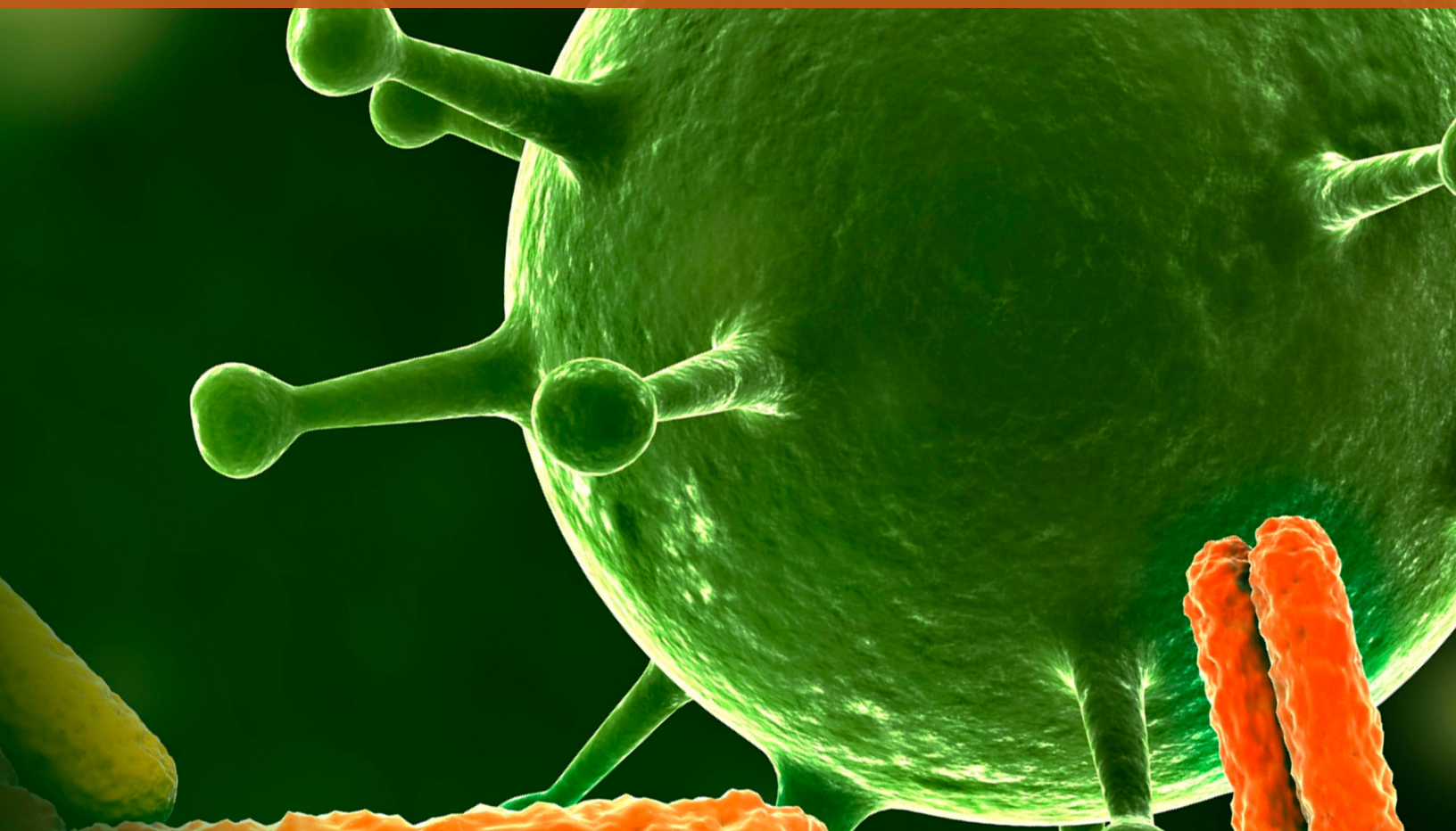
Next-Generation Monoclonal Antibodies: Challenges and Opportunities

Center for Biosecurity of UPMC

Final Report – February 2013



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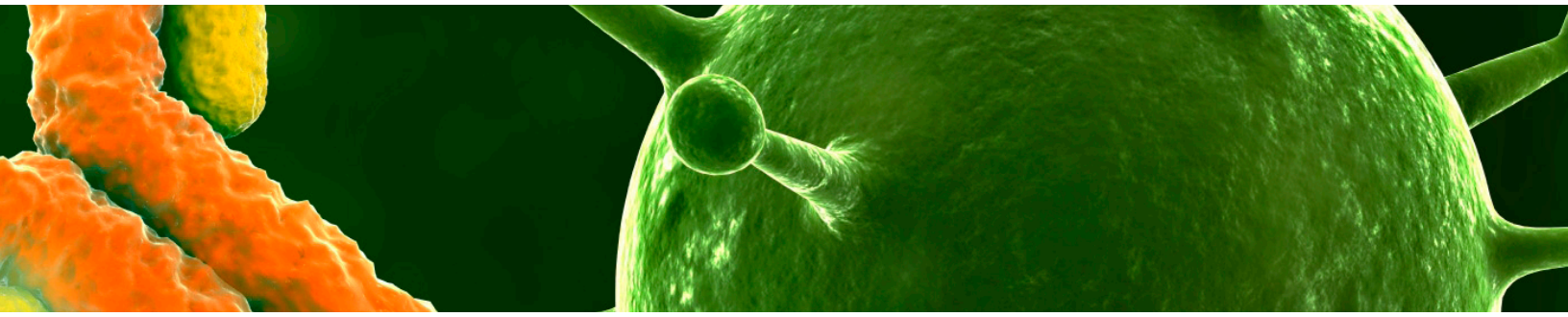


Summary of Findings: Next-Generation Monoclonal Antibodies

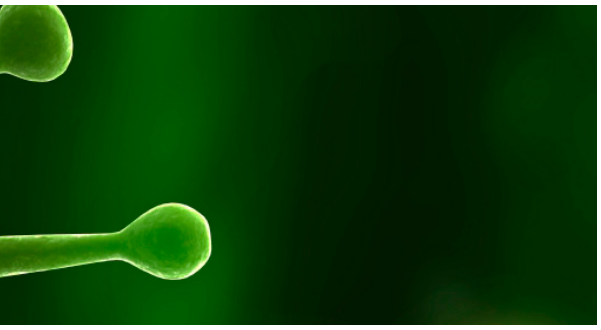
The Center for Biosecurity of UPMC conducted this study to provide leaders in the US Department of Defense (DOD) with an expert assessment of the technical feasibility and strategic implications of next-generation monoclonal antibodies (mAbs) as medical countermeasures (MCMs) for DOD personnel. Our assessment includes identification of potentially appropriate DOD investments in mAb technologies.

As a technology platform, monoclonal antibodies have value for DOD as a defense against bioweapons and emerging infectious diseases.

Monoclonal antibodies have great potential usefulness to counter biological warfare agents and naturally occurring infectious disease threats that are not addressed by currently available countermeasures. Monoclonals display exquisite specificity, are able to recruit additional host immune components to fight infection, confer near-immediate immunity once administered, can be successfully administered to all populations regardless of current immune status, and have a generally low rate of adverse reactions. Further, mAbs may offer pre- and postexposure protection in addition to potential therapeutic benefits, even in the case of antibiotic resistance. There is also a body of scientific evidence that mAbs may be effective in treating disease caused by biological warfare and natural pathogens of concern to DOD.

Although commercial development of mAb technologies is mature, mAbs are not commonly used to prevent or treat infectious diseases.

Monoclonal antibodies have become a commercial blockbuster drug platform, with the biggest portion of sales growth in the pharmaceutical industry. However, the concentrated effort in monoclonal antibody development has focused on oncological indications and immunological diseases, such as rheumatoid arthritis (RA). There is one commonly used licensed product for prevention of respiratory syncytial virus (RSV) in premature babies, another recently FDA approved for inhalational anthrax disease, and a handful of mAb products undergoing clinical evaluation for infectious disease indications, including methicillin-resistant *Staphylococcus aureus* and *Clostridium difficile*.



mAbs are poised to play a critical role in infectious disease management.

In spite of the lack of commercial attention to infectious disease mAbs, there are a number of reasons to believe they may be more desirable in the future, because of the declining clinical effectiveness of antibiotics; the large number of immunocompromised people who could benefit from mAbs; the growing recognition of the microbiome, which is disrupted by antibiotics; and the increased availability of diagnostic tests that may make mAbs more feasible to administer. In addition, because many infectious disease indications may require administration of a cocktail of mAbs, it is encouraging that the FDA has allowed cocktails of mAbs to be clinically tested as one product.

High cost per dose is a hallmark of mAbs, but costs are dropping.

Monoclonal antibodies are expensive. As a biologic class of drugs, they cost more to manufacture than small-molecule drugs, and FDA-licensed mAbs are currently among the most expensive drugs for patients and insurance companies. Many factors contribute to the cost of a particular mAb, but the most important factor influencing their price appears to be the market—the market will bear a high cost for mAbs, so they carry a big price tag. Some indicators suggest the cost of mAbs is dropping; this has been attributed to insurance company actions and greater mAb manufacturing standardization.

Monoclonal antibody products have greater regulatory success than other drug classes, but all biodefense products share common regulatory risks.

Monoclonal antibodies, in general, do not carry as much regulatory risk as other medical countermeasures, and the FDA has recent and historical experience with evaluating mAb products. This makes mAbs especially attractive for DOD, which is required to use only FDA-approved MCMs for prevention and treatment. However, biodefense products in general are riskier than other MCMs because they often require application of the FDA Animal Efficacy Rule, which allows for FDA approval based on animal model efficacy data and human safety data.

Areas for Action by DOD

As a class, mAbs will not replace vaccines or drugs in a complex MCM strategy, but they can be an important adjunct of a comprehensive approach that may be well-suited for specific DOD populations and for specific pathogens. Therefore, the question confronting DOD is not *whether* mAbs should be employed, but *how to use* mAbs technologies effectively. This report recommends that DOD take the following actions to take advantage of mAb technologies:

- Include mAbs as part of the DOD medical countermeasure strategy.
- Develop a library of mAbs that are IND-ready (ie, have attained investigational new drug status) and can be used as prophylaxis or treatment against a range of pathogens.
- Consider fast-tracking 3 mAbs for development as a proof of concept: one for treatment of a high-risk bacterial pathogen, one for prophylaxis against a fast-moving virus, and one for prophylaxis against a toxin.
- Establish partnerships with mAb developers by describing clear, specific requirements for mAbs that will be needed and pursued.
- Engage private industry and academia in mAb research and development (R&D) through clearly defined research partnerships, such as precompetitive consortia to develop new mAb technologies, which may also accelerate the lowering of production costs.
- Invest in R&D for improved means of mAb administration that meet DOD operational requirements.
- Leverage R&D of mAbs to enhance ongoing efforts to develop rapid point-of-care diagnostics.

Purpose, Methods, and Analysis

Purpose

The Center conducted this study to provide DOD leaders with an expert assessment of the technical feasibility and strategic implications of next-generation mAbs as MCMs for DOD personnel and to identify potentially appropriate mAb technologies for DOD investment.

Methods and Analysis

Review of published literature and previous reports: The Center surveyed current state-of-the-art mAb therapeutic technologies, in particular mAbs for respiratory infections, and identified new capabilities in development. We also examined the drivers of and barriers to likely advances to determine, for instance, whether the cost of mAbs could prevent or delay new development.

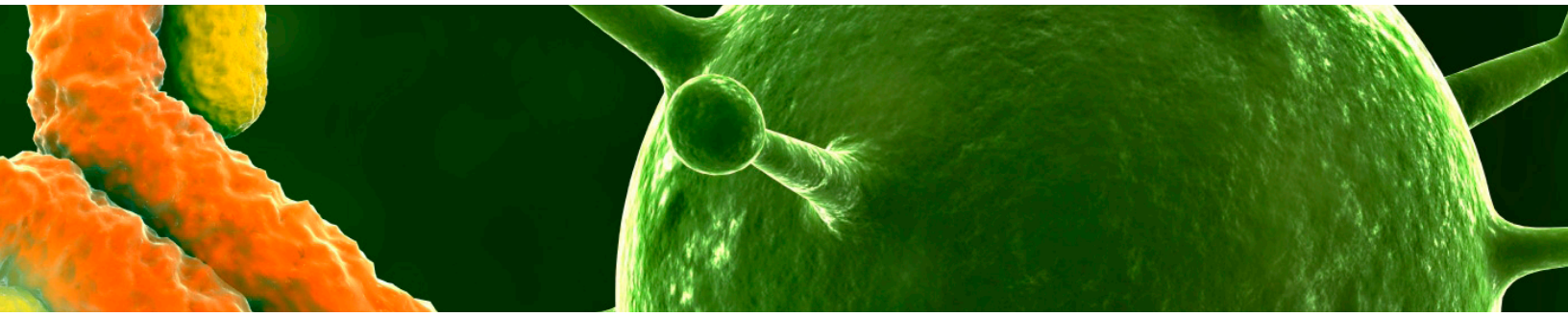
Interviews: The Center interviewed 38 technical experts, listed in Appendix B, who work with mAbs directly and who work in related fields in academia, the private sector, and government laboratories. Our goal was to ascertain the experts' judgments about evolving capabilities.

Presentations: The Center attended technical presentations at the May 2012 8th Monoclonal Antibodies Conference in London, UK, and the NIH Antibodies Interest Group, which holds periodic meetings at the National Cancer Institute in Bethesda, MD, USA.

Next-Generation Monoclonal Antibodies Meeting: The Center completed a preliminary analysis report that synthesized the results of our literature review and expert interviews. Those findings were used to facilitate the discussion held on July 13, 2012, among participants in the Next-Generation Monoclonal Antibodies Meeting held at the Center for Biosecurity in Baltimore, MD, USA. Participants included representatives of US academic institutions, private industry, and the federal government. Senior staff and leadership from the Defense Threat Reduction Agency (DTRA) attended as well. Attendees are listed in Appendix A.

Final report: This final report presents the Center's scientific and policy assessment of next-generation mAbs for DOD, informed by our expert interviews, literature review, and July 13, 2012, meeting discussions. The views expressed in this report do not necessarily reflect specific views of the meeting participants or sponsors.

Funding: This project was funded by the DTRA Chemical and Biological Technologies Directorate (DTRA/RD-CB) through TASC, Inc.



Findings

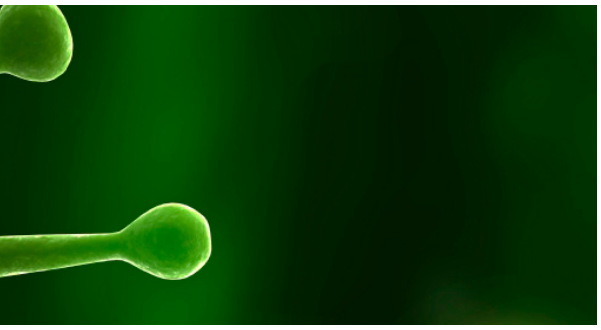
Finding 1: As a technology platform, monoclonal antibodies have value for DOD as a defense against bioweapons and emerging infectious diseases.

Monoclonal antibodies have great potential usefulness for DOD force protection against biological warfare agents and naturally occurring infectious disease threats. They display exquisite specificity, are able to recruit additional host immune components to fight infection, confer near-immediate immunity once administered, can be successfully administered to all populations regardless of current immune status, and have a generally low rate of adverse reactions.[1] Further, mAbs may offer pre- and postexposure protection in addition to potential therapeutic benefits, and they may be useful in the case of antibiotic resistance. There is also a body of scientific evidence that mAbs may be effective in treating disease caused by biological warfare and natural pathogens of concern to DOD.

This section of the report describes how monoclonal antibodies became a blockbuster commercial drug class, lists useful characteristics of mAbs, and provides an example of successful use of mAbs in an infectious disease emergency caused by the deadly Hendra virus.

Early History of Antibodies as Countermeasures

Antibodies are naturally produced by the body as part of the immune response to infection. For more than a century, they have also been used as medical countermeasures to prevent and treat infectious diseases. With a landmark series of experiments in the 1890s, Emil von Behring and Shibasaburo Kitasato demonstrated that antisera, which consists of polyclonal antibodies, could cure diphtheria. They harvested sera from guinea pigs exposed to heat-treated diphtheria toxin, and it cured guinea pigs infected with *C. diphtheriae*.[2] This passive therapy for diphtheria was commercialized in 1894 for human use, and, in 1901, von Behring was selected to receive the first Nobel Prize in physiology or medicine.[3]



In a pre-antibiotic, pre-vaccine era, antisera was the only option for treating diphtheria, a highly contagious disease that killed primarily children younger than 5 years. Vaccine became available in the early 1900s, but vaccination was not widespread. In 1925, vials of diphtheria antitoxin were transported 674 miles by dogsled from the town of Nenana, Alaska, to Nome to quench an epidemic that killed at least 5 children and threatened the lives of many more. The current Iditarod dogsled race commemorates that "Great Race of Mercy."[4]

In the years since, antisera for a variety of infectious diseases have proven effective in treating and preventing disease. The US military and the armies of other countries have routinely injected soldiers with antisera for hepatitis A and B before a vaccine became available, and antisera for rabies, tetanus, and chickenpox are still FDA-licensed and used. In most cases, antisera is administered when there is a known disease exposure and vaccination immunity has either waned or the person was never vaccinated. For example, an adult who is exposed to measles may be given both a vaccine booster and antisera to prevent infection, and a child bitten by a rabid dog would be given both a rabies vaccine and antisera.

Evolution of Monoclonal Antibodies

While antisera has been and continues to be useful, the availability of vaccines and antibiotics has diminished its relative importance in modern medicine. Diphtheria vaccine is now routinely administered as part of a childhood vaccine that also confers protection against pertussis and tetanus.[5] Antibiotics are routinely prescribed for bacterial diseases and do not require a specific diagnosis, as does antisera, before administration. Nonetheless, antibodies have exquisite binding specificity, so as soon as it became technologically possible to do so, that capacity was exploited for medical purposes with the development of monoclonal antibodies.[6,7]

In contrast to polyclonal antibodies, mAbs are derived from a single cell line and are thus identical in binding sites and binding affinities. The first monoclonal antibody therapy was licensed by the FDA in 1986.[8] It was a fully murine (mouse) mAb named Orthoclone OKT3; it binds to CD3 and was used to prevent transplant rejection.[8] Though successful, use of the mAb provoked unwanted human-antimouse immune reactions that limited the effectiveness of the treatment.[8]

Humanizing mAbs to limit adverse immune reactions thus became a research priority.[9] First, chimeric antibodies were developed, with nonhuman regions in the binding portion of the mAb and human sequences and glycosylation for the rest of the structure. Then, humanized antibodies were developed, with nonhuman sequences totaling less than 10% of the antibody structure.[10] Now, there is the potential to make monoclonals that are 100% human: Humira, which targets tumor necrosis factor (TNF) for the treatment of rheumatoid arthritis and Crohn's disease, was the first fully human monoclonal to be commercialized.[11] "Humanized" and "fully human" antibodies appear to be immunologically equivalent.[12]

The tools for mAb discovery have expanded over time as well. Some of the original commercial mAbs were found through phage display or other library systems that contained repertoires of cloned human antibody genes that were sampled and selected for binding affinity.[9,13] Many developers now use transgenic mice to generate mAbs, as they can generate human-like antibodies upon immunization.[14] In addition, some developers are able to isolate human B cells from convalescent or vaccinated subjects that produce neutralizing antibodies and generate a mAb cell line for mass production.[15,16]

Characteristics of mAbs Relevant to BW Defense and Response to Emerging Threats

Monoclonal antibodies have characteristics that distinguish them from other types of MCMs (eg, small-molecule drugs or vaccines). For instance, mAbs display exquisite specificity, in that they target specific components of a bacteria or virus that are not likely to cause unintended cross-reactions by binding to "self" proteins. Monoclonal antibodies are able to recruit immunological components to fight an infection, such as natural killer cells and complement, which may enhance pathogen neutralization. Monoclonals are also able to confer near-immediate immunity to all populations, including people who are immunocompromised. That immunity can last for months after a single administration.

In addition to their general disease prevention and treatment attributes, mAbs may provide greater protection than vaccination against some biological warfare threats. They may be particularly well-suited for DOD, given the need to provide "just in time" protection for rapidly deploying personnel.[17] DOD Directive 6205.3, pertaining to the immunization program for biological warfare defense, mandates that personnel "should be immunized against validated biological warfare threats before deployment to high-threat areas."[18] With standard vaccine for anthrax, optimum protection would not be achieved until a person had received 5 injections over the course of 18 months.[19] In contrast, with mAbs, protection against anthrax infection may be achieved immediately upon administration. In addition, mAbs may provide higher levels of protection than a traditional vaccine, as they can be administered in levels that exceed those found in vaccines. The higher level of protection may be necessary for protection in the event of a biological weapons attack, which could result in higher-than-normal levels of exposures.[17] Figure 1 summarizes mAb characteristics that have potential utility for DOD.

Figure 1: Monoclonal Antibody Characteristics of Use for DOD

- ✓ Exquisite specificity. Can be produced for specific bacterial or viral antigens without cross-reactivity for human proteins.
- ✓ Recruit immune components. Able to recruit immune components, such as NK cells and complement, to fight infection.
- ✓ Confers immunity to all populations. In contrast to vaccinations, where the immune response varies from individual to individual and where certain groups of people show poor responses to vaccine (eg, elderly, immunocompromised), monoclonal antibodies do not depend on prior immune status for function.
- ✓ Low rate of adverse reactions.
- ✓ Temporary immunity.
- ✓ Provides "just in time" protection. According to DOD Directive 6205.3, personnel "should be immunized against validated biological warfare threats before deployment to high-threat areas." In contrast to vaccines, mAbs may confer immediate immunity.
- ✓ Provides higher-than-natural protection. mAbs may be administered in higher levels than can be induced through vaccination, which is useful if BW exposure involves higher levels than natural exposure.
- ✓ Offers a pathway to protect against emerging or previously unknown threats. If humoral (antibody) responses are important to treat disease, isolating specific antibody-producing cells from survivors may offer shorter path to MCM.

As part of this project, we interviewed several DOD personnel at the Combatant Commands about their operational requirements for effective medical countermeasures. Although mAbs do not fit all of their requirements—no current or anticipated MCM does—a biodefense strategy that includes mAb technologies would meet many of the department's needs. Specifically, mAbs would: (1) address threats not covered by currently available vaccines and therapeutics; (2) be effective in spite of potential multiple antibiotic resistance; (3) provide rapid protection; and (4) provide required levels and durability of protection. The DOD operational "wish list" is highlighted in Figure 2.

There is ample scientific evidence that mAbs may be clinically effective in treating disease caused by many pathogens of concern to DOD,[17] including anthrax, smallpox, plague, Ebola, *Burkholderia*, and tularemia; toxins such as botulinum, SEA, SEB, ricin; and emerging infections including H5N1, SARS, *Acinetobacter baumannii*, and others. Table 1 outlines current mAb R&D targeting biological agents of importance to DOD, detailing the stage of development and the potential utility for DOD.

Finally, mAbs may be particularly useful to DOD because of their potential to be developed rapidly in response to an emerging or novel theat. As one expert we interviewed explained, "Thinking back to SARS and H1N1, by the time it's recognized as an epidemic, there's already someone who's survived it." If humoral immunity is important in fighting an emerging infectious disease, then antibody-producing cells can be isolated from a survivor. Alternatively, antibodies isolated from a vaccinated animal can be harvested, cloned, and tested and may be effective in preventing and treating disease. In either approach, mAbs could be identified, optimized, developed, and then produced either singly or in a multiple-mAb cocktail. Conceivably, they could be put into production within months and used during a crisis, as was the case when a mAb was used during a *Henipavirus* outbreak in 2010. To be able to accomplish this, a critical first step would be access to samples from patients who have recovered from the disease.

Figure 2: DOD Operational Considerations for MCM Use and mAb Technology Platform Suitability

Effective against threats not covered by vaccines or therapeutics?	✓ Yes
Effective against multiple antibiotic–resistant pathogens?	✓ Yes
Confers protection rapidly?	✓ Yes
Number of doses required?	✓ Depends on desired duration of immunity
Level of protection?	✓ Potentially greater than immunization
Durability of protection?	✓ Months, but not years, without additional doses
Compliance?	✓ Unknown
Costs?*	✓ Likely higher than for small-molecule drugs and vaccines

*Including both direct cost per dose and indirect logistical liabilities (cold chain, diagnostic support, ease of administration)

Table 1: mAb Research and Development Targeting Biological Agents of Importance to DOD

Biological Agent	mAb Stage of Development and Results
Category A Biothreats	
B. anthracis	Phase 1 clinical trial—Anthim: • High-affinity, humanized mAb. • Developed by Elusys. • Targets PA. • Demonstrated efficacy against anthrax infection in animal inhalational spore challenge studies. • Safe and well tolerated in humans. • IND filed in 2005. • FDA status: fast track and orphan drug.[20] FDA approved—Raxibacumab (ABthrax): • Human mAb that targets PA. • Developed by Human Genome Sciences, now part of GSK. • 65,000 doses have been ordered for and/or delivered to the SNS.[21] • Results of safety and efficacy in monkey studies indicate increased survival postexposure to lethal anthrax spores. Additional rabbit studies demonstrated efficacy. • Results of human safety studies with 400 volunteer subjects indicated raxibacumab is generally safe and well tolerated.[22] Basic research results: • Humanized mAbs derived from immunized chimpanzees have demonstrated pre- and postexposure protection against anthrax in mice. Oral mAbs given 8 and 20 hours after challenge provided significant protection against *B. anthracis*.[23] • Three chimpanzee monoclonal antibody fragments (fAbs) were humanized and demonstrated neutralization of anthrax lethal factor, with potential synergy in anti-PA antibody.[24] • Four single-chain variable fragments derived from immunized chimpanzees were developed into full-length IgG mAbs and were protective in rats.[25] • Murine mAbs derived from mice immunized against anthrax edema factor were successful in delaying disease progression in a mouse model.[26]

Biological Agent	mAb Stage of Development and Results
Y. pestis	Basic research results:[17] • Antibody efficacy has been demonstrated in mice with an inhalational plague challenge, with increased efficacy when 3 mAbs were pooled.[27] • Efficacy is expected to be demonstrated in additional studies of mAb cocktails.[17] • Results of studies of dual-function mAbs and polyclonal antibodies indicate therapeutic potential for treating pulmonary plague in mouse model.[28]
C. botulinum	Phase 1 clinical trial—XOMA 3AB: • XOMA was awarded a contract to produce mAbs against the major subtypes of BoNT A, B, and E. • Safety and efficacy were demonstrated in preclinical animal studies that supported IND application.[29] Phase 1 clinical trial—AntiBotABE: • The EU has established the collaborative AntiBotABE to discover mAbs against the same toxins; any single antibody able to neutralize multiple types of BoNTs would reduce the cost of the final product.[17] • The AntiBotABE project has so far identified promising scFvs that neutralize A1 and B1 botulinum subtypes.[30] Basic research results: • Additional research achieved systemic toxin neutralization in a mouse model using 2 mAbs against BoNT A toxin in pre- and postexposure challenges.[31]
F. tularensis	Basic research results: • mAbs derived from mice infected with *F. tularensis* LVS, an IgG2a antibody that binds to LPS. • Conferred full protection when administered either systemically or intranasally to BALB/c mice postchallenge with a lethal dose of intranasal LVS. • Three other Abs conferred prolonged survival.[32]

Biological Agent	mAb Stage of Development and Results
Ebola virus	Basic research results: • Eight murine mAbs protected mice and guinea pigs against pre- and postexposure challenge with lethal dose of Ebola glycoprotein; pooled mAbs conferred greater protection.[33] • Antibodies were generated by vaccinating mice with a VSV with Ebola Zaire glycoprotein replacing VSV glycoprotein.[34] • In recent efficacy studies, cynomolgus macaques administered 3 mAbs survived 24 hours post–lethal Ebola virus challenge.[35] • Olinger and colleagues have demonstrated passive immunity-based intervention in Rhesus macaques up to 48 hours postinfection, with 3 Ebola virus glycoprotein mAbs produced in *Nicotiana benthamiana*.[36] • Previous studies in mouse model.[37]
Marburg virus	Basic research results: • Postexposure treatment with multiple doses of polyclonal IgG antibodies from survivors studied in nonhuman primates indicate that both immediate and delayed IgG administration were completely protective and resulted in protective anti-MARV specific IgM.[38]
Vaccinia/ smallpox virus	FDA-approved sera: • VIGIV currently available from Dynport[39] and Cangene[40] Preclinical studies: • Macrogenics is creating a cocktail of 2 neutralizing antibodies for smallpox postexposure prophylaxis.[41] • With NIAID/NIH funding, Symphogen is developing sera with anti-vaccinia antibodies.[42] • Mouse model studies of mAbs derived from immunized chimpanzees are ongoing. • One mAb targeting vaccinia virus A33 glycoprotein was protective against virulent vaccinia virus challenge when administered before challenge or 2 days after.[43] • A similar study in mice demonstrated protection with pre- and postexposure administration of mAb that targeted the vaccinia virus B5 protein.[44]

Biological Agent	mAb Stage of Development and Results
Arenaviruses	Basic research results: • Two mAbs with antibodies obtained from immunized BALB/c mice given G2 ectodomain sequences of Junin and Machupo viruses were demonstrated to neutralize Junin virus *in vitro*.[45]
Category B Biothreats	
B. mallei	Basic research results: • mAb created with 4 antibodies generated by injecting mice with irradiated log phase bacteria was protective in mice as prophylactic against lethal aerosol challenge of *B. mallei*; antibodies appeared to target LPS.[46]
Venezuelan equine encephalitis virus	Basic research results: • Humanized murine mAb was demonstrated to protect mice from VEE virus, Everglades virus, and Mucambo virus (related alphaviruses) 48 hours postexposure, but was ineffective 72 hours postexposure.[47] • Human mAb prevents disease but not infection 24 hours postexposure to lethal aerosol challenge. • Mice are protected from infection when mAb is administered 24 hours preexposure by subcutaneous or aerosol challenge.[48]
C. burnetti (Q fever)	Basic research results: • Three mAbs identified, amplified, used for screening of sera from patients with Q fever endocarditis or acute Q fever in ELISA diagnostics. • Neutralization not tested[49]
B. pseudomallei	Basic research results: • Polysaccharide specific mAb protective against intranasal challenge in mice.[50]
Brucella sp.	Basic research results: • Two mAbs against *B. melitensis* cell surface protein were identified; they did not cross-react with other bacteria and reacted strongly with *B. melitensis* and surface protein in ELISA and Western blot analysis. • Neutralization not yet tested.[51]

Biological Agent	mAb Stage of Development and Results
SEB	Basic research results: • sdAb was isolated against SEB toxin B with good specificity and no cross-reactivity; this is a candidate for use in detection/diagnostics.[52] • Mice were immunized against SEB, and 4 mAbs were obtained and tested for protection against lethal challenge in mice when administered 10 minutes preexposure. Variable amounts of protection were observed with different mAbs and combinations.[53] • Synthetic human mAbs were derived from fAbs produced in *E. coli*. Converted full-length IgG mAbs were produced in *Nicotiana benthamiana* plant expression system, tested in mice postchallenge at different challenge doses of SEB, and demonstrated promising therapeutic effects in lowering IFN$_\gamma$ and IL-2 levels in mouse serum.[54]
Ricin	Basic research results: • Partially humanized neutralizing mAb IgG against ricin toxin A, expressed in a *Nicotiania* system, demonstrated protection against ricin challenge in BALB/c mice studies; efficacy was also demonstrated with administration up to 6 hours after exposure.[55] • Combination of 3 mouse mAbs against ricin toxins A and B were protective in mice with intranasal challenge and up to 7.5 hours postexposure.[56]
Category C Biothreats	
SARS CoV	Basic research results: • Crucell discovered 2 human mAbs that neutralize SARS in ferrets when administered 24 hours preexposure.[57,58]
Nipah/Hendra	Preclinical development/compassionate human clinical use • Pre- and postexposure challenge studies have tested human mAbs (m102.4) against Hendra/Nipah G glycoprotein that achieve neutralization in ferrets and monkeys. • mAbs have been administered to people in Australia as a compassionate use therapeutic option, with no reports of adverse reactions. • mAbs were derived from a large naive human phage-display antibody library and isolated as fAbs.[59]

Biological Agent	mAb Stage of Development and Results
H5N1	Preclinical studies: • Crucell partnered with Johnson and Johnson to develop a universal monoclonal antibody against influenza in 2009. Crucell's antiflu antibody, CR6261, was initially shown to neutralize a broad range of H1N1 viruses, highly pathogenic H5N1, and 2009 H1N1.[60] • In mice, CR6261 was more effective than oseltamivir in preexposure and therapeutic use following lethal H5N1 challenge.[61] • With NIH funding, Macrogenics is developing a mAb for postexposure prophylaxis for H5N1.[41] Phase 1 clinical trial completed: • Theraclone is developing an IgG mAb that binds to M2e protein, which has demonstrated *in vivo* protection against H5N1. • Theraclone is also screening human donors for broadly neutralizing anti-HA antibodies.[62]
Multiple Target Products	
Broad Spectrum (virus)	Phase 2 clinical trials—Bavituximab: • Developed by Peregrine Pharmaceuticals, Inc. • Virus-induced activation and apoptosis result in a loss of lipid asymmetry, with phosphatidylserine appearing on the outer, exposed leaflet. • Removes enveloped viruses from the bloodstream, induces ADCC to eliminate virally infected cells.[63]
Broad Spectrum (bacteria)	Preclinical studies: • Alopexx Pharmaceuticals has a fully human mAb, F598, which targets a proprietary antigen (carbohydrate on bacterial capsule PNAG) in *S. aureus* and other clinically relevant bacteria. • Alopexx entered into a partnership with Sanofi-Aventis in 2009 to develop and commercialize F598. • F598 was tested in mice with preexposure administration of mAb followed by challenge at different doses. Results indicated high *in vitro* and *in vivo* protective efficacy.[64]

Biological Agent	mAb Stage of Development and Results
Common Diseases Affecting DOD Forces	
S. aureus/ MRSA	Basic research results: • Two distinct anti-alpha-hemolysin mAbs that antagonize toxin activity and prevent human lung cell injury *in vitro* and protect animals against lethal *S. aureus* pneumonia have been identified. mAbs were derived from immunized mice and administered 24 hours prior to lethal challenge in mice.[65] • Excelimmune is developing human recombinant antibody cocktails for MRSA with mAbs cloned from human carriers; mAbs were tested in mice and protected at lethal infection levels.[66]
C. difficile	Phase 2 clinical trials: • UMass Worcester and Medarex conducted a double-blinded, randomized, placebo-controlled phase 2 clinical trial of 2 neutralizing, fully human mAbs against *C. difficile* toxins CDA1 and CDB1; mAbs significantly reduced recurrence of infection.[67] Basic research results: • Single domain antibodies derived from immunized llamas neutralized *C. difficile* toxins *in vitro*.[68] Phase 3 clinical trial: • Merck is testing MK-3415A, a human mAb, against *C. difficile* toxin B administered with single IV infusion.[69]
P. aueringosa	Preclinical studies: • Rabbit antibodies against synthetic peptides representing enzymatic domain of Pseudomonas exotoxin A have been shown to be neutralizing *in vitro*.[70] • Symphogen is partnering with Meiji Seika to make a Pseudomonas mAb cocktail.[71]
A. baumannii	Basic research results: • Five IgM monoclonal antibodies derived from immunized BALB/c mice demonstrated *in vitro* bactericidal activity in absence of iron.[72]

Biological Agent	mAb Stage of Development and Results

Abbreviation Key

Abs—antibodies; ADCC—antibody-dependent cell-mediated cytotoxicity; BoNT—Botulinum neurotoxin; CoV—Coronavirus; ELISA—enzyme-linked immunosorbent assay; EU—European Union; FDA—US Food and Drug Administration; HA—hemagglutinin; IFN—Interferon gamma; IgG— immunoglobulin G; IgG2a—immunoglobulin G2a; IgM—immunoglobulin M; IL-2—interleukin 2; IND—investigational new drug; IV—intravenous; LPS—lipopolysaccharide; LVS—live vaccine strain; mAb—monoclonal antibody; MARV—Marburg virus; MRSA—methicillin-resistant *Staphylococcus aureus*; NIAID—National Institute of Allergy and Infectious Diseases; NIH—National Institutes of Health; PA—protective antigen; PNAG—poly-N-acetyl glucosamine; SARS—severe acute respiratory syndrome; scFvs—single-chain variable fragments; sdAb—single domain antibody; SEB—Staphylococcal enterotoxin B; SNS—Strategic National Stockpile; UMass—University of Massachusetts; VEE—Venezuelen equine encephalitis; VIGIV—vaccinia immune globulin intravenous; VSV—vesicular stomatitis virus

Monoclonal Antibodies in an Infectious Disease Emergency

One potential use of mAbs is to prevent illness after a person is exposed to an infectious pathogen. The biotechnology company Crucell is pursuing this route for a rabies antibody combination product because once symptoms of rabies appear, it is too late for treatment, and the disease is nearly 100% fatal.[73] In addition to rabies, there are other diseases for which this same approach may be beneficial.

The use of mAbs for postexposure prophylaxis was already proven effective in the 2010 and 2012 outbreaks of Hendra virus in Australia. Hendra virus is shed from bats (called "flying foxes") and has spilled over to cause outbreaks in horses. Of the 7 humans who have become infected to date, 4 died. All were veterinarians and clinic workers exposed to the bodily fluids of infected horses.[74]

Though not veterinarians, Queensland, Australia, residents Rebecca Day and her daughter, Mollie, may have been exposed to the virus as they tended to their sick horse during the 2010 outbreak.[75] Only after the horse was euthanized late in the course of the disease was Hendra virus identified as the cause. Queensland health authorities immediately contacted DOD researcher Christopher Broder at the Uniformed Services University of the Health Sciences in Bethesda, Maryland, for assistance. Broder's lab had developed a mAb named m102.4 that prevented disease in laboratory animals infected with Hendra and Nipah (a close cousin of Hendra) and reduced mortality even after animals developed symptoms.[76] Given that the mother and daughter were at a "real risk" of developing the disease, the health authorities hoped that m102.4 could be sent to Australia as an experimental treatment.[75]

One of Broder's graduate students and a former postdoc pooled their frequent flier miles to hand-deliver m102.4 to Queensland. The experimental therapy was administered at a high dose (~20mgs/kg), and Rebecca Day and her daughter did not develop symptoms. To date, their infection status is not known, but, as with rabies infection, Hendra must be treated immediately because if a person is already symptomatic it may be too late.

In July 2012, another instance of high-risk exposure occurred in Queensland, and again the exposed were administered a high dose (20mgs/kg) of the m102.4 mAb prepared by Queensland Health; they did not develop disease.[77] Broder's work on m102.4 has progressed, and a horse vaccine is now being commercialized.[78]

Finding 2: Although commercial development of mAb technologies is mature, mAbs are not commonly used to prevent or treat infectious diseases.

Monoclonal antibodies have become a blockbuster drug platform, with the largest sales growth being in the pharmaceutical industry.[79] Nearly all large pharmaceutical companies have at least 1 mAb licensed product and more candidates in their pipelines. However, with the exception of 1 licensed product that is used to prevent respiratory syncytial virus (RSV) in premature babies, the concentration of effort in monoclonal antibody development has been to address oncological indications and immunological diseases, such as rheumatoid arthritis (RA).[80]

This section describes the current focus of pharmaceutical companies in mAb development, changing conditions that may make mAbs for infectious diseases more commercially attractive, and knowledge gaps that will have to be filled to produce additional infectious disease mAbs.

Despite mAb Commercial Success, Few Exist for Infectious Diseases

Monoclonal antibodies as a drug class are doing well commercially. Forecasts predict they will account for the biggest portion of sales growth in the drug industry, reaching approximately $62.7B in 2015.[79] Since 1986, when the first mAb was approved for prevention of acute transplant rejection, 34 mAbs have been approved for use in the United States, and 27 are currently marketed.[81] Nearly 350 candidates are now in the commercial pipeline, with more than 100 mAbs in Phase 2 and 3 clinical trials.[81,82] By 2009, global mAb sales topped $38B, with the 5 leading products generating $29.5B in annual revenues, and sales are expected to reach $70B by 2015.[82]

The commercial success of mAbs has occurred outside of the infectious disease market: 75% of all mAb biologics are for oncology indications or immune-related disorders.[81] Adalimumab (Humira®),[8] for RA, and infliximab (Remicade®),[8] for Crohn's, both of which block the action of TNFα, are current blockbusters. Ranibizumab (Lucentis®) is a successful fAb that is indicated for macular degeneration.[8]

In stark contrast, the state of the monoclonal antibody industry for infectious diseases is very limited.[80,83,84] There is 1 licensed product in common use, palivizumab (Synagis®), which is made by MedImmune for prevention of RSV in high-risk infants.[8] In 2010, Synagis garnered sales of $1B worldwide, $646M of which was in the United States.[85] With the recent exception of an mAb to treat inhalational anthrax, all other antibody products currently marketed in this country are *polyclonal* antisera products for the treatment of rabies, RSV, cytomegalovirus (CMV), hepatitis C (HCV), hepatitis B (HBV), vaccinia (for adverse reactions to the smallpox vaccine), hepatitis A (HAV), measles, and chickenpox.

Challenges and Changes for Infectious Disease mAbs

Infectious disease indications for antibodies were discovered first through the use of polyclonal antisera. One of the challenges to use of mAbs as medical countermeasures is that they are specific and thus require a specific disease diagnosis. A mAb that targets botulinum toxin, for example, cannot be used to treat a tetanus infection. In contrast, broad-spectrum antivirals and antibiotics do not require a specific diagnosis. Further, the broad-spectrum therapeutics tend to be more effective than mAbs later in the course of disease.[84] While most experts we spoke to believe that mAbs offer advantages in disease prophylaxis, many believe that mAbs are of limited use after disease has taken hold.

Use of mAbs in infectious diseases faces other challenges as well in that the targets and/or epitopes accessible to mAbs may be limited. There is some evidence in mice that a mAb is potentially useful for *Francisella tularensis*, which is viewed as principally intracellular bacteria[32] but may have an extracellular phase.[86] There is ongoing research into ways to target antibodies to the cytoplasm of living cells,[87] but mAbs are believed to be most effective against extracellular targets. An additional barrier is that mAbs are generally not as easy to administer as a small-molecule drug. Most commercially marketed mAbs require IV infusion, although some are administered intramuscularly or subcutaneously.

Knowledge Gaps Resulting from Lack of Commercial Interest

Because commercial interest in mAbs has focused on treatments for cancer and immunological disorders, not as much is known about mAbs for infectious diseases. The existing knowledge gaps will have to be filled before mAbs are developed for infectious diseases.

For instance, even though antisera is used routinely for some infectious diseases, the mechanisms through which immunoglobulins neutralize viral particles *in vivo* have not been fully elucidated, and it is thought that those vary by pathogen.[63] For example, immunoglobulins may activate complement, they may cause steric hindrance and interfere with the interaction between a virus glycoprotein and a cell receptor, they may opsonize infectious viral particles, they may trigger antibody-dependent cellular cytotoxicity (ADCC), or they may act in some combination of ways.[63,88]

Expanding the body of knowledge about how antibodies work in limiting infectious diseases is not a commercial priority at this time. According to an expert at the July 13, 2012, meeting, industry trends are currently focused on "adding more functionality to existing monoclonals." That is, there are a variety of strategies being undertaken to enhance the performance of mAbs, most often those with oncological indications or for chronic immunodeficiencies. Table 2 outlines mAb development strategies in commercial development. Commercial industry is also focusing on the unique characteristics that

antibody systems from other animals may offer that could be leveraged for human conditions. Table 3 describes strategies for leveraging evolution for binding.

Although adding more functionality and exploring alternative antibody structures hold considerable promise for infectious disease indications as well as cancer therapies, there are fundamental differences between targeting an epitope on a cancerous tumor and the clearance from the body of a bacterial or viral infection. The characteristics that a mAb would exhibit may well be different as a result.

As is the case for oncological indications, there is evidence that, for pathogens, multiple mAbs in a cocktail may be much more useful than a single monoclone.[63,88,93,94] In fact, a single mAb may be therapeutically insufficient, as is the case in studies of botulinum toxin, in which single mAbs neutralized toxin inadequately.[95] However, when using a cocktail that combines 3 different mAbs that bind nonoverlapping epitopes on the toxin, neutralizing potency was increased by at least 3 to 4 orders of magnitude.[95,96] The primary mechanism of action behind the increased potency of the mAb combination is the binding of 3 Fc regions to the toxin, which leads to first-pass clearance in the liver.[97,98] A similar synergistic effect of multiple monoclones was seen with tetanus,[99] rabies,[100] and Ebola.[33,35,37] Depending on the mechanism of action for a particular antibody and pathogen, it may be the case that a bi-specific antibody could yield a similar effect.[63] In addition, there are 2 manufacturers that are pursuing a recombinant polyclonal antibody, in which 1 cell line can produce 2 separate monoclones, which simplifies manufacturing and may simplify clinical testing. As one participant in the July 2012 meeting remarked, when people are infected with a pathogen, "they don't make monoclonals." And as the polyclonal, multiple monoclonal, and bi-specific approaches may be closer to the methods by which immunoglobulins clear and block infections in the human body, those approaches may ultimately become more effective mAb therapies for infectious diseases.

Table 2: Range of Creative mAb Development Strategies in Commercial Development

mAb Innovation	Purpose
fAbs	Along with other antibody fragments, may have fewer adverse events.[89]
Bi-specific antibodies	Possible to target 2 epitopes on the same pathogen, or could link cells for immune response.
Dual-variable domain (DVD-Ig) technology	Increased binding of an epitope.
Fc region engineering	This region of the antibody is being engineered for better immune recruitment and to increase the half-life of the molecule.
Broad spectrum	One example is Bavituximab, an antiphospholipid antibody, by Peregrine Pharmaceuticals. The mAb targets phosphatidyl serine, which is normally present on the inner leaflet of a membrane bilayer. In the event of cancer or infection, this phospholipid is often present in the outer leaflet.
Antibody-drug conjugates	Targeting drug actions directly at the site of need.[89]
Radiolabeled antibodies	Targeting radiation directly at a tumor.
Indirect mechanisms of action	Rather than blocking a particular epitope, mAbs are being designed as agonists/antagonists of immune receptors to modulate immune function.
PEGylation	Extends the half-life of the mAb.

Table 3: Strategies for Leveraging Evolution for Binding

Evolutionary System	Description and Advantages
Sharks	• Single domain heavy chain antibodies (5 C_H regions vs 3). • Oldest vertebrate taxon to have all components of an adaptive immune system. • vNAR (variable new antigen receptor) may target epitopes hidden from conventional mAb; potential oral availability.[90,91]
Camelids (dromedaries, camels, llamas, alpacas)	• Single domain heavy chain antibodies (2 C_H regions vs 3). • Greater tissue permeability; can access epitopes hidden from conventional mAb; potential oral availability.[90,91]
Hagfish and lamprey	• No IgG, but variable leucine receptors (VLRs), with leucine rich repeats (LRRs).[92] • May recognize mammalian antigens that are invisible to IgG-based antibodies because of self-tolerance. • According to an expert we interviewed, they are very stable: "Put them on the shelf for months, and they maintain functional integrity. You can cook them for several hours, and they still bind well."
Chimpanzees	• Already humanized. • For antibodies against vaccinia: chimpanzee fAb-displaying phage library, conversion to full-length human antibody.[43]

Finding 3: mAbs are poised to play a critical role in infectious diseases management.

In spite of the current lack of commercial attention to infectious disease mAbs, there are a number of reasons to believe they may be more desirable in the future.

This section of the report describes how monoclonal antibodies could become more commercially attractive because of the diminished clinical effectiveness of antibiotics; the large numbers of immunocompromised people who could benefit from mAbs; the growing recognition of the importance of the microbiome, which is disrupted by antibiotics; increased availability of diagnostic tests that would make mAbs more feasible to administer; and FDA allowance for cocktails of mAbs to be clinically tested as 1 product.

Diminished Antibiotic Effectiveness

The increased prevalence and rising costs of treatment for methicillin-resistant *S. aureus* (MRSA) and resistant nosocomial and community-based infections have prompted experts to declare that we are entering a "post-antibiotic era."[101,102] The commercial pipeline for new classes of antibiotics is not projected to offer a solution to this problem in the near future, which necessitates development of alternative approaches to treating infectious diseases.[84]

Large Numbers of Immunocompromised People

There are at least 10 million people in the United States (3.6% of the population) who are considered immunocompromised.[103,104] This has implications for treatment of naturally occurring infections and for response to a biological attack, because this population may be more adversely affected and may not benefit from vaccination. Conceivably, a mAb could provide protection for immunocompromised people without exposing them to the risks of live virus vaccines.

Waning Immunity or Diminished Response to Vaccine

Many childhood diseases are not confined to children, and mAbs may be beneficial as a treatment or postexposure prophylaxis for exposed adults.[105] For example, many adults have not been vaccinated against pertussis in many years, and they may benefit from a mAb to boost their immune response if they are at immediate risk for whooping cough.[106] With mumps, there is diminished herd immunity, leaving college students particularly at risk.[107] Influenza vaccine is less effective for the elderly, who are more likely to suffer the effects of the disease.[108] For all of these diseases, a mAb may be more effective than vaccine as a prophylaxis or to aid those who have become infected or are at risk of developing the disease.

Importance of the Microbiome

There is increased scientific understanding of the health maintenance role of the microbiome—the collection of microbes that live in or on the human body, including in the gastrointestinal tract, mouth, skin, nose, and urogenital tract.[109] However, the microbiome is disrupted by broad-spectrum antibiotics, which kill many microbes, alter the body's ecosystem, and affect health. There is evidence that alterations of the microbiome may contribute to disease and even to obesity.[110] As these disease pathways become better understood, reluctance to use broad-spectrum antibiotics as a first-step prophylaxis may grow.[84] A specific medical countermeasure, such as a mAb, may protect the microbiome while limiting an infection.

Increased Availability of Diagnostic Tests

In contrast to broad-spectrum antibiotics, the specificity of mAbs requires a diagnosis of disease before treatment. This has been a clear barrier in the past, but recent government efforts to develop and promote diagnostic tests for infectious diseases may allow more widespread use of mAbs for early treatment of disease.[111] As one participant in the July 2012 meeting stated, "In 5, 10 years from now, you can get 4-hour specific pathogen identification." If diseases are diagnosed routinely and quickly, there may be more opportunities to use a specific medical countermeasure like a mAb and more commercial interest in providing specific therapeutics.

Improvements in Environmental Detection

Fielded environmental biological detection capabilities offer more rapid recognition of biological agent exposures than has been available in the past. These detection systems are increasing the range of agents that can be detected and decreasing the time from collection to identification and confirmation.

Regulatory Allowance of Cocktails

There is some evidence that mAbs are more effective against infectious diseases when administered as a cocktail—a mix of 2 or more mAbs administered at once.[84] However, if those 2 mAbs had to attain FDA licensure individually, the burden and cost of clinical testing would be doubled. The FDA has allowed 1 combination product, a cocktail of mAbs against rabies (developed by Crucell/Sanofi and currently in Phase 2 clinical trials), to be tested and regulated as 1 product.[100] This approach will be advantageous for licensing mAbs for other infectious diseases that require multi-mAb treatment.[84]

Finding 4: High cost per dose is a hallmark of mAbs, but costs are dropping.

Monoclonal antibodies are currently an expensive class of biologic drugs. They cost more to manufacture than small-molecule drugs, and FDA-licensed mAbs are currently among the most expensive drugs for patients and insurance companies. Many factors contribute to the cost of a particular drug, but for mAbs, the most important seems to be that the market will bear a high price. Some indicators suggest that costs are dropping in the commercial market as a result of actions by insurance companies and increasingly standardized manufacturing. Additional factors, such as the greater regulatory success typically seen in mAb products, may also contribute to a lower cost for mAb products overall.

This section of the report describes the factors that influence the high price of mAbs, changes that may result in reduced costs, and areas in which research and investment may lead to further cost reductions.

The High Cost of Monoclonal Antibodies

Monoclonal antibodies are an expensive class of drugs for patients, insurance companies, and commercial developers. In 2008, the sale price for top mAbs ranged from $2,000/gram to $20,000/gram, with a median cost of $8,000/gram.[112] In 2012, the cost to patients can be as much as $25,000 per year.[113] Humira® for RA and Remicade® for Crohn's disease each cost about $20,000 per year.[114] The anti-RSV drug for premature babies, Synagis®, costs $900/month and is administered for 6 months, for a total cost of $5,400.[114]

Many factors contribute to the cost of a drug. It appears that mAbs are extraordinarily expensive because payers will accept their price. That said, reimbursement barriers—that is, what insurance companies will pay—and increasing competition started pressuring the pricing of mAbs, and prices have started to decline.

Pressure may also come from biosimilars, which are roughly to biologics what generics are to standard pharmaceuticals. The availability of biosimilars may exert additional downward pressure on the price of mAbs.[83,115] However, the effect of biosimilar mAbs is not expected to lower costs for off-patent mAbs to the same extent as generics did for small-molecule drugs.[114]

The European Medicines Agency has already issued guidance on similar biological medicinal products, and the FDA is expected to release guidance later this year.[83] To date, only the Korean FDA has approved a biosimilar mAb (a biosimilar version of Johnson & Johnson's Remicade). Other companies, including Amgen, Biogen Idec, Merck, AstraZeneca, and GE Healthcare, are now entering the biosimilar market space.[116]

The costs to develop monoclonals have also been decreasing because of improvements in the development pathway for mAbs and increased industrial standardization.[82] This has produced a decrease from thousands of dollars per gram to less than $100 per gram in direct productions costs (also known as the cost of goods sold, or COGS).[112,117] Estimates of the influence of COGS on the ultimate sales price range widely, from 1% to 5% to as high as 15% of sales price.[112] In 2007, the costs to develop a mAb antibody were estimated to be roughly comparable to the costs of developing other therapeutic drugs and vaccines;[118] experts at the July 2012 meeting believe that the relatively recent and precipitous decrease in COGS will be reflected in future estimates.

In the beginning of the mAb era, manufacturers were able to achieve only low antibody titers, at high cost.[112] Given the high market demand for monoclonal products, contract manufacturers built large production plants to meet the market need.[112] However, enhancements in the manufacturing and production pathways and improved purification methods eroded the need for the amount of manufacturing capacity that was established, leading to the current excess of mAb production capacity.[82,112]

Further enhancements to the manufacturing process may continue to lower the cost of goods, which may exert further downward pressure on mAb prices. Table 4 outlines manufacturing efficiencies and their effect on prices. Other factors that could affect costs for infectious disease mAbs is the amount needed for therapeutic effectiveness: As several experts noted at the July 2012 meeting, high cumulative doses (grams of product) are required for oncological indications, as compared with typically much smaller doses (ie, measured in milligrams instead of grams) for infectious disease indications.

Protein Production and Price

Most licensed mAbs use mammalian cells as a manufacturing platform. The most commonly used cell type is Chinese hamster ovary (CHO), which has been used since the licensure of tissue plasminogen activator in 1987. Another commonly used cell type is NSO myeloma cells. Both of these cell lines offer rapid growth high expression and are adapted for growth in a chemically defined media. Fed-batch processes typically accumulate titers of 1-5g/L, and production bioreactor volumes range from 5,000L to 25,000L.[112] Using the PER.C6 cell line, it has been demonstrated that 15g/L has been possible.[119]

Bacterial and yeast systems have been explored as well, although there are no approved products to date that use these systems. Interest continues, however, in part because of the expense and intellectual property challenges of CHO cell systems.[120]

Plant systems have several advantages and may offer an attractive alternative. Plant cells are not as likely as mammalian or transgenic animals to introduce adventitious pathogens; they can be engineered to perform required posttranslational modifications on transgenic proteins, and they are highly scalable for manufacturing.[121] The use of tobacco plants (*Nicotiana benthamiana*) offers significantly lower manufacturing costs than mammalian cells: Some estimate a 10-fold reduction in costs. A CHO contractor will charge from $4M to $7M to process a mAb at good manufacturing practices (GMP) standards and to generate a supply sufficient for Phase 1 clinical trials. In plants, that cost is less than $0.5M.[122] A humanized anti–West Nile virus mAb produced in plants has been found to be equivalent to that produced by a mammalian production system.[123] At the present time, however, there are no approved plant system products in the United States or Europe.

In spite of the potential for less expensive manufacturing systems to lower the cost of goods, this is not currently a priority for commercial industry. As one meeting participant said, "In terms of the decision making and hierarchy, cost of goods is actually pretty low down in a company. As long as it is within a range, that's good enough." Alternative mechanisms to produce protein are often driven more by intellectual property issues than a desire to lower the cost of goods, and the sale price for nearly all mAb products are thought to have "no direct link" between production costs and sales prices in the immediate future.[112]

Several experts at the July 2012 meeting pointed out that mAb costs for DOD would likely be different than seen commercially, and a mAb product for DOD may not be more expensive than other types of DOD countermeasures, including, for example, small-molecule drugs. Considering the lifecycle costs of a variety of countermeasure types, the typically shorter time it takes to develop a mAb countermeasure, and the greater likelihood of regulatory success to achieve an FDA-approved product, a mAb product may in the end become a less expensive option for countermeasure development.

Table 4: Manufacturing Efficiencies that Affect mAb Cost of Goods

Stage of Production	Description
Discovery	• Many strategies are available through use of phage, yeast, bacteria, viruses, mammalian cells, and memory B cell libraries.
Optimization	• Cell line optimization can increase yield (and decrease COGS). • It takes 4 months to transfect and adapt select CHO-producer cell, 1 month to build up cell-production stock for full-scale use, and several months to humanize and optimize. [119,123] • Use of plant systems or alternatives to mammalian cells could enhance yield.
Manufacturing	• All approved products use mammalian cell culture, but less costly alternatives exist. • For mammalian cell culture, there are differences in costs for dedicated facility, disposable systems, or contract manufacturing. • Elimination of cell-based production methods could streamline process.
Purification	• Currently protein A chromatography is the most expensive step ($241/g) for purification, but there are other steps, including anion-exchange, cation-exchange, virus retentive filtration, and a final spin UF/DF. • Yields possible are 70-80%, and purification concentrates up to 5g/L. The process takes 1-2 days. Could disposable membranes replace these column chromatography steps?[82,123,124]
Fill and Finish	• Biologic products, in general, have more stability problems than small-molecule drugs and require careful handling. Fill and finish and release testing are estimated to account for more than 50% of total costs ($238/g and $185/g, respectively). • Room temperature formulations could reduce costs long-term.

Finding 5: Monoclonal antibody products have greater regulatory success than other drug classes, but all biodefense products share common regulatory risks.

Monoclonal antibodies generally have less regulatory risk than other medical countermeasures. This could make them especially attractive for DOD, which is required to use only FDA-approved medical countermeasures to prevent disease caused by endemic pathogens or biological warfare agents. However, biodefense products hold more regulatory risk than other medical countermeasures, because they often require application of the FDA Animal Efficacy Rule, which grants FDA approval based on animal model efficacy data and human safety data.

This section of the report describes the DOD requirements for countermeasures, the challenges for biodefense products, and areas in which this well-known problem is being addressed.

DOD Requirements for Licensed Countermeasures

As a matter of policy, the DOD requires the use of FDA-approved vaccines and drugs to prevent diseases caused by both endemic pathogens and biological warfare agents.[18,125] DOD policy mandates that personnel "should be immunized against validated biological warfare threats, for which suitable vaccines are available, in sufficient time to develop immunity before deployment to high-threat areas."[18(p2)] Although INDs are not forbidden for military populations, they cannot be administered without informed consent unless there is a presidential waiver.[125] The operational and logistical burdens of providing informed consent, however, make INDs an unattractive option for DOD use, particularly in operational contingencies.

The decision to strongly prefer FDA-licensed products for its population places a priority on DOD support for the development of their products through FDA licensure, and it is thus an attractive quality of mAbs that they enjoy a relatively low failure rate through FDA licensure. The approval rate is consistently in the 18% to 29% range, which is at least 10% higher than that of other drug classes, and mAbs have a shorter development time to licensure.[80,115] As noted by one expert with whom we spoke, "Once you identify a good monoclonal, it's generally a straight shot to move forward. The FDA's regulatory path is clearly defined."

However, the regulatory path for biodefense MCMs is not as straightforward as the path for mAbs targeting cancers or macular degeneration. Many mAbs of interest to the DOD have to be approved using the FDA's Animal Efficacy Rule.[126] Under the rule, clinical testing in humans is conducted for safety, but efficacy trials are performed in validated animal models. The rule has been in existence since 2001, but only 4 products have been approved by this method, and all but one were already extensively used in humans but for other indications.[127,128]

One product originally rejected under the Animal Efficacy Rule is an mAb for anthrax infection, raxibacumab (Abthrax®), developed by Human Genome Science (HGS) and now is part of GSK's portfolio following the acquisition of HGS. The product is an antibody to *Bacillus anthracis*, which would presumably be used in concert with antibiotics, or by itself if the anthrax infection were antibiotic resistant. In October 2009, the FDA decided against licensing raxibacumab because it was not demonstrated to be more effective than the existing antibiotic anthrax treatment.[127,129] The FDA did not, however, consider the risk of antibiotic-resistant strains in its deliberations. In spite of the state of FDA approval, 65,000 doses were ordered for delivery to the SNS.[130] The application to FDA was resubmitted, and raxibacumab was approved by the FDA on December 14, 2012 .[131]

There are additional signs of potential improvements and clarity in the regulatory process for biodefense products. In 2009 there was no animal model qualification process in place, but there is now. FDA has offered further clarification of the rule, such as a memorandum of understanding with DARPA to develop new tools to evaluate safety and efficacy data when limited human data are available.[132]

Even though there is widespread awareness of the problem, improvements in the approval process for biodefense products may take some time. In particular, meeting participants highlighted the difficulties of developing a product that would be used for postexposure prophylaxis, noting a lack of regulatory clarity and difficulty in identifying and developing appropriate animal models. In contrast to already approved protocols for rabies, for example, in which the trigger to treat is a known exposure, animal models need to demonstrate some indication of infection before they can be treated. This is difficult to measure in many animal models and, depending on the disease, may not be feasible. Another problem discussed at the meeting was the degree to which animal models are predictive for the human condition, especially given the FDA requirement of 100% mortality in controls. Dosing of animals with 100-fold or more of LD-50 is not likely to reflect human experience.

Recommendations

This section of the report describes the authors' recommendations for actions to be taken by DOD to take advantage of the unique advantages of mAbs for the MCM armamentarium. The recommendations were informed by the Center's scientific and policy assessment of this issue, including expert interviews, literature review, and the July 13, 2012, meeting discussions, but these should not be considered consensus recommendations from either meeting participants or interviewees.

1: Monoclonal antibodies should become part of DOD's MCM strategy.

Our analysis and the opinions of the experts with whom we spoke indicate that mAbs should become a valuable MCM platform for DOD for force protection and naturally occurring disease threats. They have potential utility because they display exquisite specificity, confer near-immediate immunity, offer protection despite antimicrobial resistance, have a generally low rate of adverse reactions, and appear to be effective against many pathogens of concern to DOD (see Table 2).[1,17] While mAbs as a class will not replace vaccines or drugs in a complex MCM strategy, they have the potential to be a valuable adjunct, well-suited for specific DOD populations and for specific pathogens. The challenge to DOD should not be *whether* mAbs should be used but how to optimize mAbs for use against appropriate pathogens and for the appropriate military population.

2: Consider developing IND-ready mAb prophylaxis and treatment options for a range of pathogens.

Given the prohibitive expense of developing FDA-approved medical countermeasures for each pathogen of concern to DOD, a more prudent investment could be made in developing a range of MCMs, including monoclonal antibodies, to a stage at which increased quantities could be produced rapidly when needed. This is particularly important given the varied and expansive list of DOD pathogens of concern. There are about 50 pathogens and toxins on the Select Agent List that can harm humans; there are emerging infectious diseases that are not necessarily suitable for biological weapons but can, nonetheless, affect military populations; and new, currently unknown viruses and bacteria may emerge. The cost to DOD to develop a complete range of licensed MCMs would be well over $800M to $1B per pathogen or toxin.[118,133] Beyond development costs, there would be additional, recurring costs for stockpiling.[133] Stockpiling over a long period of time, for all of the pathogens of interest, would be resource intensive in money and time.

For these reasons, it may be beneficial to develop an array of mAbs to an IND-ready stage. This would give the DOD what some meeting experts referred to as a "warm start." If there was an immediate need for the mAb, it would be straightforward to expand the amount of monoclonal antibodies produced.

IND-ready material would already have gone through considerable efficacy testing in a model system, it would be manufactured under good manufacturing practices, and the toxicity testing would have been completed. According to interviews and discussions during the July roundtable, the costs to identify, characterize, and optimize the affinity and stability of a prototype mAb against a particular pathogen could be between $5M and $10M.

Already existing surge capacity would allow for additional protein manufacturing to suit force protection and treatment needs. As one expert at the July 2012 meeting estimated, going from IND-ready material to 1 million vials "should not take more than a few weeks, and the total cost of manufacturing will be about $100/dose." An additional advantage of this approach is that the DOD could be prepared to counter many more pathogens in a shorter period of time, as the time and resources required to complete FDA licensure tests could add years to the development of countermeasures to a more complete range of pathogens.

3: Consider fast-tracking 3 mAbs as a proof of concept: one for treatment of a bacterial biothreat for which vaccine is not available, one for prophylaxis against a fast-moving virus, and one that targets a toxin.

Monoclonal antibodies can potentially be used for prophylaxis and treatment, they have generally low toxicity, and they can be extraordinarily specific. Although as a class they have fewer adverse reactions than many other countermeasures, they are not entirely without side effects, including infusion reactions.[1] In the absence of an emergency or a clear threat of use of a particular pathogen as a weapon, it is not clear that mAb administration and potential side effects would be acceptable to military populations. Compounding the potential unease would be the need for future mAb administration. On the other hand, if the long-term effects of any medical treatment were a concern, this lack of durability for mAbs may be a benefit. Unlike the immunity produced by vaccines, mAb immunity is temporary. It can be extended with additional administrations of mAbs, so it is possible to extend immunity for months or years, but it will not last for a lifetime. It may be that treatment of disease is more acceptable to general military populations instead of vaccination, except in cases where the threat of bioweapon use is perceived to be high, and mAbs might be used both for treatment and for temporary prevention of disease.

That said, mAbs could play a critical role in treatment of a known threat for which there is no vaccine available. A monoclonal antibody could be pursued, for example, for *Burkholderia spp*, which includes biothreat agents *Burkholderia mallei* and *Burkholderia pseudomallei.* There is some evidence of mAb efficacy against those pathogens in laboratory research.[46,134-136] Given the disease prevalence of these bacterial pathogens in Asia, it might be possible to avoid use of the Animal Efficacy Rule for approval and instead pursue traditional clinical trials toward licensure.

Another high-priority need is for mAbs that could be used for designated forces entering areas with endemic pathogens that cause high-consequence viral infection. As it is not likely that forces in those areas would be able to seek medical treatment if necessary, prophylaxis, if available, would be the only feasible option. There are a number of acute viral agents for which there is a short time between presentation of symptoms and development of serious illness, including Ebola, Marburg, and Junin. Treatment would come too late for a symptomatic patient infected with any of these viruses. At the July 2012 meeting, one participant recounted DOD's decision to vaccinate all special operations forces in rabies-endemic areas against rabies, because "the possibility of being able to effectively deliver postexposure prophylaxis wasn't there. They are going to be in many instances very distant from medical support, so that your only option really is prophylaxis." This could be the case for forces in areas where Ebola, Marburg, or Junin virus are endemic.

Finally, DOD should pursue development of a mAb to a toxin amenable to neutralization that could be used in conjunction with antibiotics. There are a variety of potential targets that are biothreat agents, including ricin, SEB, or botulinum.[43,44,55,56,137-141] Developing mAbs in 3 categories would offer DOD a valuable proof of concept that could be expanded upon in additional mAb development programs.

4. DOD should establish partnerships with mAb developers by providing clear, specific requirements where monoclonals will be needed and pursued, and it should develop notional target product profiles for immunization and therapeutic applications.

Numerous reports and analyses have recommended that the US government and DOD should improve their relationships with MCM producers and the pharmaceutical and biotechnology industries.[142-147] The experts consulted for this project and the July 2012 meeting attendees agreed that, in the past, "this relationship between government and pharma has not been good. But if you can remake that relationship, you have the opportunity of getting a lot of interest." Pointing to the recent trend of pharmaceutical company interest in orphan diseases, participants expressed belief in the possibility of changing those relationships to develop more of the MCMs needed by DOD.

Clarity for requirements: A number of experts at the July 2012 meeting believe that DOD must be more specific about its requirements for manufacturers before the private sector could be engaged to develop needed MCMs. As one biotech developer stated, "It is important for DOD to think about defining your requirements. Industry can't do that for you, because you're the customer. And what industry can do is respond to you and say, 'I have that solution,' or 'I don't have it.' " Clearly defining the target population for a mAb (eg, special operations or the broader military), the desired speed of availability, quantities required, and route of administration would be a prerequisite for companies to engage with DOD. DOD could add to these components additional information typically found in a target product profile for both immunization and therapeutic applications, describing the populations for which the countermeasure will be used and the methods by which the countermeasure will be stored.

Given that the market for biodefense products is almost entirely the US government and military, companies will not satisfy DOD needs unless products are specifically requested. Without directly engaging commercial sources of mAb R&D, the focus on development for oncology and immunological diseases will continue to dominate the field.

5: DOD should engage in clearly defined partnerships with the private sector and academia through mechanisms such as precompetitive consortia.

One mechanism to improve the relationship between DOD and industrial partners is to develop precompetitive consortia that can conduct research and develop technologies that the commercial sector will not invest in but that could improve mAbs for DOD (and for other applications). Precompetitive consortia for mAb technologies could be valuable to spark research into, for instance, alternative delivery systems (eg, oral administration), mAb formulations that can be stored at room temperature (to reduce stockpiling costs), and alternative manufacturing pathways that could reduce costs for multiple manufacturers (eg, plants). Other questions need to be answered as well, such as can mAbs be used to treat diseases other than those we know of now, and how can mAb effectiveness be optimized, and how are particular pathogens cleared from the body?

Precompetitive consortia could be formed around a grand challenge that builds on DOD's unique knowledge of the immunology of military personnel. The DOD population is extensively tracked and can be, as a meeting participant described, "sampled not only in wellness but in their exposure to infectious challenge, whether it's through their normal operations or in a well-controlled challenge."

6: Invest in research and development of improved means to administer mAbs that meet likely operational requirements and constraints.

While commercial advancements are improving the identification, characterization, and optimization of candidate mAbs, commercial market forces are not necessarily going to offer new methods for administration to meet DOD requirements. Opportunities to facilitate administration in contingency or field settings, such as in micro-needle and patch delivery technologies, should be pursued and evaluated. Such research should be guided by input from combatant command and operational level medical personnel to establish both pre- and postexposure operational administration considerations.

7: Continue development of fast, point-of-care diagnostics to take advantage of monoclonal therapies and prophylaxes.

The ability to diagnose disease rapidly is important for myriad reasons: reducing morbidity and mortality, containing an epidemic, preventing further exposure, obtaining situational awareness, and determining when an epidemic is over. Clearly, diagnostics are crucial, and yet there is a dearth of accurate and

reliable diagnostic tools, and even effective tools are not well integrated into disease surveillance systems.[111,148] The US government has recognized this problem and has focused on procuring diagnostic tests and improving biosurveillance through efforts that span several government agencies.[149]

Because of the specificity of mAbs, diagnostic tests are even more important since accurate diagnosis is a prerequisite of mAb administration. For mAbs to be used as a treatment, early detection of disease will be crucial.

For all of these reasons, it is important for the US government to fund advanced development and clinical trials for diagnostic tests, to address the regulatory uncertainties involved in validating tests for rare diseases and tests that look for the presence of many diseases at once, to address the lack of standards and tools needed for diagnostic tests, and to make it easier to obtain clinical samples (including from those who have recovered from the disease in question) to validate diagnostic tests.[111]

Conclusion

This report is an expert assessment of the technical feasibility and strategic implications of next-generation monoclonal antibodies as medical countermeasures for DOD personnel. We found that mAbs have great potential to be useful for DOD force protection against biological warfare agents as well as naturally occurring infectious disease threats. Monoclonals display characteristics that would complement other medical countermeasures in a comprehensive strategy: among these, mAbs are highly specific, can be administered to all populations regardless of immune status, and offer pre- and postexposure protection as well as therapeutic benefits.

We recommend that DOD take advantage of this platform technology for force protection needs. Among other steps, we recommend developing a range of mAbs to IND status and working with mAb developers to improve means of mAb administration and usefulness for infectious disease indications. Given DOD's ongoing efforts to develop rapid point-of-care diagnostics, mAbs may become even more useful in the future for preventing and treating infectious diseases.

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Appendix A: July 13, 2012, Meeting Participants

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Kimberly Armstrong, PhD, Chemical and Biological Directorate, DTRA

Rosemarie Aurigemma, PhD, NIH/NIAID

Christopher C. Broder, PhD, Uniformed Services University of the Health Sciences, DOD

Paula Bryant, PhD, Chemical and Biological Technologies Directorate, DTRA

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Anita Cicero, JD, Center for Biosecurity of UPMC

Jeffrey Cohen, MD, National Institutes of Health

Vincent Coljee, PhD, Excelimmune, Inc.

Giora Feuerstein, MD, MSc, DTRA

William Florence, PhD, DTRA

David Frucht, MD, FDA

John Grabenstein, RPh, PhD, Merck Vaccines

Viktoria Greanya, PhD, DTRA

Gigi Kwik Gronvall, PhD, Center for Biosecurity of UPMC

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Lisa Hensley, PhD, MSPH, FDA

Jennie Hunter-Cevera, PhD, RTI International

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Larry Kauvar, PhD, Trellis Bioscience

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Gerald Kovacs, PhD, Office of the Biomedical Advanced Research and Development Authority (BARDA), HHS

James Lawler, MD, MPH, Naval Medical Research Center

Eva Lee, PhD, Georgia Institute of Technology

Anthony Macaluso, PhD, Chemical Biological Medical Systems Joint Project Management Office (CBMS-JPMO)

James Marks, MD, PhD, University of California, San Francisco (UCSF)

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Erin Reichert, PhD, Medical S&T Division (CBM), DTRA

Janice Reichert, PhD, *mAbs Journal*

Alan Rudolph, PhD, MBA, Chemical and Biological Technologies Directorate, DTRA

Philip K. Russell, MD, Sabin Vaccine Institute

Lynn Rutkowski, PhD, Ossianix

Patrick Scannon, MD, PhD, XOMA Corporation

Kristine Swiderek, PhD, Theraclone Sciences

Frank Walsh, PhD, Ossianix

Daniel Wolfe, PhD, Chemical and Biological Technologies Directorate, DTRA

Larry Zeitlin, PhD, Mapp Biopharmaceutical

Appendix B: List of Experts Interviewed by the Center for Biosecurity

Peter Sejer Andersen, PhD, Director, Antibody Discovery, Symphogen

Rosemarie Aurigemma, PhD, Chief, Biodefense Drug Development Section, NIAID

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Christopher C. Broder, PhD, Professor and Director, Emerging Infectious Diseases, Graduate Program Department of Microbiology and Immunology, Uniformed Services University of the Health Sciences

John S. Brooks, CDR USNORTHCOM

Dennis Burton, PhD, Professor, Department of Immunology and Microbial Science, Scripps Research Institute

Arturo Casadevall, MD, PhD, Leo and Julia Forchheimer Chair in Microbiology and Immunology, Albert Einstein College of Medicine

Rashid Chotani, MD, MPH, TASC, Inc.

Vincent W. Coljee, PhD, Chief Scientific Officer, ExcelImmune

Max D. Cooper, MD, Pathology and Laboratory Medicine, Emory Vaccine Center, Emory University School of Medicine

Francois Drouin, PhD, Senior Director, Product and Technology, Feldan

Jeffrey W. Froude II, PhD, Principal Investigator/ Project Leader Armed Forces Biomedical Research Institute, France

Thomas W. Geisbert, PhD, Professor, University of Texas Medical Branch, Department of Microbiology and Immunology

John D. Grabenstein, PhD, COL, USA (Ret.), Senior Director for Adult Vaccines, Merck and Co.

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Lawrence (Larry) Kauvar, PhD, Founder and Senior Vice President, Trellis Biosciences

LTC Gregory L. Kimm, CENTCOM, Health Force Protection Officer

Randall Kincaid, PhD, Scientific Director, DTRA

Michael G. Kurilla, MD, PhD, Director, Office Biodefense Research Affairs, NIAID

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Stephen H. Leppla, PhD, Microbial Pathogenesis Section, NIAID

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Anthony Macaluso, PhD, Chemical Biological Medical Systems Joint Project Management Office (CBMS-JPMO), DOD

James D. Marks, MD, PhD, Scientific Advisory Board, ImaginAb; Professor of Anesthesia, UCSF

Jennifer L. Mitcham, PhD, Senior Director, Program Management, Theraclone Sciences

Beth Rada, MS, Senior Director, Government Affairs, XOMA

Erin Reichert, PhD, Medical S&T Division (CBM), DTRA

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Philippe Thullier, MD, Biotechnology Unit, Antibodies, and Toxins, Department of Microbiology, Institute of Biomedical Research of the Army (CRSSA-IRBA)

Eric Victory, MBA, Vice President, Corporate Development and Government Project Management, MedImmune

Frank S. Walsh, PhD, Founder, CEO Ossianix, Inc.

James M. Wilson, MD, PhD, Professor of Pathology and Laboratory Medicine, University of Pennsylvania

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