The Molecularisation of Security: Medical Countermeasure Development and the Biomedical Advanced Research and Development Authority (BARDA), 2006-2015

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Abstract

How do advances in our varied understandings of biological life processes shape and influence contemporary security practices? Through an in-depth analysis of the Biomedical Advanced Research and Development Authority (BARDA), this thesis argues that security practices in the United States have undergone a process of molecularisation over the past two decades. Specifically, the thesis shows that: 1) a new molecular vision of life has emerged that operates beyond the parameters of biopolitics outlined by Foucault; 2) that this molecular conception of life is generating new notions of insecurity in the form of heightened concern with the threat of bioterrorism; and 3) that this shift in perceptions is also inciting the development of new molecular-based security technologies in the form of medical countermeasures. BARDA is the institution at the centre of government efforts in the United States to support companies in the development of medical countermeasures that aim to mitigate a bioterrorist attack. Such support is necessary as development is beset by the 'valley of death', the financial desert between preclinical research & development and procurement. Through financial and technical means BARDA facilitates the production of medical countermeasures through this valley. This support allows companies to take advantage of our ability to visualise and manipulate life at the molecular level made possible by the molecular vision of life. As this thesis demonstrates, our ability to map and manipulate DNA and visualise the bacterial structures that process DNA is essential to the development of these molecular-based security technologies. Through this exposition the way that this vision of life is driving understandings of security and insecurity in response to the threat of bioterrorism is demonstrated. In this case, our ability to visualise and manipulate life at the molecular level has characterised security in molecular terms.

Keywords: Preparedness, bioterrorism, biopolitics, molecular life, security

Abbreviations

"ARRA"	American Recovery and Reinvestment Act
ABW	Advanced Biological Warfare
AD	Atopic Dermatitis
AMR	Antimicrobial Resistance
APD	Antibody Phage Display
ASPR	Office of the Assistant Secretary for Preparedness and Response
Augmentin	Amoxacillin/Clavulanate
AVA	Anthrax Vaccine Adsorbed
BAA	Broad Agency Announcements
BARDA	The Biomedical Advanced Research and Development Authority
BLA	Biologics License Application
BSA	Broad Spectrum Antimicrobials
BW	Biological Weapons
Caltech	California Institute of Technology
CBRN	Chemical, Biological, Radiological and Nuclear
CDC	Centers for Disease Control and Prevention
CE	Common Era
cGMP	current Good Manufacturing Practices
CIADMs	Centers for Innovation in Advanced Development and Manufacturing
Cipro	Ciprofloxacin
CRE	Carbapenem-Resistant Enterobacteriaceae
CRI	Cities Readiness Initiative
CROs	Contract Research Organisations
CSG	Counterterrorism Security Group
DARPA	Defence Advanced Research Projects Agency
DHS	Department for Homeland Security
DNA	Deoxyribonucleic Acid
DoD	Department of Defence
ELISA	Enzyme-Linked Immunosorbent Assay
Elusys	Elusys Therapeutics, Inc.

EU	European Union
EUA	Emergency Use Authorization
FAR	Federal Acquisition Regulation
FDA	Food and Drug Administration
FFMN	Fill Finish Manufacturing Network
GAO	Government Accountability Office
GHSI	Global Health Security Initiative
GSK	GlaxoSmithKline
GSK'052	GSK2251052
HA	Hemagglutinin
HGS	Human Genome Sciences Inc.
HHS	The U.S Department of Health and Human Services
HHSAR	HHS Acquisitions Regulations
HPP	Hospital Preparedness Program
HSPD	Homeland Security Presidential Directive
HTS	High Throughput Screening
IAAs	Interagency Agreements
IEV or EV	Intracellular Enveloped Virion
IM	Intramuscular Injection
IMI	Innovative Medicines Initiative
IMV or MV	Intracellular Mature Virion
JAMA	Journal of the American Medical Association
JOC	Joint Oversight Committee
JOFOC	Justification for Other than Full and Open Competition
MCM	Medical Countermeasure
MDR	Multi-Drug Resistant
mRNA	Messenger RNA
MTD	Material Threat Determinations
MVA	Modified Vaccinia Ankara
NA	Neuraminidase
NASA	National Aeronautics and Space Administration

NDA	New Drug Applications
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institute of Health
NPS	National Pharmaceutical Stockpile
OMB	Office of Management and Budget
OPHEMC	Office of Public Health Emergency Medical Countermeasures
OPHEP	Office of Public Health Emergency Preparedness
OT	Other Transaction Authority
PAHPA	The Pandemic and All Hazards Preparedness Act
PAHPRA	Pandemic and All-Hazards Preparedness Reauthorization Act
PEP	Post-exposure Prophylaxis
PHEMCE	Public Health Emergency Medical Countermeasure Enterprise
PHEP	Public Health Emergency Preparedness
PPPs	Public Private Partnerships
PREP Act	Public Readiness and Emergency Preparedness Act
R&D	Research and Development
RFP	Requests for Proposals
RNA	Ribonucleic Acid
rPA	Recombinant Protective Antigen
SARS	Severe Acute Respiratory Syndrome
SBIR	Small Business Innovation Research
SIGA	SIGA Technologies
SNS	Strategic National Stockpile
SRF	Special Reserve Fund
TAMUS	Texas A&M University System
TRL	Technology Readiness Levels
tRNA	Transfer RNA
U.S.	United States
USAMRIID	U.S. Army Medical Research Institute of Infectious Diseases
VIG	Vaccina Immune Globulin
WHO	World Health Organisation

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Contents

Chapter 1: Introduction

International Relations, Global Health and Security

In the 20th century, in the fields of health and medicine, we have come to understand to a greater and greater degree the ways in which, at the molecular level, microbial life reproduces and causes disease. This understanding has supported the development of new biological weapons and medicines such as antibiotics that spurred the belief after the Second World War that infectious disease could be conquered once and for all.[1] Our growing awareness of how we can shape and alter the infectious properties of microorganisms has made intelligible the way that organisms such as bacteria and the influenza virus shift and adapt. This has led to new understandings of the mechanisms through which bacteria develop resistance to antibiotics. It has also revealed how the genetic compliment of the influenza virus drifts and shifts in the creation of seasonal and pandemic influenza respectively.[2] Our misplaced confidence in the conquering of disease has been profoundly shaken by these revelations. The emergence and understanding of the potential threats of diseases such as this and many others such as HIV/AIDS, severe acute respiratory syndrome (SARS) and Ebola have driven new understandings of insecurity and the creation of significant political concerns.

The field of International Relations has traditionally been concerned with war, peace and security among states and their consideration amongst foreign and security policy communities.[3] The fields of health and International Relations can be seen to have come together against the backdrop of globalisation and the 'real world' development of infectious disease outbreaks. Whilst the cross-border threat of disease is nothing new, by the late 20th century the scale and intensity of these health issues faced by countries became far greater

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[1] Melinda Cooper, 'Pre-empting Emergence: The Biological Turn in the War on Terror', *Theory, Culture & Society* 23, no. 4 (2006): 114.
[2] Bruce Braun, 'Biopolitics and the molecularization of life', *cultural geographies* 14, (2007): 16.
[3] Colin McInnes and Kelley Lee, *Global Health and International Relations* (Cambridge: Polity Press, 2012), 1.

than ever before.[4] Amongst other issues, infectious disease outbreaks and the changing distribution of disease vectors due to climate change challenged traditional notions of national health policy, re-territorialising it giving rise to the era of 'global heath'.[5] This rise has necessarily impacted the international system and what we must take into consideration when analysing and thinking about it as scholars of International Relations.

The rise of 'global health' and the corresponding political issues that must be investigated as a result has translated into a fertile field of research for scholars. This has included research into the legal aspects and dimensions[6] and the political and economic implications.[7] Other areas have also arisen, including global health governance[8] and investigations into global health diplomacy.[9] Over the past few years there has also been a growing link between health issues and security. This has been the result of political recognition regarding the threat emerging infectious disease poses and the efforts that must be put in place in order to prevent and prepare for it.[10] One of the most significant political statements regarding the understanding of disease as a security threat came with the passing of the United Nations Security Council Resolution 1308 in the year 2000 that emphasised the risk that the unchecked spread of HIV/AIDS could pose to international peace and security. The deliberate release of disease has also been recognised in the formation of political coalitions such as The Global Health Security Initiative (GHSI) made up of representatives from

[4] Ibid., 2.
[5] Ibid., 2.
[6] See David P. Fidler, 'Influenza Virus Samples, International Law, and Global Health Diplomacy', *Emerging Infectious Diseases* 14, no. 1 (2008): 88-94.
[7] See Anna Lugnér and Maarten Postma, 'Investment decisions in influenza pandemic contingency planning: Cost-effectiveness of stockpiling antiviral drugs', *European Journal of Public Health* 19, (2009): 516-520.
[8] See Jeremy Youde, *Global Health Governance*, (Cambridge: Polity Press, 2012).
[9] See Sara E. Davies, Adam Kamradt-Scott and Simon Rushton, *Disease Diplomacy: International Norms and Global Health Security* (Baltimore: John Hopkins University Press, 2015).
[10] See Joshua Lederberg, Robert E. Shope, Stanley C. Oaks, *Emerging Infections: Microbial Threats to Health in the United States* (Washington DC: National Academy Press, 1992); National Intelligence Estimate, *The Global Infectious Disease Threat and Its Implications for the United States* (Washington DC: National Intelligence Council, 2000).

Canada, France, Germany, Italy, Japan, the United Kingdom, the U.S. and Mexico. The World Health Organisation (WHO) has also recognised the concept of Global Health Security since 2000[11] and it has been utilised in their analysis of issues that threaten the collective health of people internationally.[12]

Global Health Security has been noted as one of the meanings of health security to emerge out of this growing political concern with health and issues of naturally emerging and deliberately released disease. The field of health security like any other area of security is essentially contested.[13] Out of this contestation the areas of global (public) health security, national security, human security and biosecurity have emerged, each constructed for a particular purpose including the promotion of a certain agenda and the privileging of certain interests over others.[14] Further, these terms have different implications for the range of health issues involved and those whose security is at risk.[15] Significant areas of research to emerge under biosecurity[16] have been those of bioterrorism[17] and the production of medical countermeasures (MCMs) to counter this threat.[18]

One currently underexplored area of research within the area of biosecurity is the issue of how exactly governments are undertaking the development of these new medicines or MCMs. In order to address this issue this thesis undertakes an analysis of the specific practices carried out by the Biomedical Advanced Research and Development Authority or BARDA.

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[11] Lorna Weir, 'Inventing Global Health Security, 1994-2005', in *Routledge Handbook of Global Health Security*, ed. Simon Rushton and Jeremy Youde (Abingdon: Routledge, 2015), 18.
[12] World Health Organisation, *The World Health Report 2007: A Safer Future* (Geneva: World Health Organisation, 2007), overview IV.
[13] Colin McInnes, 'The Many Meanings of Health Security', in *Routledge Handbook of Global Health Security*, ed. Simon Rushton and Jeremy Youde (Abingdon: Routledge, 2015), 7.
[14] Ibid., 7.
[15] Ibid., 7.
[16] See Christian Enemark, 'Life Science Research as a Security Risk', in *Routledge Handbook of Global Health Security*, ed. Simon Rushton and Jermey Youde (Abingdon: Routledge, 2015), 130-140.
[17] See Gregory D. Koblentz, 'Biological Weapons and Bioterrorism', in *Routledge Handbook of Global Health Security*, ed. Simon Rushton and Jeremy Youde (Abingdon: Routledge, 2015), 118-129.
[18] See Kendall Hoyt, 'Medical Countermeasures and Security', *Routledge Handbook of Global Health Security*, ed. Simon Rushton and Jeremy Youde (Abingdon: Routledge, 2015), 215-225.

BARDA is the institution at the heart of U.S. efforts to develop MCMs to protect the general population from a bioterrorist attack. The U.S. government is by far the largest investor in this area of biosecurity with $5.6bn dedicated to MCM development from 2004 to 2013. To date this institution has not been analysed in-depth. Such a study has the potential to significantly enhance our understanding in this area.

By looking in detail at BARDA and the way it supports MCM development, this thesis argues that contemporary security practices have been profoundly reshaped by the rise of a molecular vision of life, indeed, they have been molecularised. By analysing the way molecular understandings of life have influenced BARDA's detailed practices in this area, this thesis remains continuous with but goes beyond the Foucauldian biopolitical matrix of the body and population. It studies the development of MCMs from the perspective of molecular biopolitics and investigates the way that security practices change in this light. This introduction will now turn to the particular analytical approach taken by this thesis in conceptualising the shifting understandings of biological life in security practices.

A Biopolitical Analytics

This thesis explores in depth the way that our ability to visualise and manipulate life at the molecular level has impacted security practices in the U.S. The different ways that life has influenced politics was first recognised and conceptualised by the thinker Michel Foucault.[19] In conjunction with correlative technologies, life was made amenable to political influence at two different poles and scales – at the level of the population and the body. Commentators have emphasised aspects of Foucault's work as having considerable strengths in understanding the particular composition of today's political configurations. This includes an understanding of the historical situatedness of the phenomena that is being analysed. It has been recognised

[19] See Michel Foucault, *The Will to Knowledge: The History of Sexuality Volume 1*, trans. Robert Hurley (London: Penguin, 1998).

that Foucault proposed the concept of biopower 'after ten years of collective and individual research on the genealogy of power over life in the eighteenth and nineteenth centuries.'[20] Prioritised in the formulation of this concept was a particular historical, or genealogical, analysis[21] that emphasises the breaking down of dominant interpretations in favour of those marginalised and dispossessed. In this case, the predominance of law and sovereign power as the dominant understanding of the way power functions is problematised by the political concern with and control over biological life. The development of this notion of power cannot be divorced from the wider emergence of social power understood as govern-mentality.[22] Indeed, for Foucault new social and political strategies for managing the biological workings of the body and the population are essential to a specific form of a liberal European based govern-mentality that takes the health and welfare of the population as the end and instrument of government.[23] Biopolitical strategies are then tools of government, embody a particular govern-mentality and can be analysed in a similar fashion.

Taking a cue from Foucault, an analytical analysis of the way understandings of life have influenced politics has been developed. Such a study is concerned with the 'specific conditions under which particular entities emerge, exist and change.'[24] Similar to Foucault's genealogical method, an analytics seeks to attend to the singularity of ways of governing[25] that have emerged in correlation with particular understandings of life. By focusing on specific historical configurations it offers the chance to develop a more nuanced account of power. In contrast, other approaches have been criticised for applying the concept of biopower too broadly so removing its analytical value.[26] Often, a govern-mental and biopolitical analytics

[20] Paul Rabinow and Nikolas Rose, 'Biopower Today', *BioSocieties* 1, (2006): 199.
[21] Ibid., 199.
[22] Ibid., 200.
[23] Michel Foucault, *Security, Territory, Population*, trans. Graham Burchell (Basingstoke: MacMillan, 2009), 105.
[24] Mitchell Dean, *Governmentality: Power and Rule in Modern Society* (London: SAGE, 2010), 30.
[25] Ibid., 30.
[26] See Rabinow and Rose, 'Biopower Today', 199, 201.

has been used to understand contemporary rationalities and technologies of power.[27] One limitation, though, in emphasising the specificity of particular practices is that it would seem to deny the possibility of offering any general understanding of the processes of transformation of contemporary governmental and biopolitical practices.[28]

Commentators have noted that the area of genomic medicine is one of the key sites in understanding contemporary biopolitics. These tools offer up to medicine the opportunity to transform its basic logic from one 'based upon restoring the organic normativity lost in illness to one engaged in the *molecular re-engineering of life itself*.'[29] Indeed, this thesis is concerned with the political implications of our ability to not only understand but to (re)shape the constitution of life at the molecular level. It asks how biological processes at the molecular level are shaping and influencing contemporary security practices? In addressing this question it undertakes an analytical analysis of the biopolitical implications of these understandings. To be emphasised are the particular security configurations and processes of molecularisation that have developed in the U.S. in conjunction with our ability to shape molecular life. This analysis is carried out whilst noting the wider context of the political economic logics that Foucault recognised as predominating within the American and European based liberal governmentality that these biopolitical security practices are situated in relation to.[30] Following Foucault further, this particular security configuration is conceptualised on the basis of its contemporary techniques of power.[31]

In undertaking this analysis this thesis takes together the U.S. government's approach to the threat of bioterrorism and the technologies that have supported molecular biology's intervention into the workings of life. In this way it integrates the way molecular life is

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[27] Ibid., 202.
[28] Dean, *Governmentality*, 207.
[29] Rabinow and Rose, 'Biopower Today', 212.
[30] Michel Foucault, *The Birth of Biopolitics* trans. Graham Burchell (Basingstoke: Palgrave Macmillan, 2010).
[31] Foucault, *The Will to Knowledge*, 150.

understood and manipulated in the production of new medicines or MCMs into the discipline of International Relations. The result, it is hoped, is an interdisciplinary contribution that emphasises the way that science and technology can influence politics in what has been conceptualised as the molecularisation of security. This introduction will now turn to a description of the empirical site of analysis, the laws and institutions set up to implement the U.S. government's approach to the threat of bioterrorism.

BARDA and the Production of Medical Countermeasures

The threat posed by the deliberate creation and release of biological agents in acts of terrorism has stimulated government efforts focused on the creation and stockpiling of new medicines or MCMs. The greatest government effort in this regard has been in the U.S. Over the past decade alone, the U.S. has invested more than US$ 50 billion for civilian research on biodefense. The U.S. is not the only nation involved in such efforts though, with the European Commission announcing a Joint Procurement Agreement in 2014, enabling all European Union (EU) countries to procure pandemic vaccines and other MCMs as a group, rather than individually. As noted above, in response to flu pandemics and the deliberate release of disease, a number of governments from Europe and North America have collaborated in the GHSI. This initiative supports collaboration in a number of areas including surveillance and the procuring of vaccines and antibiotics.

In contrast to pandemic influenza many of the biological agents that could potentially be used in a deliberate attack usually cause very low rates of illness in the general population. This means that there is no ‘natural’ market for selling medical therapies that would protect people against these threats. Developing MCMs against biological attacks has therefore not been a commercial priority for pharmaceutical companies. In order to address this market failure new laws and institutions have been set up in the U.S. to incentivise and support pharmaceutical companies in the MCM development process. The Project BioShield Act,

passed in 2004, gave the federal government new authorities to develop and procure MCMs. The Pandemic and All-Hazards Preparedness Act (PAHPA) created BARDA in 2006. The development of this institution, dedicated entirely to supporting the production and stockpiling of MCMs, makes the U.S. the country that is by far the most engaged in this particular area of health security. The creation of BARDA also demonstrates the intense difficulties that are involved in supporting companies in MCM production and the material realisation of this security strategy.

New scientific developments, particularly in the field of molecular biology have been central to BARDA's preparedness efforts. These new scientific understandings, termed the molecular vision of life, have not only influenced a perception of the bioterrorist threat in the U.S. government as something which cannot be prevented but they have also made possible the creation of MCMs. In this way the preparedness efforts of the U.S. government, focused on creating and sustaining public-private partnerships (PPPs) with pharmaceutical and biotech companies, cannot be understood without taking into account the role this vision of life has played. Indeed, MCMs are a peculiar and particular manifestation of preparedness which is combined with an underlying change in the way life is understood.

The academic literature that has focused on the way different understandings of life have influenced security practices has been collected under the biopolitics of security. This literature, heavily indebted to the work of Michel Foucault, noted above, and his illustration of the way particular understandings of biological life influenced political technologies and strategies in 18th and 19th century Europe, coined the terms biopower and biopolitics. A central concern of this literature is the way particular understandings of life at the molecular level, often supported by certain technologies, influence security practices and rationales. This work to date has primarily analysed the way molecular understandings of life have shaped notions of insecurity. Despite the increasing recognition amongst governments that medicines

as tools of security are very valuable in responding to issues such as pandemic influenza and bioterrorism, this body of literature has yet to interrogate the way understandings of life at the molecular level, in particular, have shaped the creation of security tools and technologies such as MCMs.

One of the central aims of this thesis is to make an interdisciplinary contribution to the biopolitics of security literature by examining the role of the molecular vision of life in the U.S. government's decision to develop and stockpile MCMs to address the threat of bioterrorism. In doing so, this thesis builds on the current scholarship in this area by analysing the way that both notions of insecurity and the security technologies stockpiled by the U.S. government have been shaped by understandings of life at this level. Through two main avenues of investigation it is argued that the result of this process has been to characterise security in molecular terms. The first avenue analyses the financial and technical support given to companies by BARDA that is necessary to turn molecular knowledge into new pharmaceutical defences. The second investigates the key tools and technologies that have allowed us to not only understand the way life works at the molecular level but to shape it in the production of new terrorist weapons and new medicines in the form of MCMs.

BARDA forms the empirical focus and case study of this thesis as this is the institution at the forefront of U.S. efforts to incentivise and support pharmaceutical companies in the MCM development process. Through an in-depth analysis of the historical background to the development of this organisation, the way the U.S. government has adapted to meet the particular needs of companies engaged in the MCM development arena will be illustrated. By focusing on the efforts of this institution up until 2015 to support companies in the development of MCMs, the incentives utilised to support these partnerships and to overcome the lack of a natural market will be analysed. By analysing the efforts of BARDA in MCM

production we can also investigate the way particular tools and technologies have facilitated their development.

BARDA supports the molecular development of MCMs through two main mechanisms. This includes providing funding which facilitates MCM development through the carrying out of necessary studies that also help overcome the mid- to late-stage funding and development challenges known as the 'valley of death'. BARDA, through its Core Services also provides access to technologies essential to the molecular development of MCMs. In addition to these two mechanisms, as will be demonstrated, BARDA's MCM development strategy has been influenced by understandings of biological threat facilitated by the molecular vision of life. These are the three ways, then, in which BARDA has either supported the molecular development of MCMs or has been shaped by molecular knowledge. BARDA's support is necessary as there is a considerable gap between the idea, plan and strategy for MCM development and its material implementation. This thesis delves into the messy and difficult arena that is MCM development to demonstrate the way BARDA focuses efforts to overcome this gap.

Central Research Question and Theoretical Framework

The central research question informing this thesis is thereby as follows: How do advances in our understanding of biological life processes shape and influence contemporary security practices? As a means of answering this question this thesis begins by evaluating the academic literature concerned with molecular understandings of life in security processes. In this evaluation of the biopolitics of security literature the influence of understandings of life at the molecular level are demonstrated. It is further shown that this influence has to date focused primarily on the way molecular understandings of life have shaped political notions of insecurity. In this way this literature has not fully addressed the question above. This thesis, in seeking to more fully answer this question, offers a detailed account of the way the molecular

vision of life has not only supported notions of insecurity in the U.S. response to bioterrorism but how it has also facilitated the production of security technologies in the form of MCMs.

Specifically, the thesis shows that: 1) a new molecular vision of life has emerged that operates beyond the parameters of biopolitics outlined by Foucault; 2) that this molecular conception of life is generating new notions of insecurity in the form of heightened concern with the threat of bioterrorism; and 3) that this shift in perceptions is also inciting the development of new molecular-based security technologies in the form of MCMs. In so doing, this thesis makes a contribution to current scholarship in three ways: Firstly, this thesis provides a detailed empirical case study of the workings of BARDA. Through this investigation of the organisation at the heart of U.S. MCM production, it contributes to the field of health security by demonstrating the material incentives necessary to the production of these medicines. Secondly, by demonstrating the empirical basis of the workings of molecular tools and technologies in the creation of MCMs, this thesis contributes to the biopolitics of security literature by highlighting the theoretical implications of this vision of life for this field of security studies conceptualised as the molecularisation of security. Thirdly, this thesis makes an interdisciplinary contribution by elucidating the role molecular tools and technologies play in the development of MCMs in this area of science, security and International Relations.

Methodology/ Research Design

This thesis draws from a range of sources. Theoretical inspiration on the biopolitics of security literature was drawn from articles in academic journals and books. Information on U.S. biodefence was gained from a range of sources including government reports from the Government Accountability Office and Congressional Research Service. Information on the way Project BioShield funds and BARDA supports companies in these partnerships was gained from a detailed examination of BARDA's website and reports such as the Project BioShield annual reports to congress. The Government's MCM development strategy was discerned

from a range of documents including BARDA's strategic document and the Public Health Emergency Medical Countermeasure Enterprise (PHEMCE) strategy.

Information on the partnerships between BARDA and specific companies was gained through online news reports and press releases from the companies involved. There is a considerable issue involved with using online documents as references. This is mainly concerned with the changing nature of online material and the short time web pages are tied to particular addresses. All web links have been updated as regularly as possible with a copy of the page saved offline for reference in the future. Information on these partnerships and the workings of BARDA was also gained from a number of semi-structured anonymised elite interviews carried out in fieldwork in Washington D.C. whilst stationed at Georgetown University and on one separate visit. Three trips to Washington were carried out. The first involved attending BARDA's industry day in November of 2013. A second trip of three months was conducted from September to December of 2014. A third trip was conducted from the 1st to the 10th of June 2015 with telephone interviews arising from that trip, continuing until the 21st of July. On the second trip I attended the 2014 BARDA industry day in October and on the third the 13th Annual Vaccines and Therapeutics Conference from the 2nd to the 4th of June 2015.

During the second and third trips I managed to conduct a range of interviews with Congressional Researchers, representatives from global health think tanks, BARDA personnel, the FDA, representatives from lobbyist organisations and representatives from those companies that have partnered with BARDA in the development of MCMs. The opportunity to carry out these interviews was very rewarding. It was a fantastic learning experience during which I encountered a number of challenges. Most prominent amongst these was the issue of access. It took some time to arrange interviews with BARDA personnel and this was only achieved after making repeated contact with a representative that I met at the first BARDA

industry day. Having made contact, the BARDA personnel were very generous with their time and contributions.

Of those interviewed many from BARDA were willing to be recorded and attributed. Handwritten notes were taken in the case of those who declined. In the case of company representatives around half agreed to be recorded and attributed. Company representatives were particularly aware of the impact that their comments could have on their contracts with the government and kept this in mind when responding. BARDA representatives, too, did not comment on any contract, company and MCM in particular. All interviews were semi-structured, recorded on an audio device, if allowed, and were conducted having received ethical clearance from the University of Sussex. All interviews were anonymised and the codes for each participant kept on a separate computer from the data. Each participant signed a consent form detailing how they wished their information to be used. The interviews conducted with BARDA personnel were carried out in the main to clarify the process through which a company and MCM is supported both with technical and financial mechanisms. Interviews with company representatives were carried out with the aim of understanding how these support mechanisms had worked in relation to the company's expectations and needs. The interviews conducted on the third trip followed up with contacts made previously and established new contacts as a result of those met at the conference. Many of these contacts were interviewed on the phone in the weeks following.

The highly interdisciplinary nature of this project required an investigation into and education in molecular biology. This was carried out through the review of a range of literature focused predominantly on the history of this field. The analysis revealed the key milestones, discoveries and technologies essential to its development. This understanding supported an investigation into the key molecular technologies that supported the development of particular MCMs. In trying to understand the way particular technologies

worked, YouTube videos were very often an excellent primer. Understanding the workings of these technologies has allowed this thesis to demonstrate the particular way that molecular biology has made possible our ability to visualise and manipulate life at the molecular level. These factors have been essential to the development of these molecular-based security technologies and the implementation of particular political rationalities.

The choice of case studies was determined by a number of factors. Smallpox and anthrax were chosen as they are the threats that have received the most attention and resources from the U.S. government in addressing potential bioterrorist attack. BARDA's approach to the threat of antibiotic resistance through the development of broad-spectrum antibiotics was chosen as it was felt that this was an area of current and future political concern. Research in this area could contribute to these concerns and provide a platform for future endeavours. In all cases the particular MCM analysed was influenced by the relevant scientific literature that I could access and comprehend.

The Argument

How do advances in our varied understandings of biological life processes shape and influence contemporary security practices? In order to investigate the way that understandings of molecular life have influenced the politics of security in the U.S., chapter 2 engages in a detailed exposition of the molecular vision of life as set out by Nikolas Rose. In doing so it argues that a new molecular vision of life has emerged that operates beyond the parameters of biopolitics outlined by Foucault. The medical gaze he identified operated at the molar level. New scientific technologies have allowed us to gaze deep below the surface of our molar bodies. This chapter demonstrates that they have specifically allowed us to visualise and manipulate life at the molecular level. These capacities have been analysed by the literature in International Relations focused on the biopolitics of security. Significantly, this literature has predominantly focused on the way these capacities have shaped notions of

insecurity. In arguing for the way that these capacities have also supported the development of new medicines and security technologies, this chapter discusses the key discoveries regarding the molecular structure of DNA and the shift from classical to molecular biology. These shifts have not only supported the development of new medicines but also new weapons generating new security concerns for governments.

Chapter 3 goes on to support the molecuarisation thesis by arguing that our capacities to visualise and manipulate life at the molecular level generated new notions of insecurity in the form of heightened concern with the threat of bioterrorism. It does this by demonstrating the way that our ability to shape life at the molecular level, through technologies such as synthetic genomics, heightened concerns that terrorist groups may create new and more deadly biological weapons. It also analyses the way that understandings of biological life made intelligible the way bacteria evolve resistance to antibiotics. These two understandings of threat, one arising naturally and one deliberately, came together in the 'dual-purpose' argument utilised to gain support for a particular response to the threat of bioterrorism focused on preparedness and the stockpiling of MCMs. This chapter then analyses the U.S government's first attempt to partner with pharmaceutical companies in the implementation of this preparedness approach. The Project BioShield Act created in 2004 dedicated funds for the procurement of MCMs. One of the first partnerships set up to develop a new anthrax vaccine with the company VaxGen revealed the difficulties that would have to be overcome in transitioning through the 'valley of death' and moving from the vision of a preparedness response to its material realisation. Indeed, the failure of VaxGen led to the profound realisation that significant institutional adaptation in the economic, political, legal and regulatory realms would be required for the successful translation of molecular knowledge into new pharmaceutical defences.

Chapter 4 investigates the way that this institutional adaptation was implemented with the creation of BARDA in 2006. In this way it demonstrates how our shift in perceptions of what constitutes insecurity at the molecular level is also inciting the development of new molecular-based security technologies in the form of MCMs. It argues that the molecularisation of life has influenced the way BARDA works in three ways. In the first instance, BARDA's financial support through milestone based contracts, for example, allows companies to conduct vital studies in overcoming the 'valley of death' and the development of MCMs. BARDA also provides companies with access to a range of technical tools that facilitate the manipulation of molecular life in MCM development. These technical tools have taken the form of the Core Services and Centers for Innovation in Advanced Development and Manufacturing or CIADMs. These tools help meet the needs of biotech companies and prevent the failure that occurred with VaxGen. Other tools that have been used by BARDA to support the development of MCMs include the use of flexible contracting mechanisms such as the Other Transaction Authority or OT. This helps overcome the burden of the Government's most common Federal contracting mechanism and has been used to partner with large and experienced pharmaceutical companies in the development of antibiotics. Thirdly, BARDA's MCM development strategy has been significantly shaped by the molecular vision of life and our understanding of what constitutes a biological threat. This understanding of threat has manifested itself in the shift from 'fixed' to 'flexible' defences.

Our ability to shape life at the molecular level has incited the development of new institutions such as BARDA. How has it also made possible the development of MCMs? Chapter 5 demonstrates the way that both the financial and technical support offered by BARDA and our ability to specifically map and visualise DNA came together in the development of the smallpox antiviral – ST-246. The case of smallpox is taken first as this was chronologically the first biological threat to be significantly addressed by the U.S. government and that led to the stockpiling of a vaccine by the Centers for Disease Control and Prevention

(CDC) in 1999. This is the first of three empirical chapters that demonstrates the way BARDA's financial and technical support is utilised in the development of MCMs. Not only this, but these three chapters are connected in demonstrating the key ways that our understanding of the way life works at the molecular level has not only shaped the perception of insecurity surrounding a particular threat but has also been utilised in MCM development. Specifically, our ability to understand and shape DNA connects the development of the three MCMs analysed. The U.S. government's decision to develop and stockpile MCMs against the threat of smallpox was carried out in relation to a biological understanding of the threat and the potential that it could be molecularly engineered by terrorists. In response to an attack, the time it takes to administer a vaccine generates a significant window of vulnerability. This has made the development of antivirals an especially pressing concern. BARDA has supported the development of the antiviral ST-246 through the use of contracts utilising milestone payments that not only provide a market guarantee but also support late-stage development studies such as Phase III trials. Using the techniques of molecular biology, specifically High Throughput Screening and gene mapping the molecular vision of life made intelligible the workings of ST-246. Specifically, our ability to visualise and manipulate DNA in the *mapping* of genes allowed us to logically deduce the gene and protein that ST-246 targets in the inhibition of the spread of the smallpox virus within the body. Our ability to map DNA represents one path through which molecular knowledge can be translated into new pharmaceutical defences.

Chapter 6 details the way that BARDA and molecularisation made possible the development of the anthrax antitoxin Raxibacumab. Chronologically anthrax was the second threat to be significantly addressed. In a similar way to the decision to develop a smallpox antiviral, the potential threat of a molecularly engineered or antibiotic-resistant strain of anthrax stimulated efforts into the development of efficacious antitoxins. The procurement contracts for Raxibacumab run by BARDA represent the realisation of a market guarantee provided by the government. The development of Raxibacumab was also supported by the

FDA. Its development was prioritised under Fast Track Product Designation, pushing this MCM through development by enhancing communication between the FDA and the developer. The molecular vision of life made possible the development of Raxibacumab in two key ways. Molecularisation has allowed us to visualise the way that pathogens such as *Bacillus anthracis* infect and kill cells. This understanding has revealed the central role played by one specific protein that helps makes up the anthrax bacteria, the protective antigen. X-ray crystallography has allowed us to visualise the specific domain essential to the pathogenesis of the bacteria. Our ability to *manipulate* DNA into new configurations has made possible the development of phage antibody libraries. By scanning these libraries with the anthrax protective antigen, particular antibodies matching this antigen will be revealed that can be developed into the effective medicine against anthrax that Raxibacumab represents. Our ability to manipulate DNA represents another distinct path through which molecular knowledge can be translated into new pharmaceutical defences.

In chapters 5 and 6 the differing ways that we can map and manipulate DNA into new configurations is elucidated in an analysis of the development of particular MCMs against smallpox and anthrax. Chapter 7 analyses the way that the effects of BARDA and the molecularisation of life have supported the development of antibiotics. This case is taken third as chronologically it is one of the most recent threats to be addressed. The molecular vision of life has revealed the molecular processes through which bacteria develop resistance to antibiotics. In response, new antibiotics such as Eravacyline have been developed. BARDA has supported the advanced-development of this broad-spectrum antibiotic through contracts funding key studies such as those demonstrating its efficacy. Tools for visualising the structure of life at the molecular level such as cryo-electron microscopy have provided vital information on bacterial ribosomes. This tool overcomes some of the limitations of x-ray crystallography that was used in the development of Raxibacumab. It reveals the molecular structure of the bacterial ribosome essential to the processing of DNA and the development of proteins. This

makes intelligible the way that certain proteins negate the effectiveness of certain antibiotics such as the family of tetracyclines. The ability to *visualise* the cellular tools that process DNA is essential to the development of antibiotics such as Eravacycline that aim to overcome these resistance mechanisms. These three chapters then are linked by the way that the molecular vision of life has made possible the *mapping* of DNA, the *manipulation* of DNA into new configurations and the *visualisation* of DNA and the structures that process it. We have then three distinct paths through which the molecular knowledge of DNA can be translated into new pharmaceutical defences.

Chapter 2: Molecularisation, the Biopolitics of Security and DNA

Introduction

How do advances in our varied understandings of biological life processes shape and influence contemporary security practices? This is the puzzle that frames this thesis and chapter. This chapter initiates the formation of a solution that shall gain coherence as this thesis progresses. In arguing for the molecularisation of security this chapter demonstrates the emergence of the molecular vision of life as recognised by Nikolas Rose. It locates this vision of life in the work of Michel Foucault and his archaeology of medicine. The medical gaze that Foucault recognised as locating illness in the body at the molar level was central to an understanding of the way that the body and the population could be managed in the support of its health and welfare. Drawing from Foucault's notion of biopolitics this chapter demonstrates how knowledge of life at the molecular level has necessarily taken us beyond the parameters of Foucault's work, adding an additional scale at and through which we can affect the body and the population.

Central to this knowledge of life at the molecular level are the technologies that have not only allowed us to visualise and understand the workings of molecular life but have also allowed us to intervene in and manipulate these 'natural' or inherent processes. These two factors are what define the molecularisation of life. This ability has had a significant influence on the literature in International Relations. Predominantly, fellow academics that have investigated the political influence of the molecular vision of life have analysed the way notions of insecurity have been shaped. As yet, there has not been a significant focus on the way the molecularisation of life has supported understandings of insecurity *and* the development of new medicines to address these understandings. In exploring this issue and in arguing for the molecularisation of security, this chapter outlines the key scientific

understandings in biology that made possible the visualisation and manipulation of life at the molecular level.

One of the key scientific advances that made possible the creation of new medicines and new weapons is the discovery of the molecular structure of DNA. The opening up of DNA to visualisation and manipulation made possible a significant shift from classical biological techniques to molecular biological techniques. As will be demonstrated, these new techniques that support the direct editing of an organism's DNA have not only made possible the creation of new medicines but also posed the prospect of new weapons being created. These techniques have supported research of 'dual-use concern' that have demonstrated the way pathogens could be re-created or enhanced. Such research has not only provided essential information regarding the nature of deadly pathogens, it has also supported the prospect that terrorists may use such research to develop new weapons. As the next chapter will demonstrate, this prospect had a considerable influence on the U.S. government's understanding of the threat of bioterrorism.

This chapter proceeds by setting out the notion of ‘molecular biopolitics’ as understood by Rose and its links to the work of Foucault. It then goes on to review the literature in International Relations that has analysed the political effects of the molecularisation of life. It notes that aside from Elbe, little attention has been paid to addressing the role of the molecularisation of life in generating understandings of insecurity and new correlative security technologies. It then goes on to detail the significant moments of research in molecular biology that made possible the manipulation of DNA in the creation of new medicines and new weapons. This chapter concludes by noting the significant problems for governments that such research with ‘dual-use’ potential has.

Molecular Biopolitics

For Nikolas Rose, the vital politics of our own century is concerned with 'our growing capacities to control, manage, engineer, reshape, and modulate the very vital capacities of human beings as living creatures.'[1] In contrast with the vital politics of a different era focused on the quality of the population in the name of the future of the race, vital politics today is concerned with the characteristics and capacities of life itself. For Rose one of the novel aspects of contemporary biopolitics arises from the 'perception that we have experienced a "step-change", a qualitative increase in our capacities to engineer our vitality, our development, our metabolism, our organs, and our brains.'[2] This step change entails a change in the scale at which we perceive life. The common factor running through the advances in biomedical knowledge and techniques is situated in the fact that it is now at the molecular level at which life is understood, that life's processes can be anatomised and that life can now be engineered. For Rose, nothing now, it seems, is mystical or incomprehensible about our vitality, life in principle becomes intelligible in every aspect and open to calculated interventions and contestations, to politics. The molecular vision of life has opened up a new range of opportunities and threats.[3]

For Rose the molecular vision of life or molecularisation is one dimension in which medical and political perception and practice has been reshaped. Molecularisation represents a 'style of thought' of contemporary biomedicine which

> …envisages life at the molecular level, as a set of intelligible vital mechanisms among molecular entities that can be identified, isolated, manipulated, mobilised, recombined, in new practices of intervention, which are no longer constrained by the apparent normativity of a natural vital order.[4]

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[1] Nikolas Rose, *The Politics of Life Itself: Biomedicine, Power, and Subjectivity in the Twenty-First Century* (Princeton, NJ: Princeton University Press, 2007), 3.
[2] Ibid., 4.
[3] Ibid., 4.
[4] Ibid., 5-6.

As a result of this epistemic shift, medicine and politics have also been reshaped in relation to the optimal state of individual and collective human life, the values for the conduct of a life, new pastoral experts and a new economic space and capital in the form of bioeconomy and biocapital respectively. This thesis explores the impact of the molecular vision of life in the creation of new medicines or medical countermeasures (MCMs) and the new economic sites and partnerships that Project BioShield and the Biomedical Advanced Research and Development Authority (BARDA) represent.

The Medical Gaze

Rose notes the path-breaking analysis carried out in Foucault's work in *The Birth of the Clinic.* Foucault's archaeological analysis of medical perception and the clinical gaze during the 18th century situated illness in the body at the molar level. The development and use of observation as a medical technique and the assessment of disease as focused upon corporeal space and the body was noted in *Madness and Civilisation.*[5] With the shift from confinement to the asylum the order of observation became tied to classification,[6] forming objects of scientific discourse. Foucault continued this approach of determining how objects of knowledge are formed with an exposition of how the 'way to see' developed in the medical teaching clinic. As the medical eye penetrated into the body, it was the body itself which became ill.[7] The access of the medical gaze into the sick body was the result of a 'recasting at the level of epistemic knowledge (*savoir*) itself'.[8] The anatomo-clinical gaze now analyses disease from the point of view of death, with it now forming the 'essential structure of medical thought and perception'.[9] This new 'way to see' introduces a novel structure of discourse

[5] Michel Foucault, *Madness and Civilisation: A History of Insanity in the Age of Reason* (New York: Vintage Books, 1988), 115, 146.
[6] Ibid., 250.
[7] Michel Foucault, *The Birth of the Clinic: An archaeology of medical perception*, trans. A. M. Sheridan (London: Routledge, 2003), 167.
[8] Ibid., 168-9.
[9] Ibid., 177.

which constitutes disease as a distinct object of knowledge opening up but also delimiting what it is possible to think and say, its operation of *énoncés*. For Deleuze the visible and articulable result from an immanent cause that disregards form and allows it to be realised as visible matter and articulable functions.[10]

This operation of *énoncés*, creates certain objects of knowledge, not only of disease but of the patient as subject. For Foucault this dynamic correlation of power and knowledge gave rise to the many disciplines of the human sciences.[11] During the 17th and 18th centuries, in conjunction with the development of capitalism, the growth of the human sciences represented one dimension of the entry of life into history 'that is, the entry of phenomena peculiar to the life of the human species into the order of knowledge and power, into the sphere of political techniques.'[12] For Foucault, for the first time in history, biological existence was reflected in political existence, the fact of living passed into knowledge's field of control and power's sphere of intervention.[13] A new form of power emerges with biopower designating the inception of life and its mechanisms into the realm of explicit calculations, with knowledge and power now able to actively transform human life.

In conjunction with correlative technologies, life was made amenable to political influence at two different poles and scales. Disciplinary power, an anatomo-politics of the human body seeks to optimise and integrate the body into systems of efficient economic controls. Biopolitics intervenes at the level of the population to regulate biological processes such as life expectancy, birth rates and mortality. For Foucault the disciplines of the body and the regulations of the population constituted the two poles around which the organisation of

[10] Gilles Deleuze, *Foucault*, trans. Sean Hand (London: Contiuum, 2010), 33.
[11] Michel Foucault, *Security, Territory, Population*, trans. Graham Burchell (Basingstoke: MacMillan, 2009), 79.
[12] Michel Foucault, *The Will to Knowledge: The History of Sexuality Volume 1*, trans. Robert Hurley (London: Penguin, 1998), 141-2.
[13] Ibid., 142.

power over life was deployed in order to invest life through and through.[14] Crucially, this power over life emerged in conjunction with certain technologies such as the Panopticon in relation to disciplinary power and statistical calculations in the form of demography, epidemiology and risk in relation to the biopolitics of the human race.

Foucault highlights both sexuality and medicine as fields occupying a strategically vital place in the politics of the 19th century. Sexuality exists where body and population meet, making it a matter for discipline and for regularisation. Similarly, medicine is a power/knowledge that can be applied to both the body and the population.[15] In analysing both issues Foucault elucidates his method, he is not aiming for a general theory but is forming concepts on the basis of their contemporary techniques of power.[16] In a similar fashion, this thesis analyses and conceptualises the U.S. response to bioterrorism in terms of the knowledges and technologies utilised.

For Rose, though, the molar body identified by the clinical gaze and the focus of disciplinary power has been 'supplemented, if not supplanted, by this molecular gaze'.[17] In doing so it has introduced a new standard of judgement with which we can understand the workings of life. A molecular scale joins that of the body and the population in coming to dominate the way medicine functions and is understood. Biomedical research identifies the dynamics of life in terms of functionalities, identifying the differing aspects of molecular life with their particular mechanical and biological properties. In contrast to Foucault's archaeological or genealogical method, Rose utilises Ludwik Fleck's notion of 'style of thought' to understand these developments. A 'style of thought' is a particular way of seeing, thinking

[14] Ibid., 139.
[15] Michel Foucault, *Society Must Be Defended*, trans. David Macey (London: Penguin, 2004), 251-2.
[16] Foucault, *The Will to Knowledge*, 150.
[17] Rose, *The Politics of Life Itself*, 12.

and practicing and it formulates statements that are only possible and intelligible within that way of thinking.

Importantly, a 'style of thought' 'shapes and establishes the very object of explanation, the set of problems, issues, phenomena that an explanation is attempting to account for.'[18] Emphasised is the social structure of scientific activities, the socially-conditioned activity of cognition.[19] This cognition acquires meaning only in connection with a community of persons exchanging ideas and intellectual interaction as a 'thought collective'. This collective is the carrier for the historical development of any field of thought as well as for the given stock of knowledge and level of culture, designated as a thought style.[20] As styles of thought have developed they have modified their objects so that they appear in a new way with new properties, relations and distinctions with other objects.

In contrast to Rose who can be seen to focus on the 'styles of thought' that result from certain modes of knowledge or *connaissances* around a certain topic, Foucault's archaeology of medicine analyses the conditions necessary in a particular period for an object to be given to *connaissance*, conditions that allow enunciations to be formulated.[21] Focusing on *savoir* brings to light the concrete and historical *a priori* of a certain *episteme*, the necessary but equally concealed and taken-for-granted foundations of thought. Applying this method over time to a specific topic or area reveals how objects of knowledge such as disease are constituted in different ways at different times. The shifts and discontinuities that emerge occur at a fundamental level in contrast to 'styles of thought', a level which delimits what it is possible to see, think and say. The molecularisation of life can be seen then as giving rise to new modes of knowledge that are still situated within the modern *episteme*. This thesis

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[18] Ibid., 12.
[19] Ludwik Fleck, *Genesis and Development of a Scientific Fact* trans. Fred Bradley & Thaddeus J. Trenn (London: University of Chicago Press, 1979), 43.
[20] Fleck, *Genesis and Development*, 39.
[21] Michel Foucault, *Archaeology of Knowledge* trans. A. M. Sheridan Smith (London: Routledge, 2002), 16-17, note 3.

explores how this vision of life has impacted security practices. Specifically, this chapter outlines the way that this vision of life has emerged beyond the parameters of biopolitics outlined by Foucault and the ways in which it has raised questions for security. Two fundamental ways in which it has done this is through technologies that allow us to visualise and manipulate molecular life.

Molecular Technologies and Techniques – Visualisation and Manipulation

The molecularisation of life is linked to experimentation and the possibilities opened up by technological advances. The molecular knowledge of life has been advanced through experimentation, with the creation of new objects in the very process of discovery itself.[22] One significant implication of the molecular vision of life is the ability to create the molecular structure of a virus or bacteria as was the case with the SARS virus in 2003. Indeed, the pharmaceutical industry selects, manipulates, trials and develops therapeutic agents at the molecular level. It is also in molecular terms that their modes of action are explained.[23] Visualisation techniques have been important in forming life at the molecular level as a set of intelligible vital mechanisms. Techniques such as ultrasound have rendered the interior organic body visible.

Many visualisation techniques operate through digital simulation. DNA sequences visualise life in terms of manipulable strings of information. Yet visualisation alone cannot open up the vitality of life at the molecular level to intervention and manipulation. The gene was opened up to knowledge and manipulation through a number of technologies including DNA binding dyes, restriction enzymes, electrophoresis, radioactive markers and polymerase chain reaction which produced large amounts of short stretches of DNA.[24] Edwin Southern developed a method to detect specific sequences of DNA in DNA samples. The Southern blot

[22] Rose, *The Politics of Life Itself*, 13.
[23] Ibid., 13.
[24] Ibid., 14.

digests a strand of DNA into many small fragments; these fragments are then separated by gel electrophoresis based on size. The fragments are then placed on filter paper which blots them to a new medium. Once they are chemically labelled with DNA probes, the fragments can be identified and visualised.[25]

Crucially, the breaking down of vitality at the molecular level frees intervention from the normativity of a given vital order. The body can now be broken down into tissues, cells and DNA which can be rendered visible, commoditised and re-engineered by molecular manipulation, so removing their ties to their site of origin.[26] Molecularisation then strips these elements of life of their specific affinities and 'enables them to be regarded, in many respects, as manipulable and transferable elements or units'.[27] Molecularisation, in isolating these elements of life, is conferring upon them a new mobility. As Rose notes, the mobility of life is not in itself new and nor is molecularisation sufficient to make up circuits of vitality. What has been opened up by 'molecular biopolitics' are the new ways in which 'such molecular elements of life may be mobilised, controlled, and accorded properties and combined into processes that previously did not exist.'[28] These advances in the epistemological understanding of life at the molecular level have opened it up to new possibilities and so, indeed, to politics. As the next chapter will demonstrate, the fear that terrorist may create new biological organisms outside of the natural and normative vital order significantly shaped understandings of insecurity surrounding bioterrorism in the U.S. The molecularisation of life has then – as a result of visualisation and manipulation techniques – introduced a new relay through which we can affect the body and hence the population. This represents a new scale at which biopolitics can be organised and carried out in the area of security.

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[25] James Tabery, Monika Piotrowska and Lindley Darden, 'Molecular Biology' in *Stanford Encyclopedia of Philosophy*, ed. Edward N. Zalta (Spring 2016 Edition), Available at: http://plato.stanford.edu/entries/molecular-biology/. Last accessed January 7, 2017.
[26] Rose, *The Politics of Life Itself*, 15.
[27] Ibid., 15.
[28] Ibid., 15.

Biopolitics and Mechanisms of Security

For Foucault then, the emergence of an understanding of human beings as a species gave rise to biopower and to distinct mechanisms of security. These mechanisms of security in contrast to disciplinary and juridical mechanisms of power focused on the health and welfare of the population. The 'population will be the object that government will have to take into account in its observations and knowledge, in order to govern effectively in a rationally reflected manner.'[29] In his analysis of liberalism Foucault outlines how the object and subject of the population came to be governed through mechanisms of security that emerged in addition to a number of correlative technologies and events.

The need for permanent economic exchanges and for the free movement of people and goods prioritised by a liberal govern-mentality, characterised as circulation, posed 'new and specific economic and political problems of government technique.'[30] The political effectiveness of sovereignty becomes now connected to an intensity of circulations, of ideas, wills, orders and commerce.[31] Through the structuring of space one can impact the rate and effectiveness of circulations. Apparatuses of security emerge to act on this prerequisite, relying on a number of material givens and aiming to maximise the positive elements whilst acting according to probabilities. The vital elements in circulation, necessitating an open future and freedom of movement, can be made knowable, actionable and governable through the science of the state, statistics. Statistics allows for the calculation of certain events in the milieu, such as the birth rate. Further, the population, acting within this free play of circulation, reveals the naturalness of the species, with which and through which one can

[29] Foucault, *Security, Territory, Population*, 106.
[30] Ibid., 64.
[31] Ibid., 14-15.

govern. Indeed, the political project addressed to the milieu is one of the fundamental axes in the deployment of mechanisms of security.[32]

Apparatuses of security work then within the reality of fluctuations, a reality that is recognised as a nature.[33] The population, given a *laissez-faire* freedom of movement is produced as a subject, called upon to utilise this freedom and to conduct itself in such and such a fashion.[34] *Homo œconomicus* given free play to express desire in the Physiocrat's free market, acting out of private interest, will produce the general interest of the population. In doing so, by letting things take their course, the phenomena of scarcity is curbed. Letting prices rise and giving grain producers the opportunity to profit means that it is the price rise that produces the fall in scarcity. Scarcity is nullified on the basis of the reality of the movement that leads to scarcity.[35] *Homo œconomicus* given a certain freedom of movement to act on desire highlights one element of the naturalness of the population. By acting on and through this naturalness, apparatuses of security aim for a nullification of phenomena 'in the form of a progressive self-cancellation of phenomena by the phenomena themselves'.[36] This is a fundamental characteristic and importantly one which reveals 'a level of the necessary and sufficient action of those who govern.'[37] The population as that on which and towards which mechanisms are directed in order to have a particular effect is further constituted as an object.[38]

Mechanisms of security then, at the level of the population, work on an open series made governable/knowable through an estimate of probabilities. By standing back, so that one can grasp the point at which things are taking place, phenomena are understood at the

[32] Ibid., 23.
[33] Ibid., 37.
[34] Ibid., 42.
[35] Ibid., 40.
[36] Ibid., 66.
[37] Ibid., 66.
[38] Ibid., 42-3.

level of their nature or effective reality.[39] Mechanisms of security work on the basis of and within this reality, by getting the components of this reality to work in relation to each other,[40] using these components as a support to make it function as a mode of governance. Politics then acts on the domain of circulation, of freedom, a primarily economic freedom that given free play reveals its own nature and physical interactions or physics. If the end of sovereignty is internal to itself, the end of government is then internal to the things it directs.[41] As we will see, certain technologies have made intelligible, at the molecular level, the nature or internal processes that pathogens take when causing illness. They have revealed the internal principles that provide limits and the bounds within which a MCM must act to prevent disease. In order to support the development of MCMs the government must also respond to the market determined natural regularities that shape the attractiveness of MCM production to prospective companies. As will be demonstrated, significant U.S. government efforts have been devoted to incentivising and supporting partner companies in MCM production at the level of the population.

The bi-directionality of political rationalities and scientific understandings of life

Mechanisms of security are then tools that seek to ensure that the freedom of movement given to people and goods benefits the health and welfare of the population. They are employed by a distinctive liberal political rationality to achieve its aims and manage the negative elements that can arise as certain circulatory processes threaten to foment crises. The spread of disease through either natural or deliberate means is one such crisis that, capitalising on the pathways of travel and communication threatens to suddenly bolt out of control and shut down the entire system. Liberalism's focus on circulation gives rise to a

[39] Ibid., 46-7.
[40] Ibid., 47.
[41] Ibid., 99.

whole new category – or class – of security threats.[42] These 'crises' of circulation are the correlative of a particular way of rationalizing political rule according to the principles of liberalism and *laissez faire*.[43]

Security policy in addressing these sorts of threats must then not only become focused on sorting the 'good' from the 'bad' circulation but must also look to the future to anticipate and prepare for the emergence of particular crises.[44] Pandemic preparedness and the development and stockpiling of antivirals represents one way in which security policy is directed towards the future to mitigate the potentially crippling economic effects of such an occurrence. As this thesis will demonstrate, the U.S. government's efforts to incentivise private industry in the development of MCMs is another. The political need to maintain the health and welfare of the population through efficient economic flows stimulates scientific research and economic partnerships.

Government support in the U.S. in the development of any MCM often takes the form of early stage research. Organisations such as the National Institute of Allergy and Infectious Diseases (NIAID) develop potential compounds that then transition into the private sector for further development. The influence of political and economic rationalities on scientific research and understandings of life does not all flow one way though, as was well noted by Foucault.[45] As this thesis demonstrates, the way that molecular life is understood and presented as threat also shapes the security practices developed to address it. The molecular understanding of the evolutionary potential of bacteria shaped the political rationality of preparedness developed to mitigate the effects of any bioterrorist attack through the development and stockpiling of MCMs. The next section of this chapter details the way that

[42] Stefan Elbe, Anne Roemer-Mahler, Christopher Long, 'Securing Circulation Pharmaceutically: Antiviral stockpiling and pandemic preparedness in the European Union', *Security Dialogue* 45, no. 5 (2014): 448.
[43] Ibid., 448.
[44] Ibid., 448.
[45] See Michel Foucault, *The Order of Things* (London: Routledge, 2002).

particular understanding of molecular life have given rise to new forms of political rationality. Specifically, the evolutionary capacities of bacteria and the flu virus have supported the development of pre-emptive approaches to the threats of pandemic flu, infectious disease and bioterrorism.

Molecularisation and the Biopolitics of Security

Foucault's analysis of mechanisms of security, so essential to the governance and management of the population has inspired a range of research into govern-mental biopolitical security strategies. The focus of this literature has often been on the political rationalities and technologies of security deployed to enact natures within the contingent political and economic realm. Insurance, risk, 'the event', 'the contingent', 'population' and, 'circulation' are often the key organising concepts in this literature.[46] Recent research has also recognised the impact that the understandings of the workings of life at the molecular level have had in the field of security. In seeking to understand this impact a crucial question has been raised. 'What happens to the biopolitics of security when their referent object – life as species existence – undergoes profound transformation and change?'[47] Demographic changes to the population and digital and molecular advances have been recognised as critically important developments that are having a profound impact on the changing character of 'life' as the referent object of the biopolitics of security in the 21st century.[48]

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[46] See Claudia Aradau and Rens Van Munster, 'Governing Terrorism Through Risk: Taking Precautions, (un)Knowing the Future', *European Journal of International Relations* 13, no. 89 (2007): 89-115; Michael Dillon, 'Underwriting Security', *Security Dialogue* 39, no. 2–3 (2008): 309–332; Michael Dillon, 'Governing through contingency: The security of biopolitical governance', *Political Geography* 26, no. 1 (2007): 41-47; Louise Amoore and Marieke De Goede, 'Transactions after 9/11: the banal face of the preemptive strike', *Transactions of the Institute of British Geographers* 33, no. 2 (2008): 173–185; Ben Anderson, 'Security and the future: Anticipating the event of terror', *Geoforum* 41, no. 2 (2010): 227–235; Claudia Aradau and Tobias Blanke, 'Governing circulation: A critique of the biopolitics of security', in *Security and Global Governmentality: Globalization, Governance and the State*, eds. Miguel de Larrinaga and Marc G. Doucet (London: Routledge, 2010), 44-58; Stefan Elbe, 'Risking Lives: AIDS, Security and Three Concepts of Risk', *Security Dialogue* 39, no. 2–3 (2008): 177-198.

[47] Michael Dillon and Luis Lobo-Guerrero, 'Biopolitics of security in the 21st century: an Introduction', *Review of International Studies* 34, (2008): 269.

[48] Ibid., 269.

Changes in our understanding of life at the molecular level necessarily take us beyond Foucault's theorising of political strategies adapted to the body and the population. Significantly, biopolitics is critically dependent on what the sciences of life say species life is, how we can visualise it and what its thresholds of manipulation are for instance. For Dillon and Reid contemporary biopolitics has become informed by a new biophilosophical discourse, and a new form of science, the complexity sciences.[49] The biopolitics that is emerging out of this biophilosophical discourse of complexity has been termed 'recombinant biopolitics'. Life, conceived of as open complex adaptive systems, exploits connectivity through the power of recombination.[50] Code links the information and molecular sciences and is the foundation of the new biophilosophical discourse that they share.[51] The essential constituent components of life have now become conceived in terms of information as code.

Biopolitics is also critically dependent upon the mechanisms that the life sciences make available for manipulating and intervening into living processes.[52] These mechanisms and technologies include the Southern blot noted above which confer an added mobility upon the molecular elements of life. As Dillon and Lobo-Guerrero note, this added mobility, a direct result of the molecularisation of life, has transformed what we are capable of doing to and with living material.[53] New forms of manipulation represent one way in which understandings of life at the molecular level have generated new notions of insecurity. Insecurity has also arisen from the insights of molecular science and the ways in which it has transformed what we understand a living thing to be.[54] These two notions of insecurity, facilitated by the

[49] Michael Dillon and Julian Reid, 'Global Liberal Governance: Biopolitics, Security and War', *Millennium - Journal of International Studies* 30, no. 41 (2001): 42.
[50] Ibid., 44.
[51] Ibid., 50.
[52] Dillon and Lobo-Guerrero, 'Biopolitics of security', 273.
[53] Ibid., 287.
[54] Ibid., 286.

molecularisation of life, are shaped in terms of the deliberate and natural emergence of biological threats.

Bruce Braun has asked a pertinent question in this area: 'In what ways can it be said of the molecularisation of life that it has made our biological existence a political concern in new ways?'[55] In contrast to Rose's account of 'ethopolitics' or the individual management of the genetic risks peculiar to one's own body,[56] Braun outlines the ways in which the molecularised body has brought together biopolitics and geopolitics in the area of security.[57] A displaced body embedded in a chaotic an unpredictable molecular world is added to the dimension of Rose's bounded body constituted in terms of a genetic essence.[58] Molecular immunology has analysed and made visible the constituent elements of flu viruses and their mode of action when entering and exiting a cell. Hemagglutinin (HA) proteins determine how and whether a virus can penetrate human cells with Neuraminidase (NA) proteins determining whether the virus can escape and infect other cells.[59] The molecular workings of viral mutations have also been understood with genetic drift and shift referring to the slow or rapid mutation of viral genes respectively.[60] Changes to the HA proteins on the outside of the flu virus can have significant effects as to the transmissibility and virulence of a virus. Utilising the governmental method of analysis, the issue is less the accuracy of the claims within molecular immunology than *how* this understanding of molecular life has given rise to new forms of political rationality.[61]

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[55] Bruce Braun, 'Biopolitics and the molecularization of life', *cultural geographies* 14, (2007): 6; See also Bruce Braun, 'Governing disorder: biopolitics and the molecularisation of life', in *Global Political Ecology*, eds. Richard Peet, Paul Robbins & Michael Watts (Abingdon: Routledge, 2011), 389-411.
[56] See Nikolas Rose, 'The Politics of Life Itself', *Theory, Culture & Society* 18, no. 6 (2001): 1-30.
[57] Braun, 'Biopolitics and the molecularization of life', 8.
[58] Ibid., 14.
[59] Ibid., 15.
[60] Ibid., 16.
[61] Ibid., 16-7.

The human body is exposed, then, to an inherently unpredictable flu virus that may genetically mutate at any moment whilst being situated within a global economy of circulation and exchange. In this context, the threat becomes virtual, in its potentiality its emergence is immanent in every passing moment. The emergence of a virulent and highly transmissible strain of flu, is 'immanent in the present, although it cannot be known in advance.'[62] Drawing from Henri Bergson and Gilles Deleuze, Braun's recoding of the flu virus in terms of virtuality transforms our relation to the future.[63] The inherent capacity of the flu virus to genetically change and emerge reborn at any moment brings its potential emergence into the present with corresponding elements of fear and dread. This understanding has brought about a correlative political response. A speculative political logic of pre-emption has been employed in order to deal with this threat. Under a regime of 'biosecurity' an extensive system of surveillance is implemented to act pre-emptively and to detect and address the emergence of infectious diseases before they can be imported to the U.S. The molecularisation of life in this context has influenced biopolitical strategies in the protection of particular communities with correlative geopolitical effects.

In a similar fashion to Braun, Melinda Cooper has analysed the way understandings of life at the molecular level have influenced the U.S. response to bioterrorism. Cooper is seeking to understand the changes in U.S. understandings of insecurity that have precipitated the legislation of Project BioShield in 2004, authorizing $5.6 billion for the purchase and stockpiling of vaccines, drugs and other MCMs against bioterrorist threats. This occurred at the same time as a more secretive initiative to establish four research centres for the testing of biological weapons defences.[64] Cooper points to understandings of life at the molecular level

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[62] Ibid., 17.
[63] Ibid., 17.
[64] Melinda Cooper, 'Pre-empting Emergence: The Biological Turn in the War on Terror', *Theory, Culture & Society* 23, no. 4 (2006): 113; See also Melinda Cooper, *Life as Surplus: Biotechnology & Capitalism in the Neoliberal Era* (Seattle: University of Washington Press, 2008).

as central to this 'biological turn' in the war on terror. Microbiology has made visible and intelligible an understanding of the bacterial genome as highly fluid. Mobile sequences of DNA can jump across species meaning that resistance to antibiotics, for instance, can be quickly shared.[65] Noting the work of René Dubos, Cooper argues that one significant implication of this is that resistance will continually emerge. There can be no assignable limit to the co-evolution of resistance and counter-proliferation, emergence and counter-emergence.[66]

For Dubos, this engages us in a form of permanent warfare without foreseeable end, a kind of speculative warfare that is necessarily pre-emptive. Pre-emptive acts become immersed in the conditions of emergence of a threat[67] to either actively incite the occurrence of an imagined future or to negate such an occurrence, shaping the conditions of emergence to result in a more desirable end. The continuing evolution of infectious disease as inevitable, the definition of infectious disease as emerging and emergent in *essence* has had considerable influence in U.S. public health discourse.[68] Public health policy must now mobilise against emergence itself in whatever form it takes.[69] In this light, emerging infectious disease was positioned as a threat to national security and one that should be tackled in conjunction with bioterrorism. Chapter three looks at the role of the molecularisation of life in this relationship in depth. This understanding took legislative form in 2002 with the U.S. Congress passing the Bioterrorism Act outlining the same emergency response procedures for bioterrorist attacks and emerging infectious disease.[70]

Microbial resistance or the deliberate release of a biological pathogen could be incubating, threatening to emerge with catastrophic consequences at any time. In contrast to

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[65] Cooper, 'Pre-empting Emergence', 116.
[66] Ibid., 116.
[67] Ben Anderson, 'Preemption, precaution, preparedness: Anticipatory action and future geographies', *Progress in Human Geography* 34, no. 6 (2010): 790.
[68] Cooper, 'Pre-empting Emergence', 118.
[69] Ibid., 118.
[70] Ibid., 118.

classical risk theory that supports prevention, catastrophe entails the risk of something occurring without warning, instantaneously and irreversibly.[71] Significantly, as with the virtual threat, the notion of catastrophe risk 'establishes our affective relation to the future as the only available basis for decision-making.'[72] A course of speculative pre-emption is employed which intervenes in the conditions of emergence of the future before it gets a chance to befall us.[73] As a consequence, the Pentagon's Defence Advanced Research Projects Agency (DARPA) has employed aggressive counter-proliferation in order to 'create antibiotics and vaccines against infectious diseases *that have not yet even emerged*.'[74] The understanding of the nature of bacterial resistance at the molecular level has instigated a pre-emptive war against evolving infectious disease and bioterrorism that can only be of indefinite duration and economic consequence.

Sonja Kittelsen, investigating the affective consequences of bioterrorism, has argued that this threat is particularly suited to the imaginary of the displaced molecular body.[75] This arises not only from the dread of contamination from known viruses but also from the 'fear of a future possibility of exposure to new, targeted and uniquely tailored forms of biomolecular manipulation and mutation.'[76] This fear factor in addition to the *manner* in which bioterrorism strikes as elusive, indiscriminate and invisible generates a sense of dread. Much like the virtual threat and the catastrophic risk, this notion compounds the distinction between actual and imagined threat, challenges the conventional spatio-temporal relationship between 'threat' and 'security' and reinforces a sense of imminence and pervasiveness of possible attack.[77]

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[71] Ibid., 119.
[72] Ibid., 120.
[73] Ibid., 126.
[74] Ibid., 126-7.
[75] Sonja Kittelsen, 'Conceptualising Biorisk: Dread Risk and the Threat of Bioterrorism in Europe', *Security Dialogue* 40 no. 51 (2009), 61.
[76] Ibid., 61.
[77] Ibid., 52.

For Kittelsen, as for Braun and Cooper, bioterrorism's imperceptible nature means that insecurity can exist independent of an actual attack occurring.[78] This has certain political effects and implications, noted above. The distinction between the bioindustry as defender against biological threat and the bioindustry as producer of biological threat is notorious for its ambiguity.[79] Pointing to U.S. military biodefence laboratories as the source of the anthrax in the 2001 attack, the dynamic between threat and defence is highlighted as circular.[80] DARPA's pre-emptive response proliferates the threat against which it is meant to defend. When you have a threat that is a manifestation of a subjective vulnerability, shaped predominantly by the imaginary, you enter a vicious cycle in which the most dangerous form of emergence may be a political response that threatens the material realisation of the aporia of biopolitical security.

Eugene Thacker has also analysed the U.S. response to bioterrorism, seeking to understand the forms of power 'engendered by these threats and by this *biological security*.'[81] Biowar refers to all forms of biological warfare including bioterrorism in which, biology is both the weapon and the target.[82] While noting the use of biology in biowar from as early as the Black Death, the influence of the molecularisation of life is outlined on the possibility of engineering and designing novel biological weapons in contrast to already existing biological agents which are the subject of military use. For Thacker, this layer of genetic warfare, presaged by the revelations of Soviet state development,[83] is dominated by the recent advances in molecular genetics and biotechnology that have supported projects such as that focused on the Human Genome. This involves the use of techniques such as genetic engineering, gene therapy, medical genetics and genomics. For Thacker, these techniques, in

[78] Ibid., 52.
[79] Ibid., 56.
[80] Ibid., 56.
[81] Eugene Thacker, *The Global Genome* (Cambridge: MIT Press, 2006), 212.
[82] Ibid., 213-4.
[83] See Ken Alibek & Stephen Handelman, *Biohazard* (London: Random House, 1999).

light of the history of eugenics, may be used to design for the first time biological weapons that can target specific regions, ethnic groups, populations or biological resources.[84]

While the worries of a new biologically enhanced eugenics are not sustained by all commentators,[85] the prospect of genetically engineered and enhanced bioweapons is driving new notions of insecurity. Central to this is the dilemma, present in 'dual-use research of concern', that our ability to intervene in and manipulate life at the molecular level could have both beneficial and dangerous consequences.[86] Genomics and gene therapy, while offering to improve human health and well-being, have also opened up the possibility of genetically engineered pathogens.[87] Synthetic genomics, the ability to artificially synthesise biological components or organisms, supported by advances in molecular biology, have also generated security concerns.[88] A particular worry is that published research detailing the creation of synthesised viruses could be used by terrorists to reconstitute dangerous pathogens or to create novel ones. These fears discount the tacit skills and rituals not discussed in published explanations, aspects which are essential to any successful experiment and a significant obstacle to those wishing to utilise techniques from published material for nefarious ends.[89]

Elbe has also noted the ways in which the molecularisation of life has facilitated our understandings of insecurity in terms of the natural or deliberate emergence of biological threats. More than this, though, Elbe has demonstrated how the molecular vision of life is supporting the development of medicines to protect us from these threats.[90] The molecular workings of the influenza virus have demonstrated that the virus must enter living cells in

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[84] Thacker, *The Global Genome*, 222.
[85] See Rose, *The Politics of Life Itself*, 54-73.
[86] Laurie Garett, 'Biology's Brave New World', *Foreign Affairs* 92, no. 6 (2013): 32.
[87] Steven M. Block, 'Living Nightmares: Biological Threats Enabled by Molecular Biology', in *The New Terror*, eds. Sidney D. Drell, Abraham D. Sofaer, and George D. Wilson (Stanford: Hoover Institution Press, 1999), 40-75.
[88] Kathleen M. Vogel, *Phantom Menace or Looming Danger?* (Baltimore: John Hopkins Press, 2013), 71.
[89] Ibid., 104.
[90] Stefan Elbe, 'The pharmaceuticalisation of security: Molecular biomedicine, antiviral stockpiles, and global health security' *Review of International Studies* 40, no. 05 (2014): 929.

order to replicate and exit in order to infect further cells. When exiting cells, the virus relies upon the enzyme neuraminidase to dissolve the sialic acid attaching it to the surface of the host cell.[91] This mechanism of action supported the design of new antiviral medications in the form of *Tamiflu* and *Relenza*, designated as neuraminidase inhibitors.[92] Crucially though, the design of *Tamiflu* only became possible after the molecular structure of neuraminidase had been decoded.

For Elbe, the deepening knowledge regarding the molecular processes of viral replication, the emergence of scientific technologies such as x-ray crystallography capable of revealing and visualising molecular structures, and advances in computer modelling and chemical pharmacology used for the rational design and synthesis of new molecules were all key components in determining the molecular structure of neuraminidase.[93] These components also supported the design of an 'artificial' new molecule that could bind to a key site in the neuraminidase enzyme inhibiting viral replication.[94] As the case of *Tamiflu* represents, the molecular vision of life is not just highlighting new notions of insecurity but also enabling the creation of molecularly designed pharmaceutical interventions to address these threats.[95] The molecularisation of life is, then, the necessary epistemic precondition for the technical and material creation of such novel MCMs.[96] For Elbe, this vision of life, in conjunction with the development and stockpiling of MCMs, biocapital, therapeutic citizens, and flexible pharmaceutical regulation forms the core of what has been conceptualised as the pharmaceutical turn in security policy.[97]

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[91] Ibid., 930.
[92] Ibid., 930.
[93] Ibid., 930.
[94] Ibid., 930.
[95] Ibid., 930.
[96] Ibid., 930-1.
[97] Ibid., 936.

Aside from Elbe, the literature in International Relations that has analysed the impact of the molecularisation of life on security policy has focused solely on the way threats have been understood and the political rationalities they have inspired. This thesis adds to this literature by demonstrating the way that the molecular vision of life has not only played a central role in heightening concerns regarding bioterrorism but has also made possible the development of new molecular-based security technologies against this threat. Indeed, the molecular vision of life, through visualisation and manipulation has made possible the development of MCMs. The U.S. government's response to bioterrorism has undergone a process of molecularisation. In supporting this argument this chapter will now look at the key understandings and discoveries in biology and related disciplines that opened up molecular life to visualisation and manipulation.

The Discovery of the Molecular Structure of DNA

Deoxyribonucleic acid (DNA) forms the building blocks of life and our ability to visualise and manipulate DNA provides the foundation from which many of today's medicines and potential weapons can be made. This section details the key discoveries that revealed the structure and function of DNA as the carrier of genetic information. DNA was discovered in the late 1860s and many of the additional details of the DNA molecule, including its primary chemical components and the ways in which they joined with one another, were discovered in the decades after this.[98] Key discoveries included the make-up and ordering of the four nucleotide bases: Cytosine, Guanine, Thymine and Adenine that constitute DNA. It was also discovered that Ribonucleic acid (RNA) contains three of these bases in addition to that of Uracil which takes the place of Thymine. Discoveries in 1950 asserted that DNA varies among species, that the same nucleotides do not repeat in the same order and that the bases follow a

[98] See Leslie A. Pray, 'Discovery of DNA Structure and Function: Watson and Crick', *Nature Education* 1, no. 1 (2008): 100.

clear ratio.[99] In DNA, the number of Adenine bases always matches that of Thymine and the number of Cytosine bases matches that of Guanine.

The experiments that generated these understandings were crucial to the discovery by Jim Watson and Francis Crick in 1953 that the DNA molecule exists in the form of a three-dimensional double helix.[100] This discovery, owed a great deal to the ability to visualise the molecular structure of DNA. Rosalind Franklin using X-rays had produced the best X-ray diffraction images of DNA at that time.[101] These images displayed the way that the DNA molecules were positioned. From this x-ray of the molecular structure of these bases the double helix nature of DNA was ascertained. The idea that DNA contained the hereditary material was suggested in the 1940s and proved in the 1950s (expanded on in Chapter 6).[102] The discovery of the double helix also convinced the biological community that genes were composed of DNA and that this was the basis of heredity.[103] It also explained the mutability of life, as mutations both beneficial and negative would appear as a result of changes in the DNA.

The discovery of the structure of DNA was crucial to the understanding of its function as a carrier of hereditary and genetic information utilised in a range of functions in determining an organism's traits and its role in determining protein synthesis. It inspired research that led to the definition of DNA as *the* informational molecule.[104] The duplex structure of DNA was one key aspect revealed by its analysis. The genetic functions of DNA are inextricably associated with its duplex structure.[105] Particularly, the double-stranded structure

[99] Ibid., 100.
[100] Ibid., 100.
[101] Michel Morange, *A History of Molecular Biology*, trans. Matthew Cobb (Cambridge: Harvard University Press, 2000), 108.
[102] Ibid., 30-50.
[103] Ibid., 116.
[104] Joshua Lederberg, 'What the double helix (1953) has meant for basic biomedical science', in *The Philosophy and History of Molecular Biology: New Perspectives*, ed. Sahotra Sarkar (Dordrecht: Kulwer, 1996), 15.
[105] Ibid., 15.

of DNA made its potential for the replication and storage of information apparent.[106] In cell division, the genome – the complete set of genetic material in an organism – must be copied and passed on to both daughter cells. Each strand of DNA in the double helix runs antiparallel to each other with the sequence of bases running in a complementary fashion.[107] This means that upon separation each strand can act as a template for the synthesis of a new identical complementary strand of DNA.[108] The structure of DNA as a double helix, then, supports the replication of the genome before it is passed on to descendants.[109]

The directional flow of information from DNA has supported the development of the 'central dogma of molecular biology.' This is focused on the detailed transfer of sequential information.[110] The dogma regarding this flow of information has recognised the way that DNA is transcribed to RNA which is then translated into proteins which constitute the very matter of our bodies. Genes reside in sections of DNA. In protein synthesis the double-stranded DNA is turned into a single strand of messenger RNA (mRNA) in correspondence with the bases coded for in the DNA in a process of *transcription*. This mRNA is then processed by a ribosome (expanded on in chapter 7) that reads the bases to produce a corresponding chain of amino acids in a process of *translation*.[111] As a sequence of three bases is read, transfer RNA (tRNA) delivers the corresponding amino acid. Once the chain of amino acids is complete, it folds into a protein. This dogma is not an *ultima ratio* with some viruses reversing this transcription process turning RNA into DNA.[112] One of the key concepts to come out of our understanding of DNA was the gene.

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[106] Bruce Alberts et al, *Molecular Biology of the Cell Sixth Edition* (New York: Garland Science, 2015), 175.
[107] Ibid., 176.
[108] Ibid., 177.
[109] Ibid., 178.
[110] Fancis Crick, 'Central Dogma of Molecular Biology', *Nature* 227, (1970): 561.
[111] For a good visualisation of this process see Evelyn Fox Keller, *The Century of the Gene* (Cambridge: Harvard University Press, 2002), 53.
[112] Lederberg, 'What the double', 22.

The Gene and Classical and Molecular Biology

Genes have been described as segments of DNA that can be defined and manipulated as chemical entities.[113] The idea of the gene emerged in the 1860s and was popularised in the early 1900s.[114] The constitution of the gene was first unravelled in the 1940s with the understanding that DNA rather than proteins were the carriers of genetic information.[115] Experiments with bacteriophage, viruses that only infect bacteria, demonstrated that DNA was the key component necessary for viral replication passed on during infection (expanded on in Chapter 6). The discovery of the structure of DNA further convinced biologists that genes were not only real molecules but that they are made up of DNA.[116] Further, the identification of DNA as the genetic material spawned a new era of analysis in which the techniques of molecular genetics would replace those of classical genetics.[117]

One method of classical genetics to produce 'attenuated' or weakened viruses for use in vaccines is applied evolution. This has been used to produce the benign virus and antigens of the vaccinia virus used in the Imvamune smallpox vaccine. Applied evolution generates live-attenuated viruses through the serial passage of the virus in novel host cells.[118] Serial passage, first employed by Louis Pasteur, leverages the evolutionary principle that fitness is always 'specific to a particular environment, and thus high fitness in one environment may come at a cost of low fitness in another.'[119] This method has its basis in viral evolution which is known to proceed extremely rapidly due to the unique features of viral genetics and viral population dynamics.[120]

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[113] Ibid., 19.
[114] Keller, *The Century*, 2.
[115] Ibid., 3.
[116] Ibid., 3.
[117] Ibid., 3.
[118] Kathryn A. Hanley, 'The double-edged sword: How evolution can make or break a live-attenuated virus vaccine', *Evolution* 4, no. 4 (2011): 635.
[119] Ibid., 636.
[120] Ibid., 637.

Attenuation was achieved with the Imvamune vaccine by passing the vaccinia virus through chick embryos over 500 times. In this process the virus will mutate and adapt to its new host, this adaptation, ensuring fitness in one environment weakens the virus in humans. As a result of this process, Modified Vaccinia Ankara (MVA) virus, the active virus in Imvamune, has nearly 15 percent less genome in comparison to its parental vaccinia virus CVA, meaning that MVA has lost the ability to reproduce itself in a form that can cause infection in humans.[121] In this classical method of attenuation the virus' phenotype or infectious properties act as an indication of the change undergone in the serial passage process that determines its genetic make-up or genotype.[122] In contrast, our ability to understand and manipulate DNA has introduced modern techniques of molecular genetics such as rational vaccine design.[123] Understanding the molecular biology of the virus supports the genetic engineering of attenuating mutations.[124] Such mutations are engineered into a recombinant genome that, when inserted into a cell generates a recombinant and attenuated virus.[125] In this approach, the rational design and editing of a virus' genome and genotype is the primary indicator of the change expected in the phenotype or observable trait, in this case the infectious property of the virus.

The ability to understand, breakdown and manipulate DNA supported the search to fully map the human genome in the hope that the genetic blueprint detailing our complete make up will be revealed.[126] One of the most significant implications of this project was the revelation that merely understanding the sequence of a gene will not elucidate an understanding of its biological function.[127] *Structural* genomics, based on this linear notion of sequence and function has been replaced with a *functional* understanding and emphasis. This

[121] Lucas Sánchez-Sampedro et al., 'The Evolution of Poxvirus Vaccines', *Viruses* no. 7, (2015): 1739.
[122] Hanley, 'The double-edged sword', 637.
[123] Ibid., 640.
[124] Ibid., 640.
[125] Ibid., 640.
[126] Keller, *The Century*, 4.
[127] Ibid., 6.

utilises the sequence of bases as a tool to assess gene function rather than as an end product to understand the comprehensive genetic make-up and structure.[128] It has been argued that the shift to functional genomics is a consequence of the significant gap between genetic 'information' and biological meaning.[129] The idea that in discovering the molecular basis of genetic information we could fully decode and understand the make-up of an organism has been relegated as a result of the complexity of life.[130] Indeed, the complexity of life has removed it from complete understanding and manipulation. The role of the gene as the *superfold,*[131] the ultimate condition of man's constitution, is not to be realised. Despite the fact that the gene did not hold all the answers in discovering the informational basis of life, research into DNA has been central to the development of new medicines and new weapons.

Medicine Development and the Generation of (In) Security

Research into the molecular workings of DNA have also revealed ways in which it can be cut and shaped in accordance with particular restriction enzymes. Such enzymes (discussed in chapter 3) have been used to edit the genetic material of bacteria so that they produce insulin. Such insulin is then used to treat patients that have diabetes. The idea that disease has a root cause, from within or without, has not always been accepted and can be seen as a pivotal moment that facilitated the production of medicines. The 'germ theory of disease' (discussed in chapter 7), argued that diseases are caused by external agents and that the nature of these causative agents could be understood and classified.[132] This understanding, in addition to the selective binding properties of dyes, was central to the development of antibiotics. This supported the idea that specific drugs or 'magic bullets' could be discovered

[128] Ibid., 7.
[129] Ibid., 8.
[130] Ibid., 8-9.
[131] Deleuze, *Foucault*, 109.
[132] Jürgen Drews, *In Quest of Tomorrow's Medicines,* trans. David Kramer (New York: Springer-Verlag, 1999), 84.

or designed that selectively bind to the disease-causing organism or pathogen. Pathogens could now be deliberately targeted through the use of particular drugs or therapeutics.

The 'germ theory' has been supplemented by further theories of disease such as suggestions that disease arises from disturbed chemical imbalances.[133] Molecular genetics has further supplemented this chemical paradigm with an informational paradigm. This understands the emergence of disease as a result of particular genetic changes.[134] Molecular biology has supported an understanding of disease processes at the molecular (genetic) level and the determination of the optimal molecular targets for drug intervention.[135] In 2000 it was commented that drug therapy was based upon 500 molecular targets, a greater understanding of the disease-causing properties of genes has increased the number of potential molecular drug targets to between 5,000 and 10,000.[136] The use of tools such as x-ray crystallography (discussed in chapter 6), in detailing the precise molecular composition of proteins, have also supported the rational design of drugs.

Genetic engineering is a good example of the way molecular biology has supported the development of new medicines such as monoclonal antibodies for humans. One common method used to develop antibodies is to use genetically engineered or 'transgenic' mice to produce fully human antibodies.[137] Antibodies form part of the human body's adaptive immune response and are produced to target and immobilise specific unrecognised pathogenic elements termed antigens.[138] In the development of genetically engineered antibodies, human genes that produce immunoglobulin, the most abundant type of antibody,

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[133] Ibid., 85.
[134] Ibid., 86.
[135] Jürgen Drews, 'Drug Discovery: A Historical Perspective', *Science* 287, (2000): 1962.
[136] Ibid., 1962.
[137] Sirid-Aimée Kellermann and Larry L Green, 'Antibody discovery: the use of transgenic mice to generate human monoclonal antibodies for therapeutics', *Current Opinion in Biotechnology* 13, no. 6 (2002): 593.
[138] Muriel Moser and Oberdan Leo, 'Key concepts in immunology', *Vaccine* 28S, (2010): C4

are engineered to replace the equivalent genes in mice.[139] When this engineering is done successfully the immune system of the mouse recognizes administered human antigens as foreign and produces a strong immune response.[140] The antibodies produced can then be harvested and administered to human beings.

Our ability to understand, manipulate and shape the way life is constructed at the molecular level has then supported the development of needed medicines. The prospect has also been raised that these understandings and technologies could be used to enhance pathogens or develop and release new ones in premeditated and malicious acts. Accidents should also be noted as ways in which harmful biological material may enter the environment. Technologies such as genetic engineering are said to pose a 'dual-use dilemma' because it is difficult to prevent their use without foregoing their beneficial application.[141] Further, it has been recognised that many of the technologies with the potential to do the most good are also capable of causing the most harm.[142] 'Dual-use' refers then to 'materials, hardware, and knowledge that have peaceful applications but could also be exploited for the illicit production of nuclear, chemical, or biological weapons.'[143] In contrast to, say, nuclear technology, the pathogenic bacteria and viruses that are used in biotechnology are readily available from natural sources, have numerous legitimate applications in research and industry, are present in many types of facilities, such as hospitals and universities, and are impossible to detect at a distance.[144] These factors make the use of biological agents a particularly pressing dilemma.

The Dual-Use Dilemma

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[139] Larry L. Green, 'Antibody engineering via genetic engineering of the mouse: XenoMouse strains are a vehicle for the facile generation of therapeutic human monoclonal antibodies', *Journal of Immunological Methods* 231, (1999), 13.
[140] Ibid., 13.
[141] Jonathan B. Tucker, 'Introduction', in *Innovation, Dual Use, and Security*, ed. Jonathan B. Tucker (Cambridge: MIT Press, 2012), 1.
[142] Ibid., 1.
[143] Ibid., 2.
[144] Ibid., 2.

The biotechnology revolution is said to have begun in the 1970s, two decades after the discovery of the structure of DNA. One of the first discoveries in this revolution was the methodology for cutting and splicing segments of DNA from different sources making it possible to transfer genes between different species.[145] As outlined above, one of the practical applications of this recombinant DNA or genetic engineering process was the production of human monoclonal antibodies in mice. Synthetic genomics has complimented recombinant DNA techniques and has made possible the construction of entire genes and microbial genomes from scratch.[146] Scientists can now 'design a genetic sequence on a computer and convert it directly into a physical strand of DNA coding for a useful product or function.'[147] In 2010 the first self-replicating bacterial genome consisting of more than a million DNA units was synthesised by the J. Craig Venter Institute.[148] This tool has been noted as a clear example of a dual-use technology.

In 2002 synthetic genomics was used to re-create the poliovirus and prompted fears that terrorists may use this technology to re-create other more deadly viral agents.[149] In 2005 the Spanish influenza virus responsible for killing fifty million people worldwide between 1918 and 1919 was also re-created using this tool. This was done with the aim of understanding the genetic basis of its virulence so as to guide the development of effective antiviral drugs.[150] In principle it is now possible for scientists to reconstruct any virus for which an accurate genetic sequence exists.[151] This includes the variola virus, (discussed in chapter 5), that causes smallpox and against which there is little worldwide immunity with vaccination having stopped after the eradication of the disease in the late 1970s. Advances in the understandings of the human genome – genomics – and the way proteins are structured and function – proteomics –

[145] Ibid., 4.
[146] Ibid., 4.
[147] Ibid., 4.
[148] Ibid., 5.
[149] Ibid., 4-5.
[150] Ibid., 5.
[151] Ibid., 5.

amongst others, have yielded a profound new understanding of life at the molecular level.[152] They have also raised fears that potential terrorists could misuse these technologies and follow in the steps of the Soviet Union in using recombinant DNA technology to break with the natural vital order and develop genetically engineered pathogens with greater virulence, stability and antibiotic resistance.[153]

Dual-use technology then poses the problem that potential terrorists may re-create old viruses or develop new and advanced weapons of their own accord. It has been noted that there are, though, significant technical obstacles to the construction of any highly pathogenic virus from scratch. Most prominent amongst these is the cultivation of an agent and its effective delivery and dissemination.[154] These difficulties are significantly reduced if potential terrorists have access to experiments detailing the steps to be taken when seeking to develop a virus or make it more pathogenic. Such experiments conducting the latter have been termed 'gain of function' and may well be carried out with benign intent.

Such a case occurred in 2011 when Ron Fouchier, a Dutch scientist, funded by the National Institute of Health (NIH), mutated the flu virus H5N1 into something that was transmissible through the air between ferrets, the laboratory equivalent of human beings.[155] Until this time H5N1 had only infected those who had been in contact with infected birds. Fouchier and Yoshihiro Kawaoka (a researcher who had carried out a similar experiment, also funded by the NIH) were criticised for deliberately creating a mammalian strain of pandemic flu. The details of their experiments were termed a cookbook for terrorists and prevented from being published. This research was justified on the grounds that it would help anticipate

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[152] Ibid., 5.
[153] John Hart, 'The Soviet Biological Weapons Program', in *Deadly Cultures: Biological Weapons since 1945*, eds. Mark Wheelis, Lajos Rósa and Malcolm Dando (Cambridge, MA: Harvard University Press, 2006), 132-156. Cited in Tucker, 'Introduction', 5.
[154] Tucker, 'Introduction', 6-8.
[155] Laurie Garett, 'Biology's Brave New World', *Foreign Affairs* 92, no. 6 (2013), 32.

the emergence of this virus in nature, so preventing a potential pandemic through advanced vaccine production.[156]

Research of dual-use concern that had significant implications for bioterrorism agents was carried out in 2000. Australian researchers trying to develop a contraceptive vaccine for mouse populations found that inserting a single gene – interleukin-4 – into a mousepox virus rendered the normally mild pathogen highly lethal in mice and animals that had been vaccinated against the mousepox.[157] The dual-use implications arose as mousepox is closely related to the variola virus, the causative agent of smallpox. This research suggested that a similar genetic manipulation of the variola virus may increase its virulence and render it resistant to the standard protective vaccine.[158] Such research then is particularly problematic and presents governments with a dilemma. As will be demonstrated in the next chapter, the opportunities opened up by the molecular vision of life to manipulate life at the molecular level significantly influenced the U.S. government's understanding of the threat of bioterrorism.

Conclusion

This chapter has set out the key aspects of molecular biopolitics, the way it has been addressed in the field of International Relations and the key discoveries and understandings that supported this intervention into molecular life. For Rose the molecular gaze has come to supplement, if not supplant the molar gaze recognised and outlined by Foucault. Central to this supplementation has been the way this vision of life has made visible, intelligible and manipulable the molecular workings of life. International Relations has so far predominantly focused on the notions of insecurity that these tools of visualisation have inspired. The molecular vision of life, though, has not only made visible the natural processes of biological

[156] Ibid., 33.
[157] Tucker, 'Introduction', 6.
[158] Ibid., 6.

life and their connected understandings of insecurity. As Elbe has noted, it has also made possible the manipulation and intervention into molecular life outside of the natural vital order supporting the development of new medicines and security technologies. Restriction enzymes, for example, have allowed us to change the genetic make-up of organisms allowing for the production of medicines such as insulin.

Research into the workings of life has generated certain dominant understandings and interpretations. The 'central dogma of molecular biology' explains the way that information contained in DNA is transferred into proteins. Our ability to intervene in life at the molecular level has also instigated a shift in techniques in determining the genetic changes in an organism. It is now possible to directly manipulate the DNA sequence of an organism and precisely understand the way in which this change will affect its physical properties. We have come to realise, though, that the 'informational' paradigm has significant limitations in explaining the role of genes and DNA in the production of proteins. Despite the limited explanatory power of this shift, it has had a profound impact on the production of medicines. It is possible now to genetically engineer mice to produce viable antibodies to treat diseases in humans. With each scientific advance and benefit, it seems, comes a potential drawback and threat. Genetic engineering can help create new medicines but it can also be used to enhance biological weapons such as antibiotic-resistant anthrax. Synthetic genomics allows us to re-create past diseases to understand their virulence. Such research may also be used for nefarious ends. We have then the issue of the benefits and drawbacks that result not only from particular technologies but also the research that is produced from them. As the next chapter will discuss, the potential for terrorist to misuse these technologies had a significant impact of the perception of bioterrorism in the U.S. government.

Chapter 3: Molecularisation and the Emergence of Civilian Biodefence in the U.S.

Introduction

Having established in the previous chapter the way the molecular vision of life is impacting security through visualisation and manipulation, this chapter argues that this molecular conception of life is generating new notions of insecurity in the form of heightened concern with the threat of bioterrorism. In making this argument, this chapter critically examines the role of this vision of life in generating new notions of insecurity in this context. As a result of this understanding of insecurity, a preparedness response was initiated so as to produce and stockpile medical countermeasures (MCMs) to respond to a bioterrorist attack. The Project BioShield Act set out dedicated funds to support this response. This chapter then analyses the first major partnership between the U.S. government and a pharmaceutical company using Project BioShield funds. The partnership with VaxGen resulted in a publicly embarrassing failure. It demonstrated the significant difficulties and tensions inherent in the development of MCMs arising from the differing public and private expectations and the ways in which the government would have to adapt to overcome these difficulties. This led to a profound realisation that significant institutional adaptation in the economic, political, legal and regulatory realms would be required in order to translate molecular knowledge into viable pharmaceutical defences. Specifically, different financial incentives would have to be provided in order to support companies through the 'valley of death' and make use of our ability to shape life at the molecular level.

Chapter 3 argues that the molecular vision of life shaped the way the threat of bioterrorism was understood and made actionable in a number of key aspects. Through an analysis of the discourse that emerged in the U.S. government surrounding bioterrorism in the 1990s, this chapter identifies two key areas in which the molecularisation of life influenced

understandings of insecurity. Firstly, there was concern that potential terrorists may take advantage of the widespread technologies and molecular knowledge necessary for cultivating and culturing biological agents to create conventional and new biological weapons that could cause mass causality events. This resulted in prominent U.S. defence institutions investigating the ease with which this could be done. Secondly, the nature of infectious disease at the molecular level was combined with the threat of bioterrorism in the 'dual-purpose' argument to shape an actionable political response to both threats. This argument utilised the inevitable resistance of bacteria to medicines to shape the political response to bioterrorism as something which cannot be prevented and so must be prepared for through the creation and stockpiling of MCMs.

As a result of the events of September 11th 2001 and the anthrax letters that followed shortly after, the preparedness response was implemented through funding via the Project BioShield Act. The insecurity posed by the threat of bioterrorism was to be mitigated by the development and stockpiling of MCMs. Through an analysis of the U.S. government's partnership with VaxGen using BioShield funds this chapter argues that the incentives put forward to support the development of MCMs were not sufficient in this case. Significant tensions emerged from the differing public and private expectations and capabilities in this partnership. This demonstrated a wider lesson that there is a significant gap between the idea and plan of a preparedness response utilising MCMs and its realisation. As the next chapter will demonstrate, this widely publicised failure led to the profound realisation that significant institutional adaptation would be required to effectively support companies in the MCM development field.

This chapter proceeds with the key aspects of the discourse that shaped the perception of bioterrorism in the U.S. government in the 1990s. The motivation and capabilities of terrorists and the role of the 'dual-purpose' argument are set out and analysed.

It then turns to the preparedness response, dependent upon MCMs, developed and implemented in response to the anthrax letters. The Project BioShield Act is then analysed, specifically in relation to the incentives utilised and the partnership with VaxGen to develop a new anthrax vaccine. Finally, it concludes by noting the analysis of the Biomedical Advanced Research and Development Authority (BARDA) that must follow.

Molecular Life and Perceptions of Bioterrorism in the U.S.

Terrorists and Biological Weapons

The structure of DNA was revealed in the 1950s using the X-ray diffraction images derived from x-ray crystallography.[1] As noted in the previous chapter, our ability to understand and manipulate the structure and function of DNA ushered in a new era of analysis in which the techniques of molecular genetics would replace those of classical genetics.[2] In classical genetics the changes in the genetic composition of an organism had to be determined through its changed correlative physical properties. The ability of molecular genetics to change the genetic makeup of an organism has created fears that terrorists may develop new types of biological weapons, including advanced biological warfare agents and genetically modified traditional agents[3] that exist outside of the natural vital order. Combining the DNA from different organisms is possible as the genetic code of all organisms is universal. Restriction enzymes cut or 'cleave' DNA particular to certain sequences. Using specific enzymes, the same DNA sequences can be cut from different organisms. Each cut with the same enzyme leaves a complementary site at which the DNA can be bound together using another enzyme, ligase.[4] Using the right restriction enzyme the gene that produces human

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[1] Michel Morange, *A History of Molecular Biology*, trans. Matthew Cobb (Cambridge: Harvard University Press, 2000), 108.
[2] Evelyn Fox Keller, *The Century of the Gene* (Cambridge: Harvard University Press, 2002), 3.
[3] James B. Petro, et al., 'Biotechnology: Impact on Biological Warfare and Biodefense', *Biosecurity and Bioterrorism* 1, no. 3 (2003): 162.
[4] Morange, *A History*, 187.

insulin has been recombined with bacterial genetic material or plasmids. When this recombinant plasmid is placed in the bacterial cell it will produce human insulin which can be used to treat diabetes.

Genetic engineering, also known as gene splicing, recombinant DNA and genetic modification opens up the possibility that terrorists may use this molecular knowledge to create a new class of biological agents that, working outside the natural vital order, may expand the biological weapons (BW) paradigm.[5] The possibilities opened up by this technology have led to a new classification of genetically modified BW agents as a separate category of BW. As will be demonstrated below, this category of weapon influenced the U.S. government's understanding of the threat of bioterrorism and its MCM development strategy deployed in response. Potential modifications of traditional agents include antibiotic resistance, increased aerosol stability, or heightened pathogenesis.[6] It may also be possible to make it harder to detect traditional pathogens.

These molecular possibilities have also driven fears that potential terrorists may use biotechnology to generate an entirely new class of fully-engineered agents referred to as advanced biological warfare (ABW) agents.[7] Future agents may be rationally engineered to 'target specific human biological systems at the molecular level'.[8] In a move away from traditional agents, the specific biochemical pathways critical for physiological processes may be targeted by engineered agents. The capabilities of these ABW are only limited to the parallel advances in biotechnology and would pose significant problems for MCM

[5] Petro et al., 'Biotechnology: Impact', 161.
[6] Ibid., 162.
[7] Ibid., 162.
[8] Ibid., 162.

development. Molecular-based technologies have also opened up the possibility of synthesising viral genomes facilitating the creation and reconstruction of viruses from scratch.[9]

Concern regarding the ability of terrorists to shape and enhance the killing power of biological weapons rose to prominence in the U.S. in the 1990s. Foremost in shaping these concerns were the activities of the Japanese religious cult, the Aum Shinrikyo. In March 1995 the cult attacked the Tokyo subway with the chemical nerve agent sarin, killing 12 people. Following an investigation it was revealed that between 1990 and 1994 the group had attempted to produce a number of biological agents including anthrax and botulinum toxin. On nine occasions they attempted to disperse what they had produced but this caused no effect.[10] These failures occurred despite the fact that the group had access to virtually unlimited funds, four years to work undisturbed and could draw on a dozen people with graduate training. Further, despite the expenditure of several million dollars the group was unable to obtain any information concerning biological weapons from scientists that worked in the former Soviet Union's industrial-size biological weapons programme.[11]

The actions of the Aum group stoked fears that terrorists may gain access to widespread technology that could make the job of biological weapons production much easier. The U.S. government's perception of insecurity posed by bioterrorism in the 1990s was also influenced by Iraq's biological weapons development programme and the revelations from former Soviet scientists such as Vladimir Pasechnik, Kanatjan Alibekov (Ken Alibek) and Sergei Popov as to the scale and capability of the Soviet biological weapons efforts. Of particular concern was the Soviet's use of genetic engineering technologies to create an enhanced strain

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[9] Filippa Lentzos and Pamela Silver, 'Synthesis of Viral Genomes', in *Innovation, Dual-Use, and Security*, ed. Jonathan B. Tucker (Cambridge: MIT Press, 2012), 133.
[10] Milton Leitenberg, 'An Assessment of Biological Weapons Threat to the United States', in *Emerging Technologies: Recommendations for Counter-Terrorism,* eds. Joseph Rosen & Charles Lucey (Hanover: Institute for Security Technology Studies, 2001), 140.
[11] Ibid., 140.

of plague[12] and anthrax.[13] The Soviet programme was recognised as carrying out the first applications of new genetic engineering technologies to 'improve' biological agents.[14] In order to understand the weaponisation of biological agents past and future, state and terrorist, the CIA embarked on project Clear Vision in 1997. This project tested a Soviet-style bomblet and engaged in the military implications of gene splicing.[15]

Despite the failures of the Aum group's attempts to cultivate a traditional or enhanced agent, the perception in government circles was that this represented the 'index case', marking a 'threshold', in the weakening of the taboo on using chemical or biological weapons.[16] It would have significant political effects. Soon after the Aum attacks the U.S. Government responded by calling an emergency meeting of the Counterterrorism Security Group (CSG) in the Situation Room of the White House. This was the first time the Department of Health and Human Services (HHS) had ever attended a meeting of the CSG.[17] This was followed by Presidential Directive PDD/NSC39 which allocated the rapid-response capability for a chemical or biological incident to the Public Health Service of HHS.[18] As a result of this directive HHS, the principal agency for the health of all Americans, received a steep increase in funding in order to address these areas.[19] The inclusion of HHS in this response was the beginning of the integration of public health and national security to deal with the perceived threat of terrorists with biological weapons.

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[12] Judith Miller, William J. Broad & Stephen Engelberg, *Germs: Biological Weapons and America's Secret War* (New York, Touchstone, 2002), 303.
[13] Laurie Garrett, *Betrayal of Trust* (Oxford: Oxford University Press, 2002), 359.
[14] Malcolm Dando, 'The Impact of Scientific and Technological Change', in *Bioterrorism: Confronting a complex threat*, eds. Andreas Wenger and Reto Wollenmann (Colorado: Lynne Rienner, 2007), 79.
[15] Miller, Broad & Engelberg, *Germs*, 295-6.
[16] Susan Wright, 'Terrorists and Biological Weapons: Forging the Linkage in the Clinton Administration', *Politics and the Life Sciences* 25, no. 1/2 Mar. - Sep. (2006): 73.
[17] Richard A. Clarke, *Against All Enemies* (London: The Free Press, 2004), 156.
[18] The White House, *Presidential Directive NSC-39* (Washington DC: The White House, 1995), cited in Wright, 'Terrorists and Biological Weapons', 72.
[19] Ari Schuler, 'Billions for Biodefence: Federal Agency Biodefence Funding, FY2001-FY2005', *Biosecurity and Bioterrorism* 2, no. 2 (2004): 89.

Bacterial Resistance and the 'Dual-Purpose' Argument

In addition to the newly emergent threat of terrorists with biological weapons, facilitated by our ability to manipulate molecular life, at this time links were also being forged between naturally occurring infectious disease outbreaks and deliberate releases. Central to these links was an understanding of the way bacteria develop resistance to drugs such as antibiotics and share this resistance between themselves. At the centre of this lies a molecular understanding of the way bacteria exchange DNA.

Advances in molecular and microbiology have facilitated an understanding of the workings of bacteria and their resistance-sharing properties. Whereas microbes and microorganisms have been recognised since the first microscopes, the molecular structure of biological organisms was revealed in the 1930s at the sub-microscopic region between 10^{-6} and 10^{-7}.[20] This reorganisation of the gaze of the life sciences[21] has made intelligible the way bacteria can exchange sequences of DNA, often between unrelated species, through a general process of horizontal transfection.[22] The recognition of horizontal gene transfer, responsible for antibiotic resistance and the emergence of virulent strains of pathogens, have given rise to a new understanding of the fluidity of bacterial genes and genomes.[23] This understanding of the innate and irrepressible emergence of infectious disease microbes put paid to the idea developed after the Second World War and noted in the introduction that infectious disease could be conquered once and for all.[24] The way bacteria develop resistance to drugs such as antibiotics would play a key role in shaping the political response to the threat of bioterrorism. Foremost in this would be its political utilisation in the 'dual-purpose' argument.

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[20] Lily E. Kay, *The Molecular Vision of Life* (Oxford: Oxford University Press, 1996), 5.
[21] Nikolas Rose, 'The Politics of Life Itself', *Theory, Culture & Society* 18, no. 6 (2001): 13.
[22] Melinda Cooper, 'Pre-empting Emergence: The Biological Turn in the War on Terror', *Theory, Culture & Society* 23, no. 4 (2006): 116.
[23] Mae-Wan Ho, *Genetic Engineering – Dream or Nightmare?* (Bath: Gateway Books, 1998), 168-200 cited in Cooper, 'Pre-empting Emergence', 116.
[24] Cooper, 'Pre-empting Emergence', 114-6.

The 'dual-purpose' argument emerged in July 1995 at a HHS-sponsored seminar titled *Responding to the Consequences of Chemical and Biological Terrorism*. In attendance at this meeting were some of the most vociferous proponents of the link between terrorism, WMDs and biological weapons in particular. One presentation by the Nobel Laureate Joshua Lederberg addressed how the question of natural infection and emerging diseases related to the question of preparedness against biological terrorist attack.[25] Reiterating the threat stated in the Institute of Medicine report of 1992 - *Emerging Infections: Microbial Threats to Health in the United States* - infectious and parasitic disease was positioned as the preeminent source of death on a global basis, with international traffic preventing the eradication of infectious disease in any one country. The fight against resistant and virulent 'microbial predators' born out of natural exchanges of information, such as horizontal gene transfer, was positioned as a 'race' that could be won through the use of our wits and their manifestation in technology.[26]

This presentation highlighted the fact that the vulnerabilities that the release of biological agents presented – the deliberate release of the forces of nature – would generate a very similar emergency response to those that arise naturally. The vulnerabilities exposed by a biological attack were all the more real due to the irrational actions of Aum Shinrikyo that represented a new threshold of terrorism for the speaker. The research agenda, in dealing with both issues, would throw up identical problems in requirements for early detection, verification of the presence of an agent in the environment, the development of management techniques and of the new therapeutic tools to cope with these sets of infections. A call was issued for a major reconstruction of vaccine development whilst also noting the lack of a commercial market to stimulate antiviral production.[27]

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[25] U.S. Public Health Service, Office of Emergency Preparedness, *Proceedings of Seminar on Responding to Consequences of Chemical and Biological Terrorism, 11-14 July 1995* (Washington D.C.: U.S. Public Health Service, 1995), Chapter 2-171.
[26] Ibid., Chapter 2-173.
[27] Ibid., Chapter 2-178-9.

Outlined in this presentation were the key elements of a 'dual-purpose' claim that public health and counter bioterrorism shared common goals. Utilising the nature of bacterial resistance this would become a potent argument for directing the resources of the country's most prominent public health institutions into this area of security.[28] If individual battles could be won through the production of specific medicines, the war could not as infectious disease resistance would continually emerge in *essence*.[29] This vision of life at this level would be supported by the report of the U.S. National Intelligence Council titled *The Global Infectious Disease Threat and Its Implications for the United States*. Declassified in January of 2000, this national intelligence estimate highlighted the significant threat posed by infectious diseases to U.S. national security from antimicrobial resistance, a resistance which results from the constant evolution of infectious disease microbes.[30] We can see in this 'dual-purpose' claim the way that the inevitable and necessary emergence of infectious disease, drawn from the nature of bacterial evolution, comes to obscure the contingent occurrence of biological terrorism.

The 'dual-purpose' argument was advanced in two editorials in the *Journal of the American Medical Association* (*JAMA*). The first reiterated that we faced an 'ever-evolving adversary: microbes a billion fold more numerous than ourselves, vested with high intrinsic mutability and replication times measured in minutes, not years'.[31] It went on to repeat that against microbes which have developed methods of overcoming our immune systems, we have only our wits. The second emphasised the vulnerability of unprotected civilian targets that under a catastrophic biological attack would suffer the same number of casualties as a

[28] Wright, 'Terrorists and Biological Weapons', 73.
[29] Cooper, 'Pre-empting Emergence', 118.
[30] National Intelligence Council, *The Global Infectious Disease Threat and Its Implications for the United States* (Washington, D.C.: National Intelligence Council, 2000), 23.
[31] Joshua Lederberg, 'Infectious Disease – A Threat to Global Health and Security', *JAMA* 276, no. 5 (1996): 418.

nuclear attack.[32] This point drew from a U.S. Congressional report - *Proliferation of Weapons of Mass Destruction: Assessing the Risks* - which noted how biological weapons were easier to produce than chemical or nuclear weapons and relatively easy and inexpensive for any *nation* that has a modestly sophisticated pharmaceutical industry.[33] In principle, under the right conditions, biological weapons would pound for pound exceed the killing power of nuclear weapons. To be emphasised was that this power could only be unleashed against unprotected populations, effective civil defence measures are considerably easier to take against chemical and biological weapons than against nuclear weapons.[34]

Taking this forward, it was argued that unlike a nuclear attack, the outcome of a deliberate biological release could be 'profoundly altered by medical interventions, so preparedness is of the essence'.[35] Here were the basic elements of the position that would develop over the next few years, a position that proposed a grand 'dual-purpose' civilian defence research agenda that would respond at one and the same time both to the threat of emerging and re-emerging diseases and bioterrorism.[36] The fact that a bioterrorist attack could be mitigated served to reinforce the connection to infectious disease and the expansion of a research agenda that would build preparedness against this catastrophic threat. This position was advanced with the release of a special biological weapon-themed issue of the *JAMA*.

The theme of this edition focused on a 'set of timely concerns that unite national security and public health'.[37] Included was an analysis of the role of different agencies in

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[32] Joshua Lederberg and Annette Flanagin, 'The Threat of Biological Weapons - Prophylaxis and Mitigation', *JAMA* 276, no. 5 (1996): 420.
[33] U.S. Congress, Office of Technology Assessment, *Proliferation of Weapons of Mass Destruction: Assessing the Risks* (Washington D.C.: U.S. Government Printing Office, 1993), 38.
[34] Ibid., 52.
[35] Lederberg and Flanagin, 'The Threat, 420.
[36] Wright, 'Terrorists and Biological Weapons', 80.
[37] Joshua Lederberg, 'Infectious Disease and Biological Weapons: Prophylaxis and Mitigation', *JAMA* 278, no. 5 (1997): 435.

responding to incidents of chemical and biological terrorism including that of HHS which at the time was the lead agency under the Federal Response Plan for the provision of health, medical and health-related social services.[38] With the connection between infectious disease and bioterrorism a given, the focus of many of the articles was on the coordination of efforts and resources across federal, state and local levels in detecting and responding to an attack. In a similar fashion, other reports at the time focused on the need for a strategy of public health surveillance to detect both bioterrorism and emerging infectious disease, an area where public health and national security merge.[39]

We can see here how the molecular vision of life shaped the understanding of insecurity in relation to the threat of infectious disease and bioterrorism. The ever evolving potentiality of microbes places man in a constant struggle against naturally emerging infectious disease. In the 'dual-purpose' argument the identity and vision of the nature of life at this level was conflated with a newly emergent form of terrorism, a form that through the use of certain technologies can deliberately engineer a disease that breaks from the natural vital order. This argument brings two notions of insecurity together, one arising from our ability to visualise and understand the natural evolutionary processes of molecular life that lead to new diseases, and one arising from our ability to intervene and manipulate these processes in the creation of new weapons.

In this argument and conflation the threat of bioterrorism gains immediacy from the association with infectious disease. This tactical move also links infectious disease with a more traditional security threat, drawing attention and legitimating the use of additional resources.[40] This framing at once makes both threats unavoidable but at the same time

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[38] Jonathan B. Tucker, 'National Health and Medical Services Response to Incidents of Chemical and Biological Terrorism', *JAMA* 278, no. 5 (1997): 364.
[39] Christopher F. Chyba, *Biological Terrorism, Emerging Diseases, and National Security* (New York: Rockefeller, 1998), 4.
[40] Barry Buzan and Ole Wæver and Jaap de Wilde, *Security: A New Framework for Analysis* (London: Lynne Rienner, 1998), 21.

actionable through investment in and the development of a 'dual-purpose' civilian defence research agenda. The 'dual-purpose' argument serves to bind these threats together under the banner of preparedness which will merge public health and national security and give rise to a new category of medicine which conflates both, the medical countermeasure.

The Expansion of U.S. Biodefence Policy and MCM Development

So how did the 'dual purpose' argument and the heightened concern of terrorists with biological weapons manifest itself politically and shape the security response to this threat? With the threat growing, in 1998 counter bioterrorism funding for HHS jumped from US$15.9m in FY 1998 to US$173.1m in FY 1999. In addition to funding for public health infrastructure, research and development and state preparedness, US$51m was set aside to stockpile antibiotics and other medicines.[41] This would take the form of the National Pharmaceutical Stockpile (NPS), mandated by Congress and run by HHS and the Centers for Disease Control and Prevention (CDC), which was set up to distribute essential medical materiel during an emergency within 12 hours of a federal decision to deploy.[42] This was just a first step for those who saw 'terrorism-induced epidemics'[43] as the most significant threat to the U.S. The 'dual-purpose' argument would also further realise itself with the HHS counterterrorism budget rising to US$235m in 2000, marking the first time that the public health system had been integrated directly into the national security system.[44]

The framing of the threat of bioterrorism, heavily influenced by the understanding of the nature of bacterial resistance at the molecular level, had a significant impact on the political strategy and rationality that would be implemented in managing the threat of

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[41] Wright, 'Terrorists and Biological Weapons', 95.
[42] Stephen D. Prior, *Who You Gonna Call? Responding to a Medical Emergency with the Strategic National Stockpile* (Report Commissioned by the National Defence University: Centre for Technology and National Security Policy, 2004), 1.
[43] Wright, 'Terrorists and Biological Weapons', 95.
[44] Transcript: Reno, Shalala, Clarke Briefing on Terrorism 22 January 1999. Available at: http://www.apfn.net/messageboard/10-17-01/discussion.cgi.127.html. Last accessed January 7, 2017, cited in Wright, 'Terrorists and Biological Weapons', 96.

infectious disease and bioterrorism. A necessary event cannot be prevented. In preparing for these twin threats the U.S. was investing in technical solutions to all types of biological agents through biotechnology.[45] The growing awareness of this threat coupled with the terrorist attacks of 2001—9/11 and the anthrax mailings—drove the development of new funding mechanisms and new regulatory pathways such as the U.S. Food and Drug Administration (FDA) Animal Efficacy Rule to speed MCM development.[46] These mechanisms are vital in translating molecular knowledge into new pharmaceutical defences.

In 2002 the U.S. federal government prioritised civilian biodefence with funding rising from US$633m in 2001 to US$4.095bn.[47] In June of 2002 the Public Health Security and Bioterrorism Preparedness and Response Act was signed into law establishing the Strategic National Stockpile (SNS) to maintain MCMs, extending and replacing the NPS. As Cooper notes, this Act outlined the same emergency response procedures for bioterrorist attacks and emerging infectious disease,[48] further consolidating the key aims of the 'dual-purpose' argument. The National Strategy for Homeland Security of 2002 also set out the decision to develop broad-spectrum vaccine, antimicrobials and antidotes.[49] This would augment the SNS which, at that time, already contained a sufficient antibiotic supply to begin treatment for 20 million persons exposed to *Bacillus anthracis* and was projected to contain enough smallpox vaccine for every U.S. resident by the end of that year.[50]

In 2004, the Project BioShield Act was signed delivering US$5.6bn over 10 years to incentivise and encourage the private sector to partner with the U.S. government to develop

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[45] Susan Wright, 'Taking Biodefence Too Far', *Bulletin of the Atomic Scientists* 60 no. 6 (2004): 59.
[46] Andrea Meyerhoff, 'Challenges to medical countermeasures against chemical, biological, radiological, and Nuclear (CBRN) agents', in *Wiley Handbook of Science and Technology for Homeland Security*, ed. John G. Voeller (New Jersey: Wiley-Blackwell, 2010), 2534.
[47] Crystal Franco and Tara Kirk Sell, 'Federal Agency Biodefence Funding, FY2011-FY2012', *Biosecurity and Bioterrorism* 9, no. 2 (2011): 118.
[48] Cooper, 'Pre-empting Emergence', 118.
[49] The White House, *National Strategy for Homeland Security* (Washington DC: Office of Homeland Security, 2002), 39.
[50] Ibid., 44.

MCMs against biological threats and to provide a novel mechanism for federal acquisition of those newly-developed countermeasures. The Project BioShield Act and MCM development sit as a vital element in the response and recovery pillar of the 2004 Homeland Security Presidential Directive (HSPD)-10 - *Biodefence for the 21st Century*.[51] This directive notes the catastrophic threat that biological weapons pose in the hands of hostile states or terrorists. It also notes the potential of advances in biotechnology and the life sciences to create modified or novel organisms that would require equally enhanced detection methods, preventive measures, and treatments. The development of MCMs is positioned as an urgent priority to address the insecurity posed by our ability to manipulate life at the molecular level. This approach sits within the consequent management arm of the 2002 *National Strategy to Combat Weapons of Mass Destruction* - HSPD-4. We can see here how our ability to shape and alter the constitution of life at the molecular level beyond the bounds of the natural vital order has influenced the MCM development strategy of the U.S.

In arguing for the molecularisation of security, the molecularisation of life has shaped understandings of insecurity regarding the way that potential terrorists or criminals may use certain knowledges and technologies to create and disseminate novel and known biological weapons as demonstrated with the anthrax letters. Indeed, as the next chapter will show, this concern has further shaped the political strategy of MCM development that has been implemented in order to deal with this threat. This chapter will now look at the way the U.S. government set out to develop MCMs against this threat. A range of regulatory, funding, developmental and liability mechanisms had to be developed in order to support companies in MCM development and translate molecular knowledge into new pharmaceutical defences.

[51] The White House, *Biodefence for the 21st Century* (Washington DC: The White House, 2004).

Project BioShield 04-06

The Project BioShield Act of 2004 was enacted on the 21st of July 2004.[52] Project BioShield forms part of a larger strategy to defend America against weapons of mass destruction and provides HHS with new authorities to speed the research, development, acquisition and use of priority MCMs against chemical, biological, radiological and nuclear (CBRN) threats.[53] This included the creation of powerful new incentives and rewards for commercial companies to develop MCMs for diseases caused by biological agents.[54] These incentives are necessary as for CBRN countermeasures, in contrast to mainstream drugs, there is no large well-defined market or clear path to regulatory approval designated by the FDA.[55] The federal government is often the only customer. This factor in combination with the lengthy and risky development process of 10-15 years from basic research to FDA approval and estimated cost of $1bn per drug means this is not an attractive area for large experienced pharmaceutical companies.[56]

The profit margins of 20-30 percent that pharmaceutical companies seek when investing in a commercially-viable product cannot be replicated by governments. Indeed, profit margins were limited under Project BioShield to 10 percent.[57] As a result, large pharmaceutical companies face significant opportunity costs when weighing up whether to work with the government in this area. These costs often act as a significant disincentive and obstacle reducing their involvement in MCM production.[58] Particularly in relation to vaccines,

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[52] HHS, *Project BioShield Annual Report to Congress July 2004 through July 2006* (Washington DC: Office of Public Health Emergency Preparedness, 2006), 1.
[53] Ibid., 1.
[54] Stefan Elbe, *Security and Global Health* (Cambridge: Polity, 2010), 90.
[55] Jonathan B. Tucker, 'Developing Medical Countermeasures: From BioShield to BARDA', *Drug Development Research* 70 (2009): 224.
[56] Jason Matheny et al., 'Incentives for Biodefence Countermeasures Development', *Biosecurity and Bioterrorism* 5, no. 3 (2007): 228-9.
[57] Kendall Hoyt, *Long Shot: Vaccines for National Defense* (Cambridge: Harvard University Press, 2012), 151.
[58] Ibid., 152.

markets have failed to inspire socially optimal levels of innovation and consumption.[59] This chapter will now analyse how Project BioShield, the U.S. government's first attempt at incentivising involvement in MCM production, set out to support biotech and pharmaceutical companies, the tensions that emerged, the difficulties it faced and the response that was implemented.

It should be noted that the Project BioShield Act is simply a law and the funds and authorizations legislated within it have been run by various offices in HHS, including the Office of Public Health Emergency Preparedness (OPHEP) / the Office of Public Health Emergency Medical Countermeasures (OPHEMC), which is now the Office of the Assistant Secretary for Preparedness and Response (ASPR). ASPR, taking over from these offices, manages Project BioShield acquisitions and executes contracts with manufacturers.[60]

Incentives used to engage industrial participation have been categorised as either 'push' or 'pull'. Push strategies fund inputs and focus on cultivating partnerships and collaborations. Typical push incentives may reduce the industry's cost of R&D. Such efforts may be used to motivate early-stage research. Pull strategies fund or reward outputs, focusing on increasing market sustainability.[61] Typical pull incentives aim to increase industry's revenues from R&D and may be used to motivate late-stage development and production.[62]

Incentivising Private Sector Involvement in MCM Production – Four Key Authorizations

In order to address the difficult economic situation that MCM production represents, the Project BioShield Act set out four new authorities to encourage and incentivise private industry in MCM development and translate molecular knowledge into new pharmaceutical

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[59] Ibid., 4.
[60] HHS, '*Project BioShield Annual Report July 2004*', 15.
[61] National Research Council, *The Public Health Emergency Medical Countermeasures Enterprise: Innovative Strategies to Enhance Products from Discovery Through Approval: Workshop Summary*, (Washington, DC: The National Academies Press, 2010), 38.
[62] Matheny et al., 'Incentives for Biodefence', 230.

defences. This includes the *use of certain procedures regarding research and development activities that involve qualified MCMs*.[63] The streamlined procedures found in Section 2 of the Project BioShield Act and in 319-F of the Public Health Service Act include: 1) an expedited peer review to assess the scientific and technical merit of research proposals up to $1.5 million; 2) an increase of the simplified acquisition threshold from $100,000 to $25 million; 3) an expedited limited competition process in some circumstances; and 4) an increase in the micro-purchase threshold from $2,500 to $25,000.[64]

The Project BioShield Act also authorises the *use of the Special Reserve Fund (SRF) for the acquisition of MCMs for the SNS*. The SRF, provided in the Department of Homeland Security Appropriations Act, made available $5.593 billion over 10 years (FY04 to FY13) for the advanced-development and purchase of MCMs for the SNS.[65] Of this amount, $3.4 billion was obligated between FY04 to FY08. The SRF represents the guaranteeing of a federal market for new CBRN MCMs and a significant pull incentive. The market guarantee provided by the SRF represents the most important element of the Project BioShield Act. In what can effectively be seen as a new and government-backed market for MCMs,[66] the SRF allows for a guarantee that the product will be bought up to eight years before it is reasonably expected to be delivered.[67]

This act also states that no payments are made until a delivery has been made of a portion of the total number of units contracted for, acceptable to the Secretary, unless advance payment is necessary to ensure success of a project.[68] Advanced payments, that may support companies through the development stages, are limited to 10 percent of the total

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[63] HHS, '*Project BioShield Annual Report July 2004*', 4.
[64] Ibid., p. 4.
[65] Frank Gottron, *Project BioShield: Authorities, Appropriations, Acquisitions, and Issues for Congress* (Washington D.C.: Congressional Research Service, 2011), Summary.
[66] Stefan Elbe, Anne Roemer-Mahler, Christopher Long, 'Medical countermeasures for national security: A new government role in the pharmaceuticalization of society', *Social Science & Medicine* 131, (2015): 267.
[67] Frank Gottron, *The Project BioShield Act: Issues for the 112th Congress* (Washington DC: Congressional Research Service, 2012), 2.
[68] HHS, '*Project BioShield Annual Report July 2004*', 16.

contract amount. Project BioShield also allows for discounted payments for unlicensed/unapproved products with additional payment provided once the product has met the full regulatory requirements.[69] Further, the contract must be renewable for additional periods, none of which may exceed five years.[70]

The SRF, the guaranteeing of a federal market for new MCMs, represented a significant incentive for companies to partner with the government in MCM development. This financial incentive acts to 'artificially' accelerate the development of new MCMs.[71] As there is little to no natural commercial market for many MCMs, the guaranteeing of a federal market is essential, without which there would be no private-sector investment. Following Žižek's diagnosis today is characterised by the radical depoliticisation of the sphere of the liberal market economy, a situation that removes it from active discussion and political debate.[72] The issues of bioterrorism and infectious diseases in low- and middle-income countries, the need for medicines that have no market, bring the sphere of the economy into question, politicising it. It also raises a paradox that in order to protect the general population from bioterrorism, to preserve the functioning of the economic and political order, it must also question the functioning of the economy as a political entity. We can also see here the way that the U.S. government has had to intervene in the natural regularity of this market in order to incentivise participation. Given the free play to circulate, most companies would not choose to participate in this area.

A third authorization was created *regarding the procurement of security countermeasures*. The authority for this action, found in Section 3 of the Project BioShield Act and which creates Section 319F-2 of the Public Health Service Act, authorises the use of a

[69] Ibid., 16.
[70] Ibid., 16.
[71] Elbe, Roemer-Mahler and Long, 'Medical countermeasures for national security', 267.
[72] Slavoj Žižek, *The Ticklish Subject* (London: Verso, 2008), 430.

number of streamlined contracting procedures.[73] This includes the use of simplified acquisition procedures if there is pressing need for specific countermeasure procurement. These procedures also provide for a limited competition process in some circumstances, as well as the incentive and the ability to pay premiums in multiple-award contracts to vendors based on the priority of the production and delivery of an increment of the security countermeasure.[74] U.S. government procurement and acquisition is usually conducted under the Federal Acquisition Regulation (FAR), something which is often seen as a drawback when working with the government as a result of the time taken to complete the excessive paperwork.

A fourth authorization found in Section 4 of the Project BioShield Act and Section 564 of the Federal Food, Drug, and Cosmetic Act authorises the *Emergency Use Authorization (EUA) for MCMs*.[75] This permits the HHS Secretary to authorise the use of products not approved, cleared, or licensed by the HHS/FDA.[76] The Secretary has delegated this authority to the HHS/FDA Commissioner who may invoke this authority only after a declaration of emergency by the secretary. Further requirements include the fact that there is no adequate and approved alternative product available to address the specific threat that is causing the emergency declaration and that the known and potential benefits outweigh the known and potential risks.[77]

This EUA provision also empowers the FDA to approve the 'emergency "off-label" use of a commercially available anti-infective drug to treat exposure to a bioterrorist threat agent.'[78] During the response to the anthrax letters in 2001 the antibiotic ciprofloxacin (Cipro) was authorised by HHS for off-label use for inhalational anthrax. Cipro, manufactured by the

[73] HHS, '*Project BioShield Annual Report July 2004*', 16.
[74] Ibid., 4.
[75] Ibid., 1.
[76] Ibid., 1.
[77] Ibid., 2.
[78] Tucker, 'Developing Medical Countermeasures', 227.

Bayer Corporation, was pressured to lower the price of the drug by HHS. In the case of noncompliance, HHS threatened the implementation of 'compulsory licensure', which determines that intellectual property interests may be justifiably breached in order to benefit society as a whole, particularly in regard to property 'affected with a public interest'.[79] In response, Bayer acquiesced, and despite the threat not materialising, it has been argued that these actions chilled relations between the U.S. government and the pharmaceutical industry.[80] This can be seen as having a significant detrimental effect and acted as a disincentive considering the significant obstacles already present in generating partners for the government. Those working in the government at the time even went so far as to suggest that such outrageous and Mafioso tactics have plagued the government's ability to engage this industry in research.[81]

We have then four key authorizations that provided dedicated funding, streamlined contracting and development procedures and the authority to use unapproved products. These were placed within HHS as set out in the Project BioShield Act to incentivise and support companies in the MCM production process. We can see the incentives put forward to attract private industry and the elements of the Project BioShield Act which are set out to limit the risk the government has to bear when acquiring a MCM and partnering with a private company. These were not the only ones set out, though, in incentivising companies and aiding the translation of molecular knowledge into new pharmaceutical defences.

The PREP Act

[79] David B. Resnik and Kenneth A. De Ville, 'Bioterrorism and Patent Rights: "Compulsory Licensure" and the Case of Cipro', *The American Journal of Bioethics* 2, no. 3 (2002): 32-34.
[80] Tucker, 'Developing Medical Countermeasures', 227.
[81] Chuck Ludlum, *Testimony: Answers to Subcommittee Questions, Roundtable: When Terror Strikes – Preparing an Effective and Immediate Public Health Response*, Subcommittee on Bioterrorism and Public Health Preparedness, July 14, 2005. Available at: www.help.senate.gov/imo/media/doc/ludlam.pdf Last accessed January 7, 2017.

The Project BioShield Act through the four authorizations above was created to encourage the private sector to develop MCMs against CBRN terrorism agents and to provide a novel mechanism for federal acquisition of those newly-developed countermeasures.[82] Whilst these authorizations were being implemented, liability concerns emerged as a stumbling block to robust industry participation. To overcome this issue the Public Readiness and Emergency Preparedness Act (PREP Act) was signed into law in December 2005.[83] This law provides targeted liability protection in the U.S. for manufacturers and others involved in providing MCMs under defined emergency circumstances in which they would be used.[84] Following a declaration from the Secretary of HHS, those covered have immunity from tort liability but not from wilful misconduct.[85] This law assuages the fear held by companies that they may be sued following the dissemination of MCMs in an emergency and addresses one of the key issues that have to be considered when trying to entice the private sector to contribute to MCM production. Another key issue is the regulatory pathway that any successful MCM development must follow.

The Animal Rule

The translation of molecular knowledge into viable pharmaceutical products is an extremely difficult task. It is made harder by the fact that many MCMs do not have a clear regulatory pathway. In order to address the lack of a clear regulatory pathway to approval for CBRN MCMs, the FDA introduced the Animal Efficacy Rule in 2002. Aside from natural outbreaks of potentially weaponisable diseases such as Ebola in West Africa in 2014-15, exposure to a biological agent is rare. This means carrying out human clinical trials to establish efficacy is neither feasible nor ethical. In order to address the issue of efficacy, the FDA may

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[82] Gottron, *Project BioShield: Authorities,* Summary.
[83] HHS, *Project BioShield Annual Report to Congress August 2006 – July 2007* (Washington DC: Office of Public Health Emergency Preparedness, 2007), 9.
[84] Ibid*.,* 9.
[85] Elbe, Roemer-Mahler and Long, 'Medical countermeasures for national security', 267.

grant marketing approval to new drugs or biological products following efficacy trials in adequate and well-controlled animal studies.[86] The studies must demonstrate that it can reasonably be expected that the MCM provide similar protection for humans as it does for animals upon exposure. Under this rule animal studies must not only answer the same efficacy questions as human clinical trials but must also provide even more detail on disease pathogenesis and on the mechanism by which the product prevents or treats the disease.[87] The additional information of the mechanism of action takes the informational requirements above conventional studies where efficacy is the only requirement. It has been argued that the Animal Rule sets a higher standard for proof of efficacy than in conventional clinical trials and should not be considered a more expedient route to product approval.[88]

Key Factors in MCM Funding

In order to release funds from the SRF, the HHS Secretary must determine that a material threat exists and that a security countermeasure is necessary to address that threat in order to protect public health.[89] The HHS Secretary must also determine whether a given MCM is appropriate and available for Project BioShield acquisition. This decision is based on a number of factors which include the feasibility of a drug being approved and cleared within eight years, meaning that products must be in advanced-development to be eligible for acquisition under Project BioShield.[90] Another key factor is the existence or lack of a significant commercial market for the product in question.[91] The Secretaries for HHS and the Department for Homeland Security (DHS) must jointly recommend to the President the use of the SRF to acquire a MCM. The President delegated this authority to the Director of the Office

[86] Philip. J. Snoy, 'Establishing Efficacy of Human Products Using Animals: The US Food and Drug Administration's ''Animal Rule''', *Veterinary Pathology* 47, no. 5 (2010): 775.
[87] Ibid., 775.
[88] Ibid., 775.
[89] HHS, '*Project BioShield Annual Report July 2004*', 15.
[90] Ibid., 15.
[91] Ibid., 15.

of Management and Budget (OMB). Only after this approval does the HHS Secretary procure a MCM through ASPR.[92] Project BioShield is subject to government-wide competition requirements as outlined in the FAR and the HHS Acquisitions Regulations (HHSAR).[93] ASPR makes contract awards utilising the SRF following a full and open competition unless the HHS Secretary determines that this would seriously impair the Project BioShield mission. In these cases a Justification for Other than Full and Open Competition (JOFOC) is used.[94] One of the top MCM priorities for the funds dedicated under Project BioShield was a new anthrax vaccine.

The Acquisition of a New Anthrax Vaccine

Anthrax is considered to be a leading bioterrorist threat and is the only agent among the six leading biological threats known collectively as Category A Agents to have actually been used as a weapon of terror against the U.S. to date.[95] On the 20th of January 2004 the Secretary of DHS determined that Anthrax was a material threat to the U.S. population sufficient to affect national security.[96] The WMD MCM Subcommittee established national anthrax vaccine requirements, proposed ways to address them and determined the number of doses to acquire.[97] In conjunction with this an IOM report[98] stated that the nation needed a next-generation anthrax vaccine to replace the existing anthrax vaccine adsorbed (AVA), also known as BioThrax.[99] The Subcommittee recommended the acquisition of the next-generation recombinant protective antigen (rPA) anthrax vaccine to protect 25 million people in addition to a 5 million dose AVA procurement whilst the rPA vaccine was being completed.[100]

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[92] Ibid., 15.
[93] Ibid., 15.
[94] Ibid., 15.
[95] Ibid., 23.
[96] Ibid., 23.
[97] Ibid., 23.
[98] Institute of Medicine, *Anthrax Vaccine: Is It Safe? Does It Work?* (Washington DC: National Academy Press, 2002).
[99] HHS, '*Project BioShield Annual Report July 2004*', 23.
[100] Ibid., 23.

On the 4th of November 2004 VaxGen, Inc was awarded the contract for the rPA vaccine for a total of 75 million doses (25 million treatment courses) at a cost of $878 million and on the 4th of May 2005 BioPort Corporation was awarded the contract for the AVA vaccine for a total of 5 million doses at a cost of $123 million.[101] The final delivery of this AVA acquisition to the SNS was completed in February 2006.[102] On the 5th of May 2006 VaxGen received a unilateral contract modification from HHS which extended the deadlines by which VaxGen was required to complete various milestones and provide product to the government.[103] In light of the delays in the VaxGen rPA contract and to support HHS preparedness efforts, the Secretaries of HHS and DHS jointly recommended the acquisition of 5 million additional doses of AVA from BioPort.[104] On the 5th of May 2006 options were exercised under the original BioPort contract for an extra 5 million doses of AVA at a cost of $120 million and delivery to the SNS was initiated in May 2006.[105] On the 19th of December 2006 after failing to achieve a contact milestone, the VaxGen contract was terminated.[106] The failure of this procurement effort raised larger questions regarding the U.S.'s ability to develop a new anthrax vaccine and a robust and sustainable partnership between pharmaceutical and biotechnology firms and the government.[107] The biotech industry has also raised concerns regarding whether governments can clearly define its requirements for future procurement contracts.[108]

Understanding the Failure of VaxGen

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[101] Ibid., 20.
[102] Ibid., 26.
[103] Ibid., 25.
[104] Ibid., 26.
[105] Ibid., 26.
[106] HHS, *Project BioShield Annual Report August 2006,* 33.
[107] GAO, *Project BioShield: Actions Needed to Avoid Repeating Past Mistakes* (Washington DC: US Government Accountability Office, 2007), 2.
[108] GAO, *Project BioShield: Actions Needed to Avoid Repeating Past Problems with Procuring New Anthrax Vaccine and Managing the Stockpile of Licensed Vaccine* (Washington DC: US Government Accountability Office, 2007), 4.

The contract with VaxGen was the first major contract that used Project BioShield funds and it was an unmitigated failure. Government reflection on the partnership noted that this would influence the rest of the biotechnology sector who will seek to see whether the U.S. government can make partnerships such as this work.[109] The wider implications of this failure were noted beyond vaccine procurement to how the biotechnology industry responds to government invitations in the future for the development and procurement of MCMs.[110] Focused effort was put in to address and identify the factors that contributed to the failure of Project BioShield's procurement effort with VaxGen. These factors demonstrate the extremely large political and economic challenges that arise when trying to turn molecular knowledge and understanding into the creation of new pharmaceutical defences. It reveals the huge level of technical and political complexity that must be taken into consideration when supporting companies in this area.

Three major factors contributed to the failure of the contract with VaxGen. The first factor concerns the award of the contract from OPHEP/ ASPR to VaxGen which did not take the complexity of vaccine development into consideration and was overly aggressive.[111] Citing urgency, ASPR awarded the procurement contract several years before the planned completion of earlier and uncompleted National Institute of Allergy and Infectious Diseases (NIAID) development contracts with VaxGen and thus pre-empted critical development work.[112] There was a clear failure to interpret the work VaxGen was doing with NIAID as insufficient to meet the requirements set out between ASPR and VaxGen. At the time this may have come down to a lack of communication and a lack of objective criteria such as Technology Readiness Levels (TRL) to assess product maturity.[113] Whilst this may not

[109] Ibid., 4.
[110] Ibid., 4.
[111] Ibid., 14.
[112] Ibid., 14.
[113] Ibid., 16.

represent a tension between the government and the pharmaceutical company, we can see tensions arising as a result of a lack of communication between government organisations working towards the same goal.

The second factor as highlighted by the Government Accountability Office (GAO) regards the important requirements regarding the data and testing required for VaxGen's rPA anthrax vaccine to be eligible for use in an emergency.[114] These important requirements were defined in 2005 when the FDA introduced new guidance on EUA, seven months after the award to VaxGen.[115] This EUA guidance appears to require a product to be further along the development path to licensure than the previous contingency protocols would indicate. VaxGen commented that they estimated significant additional resources would be needed to meet the requirements under this new guidance.[116] NIAID also commented that EUA guidance described a product considerably further along the path to licensure (85-90 percent) than it had assumed for a Project BioShield MCM (30 percent) when it initially awarded the development contracts.[117]

Important requirements regarding the vaccine's concept of use were also not made clear, specifically the FDA's data and testing requirements for the rPA vaccine for the Phase II trial. This was important for VaxGen to be able to plan for and implement the necessary clinical and nonclinical work to generate that data and meet the FDA's requirements.[118] In addition to these two issues the introduction of BioThrax into the stockpile undermined the need for the rPA vaccine and forced the FDA to hold it to a higher standard than VaxGen had the plans or the resources to achieve. This was because EUA guidance states that the FDA will authorise an unapproved or unlicensed product – such as the rPA vaccine – only if there is not

[114] Ibid., 20.
[115] Ibid., 20.
[116] Ibid., 22.
[117] Ibid., 22.
[118] Ibid., 23.

adequate, approved and available alternative.[119] We can see definite tensions here between the differing government organisations, each with a different role to play in setting the requirements for MCMs. There seems to be a lack of communication between these organisations and a failure to understand clearly the capacities and limitations of a small pharmaceutical company such as VaxGen. This issue may be the result of a lack of overall leadership in the U.S. government guiding biodefence.[120]

The third factor concerns the unrealistic risk VaxGen took on in accepting the procurement knowing its own technical and financial limitations.[121] These risks arose from aggressive time lines, VaxGen's limitations with regard to in-house technical expertise in stability and vaccine formation - exacerbated by attrition of key staff from the company - and its limited options for securing additional funding.[122] Experts have commented that delivering 75 million filled and finished doses of a vaccine just after Phase I trials in two years is a near impossible task for any company.[123] VaxGen officials commented that they knew that at the time of the procurement award the probability of success was very low and they were counting on ASPR's willingness to be flexible with the contract time line.[124] The limited options for securing additional funding also played a key role in adding to the risk of the venture with VaxGen. The Project BioShield Act provided payment on condition of delivery of a product to the stockpile and little provision could be made contractually to support any unanticipated or additional development needed with regard to common issues such as stability or reformulation.[125] This situation meant that VaxGen, a company with limited financial

[119] Ibid., 23.
[120] See Chris Currie, *Biodefence: The Nation Faces Multiple Challenges in Building and Maintaining Biodefense and Biosurveillance* (Washington DC: US Government Accountability Office, 2016).
[121] GAO, *Project BioShield: Actions Needed to Avoid Repeating Past Problems,* 17.
[122] Ibid., 17.
[123] Ibid., 17.
[124] Ibid., 17- 18.
[125] Ibid., 19.

resources, had to attract investor capital to pay for development work needed on the vaccine.[126]

In such a firm, fixed-price contractual arrangement that was set out in Project Bioshield's original terms, whilst the developer's market risk is reduced, they assume the technical development risk[127] and the cost of the changes in development as the price is not subject to adjustment based on the developer's cost experience. Further, these terms did not mitigate the risk that the product might fail during testing and be undeliverable.[128] In this GAO report it was suggested that contracts such as this are not appropriate where there are such performance uncertainties which can be identified and whose cost cannot be calculated.[129] This case demonstrates the way that pharmaceutical companies have been adapting to meet the incentives put forward. VaxGen adopted a great deal of risk to accept a considerable government contract. Further, the fixed-price incentives set out in the BioShield contractual arrangements were inadequate to meet the financial requirements of pharmaceutical development. In the end Project BioShield's incentives failed to support VaxGen through the 'valley of death' and the translation of molecular knowledge into a new anthrax vaccine.

Project BioShield and the 'Valley of Death'

Since its enactment, Congressional policymakers have scrutinised the implementation and effectiveness of Project BioShield. A central feature in the creation of viable MCMs is the bridging of the 'valley of death', the process of translating basic research into a viable product.[130] During this period of transition when a 'developing technology is seen as

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[126] Ibid., 19.
[127] Robert Kadlec, *Renewing the Project BioShield Act: What Has It Brought and Wrought?* (Washington DC: Centre for a New American Security, 2013), 5.
[128] Gottron, *The Project BioShield Act: Issues*, 2.
[129] GAO, *Project BioShield: Actions Needed to Avoid Repeating Past Problems*, 19.
[130] Bridging the Valley of Death: How Can Academia and Pharma Best Work Together, 6 December, 2011. Available at: http://www.eln.slas.org/story/1/49-bridging-the-valley-of-death-how-can-academia-and-pharma-best-work-together. Last accessed January 7, 2017.

promising, but is too new to validate its commercial potential and unable to attract the necessary funding for its continued development',[131] many products are abandoned. The difficulties in overcoming the 'valley of death' can be seen in the case of VaxGen set out above. This situation is exacerbated when producing MCMs as many lack meaningful commercial markets and without U.S. government support would be unlikely candidates for development.[132] The unfortunate effect of this situation is that it is predominantly small biotechnology companies which do not face the opportunity cost noted above and are willing to take the development risk in producing such MCMs.

VaxGen, a small and inexperienced biotech firm, did not have the resources to support itself through the development process. The market guarantee as set out in the Project BioShield Act was aimed at specifically reducing the market risk for the company but not the development risk.[133] In this contractual and funding arrangement, the government is shielded from the notoriously risky business of MCM development. With only 10 percent of the contract amount available in advance there was no avenue for VaxGen to gain additional support should the development process require it. It was concluded that the Project BioShield Act had failed to overcome the issues presented by the 'valley of death' and in December 2006 Congress passed the Pandemic and All-Hazards Preparedness Act (PAHPA) establishing BARDA.[134] This Act recognised the fact that a different range of financial incentives and technical support would have to be provided to help companies transition through the 'valley of death' and make use of our ability to shape life at the molecular level in the development of MCMs. The next chapter will look at the ways in which BARDA was

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[131] Ibid.
[132] HHS, *BARDA Strategic Plan 2011-2016* (Washington DC: Office of the Assistant Secretary for Preparedness and Response, 2011), 5.
[133] Frank Gottron, *Project BioShield: Purposes and Authorities* (Washington D.C.: Congressional Research Service, 2009), 2.
[134] Assistant Secretary for Preparedness & Response (ASPR), *Pandemic and All-Hazards Preparedness Act: Progress Report* (Washington DC: ASPR, 2007), 1-2.

created with these incentives to adapt and overcome the limitations of Project BioShield and support pharmaceutical and biotech companies in the development of MCMs.

Conclusion

This chapter demonstrated how the molecular vision of life shaped the way the threat of bioterrorism came to be understood by the U.S. government. In doing so it has outlined the context in which the development and stockpiling of MCMs was prioritised as a viable political plan and preparedness response. The fear that terrorists would gain access to technologies to develop biological weapons became ever more real after the revelations of the Aum Shinrikyo group. The understandings of the resistance-sharing properties of bacteria, made intelligible by the molecular vision of life, were utilised in the 'dual-purpose' argument to generate support for this threat. These are the two ways in which the molecular vision of life has influenced the notions of insecurity surrounding bioterrorism in the U.S. government.

This chapter went on to demonstrate the role of the molecularisation of life in shaping the political rationality and response to this understanding of insecurity. The 'dual-purpose' claim drew heavily from an understanding of the nature of bacterial resistance at the molecular level. Such an understanding has only become possible as a result of technologies which allow us to gaze deep beneath the surface of our molar bodies. The way life works at the molecular level, made possible by this enhanced gaze, was used in a tactical move to gain support for a particular political approach. Such an approach would see the integration of public health and security in the institutional response to this threat. In response to the anthrax letters in 2001, this preparedness approach would gather significant momentum and lead to the passing of the Project BioShield Act, dedicating funding to the creation of MCMs.

This chapter has argued that the incentives set out by the Project BioShield Act were insufficient to overcome the difficulties in drug production. As the case of VaxGen demonstrated, such difficulties are enhanced with inexperienced biotech firms. With large and

experienced pharmaceutical companies put off by the opportunity cost of doing business with the U.S. government, companies such as VaxGen that are willing to participate did not receive enough support or have enough resources to bridge the 'valley of death'. This failure led to a profound realisation that significant institutional adaptation in the economic, political, legal and regulatory realms would be required for successful MCM production. Indeed, a new set of financial and technical incentives would have to be provided in order to support companies through the 'valley of death' and make use of our ability to shape life at the molecular level.

The case of VaxGen revealed the significant political and economic challenges and technical complexity involved in translating molecular knowledge into new pharmaceutical defences. At the heart of understandings of insecurity and the development of new security technologies lies our ability to harness and translate knowledge of life at the molecular level into new weapons and medicines, respectively. The next chapter will look in depth at the way in which the U.S. government adapted to overcome the problems set out in the Project BioShield Act and the failure of VaxGen in the creation of a unique institution in the form of BARDA dedicated to supporting companies such as this in the production of MCMs.

Chapter 4: BARDA and the Shift to Flexible Biodefence

Introduction

The previous chapter analysed the considerable financial and technical obstacles that prevented the smooth translation of molecular knowledges into pharmaceutical defences. This chapter demonstrates the way that the Biomedical Advanced Research and Development Authority (BARDA) adapted to overcome these obstacles to ensure that innovative molecular technologies can be transformed into viable pharmaceutical defences in the form of medical countermeasures (MCMs). As was illustrated in the previous chapter, the support and incentive mechanisms set out in the Project BioShield Act could not overcome the issues presented by the 'valley of death' which led to the failure of the partnership with VaxGen. This chapter analyses the role of the molecular vision of life and U.S. government adaptations in the response to the failure of Project BioShield and the creation of BARDA.

The way that the molecular vision of life has influenced the development of MCMs can be understood through an analysis of BARDA in three ways. BARDA is the institutional representation of the shift in perceptions that this vision of life represents. Firstly, in order to take advantage of our ability to manipulate life at the molecular level in the production of MCMs, companies have to be supported with relevant political and economic incentives and technologies to overcome the 'valley of death'. Without the financial support given to companies by BARDA, efforts at the molecular level to develop MCMs could not be implemented. BARDA's financial incentives and technical support help overcome the limitations in Project BioShield's inducements and the tensions inherent to public-private partnerships (PPPs) in this area of MCM development.

Secondly, the strategy of MCM development set out by the U.S. government and implemented by BARDA reflects the way that the molecular vision of life has influenced our understanding of biological threat. The shift from 'fixed' to 'flexible' defences not only

recognises the threat that naturally emerging diseases represent but also the way that terrorists may potentially alter known pathogens in the creation of advanced biological weapons. Thirdly, as will be shown through BARDA's Core Services, molecular knowledge is harnessed to intervene and create new technologies to secure life at the molecular level. BARDA's *raison d'être* is to deliver the technologies that support companies in the manipulation of molecular life essential to the production of MCMs. As will be demonstrated, the translation of molecular knowledges into new security technologies has required significant government intervention.

In making this argument the chapter first examines the U.S. government's response to the failure of Project BioShield's inducements. The Pandemic and All-Hazards Preparedness Act (PAHPA) created BARDA and aimed to provide financial and technical support to companies in the mid- to late-stages of product development. The range of incentives set out by BARDA would take government involvement further down the MCM development pipeline. This chapter then demonstrates the way BARDA has been set up to not only introduce a new range of political and economic support mechanisms but to also implement a wider shift in strategy and understanding that took place in the U.S. government in relation to MCM development. Importantly, this was a strategy that in response to the threat of naturally-emerging and molecularly-engineered pathogens has implemented a flexible approach to MCM development.

This flexible approach has not only influenced the MCM development strategy but has also shaped the technological platforms and contracting mechanisms employed by BARDA to support MCM development. A flexible approach to contracting has been implemented through the use of the Other Transaction Authority (OT) to remove some of the burden of the onerous obligations set out in normal federal contracts. BARDA has also set up three Centers for Innovation in Advanced Development and Manufacturing (CIADM). These PPPs harness

molecular-based knowledge to support companies in advanced-development activities and flexibly and rapidly respond to any potential future outbreaks. In doing so, this chapter first outlines the legislative acts that created BARDA and this organisation's goals and objectives. The wider background of the U.S.'s MCM development strategy is then analysed in relation to its impact of BARDA's efforts. BARDA's funding and financial incentives are then addressed along with the technical support offered to companies in the development of MCMs.

The Pandemic and All-Hazards Preparedness Act of 2006

As outlined in the previous chapter, the terms of Project BioShield were not sufficient to support VaxGen in its development of a new second generation anthrax vaccine. The Bioterrorism Act of 2002 and the Project BioShield Act of 2004 sought to prepare the country for mass casualty events such as bioterrorism and to create a federal fund for the procurement of chemical, biological, radiological, and nuclear (CBRN) countermeasures that otherwise lack a viable commercial market.[1] In 2006 the PAHPA was signed into law in response to Hurricane Katrina and the threat of a possible influenza pandemic of H5N1.[2] Title I of this legislation established the Secretary of the Department of Health and Human Services (HHS) as the lead for all federal public health and medical response to public health emergencies and incidents covered by the National Response Framework.[3] It also established the Office of the Assistant Secretary for Preparedness and Response (ASPR) in HHS, replacing the Office of Public Health Emergency Preparedness (OPHEP). The ASPR serves as the principal advisor to the Secretary of HHS on all matters related to Federal public health and medical preparedness and response for public health emergencies.[4]

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[1] Ryan Morhard and Crystal Franco, 'The Pandemic and All-Hazards Preparedness Act: Its Contributions and New Potential to Increase Public Health Preparedness', *Biosecurity and Bioterrorism* 11, No. 2 (2013): 145.
[2] Ibid., 145.
[3] Ibid., 146.
[4] HHS, *Project BioShield Annual Report to Congress August 2006 – July 2007* (Washington DC: Office of Public Health Emergency Preparedness, 2007), 16.

Title II pertained to federal funding of state and local preparedness efforts including the Center for Disease Control and Prevention's (CDC) Public Health Emergency Preparedness (PHEP) cooperative agreement grant program and the Cities Readiness Initiative (CRI).[5] Title III focused on improving medical-surge capacity through the Hospital Preparedness Program (HPP) and on improving programs set up to incorporate medical volunteers into an emergency response.[6] Title IV of this legislation took steps to accelerate the efforts of 2004 and 2006 in the arena of MCM development by modifying Project BioShield and by creating BARDA within HHS. It recognised the limitations of only supporting companies in late-stage procurement, leaving companies shouldering all of the risk in a notoriously difficult and costly development process. BARDA aims to bridge the 'valley of death', the funding gap between early-stage development often supported by the National Institutes of Health (NIH) and product procurement supported by Project BioShield's SRF. In theory BARDA works closely with the NIH to ensure a seamless transition from basic research to advanced research and development programmes in support of Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) MCM priorities.[7] This chapter will now make the first step in the argument and outline and assess the way BARDA has set out to overcome this funding gap with different funding and contracting strategies essential to overcoming the 'valley of death' and facilitating the molecular development of MCMs.

The Biomedical Advanced Research and Development Authority

The PAHPA established BARDA in 2006 as

> ...the focal point within HHS for the advanced development and acquisition of medical countermeasures to protect the American civilian population against CBRN and naturally occurring emergency threats to public health.[8]

[5] Morhard and Franco, 'The Pandemic and All-Hazards Preparedness Act', 147.
[6] Ibid., 147.
[7] HHS, *Annual Report to Congress August 2006 - July 2007,* 14.
[8] Ibid.*,* 17.

BARDA functions under the authority of the ASPR and its Director reports to the ASPR.[9] The BARDA office manages the advanced-development of MCMs for CBRN agents; the acquisition of MCMs for CBRN agents under Project BioShield; and the advanced-development and procurement of MCMs for pandemic influenza and other emerging infectious diseases that fall outside the remit of Project BioShield.[10] BARDA is then focused on the two activities of the advanced-development and procurement of MCMs. It is further charged with the dual mandate of coordinating the development of, and bridging the 'valley of death' for, MCMs determined to be critical to the Nation's health security.[11] This brings together the two aspects of development and financial support prioritised by BARDA. BARDA contracts with companies for the advanced-development of MCMs. These contracts specify development activities for the company to perform and may extend multiple years.[12] These contracts are often used to develop products which are not yet mature enough for a Project BioShield procurement contract.[13] Within these contracts BARDA also supports development by providing access to in-house scientific and technical expertise predominantly within the organisation's Core Services and personnel, such as subject matter experts, expanded on below. BARDA has taken over the management and execution of Project BioShield acquisition contracts from the Department of Homeland Security.

BARDA's strategic goals focus on: 1) An advanced-development pipeline replete with MCMs and platforms to address unmet public health needs, emphasising innovation, flexibility, multipurpose and broad-spectrum application and long-term sustainability; 2) A capability base to provide enabling Core Services to MCM innovators; 3) Agile, robust and sustainable

[9] Ibid., 17
[10] Ibid., 17.
[11] HHS, *BARDA Strategic Plan 2011-2016* (Washington DC: Assistant Secretary for Preparedness and Response, 2011), 5.
[12] Frank Gottron, *The Project BioShield Act: Issues for the 112th Congress* (Washington DC: Congressional Research Service, 2012), 10.
[13] Frank Gottron, *The Project BioShield Act: Issues for the 113th Congress* (Washington DC: Congressional Research Service, 2014), 11.

U.S. manufacturing infrastructure capable of rapidly producing vaccines and other biologics against pandemic influenza and other emerging threats; 4) Responsive and nimble programs and capabilities to address novel and emerging threats; 5) A ready capability to develop, manufacture and facilitate distribution of MCMs during health emergencies.[14] BARDA is then focused on implementing innovation, flexibility, rapid production and a nimble response.

BARDA has pursued these strategic goals[15] by predominantly focusing on collaborating in PPPs. In order to facilitate this, in 2011 BARDA set out to establish its CIADMs as well as fill and finish bulk vaccine production. BARDA has also focused on the promotion of platform technologies and the prioritisation of multipurpose products. This has resulted in investment in the Broad Spectrum Antimicrobial Programme established in January 2010. BARDA has then set out to develop a range of technologies and tools, including the CIADMs, platform technologies and Broad Spectrum Antimicrobials, to help support the advanced-development of MCMs and to develop this innovative, flexible, rapid and nimble response that has its foundation in the U.S. government's MCM development strategy.

BARDA Funding

The Department of Homeland Security (DHS) Appropriations Act of 2004 advance appropriated $5.593 billion for CBRN countermeasure acquisition through Project BioShield between FY2004 and FY2013. While this money in the SRF could be decreased or increased by Congress through rescission, transfer, or additional appropriation,[16] it sent a significant message to industry and represented a significant incentive; this money was there and dedicated to countermeasure procurement. Of this amount approximately $3.309 billion was used in this way with $2.291 billion being rescinded or transferred by Congress to other

[14] Ibid., 11-15.
[15] HHS, *BARDA Strategic Plan 2011-2016*, 8-10.
[16] Gottron, *Issues for the 113th Congress*, 7.

areas.[17] An average of $330 million has been spent on MCM procurement per year. BARDA's advanced-development support has been in significant receipt of transfers with approximately $1.825 billion being transferred for this cause.

This shift of funds from BioShield to BARDA has been seen as undercutting BioShield's market guarantee and role as a market pull mechanism and entrepreneurial model which allowed industry to pursue any development strategy of its choosing.[18] As will be seen below, in the reauthorization of PAHPA, Congress limited the amount of SRF monies that can be transferred to and used by BARDA for countermeasures development to 50 percent.[19] The greater emphasis on push incentives through milestone grants, essential in overcoming the 'valley of death', departs from Project BioShield's original approach and further require BARDA officials to micromanage the development process. Other recipients of BioShield funds have been the National Institute of Allergy and Infectious Diseases (NIAID), with $304 million transferred for basic research and $137 million for pandemic influenza preparedness during this time.[20] $25 million has been spent on rescissions. Of the $3.3 billion appropriated under Project BioShield for CBRN countermeasures, just over $3 billion or 90 percent of this money has gone in addressing just three biological threats - anthrax, smallpox and botulism - stockpiling 75 million 25 thousand MCMs. The rest of the funds were spent on acquiring radiological, nuclear and nerve agent countermeasures. Project BioShield funds and BARDA's procurement efforts have stockpiled MCMs against the three most immediate and potentially catastrophic threats.

BARDA's Financial Incentives and Support

[17] Ibid., Summary.
[18] Kendall Hoyt, *Long Shot: Vaccines for National Defense* (Cambridge: Harvard University Press, 2012), 156.
[19] Morhard and Franco, 'The Pandemic and All-Hazards Preparedness Act', 148.
[20] Gottron, *Issues for the 112th Congress*, 6.

The PAHPA amended Project BioShield to assert the role the Secretary of HHS plays in determining countermeasure priorities and national security countermeasures expressed as Material Threat Determinations (MTD).[21] PAHPA also amended the payment provisions of procurement contracts and incentives of Project BioShield to help companies overcome the 'valley of death'. This included the authorization of milestone payments of 5 percent each for achieving specific milestones in product development, up to 50 percent of the total contract amount, as deemed necessary for success of the contract.[22] Milestone payments should help companies meet the unforeseen changes in development costs and help them absorb some of the technical and development risk. Unlike the original terms of Project BioShield, before the PAHPA, these payments would not be subject to refund to the U.S. government should the contract not be fulfilled through delivery of product to the Strategic National Stockpile (SNS).[23] The original terms stipulated payment of an acquisition contract only upon delivery of a MCM to the SNS, with an exception allowing the Secretary to authorise up to 10 percent of the contract amount if deemed necessary for success.[24] This 10 percent was to be refunded to the government if the product was not delivered. The Secretary of HHS can still utilise refundable advance payment either along with or separately from the non-refundable advance payments.[25] Bavarian Nordic received a contract for a new smallpox vaccine in 2007 which utilised both authorities.[26]

One of the most attractive aspects of partnering with BARDA is the non-dilutive capital that is offered. This means that BARDA contracts do not require the sale of a company's shares in return for funding. In this way shareholder value is not diluted when funds are received. In addition to providing needed funds to a company, non-dilutive capital also allows

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[21] HHS, *Project BioShield Annual Report to Congress August 2006 - July 2007* (Washington DC: Office of the Assistant Secretary for Preparedness and Response, 2007), 10.
[22] Ibid., 10.
[23] Ibid., 10.
[24] Ibid., 10.
[25] Ibid., 10.
[26] Ibid., 10.

founding teams and existing shareholders to retain company ownership and control. Further, as funding is dependent upon approval from expert stakeholders with deep knowledge of certain domains, successful approval can act as a marker of validation for the company's products and processes.[27] This is true for products supported by BARDA as they undergo a thorough technical evaluation before contracts are awarded through tools such as TechWatch. Also, this form of funding, in reducing the upfront costs of BARDA's partners, favourably impacts their net present value calculation.[28]

The non-dilutive capital that BARDA offers represents one form of funding to support the development of MCMs. This form of capital can be found in different strands of funding which act as pull incentives. This includes BioShield procurement contracts where reimbursement is provided after the purchase of a product and its entry in the SNS. Milestone contracts, or prize payments, also act as pull incentives,[29] funding outputs and paying companies upon the advancement of a candidate to a certain developmental point.[30] Financial support such as this is key to getting a product through the 'valley of death' and in milestone contracts is tied to product-development activities. The successful translation of molecular knowledge into pharmaceutical defences is then tied to financial incentives.

Funding for MCM development and procurement was extended in 2013 with the passing of the Pandemic and All-Hazards Preparedness Reauthorization Act (PAHPRA). PAHPRA authorized up to $2.8 billion in total appropriations for Project BioShield from FY2014

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[27] James Taylor, *Non-Dilutive Financing for Biotech Startups*, 9 October 2012. Available at: http://blogs.nature.com/tradesecrets/2012/10/09/non-dilutive-financing-for-biotech-startups. Last accessed January 7, 2017.

[28] WHO White Paper on Innovative Models to Enhance Antibiotic Development, April 19, 2014. Available at: http://www.who.int/phi/implementation/7_infobrief_brada_partnering_model_innovative_models_enhance_antibiotic_development.pdf. Last accessed January 7, 2017.

[29] Institute of Medicine, *The Public Health Emergency Medical Countermeasures Enterprise: Innovative Strategies to Enhance Products from Discovery Through Approval: Workshop Summary* (Washington, DC: The National Academies Press, 2010), 38.

[30] WHO White Paper.

through to FY2018.[31] It also authorised $415 million annually for BARDA advanced countermeasure development over the same period.[32] This legislation allows but also limits the Secretary of HHS to redirect up to $1.4 billion of Project BioShield appropriations in this period to BARDA countermeasure advanced-development activities, limiting it to 50 percent as noted above. The PAHPRA also provided HHS with additional flexibility in the structuring of procurement contracts. Project BioShield procurement contracts can now be signed up to ten years before their delivery to the stockpile instead of eight and include development costs.[33]

The first new funding appropriation into Project BioShield and BARDA after the ten year advance appropriation came through the Consolidated Appropriations Act of 2014. This appropriated $255 million for Project BioShield acquisitions and $415 million for BARDA for FY2014. This appropriation act marked a significant shift from multiyear advance appropriation to annual appropriations. This also marked the first time BARDA was funded directly for advanced-development activities. Previously funds had been transferred from Project BioShield.[34] Crucially though, this money set out in the PAHPRA, in contrast to Project BioShield's original funding, was only authorised and is subject to yearly appropriations from Congress. Since the expiration of the advance appropriation, requested and appropriated funding has been less than the authorized and historic obligation rate of $330 million with $255 million appropriated for Project BioShield acquisitions in FY2014.[35] Critics have pointed to the signal yearly appropriations sends to industry. A lack of a guaranteed market over a number of years increases the difficulty of attracting investor capital, an essential resource for many small and medium biotech companies. A lack of a guaranteed market may also act as a disincentive to companies weighing up products to invest in. Products with a much more

[31] Gottron, *Issues for the 113th Congress*, 5.
[32] Ibid., 12.
[33] Ibid., 12.
[34] Ibid., 13-4.
[35] Ibid., 6, 15.

defined market represent a better investment and reduced opportunity cost in comparison to those that do not.

BARDA's Contracting Process and Incentives

BARDA contracts with companies and solicits for work through two formal mechanisms, Requests for Proposals (RFP) and Broad Agency Announcements (BAA). In RFPs the government states a specific need and defines the scope of work that is to be undertaken. Often this is focused on a specific product, service or MCM solution. This is the most common solicitation method used by BARDA to procure goods and services. A BAA is a specialized solicitation method used to procure research and development. BAAs remain continuously open and are flexible calls with which to attract and evaluate unique proposals within broad areas of interest. For both BAAs and RFPs, once a white paper or proposal is received and the submission is under consideration for award, no dialogue is permitted between potential offerors and BARDA Project Officers/Contracting Officer's Representatives.[36] This has been termed the 'cone of silence'. Under a BAA a range of contracts may be awarded including both procurement contracts and non-procurement instruments including Interagency Agreements (IAAs), Grants, Cooperative Agreements, and OTs.[37]

A BAA or an RFP is awarded under the Federal Acquisition Regulation (FAR). This is the principal set of rules which governs the acquisition process by which executive agencies of the U.S. federal government purchase or acquire goods and services by contract with appropriated funds. The FAR System regulates the activities of government personnel in carrying out that process in order to provide uniform policies and procedures for acquisition. Once a solicitation has been issued, parts of the FAR that are relevant will be specified and offerors must either

[36] Nathaniel Cohen, *Methods of Solicitation: Requests for Proposals (RFP) and Broad Agency Announcements (BAA)*, Presentation at the BARDA Industry Day November 13, 2013. Available at: https://www.medicalcountermeasures.gov/media/35770/cohen.baa_and_rfp.pdf. Last accessed January 7, 2017.
[37] Ibid.

comply, demonstrate that they can comply or claim exemption. It has been recognised that the standard federal contracting process under the FAR is not well suited to the development of MCMs. Contracting in this fashion has been seen as slow, cumbersome, inflexible and difficult to manage. These factors ultimately inhibit effective communication between program managers and contractors and make it impossible to emulate the best scientific practices in the pharmaceutical industry.[38]

The large administrative burden that contracting under the FAR represents has been used as one explanation for the reluctance of large pharmaceutical companies to become engaged in the MCM development process. This system builds in unnecessary delays in MCM development and encourages micromanagement by government officials.[39] Government prefers this as it minimizes short-term administrative risks by increasing government oversight, despite the fact that it increases the likelihood of ultimately failing to produce a MCM. Some of the key administrative tasks and burdens that the FAR imposes include in-process reviews and the earned-value management accounting system. The FAR acts then as a disincentive to large and experienced pharmaceutical companies considering partnering with the government. This, in addition to the opportunity cost of contracting with the government – on average operating margins in defence are one quarter those of biopharma[40] – makes MCM development an unattractive field for those most likely to succeed in it. It has been argued that small and innovative biotech companies have also been discouraged by profit margin limits and complex federal acquisition regulations.[41] OT authority is one contracting mechanism that has been used to overcome this disincentive.

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[38] Philip K. Russell and Gigi Kwik Gronvall, 'U.S. Medical Countermeasure Development Since 2001: A Long Way Yet to Go', *Biosecurity and Bioterrorism* 10, no. 1, (2012): 72.
[39] Ibid., 72.
[40] James Gilmore and Janet Lynch Lambert, 'Eight Strategies to Engage Industry in Biosecurity', *Biosecurity and Bioterrorism*, 3, no. 4 (2005): 359.
[41] Government Accountability Office (GAO), *Forum: Managing the Supplier Base in the 21st Century* (Washington DC: United States Government Accountability Office, 2006), 7.

Other Transaction Authority

A much more flexible contracting mechanism in the form of the Other Transaction Authority has been developed and used by various government departments. OT authority was originally given to the National Aeronautics and Space Administration (NASA) in 1958 with the enactment of the National Aeronautics and Space Act.[42] Since then seven other government agencies have been given OT authority. It has been utilised most significantly by the Department of Defence (DoD) who developed it in the late 1980s to provide the Defence Advanced Research Projects Agency (DARPA) with a new approach for research and development (R&D) work.[43] HHS was granted this authority in the PAHPA legislation in 2006.

An OT is a special vehicle for obtaining or advancing R&D or prototypes. It is limited to those agencies that have been provided OT authority and offers significant advantages in the fact that OTs are not subject to the FAR and certain procurement statutes.[44] Companies put off by the administrative burden of a FAR-based contract may be more favourable to an OT. OTs offer the option of flexible contracting arrangements that can be tailored to the project and the needs of the participants. The Government and contractor have a blank page with which to begin and structure negotiations. These arrangements can help promote more collaborative working relationships which can be more conducive to R&D.[45] There is no statutory or regulatory definition of an 'other transaction' and they are often defined in the negative in that they are not contracts, grants, or cooperative agreements. Two types of OTs are used in the government, Other Transactions for Research, the authority granted in PAHPA and Other Transactions for Prototypes.

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[42] L. Elaine Halchin, *Other Transaction (OT) Authority*, (Washington DC: Congressional Research Service, 2011), Summary.
[43] Ibid., 8.
[44] Ibid., 1.
[45] Ibid., 2.

BARDA's Broad Spectrum Antimicrobials (BSA) program was established in 2010 with the goal of re-vitalizing the antimicrobial pipeline through the support of advanced research and development of novel antimicrobial drugs.[46] As part of this programme the OT was utilised in May 2013 to construct a *de novo* partnership and strategic alliance with GlaxoSmithKline (GSK) free from regulations within the FAR. A 'Portfolio Partnership' was launched supporting an entire portfolio of candidate antibacterial therapies. The agreement with GSK which could run up to 5 years and provide $200 million in funding, possesses three central tenets: 1) flexible technical scope, 2) cost sharing, and 3) joint strategic oversight.[47] This agreement allows for product candidates to be brought into and out of development without a new agreement having to be structured upon a candidate failure as would be the case in a traditional FAR contract. A situation which in respect to the high attrition rates present in drug development does not suit large pharmaceutical companies.

Under the cost-sharing agreement, HHS will provide $40 million for the 18-month agreement and up to a total of $200 million if the agreement is renewed for the full five years. GSK researchers will conduct a range of studies to support candidates that treat illnesses caused by bioterrorism agents like anthrax, plague and tularemia, as well as address antibiotic resistance,[48] ensuring they have a 'dual-utility' application. A Joint Oversight Committee (JOC) that consists of senior leadership from both GSK and BARDA governs the agreement. Reviews are conducted every six months to determine which GSK drug candidates should be included in the portfolio and moved forward in development. BARDA conducts In-Process Reviews using federal interagency subject matter experts to provide periodic recommendations on overall

[46] WHO White Paper.
[47] Ibid.
[48] HHS forms strategic alliance to develop new antibiotics, 2013. Available at: http://www.phe.gov/Preparedness/news/Pages/strategic-alliance-130522.aspx. Last accessed January 7, 2017.

BARDA funding for the agreement.[49] In September of 2015 BARDA utilised OT to enter into an antibiotic development partnership with AstraZeneca.

The OT has then allowed BARDA to adapt and overcome the prohibitive aspects of the FAR so as to incentivise and partner with GSK, a large and experienced pharmaceutical company. For BARDA, this type of commitment sends a strong signal to the industry that the government can support partnerships with big pharma that can withstand the potential attrition rates of candidates commensurate with traditional pharmaceutical development.[50] The type of funding within the BSA program is also unique in that it is able to reimburse its partners for drug development activities in real time.[51] This stands in contrast to BioShield procurement contracts where reimbursement is only provided after the purchase of a product and milestone contracts or prize payments or where payment is received upon advancing a candidate to a certain developmental point.[52] BARDA has then utilised a flexible funding mechanism in the form of the OT to set up a portfolio approach to antibiotic development with GSK. This mechanism in particular and the BSA programme in general set out to develop MCMs with 'dual-utility' applications that can address bioterror threats such as anthrax and emerging public health threats in the form of antibiotic-resistant bacteria.

BARDA represents then a shift of focus from procurement to the advanced-development of MCMs. This has necessitated significant government financial investment and intervention in supporting companies in the translation of molecular knowledges into new security technologies. This has also exposed the government to the risk that it will pay for unusable products due to the high failure rate at this stage in product development.[53] The U.S. Government is, then, adopting development risk that contractors were expected to manage

[49] WHO White Paper.
[50] Ibid.
[51] Ibid.
[52] Ibid.
[53] Frank Gottron, *Project BioShield: Authorities, Appropriations, Acquisitions, and Issues for Congress* (Washington DC: Congressional Research Service, 2011), 9.

and that was originally meant to be balanced by the market guarantee.[54] This approach has been criticised for inserting government decision-makers into the MCM development process, something which may be better left to industry.[55] As the example of VaxGen demonstrated, the small biotech firms which are attracted to a partnership with the U.S. government often do not have the experience of bringing a product to market. In order to overcome the 'valley of death', extra financial and technical support is needed to help these companies. This financial support is necessary to make use of the molecular technologies essential to the development of a viable MCM. Political and economic inducements are then essential to the realisation of understandings facilitated by the molecular vision of life.

BARDA has introduced a range of funding and contracting mechanisms in order to help these companies. This has included milestone payments to support advanced-development activities that importantly utilise non-dilutive funding that is particularly appealing. These funds complement the procurement money set out in Project BioShield and reauthorized with PAHPRA. BARDA has also utilised the OT authority to overcome the disincentives posed by the FAR and incentivise GSK and AstraZeneca in MCM development. Financial incentives in support of product development are not the only way that the molecular vision of life has influenced BARDA's strategy. As the next section will detail, it has also influenced the MCM development strategy implemented by BARDA.

BARDA and Medical Countermeasure Development Strategy

BARDA's focus on advanced-development support and on an innovative, flexible, rapid and nimble response has its basis in the failures of Project BioShield's original inducements and the rapidly changing nature of the threat environment. As the previous chapter outlined the Project BioShield Act and MCM development were key elements in consequence-

[54] Ibid., 11.
[55] Ibid., 9.

management efforts as identified in Homeland Security Presidential Directive (HSPD)-10 and HSPD-4. In addition to these protocols, in January of 2007, HSPD-18 - *Medical Countermeasures against Weapons of Mass Destruction* was released.[56] This directive builds upon HSPD-10 and HSPD-4 in developing MCM research, development, and acquisition efforts. It does so by targeting efforts against potentially catastrophic threats; yielding a rapidly deployable and flexible capability to address both existing and evolving threats; ensuring efforts are part of an integrated WMD consequence-management approach; and a concept of operations for responding to and recovering from an attack.[57]

This directive also recognises the range of biological threats that must be prepared against. The four categories include traditional or naturally occurring agents such as anthrax; enhanced agents such as antibiotic-resistant anthrax; emerging agents that may be naturally occurring and previously unrecognized such as Severe Acute Respiratory Syndrome (SARS); and advanced agents such as novel pathogens that have been artificially engineered in the laboratory.[58] These categories recognise the way that advances in the life sciences have allowed us to understand, shape and change life at the molecular level. In doing so, the molecular vision of life has changed the way we understand what constitutes insecurity and a potential threat. As noted in the previous chapter and this directive, the possibilities opened up by genetic engineering technology have led to a new classification of genetically modified BW agents as a separate category of BW agents. Molecular-based technologies have also opened up the possibility of synthesising viral genomes facilitating the creation and reconstruction of viruses from scratch.[59] The ability to generate more dangerous pathogens by inserting drug-resistance genes through genetic engineering, for example, has also informed

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[56] George W. Bush, *Medical Countermeasures against Weapons of Mass Destruction* (Washington DC: The White House, 2007).
[57] Ibid.
[58] Ibid.
[59] Filippa Lentzos and Pamela Silver, 'Synthesis of Viral Genomes', in *Innovation, Dual-Use, and Security*, ed. Jonathan B. Tucker (Cambridge: MIT Press, 2012), 133.

BARDA's strategic focus on developing responsive and nimble programs and capabilities to address novel and emerging threats.[60]

HSPD-18 also recognises the need for a balanced strategic approach to the creation of MCMs. The creation of MCMs to address a finite number of known or anticipated agents must be employed simultaneously with a broad-spectrum flexible approach to address other current and future threats. We can see the implementation of this finite or fixed-defence approach with the stockpiling of MCMs to address the threats of anthrax, smallpox and botulism, noted above. The use of Project BioShield funds was predicated on a fixed-defence stockpiling strategy and given the time, cost and risk of vaccine development it may not make sense to stockpile a list of vaccines that can be overcome by evolution or human engineering.[61] Indeed, trying to predict threats may not be the best approach. A fixed-defence approach has limitations and inherent weaknesses then in that it cannot address enhanced, emerging or advanced agents noted above. HSPD-18 sets out the ambitious goal of structuring defences capable of responding to a wide variety of potential challenges, including a novel biological agent that is highly communicable, associated with a high rate of morbidity or mortality, and that cannot be addressed with a known countermeasure at the time of its discovery.[62]

In achieving this goal, HSPD-18 outlines a two-tiered approach which balances the immediate need to address the most catastrophic threats with agent-specific MCMs along with long-term requirements to develop more flexible, broader spectrum countermeasures to address future threats. This includes the use of platform technologies, the use of scientific tools to advance MCM development, and the use of non-pharmacological interventions to enhance a flexible biodefence capability.[63] BARDA's creation of the CIADMs and the Broad

[60] HHS, *BARDA Strategic Plan 2011-2016*, 14.
[61] Hoyt, *Long Shot,* 156.
[62] Bush, *Medical Countermeasures*.
[63] Ibid.

Spectrum Antimicrobial Programme, expanded on below, can be seen as significant efforts in this direction.

One of the key influences on the U.S. government's decision to focus on a flexible, nimble, rapid and innovative biodefence strategy was the H1N1 outbreak of flu in 2009.[64] This led to a review of the entire MCM enterprise by the PHEMCE in 2010.[65] The PHEMCE was created in 2006, is led by the ASPR and is managed by BARDA.[66] It is a coordinated interagency effort responsible for: defining and prioritizing requirements for public health emergency MCMs; focusing research, development, and procurement activities on the identified requirements; and establishing deployment and use strategies for MCMs in the SNS.[67]

The review identified key ways in which the enterprise could shift from the then current strategy of developing products aimed at countering known threats to a longer range anticipatory strategy. This approach balanced the need to produce MCMs for known priority threats with the recognition that the Nation needs the flexible infrastructure capacity to rapidly produce a MCM in the face of a new attack or unknown threat.[68] This anticipatory strategy integrates the approach outlined in HSPD-18 by developing the capabilities to respond to potential and emerging threats. The PHEMCE can be seen as the organisation responsible for implementing the strategy outlined in HSPD-18. This MCM development strategy has then been influenced and shaped by our understanding of potential deliberate and natural threat at the molecular level. This chapter will now go on to assess the way that BARDA has implemented a flexible biodefence strategy and utilised these tools in the form of financial and technical support and incentives to support the advanced-development of MCMs.

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[64] HHS, *2012 Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy* (Washington DC: Office of the Assistant Secretary for Preparedness and Response, 2012), 10.
[65] See HHS, *The Public Health Emergency Medical Countermeasures Enterprise Review* (Washington DC: Office of the Assistant Secretary for Preparedness and Response, 2010).
[66] About the PHEMCE, 2016. Available at: https://www.medicalcountermeasures.gov/phemce.aspx. Last accessed January 7, 2017.
[67] Ibid.
[68] HHS, *The Public Health,* 6.

Flexible Technical Support and Incentives

So far this chapter has assessed two ways in which the molecular vision of life has influenced the way BARDA works. Firstly, in order to overcome the financial desert between preclinical R&D and procurement[69] and make use of our ability to shape life at the molecular level in the development of MCMs, key financial and technical support mechanisms had to be put in place such as advanced-development contracts. Secondly, our understanding of molecular life shaped the perception of threat and the MCM-development strategy that BARDA must implement. This chapter will now detail the way that BARDA has supported the development of particular technologies that, in being made available to companies, make possible the manipulation of molecular life in the creation of MCMs.

In order to overcome the issues with the original Project BioShield approach, the U.S. government has added additional push factors in advanced-development support. These factors act in addition to the early-development support and push of the NIH and the market guarantee pull of Project BioShield procurement funds. In doing this the U.S. government has positioned itself earlier in the development process and adopted more risk. The government has had to adopt more risk because of the failure of Project BioShield's original inducements. These inducements, designed specifically to lure in large experienced manufacturers, cannot compete with other opportunities in the market.[70] As highlighted with the case of VaxGen, the smaller companies that respond to the government rarely have enough expertise or infrastructure to complete development and so must contract out certain stages, disrupting the development process and working relationships.[71]

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[69] Jonathan B. Tucker, 'Developing Medical Countermeasures: From BioShield to BARDA', *Drug Development Research* 70, (2009): 225.
[70] Hoyt, *Long Shot,* 152.
[71] Ibid*.,* 153.

Companies have struggled a great deal in developing the considerable expertise and capabilities required to overcome the technical, regulatory, manufacturing, commercialization, and business challenges inherent in the development of innovative MCM candidates.[72] The market push mechanisms set out in the PAHPA aims to support these smaller developers through development milestones and BARDA's advanced-development activities. BARDA's advanced-development support focuses on providing technical expertise and support to companies that are involved in the advanced stages of MCM development. The majority of this support is focused on the Core Services. These services provide technical support in the development of MCMs that complements financial and contracting aspects noted above. This represents significant government investment and intervention in the technology necessary for the translation of molecular knowledges into new pharmaceutical defences.

BARDA's Core Services

BARDA's Core Services, developed to support companies that do not have the experience of bringing a MCM through from concept to licensure, aim to provide the scientific and technical support and facilities that would otherwise be found in-house at a large pharmaceutical company. This includes the CIADMs, a Fill Finish and Manufacturing Network, a Clinical Studies Network, a Nonclinical Network, a Regulatory and Quality Affairs Division, an Analytical Decision Support Modelling Hub and a Strategic Innovations Portfolio. These services aim to provide core advanced-development and manufacturing services to MCM innovators across a range of issues[73] that must be addressed in order to overcome the 'valley of death'. This includes support to product developers with regards to specific quality and

[72] HHS, *BARDA Strategic Plan 2011-2016*, 12.
[73] Adeyinka Smith, *Nonclinical Development Network*, Presentation at the BARDA Industry Day November 13, 2013. Available at: https://www.medicalcountermeasures.gov/media/35758/smith_nonclinical_development_network.pdf . Last accessed January 7, 2017.

regulatory issues to develop a pathway in achieving FDA clearance, approval, and licensure.[74] The FDA has taken time since 2004 to construct a clear regulatory pathway that recognises the unique aspects of MCM development. They have also tried to increase the support MCM developers receive by using push incentives though designations such as Fast Track and Priority Review. Push and pull incentives have also been combined in the Orphan Drug Designation.[75] The lack of clear regulatory pathway has acted as a disincentive to companies thinking of partnering with the U.S. government. Support is also given in relation to the development and qualification of animal models,[76] clinical expertise support and oversight of MCM clinical trials[77] and modelling and analysis to assist and inform planning, preparedness and real-time response requirements.[78]

Many of the Core Services are provided by a network of Contract Research Organisations (CROs), BARDA-approved companies that in the case of clinical studies form a clinical studies network that are ready to respond to requests for the design and execution of Phase I-IV clinical trials on both routine and urgent timelines.[79] These services provide long-term flexible and sustainable capabilities as outlined in the *PHEMCE Implementation Plan of 2012* in response to the *PHEMCE Review* and in coordination with HSPD-18. Part of this involves the promotion of technologies and infrastructure with cross-cutting capabilities such as technologies with more than one application and infrastructure that can be rapidly adjusted

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[74] Regulatory and Quality Affairs. Available at: http://www.medicalcountermeasures.gov/barda/core-services/regulatory-and-quality-affairs.aspx. Last accessed January 7, 2017.
[75] Institute of Medicine, *Antibiotic Resistance: Implications for Global Health and Novel Intervention Strategies: Workshop Summary* (Washington, DC: The National Academies Press, 2010), 53.
[76] Smith, *Nonclinical Development Network*.
[77] Clinical Studies Support. Available at: http://www.medicalcountermeasures.gov/barda/core-services/clinical-studies-support.aspx. Last accessed January 7, 2017.
[78] Analytical Decision Support (ADS) Modeling Hub . Available at: http://www.medicalcountermeasures.gov/barda/core-services/modeling-hub.aspx. Last accessed January 7, 2017.
[79] Jo Ellen Schweinle, *The Medical Countermeasures Clinical Studies Network (MCM CSN)*, Presentation at the BARDA Industry Day November 13, 2013. Available at: https://www.medicalcountermeasures.gov/media/35752/schweinle_clinical_studies.pdf. Last accessed January 7, 2017.

to surge to meet new demands and respond to new threats. Many of these cross-cutting capabilities form part of BARDA's Core Services.

Technical Support for Flexible Biodefence

As noted above, HSPD-18 called for HHS to develop a flexible biodefence strategy. Using title IV authorities in the PAHPA, a rapidly deployable and flexible capability to address both existing and evolving threats is to be developed. The need for a flexible response strategy takes into consideration the extensive funding and time that drug and vaccine production necessitates. Indeed, the costs of developing and licensing a single drug or vaccine has been estimated at $880 million to $1 billion, and 8 to 10 years typically are required to reach licensure.[80] Fixed-defences or MCMs that are directed against sole agents also cannot address the possible use of enhanced, naturally emerging or advanced agents noted in HSPD-18 above. The large number of potentially destabilizing bioterror agents, the high costs of developing and procuring medicines and vaccines and the prospect of emerging infectious diseases such as pandemic flu have been the key drivers in the search for flexible and rapidly deployable alternatives.[81]

The scientific advances which have brought into focus new notions of insecurity through the possible creation and dissemination of enhanced or advanced agents have also raised the prospect of new and more efficient approaches to drug and vaccine development and production.[82] In addition to the HSPD-18, the PHEMCE strategy published in 2007 outlines HHS's intent on pursuing broad-spectrum solutions to MCM development using technologies that enhance flexibility.[83] One solution that was developed in this vein includes the development of broad-spectrum products that could be used against a wide range of threats.

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[80] Gigi Kwik Gronvall et al., 'Flexible Defenses Roundtable Meeting: Promoting The Strategic Innovation of Medical Countermeasures', *Biosecurity and Bioterrorism* 5, no. 3 (2007): 273.
[81] Ibid., 273.
[82] Ibid., 273.
[83] Ibid., 273, HHS PHEMCE Strategy of 2007 cited.

Broad-spectrum antibacterials and antivirals, for example, can be used to boost innate immunity and minimize the transmission of a contagious disease.[84] BARDA has taken up this approach with the development of its Broad Spectrum Antimicrobial Programme, established in January 2010. This programme, which includes the partnership with GSK, supports the development of antimicrobials with commercial indications provided they have a 'dual-utility' in that they also address biodefense threat agents.[85]

Another solution has been focused on the development of technologies that enable rapid, cost-effective development of drugs and vaccines against a wide range of threats.[86] This approach focuses on the development of flexible technologies in addition to flexible products such as broad-spectrum antibiotics. These technologies can be used to accelerate MCM development and production, thereby reducing development costs. The rapid development of MCMs allows for a response against unexpected threat agents, such as enhanced, naturally emerging or advanced. This also supports a response against attacks requiring quantities of MCMs that would exhaust supplies and reduce reliance on a large and expensive national stockpile.[87] Such an approach can be seen to have been institutionalised with the creation of the CIADMs.

Centers for Innovation in Advanced Development and Manufacturing (CIADMs)

The influenza outbreak of 2009 demonstrated to U.S. officials just how unprepared they were to respond to naturally-emerging threats. This raised the need to develop manufacturing facilities that could flexibly and rapidly respond to outbreaks such as this in the future. The establishment of the CIADMs was put forward in the PHEMCE Review of 2010.[88] In FY2012 and FY2013, HHS and BARDA awarded nearly $440 million in contracts to establish

[84] Ibid., 273.
[85] John K. Billington, 'The ABCs of the US Broad Spectrum Antimicrobials Program: Antibiotics, Biosecurity, and Congress' *Health Security* 13, no. 6 (2015): 350.
[86] Gronvall et al., 'Flexible Defenses Roundtable', 273.
[87] Ibid., 273.
[88] HHS, *The Public Health,* 12.

three CIADMs and a network of facilities to provide packaging support for MCM distribution, known as the Fill Finish Manufacturing Network (FFMN).[89] These contracts obligated the CIADMs to develop three activities to support flexible manufacturing for MCM development and production. This included: the manufacture of pandemic influenza vaccines during an emergency; Core Services to support the development and production of CBRN MCMs; and workforce training.[90]

In order to facilitate pandemic influenza preparedness, during the contracted periods each CIADM is expected to be able to produce 50 million doses of pandemic influenza vaccine within four months of receipt of the influenza virus strain. This surge capacity is vital to a rapid response to any naturally-emerging agent. The Core Services will assist MCM developers by manufacturing products to be used for clinical trials, for example. The workforce training programmes aim to increase expertise in CBRN MCM development. The base contracts support the building of dedicated facilities or the retrofitting of old facilities. Once this is completed they will stand ready to provide these three activities and this readiness is to be maintained through annual contract option periods. Once the facilities are ready BARDA may place task orders for any of the three activities, incurring additional payments. The FFMN supplements the CIADMs' pandemic influenza surge capacity, packaging up to 117 million doses of pandemic influenza vaccine in 12 weeks, if needed, and can also provide Core Services as CIADM subcontractors.[91]

The CIADMs are to support the development of biologics-based MCMs only. Biologics include treatments such as vaccines that, in contrast to drugs, are derived from living sources. In further contrast, the structure of most drugs that are chemically synthesized is known

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[89] Marcia Crosse, *National Preparedness: HHS Has Funded Flexible Manufacturing Activities for Medical Countermeasures, but It Is Too Soon to Assess Their Effect* (Washington DC: United States Government Accountability Office, 2014), highlights.
[90] Ibid., highlights.
[91] Ibid., highlights.

whereas most biologics are complex mixtures that are not easily identified or characterized.[92] This is one of the reasons that BARDA considers these MCMs in need of the greatest support.[93] Throughout all activities BARDA provides guidance and management oversight in terms of specific product objectives.[94]

The CIADMs differ from CROs such as the animal studies network, in that the partnership with the CIADMs removes the commercial element that restricts availability. CROs are not meant to provide a response function and when their facilities are needed they may be subject to availability. With the CIADMs BARDA is paying for 50 percent of the operating costs in order to have 50 percent of the facilities' capacity at short notice in order to respond to an emergency or to support MCM development. Upon the declaration of an emergency BARDA can direct work to one of the most suitable CIADMs avoiding the lengthy and arduous contracting process. With the recent case of the Ebola outbreak, a public health emergency was not declared. This meant that the ZMapp task order award had to go through the competition process which is just as slow as putting out a normal request for proposals and removes the immediate response capacity of the CIADMs in this context.[95] This task order was eventually awarded to the CIADM run by Emergent BioSoutions, expanded on below.

The CIADMs were created in June of 2012 as three PPPs. Emergent Manufacturing Operations Baltimore LLC heads up one center with a network of partners, including Michigan State University, Kettering University of Flint, Michigan, and the University of Maryland,

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[92] What Are "Biologics" Questions and Answers, 8 May 2015. Available at: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133077.htm. Last accessed January 7, 2017.

[93] Crosse, *National Preparedness*, highlights.

[94] Department of Health and Human Services' Centers for Innovation in Advanced Development and Manufacturing (HHS-CIADM), 2016. Available at: https://www.medicalcountermeasures.gov/barda/core-services/ciadm.aspx. Last accessed January 7, 2017.

[95] Michael Angelastro, Deputy Director for Manufacturing, Facilities and Engineering, BARDA, interviewed by author, 14 November 2014, Washington DC, audio recording, BARDA offices, Washington DC.

Baltimore. This base contract is for approximately $163 million over the first eight years.[96] Emergent will provide 31 percent of the overall construction costs in this cost-sharing contract for a biologics development and manufacturing suite and a pilot plant. This will support Core Services for the routine advanced-development of MCMs and support manufacturing of vaccines for an influenza pandemic or other threat in an emergency. After the base period of eight years, HHS has the option to extend the contract up to a maximum of 25 years. These options can be exercised with task orders. Such orders could include operational readiness reimbursement, development and manufacturing of CBRN products, warm base maintenance, surge manufacturing, and/or workforce development.[97]

The first task order issued for this or any CIADM was announced in July of 2015. Under this two-year, $19.7 million order, Emergent BioSolutions will begin the advanced-development and manufacturing activities to support an experimental monoclonal antibody drug at its Baltimore Bayview CIADM. This monoclonal antibody treatment is focused against Ebola using the same three monoclonal antibodies as ZMapp, made by Mapp Pharmaceuticals in San Diego. Emergent's manufacturing process utilises production in mammalian cells rather than tobacco plants, speeding up the process and allowing for more to be produced.[98] Emergent will transfer manufacturing processes and materials from the early-stage development work to begin advanced-development, manufacture the experimental drug for use in nonclinical and clinical studies and conduct the work necessary to scale up production to commercial volumes if studies prove successful.[99]

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[96] Department of Health and Human Services'
[97] CIADM Fact Sheet: Emergent Manufacturing Operations LLC. Available at: https://www.medicalcountermeasures.gov/media/8865/aspa_0420_20120615_aspr_pr_countermeasures_fact_sheet_emergent508.pdf. Last accessed January 7, 2017.
[98] Lisa Schnirring, Ebola vaccine called promising; HHS awards drug contract, 21 July 2015. Available at: http://www.cidrap.umn.edu/news-perspective/2015/07/ebola-vaccine-called-promising-hhs-awards-drug-contract. Last accessed January 7, 2017.
[99] HHS partnership advances experimental Ebola drug, 20 July 2015. Available at: http://www.hhs.gov/about/news/2015/07/20/hhs-partnership-advances-experimental-ebola-drug.html. Last accessed January 7, 2017.

The second center was headed by Novartis vaccines division. This leveraged existing public-private investments by HHS in a multi-purpose facility in Holly Springs, NC, in coordination with North Carolina State University and Duke University. The Novartis contract is valued at approximately $60 million over the base period of four years.[100] During this time Novartis will provide 31 percent of the overall construction costs for a clinical trials material filling suite and a technical services building. These facilities will support the advanced-development of MCMs and provide Core Services to advance product candidates to FDA licensure or approval.[101] In July of 2015 Novartis announced the completion of the sale of its influenza vaccine unit, including Holly Springs CIADM to CSL Limited. This unit is unique in that it is the first and only manufacturer with two production technologies. These consist of egg-based vaccines for seasonal, pandemic and pre-pandemic; and cell-culture-based vaccines for antibiotic-free production with the potential for rapid scale-up to protect against pandemic threats.[102] Cell-culture-based vaccine technology is used in the $1 billion vaccine plant in Holly Springs to produce vaccines such as Flucelvax, the first cell-culture-derived influenza vaccine approved in the U.S. by the FDA to act against seasonal influenza. In addition to the Holly Springs plant, Flucelvax was also developed in coordination with BARDA who spent $487 million building and certifying the plant. This facility is expected to make 150 million doses of monovalent vaccine within six months of the start of a pandemic.[103] HHS also signed a pre-pandemic contract with Novartis to fund and stockpile a synthetic genomics vaccine for H7N9 for $60 million.[104]

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[100] Department of Health and Human Services'
[101] CIADM Fact Sheet: Novartis Vaccines and Diagnostics, Inc. Available at: https://www.medicalcountermeasures.gov/media/36752/aspa_0420_20120615_aspr_pr_countermeasures_fact_sheet_novartis_v02_-_508.pdf. Last accessed January 7, 2017.
[102] Alex Philippidis, Novartis Selling Flu Vaccine Business to CSL for $275M, 27 October 2014. Available at: http://www.genengnews.com/gen-news-highlights/novartis-selling-flu-vaccine-business-to-csl-for-275m/81250520/?kwrd=HHS. Last accessed January 7, 2017.
[103] Ibid.
[104] Ibid.

The third center was led by the Texas A&M University System (TAMUS) in collaboration with GlaxoSmithKline Vaccines of Marietta, PA, Kalon Biotherapeutics of College Station, TX, and their network of institutes. This contract is valued at approximately $176 million over the first five years, with completion expected in 2017.[105] During this time TAMUS will provide 38 percent of the overall construction costs for a biologics development and manufacturing facility focused on Core Services for advanced-development and manufacturing of MCMs and the development and manufacturing of live-virus vaccine candidates. A commercial scale cGMP (current Good Manufacturing Practices) vaccine bulk manufacturing facility will also be developed to provide for large-scale surge manufacturing of pandemic vaccines. TAMUS will also develop a fill/finish facility in collaboration with LONZA of Houston, Texas. This will support the fill/finish requirements for MCMs with the added capability of processing live-virus vaccine candidates and can utilize lyophilization (freeze drying) technology.[106]

HHS has utilised the PPP model to bring together three distinct areas and strengths. Specifically, the innovative ideas of small biotech firms, the training expertise of academic institutions, and the development and manufacturing experience of large pharmaceutical companies.[107] This aims to ensure a sustainable domestic MCM infrastructure with the ability to accelerate development in times of need. Emerging and innovative technologies will also be explored in these centers to manage risk and ensure processes are as efficient as possible.[108] This three-pronged approach has been criticised for duplicating and diluting funds and technology that could have been better concentrated in one facility. This decision has been

[105] Department of Health and Human Services'
[106] CIADM Fact Sheet: Texas A & M University System. Available at: https://www.medicalcountermeasures.gov/media/8871/aspa_0420_20120615_aspr_pr_countermeasures_fact_sheet_tamus508.pdf. Last accessed January 7, 2017.
[107] Department of Health and Human Services'
[108] Ibid.

defended in light of the fact that having three sites creates flexibility and leaves backups in case a site is contaminated or attacked.[109]

The CIADMs represent a significant step in incorporating innovative technologies that will provide a more efficient model for MCM product development and provide domestic manufacturing surge capacity for a pandemic influenza vaccine.[110] The CIADMs also represent cross-cutting capabilities in MCM development and a capability to respond to unforeseen threats. As outlined above, BARDA has completed its obligations in the near term (FY12-14) by funding the initial planning and engineering activities related to the construction of the infrastructure central to the CIADMs.[111] Mid-term (FY 15-17) BARDA will support the award of contracts to the CIADMs for the advanced-development and manufacturing of MCMs.[112] While in the long term (FY 18 and beyond), BARDA will utilise the CIADMs to assist small biotech companies with technology, regulatory affairs, quality systems and manufacturing expertise to reach the goal of a licensed and readily available product for public and private use.[113] The CIADMs have been set up then to not only provide technical and advanced-development support for companies in overcoming the 'valley of death' but also to help respond rapidly to emerging threats by providing platform technologies that support the development of flexible MCM defences.

Conclusion

This chapter has analysed three ways in which understandings of molecular life have shaped the way BARDA supports the development of MCMs. In the first instance, this chapter assessed the financial support mechanisms, provided under the PAHPA to make a partnership with BARDA more attractive to developers and to overcome the 'valley of death'. These

[109] Sara Reardon, 'US biodefence facilities ramp up', *Nature* 509 (2014): 17.
[110] HHS, *2012 Public Health Emergency*, 57.
[111] Ibid., 57.
[112] Ibid., 58.
[113] Ibid., 58.

incentives, such as the payment of up to half the contract amount in milestones, addressed the considerable technical and development risk that was borne by companies under the original terms of the Project BioShield Act. These risks weigh heavily upon small companies with limited resources and were recognised as a major factor in the failure of VaxGen. Crucially, by supporting companies in these technical and development areas through funding, key product development studies can be carried out. As the next chapter will detail, such studies capitalise on our ability to manipulate life at the molecular level and are essential to the development of any viable MCM.

In the second instance, this chapter demonstrated the way that a particular understanding of the threat environment, specifically from enhanced, emerging and advanced agents, as outlined in HSPD-18, significantly shaped BARDA's focus on a flexible biodefence strategy. Such notions of insecurity draw from our ability to make intelligible the potential of molecular life to shift and change in the natural environment, generating new and emerging threats such as never-before-seen strains of flu. They also draw from our ability to shape and manipulate life at the molecular level in the creation of new weapons.

In the third instance, this chapter analysed the way that BARDA had created a range of technical support mechanisms to not only support companies in the development of MCMs but to also respond to this threat environment. The failure of VaxGen also revealed the limited expertise and infrastructure that companies such as these have in bringing a product through the necessary technical development hurdles to licensure. This limitation was addressed by BARDA in the creation of the Core Services. These services provide flexible and sustainable development support for partnering companies and act as a significant push incentive. Such efforts were recognised as placing the U.S. government further down the development pipeline and in so doing it has accepted much of the development risk previously borne by companies. Crucially, the Core Services are technical support mechanisms that

provide companies with the access to the necessary technologies needed to carry out advanced-development activities. As the next chapter will also demonstrate, such technologies provide the means through which life can be shaped into a viable MCM. BARDA then in the utilisation of financial and technical support mechanisms to facilitate the translation of molecular knowledges into new security technologies represents the significant government intervention necessary for successful MCM development.

The understanding of the threat environment made possible by the molecular vision of life has also shaped the technical support mechanisms invested in and developed by BARDA beyond the Core Services. This was seen most clearly in the creation of the CIADMs and the Broad Spectrum Antimicrobials Program that utilised the OT as a flexible contracting mechanism to incentivise and partner with large pharmaceutical companies. The CIADMs not only help support companies in the technical development of MCMs but also provide the platforms from which rapid and responsive MCM development can be carried out. The CIADMs represent, then, not only the shift from a 'fixed' to a 'flexible' defence strategy in response to the threat environment but also provide access to the technical tools necessary for companies to shape molecular life in the development of MCMs. In the next three chapters a case study analysis will be carried out regarding the key role the molecular vision of life plays in not only shaping the understanding of the threat of particular agents but in facilitating the manipulation of these agents in the development of particular MCMs.

Chapter 5: BARDA, Gene Mapping and the Production of ST-246

Introduction

This is the first of three chapters that carries out an empirical examination into the way the Biomedical Advanced Research and Development Authority (BARDA) has supported the development of medical countermeasures (MCMs) for category A threats. This chapter investigates BARDA's efforts in addressing the threat of smallpox. The case of smallpox is taken first as this was chronologically the first biological threat to be significantly addressed by the U.S. government as demonstrated by the stockpiling of a vaccine by the Center for Disease Control and Prevention (CDC) in 1999. This chapter first analyses the way the nature or biology of the virus influenced the political response to this threat in the decision to stockpile vaccines and antivirals. It then analyses the way that BARDA has supported companies through the 'valley of death' in the development of particular vaccines and antivirals. Finally, it examines the key molecular techniques and technologies that made possible the development of a particular antiviral MCM. The purpose of this chapter is to demonstrate the way that a biological understanding of the threat of smallpox and the financial and technical support offered by BARDA combined in order to successfully develop and stockpile an antiviral against the threat of smallpox.

This chapter argues that an understanding of the biology of the smallpox virus was essential to the shaping of the political threat and the production of MCMs supported by BARDA. Firstly, it demonstrates that against the background of the anthrax letters, the release of a highly contagious virus amongst a largely unvaccinated population, either through deliberate or accidental means, stimulated government efforts into the development and stockpiling of enough vaccine to protect the entire U.S. population. Key factors in this decision to heavily invest in fixed-defences included an understanding of the highly contagious nature

of the virus. Further, the modern techniques of molecular biology such as synthetic genomics have supported the engineering and enhancement of the virus by potential terrorists.

Though significant government efforts have focused on the creation and stockpiling of an efficacious vaccine, in response to an attack the time in which a vaccine can be administered post-exposure is limited. This chapter goes on to demonstrate how this understanding has driven the search for an effective antiviral. Such efforts carried out by SIGA Technologies have been supported by BARDA through a number of push and pull incentives. The antiviral developed by SIGA – ST-246 – capitalises on a pathway through which the smallpox virus spreads throughout the body. Using the techniques of modern molecular biology and drug discovery, specifically gene mapping and High Throughput Screening, it was revealed that ST-246 inhibits the action of particular proteins vital to the long-range spread of the virus within the human body. Crucially, these technologies support the mapping of DNA and the logical deduction of the specific gene targeted by ST-246. The contrasting techniques utilised in classical and modern biology are used to demonstrate the way the development of ST-246 capitalises upon our ability to understand and manipulate the workings of life at the molecular level. The mapping of DNA here, in contrast with the two other empirical chapters, demonstrates one path through which molecular knowledge can be translated into new pharmaceutical defences.

This chapter proceeds with the understanding of smallpox as a biological weapon, a basic explanation of the virus's biology and the history of smallpox vaccination. It then turns to the efforts of the CDC and BARDA in dealing with this threat through the development and stockpiling of particular vaccines and antivirals. The way ST-246 has been developed at the molecular level is then addressed with the essential tools and techniques explained.

Smallpox as a Biological Weapon

Smallpox, the disease caused by the variola virus, has been recognised as a potential biological weapon that represents one of the most serious threats to civilian populations. One of the most significant factors in this assessment is the highly contagious nature of the virus along with the very small dose required to cause infection.[1] Smallpox has a case fatality rate of 30 percent or more amongst unvaccinated populations.[2] Routine vaccination throughout the U.S. ended in 1972 and historical rates of transmission during the 1960s and 70s were as high as ten to twenty second-generation cases from a single case.[3] The Dryvax vaccine (see below) used in eradication efforts offered limited protection after 3–5 years, meaning that the majority of the population today would be susceptible.[4] Other factors influencing the understanding of this threat as a potential weapon included revelations of a Soviet biological weapons programme during the Cold War of industrial size and capacity that was able to produce many tonnes of smallpox virus annually. This was combined with revelations of Soviet efforts to molecularly enhance and produce more virulent and contagious recombinant strains of the smallpox virus.[5]

Modern techniques of molecular biology have also increased fears that the virus may be developed and disseminated. This has resulted from the fact that publicly accessible scientific literature has revealed the relatively simple and inexpensive methods for the growth, purification and genetic engineering of the smallpox virus.[6] This literature has also suggested ways in which the virulence of the virus may be enhanced via the insertion of cytokine genes.[7]

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[1] Douglas W Grosenbach, Robert Jordan, and Dennis E Hruby, 'Development of the small-molecule antiviral ST-246® as a smallpox therapeutic', *Future Virology* 6, no. 5 (2011): 653-671, NIH copy 2.
[2] Donald A. Henderson et al., 'Smallpox as a Biological Weapon', in *Bioterrorism: Guidelines for Medical and Public Health Management*, eds. Donald A. Henderson, Thomas V. Inglesby and Tara O'Toole (Chicago: AMA Press, 2002), 99.
[3] Ibid., 101.
[4] Grosenbach, Jordan, and Hruby, 'Development of the small-molecule', NIH copy 2.
[5] Henderson et al., 'Smallpox as a Biological Weapon', 101.
[6] Grosenbach, Jordan, and Hruby, 'Development of the small-molecule', NIH copy 2-3.
[7] Ibid., NIH copy 3.

These methods and avenues have increased the potential that terrorists may not only recreate the virus using tools such as synthetic genomics but also molecularly enhance its virulence. Indeed, the smallpox genome has also been published, facilitating genetic recreation and manipulation. Further, in response to an attack, post-exposure vaccination is limited to four days after exposure[8] to the virus making the need for an effective antiviral extremely pressing.

The last known case of smallpox in the U.S. was in 1949 and the global eradication programme began in 1967.[9] The Global Smallpox Eradication Program led by the WHO,[10] emphasised surveillance and containment and utilised 'ring vaccination' to identify and rapidly isolate new cases and all individuals that had had contact with those cases. Such efforts broke the chain of human-to-human transmission resulting in eventual eradication. This approach was possible as the variola virus is host-specific for humans and lacks an animal reservoir. This means that it could not be reintroduced by a mammalian or insect vector/carrier. Two other facilitators of eradication included the easy identification of infected individuals, supporting quarantine and the fact that latent infections do not occur. Individuals either die from the disease or recover and gain full immunity.[11] This chapter will now turn to the type of infection caused by the smallpox virus.

The Smallpox Virus

The scientific name for the virus that causes smallpox is variola and this presents in two clinical forms, variola major and minor. Variola virus major causes four major clinical types of smallpox: ordinary, modified, flat and hemorrhagic.[12] Ordinary represents the most common type that has occurred historically and has accounted for 90 percent or more of

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[8] Ibid., NIH copy 3.
[9] Rohit Puskoor and Geoffrey Zubay, 'Smallpox (Variola Virus)', in *Agents of Bioterrorism: Pathogens and their Weaponisation*, ed. Geoffrey Zubay (New York: Columbia University Press, 2005), 233.
[10] For a detailed account of the efforts in this astounding achievement see: F. Fenner et al., *Smallpox and its Eradication* (Geneva: World Health Organisation, 1988).
[11] Puskoor and Zubay, 'Smallpox (Variola Virus)', 233-4.
[12] Ibid., 240.

cases. A mild reaction is caused by the modified case and has often occurred in previously vaccinated persons. Flat and hemorrhagic cases are both rare and extremely severe. Variola major has historically been the most severe and most common form of smallpox, with a more extensive rash and higher fever. Variola minor causes the much milder and much less common illness alastrim with a case mortality rate of one percent or less.[13]

Infection from the variola virus occurs when virus particles or virions lodge themselves in the respiratory mucus. In ordinary-type infections symptoms manifest around eleven to fourteen days after exposure. The virus proceeds to multiply in the body after entry and two to three days after the initial symptoms of headache and backache lesions appear on the tongue and palate 24 hours before the rash emerges on the skin.[14] Lesions also appear on the larynx giving the patient a sore throat. The development of lesions in the mouth and throat mean that the virus can enter droplets and be expelled and spread by talking and sneezing, providing the main source of viral particles for airborne transmission to other individuals.[15] Those close by can inhale these droplets when they become suspended in the air and when clothing and bed linen is changed.[16] Patients with a cough and an extreme or hemorrhagic case can also expel the virus in a small particle aerosol. In this form the virus can be suspended in the air for a greater amount of time increasing the area over which it can spread.[17]

Around two weeks after infection the patient is often bedridden with a high fever and headache. A rash then appears and at this time, and until seven to ten days after this, the patient is at their most infectious. As the patient is often being cared for at this stage, infection is spread almost exclusively to household members and friends.[18] As noted, it has

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[13] Jonathan B. Tucker, *Scourge: The Once and Future Threat of Smallpox* (New York: Grove Press, 2001), 2.
[14] Puskoor and Zubay, 'Smallpox (Variola Virus)', 240.
[15] Ibid., 241.
[16] Tucker, *Scourge*, 3.
[17] Henderson et al., 'Smallpox as a Biological Weapon', 101.
[18] Ibid., 102.

also been recognised that contaminated clothing or bed linens can also spread the virus. Smallpox was used as a weapon by British forces in North America in the eighteen hundreds. Blankets that had been used by infected patients were distributed to American Indians. This created epidemics, killing more than fifty percent of many affected tribes.[19]

The last recorded person to die from smallpox was Janet Parker in 1978. Working above a research laboratory at the University of Birmingham Medical School, Parker was exposed to the virus which had spread to the floor above through air ducting. As a result of this outbreak five hundred people were placed in quarantine either at home or in hospital. Another accident occurred in 1973 with people catching smallpox after being exposed to the eggs cultivating the virus at the London School of Hygiene and Tropical Medicine.[20] Recent cases of smallpox vials being overlooked and unaccounted for in the U.S.[21] and the exposure of researchers to anthrax[22] highlight the risks that accidents generate, in addition to deliberate releases, in spreading biological agents. These are risks that will increase with the proliferation of safety labs in the U.S. in response to 9/11 and the anthrax letters.[23] This chapter will now turn to the molecular biology of the variola virus and its pathway of infection.

Molecular Biology of the Variola Virus

Viruses have been described as parasitic microscopic organisms that are capable of growth and reproduction only inside the cells of another living thing.[24] Viruses exist in many

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[19] Ibid., 100.
[20] Hugh Pennington, 'Smallpox Scares', *London Review of Books* 24, no. 17 (2002): 32-3.
[21] Brady Dennis and Lena H. Sun, 'FDA found more than smallpox vials in storage room', *The Washington Post*, 16 July, 2014. Available at: https://www.washingtonpost.com/national/health-science/fda-found-more-than-smallpox-vials-in-storage-room/2014/07/16/850d4b12-0d22-11e4-8341-b8072b1e7348_story.html. Last accessed January 7, 2017.
[22] Lena H. Sun, 'CDC says about 75 scientists may have been exposed to anthrax', *The Washington Post*, 19 June, 2014. Available at: https://www.washingtonpost.com/national/health-science/cdc-says-about-75-scientists-may-have-been-exposed-to-anthrax-and-receiving-antibiotics/2014/06/19/4b96467e-f7ea-11e3-8aa9-dad2ec039789_story.html. Last accessed January 7, 2017.
[23] Dennis and Sun, 'FDA found more than smallpox'.
[24] David A. Koplow, *Smallpox: The Fight to Eradicate a Global Scourge* (London: University of California Press, 2003), 32.

ecological sites and inside virtually all living things. Some viruses can be detected under a sophisticated light microscope, but many are exceedingly small with an electron microscope needed to be rendered visible. In fact, the first sighting of the variola virus, which was the first sighting of any virus under an electron microscope, came in 1947.[25]

Viruses are predominantly made up of either single- or double-stranded DNA or RNA. The variola virus genome is composed of double-stranded DNA comprised of around two hundred genes. The genome is surrounded by a protein coat or capsid sheath giving the virus a brick-like shape.[26] Viruses employ many different methods to infect cells with variola waiting to be engulfed by the host cell membrane. This process, known as endocytosis, is faster if the virus is encased in an envelope which helps it bind to specific receptor proteins on the outside of a particular outer cell membrane. This encasing ensures that the virus is absorbed more rapidly and efficiently, spreading the virus with greater speed.[27] As will be demonstrated, this factor and mechanism of spread and infection employed by the variola virus has been essential to the design and stockpiling of an efficacious antiviral.

By attaching and then fusing with the outer layer of the host cell, the virus's genetic material can be introduced. This is a necessary stage in the reproduction of a virus as most must take over the cells reproductive machinery in order to produce essential viral components within the cell. These components are then put together to form new viruses. Once the genetic material of the virus is in the cell, it will move into the nucleus where the cell machinery will make a copy of it. With most viruses, its DNA is duplicated and then 'transcribed' into messenger RNA. This RNA is then 'translated' by the host cell's ribosomes – the protein builders of the cell – to form virus proteins which will then be combined into a new copy.

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[25] Ibid., 33.
[26] Ibid., 33.
[27] Ibid., 34.

The variola virus is a member of the genus Orthopoxvirus, in the Poxviridae family. Unlike most viruses Orthopoxvirus do not depend upon the machinery of the host cell in order to replicate and do so using their own genetic material in the cytoplasm of the host cell.[28] In the case of the variola virus, the enzymes for DNA replication are contained within the virus, meaning that replication can start as soon as it enters the cell. Despite this, the virus still inhibits the cells normal functioning and devotes all the cells resources to its replication.[29] New copies of variola DNA are mass produced and complete new variola particles are constructed within eight hours of viral entry into the cell.[30]

The host cell will continue to be used to generate as many copies of the virus as it can hold which may be around 10,000 to 100,000 viral particles per cell.[31] Those particles that have the appropriate envelope, those that are complete and mature, can pass out of the cell and spread the infection. Other, less mature virus particles, will be released when the host cell produces so many viral copies that it bursts or lyses. Understandings of the molecular biology of the variola virus have revealed the way that its genetic code undergoes very frequent mutation. Viruses pose such an exceptional problem to the human immune system because this mutation changes the external configuration of glycoproteins that determine the antigens against which the body's immune system will produce neutralising antibodies.[32] As the glycoproteins change, they are not recognised and targeted by the body's immune system, remaining free to replicate and cause infection. Such changes in a virus' genome are also commonly seen with the influenza virus. Antigenic drift, the slow process of mutation that occurs as viruses replicate[33] is often responsible for the flu virus changing from season to season. Antigenic shift is a much more seldom occurrence and much more dramatic re-

[28] Peter B. Jahrling, Elizabeth A. Fritz and Lisa E. Hensley, Countermeasures to the Bioterrorist Threat of Smallpox, *Current Molecular Medicine* 5, (2005): 817.
[29] Koplow, Smallpox, 34.
[30] Ibid., 34.
[31] Ibid., 35.
[32] Ibid., 35.
[33] Bruce Braun, 'Biopolitics and the molecularization of life', *cultural geographies* 14, (2007): 16.

assortment of genes, often the result of two different viruses coming into contact[34] and the precursor to potential pandemics as was seen in 2009 with the emergence of the H1N1 virus and the stockpiling of Tamiflu.

Variola has an additional advantage in that it secretes proteins that can bind to and neutralise interferon gamma, the body's most powerful natural antiviral agent.[35] An additional problem in developing treatments for infection is that as viruses cause most of their harm inside the cell, attacking the virus often cannot be done without damaging the human host.[36] As will be demonstrated, ST-246 stockpiled by the U.S. government to combat the threat of smallpox has been developed to overcome this issue by targeting certain essential genes and proteins only present in viruses. In response to these factors, much of the effort in combating the variola virus has focused on preventative measures. By stimulating the body to produce the appropriate antibodies before it is exposed to the virus, it can prepare to defend itself. The most common tool through which this has been done is vaccination.

History of Smallpox Vaccination

Modern vaccination has its basis in the practice of variolation. By infecting a non-immune patient with fluid from a smallpox pustule[37] or scab, a less severe infection was induced. This provided immunity against a much more severe form of infection and utilised the natural workings of the smallpox infection to cancel out the phenomena itself, employing, for Foucault, a mechanism typical of modern security.[38] The reason for this reduced infection

[34] Ibid., 16.
[35] Koplow, Smallpox, 35.
[36] Ibid., 35.
[37] Alexandra J. Stewart and Phillip M. Devlin, 'The history of the smallpox vaccine', *Journal of Infection* 52, no. 5 (2006): 329.
[38] Michel Foucault, *Security, Territory, Population*, trans. Graham Burchell (Basingstoke: MacMillan, 2009), 59.

from scabs, used in variolation, has been made intelligible because of advances in microbiology which have revealed the tightly bound virions in the scab's fibrin matrix.[39]

Quantitative studies in London in 1776 investigating the optimal pustules for variolation led to the first introduction of study design, control groups and quantitative analysis into medical care.[40] The practice of variolation was relegated by Edward Jenner's popularisation of immunity via exposure to cowpox at the end of the 18th century. The development of a smallpox vaccine had a profound effect on the world. Until its development nearly everyone in the world contracted smallpox at some point in their lives.[41] The isolation of the Vaccinia virus, responsible for cowpox, formed a fundamental component of the vaccine – Dryvax – which was used in the WHO's Global Smallpox Eradication Program and as noted, has also been stockpiled by the U.S. government to protect its citizens from a bioterrorist attack, noted above.

Fears of such an attack were significantly heightened after the events of 2001.[42] In response, George Bush announced in December 2002 that smallpox vaccination would be offered to some categories of civilians and administered to members of the military and government in high-risk areas of the world.[43] It has been recognised that this was an extraordinary policy decision, one that sought to vaccinate people against a disease which has been eradicated with a vaccine that carried significant risks.[44] Poor communication resulted in a failure to persuade the relevant publics of the reasons behind the programme. This generated scepticism and a lack of trust and uptake amongst participants. Of the 300,000

[39] Donald A. Henderson et al. 'Smallpox as a biological weapon', *JAMA* 218, no. 22 (1999): 2129.
[40] Stewart and Devlin, 'The history of the smallpox vaccine', 330.
[41] Ibid., 330.
[42] Institute of Medicine, *The Smallpox Vaccination Program: Public Health in an Age of Terrorism* (Washington, DC: The National Academies Press, 2005), preface xv.
[43] Ibid., preface xv.
[44] Ibid., 1.

projected to be vaccinated, only 38,257 were.[45] It has been recognised more widely that the concerns about vaccine-related adverse events have compromised the implementation of a smallpox immunization program.[46]

The failure of this vaccination policy reinforces the importance of good communication in gaining the trust and cooperation of the public essential to any successful mass vaccination.[47] It also highlights the fact that if an attack were to occur, virtually the entire population would be susceptible to infection.[48] As vaccination was halted after eradication, the current world population has little immunity. In contrast to Foucault's dictum on variolisation in the 18th century which was a matter 'of the most naked empiricism',[49] today we understand the biological workings of vaccination and the length of immunity afforded to those vaccinated before smallpox was eradicated. Molecular biology has afforded us an insight into the length of time that the immune system recognises and reacts to the smallpox virus. As noted above, the Dryvax vaccine provides immunity for only 3-5 years after vaccination. Other studies have suggested that the median duration of protection from disease would range from 11.7 to 28.4 years after primary vaccination.[50]

The limited immunity of those previously vaccinated means that any outbreak today would differ substantially from other 20th century outbreaks of the disease.[51] The IOM has recognised that an outbreak in such a susceptible and mobile population would likely spread widely before being recognized and before appropriate countermeasures could be put in

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[45] Debora MacKenzie, 'US smallpox vaccination plan grinds to a halt', *New Scientist* (2003). Available at: https://www.newscientist.com/article/dn4074-us-smallpox-vaccination-plan-grinds-to-a-halt/. Last accessed January 7, 2017.
[46] Guang Yang et al., 'An Orally Bioavailable Antipoxvirus Compound (ST-246) Inhibits Extracellular Virus Formation and Protects Mice from Lethal Orthopoxvirus Challenge', *Journal of Virology* 79, no. 20 (2005): 13139.
[47] See Monica Schoch-Spana et al., 'Leading during Bioattacks and Epidemics with the Public's Trust and Help', *Biosecurity and Bioterrorism* 2, no. 1 (2004): 25-40.
[48] Institute of Medicine, *The Smallpox Vaccination Program*, 47.
[49] Foucault, *Security, Territory, Population*, trans. Graham Burchell (Basingstoke: MacMillan, 2009), 58
[50] See Hiroshi Nishiura, Markus Schwehm, and Martin Eichner, 'Still Protected Against Smallpox?', *Epidemiology* 17, no. 5 (2006): 576.
[51] Institute of Medicine, *The Smallpox Vaccination Program*, 10.

place.[52] Such concerns have heightened with the realisation that this factor makes it an increasingly attractive option for those seeking to spread terror. It has also been recognised that as the disease would probably be passed on to a second generation of cases before being diagnosed, suitable antiviral therapies would be of great value.[53] The role of the variola virus in developing new antiviral agents has been used in the debate surrounding whether the virus should be destroyed or not.[54] This chapter will now look at the way that BARDA has supported the development of particular MCMs to combat the threat of smallpox. First it will look at the efforts of the CDC to stockpile a smallpox vaccine to protect the general population.

CDC Stockpiles

Before the establishment of the Project BioShield Act and BARDA, the CDC had invested considerable efforts in stockpiling a smallpox vaccine. In 1999 the CDC smallpox vaccine stockpile was made up of Glycernated Vaccine[55] and 150,000 vials of the FDA-licensed freeze-dried vaccine – Dryvax – manufactured by Wyeth-Ayerst Laboratories Inc. in the 1970s.[56] Dryvax was one of the vaccines used in the worldwide vaccination campaign to eradicate smallpox and is prepared by harvesting live virus from lesions on the skin of infected cows.[57] This outdated technique made it virtually impossible to exclude bacterial contamination creating a level of uncertainty as to the precise content of the vaccine, a situation that would not be tolerated in biological products produced today.[58] In order to overcome these deficiencies, the CDC set out to acquire an improved vaccine. In September 2000 OraVax (Acambis PLC) was awarded a contract for the development of a cell-culture

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[52] Ibid., 10.
[53] Ibid., 35.
[54] Ibid., 47.
[55] Michael Mair & Luciana Borio, 'Key Information Regarding Smallpox Vaccine', *Biosecurity and Bioterrorism* 1, no. 1 (2003): 1.
[56] Jonathan B. Tucker, *Scourge: The Once and Future Threat of Smallpox* (New York: Atlantic Monthly Press, 2001), 242.
[57] Aysegul Nalca & Elizabeth E. Zumbrun, 'ACAM2000: The new smallpox vaccine for United States Strategic National Stockpile', *Drug Design, Development and Therapy* 4, (2010): 71.
[58] Brian W. J. Mahy, 'An overview on the use of a viral pathogen as a bioterrorism agent: why smallpox?', *Antiviral Research* 57, (2003): 3.

vaccine based on the same strain of vaccinia as the old Dryvax vaccine.[59] In response to the events of September 11th 2001, the CDC set out to stockpile enough of this vaccine to protect the entire U.S. population.[60] The nature of the threat of smallpox, its ability to rapidly spread through an unvaccinated population, heavily influenced the political response, one focused predominantly on the establishment of fixed-defences to protect the entire population of the U.S. In August 2007 ACAM2000 received FDA approval and in February 2008 it replaced Dryvax for all smallpox vaccinations.[61] Following the stockpiling of ACAM2000 all Dryvax stockpiles were destroyed.

ACAM2000, a 'second generation' smallpox vaccine now manufactured by Sanofi Pasteur Biologics Co (formerly Acambis), contains a live vaccinia virus, a virus closely related to the causative agent of smallpox, variola major.[62] Immunisation with the vaccinia virus causes a localised, self-limited infection which elicits an immune response and confers immunity to infections of smallpox[63] and provides cross-protection against all viruses in the orthopoxvirus family.[64] This process can cause complications for immunosuppressed individuals (as well as occasionally in healthy people) as their immune systems may not be able to contain the normally localised infection caused by the live-virus vaccine.[65] Vaccina immune globulin (VIG) - a concentrated solution of antibodies to vaccinia virus - is used to treat the complications that can arise with the administration of the smallpox vaccine.[66] In 2001 the CDC possessed 5,400 vials of VIG, enough for complications resulting from 3 million vaccines.[67] The higher incidence of immunocompromised conditions has increased the need for this treatment. This section of

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[59] Tucker, *Scourge,* 245.
[60] Ibid*.,* 245-6.
[61] Nalca & Zumbrun, 'ACAM2000', 71.
[62] Mair & Borio, 'Key Information', 1.
[63] Ibid., 1.
[64] Canadian Immunisation Guide: Part 4 Active Vaccines: Smallpox Vaccine, 2016. Available at: http://www.phac-aspc.gc.ca/publicat/cig-gci/p04-spox-vari-eng.php. Last accessed January 7, 2017.
[65] Mair & Borio, 'Key Information', 1.
[66] Tucker, *Scourge,* 247.
[67] Ibid*.,* 247.

the chapter will now look at the way BARDA and Project BioShield have supported the development of one vaccine - Imvamune - and one antiviral - ST-246.

Project BioShield Contracts and BARDA Support

Smallpox Vaccine

Bavarian Nordic - Imvamune

Imvamune, the first vaccine successfully developed using Project BioShield funds, is an attenuated 'third generation' vaccine designated for immunocompromised persons.[68] It is based on the Modified Vaccinia Ankara (MVA) virus,[69] which unlike conventional smallpox vaccines does not have the ability to replicate in human cells and so eliminates risk of accidental infection,[70] making it suitable for those with HIV/AIDS, atopic dermatitis (AD)/eczema, children and pregnant and nursing women.[71] As the first chapter demonstrated, as a result of the classical technique of serial passage, MVA has nearly 15 percent less genome in comparison to its parental vaccinia virus CVA, meaning that MVA has lost the ability to reproduce itself in a form that can cause infection in humans.[72]

In June 2007 BARDA awarded a contract to Bavarian Nordic for the delivery of 20 million doses of the smallpox vaccine Imvamune at a total cost of US $544 million.[73] This contract has options that if exercised extend the value to US$1.6 billion. One of the options in this contract allowed for the government to procure up to an additional 60 million doses. It also set out funds to support additional clinical studies for extending the license to include HIV-

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[68] HHS, *Project BioShield Annual Report to Congress January 2012 - December 2012* (Washington DC, Office of the Assistant Secretary for Preparedness and Response, 2012), 6.
[69] Ibid., 6.
[70] Bavarian Nordic Delivers 1 Million Doses of First Vaccine Developed Under U.S. Biopreparedness Program to the Strategic National Stockpile, 13 July 2010. Available at: http://www.bavarian-nordic.com/media/media/news.aspx?news=2041. Last accessed January 7, 2017.
[71] Bavarian Nordic Completes Delivery of 20 Million Doses of IMVAMUNE® Smallpox Vaccine to the U.S. Strategic National Stockpile, 15 November 2013. Available at: http://www.bavarian-nordic.com/investor/news/news.aspx?news=3051. Last accessed January 7, 2017.
[72] Lucas Sánchez-Sampedro et al., 'The Evolution of Poxvirus Vaccines', *Viruses* 7, no. 4 (2015): 1739.
[73] Bavarian Nordic Completes Delivery.

infected, pediatric, and geriatric populations.[74] This was the first contract to utilise advance payments as milestones in development and production are reached as set out in the Pandemic and All-Hazards Preparedness Act (PAHPA).[75] Under this contract the successful completion of a Phase II safety study with Imvamune in HIV-infected subjects in November 2008 triggered a $25 million milestone payment.[76] In October of 2011 Bavarian Nordic announced the receipt of a performance-based milestone payment of $25 million under this contract having successfully scaled-up production from three to four batches per week at its Kvistgaard facility.[77]

In May of 2012 the total value of this procurement contract was increased by $32 million to $544 million to facilitate the Phase III trial of Imvamune.[78] This study supported a Biologics License Application (BLA) submission to the FDA and was implemented after the milestone delivery of 8 million doses of Imvamune to the Strategic National Stockpile (SNS).[79] In July of 2012 BARDA announced that the population eligible to receive Imvamune in an emergency would be expanded to individuals of all ages with HIV infection or AD despite limited clinical data in children, pregnant women, and nursing mothers.[80] Previously, only certain people with HIV were eligible. Completion of this contract and final delivery of the 20 million doses was completed in November 2013.

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[74] Press Release: Bavarian Nordic Wins $1.6 Billion U.S. Smallpox Drug Deal, 5 June 2007. Available at: http://www.fiercebiotech.com/biotech/press-release-bavarian-nordic-wins-1-6-billion-u-s-smallpox-drug-deal. Last accessed January 7, 2017.
[75] Ibid.
[76] Bavarian Nordic reports successful safety data from Phase II study with IMVAMUNE®, 5 November 2008. Available at: http://www.bavarian-nordic.com/investor/news/news.aspx?news=2009. Last accessed January 7, 2017.
[77] Bavarian Nordic Receives a USD 25 Million Milestone Payment after Scaling Up for Industrial Production of IMVAMUNE®, 28 October 2011. Available at: http://www.bavarian-nordic.com/media/media/news.aspx?news=1917. Last accessed January 7, 2017.
[78] U.S. Government Supports Phase 3 Study of Bavarian Nordic's Smallpox Vaccine, 22 May 2012. Available at: http://www.bavarian-nordic.com/media/media/news.aspx?news=2033. Last accessed January 7, 2017.
[79] Ibid.
[80] U.S. Government Expands Population Eligible to Receive Bavarian Nordic's Smallpox Vaccine in an Emergency, 11 July 2012. Available at: http://www.bavarian-nordic.com/media/media/news.aspx?news=1880. Last accessed January 7, 2017.

We can see the way that BARDA has supported Bavarian Nordic in this contract and the development and stockpiling of Imvamune. In addition to paying for the stockpiling of Imvamune, the advanced-development of this product was supported through the utilisation of payments supporting the completion of safety studies and Phase III trials. These funds, essential to the development of Imvamune and overcoming the 'valley of death' (despite its classical method of development), facilitated the expansion of this vaccine to vulnerable populations. These milestone payments provided both a market guarantee and also lowered the cost and risk of development through structured funding upon completion of milestones so combining both push and pull incentives.

Imvamune - Stockpile Maintenance & Freeze-Dried Formulation

In April of 2013, following the complete delivery of the originally contracted 20 million doses, Bavarian Nordic announced the award of a contract from BARDA valued at $228 million for another 8 million doses of Imvamune® to maintain the 20 million doses stored in the SNS.[81] This contract utilised performance-based milestone payments combining push and pull incentives and is focused on ensuring the necessary manufacturing capacity for future orders, pending the availability of future funding.[82] Bavarian Nordic is guaranteed to receive $110 million for 4 million doses with the remaining $118 million for another 4 million doses, hinging on the availability of U.S. funding next year.[83]

As demonstrated in the previous chapter, the Pandemic and All-Hazards Preparedness Reauthorization Act (PAHPRA) of 2013 reauthorized the PAHPA of 2006 for another five years, extending funding for Project Bioshield and BARDA. This act authorises the appropriation of

[81] Bavarian Nordic Receives Contract Valued up to USD 228 Million from the U.S. Government Securing Continued Production and Deliveries of IMVAMUNE® Smallpox Vaccine, 16 April 2013. Available at: http://www.bavarian-nordic.com/media/media/news.aspx?news=1838. Last accessed January 7, 2017.
[82] Ibid.
[83] Kathleen Miller, Bloomberg News: Bavarian Nordic Wins $228 Million U.S. Smallpox Vaccine Award, 17 April 2013. Available at: http://www.bloomberg.com/news/articles/2013-04-16/bavarian-nordic-wins-228-million-u-s-smallpox-vaccine-award. Last accessed January 7, 2017.

up to $1.6 billion and $2.8 billion to fund BARDA and Project BioShield, respectively, between 2014 and 2018. Importantly, this authorization does not mean that these funds are immediately available and currently only $250 million has actually been appropriated for MCM procurement per year.[84] This situation has caused a great deal of unease among companies that, having invested in MCM development, now find that in the future there will be far less money for development and procurement.[85] As this case demonstrates, maintaining stockpiles depends upon the amount of funds delivered each year.

In November of 2009 Bavarian Nordic announced the award of a contract from BARDA for the development of a freeze-dried version of its Imvamune® smallpox vaccine with a total prospective value of $40 million.[86] A freeze-dried formulation offers advantages in terms of increased shelf-life and improved stability compared to the liquid-frozen formulation.[87] The base-line funding for this contract represents 33 percent of the total value that will be followed by four additional years of optional funding upon successful completion of pre-determined technical milestones.[88] In October of 2010, certain development milestones were met, releasing $14 million to support the validation of the new freeze-dried manufacturing process and associated pre-clinical and clinical studies.[89] In April of 2011 the value of this contract was increased to $94 million to provide support for additional studies and

[84] Stefan Elbe & Anne Roemer-Mahler, *Summary Report: Pharmaceuticals and Security: Strengthening Industry Engagement* (University of Sussex: Centre for Global Health Policy, 2014), 10-11.
[85] Ibid., 10-11.
[86] US Government Awards Contract to Bavarian Nordic for the Development of Freeze-Dried IMVAMUNE® Smallpox Vaccine, 17 November 2009. Available at: http://www.bavarian-nordic.com/investor/news/news.aspx?news=1977. Last accessed January 7, 2017.
[87] Bavarian Nordic in negotiations with the US authorities for the further development of IMVAMUNE®, 24 August 2009. Available at: http://www.bavarian-nordic.com/investor/news/news.aspx?news=1985. Last accessed January 7, 2017.
[88] US Government Awards Contract.
[89] US Government Exercises Next Part of Bavarian Nordic's Freeze-Dried IMVAMUNE® Contract, 12 October 2010. Available at: http://www.bavarian-nordic.com/investor/news/news.aspx?news=1935. Last accessed January 7, 2017.

manufacturing activities.[90] In April of 2014 BARDA exercised an option of this contract worth $21.9 million to fund the transfer of the already validated manufacturing process to a commercial manufacturing line with a larger capacity.[91] Development funding is then structured according to the completion of performance and technical milestones, so combining push and pull incentives in support of this formulation of Imvamune that gives it a greater shelf life.

Smallpox Antiviral

SIGA Technologies - ST-246/Arestvyr

ST-246 is the first smallpox antiviral to be supported through Project BioShield.[92] In 2003 SIGA Technologies (SIGA) purchased the rights to what became known as ST-246 and other assets from a Pennsylvania company, ViroPharma Inc., for $1 million in cash and 1 million shares of SIGA's common stock.[93] ST-246 works by blocking the ability of the virus to spread to other cells, preventing it from causing disease.[94] In May 2011 BARDA awarded SIGA a contract for the delivery of 1.7 million treatment courses of a smallpox antiviral – ST-246 – to the SNS at a total cost of $433 million.[95] This contract also supported the final stages of development needed to apply for FDA approval, including the development of techniques for scale-up manufacturing, a Phase III safety study and studies in animals to demonstrate product

[90] Bavarian Nordic's Contract for Development of a Freeze-dried Version of IMVAMUNE® Smallpox Vaccine Extended to a Total Value of USD 94 million, 11 April 2011. Available at: http://www.bavarian-nordic.com/media/media/news.aspx?news=1896. Last accessed January 7, 2017.
[91] BARDA Moves Forward on Freeze-Dried Smallpox Vaccine, 22 April 2014. Available at: https://globalbiodefense.com/2014/04/22/barda-moves-forward-on-freeze-dried-smallpox-vaccine/. Last accessed January 7, 2017.
[92] BARDA Supports first Project BioShield contract for smallpox drug, 13 May 2011. Available at: http://www.phe.gov/Preparedness/news/Pages/smallpox-antiviral-110513.aspx. Last accessed January 7, 2017.
[93] David Willman, LA Times: Cost, need questioned in $433-million smallpox drug deal, 13 November 2011. Available at: http://articles.latimes.com/2011/nov/13/nation/la-na-smallpox-20111113/2. Last accessed January 7, 2017.
[94] SIGA Technologies Awarded U.S. Government Contract Valued at Up to $2.8 Billion, 13 May 2011. Available at: http://investor.siga.com/releasedetail.cfm?ReleaseID=577406. Last accessed January 7, 2017.
[95] Ibid.

efficacy[96] under the Animal Rule, a push incentive which may reduce the risk but not the cost of development (see below). Clinical trials are expensive and Phase III trials are often the largest with 1,000 to 5,000 patient volunteers taking part in evaluating the effectiveness of a drug and the adverse reactions that arise from long-term use.[97] This would be a daunting prospect for any company that is not sure of the market for its product. BARDA's funding to support this advanced-development activity is essential to the realisation of a successful product. It not only facilitates the use of relevant technologies but also provides the funding for necessary studies, so taking away some of the risk from the developer.

In July of 2013 SIGA reached a contractual milestone with the delivery of approximately 590,000 courses of ST-246 to the SNS, qualifying for a payment of approximately $79 million for the courses delivered to date under this pull incentive.[98] ST-246 has been used in three compassionate-use cases in the U.S.[99] Compassionate use is also termed 'expanded access' and refers to the use of an investigational drug outside of a clinical trial to treat a patient with a serious or immediately life-threatening disease or condition who has no comparable or satisfactory alternative treatment options.[100] BARDA has then used contractual milestones to provide a guaranteed market and to also provide structured funding so as to support development and reduce the risk associated thus utilising both push and pull incentive mechanisms.

Early Development Support

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[96] BARDA Supports first.
[97] Jason Matheny et al., 'Incentives for Biodefence Countermeasures Development', *Biosecurity and Bioterrorism* 5, no. 3 (2007): 229.
[98] SIGA Meets Drug Delivery Condition Under BARDA Contract and Qualifies for First Payment for Delivering Arestvyr(TM), 16 July 2013. Available at: http://investor.siga.com/releasedetail.cfm?ReleaseID=777443. Last accessed January 7, 2017.
[99] Israel Taps SIGA Technologies' ST-246(R) to Combat Smallpox in Simulated Bioterror Attack, 19 January 2010. Available at: http://investor.siga.com/releasedetail.cfm?ReleaseID=438564. Last accessed January 7, 2017.
[100] Expanded Access (Compassionate Use), 2016. Available at: http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/ucm20080392.htm. Last accessed January 7, 2017.

In December 2005 ST-246 was granted Fast Track status by the FDA,[101] a significant push incentive as it facilitates drug development and expedites drug review, reducing the cost and risk of development.[102] The development of ST-246 was also supported by the NIH through a $4.8 million Small Business Innovation Research (SBIR) Phase II continuation grant announced in August of 2006.[103] In December of 2006 the FDA granted Orphan Drug Designation to ST-246, entitling SIGA to seven years of marketing exclusivity in the United States upon marketing approval from the FDA.[104] The pull incentive of market exclusivity would seem to be meaningless considering that the U.S. government is the only buyer for SIGA's product. Indeed, were MCMs a viable product in civilian domestic markets, there would be no need for BARDA at all. Orphan Drug Designation also includes the push incentive of tax credits for qualified clinical testing,[105] so reducing the cost of development.

In September 2008 SIGA announced the award of a $55 million contract from the National Institute of Allergy and Infectious Diseases (NIAID) to support the development of additional formulations and smallpox-related indications for ST-246.[106] This funding, acting as a pull incentive, was directed to the studies needed for formulation development, animal efficacy, human safety evaluations, and manufacturing.[107] Later that month a further $20

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[101] SIGA Announces Smallpox Treatment Breakthrough – SIGA Drug Completely Prevents Smallpox Disease In Preliminary Primate Trial, 18 October 2006. Available at: http://investor.siga.com/releasedetail.cfm?ReleaseID=286748. Last accessed January 7, 2017.
[102] Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review. Available at: http://www.fda.gov/forpatients/approvals/fast/ucm20041766.htm. Last accessed January 7, 2017.
[103] SIGA Announces $4.8 Million Grant for SIGA-264, It's Smallpox Candidate, 2 August 2006. Available at: http://investor.siga.com/releasedetail.cfm?ReleaseID=286751. Last accessed January 7, 2017.
[104] FDA Approves Orphan Drug Designation For SIGA's Smallpox Drug, SIGA-246, 20 December 2006. Available at: http://investor.siga.com/releasedetail.cfm?ReleaseID=286740. Last accessed January 7, 2017.
[105] Developing Products for Rare Diseases & Conditions, 2016. Available at: http://www.fda.gov/forindustry/DevelopingProductsforrareDiseasesConditions/default.htm. Last accessed January 7, 2017.
[106] SIGA Technologies Awarded $55 Million by Federal Government to Develop Broader Applications for Its Lead Drug Candidate ST-246, 3 September 2008. Available at: http://investor.siga.com/releasedetail.cfm?ReleaseID=331853. Last accessed January 7, 2017.
[107] Ibid.

million was awarded by the NIAID from BARDA to accelerate process development related to large-scale manufacturing and packaging of the drug and commercial-scale validation.[108]

In September 2009 SIGA announced the award of a Phase II grant of approximately $3 million from the NIH to continue exploring the use of ST-246 as an adjunct to the current smallpox vaccine – ACAM2000 stockpiled by the CDC – for prevention of smallpox vaccine-related adverse events.[109] Later that month SIGA announced the receipt of a $1.6 million research project cooperative agreement from the NIH to accelerate the development of its broad-spectrum antiviral candidates.[110] These funds, acting as a pull incentive, were made available through the American Recovery and Reinvestment Act ("ARRA") of 2009, which supports projects that will stimulate the economy, create or retain jobs, and have the potential for making scientific progress within two years of funding.[111]

In March 2009 BARDA, along with the NIAID, using funds which necessarily take the form of a push incentive in early development, supported SIGA's successful attempt to demonstrate its ability to manufacture commercial quantities of ST-246 in accordance with FDA-established Current Good Manufacturing Practices (cGMP).[112] cGMP provide regulations detailing the minimum requirements for drugs, including the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product.[113] These regulations clarify the drug production process and so facilitate drug development. BARDA then plays an integral

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[108] SIGA Technologies Receives Additional $20 Million From NIH for ST-246 Antiviral Therapeutic Development, 18 September 2008. Available at: http://investor.siga.com/releasedetail.cfm?ReleaseID=335511. Last accessed January 7, 2017.
[109] SIGA Technologies Receives a $3 Million Research Grant From the National Institutes of Health, 2 September 2009. Available at: http://investor.siga.com/releasedetail.cfm?ReleaseID=406615. Last accessed January 7, 2017.
[110] $1.6 Million NIH Cooperative Agreement Supports SIGA Broad Spectrum Antiviral Research, 29 September 2009. Available at: http://investor.siga.com/releasedetail.cfm?ReleaseID=412138. Last accessed January 7, 2017.
[111] Ibid.
[112] SIGA Produces FDA Registration Batches of ST-246(r) Drug Product, 30 March 2009. Available at: http://investor.siga.com/releasedetail.cfm?ReleaseID=373710. Last accessed January 7, 2017.
[113] Drug Applications and Current Good Manufacturing Practice (CGMP) Regulations, 2014. Available at: http://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm090016.htm. Last accessed January 7, 2017.

part in the MCM development pipeline, helping products transition from early-stage pre-clinical development and support from the NIH and NIAID to clinical development and review in overcoming the 'valley of death'. This chapter will now investigate the way that the molecular vision of life made possible the development of a new smallpox antiviral.

The Molecular Vision of Life and the Development of ST-246

As the analysis above of the partnerships supported by BARDA demonstrates, currently the SNS has a range of preventative measures to address the threat of smallpox. This includes a smallpox vaccine for the general population – ACAM2000 – and a smallpox vaccine for immunocompromised individuals – Imvamune. An antiviral has also been supported in the form of ST-246. ST-246, has been stockpiled to treat those individuals who are symptomatic with disease and for which the vaccine has no efficacy.[114] This addition is crucial to meeting the threat of smallpox as it has been recognised that there are currently no approved treatments for patients infected with smallpox, as opposed to preventative measures such as vaccines, for viral threats which make up a significant number of the CDC and NIAID Category A Priority Pathogens.[115] Vaccines, though, have been set out as providing post-exposure care. Category A pathogens are those that pose the highest risk to national security and public health because they require special action for public health preparedness and have the potential to be easily disseminated or transmitted from person to person, result in high mortality rates and a major public health impact, and cause public panic and social disruption.[116]

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[114] HHS, *Project BioShield Annual Report January 2014 – December 2014* (Washington DC: Office of Public Health Emergency Preparedness, 2014), 8.
[115] Chelsea M Byrd, Douglas W Grosenbach and Dennis E Hruby, 'Antiviral options for biodefense', *Current Opinion in Virology* no. 3, (2013): 537.
[116] NIAID Emerging Infectious Diseases/Pathogens, 2016. Available at: https://www.niaid.nih.gov/research/emerging-infectious-diseases-pathogens. Last accessed January 7, 2017.

Antivirals have been recognised as playing a key role in facilitating preparedness against a potential attack with smallpox. They can fill the void that is created by a reliance on vaccines. Vaccines that as we have seen in some cases are not suitable for immunocompromised individuals. Vaccines also take time to stimulate the host immune response. This lag period for antibody formation from a vaccine leaves a window of vulnerability.[117] It has been argued that antiviral therapies can fill this void and also compliment vaccination in that they reduce viral load quickly, regardless of immune status, and lower transmission rates by diminishing the virus reservoir.[118] The IOM has recommended that two antivirals of differing mechanisms of action be stockpiled.[119] Two antivirals in the form of ST-246 and Brincidofovir have been supported by BARDA. Brincidofovir releases the active ingredient cidofovir into the body that then inhibits viral replication through DNA chain termination.[120] This chapter will now explore in detail the way ST-246 inhibits the molecular pathogenesis of smallpox viral infections.

ST-246 Mechanism of Action

ST-246 has been developed using the modern techniques of molecular biology. As demonstrated in the first chapter, these techniques contrast with classical methods. In classical methods attempts at weakening a virus for use in a vaccine, for example, are determined to be successful through its phenotype or infectious properties that act as an indication of the change undergone in its genetic make-up or genotype.[121] In contrast, our ability to understand and manipulate DNA has introduced modern techniques of molecular genetics such as rational vaccine design.[122] ST-246, also known as Tecovirimat and Arestvyr,

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[117] Yang et al., 'An Orally Bioavailable Antipoxvirus Compound', 13139.
[118] Ibid., 13139.
[119] James W. LeDuc et al., 'Smallpox Research Activities: U.S. Interagency Collaboration, 2001', *Emerging Infectious Diseases* 8, no. 7 (2002): 743.
[120] Yang et al., 'An Orally Bioavailable Antipoxvirus Compound', 13140.
[121] Kathryn A. Hanley, 'The double-edged sword: How evolution can make or break a live-attenuated virus vaccine', *Evolution* 4, no. 4 (2011): 637.
[122] Ibid., 640.

intervenes upon the smallpox virus' general pathway of infection and has been developed using modern techniques of molecular genetics. As we shall see, this includes the use of technologies and techniques such as High-Throughput Screening and gene mapping.

ST-246 is a small-molecule synthetic antiviral chemical compound that is being developed to treat pathogenic orthopoxvirus infections in humans.[123] This antiviral only works against orthopoxviruses such as cow pox, vaccinia virus and smallpox (variola virus major and minor), a genus of viruses in the family Poxviridae. The mechanism of action of ST-246 targets the way orthopoxviruses replicate. Two infectious forms of orthopoxviruses result from the replication cycle.[124] As noted above, viral replication begins when the variola virus attaches itself to the surface of the host cell. As the viral and cellular membranes fuse, the core of the virus is released into the cytoplasm. Once in the cytoplasm of the host cell the core of the virus then proceeds to synthesise early proteins leading to the formation of essential viral proteins which are then assembled into progeny virus particles.[125] These immature virions or viruses eventually mature into the brick-shaped intracellular mature virion (IMV or MV) which is infectious only when released from the cell after it bursts, also known as cell lysis.

The MV particles can acquire a second membrane (see Figure 1) to form the intracellular enveloped virion (IEV or EV). These EVs can fuse with the host cell membrane, exit and then move on to fuse with another cell membrane, beginning the process of reproduction all over again. As noted, it has been suspected that those virions wrapped in a second membrane play a more critical role in cell-to-cell spread than MVs.[126] MV and EV virus particles have been recognised as two infectious but structurally and functionally different forms of the virus.[127] They represent the two ways that the smallpox virus spreads, through

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[123] Byrd, Grosenbach and Hruby, 'Antiviral options', 538.
[124] Jahrling, Fritz and Hensley, 'Countermeasures', 818.
[125] Ibid., 818.
[126] Jahrling, Fritz and Hensley, 'Countermeasures', 818; Koplow, *Smallpox*, 34.
[127] Aklile Berhanu et al., 'ST-246 Inhibits In Vivo Poxvirus Dissemination, Virus Shedding, and Systemic Disease Manifestation', *Antimicrobial Agents and Chemotherapy* 53, no. 12 (2009): 4999.

cell lysis or bursting, or through the exiting and entry of an enveloped virus.

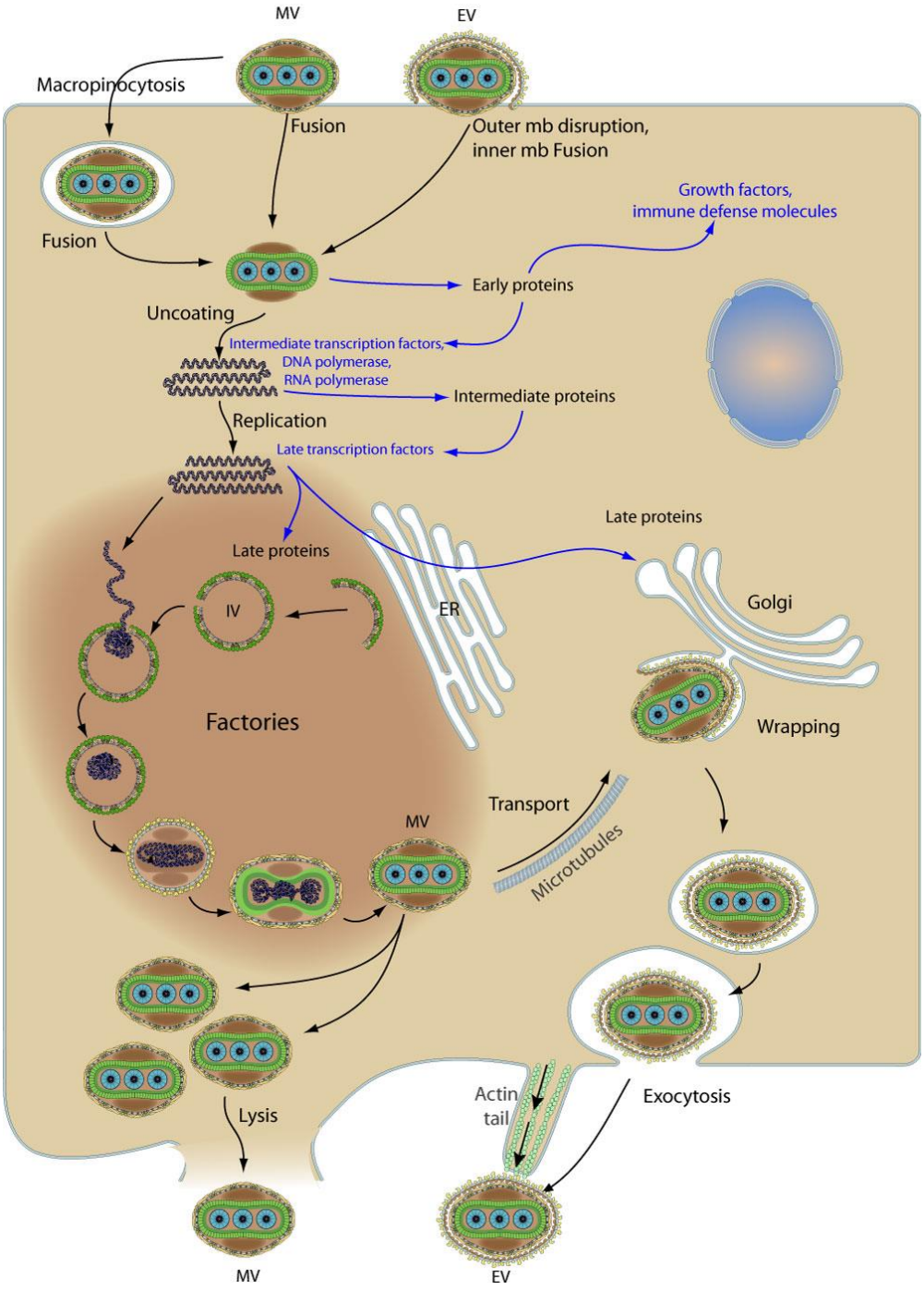

Figure 1. Image of the variola virus replication cycle. Available at: http://viralzone.expasy.org/all_by_species/4399.html. Last accessed January 7, 2017.

Armed with this knowledge, ST-246 aims to prevent the production of EV virus particles that have the ability to leave the cell and that have been implicated in the long-range

spread of the virus within the body.[128] This understanding of virus spread has been supported by the fact that in the absence of EV formation, the virus disseminates poorly from the site of original inoculation.[129] In addition to poor dissemination, lack of EV formation also reduces the virulence of the virus, making it less capable of causing disease.[130] It has been recognised that a certain poxvirus protein, p37, plays a central role in the formation of EV. P37 was identified as the target of ST-246 based on the genetic mapping of ST-246-resistant mutant viruses.[131] P37 has been identified as a very common protein amongst all orthopoxviruses and for which there is no common equivalent gene in mammals.[132] This is a key factor and overcomes the problematic fact that viruses replicate inside cells, noted above. ST-246 can be administered without the fear that it will harm human cells. P37 is essential to the wrapping of MV virus particles and EV formation. By inhibiting interaction of p37 with other cellular components, ST-246 prevents virus envelopment and cell-to-cell spread.[133] This chapter will now look at High Throughput Screening and Gene Mapping, the key molecular tools and techniques used in developing ST-246.

High Throughput Screening

ST-246 was initially discovered in 2002 using High Throughput Screening (HTS), a drug-discovery process widely used in the pharmaceutical industry.[134] The modern drug-discovery process tries to identify a specific molecular target, usually a protein, in a disease-causing organism. Advances in molecular biology, especially in genomics and proteomics, have led to the identification of numerous proteins that it is thought could be modulated by potential

[128] Grosenbach, Jordan, and Hruby, 'Development of the small-molecule', NIH copy 6.
[129] Ibid., NIH copy 6.
[130] Ibid., NIH copy 6.
[131] Ibid., NIH copy 6.
[132] Ibid., NIH copy 6.
[133] Ibid., NIH copy 6.
[134] Ibid., NIH copy 1.

drugs.[135] Key factors in this decision include whether we can design a drug to affect this target molecule. Another issue, noted with the development of ST-246, is whether the target is also found to be essential to the workings of human cells. Once a target has been identified, efforts are made to design a drug to inhibit or modify this target, preventing disease. To create a drug, a potential compound must be identified, often from a library that will interact with that target in a phase of drug development called lead discovery.

A chemical library or compound library stores a range of potential compounds. They will be screened to identify hits against the target. It has been noted that the libraries of large pharmaceutical companies approach approximately one million entities or potential compounds.[136] HTS is a heavily automated scientific method that often uses robots capable of screening 100,000 chemical compounds per day, or more.[137] This process will identify initial compounds that show potential activity against the target protein. A potential compound will then be assessed as to its viability in being developed as a drug. These compounds form the starting points from which potential drugs are refined and developed. A crucial element in evaluating a compound lies in determining its mechanism of action. A compound may inhibit the emergence of disease, but this may be for unwanted reasons that may harm the patient. Viable compounds will then be developed along the long and arduous drug-development process.

Gene Mapping

The mapping of genes was developed by Thomas Hunt Morgan and Alfred Strutevant. They studied the fruit fly (Drosophila) to demonstrate that genes travel on chromosomes. The

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[135] Jonathan Knowles and Gianni Gromo, 'Target Selection In Drug Discovery', *Nature Reviews Drug Discovery* 2, (2003): 63.
[136] Konrad H. Bleicher et al., 'Hit and Lead Generation: Beyond High-Throughput Screening', *Nature Reviews Drug Discovery* 2, no. 5 (2003): 372.
[137] Robert P Hertzberg and Andrew J Pope, 'High-throughput screening: new technology for the 21st century', *Current Opinion in Chemical Biology* 4, no. 4 (2000): 445.

rapid reproduction rate of this fly makes it particularly suited to studying the genetics of its offspring.[138] Chromosomes are packages of Deoxyribonucleic acid (DNA) that contain most of our genetic information or genome. Our DNA is broken down into 24 pairs of chromosomes that reside in the nucleus of our cells. A gene, which codes for one protein, is a section of DNA found on a chromosome. The chromosome also has portions of DNA which regulate the function of genes, turning them on and off. Each strand of DNA is made up of base pairs consisting of guanine-cytosine and adenine-thymine. Specific sequences of bases encode for amino acids which make up proteins.

In 1910, Morgan discovered that the sex of a fly determined the transmission of genes.[139] Sex cells such as the sperm and egg consist of one pair of chromosomes, not the usual two. During meiosis, a particular form of cell division that reduces the chromosome number by half and produces sperm and egg cells, portions of one chromosome swap with another, generating genetic diversity. Crucially, when these sex cells are formed, the single chromosome exchanges fragments of DNA with its partner. Morgan discovered that the closer together the genes were on the original pair of chromosomes, the rarer the exchange of fragments would be in the sperm or the egg. This rationale of recombination facilitated the ordering of genes on the chromosome and the development of chromosome maps.[140]

Fred Sanger, along with colleagues, built upon this idea of genetic mapping to develop a modern method of DNA sequencing in the 1970s. In this method heat is used to separate the double-stranded DNA into single strands. Upon a single strand, DNA polymerase, an enzyme central to the replication of DNA, is used to determine the sequence of DNA molecules.[141] This is done by separating the single strands into four samples. Each sample will

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[138] Michel Morange, *A History of Molecular Biology*, trans. Matthew Cobb (Cambridge: Harvard University Press, 2000), 16.
[139] Ibid., 16.
[140] Ibid., 16.
[141] Ibid., 237.

undergo four different reactions in order to determine the exact position of the four base pairs. In each test the DNA polymerase will reconstruct the DNA double helix by adding labelled bases to the single strand which will be used to visualize the location of each base. In each test, though, the reconstruction will halt every time it comes to a particular base pair be it guanine, cytosine, adenine or thymine. This will create DNA fragments of different lengths with each fragment directly corresponding to the position a particular base pair takes up on the strand of DNA. Using gel electrophoresis, these fragments can be separated. When an electric current is passed through the gel, the DNA fragments separate according to size with the smallest travelling the furthest to the bottom of the plate. Reading the plate from the bottom to the top allows you to reconstruct the DNA sequence from the first base pair to the last.[142] Repeated experiments yield DNA fragments of every possible length, each ending with a visually-labelled base. This way, the bases can be aligned and the sequence of the DNA determined.

The antiviral mechanism of action of ST-246 inhibits extracellular virus production and formation, or the spread of the virus from outside of a cell.[143] ST-246 was the initial 'hit' as a result of a high-throughput screen of 356,240 low-molecular-weight compounds designed to identify inhibitors of vaccinia virus replication.[144] Drug-resistant virus variants have been noted as useful tools in elucidating the mechanism of action of antiviral compounds.[145] These were used to determine the precise mechanism of action through which ST-246 prevents the spread of the virus. Gene mapping of a ST-246-resistant cowpox virus was used to understand which specific gene and consequent protein is targeted by ST-246. When the genes of a

[142] For a useful video in explaining this process see: The Sanger Method of DNA Sequencing, 11 November 2015. Available at: https://www.youtube.com/watch?v=FvHRio1yyhQ. Last accessed January 7, 2017.
[143] Yang et al., 'An Orally Bioavailable Antipoxvirus', 13142-3.
[144] Ibid., 13146.
[145] Ibid., 13143.

resistant virus were compared with those of a susceptible virus it was revealed that a single amino acid change was responsible for the difference in susceptibility.[146]

Proteins are made up of chains of amino acids that are coded for by genes and sequences of DNA. When this change was reengineered back into susceptible virus genomes, the resulting recombinants were found to be resistant to ST-246.[147] These results pointed to the cowpox virus V061 gene and the vaccinia virus F13L gene, which codes for the p37 protein, as the target of ST-246. Both genes encode for a major envelope protein required for the formation of extracellular virus.[148] As has been noted, extracellular virus particles are essential for systemic virus spread in the host and play an important role in viral pathogenesis.[149] We can see then the integral role that molecular tools and technologies, particularly our ability to map DNA, played in the discovery and development of ST-246 as an antiviral against smallpox.

Conclusion

This chapter has conducted an empirical investigation into the development of MCMs to address the threat of smallpox. It demonstrated the role that BARDA played in supporting the development of MCMs and the role that an understanding of the nature of the virus played in the development of ST-246. It has argued that the potential of terrorists to use molecular technologies to recreate or enhance the variola virus in combination with the understanding of the nature of the spread of the virus in today's unvaccinated population significantly influenced the political approach to addressing this threat through the creation and stockpiling of antivirals. The highly contagious nature of the virus, able to be spread through talking and sneezing, demonstrates the potential catastrophic consequences that

[146] Ibid., 13146.
[147] Ibid., 13144.
[148] Ibid., 13144.
[149] Ibid., 13148.

could result from a deliberate or accidental release. These consequences were brought sharply into focus as a result of the release of anthrax in the U.S. in 2001.

Following the attacks of 2001 the CDC stockpiled enough vaccine to protect the entire population of the U.S. BARDA's efforts in developing and stockpiling MCMs aim to complement these efforts and have focused on a vaccine for the immunocompromised and antivirals. Vaccines are limited in the way that they can be used post-event as they necessarily involve a lag period in stimulating the host immune response. BARDA has attempted to address this window of vulnerability by supporting the development and stockpiling of ST-246. ST-246, the first antiviral supported by BARDA, was developed using a range of financial and developmental support mechanisms from the FDA, NIH and NIAID. These mechanisms would not only help bring ST-246 through the difficult drug development pathway but also reimburse the company for delivery to the SNS.

The electron microscope revealed the variola virus in the 1940s and molecular biology further made intelligible the pathways through which the virus spreads throughout the body. The spread of the virus is greatly enhanced when the virus acquires a second membrane becoming an intracellular enveloped virion. In this form the virus can exit the host cell and fuse with another cell spreading the virus and ensuring its reproduction. By preventing the production of EV virus particles, ST-246 reduces the long-range spread of the virus within the body. High Throughput Screening, a heavily automated drug discovery tool, was used to identify potential chemical compounds that inhibit the replication of the smallpox virus. The precise mechanism of action of the drug that would be developed into ST-246 was discovered via the gene mapping of both susceptible and resistant viruses. Through the comparison of these viruses the particular gene targeted could be identified.

ST-246 in targeting the p37 protein inhibits the formation of the EV virus, preventing the long-range spread of the virus within an infected person. The case of ST-246 demonstrates

the way our ability to understand and manipulate genetic material, specifically in the deconstruction and mapping of DNA, has made it possible to inhibit the general pathway of infection that the variola virus takes. The molecular vision of life has then not only revealed the pathway through which viruses such as variola infect human cells and spread, but it has also made possible the rational design of drugs to act on and inhibit these processes in the prevention of disease. With the shift from classical to molecular biology, we move beyond Foucault's naked empiricism to the deliberate design of drugs that inhibit specific molecular processes. Our ability to shape life at the molecular level, in particular the mapping of DNA, with support from BARDA, has been translated in this case into a new pharmaceutical defence against smallpox. This is not the only way that our molecular understandings of DNA can be utilised. As the next chapter shall demonstrate, our ability to manipulate DNA into novel configurations has also supported the development of MCMs to address the threat of anthrax.

Chapter 6: BARDA, the Manipulation of DNA and Raxibacumab

Introduction

This is the second of three chapters that carries out an empirical examination into the way the Biomedical Advanced Research and Development Authority (BARDA) has supported the development of medical countermeasures (MCMs) for category A threats. This chapter investigates BARDA's efforts in addressing the threat of anthrax. The threat of anthrax is taken second as chronologically this was the second threat to be significantly addressed by the U.S. government after smallpox. *Bacillus anthracis*, the bacteria that causes the disease anthrax, has plagued human civilisation for centuries. Modern scientific understandings of this pathogen have revealed the way that the bacteria survive in unfavourable conditions. Reverting to dormant spores, the bacteria wait for human or animal contact before multiplying and spreading disease. A molecular understanding of the hardiness of these bacterial spores has been a central factor in the weaponisation of this bacteria and its use as an instrument of terror.

This chapter first analyses the way this understanding of the molecular biology of *Bacillus anthracis* shaped the need for MCMs to combat this naturally occurring threat. It then goes on to assess the way that BARDA has supported the development of antitoxins to overcome the 'valley of death' and provide a molecular-based defence against this threat. Finally, this chapter takes the case of Raxibacumab, evaluating the key molecular techniques and technologies that made possible the development of this antitoxin. The purpose of this chapter is to demonstrate the roles that both the financial and technical development support from BARDA and understandings of life at the molecular level have played in the stockpiling of MCMs to address the threat of anthrax.

This chapter argues that an understanding of the molecular workings of the anthrax bacteria have played a central role in the attractiveness of this as a weapon of war and terror

and in the MCM development strategy employed by the U.S. government to address this threat. The development of stockpiles of anthrax by the Soviet Union during the Cold War and their accidental release in Sverdlovsk in 1979 demonstrated the effectiveness of this weapon and its lethality. The anthrax letters of 2001 realised concerns that the deadliness and hardiness of the anthrax bacteria could be used to spread fear and death amongst civilian populations. Our molecular understanding of *Bacillus anthracis* has also raised worries that potential terrorists may genetically enhance a strain making it resistant to antibiotics. The limitations that an engineered or antibiotic-resistant strain of anthrax would place on antibiotics and vaccines has stimulated efforts into the development of efficacious antitoxins. As is argued, the biological understanding of the nature of the bacteria has influenced the three-pronged approach taken by the U.S. government to deal with an anthrax attack.

The window of vulnerability created by a possible clandestine release of an engineered strain has spurred the search for viable antitoxins. This chapter demonstrates that it is the nature of the biological threat that has motivated this search. BARDA has supported the development and stockpiling of Raxibacumab, developed by Human Genome Sciences Inc. (HGS) and GlaxoSmithKline (GSK). Raxibacumab targets the pathway through which the anthrax toxins enter the cells. The key active sites of a vital protein in this process have been revealed through x-ray crystallography. This chapter demonstrates the way phage display is used to find a corresponding antibody to target this specific site, preventing the entry of the anthrax toxins into the cell. In contrast to the previous chapter, in this case it is our ability to manipulate DNA into new configurations such as phage display libraries that has formed the path through which molecular knowledge can be translated into new pharmaceutical defences in the form of antibody medicines.

This chapter proceeds with an analysis of the threat that anthrax poses in the hands of terrorists who may seek to engineer and develop resistant strains. The use of anthrax as a

weapon of war and terror is then assessed before turning to the efforts of BARDA in supporting the development of antitoxins and vaccines. The key molecular tools and technologies involved in the creation of Raxibacumab are then investigated.

Anthrax as a Biological Weapon

Anthrax, a disease caused by the bacteria *Bacillus anthracis*, has been recognised as one of prime importance when considering issues of bioterrorism.[1] In 1993, a U.S. Congressional Office of Technology assessment analysis estimated that between 130,000 and 3 million deaths would follow the release of 100kg of the anthrax bacteria, on par with a hydrogen bomb.[2] One of the key factors in the lethality of this disease is the hardiness of the *Bacillus anthracis* spores. When deprived of nutrients the bacteria revert to a dormant spore that is extremely resilient and able to cause disease when returned to favourable conditions such as when in contact with a person or animal. The spores are environmentally hardy and able to survive for decades in ambient conditions.[3] As a result, the threat of infection can remain for a long time after a deliberate release, generating sustained feelings of anxiety and fear, making it an optimal agent for terrorists. Studies have revealed the molecular biology and genes responsible for spore assembly and its regulation.[4]

In order to combat the threat of anthrax, before the letters of 2001, two main defences were developed and stockpiled by the U.S. government, vaccines and antibiotics. It has been argued that antibiotics are unlikely to save the lives of people who don't begin treatment before the onset of advanced illness.[5] In addition, antibiotics may be completely

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[1] Anuj Mehta, 'Anthrax (Bacillus Anthracis)', in *Agents of Bioterrorism: Pathogens and their Weaponisation*, ed. Geoffrey Zubay (New York: Columbia University Press, 2005), 129.
[2] Thomas V. Inglesby et al., 'Anthrax as a Biological Weapon: Updated Recommendations for Management', in *Bioterrorism: Guidelines for Medical and Public Health Management*, eds. Donald A. Henderson, Thomas V. Inglesby and Tara O'Toole (Chicago: AMA Press, 2002), 65.
[3] Ibid., 67.
[4] See: Hongbin Liu et al., 'Formation and Composition of the *Bacillus anthracis* Endospore', *Journal of Bacteriology* 186, no. 1 (2004): 164-178.
[5] Luciana L. Borio and Gigi Kwik Gronvall, 'Anthrax Countermeasures: Current Status and Future Needs', *Biosecurity and Bioterrorism* 3, no. 2 (2005): 103.

ineffective against antibiotic-resistant strains of anthrax causing bacteria. Indeed, the former Soviet Union stockpiled hundreds of tonnes of *Bacillus anthracis* and transferred antibiotic-resistant genes into the anthrax bacteria.[6] It has been noted that the methods in creating resistant strains 'using genetic engineering or bacterial selection are available in the open scientific literature and do not require much sophisticated knowledge in the biological sciences.'[7] Further, understandings of the evolution of bacterial resistance to antibiotics can be leveraged to develop resistant strains. For example, growing cultures of the bacteria in diluted applications of antibiotic will lead to the eventual selection of resistance.[8] These factors have raised fears that potential terrorists may seek to employ these methods, both classical and molecular, in the development of enhanced strains of anthrax. Any successful effort, though, must overcome the difficulties in weaponisation, such as the application of additives to keep spores apart.[9] In the next chapter we will see how BARDA is supporting the development of broad-spectrum antibiotics to deal both with potential bioterror agents and antibiotic resistance.

The hardiness of the spores means that infection can be caused up to ninety days after inhalation.[10] Antibiotics are most useful when given immediately after exposure and before the patient is symptomatic.[11] Once the toxins are produced they cannot be treated with antibiotics.[12] Anthrax then is a good covert agent for any potential bioterrorist as it takes time for people to become ill, making it difficult to pinpoint the source of the release.[13] Learning about the life cycle and pathway through which the anthrax bacteria causes infection and

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[6] Alibek and Handelman, *Biohzard*, 160, cited in Susan D. Jones, *Death in a Small Package* (Baltimore: Johns Hopkins UP, 2010), 201-2.
[7] Borio and Gronvall, 'Anthrax Countermeasures', 103.
[8] Richard Danzig, *Catastrophic Bioterrorism – What Is To Be Done?* (Washington D.C.: Centre for Technology and National Security Policy, 2003), 9.
[9] Stuart B. Levy, *The Antibiotic Paradox* (Boston: Perseus Publishing, 2002), 316.
[10] Jones, *Death in a Small Package*, 234.
[11] Ibid., 242.
[12] Levy, *The Antibiotic Paradox*, 319.
[13] Jones, *Death in a Small Package*, 181.

illness has allowed us to develop defences against it.[14] It has been revealed that the toxins produced by the bacteria are responsible for disease and death.[15] Using an early version of gel electrophoresis, the three anthrax proteins that turn into toxins having entered the cell – lethal factor, protective antigen and edema factor – were separated and recognised in the 1950s as the key components in the development of disease.[16] The molecular basis of these proteins and the protective capsule supporting the hardiness of the spores was revealed via plasmid genetics at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) in the 1980s.[17] The genetic basis for these attributes was revealed to reside in two plasmids, pX01 and pX02. As will be demonstrated, this molecular understanding of the key components in the production of the anthrax toxins was central to the development of an effective antitoxin.

In addition to antibiotics, pre 2001, the U.S. government had also stockpiled a vaccine, Anthrax Vaccine Adsorbed (AVA) also known as BioThrax. BARDA has spearheaded considerable efforts at developing a new next-generation vaccine to overcome the limitations of BioThrax. One limitation of BioThrax against this threat is that it must be administered well before a person is exposed to anthrax spores.[18] Vaccination, is, however is extremely useful in protecting those carrying out decontamination of a suspect area.[19] The significant limitations of antibiotics and BioThrax in addition to the prospect that any significant aerosol anthrax release may be followed by repeated releases as the attackers reload, has stimulated calls for improvements to these defences and the development of antitoxins.[20] This chapter explores the way that BARDA has supported the development of two antitoxins through financial and technical means. As demonstrated with the threat of smallpox, the lag period for any vaccine

[14] Ibid., 186.
[15] Ibid., 196.
[16] Ibid., 199-200.
[17] Ibid., 205.
[18] Borio and Gronvall, 'Anthrax Countermeasures', 103.
[19] Ibid., 103.
[20] Danzig, *Catastrophic Bioterrorism*, 9.

creates a window of vulnerability that can be addressed through the creation of antivirals and antitoxins. An antitoxin, in neutralising the toxins produced by the anthrax bacteria that are already circulating inside the patient's body, would be invaluable against antibiotic-resistant strains. They would also be useful in cases that had been exposed before antibiotics could be administered and where the dose was so large as to overcome the protection offered by the vaccine.[21] This chapter will now outline the way that biology has revealed the pathway of infection of the anthrax bacteria.

Bacillus Anthracis

The bacteria that cause anthrax naturally occur in soil and the disease is very common in animals. It causes four types of infection in human beings: cutaneous (skin), gastrointestinal (stomach), inhalational and via injection.[22] Each type refers to the way the disease is acquired. The name anthrax is derived from the Greek word for coal, *anthrakis*, which refers to the black lesions that occur when the bacteria infect the skin.[23] It is not believed that an anthrax infection is contagious and so cannot be passed from person to person.[24] Anthrax acquired through inhalation is expected to account for the most serious morbidity and mortality following the dissemination of the bacteria via an aerosolised biological weapon.[25] Tests on non-human primates have shown that anthrax spores can remain viable in the lungs for many weeks, with the average incubation period depending on the dose.[26]

Analysis of the biology of the anthrax bacterium has revealed that it is made up of three proteins that contribute to the way it causes disease or its pathogenesis. The bacteria,

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[21] Ibid., 9.
[22] See: Roland Grunow et al., 'Injection Anthrax—a New Outbreak in Heroin Users', *Deutsches Ärzteblatt International* 109, no. 49 (2012): 843–848.
[23] Inglesby et al., 'Anthrax as a Biological Weapon', 66.
[24] Matthew Meselson et al., 'The Sverdlovsk Anthrax Outbreak of 1979', *Science* 266, no. 5188 (1994), 1205.
[25] Inglesby et al., 'Anthrax as a Biological Weapon', 66.
[26] Meselson et al., 'The Sverdlovsk', 1207.

after being inhaled enter the blood stream then attempt to invade and kill cells. As noted, the three proteins in the blood stream - protective antigen, lethal factor and edema factor - combine to form lethal toxin and edema toxin inside the cell.[27] As will be shown, molecular biology has revealed the protective antigen as the key component that facilitates binding to the surface of the host cell and allows the entry of lethal and edema factor into the human cell. Once inside the cell, lethal and edema toxin cause cell death. As will be demonstrated, the central role played by the protective antigen in the disease-causing process of the anthrax bacteria has supported the development of an anthrax antitoxin – Raxibacumab – whose mechanism of action acts on this process. This chapter will also detail the role of tools such as x-ray crystallography and phage display that support the development of this molecular-based MCM.

Anthrax has played a significant role in human history with it being responsible for numerous plagues and livestock epidemics. Its impact on human communities has meant that it was at the forefront of research and has played a key role in modern bacteriology and immunology.[28] As a result, anthrax was the first disease to be conclusively linked to a microorganism.[29] The first successful immunisation of livestock by William Greenfield occurred in 1880, with Louis Pasteur's trial of a heat-cured vaccine in sheep quickly following in 1881.[30] The prevalence of the bacteria amongst animals has been a significant issue for textile and tannery workers over the years. John Bell recognised the anthrax bacteria as the cause of inhalational anthrax, or 'wool sorters' disease'.[31] This referred to the incidences of disease that those handling or treating wool fell victim to. These incidences received their recognition in law with The Anthrax Prevention Act, passed in England in 1919.[32] Such governmental actions

[27] Inglesby et al., 'Anthrax as a Biological Weapon', 68.
[28] Mehta, 'Anthrax', 129-30.
[29] Ibid., 130.
[30] James C. Pile et al., 'Anthrax as a Potential Biological Agent', *Archives of Internal Medicine* 158, no. 5 (1998): 429.
[31] Ibid., 429.
[32] Mehta, 'Anthrax', 130.

in combination with improved disinfection methods greatly reduced the occurrence of anthrax in the developed world. Between 1944 and 1994, 224 cutaneous cases were reported in the U.S., with one occurring in 2000.[33] The last naturally-occurring case of inhalational anthrax in the U.S. occurred in 1976.[34] As of 2005 there were about 2000 cases of cutaneous anthrax reported each year worldwide.[35] This chapter will now address the way anthrax has been used of cause deliberate harm and injury.

Anthrax as a Weapon of War and Terror

The anthrax bacterium was first developed as a biological weapon during the First World War when it was used to attack animals, vital for transport and logistics. The weaponisation of the disease escalated during the Second World War with the Japanese Unit 731 conducting live experiments on prisoners of war.[36] British efforts included testing in 1942 at Gruinard Island, off the west coast of Scotland. The tests were so extensive and the island so contaminated that it had to be quarantined for 48 years.[37] The resilience of the spores means that the threat of disease can remain dormant for centuries. Efforts to decontaminate the island took several years, beginning in 1986. U.S. biological weapons research began in 1943 in response to a perceived threat from the German Army.[38]

U.S. research into biological weapons officially ended in 1969 after an executive order from President Richard Nixon. Soviet efforts, five years behind the U.S. at that time,[39] continued apace and as noted, developed into industrial size and capacity. Many nations, including the Soviet Union, would sign the Biological Weapons Convention in 1972, pledging

[33] Inglesby et al., 'Anthrax as a Biological Weapon', 66.
[34] Mehta, 'Anthrax', 131.
[35] Ibid., 131.
[36] Ibid., 131.
[37] Ibid., 131.
[38] Ibid., 132.
[39] Ibid., 132.

not to use or develop biological agents for military purposes.[40] It is thought that research continued in numerous countries despite the signing of this convention. The anthrax outbreak in Sverdlovsk, Russia, in 1979 confirmed suspicions of continued Soviet research. Reports of an anthrax epidemic in Sverdlovsk, a city of 1.2 million people 1400 km east of Moscow, appeared in the Western Press in 1980.[41] The emergence of gastrointestinal anthrax was originally attributed to eating contaminated meat and cutaneous anthrax to contact with diseased animals.[42] This explanation for the 96 cases of human anthrax, 79 gastrointestinal and 17 cutaneous leading to 64 deaths was heavily questioned and debated.[43] An investigation by independent scientists mapped the geographical distribution of human and animal cases in conjunction with wind and meteorological conditions. It concluded that the outbreak resulted from the windborne spread of an aerosol of anthrax pathogen.[44] In May of 1992, President Boris Yeltsin, the chief Communist Party official of the Sverdlovsk region in 1979, confirmed that the Soviet military was responsible for the release.[45] The largest documented outbreak of human inhalation anthrax was the result of an accidental release from a military microbiology facility on Monday, 2 April 1979.[46]

Up until 2001, the only known data on inhalational anthrax came from the eighteen cases reported in the U.S. from 1900 to 1976[47] and the data from Sverdlovsk. The Sverdlovsk incident provided the data on the only known aerosol release of *bacillus anthracis* spores resulting in an epidemic.[48] These cases made it difficult to calculate the mortality rate of this type of anthrax as most of those in the U.S. occurred before the development of antibiotics and critical care units, whilst the Sverdlovsk data varies widely with recent analyses suggesting

[40] Ibid., 132.
[41] Meselson et al., 'The Sverdlovsk', 1202.
[42] Ibid., 1202.
[43] Ibid., 1203.
[44] Ibid., 1206.
[45] Ibid., 1203.
[46] Ibid., 1206.
[47] Inglesby et al., 'Anthrax as a Biological Weapon', 66.
[48] Ibid., 65.

as many as 250 cases with 100 deaths.[49] During the first Gulf War, Iraq's biological weapons programs stoked fears that it may use 6500 L of its weaponised anthrax.[50] Fears that terrorists may deliberately use anthrax emerged with the attempts of the Aum Shinrikyo cult, noted above, and were unfortunately realised with the anthrax letters a few years later.

The Anthrax Letters of 2001

On the 18th of September and 9th of October 2001, officials believe five letters were sent (four were recovered) to the offices of *NBC Studios* and the *New York Post* in New York City and to Senators Daschle and Leahy of the U.S. Senate.[51] To date, responsibility for this release has not been confirmed and it has been interpreted as both a criminal and terrorist event. Contained within these letters were 1-2 grams of anthrax spores. Outbreaks of disease occurred in Florida, New York, New Jersey, Connecticut, Capitol Hill in Washington D.C. and the Washington D.C. regional area, including Maryland and Virginia.[52] Twenty two people fell ill, eleven with the cutaneous form of the disease and eleven with the inhalational form of the disease, five of which died.[53] Of these five, two were members of the U.S. Postal Service.[54] After tests, the anthrax sent in the letters was described as 'weapons grade' and identified as the Ames strain developed by the USAMRIID within the previous two years.[55]

The response to these attacks was complicated by a number of significant issues including the recent events of September the 11th, the unfamiliarity of physicians to the clinical presentation, diagnosis or treatment of anthrax patients and the enormous crime scene investigation and communication problems between investigating federal agencies.[56] The lack

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[49] Ibid., 70.
[50] Mehta, 'Anthrax', 134.
[51] Jeffrey Ryan and Jan Glarum, *Biosecurity and Bioterrorism* (Oxford: Butterworth-Heinemann, 2008), 146.
[52] Ibid., 146.
[53] Ibid., 146.
[54] Jeanne Guillemin, *Biological Weapons: From the Invention of State-Sponsored Programs to Contemporary Bioterrorism* (New York: Columbia University Press, 2005), 177.
[55] Christian Enemark, *Disease and Security* (Abingdon: Routledge, 2007), 144.
[56] Ryan and Glarum, *Biosecurity,* 282.

of scientific certainty as to the properties of the anthrax in question led to differing policies and recommendations and did not allow the Center for Disease Control and Prevention (CDC) to offer concrete public health advice which generated mistrust amongst the public.[57] The issues that were not addressed soon enough include the number of spores that would cause a lethal dose, how the spores might disperse from an envelope and whether closed envelopes would leak spores.[58]

In addition to not knowing the threshold for the range of infection, neither the CDC nor FBI was practiced in gauging the risks of anthrax.[59] These factors meant that it was difficult to ascertain who was at risk of exposure. This fed into effective treatment as the antibiotics used - Ciprofloxacin and Doxycycline drawn from the stockpile established by the Clinton administration - had to be delivered before the anthrax toxins were produced.[60] The need for effective post-exposure treatment was further revealed. These failures would prove fatal for two postal workers who continued to work at the Brentwood postal facility despite the closure of Senate offices upon suspicion of leakage from the letters.[61] Government Accountability Office reports concluded that poor communication prevented alerting public health agencies and the United States Postal Service to the real risks involved.[62] Further, the risks of inhalational anthrax and its symptoms were not described to the postal workers, nor were local physicians told to be on the watch for any patients from postal facilities.[63] In response, the U.S. government decided to invest in a new range of vaccines and therapeutics to address the threat of anthrax. This chapter will now assess the way BARDA has supported the

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[57] Elin Gursky, Thomas V. Inglesby & Tara O'Toole 'Anthrax 2001: Observations on the Medical and Public Health Response', *Biosecurity and Bioterrorism* 1, no. 2 (2003): 103.
[58] Guillemin, *Biological Weapons,* 173.
[59] Ibid*.,* 174.
[60] Ibid*.,* 174-5.
[61] Ibid*.,* 176.
[62] GAO, *Bioterrorism: Public Health Response to Anthrax Incidents of 2001*. (Washington DC: US Government Accountability Office, 2003), 5; See also GAO, *U.S. Postal Service: Better Guidance Is Needed to Improve Communication Should Anthrax Contamination Occur in the Future* (Washington DC: US Government Accountability Office, 2003).
[63] Guillemin, *Biological Weapons,* 177.

partnership with pharmaceutical and biotech companies central to the development of two antitoxins.

Project BioShield Contracts and BARDA Support

Anthrax Therapeutics/Antitoxins

Elusys Therapeutics Inc - Anthim

As demonstrated above, antibiotics and the BioThrax vaccine have significant limitations in responding to a terrorist attack using anthrax. These factors in addition to the prospect that any significant aerosol anthrax release may be followed by repeated releases as the attackers reload, has stimulated calls for improvements to these defences and the development of antitoxins.[64] Anthrax antitoxins are used as a post-exposure prophylaxis for anthrax. Along with vaccines and antibiotics, antitoxins form one part of a three-pronged approach taken by the U.S. government to deal with an anthrax attack.[65] Elusys Therapeutics, Inc. (Elusys) has been involved in efforts to develop an anthrax therapeutic - Anthim. Anthim is a monoclonal antibody being developed for the treatment and prophylaxis of inhalational anthrax disease. In a similar fashion to Raxibacumab, Anthim binds to Domain IV of the *bacillus anthracis* protective antigen - the region responsible for binding to host cell receptors[66] - and inhibits this protein from binding to the host cell.[67] Anthim prevents the protein from binding to cells and, thereby, inhibits the formation of toxins which are responsible for the bacteria's high mortality.

Anthim has been supported in the main by two advanced-development contracts from BARDA. The first of these included a contract announced in January of 2010 potentially

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[64] Danzig, *Catastrophic Bioterrorism*, 9.
[65] HHS, *Project BioShield Annual Report to Congress January 2012 - December 2012* (Washington DC: Office of the Assistant Secretary for Preparedness and Response, 2011), 4
[66] Leslie W. Baillie, 'Is New Always Better than Old? The Development of Human Vaccines for Anthrax', *Human Vaccines* 5, no. 12 (2009): 810.
[67] Zhaochun Chen, Mahtab Moayeri, & Robert Purcell, 'Monoclonal Antibody Therapies against Anthrax', *Toxins* 3, (2011): 1007.

totalling up to $143 million to complete the final development, commercial manufacturing and licensure of Anthim.[68] Under this contract $16.8 million of funding was provided in the first year with options for additional funding over the following four years. We can see here how this contract, one of the largest awarded by BARDA for advanced-product development, will be structured. This contract will support Elusys in developing the company's clinical and commercial strategy, including scaling up manufacturing, expanded human safety trials and pivotal, non-clinical effectiveness studies in animals, through to FDA licensure.[69] The third year of funding of $50.2 million was awarded by BARDA in August of 2012.[70] This advanced product development contract supports manufacturing activities, human safety trials and non-clinical effectiveness studies in animals and efforts to gain FDA licensure.

The second contract announced in September of 2011 was the first U.S. Government contract to develop an antitoxin for pre- and post-exposure prophylaxis (PEP) use via intramuscular injection (IM).[71] This five year contract supports multiple animal efficacy studies as well as human safety studies to further demonstrate the utility of Anthim, to prevent disease and death from exposure to anthrax when administered intramuscularly before symptoms of disease are present. Intramuscular administration is a significant benefit as it allows for the rapid administration of a single dose of antitoxin to large numbers of people outside of a hospital or medical setting. In September of 2012 Elusys announced the award of additional funding, valued at $14.5 million, to support expanded human safety studies.[72]

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[68] Elusys receives contract for up to $143 million from the U.S. federal government to fund advanced development of Anthim®, a new treatment for Anthrax, 4 January 2010. Available at: http://www.elusys.com/#/news/010410. Last accessed January 7, 2017.
[69] Ibid.
[70] Elusys awarded additional $50.2 million under an existing U.S. government contract to support final stages of development of ETI-204, for treatment of inhalational Anthrax, 1 August 2012. Available at: http://www.elusys.com/#/news/080112. Last accessed January 7, 2017.
[71] Elusys awarded $68 million contract to develop Anthim for intramuscular pre- and post-exposure prophylaxis of Anthrax infection, September 8, 2011. Available at: http://www.elusys.com/#/news/090811. Last accessed January 7, 2017.
[72] Elusys awarded additional $14.5 million under existing U.S. government contracts supporting expanded human safety studies of ETI-204 for treatment of inhalational Anthrax, September 13, 2012. Available at: http://www.elusys.com/#/news/091312. Last accessed January 7, 2017.

We can see here with these two contracts the way that BARDA has supported the development of Anthim. One contract supported the overall development of Anthim including funding for Phase III safety studies, essential for the development of any viable MCM.[73] The yearly funding contract mechanism supports companies such as Elusys throughout the MCM development pathway and provides financial support through the 'valley of death'. Another contract supported the development of a specific product benefit focused on developing Anthim for intramuscular administration. In both contracts milestone payments help push the product through development. This funding structure lowers the cost and risk of development that the company faces and represents a significant push incentive in the facilitation of MCMs. In addition to this, Anthim was supported by being granted Fast-Track status and Orphan Drug Designation by the FDA in 2006 and is being developed under the Animal Rule.[74] All these incentives, predominantly focused on pushing the product through development, combined with the significant pull incentive of the market guarantee provided by Project BioShield and MCM procurement. In November of 2015, Anthim was procured as an investigational agent for the treatment of inhalational anthrax infection for $44.9 million.[75]

Human Genome Sciences/GlaxoSmithKline - Raxibacumab

Raxibacumab (formerly ABthrax) is a recombinant, fully human monoclonal antibody that was originally developed by HGS in collaboration with Cambridge Antibody Technology.[76] In August of 2012 GSK announced that it had completed the acquisition of HGS for $3.6

[73] Elusys announces results from three phase 3 safety studies of its Anthrax anti-toxin, Obiltoxaximab (ETI-204), in adult volunteers and completion of its phase 3 clinical development program, September 22, 2014. Available from: http://www.elusys.com/#/news/092214. Last accessed January 7, 2017.
[74] Elusys' Anthim™ dramatically improves survival of animals treated after active Anthrax infection, April 22, 2008. Available from: http://www.elusys.com/#/news/042208. Last accessed January 7, 2017.
[75] Elusys therapeutics receives first delivery orders from U.S. government for Anthim® (Obiltoxaximab) for treatment of inhalational anthrax, November 12, 2015. Available from: http://www.elusys.com/#/news/111215. Last accessed January 7, 2017.
[76] U.S. Government Agrees to Purchase ABthrax(TM) From Human Genome Sciences for the Strategic National Stockpile, 20 June 2006. Available at: http://www.thefreelibrary.com/U.S.+Government+Agrees+to+Purchase+ABthrax(TM)+From+Human+Genome...-a0147248403. Last accessed January 7, 2017.

billion.[77] Two contracts were awarded utilising Project BioShield funds for the procurement of Raxibacumab.[78] Both contracts did not originally draw from the Special Reserve Fund (SRF) but were modified to do so under BARDA. The first of these contracts was awarded in September 2005, completed in 2009 and delivered 20,000 treatment courses at a cost of $174 million. The second contract was awarded in July of 2009, completed in 2011 and delivered 45,000 doses at a cost of $152 million in 2009 and $8 million in 2011.[79]

In these contracts the SFR acted as a market guarantee that under the original terms of Project BioShield only authorised advanced payment of 10 percent of the total contract amount. Crucially, the Pandemic and All-Hazards Preparedness Act (PAHPA) authorised BARDA to pay up to 50 percent of the total contract amount in milestone payments. During its development, Raxibacumab received a Fast Track Product designation from the FDA, as well as an Orphan Drug Designation for its use in the treatment of inhalational anthrax disease in 2003.[80] An important feature of Fast Track Product designation is that it emphasises the critical nature of close early communication between the FDA and the sponsor to improve the efficiency of product development.[81] By doing this the requirements of drug development are clarified and the time and risk reduced.

Orphan Drug Designation is given to drugs which address diseases/disorders that affect fewer than 200,000 people in the U.S., or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug.[82] Orphan

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[77] GSK completes acquisition of Human Genome Sciences, 3 August 2012. Available at: https://us.gsk.com/en-us/media/press-releases/2012/gsk-completes-acquisition-of-human-genome-sciences/. Last accessed January 7, 2017.
[78] HHS, *Project BioShield Annual Report to Congress January 2009 - December 2009* (Washington DC: Office of the Assistant Secretary for Preparedness and Response, 2009), 7.
[79] HHS, *Project BioShield Annual Report to Congress January 2012 - December 2012*, 5.
[80] U.S. Government Agrees.
[81] Fast Track Designation Request Performance, 2016. Available at: http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cber/ucm122932.htm. Last accessed January 7, 2017.
[82] Developing Products for Rare Diseases & Conditions, 2016. Available at: http://www.fda.gov/forindustry/DevelopingProductsforrareDiseasesConditions/default.htm. Last accessed January 7, 2017.

designation qualifies the sponsor of the drug for various development incentives,[83] including tax credits for qualified clinical testing and the sale of the drug without competition for a certain number of years, a market guarantee which has been used to block competition.[84] As has been noted above a combination of push and pull incentives are included in this designation.

In September 2013 GSK announced a contract with BARDA for the delivery of 60,000 doses of Raxibacumab.[85] This contract, which provides delivery over four years for $196 million, is part of a broader five year base contract. Raxibacumab was approved by the FDA in December 2012 for the treatment of inhalational anthrax in combination with appropriate antibacterial drugs and for prophylaxis of inhalation anthrax when alternative therapies are not available or are not appropriate.[86]

Inhalational anthrax is associated with high mortality primarily due to toxin-mediated injury.[87] The virulence of anthrax comes from the combination of three proteins known as protective antigen, lethal factor, and edema factor.[88] As noted above, on their own these proteins are not toxic to cells but the combination of the protective antigen with lethal factor or edema factor results in the formation of the cytotoxic lethal toxin and edema toxin,

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[83] Designating an Orphan Product: Drugs and Biological Products. Available at: http://www.fda.gov/forindustry/developingproductsforrarediseasesconditions/howtoapplyfororphanproductdesignation/default.htm. Last accessed January 7, 2017.
[84] Andrew Pollack, 'Orphan Drug Law Spurs Debate', *The New York Times*, 30 April 1990. Available at: http://www.nytimes.com/1990/04/30/business/orphan-drug-law-spurs-debate.html. Last accessed January 7, 2017.
[85] Press Release: GSK signs a multi-year agreement with BARDA to supply the US government with anthrax treatment, 19 September 2013. Available at: http://www.gsk.com/en-gb/media/press-releases/2013/gsk-signs-a-multi-year-agreement-with-barda-to-supply-the-us-government-with-anthrax-treatment/. Last accessed January 7, 2017.
[86] Ibid.
[87] Thi-Sau Migone, et al., 'Raxibacumab for the Treatment of Inhalational Anthrax', *New England Journal of Medicine* 361, no.2 (2009): 135.
[88] Nutan Mytle, et al., 'Evaluation of Intravenous Anthrax Immune Globulin for Treatment of Inhalation Anthrax', *Antimicrobial Agents and Chemotherapy* 57, no. 11 (2013): 5684.

respectively.[89] Preventing or blocking the binding of the protective antigen can prohibit the toxins from entering the cells.

Raxibacumab inhibits the protective antigen from binding to the anthrax toxin receptor[90] and so confers 'passive immunity' to the body by transferring readymade antibodies. In contrast, vaccines confer 'active immunity' by exposing the body to live, killed or sub-components of a pathogen and its antigens, so stimulating the body's own production of antibodies. Vaccines represent an auto-immune enhancement at the molecular level whilst antitoxins can be seen as some sort of sovereign defence. The U.S. government in creating and providing people with antitoxins is fighting anthrax on their behalf, in their body, at the molecular level. Raxibacumab in contrast to a vaccine offers immediate protection and in contrast to antibiotics may also prevent and treat infections caused by antibiotic-resistant strains of anthrax.[91] As will be demonstrated now, our ability to visualise and manipulate life at the molecular level has been crucial to the development of Raxibacumab.

The Molecular Vision of Life and the Development of Raxibacumab

The Structure and Function of Anthrax

Since their development and use in the 1980s, monoclonal antibodies have primarily been designed to target cancer and diseases of the immune system.[92] As a result of the anthrax letters sent soon after the attacks of September 11th 2001, significant efforts were directed towards the potential of monoclonal antibodies to work against infectious disease in general and the threat of anthrax in particular. One key aspect in this search was focused on determining the structure of the anthrax protein toxins that act within cells and which are

[89] Ibid., 5684.
[90] Migone, et al., 'Raxibacumab for', 136.
[91] U.S. Government Agrees.
[92] Sohini Mazumdar, 'Raxibacumab', *mAbs* 1, no. 6 (2009), 531.

critical for understanding how the anthrax toxins access cells.[93] Utilising one tool of molecular biology – x-ray crystallography – the structure of the key components of anthrax could be understood.

X-ray Crystallography and Drug Discovery

X-ray crystallography came to prominence after the Second World War as a result of its use in providing 'conclusive proof of the structure of penicillin'.[94] X-ray crystallography provided the three dimensional molecular structure of penicillin from which it was able to determine the active sites essential for its antibacterial function. It was determined that the four-membered β-lactam ring inhibits the growth and division of bacteria causing them to shed their cell walls. This contribution led to this scientific method being recognised as an important analytical tool for the structure determination of complex biological molecules.[95]

X-ray crystallography exposes a purified and highly concentrated crystal, of what is usually a protein, to an x-ray beam. The diffraction patterns that result can be used to determine the symmetry and size of the units that form the crystal. The intensity of diffraction spots can be used 'to determine the "structure factors" from which a map of the electron density can be calculated.'[96] It is the 'variation in the intensities of each of the spots that contains the structural information and which is extracted during the data processing'.[97] Through refinement of the measured intensity of a diffracted spot, it is possible to determine the structure factor from which the arrangement of the atoms in the unit cell can be calculated. The electron density map that results will form the three dimensional contours

[93] H. Katayama et al., 'Three-dimensional structure of the anthrax toxin pore inserted into lipid nanodiscs and lipid vesicles', *Proceedings of the National Academy of Sciences* 107, no. 8 (2010): 3453.
[94] Soraya de Chadarevian, *Designs for Life: Molecular Biology after World War II* (Cambridge: Cambridge University Press, 2002), 65.
[95] Ibid., 65.
[96] M S Smyth, J H J Martin, 'x Ray crystallography', *Journal of Clinical Pathology: Molecular Pathology* 53, (2000): 8.
[97] Ibid., 11.

into which the protein structure will be built. Once this map is of sufficient quality, using a computer graphics programme the molecular structure can be built using the protein sequence. The aim of this tool is to obtain a three dimensional molecular structure from a crystal.

As noted, the anthrax toxin is composed of two binary combinations made up of one protein of either lethal factor or edema factor and a common binding component known as protective antigen. Lethal toxin is formed when the protective antigen binds with lethal factor and edema toxin is formed when the protective antigen binds with edema factor.[98] Through x-ray crystallography the distinct components and domains of the protective antigen have been determined with Domain I recognised as the site for binding to lethal and edema factor, with Domain IV implicated in host-cell binding[99] (see Figure. 1). This has facilitated an understanding of the protective antigen as a protein that mediates binding to its receptors in the cell membrane of host cells and also combines with the other proteins to produce toxins. Crucially, this allows for the mechanism of action to be determined with the protective antigen facilitating translocation of the enzymes and their toxins into the cell cytosol once it has bound successfully with receptors in the host cell and either enzyme. [100]

[98] Jeffrey W. Froude et al., 'Antibodies for biodefence', *mAbs* 3, no.6 November/December (2011): 517.
[99] Carlo Petosa et al., 'Crystal Structure of the anthrax toxin protective antigen', *Nature* 27 February 385 (1997): 833-4.
[100] Carlos E. Kummerfeldt, 'Raxibacumab: potential role in the treatment of inhalational anthrax', *Infection and Drug Resistance* 7, (2014), 102.

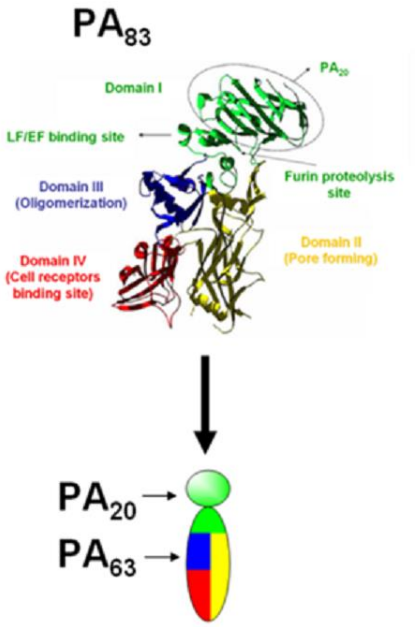

Figure 1. Molecular structure of the protective antigen with the Domain IV highlighted in cell binding.[101]

Once this mechanism of action has been determined, a drug target in the form of the protective antigen can be identified. This now presents the problem of designing a small molecule or protein that can modify the target.[102] One of the most common tools utilised in this regard are antibodies. The protective antigen has been regarded the most important target of neutralizing antibodies because it plays a central role for the formation of both toxins, it is involved at the earliest stages of the intoxication process, and vaccines composed of protective antigen have showed that antibodies binding to this protein effectively limit the pathogenicity of the anthrax bacteria.[103] Antibodies are proteins which identify and neutralise pathogens such as bacteria and viruses. They are usually produced by plasma cells in the body's immune system. The tip of the Y shaped antibody targets the specific molecular site of the pathogen called the antigen. The paratope on the end of the antibody locks with the

[101] Jeffrey W. Froude II, Philippe Thullier and Thibaut Pelat, 'Antibodies Against Anthrax: Mechanisms of Action and Clinical Applications', *Toxins* 3, no. 11 (2011): 1434.
[102] Jürgen Drews, 'Strategic trends in the drug industry', *Drug Discovery Today* 8, no. 9 (2003): 416.
[103] Froude II, Thullier and Pelat, 'Antibodies Against Anthrax', 1436.

specific epitope of the antigen. One of the major advantages of antibodies as a response tool is that they bring immediate protection against a pathogen.[104] In contrast, vaccines must elicit a host immune response to be effective and may often require booster injections.

Recombinant antibodies, those selected, engineered or expressed utilising DNA-based molecular biology techniques may be administered in quantities that exceed that elicited by vaccines. This higher level of protection is useful as exposure to a biological agent may involve elevated levels compared to natural exposure.[105] Monoclonal antibodies can be produced in three different ways. As demonstrated in the first chapter, in one method they can be generated as mouse antibodies that are then 'humanised' by recombination with human antibody genes. In an alternate method, human antibodies can be directly raised in nude mice grafted with human immune cells. Thirdly, antibodies can be made by phage display techniques.[106]

Monoclonal Antibodies and Phage display

Bacterial viruses or bacteriophages are found wherever bacteria proliferate and are estimated to be one of the most widely distributed and diverse entities in the biosphere.[107] Research on phages has been central to some of the most significant discoveries in the biological sciences including the identification of DNA as the genetic material and the deciphering of the genetic code.[108] Bacteriophages and their interactions with bacterial cells were first visualised using an electron microscope.[109] Research employing bacterial viruses as conceptual models of gene action began in the late 1930s with the establishment of the 'phage

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[104] Froude et al, 'Antibodies for biodefence', 517.
[105] Ibid., 517.
[106] Jürgen Drews, 'Drug Discovery: A Historical Perspective', *Science* 287, (2000): 1962.
[107] Olivia McAuliffe, R. Paul Ross, and Gerald F. Fitzgerald, 'The New Phage Biology: From Genomics to Applications', in *Bacteriophage: Genetics and Molecular Biology*, ed. Stephen McGrath and Douwe van Sinderen (Norfolk: Caister Academic Press, 2007), 1.
[108] Ibid., 2.
[109] Ibid., 4.

school' at the California Institute of Technology (Caltech) under the leadership of Max Delbrück.[110] Delbrück applied principles derived from nuclear physics to study the gene.[111] This research programme has been generally recognised as one of the most fruitful approaches to the gene problem and a principal turning point in the history of molecular biology.[112]

The 'modern' era of bacteriophages in biology is said to have emerged with the work of Delbrück in the late 1930s and the analysis of replication and genetic changes resulting from infection. Al Hershey and Delbrück worked closely together on the issue of phage, designing experiments to provide decisive evidence for the primacy of DNA during replication and mutation of phage.[113] One of the most significant experiments in this area was that conducted by Hershey and Martha Chase in 1952 proving that DNA is the molecule that transmits genetic information. In these experiments, the protein shells of bacteriophages were labelled with radioactive isotopes; upon infecting bacteria, the labelled phage coats remained outside of what was passed on thus demonstrating that DNA, not protein, was the genetic material.

Up until this point, it was not known whether protein or DNA carried the information regarding viral replication.[114] This conclusion can be seen to be the end-point of a long series of convergent experiments that included Oswald Avery's research on the transformation of the pneumococcal bacteria in 1944 which pointed to the role of DNA rather than a protein.[115] The significance given to the Hershey and Chase experiments in light of Avery's work demonstrate the extent to which a scientific experiment only has value in relation to a theoretical,

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[110] Lily E. Kay, *The Molecular Vision of Life* (Oxford: Oxford University Press, 1996), 12.
[111] Michel Morange, *A History of Molecular Biology*, trans. Matthew Cobb (Cambridge: Harvard University Press, 2000), 41.
[112] Kay, *The Molecular Vision of Life*; See also John Cairns, Gunther S. Stent and James D. Watson, eds., *Phage and The Origins of Molecular Biology* (New York: Cold Spring Harbour Laboratory, 1968).
[113] Kay, *The Molecular Vision of Life*, 249.
[114] McAuliffe, Ross, and Fitzgerald, 'The New Phage Biology', 4.
[115] Morange, *A History of Molecular Biology*, 31-2.

experimental and social framework.[116] Following these discoveries regarding the structure and replication of viruses for which Delbrück, Hershey and Salvadore Luria shared a Nobel Prize in 1969, it was possible to answer complex biological questions using bacteriophage as a model, including the nature, mutations, replication and expression of genes.[117]

The ability to manipulate genes in the production of recombinant antibodies is essential to the production of phage antibodies and phage display technology. The recombinant DNA revolution has facilitated the isolation and manipulation of genes using enzymes. These modified genes can then be inserted into the genome in question. Antibodies were the first proteins to be successfully displayed on the surface of phage through the manipulation of genes.[118] Antibody phage display (APD) is based on genetic engineering of bacteriophages and repeated rounds of antigen-guided selection and phage propagation.[119] As a result of the understanding that DNA carries the genetic information, coding for the phenotype or physical properties of an organism, manipulation of the sequence coding within a phage particle will change the nature of the protein to be displayed on the surface of the bacteriophage. The 'physical link between the phenotype and genotype of the expressed protein and the replicative capacity of phage are the structural elements that underpin all phage display technology.'[120] The proteins displayed on the surface of phage that are used to bind to the antigen are derived from the genes encoding the key elements of the antibody. Our ability to recombine genes breaks the normativity of the natural vital order.

Recombinant antibody technology involves recovering, amplifying and cloning genes into an appropriate vector. This vector is then introduced into a host which will express

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[116] Ibid., 49.
[117] McAuliffe, Ross, and Fitzgerald, 'The New Phage Biology', 4.
[118] Hennie. R. Hoogenboom, 'Antibody Phage Display Technology and its Applications', *Immunotechnology* 4, (1998), 3.
[119] Christoph M. Hammers and John R. Stanley, 'Antibody Phage Display: Technique and Applications', *Journal of Investigative Dermatology* 134, no. 2 (2013), 1.
[120] William G. T. Willats, 'Phage display: practicalities and prospects', *Plant Molecular Biology* 50, (2002) 837.

adequate amounts of functional antibody.[121] The ability to manipulate antibody genes makes it possible to generate new antibodies in vitro, outside the cell, or body. As noted, antibodies can be engineered to express certain proteins through the alteration of antibody structure and functional properties by recombinant DNA methods. Methods of in vitro mutagenesis, changing the genetic information of an organism, can be applied to insert, delete or change particular amino acids or entire variable domains.[122] Crucially, this can only be done once the DNA sequences of the variable regions are known and from which the amino acid sequences can be deduced. These techniques allow for the creation of many different protein expressions and for a wide range of phage antibodies which will make up the phage display library. One significant advantage of this technique is that antibodies can be produced that would be difficult or impossible to obtain in animals.[123]

Another key element of antibody engineering is the ability to model the combining site and visualise antibody-antigen interactions in three-dimensional space. X-ray crystallography has been used in this regard to determine the structures of many antibodies at the atomic level and resolution.[124] These structures have been stored and can be used to construct computational models of new antibodies to guide subsequent engineering and mutagenesis steps. Specific software packages using established crystallographic structures have been used to build antibody models from amino sequence data.[125] This tool can be used as an aid in building models of antibodies that bind to specific antigens.[126] One advantage of using recombinant antibodies is that they are less antigenic and more stable for human clinical diagnostic and therapeutic applications.[127] Antibodies developed in mice may have an

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[121] Alexander E. Karu, Christopher W. Bell, and Tina E. Chin, 'Recombinant Antibody Technology', *ILAR Journal* 37, no. 3 (1995), 134.
[122] Ibid., 137.
[123] Ibid., 137.
[124] Ibid., 137.
[125] Ibid., 137.
[126] Ibid., 137.
[127] Ibid., 137.

undesired immune response in humans. Another advantage of engineering antibodies in vitro is that it removes the requirement that the antigen produce an immune response[128] in the host, usually mice.

The three key elements in creating recombinant antibodies include then the technology based on advances in the understanding of antibody structure and function, the biology of bacteriophage replication and new techniques for DNA manipulation and mutagenesis.[129] X-ray crystallography has also revealed that all antibodies share similar structural features.[130] Using these techniques, a phage display library can be created by using DNA which can encode for millions of variations of certain ligands, such as proteins which will be displayed on the surface of the phage.[131] This library will contain a range of recombinant antibodies, each displaying a unique antibody protein. The library will then be screened for phage binding to an antigen through its expressed surface monoclonal antibody by a technique called (bio-)panning.[132] There are multiple rounds of possible binding and at each stage those antibodies which bind to the antigen will be retained while those that do no will be washed away. Those that bind can then be recovered, re-infected into bacteria and regrown for further enrichment and for analysis of binding.[133] The process of phage antibody selections involves the sequential enrichment of specific binding phage from a large excess of non-binding clones.[134] Those that bind successfully can then be developed into a viable medicine or MCM as was the case with Raxibacumab.

Raxibacumab

[128] Willats, 'Phage display', 846.
[129] Karu, Bell, and Chin, 'Recombinant Antibody Technology', 132.
[130] Ibid., 133.
[131] Hoogenboom, 'Antibody Phage Display Technology', 2.
[132] Hammers and Stanley, 'Antibody Phage Display', 2.
[133] Hoogenboom, 'Antibody Phage Display Technology', 2.
[134] Ibid., 8.

The two techniques of x-ray crystallography and phage display were used to develop the anthrax antitoxin Raxibacumab. As noted, this antibody targets the protective antigen mechanism of action in the anthrax highlighted by the technique of x-ray crystallography. Raxibacumab, a recombinant fully human immunoglobulin monoclonal antibody, is directed against Domain IV of this protein and acts by inhibiting its interaction with cell receptors.[135] By binding to this protein at the Domain IV epitope, the specific piece of the antigen that an antibody binds to, Raxibacumab prevents its binding to the cell receptor, thereby inhibiting pore formation and internalization of lethal and edema factor. In doing so, Raxibacumab confers passive immunity to the body by transferring readymade antibodies to inhibit the protective antigen. Given intravenously as a single dose, its current FDA-approved indications include use as therapy for and prevention against inhalational anthrax.[136]

Raxibacumab was derived from a phage display library licensed by HGS (GSK, Research Triangle Park, NC, USA) from Cambridge Antibody Technology.[137] As noted, an antibody library made up of phage, each expressing unique antibodies is screened for those that bind to a specific antigen. In this case the Domain IV epitope of the anthrax protective antigen would have been used to find an antigenic match. This is done through its expressed surface monoclonal antibody and (bio-) panning.[138] This technique facilitates multiple rounds of phage binding to antigens pulling out potentially very rare antigen-binding clones. During each round non-binders are washed away and specific binders are selected out. After cyclic panning, the result is a phage pool, a mixture of all the phages that bind to the antigen chosen. These pools are then tested in phage Enzyme-Linked Immunosorbent Assay (ELISA) to confirm antigen binding. The nucleotide encoding for the monoclonal antibody that bound to that antigen is then sequenced before the monoclonal antibodies are purified and subjected to further

[135] Froude II, Thullier and Pelat., 'Antibodies Against Anthrax', 1437.
[136] Kummerfeldt, 'Raxibacumab', 107.
[137] Mazumdar, 'Raxibacumab', 532.
[138] Hammers and Stanley, 'Antibody Phage Display', 2.

downstream analysis.[139] The development of Raxibacumab was made possible then not only by molecular tools such as x-ray crystallography and our ability to manipulate DNA into new configurations in phage display but also the economic and development support provided by Project BioShield funds and BARDA.[140]

Conclusion

In this chapter we conducted an empirical investigation into BARDA's efforts to support the development of MCMs to address the threat of anthrax. The potential of terrorists to genetically engineer and develop antibiotic-resistant strains of anthrax shaped the approach employed by the U.S. government in its decision to stockpile antitoxins in addition to vaccines and antibiotics. We also saw the key role that an understanding of the general pathway of infection taken by the bacteria played in the creation of the antitoxin Raxibacumab. The apparent ease with which antibiotic-resistant strains of anthrax could be developed has stimulated efforts in the creation of a broad range of MCMs to deal with this one threat. This factor, in combination with a molecular understanding of the hardiness of the spores, has made this one of the prime tools of state and terrorist biological weapons efforts. Such efforts were developed to industrial capacity by the Soviet Union with attempts to spread terror realised with the anthrax letters of 2001.

The hardiness of the spores means that people may become sick long after an accidental or deliberate release, as was revealed by the outbreak in Sverdlovsk. The implications of this impact the treatment measures that can be implemented. As noted, antibiotics are most useful right after the victim is exposed and before the patient becomes symptomatic. This chapter outlined this threat environment, one shaped by the biological

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[139] Ibid., 2.

[140] Other thinkers that have identified similar economic formations include: Kaushik Sunder Rajan, *Biocapital: The Constitution of Post-genomic Life* (London: Duke University Press, 2006); Cooper, *Life as Surplus*.

workings of the anthrax bacteria. In response, BARDA supported the development of Raxibacumab to fill the therapeutic gap created by a reliance on vaccines and antibiotics. We saw the way development was supported by the FDA through particular tools such as Fast Track and orphan designation. BARDA's procurement contracts, made possible by the dedicated funding set aside under the Project BioShield Act, acted as a market guarantee and key pull incentive. This guaranteed market also provides reassurance not only to companies but also to investors that efforts and investments will be rewarded.

The molecular components of the anthrax bacteria were revealed through gel electrophoresis in the 1950s. The understanding of the different components of three anthrax proteins revealed the central role played by the protective antigen in causing the entry of the other proteins into the cell and their formation into toxins in cell death. This understanding was central to efforts focused on stimulating the innate immune response through vaccination. The central role played by this protein in causing cell death also formed the platform for the development of monoclonal antibodies seeking to confer 'passive immunity' in the body. As this chapter has assessed, before Raxibacumab could be developed, an active site within the protective antigen had to first be revealed. X-ray crystallography, a fundamental tool in the development of molecular biology in general and the discovery of DNA in particular, played a central role in revealing this target. The protective antigen, in crystal form, reveals its molecular structure when x-rays are passed through it. This structure supported an elucidation of the key components that correspond to the specific functions carried out by this protein. Domain IV, implicated in the process of binding to the outside of the cell so supporting the entry of toxins, was revealed as a viable target for drug discovery.

If the structure of the protective antigen was made possible as a result of our ability to view the molecular structure of life at the molecular level, the discovery of Raxibacumab is a result of our ability to manipulate it. Our ability to manipulate the protein-producing powers

of genes through the use of enzymes has supported the development of libraries of phage antibodies. Phage antibodies are the result of certain genetic sequences that display certain proteins. The creation of many different genetic combinations produces a range of proteins or a library. Raxibacumab was discovered by scanning this library for an antibody that selectively binds to the Domain IV site on the protective antigen, preventing its binding to the cell wall, the entry of toxins and cell death. Through the visualisation and manipulation of life at the molecular level, specifically the manipulation of DNA into new configurations, Raxibacumab, an anthrax antitoxin, could be developed that inhibits the general pathway of infection of the anthrax bacteria. In the previous chapter we saw how our ability to map DNA made possible the development of ST-246. In this case our ability to manipulate it into new configurations provides the pathway through which molecular knowledge can be translated into new pharmaceutical defences in the form of an anthrax antitoxin. As will be demonstrated in the next chapter there is yet still a third way in which our ability to understand DNA can be utilised in the development of new medicines. Specifically, our ability to visualise the structures that process bacterial DNA has provided the pathway for the development of a new range of broad-spectrum antibiotics.

Chapter 7: BARDA, the Structural Processing of DNA and Eravacycline

Introduction

This is the third empirical examination into the way the Biomedical Advanced Research and Development Authority (BARDA) has supported the development of medical countermeasures (MCMs) for category A threats. This case is taken third as chronologically it is one of the most recent threats to be addressed. This chapter is focused on the way that BARDA has supported the development of broad-spectrum antibiotics to combat both the issue of antibiotic resistance and the bacterial pathogens that fall into this category and are considered potential agents of bioterrorism. It first sets out BARDA's Broad Spectrum Antimicrobial Programme and investigates the problem of antimicrobial development and the ways that it differs from the production of MCMs that we have looked at in the previous chapters. It then analyses the nature of antibacterial resistance, assessing the biological and molecular mechanisms that contribute to this phenomenon. The range of incentives that BARDA has utilised to support a range of companies in the development of MCMs to combat this issue is then addressed. Finally, this chapter takes the case of Eravacycline and analyses the way the molecular vision of life made possible the development of this antibiotic focused on addressing the resistance mechanisms of bacteria. The purpose of this chapter is to bring together BARDA's efforts at addressing the unique market failure antibiotics represent in combination with the molecular biological understandings of resistance that have made the development of new antibiotics possible.

This chapter argues that the biological nature of the development of antibiotic resistance, an inevitable consequence of bacterial evolution, has not only shaped the unattractiveness of the market for potential developers but has also made possible the creation of antibiotics as a solution to this threat. In order to do this, it first demonstrates the way the particular nature of antibiotic resistance, as a slow-developing and uncertain threat,

has reduced the attractiveness of this market to drug developers. Further, the way antibiotic resistance develops, under the selective pressures present in the environment, has relegated newly developed antibiotics to drugs of last resort, meaning potential sales of any new drug will be of low volume. These factors, driving drug developers away from this unprofitable market, have stimulated the efforts of the U.S. government into implementing a range of new incentives to encourage company involvement.

Taking the case of Eravacycline, an antibiotic developed in the tetracycline class, this argument is further supported through an investigation into the molecular techniques utilised to understand not just the biological workings of bacteria but also the details of the resistant mechanisms developed. The role of x-ray crystallography and cryo-electron microscopy is analysed in highlighting both the structure and function of the bacterial ribosome. Indeed, these tools allow us to visualise the structures of the bacterial cell that process DNA and proteins essential to its functioning. Such an understanding highlights the way the tetracycline class of antibiotics work. The mechanism of action naturally produced by bacteria seeking to maintain dominance in a competitive natural environment is revealed. These molecular technologies, cryo-electron microscopy in particular, have also revealed the mechanisms through which bacteria have developed resistance to tetracycline antibiotics. In elucidating this process, the biological understandings of the molecular mechanism of antibiotic effectiveness and resistance have made possible the further development of drugs to overcome these resistance mechanisms. This understanding of the role of bacterial structures that process DNA represents a third pathway and mechanism through which molecular knowledge can be translated into new pharmaceutical defences.

This chapter proceeds by setting out BARDA's antimicrobial programme in relation to the problem of antibiotic development and the nature of antibiotic resistance. It then turns to the contracts supported by BARDA and the incentives utilised in the development of new

antibiotics. The crucial understandings of the way antibiotics work and the resistance mechanisms developed in response is then assessed in relation to the development of Eravacycline.

BARDA's Broad Spectrum Antimicrobial Program

BARDA's Broad Spectrum Antimicrobial Program was established in 2010 and is 'focused on developing novel antibacterial and antiviral drugs for the treatment or prevention of disease caused by currently defined and future biological threats.'[1] BARDA's support of public-private partnerships (PPPs) in the creation of new antimicrobials recognises the increasingly prevalent public health threat of antibiotic/antiviral resistance. It also recognises the role resistance may play in complicating the primary treatment of a wide array of threats, including that posed by bioterrorist agents. According to the 'dual utility' rationale employed in this programme, BARDA will support the development of antimicrobial candidates with commercial and clinically prevalent infectious disease indications provided they also have indications against potential bioterrorist agents.[2] One important consequence and limitation of this approach is that BARDA must turn down potential candidates for support that lack a viable biodefense justification.[3]

Despite the focus of this programme on both antibacterial and antiviral drugs, this chapter will just focus on BARDA's support for antibacterial drugs that also have a public health application and seek to address the threat of antimicrobial resistance (AMR). BARDA set up this programme in the knowledge that new antimicrobials are needed immediately to address the increasingly prevalent public health threat of antibiotic resistance. Through BARDA's monetary incentives and development support, it hopes to revitalize the

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[1] HHS, *BARDA Strategic Plan 2011-2016* (Washington DC: Assistant Secretary for Preparedness and Response, 2011), 9.
[2] Ibid., 9.
[3] John K. Billington, 'The ABCs of the US Broad Spectrum Antimicrobials Program: Antibiotics, Biosecurity, and Congress,' *Health Security* 13, no. 6 (2015), 351.

antimicrobial pipeline and engage or reengage pharma and biotech companies in antimicrobial development.[4] As noted, a significant element of this monetary incentive is the non-dilutive funds available. This funding strategy provides BARDA's partners with capital to support product development and supplement existing equity. As discussed, the development support set out in BARDA's Core Services includes technical consulting support for preclinical studies, clinical studies (Phase I-III), manufacturing, and regulatory activities. Potential category A threats that could be targeted by the design and development of antibiotics include: *Bacillus anthracis* (anthrax), *Clostridium botulinum* toxin (botulism), *Yersinia pestis* (plague) and *Francisella tularensis* (tularemia).

BARDA's Broad Spectrum Antimicrobial Program also represents a move towards more flexible defences in contrast to the 'fixed-defence' approach implemented with the stockpiling of anthrax and smallpox analysed in the previous chapters. This programme meets the need for multipurpose products, prioritised in BARDA's strategic plan.[5] In addition to the CIADMs, this programme contributes to the achievement of one of the organisations major goals focused on establishing an 'advanced development pipeline replete with medical countermeasures and platforms to address unmet public health needs, emphasizing innovation, flexibility, multi-purpose and broad-spectrum application, and long-term sustainability.'[6] BARDA's Antimicrobial program supports the achievement of this goal through the development of flexible, multiproduct platforms and countermeasures with broad-spectrum activity.[7] This chapter will now outline nature of the problem facing the development of efficacious antibiotics.

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[4] Broad Spectrum Antimicrobials, 2016. Available at: https://www.medicalcountermeasures.gov/barda/cbrn/broad-spectrum-antimicrobials.aspx. Last accessed January 7, 2017.
[5] HHS, *BARDA Strategic Plan*, 8-9.
[6] Ibid., 11.
[7] Ibid., 11.

The Problem of Antibiotic Development

The problem of antibiotic development is closely related to but slightly different from that facing the development of MCMs for biological threats. The main distinction is that there is a commercial market for antibiotics. The U.S. market for antibiotics at about $40 billion of sales a year is quite large.[8] Crucially, only about $4.7 billion of this total is from the sale of patented antibiotics. In perspective, this amount represents the yearly sales for one top selling cancer drug. This small commercial market, then, is not attractive to large pharmaceutical developers. Other factors that have made this an unattractive market to invest in include the fact that the uncertainty of any successful investment in drug development is exacerbated in the area of antibiotics. This arises as it is hard to predict how big the health need will be at early stages of investment.[9] For many other diseases there is often demographic information that supports the prediction of the size and nature of future patient populations.[10] With antibiotics, generic products can often be used to treat most infections other than resistant ones. This means that the market for a new antibiotic is normally limited to a subset of patients with resistant infections, a population that may be very small and irregular.[11] As resistant rates change quickly and unpredictably, it is difficult for drug developers to estimate with any certainty the future size of the market for any new antibiotic.[12] This precludes an essential activity that must be completed many years before a drug reaches the market.

In addition to the uncertainties of the market, another factor reducing the attractiveness of investment in this area is the fact that any new drugs will initially be reserved as last-line treatments.[13] As bacterial resistance almost always emerges in response to new

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[8] The Review on Antimicrobial Resistance, *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations* (London: The Review on Antimicrobial Resistance, 2016), 6.
[9] The Review on Antimicrobial Resistance, *Securing New Drugs for Future Generations: The Pipeline of Antibiotics* (London: The Review on Antimicrobial Resistance, 2015), 10.
[10] Ibid., 10.
[11] Ibid., 10.
[12] Ibid., 10.
[13] Ibid., 16.

antibiotics, new drugs will likely become first- and second-line treatments only many years after they have been developed. They will predominantly only be introduced after older drugs have been lost to resistance.[14] This is often many years after it has been licenced when the drug may be off-patent and available as a generic, thus removing the certainty of a financial return on the drug developer's investment.[15] Two of the largest selling and most widely used generic form of antibiotics include amoxacillin/clavulanate (Augmentin) and ciprofloxacin (Cipro), distributed in response to the anthrax letters.[16]

In response to this situation, companies often wait until resistance is already rising in an area before deciding to invest.[17] This lag means that new drugs will only be developed in response to established medical problems. These issues have led to a rethinking of the value of these drugs, one that reflects better the benefits they offer society in the long term instead of the limited time which this drug is 'on patent'[18] and financially profitable. A system of financial reward must be developed that reflects the societal 'insurance value' of having an effective supply of antibiotics.[19] The problems facing companies in the production of antibiotics then are focused on an uncertain market and one that when it does emerge, is of low volume. BARDA has tried to overcome both of these issues by providing a guaranteed government backed market for the creation of broad-spectrum antimicrobials.

In the U.S. it has also been noted that the FDA approval process is another significant obstacle to developing novel antimicrobial drugs.[20] The FDA utilises noninferiority trials to evaluate all experimental drugs for indications for which treatments already exist.[21] In these

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[14] Ibid., 12.
[15] Ibid., 12.
[16] Steven J Projan, 'Why is big Pharma getting out of antibacterial drug discovery?', *Current Opinion in Microbiology*, 6, (2003): 428.
[17] The Review on Antimicrobial Resistance, *Securing New Drugs*, 12.
[18] Ibid., 12.
[19] Ibid., 12.
[20] Institute of Medicine, *Antibiotic Resistance: Implications for Global Health and Novel Intervention Strategies: Workshop Summary* (Washington, DC: The National Academies Press, 2010), 36.
[21] Ibid., 38.

trials a standard comparator drug already on the market is compared with the experimental drug. As there is no comparison to a placebo in these tests, the results of the trials will either demonstrate that both drugs are better than placebo or neither drug is better than placebo. If, though, the comparator drug has already demonstrated to be superior to a placebo in previously conducted randomized, controlled studies and the experimental drug has been shown to be noninferior in efficacy to this drug, the experimental drug will be inferred to be noninferior as well.[22] As a result, the FDA has come to insist that comparator drugs used in these trials be previously shown to be superior in efficacy to placebo. This has generated great difficulties as the first antibiotics, unquestionably effective, predate the advent of randomized, placebo-controlled studies by two decades.[23] Another factor complicating this approach is that it is unethical to treat sick patients with a placebo, prohibiting such trials today. One suggested solution to this problem has been to use the results of early studies conducted between 1936 and 1950 that were sufficiently controlled to permit valid comparisons between patients who received antibiotics and those who did not.[24]

In contrast, antimicrobial effectiveness permits the use and development of other medical advances, such as transplantation and cancer chemotherapy, and of surgery in general.[25] This has been noted as a significant factor in incentivising the pharmaceutical industry into the development of antimicrobials. Indeed, how significantly would the pharmaceutical industry be negatively impacted if the many extremely profitable medical procedures dependent upon antibiotics could not be performed? This chapter will now turn to the historical background to antibiotic development.

[22] Ibid., 38.
[23] Ibid., 38.
[24] Ibid., 39.
[25] Ibid., 54.

The Nature of Antibiotic Resistance

The Antibiotic Era

Antibiotics have been termed a medical treasure and perhaps the most important therapeutic discovery in the history of medicine.[26] The beginning of the antibiotic era is associated with scientific developments that took place in the late 19th century into the 20th. Prominent amongst these developments was the conceptualisation of the idea of a 'magic bullet' that selectively targets only disease-causing microbes and not the host.[27] This was based on the observation that aniline and other synthetic dyes could stain specific microbes but not others.[28] The use of dyes in medicine had its basis in the discovery that tar contained many substances that could be used as dyes in the textile industry.[29] Their use grew in connection with two additional factors of understanding. The first regarded the nature of infectious disease and in particular that diseases could be caused by outside agents and external causes. This theory of infection first emerged in the 16th century and had to be confirmed by the work of Louis Pasteur and the field of scientific microbiology.[30] The modern doctrine of infection found practical application in disinfection during surgery resulting in a drastic reduction of peri- and postoperative infections and the beginning of modern surgical practices.[31]

The second factor was the use of dyes to colour human and animal tissues to reveal cellular and sub-cellular structures more clearly under a microscope.[32] Questioning and experimentation led to the idea that there are chemical affinities between particular dyes and

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[26] Stuart B. Levy, *The Antibiotic Paradox* (Boston: Perseus Publishing, 2002), 57.
[27] Rustam I. Aminov, 'A brief history of the antibiotic era: lessons learned and challenges for the future' *Frontiers in Microbiology* 1, no. 134 (2010): 2.
[28] Ibid., 2.
[29] Jürgen Drews, *In Quest of Tomorrow's Medicines,* trans. David Kramer (New York: Springer-Verlag, 1999), 24.
[30] Ibid., 61.
[31] Ibid., 61.
[32] Ibid., 61-3.

tissues or cellular components. Dyes were used to explore the binding properties of biological structures and chemical compounds. Based on this work, it was asserted that all cells carry particular receptors and that there exist corresponding dyes that bind with greater selectivity to certain types of tissue or even certain parasites.[33] The task of chemotherapy was designated as finding those substances that are poisonous but that only bind to cells that one wishes to eliminate from the body of the patient.[34] Any viable substance must then poison only that which it binds to. Antitoxins represent one viable substance that, as we saw with Raxibacumab, acts only on the anthrax pathogen. The discovery of antitoxins was lauded in the early 1900s as 'magic bullets' as they acted exclusively on the parasites and not on the organs.[35] Dyes then revealed the selective binding properties of certain substances. This made possible the discovery of a new class of drugs and led to the era of antibacterial chemotherapy.[36]

Soon after this discovery a large-scale and systematic screening program was carried out in 1904 to find a drug against syphilis, a disease that was endemic and almost incurable at that time.[37] Systematic screening became a fundamental component of research strategies in the pharmaceutical industry and resulted in thousands of drugs, including antimicrobials, being discovered and used in clinical practice.[38] Penicillin was discovered in well-known fortuitous circumstances by Alexander Fleming in 1928. This discovery pursued an understanding regarding mould that has persisted since ancient times. Research has revealed that the exposure to antibiotics is not confined to the modern 'antibiotic era' discussed above.[39] Traces of tetracycline, an antibiotic that can be found in nature, have been found in human skeletal

[33] Ibid., 64-5.
[34] Ibid., 65.
[35] Ibid., 65.
[36] Ibid., 68.
[37] Aminov, 'A brief history', 2.
[38] Ibid., 2.
[39] Ibid., 1.

remains dating back to 350–550 Common Era (CE).[40] Tetracyclines support such dating as they are incorporated into bones as well as tooth enamel and thus provide permanent markers of exposure.[41] The natural history of antibiotic-resistant genes has also revealed the long-term presence of genes conferring resistance to several classes of antibiotics in nature well before the antibiotic era.[42] The emergence of this era and the development of antibiotics was closely tied to the understanding of the role of bacteria as the causative agents of disease.

Bacteria and the Development of New Medicines

Bacteria represent a major component of our bodies. They are independently multiplying microscopic single-cell organisms.[43] Every day we are continually interacting with these ordinarily invisible microorganisms. They were first viewed in the 17th century under a homemade microscope.[44] The idea that microorganisms shared our environment and caused disease, the basis of the 'germ theory of disease', remained controversial well into the 19th century.[45] The arguments within this theory, advanced by Pasteur, would eventually be formally endorsed by the French Academy of Sciences in 1864. The understanding of the role of bacteria as active participants in our environment, from the decay of living tissue to food production, supported their interpretation as causative agents of human disease. Following the acceptance of this view, many of the afflictions of the human body could now be attributed to a single microbial cause.[46] With the growth of bacterial colonies on agar plates, bacterial types could be generated and specific bacteria could be identified with a particular disease.[47]

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[40] Ibid., 1.
[41] Ibid., 1.
[42] Ibid., 1.
[43] Levy, *The Antibiotic Paradox*, 18.
[44] Ibid., 15.
[45] Ibid., 15.
[46] Ibid., 16.
[47] Ibid., 17.

Under an electron microscope, magnified 3000 fold, bacteria are visualised as clear and distinct organisms. Bacteria multiply by simple division and exist in large numbers of colonies, each often representing the progeny of a single cell.[48] Colonies of non-pathogenic bacteria exist on the skin and in the intestinal tract in their tens of thousands of billions. Pathogenic or disease-causing bacteria must multiply into the millions in order to cause illness. Pathogenesis is the ability of bacteria to cause an infection, a form of organ destruction.[49] Bacteria are generally distinguished on the basis of their differential abilities to retain an iodine-crystal violet stain when treated with organic solvents such as alcohol.[50] Stain or Gram-positive bacteria are turned deep purple by this stain and retain the colour during washing. Those bacteria that lose the dye and are able to be counterstained with another lighter dye that colours them pink are called stain or Gram-negative.[51] This distinction derives from the particular composition of the bacterial cell walls. Gram-negative bacteria such as that which causes meningitis, have a three-layered cell wall[52] or double-cell membrane, which shields them from many antibiotics.[53] The outer layer, made up of sugars attached to fats does not hold onto the stain. Gram-positive bacteria such as that which causes strep throat, have only a single-cell wall that retains the colour of the Gram stain during washing.[54]

An antibiotic is a substance made by one microorganism that inhibits the growth of another microorganism.[55] Despite the antibacterial properties of penicillin being discovered in 1928, it was not used as a therapeutic agent to treat infections in humans until the 1940s and was originally preserved as a tool for the military. This has been attributed to the lack of biochemical and microbiological expertise at the time and also a mentality that discouraged

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[48] Ibid., 20.
[49] Ibid., 24.
[50] A. D. Russell and I. Chopra, *Understanding Antibacterial Action and Resistance* (Chichester: Ellis Horwood, 1990), 18-9.
[51] Levy, *The Antibiotic Paradox*, 21.
[52] Ibid., 21.
[53] Institute of Medicine, *Antibiotic Resistance*, 62.
[54] Levy, *The Antibiotic Paradox*, 22.
[55] Ibid., 33.

the possibility of finding substances to treat infectious disease that could be used internally.[56] The properties of dyes would again play a significant role in changing this perception. Prontosil, a man-made and newly patented dye in the 1930s, had been found to work against certain forms of bacteria when injected into mice. It was discovered that it was not the dye part of the molecule which worked against the bacteria but the sulphonamide chemical attached to it.

The effectiveness of Prontosil and other sulphonamide derivatives demonstrated that it was possible to create agents that were nontoxic, stable and could work when taken internally. This understanding has been seen as a critical event that led to the resurgence of interest in antibiotics at that time and the search for other 'magic bullets'.[57] One context in which this search took place was the soil. The first major finding of an internally-useful antibiotic occurred in 1943. Streptomycin, effective against Tularemia, was also the first drug of any kind to work against Tuberculosis.[58] Today it has been recognised that most of the infectious, disease-causing bacteria that were previously universally susceptible to antibiotics are resistant to at least some and in many cases to a large number of drugs.[59] This chapter will now turn to the mechanisms bacteria employ in generating resistance.

Mechanisms of Antibiotic Resistance

Antibiotic resistance can be understood as evolution 'in real time' in response to the drugs used to combat disease.[60] Resistance is an inevitable factor and indeed it has been argued that there is no man-made defence that cannot be outmanoeuvred by microbial evolution and adaptation.[61] Antimicrobial and antibiotic resistance is both a global public

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[56] Ibid., 39.
[57] Ibid., 41.
[58] Ibid., 45-6.
[59] Ibid., 71.
[60] Institute of Medicine, *Antibiotic Resistance*, 1.
[61] Ibid., 3.

health and environmental catastrophe and has been termed a 'classic' example of the 'tragedy of the commons'.[62] This term was developed by Garrett Hardin to discern the failure of common resources that result when each individual tries to realise his material potential without limit.[63] Antimicrobial resistance represents a tragedy in line with land use, global climate change and access to clean and fresh water resources. Antibiotic resistance has also revealed a serious dilemma in that individuals acting without restraint to maximize personal short-term gain through the use of antibiotics can cause long-range harm to the environment, themselves and others. The excessive use of antibiotics demonstrates 'the logic of the commons' in that those natural resources held in common to be freely used and consumed eventually leads to its collapse and the demise of those that depend upon them.[64]

As early as 1945 there had been warnings that the misuse of penicillin and other drugs could lead to the selection and propagation of mutant forms of resistant bacteria.[65] The growth in resistant bacteria has been put down to the indiscriminate and inappropriate use of antibiotics in outpatient clinics, hospitalized patients and in the food industry.[66] Bioterrorist or bio-crime events, such as the unresolved anthrax letters, can also lead to a surge in antibiotic use amongst the public. Following the letters there was a run on Cipro, with estimates suggesting two percent of Americans had acquired the drug.[67] The millions of people self-diagnosing and self-medicating with this antibiotic and not completing regimens will cause a significant change in the microbial environment and raise the particular risk of the accelerated evolution of resistance.[68]

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[62] Ibid., 6.
[63] See Garrett Hardin, 'The Tragedy of the Commons' *Science* 162, no. 3859 (1968): 1243-1248.
[64] Institute of Medicine, *Antibiotic Resistance*, 6.
[65] Levy, *The Antibiotic Paradox*, 7.
[66] Alfonso J. Alanis, 'Resistance to Antibiotics: Are We in the Post-Antibiotic Era?', *Archives of Medical Research* 36, (2005): 697.
[67] Levy, *The Antibiotic Paradox*, 317.
[68] Ibid., 318-9.

The first cases of antimicrobial resistance occurred in the late 1930s and 1940s and was predominantly a problem for hospitalized patients.[69] The spread of resistant bacteria outside the hospital has now caused community-acquired infections.[70] In 2005 it was stated that over the years at least one or more mechanism of resistance has developed to each of the 17 different classes of antibiotics developed.[71] In some cases bacteria have been able to develop simultaneous resistance to two or more antibiotic classes, making treatment increasingly costly and leading to high rates of morbidity.[72]

Most antibiotics in use today are produced by bacteria themselves and serve as a kind of chemical warfare against other forms of bacteria.[73] Humans did not invent antibiotics; we have merely observed that 'bacteria and other microorganisms produced biological compounds capable of killing or suppressing the growth and reproduction of other bacteria.'[74] Bacteria that produce antibiotics must also then have resistance properties as well. Bacteria use a variety of methods to protect themselves, including altered membrane permeability or binding sites, efflux pumps that export incoming antibiotics, and antibiotic-degrading enzymes.[75]

An understanding of the molecular basis for the development of resistance is important in developing new approaches against infection and new strategies in the development of new treatments.[76] Generally, resistance is the result of changes in the genetic make-up of bacteria that either take place via a mutation or by the introduction of new genetic

[69] Alanis, 'Resistance to Antibiotics', 698.
[70] Ibid., 698.
[71] Ibid., 698.
[72] Ibid., 699.
[73] Institute of Medicine, *Antibiotic Resistance*, 45.
[74] Jose L. Martinez, 'The role of natural environments in the evolution of resistance traits in pathogenic bacteria', *Proceedings, Biological Sciences* 276, no. 1667 (2009): 2521–2530, cited in Institute of Medicine, *Antibiotic Resistance*, 8
[75] Institute of Medicine, *Antibiotic Resistance*, 9.
[76] Alanis, 'Resistance to Antibiotics', 699.

information.[77] These genetic changes are expressed in the biological mechanisms of the bacteria and determine the specific type of resistance that is developed.[78]

Bacteria undergo random genetic mutations. This can lead to resistance to certain antibiotics. This resistance is then either spread horizontally or vertically. Vertically, the critical unit of AMR transmission – the resistance-associated gene or gene cassette – is passed on through inheritance as bacteria replicate and divide.[79] Resistant genes are often situated on plasmids. Plasmids complement the chromosomal DNA of bacteria and carry traits that ensure the survival of the bacteria in adverse conditions.[80] They exist as independent, self-duplicating genetic elements with many copies of many different plasmids residing in a cell.[81] Horizontally, the resistant gene can be transferred amongst bacteria through many mechanisms; the most common are conjugation, transformation and transduction. In this process, plasmids are often the genetic vehicle in the transfer of resistance. The most important and the most common mechanism of transmission of resistance in bacteria is conjugation.[82] Via a protein structure called a 'pilus', one bacteria reaches out and draws another to it. Once they are together, duplicate plasmids can be transferred, passing on resistant genes.[83]

Despite the way a gene is transferred to a bacterium, resistance occurs when 'the gene is able to express itself and produce a tangible biological effect resulting in the loss of activity of the antibiotic.'[84] One form of resistance is generated when the bacteria produces one or more enzymes that either degrade or modify the antimicrobial, making them inactive against

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[77] Ibid., 699.
[78] Ibid., 699.
[79] Institute of Medicine, *Antibiotic Resistance*, 18.
[80] Levy, *The Antibiotic Paradox*, 72.
[81] Ibid., 72.
[82] Alanis, 'Resistance to Antibiotics', 700.
[83] Levy, *The Antibiotic Paradox*, 83.
[84] Alanis, 'Resistance to Antibiotics', 700.

the bacteria.[85] Antibiotic-active efflux is another resistance mechanism, common against tetracycline that acts against antibiotics that work inside the bacteria. It results from the development of an active transport mechanism that pumps the antibiotic molecules that penetrated outside the bacteria until the concentration of antibiotic is below that necessary for it to have any activity.[86] A third form of resistance, receptor modification, occurs when the target or receptor of the drug is altered by the bacteria, resulting in the lack of binding and a lack of antibacterial effect.[87] This chapter will now assess the way that BARDA has supported companies in the development of antibacterial drugs to address the dual threats of resistant bacteria and potential bioterrorist agents.

Project BioShield Contracts and BARDA Support

Achaogen

In August of 2010 Achaogen was awarded a contract by BARDA to fund the development, manufacturing and regulatory activities that would position ACHN-490/plazomicin as a treatment for plague, tularaemia and current and emerging multi-drug resistant (MDR) pathogens.[88] This contract includes a fixed-fee two year base period of $27 million and can be extended annually for an additional three years which would bring the total value of the contract to $64.5 million.[89] This contract represents the first time that BARDA research and development funds have been used in the broad-spectrum antimicrobial initiative set up in 2010.[90] In 2012 and April of 2013 BARDA exercised a $16 million and $60

[85] Ibid., 700.
[86] Ibid., 700.
[87] Ibid., 700.
[88] Achaogen Awarded Contract Worth up to $64 Million by BARDA for the Development of ACHN-490, 30 August 2010. Available at: http://investors.achaogen.com/releasedetail.cfm?ReleaseID=827159. Last accessed January 7, 2017.
[89] Ibid.
[90] Robert Roos, 'HHS funds development of drug for plague, tularemia', *CIDRAP*, 30 August 2010). Available at: http://www.cidrap.umn.edu/news-perspective/2010/08/hhs-funds-development-drug-plague-tularemia. Last accessed January 7, 2017.

million contract option, respectively, bringing the total value of the contract to $103 million.[91] This latest option supports a global Phase III superiority study that will evaluate the efficacy and safety of plazomicin in treating patients with serious Gram-negative bacterial infections due to carbapenem-resistant Enterobacteriaceae (CRE).[92] Through the Special Protocol Assessment procedure the FDA has agreed that the design and planned analyses of the single pivotal Phase III trial adequately address objectives in support of a New Drug Application. The FDA has also granted Fast Track designation for the development and regulatory review of plazomicin to treat serious and life-threatening CRE infections.[93]

Cempra Pharmaceuticals

In May of 2013 BARDA awarded a two-year $17.7 million contract to Cempra Pharmaceuticals. This contract will support the development of Solithromycin, an antibiotic that could potentially treat children infected with anthrax, tularaemia or community-acquired bacterial pneumonia.[94] Studies of the drug's use in treating anthrax or tularaemia will be conducted under the FDA's Animal Efficacy Rule.[95] This contract is for a two year base period with guaranteed funding of $17.7 million and is extendable up to five years, bringing the value of the total contract to $58 million.[96] This contract will support Phase I, II and the majority of II/III studies and the Paediatric as well as the Animal Rule New Drug Applications (NDA). If approved, solithromycin would be the first orally-administered antibiotic approved since

[91] Achaogen Awarded $60M Contract Option by BARDA for the Clinical Development of Plazomicin, 24 April 2013. Available from: http://investors.achaogen.com/releasedetail.cfm?ReleaseID=827153. Last accessed January 7, 2017.
[92] Ibid.
[93] Plazomicin. Available from: http://www.achaogen.com/plazomicin/. Last accessed January 7, 2017.
[94] HHS funds drug development for bioterror infections, pneumonia, 24 May 2013. Available at: http://www.phe.gov/Preparedness/news/Pages/infections-130524.aspx. Last accessed January 7, 2017.
[95] Ibid.
[96] Cempra Awarded $58 Million Contract to Develop Antibiotic for Paediatric Use and Biodefence by Biomedical Advanced Research and Development Authority (BARDA), 28 May 2013. Available at: http://investor.cempra.com/releasedetail.cfm?ReleaseID=767526. Last accessed January 7, 2017.

1991.[97] Solithromycin is a highly potent next-generation macrolide, the first fluoroketolide, which has potent activity against most macrolide-resistant strains.[98]

GSK - GSK '052

In September 2011 BARDA awarded GSK a contract for the development of GSK2251052 (GSK'052), an experimental antibiotic against a novel target, the bacterial enzyme leucyl tRNA synthetase.[99] In addition to working against Gram-negative hospital pathogens, it was hoped this antibiotic will work against the pathogens which cause plague and anthrax.[100] This contract awarded GSK $38.5 million over two years with options to extend the contract for a total of four years up to a total of $94 million.[101] It supported studies to evaluate efficacy and carry out Phase II & III clinical trials. In addition to financial support, BARDA also provides technical support, so sharing the risk and cost of drug development.[102] Anacor Pharmaceuticals licensed GSK'052 to GSK in July 2010 under the company's on-going research and development collaboration.[103] In February of 2012 GSK announced the suspension of all clinical trials for GSK '052.[104] The failure of this contract for technical reasons spurred efforts to develop a more flexible and appealing way of developing products like these. This led to the utilisation of the Other Transaction Authority (OT) noted in the chapter above.

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[97] Ibid.
[98] Products: Solithromycin, 2016. Available at: http://www.cempra.com/products/Solithromycin-cem-101/. Last accessed January 7, 2017.
[99] GSK awarded contract by BARDA to support research on potential novel antibiotic, 6 September 2011. Available at: http://www.gsk.com/en-gb/media/press-releases/2011/gsk-awarded-contract-by-barda-to-support-research-on-potential-novel-antibiotic/. Last accessed January 7, 2017.
[100] Ibid.
[101] BARDA partners to develop new class of antibiotic, 6 September 2011. Available at: http://www.phe.gov/Preparedness/news/Pages/gramnegative-110906.aspx. Last accessed January 7, 2017.
[102] Ibid.
[103] Anacor's Partner GlaxoSmithKline Awarded up to $94 million in U.S. Government Funding to Support Development of GSK '052, 7 September 2011. Available from: http://www.fiercebiotech.com/press-releases/anacors-partner-glaxosmithkline-awarded-94-million-us-government-funding-su. Last accessed January 7, 2017.
[104] Edward Su, GSK halts trials of novel antibiotic licenced from Anacor, 7 February 2012. Available at: http://www.pharmatopics.com/2012/02/gsk-halts-trials-of-novel-antibiotic-licenced-from-anacor/. Last accessed January 7, 2017.

GSK – Strategic Alliance with BARDA & GSK'944

In May of 2013 BARDA formed a strategic alliance with GSK utilising a portfolio approach to develop novel antibiotics to simultaneously combat bioterrorism and antibiotic resistance.[105] This 'Portfolio Partnership' is a flexible agreement where, during joint semi-annual portfolio reviews, drugs can be moved in or out of the portfolio based on the advanced-development stage and technical considerations. This approach is seen as more efficient[106] and also balances the business risk for the federal government and GSK. Supporting multiple drug candidates also increases the likelihood that one or more will advance to the level at which the company can apply for FDA approval. Novel antibiotics may also be made commercially available reducing the need and cost of stockpiling. BARDA and GSK's antibiotic group will manage and fund the portfolio initially over 18 months and potentially up to five years. Under the cost-share arrangement, the Department of Health and Human Services (HHS) will provide $40 million for the 18-month agreement and up to a total of $200 million if the agreement is renewed for the full five years.[107]

Within this strategic alliance HHS used for the first time the OT granted under the Pandemic and All-Hazards Preparedness Act (PAHPA) of 2006. As discussed previously, an OT is distinct from a contract, grant or cooperative agreement and provides a funding and collaboration vehicle to promote innovation in technology for advanced research and development.[108] As the OT is not subject to the Federal Acquisition Regulation and certain procurement statutes, it gives agencies the flexibility necessary to develop agreements tailored to national needs presented in particular scenarios such as biodefense.[109] GSK'944 is

[105] HHS forms strategic alliance to develop new antibiotics, 22 May 2013. Available at: http://www.phe.gov/Preparedness/news/Pages/strategic-alliance-130522.aspx. Last accessed January 7, 2017.
[106] Gunjan Sinha, 'BARDA to pick and choose next generation antibiotics', *Nature* 31, no.8 (2013): 665.
[107] HHS forms strategic.
[108] Ibid.
[109] Ibid.

one of the antibiotics to be further developed under this agreement, a drug which has protected or successfully treated animals suffering from anthrax, plague, or tularaemia. This programme will fund studies to support the use of GSK'944 for the treatment of anthrax, plague and tularaemia and to pursue the development of the use of GSK'944 to treat hospital- and community-acquired drug-resistant bacterial infections.[110]

Basilea Pharmaceutica International Ltd

In June of 2013, the Basel, Switzerland-based Basilea Pharmaceutica, Ltd., was awarded a contract from BARDA to support the development of BAL30072, an antibiotic to treat glanders, melioidosis and other severe infections caused by antibiotic-resistant bacteria.[111] This contract creates a cost-sharing PPP between BARDA and Basilea that can be extended up to a total of six years. In the first, 22 month phase of this contract BARDA will contribute $16.8 million and up to a total of $89 million if the contract is extended for the full six years.[112] The exercise of these options is based on the successful completion of pre-defined milestones, including microbiological, pre-clinical, clinical, manufacturing and associated regulatory activities.[113]

This contract is funded under BARDA's Broad Spectrum Antimicrobials Program and will support Basilea in conducting studies evaluating the safety and efficacy of BAL30072, the results of which will support the eventual filing of a new drug application with the FDA.[114] Early studies have shown the potential of BAL30072 to treat a broad range of multidrug-

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[110] Ibid.
[111] HHS awards $16.8 million grant for antibiotic to fight glanders, melioidosis, 27 June 2013. Available at: http://bioprepwatch.com/countermeasures/medical/hhs-awards-16-8-million-grant-for-antibiotic-to-fight-glanders-melioidosis/330995/. Last accessed January 7, 2017.
[112] BARDA supports new broad-spectrum antibiotic, 25 June 2013. Available at: http://www.phe.gov/Preparedness/news/Pages/broad-spectrum-June2013.aspx. Last accessed January 7, 2017.
[113] Basilea awarded contract by BARDA of up to USD 89 million for the development of its novel antibiotic BAL30072, 25 June 2013. Available at: http://www.basilea.com/News-and-Media/Basilea-awarded-contract-by-BARDA-of-up-to-USD-89-million-for-the-development-of-its-novel-antibiotic-BAL30072/7d4bd82d-306d-c22d-674d-e36f1889026d. Last accessed January 7, 2017.
[114] BARDA supports new.

resistant Gram-negative bacteria commonly found in hospitals. As part of a combination therapy with other licensed antibiotics, the drug also has shown promise in treating severe infections, including hospital-acquired pneumonia, complicated intra-abdominal infections, cystic fibrosis lung infections, and complicated urinary tract infections.[115]

Rempex Pharmaceuticals/The Medicines Company

In February of 2014 Rempex Pharmaceuticals, a wholly-owned subsidiary of The Medicines Company, was awarded a contract to fund the development of Carbavance.[116] Carbavance is being developed to protect against melioidosis and glanders and potentially provide a new option to treat antibiotic-resistant infections. Carbavance is a combination of a carbapenem antibiotic with a novel beta-lactamase inhibitor for treatment of MDR Gram-negative infections.[117] This contract includes an initial commitment of $19.8 million with option periods over 5 years that would bring the total value of the award to approximately $90 million.[118] This contract is a cost-sharing arrangement that includes funds for non-clinical development activities, clinical studies, manufacturing, and associated regulatory activities designed to gain U.S. approval of Carbavance for treatment of serious Gram-negative infections and to assess the drug's potential usefulness for the treatment of melioidosis and glanders.[119]

AstraZeneca/Allergan - ATM-AVI

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[115] Ibid.
[116] HHS supports development of anti-bioterrorism drug, 7 February 2014. Available at: http://bioprepwatch.com/biological-threats/bioterrorism/hhs-supports-development-of-anti-bioterrorism-drug/335865/. Last accessed January 7, 2017.
[117] BARDA Awards Contract Worth up to $90 Million to The Medicines Company/Rempex for Development of Gram-Negative Antibiotic, 5 February 2014. Available at: http://www.themedicinescompany.com/investors/news/barda-awards-contract-worth-90-million-medicines-companyrempex-development-gram. Last accessed January 7, 2017.
[118] Ibid.
[119] Ibid.

In September of 2015 it was announced that BARDA would be entering into a PPP with AstraZeneca to develop a portfolio of drug candidates with 'dual use' potential in treating illnesses caused by bioterrorism agents and antibiotic-resistant infections.[120] This partnership utilises the OT authority and is the second time this has been used to develop a portfolio of antimicrobial drug candidates. Under a cost-sharing arrangement BARDA will provide $50 million towards product development. This could rise up to a total of $170 million for development of additional products in the portfolio over the five-year period.[121] The portfolio of drug candidates is reviewed annually by both sides to determine which to move in or out. These assessments are based on technical and financial considerations and the development progress of each drug candidate.[122]

The first drug candidate – ATM-AVI – is being developed to treat Gram-negative infections and illnesses caused by bioterrorism threats such as meliodosis, glanders and plague.[123] BARDA's support for ATM-AVI, a combination of aztreonam and avibactam, is being complemented by the European Union's Innovative Medicines Initiative (IMI). The IMI is currently supporting the Phase II clinical study of ATM-AVI in Europe under a project called COMBACTE-CARE.[124] The IMI, a partnership between the European Union and the European pharmaceutical industry, will also fund additional clinical studies needed to apply for regulatory approval of ATM-AVI. These efforts represent the implementation of the particular calls to action as outlined in the National Action Plan for Combating Antibiotic-Resistant Bacteria.[125] This included the establishment of international collaborative efforts and the creation of at least one additional portfolio partnership by March 2016 to accelerate

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[120] HHS enters into strategic alliance to accelerate new antibiotic development, 16 September 2015. Available at: http://www.hhs.gov/about/news/2015/09/16/hhs-enters-strategic-alliance-accelerate-new-antibiotic-development.html. Last accessed January 7, 2017.
[121] Ibid.
[122] Ibid.
[123] Ibid.
[124] Ibid.
[125] See The White House, *National Action Plan for Combating Antibiotic-Resistant Bacteria* (Washington DC: The White House, 2015).

development of new antibacterial drugs.[126] In January of 2016 it was announced that the company Allergan will partner with AstraZeneca to develop and market ATM-AVI.[127] Under this agreement Allergan will maintain commercial rights in the U.S. with AstraZeneca maintaining these rights in all other countries. The IMI is also now supporting global Phase III clinical development for ATM-AVI before regulatory approval for this treatment is sought.[128]

CUBRC/ Tetraphase

In January of 2012 CUBRC, Inc. in collaboration with Tetraphase Pharmaceuticals, Inc., received a five-year contract worth up to $67 million from BARDA for the development, manufacturing and clinical evaluation of TP-434/Eravacycline.[129] Eravacycline is as a broad-spectrum intravenous and oral antibiotic for the treatment of MDR infections, including those caused by Gram-negative bacteria.[130] CUBRC serves as the prime contractor and Tetraphase as lead technical expert in this contract which includes a 12-month base period with committed funding of $11.5 million and subsequent option periods that, upon completion, would bring the total to $67 million.[131] This contract includes funding for pre-clinical efficacy and toxicology studies, clinical studies, manufacturing activities and associated regulatory activities. These studies are intended to develop Eravacycline as a MCM for the treatment of inhalational anthrax, tularaemia and plague. Eravacycline is also being developed as a

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[126] Ibid., 7-8, 47.
[127] Ben Adams, Allergan links with AstraZeneca on new antibiotic treatment, 29 January 2016. Available from: http://www.fiercebiotech.com/biotech/allergan-links-astrazeneca-on-new-antibiotic-treatment. Last accessed January 7, 2017.
[128] Ibid.
[129] CUBRC Awarded BARDA Contract Worth up to $67M, 20 January 2012. Available at: http://www.cubrc.org/index.php?option=com_content&view=article&id=89:cubrc-awarded-barda-contract-worth-up-to-67m&catid=19:press-releases&Itemid=6. Last accessed January 7, 2017.
[130] Pipeline, 2017. Available at: https://www.tphase.com/our-science/pipeline/. Last accessed January 7, 2017.
[131] BARDA Awards Contract Worth up to $67 Million for the Development of a Novel Tetraphase Antibiotic, 16 February 2012. Available at: http://ir.tphase.com/releasedetail.cfm?ReleaseID=747629. Last accessed January 7, 2017.

potential therapeutic agent for serious hospital infections, including those caused by multidrug-resistant aerobic and/or anaerobic Gram-negative and Gram-positive pathogens.[132]

We can see the range of support mechanisms that BARDA has utilised to support companies in the advanced-development of broad-spectrum antibiotics. BARDA structured contracts to provide funding upon the successful completion of contract milestones. The milestones were often linked to the completion of essential advanced-development studies measuring, amongst other areas the efficacy and safety of potential broad-spectrum antibiotics in clinical trials run from Phase I to III. These studies and trials can be done utilising BARDA's contract research organisations and Core Services and are essential on overcoming the 'valley of death'. We also saw how the failure of a product under the partnership with GSK led to the utilisation of a much more flexible contracting and funding structure provided for with the OT. The flexibility afforded under this contracting mechanism was also used to incentivise and partner with another large pharmaceutical company, AstraZeneca. This chapter will now assess the way the understanding of life at the molecular level has supported the development of these new antibiotics and particularly the development of Eravacycline.

The Molecular Vision of Life and the Development of Eravacycline

As has been noted above, antibiotics at their most basic are chemical compounds that kill or inhibit the growth of bacteria. In nature microbes/bacteria produce antibiotics to protect themselves against competitors. The death of other microbes means that those remaining have greater access to surrounding resources. Competition between microbes has led to the generation of sophisticated antibiotic molecules. All antibiotics disrupt a critical function in the bacterial cell. Penicillin, for example, prevented the bacterial cell wall from renewing during growth. Making penicillin generally available for medicines presented a

[132] Ibid.

formidable problem both in terms of research and large-scale production.[133] Efforts by Britain and the U.S. in the 1940s involving 39 laboratories culminated in the isolation of pure penicillin, the determination of its structure, and the method for large-scale production.[134] The significant obstacles that had to be overcome included the low concentrations that could be derived from the original mould cultures and from the chemical instability of penicillin.[135] The key activities undertaken to make large-scale production practical and cheap included the isolation of improved strains of penicillin using selection and mutation methods and improved culture conditions.[136]

Eravacycline is a novel, fully-synthetic broad-spectrum tetracycline designed to treat plague, tularemia and complicated intra-abdominable and urinary tract infections.[137] As noted above, tetracyclines are amongst the oldest discovered antibiotics in the world. Tetracyclines can be divided into two groups, atypical and typical.[138] Atypical tetracyclines function by disrupting bacterial membranes, while the typical form bind to the ribosome and inhibit protein synthesis.[139] Bacteria are prokaryotic cells and have a different ribosome structure from human cells which are eukaryotic cells. Ribosomes were discovered in the 1950s,[140] and a prokaryotic ribosome is made up of 30S and 50S subunits that together form a 70S ribosome.[141] Prokaryotic cells are the oldest and simplest cells and lack a nucleus. This difference in ribosome composition between prokaryotic and eukaryotic cells is key and is the reason why tetracycline antibiotics only harm bacterial ribosomes and not those present in

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[133] T. J. Franklin and G. A. Snow, *Biochemistry and Molecular Biology of Antimicrobial Drug Action*, (New York: Springer, 2005), 8.
[134] Ibid., 8.
[135] Ibid., 8.
[136] Ibid., 8.
[137] Joe Larsen, *BARDA's Broad Spectrum Antimicrobial (BSA) Program*, March 2015. Available from: https://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/Larsen,%20Joe.pdf. Last accessed January 7, 2017.
[138] Sean R. Connell et al., 'Ribosomal Protection Proteins and Their Mechanism of Tetracycline Resistance', *Antimicrobial Agents and Chemotherapy* 47, no. 12 (2003): 3675.
[139] Ibid., 3675.
[140] Peter B Moore, 'The ribosome returned', *Journal of Biology* 8, no. 8 (2009): 8.1.
[141] Franklin and Snow, *Biochemistry and Molecular Biology*, 86.

human cells.[142] Indeed, these antibiotic compounds would have evolved to only target the ribosomes of other bacteria.

Ribosomes are a key component of protein synthesis in bacterial cells. They play a central role in turning the genetic code into proteins.[143] DNA sequences make up genes that code for the amino acids that make up proteins. Each sequence of nucleotide bases, made up of complimentary pairs of adenine and guanine, thymine and cytosine in a strand of DNA, codes for the sequence of amino acids.[144] When proteins are made, this DNA has to be changed into another form in order for its sequencing information to be read by the ribosome. Under a process known as *transcription*, a single strand of messenger RNA (mRNA), as opposed to the double-strand of DNA, is created and is complementary with the DNA coded for in the gene.[145] This mRNA must then be *translated* by the ribosome. As the ribosome moves along the mRNA, it reads the code and produces a corresponding chain of amino acids. These amino acids are carried to the ribosome by transfer RNA (tRNA). This chain, when complete, forms the protein. Eravacycline inhibits protein translation in the bacterial cell by binding to the 30S ribosomal subunit and blocking the entry of tRNA molecules into a particular site of the ribosome.[146]

Proteins are the most important components of organisms and carry out a number of roles in the cell. As enzymes, proteins help catalyse or speed up reactions within the cell.[147] Proteins also help give structure to the cell and also bind to genes to control their activity.[148]

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[142] Denis L. J. Lafontaine and David Tollervey, 'The Function and Synthesis of Ribosomes', *Nature Reviews Molecular Cell Biology* 2, (2001): 516.
[143] David J. C. Knowles et al., 'The bacterial ribosome, a promising focus for structure-based drug design', *Current Opinion in Pharmacology* 2, no. 5 (2002): 501.
[144] Michel Morange, *A History of Molecular Biology*, trans. Matthew Cobb (Cambridge: Harvard University Press, 2000), 257.
[145] Ibid., 257.
[146] Trudy H. Grossman et al., 'Eravacycline (TP-434) Is Active *In Vitro* against Biofilms Formed by Uropathogenic *Escherichia coli*', *Antimicrobial Agents and Chemotherapy* 59, no. 4 (2015): 2448.
[147] Morange, *A History*, 255.
[148] Ibid., 255-6.

Ribosomes are the target for seven different classes of antibiotics including tetracyclines.[149] Tetracyclines, in targeting the bacterial ribosome, aim to interfere with these cellular activities and in contrast to other antibiotics are bacteriostatic. This concerns antimicrobial exposure that inhibits growth with no loss of viability.[150] Proteins such as *FtsZ* have been recognised as playing a central role in bacterial cell division. Preventing the formation of such proteins through ribosomal inhibition can then prevent the division of bacterial and the spread of infection. Bactericidal antibiotics, on the other hand, relate to antibiotic exposure that leads to bacterial cell death.[151]

Antibiotic design focused on the ribosome has gone hand in hand with recent outstanding advances in structural biology and the development of new laboratory and computational tools.[152] The structure of the ribosome has recently been determined by X-ray crystallography, revealing the molecular details of the antibiotic-binding sites.[153] The data from these crystallographic studies has explained many earlier biochemical and genetic observations, including how drugs exercise their inhibitory effects and how alterations to ribosomal components confer resistance.[154] This has supported research into how existing drugs may be used or new drugs developed to improve binding and circumvent resistance.[155] Ribosomes have been recognised as nature's largest and most complex enzyme consisting of more than fifty different proteins.[156] They also represent a complex system made up of interdependent components that require a particular arrangement to function.[157] In a way,

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[149] Knowles et al., 'The bacterial ribosome', 501.
[150] Michael A. Kohanski, Daniel J. Dwyer and James J. Collins, 'How antibiotics kill bacteria: from targets to networks', *Nature Reviews Microbiology* 8 (2010): 423.
[151] Ibid., 423.
[152] Knowles et al., 'The bacterial ribosome', 501.
[153] Jacob Poehlsgaard and Stephen Douthwaite, 'The Bacterial Ribosome as a Target For Antibiotics', *Nature Reviews Microbiology* 3, (2005): 870.
[154] Ibid., 870.
[155] Ibid., 870.
[156] Ibid., 870.
[157] Ibid., 870.

tetracyclines aim to disrupt the optimal arrangement of the component parts that ensure the ribosome's successful functioning.

They do this by lodging between crucial components, so disrupting the manner in which they operate and therefore interfering with the synthesis of new proteins.[158] Many antibiotics overlap in the sites that are targeted. Atomic-level structures of the ribosome obtained by X-ray crystallography have revealed how many of these antibiotics recognize their binding sites.[159] Utilising the tools of electron microscopy and later cryo-techniques, the overall shape and dimensions of the ribosome were first visualized and the various stages of translation captured.[160] The mRNA passes through the ribosome like a piece of tape passing through a video player with the tRNA bringing an amino acid every time three base pairs are read. The passage of the tRNA through the ribosome has been broken down into a number of different sites.[161] During protein biosynthesis, the first site that the t-RNA carrying the amino acid attempts to bind to is the A-site of the ribosome.[162] The A-site is the first stage of three through which the t-RNA moves when delivering the amino acid. 'Tetracycline directly inhibits binding of aminoacyl-tRNAs to the A site by binding to an overlapping site on the ribosome'.[163] Tetracyclines, by blocking the pathway of the tRNA through the ribosome prevent the chain of amino acids from successfully being put together in the bacterial cell and in so doing prevent protein formation.

Bacterial resistance to tetracyclines has been attributed to the presence of separate enzymes that either export it outside of the cell via efflux, chemically modify the drug to

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[158] Ibid., 870.
[159] Ibid., 870.
[160] Ibid., 871.
[161] See the diagram in Poehlsgaard and Douthwaite, 'The Bacterial Ribosome', 872.
[162] Akul Mehta, Mechanism of Action of Tetracyclines, May 27, 2011. Available at: http://pharmaxchange.info/press/2011/05/mechanism-of-action-of-tetracyclines/. Last accessed January 7, 2017.
[163] Lafontaine and Tollervey, 'The Function and Synthesis', 516.

render it inactive, or are able to release the antibiotic from the ribosome.[164] Ribosomal protection has been recognised as an important tactic for promoting tetracycline resistance in both types of bacteria.[165] Studies have demonstrated the workings of ribosomal protection proteins that negate the workings of tetracycline. These proteins actively dislodge tetracycline from the ribosome.[166] It has been demonstrated that the proteins Tet(O) and Tet(M) confer tetracycline resistance by releasing tetracycline from the ribosome, thereby freeing it from the inhibitory effects of the drug, such that the tRNA can bind to the ribosome and protein synthesis can continue.[167] The role of these proteins in the inhibition of tetracycline has been made intelligible through the use of cryo-electron microscopy or cryo-EM.[168]

Cryo-electron Microscopy

Cryo-EM is a technology used to study the architecture of cells, viruses and protein assemblies at molecular resolution.[169] It is based on the workings of electron microscopes that photograph images using electrons. These microscopes utilise the wavelength of electrons that can be up to 100,000 times shorter than that of ordinary light. Such small wavelengths can produce detailed images of some of the smallest organic components. Cryo-EM density maps are often combined with images from tools such as x-ray crystallography and nuclear magnetic resonance spectroscopy to achieve atomic-resolution models of complex, dynamic molecular assemblies.[170] One drawback in using x-ray crystallography is that it requires the sample to undergo the difficult process of crystallisation. Despite 90 percent of the 100,000 entries in the Protein Data Bank, a repository of protein structures, being solved using this

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[164] Ditlev E. Brodersen et al., 'The Structural Basis for the Action of the Antibiotics Tetracycline, Pactamycin, and Hygromycin B on the 30S Ribosomal Subunit', *Cell* 103, (2000): 1144.
[165] Connell et al., 'Ribosomal Protection', 3675.
[166] Ibid., 3677.
[167] Ibid., 3677.
[168] Ibid., 3678.
[169] Jacqueline L. Milne et al., 'Cryo-electron microscopy – a primer for the non-microscopist', *FEBS Journal* 280, no. 1 (2013): 28.
[170] Ibid., 28.

technique, it can take years to find ways of forming some proteins into large crystals that are suitable for analysis.[171] In traditional electron microscopy it has been recognised that the passage of electrons through an organic sample can cause extensive damage through irradiation and the breaking of chemical bonds.[172] Approaches responding to this issue have found lower electron doses to produce images of too poor a quality, whereas doses that are high enough to get a good image lead to unacceptable levels of specimen damage.[173]

Cryo-EM aims to overcome some of the limitations of x-ray crystallography and electron microscopy by carrying out imaging of frozen specimens maintained at either liquid nitrogen or liquid helium temperatures.[174] Liquid nitrogen freezes the sample at around -150 degrees Celsius. Imaging at this temperature reduces the extent of radiation damage by as much as six-fold compared to ambient temperatures, allowing for higher electron doses and higher quality images.[175] This problem is not entirely removed though and low contrast images are sometimes the inevitable consequence of the radiation sensitive nature of biological objects.[176] This variable notwithstanding, both liquid nitrogen and liquid helium have been used successfully to obtain 3D reconstructions at near-atomic resolution.[177] This has included the structural analysis of the ribosome.[178]

Crucially, these models reveal how the machinery of the cell operates and how molecules involved in disease might be targeted with drugs, including antibiotics.[179] It has been noted that ribosomes, as stable molecules often built from dozens of proteins, are well

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[171] Ewen Callaway, The revolution will not be crystallized: a new method sweeps through structural biology', *Nature* 525, no. 7568 (2015): 173.
[172] Milne et al., 'Cryo-electron microscopy', 30.
[173] Ibid., 30.
[174] Ibid., 30.
[175] Ibid., 30.
[176] Werner Kühlbrandt, 'Microscopy: Cryo-EM enters a new era', *Elife* 3, (2014): 2.
[177] Milne et al., 'Cryo-electron microscopy', 30.
[178] See Yaser Hashem et al., 'High-resolution cryo-electron microscopy structure of the Trypanosoma brucei ribosome', *Nature* 494, no. 7437 (2013): 385–389.
[179] Callaway, 'The revolution will not be crystallized', 173.

suited to analysis via cryo-EM.[180] The structure of ribosomes was solved using x-ray crystallography, with three chemists receiving a Nobel Prize for the work in 2009.[181] Despite this, researchers using cryo-EM have published dozens of structures of ribosomes from a number of organisms in recent years.[182] Another advantage of cryo-EM is that the mechanism by which a protein works can be deduced by flash freezing it in several conformations in contrast to the single, static pose employed in x-ray crystallography.[183]

It has been noted that the ability to solve the structure of cellular elements such as ribosomes in atomic detail is an essential prerequisite for the development of novel antibiotics and drugs.[184] Further, the molecular mechanisms of antibiotics were not clear in the absence of high-resolution structures.[185] Structures developed using the tools above have supported the rationalisation of much of the biochemical and genetic data on antibiotics and models for their mode of action.[186] These structures have provided information on the way DNA is processed in the production of certain proteins that generate resistance. The detailed knowledge of antibiotic binding sites in the 30S ribosome also supports the design of innovative drugs that target bacterial protein synthesis.[187]

In the case of the tetracyclines in general and Eravacycline in particular, the tools of x-ray crystallography and cryo-EM have played an integral role in their understanding and development. They have made intelligible the mechanisms of action of the antibiotic class tetracyclines. They have also demonstrated the workings of resistance mechanisms developed by bacteria in response to these antibiotics. The proteins Tet(O) and Tet(M) release the

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[180] Ibid., 173.
[181] Ibid., 173.
[182] Ibid., 173.
[183] Ibid., 173.
[184] Kühlbrandt, 'Microscopy', 1.
[185] Andrew P. Carter et al., 'Functional insights from the structure of the 30S ribosomal subunit and its interactions with antibiotics', *Nature* 407, no. 6802 (2000): 340.
[186] Ibid., 340.
[187] Ibid., 347.

tetracycline from the A-site allowing the tRNA to bind successfully and deliver the chain of amino acids necessary for protein creation. This understanding and knowledge of the workings of antibiotics and resistance mechanisms developed in response has been vital to the development of new antibiotics and new pharmaceutical defences such as Eravacycline that attempt to target new molecular sites in the ribosome in the fight against antibiotic resistance and bacteria that could be used by potential bioterrorists.

Conclusion

This chapter has carried out an empirical investigation into the partnerships supported by BARDA in the development of broad-spectrum antibiotics. BARDA's Broad Spectrum Antimicrobial Programme was set up to overcome the issues that inhibited the involvement of pharmaceutical companies in the development of new antibiotics. The uncertainty of the market's needs and the low volume of antibiotics bought at any one time were identified as two key factors. Both of these factors are directly related to the nature of antibiotic resistance. Indeed, the emergence of resistance is something that is extremely hard to predict. Though bacteria are continually evolving resistance to the environmental stresses they encounter, the therapeutic need for new antibiotics cannot be predicted as would normally be done in other areas. As resistance necessarily emerges in response to new antibiotics, any new drug will automatically be reserved and used as a first-line treatment many years after the company producing it can turn a profit. The previous two chapters demonstrated how BARDA attempted to overcome the lack of a commercial market. In contrast, this case demonstrates the way the nature of antibacterial resistance influenced the economics of drug development in this area.

In trying to address the threats posed by antibiotic resistance and bacterial pathogens that could be used as potential bioterror agents, BARDA has focused on establishing flexible defences with a broad-spectrum of application. Further, the guaranteed government-backed

market that BARDA represents also aims to overcome the disincentives noted above. In supporting companies in this area BARDA has utilised the OT, allowing it to work with a company across a broad portfolio of products. This adds flexibility into the government contracting mechanism and has supported partnerships with large pharmaceutical companies such as GSK and AstraZeneca. These companies, previously put off by the restrictive requirements under the FAR, can now share the costs of drug development with BARDA and jointly provide oversight as to the drugs to be prioritised and the developmental process to be followed.

Advances in medicine supported the idea of a 'magic bullet', a drug or compound that selectively targets the disease-causing organism. Understandings of the properties of dyes revealed their particular affinity with certain tissues or cells. This idea, in combination with the notion that disease was caused by external agents in the 'germ theory' of disease, provided the grounding for antibiotic chemotherapy. The benefits that emerged from this understanding led to an unexpected victory over infectious disease and the emergence of the antibiotic era. The spread of antibiotics and their misuse has revealed the limited nature of this victory. Bacterial resistance will continually emerge and require the constant investment in and development of new antibacterial therapies.

The case of Eravacyline demonstrated the key role that the molecular vision of life has played in supporting the development of new antibiotics. We first saw how the mechanism of action employed by tetracyclines was revealed through x-ray crystallography. This tool, in revealing the structure of the prokaryotic ribosome, demonstrated the active sites targeted by this antibiotic. By blocking the passage of the tRNA through the ribosome, tetracylines prevent the formation of bacterial proteins essential for continued functioning and reproduction. In doing so, the natural workings of antibiotics produced as a result of bacterial competition were revealed. Cryo-EM has further revealed the mechanisms through which bacteria have

developed resistance to tetracyclines. This method, by freezing samples at -150 degrees Celsius, overcomes some of the limitations of x-ray crystallography and has elucidated the structure of certain samples at near-atomic resolution. The role of proteins such as Tet(O) and Tet(M), made intelligible via this method, have supported the development of Eravacycline and other antibiotics that can overcome these resistance mechanisms. We can see, then, the vital role played by these technologies in revealing the molecular structure of the ribosome. This has also demonstrated the a third pathway through which our molecular understanding of DNA, in this case how it is processed in the formation of vital proteins, has supported the development of new pharmaceutical defences in overcoming the mechanisms of action and resistance employed in the evolutionary battle between bacteria.

Chapter 8: Conclusion

Chapter and Argument Review

How do advances in our varied understandings of biological life processes shape and influence contemporary security practices? This is the question that has framed this thesis and has been addressed through an in-depth analysis of the Biomedical Advanced Research and Development Authority (BARDA). In doing so, this thesis has argued that, in this case, security practices in the U.S. have undergone a process of molecularisation over the past two decades. This has been supported though an investigation into the way that molecular understandings of life have not only influenced notions of insecurity surrounding the threat of bioterrorism, but have also made possible the development of new molecular-based security technologies.

In making this argument, chapter 2 argued that a new molecular vision of life has emerged that operates beyond the parameters of biopolitics outlined by Foucault. The ground-breaking work carried out by Nikolas Rose has identified a new scale at which we can understand and shape the workings of life. These understandings, facilitated by the emergence of particular technologies, have allowed us to visualise and manipulate life at the molecular level. Significantly, these abilities have made intelligible a range of new insecurities from the way that the flu virus mutates in the potential creation of new pandemics to the genetic engineering of bacteria in the creation of new pathogens. These insecurities have shaped the security logics that seek to address the threats to the movement of people and goods so prized by the political rationality of liberalism. To support the principles of *laissez faire*, security policy has directed its concerns towards the anticipation of an uncertain future. Governments have directed resources towards the management of potential crises of circulation shaping scientific research efforts and demonstrating the bi-directional relationship between political rationalities and scientific understandings of life. The literature in International Relations has so far only focused on the way that new understandings of life have

generated new insecurities. This chapter demonstrated the way that our understandings of the workings of DNA have made possible not just the development of new weapons but also new medicines. The technologies at the centre of these possibilities have 'dual-use' potential that creates a security concern for governments.

In chapter 3 it was argued that this molecular conception of life is generating new notions of insecurity in the U.S. in the form of heightened concern with the threat of bioterrorism. Our ability to visualise and manipulate life at the molecular level shaped an understanding of insecurity surrounding bioterrorism in the U.S. The idea that terrorists may use molecular technologies to manipulate life at the molecular level in addition to our ability to visualise the way bacteria share resistance was combined in the 'dual-purpose' argument. This argument, drawing from the inherent characteristics or nature of life at the molecular level, framed the threat of bioterrorism as something that cannot be prevented and so must be prepared for through the development and stockpiling of medical countermeasures (MCMs). This logic and rationality of preparedness was implemented in the first instance with the passing of the Project BioShield Act. This chapter went on to assess the inducements set out in this Act. The case and failure of VaxGen led to a profound realisation of the significant institutional adaptation in the economic, political, legal and regulatory realms that would be required to support companies in this endeavour and harness our ability to shape life at the molecular level in the development of viable MCMs.

Chapter 4 argued that this shift in perceptions is also inciting the development of new molecular-based security technologies in the form of MCMs. This shift in perceptions has taken institutional form with the creation of BARDA. BARDA provides the financial and technical support necessary for the harnessing of life at the molecular level and the development of MCMs. This support has taken the form, for example, of advanced-development contracts and BARDA's Core Services. Further, the molecularisation of life has

also shaped the strategy employed by BARDA in the production of MCMs. Indeed, the understanding of the way new biological threats can emerge either naturally or deliberately beyond what has already been seen and addressed has influenced a more 'flexible' strategy in the creation of MCMs. This flexible approach has been implemented with the creation of the Centers for Innovation in Advanced Development and Manufacturing or CIADMs. These centers not only provide technical development support to companies but also aim to facilitate a rapid response to emerging threats.

The way that these financial and technical mechanisms have been utilised in the development of specific MCMs was addressed in the three empirical chapters. These chapters also detailed and linked three distinct pathways through which our molecular knowledge of DNA can be translated into new pharmaceutical defences. The first of these looked at the way in which the threat of smallpox was addressed. The understanding of the molecular biological workings of the variola virus shaped the way that the threat was understood and should be prepared for. The variola virus is highly contagious and would spread widely amongst today's unvaccinated population and could be synthesised by potential terrorists using today's molecular technologies. The time it takes to vaccinate a population leaves a certain window of vulnerability that has been addressed through the development and stockpiling of antivirals. ST-246 was supported through contracts funding advanced-development studies and procurement. Our ability to map DNA was crucial to the development of ST-246. High Throughput Screening having highlighted the potential of this compound to act against and inhibit the variola virus had not revealed its mechanism of action. By mapping the genes of viruses that were susceptible and resistant, the key gene targeted by ST-246 could be identified. Indeed, through this process of logical deduction and exclusion it was revealed that ST-246 targets the p37 protein so inhibiting the formation of the enveloped virus preventing the long-range spread of the virus within the body of an infected person. The molecular vision of life has in this case not only revealed the natural pathway of infection that the variola virus

takes within the body. Through the manipulation of genetic material, specifically in the mapping of DNA, it has also allowed us to understand the workings of MCMs that can act upon and inhibit this process.

Having addressed the way that the molecular vision of life has supported the mapping of DNA in the elucidation of the working of this smallpox antiviral, the next chapter assessed its role in the development of an antitoxin against the threat of anthrax. The possibility that terrorists may use molecular base technologies to edit the genetic constitution of the *Bacillus anthracis* bacteria by making it resistant to antibiotics, for example, has driven the search for antitoxins. The antitoxin Raxibacumab was supported in its development and procurement by the dedicated funding set aside under the Project BioShield Act that acts as a market guarantee and pull incentive. The regulatory aspects of development that can be enhanced through clear communication with the FDA were also recognised and aided through Fast Track and orphan designation. Molecular biology has revealed the pathway of infection and pathogenesis that *Bacillus anthracis* takes once in the body. The components that make up this process have also been elucidated, with the protective antigen playing an essential role in facilitating the entry of the toxins into the cell. Molecular biology has not only made visible this pathway of infection, but through tools such as x-ray crystallography it has made visible the key sites of the protective antigen and their role in causing disease. The Domain IV site of the protective antigen could now be targeted through the design of a monoclonal antibody. Our ability to manipulate DNA into new configurations offered up another pathway for MCM development and was essential to the creation of a library of phage antibodies. Scanning this library for antibodies that bind to and match the Domain IV site of the protective antigen resulted in a positive match and development of what would eventually become Raxibacumab.

The previous two chapters detailed the way that the molecular vision of life supported the mapping of DNA and its manipulation into new configurations. Two distinct pathways

essential to the development of new medicines and pharmaceutical defences were identified. The final empirical chapter of this thesis analysed the way that the development of broad-spectrum antibiotics was supported. The antibiotic Eravacycline was supported by BARDA in its advanced-development through contracts funding particular activities, including regulatory activities and efficacy studies. The molecular vision of life has made visible the structures that process DNA inside the bacterial cell. It has revealed through x-ray crystallography the precise sites on the bacterial ribosome which the tetracycline class of antibiotics bind to. Bacteria have however evolved mechanisms through which the action of these antibiotics can be resisted and prevented. Cryo-electron microscopy has revealed the role that certain proteins play in releasing the tetracycline antibiotic molecules so conferring antibiotic resistance. Cryo-electron microscopy tries to overcome some of the limitations of x-ray crystallography and has been used to generate higher resolution molecular images. This tool has revealed the natural pathway or inherent process through which the proteins conferring resistance are produced in the ribosomal processing of DNA. This visualisation of the bacterial structures that process DNA in the creation of these proteins revealed a third pathway through which molecular knowledge has made possible the creation of new antibiotics, such as Eravacycline, that can respond to and overcome these resistance mechanisms.

Thesis Contributions and Implications

BARDA and the Molecularisation of Security

This thesis has made a contribution to current scholarship in three ways. Firstly, this thesis provides a detailed empirical case study of the workings of BARDA. Through this investigation of the organisation at the heart of U.S. MCM production, it contributes to the field of health security by demonstrating the material incentives and support necessary for the production of these medicines. The historical background that gave rise to the need for BARDA and the way that it was created to overcome the limitations of the Project BioShield

Act were outlined. Key adaptations in financial and technical areas helped companies to overcome the 'valley of death' in the production of MCMs. We saw how messy and difficult the MCM development arena is and the significant effort needed in moving from the desire for an efficient MCM development pathway to its reality. This has been the first in-depth analysis of an organisation of this kind and one that will, hopefully, contribute to a debate regarding those investigated in the future.

Secondly, it demonstrates the empirical basis of the workings of molecular tools and technologies in the creation of MCMs. In doing so this thesis contributes to the biopolitics of security literature by highlighting the theoretical implications of this vision of life for this field of security studies here conceptualised as the molecularisation of security. As has been noted, this literature to date has not sufficiently investigated the way that understandings of life at the molecular level have supported the development of new medicines or MCMs. This thesis has analysed the way that the molecular vision of life, through visualisation and manipulation, supported not only understandings of insecurity but also the development of new molecular-based security technologies. The central role this vision of life has played in shaping both security and insecurity in this case has facilitated the characterisation of security in molecular terms. Contemporary security practices have then been profoundly reshaped by the rise of the molecular vision of life. Crucially, the molecular vision of life has revealed the nature or inherent characteristics of life at the molecular level.

This revelation is intimately connected to the third and interdisciplinary contribution that this thesis makes. It has undertaken an analysis of the key tools and technologies that have made possible the development of three MCMs. In doing this it has demonstrated attentiveness to the nuanced ways in which these technologies have enabled the transition of the molecular knowledge of DNA into new pharmaceutical defences. Scientific understandings and the possibilities they offer influence security practices. Such practices seek to capitalise

upon these understandings in the creation of MCMs to address specific threats. In this way we can see how science and security coproduce, reinforce and extend each other. The way these technologies reveal the nature of life at the molecular level is also a key element in this contribution. Indeed, this is the fundamental factor that has supported understandings of insecurity but also the development of new medicines or MCMs. Theoretically, this central thread allows us to recognise the way that security has been characterised in this case, in molecular terms. This conclusion will now turn to the implications of this characterisation.

Natures, Inherent Regularities and Political Economy

This thesis has then advanced the argument through various stages that security practices in the U.S. have undergone a process of molecularisation. In doing so, it has demonstrated the way both understandings of insecurity were shaped by molecular processes and our ability to shape life at the molecular level. In response to this, security technologies, in the form of MCMs, have been developed to intervene in the natural pathway through which pathogens cause disease and resistance to antibiotics is developed. So what is the significance of this research in understanding the way that security and governance is changing in correlation with new understandings of life?

In the second chapter we saw how the need for permanent economic exchanges and for the free movement of people and goods prioritised by a liberal govern-mentality, characterised as circulation, gave rise to the subject and object of the population. Inherent regularities in the population were revealed by statistics. Given free play to circulate, the levels of mortality from certain diseases, for example, can be recorded and shaped through vaccination programmes. Mechanisms of security work then upon an open series. By standing back, one can grasp things at the level of their nature or effective reality. As a tool of government focused on the health and welfare of the population derived though economic circulation, biopolitical mechanism of security must be attentive to the internal principles or nature of the object of governance revealed by this circulation. In this case, the level of

disease within a certain population will have its own internal regularities that must be worked with and through if any political strategy is to be implemented.

It has been asserted that any biopolitical security practice such as vaccination seeks to enact the 'nature'[1] of the living entity in question. This thesis has argued that in the U.S. in response to scientific advances that have revealed the inherent characteristics or 'nature' of life at the molecular level, these practices have undergone a process of molecularisation. The shift in security practices outlined above has been possible because the molecular vision of life has revealed the often linear and inherent disease causing characteristics of pathogens, such as the variola virus and *Bacillus anthracis*. Foucault argued that the state is the correlative of a particular way of governing and that the problem is how this way of governing develops, expands, contracts and is extended to a particular domain.[2] Modern liberal governmental reason seeks to establish an internal limitation to its own practices of government.[3] The principle of limitation is found in what is internal to governmental practice, in the objectives of government.[4] Crucially, the internal limitation of governmental practice is in correspondence with the nature and regularities of the object being governed. Governmental reason will have to respect these internal limits inasmuch as it can calculate them on its own account.[5] For Foucault, political economy made possible the self-limitation of governmental reason.[6] Political economy reflects on governmental practices in terms of its effects. Further,

> …it discovers a certain naturalness specific to the practice of government itself. The objects of governmental action have a specific nature. There is a nature specific to this governmental action itself and this is what political economy will study.[7]

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[1] Michael Dillon and Luis Lobo-Guerrero, 'Biopolitics of security in the 21st century: an Introduction', *Review of International Studies* 34 (2008): 267.
[2] Michel Foucault, *The Birth of Biopolitics* trans. Graham Burchell (Basingstoke: Palgrave Macmillan, 2010), 6.
[3] Ibid., 10.
[4] Ibid., 11.
[5] Ibid., 11.
[6] Ibid., 13.
[7] Ibid., 15.

The understanding of nature will then transform with political economy, it becomes something that 'runs under, through, and in the exercise of governmentality. It is, if you like, its indispensable hypodermis.'[8] The natural regularity inherent to an object of governance is then one face of govern-mentality, the other being the rationale of action or political logic taken in response to this regularity.[9] The two are permanently correlative.[10]

We can here draw out the reason for the focus on technologies of power and rationalities noted as the focus of many biopolitical analyses.[11] As this thesis has shown, certain technologies reveal the natural or inherent regularities in the threat to be addressed or the object to be governed. For example, the inherent processes through which bacteria develop resistance to antibiotics was made intelligible through technologies that revealed life at the sub-microscopic region. We saw how this understanding of the inevitable way that resistance develops shaped the political rationality of preparedness deployed in dealing with this threat and that of bioterrorism. The political rationality must act in accordance with the nature of the object as it is understood. As Braun notes in relation to pandemic flu, key here is less the accuracy of the scientific observation than how this understanding of molecular life and the discourses it gives rise to transform our understandings of our own biological existence and given rise to new forms of political rationality.[12]

Political economy is then the intellectual instrument, the form of calculation and rationality that makes possible the self-limitation of governmental reason.[13] Political economy recognises that the nature specific to the objects and operations of government must be respected.[14] This understanding shapes the way that apparatuses of security work. They work

[8] Ibid., 16.
[9] Ibid., 16.
[10] Ibid., 16.
[11] Paul Rabinow and Nikolas Rose, 'Biopower Today', *BioSocieties* 1, (2006): 202.
[12] Bruce Braun, 'Biopolitics and the molecularization of life', *cultural geographies* 14 (2007): 16-17.
[13] Foucault, *The Birth of Biopolitics*, 13.
[14] Ibid., 16.

within the reality of fluctuations, a reality that is recognised as a nature.[15] By acting on and through this naturalness, apparatuses of security aim for a nullification of phenomena 'in the form of a progressive self-cancellation of phenomena by the phenomena themselves'.[16] This is a fundamental characteristic and one which reveals 'a level of the necessary and sufficient action of those who govern.'[17] Vaccination is again a useful example. Foucault notes the way that the exposure to smallpox scabs produced a much-reduced immune reaction and inoculated individuals against the full effects of smallpox. Much like the management of scarcity through the natural regularities of commerce, vaccination too finds its direct point of support in the reality of the phenomena itself.[18] Vaccination or variolisation was used as a preventative measure and was applied in coordination with a statistical analysis of the occurrence of smallpox within a population.

The effects of political economy at the level of the population and the body are well documented then by Foucault. One of the key implications of this thesis has been to detail the way in which the self-limiting rationale of political economy has continued to exercise its influence on the understanding and governance of life at the molecular level. This thesis has shown the central way that the understanding of the natural regularities inherent to particular pathogens have not only shaped the particular political approach to the threat of bioterrorism but are central to the development of these molecular-based security technologies. Indeed, our ability to visualise and manipulate life at the molecular level has driven the understanding of the nature of molecular life but also ways in which this must be respected and acted upon in order to prevent illness. As the three case studies have shown our ability to map and manipulate DNA into new configurations as well as visualising the bacterial structures that process DNA, have been essential to the development of new MCMs. Crucially though, these

[15] Foucault, *Security, Territory, Population*, 37.
[16] Ibid., 66.
[17] Ibid., 66.
[18] Ibid., 59.

efforts could not have been carried out without an understanding of the inherent way in which DNA is structured, transcribed and translated into proteins outlined in the first chapter.

The specific MCMs described in the case studies act in a way that respects the inherent regularities of the organism in question. ST-246 prevents the spread of the variola virus within the body by acting upon the gene that produces the protein which envelops the virus. Raxibacumab prevents the *Bacillus anthracis* protective antigen from binding to the wall of the cell so preventing toxin entry. Eravacycline has been developed in response to an understanding of the way in which bacteria develop resistance mechanisms to the tetracycline class of antibiotics. In each case the natural process of infection or resistance is relied upon to support the development of a MCM that can produce an intervention and lead to the negation of the phenomena itself. A subtle difference to the example of variolisation given by Foucault is that this intervention is not the direct result of the process itself but removed from and yet made possible by it. The necessary and sufficient level of interaction and governance is derived from an understanding of this inherent process. One implication of this thesis then has been to demonstrate the influence, role and expansion of this political economic rationale into understandings of life at the molecular level and this biopolitical security practice.

While noting this implication, we should also note the limitations of this study. As noted in the introduction, this thesis has taken an analytical approach to the issue of biopolitics. It has assessed the way that the nature of life at the molecular level has been understood in one particular political process and logic. The limitations of this approach mean that it cannot make statements about security writ large. The molecular vision of life may well be influencing security practices in other ways but they will have to be defined on their own terms. The way life is being understood through the development of particular technologies is constantly changing. New ways of understanding and manipulating life are generating new

security concerns.[19] Future research coming out of this thesis will need to remain attentive to the new ways that life is conceived through technological advancement and the security concerns that it gives rise to.

Further research could take the understanding of the way the molecular vision of life has developed and apply it to different political rationalities and arenas. One particular avenue of research that may be fruitful would be to apply molecular biopolitics to the area of resilience studies. The development of MCMs is noted in U.S. Homeland Security documents as specifically implicated in the mitigation and reduction of vulnerability. The understanding of the way that bacteria develop resistance to antibiotics, an essential and inherent characteristic, was used to generate support for a specific approach to the threat of bioterrorism. The logic of preparedness was developed through a securitising move. Further research could investigate other instances where biological understandings of life have generated similar moves in relation to different threats.

Concluding Thoughts

This thesis then has investigated the implications of the question raised as to 'how security practices also change, if at all, as a result of their growing concern with a wide range of contemporary international health issues.'[20] It has looked specifically at the advances in our understanding of biological life processes and has asked how they are shaping and influencing contemporary security practices. As a result of understandings of life at the molecular level, it has argued that security practices in the U.S. have undergone a process of molecularisation. Our ability to visualise and manipulate molecular life in particular has facilitated understandings of insecurity and has also made possible the development of new security

[19] Emily Mullin, Obama Advisers Urge Action Against CRISPR Bioterror Threat, 17 November 2016. Available at: https://www.technologyreview.com/s/602934/obama-advisers-urge-action-against-crispr-bioterror-threat/. Last accessed January 7, 2017.
[20] Stefan Elbe, *Security and Global Health* (Cambridge: Polity Press, 2010), 14.

based technologies that act upon the inherent processes of life at this level. This thesis has also sought to draw attention to the logics that run through understandings of life and attempts to govern it. These logics seek to govern and manipulate in relation to the inherent characteristics of the object. Scientific understandings of life made possible via various technologies also identify and highlight the same factors in their attempts to shape molecular life through the creation of medicines such as MCMs.

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