BIOTERRORISM BY BIOTECHNOLOGY: IMPLICATIONS FOR CLINICAL MEDICINE

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Contents

Summary

Advancement in the field of biotechnology has lead to the genesis of novel biological weapons **[**see also *Biowarfare and Bioterrorism*]. This article reviews biotechniques involved in the development of altered bioweapons and the next generation clinical countermeasures effective against them. The arsenal of advanced bioweapons is

complex and difficult to disarm. Rapid strides in biotechnology have made high level techniques affordable and accessible. Consequently, rampant proliferation in bioweaponeering is anticipated. Potential difficulty in confirmatory diagnosis and medical management of deliberately altered microbes could be addressed, by employing a new level clinical approach. Clinicians, health care personal and first responders would benefit from considering the possibility of genetically engineered organisms while dealing with any outbreak or epidemic. A new innovative set of anti-infectives, molecular approaches, vaccines and adjuvants have been synthesized using biotechnology and some are in development. Research in areas of medical biotechnology along with familiarity of biologically modified organisms, might be the crucial step in managing and preventing bioterrorism.

1. Introduction

Bioterrorism is the intentional dissemination of a biological agent or its toxins, intended to kill or incapacitate the target individual or population. A disease causing microbe or its components can be used as an instrument of terror. The uniqueness of 21st century bioterrorism is that it has evolved to be more complex and sophisticated due to nefarious exploitation of recent advances in biotechnology. Compared with nuclear weapons, which have to face ongoing disarmament and control programs, biological weapons continues to proliferate due to its stealth nature. The initial design of medical management is to administer routine antibiotics and vaccines. However, the potential for deploying genetically modified organisms, as a result of universal access to biotechnology and microbiology, calls for more advanced clinical counter measures.

Paradoxically, the very same technology which aids in bioweapons creation also plays the most crucial role in manufacturing new generation antidotes, vaccines and other therapies. There is a strong prediction among civilian and military biofense communities, that in the near future a bioterrorist event is imminent. Bioterrorism also forms the main arm of asymmetrical warfare and stands out as a possible option due to its low cost of production and the disproportionate damage it can evoke. One of the main aims of clinical management is to create state of the art sustainable counter measures against the perceived bioterrorist threats involving novel agents. It's an encouraging trend that the policy to fast track clinical trials and permit early availability of experimental molecules and vaccines has been adopted by drug regulation agencies. Initiatives like project biosheild, journal restriction protocols, controlled sale of dual use equipments, awareness creation, limiting select agents, health care training, stockpiling antidotes etc have greatly enhanced biosecurity and biodefense levels.

2. Biotechniques in Bioweaponeering

Covert science and open access to biotechnology makes confronting biologically modified bioweapons a formidable task. History of bioterrorism predates the birth and evolution of microbiology and biotechnology. But recent advancement in laboratory techniques, permit endless creation of designer bioweapons. While, infectious disease modeling and computational biology helps in overcoming lengthy animal testing procedures. Intertwining of legitimate research with offensive research helps in defying detection. As with any technological advancement, biotechnology has a sinister side

which is comparatively difficult to identify and prohibit. There is a consensus among biodefense experts that creating awareness of the biohazards could be the first step in preventing proliferation. The following parts of the article, illustrates the nature of the problem by highlighting techniques which could be adopted to create novel bioweapons. Some of the techniques have already found application in bioweaponeering and others might be considered in the future.

2.1. Genetic Engineering

The advent of genetic engineering has opened a new era in creating and experimenting with biological weapons. Recombinant rDNA technology and gene splicing offer unprecedented control in the manipulation and modification of an organism [see also *Genetic Manipulation of Bacteria*]. Genetically altered microbes find wide application in medicine and science. At the same time biotechnology could be utilized to produce pathogens with characteristics previously not encountered. A bioweapon created employing such methods would exhibit increased virulence, modified transmission dynamics, evasion of human immune system and could be rendered refractory to currently available therapies.

Reports emerging on such efforts indicate antigenically altered *Bacillus anthracis* resistant to a spectrum of recommended antibiotics including Ciprofloxacin and Doxcycline. Antibiotic resistant genes inserted into regular disease pathogens make them impossible to treat with conventional antimicrobials. Similarly, recombinant *Orthopox viruses* constructed by insertion of foreign genes will be resistant to any mass vaccination attempts. Genetically modified *Filoviruses* poses a greater threat, due to its mortality rate and lack of effective therapies or vaccines. Weaponization of these agents (*Ebola, Marburg)* will make them almost impossible to contain. Experimental vaccines and antidotes might not be widely available and would be inaccessible to most of the global population.

Francisella tularensis a category -A agent (the causative organism of Tularemia) which posses a very high infectivity potential was further genetically modified to be hypervirulent. This eventually lowered the minimum dose of organism required for infectivity. *Bacillus thuringiensis* is widely used in biotechnology and a common industrial microbe carrying antibiotic resistant plasmid. This antibiotic resistant plasmid, introduced into *Vibrio cholerae* by transfection using a suitable bacteriophage vector system, will render the strain of cholera multidrug resistant.

Altering virus envelope proteins extends the host range and modifies target cell tropism. Widely found animal viruses have been manipulated to target human cells. Modification of feline *Coronavirus* viral envelope spike glycoprotein using targeted RNA recombinant technology resulted in a strain which switched species tropism. Certain bacterial enzymes can induce resistance and neutralize beta-lactam antibiotics. Using DNA shuffling technique on recombinant *β-lactamase* enzyme has shown to create enzymes which are thousand fold more potent. This kind of compounds would exhaust the existing armamentarium of *β-lactam* antibiotics. A range of designer microbes could be created with the tools of biotechnology which are rapidly advancing and accessible to many bioweaponeers.

2.2. Synthetic Biology

In this century, laboratory based chemical synthesis of primitive life forms like a bacteriophage *Φ x 174* and *Polio* virus have been successful. Large scale genome synthesis has been possible by biotechnology techniques like oligonucleotide synthesis, DNA sequencing and amplification. The potent risk of deliberate use and release of such organisms into the environment and population are high. With a huge biotechnology sector involved in synthesizing efforts, like the genomes of eukaryotic life forms (i.e. bacteria, viruses and rickettsiae) this emerging tool offers an unprecedented biosecurity threat. Harnessing this new biological system for legitimate medical and industrial purpose is permitted, at the same time the potential danger of dual use cannot be overlooked.

Several repositories offer biobricks or sequences of DNA which could be used as building blocks to fabricate the genome of an entirely new organism using various design protocols. Synthetic biology aids in custom creation of weapons grade pathogens with unique properties, morphology and replication patterns. A new synthetic species of microbe will greatly change the equation in the medical therapeutic arena. As antidotes and vaccines are only created and stockpiled for known organisms and their disease outcomes.

2.3. Nanotechnology

Advancement in material science and biotechnology has lead to the fabrication of micro-encapsulated organisms using poly DL-lactide-co-glycolide microspheres, liposomes, nanomaterials, silica and polymers. This increases the environmental survival of biological weapons which would other wise be degraded by the action sunlight, wind, temperature and humidity.

Furthermore, the application of nanobiotechnology [see also *Nanomedicine and Medical* Nanorobotics] for engineering biological weapons opens pathways for an entirely new class of biology based nanoweapons. They could be self-replication or non-replicating, remotely operable and extremely destructive. The current availability of such technologies and rapid advances in nanoscience, poses a new level of threat previously unseen.

2.4. Dual Agent Fabrication

These groups of novel bioweapons display unique properties. They are engineered by manipulating the genome of a microbe through insertion of an alien gene to perform different set of functions, which is not a part of the organism's characteristics. For example, *Yersinia pestis* (the causative agent of plague) expressing *epsilon* toxin under the control of antibiotic-induced expression system is a classical example of a dual agent. The administration of antibiotic chemotherapy could be counterproductive as this type of weapon multiplies in the presence of antibiotics.

Genetically modified *Legionella pneumophila* strains, that expresses human myelin protein which elicits an immune response directed against nerve myelin, has been

successfully created in the laboratory. The use of this type of agent could lead to complete demyelination of the human nervous system followed by complete paralysis and death. A recent legitimate scientific research produced recombinant mousepox virus *Ectromelia* with inserted genes that expressed mouse *IL-4*. This helped in overcoming the vaccine induced immune response. If the same methods are applied for smallpox virus *Variola major*, it would have catastrophic consequences even among vaccinated population. Many of the biodefense efforts like mass vaccination could be effectively countered.

2.5. Bioregulators Production

Naturally occurring endogenous chemical compounds which have profound effect on human physiology by affecting several regulatory biochemical pathways, have shown to be potential biological weapons. Some of the well established bioregulators are cytokines, neurotransmitters, vasoactive amines, synthetic hormones, eicosanoids, plasma proteases and nucleotides. Bioregulators can have a range of toxic effects on the cardiovascular, gastrointestinal, neurovascular and immune systems leading to incapacitation and death in minutes.

Traditional bioweapons like bacteria and viruses require time for incubation while bioregulators have a rapid onset of action. Their presence in miniscule amounts prevents detection in standard forensic assays. The clinical manifestations are varied, compared to the expected symptoms in the algorithms of biodefense syndromic surveillance systems. The management becomes complicated as most of these agents are not included in the standard list of bioweapons. Vaccination and antidotes will be ineffective or theoretically impossible against this group of endogenous compounds. Bioregulator genes could be cloned in a bacterial plasmid or a viral vector as a modified delivery system. Further, various industrial biotechnology methods contribute to the large scale synthesis of this new class of non-traditional biological weapons.

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His present work is concerned with Management and research on public health human virology