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ScienceDirect
Antiviral Research 77 (2008) 1–5
Antiviral Research
www.elsevier.com/locate/antiviral

Review

# Discovery and development of antiviral drugs for biodefense: Experience of a small biotechnology company

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Received 13 June 2007; accepted 16 July 2007

**Abstract**

The unmet need for effective antivirals against potential agents of bioterrorism and emerging infections is obvious; however, the challenges to develop such drugs are daunting. Even with the passage of Project BioShield and more recently the BARDA legislation, there is still not a clear market for these types of drugs and limited federal funding available to support expensive drug development studies. SIGA Technologies, Inc. is a small biotech company committed to developing novel products for the prevention and treatment of severe infectious diseases, with an emphasis on products for diseases that could result from bioterrorism. Through trials and error SIGA has developed an approach to this problem in order to establish the infrastructure necessary to successfully advance new antiviral drugs from the discovery stage on through to licensure. The approach that we have taken to drug development is biology driven and dependent on a dispersive development model utilizing essential collaborations with academic, federal, and private sector partners. This consortium approach requires success in acquiring grants and contracts as well as iterative communication with the government and regulatory agencies. However, it can work as evidenced by the rapid progress of our lead antiviral against smallpox, ST-246, and should serve as the template for development of new antivirals against important biological pathogens.


*Keywords:* Antiviral; Drug development; Smallpox; Hemorrhagic fever virus; Category A; Biothreat agents

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## 1. Introduction

Highly pathogenic viruses such as Ebola and variola pose a significant threat to human health, yet in most cases, therapies to prevent or treat these diseases are lacking. Project BioShield was put forward in 2004 by the U.S. President George W. Bush to help address this issue by expediting research and development of medical countermeasures against biothreat agents. In theory, this legislation gives the Food and Drug Administration (FDA) the ability to make promising treatments available quickly in emergency situations, and ensures that resources are available to pay for "next-generation" medical countermeasures. Project BioShield is a comprehensive effort overseen jointly by the Department of Health and Human Services (DHHS) and the Department of Homeland Security (DHS) with involvement from other federal agencies, including the Department of Defense (DOD), as appropriate. Recognizing the limitations of BioShield, additional legislation was passed in 2006 to help drug companies to bridge the "Valley of Death", the crucial middle phase of drug development between basic research and the acquisition of final products, which includes many of the late stage development activities required to support a New Drug Application (NDA). The Biomedical Advanced Research and Development Authority (BARDA) was created to facilitate col-

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doi:10.1016/j.antiviral.2007.07.003

laboration between companies and the federal government and to promote innovation. These measures are helpful, but there is still a significant disconnect between recognizing what needs to be done and actually accomplishing it in a timely fashion. We are committed to trying to bridge this gap. In the sections below, we will discuss the major challenges to develop these new antivirals and the approach we have taken for the development of new therapeutics against Category A viral biothreat agents.

## 2. Challenges to development of antivirals for biothreat agents

The first challenge that drug developers face is the paucity of available information about many of these exotic pathogens. Because these are primarily tropical diseases, endemic in developing countries, relatively little research attention and funding has been focused on them until recently. The hemorrhagic fever viruses are commonly lumped together into a group of "similar" diseases caused by four very different types of viruses: arenaviruses, bunyaviruses, filoviruses, and flaviviruses. While it is true that the clinical symptoms produced by these viruses are similar, each of the viruses has a different genome and replication strategy, so it is highly unlikely that a single drug will be developed that can treat all of these diseases.

Most of these pathogens require biosafety level 4 (BSL-4) containment, which is in short supply and has limited access. One alternative that is being explored is the use of surrogate viruses (e.g. Tacaribe instead of Junin, for the New World arenaviruses) that requires lower levels of bio-containment. This can be useful, but both granting and regulatory agencies consider the authentic pathogen as the "gold standard" for demonstrating therapeutic efficacy. A second alternative is the development of pseudotype virus assays or replicon systems, in which the envelope proteins of a pathogen enwrap a non-replicating genome expressing a convenient reporter gene, a "sheep in wolf's clothing". Although suitable for use in BSL-2 laboratories and amenable to high throughput screening, the limitation of these systems is that they are not live viruses in the truest sense and may not allow certain virus functions to be recapitulated as drug targets.

Work with the authentic agents requires BSL-3 or BSL-4 facilities, which are available in only a few locations in the U.S.: the United States Army Medical Research Institute for Infectious Diseases (USAMRIID), University of Texas Medical Branch (UTMB) Galveston, Southwest Foundation for Biomedical Research (SFBR) and the Centers for Disease Control and Prevention (CDC). Even more restrictive is the limited space available in which to conduct BSL-4 animal studies. This is a particular problem with non-human primates, which will likely be required for product licensure. Current facilities can only handle a small number of animals which limit the experiments that can be done and the statistical significance of the results obtained. Recognizing this problem, the National Institute of Allergy and Infectious Diseases (NIAID) is providing funding to build two new National Biocontainment Laboratories, one at Boston University and one at UTMB Galveston, both of which should be ready near the end of 2008. NIH is also building a new BSL-4 facility in Frederick, MD, next to USAMRIID at Fort Detrick that will be completed in 2008. The criteria for access to these facilities are not easily defined. The first and foremost requirement is money to fund the studies, followed by the scientists who are willing to work on the appropriate select agent and develop appropriate animal models. After that it is a matter of politics; what is the high profile agent of choice, is the particular government agency interested in it, have you proven that the small molecule is worthwhile and ready to be tested in animals? Insurance that these resources are effectively being used is of utmost importance.

As mentioned previously, there have been several animal models developed using surrogate BSL-2 and BSL-3 RNA viruses, but efficacy studies against the actual pathogens in BSL-4 will likely be required by the FDA for approval of a new therapeutic. Appropriate animal models will need to be developed and validated for each pathogen which will require finding the appropriate animal species and collecting enough natural history of infection to support their use in regulatory applications. Also, the chosen animal models will need to recapitulate human disease as closely as possible. This will involve obtaining disease information on infected humans, which is quite rare for some viruses; furthermore natural outbreaks of these diseases mainly occur in undeveloped countries which have limited surveillance and epidemiology capabilities. Another nuance of the animal models is the delineation of what point of intervention constitutes prevention versus treatment. Answers to these questions will greatly impact what indication a new antiviral drug receives from the FDA.

RNA viruses have relatively high mutation rates (around 1 per genome per replication event) because they lack proof-reading capacity in their replicases. In contrast, DNA viruses have considerably lower mutation rates (approximately 0.003 per genome per replication event) due to the proof-reading ability of DNA polymerases within the host cell. This trait predicts that RNA viral pathogens will be able to rapidly evolve resistance in the presence of antiviral drug selection. Thus, treatment for RNA pathogens may require combination of therapeutic modalities or the use of antiviral drugs that circumvent resistance, i.e., where induced mutations render the resistant virus less fit and unable to productively produce an infection. Combination therapy comes into play when the antiviral is used long term for chronic diseases such as the case of human immunodeficiency virus (HIV) treatment or in the event that the drug had to be given prophylactically for a long period of time. One would not expect acute use of an antiviral to produce significant resistance problems.

The clinical development pathway for antivirals against biothreat agents is convoluted, to say the least. Since most of these pathogens are not endemic in the United States and may be rare even in endemic areas, it is difficult to perform human efficacy studies with clinical rigor. Recognizing this problem, the FDA developed the Animal Rule (21 CFR 314.600). The FDA Animal Efficacy Rule (finalized May 2002) applies to the development/testing of drugs/biologicals to reduce or prevent serious/life-threatening conditions caused by exposure to lethal/permanently disabling toxic agent (chemical, biological, radiological, or nuclear substances), where human efficacy trials