The Application of the Aethlon Medical Hemopurifier™ in Biodefense

Ken Alibek, MD, PhD, ScD
and
Charles Bailey, PhD

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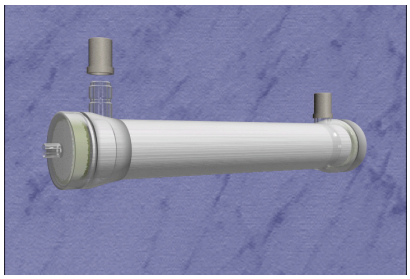
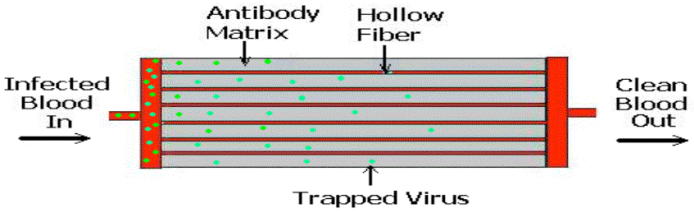
Executive Summary

Following the anthrax mailings in 2001 the importance of having a effective biodefense has never been more obvious or greater. The 2001 attack and subsequent scares highlight the flaws in current treatment options for biological weapons attacks.

Policymakers were awakened to the inherent powers of biological research and their potential for abuse in the wrong hands. This awareness has translated into specific governmental programs that represent a new business opportunity, for which **Aethlon Medical's Hemopurifier treatment technology** is uniquely suited. Government spending on research and product development has financial benefits that reduce the impact of research spending and extend patent, product liability and market protections for companies willing to participate in the effort.





Aethlon clearly fills a large void in the armamentarium of available treatments for several organisms that may be released either as 'natural' epidemics or deliberately as weapons of bioterror. **Aethlon Medical's Hemopurifier is an effective weapon that could be rapidly deployed even against genetically altered biowarfare agents**. The Hemopurifier is a modified hollow-fiber hemodialysis cartridge containing an affinity matrix comprised of antibodies or lectins and antisense DNA that selectively removes pathogenic viruses, bacteria, and toxins from circulating blood.

In preclinical human blood trials, **the Hemopurifier has already demonstrated its ability to effectively remove HIV (the AIDS Virus), HCV (Hepatitis C Virus), and related protein toxins from infected blood**. Aethlon scientists are submitting a proposal to the National Institutes of Health to further test this technology. This team believes these cartridges will also be capable of binding a wide variety of pathogenic enveloped viruses, including some hemorrhagic fever viruses that have already been weaponized and for which there is no effective treatment. The proposal will focus on the treatment of late stage inhalational anthrax and orthopox virus infections, which have proven impossible to treat with antibiotic therapy alone.

The ability to rapidly develop and test new treatments, coupled with special programs within the FDA and the Bioterrorism Act of 2002, allow for the approval of new treatments based solely on animal and human safety trials. These programs allow for Aethlon's technology to be a prime candidate as a first responder to biological threats even from microbial biological weapons which have never been seen before.

Taken together, these factors provide a compelling rationale for Aethlon to expand its market focus to participate in this rapidly growing opportunity in Biodefense.

Advantages of the Technology

- **Rapid Development of New Treatments**

The Hemopurifier technology can be rapidly developed, tested, and deployed to remove new, resistant strains of biological warfare agents from soldiers and civilians. In contrast to the situation with drugs and vaccines, development and initial deployment times of a few months are feasible even for a new agent. For example, should a terrorist group develop a new vaccine resistant strain of smallpox, Aethlon need only find or generate an antibody that reacts with the new virus or toxin. Once an antibody is available, Aethlon can build, and test a new Hemopurifier in a few weeks. In a recent test scenario Aethlon made and tested a new binding agent in six days.

- **Rapid Deployment after Approval**

Even for already approved vaccines or drugs problems developing sufficient inventories to treat even selected portions of the population exist. The reality that Aethlon can utilize a existing global manufacturing infrastructure for related dialysis cartridges, provides for additional competitive advantage for the deployment of new bioterrorism treatments.

- **Simplicity of Use in the Field**
    - In civilian use, the Hemopurifier treatment would most likely be implemented in intensive care facilities staffed by trained medical personnel. In the ICU, many patients are currently treated for acute renal failure as the result of trauma or surgery. Such facilities have the equipment and expertise to establish an extracorporeal circuit and pump the patients' blood through the Hemopurifier.

    - Use of the Hemopurifier in a military setting will significantly contribute to the ability of military medical personnel to respond to battlefield events. In the field, the device can be operated with only needles, tubing and tape to connect the patient to the device. The patient's own blood pressure drives the filtration process, eliminating the need for additional equipment.

- **Potential for use as a wearable device**

The Hemopurifier's compact size means it can be worn by an individual, which would make it possible for patients to conduct limited functions with the device attached.

The Market for Biodefense

The market for diagnostics and treatments for the agents of bioterrorism have grown remarkably in response to the events following September 11, 2001. Although it is clear that newly emerging pathogens such as SARS also represent a major threat, the only real customer capable of addressing the threat in the Biodefense market is the federal government.

Aethlon is well positioned to expand its focus to tap into these resources. Funding obtained from these sources can be used to broaden the spectrum of diseases that threaten both the military and civilian communities even if they are not released as intentional weapons of terror.

Public Policy Defines the Market

In July 2004, President Bush signed into law "Project Bioshield", which designates $5.6 billion over ten years to the development of new ways to counter the bioterrorist threat. The program provides a government-backed funding source as well as a guaranteed buyer for products that are cutting edge but may not have other commercial value. Treatments for anthrax, plague, smallpox, ebola, and botulism, are among the program's priorities.

The most significant component of the bill is the provision of a 'permanent, indefinite, funding authority', and indemnification. Tony Fauci, director of the National Institute of Allergy and Infectious Diseases is optimistic that Project Bioshield has removed a major roadblock for many companies. "Companies would be hesitant to develop something if they didn't know what was at the end of the rainbow. If you deliver the product, we will guarantee you get money." (*Washington Post, July 26, 2004)* The program has several measures built in to protect consumers as well as to ensure that the biotechnology companies do not drag out the process of developing their products.

Bioshield II legislation is already in development and will likely address liability and intellectual property issues in order to encourage pharmaceutical and biotechnology firms to become involved in the biodefense effort.

Additionally, beginning in 2001, the Federal government instituted legislative methods for regulating and controlling relevant facilities. The Patriot Act (2001) criminalized possession of biological agents unless justified by a "prophylactic, protective, bona fide research, or other peaceful purpose."

The Public Health Security and Bioterrorism Preparedness and Response Act (2002) provided for markedly enhanced research and development funds for research institutions and companies seeking to develop new diagnostic and therapeutic techniques to identify and treat these new weapons of mass destruction. The Act also provided for certain commercial and financial benefits to companies willing to become involved in the Biodefense effort including research tax credits and other incentives.

Lobbying for New Programs

Senator Joseph Lieberman, who led the way for the creation of the Department of Homeland Security, sees biotechnology as the best place to develop counter-bioterror tools. "We aren't yet ready for the next chemical and biological arrows that may be shot at us by terrorists," Lieberman says. "We need to encourage our biotechnology and pharmaceutical industries to build the shields that will protect us." Senator Lieberman's bill (S-3148), provides for generous tax incentives, "guaranteed" markets for

successful products, and special patent protection. The government will specify the nature of the market, and contract terms for a successful product, before the research is started.

One major effect of all this is a surge of interest in microbial biology. Researchers want to find out which genes make microbes virulent and where their weak spots are. They also want tools to detect deadly infectious agents quickly and to distinguish natural epidemics from "terrorist-made" ones.

Increased funding for research on bioterrorism agents will pay dividends in discoveries in other areas. In recent years, we have witnessed several emerging and reemerging infectious diseases that have presented us with many of the same challenges as bioterrorism, namely identifying changing threats and preparing for them to appear at any time. People lack immunity to emerging diseases, and effective treatments are not always known. The influx of resources and renewed energy into infectious diseases research will no doubt help us enormously in tackling naturally occurring illnesses such as drug-resistant tuberculosis and influenza.

Aethlon clearly has the potential to fill a large void in the armamentarium of available treatments for several organisms either as 'natural' epidemics or deliberately released as weapons of bioterror. Aethlon's ability to rapidly develop new treatments creates a unique niche within the Biodefense market that the company can exploit to expand its markets.

Specific Programs Funding Bioterrorism Research

Funding for Biodefense has increased dramatically since 2001 in terms of both the number of government organizations involved and the amount of money allocated. Between fiscal year (FY) 2001 and 2004, $14.5 billion was distributed for civilian Biodefense and an additional $7.6 billion has been budgeted for FY 2005. The Department of Health and Human Services (HHS), the Department of Homeland Security (DHS), and the Department of Defense (DOD) are the primary government agencies involved in Biodefense research and development.

Department of Health and Human Services (HHS)

HHS is the only agency that has a comprehensive section for Biodefense spending in its annual budget. There are three areas in which HHS Biodefense efforts fall: support for local and state public hospitals; surveillance of disease outbreaks, and countermeasures for research. HHS's projected budget for FY 2005 is just over $4 billion. Among the various agencies that fall under HHS, several are involved in human medical Biodefense research:

- *National Institutes of Health (NIH)*

  Over the last decade, NIH had one of the largest increases in funding for Biodefense. In FY 2002, for example, NIH spent $291 million on biodefense. The projected budget for FY 2005 is $1.6 billion (an additional $1.4 billion is budgeted for HIV research).

  The main institute involved in Biodefense research is **the National Institute of Allergy and Infectious Disease (NIAID)** which has a projected budget of almost $1.5 billion. The NIAID's Counter Bioterrorism Research Agenda describes the highest priorities of an accelerated program to research bioterror agents, specifically Category A agents, which include anthrax, smallpox, plague, tularemia, and viral hemorrhagic fevers. Significant funding is also available for research on more exotic agents that can be used for military purposes. Specific research areas include combating potential bioterror agents and the development of next-generation therapeutics and diagnostic tests.

- *Centers for Disease Control and Prevention (CDC)*

The CDC falls under the umbrella of HHS. The CDC's biodefense agenda includes providing grants to state and local public health departments to help improve readiness for a biological weapons attack. $1.1 billion is allocated to the CDC in the FY 2005 budget.

- *Food and Drug Administration (FDA)*

The FDA oversees the testing and approval for new drugs, vaccines, medical devices, and diagnostic products as well as food and cosmetics. No new treatment, medical device, food or cosmetic can be sold without the administration's approval. Given the vast responsibility to protect the health of the nation, the FDA plays a vital role in combating bioterrorism. Its projected budget for FY 2005 is $1.1 billion (up from $128 million in FY 2001).

One of the main problems facing the agency is and has been the need to ensure public safety while at the same time preventing unsafe treatments from reaching the public. The balance between these competing pressures has resulted in a long and deliberate process for approving new treatments, which is not responsive to the urgent need for new treatments presented in the era of bioterror. For most drugs, the principal research and development phases takes 1 to 3 years before a drug is even submitted to FDA for testing. The clinical research program takes 2 to 10 years, depending on the agent and clinical indication. The marketing application review period requires an average of 1 year. Once a product is approved for market, long-term post-marketing surveillance, inspections, and product testing must be performed to ensure the quality, safety, and efficacy of the product, as well as appropriate product labeling.

Many biological warfare defense products pose difficult problems with regard to obtaining clinical efficacy data. For deadly infectious agents and toxins, human efficacy trials cannot ethically be performed, as such studies would involve exposing healthy human volunteers to a lethal or permanently disabling agent without proven therapy and field trials. In most cases, field trials are not feasible because pockets of natural exposure do not exist.

Recognizing this issue, FDA has proposed standards in approving new treatments to counter chemical and biological weapons based solely on animal tests that predict efficacy in humans. Some scientific considerations for animal studies include the toxic agent's pathophysiologic mechanism, how the test treatment prevents toxicity and the validity of the clinical endpoint in humans. In addition, data showing that treatment safety in humans is required.

For therapeutic products, these mechanisms include expedited review and fast-track development, as well as accelerated approval and priority review of marketing applications. For licensure, a biological warfare defense product must have an acceptable quality, safety, efficacy, and potency profile. Likewise, the product must have acceptable stability characteristics and be produced in compliance with current good manufacturing practices. Product safety will still be evaluated in healthy human volunteers at doses and routes of administration anticipated in field use. The net result is that a complete review of the marketing application for a priority product can be accomplished in as little as six months. FDA also requires that product recipients be given follow-up after treatment to affirm product safety and efficacy.

Department of Homeland Security (DHS)

The DHS was created by the Homeland Security Act of 2002 and is responsible for unifying national efforts to secure the United States. Biodefense funding for FY 2005 is expected to be just over $4 billion. There are three directorates within DHS: the Emergency Preparedness Directorate, Information Analysis and Infrastructure Protection Directorate, and the Science and Technology Directorate. The majority of the proposed funding is allocated to two programs:

- *Project Bioshield*

Project Bioshield is part of the Emergency Preparedness Directorate and enables the government to make large-scale procurement of countermeasures quickly. Though not finalized, the FY 2005 budget for this program is over $2.5 billion.

- *Homeland Security Advanced Research Projects Agency (HSARPA)*

HSARPA is responsible for late stage development of new homeland security technology.

Department of Defense (DOD)

The DOD's Biodefense focus is primarily in a military setting but there are programs that support civilian Biodefense efforts. It is estimated that the DOD spent $2 billion on civilian Biodefense in FY 2004.

There are several organizations within the Department involved in civilian Biodefense.

- *Defense Advanced Research Projects Agency (DARPA)*

DARPA is the central research and development organization for the DOD. Research areas include basic and applied research and development. Biological weapons defense programs, which began in the mid-1990's, are managed within two offices: the Special Projects Office (SPO) and the Defense Sciences Office (DSO). One program, the Unconventional Pathogen Countermeasures Program, which is part of the DSO, focuses on the development of revolutionary, broad-spectrum medical countermeasures against significantly pathogenic microorganisms and/or their pathogenic products. These countermeasures will be versatile enough to eliminate biological threats, whether from natural sources or modified through bioengineering or other manipulation.

The specific strategies sought by DARPA in this initiative include:

1. Defeat of a pathogen's ability to enter the body, traverse the bloodstream or lymphatics, and enter target tissues.

2. Identification of novel pathogen vulnerabilities based on fundamental, critical molecular mechanisms of survival or pathogenesis, e.g., Type III secretion, cellular energetics, virulence modulation.

3. Construction of unique, robust vehicles for the delivery of countermeasures into or within the body.

4. Modulation of the advantageous and/or deleterious aspects of the immune response to significantly pathogenic microorganisms and/or their pathogenic products in the body.

Aethlon's technology is highly suited to play a role in aiding the body in its defense against invading pathogens or toxins and should be a good candidate to participate in this initiative.

- *United States Army Medical Research and Materiel Command (USAMRMC)*

The USAMRMC manages special programs funded by Congressional Special Interest Medical Programs (CSI) which are added to the DOD's budget by Congress. The purpose of USAMRMC is

to "ensure sponsorship of good science, advanced development and procurement as required by Congress, that can benefit the DOD and the civilian sector." (USAMRMC website)

There are several programs within the USAMRMC that deal specifically with medical Biodefense. The Medical Chemical and Biological Defense Research Program (MCBDRP), one of four research area directorates, is focused on providing a strong medical defense against chemical and biological weapons.

- *Defense Threat Reduction Agency (DTRA)*

DTRA provides "a unified, consistent approach to deterring, reducing, and countering Weapons of Mass Destruction." (DTRA website) Chemical and Biological defense is a key part of this mission. DTRA's Chemical and Biological Defense Program is involved in the development and procurement of, among others, protective equipment and medical countermeasures including prophylaxes, diagnostics, and therapeutics.

- *United States Army Research Office (ARO)*

The ARO funds basic research that may produce far-reaching technological discoveries that will enhance the Army's defense capabilities.

Biotechnology in the future

Biotechnology can be defined as the use of cellular and biomolecular processes to solve problems or make useful products (from Biotechnology Industry Organization). Biotechnology tools and techniques aid in product discovery and development by detecting new targets and tailoring products to address specific needs.

The biotechnology industry is one of the fastest growing industries in the United States. There are over 1500 biotechnology companies in the United States with California, Massachusetts, North Carolina, and the Washington, D.C. metropolitan area having the largest number of such companies. Over 370 biotechnology products, which target over 200 infectious and non-infectious diseases, are currently in clinical trials. Revenues from biotechnology products have ballooned from $8 billion in 1992 to almost $30 billion in 2002.

The biotechnology industry is also one of the most research intensive industries in the world. Many biotechnology companies have diverted focus from traditional research to Biodefense research. Since 2001, the U.S. government has spent billions on Biodefense and the proposed FY 2005 budget indicates the trend will continue. Many projects have been put on the fast track due to their importance to national security. In addition to biotechnology companies, universities and other non-profit organizations are moving to Biodefense research providing opportunities for collaboration and network building.

It is clear that many companies previously developing products for the commercial market are adapting to help fight bioterrorism. Aethlon Medical shares this advantage since biodefense is clearly an expansion of the company's current market opportunities. In addition to available funding and other financial incentives, FDA fast track developments with regard to biodefense could enhance the likelihood of other Aethlon products successfully reaching market.

Defining the Threat of Bioterrorism

The horrendous terrorist attacks of September 11, 2001 had the immediate effect of raising our level of consciousness about future terrorist attacks. We now know beyond a shadow of doubt that those who seek our destruction have no limitations whatsoever regarding the lengths that they will go to in order to achieve their aims. Bioweapons pose a particularly severe threat because small quantities can be deadly or incapacitating over a widespread area and they are relatively easy to produce and conceal.

The Department of Health and Human Services now maintains a list of select agents that are likely to be used in a terrorist attack. Table I summarizes the most important of these bioweapons. Class A agents are defined as organisms that pose the greatest threat to national security because they can be easily disseminated, have a potential for major public health impact, may result in high mortality rates, or may be transmitted from one person to another. Class B agents are the second highest priority because they too are relatively easy to disseminate, they result in moderate morbidity rates and low mortality rates, and require specific diagnostic and disease surveillance enhancements. Class C agents include emerging pathogens that could be disseminated in the future because of their availability, ease of production and deployment, and their potential for high morbidity and mortality rates.

Table I. Select Agent Bioweapons by Classification

Weapon	Scientific Name or Type	Class
Bacteria		
Anthrax	*Bacillus anthracis*	A
Botulism	*Clostridium botulinum*	A
Plague	*Yersinia pestis*	A
Tularemia	*Francisella tularensis*	A
Brucella	*Brucella*	B
Glanders	*Burkholderia mallei*	B
Melioidosis	*Burkholderia pseudomallei*	B
Q fever	*Coxiella burnetii*	B
Typhus	*Rickettsia prowazeki*	B
Viruses		
Dengue		A
Ebola	Filoviridae	A
Lassa fever		A
Marburg	Filoviridae	A
Rift Valley fever	Bunyaviridae	A
Smallpox (*Variola major*)	Poxviridae	A
Venzuelan equine encephalitis	Alphaviruses	B
West Nile viruses		B
Crimean-Congo hemorrhagic fever		C
Rotavirus		C
Tick Borne Encephalitis		C
Yellow fever	Flaviviridae	C
Toxins		
Aflatoxin		
Botulinum	*Clostridium botulinum*	A
Ricin		B
Trichothecene mycotoxins		

In its broadest sense, biological threats include deadly or incapacitating epidemics generated by the emergence of new pathogens through both natural mutations and sinister or inadvertent human intervention. Thus the problems that bioterrorism presents are common to the issues that the medical community has faced for as long as humans have existed. Seen in that context, the identification and solution of the problems for the biological threats is part of a much broader effort to control infectious disease.

Table II. Worldwide Development of the Weapons of Bioterror					
Agents	**Russia**	**Iraq**	**Japan**	**South Africa**	**US**
Viruses					
Lassa fever					
Crimean-Congo hemorrhagic fever					
Rift Valley fever					
Bolivian hemorrhagic fever					
Venzuelan equine encephalitis					
Ebola					
Marburg					
Yellow fever					
Camelpox					
Smallpox					
Rabies					
Bacteria					
Anthrax					
Typhus					
Glanders					
Melioidosis					
C. perfringens					
Plague					
Tularemia					
Q fever					
Psittacosis					
Cholera					
Toxins					
Aflatoxin					
Botulinum toxin					
Ricin					
T2 Toxins					
Staphylococcal enterotoxin B					
Superbugs					
Antibiotic-resistant anthrax.					
Tularemia - drug resistant					

Yellow = researched Red = weaponized
Blue = developed Green = assassination weapon

Many people may feel that the federal government is overreacting to recent events. A simple examination of Table II shows that a large number of the agents on the select list have in fact already been weaponized in countries around the world.

The threat is therefore very real, both in terms of magnitude as well as diversity. Many infectious agents or biological toxins could be engineered for deliberate use as a weapon. Numerous organisms are available but most are not widely used as biological weapons – yet! The large-scale effects of these agents, if released as biological weapons, are largely unknown, hence the fear of what they could do in the wrong hands. Experts in the field believe that anthrax, botulism, plague and smallpox pathogens are most likely to be used; however this may be precisely why terrorists would try to use some other organisms or toxins for which we are unprepared.

Aethlon Medical's technology should prove to be capable of treating exposure to many of these agents, which are resistant to treatment by more traditional methods.

Problems with Current Treatment Options

As recent events have highlighted, there are many problems, both theoretical and practical, with current efforts to defend against biological threats. The truth is that no adequate treatments exist for many of the known weapons, let alone those which might easily be developed. Even when effective vaccines or therapies are available, shortages of drugs or the failure to use vaccines prior to an attack may seriously limit our ability to prevent or otherwise respond to an outbreak. More important is the fact that a wide range of pathogens that can be employed by a relatively unsophisticated terrorist for which no real prevention treatment options exist.

The problem with developing new therapeutics is that they take too long to get approved. To illustrate the point, consider the current treatment options for Biodefense.

Antibiotics and Anti-Viral Drugs

Antibiotics are the most immediately available first line of therapy for bacterial infections. Unfortunately, bacteria, previously controlled through the application of antibiotics, are developing widespread resistance to available treatments. Several bacteria have become completely resistant to many existing antibiotics and developing new antibiotics is a long, time consuming process. In addition, problems of availability in sufficient quantities, which antibiotics are appropriate to use, efficacy against the particular organism, adverse reactions, timely initiation of therapy and completion of treatment regimens.

For viral infections, specific drugs can be effective, but there are no drugs that are effective against the broad-spectrum of known pathogenic viruses. At present, only a few antiviral drugs are available to treat the multitude of viruses that may be used as biological weapons. For example, Ribavirin is the treatment of choice for certain hemorrhagic fever viral infections, but has no current application to Ebola and Marburg infections. Some newer antiviral drugs such as Cidofovir have shown significant promise in animal models, and limited case reports in humans are encouraging. The lack of broad-spectrum antivirals takes on added significance in light of the ability of many viruses to rapidly develop resistance. One need look no further than AIDS to see both the need and the problem.

Current efforts to define the genetic details of normal and pathogenic agents on a molecular level promise the hope for new points of attack. Genomic analysis of the viral pathogen and the animal model response to infection provides valuable information enabling the development of novel treatment and prevention strategies. However, even the rapid elucidation of the genetic structure of a specific pathogen does not provide sufficient information to design an effective cure. For example, while SARS has been known for more than a year and several strains have had their complete genetic sequence determined, no effective treatment has yet emerged.

One promising approach in drug development has been the advent of combinatorial chemistry, which provides the ability to rapidly synthesize huge libraries of related compounds, many of which have never been seen before. However, the real roadblock to progress is the need to laboriously screen each new compound for efficacy in fighting a particular disease. In that sense, combinatorial drugs confront the same problem as the traditional method of screening of plant and animal extracts for active compounds that block viral or bacterial replication.

Thus while science can radically increase the number of drug candidates, the slow step will always be showing that they are both effective and safe. And more to the point, even effective new drugs represent an irresistible selective pressure on natural and un-natural pathogens to develop resistance, something at which they are clearly very efficient.

Vaccines:

Historically, our most effective tool in controlling infections have been vaccines. Polio, measles, mumps and many other viral illnesses are now controllable and smallpox has been eradicated from nature. Licensed vaccines for hemorrhagic fever viruses are limited to yellow fever (though others are in the trial phase of approval). Promising vaccines are being tested for some of the other diseases, but research is hampered by the need to conduct the studies in secure laboratories.

There are other problems with relying on vaccines as our primary protection against a biological weapons attack. While vaccination may be an effective prophylaxis in a military setting, it would not work for civilian populations for several reasons:

- For vaccination to be effective, the target populate must be known and limited. Expense and logistical challenges would make it virtually impossible to vaccinate the entire population of the United States against even a single agent.

- The agent used would have to be known prior to its deployment. With the exception of the smallpox vaccine, vaccination is of no use post-exposure to a pathogen.

- Even if every person in the United States could be vaccinated, it would be impossible to vaccinate him or her against every agent for which a vaccine is available.

- Even if a vaccine is available, it would only be useful if the agent involved has not been genetically altered so that it is drug or vaccine resistant.

Vaccines that are both efficacious and safe are notoriously difficult to develop. History has shown that developing vaccines can be a slow process and may not even be possible for highly mutable pathogens like HIV and Hepatitis C. Moreover, current vaccine strategies often carry significant risk for complications. For example, smallpox vaccine, which uses attenuated strains of a live virus, can occasionally cause illness or death by infection from the very organism that usually provides protection.

In terms of a bioterrorist attack, anthrax vaccine can serve as an example of our capability in treating a well recognized threat. Only one anthrax vaccine, licensed in 1970, is available. This vaccine, produced by the Bioport Corporation, consists of a membrane-sterilized culture filtrate of an avirulent, non-encapsulated strain of anthrax. The data in support of the license consisted of a single field study. The vaccine efficacy was 92.5% effective in this small trial. In December 1985, 15 years after the vaccine was licensed, the FDA's advisory panel reviewed the efficacy of the anthrax vaccine but did not respond to the effectiveness of the current vaccine to inhalational exposure anthrax infection.

The shortcomings of the current vaccine have spurred studies of new anthrax vaccine products. The new vaccines include protective antigen–based vaccines, e.g., purified protein from *B. anthracis* culture or live-attenuated spore vaccine. One of the immune correlates of protection of anthrax vaccines is likely to be the antibody response to protective antigen. However, the quantitative relation of anti-protective antigen antibody to protection has not been established in humans. The relationship between neutralization of protective antigen and the lethal effects of anthrax is currently being investigated by the Department of Defense.

Because of the difficulties associated with the classic vaccine development, new methods for generating vaccines are being researched. Recombinant DNA technology combined with combinatorial biochemistry is now being employed in an attempt to rapidly identify and develop vaccine candidates and passive immunotherapies. In the phage display system, cloned viral or bacterial proteins, or even cloned antibodies, are individually displayed on the surface of bacterial viruses. Phage proteins can be rapidly screened to find out which ones are the most immunologically reactive. Directed evolution can then be

used to make even more effective antigenic materials. Even better, the best of these are already in a form that can be used to produce enough of the material to test in animals.

The principal drawback to the system is the need to use fermentation techniques to produce sufficient quantities of purified material, uncontaminated by the organisms used to produce them. The amount of material required to inoculate a sizeable population requires large fermentation systems, which are expensive to set up and already in short supply. The restriction on medical fermentation capacity is already so severe that many companies have had to delay offering approved products to the public.

Because of these obvious shortcomings, other methods of mitigating the situation are now being sought. What is urgently needed is a system to treat newly emerging bioweapons' infections that can be developed quickly rather than the years required for drugs and vaccines. Aethlon's Hemopurifier technology is potentially suited to fill many of these needs.

The Hemopurifier as a Solution to Biodefense Problems

Table III. Bioweapons Potentially Treatable Using Hemopurification

Bioweapon	Scientific Name	Lethality (untreated)	Class
Bacterial Toxins			
Anthrax	*Bacillus anthracis*	*10,000-20,000 spores*	A
Tularemia	*Francisella tularensis*	*10-100 organisms*	A
Plague	*Yersinia pestis*	*500-1,500 organisms*	A
Q fever	*Coxiella burnetii*	*1-3 organisms*	B
Brucella	*Brucella*	*100-400 organisms*	B
Typhus	*Salmonella typhimurium*	*No inhalational dose*	B
Glanders	*Burkholderia mallei*	*100-200 organisms*	B
Viruses			
Ebola	*Ebola virus*	*60-90% (3-10 virions)*	A
Smallpox	*Variola major*	*40% (5-100 virions*	A
Marburg	*Marburg virus*	*20-30% (3-10 virions)*	A
Yellow fever		*10-50% (1-10 virions)*	C
Lassa fever		*17% (10-100 virions)*	A
West Nile viruses		15%	B
Venezuelan equine encephalitis		0-10%	B
Dengue			A
Rift Valley fever			A
Toxins			
Aflatoxin		*Potent carcinogen*	
Botulinum/Botulism	*Clostridium botulinum*	*LD_{50} = 0.9µg*	A
Ricin		*LD_{50} = 3 mg*	B
Trichothecene mycotoxins		*LD_{50} = 85 g*	
Abrin		*LD_{50} =3µg*	

While not all potential threats are suitable for treatment, the Hemopurifier platform is well designed to treat many of the most dangerous bioweapons, as depicted in the Table above. Target weapons amenable to treatment using the Hemopurifier approach are those that are distributed to their target organs in the bloodstream. Another requirement is that the organism or toxin be of a size that can pass into the cartridge and be captured. Using current cartridge designs, the only excluded organisms would be blood-borne bacteria and a few very large viruses that are too large to pass through the pores in the membrane inside Aethlon's Hemopurifier. However, most pathogenic bacteria are lethal as a result of potent protein toxins that they produce. These toxins are distributed by the blood and can be captured with very high efficiency.

Based on these considerations, one can define a large number of important potential biowarfare targets for the Hemopurifier. These targets include anthrax and botulinum toxin, smallpox, and hemorrhagic fever viruses. Larger viruses and bacteria such as plague or tularemia can be captured by direct hemofiltration by a modification of the current technique.

Beyond the ability to treat many of the most urgent bioterror threats, Aethlon's biggest asset is its ability to rapidly respond to unanticipated developments and to get those treatments to the people most in need.

Milestones, Timelines and Estimated Costs

Timelines for Treatment Development

The table below projects suggested timelines for the generation and testing of the current targets and a plan for larger pathogenic bacteria. The timelines presuppose the development of a working relationship with government or private agencies capable of handling biowarfare agents.

Biowarfare Agent Development Timelines

Process	2 months	4 months	6 months	8 months	10 months	12 months
Obtain Toxins	Anthrax toxins					
	Botulinum toxin					
Obtain/Grow Cultures	Smallpox purified virus					
Isolate virus stocks		Ebola (Reston) purified virus				
		Marburg - purified virus				
			Plague surface proteins			
			Tularemia surface proteins			
Develop/Obtain antibodies		Anthrax toxins Antisera				
		Botulinum toxin antiserum				
			Smallpox surface proteins MAb			
				Plague surface proteins MAb		
				Tularemia surface proteins MAb		
Build/Test Hemopurifier	Develop Hemofiltration polymer					
			Anthrax (Antisera) - guinea pigs			
			Botulinum toxin (Antiserum) - guinea pigs, dogs			
				Ebola (Reston) - lectin capture - guinea pigs, monkeys		
				Marburg - lectin capture - guinea pigs		
					Smallpox - antibody capture, monkey	
					Plague - antibody capture, guinea pig	
						Tularemia - rabbit

Strategic Issues

The strategic issues Aethlon faces in implementing a Biodefense program include:

- Complete manufacturing agreements that allow for mass deployment the Hemopurifier cartridges.
- Partnering with the Department of Defense, The National Institutes of Health, and other government agencies as a means to fund product development.
- Partnering with existing biocontainment facilities such as Fort Detrick and the Centers for Disease Control or independent biocontainment facilities such as those available at the University of California at Davis to perform the animal studies in BSL-4 maximum containment.

Summary and Conclusions:

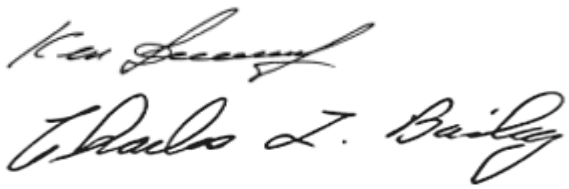
Aethlon's Hemopurifier technology provides an exciting and important method for treating a variety of infectious diseases. The potential of the Hemopurifier has been demonstrated in pre-clinical trials where, among others, HIV, Hepatitis C virus and related protein toxins have successfully been removed from infected blood. The need for such a technology has never been greater as the threat of biological weapons (such as anthrax and smallpox) and newly emerging infectious diseases (such as SARS) grows daily.

We believe that the Hemopurifier will be an essential tool in the country's biodefense arsenal. Aethlon's Hemopurifier offers several key advantages, among them rapid product development and deployment. Compared to traditional treatment methods such as drugs and vaccines, the time between tailoring Hemopurifier cartridges to deploying them is drastically reduced. The Hemopurifier is also easy to use in civilian intensive care units as well as on the battlefield. It is compact enough to potentially allow patients being treated with the Hemopurifier to participate in restricted activity.

The market for novel technologies has grown substantially in recent years, and this trend will surely continue. The recent anthrax attack and emergence of SARS have driven the federal government to dramatically increase spending for the biodefense effort. The projected budget for civilian biodefense funding alone (through various agencies within the Department of Health and Human Services, the Department of Homeland Security, and the Department of Defense) in FY 2005 is an astounding $7.6 billion. Recent growth, in terms of the number of companies and revenue, in the research intensive biotechnology industry exemplifies the potential that innovative and proven technologies can achieve.

Technology that can be used against agents that have been or could be developed into biological weapons is particularly desirable. Biological weapons pose a substantial threat because they are relatively inexpensive and easy to produce, and if they are deployed in even a small amount, they can have catastrophic results. A significant number of biological agents have already been weaponized by countries such as the former Soviet Union, Iraq, Japan, South Africa, and the United States. Aethlon's Hemopurifier is capable of treating many of the infections, such as anthrax, tularemia, smallpox, and botulinum and ricin toxins, that would result if these weapons were ever deployed.

Our current treatment options for many of the diseases that could result from a biological weapons attack are grossly inadequate. The growing number of antibiotic resistant bacteria, the lack of effective anti-viral drugs, and the enormous amount of time and money that is necessary to develop new drugs and have them approved all create a huge void in the medical countermeasures available to respond to a biological attack. Prophylactic measures such as vaccines are also ineffective for various theoretical and logistical reasons. Through its Hemopurifier, Aethlon is poised to fill a significant part of this void, thus strengthening our ability to treat victims of a bioterrorist attack and saving countless lives.



About the Authors:

Dr. Ken Alibek, Executive Director of Education, National Center for Biodefense

Dr. Kenneth Alibek, the Executive Director of Education for the National Center for Biodefense (NCBD), is the former First Deputy Director of the Biopreparat, the Soviet Union's offensive biological weapons program. Dr. Alibek has extensive knowledge of multiple biological weapons agents and is dedicated to developing new forms of protection against biological weapons and other infectious diseases. As a result of his expertise in this field, Dr. Alibek has consulted with and testified for numerous government agencies. Dr. Alibek holds a M.D., a Ph.D. in Microbiology, and a Sc.D. in Biosciences/Biotechnology and currently serves as a Distinguished Professor of Medical Microbiology and Immunology at GMU.

Dr. Charles Bailey, Executive Director of Research, National Center for Biodefense

Dr. Charles Bailey is a specialist in infectious diseases at George Mason University. His primary role is Executive Director of Research for the University's National Center for Biodefense, with an ancillary role as Distinguished Professor of Biology. Dr. Bailey networks with government leaders and contractors in the biodefense and homeland security arena in funding development. Dr. Bailey spent 25 years in both research and development and in managerial roles for the U.S. Army in the field of infectious diseases and biological warfare defense. Over a continuous 13-year period, he served as a research scientist, deputy commander for research, deputy commander and commander at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID).

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About Aethlon Medical:

Aethlon Medical is pioneering the development of viral filtration devices to treat HIV/AIDS, Hepatitis-C (HCV), and pathogens that are mass casualty biological warfare candidates. Each treatment application employs the use of a proprietary technology known as the Hemopurifier™, which is designed to rapidly reduce the presence of infectious disease and toxins in the body. The Hemopurifier converges the established scientific principals of affinity chromatography and hemodialysis as a means to augment the immune response of clearing viruses and toxins from the blood before cell and organ infection can occur. More information is available at www.aethlonmedical.com.

Aethlon Medical Contact:

James A. Joyce
Chairman, CEO
3030 Bunker Hill Street, Suite 4000
San Diego, California 92109

Email: jj@aethlonmedical.com
Phone: (619) 459-7800 x301
Mobile: (619) 368-2000