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**Biodefense Market Report: Vaccines,
Therapeutics and Diagnostics for
Bioterror Agents**

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Chapter 8. Arenaviruses

Background

The arenaviruses are a family of rodent-borne RNA viruses endemic to specific geographic regions around the world. Viral particles are spherical with an average diameter of 110 to 130 nanometers, and they are enclosed in a lipid membrane. Each individual arenavirus is associated with a specific rodent host. For example, Lymphocytic choriomeningitis virus (LCMV) is carried by the common house mouse, *Mus musculus*, and Lassa virus is transmitted by the “multimammate rat” of the genus *Mastomys*.

Incidence

Arenaviruses that infect humans and the resulting diseases are shown in Table 11, along with the geographic region of infection and the incidence of infection.

Table 11. Arenaviruses that infect humans

Virus	Disease	Geographic Region	Incidence
Lymphocytic choriomeningitis virus (LCMV)	Lymphocytic choriomeningitis	Europe, N. and S. America, Australia, Japan	Historically underreported, approximately 2-10% of urban dwellers have serologic evidence of past infection
Lassa virus	Lassa fever	West Africa	100,000-300,000 per year
Junin virus	Argentine hemorrhagic fever	Agricultural regions of Argentina	Less than 100 cases per year since widespread immunization began
Machupo virus	Bolivian hemorrhagic fever	Beni province of Bolivia	Sporadic epidemics in Bolivia, most recently 1994 with 9 cases
Guanarito virus	Venezuelan hemorrhagic fever	Guanarito region of Venezuela	Intermittent epidemics and intermittent cases. Most recent epidemic in 1990 with 104 cases and 26 deaths
Sabia virus	Brazilian hemorrhagic fever	Brazil	3 cases reported worldwide since discovery in 1994, 2 of which were laboratory infections

Arenaviruses typically infect humans who have come into contact with contaminated excretions of infected rodents, either through ingestion of contaminated food or by direct contact with

broken skin. Additionally, aerosol transmission of small particle aerosols of virus has been reported from both rodent vectors and infected humans. A few arenaviruses, such as Lassa virus and Machupo virus, also spread person-to-person by direct contact with blood or excretions containing viral particles in home or health care settings.

Some arenaviruses, such as LCMV, can cause meningitis, encephalitis and meningoencephalitis while others, such as Lassa virus, can cause hemorrhagic diseases. The mortality of arenaviruses is generally low, 1 to 10 percent, although during epidemics, mortality can reach 50 percent. LCMV infections have a mortality of less than one percent. Hospital admissions are required for LCMV patients with meningitis and encephalitis, although only supportive care is generally given. Lassa fever is normally mild or asymptomatic in 80 percent of people infected with Lassa virus, with a mortality of less than one percent, although 15 to 20 percent of patients admitted to hospitals for Lassa fever eventually die. Treatment for patients with Lassa fever includes administration of ribavirin, an antiviral drug, and supportive care. A live attenuated Junin viral vaccine has been successfully administered in Argentina, reducing the number of cases of Argentine hemorrhagic fever to less than 100 per year. Ribavirin may be used to treat Argentine hemorrhagic fever as well as Machupo, Guanarito and Sabia viral infections.

Because the symptoms of infection with arenaviruses in the early stages, including fever, malaise, headache, muscle ache, nausea and vomiting, are common to many infectious diseases, cases of arenavirus infection are often undiagnosed and are probably underreported. However, in the U.S., even one case of an arenaviral infection without travel to a region with endemic infection or known contact with a victim from an affected area may represent an act of terrorism. The CDC classifies arenaviruses as Category A agents, the highest priority, for possible use in bioterrorism.

Companies and Institutions with Products in Development

Table 12 lists the companies and universities with products in development as vaccines or therapeutics against arenaviruses. Individual product development details are given in the text following the table.

Table 12. Products in development for arenaviruses

Company/Institution	Product Name	Progress
Crucell NV	Lassa virus vaccine	Preclinical
Cyntellect Inc.	Thioaptamer viral hemorrhagic fever therapy	Preclinical
Idenix Pharmaceuticals Inc.	Hemorrhagic fever virus inhibitor research program	Preclinical
Peregrine Pharmaceuticals Inc.	Antiviral agent research program	Preclinical
SIGA Technologies Inc.	Biodefense antiviral research program	Preclinical
University of Buenos Aires	Junin virus brassinosteroid analogue	Preclinical
University of Buenos Aires	NSC 20625	Preclinical

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Crucell and the NIAID's Dale and Betty Bumpers Vaccine Research Center (VRC) entered a CRADA in May 2002 to develop an Ebola vaccine. This agreement was expanded to include vaccines against Marburg virus and Lassa virus in August 2002. Under the agreement, NIAID researchers provided Crucell with modified Ebola, Marburg and Lassa genes that are nonpathogenic. Crucell announced in March 2005 that the CRADA with the NIAID had been extended. In the extended CRADA, Crucell and the VRC will continue to develop the Ebola vaccine and use results derived from it in the development of Marburg and Lassa vaccines. The NIAID will provide funding for experiments performed at the VRC and for animal studies performed at USAMRIID. Crucell has the option for exclusive global commercialization rights to the resulting vaccines.

In October 2002, Crucell signed a manufacturing contract with NIAID's VRC. The manufacturing contract was expected to last for two-and-a-half years. Under the terms of the agreement, Crucell will manufacture clinical grade vaccines for Lassa, Ebola and Marburg viruses. These vaccines will utilize Crucell's AdVac adenoviral vaccine technology and will be produced in Crucell's PER.C6 human cell line.

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Cyntellect was spun out of Oncosis Inc. in May 2002. In August 2002, the company announced that it had been awarded an SBIR grant for collaborative research with faculty at the University of Texas Medical Branch at Galveston. The grant funds research on the effectiveness of anti-NF- κ B thioaptamers against bioterror agents. Thioaptamers are chemically modified DNA decoys. Cyntellect will use its proprietary LEAP technology for high throughput screening of a library of thioaptamers. LEAP loads cells with thioaptamers using laser-based techniques, then screens the injected cells to identify active thioaptamers. Cyntellect reported improved survival in an animal

model of arenavirus-induced hemorrhagic fever following pretreatment with a candidate thioaptamer.

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Idenix, formerly known as Novirio Pharmaceuticals Ltd., announced a collaboration with the Paris, France-based Institut Pasteur in February 2002. Institut Pasteur planned to evaluate Idenix's proprietary library of compounds against Ebola, Marburg and Lassa viruses. Institut Pasteur conducts research on arenaviruses in the Jean Mérieux BSL-4 laboratory that is located in Lyon, France. This facility has been administered by INSERM since 2004. Idenix's principal disease targets include hepatitis B, hepatitis C and HIV/AIDS

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In November 2003, researchers at the University of Texas Southwestern Medical Center at Dallas received a \$1.68 million grant from the NIAID to examine Peregrine's anti-aminophospholipid antibodies as a potential treatment for Lassa fever. The antibodies direct an immune response to phospholipids in the viral envelope. Arenaviruses were selected as the primary target, but the anti-aminophospholipid antibodies could be effective against other viruses with similar viral envelopes, including smallpox and avian flu. Peregrine was looking for partners for its Lassa fever program in October 2005. One of Peregrine's monoclonal antibodies, Tarvacin, was effective in a rodent model of Pichinde virus, which is an established model for

Lassa fever. A Phase I clinical trial of Tarvacin for the treatment of patients with chronic hepatitis C was initiated in August 2005.

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SIGA acquired selected antiviral programs from ViroPharma Inc. for \$1 million in cash plus one million shares of SIGA common stock in June 2004. The programs included lead compounds, assays and scientific knowledge related to the development of antiviral drugs, including drugs targeting smallpox and hemorrhagic fever viruses. In August 2004, SIGA announced that the NIH awarded it two grants for a total of approximately \$12 million to support the development of the antiviral program acquired from ViroPharma. The grants specifically support the preclinical development of antiviral products targeting smallpox and arenaviruses, and drug discovery programs for other hemorrhagic fever viruses including Ebola. In March 2006, SIGA and PharmAthene Inc. (Annapolis, Md.) announced plans to merge. The resulting company will operate under the name PharmAthene and focus on biodefense products.

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Wachsman et al. published “Antiviral effect of brassinosteroids against herpes virus and arenaviruses” in the journal *Antiviral Chemistry and Chemotherapy* (2000 Jan;11(1):71-7). The article reported that a natural brassinosteroid and a series of synthetic derivatives were potent inhibitors of arenavirus replication in cell culture. Arenaviruses were susceptible to the brassinosteroid compounds throughout replication.

The University of Buenos Aires is also evaluating NSC 20625, a zinc finger antiretroviral agent that originated at the NIH National Cancer Institute.