China, regarding perceptions of inter-relatedness and forms of transnational solidarity and community formation.

Shortcomings and limitations of study

Not all aspects of the research mentioned here could be explored to an equal depth. I tried to triangulate my claims using different data sources where possible, but triangulation was sometimes impossible. Much of the information about the

organization of the Network, and of the difficulties that emerged, was obtained from the Network's founder, Dr Wise Young, from several hours of interviews, as well indirect sources, such as commentaries and participation in debates on *CareCure*.

This has resulted in an invaluable pool of information about the operation of the organization, and provided insights from a leadership perspective, that would otherwise not have been possible.

A challenge in this respect is, however, that some of the more interesting statements and findings could not be triangulated by other sources or informants. Despite my best efforts at triangulation, several specific claims have not been verifiable through other sources. As a result, some of the conclusions that have been reached in particular chapter sections are presented as suggestions, rather than unequivocally confirmed facts.

Positioning myself in the field

In the course of this research, I tried to maintain a detached perspective in order to analyze the operation of the Network in as objective and unbiased a way as possible. However, in the course of my fieldwork, I developed a sympathetic appreciation of the organization, and of the manner in which clinical research is conducted. This has to be understood in the context of countless for-profit experiments that patients are increasingly subjected to in China (both international and domestic patients). Enrolment in such studies often follows false claims and financial motive, rather than the simple goal of systematically testing out a new approach or therapy. Such trials subject patients to significant physical risks and emotional risks, and can also have a negative effect on the financial state and life in general of participants.

The way in which clinical experiments are conducted by the China SCI Net is completely different. Their research is committed to the establishment of valid data on the safety and efficacy of a tested treatment approach, and this is carried out in a highly systematic and responsible way. Patients are fully informed about the risks and uncertainties regarding efficacy of the intervention. Various safeguards are in place to assure the physical and psychological integrity of all participants; this involves international advisory bodies, multi-level IRB review, and audits by drug regulatory agencies.

It should be pointed out that sympathetic appreciation does not diminish an independent and dissociated analytical capacity. It is important to know that my goal in this study was neither to support the Network nor to criticize it. Rather, it was to take the formation of the China SCI Net as a case study, to explore international academia-driven clinical trial collaborations across the context of scientific multipolarization, and to try to trace the lines of transformation, changing patterns of opportunities and inter-relatedness and observe the types of transnational research organization that emerge.

The China SCI Net turned out to be a fascinating study in this respect, because it initiated transnational academic research collaborations that seem, in many respects, unprecedented, and that may have provided hints regarding the direction clinical research would take in the near future. I am extremely grateful to the researchers and organizational staff who took part in the Network during my involvement with it, for their openness and generosity in providing so much detail on their work; it has allowed me to fully understand the organizational aspects of the Network, and the challenges faced in getting this project to succeed across highly diverse regulatory, cultural and institutional boundaries.

Chapter III

Foundation and history of the China SCI Net and transcontinental scientific exchanges

Introduction

In this Chapter I will first describe the background of the China Spinal Cord Injury Network. Then I will elucidate the motivating forces and reasons behind the decision to build up a collaborative research platform in China. The chapter illustrates that trans-polar scientific partnerships, such as that which exist between China and the USA, not only open up new financing pathways, but also offer access to other crucial research resources. These range from high-level clinical facilities, to unprecedented clinical experiences, highly motivated staff, and human research participants. As I will show, on the basis of data from the China SCI Net, the existence of high-profile capacities in China, in combination with some vital structural differences in relation to the USA, has a strongly enabling effect and is giving rise to novel research possibilities. Hence, what the scientific pole China offers is new funding opportunities and an advanced clinical infrastructure that is characterized by state-of-the-art hospitals, the latest medical technologies, and competent staff.

With regard to structural differences between China and the USA, three factors are significant. First, there are important differences in terms of labor and research costs, which reduce the expense of clinical trials in China by a factor of three to five. Second, the greater population size facilitates easier access to patients, particularly with respect to medical disorders with low incidence rates. Recruitment of patients for clinical trials is further facilitated through socioeconomic differences and diverging healthcare arrangements, which often put a higher burden on people in China with a specific disease or condition, and on their families.

This combination of factors has a facilitating effect – particularly for academia-initiated clinical research partnerships, which are confronted by enormous costs, and highly finite resources. As shown by the China SCI Net, the partnering of researchers from China and the USA can facilitate the creation of independent and large-scale academia-driven clinical research projects, which in one of these two scientific center regions alone, could not (or only with great difficulty) be realized. In this respect, the formation of the China SCI Net constitutes a highly creative effort to maximize financial and human resources that would normally be out of reach for academic researchers in the USA, unless they obtain funding from industry. In this sense, the China SCI Net makes full use of the opportunities offered through the collaboration between the scientific poles of China and the USA.

PART I: A brief history of the China SCI Net

The origination of the China SCI Net is intrinsically linked to the initiative of Professor Wise Young, the founding director of the W.M. Keck Center for Collaborative Neurosciences at Rutgers University, New Jersey, USA. Young, who was born in Hong Kong and spent parts of his childhood in Japan, arrived in the USA in 1970 at the age of eighteen, and studied medicine at Reed College and Stanford University. After completing a PhD at the University of Iowa he settled for a career as neurosurgeon at New York University (NYU), where he became director of neurosurgery research in 1984.⁸

Young has been involved in spinal cord injury research for more than 30 years. In the 1980s and early 1990s, during his time at NYU, he played a key role in the discovery and clinical study of methylprednisolone, the first drug to show any effectiveness in patients with acute spinal cord injuries. In 1997, after the drug was brought to the market by Pfizer, Young left NYU and founded the W.M. Keck Center at Rutgers University, where his studies shifted focus from acute spinal cord injury to chronic injury (Young 2009a).

At Rutgers he formed a team capable of carrying out cell transplantation, manipulating cells genetically, as well as methods for adequately assessing regeneration (*ibid.*). They performed animal studies on olfactory ensheathing glial

⁸ The W.M. Keck Center: Faculty and Staff, URL: <http://keck.rutgers.edu/center/center.html>, (site accessed August 21, 2012).

cells, neural stem cells and umbilical cord mononuclear cells; more recently they have worked with mesenchymal stem cells, embryonic stem cells and induced pluripotent stem (iPS) cells. Young recalled this time as follows:

All this was new for me. In 1998, we were just beginning to learn about stem cells and the existence of adult stem cells was still controversial. We did not know how to grow stem cells or how to manipulate them genetically. It also became clear to me that it would be a long and uphill road to clinical trials of cell transplants in the United States. Not only are neurosurgeons extremely skeptical that any treatment could be beneficial for chronic spinal cord injury, but most of them are frankly afraid of exposing the injured spinal cord. (Young 2009b)

As stated on its website, the W.M. Keck Center was, from its inception, ‘dedicated to multidisciplinary collaborative research’ and ‘to accelerating the translation of scientific discoveries into effective human therapies’.⁹ To realize these purposes, Young promoted a strongly interactive approach that emphasized multidisciplinary, partnerships with research hospitals, and close cooperation with the SCI community.¹⁰ He has actively participated in advocacy initiatives for increases in public funding, and has held monthly open-house sessions at which people with spinal cord injury learned about and discussed novel research and approaches to rehabilitation. In 2001, Young founded the website *CareCure*, which has more than 45,000 registered members and is now one of the world’s largest interactive community websites for people with spinal cord injury.¹¹ As of August 26, 2012, Young had posted 37,480 contributions to discussions with the website’s members.¹²

The *CareCure* community website, as I will show in Chapter VIII, has evolved into an important instrument for patient activism, in particular regarding the uptake of clinical trials. In this respect, the debates occurring on *CareCure* reflect an important trend that has taken place in the SCI community in the USA since the mid-1990s;

⁹ The W.M. Keck Center – Introduction. URL: <http://keck.rutgers.edu/main.html> (last accessed August 21, 2012).

¹⁰ Same source as in previous footnote.

¹¹ John E Smith, one of the site’s moderators, claims that *CareCure* is even the world’s largest SCI community website. URL: <http://cakassel55.healthblogs.org/2008/12/16/closing-out-2008/> (last accessed August 26, 2012). The number of members on August 26, 2011 was 45,624. URL: <http://sci.rutgers.edu/forum/memberlist.php> (last accessed August 26, 2012).

¹² URL: <http://sci.rutgers.edu/forum/member.php?u=10073> (last accessed August 26, 2012).

namely, there has been a shift in patient advocacy from primary efforts to improve ‘care’, toward the gradual realization of seeking ‘cure’ (Olkin and Pledger 2003).

In the SCI community, the ‘pro-cure’ members were initially been represented by Christopher Reeve, the actor of the *Superman* movies, who was left paralyzed from the shoulders down after a horse-riding accident in 1997. The advocacy of Reeve served to pull both public opinion and attitudes within the SCI community in a new direction, whereby there was widespread activism for innovative translational research, in particular for that involving stem cells. This push for seeking cure was continued after Reeve’s death, in 2004, by his wife Dana; this gave rise to an expansion of research activity and funding, and has resulted in the passing of an Act – the Christopher and Dana Reeve Paralysis Act – in 2009. As a result of this Act, research activity on paralysis within the USA has increased further.¹³

This spirit of pro-cure activism is still reflected on the *CareCure* website, which is playing an increasingly important role in the North American SCI community. For example, many of the website’s members are engaged in fundraising for research projects in the USA, and there are widespread calls for new therapies and clinical trials. In contrast to Reeve, however, who targeted efforts at the development of innovative basic research, Young and numerous other present-day contributors to the *CareCure* website push actively for clinical testing of potentially effective treatments.¹⁴

This degree of collaboration and alignment of interests within the SCI community is based on close interaction, poly-vocal dialogue, and joint advocacy between patients and experts, and forms a clear manifestation of what Rabinow has labeled ‘biosociality’ (Rabinow 1996). There are correlates, too, with the participatory approaches and forms of collaborative research found in development and the social sciences (Selener 1997; Lassiter 2008). As I will show in Chapter VIII of this dissertation, with the formation of the China SCI Net these elements of *participation*, *activism* and multi-level *interest-alignment* gain interesting transnational dimensions. In the context of academia-initiated international clinical trial collaborations, they are in many respects unprecedented.

¹³ Christopher and Dana Reeve Paralysis Act: Summary of Legislation. URL: http://www.christopherreeve.org/site/c.ddJFKRNoFiG/b.4442895/k.BCD7/Christopher_and_Dana_Reeve_Paralysis_Act_Explained.htm (last accessed August 26 2012).

¹⁴ Interview Wise Young, August 29 2010, Hong Kong.

First visits to China

Between 1999 and 2003, Young travelled on a regular basis to China, where he gave lectures sponsored by Pfizer on the use of methylprednisolone in patients with spinal cord injury. Even though Young was born in Hong Kong, and his father came from Ningbo, his first visit to the Chinese mainland was in 1999 (IBTV 2010). During his initial visits, Young visited dozens of spinal cord injury units and research centers. Through his conversations with doctors and staff he developed a gradual understanding of the situation for people with spinal cord injury in China, and of the treatment and rehabilitation options and approaches to research (Young 2008). It is likely that the idea to build a collaborative clinical trial infrastructure in China emerged at this time.

From concept to reality

In March 2002 my son was injured and since then we were looking for a therapy. At that time I had no knowledge about spinal cord injury. And I was not aware that it is an irreversible condition. But as times went by me and my son realized that it is not reversible, and we saw he would not recover, because he is completely injured. We started rehabilitation in Hong Kong, for two and a half months, and after this he was able to take care of himself. In Western medicine you receive rehabilitation only, but you have no hope to recover. And so we went to Beijing, to search for Chinese traditional therapies. We were just praying, hoping, because we did not want to sit there, without any recovery. Many different kinds of doctors came, and they offered their skills, like acupuncture, or some massage, or heating techniques, and some herbal medicines. Whatever they were doing, they were offering to us. And everyone said it would help. But after trying for several months, honestly, nothing happened from the traditional Chinese medicine. At the same time I read books, written by Christopher Reeve, and I learned something about what is going on with [then emerging approaches in] Western therapies, for example, weight-bearing treadmills. I did not understand how it worked, and whether it worked, and for what kinds of patients. But I just read that it had helped some patients. [...] From the book I also learned about John McDonald (the head doctor of Christopher Reeve), and I flew [from Hong Kong] to Chicago to meet him. He was doing something with embryonic stem cells, and had a publication on that in that time. I asked him what I could do, and whether I

should take experimental treatments either from China or Taiwan. And he told me to wait for five years. [...] At that time, in 2003 he told me to wait for another five years! ¹⁵

The China SCI Net came into being when Young met Suzanne Poon, whose son, Richard Poon, had been injured during a skiing accident in Japan at the age of sixteen in 2002. After the meeting with McDonald, Poon met Young in September 2003 in Hong Kong. Contrary to her initial hopes, unfortunately, Young was also unable to help her son, and like McDonald before, he advised against the use of experimental therapies (*ibid.*). Waiting five years doing nothing, however, was too long for Poon. Her own discussions with patients who had undergone experimental cell treatments in Beijing, and the writings of Christopher Reeve, had instilled in her a conviction that a therapy for spinal cord injury was imminent. When she asked Young what she could do, he proposed that she should work together with him to initiate a clinical trial infrastructure for spinal cord injury in Hong Kong and the Chinese mainland. Rigorous clinical trials, he stated, were the only way in which candidate therapies could reliably be tested and treatments developed, albeit gradually.

For Poon this was a fundamental turning point. First, any hope she had had that her son could be instantly cured was shattered; second, as she later told me, the motivation to help her son was transformed into determination to support the struggle for a cure, with the aim of helping anyone with spinal cord injury, in the long term. Poon pinpoints this shift to her meeting with Young, as well as the activism expressed in the writings of Christopher Reeve and of the hundreds of injured people she communicated with on the *CareCure* website.

CareCure and Christopher Reeve have changed me. I learned from both that we have to advocate. We have to do something. [...] I do not mind if the complete therapy for SCI will come in fifty or in [a] hundred years, but if we do not work harder... in the coming years – this is my strong believe – if we can bring the therapy closer for five or ten years, how many people will benefit worldwide? This is the drive behind me. First it was my son. But eventually I felt that it is everyone in the world. ¹⁶

After her decision to work with Professor Young, things progressed swiftly. Poon introduced Young to Paul Tam, who was, at that time, the Pro-Vice Chancellor

¹⁵ Interview Suzanne Poon, August 30 2010, Hong Kong.

¹⁶ Same source as in previous footnote.

Research of Hong Kong University (HKU), and a family friend of the Poon. Tam signaled interest in the project, and suggested the HKU as an umbrella organization. Then, in March 2004, Poon arranged a meeting for the two men in Beijing with Xifu Huang, a deputy minister of the Ministry of Health (MOH) in China. At that time, no partner institutes in mainland China had been selected. However, as Young recalls, the deputy minister gave his official blessings to the project, exhorting them to do ethical research (Young 2010a). After that meeting, the deputy minister drafted a document that both publicly announced and formalized the project. The China SCI Net was brought into official existence.

One day later, in Hong Kong, Tam called for a meeting with various individuals at HKU: Kwok-Fai So, the head of the anatomy department, Keith Luk, the head of the orthopedics department, and Johan Karlberg, the director of the Clinical Trial Center. During a joint interview of Suzanne Poon and Young, they recalled that moment in the following way:

SP: All the important components of the network were now gathered together. It was 8 am in the morning. And Paul had a flight at 12 ...

WY: Yes, and HKU agreed to be the umbrella, our heads, during an initial period of time, which was crucial, since this is [a] very difficult [stage] for a clinical trial network.¹⁷

The outcome of this meeting was as follows. Paul Tam was to be a member of the advisory board of the network; Luk and Karlberg were to pull together an executive committee, with the Clinical Trial Center being responsible for protocol development and related controls; Poon would chair the HKU China SCI Fund with the purpose of attracting financial resources for the project; and So and Young were to be the network's co-directors (HKU SCI Fund 2005a, 2005b). The concrete organizational modalities of the network, the forms of collaboration it has given rise to, and its financial operation will all be discussed in greater detail in Chapter VIII.

¹⁷ Interview with Suzanne Poon and Wise Young, August 30 2010, Hong Kong.

Selection of clinical partners

The next step in building the network involved attracting suitable clinical partners. The focus lay initially on the selection of qualified research hospitals in mainland China. Fifteen hospitals in seven cities were enrolled between the summer of 2004 and the spring of 2005. Together with Queen Mary Hospital of HKU, and the Prince of Wales Hospital of the Chinese University Hong Kong, the China SCI Net comprised seventeen hospitals by the summer of 2005.

The first observational study of spinal cord injury patients was launched in October 2005 (China SCI Net 2008). Between 2005 and 2008, nine additional hospitals were selected, seven from mainland China and two from Taiwan. The selection process occurred primarily through a group of senior researchers from the Chinese mainland and Hong Kong, some of which Young had known since 1999 (Young 2004, 2008). One senior researcher who was involved in the process pointed out that the idea was, in brief, to identify hospitals that had gained a good reputation for the treatment of spinal cord injury and would be able to conduct rigorous clinical research and high-quality cell transplantation. The selected hospitals were usually affiliated to the highest ranked medical schools in China, of both civil and military universities. By his inclusion of the military hospitals, Young was primarily following the suggestions of his advisors – after all, the top-ranked military hospitals and medical universities have an outstanding reputation in China. They excel in their research, they offer state-of-the-art treatments, they are tightly organized and well equipped.

The two hospitals in Taiwan were included in 2007. One hospital was from the Buddhist Tzu Chi Order, which approached Young in 2007 to advise on the foundation of a stem cell research center (Young 2008). The other hospital was the Chinese Medical University Hospital in Taichung. The neurosurgery division at this hospital was run by John Lin, who had longstanding experience with stem cell-based clinical trials, and was engaged in two additional clinical trial collaborations with companies in the USA (Neuralstem 2008; Young 2008; Lin 2011). The two hospitals in Taiwan will become more involved when the China SCI Net launches its multicenter Phase III trial in 2013/14.

In 2007, the directors of the China SCI Net decided to leave the umbrella organization HKU and to register as a non-profit organization. A small office was

rented in the Wan Chai District of Hong Kong Island, where a small team of professionals was set up to coordinate the organization's clinical trials and associated hospitals. The personal structure of the board of directors remained unchanged. The board continues to be involved in any central decisions and changes within the China SCI Net, and to function as a vehicle for external advice.

Treatment approach tested by the China SCI Net

In its first series of clinical trials the China SCI Net tested a combination treatment in chronic spinal cord injury patients that comprised three components:

- (i) surgery-based injection of human umbilical cord blood-derived mononuclear (UCBM) cells into the spinal cord,¹⁸
- (ii) a six-week course of oral lithium, and
- (iii) a one-off high dose of methylprednisolone following UCBM cell injection.

The therapeutic rationale behind this treatment combination was to facilitate axonal regeneration across the injured part of the spinal cord in three complimentary ways. The UCBM cells were expected to facilitate formation of a cellular bridge at the injury site to enable re-growth of nerve axons across the damaged tissue environment from above and below. The lithium was administered to stimulate the production of neuronal growth factors (neurotrophines) in both the implanted cells and the cells of the surrounding spinal cord and thus promote the growth of the axons across the newly built bridge over an extended time period. The methylprednisolone was used to increase the survival of the transplanted cells by acting as a blocker of growth inhibitors at the injury site that can prevent the re-growth of axons and other neural cells (Young 2009b).

As can be seen in Table 1, a total of eight clinical trials are currently being conducted by the China SCI Net. Of these, the first is a non-interventional observation trial (study CN100). Lithium was first tested separately in a Phase I study for safety and a Phase II study for safety and efficacy (studies CN101 and CN102). UCBM cells were initially tested separately in patients in two analogous Phase I/II trials, in which a

¹⁸ UCBM cells contain various types of neuronal stem and progenitor cells that differentiate into neural cells after transplantation into the spinal cord. The transplanted cells are HLA-matched to the recipient, to improve therapeutic efficacy and prevent side effects from immune rejection.

first step aimed to establish the safety, appropriate dosage and preliminary efficacy of the cell injection alone; the second step involved testing for safety and efficacy of the cell injection in combination with lithium alone, and in combination with lithium plus methylprednisolone (studies CN102b and CN102b_KM). At the time of writing, follow-up investigations are still ongoing; when the results of these two Phase I/II studies become available, the decision will be made whether or not to proceed with the Phase III study (CN103).

Table 1:

Our Studies

Around the world thousands of scientists are working hard to find a way to cure spinal cord injury. Most of the studies are in laboratories and many of them have had good results. But it may take a long journey for the promising therapies from the laboratory results to clinical practice. ChinaSCINet would like to speed up the transition by organizing different clinical studies. The studies include:

CN100: Observational Study

This multicentre observational study started in October 2005 to collect the acute and chronic spinal cord injured patients data outcomes and follow up for a period of one year or 6 months from 22 hospitals in Mainland China, Hong Kong and Taiwan. This established a solid foundation for the ChinaSCINet to perform clinical trials to test promising SCI therapies following international standards and guidelines. The study finished by the end of 2008.

CN101: Phase I Lithium Trial

This Phase 1 clinical trial in 2007 in Hong Kong was to assess the safety and pharmacokinetics of 6-week course of oral lithium in 20 patients with chronic spinal cord injury. The study finished by the end of 2008. Participating site: the University of Hong Kong, MacLehose Medical Rehabilitation Centre.

CN102a: Phase II Lithium Trial

This Phase 2 randomized double-blind placebo-controlled trial is to assess the efficacy of 6-week course of oral lithium in patients with chronic spinal cord injury. It was conducted by China Rehabilitation Research Center, Beijing, in 2008-2009 and by Buddhist Tzuchi Hospital, Taichung, in 2009-2010.

CN102b: Phase I/II UCBMC Transplant Trial

This umbilical cord blood mononuclear cell transplants trial is to investigate the safety and feasibility of transplanting cord blood mononuclear cells into 20 chronic spinal cord injury patients. The study was launched in Jan 2010 and it is now recruiting subjects. Participating Sites: The University of Hong Kong, The Chinese University of Hong Kong.

CN102b_KM: UCBMC Transplant with Rehabilitation Trial

This trial is to assess the safety and feasibility of umbilical cord blood mononuclear cell transplant followed by locomotion rehabilitation in the treatment of chronic spinal cord injury. Launched in September 2011, it will enroll 20 eligible subjects. Participating site: PLA Kunming General Hospital, Kunming.

CN102c: Lithium+UCBMC Trial

This trial is to assess the safety and efficacy of lithium, umbilical cord blood mononuclear cell transplant and their combination in the treatment of acute/subacute spinal cord injury. Started in September 2011, this trial is going to recruit 60 subjects. Participating site: PLA Kunming General Hospital, Kunming.

CN103 Phase 3 Cord Blood Mononuclear Cells ± Lithium Trial

Provided the adequate regulatory approvals and funds are available, ChinaSCINet hopes to carry out a pivotal phase 3 clinical trial assessing umbilical cord blood mononuclear cell transplants and randomized placebo-controlled lithium in 400 patients with spinal cord injury in Mainland China, Hong Kong and Taiwan.

PART II: New opportunities through collaboration

In the second part of this chapter I will explore the opportunities and resources that the China SCI Net has been able to mobilize by collaborating with hospitals and research institutes in Hong Kong and China. I will first examine the possibilities that result from the processes of economic growth and scientific capacity building that have characterized the situation in China in recent years. Then I will look at the role of structural differences between China and the USA, and on the enabling aspects of these differentials in the context of the formation of the China SCI Net. Three types of factors will be explored at this point: first, the differentials in terms of labor and research costs; second, the differences in population size and the epidemiology of spinal cord injury; and third, socioeconomic differences and disparities in healthcare arrangements.

Scientific capacity building in China – opportunities for collaborations

Since 2002, the total R&D expenditure in China has increased by roughly 20 per cent each year (Qiu 2012a). Large investments have been made to promote independent innovation policies, including the endorsement of medical research. Within this field, drug discovery and regenerative medicine are key areas (*ibid.*: 2). The development of stem cell-based treatments for diseases including age-related disorders like Parkinson's disease, Alzheimer's disease, diabetes and cardiovascular disease has been targeted in particular through what is known as the '863' program' (Pei 2009). More recently, the Chinese government's commitment to stem cell research and regenerative medicine has been re-confirmed in the 'Innovation 2020' program, in which both fields of study were defined as one of seven key areas in the sciences (Qiu 2012b). This investment in research has for many years gone hand in hand with the promotion of medical education, and the development of encompassing clinical infrastructures, particularly in urban areas. In 2009, the National People's Congress called for the creation of 9,000 new medical institutions, and earmarked 850 billion Chinese Yuan for spending on new healthcare infrastructure; this is in addition to the

regular budget for government health expenditures (Sysmex 2010).¹⁹ The total amount of money spent on healthcare and medical infrastructure between 2009 and 2011 has been estimated at twelve trillion Chinese Yuan [ca. 1.9 trillion US dollars] (Olympus 2011).

As has widely been reported, China now has many high-profile hospitals and medical schools, all of which offer good opportunities for collaboration (Gallin 2011), and are increasingly popular with the pharmaceutical industry (Cooper 2008a). Interest in intensifying medical research partnerships with China has been shown by the NIH, which has been holding joint symposia with the Chinese Academy of the Medical Sciences annually since 2009; the purpose of these symposia is ‘to form a network of translational medicine centers’ (Chen 2011: 7) that operate closely with the NIH (Gallin 2011). These efforts toward Sino–American clinical research partnerships also coincide with NIH-initiated training partnerships on clinical research principles and practices that have been in effect since 2008. These are provided in collaboration with the not-for-profit Global MD Organization (Ognibene *et al.* 2011). There is a strong consensus that collaborative translational research between the USA and China may provide an effective platform for tackling global public health challenges, as well improve healthcare delivery and facilitate rapid access to new drugs in both China and the USA (Gallin 2010; Chen 2011).

The well-equipped hospitals and quality of care found in China, in combination with the presence of highly experienced medical specialists there, has also been pointed out by Young (2008). Delivering a presentation at the Bedford SCI Workshop in 2008, Young introduced these issues as central enabling factors for clinical collaborations with China:

There are some misconceptions [with regard to China]. [...] [One is] the assumption that the quality of care is low. And I agree that there is enormous variability in care, but there are some centers in China whose care is as good as in the United States. And even more interesting, many surgeons or doctors here, in the US, would be absolutely astounded on how good, and how well equipped these hospitals are. I would say that almost every hospital in China has now multiple 3.0 Tesla machines [MRI picturing technology]. They are using diffusion tensor [imaging] analysis, which is routine when they are doing all their examinations of the spinal cords. [R]ecently we had a consensus conference, on

¹⁹ <http://www.cecc.gov/publications/annual-reports/2009-annual-report> (last accessed August 26 2012).

what is the best way to transplant cells into the spinal cord. And I asked the group, how many of you have CT (computed tomography)[square brackets?] guidance [an image-based navigation system for surgical operations]? Every hand went up. [China] has taken its huge trade imbalance and has translated this into equipment for hospitals. And many of the top-of-the-line hospitals look like high regencies. They are glass and steel towers. If you go to Shanghai or Beijing, or wherever, this is what it looks like. Really, it is a different world now, just in the last ten years. Finally, there are a lot of people who are saying Chinese doctors are not as good. In my opinion, Chinese doctors, at least in surgery, are much more experienced than US doctors. And they, they have experienced everything. They have seen everything, and they typically operate on ten times more cases than the average US surgeon. (Young 2008)

A second enabling factor, according to Young, which is closely related to the final point above, is that orthopedic and neurosurgeons in China often have considerable clinical experience with stem cell transplantations in humans, as well as knowledge of related surgical procedures. This point is emphasized on the website of the China SCI Net.

China was the logical place to start cell transplant trials because the doctors there have more experience with cell transplants than in any other country in the world. While most other countries were just dipping their toes in the water, injecting the cells intravenously or intrathecally, Chinese neurosurgeons were routinely injecting cells directly into the spinal cord of people with chronic spinal cord injury. Dozens of centers there have transplanted several types of cells into the spinal cords of many dozens and even hundreds of patients. We should learn from the breadth and depth of surgical transplantation experience they have in China, about what works and what doesn't work. Over the past five years, we have trained over twenty-five centers in China to carry out standardized neurological examinations and how to run clinical trials. (Young 2009a)

The availability of unprecedented insights and experiences, that in the context of the USA, due to more stringent regulatory controls could not be made, have informed the clinical trial protocols of the China SCI Net in particular, with regard to the selection of surgical and injection procedures. The availability of these local experiences has not, however, influenced the choice of the cell type that is tested by the Network. The umbilical cord blood (UCB) mononuclear cells that are used in the organization's clinical trials are imported from the USA, and have a proven safety record in humans

in the case of leukemia and various other blood diseases. In the US they are offered to patients, in the context of the FDA regulation for the use of human cord blood (Reuters 2011; NMDP 2012). Even though, the clinical experiments in China form the first transplantations of this type of cells into people with spinal cord injury. This is the reason, why (despite the established safety record in human in the case of blood diseases) dose escalating Phase I safety studies have been conducted in Hong Kong and Kunming.

A third type of opportunity that the gradual ascend of China to a global scientific center region has offered to the China SCI Net is finance. In fact, the daily operations of the China SCI Net have almost completely been funded through funds that have been mobilized in Hong Kong and mainland China (see Chapter VIII). While the cells are sponsored by Stemcyte, a US–Taiwanese Cord Blood Therapeutics Company, the preparation and execution of the clinical trials have predominantly been funded locally, through charity fund-raising in Hong Kong on the one hand, and access to funds from local hospitals, urban and provincial governments, as well as the health department of the Chinese military (Rosemann 2013b). In Chapter VIII I will describe in greater detail the funding opportunities that have arisen in the context of the China SCI Net. For now, suffice it to say that the mobilization of funds from within China for international research projects is a fairly new phenomenon, of the kind that has not been reported in the literature before.

The enabling effects of structural differences

The second part of this analysis concerns the enabling effects on international clinical collaborations relating to structural differences between China and the USA. Three factors in particular will be mentioned: differentials in terms of research costs; differences in population size and epidemiology; and the effects of socioeconomic differences and diverging healthcare arrangements.

(i) Differentials in research costs

According to Mark Engel, the Chief Executive Officer of a large contract research organization (CRO), the costs for conducting clinical trials in China in 2008 were five or six times lower than those in the USA (Engel 2008: 3). The reasons for this relate to cheaper labor costs and the lower prices charged by hospitals in China (*ibid.*: 5). These

favorable conditions certainly had an enabling effect on the operation of the China SCI Net. As an independent, academia-initiated clinical trial infrastructure, which runs on a financial shoestring, the lower-cost environment in China has provided clear incentives as well as novel opportunities. As Young clarified in a 2009, during an interview with the *Lancet*, the costs of surgery in China are about five times less than in the USA (Qiu 2009). In a blog contribution on the *CareCure* website, he states:

Doing the trials in China is advantageous because trial costs are lower, large numbers of patients are available, and the doctors are experienced and enthusiastic about cell transplantation. In the US trial costs may be five times higher, there are fewer patients, and most doctors have little or no experience with cell transplants.²⁰

From this perspective it can be seen that the testing of cell-based therapies in China be done ‘more quickly and cheaply’ (Young, cited in Qiu 2009), and with more experienced doctors. The link between higher speed and lower costs will be expanded on in the next section.

(ii) Differences in population size and epidemiology of spinal cord injury

As stated by Engel, the huge population in China means patients are available in large numbers even for trials with orphan diseases.²¹ Furthermore, large concentrations of patients in huge hospitals allow for fast recruitment, which in turns facilitates the rapid completion of trials, and the saving of additional costs (Engel 2008: 6).

This assessment holds true, too, for spinal cord injury. Between one fifth and one third of all people with spinal cord injuries in the world are expected to live in China. The number of cases is estimated at 500,000 to 1,000,000, and the total prevalence lies between two and three times more than that in the USA (Li 2005: 2; Luk 2005: 3). The yearly incidence rate in urban areas of China appears to have continuously risen since the 1980s, and now lies in the region of 60 per million – that is a third more than the US average (Li 2005: 2). This high incidence rate can be traced back to China’s construction boom, as well as less rigorous work safety

²⁰ Blog contribution of Wise Young on *CareCure*, June 25, 2012. URL: <http://sci.rutgers.edu/forum/showthread.php?t=160146&page=9> (last accessed August 26, 2012).

²¹ The McGraw-Hill Concise Dictionary of Modern Medicine defines “orphan disease” as: ‘Any disorder affecting less than 200,000 people in the US (less than one per 1,000 people)—regarded by the pharmaceutical industry as too rare for developing commercially viable products’. URL: <http://medical-dictionary.thefreedictionary.com/Orphan+Disease> (last accessed September 20, 2012).

arrangements (Li *et al.* 2004). These conditions facilitated the recruitment of patients also in the context of the China SCI Net. In comparison to Hong Kong, with its comparably small population and a yearly SCI incidence rate of just 20 per million (Luk 2005: 3), recruitment of patients in China is much easier. Young reported the following in this respect:

Lack of patients in Hong Kong is a problem because there are relatively few people with spinal cord injury in Hong Kong. I suppose that we could have gotten more patients by hyping the therapy but this is not the way we do things. [...] Lack of patients in China [on the other hand] is not a problem; there are plenty of people who are willing to volunteer.²²

A close link also exists, of course, between the size of the population in an area and market-size. The simultaneous testing and joint regulatory approval of a new treatment in both China and the USA (or another country) amplifies market opportunities and increases the chances for investments from the pharmaceutical industry. The formation of the China SCI Net, and its sister network in the USA (the SCI Net USA) facilitates such processes. As I will show in Chapter VIII, the creation of this trans-polar clinical research economy is hoped to encourage new flows of investment at a later time, and to boost drug development in the SCI field on a previously unprecedented scale.

(iii) Socioeconomic differences and diverging healthcare arrangements

Large population size, as has been shown, simultaneously facilitates both patient recruitment and lowers costs. Recruitment of patients, however, is not only linked to population size, but also to socioeconomic differences and diverging healthcare arrangements, both across and within the two countries. In China, for instance, the overwhelming numbers of people with spinal cord injuries come from poorer socioeconomic backgrounds, and many of these people have lost income opportunities due to their injury (Li 2005: 3). Healthcare arrangements, particularly among the rural population and migrant workers in the big cities, are limited; in general, only 30 per cent of medical costs are covered by the government. Furthermore, rehabilitation is currently available only for a minority (Young 2008). Against this background it

²² Blog contribution of Wise Young on *CareCure*, January 21, 2012. URL: <http://sci.rutgers.edu/forum/showthread.php?p=1480260> (last accessed August 26, 2012).

appears that the willingness of these patients to partake in human or early-stage clinical trials is considerably higher than in high-income countries that have strong healthcare systems. Young clarifies this point, again, in relation to the situation in Hong Kong:

In Hong Kong, in particular, where there is cradle-to-grave healthcare, there is really no reason for people to volunteer for trials. Why not wait until the trials show that the treatment is safe and effective? ²³

In a later passage of the same text, Young concludes that conducting large clinical trials with multiple centers in countries with large population sizes may be the only way to overcome this challenge.

Lack of volunteers is likely to be a problem for the world. We may have trouble finding 20 patients for a phase 1/2 trial in Norway, France, or the United States. However, this is one of the reasons why we must have networks with multiple centers. Networks are the only way to get the numbers that we need to show therapeutic efficacy. ²⁴

Conclusions

In this chapter, I have described the opportunities and resources that can be mobilized by the formation of a transnationally operating clinical trial infrastructure in China. In this context, two different kinds of factors were explored. First there were the resources and possibilities related to the efforts put into the infrastructure and capacity-building in China during the last three decades. In this respect, I have pointed to the availability of high-level clinical facilities, unprecedented experiences in the field of surgery-based transplantation medicine, and the multifaceted opportunities for acquiring research funds in China. The second set of issues explored in this chapter were the enabling factors that can be traced back to a number of structural differences that exist between China and the USA. In this respect, I have highlighted the role of differences in costs, population sizes and epidemiological population profiles, as well as those in socioeconomic circumstances and healthcare arrangements. These findings

²³ Same source as in previous footnote

²⁴ Same source as in previous footnote

refer to the continuing significance of structural asymmetries between rapidly developing countries such as China, and more evenly developed countries such as Hong Kong, or the USA, where the overall level of wealth is still higher, and health care insurance as well as social care arrangements for people with disability are more comprehensive. The case of the China SCI Net has shown, in this respect, that the increasing availability of new types of resources in emerging scientific and economic center regions such as China and India, together with the persistence of socio-economic divisions, poverty, as well as limited access to comprehensive health care, offer powerful opportunities and incentives for international clinical research collaboration, in particular regarding the lessening of research costs, and processes of patient recruitment.

From a more positive reading, this situation may have a strongly enabling effect, and facilitate the development of large-scale international research projects, that may advance processes of medical innovation and that in the long-term benefit local patient and research communities. From a more negative reading, the coalescence of new types of material, technological and knowledge resources on the one hand, and the persistence of global (as well as inter- and intra-regional) inequalities on the other hand, may give rise to well-known dangers such as exploitation, vulnerability and inadequate forms of exchange and benefit sharing. In case of more responsible forms of clinical research collaborations such as the China SCI Net, where patient recruitment occurs by full disclosure of medical risks and without exaggerated claims (see Chapter IV), and multiple levels of regulatory approval are sought (see Chapter VI) the risk of exploitation and undue harm to patients, may only be small. In other projects, however, the dangers for patients may be much higher.

It is noteworthy that such risks are not necessarily related to international research collaborations with partners in highly developed countries such as the USA, the EU and Japan. With the ascend of China, India and other parts of the world to global scientific and economic center regions, the strategic use of inequalities and vulnerabilities, and related forms of instrumentalization and misuse, may increasingly come from within these regions. Exploitation of patients and other vulnerable groups is likely to surface both in domestic and international projects, which are initiated by researchers and scientific entrepreneurs from within these countries.

Chapter IV

Conducting a stem cell-based clinical trial for spinal cord injury

Introduction

A central theme in this dissertation is the ‘systemic properties of science’, that is the ways in which the production of scientific data in hospital and laboratory is grounded within the socio-material texture of societies (Star 1995). In this chapter, however, the focus on these relationships is given instead, to the micro-organizational and work practices in the context of the clinic. More specifically, I will concentrate on the situated interaction processes and clinical procedures encountered in the first clinical trial of stem cells conducted by the China SCI Net (clinical trial CN102b; see Table 1 on page 34) in Hong Kong. Four central aspects of the trial will be discussed: the recruitment of patients; the preparation of cells; the surgery and cell injection; and the procedures for outcome measurement. These elements will be explored from several perspectives: (1) the formalized specifications of the research protocol, (2) the practice-based perceptions of clinical staff and researchers, and (3) the corporeal experience of a clinical research participant.

The complex everyday activities of the clinic, in which the surgery-based clinical trials with stem cells (a potentially important form of future medicine) were based, have not yet been explored in the literature. In the context of this dissertation, however, it is important to elucidate the methodological and procedural aspects of the experimental clinical labor for two reasons. First, the execution of the clinical procedures that are introduced in this chapter form the practical core and central purpose of all organizational activities of the China SCI Net (these are discussed in Chapters III, VI, VII and VIII of this dissertation). Second, appreciation of the situated clinical practices and challenges of stem cell-based clinical trials is important for increasing understanding of the scientific and regulatory controversies in this area of research (these will be the object of analysis in Chapters V and VI).

The structure of this chapter is as follows. First is a brief introduction to the different types and stages of clinical trials, and then the place of the China SCI Net’s

CN102b study in this will be explained. The logistical aspects of the trial will follow, and then I will continue with the themes of patient recruitment, cell preparation, surgery and injection, and outcome measurement. The chapter ends with a conclusion.

Locating the trials

Experimental clinical interventions with stem cells in China, as I will show in Chapter V, have been conducted in many different forms, ranging from unproven experimental, for-profit therapies, to semi-standardized clinical trial-like studies and highly systematized clinical trials. In contemporary drug research, randomized placebo-controlled clinical trials are now widely seen as the methodologically most reliable form of clinical research. In most countries they have become an obligatory passage point for the approval of new medicines. Drug regulatory authorities commonly require three subsequent phases of randomized clinical trials (RCTs) in order to approve a new drug, and these studies should involve increasing numbers of research subjects, and testing of the efficacy and safety of the new drug in sufficiently large and diverse study populations.

Phase I trials are safety studies. They test a new product in increasing doses in a small number of usually healthy human volunteers. In Phase II and III trials, the number of participants is gradually increased, with the purpose of systematically determining the efficacy and identifying any adverse effects. Drugs based on chemical compounds (i.e. the majority of drugs we use) are often tested further still, in a Phase IV post-approval trial. This occurs after the drug has been put on the market.

If testing in healthy individuals is seen as unethical (as in case of surgical-based procedures), or if the experimental interventions are thought to be of potential benefit to sick people for whom no other treatment exists, then a new drug or therapeutic approach may be tested directly on patients in a Phase I study. Such investigations are commonly labeled phase I/II trials, that is the first in-human studies to investigate the safety, dosage levels and first indications based on treatment responses among a small number of patients.²⁵

The CN102b clinical trial in Hong Kong described in this chapter was set up as an open-label (non-randomized), dose-escalating phase I/II trial whose purpose is ‘to

²⁵ Information from National Cancer Institute, USA: <http://www.cancer.gov/dictionary?cdrid=45832> (last accessed August 10, 2012).

investigate the feasibility, safety, and efficacy and optimal dose of umbilical cord blood mononuclear cell transplant in the treatment of chronic spinal cord injuries'.²⁶ The study was the first clinical trial with stem cells to be conducted by the China SCI Net. It is also the first trial of umbilical cord blood (UCB) mononuclear cells that have been HLA-matched (that is, the donor and recipient share the same class of protein markers known as human-leukocyte antigens) and, in the context of a systematic clinical study, transplanted into the human spinal cord of a patient. According to the study protocol the trial required 20 patients with chronic spinal cord injuries and a neurological status as specified as 'A' on the ASIA (American Spinal Injury Association) impairment scale (where A signifies a complete loss of sensory and motor function below the level of the injury). The neurological level of these patients has to be between cervical level C5 and thoracic level T10 (see Figure 1). In addition, the spinal injury must have taken place more than one year before commencing on the trial.

To determine the best possible dosage of cells, and to assess the safety, feasibility and preliminary efficacy of the transplanted UCB mononuclear cells, the study protocol divided participating patients into five groups, each with four patients. One group was to be treated after the other, that is sequentially rather than all five at once. Groups I, II and III were to receive an injection of HLA-matched UCB mononuclear cells alone, but in increasing doses: 4 microliter (1.6 million cells) for Group I; 8 microliter (3.2 million cells) for Group II; and 16 microliter (6.4 million cells) for Group III – the highest dose to be administered in the trial. This was to establish the highest possible *safe* dose for future stages of the trial.

Once determined, Groups IV and V would receive this highest safe dose of cells, plus the other components of treatment, thus: Group IV would receive the safe dose of cells plus an intravenous injection of 30 mg/kg methylprednisolone; Group V would receive the safe dose of cells plus the methylprednisolone plus a six-week course of oral lithium carbonate. Group V would be the only patients to obtain the full treatment. This full treatment combination will be tested in a subsequent Phase III study in 2013/14. (For a full review of the treatment rationale, see Chapter III.)

²⁶ A summary of the study protocol of trial CN102b, from which this quotation is taken, can be found on the clinical trial registry of the US NIH site, ClinicalTrials.Gov. <http://www.clinicaltrial.gov/ct2/show/NCT01046786?term=spinal+cord+umbilical+hong+kong+china&rank=1> (last accessed August 10, 2012).

The trial was approved in 2009 by the Department of Health in Hong Kong (the city's drug regulatory authority). It was being conducted by two teams of neurosurgeons in Hong Kong University's Queen Mary Hospital, and the Prince of Wales Hospital of the Chinese University of Hong Kong. A more detailed description of the way in which the trial obtained regulatory approval is provided in Chapter VI.

The first patient was injected with UCB mononuclear cells in November 2010. Due to difficulties in recruitment in Hong Kong, however, there were only eight participants, and in April 2012 the trial was still open for new patients. To counter this unexpected challenge, the leadership of the China SCI Net decided in early 2011 to conduct a parallel study in Kunming, the capital of Yunnan Province in China, where there was a larger prevalence of people with spinal cord injury, and where recruitment was expected to be faster.

The clinical trial in Kunming (CN102b_KM; see Table 1 on page 34) was begun after my fieldwork was completed, and could therefore only be followed through data published on the Internet and a few interviews. Twenty chronic SCI patients, as specified in the Kunming protocol, were given cell transplantations, but the outcome measurement is still ongoing. In this chapter, therefore, the primary focus is on the CN102b trial in Hong Kong, although the Kunming trial will be used for the occasional reference point. It should be noted that the generosity of researchers, clinical staff and patients in the Hong Kong trial, in sharing their perceptions and experiences with me, has resulted in this unique opportunity to document the very first UCB mononuclear cell transplantations in people with spinal cord injuries in the world, in the context of a systematized clinical trial.

I will now discuss the different aspects of the trial in greater detail. I will first speak about the organization and logistics of the trial, and then introduce four main aspects of the study: (i) the recruitment and initial neurological assessment procedures; (ii) the origin and preparation of the cells for transplantation; (iii) the surgery and process of cell transplantation; and (iv) the outcome measurement procedures. It is important to note that these four elements constitute the central, and fully standardized, clinical building blocks of the current clinical trial series of the China SCI Net. They not only form the basis of the trials in Hong Kong and Kunming, but also will be replicated in the Phase III multicenter clinical study due to start in 2013/14.

The following sections are based on information provided by staff from the China SCI Net headquarters in Hong Kong, and the PIs and clinical staff from both, Queen Mary and Prince of Wales Hospitals. However, descriptions of the logistical aspects of the trial, as well as cell preparation and surgical procedures are derived primarily from the experiences of the team in the Prince of Wales Hospital.

Logistical aspects of the trial

The preparation and execution of the CN102b trial in Hong Kong is based on a complex range of organizational activities and interplay between numerous departments, institutions, organizations and individuals from Hong Kong, mainland China, Taiwan and the USA. The central organizational nodes in this are the China SCI Net headquarters in Hong Kong, two clinical trial coordinators in two Hong Kong hospitals, the scientific committees of the trial, and the Network's board of directors. The study protocol of CN102b and related execution pathways are defined by three scientific committees, namely the treatment protocol committee, the outcome measure committee, and the implementation committee. These committees include the two PIs and other medical specialists from the two hospital teams, directorial board members, and a legal advisor. While the treatment combination and surgical procedure were determined beforehand, the committees served to refine any decisions made and add or revise particular elements in relation to the local conditions and any unforeseen circumstances (see section (i) on patient recruitment).

Coordination of the trial in terms of its execution lies in the hands of the PIs, the clinical trial coordinators in the two hospitals, and the Vice-President of the China SCI Net headquarters, Dr Wendy Cheng.²⁷ Two management levels interact at this level: the management of the Network as a whole, and the management of the trial in each of the two hospitals. Executive management at the level of the Network as a whole lies in the hands of Dr Cheng. Regarding CN102b, her tasks are primarily to facilitate and monitor the trial's implementation and to observe whether the two hospitals meet the administrative requirements set out by the Network. This involves providing technical and financial support, overseeing the approval procedures of the

²⁷ Some of the names of persons in this chapter, are made anonymous (i.e. are given different names), on behalf of the wish of the interviewees. Consultations with interviewees regarding the use of names and representations of the trial in publications, are currently being held.

ethics committees, and dealing with informed consent forms and insurance arrangements, as well as the controls of clinical trial documentation, GCP (good clinical practice) standards, and incoming data. The same tasks apply to the Kunming trial CN102b_KM. Because the data from the two trials CN102b and CN102b_KM will be compared, a number of basic standardized requirements must be met by all of the participating institutes.

The management of the trial in the two hospitals in Hong Kong lies primarily in the hands of two clinical trial coordinators who operate under the supervision of the PI in each institute, and in close collaboration with Dr Cheng. The role of the trial coordinator is, in essence, to facilitate the logistics for the implementation of the clinical trial protocol.

As reported by Dr Jennifer Zhao,²⁸ the coordinator of the CN102b trial at Prince of Wales Hospital, this includes the following tasks: organizing all medical assessment and measurement procedures, from neurological examinations of patients in the recruitment phase, to the safety and efficacy outcomes; entering study data into a web-based recording system; carrying out controls regarding the availability and standardization of required tests and equipment (such as laboratory tests and MRI picturing technology); ensuring that the trial is conducted according to the criteria set out by the China SCI Net and the rules and legal requirements of the hospital; and coordinating the locations and staff when a new patient is scheduled for surgery.

Dr Zhao describes this last point as her most challenging responsibility:

From the role of organizing this research, the most difficult part is to get all the different parties together. If you have a patient to be operated next Monday, then we have to make sure that every party is okay with the operation date. We have to make sure that Dr Tsai (the head of the transplantation lab) is available for the cell culturing, so that the cells are ready. We have to make sure that there is an operation theatre for the patient, and [book] the occupational therapy and physiotherapy assessments. Then we have to make sure that there is a bed in the ward for the patient.

Altogether, around twenty people were involved in the trial at the Prince of Wales Hospital. The PI of the study was the neurosurgeon Professor Ming Luk, who is also

²⁸ Some of the names of persons in this chapter, are made anonymous (i.e. are given different names), on behalf of the wish of the interviewees. Consultations with interviewees regarding the use of names and representations of the trial in publications, are currently being held.

the head of the Department of Neurosurgery. He and his neurosurgeon colleague, Professor Ya Jin were responsible for the surgery and the transplantation of the UCB mononuclear cells. The cells were prepared for transplantation by Professor Hui Tsai, who is the head of the Blood and Marrow Transplant Laboratory at the Prince of Wales Hospital. The work of these specialists will be described in greater detail in sections (ii) and (iii) below.

The responsibilities of Dr Zhao, the trial coordinator at the Prince of Wales Hospital, have already been touched on above, and will be explained further in subsequent sections. She was assisted by Melanie Zhang, whose responsibilities included monitoring the assessment protocols of patients. The two neurosurgeons Profs Luk and Jin and Dr Zhao were assisted by four junior doctors and a number of nurses, all of whom were affiliated to Professor Luk's department. The nurses were primarily involved in clinical care work after surgery, while the junior doctors were concerned with data collection, examination procedures, and the organization of pharmacokinetic and other medical tests, some of which are done at laboratories in the hospital and others at specialist laboratories elsewhere. Their work took place during the patient recruitment process, and later in the follow-up period.

Standardized neurological assessment of the patients was not carried out at the Prince of Wales Hospital, but at the MacLahose Rehabilitation Center on Hong Kong Island. A specifically trained physiotherapist and occupational therapist conducted the assessments for all participants in the CN102b trial from both the Prince of Wales and Queen Mary hospitals. Their work, like that of the four junior doctors, was during the recruitment and follow-up periods. These are the subject of the next sections of the chapter.

(i) Patient recruitment and neurological assessment

Recruitment of patients was on the basis of rigidly defined inclusion and exclusion criteria. The inclusion criteria were as follows: the study was open to chronic spinal cord injury patients, with an injury between the spinal levels of C5 and T10 (see Figure 1). The injury must have happened more than a year before the trial, and the neurological examination results must have been stable for at least six months. The neurological status of the patients had to be 'A' on the ASIA impairment scale, involving complete loss of sensory and motor function below the injury site. Patients

could be of either sex, and aged between 18 and 60 years. They were required to fully understand the aims, procedures and risks of the trial, and sign the IRB-approved informed consent form (Leung 2010).

Participants were not eligible to take part in the trial if the length of their spinal cord lesion exceeded three segments, or if they had a cyst in their spinal cord. Other exclusions included patients with significant renal, cardiovascular, hepatic or psychiatric disorders, or other severe medical diseases or infections. Pregnant or breastfeeding women, or those of child-bearing age who refused to use contraception, were not allowed to participate. Additional exclusion criteria were the unavailability of HLA-matched umbilical cord blood cells, and patients contraindicated for laminectomy procedures (surgery on the lamina bones of the spinal vertebrae) or the drugs methylprednisolone or lithium carbonate (*ibid.*).²⁹

Eligibility to participate in the trial was assessed by the PIs and medical staff in both hospitals. Evaluation of the neurological status of patients, on the basis of the ASIA impairment scale, was done by specially trained physiotherapists and occupational therapists at the MacLahose Rehabilitation Centre. A discussion of the assessment and informed consent procedures follows below.

Recruitment in Hong Kong

The recruitment of patients for the CN102b trial in Hong Kong was very challenging. Recruitment started in May 2010, four months after approval for the study was obtained from the Hong Kong Department of Health.

Information on the trial was distributed in many ways to the patients. The website of the China SCI Net provided a downloadable information sheet giving details of the trial's objectives and procedures. Two public lectures were also given by the China SCI Net, to invited members of various SCI organizations and the wider community in Hong Kong. The two PIs and Dr Young delivered one and a half hours of detailed information to interested patients, explaining the purpose of the study, the surgical and injection procedures, and the related risks. The third source of

²⁹ The inclusion and exclusion criteria mentioned here, and other details of the CN102b trial in Hong Kong, can be found on the U.S. NIH Clinical Trials Registry *ClinicalTrials.gov*. URL: <http://clinicaltrials.gov/ct2/show/NCT01046786?term=CN102b&rank=1> (last accessed September 20, 2012)

information was through registration at the USA trials registry, *ClinicalTrials.gov*.³⁰ This website provided details on the study's purposes and protocol and announced that the study was recruiting patients. Detailed information and ongoing updates on the Hong Kong trial were also available on the *CareCure* website, which is available also to people from Hong Kong and mainland China.

Challenges to recruitment

Despite this high level of visibility, the recruitment of patients for the trial in Hong Kong was highly problematic, and there were severe delays. By February 2012, only eight patients had been successfully enrolled out of the intended twenty.

There are various reasons why the recruitment process in Hong Kong was so challenging. Among these was the relatively low number of eligible patients for the study. Of the city's 6.8 million inhabitants, approximately 800 to 1000 had some sort of spinal cord injury. The total number of people with chronic injury was around 400. Of these, less than half had an ASIA A impairment, which is one of the central inclusion criteria; and of this group, comprising fewer than 200 patients, only half had lesions between C5 and T10 – another inclusion criteria. The range of eligible patients was also restricted by age, because the trial was recruiting people between the age 18 and 60 years.³¹

By June 2010, the doctors in Hong Kong had screened some 40 likely participants, but most had to be rejected because they did not 'fully' qualify as ASIA A in the neurological assessment, or they had metallic implants so they could not undergo MRI scanning. This was important because MRI technology was one of the ways in which safety outcome would be measured. Other patients were ineligible because they had a lesion that was slightly too high (between spinal levels C4 and C5) or too low (between T10 and T11) for eligibility in the trial.³²

In addition to the selection criteria, one more issue led to the withholding of eligible people from participating in the trial, related to the fact that this was the first in-human safety study. At a public lecture by the China SCI Net in 2010, I met a young man called John Lee who had a chronic spinal injury, and we became friends over time. John told me that because the study was then only testing for safety – rather

³⁰ Same source as in previous note.

³¹ Interview with Prof Ming Luk, Hong Kong, June 26 2010.

³² Interviews with (1) Prof Ming Luk, Hong Kong, June 26 2010; (2) Prof Yi Hwong, Hong Kong, August 21 2010; (3) Prof Ya Jin, Hong Kong, August 24, 2010.

than efficacy – and they knew that only four out of twenty patients were going to receive the full treatment combination. This meant that expectations of the trial were low, and some patients wanted to wait for the Phase III study, when a safe dosage had been established, and the treatment would be more mature. People were also reluctant to participate because of their perceptions of risk from the surgery. According to John, several of them were concerned that their physical conditions would worsen rather than improve because of surgical complications.³³

These concerns correlated with the openness with which the study's investigators communicated with the patients about the risks involved. Honest reporting of such risks and uncertainties is a legal pre-requisite in contemporary clinical drug trials, which contrasts markedly with many of the experimental for-profit therapies offered to people with spinal cord injuries in mainland China. For example, the description of Phase II of the trial on the Network's website made no claims regarding efficacy of the treatment at that stage of the study; this would be tested for later, in a Phase III study. The site clearly pointed out that 'based on the results of this Phase I/II trial, a phase III trial will be decided'. Thus if the treatment were found to be unsafe or to have no efficacy, the study would go no further than Phase II.³⁴ This information was also communicated to patients on the *CareCure* website. On September 1, 2010, for example, Young stated that if the treatment did 'not show beneficial effects or even deleterious effects, we will of course not continue onto the phase III trial'.³⁵

The fact that risks and expectations of the trial were communicated in an open and unbiased way to patients was confirmed in several ways: through interviews with various trial investigators, through attendance at a public lecture, and through conversations with John and another patient, both of whom went through the informed consent procedure. At the public lecture in Hong Kong, organized to attract new study participants, no overstated expectations were given regarding efficacy of the treatment; for example, Professor Yi Hwong the PI of the study in Queen Mary Hospital who introduced the study protocol stated twice that they could make no promises regarding efficacy. There was mention of the animal research that had first

³³ Interview with John Lee, Hong Kong, January 2 2011.

³⁴ URL: http://www.chinascinet.org/index.php?option=com_content&task=view&id=125&Itemid=167&lang=en (last accessed September 21, 2012).

³⁵ Blog contribution of Wise Young on *CareCure*, January 9, 2010. URL: <http://sci.rutgers.edu/forum/showthread.php?t=139662&page=2> (last accessed September 21, 2012).

indicated the benefits of transplanting UCB mononuclear cells, in the context that ‘perhaps’ the tested therapy would ‘lead to improvements in neurological functions’ in humans (Leung 2010).

In Hong Kong, I talked with three of the four key neurosurgeons involved in the study, who mentioned independently that the surgery was technically simple and not particularly risky. However, all three acknowledged that there were certain risks and temporary adverse effects associated with the study. It was pointed out during the lecture that patients might experience a decrease in neurological function and sensory perception for several days after the surgery, and that there were other risks related to the surgery and cell injection, such as bleeding and inflammation (including inflammation of the meningeal linings around the brain, causing meningitis).

Other risks mentioned during interviews were related to anaesthesia, neuropathic pain, sensory losses and, in extreme cases, loss of neurological function (Leung 2010).³⁶ To minimize the risk of functional loss, two safety features were built into the study protocol. First, chronic ASIA A patients were selected for, because they had complete loss of motor and sensory function below the injury site. Second, patients were selected in whom C5 was the highest neurological level affected, because a surgical mistake at level C4 or higher can impair breathing function.³⁷ Although these selection criteria minimized the risk of functional loss below the injury site, there was still a small risk of partial loss of function *above* the injury site. However, as pointed out by all three physicians, this risk was very small.

The three neurosurgeons communicate the full range of risks and potential adverse reactions to participants. Dr Hwong, for instance, said he explains patients the entire procedure, in detail, to clarify all the risks. According to this researcher, the complete disclosure of potential risks was particularly important, because the participants had no acute medical conditions that required surgery which the patient would gain unquestionable improvement from.

That chance for efficacy, and potential risks are candidly communicated to patients was confirmed by two patients – John, as described previously, and Catherine Chen, to whom I was introduced by John. They both applied to participate in 2010 while I was conducting my fieldwork. Catherine and John were both fully aware that,

³⁶ Interviews with (1) Prof Ming Luk, Hong Kong, June 26 2010; (2) Prof Yi Hwong, Hong Kong, August 21 2010.

³⁷ Interview with Prof Yi Hwong, Hong Kong, August 21 2010.

even though participation might have some beneficial effects, the chance of benefitting from these was lower in the dose-finding trial than in any phase III trial that might follow.³⁸ They both had a comprehensive understanding of the risks involved. John, for instance, who had a very high injury level (C5/C6), was told by one of the investigators during the informed consent procedure that a problem with the surgery might result in him not being able to move his hands. John decided to continue with his application despite this. However, he was later barred from participation because in the neurological evaluation he did not fully meet the inclusion criterion. As he recalls:

Participation in the trial requires ASIA A especially. I had thought I met this requirement. When I visited the Rehabilitation Hospital for the medical assessment I saw my medical record on the computer of the doctor [based on previous neurological assessment], and I saw 'ASIA A'. But, in the assessment procedure that followed, the physiotherapist said I was assessed as not completely ASIA A. So I could not participate.³⁹

For John this was a great disappointment, because he had considered participation in the study as an important opportunity. Not long after, however, his initial feelings of discontent became more constructive. He postponed his former plan to take up a PhD in Public Care, and instead began working in a non-governmental organization (NGO) that was striving for improved care and realization of rights for people with severe physical disabilities in Hong Kong.

Similarly, Catherine Chen's hope outweighed her fears of emotional distress and physical risks. In response to my question on why she had decided to take part in the trial, she emailed the following response:

If you ask me why I chose to take part in this research, I'd tell you that undoubtedly there is no SCI patient who wants to be bound to the wheelchair for the rest of her life. I got injured when I was 19. I spent almost 5 years to resume my normal life in the society. Since my mum was a traditional woman, she really minded on how other people would view me as disabled and about all the gossip. [...] Over the past many years, I had no choice but accept the fact that I was wheelchair-bound, but still there are so many problems that made me feel annoyed: incontinence, relations with family members, and work. [...] I signed up for the stem-cell treatment by phone and email immediately when

³⁸ Interviews (1) John Lee, Hong Kong, January 2, 2011; (2) Catherine Chen, Hong Kong, July 5 2011.

³⁹ Interview John Lee, Hong Kong, July 5, 2011.

I saw relevant information regarding the research of SCI from newspaper in 2004. Having been waiting for several years, I really hope that the success will come and I can recover. I also hope that I no longer need to go through so many ‘assessment’ with my career development. Perhaps my hope for the research and technological advancement has been significantly motivating me to persist till now.⁴⁰

This statement clearly shows the difficulties Catherine encountered in the aftermath of her injury, and her hope that participation in the trial would result in some form of recovery; this hope was kept her going. Unlike John, Catherine met the initial inclusion criteria, and she underwent the surgery in the spring of 2011. A more detailed account of her experiences can be found in section (iii) on surgery and transplantation that follows later.

Recruitment in Hong Kong versus recruitment in Kunming

In the Chengdu Army General Hospital in Kunming, there was a fundamentally different situation to that in Hong Kong. Patient recruitment for the CN102b_KM trial was rapid and without complication. The trial started in September 2011, and three months later 18 patients had been selected.⁴¹ This is no surprise. Situated in the capital city of Yunnan Province (with a population of 46 million), close to the border of neighboring Sichuan Province (with a population of 80 million), the hospital housed the largest spinal cord injury unit in Southeast China and was the hub for treatment and rehabilitation research. It attracted patients from many other parts of China.⁴² Once it was clear that the Phase I/II trial would also be carried out in Kunming, a list of aspiring participants soon built up, prompting doctors to recruit patients on the basis of personal invitation. I am not aware of the details of this process.⁴³

In addition to the differences in size and population in the two locations, another important factor to impact on the process of patient recruitment was the extent and quality of healthcare arrangements at that time. I am not able to provide systematic quantitative data on this issue, but several of my qualitative observations point in this direction. In mainland China, the healthcare service is extensively

⁴⁰ Email from Catherine Chen to author, April 6, 2011.

⁴¹ Blog contribution of Wise Young on *CareCure*, January 6, 2012. URL: <http://sci.rutgers.edu/forum/showthread.php?t=139662&page=52> (last accessed September 21, 2012).

⁴² Interview Prof Kwok-Fai So, Hong Kong, June 11, 2010.

⁴³ That recruitment is by invitation only, was reported on *ClinicalTrials.gov*, URL: <http://clinicaltrials.gov/ct2/show/NCT01471613> (last accessed September 21, 2012).

privatized, with comprehensive care arrangements available only to a smaller number of people with disabilities: these are employees of the government and staff of companies who provide private health insurance, and those who can pay from their own pocket. The majority of people with chronic spinal injury fall outside these categories, causing a strong health burden and high financial pressures on the patients themselves and their families.⁴⁴

This contrasts to the situation in Hong Kong, where there are far more comprehensive care arrangements for people with disabilities, targeted particular at those of low or middle incomes. The government covers the costs of hospitalization, surgical and other treatments, as well as outpatient services. People who have received an injury can also apply for Comprehensive Social Security Assistance (CSSA). They are provided with a flat with disability-compliant modifications, and basic equipment such as wheelchair and lifts; they also receive rehabilitation and occupational therapy. Furthermore, depending on the financial situation of their families people with SCI can apply a disability allowance and access a government-initiated job scheme.⁴⁵ Those who are not (or only partly) eligible for government support, can apply for practical support and financial assistance through a series of local NGOs.⁴⁶ Even though, as some of my informants have pointed out, the care of people in wheelchairs is far from optimum and the job schemes are not entirely satisfactory, the situation is very much more comprehensive and inclusive than in mainland China.⁴⁷ The absence of comprehensive care in mainland China combines with social pressure on the patients themselves, which often leads to various forms of stigmatization and extreme situations in which people are confined to their homes.⁴⁸

Such factors are likely to increase the willingness of people in mainland China to participate in clinical trials, as well as unproven for-profit experimental therapies. The reluctance observed among some patients in Hong Kong to take part in the CN102b safety trial, may to some extent be traced back to the better care they receive.

⁴⁴ The information in this paragraph is based on interviews with three SCI patients and two doctors from the rehabilitation unit of the Second Affiliated Hospital of the Medical School of Xi'an Jiaotong University, Xi'an, China; September 18, 2010.

⁴⁵ Interviews John Lee, Hong Kong, January 2, 2011.

⁴⁶ Same as previous note.

⁴⁷ Interviews (1) John Lee, Hong Kong, January 2, 2011; (2) John Lee, Hong Kong, July 5, 2011; (3) Catherine Chen, Hong Kong, July 5, 2011; (4) Prof Ming Luk, Hong Kong, June 26 2010; (5) Prof Yi Hwong, Hong Kong, August 21 2010.

⁴⁸ Interviews (1) John Lee, Hong Kong, January 2, 2011; (2) Catherine Chen, Hong Kong, July 5, 2011

This may explain also why several people with SCI decided to wait until the Phase III study, where the likelihood of treatment success appeared greater.⁴⁹

I continue now with a section on the sourcing, transportation and preparation of the cells in the CN102b trial.

(ii) Origins and preparation of UCB mononuclear cells

The umbilical cord blood (UCB) mononuclear cells used in the China SCI Net clinical trial had a long geographical and institutional journey before reaching their final destination in Hong Kong for transplantation into patients. Collecting, preserving and storing of the UCB units, as well as the subsequent isolation and processing of the mononuclear cells, was carried out by Stemcyte, a global umbilical cord blood therapeutics company, with its headquarters in Covina, California, USA.⁵⁰ According to their website Stemcyte is ‘the world’s largest, most racially diverse, and highest-quality public bank of UCB stem cell products in the world’.⁵¹ The company generates revenue from a combination of private and public banking, and has UCB banks and laboratories in the USA, Taiwan, and India.⁵² Among its investments are clinical trials for thalassemia, spinal cord injury and stroke; for all conditions it aims to establish its UCB products as IND-approved therapies.⁵³

Their laboratories and storage facilities in the USA and Taiwan are approved under the US National Marrow Donor Program (NMDP 2012), which holds an FDA IND protocol, that permits the use of UCB units (from Stemcyte as well as certain other cord blood companies) for treatment of several FDA-specified indications.⁵⁴ To take part in this protocol, the company has AABB accreditation, a California Biologics License, a Clinical Laboratory License, and is regularly inspected by the FDA.⁵⁵

The cord blood units used in the China SCI Net trials in Hong Kong and Kunming were collected in Taiwan from Taiwanese donors. This is because before

⁴⁹ Interview John Lee, Hong Kong, January 2, 2011.

⁵⁰ URL: <http://www.stemcyte.com> (last accessed September 21, 2012).

⁵¹ URL: <http://www.stemcyteindia.com/stemcyte-usa.php> (last accessed September 21, 2012).

⁵² URL: <http://www.stemcyte.com/public-banking> (last accessed September 21, 2012).

⁵³ URL: <http://www.stemcyte.com/index.php/why-save-cord-blood/research-developments> (last accessed September 21, 2012).

⁵⁴ URL: <http://m.prnewswire.com/news-releases/stemcyte-adds-world-class-talent-to-its-north-american-and-global-operations-135523473.html> (last accessed September 21, 2012).

⁵⁵ URL: <http://www.stemcyte.com/index.php/why-choose-stemcyte/our-accreditations> (last accessed September 21, 2012).

transplantation the cells must be HLA-matched to the recipients and there is a better chance of finding a match between people who have a closer level of genetic proximity, thus donors from East Asia are more suitable than donors from the USA (Young 2008).

The blood is collected from the umbilical cords of newborn babies. This is carried out in the maternity wards of hospitals, after the parents have agreed to donate the cord blood for 'public banking' under the Stemcyte scheme. The company offers public donation as free service. Expectant parents decide whether or not to take part in the scheme before arriving at the hospital; sometimes they are recruited through advertisements or by contracted staff in the hospital.⁵⁶

After collection, the units are shipped to Stemcyte's central laboratory and storage facilities in Covina, Los Angeles in the USA, where they are processed, tested for sterility, screened for infectious diseases, and frozen in tanks of liquid nitrogen. Then they are stored until required (see Figure 2).⁵⁷

When a patient is recruited onto the trial, a sample of his or her blood is sent to Stemcyte's HLA laboratory in Covina, to identify the particular type of HLA (human leukocyte antigen) in the blood through genetic sequencing. Then a match is searched for in the company's inventory. As specified in the trial protocol, the donor cord blood units must match by a ratio of 4 to 6 or higher with those of the recipient. The better the match, the greater the chance for successful engraftment, regeneration activity and long-term survival.⁵⁸

When an HLA-matched cord blood unit is found, and a concrete date for the surgery identified, the frozen cord blood unit is transferred to VISTA Biologicals Corporation in Carlsbad, California, seventy miles from the Stemcyte headquarters and storage facility in Covina. VISTA is a contract laboratory that provides specialized cell culture and manufacturing services for preclinical and clinical research in industry and academia. Here, the units are thawed and the mononuclear cells are isolated and purified in compliance with FDA guidelines for current Good Manufacturing Practices (GMP). As their name suggests, these mononuclear cells

⁵⁶ Interview with Senior Manager of Stemcyte Taiwan, Taipei, August 11 2010. Website of Stemcyte Taiwan, Service Flow Chart (fuwu liucheng tu); URL: <http://www.stemcyte.com.tw/?mode=ourservices&cmd=c> (last accessed September 21, 2012).

⁵⁷ Interview with Senior Manager of Stemcyte Taiwan, Taipei, August 11 2010. Website of Stemcyte USA,

⁵⁸ Blog contribution of Wise Young on *CareCure*, June 28, 2007, URL: <http://sci.rutgers.edu/forum/showthread.php?t=83856&page=5> (last accessed September 21, 2012).

have a single large nucleus. They comprise various cell types including monocytes, lymphocytes, and hematopoietic progenitor cells that express specific surface antigens (CD34+, CD133+, CD45+) and other protein markers for pluripotent hematopoietic stem cells. The intention is for these cells to regenerate the damaged nerve tissue in the spinal cord (Young 2009b).

After purification and certain control procedures, the cells are dispersed into a medium favorable for the transfer. The cells are not frozen, but are maintained at a stable room temperature in a sterile polyethylene bag within an insulated Styrofoam box. They are transported by air express courier, and reach their destination around thirty-six hours after departure (see Figure 3).⁵⁹

On arriving in Hong Kong, events are very fast (see Figure 4). The cells are unpacked, separated from the transport medium and re-suspended in a medium that is good for injection. The integrity of the cells is tested next, in terms of their viability, clonogenicity, overall number, and the presence of cells carrying CD34+ and CD133+ antigens, and sterility tests are run to rule out any microbial contamination (Tsang 2011). Then the cells are concentrated into a volume of 100,000 cells per microliter, and put into antiseptic injection vials (see Figure 5). Within two hours of arrival at the laboratory, the vials are ready to be transferred to the operating theatre for transplantation (*ibid.*).

The total length of time taken to thaw and process the cells at VISTA Biologicals to their reconstitution and transplantation in Hong Kong is no more than 48 hours.⁶⁰

⁵⁹ Interview with Prof Hui Tsai, Hong Kong, January 7 2011.

⁶⁰ Same source as in previous note.

(iii) Surgical and cell transplantation procedure

Before transplantation of cells into the patient's spinal cord, a small-scale resection operation must be performed. The clinical trial protocol described in detail the following procedure: the patient is anesthetized (with general anesthetic). After making a spinal incision, the thick membrane enveloping the spinal cord (the dura mater) is exposed in two locations, one above and one below the injury site, over an area of one centimeter by two centimeters (Leung 2010). The dura is opened at these two points, to enable access for the injection. A total of four injections are made, two at each of the two surgical sites (see Figure 6). A hand-held 27-gauge butterfly needle is entered at a 45-degree angle through the dorsal root zones on the right and left side of the spinal cord at each site (see Figure 7). The needle is inserted to a depth of three millimeters before the cells are injected (Young 2009b). Following the injection, the dura is closed up, and the two incision sites are sutured and medicated.⁶¹

The operation should take between one and two hours, and the patient is required to stay in the hospital for three to seven days, according to the judgment of the doctors (Leung 2010).

Challenges of surgical procedure

This process sounds very straightforward, but in practice the process faced certain challenges. For one thing, surgeries are not commonly carried out on the spinal cord one year or more after an injury, and surgeons can be confronted with very irregular patterns of adhesions and scar tissue that can complicate the operation. Furthermore, the injured segments of the spinal cord in different patients can present very variable physiological features, mainly because of the diverse circumstances under which the original trauma occurred. Both factors can complicate the surgery, and prevent precise identification of the injection site. It is also important to realize that for the clinicians in Hong Kong this specific treatment approach was novel at that time, so the surgeons performing it, were breaking new ground; in various respects it exceeded their routine repertoire of internalized practices and experience (see Figure 8). Professor Ya Jin,

⁶¹ Interviews with (1) Prof Ming Luk, Hong Kong, June 26 2010; (2) Prof Yi Hwong, Hong Kong, August 21 2010; (3) Prof Ya Jin, Hong Kong, August 24, 2010.

one of the neurosurgeons involved with the first patients in Hong Kong, described these issues in an interview as follows:⁶²

YJ: After the trauma... there can be some adhesions or scarring, around the tissue, including the skin, and, you know, the soft tissue, even the bone, and the dura. [...] Not many people have seen the spinal cord after the injury, after more than one year [post injury].

AR: Yes.

YJ: You know, no person would [normally] like to open the spinal cord of an old [chronic] spinal cord injury patient. So there are not many people who have seen such cord. And we do see this [now]. You know, the cord... normally it is like one of my fingers. In terms of the size. But now, even smaller than my little finger... that area. So probably [this is] because of the trophic changes, after the long-term injury.

AR: I see.

YJ: The first case we did, we saw... a lot of vascular... you know vessels... outside the spinal cord. But the second case, we wouldn't see them.

AR: You mean blood vessels that would grow... in a kind of unruly way?

YJ: Yes, just like the roots of a tree, grappling around the spinal cord. In the first case. But in the second case we didn't see the same phenomenon. So I assume this is incidental.

AR: And could you get your way through this?

YJ: It was a bit difficult... again there is quite a lot of the scar... you know at the surface of the spinal cord, and we had to cut off the scar tissue. So we lost a little bit of time to do that. [...] But anyway, the spinal cord is smaller in size and... the appearance is not the same as in the normal spinal cord. [...] And then, [after opening the dura] there was some adhesion that we had to clear, before doing the injection. [...] Well, this was not a big deal in fact. It involves maybe some experience, or techniques. But it is not a big deal. The big deal is actually – injecting the cells [laughs].

⁶² All quotations in this section stem from an interview with Prof Ya Jin, Hong Kong, January 6, 2011.

The injection of the cells was carried out in a highly standardized way, but it was a taxing issue for the neurosurgeons. As Dr Jin explained, the angle, depth and entry point of the injection were well controllable. The first challenge, however, was to be sure that the prescribed cell volume actually reached its target destination, without losses into peripheral areas, and taking into account variations in dose that arise from the delivery method. This issue will be discussed now.

As the following passages show, aspects of the procedures were subjected to ongoing reflection in order to prepare for such possibilities. The surgical team performed preoperational training and test procedures, and made slight adjustments of the surgical and injection protocols, so as to ensure further standardization.

YJ: You know, you want to inject into the right place; [and] you want to inject in the right volume, the correct amount of cells. And this is very difficult, because we are talking about a very small size, a very small volume. And we have to make sure that everything is accurate. That is why each time before the operation we [...] have a [test] trial, [where we] inject by dead material operator. To see whether we are really injecting the volume that we are wanting to. You know, we are only talking about microliter.

AR: Yes, so few.

YJ: Only four micro liters, even a little drop, is already quite an amount of microliter. So this is the most demanding part of the whole surgery. We are still developing the ideal, the optimal way to do that. We have to standardize everything. We cannot do one patient in one way, and one in another way, because then we cannot really compare. [...]

When you are injecting, even the needle, the volume inside the needle, will affect the accuracy of the amount of cells that you are getting into the spinal cord. So we have to check all the system, to make sure the dead space is filled up. [...]

So, the surgery is not a big deal, compared to... Well... to be humble.

AR: Well yes...

YJ: [laughs] No, the surgery is difficult. But the surgery, this is like our job. Our daily job. This is what we are paid for anyway. So, we did the surgery in a usual way. But the difficulty is really, how to inject the cells accurately. So this is the main, issue. That's why we first meet here [in the transplantation lab], and discuss that this is done properly.

AR: What about finding the precise position, where you put the needle through? Is it really possible to find it? And what about the depth of the injection, and about injecting at a 45-degree angle?

YJ: To find the [injection] position, we are able to find the position. You know, the position is actually where the nerve is coming out. Where the dorsal root nerve is coming out. So we can still identify the nerve. So, we can see the site that we are going to inject. About the 45 degrees. Because we cannot have a compass, to really measure whether it is 45 or 45.1 degree. But I think approximately we just inject it obliquely. Depth, we can control, because we know where the buffer of the needle is [after 3mm]. The ratio and depth we can control.

Another important challenge was to identify the precise surgical locations at which to open up the dura, and to guarantee that the injections go directly into the two corresponding areas immediately above and below the injury site. To identify the locations, the team worked with four different tools: MRI (magnetic resonance imaging) technology, a neuro-navigation system, the experienced surgical eye, and ultrasound. This is what Dr Jin had to say on the procedure:

AR: And the locations, to identify the spots for the surgery. Is this difficult? I mean you have the MRI, and you can see where the injury site is, so that you can identify the injury site. Or not?

YJ: The interesting thing... theoretically yes and no. We can see the image from the MRI. And also we can see the spinal cord in the real patients. But how can we know that this site is corresponding to that side? So one way to do this is to use a system that is called neuro-navigation. Neuro-navigation is just like a navigation system, just like a GPS. Basically you just turn the computer on, put the data into the computer, of the patient's spinal cord. And then you register with the computer. Just to make them know the reference point. And then, [when you want to start the surgery], the computer will tell you where your point is, in the picture that the computer is producing. Just like a GPS. You can know where you are, on the globe. In theory, by using this system, we can make a very small incision, and just inject the cells into the spinal cord. According to the [data provided by the] neuro-navigation. But in reality we think it is not safe.

AR: In which sense?

YJ: Because the spinal cord is something mobile. And also because... as I have said, because there are a lot of blood vessels on the surface, and the computer does not tell you where the blood vessel is. So if you inject blindly, by just following the picture, then you may directly inject into the blood vessel.

AR: And then the cells are lost. They do not go to the right place.

YJ: Yes, and in the end, you would completely not be sure whether you are injecting into the right place. Because you have no way of checking it out. [...] That is why we prefer to open it up [i.e. to expose the whole dura above the injury site, in one go]. To really have a look. And in the next patient that we are going to do, we are trying to use the ultrasound, to see whether we can identify the site still better.

What Dr Jin referred to above when he said ‘That is why we prefer to open it up’ is that – in contrast to the original protocol – the surgical team decided before doing its first patient to open up the complete area around the injury site in one piece, instead of a small area above and another below the injury site. The reason for this decision was to better spot the injury site, and to identify the optimum point for opening up the dura.

As reported by Prof Luk, the PI of this group, the lesion of that first patient was relatively small – the opening was in total five to eight centimetres.⁶³ This decision was considered to be particularly good because due to the injury the patient’s spinal column was twisted around 90 degrees to the side, and there were many small blood vessels (as reported by Dr Jin above). According to Luk, with only small openings above and below the injury site, the injections could not have been performed successfully.⁶⁴

Patient perspective on the procedure

I will now provide an account of the trial from the perspective of Catherine Chen, who underwent surgery and cell injection three months before we met. Catherine was in her late thirties then. She had suffered a chronic spinal cord injury at neurological thoracic

⁶³ Reported during a presentation at a PI meeting in Hong Kong, April 19, 2011.

⁶⁴ Same source as in previous note.

level T10 (see Figure 1) in the mid-1990s. Not long after the injury, Catherine opened and ran a flower shop, but it had to be closed. A long period of painful rejections in the job market followed. After almost sixty applications, she finally found employment as a teacher of flower decorating, which she had done ever since. In contrast to other people with SCI in Hong Kong, who chose to wait for the Phase III trial, Catherine opted for instant participation. She considered that if she did not make the decision at that point, it might take many more years for another opportunity to arise.

Part of Catherine's decision to take part in the study, she told me in an interview, was based on the fact that she was independent, with no spouse or children, and she was also free from the obligation to care for her father. Unlike some of her friends, who worried about their families and their ability to take care of their children, Catherine felt free enough, and psychologically strong enough, to accept the potential risks of the trial, and to face the unexpected outcomes. As she put in an email:

Indeed I had high expectations on the outcome of the surgery since I have been waiting for this long. What I have to do is to face the future whether I am going to recover or not. Perhaps, unlike other people, I didn't get spoilt in my childhood. I am sure I'll be psychologically strong enough to accept and go through any 'unexpected outcome' with my great resilience. My brother and sister will take up the caring responsibility to my father. Thus it seems there is nothing I have to deal with at this point.

In the light of her hopes for substantial recovery, Catherine was slightly disappointed when the investigator, who underwent the informed consent procedure with her, did not tell, or make any promises about, the kinds of benefits she had hoped for. The PI, she recalls, highlighted in particular the potential risks of the study, which were explained during the process of going through the consent form.

After a brief period of reflection, she decided to take part in the study. Arrangements were made with her employer, and dates were set for the preliminary clinical examinations and the surgery. I received a first indication of how the operation went, and of the physical and emotional state Catherine was in, in an email sent one month after her stay in the hospital. In it she recalled:

The surgery was more complicated than expected. During the operation, Dr Hwong found that my T9 is a bit 'loose' and a crack was found there. That's why a [metal] stabilizer has

been put in it, to give additional support to that area. I was required to put on a waist brace for three months after the surgery, so I'm now not allowed to drive and do any manual work. What I remember most is that I got fever after the surgery, and that my wound felt extremely painful. I had also a strong headache. [...] I was in distress throughout the 5-day stay in intensive care unit [ICU]. I started questioning, seemed to have many question marks in my mind. I'd been in the hospital for ten days. After discharge, I was asked to take rest in bed. But I could still feel strong pain in the wound.⁶⁵

The discovery of the crack in the T9 vertebra was significant. It was feared that it might cause long-term complications, and undertaking fixation with a metal stabilizer forced the surgeons to diverge significantly from the original surgical protocol. With detection of the crack, a new medical situation had emerged. The priority of successfully completing the clinical research was replaced by a new demand: to solve a medical problem the surgeons were unexpectedly confronted with.

This change in surgical protocol also meant that Catherine's experience of the surgery was non-representative of other trial participants. Not only was her spinal cord opened on a much larger scale than the other participants, but additional surgical procedures had to be performed. As Catherine told me in an interview, in addition to fixation with the metal stabilizer, a bone fragment was removed, which had exerted pressure on a part of the spinal cord, close to the injury site. Accordingly, her side effects and corporeal experiences during the hospitalization period were different, and more extreme, than those of the other patients. Furthermore, the healing process was different, both in terms of its duration and preventing her from everyday activities such as driving and work.

For Catherine, at least, the surgery was a difficult experience. After being discharged from hospital, she could not leave her bed for another fourteen days, with severe pain in the muscles surrounding the injury site for one month. For the other patients, the side-effects and experience of surgery were less severe.⁶⁶ Catherine's case is an important reminder, nonetheless, that participation in a surgery-based clinical trial involves significant personal sacrifice by some patients, even intense moments of suffering. Indeed, the surgical and corporeal aspects of stem cell-based interventions, as well as related risks, have been little explored in commentaries on stem cell-based

⁶⁵ Email from Catherine Chen to author, June 30 2011.

⁶⁶ As reported by Prof Ming Luk, in a presentation at a PI meeting in Hong Kong, April 19, 2011

clinical trials and experimental treatments. Surgery is an inevitable part of optimized delivery for stem cell-based therapies. Greater attention to the surgical aspects of these treatments in regulatory and ethical debates seems essential, particularly with respect to experimental for-profit therapies, in which the surgery and injection procedures are likely to occur in a less-controlled, less-responsible way.

A final issue to be addressed in this section is the corporeal experience of physical changes and improvements from the treatment. For instance, Catherine reported that:

A month later [after the injection], I found that there was a little improvement in my right thigh and waist in terms of touch sensation. But the touch sensation was not as strong as the able-bodied have. Now the numbness I feel in the lower limbs is stronger than ever. The ache may cause me insomnia at night. Nevertheless, Dr Hwong says that the outcome still remains unknown until six to twelve months after the operation.⁶⁷

In theory, the transplanted cells exert their therapeutic effects by creating a bridge of nervous tissue through which the axons of nerve cells can grow, thus potentially restoring functional nervous pathways that had been lost after the initial trauma. However, this axonal re-growth through the cellular bridge is an uncertain and extremely slow process. The axons grow only about two millimetres per month (Young 2009b), so any therapeutic effects are expected to emerge after some time, over the course of several months and up to one year. From the perspective of the patient, this means a period of carefully paying attention to the changes and reactions of one's own body. As clarified by Catherine in an interview held three months after surgery, this period remains a time of hope, but also of sorrow. With respect to hope, Catherine stated that she still anticipated an improvement in motor function over the following months. A landmark event for her would be to be able to stand up with a standing frame, so she could occasionally stretch her body in an upright position. She added that her expectation was probably beyond what was practically achievable, but she had not given up hope, and was willing to pursue her goal further in a subsequent clinical trial.

As for sorrows, she expressed repeated concerns about unfavourable outcomes of the treatment. One source of distress was the gradual regaining of her touch sensation.

⁶⁷ Email from Catherine Chen to author, June 30 2011.

While the return of bodily sensation is commonly desired by people with paralysis, she realised that the process can cause pain and peculiar bodily sensations. The problem was particularly pronounced in her lower limbs:⁶⁸

CC: The feeling is in the lower limbs. I want to move my feet, but then cannot. It is not a good feeling, and it prevents me from sleeping. Sometimes there is also pain. Initially this feeling was only sometimes, but now it happens every day, and sometimes it is very strong.

AR: You think there is a causal relation with the treatment?

CC: Yes, yes [gets a bit breathless]. That feeling now is as if... somebody is touching your skin, but it is inside, not from the outside.

Catherine feared that these feelings might be long-lasting, or even get worse. As the final section on outcome measurement in this chapter will show, the expected treatment outcomes in the CN102b trial, both sensory and motor, are determined on the basis of extensive and standardized methods and measurement protocols. These systematized measurement procedures enable statistically significant comparisons to be made across large numbers of patients, from one or multiple hospitals.

(iv) Outcome measurement

The final element of the CN102b study is described in this chapter, namely the procedures used to measure the clinical outcomes. After surgery and cell transplantation, the participants underwent follow-up and outcome measurement procedures at days 3, 7 and 14, then at weeks 6, 24 and 48 after the operation date.⁶⁹ To determine the efficacy of the investigation, the tests were done with grading-scale systems that index for various forms of improvement. These procedures constitute standardized methodological packages, uniformly applied across the hospitals, to

⁶⁸ Interview with Catherine Chen, Hong Kong, July 5 2011; translation from Cantonese to English by John Lee.

⁶⁹ Details of the study protocol can be found at: <http://www.clinicaltrials.gov/ct2/show/NCT01046786?term=nct01046786&rank=1>, (last accessed August 27, 2012).

assure the collated data are valid for systematic statistical analysis and comparison (Leung 2010).

The most important measurement instrument used in the China SCI Net trial (and its sister network in the USA), was the neurological grading scale of the American Spinal Injury Association (ASIA). The ASIA scale was designed to determine changes in both the sensory and motor function of people with spinal cord injuries. However, various additional measurement scales were also applied, such as the Modified Ashworth Scale (MAS) to measure spasms, the Walking Index for Spinal Cord Injury (WISCI) to test walking capacity, the Visual Analog Scale (VAS) for evaluation of pain, and the Spinal Cord Independence Measure (SCIM) to assess the ability to self-care, mobility, respiration and sphincter management.

The timing of these examinations, and other pharmacokinetic and physiological examinations conducted in the course of the trial, are summarized in the flow diagram of the CN102b trial. The inclusion and exclusion criteria, outcome measurements, and surgical and injection procedures described in this chapter also applied to the parallel Phase II study conducted in Kunming (as well as the future Phase III multicenter trial). I will show in Chapter VII that the standardized use of these measurement and intervention procedures in the Network's associated hospitals was not a consequence of their longstanding routinization, but the outcome of intensive training. The ASIA neurological grading system, for instance, was introduced to supersede a range of local assessment forms, which reportedly lacked a common language, and produced widely variable outcomes.

Chapter Summary

In this chapter I have focused on the micro-organizational and work practices of the first clinical trial with stem cells to be conducted by the China SCI Net. In doing so, I introduced the central methodological building blocks on which the current series of clinical trials being carried out by the network is based: the selection of patients on the basis of strictly defined inclusion and exclusion criteria; the choice and preparation of cells; the performance of surgical and cell injection procedures; and the systematized measurement of outcomes. These practices have been explored from multiple viewpoints, including the directives of the clinical research protocol, the practice-

based perceptions and experiences of clinical staff and researchers, and the corporeal experiences and understandings of the people with spinal cord injuries who applied for, or took part in, the study.

A focus on actual treatment practices, in particular with respect to the surgical and cell injection procedures, has shown that the translation of clinical procedures from the study protocol to the real-world level of the clinic, confronted the involved neurosurgeons with various challenges. These challenges, as has been shown, could in the first place be traced to the variable physiological conditions encountered within the spinal cords of the chronic injured patients, the precise characteristics of which only became visible during the operation.

Other challenges were the identification of the optimum location for opening the dura, and ensuring the standardized delivery of the cells, so as to guarantee that the exact amount of cells reach their target. It has become clear that these procedures were subject to continuous reflection. Preoperational training and test procedures were performed, and minimal adjustments were made to the surgical and injection protocols in order to take the standardization to a higher level.

Another aspect that has been discussed in this chapter concerned the challenges of patient recruitment in Hong Kong. The situation in Hong Kong was compared with that in Kunming, and discussed with respect to their different population sizes and healthcare arrangements. Sound quantitative and additional qualitative data is required to get a true understanding of this issue. Nonetheless, the data presented in this chapter have suggested that structural differences, in particular differences in access to healthcare, played a central role in influencing the patients' behavior during the recruitment stages of the trials.

In the following chapters, I will leave the micro-contexts of the clinic and research laboratory, and move further to the wider sets of relationships, organizational procedures, and regulatory and audit practices through which the clinical studies of the China SCI Net have been enabled and legitimized.

I shall continue in Chapter V by focusing on the regulatory situation for clinical stem cell research and applications in mainland China, and on the highly contrasting forms of clinical experimentation the situation has given rise to.

Figures Chapter IV:

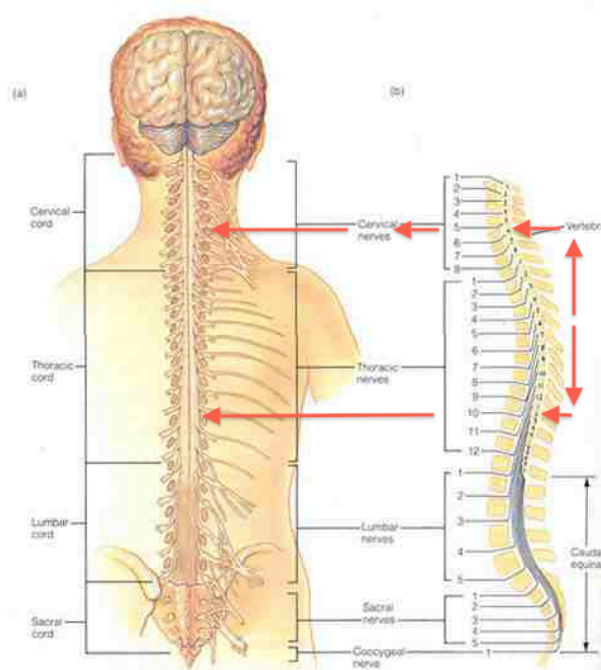


Figure 1: the neurological level of SCI patients admitted to the CN102b trial has to be between cervical level C5 and the thoracic level T10 (see red arrows).



Figure 2: Cryopreservation of Cord Blood Unit in Covina, California, USA.



Figure 3: Unit of UCB mononuclear cells in insulating Styrofoam box, with temperature measurement device. Opened in Hong Kong after shipment from the USA.

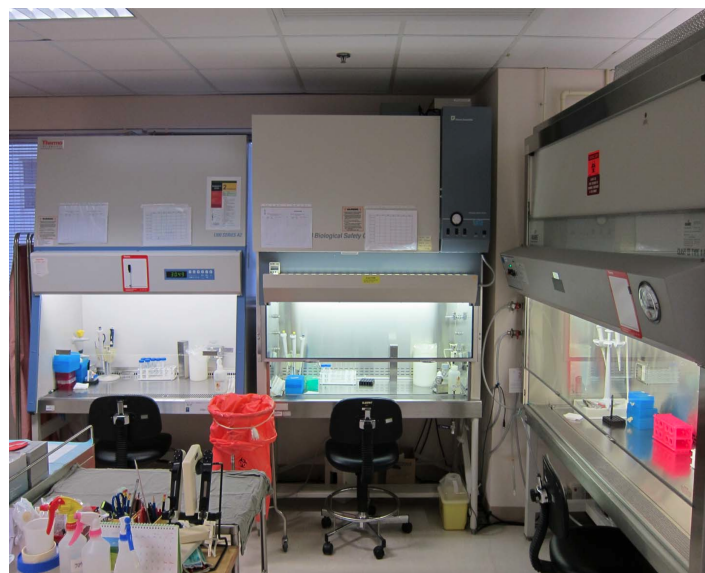


Figure 4: Work places at the Blood and Marrow Transplant Lab in Prince of Wales Hospital, Hong Kong.

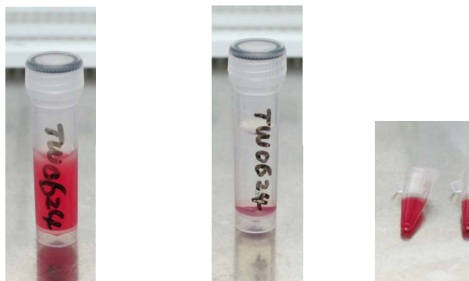


Figure 5: Vials with the concentrated mononuclear cells minutes before transplantation.

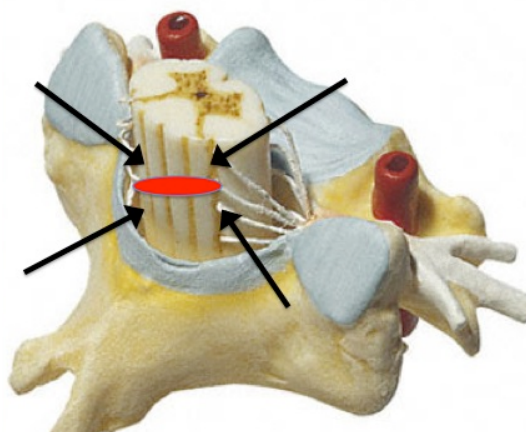


Figure 6: Model of a section of the spinal cord indicating the four injection points above and below the injury site.

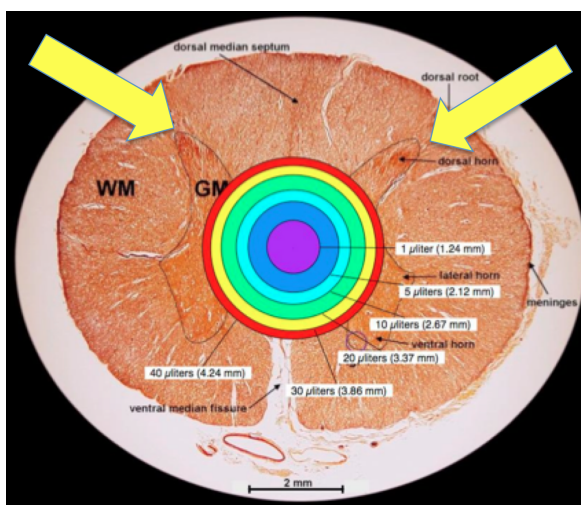


Figure 7: Model that indicates the injection pathway through the dorsal root entry zone and the grey matter of the dorsal horn into the center of the spinal cord.



Figure 8: The neurosurgical team in the operation theatre: surgery of the first patient of the CN102b trial in Hong Kong

Chapter V

Situating the Network in the context of China

Introduction

In this fifth chapter, I will place the China SCI Net in the wider landscape of clinical stem cell research and applications that have evolved in China over recent years. For this purpose, I will trace the institutionalization of experimental clinical stem cell research and applications in China, its stepwise problematization, and metamorphosis into an object of regulatory concern and intervention. My interest is in particular on the stakeholder groups that push toward integration of clinical stem cell research into the international arena of high-profile science, and on the motivations that propel this dynamic. The activities of these stakeholders, of which the China SCI Net is one, will be analyzed against the background of a well-established landscape of informal and frequently for-profit forms of clinical experimentation with stem cells. It will become clear that the transition toward adoption of an internationally recognized standard system in the stem cell field is a complex and highly contested process. The longstanding absence of a coherent state-centered regulatory approach for research and application of stem cells in China, has not only given rise to the realization of new economic opportunities, but also to a multi-stranded innovation culture, which is characterized by knowledge exchanges and collaborations between highly diverging socio-technical and epistemic communities. I will make sense of these processes through the concept of ‘national experimental pluralism’. In the wider structure of this dissertation, this chapter is essential for understanding the operation and activities of the China Network in two major respects. First, it provides background information on the challenges that the Network has encountered in obtaining regulatory approval in China (this will be a central theme of Chapter VI). Second, it offers contextual understanding for the processes of capacity building, education and self-regulation, through which the China SCI Net has worked to restructure local research and innovation infrastructures in associated partner institutes. The information within this

chapter is also important because it elucidates the motivations of associated partners for joining the Network.

The chapter is divided in three parts. In Part One I provide an overview of the diverging modalities of stem cell-based clinical experimentation in China, and introduce the stakeholder groups that push for the adoption of internationally recognized research standards and regulatory protocols. In Part Two, I focus on the problematization and emerging regulatory situation of the clinical stem cell field in China. Then, in Part Three, I analyze clinical innovation processes in the field, through the concept of ‘national experimental pluralism’.

PART I: Experimental SC research and applications in China

Clinical research for new drugs and medical technologies in China has in recent years been marked by the striving toward independent innovation and the strengthening of domestic research, testing and production infrastructures (Ding *et al.* 2011). This trend has been accompanied by the adoption of international scientific and ethical clinical research standards, promulgated in regulations for the administration of clinical trials, their ethical review, and mandatory certification of research hospitals according to Good Clinical Practice (GCP) guidelines (Cure 2009; Li 2011). International standards are also manifest in closer adherence to evidence-based medicine (EBM) protocols for the evaluation of new medicines observed by the Chinese State Food and Drug Administration (SFDA), especially since its reform in 2007 (Li, Sun & Wang 2008). The propagation of international standard regimens initially focused particularly on the development of conventional drug products, but was extended more recently to the evaluation procedures in Traditional Chinese Medicine (Tang *et al.* 2008), for gene therapies (Peng *et al.* 2008), and other advanced medical technologies (Qiu 2009; Zhang 2012).

In contrast, clinical stem cell research and applications, focused on in this chapter, have only lately become the object of regulatory attention in China. A first attempt, within the context of a regulation for novel medical technologies, was introduced in 2009 (Cyranoski 2009). However, this attempt was never completed and a new and more comprehensive regulatory approach has been in preparation since 2008. The Chinese Ministry of Health (MoH) has issued a first phase of this evolving

regulatory framework in January 2012 (MoH 2012). Harmonization with the international system, however, has with this initial step not yet been realized.

Four basic modalities of clinical experimentation

Experimental interventions using stem, or stem cell-like, cells have been carried out in China for more than ten years (Song 2010). Enabled by the long-standing absence of state regulation for this new research field, a broad range of experimental approaches using stem cells has emerged during this period. These interventions range from cases of obvious fraud (BBC 2009), through to highly formalized SFDA-approved clinical trials. The overwhelming bulk of experimental implantations of stem cells in China, however, fall in between these two poles. They are carried out as (1) patient-driven experimental treatments, (2) profit-driven experimental therapies, (3) research-driven observational or clinical pilot studies. A fourth group is comprised of the highly systematized phase I and II (soon III) clinical trials that have intermittently been approved by the SFDA since 2004 (Liao and Zhao 2008). While the forms of clinical experimentation with stem cells in China do often diverge from international standard regimens, a slow but steady move toward the adoption of internationally recognized clinical research protocols is evident in recent years.

Significantly, this transition process has not primarily been propelled by the state, but by the agency of a select group of Chinese high-profile researchers and their international research partners. These groups have worked continuously to transform and standardize local research infrastructures and to harmonize conceptions of clinical research methodology and ethics with international standards. These efforts have taken place through capacity building and scientific self-governance efforts in the context of concrete clinical projects and beyond the level of state agency. The Chinese Ministry of Health (MoH), which is the responsible government unit for clinical SC research, has for many years been hesitant in its approach to the governance of clinical SC research and applications in China.⁷⁰ The MoH has, however, facilitated the adoption of international standards in the SC field indirectly, by promoting EBM in medical education (Li, Su and Wang 2008), by imposing stringent regulations for drug

⁷⁰ Note: while basic SC research falls under the joint responsibility of the Ministry of Health and the Ministry of Science and Technology [see Salter and Qiu (2009)], clinical research and applications falls solely under the responsibility of the MoH.

evaluation procedures by the SFDA, and by demanding GCP certification for research hospitals (Li 2011). Furthermore, as will be shown in Part Two, the MoH is currently in the process of issuing a comprehensive regulatory approach for clinical SC research and applications. This step will undoubtedly propel and formalize the transition toward the adoption of international standards further. Before commenting on these issues in greater detail, however, I provide a brief overview of the four central modalities of experimental clinical intervention with SC that can be observed in China today: patient-driven, profit-driven, and science-driven forms of clinical experimentation.

Patient- versus profit-driven experimental interventions with SC

Patient-driven forms of clinical SC applications are experimental clinical interventions in which doctors test an unproven treatment. These typically involve a seriously ill patient whose life expectancy is low and for whom all existing treatment options have failed. With informed consent, such experimental intervention is allowed in paragraph 35 of the Declaration of Helsinki (DoH 2008), and practiced in many countries in the world. Numerous such interventions have been carried out in China, with some having been reported in medical journals (Gu *et al.* 2003; Zhu 2006) and shown repeatedly on state television (see for example: CCTV 2007, 2010). Such patient-driven forms of experimental treatments are commonly provided by doctors in first-tier hospitals, and are not usually linked to commercial interests. As the head of a clinical research institute in a large hospital in Beijing pointed out, fees may be charged, but these are restricted to operating expenses for hospital beds, material and equipment. Costs for patients or their families do not involve the salary for hospitals or doctors.

Experimental treatments are commonly provided to patients of a clinical specialist, who tests a newly developed treatment approach, on a small number of his or her most seriously ill patients. Sometimes, particularly if conducted in first-tier hospitals, the results of these clinical experiments are recorded and presented at medical conferences, and occasionally published in peer-reviewed medical journals (Peng *et al.* 2005; Li *et al.* 2007).

Profit-driven experimental therapies, on the other hand, follow a different pattern. The provision of potential help to patients in need is here part of a logic of commercial calculation, and the object of strategic investment. A novel type of economy has thus emerged based on new sets of relationships between clinical service providers, scientists, local investors, government officials and patients. Services are

usually offered to a very broad patient clientele with different disease types and at various disease stages. For example, some companies apply one or two experimental methods to more than seventy different disease conditions.⁷¹ Experimental for-profit treatments are generally provided in private hospitals, military hospitals or in privatized units of first and second-tier public hospitals, which are often especially designed for the purpose of SC therapy (Qiu 2009; Song 2011). Providers of commercial experimental SC therapies, as stated by the sales manager of a large healthcare equipment supply company, do only in few cases engage in more systematic and long-term collection of clinical data, and commonly eschew peer-reviewed publications, so as to hide technological details, to cover up negative data, flaws or adverse effects.

Occasionally, however, the boundaries between patient- and profit-driven forms of experimental treatments are blurring. Therapeutic procedures that have been applied as non-profit first-in-human experiments are then rapidly provided as for-profit experimental therapies. An example is the General Hospital of Armed Police Forces in Beijing. After some animal studies and initial experiments in patients with neural SC in 2003, the hospital converted its services to for-profit. In 2011 it had conducted 2847 treatment episodes.⁷² What happens in such cases, is the on-the-spot routinization of a non-systematically proven experimental treatment approach where some degree of efficacy, and no apparent adverse effects, can be observed. This rapid move from non-profit to for-profit is enabled by the fact that controls for experimental treatments with SC in China currently lie exclusively in the hands of hospital IRBs, without any forms of external supervision (Cure 2009). Furthermore, the shift is facilitated because patients expect to pay for experimental treatments in the strongly commercialized health-care system of China. This has been pointed out in interviews with both, clinicians and patients. Consequently, some of these clinical service providers make substantial amounts of money. Beike Company, for instance, which has treated more than 9000 patients, has reportedly generated one hundred million US dollars until 2010 alone (Sipp 2012). An estimate in the journal *Nature* states that there were between 100-150 for-profit stem cell clinics in China in 2009, but the actual number is uncertain (Cyranoski 2009).

⁷¹ See the list with “treatable diseases” on the website of Beike Biotech: <http://stemcelltreatmentnow.com/index.php/treatment/treatable-diseases.html>

⁷² <http://www.neuralstemcell.com.cn/ksjj/>

Research-driven experimentations with SC

A broad range of research-driven clinical SC applications is going on in China. These experiments gather structured forms of evidence, but their protocols do not conform fully to international scientific requirements set out by other drug regulatory authorities or top international journals. At the less systematic end, in terms of research methodology, one finds open-label observational studies, some of which contain cross-sectional elements that compare the results from different types of treatment intervention. For example, the gastroenterology department of a first-tier Military hospital in Central-South China, started to test an autologous SC treatment in 2009 and later a treatment based on mesenchymal stem cells (MSC) in patients with acute liver failure. A high risk of rapid mortality, together with high costs and long waiting times for liver transplantation, form severe challenges to these patients in China (Wang 2009). These conditions, and the apparent success of the experimental treatment in a first patient, justified more interventions and, prior to September 2010, more than 130 experimental treatment episodes had been provided (Chen 2010). As reported by the PI of this study at a SC conference in China in 2010, systematic records of the treatment results were taken of all patients along some standardized outcome measures (*ibid.*). A colleague of this researcher commented, however, that the design and results of such observational treatment series are far from systematic enough to be accepted by a good journal. In his view, though, these data provide important precursory information on the efficacy and safety of specific treatment pathways, which then can be tested in systematic clinical trials later.

In addition to such semi-systematized observational studies, however, a larger number of more systematically designed clinical studies have been carried out in China. These studies qualify either as clinical pilot studies or as randomized clinical trials, of which only very few involve control groups (see for example Wang *et al.* 2007). Liao and Zhao, in a review of 18 publications of clinical SC research in China, concluded in 2008 that, even though important progress in the field has been made, some of the trials were not done well. In certain hospitals, for instance, cells were used that were not well characterized (2008: 613). They argue that without mandatory SFDA approval of SC clinical trials, data on the safety and efficacy of these studies cannot be guaranteed (*ibid.*).

The Move toward International Integration

What can be observed in the clinical SC field in China today is a slow but steady move toward the adoption of internationally recognized standard protocols. Two parties in particular propel this transition. The first is a small group of high-profile researchers in China who aim to develop SFDA-approved SC-based medicinal products, which can be formally marketed in China, and reported on in international top journals. The second is investigator-initiated international clinical trial partnerships that are preparing multi-centered clinical trials in China and other countries. Necessarily, these must accord with international approval and review protocols in order to produce credible data.

Clinical SC researchers in China, who seek SFDA-approved clinical trials in the context of an investigational new drug (IND) procedure, are currently a rather small group. These persons have usually obtained training or professional experience abroad, and have a dual educational background as both research scientists and medical doctors. These researchers do mostly oppose the uncontrolled experimental research landscape with stem cells in China, and call for far-reaching regulatory controls. According to a high-ranked researcher from a renowned military hospital in Beijing, for instance, China should use the same approval and review protocols as handled in the USA, if it comes to SC-based clinical trials. From the viewpoint of this researcher, the diluting of internationally recognized standards, by adjusting them to specific conditions found in China, will result in isolation, and pre-empt possibilities for publications in international journals and high-level international collaborations. It will pre-empt, furthermore, the development of stem cell-based medicinal products or technologies in China that can be internationally licensed and marketized. This view corresponds to the approval protocols for efficiency and safety of drugs and pharmaceuticals that are currently used by the SFDA, which follows procedures set out by the US Food and Drug Administration (FDA) (RJS 2010).⁷³

However, such harmonization has not yet occurred in the clinical SC field. In fact, review and approval protocols for IND applications of SC products have not yet been publicly issued by the SFDA. Because comprehensive evaluation directives for the licensing of SC therapeutic products are still in a process of negotiation, the SFDA

⁷³ <http://www.sfdachina.com/info/50-1.htm>

appears to have taken an extremely careful stance in recent years. According to a SC researcher who acts as external advisor to the SFDA, the agency approves the step from preclinical to clinical studies currently only for SC products that have previously obtained approval by a drug regulatory agency in the USA or Europe. Numerous researchers I talked to expressed severe complaints in this respect. This situation was widely assessed as slowing down clinical innovation processes in China, as preventing international integration and recognition, and as increasing the number of clinical trials carried out exterior to review by a drug regulatory agency.

A related issue is that SFDA responsibilities are limited to the review of clinical trials with standardized SC-based medicinal products. Since therapeutic approaches that are based on the transplantation of cells from one-donor-to-one-patient, are categorized as medical technology, and not as medicinal products, they fall out of the jurisdiction of the SFDA. Until January 2012, however, clinical trials with SC-based medical technologies had to be subject exclusively to hospital intern IRB review. While this situation has amplified possibilities for clinical experimentations, it has simultaneously deprived several researchers of the chance to obtain approval and feedback by a national-level drug regulatory authority. According to the founder of a stem cell R&D company in Northern China, this has in many institutes prevented a boost in research quality, and has increased safety risks for partaking patients.

International clinical research collaborations are another important vector, which push segments of the SC field toward the adoption of international standard protocols. Such projects are commonly committed to rigorous EBM standards, and seek approval and review procedures of drug regulatory authorities in several countries simultaneously. To my knowledge, the China SCI Net is currently the only multi-sited international clinical trial infrastructure that already conducts SC-based clinical trials in China, but at least two other projects are in preparation. As I will show in greater detail in chapter seven, the network has since 2006, in the context of a long-term capacity building program, carried out intensive training and educational activities. The purpose of this program has been to enable standardization of research design, ethics protocols, quality assurance measures, cell transplantation methods, and GCP requirements. These activities do clearly facilitate the integration of associated institutions and researchers into the international arena. Joint publications in top international journals, for instance, have already been launched (Wong *et al.* 2011; Yang *et al.* 2012). Despite these benefits, however, international collaborative clinical

research projects are not yet very popular in the clinical stem cell field in China. The reasons for this include: the unclear regulatory situation for clinical SC research in China, language barriers, and the enormous time and money-intensive process of building up a cross-continental multi-sited clinical infrastructure that produces reliable and standardized data. However, due to the relatively low labor costs in China, the availability of good clinical facilities and CRO services, the high numbers of available patients, and the market potential in China, there is a huge interest among both academic investigators and biotech companies to get collaborations going in China. A range of seed partnerships indicate that the formation of clinical innovation through international clinical trial partnerships will, in the coming years, play an important role in the SC field in China.⁷⁴ If this happens, these alliances will play a crucial role in the transition to the widespread adoption of systematic science-driven forms of experimental clinical research with stem cells in China.

PART II: Problematization and regulation

I turn now to the contrasting forms in which clinical research and applications with stem cells have emerged as problems in China, and to the conceptions of ethics and research governance that underlie these positions. I then analyze the ways in which these local forms of problematization have informed the evolving regulation for clinical experimentation with stem cells in China, and show how this emerging regulatory approach relates to international standard regimes for clinical stem cell research. The ethics to which I refer here concerns the diverging logics, interests and experiences which emerge at the interface of technology research, politics and culture (Ong 2010: 13). Articulations of ethics can evolve at different levels and scales (i.e. patients, professional groups, states, companies, religious collectivities, etcetera), and reflect tensions between the priorities and worldviews of specific stakeholders or social groups. They are, furthermore, closely bound to issues of power and representation (Sleeboom-Faulkner 2010). Regulation, in contrast, refers here to the efforts of states to shape the governance of technology research in relation to public interests (Van Zwanenberg, Ely and Smith 2011: 12).

⁷⁴ See BioTimes Asia: (<http://biotimeasia.com/>)

In regulatory debates on clinical SC research in China, a tension can be observed between forms of ethical reasoning that prioritize the stringent protection of human experimental subjects, and opinions that emphasize the value of rapid scientific progress for economic and social development. In the latter register, we see a climate of high expectations and hope that has been initiated by the media, scientists, clinical service providers, as well as politicized innovation and development discourse. The first experimental treatments with stem- or stem cell-like cells in the early 2000s, for example, were by the media celebrated as important breakthrough advancements (Liu and Xing 2002; CCTV 2002), and as indicators of China's rapid scientific progress (CCTV 2003). Supportive coverage on experimental stem cell therapies in China's state television has continued over the years, with treatment episodes framed as indicators of scientific development and hope for patients (CCTV 2003, 2007, 2010). Positive associations with experimental for-profit stem cell therapies in China have been reinforced furthermore, through high profile advertising campaigns launched by stem cell clinics, who use photos of high-ranked politicians posing with clinical service providers, and a political discourse that highlights rapid and independent innovation and technology-driven economic development (Song 2011; Sipp 2012). Risks for patients and doubts regarding the efficacy of experimental SC therapies are commonly downplayed in such representations.

Notwithstanding these campaigns, the safety, feasibility and profit-driven character of these treatments have in recent years been the subject of critical commentary and debate in various print media. The news magazine *New People's Weekly*, for example, launched a front page story in 2007 titled: 'A Truth Inquiry of Stem Cells: "Gambling" on the Hospital Bed', which cast serious doubts on both the safety and efficacy of experimental SC treatments. The chapter asks for greater standardization, and specification of clear application norms (Huang 2007). Calls for systematized forms of evidencing were also demanded by the influential news magazine *Southern Weekend*, which asked whether an initially highly praised experimental treatment for SCI is a "science bubble" rather than a "striking breakthrough". The chapter concludes with a plea for more controlled randomized clinical trials in China (Southern Weekend 2006). Furthermore, calls for reliable regulation have come from high-profile, Chinese researchers (Liao and Zhao 2008), as well by scientists and commentators from abroad (Cyranoski 2009, 2012; ISSCR 2008; Hyun 2010).

The Chinese Ministry of Health (MoH), which is the government unit responsible for the regulation of clinical research and applications in China, has reacted to these demands in three ways. First, in 2007, it decided to regulate experimental for-profit SC therapies in the context of a regulation for new medical technologies, which was launched in 2009 (Chen 2009). Second, in 2008, it assigned an expert committee in Shanghai to develop a draft regulation for the entire field of clinical SC research (Qiu *et al.* 2010). A draft was submitted to the MoH in 2010, and is now in a phase of internal finalization. Third, a notification of the MoH has been issued in January 2012, which has introduced a phase of evaluation and preliminary rectification.

The 2009 regulation and its impact

On May 1 2009 the MoH promulgated the *Management Measures for the Clinical Use of Medical Technologies*, a regulation that classified a range of new medical technologies and procedures into three categories. Stem cell transplant technology was grouped into category III, which included technologies considered as risky, ethically controversial and in need of clinical verification (Qiu 2009). To implement the regulation the MoH assigned five institutions (Chen 2009: 271), among them the Chinese Medical Association, the Chinese Hospital Association and the Chinese Doctors Association. According to an associate of the MoH in Beijing, clinics that used SC transplantation technology were summoned to register at these institutions. These organizations in turn were assigned to grant licenses on the basis of newly formed assessment criteria and review and inspection committees. In practice, this regulation has not yet been implemented for SC transplantation technologies. As stated by a senior SC scientist, who as a member of the Chinese Doctors Association was involved in the formulation of review criteria, there were widespread disagreements among experts of the assigned five institutions, over the precise characteristics of these criteria, over feasible implementation pathways, as well as the extent to which the situation should be controlled.

It is noteworthy that the 2009 regulation, despite its non-implementation, has impacted the clinical SC field in China in several ways. According to a clinical researcher from the People's Hospital in Beijing, for example, the hospital issued a ban on all forms of (non-SFDA approved) experimental SC research and clinical trials,

until reliable regulatory structures are in place. Similar decisions can be reported from other first-tier hospitals. Clinical researchers from three renowned state hospitals told me their departments had halted clinical experimentations with stem- or stem cell-like cells after May 1 2009. One reason for this was fear of legal prosecution, since none of the hospitals was yet able to receive an official license for the use of clinical SC technology, as demanded in the MoH regulation.

The delimiting impact of this regulation has been much lower, however, in private and lower-ranked state and military hospitals. According to the China marketing manager of a multi-national supply firm for laboratory equipment, for instance, a market evaluation revealed that the purchase of CO₂ incubators for the culturing of mammalian cells had increased in the third and fourth quarter of 2009 by more than fifty percent. Allegedly, virtually all orders in that period were issued by private hospitals functioning as cell therapy centers. According to this marketing specialist, the increase in CO₂ incubator purchases to commercial providers of SC therapies is explained by the fact, that the 2009 regulation addressed SC technology only in a very minimalist way; without any specification of review criteria and implementation pathways. To commercial providers of cell therapies this move signaled that stringent controls for experimental SC therapies were unlikely to be carried out in the near future. In the light of a growing demand for these therapies, these providers decided upon investment and market expansion.

The emergence of a comprehensive regulation

In 2008 the Science and Education unit of the MoH authorized an expert committee of medical ethics chaired by Prof Chingli Hu, to develop a comprehensive draft regulation for clinical research and applications with human SC in China. After a two-year consultation and preparation process, a draft was submitted to the MoH in October 2010. This proposal has subsequently been under internal consideration, and is expected to form the foundation of a finalized version that is expected soon.⁷⁵

A central premise of this draft is the promotion of standardized and rigorous scientific forms of clinical SC research (Hu 2010: 27). It asks for methodical preclinical studies and the generation of reliable safety data, as well as standardized

⁷⁵ This information is based on a presentation of this draft regulation, generously provided by Prof Chingli Hu and his team in Shanghai, on January 21, 2011.

clinical trials that precede clinical applications (27). These trials shall be subject to approval and review procedures under the MoH and the SFDA (which since 2008 has been a subunit of the MoH). Only qualified and licensed hospitals would be able to provide approved clinical applications (37). Furthermore, the draft stipulates that the quality and safety of used cells must be subjected to reliable controls and documentation (32). Medical institutions that violate these principles will be forced to stop SC-based clinical trials or applications for a period of five years (37).

The draft specifies approval and review procedures for three central forms of clinical research and applications with SC. First is approval of clinical trials and applications of *stem cell based drug products*, i.e. standardized batch products based on amplification of cells from one or multiple donors. Responsibilities for evaluation and market approval of these ‘off-the-shelf’ SC products (commonly regarded as the most risky treatment form with SC) shall be handled by the SFDA, and be based on systematic preclinical studies and closely reviewed Phase I-III clinical trials (36). Second is approval of clinical trials and applications of *modified SC from a single donor to single recipient*. With reference to the 2009 regulation these treatment forms were defined as medical technology. Regulatory distinctions are made in this respect between autologous/allogeneic SC, and minimally/extensively manipulated SC. Approval of minimally processed autologous SC, which are seen as the least risky group of cells, shall occur through the MoH Bureau of Medical Administration. More extensively manipulated cells, particularly from allogeneic sources, shall be approved by the MoH Bureau of Science and Education. Application and review procedures shall be handled by the thirty-one province-level sub-branches of the MoH, with the MoH in Beijing as the central supervising agency. Third is approval of *experimental therapeutic approaches with SC*. Experimental for-profit applications shall be strictly delimited. In accordance with chapter 35 of Helsinki Declaration first-in-human experimental treatments with SC shall be allowed, but in a low number of patients, and according to clear approval criteria. Applications and oversight shall occur through specialized ethics committees, at the provincial MoH branches.

With this draft regulation, a clear step toward international harmonization has been set into motion. In regulating medical procedures with SC proportionate to risk, for example, the Chinese draft regulation follows essentially the approach that is also taken in the EU (Faulkner 2009: 641). Differences exist, however, with respect to terminology and the allocation of responsibilities. In the EU, all experimental medical

procedures with SC (including autologous SC for non-homologous use) have since 2007 been classified as *advanced therapy medicinal products*. These are regulated under the centralized auspice of the European Medicines Agency (EMA) (*ibid.* 2009; EMA 2012). The 2010 draft regulation for China, on the other hand, follows a slightly different strategy. For one thing, approval procedures are divided between the categories ‘medical products’ and ‘medical technologies. For the other thing, responsibilities are not done by a centralized drug regulatory agency, but split across three administrative units of the MoH, each with its own subsidiary branch organizations at a provincial level. Since the draft regulation is likely to still undergo significant revisions, it is too early to say what the implications of these differences for processes of regulatory harmonization and international collaborations will be. Further research into these directions, together with a focus on local implementation, will be of interest.

The January 2012 notification

On January 6 2012, the MoH issued a regulatory document called *Notification on Self-Evaluation and Self-Correction Work regarding the Development of Clinical Stem Cell Clinical Research and Applications*.⁷⁶ With this document an initial one-year phase of a more comprehensive regulatory approach has been initiated, whose precise details have not yet been publicized. In the January 2012 document, four subsequent stages of this forthcoming approach have been announced: self-evaluation (*zicha*), self-correction (*ziji*), re-certification (*chongxin renzheng*), and standardized management (*guifan guanli*).

The initial one-year phase that is set out in the 2012 document, however, addresses only the first two of these stages: self-evaluation and self-correction. Self-evaluation of the hospitals that carry out SC-based clinical research and applications shall occur in the following way. First, clinics are required to fill in the ‘Self-Evaluation Form for Inquiry into Conditions of Stem Cell Clinical Research and Applications’.⁷⁷ In this form, clinics are asked to report truthfully on previously and currently developed kinds of clinical research and applications with stem cells.

⁷⁶ <http://www.moh.gov.cn/publicfiles/business/htmlfiles/mohkjjys/s3582/201201/53890.htm>

⁷⁷ This document has been put on the MoH website.

<http://61.49.18.65/publicfiles///business/cmsresources/mohkjjys/cmsrsdocument/doc13829.docx>
Translations of these two documents can be requested from the author of this chapter per email.

Information is requested on (1) types of cells and forms of cell-processing, (2) the disease types for which cells have been used, (3) forms of ethics and regulatory approval mechanisms, (4) informed consent procedures, (5) information on risks and experienced problems, (6) sources of funding and patient fees, (7) number of patients experimentally treated, and (8) publications or summarizing reports from clinical trials or other types of clinical studies. Second, this information is evaluated by province-level MoH workgroups, which are coordinated by the ‘Stem Cell Clinical Research and Application Standardization and Rectification Work and Leadership Group’, co-founded by the MoH and SFDA in Beijing (paragraph 2). The task of these province-level workgroups is to appraise the incoming data, to produce summarizing reports to Beijing (paragraph 4), and during later stages, to play an active role in the implementation and enforcement of the regulation (paragraph 2).

Self-correction means that all institutes that have not yet received approval, either by the MoH or the SFDA, must stop clinical stem cell research or application activities until approval has been obtained. Institutes that continue to carry out unauthorized clinical research or applications have been announced to be targeted as focal points for rectification (paragraph 2). On the other hand, clinical trials for stem cell products that have obtained approval by the SFDA are expected to act in strict accordance with the requirements set out by the SFDA, and in compliance with the Chinese GCP standards (paragraph 2). The document has announced that no registration applications will be accepted by the MoH or the SFDA until July 1 2012 (paragraph 2). Information on how applications for registration will be handled, however, has not been provided in the text. Uncertainty also remains as to how non-compliance will be dealt with, and which role the MoH and its province-level workgroups will play in this. It is not clear, furthermore, whether military hospitals (that operate under the command of the Health Department of the Army General Logistics Department), will be subjected to the same review and approval procedures as state hospitals, or whether a different regulatory approach shall apply.

Part III: Medical innovation and national experimental pluralism

With the January 2012 notification, and the draft regulation of 2010, the ministry has signaled that it is committed to methodical preclinical studies, approval procedures based on systematic clinical trials, controls of cell processing and manufacturing, and to the penalization and shutting down of clinics that do not meet required standards. These issues reflect, by and large, the benchmarks set out in the ‘Guidelines for the Clinical Translation of Stem Cells’ of the International Society for Stem Cell Research (ISSCR 2008), which formed a central reference point for the regulation prepared by the drafting committee led by Chingli Hu (Hu 2010: 23-4). If successfully implemented these steps will bring governance of the clinical SC field in China into line with the international standard system.

In creating congruence with internationally recognized clinical standards in the stem cell field, the ministry is gradually establishing new boundaries of inclusion and exclusion. Many of the forms of clinical experimentation that have become institutionalized and widely sought after in recent years, will be delegitimized. However, this change in status may be some time off. Not only will technical standards and implementation pathways of the emerging regulatory framework have to be defined in detail, but there is also the challenge of developing adequate enforcement mechanisms. According to a Nature report from April 2012, not one clinic had signed up at the ministry in the required way, and many hospitals continued to offer treatments, despite the decree applications that have not yet received approval by the MoH or SFDA should not proceed (Cyranoski 2012). Accordingly, until stringent enforcement procedures are in place, the landscape of clinical experimentations with SC in China, will remain characterized by the coexistence of multiple and highly diverging forms of experimentality.

In this respect, a complex and multi-stranded clinical innovation culture has developed in the SC field in China. This culture is characterized by collaborations and knowledge exchanges between highly contrasting socio-technical and epistemic communities. Let me explain this briefly through the concept of “national experimental pluralism”. The term refers to the deployment of divergent modalities of experimental clinical application through different communities of practice, under a shared national jurisdiction. In the clinical SC field in China, as I have shown above,

multiple forms of clinical experimentation exist side-by-side. These differ with regard to recruitment strategies, clinical methodologies and the epistemic and discursive practices through which claims on efficacy, safety and ethical validation are created and justified. These disparate forms of experimental clinical intervention (and the goals, values and legitimization frameworks on which they are based) are situated in diverging socio-technical communities that have evolved under the permissive regulatory approach to clinical SC applications in China. I suggest that this pluralization of experimental practices and communities, has given rise to a clinical innovation culture that in many respects diverges from linear lab-to-clinic models of drug development, as drug regulatory authorities, such as the U.S. FDA or the Chinese SFDA, promote them. Due to the long-standing absence of a regulatory framework for clinical SC research in China, a more dynamic and circular process of clinical innovation can be observed. Promising approaches with new cell types may be tested first in patients, then moved to the lab, and subsequently back to the clinic; either in form of (more) systematized pilot-studies or clinical trials, or as for-profit experimental therapies.

As Webster *et al.* have pointed out recently, similarly pragmatic pathways of clinical translation can also be observed in the USA and Western Europe, in experimental clinical work with autologous stem cells (2011: 411). As the authors note, rapid translation from bench to clinical trials, with return feedback loops to the lab, before a phase of re-testing in the clinic, can be frequently observed in the development of autologous SC treatments (*ibid.*: 411). In China, however, the situation is still different. For one thing, such circular patterns of clinical translation exist not only with autologous stem cells, but also with allogeneic cell sources, which are considered more risky. Furthermore, multi-directional knowledge transfers between bench and clinic in the SC field in China can occur across highly diversified institutions and stakeholder groups, which employ starkly contrasting forms of data collection, ethical standards, and approval procedures. This contrasts significantly with the situation in the USA or Western Europe, where knowledge exchanges between labs, clinics, research institutes and companies unfold in a context of homogenized regulatory practices, unified technical and ethical standards, and a widespread commitment to clinical trials.

An illustration of the opportunities that arise from the multi-directional knowledge flows between diverging sites and frameworks of experimentality in China,

is the use of allogeneic mesenchymal stem cells (MSC). Since 2004, MSC have experimentally been used in patients in China (Chen *et al.* 2004). These early studies, in combination with encouraging findings from abroad, have triggered a massive wave of basic, preclinical and clinical research with MSC (Liao and Zhao 2008), as well as countless experimental for-profit applications. Research with MSC in China has resulted, moreover, in at least four standardized MSC-based medicinal drug products, which have applied for SFDA approval. Additionally, a large number of non-SFDA reviewed clinical trials and clinical trial-like studies with MSC have been conducted, for several disease conditions (Liao and Zhao 2008, Han et al 2011).

This co-existence of rapid clinical applications alongside systematic preclinical and basic research opens up possibilities that in the UK, for instance, would be unthinkable. For one thing, it has created opportunities for fast “tryout” trials, e.g. the precursory testing of a new SC product in patients with different disease types, to identify the most promising uses for subsequent (and highly cost-intensive) IND application. For instance, in 2010 a senior researcher presented findings at an international conference. These findings were taken from clinical pilot studies for seven disorders in altogether 153 patients, with a standardized MSC product developed in this researcher’s lab. These studies were based on collaborations with local hospitals and aimed to create preliminary efficacy and safety data, on which basis to detect the most promising approaches for a planned SFDA application. Due to the absence of a regulation for SC-based clinical trials in the past, pilot-trials that precede IND applications at the SFDA have in fact been legal (provided IRB approval in involved hospitals has been obtained). Many researchers see such studies as a central element for clinical SC innovation in China because they allow for rapid and unproblematic evaluation of the clinical utility and feasibility of new products which can be tested more systematically later on. Many of the high-profile researchers with whom I spoke, nonetheless, reject such informal trials, and insist wholly on lab-to-clinic translations under review of the SFDA or MoH.

The coexistence of rapid clinical experimentations, often for-profit, alongside systematic preclinical studies and formalized clinical trials has created various other effects, which have benefitted the field of clinical SC research in China. Several researchers reported, for instance, that the high number of experimental treatments with MSC in patients with different diseases have delivered important preliminary insights regarding the treatment potential of these cells, and a rough estimate that MSC

(after use in thousands of patients) are apparently comparably safe. According to Liao and Zhao, experimentations with MSC in clinical trials have also provided new questions for basic research in China (2008: 616). But feedback loops from clinic to lab occur also in the context of for-profit experimental treatments. Clinical service providers of for-profit MSC therapies, for instance, publish regularly together with basic scientists from key-state institutes and hospitals, in particular on mechanisms of functional recovery (Li *et al.* 2010; Tang *et al.* 2012). The market potential and widespread clinical applications with MSC in China have also intensified research on the sourcing, quality control, and storage of MSC. AmCellGene Co. Ltd., for instance, a SC R&D company from Tianjin, has developed a standardized manufacturing procedure for the clinical use of umbilical cord derived MSC. This procedure encompasses cell collection, isolation, cryopreservation, characterization and administration, for the manufacturing of clinical grade MSC in the context of good manufacturing practice (GMP) compliant laboratories (Gong *et al.* 2012). Most important maybe, the large number of clinical applications with MSC has given rise to crucial hands-on experiences, in particular regarding cell transplantation and related surgical procedures, and to the availability of a clinical infrastructure, which can be used for systematic and multi-center clinical trials in the future.

National experimental pluralism and the China SCI Net

The coexistence of, and collaboration between, diverging communities and forms of clinical experimentation with stem cells in China, have been of some advantage for the Network. As I demonstrated in Part One of Chapter III, the lack of clinical experiences with stem cell-based approaches in spinal cord injuries was defined as a central barrier for clinical translation in the US context. In China, however, clinical experimentations with stem cell-based approaches in this field have been conducted widely. The availability of clinical experiences with stem cells among network-affiliated researchers informed the study protocol of the China SCI Net, particularly with respect to the surgical and cell injection methods. The surgery and injection procedure described in Chapter IV had been developed by two clinical Network teams in Mainland China (Young 2010). China has a breadth of experience with cell transplantation, as explained before, which has clearly been facilitated by the longstanding absence of formalized state-centered regulatory and oversight structures

for clinical stem cell research and its applications. The tapping of insights that result from these experiences, and their translation from the context of China to a transnationally operating high-profile science collaboration, is a clear example of the emerging scientific opportunities and related ethical dilemmas that clinical partnerships (against a background of scientific multipolarization) are giving rise to.

Conclusions

In this chapter I have provided an overview of the regulatory situation for clinical stem cell research and its applications in China, and of the diverging modalities of stem cell-based clinical experimentation that this situation has enabled. I have shown that although the initial steps toward regulatory harmonization have been undertaken, more specific regulatory instruments will be required if the process is to be implemented. Presently, the situation is characterized by what I have called ‘national experimental pluralism’, that is the coexistence of highly diversified modalities of clinical experimentation under a shared national jurisdiction. In this respect, I have suggested that the side-by-side of distinct experimental forms in the clinical stem cell field in China has given rise to a highly complex clinical innovation culture, which is characterized by multi-directional flows of knowledge and resources across starkly contrasting socio-technical and epistemic communities. This point was illustrated by referring to clinical innovation processes with a specific type of stem cells -- mesenchymal stem cells -- whereby knowledge exchanges and collaboration between diverging experimental communities have created possibilities for fast ‘try-out’ trials, technology development, and additional questions for basic and preclinical research.

Exchanges of knowledge and transfer of experience between previously isolated and, in methodological terms, starkly contrasting communities of clinical practice, have played an enabling role also for the China SCI Net. As I highlighted in the final section of this chapter, surgical transplantation experiences of domestic clinical partners in China were integrated into the organization’s study protocol, and applied in an international context. I suggested in this respect that the draining off of these clinical insights and experiences in China, and their integration into a multi-country, high-profile research project, forms a noteworthy example of the new kinds of opportunities and resources offered by collaborations in the context of global

scientific multipolarization. The use of these opportunities implies, however, an alteration of the current practices through which clinical translation in highly regulated countries such as the USA is currently conducted and legitimized. More research into these and similar processes would be beneficial.

The high level of clinical experimental freedom with stem cells in China has given rise to novel economic and scientific opportunities. In the light of these new possibilities, incentives for the harmonization of clinical research practices with the international system have remained low for many medical institutions. Stakeholders that promote the integration of the clinical stem cell research in China into the international arena are a relatively small group of high-profile researchers and R&D (research and development) companies, as well as researchers that take part in international clinical research collaborations. The China SCI Net has, in this context, been identified as the only multi-sited international clinical trials network that is currently active in the stem cell field in China. The key incentives for these stakeholder groups are the development of formally approved medicinal stem cell products that can be accessed and marketed in multiple countries, and the opportunity to be published in top international journals. To achieve compliance with international clinical research and ethics protocols, these groups must rely on extensive forms of capacity building and scientific self-governance.

In contrast, providers of for-profit therapies, and clinical researchers for whom international recognition is not important, have little incentive to comply with international standard regimens. Many of the activities and economic undertakings of these groups would come under pressure through a shift toward consistent regulatory harmonization in China. At present, in any case, no regulatory mechanisms exist in China to enforce compliance with international standards in the clinical stem cell field. Even though, as I have shown in this chapter, oversight and approval mechanisms are now endorsed by the state, there is a widespread consensus that regulatory controls should not be too stringent, so as not to inhibit scientific progress and delay public health and economic benefits.

Against this background, internal pressures for conformity with the international system are expected to remain low. However, external forms of pressure for regulatory harmonization in the stem cell field are currently also not very strong. In contrast to pharmaceutical drug research, in which international harmonization has been enforced by drug regulatory agencies and the pharmaceutical industry, the

pressure is still low in regenerative stem cell medicine. A key reason for this, I suggest, is that the regenerative medicine field is still in an early development stage. Until now, the therapeutic potential of stem cell-based therapies has only in a few cases been demonstrated convincingly. Cross-border marketing of stem cell-based products or procedures is still low, and it is mainly restricted to the informal sector. Investments from the pharmaceutical industry, moreover, have remained small. In the light of this situation, and the concrete forms of exchange and use value that the stem cell mode-of-production in China is already generating, the broad spectrum of experimental scientific and ethical practices to which this chapter has referred to is well likely to persist. In the next chapter I will focus on China SCI Net's experiences and interactions with the regulatory system in China, from the perspective of the China SCI Net.

Chapter VI

Regulatory approval and controversies

Introduction

In this chapter I focus on the experiences and interaction processes within the regulatory system for clinical stem cell research in China, from the perspective of the China SCI Net. I will do this by concentrating on the approval procedures of the first two clinical trials with stem cells that the Network conducted. These are trials CN102b and CN102b_KM which were conducted in Hong Kong and Kunming, respectively (as described in Chapter IV). Based on these data, two lines of argumentation are developed upon.

The first points to the differences in regulatory structures across countries; these are often associated with enabling effects on projects of international drug development. It has been suggested, for instance, that the strategic utilization of regulatory loopholes reduces costs, expedites recruitment procedures (Petryna 2009), and enables research and commercial applications that would not be possible in more stringently regulated zones (Sleeboom-Faulkner and Patra 2011). The aim of this chapter, however, is to show that the existence of diverging regulatory frameworks, in the context of international clinical research projects, can also present important barriers to multi-national drug development. As the example of the China SCI Net shows, the unsettled regulatory situation of clinical stem cell research in China has caused significant time delays for the Network, as well as increased costs and many organizational challenges.

The second line of argument involves the review and approval procedures for clinical trials; this concerns the evidence and principles on which basis decisions are made about when and in what way to proceed from laboratory testing to clinical experimentation in human beings. A related issue is who makes these decisions and in what form. Part Two of this chapter further elucidates these issues; they not only underlie the review procedures of Institutional Review Boards (IRBs), drug regulatory

authorities and national ethics committees, but they are also crucial for patients and their families, and the scientists. I will show that contrasting opinions with regard to the timing, speed, criteria and evidence for clinical translations can be observed not only across countries (or other kinds of homogenized regulatory zones), but also *across* and *within* specific disease fields in each country.

These issues will be addressed by exploring a number of controversies that have arisen with respect to the timing and form of clinical translation as handled by the China SCI Net. I will focus, first, on debates led among clinical researchers in China; second, on debates among scientists and patients in the USA. Attention is also given to a recent debate on clinical translation in the US spinal cord injury research community, in which interesting comparisons were made to clinical research in other disease types, especially multiple sclerosis and HIV/Aids.

PART I: Interacting with the regulatory system - Experiences and challenges

Chapter V provided a more general overview of the evolving regulatory situation for clinical stem cell research and applications in China. In this chapter, I will build on these observations as I explore the interface between clinical researchers and regulatory agencies through one specific example: that is, through the approval procedures that preceded the first two clinical trials of the China SCI Net, conducted in Hong Kong and Kunming. The data presented in this section stem from several sources, among which were the *CareCure* community website, interviews, the trial protocols and media analysis.

Clinical trial CN102b, the Phase I/II safety study described first in Chapter IV, was originally meant to be conducted at the Chengdu Army General Hospital in Kunming. This hospital houses one of the largest and most advanced spinal cord injury research and rehabilitation units in China. However, a long, drawn-out institutional odyssey ensued that led to the trial being launched in Hong Kong, rather than Kunming, two years after the intended starting date of 2008.

This will require some explanation. The initial plan of the China SCI Net was, until to the end of 2007, to seek approval for its stem cell transplantation trials by the Chinese SFDA (the central drug regulatory authority in China), in the context of an investigational new drug (IND) application procedure. The choice of the SFDA was logical. SFDA approval for such trials is not mandatory in China, but the filing of an IND application would be advantageous in two ways: one, it would allow for formalized marketing of the tested treatment combination in China (provided it was proven to be efficient and safe, and two, it would facilitate approval procedures for subsequent clinical trials in the context of an IND application with the US Food and Drug Administration (FDA). Thus, additional insights would be gained and the tested treatment combination could be taken to the market in the USA.

Informal inquiries on how best to achieve approval for the trials were made by approaching staff from the SFDA as well as the Ministry of Health (MoH); this process began in 2005 (Young 2007). In 2006, however, a completely unforeseen event occurred: the SFDA was shaken by a scandal on a grand scale. The former head of the institution, and various members of the staff, faced severe charges of bribery,

and were accused of abusing rules in the renewal of drug production licenses. It is reported that at least ten people died because substandard medicines had been approved (Jia 2007). As a result, the agency was provisionally shut down. Everyone at the senior leadership level was replaced and the organizational procedures were restructured. The institution was re-opened as a sub-unit of the MoH. The agency's former head was sentenced to death and publicly executed in July 2007 (China Daily 2007).

When these events unfolded, the China SCI Net was still preparing its IND application. It was hoped that the application could be submitted soon after restructuring of the agency. Professor Young attended a meeting with new staff of the SFDA, early in 2007, and had the following to say: 'The current SFDA is embattled but we were very surprised in a visit to them last week that they really want to help us'.⁷⁸ Two months later, in March 2007, things were still progressing according to plan:

It is now 2007 and while we are well on our way to completing the observational trial and our Phase 1 [lithium] trial is just beginning, we are [...] now applying to the SFDA and MoH for the Phase 2 studies [the lithium Phase II study CN102a, and the Phase I/II umbilical cord blood cell/lithium combination study CN102b]. They may not be approved until later on in the year.⁷⁹

In the same contribution Young also reported:

Because there has never been a clinical trial of a combination cell transplant and drug therapy the China SCI Net trial must be approved by two agencies: the SFDA and the Ministry of Health. We have a lot of work to do to put together the safety packages and applications.

Unexpectedly, however, when the SFDA started to operate under its new rules, which had only been introduced in July 2007 (Jia 2007), the agency was not surprisingly exercising extreme caution in the approval of new medical approaches. It is reported that the organization refused to even accept an IND application from the China SCI

⁷⁸ Blog contribution of Wise Young on *CareCure*, January 28, 2007. URL: <http://sci.rutgers.edu/forum/showthread.php?t=76460> (last accessed September 25, 2012).

⁷⁹ Blog contribution of Wise Young on *CareCure*, March 11, 2007. URL: <http://sci.rutgers.edu/forum/archive/index.php/t-78638.html> (last accessed September 25, 2012).

Net at that point. According to one researcher at the Network, Young and other senior investigators met several times between 2007 and 2008 with officials from the MoH in order to explore their options. However, the MoH insisted that no application could be launched for an unspecified time.⁸⁰ The precise reasons for this were never entirely clear. However, this researcher did state that the rejection was probably politically motivated. In the months that followed the SFDA scandal, the MoH tried to avoid approving anything that might cause public controversy.⁸¹

For the China SCI Net this temporary rejection resulted in uncertainty and serious delays. In 2008, when it became clear that SFDA approval for the Phase I/II study might take several years, two further options were considered. The first was to apply to the Hong Kong Department of Health (DoH), in order to carry out the study in affiliated hospitals located there. The second was to apply to the Health Division of the Army General Logistics Department in China (the national drug regulatory authority of the military) with respect to the CN102b trial. The headquarters of the Logistics Department is located in Beijing, and their province- and district-level health bureaus are scattered all over the country. It operates independently of the MoH, and handles its own regulatory, approval and review procedures. The central task of the agency is to oversee and approve clinical research and treatments that are developed in the medical universities and hospitals of the Chinese military. The CN102b trial was initially to be carried out the Chengdu Army General Hospital in Kunming, which falls under the jurisdiction of the military, therefore this application was a feasible and lawful alternative. In this way, the trial would be approved by a national-level health authority, and the study could finally be launched.

In 2008, the decision was taken to apply for approval of CN102b at the Army Health Division and thus to carry out the trial in Kunming. Due to the large number of patients in the hospital's spinal cord unit, and the high technical standards and vast research experience found there, the Chengdu Army General Hospital in Kunming was an optimal choice.⁸² However, on May 1, 2009, there were further unforeseen events. The China MoH issued new regulations on the clinical use of medical technologies,

⁸⁰ Interview Nr 24, senior researcher, North China, February 14 2011.

⁸¹ All names of persons in this chapter (with exception of Wise Young), are made anonymous (i.e. are either referred to as 'researcher', or 'senior researcher', or given different names), on behalf of the wish of the interviewees.

⁸² Interview Nr. 32, senior researcher, Central China, September 15 2010.

including the use of stem cells (see Chapter V). Wise Young reported the matter to the US spinal cord injury community thus:

On May 1, 2009, the Ministry of Health of China issued new regulations that would take place in November 2009. These new regulations require all hospitals that provide cell transplantation treatments to be accredited and all cell transplant procedures to be approved. We were in the process of getting a clinical trial approved at the Kunming Army General Hospital and had all but obtained permission and a grant to do so when this ruling came out that we were told that we need approval from the Ministry of Health.⁸³

As reported in Chapter V, the May 1, 2009 regulation was never enforced with respect to cell transplants, but it still had a significant impact on research in that area. Many of the for-profit practices continued their research regardless, researchers in more reputable institutes withdrew from clinical experimentation with stem cells until such time as clear regulatory procedures were in place. In the light of the uncertain regulatory situation, the military health authority would not independently approve the trial after all. Responsibility for approval of the trial now lay solely in the hands of the MoH. When senior staff of the China SCI Net approached officials in the MoH, however, a bureaucratic game of ping-pong was set into motion; the researchers were sent back and forth between different units in the MoH, as Young reported in August 2009:

We have now met senior officials of the Ministry of Health. One department head told us that our trial was not the responsibility of his department and referred us to another. That department in turn said that it wasn't their responsibility and referred us to the SFDA. We wrote to the SFDA and just received a reply saying that this was the jurisdiction of the Ministry of Health. In short, nobody is making any decisions or taking responsibility for approving clinical trials involving cell transplants. I suspect that it may be many months before this bureaucratic issue is resolved.⁸⁴

⁸³ Blog contribution of Wise Young on *CareCure*, August 22, 2009. URL: <http://sci.rutgers.edu/forum/showthread.php?t=123088> (last accessed September 25, 2012).

⁸⁴ Blog contribution of Wise Young on *CareCure*, August 22, 2009. URL: <http://sci.rutgers.edu/forum/showthread.php?t=123088> (last accessed September 25, 2012).

Several Network researchers confirmed this multi-directional administrative journey during my fieldwork. The SFDA's refusal to take responsibility for approving stem cell-based clinical trials was independently reported by other researchers in China. Evidence provided by personnel with connections to the MoH indicated there was some conflict between different units, such as the SFDA, the Department of Science and Education, and the Department of Medical Administration. At debate were not only issues about how the research should be regulated in a technical sense, but also how specific roles and responsibilities should be distributed across the organization's subunits. According to a senior researcher from Beijing, after three meetings with representatives from these departments, there was no conclusive outcome. Faced by this institutional merry-go-round, the Network decided to pursue its contingency plan, namely to apply for regulatory approval of CN102b via the Department of Health in Hong Kong, and thus conduct the trial there.

Approval of the trial in Hong Kong

In contrast to the difficulties experienced in obtaining approval for the trial in mainland China, the process in Hong Kong was uncomplicated and rapid. The first step involved applying for IRB approval from Queen Mary Hospital at Hong Kong University and the Prince of Wales Hospital from the Chinese University of Hong Kong. Approval from their two ethics committees was obtained in Autumn of 2009. Subsequently an application was filed at the Pharmaceutical Registration Unit with the Pharmaceutical Services Division of the Hong Kong DoH.⁸⁵ The trial was officially approved in January 2010.

The clinical use of cells for research is regulated in Hong Kong as follows: as with other human tissues and blood products, stem cells are classified as a medical ‘device’. As specified in the *Classification Rules for Medical Devices*: ‘all devices manufactured from or incorporating animal or human cells/tissues/derivatives thereof, whether viable or non-viable’ are to be classified as Class IV (DoH: 2010). Class IV is the highest risk category, as defined in the DoH *Medical Device Administration Control System* (MDACS) which has been implemented gradually since 2004. This process is still ongoing.⁸⁶ The *Classification Rules for Medical Devices* document mentions that ‘currently’ (in 2010) these cell and tissue products do not yet ‘fall within the current scope of the MDACS’; however, it stated that a specific regulation for these products was in preparation (DoH: 2010).

In other words, the clinical use of cells and stem cells was, at the time of writing, not regulated as a distinct regulatory category in Hong Kong. This did not mean that their use was without regulatory control. Approval for clinical experimentations with such cells had to be obtained at two different levels: by hospital internal ethics committees, and by one of the six ‘cluster ethics committees’ in Hong Kong that oversee research in all hospitals under the Hospital Authority (another part of the DoH). They also review clinical research in compliance with the ICH Good Clinical Practice (GCP) guidelines (HA 2010).

⁸⁵ Please note that the names of the administrative units in the Hong Kong DoH have changed since the time of writing. Approval of new drugs is now no longer handled by the Pharmaceutical Service Division, but by the Drug Office.

⁸⁶ Information specified on the website of the DoH *Medical Device Administration Control System*. URL: <http://www.mdco.gov.hk/english/mdacs/mdacs.html> (last accessed September 25, 2012).

However, the use of stem cells together with a drug (as proposed by the China SCI NET) is a fundamentally different situation. Approval by the DoH is then mandatory. IND applications at the Pharmaceutical Registration Unit of the Hong Kong DoH are based on a standard procedure that includes the evaluation of (i) the proposed study protocol, (ii) preclinical studies of the tested medicinal products, (iii) evidence that the trial medication is manufactured in accordance with Good Manufacturing Practices (GMP), (iv) sample certificates of analyses of the used medication, (v) approval letters from the hospital ethics committees, (vi) the proposed patient consent forms, and, if applicable, (vii) clinical trial certificates and data from previously completed clinical studies (MDACS: 2010). Applications are then approved by specialist teams in the Pharmaceutical Registration Unit, if necessary under inclusion of external experts (*ibid.*).

I am not aware of the precise details of the application procedure for the CN102b trial with the Hong Kong DoH, but according to the Executive Manager of the China SCI Net (Dr Wendy Cheng in Hong Kong) who filed the application, all submitted documents were accepted, and there were no complications. A senior Network researcher mentioned that the trial was approved without difficulty or requests for further preclinical study data because the tested umbilical cord blood (UCB) mononuclear cell product was GMP-certified and had a long safety record of in-human application in blood diseases; furthermore, a Phase I and II trial on lithium in spinal cord-injured patients had already been completed by the Network.

The Network started to recruit patients for the trial immediately after approval in January 2010. The take-up was extremely slow, however, as documented in Chapter IV. Only two patients were enrolled on the study by the end of 2010. Nevertheless, after the long history of delays and complications experienced by the Network, the announcement of the first successfully operated patient on *CareCure* was met by a long wave of enthusiastic replies. Young gave the news as follows:

The first case was done on the 29th of November. It was, I believe, the first spinal cord injury cell transplant operation in Hong Kong history. The surgery went well. The patient did not have any neurological change afterward. In addition to the daily care and exams, the subject will be receiving formal examinations at 6 weeks, 6 months, and a year. I am hopeful, of course. The next case has been tentatively scheduled for around the middle of

December.⁸⁷

Here are a selection of excerpts from the long list of replies posted on the *CareCure* website by people from the spinal injury community in the USA:⁸⁸

Wow! Hope!! Thank you Dr Young!

Way to go Wise! I am so happy for you and our community.

Dr Young, thank you so much for the update and everything you do for us, and congratulations! May God bless you and be with us all.

I can't tell you how much I appreciate what you and everybody involved in these trials are doing for all of us Dr Young! I hope and pray for great results!

The importance of beginning clinical trials cannot be over-estimated, regardless of initial results. The cure is a process; this is another step toward achieving that goal.

The enthusiasm expressed in the fifty or more responses to Young's announcement was completely understandable. Four years after initial attempts to get the trial approved by the SFDA in China, this first injection of UCB mononuclear cells into the spinal cord of a patient was a significant achievement.

Re-application of the trial in Kunming

The challenge of recruiting eligible patients in Hong Kong was still a disappointment for the organization, both at the leadership level of the Network and among the PIs and staff of the associated hospitals. After so many complications and delays, this problem jeopardized successful completion of the trial. Therefore, the organization decided to

⁸⁷ Blog contribution of Wise Young on *CareCure*, December 1, 2010. URL: <http://sci.rutgers.edu/forum/showthread.php?p=1290098#post1290098> (last accessed September 25, 2012).

⁸⁸ These replies can be found on the following web pages of *CareCure*:
 URL 1: <http://sci.rutgers.edu/forum/showthread.php?t=139662&page=11>,
 URL 2: <http://sci.rutgers.edu/forum/showthread.php?t=139662&page=12>,
 URL 3: <http://sci.rutgers.edu/forum/showthread.php?t=139662&page=13>,
 (all sites last accessed on September 25, 2012).

re-apply to the Health Division of the Army General Logistics Department in mainland China. The purpose was to conduct the CN102b trial as a multi-center study simultaneously in Hong Kong and in Kunming. In doing so, they were more likely to recruit adequate numbers of patients.

In the summer of 2010, when this decision was taken, the regulatory situation in China seemed more relaxed again. As a senior researcher of the Network in Hong Kong recounted, the researchers in Kunming indicated that approval for the trial by the Health Division of the General Logistics Department of the People's Liberation Army (PLA) was once more an option. This was not surprising. A stem cell scientist in Beijing reported in February 2011, that during the course of the previous year (2010) it had become clear that the May 1 2009 regulation would be enforced by the MoH *only* after further review criteria and implementation procedures were issued. This was expected to take a couple of years. Under the revised conditions, it was therefore feasible to renew application attempts for approval from the Army's Health Division. Moreover, the CN102b study protocol had by then been approved by the DoH in Hong Kong, so the investigators were in a far stronger position than before.

The application, according to a senior researcher from the Network in mainland China, was handled by the headquarters of the Military Health Department in Beijing. After internal evaluation of the protocol and submitted documents and data, the PI of the study in Kunming was ordered to Beijing to defend the trial before an independent expert committee. According to this researcher, specialists were recruited from an 'expert bank', that is a centralized registration system containing the names of medical specialists in different disciplines from military universities and hospitals throughout China.⁸⁹ The hearing was successful.

The Military Health Authority approved the trial in Kunming in February 2011.⁹⁰ On February 14, 2011, the trial was registered under the name CN102b_KM on the US clinical trials registry *ClinicalTrials.gov*. The first patient underwent surgery and cell injection in September.⁹¹ Seven months later, all twenty patients had received cell transplants. An additional six patients were treated during the same time

⁸⁹ Interview Nr. 32, senior researcher, Central China, September 15 2010.

⁹⁰ Same source as previous note.

⁹¹ Blog contribution of Wise Young on *CareCure*, September 29, 2011. URL: <http://sci.rutgers.edu/forum/showthread.php?t=165693> (accessed September 25, 2012).

in Hong Kong. On May 14, 2012 Young reported on *CareCure* that recruitment for the two trials was closed.⁹²

Additional forms of approval for the CN102b and CN102b_KM studies

Two additional forms of review and approval for the CN102b and CN102b_KM studies, from outside China, deserve special mention. The first was an external review procedure carried out by Western IRB, Olympia, USA. The second was the control of the GMP status of the laboratories in the involved hospitals by the US FDA. Approval of the CN102b study by Western IRB was sought voluntarily, and conferred an additional element of compliance with the international standard system. It also should help paving the way for approval of the treatment with the US FDA.

The Western IRB is an independent, for-profit IRB. It is accredited and reviewed by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). It serves to carry out IRB review procedures for many of the leading medical universities and university hospitals in the USA, as well as pharmaceutical and biotech companies. The organization has experience of review procedures for human research in more than fifty countries.⁹³ According to the *Oxford Handbook of Clinical Ethics*, Western IRB carries out ethics reviews for more than half of all new drug submissions to the US FDA (Ezekiel *et al.* 2011: 753). The company approved the CN102b study protocol in 2009, apparently without complaint.⁹⁴

External controls of the GMP status of the transplantation laboratories were required mandatorily by the US FDA. The Head of one of the two laboratories involved in the Hong Kong trial explained the procedure as follows:

Because the clinical use of the UCB mononuclear cells from Stemcyte in the USA is subject to a special IND procedure, under the control of the FDA, the FDA also carries out controls of laboratories when the cells are destined for use abroad. The controls undertaken for the stem cells for the CN102b trial in Hong Kong were carried out in the following way. First, the study protocol was sent to the US FDA. They sent

⁹² Blog contribution of Wise Young on *CareCure*, May 14, 2012. URL: <http://sci.rutgers.edu/forum/showthread.php?t=186632&page=2> (accessed September 25, 2012).

⁹³ Western IRB, Global Services. URL: <http://www.wirb.com/Pages/GlobalServices.aspx>, (accessed September 25, 2012).

⁹⁴ Interview Prof Kwok-Fai So, Hong Kong, June 11, 2010.

an inspection team to Vista Biologicals in San Diego, which is where the cells were processed and packaged for distribution to Hong Kong and mainland China. The inspectors evaluated whether the laboratory was fully GMP compliant and GTP (Good Tissue Processing) compliant. Then the FDA focused on the transplantation laboratories in Hong Kong. The relevant documentation, certificates, standard operating procedures (SOPs), scientific papers and institutional charts were sent to the FDA. After a review process in the USA, the Head of the laboratory was interviewed by telephone. In this way it was ascertained that the laboratory met all the required standards. Approval was given for the preparation of the cells for transplantation, and approval was obtained for their shipment from the US.⁹⁵

⁹⁵ Interview Prof Hui Tsai, Hong Kong, January 7 2011.

Interim Summary

In the previous sections I have shown that the unclear regulatory situation for clinical stem cell research in China at that time was very challenging for the China SCI Net. The repeated refusals of the MoH and SFDA to take responsibility for the trial's review and application procedure caused significant delays, as well as increased costs, and the decision to relocate the trial to Hong Kong, necessitating yet more regulatory applications. These problems not only reveal the importance of a reliable and clearly defined regulatory framework for multi-country science projects, but also highlight what happens when such frameworks are not in place.

A frequently made claim in the social science literature on international clinical research collaborations is that the existence of regulatory divergence across national jurisdictions opens up new opportunities for international drug research and commercial applications. A drug product that could only with great difficulties (and immense costs) be tested in a stringently regulated country can be tested in another country, where the regulations are more lenient. Sleeboom-Faulkner and Patra (2011), for instance, report on a medical entrepreneur who clinically tested and marketed stem cell treatment technology in India; this had been developed – but not approved – in Japan. Petryna (2009) describes how pharmaceutical companies profit from the off-shoring of clinical trials to low-regulated zones, and how clinical data generated in these areas are used to apply for regulatory approval in high-regulated countries.

The experience of the China SCI Net shows that the existence of divergent levels of regulatory stringency across countries, in the context of international clinical research projects, can create barriers to multi-country drug research. While it is true, as shown in Chapter V, that the Network benefitted from the surgical and cell transplantation experience of clinical researchers in China, the absence of a consistent regulatory approach for clinical stem cell research almost deprived it of official regulatory approval for its trials. For clinical providers of informal stem cell therapies in China, or for clinical researchers who experiment with a particular cell type in a few patients, approval by a drug regulatory authority is essentially of no use. But for an internationally operating, high-profile clinical research infrastructure such as the China SCI Net, the very purpose and effort of conducting trials is meaningless without such approval. It means that a tested product cannot be brought to the market, and the research data will not be acceptable for approval in other countries. However, as I will

show in Chapter VII, even with official regulatory approval, international clinical research projects such as that of the China SCI Net are forced to balance out regulatory differences across national jurisdictions through active forms of self-regulation and capacity building.

PART II: Controversies

On a more general level, the pivotal issues underlying the approval and review procedures of first in-human trials are (1) ethical principles (in relation to the risks of a candidate treatment), (2) preclinical evidence (that indicate the treatment's safety and efficacy), and (3) the level of urgency around efforts to control a particular disease (usually higher in case of epidemic diseases, such as HIV/Aids).

These are the central criteria, on whose basis decisions to move from preclinical to clinical research are taken. Related to this is the matter of who should make these decisions, and in what form they should be made. Such issues are debated by expert committees, national ethics councils, drug regulatory authorities, hospital IRBs and other regulatory agencies.

In the following paragraphs I make a shift in perspective. I will show how the methodological forms, legitimization criteria and the speed of laboratory-to-clinic translations are critically debated also at the 'grassroots' level, that is within the specific biosocial communities that characterize contemporary assemblages of global drug development. These debates take place among patients, their families, and clinical researchers, often in a highly dialectical way. In the remainder of this chapter, I will explore these 'grassroots' perceptions by focusing on a number of controversies with regard to the timing and form of clinical translation, as handled by the China SCI Net. These issues will be examined from three analytical angles: the first concentrates on debates led among clinical researchers associated with the China SCI Net in mainland China; the second involves exploration of a controversy among clinical spinal cord injury researchers in the USA; the third focuses on the viewpoints of people with spinal cord injury who make comments on the *CareCure* website.

One theoretical point to be highlighted relates to the unit of analysis through which variations in laboratory-to-clinic translations are studied. In the literature, differences in the way in which clinical translation is practiced and legitimized are usually discussed by referring to contrasts in research regulation and the role of regulatory agencies across countries. Chen and Gottweis (2011), for instance, speak of a 'regulatory patchwork', whereby differences in national regulatory frameworks result in widely divergent forms of clinical translation, across tightly or low-regulated

countries (*ibid.*: 4). I will show in this respect that variations in speed, forms and legitimization rationales of clinical translation can be observed not only across countries (or regional and supranational jurisdictional zones), but also across particular disease fields within a country. As will become clear, there is also great variation within specific disease fields, at the level of individual researchers and research groups.

Debates among clinical spinal cord injury researchers from mainland China

Perceptions and debates on the timing, forms and organizational models of clinical translation relating to the aims of the China SCI Net, will first be explored from the perspective of affiliated researchers from mainland China. The following issues will be considered: perceptions about the reasons for conducting the trial in China; the controversy surrounding the use of a randomized controlled clinical trial; opinions on the use of sham surgery for the control group.

The reasons for conducting the trial in China

There was widespread consensus among affiliated researchers that the existence of the Network and its research aims had widely beneficial effects (more on this in Chapter VII) for spinal cord injury patients in China, for the field of spinal cord injury research as a whole, and for affiliated researchers and institutions. During the initial formation of the Network, however, the motivations of Professor Young to plan and conduct clinical trials in China were subject to critical scrutiny and suspicion.

Dr Qiong Song, a clinical researcher whose department joined the organization at an early stage, related the fact that various hospitals refused to take part in the Network – the main reason, according to Dr Song, was that people objected to the idea that trials in China were initiated by an American researcher.⁹⁶

At that time (in 2005) research with stem cells was still viewed with great controversy within the US. Even though criticism in the USA was primarily directed against human embryonic stem cell research, some researchers in China supposed that Young's motive was to conduct trials in China, because they could not be done in the

⁹⁶ Interview Nr 24, senior researcher, North China February 14 2011.

USA. As Song went on to explain, these researchers thought that it was more appropriate to conduct the trial on American patients before Chinese patients.

In Song's opinion, these suspicions about the organization's motives played a role also in the problems faced by the Network during its early attempts to register the trial with the SFDA. Allegedly, government officials and the SFDA questioned why the proposed trials should be done in China rather than the USA.⁹⁷

Song points out that this way of thinking reflected a general precautionary stance regarding clinical trial collaborations with foreign institutes. The potential risks for patients make this a sensitive issue that frequently tends to result in criticism from the media, politicians and the public. This claim cannot be confirmed by other data in this dissertation, but it is highly likely that the foundation of such an international network, with its intention to conduct clinical trials in China, was initially met with suspicion. It is not certain, however, whether the difficulties the Network encountered with regard to approval for the first trial were related to this issue.

Dr Lingfang Li, a researcher from another team in the Network who helped identify potential partner hospitals in mainland China, gave another reason for the reluctance of some hospitals to join the organization; this was because the clinical trials had not yet been officially approved by the MoH. In fact, when the hospitals were being recruited, various candidate treatments were still under consideration, thus a concrete approach had not been decided, and official approval from the MoH was therefore not possible. Dr Li found that some of the departmental and hospital heads he approached found this problematic. They were reluctant to test a treatment that may not have developed by themselves, and they refused to take any responsibility until official approval was granted by the MoH or SFDA. According to Dr Li, some researchers insisted that they would only join the Network after seeing an official approval document.⁹⁸

Most of the hospitals, however, particularly the larger and more renowned ones, accepted that a definite treatment approach for the trials had not been determined, and that approval for the trials would be obtained in due course.

⁹⁷ Same source as in previous note.

⁹⁸ Interview Nr. 32, senior researcher, Central China, September 15 2010.

Other controversies among researchers in China

Chapter IV explained how the clinical trials of the China SCI Net followed stringent evidence-based medicine (EBM) clinical research standards, with the three-phase randomized controlled trial (RCT) format as its central methodological instrument. I will show in Chapter VII how – in order to achieve this – the organization set out to significantly alter certain research practices and concepts in affiliated partner institutes. The Network's attempts at restructuring in the affiliated research hospitals in mainland China resulted in a number of controversies, involving the roles and values of the clinical trials, the use of sham surgery as a control treatment, and the acceptability of financial contributions from patients. This shall be discussed now.

i. Roles and values of the clinical trials

The vast majority of researchers affiliated to the China SCI Net with whom I spoke were strongly supportive of RCTs, and were generally in favor of adopting such clinical trial protocols for stem cell research in China. Some of the interviewees, however, expressed a less accepting opinion. While the role and value of trials were widely acknowledged, there was discontentment with regard to the status of clinical trials as the *only* acceptable clinical research methodology. Some of the researchers I spoke with mentioned the possibility of other more patient-driven approaches; they insisted that potentially helpful treatments could be given to patients outside the clinical trial format, and these options should not be abandoned. One researcher, for example, argued that although RCTs result in strong evidence, and therefore help patients to obtain efficient treatments, the trials take a long time to complete and only limited numbers of patients can take part, which means that large numbers of patients are denied access to the potentially helpful treatment. According to this clinician, the RCT approach means that people whose quality of life could be vastly improved often have to wait for many years; in some situations and diseases, patients die before a tested treatment is approved. Therefore, clinical research should be more flexible, with systematic clinical trials being practiced alongside less rigorous forms of clinical experimentation.⁹⁹

⁹⁹ Interview Nr. 23, senior researcher, North China, September 23, 2010.

Another researcher rejected this view, pointing out the potential for exploitation of patients, who may be lured into experimental treatments on the basis of false claims. According to this researcher, experimental treatments are acceptable only if they are provided on a non-profit basis – and provided there are clear indications that the treatment appears to help patients, and has no severe adverse effects. Experimental for-profit applications were therefore rigorously rejected by this person.¹⁰⁰

It is important to note that before the introduction of EBM-based clinical research methodology into medical education and regulation in China during the 1990s and 2000s patient-centered (rather than rigorous science-centered) forms of clinical experimentation have for a long time constituted the central dogma in experimental medicine. As reported by several researchers in China (not related to the Network), a shift toward systematic clinical trials and the formation of multicenter clinical trials networks occurred first in the field of cancer research, and only later in the fields of orthopedics and neurosurgery.¹⁰¹ In these latter fields, the shift toward EBM and multicenter RCTs was, at the time of my research, in many respects an ongoing process.

That this process was progressing rapidly became clear during my visits to the hospitals of the China SCI Net in mainland China. Most of the eight departments involved had conducted Phase I/II clinical trials or had prepared such trials.¹⁰² Previous studies tended to be conducted without the inclusion of control groups, but these later studies all included controls. One of the hospitals was already planning a larger Phase III trial, and had set up a province-level multicenter clinical network to this end.¹⁰³

¹⁰⁰ Interview Nr. 28, seniore researcher, East China, January 19, 2011.

¹⁰¹ Interview Nr. 50, seniore researcher (hematologist), Beijing, February 8, 2011; Interview Nr. 59, seniore researcher (hematologist), Shanghai, January 21, 2011; Interview Nr. 64, seniore researcher (hematologist), Tianjin, January 27, 2011.

¹⁰² Note: Only some of these trials were with cells or stem cells. Others were surgical trials, comparing different techniques and operation times.

¹⁰³ Interview Nr. 20, senior researcher, South East China, September 7, 2010.

ii. Sham surgery

Another issue of great controversy were debates regarding the use of sham surgery as a control group.¹⁰⁴ The possibility was discussed in an expert panel of the first international symposium organized by the Network in 2005 in Hong Kong. In the USA, sham surgery is acceptable under very specific conditions, but among the orthopedic and neurosurgeons I interviewed in mainland China, the proposed use of sham surgery was completely unacceptable.

The main reason was that patients would be exposed to the risks of surgical procedures without the chance of any medical benefit. Researchers in China saw this as unethical and as intolerable for their patients. Dr Xinjan Liu, an orthopedic surgeon affiliated to the China SCI Net in mainland China, acknowledged that the use of placebo control groups is very important in drug trials, and that the methodology was extensively adopted in China. However the use of sham surgery control groups was totally different. Liu readily accepted the scientific rationale, but argued that a sham surgical procedure – unlike the administration of a placebo product – involves much greater risks for the patients (in particular anesthetic risks) and brings about some degree of suffering, from fake incisions and stitches. The idea of exposing patients to needless postoperative pain was highly problematic to this person, especially if there was a chance that the treatment group received some benefits from the trial. For these reasons, the use of sham surgery was entirely rejected.¹⁰⁵

Dr Liu also pointed out that patients in China were very unlikely to take part in any trial if they knew they might receive sham surgery. Dr Qiong Song was of the same opinion. He acknowledged that a clinical trial without a sham control would result in less robust data, but he considered the mimicking of a potentially beneficial surgical procedure to be unacceptable. According to him, a sham surgery-controlled trial would simply not gain approval by ethics committees or regulatory agencies in China.¹⁰⁶

¹⁰⁴ A sham surgery control group is the equivalent of a placebo-control group. It is occasionally used in surgical clinical studies. A patient is anesthetized and obtains a few surgical incisions that make the patient believe s/he may have undergone treatment-active surgical procedures. It is a methodological instrument to increase the validity of data in surgical studies, by testing 'placebo' responses (i.e. sham surgery-based placebo responses) in a control group. Surgical incisions in sham surgery patients are usually kept on a minimum level.

¹⁰⁵ Interview Nr. 22, senior researcher, South East China, September 5, 2010.

¹⁰⁶ Interview Nr 24, senior researcher, North China, February 14 2011.

Dr Ma Qiao, an orthopedic surgeon from one of the affiliated hospitals, expressed himself in particularly dramatic terms. He believed that demands for a rigorous study design that involved sham surgery completely overrules the needs of the patients, that exposing them to sham surgery reduces their status to that of laboratory animals. He also felt that such a proposal had parallels with the medical experiments conducted during World War II by Japanese doctors on Chinese patients and prisoners of war.¹⁰⁷

In the context of the China SCI Net, the option of a sham surgery control group was publicly discussed by a research protocol panel at the first international symposium of the organization in 2005 in Hong Kong.¹⁰⁸ During this discussion it was very clear that the use of sham surgery as a control – while endorsed by some of the invited experts from the USA – was simply not an option for researchers in China. A consensus was formed that clinical trials conducted by the Network should be ‘active comparator’ studies, whereby all the patients groups would be exposed to some form of experimental intervention. In case of the planned Phase III trial, therefore, these treatments would involve different combinations of UCB mononuclear cell transplantation, lithium administration and methylprednisolone administration. These would be tested against a control group of patients that received a cell transplant alone.¹⁰⁹

iii. Financial contributions from patients

Another contentious area was the concern about financial contributions from patients taking part in the trial. As reported in Chapter V, there is generally insufficient funding for academia-initiated clinical trials in China, and it is widespread practice to charge patients for the operational expenses of a trial, including costs of treatment, hospitalization and rehabilitation. Depending on how much money from government grants is available, the costs to patients can be reduced or waived completely. In the case of the China SCI Net trials, all costs were covered by the organization itself, thus the participants were completely free from financial contributions.

¹⁰⁷ Interview Nr. 23, senior researcher, North China, September 23, 2010.

¹⁰⁸ The panels and presentations of this conference were recorded on video, and a CD Rom was made available for analytical purposes.

¹⁰⁹ Interview Nr. 32, senior researcher, Central China, September 15 2010.

However, in some institutes affiliated to the China SCI Net, financial contributions by patients remained common practice in clinical studies (not organized by the Network).

Almost all researchers with whom I spoke preferred to refrain from charging trial participants, however the situation was not that straightforward. One of the spinal cord injury researchers, Dr Judi Hu, explained how money for spinal cord injury research was available in China, but funds for clinical trials were very scarce. In fact, they were reportedly non-existent at that time for systematic multicenter clinical trials. Some funding was in place for smaller trials, but this was extremely limited. Dr Hu concluded that charging patients for parts of the treatment in academic clinical trials (other than the studies of the China SCI Net, in which all trial expenses are covered by the organization) was unavoidable. Without doing so, it would not be possible to conduct investigator-initiated clinical trials at all.¹¹⁰

Another spinal cord injury researcher, Dr Yun Wang, added that the situation would not change if the government did not provide more funding for clinical trials. According to him, financial contributions of participants in academia-initiated clinical studies were (at the time of my fieldwork in 2010/2011 at least) a firm part of China's clinical research culture. Under the significantly privatized healthcare system at that time, patients had become so used to paying for treatments that they expected to pay for experimental procedures.¹¹¹

The few spinal cord-injured patients I spoke with in mainland China all confirmed this view. They saw payment for participation in a clinical trial as both reasonable and acceptable. Further research into the perceptions of patients at that time would be the only way to acquire a greater understanding of the situation, however the truth of the situation was clearly reinforced by the findings of my fieldwork.¹¹²

¹¹⁰ Interview Nr. 28, senior researcher, East China, January 19, 2011.

¹¹¹ Interview Nr. 27, senior researcher, East China, January 19, 2011.

¹¹² Interview Nr. 82, person with SCI, Central China, September 16, 2011; Interview Nr. 83, person with SCI, Central China, September 16, 2011; Interview Nr. 84, person with SCI, Central China, September 16, 2011.

Debates among clinical spinal cord injury researchers in the USA

In the following section I will introduce the debate on the preclinical evidence and timing of the clinical translation of the China SCI Net research, which was led by Professor Young and Jerry Silver, a senior spinal cord injury researcher from Case Western Reserve University in the USA. I will continue in the wider context of the considerations and organizational frameworks under which processes of clinical translations occur. It will become clear how, in the USA, there are huge differences between various disease fields with respect to the scientific criteria and legitimization rationales underlying translation of research projects from the laboratory to the clinic. With respect to spinal cord injury, I will show that positions and review criteria regarding time-points and forms of clinical translation are dynamic and are constantly being negotiated.

The Young–Silver debate on the solidity of preclinical studies

In November 2011 a noteworthy debate surfaced regarding the preclinical study data for the treatment combination to be tested by the Chinese and USA spinal cord injury Networks, and whether the data were strong enough to justify translation to the clinical arena. Jerry Silver stirred up the debate on the *CareCure* website by arguing that there are ‘zero published data showing that umbilical cord blood stem cells plus lithium has been effective to foster recovery in an appropriate animal model of spinal cord injury at long chronic stages’.¹¹³ What Silver points out is that the preclinical data that indicated the efficacy of the stem cells was derived from animal models with only acute and sub-acute spinal cord injury. He asked for a pilot experiment to be conducted ‘in an animal model of *chronic* spinal cord injury using a strategy similar to that used in humans [that is, the combination of cell transplantation and lithium] to show that this can have even a minimal beneficial effect’.^{114 115}

¹¹³ Blog contribution of Jerry Silver on *CareCure*, October 21, 2011. URL: <http://sci.rutgers.edu/forum/showthread.php?s=1d0396a724ec51d144062720e289c296&p=1436211#post1436211> (accessed September 26, 2012).

¹¹⁴ Blog contribution of Jerry Silver on *CareCure*, November 8, 2011. URL: <http://sci.rutgers.edu/forum/showthread.php?t=168731&page=5> (accessed September 26, 2012).

¹¹⁵ For contextual understanding I repeat here briefly the rationale behind the combination treatment tested by the China SCI Net: (1) The UCBM cells are expected to facilitate formation of a cellular bridge at the injury site to enable re-growth of nerve axons across the damaged tissue environment from above and below. (2) Lithium is administered (in a six week oral course) to stimulate the production of

Young responded to the suggestion of ‘zero published data’ by providing a summary of twenty-six studies on which the decision to bring the lithium/cell combination was based.¹¹⁶ In this response he also referred to the absence of preclinical research data from an animal model with *chronic* spinal cord injury:

We have shown that lithium stimulates umbilical cord blood mononuclear cells to proliferate and to secrete neurotrophins (Young 2010). Unfortunately, we were unable to test the combination of lithium and HLA-matched cord blood cell transplants in animals. First, it is difficult to get umbilical cord blood from animals. There is no source of HLA-matched umbilical cord blood from animals. Non-HLA-matched allogeneic or xenograft cells [transplanted human cells] are immune-rejected from the spinal cords. Second, when we used cyclosporin [ciclosporin] or FK501 to immune-suppress the animals and prevent rejection of the cells, we found that the immunosuppression by calcineurin blockers *blocked the effects of lithium* [my italics]. Third, human umbilical cord blood cells contain large numbers of CD34+, CD133+ and other cells that may not be present in neonatal rat blood. We are continuing to work to test the cells in rat spinal cord injury models.¹¹⁷

One of his observations was about ciclosporin (then called cyclosporine), which is used to suppress HLA-based rejection symptoms after the transplantation of human cells into animal models. The fact that ciclosporin can inhibit tissue regeneration in xenotransplanted animal models is widely accepted. According to Naomi Kleitman (2008), Director of the spinal cord injury research cluster at the National Institutes of Health (NIH) this problem is also recognized by the US Food and Drug Administration (FDA), which asks for efficacy data *only* on the basis of preclinical studies that involve transplantation of cells within the *same* species (*ibid.*). Xenotransplants, which entail the transplantation of human cells, are required only to prove the safety of the transplantation of a particular type of cell; for toxicity and tumorigenicity studies the administration of ciclosporin poses no problem (*ibid.*).

neuronal growth factors (neurotrophines) in both the implanted cells and the cells of the surrounding spinal cord and thus promote the growth of the axons across the newly built bridge over an extended time period. (3) The methylprednisolone is used to increase the survival of the transplanted cells by acting as a blocker of growth inhibitors at the injury site that can prevent the re-growth of axons and other neural cells. (Based on: Young 2009; reported already in Chapter III).

¹¹⁶ Blog contribution of Wise Young on *CareCure*, November 10, 2011. URL:

<http://sci.rutgers.edu/forum/showthread.php?t=168731&page=5> (accessed September 25, 2012).

¹¹⁷ Same source as in previous note.

As Young then pointed out during an interview, his team had tried to address the xenotransplantation/immune rejection problem by creating an appropriate rat spinal cord injury model, but ultimately this failed. In 2007 they had begun development of a transgenic mouse model. Young expected this model would soon be capable of receiving human UCB cell transplants without immunosuppression syndromes.¹¹⁸ I was not fully informed on the progress of this research, however, and at the time of writing was unable to find any publications on the subject.

The differences in opinion of Silver and Young touched on a central and unresolved question within the US American spinal cord injury community: of what kind and what quality should the preclinical efficacy data be in order to legitimize translation from the research laboratory into the clinic. In her role as Head of the NIH funding committee that decides on grant applications for clinical research in the spinal cord injury field in the USA, Naomi Kleitman (2008) explained how there was no consensus on the issue or existence of any clear-cut criteria.

The first and biggest barrier [for translation toward a clinical trial] is: the community has reached, as far as I can tell, absolutely no consensus on how much preclinical efficacy is necessary, or advisable. [...] [P]ushing drugs or cells to clinical use, without adequate trial design, simply wastes rather than saves time. But to be perfectly honest, striving for perfection in an imperfect animal model, may only delay important clinical testing. Finding the appropriate balance between those two – should essentially be the goal [...]. There will never be a 100% agreement, but there should certainly be a better agreement than we have today. (Kleitman 2008)

Young and Silver were operating at opposite ends of what was viewed as permissible in the US context. While Silver argued that ‘it is a moral obligation to enter into clinical trials where people’s lives are at stake with preclinical data that are far stronger’,¹¹⁹ Young maintained that the existing preclinical data were sufficient, rather than optimal, to permit moving on to clinical trials.¹²⁰ His case was supported by the established safety record of the GMP-certified (Good Manufacturing Practice) and FDA-registered Stemcyte product he used (see Chapter IV), and the fact that UCB

¹¹⁸ Interviews with Wise Young, Hong Kong, August 29, 2010.

¹¹⁹ Blog contribution of Jerry Silver on *CareCure*, November 8, 2011. URL: <http://sci.rutgers.edu/forum/showthread.php?t=168731&page=4>, (accessed September 25, 2012).

¹²⁰ Blog contribution of Wise Young on *CareCure*, November 10, 2011. URL: <http://sci.rutgers.edu/forum/showthread.php?t=168731&page=5>, (accessed September 25, 2012).

cells were widely used in experimental for-profit therapies. He argued that the trials of the China and US spinal cord injury Networks were providing an important opportunity to shut down these (for-profit) applications in the future, if the cell transplant and lithium combination tested by the two Networks proved to be without benefit.

In my opinion, it is worthwhile testing the combination of lithium and UCBMC transplants in human chronic spinal cord injury. [...] As you and everybody else here [on the *CareCure* forums] knows, we have been focusing on chronic spinal cord injury. Many clinics are now giving umbilical cord blood cells to people with chronic spinal cord injury in Mexico, China, India, Thailand, and other countries, often delivering the cells intravenously or intrathecally. Our trials, which are rigorously carried out with direct transplantation of HLA-matched umbilical cord blood mononuclear cells into the spinal cord around the injury site, will definitively assess the effects of umbilical cord blood cells alone and in combination with lithium.¹²¹

What Young referred to here was the positive value of *negative* study results, that is the proof of inefficacy of a tested treatment. This would allow the use of UCB for spinal cord injury by for-profit experimental therapy providers to be halted (Young 2008). Be this as it may, the debate showed that there were important variations in the USA with regard to several aspects of preclinical research, namely the evidence, speed, review criteria and legitimization rationales used to make collective decisions for moving toward clinical experimentation in human patients.

Variations in requirements for different field of research

I will now show that an even larger level of variation exists in the ways in which these decisions are made across different disease fields. The matters addressed by Kleitman above, about the type and quality of preclinical efficacy data, and the feasibility and precision of animal models, are dealt with in highly divergent ways across different research communities. To illustrate this, I will briefly compare research in the areas of spinal cord injury, human immunodeficiency virus (HIV), and multiple sclerosis. The data I draw upon stem from panel discussions of the 2008 and 2009 Bedford spinal

¹²¹ Same source as in previous note.

cord injury Conference entitled ‘Barriers to Cure’ (this was referred to in Chapter III), and are triangulated with secondary sources.

According to Ann Kissling, Head of the Bedford Stem Cell Center in the USA, and a researcher into transmission of HIV through seminal fluid,¹²² the earliest candidate therapies for Aids were brought to clinical trial in the absence of any animal model, and with very little preclinical data (Kissling 2008). She explained that the clinical translation process for HIV and funding for this from the NIH, followed an almost entirely patient—applicant-driven approach. In the light of the public health threat posed by HIV/Aids at that time, conventional review criteria became less stringently applied, and ‘cure’ as a trial outcome was privileged above the proof of presumed treatment mechanisms (Kissling 2008). The lack of workable animal models for HIV/Aids, at least during the first two decades of research into the disease, is a well-established fact in the literature (Lo 1992; Wolf and Lo 1995; 2001). Compared to other disease fields, it was been reported that HIV vaccine trials went ahead ‘with less preclinical evidence of efficacy than other interventions’ because:

A good animal model does not exist, [and] HIV is highly variable and undergoes rapid mutation, and there is little information about how to build protection against HIV. Nevertheless, because of the enormous suffering caused by HIV, such trials are ethically appropriate if there are credible scientific reasons to believe the candidate vaccine may be effective’ (Wolf and Lo 1995).

The high speed and the low level of preclinical evidence were thus legitimized on the basis of the high disease burden of HIV, and on the notion of urgency in light of the disease’s transmission rate.

Clinical translation of research with sub-optimal animal models occurs in other disease fields, where public perceptions of urgency are lower. One example is multiple sclerosis (MS) research. The most commonly used animal model is a mouse with experimentally-induced encephalomyelitis (the so-called EAA model). This model, however, has been described as being ‘totally different clinically, immunologically and histologically from MS’ (Behan, Chaudhuri and Roep 2002: 245). Attempts to extrapolate findings from the mouse model to the pathogenesis of human MS have

¹²² Bedford Stem Cell Research Foundation, ‘About the Director’, URL: http://www.bedfordresearch.org/aboutus/aboutus.php?item=about_director (accessed September 25, 2012).

been highly erratic (*ibid.*), with ‘many failures to clinically translate experimental findings in EAE into MS’ (Sriram and Steiner 2005; Baker and Jackson 2007: 10). Despite these problems, however, there have been many more clinical trials for MS than for spinal cord injury; in fact, seven FDA-approved medications have been developed based on preclinical evidence from the EAE model (MD Biosciences 2010).

According to the US clinical trials registry *ClinicalTrials.gov* since 2001 there have been nearly three times more interventional Phase I studies for MS than spinal cord injury,¹²³ even though the prevalence of spinal cord injury is about one and a half times higher than that of MS.¹²⁴

‘Review’, as Naomi Kleitman has put it, ‘is largely an issue to get peers to agree’ (Kleitman 2008). While the NIH handles a number of general review parameters, the precise criteria used for funding applications for the translation of clinical research vary across disciplines and disease fields, and depend on different consensus regarding the kind, quality and quantity of preclinical data required.

Controversies among patients

The skepticism of Silver, who was resolved to ‘cross his fingers for the trial’,¹²⁵ and the drawn-out debate with Young on *CareCure*, was reflected by the wider spinal cord injury community. On the *CareCure* and other spinal cord injury websites, a wide variety of opinions and levels of support were expressed for Young and the trials of the transnational Network. The number of supportive statements for Young and the trials far outweighed those of critics, but the questions Silver raised about the kind and quality of preclinical study data were echoed by some patients with spinal cord injuries or advocates of those with injuries.

‘Grammy’ was one member of the *CareCure* website who frequently entered into dialogue with Professor Young since 2007. In a posting on October 2011, Grammy

¹²³ Specifically there have been sixteen interventional Phase 1 studies for MS, and six for spinal cord injury. Source: www.clinicaltrial.gov.

¹²⁴ Data from Paralysis Resource Center, Christopher Reeves Foundation (http://www.christopherreeve.org/site/c.mtKZKGMWKwG/b.5184255/k.6D74/Prevalence_of_Paralysis.htm).

¹²⁵ Blog contribution of Jerry Silver on *CareCure*, October 21, 2011. URL: <http://sci.rutgers.edu/forum/showthread.php?s=1d0396a724ec51d144062720e289c296&p=1436211#post1436211> (accessed September 26, 2012).

was highly critical about the testing of the combination of UCB mononuclear cells with lithium:

I've read through as many of the papers that have been listed which constitute the rationale behind umbilical cord stem cells and lithium. All the papers used the stem cells at 'acute' stages, (most after 1 week following spinal cord injury). Nothing at 'chronic' stages. All the studies show a very modest effect of these particular stem cells of about 2 BBB points [Basso, Beattie and Bresnahan Scale: to test locomotor functions in paralyzed lab animals] beyond that of cyclosporin [ciclosporin] which is used to prevent rejection. Not so good. There is no evidence that lithium promotes stem cell survival in the injured cord. The Wu paper examined lithium effects on stem cell proliferation when placed into the normal spinal cord only. The second Wu paper (2007) saw no effect of lithium alone on regeneration. There was only one additional paper on this subject, which was carried out only *in vitro*. All of the papers are in low-impact journals. This does not give me much hope at all. I wish you only the best Christopher [another blogger on *CareCure*] if you should decide you want this UCB cell/lithium injection. Perhaps the decompression and intense rehab would be helpful. I'm fearful this concoction will not be quite what you are looking for in regards to actual regeneration or plasticity.¹²⁶

This quote is an interesting testimony to the scientific literacy exhibited by some of the bloggers and activists on the *CareCure* website. It is also an interesting example of the critical and inquisitive spirit of questioning commonly found on the *CareCure* forums.

'Hope' and its discontents

Another issue that sparked off controversy in the North American spinal cord injury online community was the promotion of 'hope'. A talk given by Young in New Zealand in 2011 led to vigorous debate on a spinal cord injury community website named *Apparelyzed*. This debate centred on the sustained propagation of hope by Young, and his belief that a cure for spinal cord injury could be achieved in the foreseeable future. The passage that triggered the controversy was as follows:

¹²⁶ Blog contribution of 'Grammy' on *CareCure*, October 9, 2011. URL: <http://sci.rutgers.edu/forum/printthread.php?t=162836&pp=10&page=21>, (accessed September 25, 2012).

I am very hopeful that the recovery is going to be very substantial. Because, we know, that in the spinal cord, if you have ten percent of your axons, you'll be able to walk. So, I believe that the therapies, if they work, will actually generate very substantial recovery. Not just incremental small changes. That this will be a big change. And I think this will be what will be so surprising about these trials. [...] Our goal in spinal cord injury is to convert someone with a complete injury, or a severe incomplete injury into one that is [a] less severe, incomplete injury. And they can recover sufficient function, so that they are independent, they can do almost everything that they did before, and a third party, who does not know them, seeing them for the first time, wouldn't even guess that they are spinal injured. To me that is a cure. (Young 2011b)

The forward-looking confidence expressed in this statement was met with fierce criticism on *Apparelyzed*. This is from one contributor and potential patient known as 'sci1998':

After reading what Wise Young said about how soon a cure is coming and that you wouldn't be able to tell the difference from an AB [able-bodied person], I really think that is a helluva lot of wishful hype and marketing. I think it would rather be you couldn't tell the difference between the control group and the ones that receive the treatment.¹²⁷

In another posting from the same contributor:

Wise (and not just him but we are talking about sci [spinal cord injury]) has such a grip on desperate people. I am sci but I won't ever give my soul to unproven research. I despise being used by legit research [...]. I do have a hope I will be, but I think your all-out love of one researcher who has in my opinion only used his salesmanship to sell his [...] bill of goods only puts a cure further away.¹²⁸

Both of these posts were from a person who repeatedly criticized Wise Young, and who verbally attacked other bloggers on various sites, often in a strongly offensive manner. Despite the argumentative tone of this blogger, however, the criticism that

¹²⁷ Blog contribution of 'sci1998' on *Apparelyzed*, June 30, 2011. URL: <http://www.apparelyzed.com/forums/topic/19736-dr-wise-young-speaks-about-spinal-injury-umbilical-cord-blood/>, (accessed 25 September 2011).

¹²⁸ Blog contribution of 'sci1998' on *Apparelyzed*, July 14, 2011. URL: http://www.apparelyzed.com/forums/topic/19736-dr-wise-young-speaks-about-spinal-injury-umbilical-cord-blood/page__st__30, (accessed 25 September 2011).

Young ‘sells hope and who wouldn’t want that’¹²⁹ is echoed among various other persons in the spinal cord injury community.

A pattern that was observed in this respect was the division among older people with spinal cord injury, who were long-term injured, and younger persons, or people who were injured more recently. The former group was commonly more skeptical, and often cynical, about the idea of cure, while those in the latter group, tended to strongly endorse the notion that a cure might be achieved, and engaged in active support for the realization of research and clinical trials with this aim. Here are two extracts representing people from each of the two groups. The first is from ‘Tetracyclone’

Dr Young is in his 50s and I greatly respect him as a person, and his work. He gives a huge amount of time to communicating with spinal cord injured individuals over the Internet over on *CureCare*. [...] I have a difference of opinion with him in this way -- he offers constant hope-for-a-cure to us all, yet many of us suffer permanent secondary physical degradation, which make the notion of recovery just plain silly. What good would it do to repair someone's nerve function when their bones are so brittle they cannot transfer safely? As many say, getting back control of bladder and bowel would be grand - - no lie. [...] Yet it is not healthy that some of us who could never stand again even with a ‘cure’, literally ‘live for’ the hope of one. It is creepy. Those folks do not frequent this forum. I'm not saying that is Young's fault. It is not his mission to be a psychologist, but to be a scientist.¹³⁰

The second is from ‘Love and Hate’, written in response to Tetracyclone and another blogger:

I understand where you guys are coming from with your pessimism but I don’t think you are giving enough credit where credit is due. There are a lot of young people with spinal cord injury and this is something important for us. When I read some of the posts above I feel sad and disappointed at the same time. I think it is something we should be happy and excited about. If not for us then for future generations of spinal cord injury. I feel like people are selfish and they just think about themselves. [...] Dr Wise unlike any other pro

¹²⁹ Blog contribution of ‘bob’ on *NJN Network*, September 30, 2011. URL: <http://njnnetwork.com/2011/09/whats-wrong-with-the-rick-hansen-foundation/>, (accessed 25 September 2011).

¹³⁰ Blog contribution of ‘Tetracyclone’ on *Apparelyzed*, June 22, 2011. URL: <http://www.apparelyzed.com/forums/topic/19736-dr-wise-young-speaks-about-spinal-injury-umbilical-cord-blood/>, (accessed 25 September 2011).

in this field is constantly communicating with community sharing his knowledge with us. Keeping us on track. If those trials will end with failure he will let us know. It's not like he's up there to take our life savings like many other 'companies' around the world. [...] The true [truth] is that Dr Wise's trials are one of the most promising from all of them and one that we need to keep an eye on. Safety trials are already on the way with so far good results.¹³¹

I observed on *CareCure*, *Apparelyzed* and other spinal cord injury community websites overall wide-ranging support for the trials conducted by the China SCI Net and the SCI Net USA; critical comments existed, but were the exception rather than the rule. 'Hope' was an over-riding paradigm that was evident in many of the contributions, particularly in those in support of the idea of cure. Numerous activist and fundraising projects were seen, some of which were in support of Young's project, others in support of other projects, as well as more independent community-organized conferences that aimed to bring together researchers, companies and spinal cord injury activists, in order to learn from each other and trigger new lines of research.¹³²

The perceptions of the blogger 'sci1998' on *Apparelyzed*, who diagnosed a 'cult-like following' of Young on *CareCure*, is clearly misleading. In the light of the controversies and critical comments found on the website, *CareCure* represents a pool of widely contrasting opinions and constructive dissonances as well as a space for critical debate and expert quarrels. It remains a place for communication and comfort also for those who have no hope, and for those who over time lost their hope, of a cure. Look at the following contributions from two bloggers, 'Chris Chappel' and 'Spidergirl'.

Hope, for some, is a very raw, painful emotion and process. When one decides to close the door of hope it is very difficult for them when others start knocking. Time and time again I meet many who have closed the door and padlocked it. We all have our own way of dealing with trauma. It's not our job nor our right to try and convince others to believe in something that they don't. To each his own.¹³³

¹³¹ Blog contribution of 'Love and Hate' on *Apparelyzed*, June 23, 2011. URL: <http://www.apparelyzed.com/forums/topic/19736-dr-wise-young-speaks-about-spinal-injury-umbilical-cord-blood/>, (accessed 25 September 2011).

¹³² An example here are the annual Working 2 Walk conferences, URL: <http://www.u2fp.org/organize/events/working-2-walk/agenda/>, (accessed 25 September 2011).

¹³³ Blog contribution of 'Chris Chappel' on *CareCure*, August 15, 2004. URL: <http://sci.rutgers.edu/forum/showthread.php?t=19886&page=3>, (accessed September 25, 2012).

I am sorry to be negative, but I just don't believe in a natural cure. I believe in robotic assisted devices in the future. I am not convinced. It's not Dr Wise... (I believe he's doing more than anyone) – it's just the community as a whole is lost... It's just toooo MUCH!!!¹³⁴

Conclusions

In Part One of this chapter, I pointed to the challenges that the China SCI Net encountered in its interactions with regulatory agencies in China when applying for regulatory approval of the organization's first clinical trial with umbilical cord stem cells. It became clear that the Network, as a result of the unclear regulatory situation for clinical stem cell research in China, experienced severe challenges, which almost brought their activities in China to a halt. I suggested that the existence of regulatory divergence in the context of clinical research partnerships poses significant barriers to multinational drug development. A focus on the strategic instrumentalization of regulatory differences across national jurisdictions, which has been a central concern in the social science literature on international drug research, falls short of grasping the complex implications of situations of regulatory multiplicity with respect to international clinical research projects.

It is important to focus on the constraining effects of regulatory differences, and the ways in which clinical researchers try to balance out any disparities so as to create legitimacy and trust in multiple contexts simultaneously; in fact, as I will argue at greater length in Chapter VII this is a fundamental aspect of understanding the global operation of science in the contemporary era.

In Part Two of the chapter, I explored issues surrounding the principles, the methodological forms, the preclinical criteria, the timing and the speed of laboratory-to-clinic translations. Controversies on these issues have been explored from three different perspectives: from that of the researchers affiliated to the China SCI Net; from that of clinical researchers in the spinal cord injury field in the USA; and from that of the patients with spinal injuries who post their comments on the *CareCure* and *Apparelyzed* spinal cord injury community websites. Among researchers of the China

¹³⁴ Blog contribution of 'Spidergirl' on *CareCure*, July 18, 2010. URL: <http://sci.rutgers.edu/forum/showthread.php?p=1235917>, (accessed September 25, 2012).

SCI Net, controversy was observed with respect to the advantages and disadvantages of EBM research approaches, the debated use of sham surgery controls, and the motives behind carrying out trials in China rather than the USA. Controversies in the spinal research community in the USA, on the other hand, centered especially on the type and quality of preclinical evidence, on which basis the first-in-human trials would be legitimized. Wise Young and Jerry Silver, the main protagonists in the unfolding debate, seemed to have views at the opposite ends of what, in the context of the USA, is seen as legitimate.

A related point was that in the US spinal cord injury research community, no consensus or clearly defined criteria seemed to exist regarding the level of preclinical efficacy data required to move from laboratory to clinic. Similarly, it became clear that the comparative analysis of ‘regulations’ (national or regional) to explain variations in laboratory-to-clinic translation, is unsatisfactory. As this chapter has shown, large variances were observed regarding the timing, scientific criteria and ethical principles on the basis of which clinical translations are permitted in different countries, and within specific disease fields.

Further controversy was found regarding the clinical translation of the cell transplantation therapy augmented with lithium administration. There was some dispute about the amount of supporting preclinical data for this therapy among the China SCI Net as well as contributors to the *CareCure* website. Another area of discontent highlighted by events on *CareCure* concerned the issue of ‘hope’, in particular the ways and extent in which hope should be promoted as an organizing principle in projects of clinical translation. Diverging opinions were expressed by older and longer-term spinal-cord injured people compared to younger people or those who had been injured more recently. The more recently injured and younger group typically endorse quite strongly the idea that ‘cure’ is achievable; the older and/or long-term injured group were often far more cynical and skeptical about the idea of a cure. Far more research is warranted into the perceptions of such people in order to confirm these claims.

Chapter VII

Restructuring Local Grounds

Introduction

In this seventh chapter of the dissertation, I will explore how the China SCI Net worked to transform local clinical research and innovation practices in affiliated partner institutes. These trans-local forms of restructuring are necessary to assure the generation of standardized clinical research data, which will be accepted by the international research community, top international journals and drug regulatory authorities. I will make sense of these processes through the concept of ‘transnational scientific self-governance’. The term refers to project-internal forms of self-regulation and capacity building for creation of a standardized trans-institutional research infrastructure that is compliant with multi-regional regulatory requirements and the international scientific standard system. In this chapter, I will explore these transnational forms of scientific self-governance by focusing on two interrelated aspects: the objectives and domains of restructuring, and the methods and techniques of restructuring through which intended changes are to be achieved.

The objectives and domains of restructuring are explored in Part One of this chapter. These will be investigated from the perspective of the leadership and coordination level of the Network on the one hand, and from the viewpoint of associated partners in mainland China on the other. I am interested, in particular, how changes promoted by the leadership correspond to the problematizations of local research practices, as articulated by affiliated clinical researchers. I am interested, furthermore, in the conceptions of benefits and incentives, on which basis local researchers decided to take part in the Network, and to accept and implement changes in clinical research practice.

Then, in Part Two, I focus on the methods and techniques of restructuring, and the way in which local partner institutes were incorporated into a standardized trans-national research infrastructure. I will analyze these processes by highlighting three specific aspects – selection, restructuring, and international integration. The ultimate

proof of completion of these phases is the generation of valid and standardized clinical research data, in the context of the organized clinical trials. By generating these data, Network-affiliated hospitals immediately confirm their status as members of the China SCI Net, and gradually evolve into recognized components of the global system of high-profile science. Successful incorporation into the China SCI Net, in other words, places the affiliated clinics at the intersection of previously distant social worlds, such as foreign drug regulatory authorities, the US spinal cord injury research community, transnational patient advocacy networks, and globally operating biotech and pharmaceutical companies. It will become clear during the discussion that this integration process, even though initiated by a researcher from the USA, was a deeply collective effort, one that was systematically driven by researchers from within the affiliated institutes in China.

In Part Three these issues will be discussed in the light of a theoretical discussion on the global distribution of evidence-based-medicine (EBM), and the travel and trans-local re-embedding of international clinical research standards. In this respect two claims will be made. I will suggest first that the local alterations in clinical research practices, as instigated by the China SCI Net, were employed in highly context- and situation-specific ways. The newly promoted schema of the randomized controlled clinical trial (RCT) was used next to previously institutionalized practices of clinical experimentation, which were deployed in different situations, and for contrasting purposes.

In an additional strand of this analysis I will show that the homogenization of clinical research practices, which can be observed in the context of the global journey of EBM research standards, is also producing areas of discontentment and resistance, and what I will refer to as practices of ‘alter-standardization’ and the ‘pluralization of the international’.

PART I: Objectives and domains of restructuring

What we are trying to do is really to bring the international standards of clinical trials to China. So, what we are doing is to bring in the concept of using all the modern standards on how to run a clinical trial, as is recognized in the West, in the current time. All the conceptions of leading this network [...] evolve around that concept, right? Obviously, in order to get it to work, first of all we had to promote the interest that we are dealing with a

very important unresolved clinical problem, which is true. So this [spinal cord injury] is an important clinical conundrum, and we have tried to bring in experts from around mainland China, Hong Kong, Taiwan. [...] To [let them] know that they are the target groups. So this is the first level [...], to bring in these people, to provide a platform. For them to be able to interact. That is the first level. And of course, the second level is, we would then bring in the knowledge as to how a clinical trial should be run, in an internationally recognized manner. So that is the second level.¹³⁵

A central objective of the China SCI Net, as the organization's Co-Director Prof Kwok-Fai So states above, is the promotion of internationally recognized clinical trial standards in China. In the first place, of course, the aim was to restructure local clinical research practices in hospitals affiliated to the Network, so as to successfully complete the proposed series of clinical trials. However, there was still a deeper, further-reaching vision of restructuring underlying activities of the Network: that is, to advance contemporary clinical trial methodology to the field of clinical stem cell research in China in a more general sense.¹³⁶ This vision of promoting systematic clinical research standards to transform the situation of clinical research in the stem cell field in China was widely shared among affiliated researchers in China. The motivations underlying this vision were found in two inter-related sets of factors: discontent with local clinical research practices in the fields of orthopedic surgery and neurosurgery, and the conceptualization of specific benefits that would result from the promoted changes. Let me start with the first of these – problematization of local research conditions.

¹³⁵ Interview Prof Kwok-Fai So, Hong Kong, January 7, 2011.

¹³⁶ Two things should be noted in this respect:

- 1) These efforts relate exclusively to the situation in Mainland China, not to Hong Kong and Taiwan, where systematic clinic trial standards, and related government controls, have been methodically promoted for some time.
- 2) Internationally recognized clinical trial standards and methodology has of course also been promoted in Mainland China (see Chapter V, Part I) in clinical stem cell research, however (as shown in Chapter V, Part I), the use of RCTs is still rare.

Problematizations of local research conditions

Researchers from the China SCI Net expressed discontent with local clinical research conditions, in particular with regard to methodological issues.¹³⁷ Dr Yunfa Zhu, a clinical researcher from a hospital in South China mentioned that clinical studies in the orthopedic and neurosurgery fields in China are often characterized by a lack of rigor in terms of outcome measurements and long-term follow-up of patients. One particular problem was that for many years multiple outcome measurement scales were used in the spinal cord injury field in China, some of which were developed by individual researchers. The use of these non-standardized measurement protocols not only made it difficult to assess the reliability of study results, but also prevented systematic reviews and meta-analyses, on which basis the efficacy and safety of a particular treatment approach could be determined.¹³⁸

According to Dr Jiayou Qiu, one of the researchers based in Central China, problems with the quality of data can sometimes be traced back to the non-systematic handling of inclusion and exclusion criteria of patients in trials; this results in non-homogeneous study samples, and thus reduces data validity.¹³⁹ Comparisons of data from clinical studies in the spinal cord injury field in China were further complicated due to the widespread lack of control groups. This issue was addressed by Dr Jianxin Huang from one of the partner hospitals in Central China. He pointed out that, although the RCT format had become common in many medical fields in China (especially cancer research), the use of control groups was still rare in the fields of orthopedics and neurosurgery. One reason for this was the overwhelming rejection of the sham techniques used as a control method in surgical trials, which is widely considered as unethical (see Chapter VI) However, controlled clinical trials that included an active comparator (treatment) group have, according to this researcher, become more common.¹⁴⁰

Another methodological challenge reported by researchers of the China Network was the absence of multicenter clinical trials in both the field of clinical stem cell research more generally, and orthopedic and neurosurgery in particular. Dr Yunfa

¹³⁷ All names of persons in this chapter (with exceptions of the Co-Directors Wise Young and Kwok-Fai So), are made anonymous (i.e. are either referred to as ‘researcher’, or ‘senior researcher’, or given different names), on behalf of the wish of the interviewees.

¹³⁸ Interview Nr. 19, senior researcher, South China, September 10, 2010.

¹³⁹ Interview Nr. 35, senior researcher, Central China, September 15, 2010.

¹⁴⁰ Interview Nr. 32, senior researcher, Central China, September 14, 2010.

Zhu, for instance, pointed out that the lack of multicenter trials in the field posed a serious threat to credibility and reputation. In China, clinical studies with large patient cohorts have been conducted in individual clinics, but these studies are commonly not considered robust enough methodologically to get through the peer review process of the major international academic journals, and accordingly they are not published.¹⁴¹

The scarcity of multicenter trials in China might be explained by several factors. Dr Xinjian Liu, from South China, highlighted the complex organizational challenges of planning and conducting multicenter studies, and emphasized the lack of funding to cover the high costs of such trials.¹⁴² Dr Jiayou Qiu, described a different challenge, that is motivating people to collaborate in large-scale projects; due to competition a tendency exists apparently among many researchers in China to work with one's own team in isolation. A related problem is mistrust of data from pre-clinical or clinical pilot studies conducted by colleagues, which are used for decision-making by potential partners in collaborative trials. According to Dr Huang, this lack of trust in the work of one's colleagues forms a significant demotivating factor for multicenter collaborations.¹⁴³

Dr Bo Jian, from another institute in North China, pointed to the relatively recent introduction of EBM in the standard medical curriculum in China, and a lack of knowledge on how to carry out systematic clinical trials particularly among older clinical researchers. According to Dr Jian the eagerness to engage in multicenter studies is also low because of the small chance of being the first-named author of any publication on such large studies, thus conflicts can arise.¹⁴⁴

Conceptualizations of benefits

Despite these challenges, many researchers perceived the formation of the China SCI Net as a valuable opportunity. Participation in the Network was widely seen to contribute to positive change and improvements in local research conditions, for affiliated researchers, for spinal cord injury patients, and for spinal cord injury research in China in a broader sense. Dr Yunfa Zhu, for example, told me that he hoped the trials conducted by the Network would gradually set a new standard for cell

¹⁴¹ Interview Nr. 19, senior researcher, South China, September 10, 2010.

¹⁴² Interview Nr. 22, senior researcher, South East China, September 5, 2010.

¹⁴³ Interview Nr. 35, senior researcher, Central China, September 15, 2010.

¹⁴⁴ Interview Nr. 32, senior researcher, Central China, September 14, 2010.

transplantation trials in China. His expectation was that the success of the Network, in particular the appearance of its publications in high-ranking scientific journals, would highlight the importance of systematic clinical research methodology, and the benefits to be gained from it.¹⁴⁵ On a more general level, the researchers were able to specify several advantages of the Network.

First of these was the promotion of EBM standards and highly systematic clinical research methodology. Dr Jin Luo, for instance, a researcher in a large hospital in Central China, referred to the trans-institutional standardization of research practices and measurement protocols. The use of these standardized methodological procedures, in the context of a multicenter clinical trial infrastructure, would not only generate high-quality data, but also convince peers, both in China and internationally, of the validity of the findings, and of the credibility of the Network.¹⁴⁶

Second was the potential for high-profile publications; the expectation was that these trials would produce articles for publication in the top international medical journals. Such publications would boost the status of the researchers and institutes involved, and further the reputation of China as a leading player in clinical spinal cord injury research.

The third advantage was the creation of trust in the international arena. As mentioned by Xinjian Liu, the successful completion of the Network's clinical trials would significantly increase international trust regarding clinical stem cell research in China. The completion of the trials would show that academia-initiated clinical trial partnerships with qualified hospitals in China can form an important pathway for future clinical research innovations.¹⁴⁷ Indeed, various researchers outside of China had questioned the capacities and credibility of the Network. Volker Dietz, for instance, who headed a multicenter clinical spinal cord injury study center in Europe, commented in 2007 that 'China is not the right place to test these new therapies' (Dietz; cited in Schuster 2007). Dietz considered that standards of care in China were too low, so that systematic and long-term follow-up of patients would not be possible, and thus the results would not reach internationally recognized standards. 'New therapies', Dietz said, 'ought to be tested in seasoned networks of the West for the results to receive international acceptance' (*ibid.*).

¹⁴⁵ Interview Nr. 19, senior researcher, South China, September 10, 2010.

¹⁴⁶ Interview Nr. 30, senior researcher, Central China, September 16, 2010.

¹⁴⁷ Interview Nr. 22, senior researcher, South East China, September 5, 2010.

The fourth benefit put forward by the researchers of the China SCI Net was the capacity of the Network to regularly bring together numbers of recognized researchers in China, over a prolonged period of time. Jin Luo, one of the principal investigators (PIs) in China, mentioned that these meetings resulted in important exchanges of knowledge and experience, and led to a detailed understanding of what people in other Chinese spinal cord injury centers do. Moreover, the majority of the Network's meetings and training sessions were also attended by international experts from abroad, which increased awareness of what was going on outside mainland China, in Hong Kong, Taiwan, and the USA, for example.¹⁴⁸

The final, fifth benefit related to people with spinal cord injury themselves. The view that the China SCI Net offered opportunities for these patients in China was shared by all of the affiliated researchers. According to the Director of China's leading spinal cord injury rehabilitation research center in Beijing, Jianjun Li, the Network offered important possibilities for these patients to access new and methodically proven treatments and rehabilitation approaches (Li 2005). As pointed out by researcher Bo Jian, the Network would also encourage the development and testing of new therapeutic approaches, and allow patients to take part in systematic and carefully conducted clinical trials.¹⁴⁹ One benefit for patients was repeatedly mentioned by researchers; that is, the gradual 'ruling out' of non-systematically proven, for-profit experimental therapies. Yunfa Zhu referred to the current series of clinical trials with umbilical cord blood (UCB), which in its non-HLA-matched form is offered by various clinics in China. As Zhu pointed out, if the Network's series of clinical trials showed that the use of UCB mononuclear cells was ineffective, then for-profit providers of experimental UCB therapies would be discredited. Zhu defined this as the 'positive value' of 'negative' clinical trial data (i.e. proof of inefficacy).¹⁵⁰ In short, the adoption of EBM standards, RCTs and the formation of a multicenter trial infrastructure were widely seen as providing important opportunities to researchers of the China SCI Net, as well as the spinal cord injury research field and spinal-cord injured patients in China in general.

Acceptance of restructuring at a local (clinic) level was facilitated by the widespread discontent among researchers with local research practices in the stem cell

¹⁴⁸ Interview Nr. 30, senior researcher, Central China, September 16, 2010.

¹⁴⁹ Interview Nr. 32, senior researcher, Central China, September 14, 2010.

¹⁵⁰ Interview Nr. 19, senior researcher, South China, September 10, 2010.

field, and related concerns for patients. It was hoped that participation in the China SCI Net would help to change this situation, and set an example for a new standard of cell transplantation trials in China. In order for this to happen, however, local clinical research practices in network-affiliated hospitals have to undergo a transformation themselves. Moving on, I can show how this was attempted, and what challenges emerged along the way.

PART II: Methods and techniques of restructuring

The formation of the China SCI Net was based, in essence, on the voluntary and situation-specific merging of previously separated research centers into an evolving trans-continental clinical research infrastructure and economy. In its pursuit to create systematic, internationally acknowledged scientific knowledge, this project aimed to unite multiple communities, institutions, and organizations into an evolving global research assemblage that allows for the realization of multiple, but inter-related interests, purposes, resources and benefits. As I will show in the following sections, the forming of this transnational research economy rested on an interconnected sequence of organizational mechanisms, training programs and monitoring activities. Together, they aimed toward the transformation of local research conditions and practices, so as to integrate multiple and heterogeneous local institutes into a single homogenized institutional framework, in which standardized investigations in line with current international clinical research standards would be possible.

This trans-local instilment of novel principles and rules is a complex and drawn-out task. As a senior partner of the Network in mainland China commented, to achieve transformations in clinical practice, older and often deeply engrained practices, habits and convictions have to be overcome, and consensus on fundamental issues must be reached.¹⁵¹ In the following discussion, I will explore how the China SCI Net attempted to tackle these challenges, and how the vision of a cross-continentially-operating, homogenized clinical trial infrastructure that allows for the generation of internationally acknowledged research data could be realized. I will analyze these issues by focusing on three key stages: selection, restructuring, and international integration.

¹⁵¹ Interview Nr. 32, senior researcher, Central China, September 14, 2010.

Selection

Initial information on the selection of centers in mainland China, Hong Kong and Taiwan for the Network has already been provided in Chapter III. In this section, I will build upon these insights by highlighting the mechanisms of selection, and by pointing out that selection is an ongoing process that involves long periods of training, assessment and qualification. The selection process of centers destined to take part in the first multicenter clinical trial was ongoing at time of writing. Therefore it was not known how many of the twenty-five centers that initially agreed to join the Network for the Phase III trial would (in 2013/2014) be participating.

Selection depended on the ability of each center to provide evidence that they met certain criteria relating to technical benchmarks, institutional qualifications, and adjustments in their infrastructure, behavior and organization, all of which are required for a successful multicenter clinical trial. A combination of external and internal parameters had to be met. The external qualifications included a number of evaluations to be carried out in addition to the controls carried out within the Network itself. These included mandatory testing GCP (Good Clinical Practice) certification of each hospital wanting to participate in the multicenter Phase III trial. GCP certification is based on an inspection and examination by the Chinese Government. Candidate centers also had to have a GLP (Good Laboratory Practice) certified laboratory facility. They also needed to pass the controls specified by the US Food and Drug Association (FDA) because the cells that would be used for transplantation are an FDA-approved cell product that is manufactured in and imported from the US (for more detail see Chapter V). Each center was also required to obtain hospital-internal IRB (Institutional Review Board) approval for the clinical trial.¹⁵²

The internal qualifications handled within the Network can be divided into those that are ‘performance-based’ and those that are ‘organizational’. Performance-based criteria cover aspects such as protocol compliance, which involves the correct handling of inclusion and exclusion criteria, accurate completion of data sheets, and proper conduct of physiological examinations and follow-up investigations, and informed consent. Among the organizational criteria are checks of IRB approval

¹⁵² Interview, Nr. 17, Hui Tsai, Hong Kong, January 7 2011.

procedures, availability of GCP facilities, technical instrumentation, specialists and motivated staff, and adherence of the center to basic contractual conditions.¹⁵³

Role of the Network's headquarters

These monitoring tasks, together with the coordination of the Network as a whole, were done from the Network's headquarters in Hong Kong. Located on the eighth floor of a mid-size office tower in Wanchai district of Hong Kong Island, the office is permanently staffed by the Network's Vice-President Dr Wendy Cheng, as well as GCP monitor Jenny Yu.¹⁵⁴ The office was also used by part-time staff, for the coordination of funding campaigns and statistical analysis, and by Dr Young during his frequent stays in Hong Kong. The office was registered as a non-profit company under the name China Spinal Cord Injury Network Company Limited, with the Hong Kong Spinal Cord Injury Fund Limited as the collaborating partner organization. The Hong Kong Spinal Cord Injury Fund exists solely to support the Network's organization.¹⁵⁵

The Hong Kong office is the nerve center of the China SCI Net. All operations of the organization, as well as communications with affiliated hospitals, stem from here. Wendy Cheng, in her role as Vice-President and central coordinator of the Network, executes and oversees a complex range of tasks. Her main function, as she described during an interview, is to hold the Network together through provision of all kinds of support and regular communication. Together with Jenny Yu, and in dialogue with Dr Young, Dr Cheng had been building up the legal and organizational infrastructure of the Network since 2008, and is arranging the logistics of past and upcoming trials. Besides interacting with participating hospitals, monitoring their activities and performance, Wendy Cheng and Jenny Yu were responsible for organizing training programs, workshops, principal investigator meetings, scientific symposia, and scheduling gatherings of the Network's scientific committees (such as the treatment protocol committee, the outcome measure committee and the implementation committee) as well as board of directors meetings.

¹⁵³ Interview Dr. Wendy Cheng, Hong Kong, June 9, 2010; Interview Wise Young, Hong Kong, June 24, 2010.

¹⁵⁴ Interview Dr. Wendy Cheng, Hong Kong, June 9, 2010; Interview Wise Young, Hong Kong, June 24, 2010.

¹⁵⁵ Website of Hong Kong Spinal Cord Injury Fund, URL: <http://www.hkscifund.org> (accessed August 27, 2012).

Thus the headquarters of the China SCI Net in Hong Kong played a central role in both the restructuring and selection of participating centers. Practices of ‘selection’ were intrinsically intertwined with project-internal processes of ‘restructuring’ and related procedures of training and assessment. Selection, in this sense, was based on the ongoing monitoring of assent to and adoption of required clinical research standards and related institutional prerequisites. This is the subject of the following paragraphs.

Restructuring

The central objective of the China SCI Net, as above indicated by Professor Kwok-Fai So, and as endorsed by most of the affiliated researchers, was to transform local clinical research practices and conditions in related institutions in a way that allows the execution of internationally recognized clinical trials. In this way these centers would be integrated into the international arena of high-profile science in the field of spinal cord injury research and other areas of neurodegenerative research. Realization of this transformation process was based on extensive training as well as performance assessment procedures, and these were accompanied by feedback, and adjustments in documentation, control and monitoring procedures. I will pass comment on each of these aspects in turn.

Training and standardization

Training for staff of the twenty-five affiliated research centers and hospitals began in 2005, with three to four meetings per year until 2009. An initial target was the carrying out of standardized neurological examinations, to ensure valid and replicable assessment of the injury grade of patients on the trial.

When we first came here, the neurological assessment of spinal cord injury – almost everywhere – was completely haphazard. It ranged from, eh, you know ... you take a pin, you put it here, you touch a patient, ask ‘Can you feel it?’ Eh ... there was no disciplined [way]... no common languages, no common neurological assessment of the patients. And they had not really adopted the American Spinal Injury Association [ASIA] method, which was adopted by the International Spinal Cord Society. So, it has become an international classification system. And I coached the committee in the early 1990s to help that system

develop. So our goal is to train our people to do the collection of data for clinical trials. And we train them so that we can trust what they say, so that a patient is an ASIA A, and we know this is real.¹⁵⁶

Standardization of neurological assessment procedures was the first in a long line of critical issues that were addressed. Training sessions fell into three basic categories: training on how to do clinical trials for spinal cord injury; education on recent research and rehabilitation approaches; and education on evidence-based strategies for the identification of new therapies.¹⁵⁷ The first of these – training on clinical trials – aimed to address aspects of clinical trial design, such as protocol development, quality assurance measures, the reliable use of outcome measures and the ethical and legal issues of clinical trials, as well as requirements by foreign drug regulatory authorities and international journals. The second category included a wide range of insights from recent research on spinal cord injury from both China and the USA, covering treatment, rehabilitation and care, the surgical management of spinal cord injury, and the latest basic research strategies. The third category, on education, addressed the identification of new therapies and was targeted first at younger staff and those in the middle of their careers. Education aspects included EBM protocols for preclinical research, ensuring replicable work with animal models, and strategies for translation from discovery to clinical trial.

As I shall point out in Chapter VIII, the central motivation behind all of this was really to facilitate the development of innovative preclinical and clinical studies among researchers within the China SCI Net. This would make the Network an active innovation platform that could be used for the systematic testing of novel therapies generated in China.¹⁵⁸ Training sessions were held in the context of large symposia and workshops organized by the trial, and by a team of instructors who travelled around China holding workshops for the research teams in collaboration with affiliated

¹⁵⁶ Interview Wise Young, Hong Kong, June 24, 2010.

¹⁵⁷ An overview of investigator workshops can be found on the website of the China SCI Net at http://www.the.China.SCI.Net.org/index.php?option=com_content&task=view&id=33&Itemid=59, (accessed August 27, 2012).

Additional training sessions were organized in the context of the four International Spinal Cord Injury Treatment and Trials (ISCITT) Symposia, which the China SCI Net organized in 2005, 2006, 2008, and 2012. Available at <http://iscitt.org/> (last accessed August 27, 2012). The presentations of the symposia of 2005 and 2008 have been video-recorded, and can be viewed online (accessible via <http://iscitt.org/>).

¹⁵⁸ Interview Wise Young, Hong Kong, June 24, 2010.

institutions.¹⁵⁹ Spinal cord injury researchers from the USA were invited to spinal cord injury departments and rehabilitation centers in China, to witness demonstrations of surgical procedures, approaches to rehabilitation and forms of cell transplantation that were not available in the US at that time.

The principal investigators of the China SCI Net were invited to the W.M. Keck Center at Rutgers University in New Jersey to witness approaches to care and research developments there.¹⁶⁰ The W.M. Keck Center also hosted long-term visits from several young and mid-career researchers from China, where they obtained advanced training and experience in basic and preclinical research.¹⁶¹ In its training and education program, the China SCI Net did not work with an examination system. Instead, as the next section will show, new contents were transmitted through demonstrations and educational materials in training sessions, and compliance to introduced standards and practice parameters was then tested in practice, first in the multicenter observational study (CN100), and then during the first Phase I/II clinical trials (which involved only a few centers).

Help with the training of researchers for clinical trials came unexpectedly from the Chinese Government. In 2004 it imposed a mandate on research hospitals to obtain GCP certification within four years of opening. This four-year limit was not handled strictly, however, and some of the hospitals affiliated to the China SCI Net were still not GCP-certified after this time. The required GCP examinations of the Government helped the Network to transmit some of its core messages and educational contents to affiliated research hospitals.¹⁶² Successful GCP qualification was a selection criterion for inclusion in the planned multicenter Phase III trial.

Reception of the training program by researchers

All in all, the training and education program of the China SCI Net was highly regarded by participating researchers. I conducted interviews with thirty researchers affiliated to the Network, and found that virtually all of them, even the most senior

¹⁵⁹ Investigator Workshops of China SCI Net, URL: http://www.the China SCINet.org/index.php?option=com_content&task=view&id=33&Itemid=59, (accessed August 27, 2012).

¹⁶⁰ Two workshops were held at Rutgers University in New Jersey on August 2—12, 2006 and November 13—16, 2006. See http://www.the China SCI Net.org/index.php?option=com_content&task=view&id=33&Itemid=59#Nov13-16,2006 (last accessed August 27, 2012).

¹⁶¹ Several of the researchers and younger staff in the China Network-affiliated hospitals and research institutes I visited had spent some time at the W.H. Keck Center.

¹⁶² Interview Wise Young, Hong Kong, June 24, 2010.

amongst them, praised the content and learning effects of the sessions. They also appreciated having the unprecedented opportunity to engage in intensive exchanges of knowledge with colleagues from within China and from the USA. Dr Xin Liu, for example, the Vice-Director of a research institute in Southeast China, mentioned that he learned many new things about spinal cord injury, particularly about existing treatment options and research. He pointed out that since joining the Network and participating in the training sessions, he had done more research on animal models and instigated more international collaborations in basic/preclinical research, as well as having articles on spinal cord injury published in international journals.¹⁶³

Dr Bao-Zhi Du from Southeast China described how the training sessions and workshops provided a solid basis for overcoming the challenge of establishing consistent clinical research standards and observation methods across different centers. To him the combination of formal training and practical hands-on experience in the workshops, and the conducting of an observational study (more on this study below), formed a suitable method that changed research practices in his clinic; also beyond the context of the China SCI Net trials.¹⁶⁴

Systematic measurement of the impact of these training sessions was not conducted as part of my fieldwork, but various researchers reported launching new preclinical studies, often using the ‘rat spinal contusion model’, which was introduced during the China SCI Net workshops.

Furthermore, four out of the eight centers I visited in mainland China revealed plans for carrying out systematic Phase I to Phase III clinical trials that would involve randomized control groups. Dr Judi Hu, a researcher in a large hospital in East China, stated that many researchers who took part in the training program realized that clinical research in China often did not match the level of methodological systematization observed in Western countries, and that for this reason their studies were not accepted for publication in international journals. According to Dr Hu, this increased their motivation to adopt new patterns of research practice and methodology and to start working in a more rigorous manner.¹⁶⁵

¹⁶³ Interview Nr. 26, senior researcher, Southeast China, January 20, 2011.

¹⁶⁴ Interview Nr. 21, senior researcher, Southeast China, September 8, 2010.

¹⁶⁵ Interview Nr. 28, senior researcher, East China, January 19, 2011.

Observational study CN100

Training was only the first element by which the restructuring of clinical research practices and related institutional arrangements was implemented. Another closely intertwined element was the active assessment of performance in the multicenter observation trial, CN100. The purpose of this study was to collect long-term data from 600 chronic and acute spinal cord injury patients, in accordance with international clinical trial protocols. Besides the scientific value of this study – which was the first longitudinal observational study of chronic and acute spinal cord injury patients in China – it fulfilled two central functions for the Network: it served as a test trial of the ability of affiliated centers to recruit patients, to conduct standardized neurological assessments, to carry out long-term follow-ups, and to document data and data-collection procedures in the prescribed fashion. As it was an observational trial, it did not involve any therapeutic intervention. However, it provided a pool of potential spinal cord injury patients who could be recruited on subsequent trials.

The Network decided to carry out the observational study in 2005, and it was launched that same year, after receiving approval of hospital-internal IRBs. Since some centers joined the Network only after that point, the study lasted until 2008. The data are currently being prepared for publication.¹⁶⁶

As Wise Young commented during an interview, several hospitals were unable to meet the set targets.¹⁶⁷ This meant that instead of the intended 600 patients, only 386 profiles were completed. The main reason for this was that many patients lived at a distance from the centers, and were not sufficiently motivated to return for follow-up treatments. In some cases, data charts were also incomplete – or bogus. Dr Young recalls this situation as follows:

The first trial we held was an observational trial. To show that the hospitals can deliver the data. We paid at that time an absorption sum of 1000 US\$ a patient for the [completed] data. Now this study revealed a lot of problems I actually had heard about, but never really encountered, until to this point. The number one problem in China is really to get patients to come back. [...] The most well-known, the most famous hospitals, they had the worst

¹⁶⁶ The study protocol and details of the trial can be found on *ClinicalTrials.gov* at <http://www.clinicaltrials.gov/ct2/show/NCT00517374?term=CN100&rank=1> (last accessed August 27, 2012). Additional information in this section is taken from: interview Kwok-Fai So, Hong Kong, January 7, 2011.

¹⁶⁷ Interview Wise Young, Hong Kong, June 24, 2010.

follow-up rates. [This is because] they get patients from all over the country. [...] You know, whenever someone with spinal cord injury travels, there is a wife, there is a whole family almost, and that costs money. And, for a patient, to come three times to a hospital, just to get examined, without a therapy, [even though] the largest part of the 1000 US\$ went to the patients, [but] these very, very big famous hospitals, they just couldn't give us follow-up data. It is very interesting. The local hospitals and also the military hospitals, they delivered the best results.

Later in that interview he added:

We... in the observation trial did not use CROs [Contract Research Organizations]. But we observed data that just could not have been. You know – patient data would be the same, over the whole year period. Suggesting that someone had examined the patients very carefully... It became very clear to us that we need to have very good controls of the protocol. That is when we began the supervisor–principal investigator signing system. Yes, and then... when we do the [Phase III] efficacy study we put a CRO in it. [...] We still have some problems to solve, with the significant adverse effects, for example. I have to say, these adverse events, a lot of people don't report them. And that... you know, the patient has a fever... And they say... 'Oh, all patients have fever. It is not a significant adverse effect'. And they do not fill out the form and they don't send it. [...] This is not that people are trying to cheat, or anything like that, but this is just... these are people who have never done clinical trials before, and often don't know how clinical trials are done. [...] We found that the best units were always the units where the PI was hands on it... in the process. But if you have the chairman of a department delegating it to, you know, some of the junior people, we got a lot of excuses and the data weren't enough. So, it is very possible, that out of the twenty-five centers, ten will not be able to make it and we cut it down to fifteen.¹⁶⁸

Identification and analysis of the challenges that became visible during observational trial CN100 provided Young and the leadership level of the Network with fundamental insights into local conditions. These ranged from the characteristics of different types of hospitals and patient behavior, to logistical problems in individual departments, as well as attitudes and practices that prevented protocol compliance.

These insights resulted in some fundamental adjustments of the control and monitoring structures through which the Network operated, such as the introduction of

¹⁶⁸ Interview Wise Young, Hong Kong, June 24, 2010.

a supervisor–principal investigator signing system. With this system, each doctor or nurse involved in examination of patients has to ‘sign off’ the data collection sheet with his or her supervisor as well as the principal investigator in the institute.

Documentation protocols were changed from paper to a computerized web-based system for data entry, in order to enhance data insertion and data analysis, and to permit spontaneous checks by the headquarters in Hong Kong.

Identification of challenges in the observational study gave rise to adjustments of training procedures, as well as the decision to work with a CRO during the forthcoming Phase III trial. Successful completion of the Phase III study would be proof that the Network works in its current form, and will therefore be able to conduct future clinical studies.

International integration

The final phase, integration of network-associated clinics into the international system of high-profile science, occurs through participation in the organization’s clinical trials, and the generation of valid and standardized clinical research data. The ultimate proof of integration is the acceptance of these data by top international journals, and drug regulatory authorities such as the US FDA, in the context of IND [Investigational New Drug] applications of the tested treatment procedures overseas. The acceptance of research data by these institutions, in other words, establishes network-affiliated hospitals as recognized components of the global system of high-profile science, and places them at the intersection of previously distant social worlds like international peer-review communities, transnational advocacy networks, and foreign biotech and pharmaceutical companies.

The China SCI Net, as I will explain in greater detail in Chapter VIII, functions in this respect as an integrating device, to build bridges between regions, research institutes and communities; its knowledge products would otherwise remain excluded from and unrecognized in the international science arena.

This integration process, as I have illustrated in the previous sections of this chapter, is based on extensive forms of transnational scientific self-governance, that is, project-internal efforts of self-regulation and institutional restructuring, in order to ensure compliance with both domestic and international scientific standards. I illustrated these processes first with relation to the objectives of restructuring that were

articulated within the China SCI Net; then I explored the tactics and techniques of restructuring, on which basis these objectives would be realized. It is clear that this Network-internal process of restructuring is a collective and voluntary process, the impetus of which comes not only from the leadership level of the organization, but also from affiliated PIs and staff in mainland China.

Motivation to endorse and participate in the restructuring of clinical research practices in China, as I have shown, is based on discontentment and criticism of conditions observed in the local research arena. It also relates to a range of benefits anticipated to arise through participation in the Network. These benefits range from personal benefits to institutional benefits, in addition to benefits for patients. There is also the hope that clinical studies conducted by the Network might lead to a new standard of cell transplant trials in China.

PART III: The global distribution of evidence-based medicine:

Homogenization and heterogenization

Evidence-based medicine (EBM) is a massive global move toward standardization in the life sciences and health sciences (Timmerman and Epstein 2010). The instigation of the China SCI Net offers an important opportunity to understand how the global distribution of evidence-based medicine – and its central epistemological instrument, the RCT – takes place. The transnational processes of scientific self-governance and capacity building described in this Chapter provide a valuable lens through which to understand how this dynamic is promoted, perceived, facilitated and resisted by local agents in multiple geographical and institutional contexts and subject positions.

Two lines of argument will be put forward in this respect. The first is that the adoption of EBM research protocols in *heterogeneous* global assemblages (within which scientific data are now often generated) is not necessarily a stable or constant process. Rather, EBM standards are instilled and activated in highly situation-specific contexts, but deactivated in other research situations. Established and newly adopted forms of clinical experimentation exist side-by-side with each other, and researchers switch back and forth between these divergent schemas, depending on the partners they work with, their purposes, and the geographic scale of the research project itself.

In the second line of analysis I will temporarily move away from the China SCI Net, and focus on the situation of clinical SC research in mainland China at a more general level. I argue, in a nutshell, that the increasing adoption of EBM research protocols is resulting in substantial forms of discontentment and resistance. These forms of opposition, I contend, are resulting in processes that I refer to as “alter-standardization”, and the “pluralization of the international”. These claims will be illustrated through a case study of the International Association of Neurorestoratology (IANR), an international professional society that centers around the foundation of a new sub-discipline of the neurosciences – neurorestoratology. Both, the field of neurorestoratology and the IANR, have been initiated by a researcher from Beijing, who has also ties with the China SCI Net.

The situation-specific character of transnational technological zones

A way to make sense of the processes of scientific self-governance that have been employed in the context of the China SCI Net, is to appreciate these as establishing what Barry has called a ‘technological zone’, that is a ‘space within which differences between technical practices, procedures and forms have been reduced, or common standards have been established’ (Barry 2006: 239).

In the case of the China SCI Net, as shown previously, a standardized operational zone has been formed around internationally recognized EBM standards, with the RCT as its central methodological tool. The creation of this standardized trans-local space is built upon (and overlays) a context of geographic, cultural, institutional, and regulatory heterogeneity. In this standardization process, the methodological form of the RCT changes from being an object of contestation, to a gradually normalized and trans-locally implemented component of the everyday. In the terminology of Star, a metamorphosis occurs where the ‘boundary object [does] change into infrastructure, [and] into standards’ (Star 2010: 605). Initially, in the act of being moved across borders, the RCT is a flexibly defined ‘boundary object’, whose practices are contested and tailored to local needs across institutions and research communities (*ibid.*: 602). Over time, however, the format of the RCT transforms to a standardized methodological arrangement, whose procedures are replicated and solidly entrenched in multiple geographic and institutional contexts and communities of practice.

As I have shown in this chapter, using the example of the China SCI Net, this transformation is the result of the transnational self-regulatory activities of scientists – not of the agency of states.

It is important to note, though, that the formation of a standardized technological zone across transnational heterogeneous contexts does not necessarily mean the establishment of constant or complete transformations of the socio-technical and methodological practices employed in this zone. Instead, the existence of a standardized trans-local operational zone can be limited in time, and can depend upon its activation in specific situational contexts. This is well illustrated by the China SCI Net. Standardized methodological norms and work arrangements across network-affiliated hospitals are activated especially in the context of the Network's clinical trials; outside the context of these trials, heterogeneous clinical practices continue to exist.

As shown previously in this chapter, systematic RCTs and multicenter clinical studies were increasingly adopted in hospitals affiliated to the China SCI Net (beyond the clinical trials organized by the Network), but a stream of highly divergent forms of clinical experimentation has been observed. In one clinic in South China, for example, the performance of systematic RCTs co-existed with less systematic clinical studies. Larger cohorts of patients were treated with new cell types and other experimental treatment approaches in a methodological format that did not conform to international EBM standards, and which would not be acceptable to the top academic journals, and the review procedures of drug regulatory authorities. Professor Young considered, in this respect, that the trans-institutional replication of the methodological research standards demanded by the Network was not always based on inner conviction among the associated clinicians. Older conceptions of clinical research practice often still have greater weighting, or are seen as being more practicable than new ones, and continue to be reproduced alongside the standardized research work being conducted for the Network.

This situation-specific character of technological zones, in which established standards can lay dormant for a while, and which can be switched on and off in relation to contextual demands, has not yet been described in the literature. These insights are, however, vital theoretical additions to Barry's concept of 'technological zones'. I suggest, therefore, that the polymorphous, situation-specific character of technological zones is likely to be most pronounced in the context of zones that stretch

out over extensive transnational spaces, and heterogeneous institutional, cultural and regulatory milieus.

I have explained how within these complex transnational spaces of collaboration, highly systematic research practices can exist alongside less systematic forms of investigation. The researchers move between them according to the needs of the particular study they are undertaking and the partners they work with. In these extended transnational zones, standardized technological practice can be activated and deactivated on command, with respect to situation-specific needs and regulatory requirements.

Alter-standardization and the pluralization of the international

Resistance to standardization in the context of the global distribution of EBM and the RCT has been widely reported in the literature (Timmerman and Berg 2003, Mykhalovskiy and Weir 2004; Bharadwaj and Glasner 2008; Timmerman and Epstein 2010). In the clinical stem cell research field in China, opposition to the adoption of international clinical research protocols has been particularly pronounced (*Nature* 2012). As reported in Chapter V, the Chinese Government has been increasingly committed to bringing the governance of clinical stem cells research into line with international standards.

The move toward international integration, however, is not without vital forms of contestation and resistance. I suggest, in this context, that the set character of stem cell-based clinical experimentation in China, which is represented by well-established communities of practice, high popularity among patients, and lucrative profit margins, significantly increases the potential for regulatory conflict in China. In fact, the widespread existence of these ‘informal’ forms of clinical experimentation has been challenging to various international standards for some time. It has given rise to claims for the acceptance of less rigorous research regimens, which allow rapid clinical translations, and the legitimization of types of clinical studies beyond the randomized trial, such as cohort studies, or experimental studies based on self-comparison by patients (Huang 2010: 130).

What is at stake here is, in essence, a clash between an emerging – and in many respects imported – form of regulatory authority (as embodied by EBM and

international standard and approval regimes for systematic clinical trials), and local forms of professionalism and research validation that have arisen on the basis of preexisting manifestations of clinical experimentality with stem cells in China. I suggest in this context that these confrontations have given rise in practice to a ‘pluralization’ of ethical and scientific practices and categories. As shown in Chapter V, the introduction of novel rules and practices has given rise to forms of hybridization and the coexistence of multiple forms of experimentality. The stepwise adoption of international standards has transformed and pluralized the local forms, but it has not superseded or replaced them.

In the final paragraphs of this chapter I shall contend that what is currently happening in China is not only a pluralization of ethical and scientific forms and practices on the ground, but a gradually evolving move toward the pluralization of the international itself. What I mean by this is the creation of novel transnational spaces of ‘alter-standardization’, that is, the formation of novel transnational networks, institutional spaces, rules, communities of practice, and platforms of knowledge sharing and publication, that endorse and validate alternative forms of experimental research, with ethical and research protocols that, in various respects, diverge from the current international scientific standard.

The international pluralizes: The case of the International Association of Neurorestoratology

Let me illustrate these claims by referring to the International Association of Neurorestoratology (IANR). This body was initiated in 2008 by Dr Huang Hongyun, a Beijing-based neurosurgeon, in collaboration with Chinese and international partners. Since the early 2000s, Dr Huang has offered experimental (for-profit) therapies with a type of stem cell – the fetal olfactory ensheathing cell – to large numbers of patients with neurodegenerative disorders. His approach was initially celebrated as an important breakthrough (CCTV 2002), but harsh criticism followed in 2006 (Cyranoski 2006; Dobkins and Guest 2006). In response to these objections, Huang has continually tried to prove the scientific basis of his work, and the efficacy of the cells and the procedures he uses. In doing so, he has become an important trail-blazer for the recognition of advances made in experimental treatments, and the acknowledgment of assessment forms beyond randomized clinical trials (Huang

2010). Huang has crossed the boundary between for-profit treatments and research-driven experimental therapies since his initial experiments in humans in 2001. Unlike most for-profit providers, he presents full details of his procedures and his (co-)published case studies (Zhao *et al.* 2008) and observational studies (Huang *et al.* 2003, 2006, 2008, 2009) and, more recently, a RCT that was issued by a first-rate international scientific journal (Chen *et al.* 2010).

The foundation of the IANR might be viewed as an unswerving extension of Huang's striving for recognition of more accommodating methods of bench-to-clinic translation. The Association's focus, however, is much broader. It centers on the promotion and development of a new sub-discipline and branch of the neurosciences – neurorestoratology (Huang, Chen and Sanberg 2010). The research of this emerging field focuses on therapeutic strategies from various subject areas of the neurosciences: from transplantation of cells and tissue, to the use of biomaterials and bioengineering, neuromodulation, and pharmaceutical and chemical therapies. These approaches share the goal of neural regeneration and repair, with the aim of replacing damaged components of the nervous system in humans (Huang 2010: 15). The core objective of this developing sub-discipline is to 'restore neurological functions in patients' and 'to improve their quality of life' (Huang 2010: 129).

The IANR brings together scientists and clinicians from all over the world and numerous branches of the neurosciences (IANR 2010). It provides a professional platform for exchange of knowledge dedicated to the transfer of basic and pre-clinical research findings into new clinical strategies and interventional therapies (*ibid.*). An explicit purpose of the association is to facilitate and 'shorten the process of bench to bedside' translation (*ibid.*). To promote this goal, the IANR explicitly endorses the use of efficacy assessment procedures other than RCTs, including a method of self-comparison by patients.¹⁶⁹

The situation is multifaceted and complex. On the one hand, the association promotes clinical trials and it proclaims to 'support the highest standards for clinical trials to evaluate the safety and efficacy of its neurorestorative therapies' (IANR 2009). But on the other hand, it claims for many patients with deteriorating neurodegenerative diseases that 'self-comparison is the best way and the simplest tool

¹⁶⁹ Self-comparison is the cross-case documentation of treatment efficacy on the basis of before---after (treatment) comparison by patients themselves; mainly based on subjective experience and anecdotal evidence.

to assess the effect of a treatment’ (Huang 2010: 130). In these cases, it is ‘a much better assessment method [...] than randomized double-blind control[-led clinical trials], for ethical, lawful and scientific reasons’ (*ibid.*: 129). Neurorestoratology and the IANR, according to Huang, strongly support physicians and scientists to use these ‘reasonable and practical research methods to do study’, instead of indiscriminately following the ‘doctrinal, or rigid way’, as defined by EBM and the international standard system, with RCT as the only validated assessment instrument (*ibid.*: 130).

In this way, the IANR diverges drastically from international scientific standard protocols, such as those used by the top journals, whereby rigidly followed EBM protocols and RCTs are a precondition for publication. With the initiation of a transnational research community in which this orthodoxy is partly challenged, the IANR has instigated a vital institutional space, which simultaneously allows critiquing of the range of international standards, while enacting and legitimating forms of clinical experimentation that lie outside of it. What is being created is an alternative system of research standardization and validation, which is stabilized by the creation of cross-national alliances and institutional arrangements, and the instigation of novel platforms for global research communication and publication. I can briefly illustrate this as follows.

First, the IANR has succeeded in initiating important strategic partnerships with well-known international scientists and editors of international scientific journals. The *Journal of Cell Transplantation*, for example, which ranks second in the world in its category, has reserved a yearly section for the IANR (Huang 2010: 129), and its Editor in Chief, Paul Sanberg, has actively promoted neurorestoratology as a novel sub-discipline (IANR 2009; Huang, Chen and Sanberg, 2010). An alliance has been formed also with the *American Journal of Neuroprotection and Neuroregeneration*, which is described on the Association’s website as the ‘second official journal of the IANR’ (IANR 2010). The newly founded journal *Frontiers in Neurorestoratology* – a specialty section of the online open-access journal *Frontiers in Neurosciences* – is a permanent outlet of the IANR (*ibid.*).

A second way in which the IANR creates possibilities for knowledge-sharing is through its annual conferences. These are huge events that bring together an interesting mixture of internationally recognized and less-recognized scientists, clinical researchers, and experimental therapy providers from China, Asia, the USA, Europe, the Middle East, and South America (IANR 2010, 2011). These conferences

form important platforms for community building and sharing of novel (pre)clinical strategies and results from experimental clinical research that would normally be unacceptable to the international top journals, and thus remain invisible to wider scientific circles and the public.

Thus the formation of neurorestoratology as a new sub-discipline, and the IANR, play a pivotal role in gradually transforming previously marginalized forms of experimental clinical research from being unacceptable and criticized, to a slowly tolerated component of the ordinary. This suggests the occurrence of a gradual renegotiation of the terms defining the limits between the recognized and the ineligible in the international arena of clinical high-profile science. This process, I assert here, is propelled by the gradual pluralization of the institutions, sites, actor circuits, and rules through which these boundaries are specified, enacted and reproduced. This pluralization is enabled by the forging of strategic alliances and the extension and strengthening of professional networks, all of which facilitate stabilization of alternative categories and practices that are designated as ‘shared’, and increasingly ‘international’ (*cf.* Latour 1987).

The formation of these novel transnational spaces of alter-standardization emerges in direct response to the fault-lines that are created in the context of the global diffusion of EBM and RCTs. It is a form of resistance that targets the re-valuation and re-legitimization of forms of clinical experimentation that, due to their lack of conformity with current international standards as employed by top journals and drug regulatory authorities, have been de-valued and de-legitimized.

Conclusions

In this chapter I focused on the ways in which the China SCI Net worked to restructure local clinical research practices, with the purpose of creating homogeneity within the current international standard system.

In Parts One and Two of the chapter, these processes were explored through the concept of transnational scientific self-governance, which I defined as project-internal forms of self-regulation and capacity building for creation of a standardized trans-institutional research infrastructure that is compliant with multi-regional regulatory requirements and the international scientific standard system. Part One looked at the objectives and domains of restructuring. It became clear that the introduction of international clinical trial standards in the context of the China SCI Net was broadly supported among the affiliated researchers. The creation of a multicenter clinical trial infrastructure, in particular, was seen as opening up important opportunities, not only for the involved researchers but also patients with spinal cord injury and, in a more general sense, anyone working in that field of research in China.

Motivation to take part in the restructuring of local clinical research practices was shown to be subject to widely shared criticism of the often non-systematic and profit-driven character of experimental research applications with stem cells in China. The foundation of the China SCI Net was seen, in this regard, as a positive example capable of instilling a new standard for cell transplantation trials in China.

Motivations to join the China SCI Net, in other words, and to consent to and take part in local forms of restructuring, were partly driven by differences in clinical research methodology and standards. The Network was perceived as a platform offering access to a new methodological repertoire, which would allow the acceptance of clinical research conducted in associated hospitals in China, in the international arena of high-profile science.

Part Two explored the methods and techniques of restructuring through which set objectives to be translated into practice. I analyzed these processes by focusing on three inter-related stages: selection, restructuring, and integration.

The selection of affiliated hospitals was shown to be an ongoing process, based on mandatory qualifications (such as Good Clinical Practice (GCP) certification) and

performance-based assessment criteria, through which the adoption of the required technical and behavioral protocols is monitored.

The restructuring of clinical research and innovation practices occurred through a combination of education, practice-based learning and external controls. Training and educational programs were found to be focused on standardized neurological assessment procedures, clinical trial design and protocol development, as well as evidence-based strategies for the identification of new therapies. Practice-based learning occurred through a multicenter observational study, in which the associated hospitals were asked to collect standardized and longitudinal neurological and physiological assessment data from people with spinal cord injuries, over a period of one year. A variety of external control mechanisms were applied to monitor protocol compliance and validity of the data. Any identifiable problems were used to adjust the monitoring and control structures, so as to improve clinical performances in subsequent clinical trials.

Integration of the Network-affiliated hospitals into the international arena occurred, in essence, through the generation of clinical data that were accepted by top international journals and drug regulatory authorities. The acceptance of data by these institutions led to (full) membership of the hospitals in the China SCI Net; they gradually become established as recognized components of the global system of high-profile science.

In Part Three, I linked the transnational efforts of scientific self-governance that the China SCI Net has conducted to Barry's (2006) concept of 'technological zones'. I argued that the transformation of local research practices, in the pursuit of the creation a standardized trans-local research zone, does not inevitably mean the complete or constant restructuring of methodological and socio-technical standards. I suggested in this respect that in extensive transnational technological zones, such as that formed by the China SCI Net, which stretches out over heterogeneous institutional, regulatory and cultural milieus, the adoption of standardized research practices is not permanent; instead it is highly context- and situation-specific.

Established and newly adopted forms of clinical experimentation exist alongside formerly institutionalized forms of clinical research practice. Researchers switch back and forth between these divergent schemas, depending on the purposes of their investigations, the partners they work with, and the regulatory requirements that result from collaborations with institutes in different countries. Standardized

technological zones, from this perspective, can be switched on and off in relation to contextual demands. In the case of the China SCI Net, for instance, standardized trans-institutional methodological practices are activated only at the time of the Network's clinical trials. Even though systematic randomized controlled trials (RCTs) are increasingly adopted in affiliated hospitals, heterogeneous clinical research practices continue to exist.

A further line of analysis in Part Three focused on the observed forms of discontentment and resistance to the global distribution of evidence-based medicine research protocols, with the randomized controlled clinical trial as the key epistemological instrument. To this end, I moved away from the China SCI Net and explored on the state of clinical stem cell research in China at a more general level. On this issue, I argued that the promotion of EBM research protocols results in substantial forms of discontentment and resistance. These forms of contestation, I propose, are gradually resulting in processes of 'alter-standardization', which I define as the formation of emerging transnational networks, institutional spaces, rules, communities of practice, and platforms of knowledge sharing and publication, that endorse and validate alternative forms of experimental research. These claims were empirically illustrated by an example of the International Association of Neurorestoratology (IANR). Their activities led me to conclude that what is currently happening in China is not simply a pluralization of ethical and scientific forms and practices at the level of individual institutions, but a gradually evolving move toward the pluralization of norms, definitions and practices designated as 'international'.

Together, these findings show that a focus on processes of transnational scientific self-governance, as employed within multi-country collaborative research projects, provides a unique analytical lens through which to understand the global distribution and trans-local adoption of EBM standards; light is shed on the controversies, forms of resistance and alternatives that arise with this trend. By departing from the activities, perspectives and challenges of the scientists and professional staff who run and take part in contemporary transnational science projects, several profound and practice-based insights can be gained into the interplay between the diverging forms of legal authority that shape present-day projects of science, and the way that these processes play out against the background of scientific multipolarization.

Chapter VIII

Organizational Basis of the China SCI Net

Introduction

In this eighth and final chapter of the dissertation I will discuss the organizational aspects of the Network. To this end, the chapter is structured in three parts. Part One introduces the financiering model of the Network, and shows how it is intrinsically connected to a project of community formation and activism. Part Two describes the organizational structure of the Network, particularly with respect to division of labor and benefit-sharing; this approach is analyzed in contrast to those of international clinical research partnerships as organized by the huge pharmaceutical companies known collectively as ‘Big Pharma’. Part Three focuses on the integration of people with spinal cord injury into decisions for future trials conducted by the Network.

This chapter departs from the insight that the creation of a transnational research infrastructure (as exemplified by the China Network) is intrinsically intertwined with a process of community building, and complex forms of activism and social movement (*cf.* Clarke and Star 2008). The organizational model of the China SCI Net is, in essence, based on the reconstruction of an academic partnership approach, which ties together a broad range of stakeholders, organizations and institutions within an extended transnational space. These efforts have resulted in an unprecedented trans-continental research assemblage, in which processes of clinical innovation and research are brought to fruition largely independently of conventional forms of research financiering and organization (as represented by the innovation infrastructures of state governments and pharmaceutical companies of the Triad countries). Indeed, the operations of the China SCI Net in Hong Kong, mainland China and Taiwan are almost completely funded from within these regions.

My argument in this regard is that the formation of the China SCI Net, as part of an evolving transcontinental academia-centered clinical research infrastructure, is giving form to a new modality of transnational clinical research and trial organization,

which differs in a number of fundamental respects from more conventional forms of international clinical partnerships as embodied by the pharmaceutical industry, and as described (for example) by Adriana Petryna (Petryna 2009). What the China SCI Net exemplifies is not the transfusion of a capital-oriented pattern of drug development (as propelled by Big Pharma) to yet another field of promising research, but the evolution of an alternative, and in many ways, unprecedented model of clinical research organization and infrastructure formation. With the underlying core of this model currently lying in academia, the Network has been formed independently from the agency and the capital flows of both large-scale drug companies and ‘first world’ government agencies.

Four central differences with more conventional forms of global drug research will be addressed now: first is the flattening of hierarchies and opening up of decision-making processes; second are the differences in benefit-sharing and ownership; third is the evolving of a collectivist approach of knowledge production; and fourth is the facilitation of domestic forms of innovation in China.

I propose that the diagnosed shift toward recognition of involved partners ‘as equal’ (in the sense that labor, benefits, costs and decision making processes are shared on an equal basis) indicates a number of issues of theoretical importance. In fact, a communalist ethos is not only emerging with respect to issues of benefit-sharing, but also in the context of decision-making processes regarding future research. This suggests there is a gradual blurring of conceptualizations between ‘intellectual creation’, as done in ‘developed’ countries, and ‘intellectual stewardship’ or ‘hands-on work’ as seen in ‘developing’ countries. In the context of the global organization of clinical trials by Big Pharma, such divisions may still hold water, but in the emerging modality of transnational research partnerships I am describing here, these boundaries are gradually dissolving. This shift then results in a form of organization that is intrinsically linked to the growing scientific and economic significance of China, and a progressive transition from a production society to an innovation society. Thus, in the light of these developments, and the gradual transfer of influence from West to East, older modes of collaboration – couched as they still are in terms of ‘development’ and based on notions of (paternalist) ‘benefaction’ – have become increasingly obsolete and contested.

PART I: Funding of the China SCI Net

Funding of the Network was based on a highly complex organizational model. As I will show in this section, money for the activities and managerial basis of the Network was raised in innovative and diverse forms. These have included charity funding, cross-continental alliances with patient advocacy groups in North America, company sponsorships, grants from local hospitals, the Chinese Army and provincial governments in China, and the incorporation of clinical labor into the work routines and research obligations of associated researchers and staff.¹⁷⁰

This multi-stranded funding model was developed in relation to two trends that characterized the funding situation for stem cell-based clinical trials in both China and the USA from the early 2000s: the reluctance of pharmaceutical companies to invest in stem cell-based medicinal approaches (Keirstead 2008); and the scarcity of funds for investigator-driven clinical trials with stem cells from state governments (*ibid.*). The funding model of the China and US networks comprised a number of creative ways for counterbalancing this situation, and for carrying out internationally recognized Phase I–III clinical trials.¹⁷¹

Six key themes will be introduced now and discussed one by one in the sections that follow. These are: (i) the creation of an academia-based transnational partnership model that operates in a low cost environment; (ii) a model of charitable funding outside of the USA; (iii) transnational funding alliances; (iv) tapping into state-allocated funding resources in China; (v) the integration of clinical trial costs into the routine labor processes of associated researchers; and (vi) the relationship between the China SCI Net and the SCI Net USA

The discussion that follows draws on comparisons with other international academic trial collaborations, and debates on the globalization of clinical trials, with a particular focus on the assumptions related to instrumentalization and exploitation.

¹⁷⁰ All names of persons in this chapter (with exceptions of the Co-Directors Wise Young and Kwok-Fai So), are made anonymous (i.e. are either referred to as ‘researcher’, or ‘senior researcher’, or given different names), on behalf of the wish of the interviewees.

¹⁷¹ In this section I will primarily focus on the China SCI Net, but refer to the funding scheme of the SCI Net USA as appropriate.

(i) Academic partnering in a low-cost environment

As already pointed out in Chapter III, in contrast to the high-cost area – the US – the formation of a transnationally operating academia-based partnership models in China is significant for cost reduction. This becomes clear by comparing the expected expenses of the Phase III trial in China with the parallel Phase III trial to be carried out by the Spinal Cord Injury Net in the USA.

We estimate that CN103 [the Phase III trial in China] will cost about US\$ 6 million. US103 [the phase III trial in the USA] will cost about US\$ 24 million.¹⁷²

[In the USA] just testing a patient, preparing the cells in a GMP [Good Manufacturing Practice] facility, operating and transplanting the cells, doing six weeks of rehabilitation, and evaluating the patient for a year will cost \$100,000 per patient. The Phase III trial we are planning has four groups of 60 patients (lithium, cell transplant, cell transplant plus lithium, rehabilitation only) or \$24 million.¹⁷³

(ii) Charity funding in Hong Kong outside of the USA

The central financial pillar of the China SCI Net is the Hong Kong Spinal Cord Injury Fund Limited, a charity funding association registered in Hong Kong that was founded to support the Network.¹⁷⁴ Under the motto ‘Lightening a way to a cure’, the organization generated more than three million US dollars between 2005 and 2010.¹⁷⁵ Presided by Suzanne Poon, it started under the umbrella of Hong Kong University, before becoming an independent non-profit organization. With a team of friends and volunteers recruited by Poon, and the help of a professional fundraiser, the foundation initiated a broad range of functions in the winter of 2004: television shows including a documentary, as well as gala dinners, sporting and cultural events, involving local and international celebrities from stage, screen and sports people – Kung Fu artists,

¹⁷² Blog contribution Wise Young on *CareCure*, July 9, 2010. URL: <http://sci.rutgers.edu/forum/showthread.php?t=125364&page=6>, (accessed September 27, 2012).

¹⁷³ Blog contribution Wise Young on *CareCure*, July 5, 2010. URL: <http://sci.rutgers.edu/forum/showthread.php?p=1233269#post1233269>, (accessed September 27, 2012).

¹⁷⁴ Website of the Hong Kong SCI Fund, URL: http://www.hkscifund.org/index.php?option=com_content&task=view&id=21&Itemid=33&lang=en, (accessed September 27, 2012).

¹⁷⁵ Interview Suzanne Poon, Hong Kong, August 28, 2010.

athletes, and even the FC Barcelona.¹⁷⁶ The money raised in this way was used for training sessions in Hong Kong and mainland China, towards expenses at the Hong Kong headquarters, and toward expenses of the observational trial (CN100), and parts of Phase I (CN101) and Phase II (CN102a and CN102b).¹⁷⁷

(iii) Transnational funding alliances

Involvement of scientists and people with spinal cord injury from the USA

Various transnational dimensions characterized the funding model of the China SCI Net from the outset. There was the involvement of scientists and spinal cord injury patients from the USA in funding campaigns in Hong Kong; for example, some scientists and patients and the Governor of New Jersey were invited to join the first large-scale television show of the organization in autumn 2005. A North American spinal cord injury clinical trials activist and rap artist, Richard Gaskin, provided the entertainment alongside a number of celebrities from Hong Kong; a song was presented in honor of Christopher Reeve who had died a couple of months before.¹⁷⁸

These fundraising activities were noticed by the spinal cord injury community in the USA and actively debated. Many patients in the US thus began to identify with the Network in China, and began to see it as a constituent of their own struggle, and their hope for cure. ‘BigBob’, a member of the *CareCure* community website, posted the following in November 2004:

Suzanne [Poon], it is nice to know that you have helped tremendously [...]. I look forward to the days when we can look back at these times while we struggled to motivate the cure. I forever will be grateful to you. Your unselfish labor, and devotion, is what puts my son closer to recovering. Thanks.¹⁷⁹

¹⁷⁶ Hong Kong SCI Fund , organized fundraising events between 2004 and 2012, URL: http://www.hkscifund.org/index.php?option=com_content&task=view&id=59&Itemid=77, (accessed September 27, 2012).

¹⁷⁷ Interview Suzanne Poon, Hong Kong, August 28, 2010. Interview Wise Young, Hong Kong, June 24, 2010.

¹⁷⁸ Information from: (1) Interview Suzanne Poon, Hong Kong, August 28, 2010. (2) Website of Hong Kong SCI Fund , organized fundraising events between 2004 and 2012, URL: http://www.hkscifund.org/index.php?option=com_content&task=view&id=59&Itemid=77, (accessed September 27, 2012).

¹⁷⁹ Blog Contribution of ‘BigBob’ on *CareCure*, November 20, 2004, URL: <http://sci.rutgers.edu/forum/archive/index.php/t-20589.html>, (accessed September 27, 2012).

Identification of people with spinal injuries and their families with the China SCI Net through *CareCure* was actively encouraged by Young, who posted regularly on the progress and developments of the Network from its earliest stages. The hope and increasing identification of patients in the US were also expressed in requests for donations to the Network. ‘Suzanne,’ asked one *CareCure* member in November 2004, ‘how do I donate money to the Network?’ which triggered a number of similar requests over the following days.¹⁸⁰ However, a formal funding campaign for the China SCI Net in the US was never launched. As Poon pointed out in an interview, there were some relatively minor donations from US patients, but the majority of the capital raised by her organization came from citizens and companies in Hong Kong.¹⁸¹ In the US, fundraising programs for the project were only initiated after the formation of the sister network in North America in 2008.

Sponsorship from overseas charitable institutions

Funding was also secured in Taiwan by the Buddhist order known as Tzu Chi, a charity-based organization led by Master Chen, a 77-year-old Buddhist nun from a monastery in Taipei. The order is engaged in worldwide relief of catastrophes as well as various educational activities, and it runs four large hospitals in Taiwan. The order went on to create a stem cell research center in Hualian, and the Tzu Chi Hospital in Taichung became an associated partner of the China SCI Net in 2008. The organization does not specifically raise money for the Network, as does the Hong Kong funds, but it will fund parts of the Taiwan arm of the Phase III trial.¹⁸²

At the time of writing, no charity funding had been mobilized from mainland China. While the Network has an interest in obtaining this, there are practical obstacles. Not least is the fact that charity funding is not a popular model for clinical research in China. Furthermore, no organization or local partner was found who would undertake the task and apply for permission from the Chinese authorities. The fact remains that most money for the China SCI Net was raised in Hong Kong, yet it was used to build capacity and infrastructure in mainland China – this is yet another example of the transnational dimension of the Network’s funding model.

¹⁸⁰ Blog Contribution of ‘Schmeky’ on *CareCure*, November 20, 2004, URL: <http://sci.rutgers.edu/forum/archive/index.php/t-20589.html>, (accessed September 27, 2012).

¹⁸¹ Interview Suzanne Poon, Hong Kong, August 28, 2010.

¹⁸² Interview Wise Young, Hong Kong, August 29, 2010.

In April 2011, the Hong Kong Spinal Cord Injury Fund made a partnership agreement with the Rick Hansen Foundation from Canada. This related to funding a campaign for the upcoming Phase III trial of 400 patients. Rick Hansen is a former Para-Olympic champion; in the 1980s he travelled across all five continents in his wheelchair to increase awareness for the rights and potential of people with disabilities. Since then, the organization has become the largest spinal cord injury foundation in Canada that invests actively in research, as well as novel rehabilitation and care approaches.¹⁸³

Cooperation between the Hong Kong Fund and the Rick Hansen Foundation was forged in the context of Hansen's visit to Hong Kong, precisely twenty-five years after his presence in China during his world tour, when he had climbed the Great Wall and crossed the whole of China in his wheelchair (Russel 2011). Cheered on by 1500 schoolchildren, to the rhythm of a local marching band, Hansen rolled into the arena of Hong Kong's Sha Tim race course. Here he gave the Foundation's Difference Maker Award medals to people who had made a significant contribution to research and the well-being of people with spinal cord injuries. Among the honored guests were two key members of the China SCI Net – Suzanne Poon and Professor Kwok-Fai So. The event was followed by a huge gala dinner and fundraising show at the race course. This was recorded by Hong Kong's station ATV and broadcast ten days later.¹⁸⁴

Young posted on the *CareCure* website to say that the gala dinner alone had generated 8.2 Hong Kong dollars (the equivalent of around 1.1 million US dollars) for the Network.¹⁸⁵

Involvement by overseas companies

Another source of support for the current series of clinical trials carried out by the China SCI Net was Stemcyte. Stemcyte is a highly accredited, internationally operating, commercially operated cord blood bank producer, with headquarters in the US, that provides FDA-registered transplant cells worldwide. Stemcyte entered into a

¹⁸³ Website of the Rick Hansen Foundation, URL: <http://www.rickhansen.com/>, (accessed September 27, 2012).

¹⁸⁴ The highlights of these events can be seen via the website of the Hong Kong SCI Fund, URL: http://www.hkscifund.org/index.php?option=com_content&task=view&id=50&Itemid=77, (accessed September 27, 2012).

¹⁸⁵ Blog contribution Wise Young, *CareCure*, April 21, 2011. URL: <http://sci.rutgers.edu/forum/archive/index.php/t-153237.html>, (accessed September 27, 2012).

formal licensing and research agreement with Rutgers University in 2008, to formalize the use of the company's proprietary umbilical cord blood (UCB) mononuclear cells in the contexts of the CN102b and CN103 trials.¹⁸⁶

Through this, the company received exclusive commercialization rights for the combination of UCB mononuclear cells and lithium in spinal cord injury patients, provided the treatment is proven to be efficient and safe. A patent for this invention was filed, through which the IP rights of the treatment combination were ascribed to Stemcyte.¹⁸⁷

As Young reported, the purchase price of the donated cells was about US\$ 22,000 per unit (excluding transportation and processing costs before transplantation). This adds up to US\$ 880,000 for the two Phase II trials (in Hong Kong and Kunming) that had twenty patients each, and US\$ 8.8 million for the multicenter Phase III study with 400 patients.¹⁸⁸ According to a senior staff member at Stemcyte, this investment was of value to the company in case even if there were negative research findings. By engaging in FDA-approved clinical trials, and by collaborating with high-profile researchers such as Young, the company proved it was committed to the highest quality and scientific standards, and thus fostered trust among (potential) clients. As well as being a form of promotion, these research partnerships result in the harvesting of new information about the cells, and their potential in different disease and transplantation contexts.¹⁸⁹

Smaller amounts of money were also raised from some internationally operating medium-sized and large biotech and pharmaceutical companies, such as BIOGEN Inc., Acorda Diagnostic and Pfizer. These companies acted primarily as sponsors for the large international conferences and workshops organized by the Network.¹⁹⁰

(iv) Accessing state allocated resources in China

Another source of funding was grant money from institutions and government agencies in China and Hong Kong. For an internationally operating research network

¹⁸⁶ Interview Wise Young, Hong Kong, June 24, 2012.

¹⁸⁷ Filed as US patent US 2010/0189696 A1 (July 29 2010). The patent can be accessed via 'Google Patents', URL: <http://www.google.com/patents/US20100189696>, (accessed September 27, 2012).

¹⁸⁸ Interview Wise Young, Hong Kong, June 24, 2012.

¹⁸⁹ Interview with Senior Staff member of Stemcyte, Taipei, August 11, 2010.

¹⁹⁰ Interview with Suzanne Poon, Hong Kong, August 28, 2012.

initiated by an overseas researcher, tapping into such financial resources in China is very unusual – probably unprecedented. Money was acquired from three sources: from within collaborating hospitals, from provincial governments, and from the health division of the People’s Liberation Army. Capital from national-level science funding programs had not been applied for at the time of writing, but in the context of the Phase III study it was hoped to attract money directly from the Ministry of Health.¹⁹¹

The acquiring of funding from within institutions in China and Hong Kong was initiated and arranged through affiliated investigators. In Kunming, for example, investigators organized financial support from within their own hospital, the domestic government of Yunnan province, and the People’s Liberation Army.¹⁹² In Hong Kong, funding was obtained by the two hospitals for laboratory costs and surgeries, but this covered only part of the total costs of the trial; the largest part of the expense was paid for by the Hong Kong Spinal Cord Injury Fund.

The generation of funding from government agencies and affiliated hospitals was an indication of the high level of trust and motivation that Young was able to generate among partners in China. It indicates, furthermore, that the China SCI Net was primarily perceived as a Chinese project, with benefits for researchers and patients in China, and the wider field of spinal cord injury research (Li 2005).

(v) The integration of clinical trial costs into routine labor processes of associated researchers

An important way in which the China SCI Net was able to reduce the operational costs of its trials, was the integration of research expenses and labor into the everyday work and research activities of affiliated investigators and related staff. In contrast to industry-sponsored clinical trials, whereby hospitals receive reimbursement of several thousand US dollars per patient (depending on the research protocol, precise procedures and study duration), no such payments were required in the context of the China SCI Net. Surgery, investigations, and care of patients were conducted as part of the daily work routines of the investigators and staff. The Network, in turn, paid the

¹⁹¹ Interview Kwok-Fai So, Hong Kong, January 7, 2011.

¹⁹² Blog contribution Wise Young on *CareCure*, May 1, 2011, URL: <http://sci.rutgers.edu/forum/showthread.php?t=153611>, (accessed September 27, 2012).

costs of the technology, medication and neurological assessments of patients through external specialist staff.

The ways in which costs are integrated into participating institutions, however, differ significantly across hospitals and regions in which the China SCI Net is active. In Hong Kong, for example, the hospitalization costs of patients is covered by its public healthcare system, which is not possible in mainland China.¹⁹³ In Kunming, for instance, hospitalization expenses are covered by the Network and grants raised in participating hospitals. Some of the principal investigators in other hospitals in mainland China however expect the China SCI Net to re-imburse the clinical.¹⁹⁴

(iv) The relationship between the China SCI Net and the SCI Net USA

An additional aspect of transnational funding emerged with the formation of the sister network in the US in 2008 – the Spinal Cord Injury Net USA. As mentioned above, members of the *CareCure* community had started to conceive of and identify with the China SCI Net as part of their own agenda and purpose – the realization of potential therapies through new research and clinical trials. The links between the organization in China and the community in the US intensified after the formation of the US Network. Because the two networks were dedicated to the testing of the same treatment combination, a large-scale standardized transatlantic research infrastructure was able to emerge, with the gradual blurring of regional and institutional boundaries. This alignment of interests, research protocols and institutions also resulted in the partial blurring of boundaries regarding research financing.

At an organizational level, a clear-cut distinction between the two organizations was drawn. Money raised in China, Taiwan and Hong Kong is intended for exclusive use of the China SCI Net; while money raised in the US was for the use of the US Network. In practice, however, with the integration of research protocols, data and hospitals in a joint project, such divisions are difficult to maintain. This is because the two networks have formed one large project, in which one builds upon the work of the other, with processes of mutual learning and maximization of credibility.

The integration of the China and US networks into one also facilitated the integration of the China SCI Net into a large-scale project of community formation

¹⁹³ Interview with Prof Yi Hwong, Hong Kong, August 21 2010.

¹⁹⁴ Interview Nr. 27, senior researcher, East China, January 19, 2011.

and patient activism that has been unfolding since the late 1990s in the US. With the formation of the US part of the Network, attention to both intensified.

Since the data of the Phase II trials is to be used for gaining FDA-approval for further trials in the USA, the China SCI Net has become the focus of hope and attention of the US pro-cure movement, which was initiated by Christopher Reeve, and pushed further by Professor Young and numerous other researchers, as well as patient advocacy groups and spinal cord injury community leaders. However, as I will show in Part Two of this chapter, the integration of these two networks does not imply ‘an absorption’ of the China SCI Net into US interests. While a common interest is pursued, the two organizations are meant to function both collaboratively and independently. Both networks, as I will show below, are designed to function as self-governed innovation and testing platforms, aside to being involved into large-scale transnational projects.

In terms of funding, the SCI Net USA had a strategy very like that of the China SCI Net. Money was sought from every source possible, through state funding, hospital funding, foundations and companies, and several organizations were involved in fundraising for the planned trials in the US. There was one difference from the China Network, however, in as much as the model of the US Network relied on more intensive fundraising from within the spinal cord injury community, which has not yet been achieved in Hong Kong, Taiwan or mainland China. Leaders in the community, in cooperation with Young, initiated these campaigns aimed at the community itself. The most successful venture at the time of writing was the ‘Just A Dollar, Please’ campaign that followed a similar method to that of the Buddhist Tzu Chi organization:

195

The concept behind the \$1 a day project is to find about 10,000 people in each city/region to support a clinical trial program. If 10,000 people donate 1\$ a day that adds up to \$3.65 million a year, that will support the hospital there to 1–2 years of clinical trials.¹⁹⁶

¹⁹⁵ Website of ‘Just A Dollar Please’, URL: <http://www.justadollarplease.org/>, (accessed September 27, 2012)

¹⁹⁶ Blog Contribution Wise Young, *CareCure*, July 5, 2010, URL: <http://sci.rutgers.edu/forum/showthread.php?t=125364&page=4>, (accessed September 27, 2012).

People needed to be motivated into donating. This was the task of Jim Bennett, who suffered from a spinal cord injury himself and who had a coordinating role in the US Network. He set up a network of recruiters called the Clinical Trial Support Squad, whose goal it was to procure donations from 100 people with spinal injuries and their families. They used *CareCure* as a platform for discussion and ‘social networking websites such as *Facebook*, *MySpace* and *Twitter* to reach potential donors’.¹⁹⁷

A further initiative launched by the spinal cord injury community involved selling blue plastic bracelets bearing the inscription ‘Supporting Clinical Trials Now!’ These were sold online for six US dollars each, or for less if purchased in bulk. By September 4, 2012, some 9800 bracelets had been sold.¹⁹⁸

Funding advocacy from within the spinal cord injury community in the US is now a widespread phenomenon. Support groups for the Network compete with advocacy groups for other research projects, and ‘advocacy toolkits’ are now available online.¹⁹⁹ In the light of this competition, it is not easy to maintain motivation and decide which organization and what kind of research to support. One of the bloggers on *CareCure*, known as ‘Scaper1’, who is also a member of the Clinical Trial Support Squad, expresses his confusion in this respect:

It's not easy to keep believing in a cure and to know which research to support. That said, I think that Wise's clinical trial networks are amazing achievements and one of our best chances, so I'm willing to keep trying.²⁰⁰

The ambivalence revealed by Scaper1 is a recurring theme on *CareCure*. As shown in Chapter VI, people with spinal cord injury are often highly critical in their questioning of the research projects they are asked to support. The quotation above also demonstrates that the China and US networks are conceived as inter-related parts of a single project. Support for the two networks, which can be witnessed on community websites such as *CareCure* and *Apparalyzed*, is clearly related to the scale of the two projects. In combination, the China SCI Net and SCI Net USA promise to become the

¹⁹⁷ Blog contribution of Jim Bennet, *CareCure*, April 20, 2009. URL:

<http://sci.rutgers.edu/forum/archive/index.php/t-117784.html>, (last accessed September 27, 2012).

¹⁹⁸ SCI Bracelets – Clinical Trial Now!, Website, URL: <http://www.scibracelets.com/>, (last accessed September 27, 2012).

¹⁹⁹ See <http://unite2fightparalysis.org/advocacy>, (last accessed September 27, 2012).

²⁰⁰ Blog contribution of ‘Skyper1’, *CareCure*, May 19, 2011, URL: <http://sci.rutgers.edu/forum/showthread.php?t=138661&page=8>, (last accessed September 27, 2012).

largest infrastructure for clinical trials in the spinal cord injury field in the world, with plenty new research opportunities.

In summary, the close interaction between Young and the spinal cord injury movement in the US made the China SCI Net, from its very beginnings, a focal point for hope among the patient community in the US. This trend was strengthened with the formation of the SCI Net USA, and the integration of the two networks into an evolving large-scale transnational research economy. Furthermore, the fact that the US Network is concerned with testing the same treatment combination as the Chinese Network (with some variation in the control groups and patient categories) has made the researchers, hospitals and patients of the China SCI Net part of a wider project of community building and patient activism in the USA.

As I will show now, in Part Two of this chapter, the entwinement of the two networks, and the significance of the China Network for people with spinal cord injury in the US, in no way meant that the institutes or investigators in China were relegated to a role of stewardship in order to serve US interests. On the contrary, what was observed was the tactical pooling together of resources in relation to a set of shared goals, with the development of treatment approaches to spinal cord injury as the focal point of communal commitment. In the course of my discussion, I will show how participation in the China SCI Net is associated with the generation of significant benefits for the affiliated partners, and enables the use of the Network for independent domestic innovation trajectories.

PART II: A new modality of transnational clinical research

In the second part of this chapter I argue that the establishment of the China SCI Net as part of an evolving transnational academia-driven clinical research infrastructure, exemplifies how a new modality of transnational clinical research and trial organization can take shape. The organizational forms of this modality differ from more conventional forms of international clinical partnerships – such as those embodied by Big Pharma, and those described, for example, by Adriana Petryna (2009) – in some very fundamental respects. As I will elucidate below, the main differences exist with regard to labor division, benefit-sharing, ownership issues, decision-making processes, and the possibility of independent use of the infrastructure

by associated investigators (in China). I suggest that this type of clinical research modality opens up an interesting alternative pathway to established corporate-based models of drug development; and this is not only more cost effective but also provides more leverage and independence to the academic investigators and institutions involved.

A more general difference with this new modality is that, in contrast to industry-sponsored forms of drug development, the China SCI Net does not manifest a capital-oriented pattern of drug development. Rather, it is an academic partnership model, which is dedicated to the clinical evaluation of both established and new therapeutic forms. This includes rehabilitation approaches and surgical procedures, both of which are not normally innovated by the pharmaceutical industry. The therapeutic options that arise, therefore, are not selected according to their marketability and the size of the potential market, but on the basis of patient need – in this case, in a disease field that pharmaceutical companies have often neglected, due to its limited size.

Having said this, because the Network collaborates with corporate sponsors, and intends to intensify its collaboration with the private sector in the future, the boundaries between academic and commerce-oriented research are not clear-cut. I will continue my argument with a brief overview of the common organizational underpinnings of industry-sponsored clinical trials, and then introduce four central aspects, along which the organizational structure of the China SCI Net differs from established forms of international drug research.

Industry-sponsored multi-country trials and their organizational basis

Multi-country drug research is frequently associated with the outsourcing of clinical trials to low-income and population-rich countries, as initiated by Big Pharma. Petryna, for instance, has described how this trend often follows older forms of global labor division and exploitation, with relatively one-sided flows of economic and scientific benefits, and the strategic utilization of differentials in costs, regulations, and biological characteristics of populations (Petryna 2009).

Asian societies, in particular, have experienced a significant increase in internationally organized clinical trials in their own countries in recent years. In fact,

33.8% of all industry-sponsored Phase III trials carried out in the world between April 2008 and March 2011 were conducted within Asia; the most were in Japan, followed by India, South Korea, mainland China, and Taiwan (Clinical Trial Magnifier 2011). Despite a great deal of criticism about the moral and ethical underpinnings of this kind of outsourcing of clinical trials to population-rich, low-income countries (Angell 2004; Cooper 2008a; Rajan 2010), the implementation of international industry-sponsored clinical trials is often actively sought by state governments, and is associated with numerous advantages. In the context of China, for example, Enchang Li from the *Chinese Journal of Medical Ethics* has pointed out that industry-sponsored international clinical trials in China constitute an important form of capacity building; they result in access to new drugs, bring about new medical investments, introduce novel technologies and know-how, and stimulate the development of independent pharmaceutical research in China (Li 2009). According to Li, these trials also form, in many instances, a source of valuable medical care for patients who either cannot afford such care, or for whom no other treatment possibilities exist (*ibid.*).

Other than these potential advantages, it is obvious that – from an organizational perspective – the rules and roles of industry-sponsored clinical trial collaborations are fixed, and unmistakably defined by the sponsor. The administrative model on which the international outsourcing of clinical trials is based is, in essence, a hierarchized form of contract labor, in which local clinicians, hospitals and Contract Research Organizations (CROs) are assigned the role of facilitators and technicians. The initial act of innovation that underlies the tested approach has normally occurred elsewhere, and the research findings flow back from the local clinical trial sites to the original sponsor, who is usually in a different country, and who legally owns the data and thus transforms them into profit (Rajan 2010).

The organizational model of the China SCI Net, in contrast, is based on a more collectivist approach to knowledge production. It is characterized by (i) the sharing of costs and labor among associated partners, (ii) the sharing of benefits, as well as a communal approach to ownership, (iii) the flattening of hierarchies and decision-making processes, and (iv) the formation of a domestic innovation platform. Let me illustrate these four important features now in some detail.

The sharing of costs and labor among associated partners

The China SCI Net is legally registered as a non-profit corporation in Hong Kong. In the words of Professor Wise Young, the Network constitutes a ‘membership-based corporate organization with a non-profit character’.²⁰¹ The term ‘corporate organization’ is not meant here in the conventional sense of ‘company’ or ‘commercial corporation’, but rather (as stated by Young) as a ‘professional society’, meaning a group of people who are legally authorized to act as an organizational entity.²⁰²

The non-profit character of the China SCI Net is affirmed by the fact that buying or trading shares of the organization is not possible; there is also a self-imposed debarment on the generation of profits from any products or services provided or developed by the group. Money for the organization is currently received exclusively through a model of charity funding, but its operations – as indicated in the preceding sections – are supplemented by government grants and forms of company sponsorship. As Young stated, all incoming money is ‘always spent to fund the mission’ of the organization.²⁰³

This academia-centered, non-profit organizational model goes along with a collectivist approach to knowledge production. As I demonstrated above, labor and research costs are, in several respects, integrated into the routine work processes of participating investigators and related staff, and expenses are shared between involved institutions if additional grants from hospitals or from government can be attracted. Research costs are broken down in this way, into comparably small and do-able portions. Compared to industry-sponsored clinical trial partnerships, in which technological, biological and human resources are in every respect hired and paid for, this organizational model forms a more collectivist and inventive form of cost reduction, which allows the carrying out of high-profile clinical trials ‘far below’ the operational ‘expenses of the pharmaceutical industry’.²⁰⁴

Of course, the integration of clinical trial labor into the everyday duties of investigators, in the context of academic clinical trials, is not new (OECD 2011). However, this occurs in the context of a transnational clinical trial infrastructure that

²⁰¹ Interview Wise Young, Hong Kong, June 24, 2010.

²⁰² Same source as in previous footnote.

²⁰³ Same source as in previous footnote.

²⁰⁴ Same source as in previous footnote.

has been initiated by a researcher from the USA, but which is almost completely funded from within the ‘science pole’ of China. The possibility of acquiring funds from Chinese hospitals, state agencies and the military for international clinical research collaborations, is a novel – perhaps even unprecedented – phenomenon, which has not been reported in the literature before.

The mobilization of financial, technical and labor resources in China clearly reflects the increasing opportunities that emerge for academic clinical research collaborations, in the context of a multi-polarizing science world. I suggest in this respect that access to these resources in the context of the China SCI Net, has only been possible because of a strongly communalistic approach to knowledge production, in which the benefits, the scientific data generated therein, and the decision-making processes are collectivized and shared among the associated academic partners. These issues will be discussed in the next section.

A communal approach to ownership and the sharing of benefits

Since participation in the Network is voluntarily, and the work of investigators is not currently financially remunerated, a benefit and incentive system has been developed that differs markedly from conventional models of the pharmaceutical industry. This is reflected (i) in a distinct approach to data ownership, and (ii) unrestrained use of potential applications of the tested treatment (provided it is proven efficient) by network partners.

Data ownership

As to data ownership, two central principles apply. The first relates to publication of the research. The contributions and work of the participating investigators are fully acknowledged in joint academic journal publications. Data are administered and statistically analyzed at the China SCI Net headquarters in Hong Kong²⁰⁵ and the articles are prepared by a writing committee that involves the two Network directors and the investigators who were most closely involved with the relevant studies. In the case of the smaller Phase I and II trials, the all-important lead authorship status is

²⁰⁵ Interview Dr. Wendy Cheng, Hong Kong, June 9, 2010.

awarded to the principal investigators of the hospitals in which the trials were conducted.²⁰⁶ Draft articles for Phase III trials are prepared by the committee and distributed for feedback from all involved investigators. In this case, first authorship is determined on merit to the individual who made the greatest contribution to the trial. Every investigator involved in the project is named as a co-author.²⁰⁷ The research is then submitted for publication in first-rate medical journals, which, as I determined during interviews with investigators in mainland China, is consistently seen as a strong incentive for participation in the trial.²⁰⁸

The second principle is that the data produced within a participating institution remain the legal property of that institution. This means that after completion of any collective publications through the China SCI Net, the data can freely be used by the investigators at these clinics or hospitals, for any publication they produce in their own name.

Potential applications of tested treatment

In contrast to drug trials in the pharmaceutical industry, where tested treatments are often marketed overseas but remain unavailable in the countries in which (large parts of) the clinical testing has been done (Rajan 2010), trials by the China SCI Net were designed to provide full access of the tested treatments to local patient populations. If the safety and efficacy of the tested cell/lithium combination treatment is established in the context of an IND [investigational new drug] application at the Chinese SFDA, then in principle all the spinal cord injury centers in mainland China, Hong Kong and Taiwan will be able to offer the treatment to their patients.

The following observations are very important. The surgical and cell transplant procedures used for the treatment method, which were an innovation of the Network researchers in China, are not rights protected; they will be published and be freely available, without any intellectual property restrictions attached.²⁰⁹ This means that, in principle, doctors all over the world will be able to use them in cell transplantation trials for spinal cord injury with other cell types.

²⁰⁶ Interview Nr. 10, senior researcher, Hong Kong, June 26 2010

²⁰⁷ Interview Nr. 35, senior researcher, Central China, September 15 2010; Interview Wise Young, Hong Kong, June 24, 2009.

²⁰⁸ The Phase I/II studies on the safety and efficacy of lithium in spinal cord injury patients were published in in 2011 and 2012 in the journal *Spinal Cord* – part of the *Nature* group. See references: (Wong 2011; Yang 2012).

²⁰⁹ Interview Kwok-Fai So, Hong Kong, January 7, 2011.

However, the situation is different with regard to the cell/lithium combination: in theory, hospitals offering this treatment in the future (if proven safe and efficient), would be required by international patent law to purchase their cells from Stemcyte. The reason for this is because a licensing agreement has been made between Rutgers University and Stemcyte protecting the intellectual property rights for the application of Stemcyte's UCB mononuclear cell product in combination with lithium. In practice, though, the legal prosecution of clinics in China that offer the combination treatment with UCB mononuclear cells not purchased from Stemcyte is unlikely.

Accordingly, competing approaches are expected to be seen in the market soon. Alternative UCB products for the treatment of spinal cord injury can also emerge in a formalized way, if competing UCB producing companies convince the SFDA (or other drug regulatory authorities) of the equivalence of their products to the Stemcyte cell product. For this to happen, however, additional clinical trials would be required, which takes a long time. For Young, the emergence of similar UCB products (officially approved, or informally applied) is a predictable consequence of market competition, with a price drop and decreasing market size of the Stemcyte UCB product as interrelated consequence:

All of the UCB companies have marketing agents, and they say... ok, we also do it... what is the difference between this treatment and that treatment, and we will lower the prices down. And then, Stemcyte will lower the prices. And ... all that IP [intellectual property] stuff that does not last that long. Someone will find a different version of UCB for this, and so on. It is only a temporary protection. So, Stemcyte might make two or three years profit, and they are actually competing with all the other companies, and the prices will fall. And eventually it will become generic.²¹⁰

The licensing agreement made with Stemcyte shows also that the boundaries between non-profit and for-profit are becoming increasingly blurred in the case of the China SCI Net, and that commercial and non-commercial interests are intertwined in complex ways. While the Network operates as a non-profit organization, they do have corporate sponsors, therefore some commercial considerations and intellectual property rights issues are unavoidable in the organization and planning of the Network's clinical trials.

²¹⁰ Interview with Wise Young, Hong Kong, June 24, 2010.

In summary, this section has shown how the issues of benefit-sharing, data ownership, patient access, and potential applications of the therapy tested by the China SCI Net differ from industry-sponsored international clinical trial partnerships. These differences relate to several aspects. (i) The contributions and work of the affiliated investigators, for example, are fully acknowledged in articles published in the top international academic journals. (ii) The participating institutes and hospitals can retain legal ownership of the data they produce, and they can be used for any independent publications the investigators prepare after the collective publications with the China SCI Net are completed. (iii) Any spinal cord injury center in China will be able to offer the safe and efficacious treatment (as proven in the context of an IND application) to patients. (iv) The innovative surgical and cell transplantation techniques used by the Network will be freely available for other types of intra-spinal cell transplantation. (v) All royalties obtained through the licensing agreement with Stemcyte are not to be used for private purposes, but will be allocated to Rutgers University toward future research.

Flattening hierarchies and opening up of decision-making processes

The third major difference from industry-sponsored clinical trials is that the organizational hierarchy is de-emphasized, or flattened. Decision-making procedures are also opened up. This step-wise deployment of an ethos of equity and communalization is based on the collective generation of academic and public health benefits.

The hierarchical distinctions seen between sponsors, intellectual creators and facilitating technicians in industry-driven clinical trials are either blurred or consciously de-emphasized within the China SCI Net. This is significant because, for example, funding is attracted by the collective efforts of the organization as well as individual investigators, so the financiering and technical performance aspects of the work in clinical trials normally tend to fall into the hands of the same people. Furthermore, many of the Network-affiliated investigators made important intellectual contributions to the development of the treatment tested by the Network; for example, lithium's effect on cell proliferation and its potential role in spinal cord injury was discovered by researchers at Hong Kong University (Yick *et al.* 2004; Su, Chu and

Wu 2007) and preclinical evidence was obtained in rats for the use of UCB cells in spinal cord injury by researchers from mainland China (Zhao *et al.* 2004). Moreover, investigators from China contributed their experiences relating to spinal surgery and cell transplantation.²¹¹ This sloping down of boundaries between the sponsor, creator and facilitator, as shown in the preceding sections, is brought about through a process of collaborative labor and resource mobilization, and it goes along with a more egalitarian mode of data-sharing and benefit-sharing, with a markedly less exclusive property regimen.

The communal and more egalitarian approach (compared to industry-sponsored trials) achieved by the China SCI Net is also reflected in a broad series of collective decision-making processes. A range of events can be observed here. First was the collective discussion and evaluation of candidate approaches, which took place primarily during the establishment period of the Network (in 2004 and 2005), through investigator meetings and a huge international symposium held in Hong Kong in the autumn of 2005. The evaluation processes of diverging options included Network-affiliated investigators and a wide range of international experts; they commented on the feasibility of different approaches as well as certain organizational and protocol issues, in order to get the planned trials internationally approved and published. These pivotal open discussions of the conference panels were captured on video; they provide valuable insights into the variety of positions and preferences at that time, and show how initial support for trials based on findings with olfactory ensheathing cells gradually shifted support toward the lithium–UCB cell combination.

In terms of recapturing the decision-making procedures underlying some of the difficult choices regarding selection of a treatment (and related information), the following pattern could be observed. The first phase was characterized by the following steps: (i) presentation of the options; (ii) open debate and collective evaluation; (iii) set up of panels and discussions in order to reach consensus. Young pointed out that the Network had never implemented a formal majority-vote system, but it had worked toward the formation of consensus, in which the best possible option were collectively discussed and then supported by (ideally) general agreement.²¹²

²¹¹ Interview Nr. 32, senior researcher Central China, September 14, 2010. Interview Nr. 23, North China, September 23, 2010; Interview Wise Young, Hong Kong, June 24, 2010.

²¹² Interview Wise Young, Hong Kong, June 24, 2010.

The second phase involved the opinion of independent experts; decisions were made by the board of directors regarding the treatment combination and the concrete series of trials through which the combination should be tested.²¹³

In the third phase, each trial had its own specific committee to develop the trial treatment protocol. In the observational trial (CN100) and the Phase I lithium study (CN101), this task was carried out by the Clinical Trial Center of Hong Kong University, but for the Phase II lithium study (CN102a) the task was taken over by the China SCI Net itself. Certain elements of the clinical trial protocols were developed through close collaboration with investigators, via specifically designed consensus meetings to address crucial issues, such as concerns regarding the standardization of the surgery and transplant technique. For this purpose, various teams of the Network came together in 2008 and presented a range of possibilities; a consensus was reached on one technique that very day.²¹⁴

Other aspects of the treatment protocols, particularly the technical aspects, were dealt with by experts on specialist committees; among these were the treatment protocol committee, the outcome-measure committee, the regulatory approval committee, and the implementation committee. Each of these involved the investigators of the hospitals in which the study was carried out, as well as members at the leadership level of the Network, and external staff and experts if required. These committees were formed for each clinical trial.²¹⁵

Transnational consensus meetings have also been held. For the first clinical trial conducted by the Network in the USA, for instance, a group of US investigators visited rehabilitation centers in Beijing and Kunming in 2010. These centers had apparently developed a ground-breaking intensive rehabilitation program. The investigators participated in a consensus conference about the rehabilitation protocol to be used in the US trials.²¹⁶

²¹³ Interview Nr. 32, senior researcher Central China, September 14, 2010.

²¹⁴ Interview J. Karlberg, Director of Clinical Trial Center Hong Kong, January 8, 2011; Interview Wendy Cheng, Hong Kong, June 12, 2010.

²¹⁵ Interview Wendy Cheng, Hong Kong, June 12, 2010.

²¹⁶ Interview Wise Young, Hong Kong, June 24, 2010.

Formation of a domestic innovation platform

Another deviation from industry-initiated ‘top-down’ forms of clinical research alliances is the targeting of indigenous forms of innovation and knowledge production, and their integration and positioning within the internationally recognized circuit of high-profile science. The China SCI Net functions, in this respect as both a platform for domestic knowledge production, and as a device for international integration. In its former function, the Network operates as a structure in which promising therapeutic approaches developed by associated partners in China can be clinically tested. In its latter function, the Network works as an integrating device, by building bridges between regions, places, institutes, and hospitals whose knowledge products would otherwise remain unrecognized, and by positioning these inventions in the arena of internationally recognized science.

Wise Young clarified how, from the start, he wanted the China SCI Net to be able to operate as an independent platform for innovation – one that would not only test therapies from the US, but also therapies from China, which were developed by network-affiliated researchers. For this purpose, between 2006 and 2009 he initiated two or three educational workshops per year aimed at junior and mid-level personnel of the affiliated hospitals, and he targeted pre-clinical research strategies. The aim is described below.

[...] they regard themselves as being a part of the pipeline for the therapies. They are discovering therapies. They don't regard themselves as just a tester of therapies. You know – just testing things that other people have made is not as... I guess... you are being a technician... you are applying... But the discovery process is something that we have started in China. [So that] things grow beyond us... And already it is happening. The first thing is the discovery of the intradural decompression study. And that is a Chinese story, and there is great pride in this. [...] And by the way, lithium, in Hong Kong University discovered. It is not [imported]. And this is one of the very attractive things why we have chosen it. Because it is not something discovered in the US, but it is discovered by one of our centers.²¹⁷

²¹⁷ Interview Wise Young, Hong Kong, June 24, 2010.

The idea, in other words, that domestic forms of research innovation in China could be developed and tested by the Network, and be published and positioned internationally, formed a key motivation behind the foundation of the research from its beginning. As Young mentions here, the integration of domestic innovations has been realized already, with discovery of lithium enhancing survival and growth of transplanted umbilical cord blood stem cells (Su, Chu and Wu 2007), and the development of the intradural decompression surgical technique in Kunming.

PART III: Involvement of spinal cord injury patients in decisions about future trials

Yet another line of differentiation between the Network trials and industry-sponsored clinical trials is the integration of patients with spinal cord injury into decisions for trials to be conducted in the future. The China SCI Net, as I have shown in Chapter VII, forms an important catalyst for an emerging global research environment that is giving rise to new forms of patient activism and community building, with wide-ranging transnational dimensions. In this regard, I pointed in particular to the involvement of patients in fundraising procedures. Funding activism on behalf of spinal cord-injured people and their families, as has become clear, is more extensive in the USA than in Hong Kong. The Hong Kong Spinal Cord Injury Fund was shown earlier in this chapter to have evolved into an important hub for fundraising in the field, having close links to the *CareCure* community in the USA and other international spinal cord injury organizations such as the Rick Hansen Foundation in Canada. However, at the time of writing, there was no involvement of spinal cord injury organizations in Hong Kong. Even though there are community organizations and forms of activism for spinal cord injury patients in Hong Kong, their goals primarily relate to quality of life issues and the improvement of local care conditions.²¹⁸ Funding activism for research is still the domain of the Hong Kong Spinal Cord Injury Fund. However, as Suzanne Poon commented, it is hoped that closer linkages with the spinal cord injury community in Hong Kong are established in the future.²¹⁹

²¹⁸ Interview with John Lee, Hong Kong, January 2 2011.

²¹⁹ Interview with Suzanne Poon Hong Kong, August 28, 2010.

Patient involvement in the global spinal cord injury network

Increasing forms of patient activism and the increasing involvement of the spinal cord injury community in the funding of clinical research must, in the view of Young, go hand in hand with the inclusion of those affected by spinal cord injuries and their families into the decision-making processes for future clinical trials. This will be even more important when the China SCI Net becomes a global research economy that not only includes the US Network, but also additional multicenter clinical trial networks in Europe, India and even the Middle East. These projects are driven by local partners in these regions, and are still in preparation and have uncertain outcomes.

One important and challenging issue here is how such a large-scale clinical research infrastructure will be governed and how decisions are made for therapeutic approaches to be tested in future trials. For Young, people with spinal cord injury play a crucial role in these decision-making processes, especially if some of the money for these trials is raised through forms of activist fundraising from within the community itself. To understand this point better, what follows is a long fragment of conversation between Dr Young and myself in an interview held in Hong Kong. Here, he sketches out initial ideas for realizing a robust and fair governance model for such a global spinal cord injury network.

WY: So, the first major problem is funding. The second major problem is – who chooses the therapies? How – who makes the decisions? Because what happens is, that this is a very corruptible process.

AR: In which sense precisely? Can you explain in some detail?

WY: Oh yes, if I got a million dollars from a drug company to test their therapies, which costs them, you know... much less with the China SCI Net, I would like... giving a gift to this company, and this company would be more than happy to buy me a house, or whatever, or something. The process is extremely corruptible, extremely corruptible! [...] And that is why... so how do you ensure objective, non-corrupted, rational decisions, in terms of what therapies you do? And that, now that takes a... Now, one of the approaches that people have is that they want to have big names, scientists in scientific advisory boards and so on. Em... I have a radical idea. I think that the decisions

should be made as a decision-making process in the same way the congress and the senate does things. This has to do with the government. [...] So, I would like to have two committees, one of the committees would be the senior scientific advisors – experts. A committee of experts. And these would be like the senators. There would be relatively few of them. And their jobs are to argue, and to consider, and to build faith and so forth. And I would like to have a *group of advocates* [people from the community organizations], and some doctors on the other sides. And it is the two bodies, which have to both decide together. Whatever therapy they must approve, must be agreed upon by both sides.

AR: That sounds maybe as a... workable model, for such a large-scale institutionalized apparatus, that includes so many different people and interests.

WY: You have to have the stakeholders. Now it makes sense that you do this, because... the dollar-a-day people are those who pay. I mean those guys pay, those are the stakeholders; they need to be part of the decision-making of what therapies are going in. But you want to make sure that these therapies are scientifically solid.

AR: Yes.

WY: Right, so that is why you have a senate, why you have a congress, right? You have the people. And by the way, I consider doctors kind of in the same looping, as people with spinal cord injury. You have a group that is considered as the experts, and you have a group that you consider as the advocates. Right? Presumably, the advocates group would be bigger, like maybe thirty people. The scientific advisory board, I think, would take ten. [...] Either side can propose therapies, but both sides have to agree, before it actually gets passed on to the executive committee. So, the PIs [principal investigators] of the Network will have vetoing power of course; they can decide not to do it.

AR: It sounds promising.

WY: How about mothers and fathers? How about... And how... is this going to be democratic? You know, I mean... everybody who gives a dollar a day, they get to vote? I mean... [they want to know] what do you do? We have to somehow give advocates a role. You know, they are stakeholders, and to expect people [to pay] and to have no influence on the processes so that is... So anyway, you have seen an outline to where I

am heading. [...] You know, [the challenge is] how to set up a system that can make rational, and yet passionate choices.²²⁰

I will not engage here in a discussion of this approach. What I want to do primarily is to illustrate Young's concept of the inclusion of representatives of patient advocacy groups into a future governance structure of a gradually evolving global network. If it achieved realization, it would be a radical step in drug development studies, where patients play an increasingly important role, not only as funders but also as stakeholders, in the decision-making processes of the projects that may take us to our regenerative futures.

Conclusions

In this chapter, I introduced the financiering model and the organizational structure of the China SCI Net, concentrating in particular on aspects of labor division and benefit sharing. I also focused on ideas for the inclusion of people with spinal cord injury into decision-making processes for future clinical trials, in the context of an evolving global research network in this field. Funding for the China SCI Net, as I have shown, is based on a multi-stranded organizational strategy, and has almost exclusively been raised with respect to Hong Kong and China. The tapping of financial resources from local hospitals, provincial governments and the Health Division of the People's Liberation Army in China, in the context of a transnational research project, is most likely unprecedented in the history of international collaborations in clinical medicine in China. The acquiring of these funds, in combination with the money raised through charity fund-raising throughout Hong Kong, and the sponsorship of the umbilical cord blood (UCB) stem cells by Stemcyte has enabled the Network to finance its operation independent of support from the pharmaceutical companies and state resources from US funding agencies. Access to these resources, as I have suggested, has been possible only because the Network has been organized and perceived as a project that creates benefits in the first place for both researchers and patients in China, while simultaneously functioning as part of an international clinical research infrastructure.

²²⁰ Interview Wise Young, Hong Kong, June 24, 2010.

The organizational structure of the China SCI Net was discussed by comparison with international clinical trial partnerships organized by the pharmaceutical industry. Four fundamental differences were identified, all of which refer to a far more collectivist approach of knowledge production. This implies that costs and labor are, to a large extent, shared among the involved partners. The work of associated researchers is not financially remunerated, as in the case of collaborations with pharmaceutical companies. However, the division of costs and clinical labor goes alongside a highly communalistic approach to knowledge production, which is characterized by various forms of reciprocity. Three attributes have been mentioned in this respect: a communal approach to ownership of generated data and medical procedures; the flattening of hierarchies and the opening up of decision-making processes; and the formation of a domestic innovation platform that can be independently used by researchers in China.

In Part Three of the chapter, it became clear that there are plans to integrate people from the spinal injury community into decisions regarding treatment approaches that are to be tested in future clinical trials. It is my suggestion that the organizational model of the China SCI Net represents a highly unconventional form of international clinical research and trial organization. In many regards it is an unprecedented modality of international clinical research collaboration and it provides an interesting alternative to corporate-based models of drug development; it is not only cost-saving, but also provides more leverage and independence to academic investigators and institutions.

International academic clinical research partnerships are not a new phenomenon, of course. However, academic clinical trial collaborations with clinical partners in low-cost, low-income countries have in the past usually been based on sponsor--host relationships, in which the investigators from high-income countries assume also the role of financial sponsor (OECD 2011: 52). The reason for this is commonly the non-availability of local forms of funding, with the bulk of the funding for international projects being acquired in the Triad countries. This, however, creates dependency structures, and the solidification of geographically bound hierarchies (Sariolla and Simpson 2012). In the case of the China SCI Net, such spatialized patterns of inequality are largely transcended, since virtually all of the money for the organization and execution of the Network's clinical trials is acquired locally; through the investigators in China and fundraising in Hong Kong. The local and communalistic

character of the project, as suggested above, is reflected also in the fact that the Network can be used as an independent innovation platform for the clinical testing of novel therapeutic approaches developed in affiliated hospitals in China. This is a second core difference from conventional forms of international academic clinical research partnerships.

This availability of financial, technical and infrastructural resources within China, in the context of international joint projects, clearly reflects the increasing scientific and economic significance of China, and its continuing transition from a production society to an innovation society. Furthermore, the acquiring of resources from within the evolving science-pole of China epitomizes the opportunities that emerge for academic research collaborations in the context of a multipolarizing science world. The case of the China SCI Net also suggests that increasing access to local resources is likely to occur along with important transformations in the ways that international academic clinical research collaborations are organized.

Against the background of scientific multipolarization, the roles and responsibilities of all involved partners are gradually redefined, and the processes of clinical labor, decision-making and benefits sharing are allocated on a more equivalent basis. It is too early, however, to extrapolate these findings to a level of generalization beyond the case of the China SCI Net. Further research into the transfigurations of the organizational modalities of international clinical research co-operations in the context of the current trend of scientific multipolarization will be required.

Chapter IX - Conclusions

The empirical focal point of this dissertation was the formation of the China SCI Net, an international, academic clinical research infrastructure that is active across the contexts of mainland China, Hong Kong, Taiwan, and the USA. The establishment of this evolving transnational research economy has provided a unique opportunity to generate insights into the processes and challenges involved in the development, organization and governance of large-scale, trans-continental clinical research collaborations in the field of regenerative stem cell medicine. It has also led to an initial understanding on how the formation of such international infrastructures is facilitated and shaped by the availability of new types of resources, expertise and opportunities globally, which is a process driven by the emerging of new economic, geopolitical and scientific center regions in the world. In this dissertation, I explored these issues through three inter-related analytical levels.

At the first level, I examined the China SCI Net as the establishing of a transnational standardized research zone that is evolving against a background of regulatory, institutional and cultural heterogeneity. I analyzed this process in light of debates on the global distribution of evidence-based clinical research standards, and the local responses and forms of contestation that surround this trend. At the second level, I explored the ways in which the organizational forms of projects such as the China SCI Net are changing, in relation to the impact of the unfolding dynamic of scientific multipolarization (as explained in the Introduction). In this dissertation, I investigated this dynamic, in particular from the regional standpoint of China. At the third level, I set out to examine the theoretical implications of the trend toward scientific multipolarization. Guiding questions in this respect were: What kinds of analytical tools are needed to identify, map and make sense of these changes? Are existing theoretical approaches sufficient to capture this complex dynamic: the changing forms of partnership and activity, as well as the redirections of global flows, power, property and infrastructure that are occurring in the evolving ‘multipolar’ scientific world system? A central concern in this respect was to engage in a reflective dialogue with the analytical possibilities and limitations of postcolonial approaches to the study of science and technology, and the search for complementary analytical

perspectives, through which the empirical transformations and impact associated with the move toward a multipolarizing science system, can be captured in a more nuanced, and comprehensive manner.

Each of these three analytical levels will now be discussed in detail, in relation to the empirical findings of this study and the relevant literature. I will then define some analytical dimensions through which the transformations and the local, regional and global impacts of the transition to a multipolar science world can be identified and mapped at a more open and broad level, extending beyond the topic of international collaboration that has been central to this dissertation. By developing a ‘multipolar technoscience’ framework, I aim to look ahead and identify future lines of research, analysis and theorization. This will allow the connections between science, globalization and geopolitical diversification to be examined from new perspectives.

Analytical Level I: Clinical stem cell research as a global collaborative project

In the sociological and anthropological literature on experimental clinical research with stem cells, research on the formation of international clinical trial collaborations is a neglected area. As discussed in the Introduction, in contexts other than the USA and Europe, analysts have focused almost exclusively on unproven, for-profit stem cell therapies; they have not examined the emergence of more systematic forms of clinical research. This is an important analytical shortcoming. It overlooks the fact that international clinical trial partnerships have had a more significant role in the stem cell field in recent years. It also misses a number of important analytical opportunities. Importantly, a focus on the travel and trans-local re-embedding of randomized controlled clinical trial (RCT) standards, in the context of inter-continental clinical stem cell research collaborations, offers a valuable opportunity to understand how the promotion and global distribution of evidence-based medicine (EBM) research protocols plays out in a newly emerging field of clinical medicine, for which national regulatory frameworks are emerging only gradually, and no internationally harmonized research standards have been defined. Such insights are of value not only with respect to current developments in regenerative stem cell medicine, but also other evolving spheres of science, technology and medicine research. In this dissertation, I examined three inter-related analytical themes in this respect: (i) the first concerned the role and forms of scientific self-governance, through which the emergence of standardized trans-continental clinical research zones (such as the China SCI Net) is advanced and institutionalized; (ii) the second addressed the ways in which trans-local distribution and re-embedding of EBM clinical research protocols impact and transform local clinical research and innovation practices; (iii) the third concerned the local responses and forms of resistance to these trans-local forms of restructuring. These three themes will now be discussed in detail.

The role and forms of scientific self-governance

The heterogeneity of regulation, clinical research methodologies and practices of commercialization that can be observed in the clinical stem cell field at a global level, poses significant challenges to the development of international clinical stem cell

research projects. In the literature, the challenges related to the increasing internationalization of research in the life and health sciences have been addressed primarily from the perspective of adequate adjustments of national regulatory systems (Wahlberg et al. 2013) or the development of global governance frameworks (Peel 2010, Zwanenberg, Ely and Smith 2011). The forms, role and implications of the ways in which scientists themselves address these challenges, in the context of collaborative cross-continental clinical research projects, have received little attention to date. In the case of emerging technologies in which state regulations evolve only gradually, and internationally harmonized regulatory frameworks are not yet in place, important analytical insights can be gained by focusing on the self-regulatory efforts of the researchers and staff who run and organize such collaborative projects. I have shown in this dissertation how, in evolving fields of medicine such as clinical stem cell research, the creation of standardized trans-national research zones that try to operate in an internationally recognized way depend on extensive forms of scientific self-governance. These project-internal forms of self-regulation, capacity building and institutional restructuring are judicious attempts to navigate through an internationally diverse regulatory environment; the aim is to create compliance with the variable requirements of the drug regulatory authorities and related processes of peer review in different countries.

The China SCI Net, as I have shown, is a standardized international research zone in the making. As shown in Chapter VII, scientific self-governance involved continuing efforts of assessment, selection, and institutional restructuring. These procedures aimed at the consistent implementation of standardized clinical research protocols. In contrast to multicenter clinical trials that are conducted in a single country, the project-internal forms of self-regulation, capacity building and institutional restructuring that were described in Chapter VII constitute a long-term strategic endeavor to create congruence with the auditing demands of widely varying regulatory and legal systems. At the time of writing, the clinical trials of the Network had been approved exclusively by the regulatory authorities in Hong Kong and mainland China, but the data from these trials will be used for investigational new drug applications (INDs) in the USA; this required an enduring anticipatory engagement with the review and approval criteria of the US FDA with respect to the ‘acceptance of foreign clinical studies not conducted under an investigational new drug application (non-IND foreign clinical studies) (FDA 2008). This constant need

for forms of ‘anticipatory audit’ (Strathern 2008: 308) requires the identification and forestalling of regulatory gaps between national jurisdictions from an early stage of the clinical translation process. Let me illustrate this point briefly through an example: At the time of writing, the Health Department of the Army General Logistics Department in China (the regulatory agency that approved the China SCI Net’s clinical study CN102b_KM, conducted in Kunming) did not mandatorily require that clinical studies should be conducted in compliance with ICH-GCP standards. Nor did it require the clinical trials to be conducted exclusively in hospitals certified by the Chinese MOH as officially recognized clinical trial units. However, the US FDA’s list of requirements for the acceptance of ‘non-IND foreign trials’ (in the context of IND applications at the US FDA), states that ‘accordance with good clinical practice (GCP), including review and approval by an independent ethics committee (IEC)’ is obligatory (Federal Register 2008). The China SCI Net recognized these discrepancies from the outset and (as reported in Chapters VI and VII) ensured their clinical trial protocols were fully GCP compliant and only MOH-certified hospitals were selected; independent ethics committee review was also sought by an external commercial IRB in the USA.

Trans-national scientific self-governance is a key aspect of the global operation of science particularly in emerging fields of technology research, for which there are no internationally harmonized regulatory frameworks. Against this background, it is surprising that the forms, role and implications of the self-regulatory activities of biomedical scientists in the context of real-world cross-border projects, have received comparatively little attention to this point. I suggest in this regard, that a focus on trans-national processes of scientific self-governance within evolving global projects such as the China SCI Net provides important analytical opportunities. In emerging fields of technology research such as regenerative stem cell medicine, an understanding can be gained, for example, about processes of cross-border harmonization and standardization – both before and during the establishment of fully developed state regulations, and/or the development of internationally harmonized regulatory frameworks. The China SCI Net, for instance, offers one of the first opportunities to observe processes of cross-border harmonization and standardization (and the ways these processes relate to the contrasting demands of multiple regulatory regimes) in the field of stem cell medicine.

Review of these processes also provides a unique analytical lens through which to understand the global distribution and trans-local adoption of EBM standards in emerging (and controversial) fields of medical research, from a grassroots perspective. Above all, important insights can be gained into (a) the ways in which local clinical research and innovation practices are transformed in the context of international research projects, and (b) the interplay and conflicts between the divergent values, normative systems and forms of legal authority underlying the creation of standardized trans-national research zones. These are the issues to which I now turn.

Transformation of local clinical research and innovation practices

As pointed out by Brunsson and Jakobsson, standards serve to coordinate assemblages of things and people into new configurations, and in doing so they transform existing practices, institutional arrangements, and related social orders (2000: 49). I will now reconsider the transformations of local clinical research and innovation practices that can be associated with processes of standardization in the context of the China SCI Net.

In 2004, when the China SCI Net was launched, the organization of an academia-driven, multicenter clinical trial infrastructure was a radical novelty in the Chinese landscape of stem cell research. Standardized multicenter drug trials, as I had shown in Chapter V, had been conducted in China by multinational pharmaceutical companies from the early 1990s (Cooper 2008a). Clinical experiments with stem cells, though, followed for many more years primarily an “art-of-medicine” approach, whereby tailor-made experimental treatments were designed according to the unique needs and disease conditions of individual patients (Rosemann 2013a). Some of these emerging therapeutic strategies were rapidly transformed into experimental for-profit applications, and were applied to large numbers of patients; others were tested in more scientific ways. By 2010, relatively few systematic clinical trials with stem cells had been conducted in China. Moreover, as reported by Zhang (2012), until that time stem cell research centers in China mostly operated in isolation, with rather little collaboration between researchers. Against this background, the formation of an internationally operating multicenter clinical trial infrastructure that would allow the testing and marketization of stem cell-based medicinal products, not only in mainland China, but also in Hong Kong, Taiwan and sometime later in the USA and possibly other countries, was a radical and fundamentally new concept. With its international

scope and dedication to cross-institutional cooperation, the China SCI Net embodied a paradigmatic turning point in the field of stem cell research in China. This involved three important changes: (a) the promotion of multicenter clinical research partnerships; (b) international integration and multi-country regulatory approval; and (c) the adoption of internationally acknowledged EBM clinical research standards. Regarding the first two changes, the China SCI Net has functioned until now as both a platform for collaborative knowledge production and as an integrating device, that builds bridges between previously isolated research institutes, hospitals and communities. At a domestic level, within China, as illustrated in Chapters VII and VIII, the Network has transcended existing institutional boundaries, by enabling new forms of communication, exchange and collaborative research practices between formerly unrelated – and competing – hospital units and researchers. At an international level, the Network has initiated new linkages with foreign research and corporate and regulatory communities. By participating in an international clinical research project that is striving for multi-country certification of tested therapeutic products, the Network-affiliated hospitals in China gradually evolve into recognized components of the international system of high-profile science. These hospitals then find themselves at the intersection of previously distant social worlds, with access to international research and peer-review communities, foreign biotechnology companies, overseas drug regulatory agencies, and trans-national advocacy networks (Rosemann 2013b). In doing so, the Network has facilitated the positioning of clinical innovations from China (that would otherwise be recognized only at a domestic level) into the arena of internationally recognized science.

At the center of this integration process, as described in Chapters IV and VII, was the promotion and systematic adoption of internationally recognized EBM clinical research standards. To better understand these changes, I provided in Chapter IV an overview of the range of clinical practices and procedures that were affected by the trans-institutional implementation of internationally recognized trial standards in the context of the Network's clinical studies. These aspects ranged from the standardization of elementary methodological principles, to the standardization of intervention procedures, diagnostic patient examinations, outcomes measures, and other aspects of RCT protocols. The methods, techniques and organizational procedures through which these forms of standardization were achieved, have been described in Chapter VII. What interests me here is the level of sustainability of these

changes, and the precise situations under which international clinical trial standards are either applied – or abandoned.

As I suggested in Chapter VII, the creation of standardized research zones in the context of inter-continental collaborative clinical research projects, such as the China SCI Net, does not necessarily typify the constant or complete transformation of the socio-technical and methodological practices performed in the institutions that are part of the project. Rather, the adoption of homogenized, internationally recognized clinical research standards was shown to be temporary, and was only activated in highly specific situations. This situation was well illustrated by the China SCI Net. Locally evolved and newly adopted forms of clinical experimentation (implemented in the context of the Network's clinical trials) continued to exist alongside each other in several of the Network-affiliated institutions I visited. Internationally recognized clinical trial standards that would match up with the review criteria of specific top international journals, were taken up first and foremost in the context of the clinical trials organized by the Network; in independent clinical studies of individual investigators (outside the context of these trials) less rigorous research standards were often employed – one hospital continued to provide experimental for-profit treatments. As outlined in Chapter VII, though, a shift toward the employment of more systematic clinical studies was widely reported in Network-affiliated hospitals. The overwhelming majority of clinical researchers with whom I spoke mentioned plans for trials with the use of control groups, more robust criteria for inclusion and exclusion of patients, as well as systematic multi-center Phase III studies (also independently from the China SCI Net).

Barry, as indicated in Chapter VII, has in this respect spoken of the creation of 'technological zones', within which 'differences between technical practices, procedures and forms have been reduced, or common standards have been established' (2007: 239). The borders of these zones, Barry argues, 'increasingly [do] not correspond to the borders of nation states' (*ibid.*). However, Barry acknowledges that the development and implementation of shared standards in these trans-territorial zones is usually closely linked to the regulatory norms and qualification mechanisms of national state governments and other dominant political entities. A common phenomenon in this respect is the extension of regulatory standards from one territorial or jurisdictional domain to another domain, where they are inflicted on domestic repertoires (normative, professional, etc.) and jurisdictional frameworks. Broadly

speaking, this situation was observed in the case of the China SCI Net. Internationally recognized EBM clinical research standards were transported to new institutional contexts, where they were mapped on (and tried to supersede and unify) a heterogeneous range of locally evolved clinical research practices.

A point not mentioned by Barry, however, relates to the fact that the formation of such standardized trans-national zones can be highly temporarily and situation specific. In the case of the China SCI Net, it would seem that older conceptions of clinical research practice can continue to exist, and be reproduced in the institutes that constitute such trans-national research zones. This situation-specific character, in which newly established standards can lay dormant for some time and be switched on and off in relation to contextual demands, has not been systematically explored in the literature to date. The China SCI Net indicates in this regard, that researchers do switch back and forth dynamically between different schemas of scientific and ethical practice, depending on the purposes of their research, the partners they work with, the geographic scale of the project, and the contrasting requirements for regulatory review that arise from these differences.

Forms of resistance and alter-standardization

Standardization constructs a state of stability and order across a situation of diversity and multiple possibilities (Timmermans and Epstein 2010: 71). However, the use of unified standards in global medicine research is also a form of stratification. As Thévenot has pointed out, the recognition of some forms of clinical research practices as being internationally more acceptable than others creates new boundaries of inclusion and exclusion between individuals, groups, things, spaces, practices, values and concepts (Thévenot 2009). Alternative – and less costly – types of therapy development, outside the RCT format, such as the experimental provision of new treatment options for patients with few or no medical alternatives, have been increasingly devaluated (Hyun 2010). The RCT is now a binding global standard in more conventional forms of medical research (based on the clinical testing of compound-based or small molecule-based drugs), but in emerging fields of research such as regenerative stem cell medicine the situation is far more variable. As documented in Chapter V, China made international headlines with the experimental provision of non-systematically proven cell and stem cell treatments to patients on a for-profit basis (Cyranoski 2009; Sipp 2010). I have shown that the widespread

availability of experimental therapies in China is connected to the longstanding absence of a consistent regulatory framework for clinical stem cell applications, which has resulted in the generation of new forms of profit, and novel scientific and medical opportunities. The situation is complex, however. Chapter V highlighted two overall trends. The first was the increasing adoption of RCT methodology in the clinical stem cell field in China. Since 2012, this shift has also been endorsed in an evolving state regulation. The second trend involved the emergence of a trans-national politics of resistance with its roots in China, that reverberates positively with the interests of numerous clinical researchers, clinics and companies in a broad range of other countries, including the USA, Japan and Europe.

In connection with this point, I argued in Chapter VII that the forms of resistance and resentment toward adopting RCTs that can be observed in the clinical stem cell field in China, are of an increasingly organized and trans-national form. What was observed was not only the diversification of ethical and scientific forms at the level of individual institutions, but a gradual move toward a ‘pluralization of the international’ itself – a shift toward the pluralization of the standards, categories and practices designated as ‘international’ and ‘shared’. What I mean by this is the creation of novel trans-national spaces of ‘alter-standardization’, i.e. the formation of novel trans-national networks, institutional spaces, rules, communities of practice and platforms of knowledge-sharing and publication, that both, endorse and validate alternative forms of experimental research. These alternative forms employ ethical and research protocols that, in several respects, diverge from the current canon of international scientific standards. These findings were illustrated through a case study of the International Association of Neurorestoratology (IANR), a professional society that centers on the foundation of a new sub-discipline of the neurosciences known as neurorestoratology. Both the field of neurorestoratology and the IANR were initiated by a researcher from Beijing, in close collaboration with other scientists from China, India, the UK, USA and the Middle East.

Forms of resistance in the context of the global distribution of EBM standards and the carrying out of RCTs have widely been reported in the literature (Timmerman and Berg 2003, Mykhalovskiy and Weir 2004; Bharadwaj and Glasner 2009; Timmerman and Epstein 2010). In China, in the clinical stem cell research field, opposition to the adoption of international clinical research protocols has been particularly pronounced (Rosemann 2013). The reasons for this, as illustrated in

Chapters V and VII, are the “set” character of stem cell-based clinical experimentation in China, which is represented by well-established communities of practitioners, high popularity of stem cell therapies among patients, and the existence of lucrative profit margins. This situation significantly increases the potential for regulatory conflict in China. As the case of the IANR indicates, the widespread acceptance and availability of more informal forms of clinical experimentation has given rise to claims for the acceptance of less rigorous research regimens that allow rapid clinical translation and the legitimization of types of clinical studies beyond the RCT such as open-labeled, non-controlled cohort studies, or experimental studies based on self-comparison by patients (Huang 2010: 130).

What is at stake here, broadly speaking, is a clash between an emerging – and in many respects imported – form of regulatory authority (as embodied by EBM and the international standard regimens for RCTs) and local forms of professionalism and research validation which have arisen on the basis of pre-existing manifestations of clinical experimentality with stem cells in China. As suggested above, such confrontations have brought about a ‘pluralization’ of ethical and scientific practices and categories. The introduction of novel rules and practices has given rise to forms of hybridization and the coexistence of multiple forms of experimentality. The stepwise adoption of international standards has transformed and pluralized local forms and practices, but it has not superseded or replaced them.

Analytical Level II: International Clinical Research Collaborations in a Multipolarizing Science World

At the second analytical level in this dissertation, I was concerned with the empirical impact of the current dynamic of ‘scientific multipolarization’ on the development and organization of international clinical research collaborations. With the concept of ‘scientific multipolarization’ as spelled out in the Introduction, I refer to the materialization of ‘novel’ scientific center regions in the world, a trend that is closely linked to the emergence of new global centers of geopolitical and economic influence, which have been unfolding since the end of the Cold War. The increasing significance and global role of these developing scientific hubs is epitomized by the increasing accumulation of research capacity, expertise and know-how, and the availability of high-level technological infrastructures, large amounts of funding, well-trained scientific staff, and a growing record of breakthroughs and techno-scientific innovations. These changes, as is now widely asserted, give rise to an intensification of global competition, and also create new opportunities for facilitating international science and technology cooperation (Bound *et al.* 2013). My working assumption, in this respect, was that the emergence of these new scientific centers in the world is associated with significant changes in organizational forms, types of exchange, and the interactions and subjectivities that arise during international research collaborations. Changes can also be expected with respect to the reasons behind initiating collaborative projects, and the criteria and mechanisms by which these projects are judged, appraised and legitimized.

In the context of this dissertation, I set out to explore these presumptions by restricting myself to the study of international academic clinical research collaborations in the field of regenerative stem cell medicine. My geographic focus was exclusively on collaborations involving medical institutions in China, as exemplified by my central case study on the China SCI Net. In order to identify and understand the lines of transformation that can be associated with the current ascent of China to the status of a global scientific center region, I proposed four interrelated analytical dimensions. These dimensions were:

- 1) Emerging forms of sociality and social movement.

- 2) Patterns of research financiering / and ownership.
- 3) The organizational modalities of trans-national research alliances, especially:
 - a. the forms and processes of labor division between associated stakeholders and partners
 - b. the decision-making processes
 - c. involved exchanges and transactions, and
 - d. forms of profit and benefit sharing.
- 4) Patterns of exchange and resource mobilization from within and between the involved center regions (in this dissertation, China and the USA), including the mobilization of human, biological, technological and infrastructural resources.

Before discussing these dimensions one by one, a brief summary of key findings. The case study of the China SCI Net has indicated, that the ongoing changes, increasing opportunities, and availability of new types of resources in the context of China, are resulting in significant transformations of the ways in which trans-national clinical research collaborations are initiated, organized and justified. As I have shown, the organizational model of the China SCI Net differs from both the organization of clinical trials by the drug industry, and other forms of academic clinical research collaborations, between high- and low- to-middle-income countries. Funding for the China SCI Net, as I have illustrated, has almost exclusively been raised domestically, within Hong Kong and mainland China. In the context of a large-scale trans-national research project, the tapping of financial resources from local hospitals, provincial governments and the Health Division of the People's Liberation Army in China appears to be unprecedented in the history of international collaboration in clinical medicine in China. The money raised through charity fund-raising throughout Hong Kong, in combination with the funds from mainland China, has enabled the Network to finance its clinical trials independently of support from the drug industry and state resources from funding agencies of the US or other developed countries. I have suggested in this respect, that the far-reaching access to the financial, technical, infrastructural, human and knowledge resources in China has only been possible because the China SCI Net is set up around a highly collectivist model of international knowledge production, that creates substantial benefits for local spinal cord researchers, patients and hospitals in China. This collectivist approach is manifest not only in the collective mobilization of financial resources and the sharing of costs and

labor, but also in (a) the incorporation of local research innovations, (b) the sharing of research benefits, (c) the flattening of decision-making processes, (d) the use of the Network as platform for domestic innovation, and (e) by providing local access to effective and safe treatments.

Emerging forms of sociality and social movement

As the case of the China SCI Net has shown, the expertise, infrastructure and research possibilities that the ‘science pole’ China offers, do increasingly encourage the formation of complex trans-continental research assemblages. The massive availability of resources and knowhow in China has facilitated clinical research and innovation processes, that could not have been accomplished in one of the involved scientific center regions (i.e. China and the USA) alone (or that could only have been accomplished with great difficulty). The core of the assemblage consists of a hospital infrastructure in China and, more recently, a sister Network in the USA known as the SCI Net USA together with its US-based hospital infrastructure. Participation in the Network’s clinical trials placed the participating clinics in China at the intersection of previously distant social worlds, including interactions with overseas drug regulatory authorities, the spinal cord injury (SCI) research community in the US, trans-national patient advocacy networks, globally operating biotechnology and pharmaceutical companies, and the editorial boards of the top academic international journals.

The creation of a hospital infrastructure in China has been intrinsically linked to a project of trans-national community formation and complex forms of activism and social movement. The close interaction of the Network’s founding Director, Professor Wise Young, with the SCI pro-cure movement in the USA, meant that the China SCI Net was from its very beginning a focal point of attention and for hope among the SCI community in Northern America. Members of the *CareCure* community website, for instance, started to conceive of – and to identify with – the China SCI Net as part of their own agenda and purposes: the realization of potential therapies through new research and clinical trials. The links between the China SCI Net and the SCI research and patient community in the USA were intensified with the formation of the SCI Net USA. This forms a parallel network to the one in China, and its foundation has consolidated the integration of the hospitals of the China SCI Net in a large-scale standardized trans-Pacific clinical research infrastructure. Even though organized and

financed independently, the two networks form, in essence, one large project, in which one builds upon the work and clinical data of the other. With the formation of the SCI Net USA, the interest among patients in the US in the work and progress of the Network in China clearly increased. Since the data of the Phase II trials in Hong Kong and Kunming shall be used for US Food and Drug Administration (FDA) applications relating to subsequent trials in the USA, the China SCI Net has become the target of hope and attention among larger segments of the US pro-cure movement. The integration of the China and USA networks into one joint project implies, therefore, the incorporation of the China SCI Net not only into a transcontinental clinical infrastructure, but also into a large-scale project of patient activism and trans-national community formation. Community building processes among patients in the context of the USA, as I have shown in Chapter VIII, occurs in particular through the involvement of people with SCI into collective processes of fundraising (for the SCI Net USA). Some people with SCI from the USA have travelled to Hong Kong and China to participate in fundraising campaigns and international symposia organized by the Network there, but for most people in the US community the links with China and the China SCI Net occur solely at an ideational and identificational level.

Trans-national forms of sociality among researchers in the field, on the other hand, are of a more tangible nature. Many SCI researchers from the USA have flown to China to take part in conferences, to witness demonstrations of surgical procedures, and to learn more about approaches to cell transplantation and rehabilitation. Researchers from the US research community have also been involved in processes of review and feedback, and have been engaged in the training of evidence-based research standards and clinical trial design. Similarly, researchers of the Network in China have travelled to the USA, to New Jersey, to learn about developments in research and rehabilitation. A selection of mid-career researchers stayed for several months at Rutgers University in the USA for advanced training in research and to participate in basic and pre-clinical research. This is part of an important process of community formation. A process of community formation, as suggested in Chapter VI, also occurred among SCI researchers *in* China. In forming a sustained multi-center clinical research platform, the China SCI Net brought together a large number of recognized researchers in China who had previously operated separately from each other. The integration of these researchers within a joint project created opportunities

for exchange of knowledge and to develop a nuanced awareness of what other researchers in China were doing.

In summary, what has been observed is the emergence and evolution of an extended trans-national assemblage of biosociality, which centers on the integration of two independently organized research networks into a trans-Pacific joint project.

The patterns of research financiering and ownership

Funding of the network, as I have shown in Chapters III and VIII, is based on a highly complex organizational model, which involves the acquiring of monetary resources through multi-stranded pathways and opportunities. With exception of the sponsorship of the umbilical cord blood (UCB) stem cells through Stemcyte, the operational expenses of the China SCI Net have almost exclusively been met locally, within China and Hong Kong. Most of the money has been obtained from charitable funds in Hong Kong, and has been complemented by the tapping into resources from local hospitals, as well as grants from provincial governments in China and from the Health Division of the People's Liberation Army. I have suggested, in this respect, that – in the context of an internationally operating research network initiated by an overseas researcher – tapping into financial resources within China is highly untypical, and probably unprecedented. Furthermore, costs could be reduced by integrating the expenses for surgery and other forms of clinical labor into the routine work obligations of associated (principal investigators) PIs and clinical staff. Of course, the lower labor costs in China coupled with the lower prices charged by hospitals for technical and care services, means conducting clinical trials in China constitutes an important cost-reduction measure.

The opportunities that have arisen in this joint project, as suggested in Chapter III, are of particular relevance to academic international clinical research partnerships. The case of the China SCI Net exemplifies that tapping into both financial resources and expertise in China allows two central barriers to be overcome, which have hampered the clinical testing of stem cell-based treatment approaches for SCI in the USA: these are: hesitancy of the pharmaceutical industry to invest; and limited availability of funding for academic clinical trials by the government. An argument was developed in relation to this situation, as shown in Chapter VIII, whereby access to finance and other forms of resources in China has been possible *only* because the

China SCI Net has been organized and perceived as a project that creates *benefits* for China – that is, it benefits both SCI researchers and SCI patients in China, and it leads to the opportunity to function as part of an international clinical research infrastructure.

The organization of the China SCI Net as a sustainable research infrastructure on both domestic and international levels has been realized through a highly communalistic mode of knowledge production. In this model, labor, benefits, the generation of scientific data and decision-making processes are, to a large extent, collectivized and shared among associated research partners. The case of the China SCI Net suggests that access to local resources and know-how in the context of trans-polar clinical research collaborations is likely to go hand in hand with significant transformations in the ways that international academic clinical research collaborations are organized. This issue is addressed in the next section, on research organization.

The organizational modalities of trans-national research alliances

The organizational model of the China SCI Net is based, in essence, on an academic partnership, which ties together a large number of clinical researchers, scientists, academic and military research hospitals and research centers, and one company, into an extended trans-national research economy. I have argued in this respect that the formation of the China SCI Net as part of an evolving transcontinental academia-centered clinical research infrastructure, means that a new modality of trans-national clinical research and trial organization is taking shape, which – in several fundamental aspects – differs from international clinical research partnerships organized by the pharmaceutical industry.

Four distinct differences can be highlighted in this respect, which relate to (1) the sharing of costs and labor, (2) a communal approach to ownership and benefit-sharing, (3) the flattening of hierarchies and decision-making processes, and (4) the formation of an independent platform for innovation. Hierarchical distinctions commonly occur between the sponsor, the intellectual creators and the facilitating technicians in industry-sponsored clinical trials, but in the organizational model of the China SCI Net these hierarchies are blurred. Since funds are raised collectively, with the active involvement of local PIs in China, the acts of financing and technical

performance of clinical trial labor fall, to a significant extent, into the hands of the same individuals. Furthermore, researchers who are affiliated to the Network make important intellectual contributions to the approach that is being tested by the organization. I have shown in Chapter VIII that this sloping down of boundaries between sponsor, creator and facilitator, through collaborative processes of resource mobilization, labor and invention, goes alongside a more egalitarian mode of data-sharing and benefit-sharing, and a less exclusivist property regimen. The step-wise deployment of an ethos of equity and communalization seen in the Network is based on the collective generation of academic and public health benefits, rather than the generation of financial profits. International academic clinical trial partnerships based on collective forms of fund-raising and the integration of processes of clinical labor into the routine work of collaborating investigators, are not a new phenomenon. However, as pointed out in Chapter VIII, academic clinical research collaborations with clinical partners in low-cost and low-income countries have in the past typically been characterized by substantial funding imbalances. This has resulted in sponsor–host relationships in which investigators from high-income countries have usually taken on the role of financial sponsor (OECD 2011: 52). This, in turn, has created dependency structures, and the solidification of geographically bound inequalities and hierarchies (Sariolla and Simpson 2012). In the case of the China SCI Net, these geographically based patterns of inequality have been largely transcended. As reported above, the largest source of funding for the Network and its clinical trials was acquired on a local basis.

An additional distinguishing feature that separates the Network from conventional forms of international academic clinical research partnerships is that this independent form of clinical research innovation has been instigated through training in basic and preclinical research; it is thought to function also as an independent innovative platform for the testing of novel therapeutic approaches that are developed in affiliated hospitals in China. I have suggested that this (in many respects unprecedented) modality of international clinical research collaboration provides an interesting alternative to corporate-based models of drug development; it is not only cost-saving, but also provides more leverage and independence for academic investigators and institutions. The boundaries between non-profit and for-profit organizations, as I have shown, are becoming less clearly defined, however. While the Network operates as a non-profit organization, it is partially dependent on corporate

sponsors, thus commercial considerations and intellectual property rights issues are unavoidable when it comes to the organization and planning of clinical trials.

In summary, my analysis of the China SCI Net suggests that the far-reaching access to human, technical and knowledge resources in China is resulting in vital changes in the ways that international academic clinical research collaborations are defined and organized, in the context of a multipolarizing science world. The roles and responsibilities of the partners are shared more evenly, with one-sided exchanges becoming more difficult to institutionalize and to justify. Processes of collective financing and joint innovation inevitably sit alongside re-articulations of patterns of labor division, decision-making, benefit-sharing, profit-sharing, and revised forms of ownership regarding inventions and research data. For now, however, these claims should be treated as hypothetical, rather than confirmed facts. After all, this argument has been derived from one single case study – on the China SCI Net – therefore extrapolations to a more general level should be met with caution, until such point as additional empirical research tests this argument in other cases of international academic clinical research collaborations

The patterns of exchange and resource mobilization from within and between the involved center regions

As argued in Chapters III and VIII, the availability of financial, technical and infrastructural resources within China for an international joint project like the China SCI Net clearly reflects the increasing scientific and economic significance of China, and the country's ongoing transition from a production society to an innovation society. The acquisition of financial, technical and knowledge resources from within the evolving science-pole of China epitomizes the evolving possibilities that emerge for academic research collaborations in the context of a multi-polarizing science world. Analytical distinctions between processes of "intellectual creation", as related to developed countries, and "technical stewardship", as related to developing countries, are becoming increasingly difficult. Indeed, in the context of the current trend toward scientific and economic multipolarization, geographic concepts of "developed" and "developing" countries also become more and more complex and problematic.

I will now concentrate on the specific flows and exchanges on which the operation of the Network is based. A first order of exchange concerns the resources that are made available in the context of the organization's clinical trials, from within associated institutions in China. As shown in Chapter III, these comprise access to SCI patients, technological resources, scientific innovations, experience in unprecedented surgical and cell transplant techniques, clinical facilities, sufficient numbers of medical specialists and hospital staff, as well as access to finance. The availability of these resources, as suggested in Chapter III, has a strongly enabling effect, as seen in the case of the China SCI Net, and allows for the organization of a research project and infrastructure which would have been much more difficult and considerably more expensive in the USA. Access to patients for the Network's clinical trials was relatively simple in China for a number of reasons; these were structural differences relating to larger population sizes, socio-economic differences and disparities in national healthcare arrangements.

Access to SCI patients and the availability of technical, ideational and clinical resources from within the science pole China, and their integration and flow in a trans-national research economy, is based on a clearly specified set of return flows and reciprocal exchanges from the side of the leadership level of the China SCI Net. On the one hand, as reported in Chapter VII, participation in the Network occurs alongside the gradual integration of participating institutions into the international system of high-profile science. This opens up opportunities for the publication of papers in the major academic medical journals, for the registration of medicinal approaches developed in China by overseas drug regulatory authorities, for future collaborations with US researchers and pharmaceutical companies, for instance, and for a rise in prestige and status on the domestic research scene. Motivations to participate in the network and to offer expertise, know-how, finance and forms of social and technical capital, are based on the assumption of long-term positive changes and improvements in local research and care conditions in China; it was widely expected that such improvements would benefit researchers, patients, and SCI research on a general level. These benefits and reciprocal exchanges involve installing a standardized multicenter clinical research infrastructure that can be used for the development of domestic medical innovations, training in evidence-based medicine (EBM) and clinical trial methodology, rapid access to new treatments and rehabilitation approaches for people with SCI in China; they also involve introducing a

higher standard and level of systematization for clinical trials in the field of cell-transplantation medicine.

Summary

The findings presented here are significant. International clinical research has for many years involved geographically bound hierarchies between the sponsors, intellectual creators and facilitating technicians of the research. In the case of the China SCI Net, these boundaries are in significant respects transcended. A form of trans-national clinical research organization may be taking shape here, which in important regards resembles academic clinical-research partnerships within developed countries. I contend, in this respect, that these organizational changes are intrinsically linked with the current dynamic of global scientific multipolarization. The increasing availability of funding in China, high-end technology, dependable clinical infrastructures, and a rich pool of clinical experience and competent staff, is resulting in new socio-economic demands, forms of joint leadership, revised patterns of benefit sharing, and more active forms of intellectual participation. In summary, my analysis of the China SCI Net suggests that the far-reaching access to human, technical and knowledge resources in the evolving science pole China, is resulting in vital changes in the ways that international academic clinical research collaborations are defined and organized. The roles and responsibilities of involved partners are shared more evenly, with one-sided exchanges more difficult to institutionalize and justify. Processes of collective financiering and joint-innovation, inevitably sit alongside re-articulations of patterns of labor division, decision-making, benefit sharing, profit sharing and revised forms of ownership regarding inventions and research data. An open question is, in this respect, whether and to what extent similar developments can be observed also in other international clinical research projects, and in the context of co-operations with institutions from evolving global scientific center regions, other than China. Further research will be required to determine whether the insights of this study can be extrapolated to a more general level.

Analytical Level III: The theoretical implications of the scientific multipolarization trend

At the third analytical level in this dissertation, I set out to explore the theoretical implications of the current move toward a multipolarizing global science system. Issues arose regarding the types of analytical tools needed to identify, map and make sense of the transformations that are associated with the evolving of new scientific center regions in the world. Are existing theoretical approaches sufficient to capture this complex global dynamic, the changing forms of partnership and activity, and the redirection of global flows, power, property and infrastructure that are occurring in the evolving ‘multipolar’ science world?

The findings of this dissertation clearly underpin the need for a critical awareness of the empirical and theoretical impact of the multipolarization trend that is gradually unfolding in the sciences. Such awareness should involve a reflective evaluation of the conceptual, methodological and ideological presumptions of existing theoretical approaches to the study of science and globalization. A central analytical concern this dissertation, was a reflective engagement with the possibilities and limitations of postcolonial approaches to the study of science and technology. Postcolonial studies of science and technology, as I showed in the Introduction, have been crucial to our understanding of both, the globalization of the sciences – and of the role of technology and science in processes of globalization. Postcolonial theory, has introduced new analytical perspectives, and important reflexive projects and insights, and has stripped off the primary fixation with science in the USA and Western Europe that has been prevalent in STS for a long time. Furthermore, it has opened a critical historical awareness that has clarified that the development of the sciences in ‘the West’ has been intrinsically bound to the colonial legacy, and that contemporary forms of exploitation, expropriation and domination can, to some extent at least, be explained as a consequence of this historical dynamic.

In the Introduction I also explained that postcolonial technoscience studies have a lot to offer the study of science and globalization, also with respect to geopolitical, economic and scientific multipolarization. The analytical themes that postcolonial theory brings to the study of science and globalization – namely,

hybridity, heterogeneity, concern with global asymmetries and the emergence of forms of contestation and resistance, together with a focus on science-as-practice – will remain of central importance to a nuanced understanding of the operation of science in a multipolarizing world system. At the same time, the preoccupation of postcolonial theory with issues of historicity, relationality and positionality – together with its concerns about reflexivity and criticality (Rizvi 2009: 109) – will continue to form crucial analytical tools in the study of science, also in the context of multipolar globalization.

As I had outlined in the Introduction, however, there are also some analytical limitations, that can be associated with the use of postcolonial approaches to the study of science and globalization in the contemporary world. A first point was that the predominant focus of postcolonial studies on the residual effects of colonialism, and the global impact of—and local responses to—more recent forms of Euro-American dominance, neglects a systematic engagement with the implications of the gradual emergence of new centers of global power. If, however, postcolonial analytical perspectives, as suggested by Anderson and Adams (2008), shall be used for the study of science and globalization at a more open and general level (i.e. beyond the impact of Euro-American forms of power), a systematic concern with the manifestations and effects of current processes of geopolitical and economic diversification will be indispensable. This is well exemplified by the case of China, which is now self-consciously seeking a place at the center of the global stage, and develops and internationally promotes its very own trajectories of modernization, civilizational power and globalization, that differ in vital respects from Euro-American blueprints, concepts and values (*cf.* Pieke 2008). The exploration of non-western knowledge systems and conceptions of modernity and development has, of course, been a central theme in postcolonial studies. A central difference is now, however, that these region-specific forms and perspectives of modernization and development start to ‘globalize’ themselves, i.e. are employed in new types of global projects, and in geographic configurations that operate independently—and often in strategic competition to—the interests of the USA and Europe. China’s increasing engagement in African societies, which combines a market-driven agenda of economic and social development, with a strategic politics of oil and natural resources, is an example.

A closely related point concerns the historical and political situatedness of postcolonial theory. Following the demise of colonialism, postcolonial studies

emerged as an indispensable critical and emancipatory political project, which aimed to deconstruct and overcome colonial assumptions, definitions and stereotypes. This high level of politicization has—for obvious and much needed reasons—anchored postcolonial theory not only into a specific historical territory but also into a concrete moral agenda, with its own forms of problematization and values, lines of ideological presumptions and critique, sets of political opposition, and objectives of social change. The practices, techniques and discourses of domination, and their trans-local responses, that postcolonial scholars have studied, moreover, have grown out of highly specific historical, cultural and geopolitical conditions. In both, Western colonialism and more recent forms of ‘neo-imperialism’, described by scholars such as Harding (2012) and Escobar (2011), we see a top-down transfer of knowledge and technology from ‘North’ to ‘South’, that has been legitimized by a discourse of ‘development’, ‘aid’ and ‘modernization’ (Escobar 1988; Ferguson 1990; Sachs 1992). As shown in a report of Apffel-Marglin and Marglin (1990), local knowledge systems have in the context of these hierarchical endeavors commonly been marginalized, or rendered amenable for capitalist utilization (Apffel-Marglin and Marglin 1990; Hayden 2003).

While top-down forms of technology and knowledge transfer continue to exist, a considerably more complex situation can currently be observed. In countries such as China, South Korea, Taiwan, Singapore, Russia and others, the engagement with ‘Western’ knowledge forms, technologies and scientific research is typically voluntary, and intensely promoted from within—not imposed from the outside. In this process, imported forms are strategically disassembled, locally transformed, merged with other knowledge practices, and developed further. These hybrid forms, and domestically derived inventions, moreover, are utilized for projects of economic development, independent innovation, and national self-strengthening. Clearly this does not apply to the poorest countries in the world, but it is valid for a larger number of countries, in particular the economic growth regions in Asia, whose domestic development strategies are typically structured around intensive investments in science and technology (NSF 2012). Whether and where concepts of ‘foreign’ and ‘domestic’ start and end in light of the complex, trans-local joint production of scientific forms, escalating interdependencies and multi-directional flows of knowledge, is increasingly difficult to say. The building of scientific capacity in the emerging economic and geopolitical center regions in the world, moreover, has resulted in a scenario of more intense global competition for innovations and access to talent, capital and markets

(Scholtissek 2008). This is exemplified also by the sizeable increase in outward FDIs from the emerging economies in recent years (Sauvant, Maschek and McAllister 2010), and the growing number of the merging and acquisition of companies in the USA and Europe, by companies from other world regions (DeCarlo 2012). Together, these processes have significant implications for the production of science in the historically longer-established scientific centers of the Triad regions (Royal Society 2011), and it is now widely stated that the growing science base in China and other countries, form a challenge to the viability of the knowledge economies in these regions (Bound et al. 2013).

In sum, the present situation differs from the historical conditions and antecedents of the decades following the end of colonialism in some fundamental aspects. While the current world system is—in many regards—still dominated by ‘the West’, particularly by the USA, the partly declining influence of European societies, and the emergence of new centers of economic, political and scientific significance, have given rise to a fundamentally altered global situation, that requires careful reflection. These changes do not mean, of course, that postcolonial studies have become outdated, or that the impact of colonial or other forms of political and economic control have ceased to play a vital role in the present—far from it. It means, however, that—as a result of the historical and political situatedness of postcolonial studies—the application of postcolonial theory and insights to new historical contexts, must be combined with a critical appraisal of its methods and concepts, and the underlying presumptions, values and political agendas on which they are based. This requires a nuanced awareness of the current historical and geopolitical transformations that drive the formation of global scientific centers outside of Europe and Northern America, and a nuanced understanding of the local, regional and global implications of these processes. It requires too, a careful exploration of the ideological underpinnings and political objectives that underlie postcolonial studies. To what extent, for instance, and in which ways, can the critical agenda of postcolonial science and technology studies (that has evolved in correspondence to the hegemonic role of Europe and later the US) be transferred to the practice and politics of science, development and globalization in other global center regions? Can the striving for economic growth and technoscientific advancements in other world parts really be measured with the same criteria, and along the same parameters of analysis, criticism and moral judgment, that have been applied to the expansion of Europe and the USA?

This dissertation underpins the need for such critical questioning. Some of its findings sit uneasily with several of the ontological assumptions that are frequently associated with post-colonial science and globalization theory. The forms of scientific collaboration, exchange, and benefit sharing to which this dissertation has referred, run in many regards counter to notions of subalternity, unequal exchange and exploitation, that are often taken for granted in post-colonial studies, as inevitable consequences of the histories and political-economic relations that shape contemporary global scientific flows. As pointed out in Part II of this Conclusion, the ongoing changes, increasing opportunities, and availability of new types of resources, funding and high-level technological infrastructures in China, seem to result in significant transformations of the ways in which international clinical research collaborations are organized, initiated and justified. Access to these resources is resulting in new socio-economic demands, forms of joint-leadership, and revised patterns of transnational research collaboration, in which geographical hierarchies are partially transcending, new practices for socio-economic and intellectual participation emerge, and lop-sided exchanges are increasingly difficult to institutionalize and legitimize. These changes do not mean, of course, that under the influence of global scientific multipolarization, asymmetric exchanges come to an end. It means, however, as I suggest here, that the increasing availability of funding, expertise, knowledge and technological infrastructures in the evolving scientific center regions in the world, is about to result in important re-articulations of the organizational forms and the kinds of transactions and subjectivities that characterize international research partnerships. A critical engagement with the global role of science and power in the West remains in this respect vital. However, the fact that the production of science is now increasingly marked by multiple vectors and plural geopolitical force fields means clearly, that many of the forms of subjectification, utilization, peripheralization and dependency that are likely to emerge in the context of the evolving multi-polar scientific world system will be related to the activities of global spheres other than North America, Europe, or Japan. This reconfiguration of flows, global asymmetries and changing forms of inequality will remain an important field of analysis in science and technology studies.

Bibliography

- Abraham, I. (2006) The Contradictory Spaces of Postcolonial Techno-science, *Economic and Political Weekly*, 21 January 2006, 210-219.
- Ackerman, T. (2012). Medical board's proposed stem-cell policy under fire. April 8, 2012, The Houston Chronicle, URL: <http://www.chron.com/news/houston-texas/article/Medical-board-s-proposed-stem-cell-policy-under-3467573.php>, (last accessed September 26, 2012).
- Anderson, Warwick. (2002). "Postcolonial Technoscience." *Social Studies of Science* 32:643-658.
- Anderson, W., and V. Adams (2007). Pramoedya's Chickens: Postcolonial Studies of Technoscience, in E.J Hackett, O. Amsterdamska, M. Lynch and J. Wajeman (eds), *The Handbook of Science and Technology Studies*, 3rd edn, Cambridge, MA: MIT Press, 2007, pp 181-207.
- Anderson, W. (2009). From subjugated knowledge to conjugated subjects: science and globalisation, or postcolonial studies of science?, *Postcolonial Studies*, 12:4, 389-400.
- Appadurai, A. (1991). Global ethnoscaples: notes and queries for a transnational anthropology. In R.G. Fox (ed.) *Recapturing Anthropology*. Santa Fe: School of American Research Press.
- Appadurai, A. (1996). *Modernity at Large: Cultural Dimensions of Globalization*, Minneapolis: University of Minnesota Press.
- Apffel-Marglin, F., and S. Marglin (1990). *Dominating Knowledge: Development, Culture, and Resistance*, Oxford: Clarendon Press.
- Arrow, K. J., et al. (2008). To the Honorable Barack H. Obama, President-Elect of the United States, <http://michaelwest.org/testimony/totheHonorableBarackObama.pdf>, (last accessed August 27, 2012).
- Baker, D., and S. Jackson (2007) Review Article: Models of Multiple Sclerosis. *Journal for Advances in Clinical Neuroscience and Rehabilitation*, 6(6), 10-12.

- Barry, A. (2006). Technological Zones. *European Journal of Social Theory*, 9(2), 239-253
- Bender W., Hauskeller, C. and A. Manzei (2005). *Crossing Borders: Cultural, Religious and Political Differences Concerning Stem Cell Research*. Munster: Agenda Verlag
- Bharadwaj, A. (2005). Cultures of embryonic stem cell research in India. In: W. Bender, C. Hauskeller and A. Manzei (eds), *Crossing borders: cultural, religious and political differences concerning stem cell research*, Munster: Agenda Verlag: 325-41.
- Bharadwaj, A. (2012a). Enculturating Cells: The Anthropology, Substance, and Science of Stem Cells. *Annual Review of Anthropology*, 41: 303-317.
- Bharadwaj, A. (2012b). *Conceptions: Infertility and Procreative Modernity in India*. London: Berghahn Books.
- Bharadwaj, A. (2013). Ethic of consensibility, subaltern ethicality: The clinical application of embryonic stem cells in India. *BioSocieties*, 8(1): 25-40.
- Bharadwaj A, and Glasner P. (2009). *Local Cells, Global Science: The Rise of Embryonic Stem Cell Research in India*. London: Routledge.
- BBC Panorama (2009). Stem cells and miracles. TV documentary. URL (accessed July 5 2011): http://news.bbc.co.uk/panorama/hi/front_page/newsid_8040000/8040872.stm
- Behan. P.O., Chaudhuri, A., and B.O. Roep (2002). The pathogenesis of Multiple Sclerosis revisited. *Journal of the Royal College of Physicians*, 32, 244-265.
- Blumer, H. (1954). What's wrong with social theory?, *American Sociological Review*, 19(1), 3-10.
- Bowker, G. C., and S. L. Star. 1999. *Sorting Things Out*. Cambridge, MA: MIT Press.
- Bound, K. et al. (2013) China's Absorptive State: Research, innovation and the prospects for UK-China collaboration, Nesta, URL: <http://www.nesta.org.uk/publications/chinas-absorptive-state-innovation-and-research-china>

Brennan, P. (2011). Geron Corp. shuts down world's first stem cell trial. OC Science, URL: <http://sciencedude.ocregister.com/2011/11/16/geron-corp-shuts-down-worlds-first-stem-cell-trial/159883/>, (last accessed August 26, 2012).

Brown, N., (2007). Shifting tenses: reconnecting regimes of truth hope? *Configurations*, 13(3): 331–355.

Buergi, B. R. (2012). Buying In, Edging Out: Perspectives on Contemporary Global Health Financing among Thailand's Malaria Community. *Science Technology and Society*, 17(1): 123-142.

BW Panel (2009) Bedford SCI Workshop: Faculty Panel Discussion – what are the barriers to cure?. Video of Faculty Panel Discussion, *Spinal Cord Injury – what are the barriers to cure?, Workshop*, University of Georgia, April 4, 2009, URL: <http://www.spinalcordworkshop.org/portfolio-type/2009-faculty-panel-discussion/>, (last accessed August 26, 2012).

CCTV (2002). Hope for the cure of Spinal Cord Injury. Transcript of TV program (in Chinese). CCTV 10, February 4 2002. Program name: Jiangkang Zhilu [The Healthy Way]. URL (accessed August 12 2011): <http://www.cctv.com/life/jiankangzhilu/index020204.html>

CCTV (2003). Chinese biotechnology moves further to the next level. Transcript of TV program (in Chinese). CCTV 4, February 20 2003. Program name: Zhongguo Baodao [China Report]. URL (accessed August 12 2011): <http://www.cctv.com/lm/522/more41.html>

CCTV (2007). A 38 year old paraplegic relearns to walk after calamity caused by collapsing building. TV program. CCTV 10, January 19 2007. Program name: Jiangkang Zhilu [The Healthy Way]. URL (accessed August 12 2011): <http://discovery.cctv.com/20070119/104142.shtml>

CCTV (2010). Stem cell transplantation therapy expert: YANG Xiaofeng. TV program. CCTV 10, June 11 2010. Program name: Keji Renwu [Science & Technology Life]. URL (accessed August 12 2011): <http://www.ihealth.org.cn/chapter-1087-2.html>

Chakma, J., Sammut, S., and A. Agrawal (2013). Life sciences venture capital in emerging markets. *Nature biotechnology*, 31(3): 195-201.

Chen, D.F. (2010). The application of stem cell transplantation in acute and sub-acute liver failure. Conference Presentation (unpublished). Workshop of Frontiers Cell Therapy Research, Tianjin, September 24 2010.

Chen, H. (2009). Stem cell governance in China: from bench to bedside?. *New Genetics and Society*, 28(3), 267–282.

Chen, L., *et al.* (2010). Intracranial transplant of olfactory ensheathing cells in children and adolescents with cerebral palsy: A randomized controlled clinical trial. *Cell Transplantation*, 19(2), 185–191.

Chen, S., *et al.* (2004). Effect on left ventricular function of intracoronary transplantation of autologous bone marrow mesenchymal stem cell in patients with acute myocardial infarction. *American Journal of Cardiology*, 94: 92–95.

Chen, Z. (2011). National Plan on Translational Medicine in China: Promoting Health Care Reform and Improving People's Health. E-booklet: Selected Presentations from the 2011 Sino-American Symposium on Clinical and Translational Medicine, June 24, 2011, pp. 7, URL: http://www.sciencemag.org/site/products/2011_Sino-American_Symposium_booklet.pdf, (last accessed August 26, 2012).

Chen, H.D., and H. Gottweis (2011). Stem Cell Treatments in China: Rethinking the patient role in the global bio-economy. Bioethics, Early View Online Version, DOI: 10.1111/j.1467-8519.2011.01929.x, 1-14.

Chen, H.D., and G. Clancey (2013) Special Issue: Asian Biopoleis–Biomedical Research in ‘The Asian Century’, *Science, Technology and Society*, 18(3), 267-420.

China Daily (2007). Former SFDA chief executed for corruption, China Daily, July 10, 2007, URL: http://www.chinadaily.com.cn/china/2007-07/10/content_5424937.htm, (last accessed August 26, 2012).

ChinaSCINet (2008). Newsletter April 2008. URL: http://www.chinascinet.org/downloads/newsletter/newsletter_apr08.pdf, (last accessed August 26, 2012)

Clancey, G. and C. Graham (2013). Subject Issue on Asian Biopoleis: Practice, Place, and

Life, *East Asian Science and Technology Studies*, 7(1): 1-173.

Cooper, M. (2008a). Experimental Labour: Offshoring Clinical Trials to China. *EASTS East Asian Science, Technology and Society: An International Journal*, 2(1), 73-92.

Cooper, M. (2008b). *Life as Surplus: Biotechnology and Capitalism in the Neoliberal Era*. Seattle, WA: Washington University Press

Coopmans, C., Graham, C., Gelfert, A., and G. Clancey (2012) Special Issue: Technologies, Lives and Futures in Asia. *Science, Technology and Society*, 17(1): 1 – 164.

Cribb, A., et al. (2008). Towards the applied: the construction of ethical positions in stem cell translational research. *Medicine, Health Care and Philosophy*, 11: 351-361.

CURE (2009). Medical Research Council: CURE Committee Report. URL: <http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC006303> (accessed September 27, 2012)

Cyranoski, D. (2006). Patients warned about unproven spinal surgery. *Nature*, 440, 13.

Cyranoski, D. (2009). Stem-cell therapy faces more scrutiny in China: but regulations remain unclear for companies that supply treatments. *Nature*, 459, 146–147.

Cyranoski, D. (2012). China's stem cell rules go unheeded. *Nature*, 484, 149-150.

DeCarlo, S. (2012). A Regional Look At The Forbes Global 2000, Forbes, <http://www.forbes.com/sites/scottdecarlo/2012/04/18/a-regional-look-at-the-forbes-global-2000-3/> (accessed August 21, 2012)

De Vasconcelos, A. (2008). "Multilateralising Multipolarity", in Giovanni Grevi and Alvaro de Vasconcelos (ed.), *Partnerships for Effective Multilateralism: EU Relations with Brazil, China, India and Russia*. Chaillot Paper 109, Paris: EU Institute for Security Studies, May 2008, p. 24.

Dickenson, D. L. (2006). The lady vanishes: what's missing from the stem cell debate. *Journal of Bioethical Inquiry*, 3(1-2): 43-54.

Ding, J.X., *et al.* (2011). From imitation to innovation: a study of China's drug R&D and relevant national policies. *Journal of Technol. Management Innovation*, 6(2), 1-13.

Dobkin, B.H., Curt, A., & Guest, J. (2006). Cellular transplants in China: observational study from the largest human experiment in chronic spinal cord injury. *Neurorehabil. Neural Repair*, 20, 5–14.

DoH [Department of Health Hong Kong] (2010). Classification Rules for Medical Devices. Issued January 4, 2010. URL: http://www.emergogroup.com/files/hong_kong_tr003e_en.pdf, (last accessed August 26, 2012).

DoH (2008). World Medical Association Declaration of Helsinki. URL (accessed August 12 2011): <http://www.wma.net/en/30publications/10policies/b3/>

DOUGLAS-JONES, R. (2012) *Locating Ethics: capacity building, ethics review and research governance across Asia*. Doctoral thesis, Durham University.

Engel, M. (2008). Drug Development in China: Opportunities and Challenges – A clinical trial perspective. URL: www.burrillandco.com/content/content_files/MarkEngel11606.ppt, (last accessed August 27, 2012).

Epstein, S. (1996). *Impure Science: AIDS, Activism, and the Politics of Knowledge*. Berkeley: University of California Press.

Epstein, S. (2008). Patient groups and health movements. In: *Handbook of Science and Technology Studies*, E. Hackett, O. Amsterdamska, M. Lynch, and J. Wajcman (eds.), Cambridge, MA: MIT Press, pp. 499–540.

Escobar, A. (1988). Power and visibility: Development and the invention and management of the Third World. *Cultural Anthropology*, 3(4): 428-443.

Escobar, A. (2011). *Encountering Development: The Making and Unmaking of the Third World*. Princeton: Princeton University Press.

Ezekiel, J. (2011). *Oxford Handbook of Clinical Ethics*, Oxford /New York: Oxford University Press.

EMA (2012). Reflections paper on classification of advanced therapy medicinal products. URL:http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500126681.pdf (accessed September, 2012):

Fallone, E. (2011). Funding Stem Cell Research: The convergence of science, religion and politics in the formation of public health policy. Marquette University Law School, Research Paper Series, URL: http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1747802, (last accessed August 27, 2012).

Faulkner, A. (2009). Regulatory policy innovation. *Research Policy*, 38, 637-646.

Federal Register/Vol. 73, No. 82/Monday, April 28, 2008/Rules and Regulations
FDA (2008) Human Subject Protection; Foreign Clinical Studies Not Conducted Under an Investigational New Drug Application, *Federal Register*, 73(82), pp. 22800-22816, URL: <http://www.gpo.gov/fdsys/pkg/FR-2008-04-28/pdf/E8-9200.pdf> (last accessed 20.01.2014).

Ferguson, J (1990) The Anti-Politics Machine: "Development," Depoliticization, and Bureaucratic Power in Lesotho. Cambridge: Cambridge University Press.

Fischer-Tiné, H. (2011) Postcolonial Studies, European History Online, <http://www.ieg-ego.eu/en/threads/europe-and-the-world/postcolonial-studies/harald-fischer-tine-postcolonial-studies>, (last accessed August 21, 2012)

Franklin S. (2003) Ethical biocapital: new strategies of cell culture. See Franklin and Lock 2003b, pp. 97–128

Franklin, S. (2006). Embryonic economies: the double reproductive value of stem cells. *BioSocieties*, 1(1): 71.

Franklin, S., and M. Lock (Eds.). (2003). *Remaking life & death: toward an anthropology of the biosciences*. Santa Fe, NM: School of American Research Press.

Franklin, S., and L. Kaftantzi (2009). Industry in the middle: Interview with Intercytex Founder and CSO, Dr Paul Kemp. *Science as Culture*, 17(4): 449-647.

Gallin, J. (2011). Report on 2011 Sino- American Symposium on Clinical and Translational Medicine. E-booklet: Selected Presentations from the 2011 Sino-American Symposium on

Clinical and Translational Medicine, June 24, 2011, pp. 4, URL: http://www.sciencemag.org/site/products/2011_Sino-American_Symposium_booklet.pdf, (last accessed August 26, 2012).

Geeraerts, G. (2011). China, the EU and the New Multipolarity. *European Review*, Vol. 19, No. 1, 57–67

Geesink, I., Prainsack, B., and Franklin, S. (2008). Stem cell stories 1998–2008. *Science as Culture*, 17(1): 1–11.

GAAN [Goldsea Asian American News] (2013) South-Korea leads in commercial stem cell therapies, 25.01.2013, URL: <http://goldsea.com/Text/index.php?id=12433> (last accessed 20.01.2014).

Gong, W., *et al.* (2012). Banking Human Umbilical Cord-Derived Mesenchymal Stromal Cells for Clinical Use. *Cell Transplantation*, 21, 207–216.

Gottweis H., Salter B., and C. Waldby (2008). *The Global Politics of Stem Cell Research: Regenerative Medicine in Transformation*. London: Palgrave, 2008.

Gottweis, H. (2009) Special Issue: BIOPOLITICS IN ASIA, *New Genetics and Society*, 28(3): 201–300.

Gramsci, Antonio (1992). Cultural Hegemony, in: J. A. Buttigieg (ed.) *Prison notebooks*. New York City: Columbia University Press, 233–38

Gu, Y.Q., *et al.* (2003). Treatment of diabetic foot with autologous bone marrow cells: a case report. *Zhong Guo Shi Yong Wai Ke Za Zhi* [Chinese Journal of Practical Surgery], 23, 670.

Gupta, J. A. (2011). Exploring appropriation of “surplus” ova and embryos in Indian IVF clinics. *New Genetics and Society*, 30(2): 167–180.

HA [Hospital Authority Hong Kong] (2010). Review on Clinical Governance in Hospital Authority. URL: http://www.ha.org.hk/haho/ho/cad_bnc/AOM-P810.pdf, (last accessed August 26, 2012).

Harding, S. (1994). Is science multicultural? Challenges, resources, opportunities,

Configurations, 2, pp. 301 – 327.

Harding, S. (1998). *Is Science Multicultural? Postcolonialisms, Feminisms, and Epistemologies*, Bloomington and Indianapolis: Indiana University Press.

Harding, S. (2009): Postcolonial and feminist philosophies of science and technology: convergences and dissonances, *Postcolonial Studies*, 12:4, 401-421

Hayden, C. (2003) *When Nature Goes Public: The Making and Unmaking of Bioprospecting in Mexico*, Princeton: Princeton University Press.

Herolf, G. (2011) Multipolar World at the End of the First Decade of the 21st Century: How about Europe?. *Central European Journal of Public Policy*, 5(1), 4-22.

HKU SCI Fund (2005a) Hong Kong University SCI Fund Newsletter. URL: http://www.chinascinet.org/downloads/newsletter/newsletter_oct_no1.pdf (last accessed August 26, 2012)

HKU SCI Fund (2005b) Hong Kong University SCI Fund Press Release: HKU – SCI Fund Global Advancement in the Treatment of Spinal Cord Injury. URL: <http://www.hkscifund.org/downloads/Press%20Conference/Dec05/051216press-releaseeng.pdf> (last accessed August 26, 2012)

Hu, C.L., *et al.* (2010). Ethical guidelines for the clinical research and application of stem cells. URL (accessed August 11 2011): <http://wenku.baidu.com/view/f52fd4886529647d27285223.html>

Huang, H., *et al.* (2003). Influence of patients' age on functional recovery after transplantation of olfactory ensheathing cells into injured spinal cord injury. *Chinese Medical Journal (English)*, 116(10), 1488–1491.

Huang, H.Y., *et al.* (2006). Influence factors for functional improvement after olfactory ensheathing cell transplantation for chronic spinal cord injury. *Zhongguo XiuFu Chongjian Waike Zazhi* [Chinese Journal of Surgical Repair and Reconstruction], 20(4), 434–438.

Huang, H.Y., *et al.* (2008). Fetal olfactory ensheathing cells transplantation in amyotrophic lateral sclerosis patients: A controlled pilot study. *Clinical Transplantation*, 22(6), 710–718.

Huang, H.Y. (2009). Olfactory ensheathing cells transplantation for central nervous system diseases in 1255 patients. *Zhongguo Xiufu Chongjian Waike Zazhi* [Chinese Journal of Surgical Repair and Reconstruction], 23(1), 14–20.

Huang, H.Y. (2010). Neurorestoratology, a distinct discipline and a new era: A brief introduction to the First IANR Section. *Cell Transplantation*, 19(2), 129-31.

Huang, H.Y., Chen, L., & Sanberg, P. (2010). Cell therapy from bench to bedside translation in CNS neurorestoratology era. *Cell Medicine, Part B of Cell Transplantation*, 1, 15–46.

Huang, Q. (2007). Fact Inquiry of Stem Cells: “Gambling” on the hospital bed. *New People’s Weekly*, September 20 2007. URL (accessed August 11 2011): <http://scitech.people.com.cn/GB/6290699.html>

Hyun, I.S. (2010). Allowing Room for Innovative Stem Cell-Based Therapies Outside Clinical Trials: Ethical and Practical Challenges. *Journal of Law, Medicine, and Ethics*, 38(2), 277-85.

IANR (2009). Beijing Declaration of International Association of Neurorestoratology. *Cell Transplantation*, 18(4), 487.

IANR (2010). Introduction of International Association of Neurorestoratology. URL (accessed August 12 2011): <http://www.ianr.org.cn/english/jianjie.asp?id=66,131>

IANR (2011). Scientific Program: IANR IV and 8th GCNN Conference April 27-30, Amman, Jordan. URL (accessed August 12 2011): <http://www.ianr.org.cn/english/innn.asp?id=1274>

IBTV (2010). IBTV Show II: DR WISE YOUNG. URL: <http://blip.tv/professirx/ibtv-show-ii-dr-wise-young-3515377> (last accessed August 26, 2012)

ISBC (2010). International Science and Bioethics Collaborations Project: End of Award Conference, Cambridge, <http://www.isbc-project.org.uk/wp-content/uploads/2010/08/FULL-COLLOQUIUM-PROGRAMME-FOR-WEB.pdf>, (last accessed August 21, 2012)

ISSCR (2008). ISSCR Guidelines for the Clinical Translation of Stem Cells, URL (accessed July 15 2012): <http://www.isscr.org/GuidelinesforClinicalTranslation/2480.htm>

Jia, H.P. (2007). China drugs agency must play by new rules, Science and Development Network, URL: <http://www.scidev.net/en/news/china-drugs-agency-must-play-by-new-rules.html>, (last accessed August 26, 2012).

Jiang, R.H., et al. (2011). Transplantation of placenta-derived mesenchymal stem cells in type 2 diabetes: a pilot study. *Frontiers of Medicine*, 5(1), 94–100.

Kato M, and M. Sleeboom-Faulkner (2011). Meanings of the embryo in Japan: narratives of IVF experience and embryo ownership. *Sociology of Health and Illness*, 33(3): 434–47

Kaufman, S. R., and Morgan, L. M. (2005). The anthropology of the beginnings and ends of life. *Annual Review of Anthropology*, 34: 317-341.

Keating, P., and A. Cambrosio (2012). *Cancer on Trial: Oncology as a new Style of Practice*. Chicago and London: Chicago University Press.

Keirstead, H., et al. (2005). Human Embryonic Stem Cell-Derived Oligodendrocyte Progenitor Cell Transplants Remyelinate and Restore Locomotion after Spinal Cord Injury. *The Journal of Neuroscience*, 25(19), 4694 – 4705.

Keirstead, H. (2008). Challenges to the clinical viability of stem cell technology. Video of conference presentation, *Spinal Cord Injury – what are the barriers to cure?*, Workshop, Bedford Massachusetts, March 29, 2008, URL: <http://www.spinalcordworkshop.org/portfolio-type/hans-keirstead-phd-challenges-to-the-clinical-viability-of-stem-cell-technologies/>, (last accessed August

Kent, J. (2012). *Regenerating bodies: tissue and cell therapies in the twenty-first century*. London and New York: Routledge.

Kissling, A. (2008). 2008 Spinal Cord Workshop Panel Discussion. Video of conference presentation, *Spinal Cord Injury – what are the barriers to cure?*, Workshop, Bedford Massachusetts, March 29, 2008, URL: <http://www.spinalcordworkshop.org/portfolio-type/2008-spinal-cord-workshop-panel-discussion-part-2-of-2/>, (last accessed August 26, 2012)

Kissling, A. (2009). Introduction: What are the Barriers to Cure. *Workshop*, University of Georgia, April 4, 2009, URL: <http://www.spinalcordworkshop.org/portfolio-type/ann-a-kiessling-phd-2009-spinal-cord-workshop-introduction/>, (last accessed August 27, 2012).

Kitzinger, J. (2008). Questioning hype, rescuing hope? The Hwang stem cell scandal and the reassertion of hopeful horizons, *Science as Culture*, 17(4): 417–34

Kitzinger, J., and C. Williams (2005). Forecasting science futures: legitimizing hope and calming fears in the embryo stem cell debate, *Sociology of Science and Medicine*, 61: 731–40

Kitzinger, J., Williams, C., and L. Henderson (2007). Science, media and society: the framing of bioethical debates around embryonic stem cell research between 2000 and 2005. In: *New Genetics, New Social Formations*, P. Glasner, P. Atkinson, and H. Greenslade (eds.), London: Routledge, pp. 204–30.

Kleitman, N. (2008). Translating SCI Research: What are the challenges?. Video of conference presentation, *Spinal Cord Injury – what are the barriers to cure?*, *Workshop*, Bedford Massachusetts, March 29, 2008, URL: <http://www.spinalcordworkshop.org/portfolio-type/naomi-kleitman-phd-translating-sci-research-what-are-the-challenges/>, (last accessed August 26, 2012)

Knoepfler, P. (2012). Celltex responds in press release: FDA problems result of their Texas lab being run by Koreans, not Texans, Knoepfler Lab Stem Cell Blog, URL: <http://www.ipscell.com/2012/06/celltex-responds-in-press-release-fda-problems-result-of-their-texas-lab-being-run-by-koreans-not-texans/>, (last accessed September 26, 2012).

Konrad, M. (2007). International biodiplomacy and global ethical forms: Relations of critique between public anthropology and science in society. *Anthropological Quarterly*, 80(2): 325–353.

Konrad, M. (2012). *Collaborators Collaborating: Counterparts in Anthropological Knowledge and International Research Relations*. Berghahn Books.

Krucken, G. and G.S. Drori (2009). *World Society: The Writings of John W. Meyer*, Oxford: Oxford University Press.

Kurlantzik, J. (2009). How China Is Capitalizing on the Economic Crisis. *Time Magazine*,

April 13 2009.

Lassiter, L. E. (2008) Editor's Introduction. *Collaborative Anthropologies*, 1, pp. vii-xii

Leung, G. (2010). Umbilical Cord Blood Stem Cell Transplantation Therapy for Chronic Spinal Cord Injury. [Qidaixie xibao yizhizhiliao manxing jisui sunshang], Public Lecture China SCI Net, Hong Kong, August 29 2010.

Leydesdorff, L., Carley, S., and I. Rafols (2013). Global Maps of Science based on the new Web-of-Science Categories. *Scientometrics*, 94(2): 589-593.

Li, J.J., et al. (2004). 2002 Nian Beijing shi Jisui Sunshan Fabinglü Diaocha [Spinal cord injuries in Beijing : a epidemiological survey in 2002], *Zhongguo Kangfu Lilun yu Shijian*. Chinese Journal for Health Ethics and Practice, 23, 453-459.

Li, J.J. (2005). Rehabilitation Management of Spinal Cord Injury in China Present Situation: Prospects for 21st Century, Conference Presentation, International Spinal Cord Injury Treatments & Trials (ISCITT) Symposium, Hong Kong, 17 December 2012.

Li, J.J. (2011). GCP implementation status in China. Presentation State Food and Drug Administration, URL (accessed August 13 2011):
http://www.pmda.go.jp/english/past/2010_sympto/file/201005_04.pdf

Li, J.M., et al. (2010). Human mesenchymal stem cell transplantation protects against cerebral ischemic injury. *Brain Research*, 1334, 65-72.

Li, Y.I., Su, X., & Wang, L. (2008). Evidence-Based Medicine in China. *Value in Health*, 11 (Supplement 1), 156-8.

Li, Z., et al. (2007). The clinical study of autologous peripheral blood stem cell transplantation by intracoronary infusion in patients with acute myocardial infarction. *International Journal of Cardiology*, 115, 52-56.

Lo, B. (1992). Ethical dilemmas in HIV infection: What have we learned?. *Journal of Law, Medicine and Ethics*, 20(12), 92-103.

Liao, L.M., & Zhao, C.H. (2008). An overview of stem cell based clinical trials in China. *Stem Cells and Development*, 17, 613-18.

Lin, S.Z. (2012) Study of Purified Umbilical Cord Blood CD34+ Stem Cell on Chronic Ischemic Stroke. ClinicalTrials.gov, URL: <http://clinicaltrials.gov/ct2/show/NCT01438593>, (last accessed August 26, 2012).

Liu, H.Z., & Xing, R.J. (2002). Neural stem cell transplantation: cerebral palsy successful, *Xinhua News Agency*, January 16 2002.

Luk, K. (2005). Orthopedic Management for the Chronic Spinal Cord Injured. Conference Presentation, International Spinal Cord Injury Treatments & Trials (ISCITT) Symposium, Hong Kong, 17 December 2012, URL: http://www.iscitt.org/iscitt1/051217/Session1A_partI/English%20Version/msh.htm, (last accessed August 26, 2012).

McMahon, D., and H. Thorsteinsdóttir (2013). Pursuing endogenous high-tech innovation in developing countries: A look at regenerative medicine innovation in Brazil, China and India. *Research Policy*, 42 (4): 965-974.

Meyer, J. (2007). Globalization: Theory and Trends." *International Journal of Comparative Sociology*, 48, 4-5: 261-273. 2007

NSF National Science Foundation (2012). Science and Engineering Indicators 2012. <http://www.nsf.gov/statistics/seind12/pdf/seind12.pdf> (accessed August 21, 2012)

McNeil, M. (2005). Introduction (to special issue): Postcolonial Technoscience. *Science as Culture*, 14(2): 105-112.

Martin, P., Brown, N., and Kraft, A. (2008). From bedside to bench? Communities of promise, translational research and the making of blood stem cells. *Science as Culture*, 17(1): 29-41.

Massey, M. (2009) Responsibilities over distance", Interview chapter in *Globalizing the Research Imagination*, eds, Kenway, J. and Fahey, J., Oxford: Routledge, New York: Taylor & Francis Inc., 2009, pp.73-85.

MD Biosciences (2010). The Experimental Autoimmune Encephalomyelitis (EAE) model is associated with all Seven FDA Approved MS Drugs and Fingolimod, MD Biosciences Preclinical Drug Discovery Blog, URL:

<http://www.mdbiosciences.com/blog/?Tag=Multiple%20Sclerosis>, (accessed September 3, 2012)

MDACS [Medical Device Application Control System, Hong Kong] (2010). Guidance Notes for Applicants of the Certificate for Clinical Trial on Medical Device - Annex III: Clinical Trial Check List. URL: http://www.mdco.gov.hk/english/mdacs/mdacs_gn/files/dgn_eng.pdf, (accessed September 3, 2012).

MOH (2012). Guanyu Fazhan Gan Xibao Linchuang Yanjiu he Yingyong zicha ziji gongzuo de tongzhi [Notification on Self-Evaluation and Self-Correction Work regarding the Development of Stem Cell Clinical Research and Applications], MOH, China, 6 January 2012, URL: <http://www.moh.gov.cn/publicfiles/business/htmlfiles/mohkjjys/s3582/201201/53890.htm>, (last accessed August 26, 2012).

Mykhalovskiy, E, and Weir, L. (2004). The problem of evidence-based medicine: directions for social science. *Social Science & Medicine*, 59, 1059–69.

Nature (2012). Editorial: Buyer Beware. *Nature*, 484, 141.

Neuralstem (2008). Neuralstem Collaborates with Hospital in Taiwan to Develop Additional ALS Stem Cell Clinical Trials, Neuralstem Inc. Investor Information, URL: http://investor.neuralstem.com/phoenix.zhtml?c=203908&p=irol-newsArticle_print&ID=1231450&highlight=, (last accessed August 26, 2012)

NIH (2011). National Institute of Health FY 2011 President's Budget. URL: <http://officeofbudget.od.nih.gov/pdfs/FY11/Summary%20of%20the%20FY%202011%20Presidents%20Budget.pdf>, (last accessed August 26, 2012).

NMDP (2012). National Marrow Donor Program: Understanding FDA Cord Blood Regulation, URL: http://marrow.org/HD/Payor/NP00507_Payor_Guide-FDA_CordBlood.aspx, (last accessed August 27, 2012).

OECD [Organisation for Economic Co-operation and Development] (2011). OECD Global Science Forum: Facilitating International Cooperation in Non-Commercial Clinical Trials, URL: <http://www.oecd.org/science/scienceandtechnologypolicy/49344626.pdf>, (accessed September 27).

Ognibene, F. P., et al. (2011). Global Outreach in Clinical Research by the NIH Clinical Center: Building Training Partnerships with China. E-booklet: Selected Presentations from the 2011 Sino-American Symposium on Clinical and Translational Medicine, June 24, 2011, pp. 8, URL: http://www.sciencemag.org/site/products/2011_Sino-American_Symposium_booklet.pdf, (last accessed August 27, 2012).

Olkin, R. and C. Pledger (2003). Can disability studies and psychology join hands?. *The American Psychologist*, 58(4), 296-304.

Olympus (2011). Annual Report. URL: <http://www.olympus-global.com/en/corc/ir/annualreport/2011/pdf/ar2011.pdf>, (last accessed August 27, 2012), pp. 12.

Ong, A. (2010). Introduction. In: A. Ong and N.N. Chen (eds). *Asian Biotech*. Durham: Duke University Press.

Ong and N.N. Chen (2010). *Asian Biotech*. Durham: Duke University Press.

Ozolina, Z., et al. (2009). Global Governance of Science: Report of the Expert Group on Global Governance of Science to the Science, Economy and Society Directorate. European Commission, http://ec.europa.eu/research/science-society/document_library/pdf_06/global-governance-020609_en.pdf (accessed August 21, 2012)

Patra, P.K., and M. Sleeboom-Faulkner (2009). Bionetworking: experimental stem cell therapy and patient recruitment in India. *Anthropology of Medicine*, 16(2):147–63

Patra, P.K., and M. Sleeboom-Faulkner (2011). Recruiter-patients as ambiguous symbols: Bionetworking and stem cell therapy in India. *New Genetics and Society*, 30(2): 155-166.

Pei, X.T. (2009). Human Stem Cell Research and Ethical Regulations in China. In O. Doering (ed.), *Life Sciences in Translation – A Sino-European Dialogue on Ethical Governance of the Life Sciences*, BIONET Textbook delivery to the EU Commission, 168-179

- Peng, Y., *et al.* (2005). Treatment for patients with severe liver damage by transplantation of autologous bone marrow stem cells. *Shiyong Yixue Zazhi* [Journal of Practical Medicine], 21, 2143–2145.
- Peng, Z., *et al.* (2008). The application of gene therapy in China. *Drugs*,
- Petryna, A. (2009). *When experiments travel: clinical trials and the global search for human subjects*. Princeton University Press.
- Petty, J.L., and C.A. Heimer (2011). Extending the rails: How research reshapes clinics, *Social Studies of Science*, 41(3): 337–360.
- Pieke, F. (2012) Anthropology and the Chinese century. Inaugural Lecture, Leiden University, March 2, 2012.
- Prainsack, B., Geesink, I., and S. Franklin (2008). Stem cell technologies 1998–2008: Controversies and silences, *Science as Culture*, 17(3): 351-362.
- Prasad, A. (2008). Science in motion: what postcolonial science studies can offer, *Electronic Journal of Communication, Information, Innovation in Health*. 2(2), p.35-47.
- Qiu, J. (2009). China Spinal Cord Injury Network: changes from within. *The Lancet*, 8(7), 606-607.
- Qiu, J. (2012a). China's budget backs science, *Nature News*, 13 March 2012, URL: <http://www.nature.com/news/china-s-budget-backs-science-1.10209>, (last accessed August 26, 2012).
- Qiu, J. (2012b). China sets 2020 vision for science, *Nature*, 470(15), URL: <http://www.nature.com/news/2011/110202/full/470015a.html>, (last accessed August 27, 2012).
- Qiu, X.X., *et al.* (2010). Reinvestigation on ethical issues in stem cell research and clinical use: results and recommendations. *Yixue yu Zhexue: Renwen Shehuiyixue* [Medicine & Philosophy: Humanistic & Social Medicine Edition], 31(2), 5-18.

Rabinow, P. (1996). *Essays on the anthropology of reason*. Princeton, N.J.: Princeton University Press.

Rajan, K.S. (2006). *Biocapital: The Constitution of Postgenomic Life*. Durham/London: Duke University Press.

Rajan, K.S. (2010) 'The Experimental Machinery of Global Clinical Trials: Case Studies from India', in A. Ong and N. Chen (eds.) *Asian Biotech*. Durham and London: Duke University Press

Rajan, K. S. (2012). *Lively Capital: Biotechnologies, Ethics, and Governance in Global Markets*. Duke University Press Books.

Reuters (2011) StemCyte Adds World Class Talent to its North America and Global Operations. URL: <http://stemcellnetwork.blogspot.co.uk/2011/12/stemcyte-adds-world-class-talent-to-its.html>, (last accessed August 26, 2012).

Rizvi, F. (2008). 'Mobile Minds', an interview in Kenway, J. & Fahey, J. (eds) *Globalizing Research Imagination*, London & New York: Routledge, 65-73.

RJS [RJS Medical Technology Inc] (2010). Introduce of China SFDA. URL (accessed August 11 2011): <http://www.sfdachina.com/info/50-1.htm>

Robertson, R. (1992). *Globalization: Social Theory and Global Culture*, London, Thousand Oakes (CA): Sage

Rosemann, A. (2009). The IVF-stem cell interface in China: ontologies, value perceptions and donation practices of embryonic forms of life. In: *Life Sciences in Translation: A Sino-European Dialogue on Ethical Governance of the Life Sciences*, O. Doering (ed.). London: BIONET Textbook delivery to the EU Commission.

Rosemann, A. (2011). Modalities of value, exchange, solidarity: the social life of stem cells in China. *New Genetics and Society*, 30(2): 181–92.

Rosemann, A. (2013a) Medical Innovation and National Experimental Pluralism: Insights from Clinical Stem Cell Research and Applications in China. *Biosocieties*, 8(1): 58-74.

Rosemann, A. (2013b). Scientific Multipolarisation: Its Impact on International Clinical Research Collaborations and Theoretical Implications. *Science Technology and Society*, 18(3): 339-359.

Rottenburg, R. (2012). Workshop: Relocating Science and Technology, Halle, http://www.engagiertewissenschaft.de/de/newsletter-beitrag/Workshop_Relocating_Science_and_Technology_Halle_18_20_Juli_Anmeldung_bis_156, (last accessed August 21, 2012)

Rouse. J. (1996) *Engaging Science: How to Understand its Practices Philosophically*, Cornell University Press.

Russel, R. (2011). Rick Hansen concludes China tour at Hong Kong SCI Youth Rally, Website of Rick Hansen Foundation, URL: <http://www.rickhansen.com/Media-Room/Media-Article-View/Article/24/rick-hansen-concludes-china-tour-at-hong-kong-sci-youth-rally.aspx>, (accessed September 27, 2012).

Sachs, W. (Ed.). (1992). *The development dictionary: A guide to knowledge as power*. London: Zed Books.

Saini, A. (2011). *Geek Nation*. Hachette UK.

Salter, B., and R.Z. Qiu (2009). Bioethical governance and basic stem cell science: China and the global biomedicine economy. *Science and Public Policy*, 36(1), 47-59.

Sariola, S., and B. Simpson (2011). Theorising the 'human subject' in biomedical research: International clinical trials and bioethics discourses in contemporary Sri Lanka. *Social Science & Medicine*, 73(4): 515-521.

Sariola, S., and B. Simpson (2013). Precarious ethics: Toxicology research among self-poisoning hospital admissions in Sri Lanka. *Biosocieties*, 8(1): 41-57.

Sauvent, K.P., et al. (2010). *Foreign direct investments from emerging markets : the challenges ahead*. New York, Palgrave Macmillan.

Scholtissek, S. (2010). *Multipolare Welt. Die Zukunft der Globalisierung und wie Deutschland davon profitieren kann*. Hamburg: Murmann Verlag.

Schukman, D. (2013). China: Opportunity and risk for hi-tech, BBC News, 14.10.2014, URL: <http://www.bbc.co.uk/news/science-environment-24520694> (last accessed 20.01.2014)

Seth, S. (2009). Putting knowledge in its place: science, colonialism, and the postcolonial, *Postcolonial Studies*, 12(4), 373-388.

Selener, J. D. (1997). *Participatory action research and social change: approaches and critique*. Ithaca, New York: Cornell University Press.

Sheridan, K. (2011). First US embryonic stem cell trial is halted. AFP, URL: <http://www.google.com/hostednews/afp/article/ALeqM5hLgxf2AexXGLZaet7mab5xYSGx4g?docId=CNG.74e1e8ebf81a22e8b2b0577c5462a0cc.11>, (last accessed August 26, 2012).

Simpson, B. (2011). Capacity Building in Developing World Bioethics: Perspectives on biomedical ethics in contemporary Sri Lanka. In: C. Myser (ed.) *The Social Functions of Bioethics Around the Globe*. Oxford: Oxford University Press.

Simpson, B. (2013). Building Capacity: A Sri Lankan Perspective On Ethics And Accountability. In: M. Konrad (ed.) *Collaborators Collaborating: Counterparts in Anthropological Knowledge and International Research Relations*. Oxford: Berghahn.

Simpson, B., and S. Sariola (2012). Binding authority: Randomised clinical trials and the production of global scientific knowledge in contemporary Sri Lanka. *Science Technology and Human Values*, Online before print, March 30 2012, doi: 10.1177/0162243911432648.

Sipp, D. (2012). Clinical translation of stem cell research in Asia: Strides forward and missteps. Invited Lecture, Sussex University, 19.04.2012

Siram S., and I. Steiner (2005). Experimental allergic encephalomyelitis: a misleading model of multiple sclerosis. *Annals of Neurology*, 58, 939-45

Sleeboom-Faulkner, M. (2004). *Genomics in Asia: a clash of bioethical interests?*. New York and London: Routledge.

Sleeboom-Faulkner, Margaret, ed. (2009) *Human genetic biobanks in Asia: politics of trust and scientific advancement*. Routledge contemporary Asia series . Routledge. ISBN

9780710313416

Sleeboom-Faulkner, Margaret, ed. (2010) *Frameworks of choice: predictive & genetic testing in Asia*. IIAS publications series. Edited volumes, 3 . Amsterdam University Press. ISBN 9789089641656

Sleeboom-Faulkner, M. (2010). Embryo controversies and governing stem cell research in Japan. In: A. Ong and N.N. Chen (eds). *Asian Biotech*. Durham: Duke University Press.

Sleeboom-Faulkner, M. (2011). Looking beyond the regulatory exteriors of stem cell research in Asia—discussion. *New Genetics and Society*, 30(2): 137-290.

Sleeboom-Faulkner, M. and P.K. Patra (2011). Experimental stem cell therapy: Biohierarchies and bionetworking in Japan and India, *Social Studies of Science*, 41(5), 645-666.

Sleeboom-Faulkner, M. and B. Simpson (2013) Special Issue: Experimental Ethics, *Biosocieties*, 8(1), 1-103.

Sleigh, A., and H. Van Lewinski (2006). China: Moving up the value chain, Accenture, <http://www.accenture.com/us-en/outlook/Pages/outlook-journal-2006-china-value-chain.aspx>, (last accessed August 21, 2012).

Spelman, M. (2009). An interview with Mark Spelman, Accenture. Podcast Transcript, http://www.accenture.com/SiteCollectionDocuments/PDF/Multi_Polar_World_Mark_Spelman_Podcast_Transcript.pdf (last accessed August 21, 2012)

Song, P. (2010). Biotech pilgrims and the transnational quest for stem cell cures. *Medical Anthropology*, 29(4), 384-402.

Song, P. (2011). The proliferation of stem cell therapies in post-Mao China: problematizing ethical regulation. *New Genetics and Society*, 30(2), 141–153.

Southern Weekend (2006). Huang Hongyun: Striking Breakthrough or science bubble. *Nanfang Zhoumo* [Southern Weekend], July 21 2006, URL (accessed on May 14 2011): <http://www.bioon.com/biology/chinese/185809.shtml>

Star, S.L. (1995). Introduction, in S.L. Star (ed), *Ecologies of Knowledge*, Albany: State University of New York Press, pp.1-38.

Star, S.L. (2010). This is Not a Boundary Object: Reflections on the Origin of a Concept. *Science Technology Human Values*, 35(5), 601-617.

Strathern, M. (2012). Currencies of collaboration. In: M. Konrad (ed.) *Collaborators Collaborating: Counterparts in Anthropological Knowledge and International Research Relations*, Berghahn Books, pp.109 -134.

Swayne, M. and A. Messer (2011). U.S. Will No Longer Dominate Science And Research, <http://live.psu.edu/story/51436#> (accessed August 21, 2012).

Sysmex (2011) Key Strategies for Future Growth: An Interview with the CEO. URL: http://www.sysmex.co.jp/en/ir/data_irreport/annual/pdf/2010/sysmexAR2010_5.pdf, (last accessed August 26, 2012).

Tang, J.L., *et al.* (2008). Traditional Chinese Medicine. *Lancet*, 372, 1938–40.

Tang, Y., *et al.* (2012). Cell viability and dopamine secretion of 6-hydroxydopamine-treated PC12 cells co-cultured with bone marrow-derived mesenchymal stem cells. *Neural Regeneration Research*, 7(14), 1101-1105.

The Royal Society (2011). Knowledge, networks and nations: Global scientific collaboration in the 21st century, http://royalsociety.org/uploadedFiles/Royal_Society_Content/Influencing_Policy/Reports/2011-03-28-Knowledge-networks-nations.pdf, (last accessed August 21, 2012)

Thevenot, L. (2009). Governing life by standards: a view from engagements. *Social Studies of Science*, 39, 793–813.

Thompson, C. (2010) Asian Regeneration? Nationalism and Internationalism in Stem Cell Research in South Korea and Singapore, In: Ong and N.N. Chen (eds). *Asian Biotech*. Durham: Duke University Press.

Timmermans, S., and Berg, M. (1997). Standardization in Action: Achieving Local Universality through Medical Protocols. *Social Studies of Science*, 27: 273-305.

Timmermans S, and Berg M. (2003). *The Gold Standard: The Challenge of Evidence-Based Medicine and Standardization in Health Care*. Philadelphia, PA: Temple Univ. Press

Timmermans, S., and Epstein, S. (2010). A world of standards but not a standard world: toward a sociology of standards and standardization. *Annual Review of Sociology*, 36, 69-89.

Tsang, K. (2011) CN102b Trial: Cord Blood Cell Preparation, China SCI Net Investigator Meeting and Workshop on Cell-based Therapies, Hong Kong, April 19 2011.

Van Kemenade, W. (2008). *Détente Between China and India The Delicate Balance of Geopolitics in Asia*, Netherlands Institute of International Relations Clingendael, The Hague, <http://www.willemvk.org/downloads/DetentebetweenChinaandIndia.pdf> (accessed August 21, 2012).

Van Zwanenberg, P., Ely, A., and A. Smith (2011) *Regulating Technology*. London, Earthscan.

Veugelers, R. (2008) Towards a multipolar science world: trends and impact, https://lirias.kuleuven.be/bitstream/123456789/213469/1/MSI_0808.pdf (accessed August 21, 2012).

Wagner, C. (2011) *The New Invisible College: Science as a Social Network*, Washington, AAAS Meeting, <http://aaas.confex.com/aaas/2011/webprogram/Paper3680.html>, (accessed August 21, 2012).

Wahlberg, A., and T. Streitfellner (2009). Stem cell tourism, desperation and the governing of new therapies. In: *Life Sciences in Translation: A Sino-European Dialogue on Ethical Governance of the Life Sciences*, O. Doering (ed.). London: BIONET Textbook delivery to the EU Commission.

Wainwright, S., Williams, C., Michael, M., Farsides, B., and A. Cribb (2006). From bench to bedside? Biomedical scientists' expectations of stem cell science as a future therapy for diabetes, *Sociology of Science and Medicine*, 63: 2052–64.

Wainwright, S., and C. Williams (2009) Spaces of speech and places of performance: an outline of a geography of science approach to embryonic stem cell research and diabetes. *New*

Genetics and Society, 27(2): 161-173.

Waldby, C. (2002). Stem cells, tissue cultures and the production of biovalue. *Health*, 6(3): 305-323.

Waldby, C., and S. Squier (2003). Ontogeny, ontology, and phylogeny: embryonic life and stem cell technologies. *Configurations*, 11(1): 27-46.

Waldby, C., and R. Mitchell (2006). *Tissue economies: Blood, organs, and cell lines in late capitalism*. Duke University Press.

Waldby, C. (2008). Oocyte markets: women's reproductive work in embryonic stem cell research. *New genetics and society*, 27(1), 19-31.

Waldby, C., and M. Cooper (2010). From reproductive work to regenerative labour The female body and the stem cell industries. *Feminist Theory*, 11(1): 3-22.

Walters, L. (2004). Human embryonic stem cell research: an intercultural perspective. *Kennedy Institute of Ethics Journal*, 14(1): 3-38.

Wang, S. (2009). Chongqing: the first successful case of autologous bone marrow stem cell treatment for liver cirrhosis. Newsletter Daping Hospital, Research Institute of Surgery.

Wang, X., *et al.* (2007). Transplantation of autologous endothelial progenitor cells may be beneficial in patients with idiopathic pulmonary arterial hypertension: a pilot randomized controlled trial. *Journal of American Coll. Cardiology*, 49, 1566–1571.

Webster, A., *et al.* (2011). Experimental heterogeneity and standardization: stem cell products and the clinical trial process. *Biosocieties*, 6(4), 401-419.

Will, C. (2007). The Alchemy of Clinical Trials. *BioSocieties*, 2(1): 285–99.

Wilsdon, J., and J. Keeley (2007). China: The next science superpower?. E-booklet, DEMOS, URL: http://www.demos.co.uk/files/China_Final.pdf?1240939425, (last accessed August 26, 2012).

Wilson-Kovacs, D, and C. Hauskeller (2011). The clinician-scientist: professional dynamics in

clinical stem cell research, *Sociology of Health and Illness*, 34(4):1–16

Wilson-Kovacs, D., S. Weber, and C. Hauskeller (2010). Stem cells clinical trials for cardiac repair: regulation as practical accomplishment, *Sociology of Health and Illness*, 32(1): 89–105

Wirth, E. (2010). Preclinical and Phase 1 Development of Oligodendrocyte Progenitor Cells Derived From Human Embryonic Stem Cells for the Treatment of Spinal Cord Injury. Conference Presentation, The International Conference of Stem Cells and Regenerative Medicine for Neurodegenerative Diseases, Hualien, Taiwan, April 24, 2012.

Wolf, L.E., and B. Lo (2004). Aids: Healthcare and research issues. Encyclopedia of Bioethics, URL: <http://www.encyclopedia.com/article-1G2-3402500041/aids-ii-healthcare-and.html>, (accessed September 3, 2012)

Wolf, L.E., and B. Lo (2001). Ethical Dimensions of HIV/Aids. HIV InSite Knowledge Base, University of California San Francisco, URL: <http://hivinsite.ucsf.edu/InSite?page=kb-08-01-05>, (accessed September 3, 2012)

Wong, Y.W. et al. (2011), A three-month, open-label, single-arm trial evaluating the safety and pharmacokinetics of oral lithium in patients with chronic spinal cord injury, *Spinal Cord* 49, 94-98.

Yang, M.L. (2012). Efficacy and safety of lithium carbonate treatment of chronic spinal cord injuries: a double-blind, randomized, placebo-controlled clinical trial, *Spinal Cord* 50, 141-146

Young, W. (2004). China SCI Network Update. URL: <http://sci.rutgers.edu/forum/showthread.php?t=20729>, (last accessed August 26, 2012)

Young, W. (2008). SCI: Is the cure in China?. Video of conference presentation, *Spinal Cord Injury – what are the barriers to cure?*, Workshop, Bedford Massachusetts, March 29, 2008, URL: <http://www.spinalcordworkshop.org/portfolio-type/wise-young-md-phd-spinal-cord-injury-is-the-cure-in-china/> (last accessed August 26, 2012)

Young, W (2009a). ChinaSCINet & SCINetUSA. URL: http://www.chinascinet.org/index.php?option=com_content&task=view&id=97&Itemid=155, (site accessed August 21, 2012)

Young, W. (2009b). Spinal Cord Injury: The Next Generations of Therapies. The Spinal Cord Workshop: What are the Barriers to Cure, University of Georgia, April 4, 2009, URL: <http://www.spinalcordworkshop.org/portfolio-type/wise-young-md-phd-spinal-cord-injury-the-next-generation-of-therapies/> (last accessed September 21, 2012).

Young, W (2011a). Regulatory agencies are not the problem. Blog Contribution on CareCure, URL: <http://sci.rutgers.edu/forum/showthread.php?t=157952#post1382709>, (last accessed August 27, 2012).

Young, W. (2011b). Dr Wise Young speaks about Spinal Injury & Cord Blood. Talk given at a Umbilical Cord Blood Bank in New Zealand, transcript of video-recording; URL: <http://www.cordbank.co.nz/cordbank-news/dr-wise-young-speaks-about-spinal-injury-cord-blood/>, (accessed September 3, 2012)

Zhang, J. Y. (2012). *The Cosmopolitanization of Science: Stem Cell Governance in China*, Basingstoke: Palgrave Macmillan

Zhao, J., *et al.* (2008). Olfactory ensheathing cell transplantation for 5 patients with persistent vegetative state. *Zhongguo zuzhi gongcheng yanjiu yu linchuang kangfu* [Journal of Chinese Clinical Rehabilitative Tissue Engineering Research], 12(34), 6739-42.

Zhu, J., *et al.* (2006). Tracking neural stem cells in patients with brain trauma. *New England Journal of Medicine*, 355, 2376–3378.