



Corporate Profiles

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Lentiviral Vector Assists Gene Therapy **VIRxSYS's HIV Treatment Highlights the Potential of the Approach**

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VIRxSYS (www.virxsys.com) is developing a unique technology that is advancing both gene therapy and HIV treatment. VRX496 uses a lentiviral vector to deliver a payload to block the replication of HIV. In a recent Phase I trial, VRX496 suppressed viral loads and restored the immune system responses in chronic HIV patients. "This is an important milestone in the development of what we believe could be the next generation of HIV therapy," says Riku Rautsola, Ph.D., president and CEO of VIRxSYS.

VRX496 is the first and only lentiviral vector therapy approved by the FDA for clinical trials, according to VIRxSYS. The backbone of VRX496 consists of a genetically engineered version of HIV in which all the infectious components are removed and replaced with the therapeutic payload—a long antisense sequence that targets the HIV envelope protein and cripples the virus.

Preclinical studies show that HIV is unable to mutate around VRX496, which should prevent the formation of resistant strains. "We have seen no resistance develop to our therapy in vivo or in vitro," says Gary McGarrity, Ph.D., executive vp of scientific and clinical affairs at VIRxSYS.

Successful Phase 1 Results

VRX496 is an autologous therapy that uses a patient's own cells. Clinical sites collect white blood cells from individual patients by apheresis. VIRxSYS scientists purify the white blood cells to isolate CD4 T cells, which are transduced with VRX496. The genetically modified cells are expanded and reinfused into the patient.

When HIV enters CD4 T cells to replicate, the antisense payload of VRX496 is transcribed, which binds the virus and destroys it. The goal is to repopulate a patient's immune system with genetically engineered cells that promote immunity against HIV and prevent the progression to AIDS. Although not a cure, VRX496 could improve the quality of life for HIV patients by bringing viral loads down to low levels. This approach could slow or even reverse a patient's progression to full-blown AIDS.

In a Phase I trial, five chronic HIV patients, who had failed to respond to multiple standard antiretroviral drug regimens, received one infusion of VRX496. All patients showed stable or decreased viral loads as well as stable or increased immune responses to HIV antigens. Four of the five had stable or increased CD4 T cells. Some patients have maintained these positive outcomes for up to three years, and the genetically modified CD4 T cells remain in circulation.

In addition, no toxicities or adverse events related to VRX496 have been observed. The results are described in the November 7, 2006, issue of PNAS.

A Phase II study is under way in 40 chronic HIV patients to further establish the safety and tolerability of VRX496 and to determine the optimal dose.

Current anti-HIV drugs are small molecules that are highly toxic. Because HIV mutates rapidly, it often becomes resistant to conventional drug regimens taken by patients. VIRxSYS' alternative gene therapy is designed to block all the mutation sites on HIV, preventing resistance. Thus VIRxSYS says that VRX496 overcomes the problems of toxicity and resistance.

Moreover, people who live with chronic HIV infections take an average of seven antiviral drugs daily to suppress

the virus. VRX496, which is intended as a short-term therapy that offers long-term benefits, may be more convenient for patients by eliminating the need for multiple daily pills.

Carl June, M.D., who was a coprincipal investigator of the Phase I trial at the University of Pennsylvania Cancer Center in Philadelphia, started a new clinical trial. He's treating early-stage HIV patients with six infusions over several weeks to determine whether VRX496 will allow them to stop standard HIV medications.

Gene Therapy

VIRxSYS was founded in 1998 to develop gene-based therapies based on a lentiviral vector platform exclusively licensed from Johns Hopkins University. The privately held VIRxSYS has a unique financing model. A group of private shareholders provides funds, and the company has not had to rely on traditional venture capital. "We are fortunate to have loyal shareholders who finance us," Dr. Rautsola says.

VIRxSYS designs, builds, and manufactures its lentiviral vectors at the company's in-house GMP facility. The processing of patient cells and their transduction with VRX496 is also performed at the company's laboratory. Moreover, VIRxSYS developed proprietary methods for the processing of viral vectors and the transduction of target cells.

In addition to HIV, VIRxSYS has preclinical programs for hemophilia and atherosclerosis that use lentiviral vectors carrying gene-based therapies.

Gene therapy in the early 1990s offered enormous promise for treating diseases, but the lack of convincing clinical data and some adverse clinical events sent the technology into a recession. "Gene therapy was failing not because we did not understand genomics but because we did not have good delivery mechanisms," Dr. Rautsola says. Lentiviral vectors can solve the delivery and safety problems and "elevate gene therapy to a totally new level."

The first gene-therapy experiments in people used Moloney leukemia virus (MLV) derived from mice to infect cells and deliver a payload. Unfortunately, MLV inserts randomly into genes, including oncogenes, raising the risk for leukemia in treated patients. In studies observed so far, lentiviral gene vectors do not cause this insertional mutagenesis or immune reactions that plagued early gene-therapy trials. "Many animal models show that lentiviruses are not oncogenic," says Dr. McGarrity, "and we continue to collect patient safety data to monitor this."

Like other new technologies, gene therapy has not lived up to its initial hype and grand expectations. Now that VIRxSYS is solving the delivery and safety problems, "we feel that we are positioned to deliver the promise of genetic medicine and begin to see clinical successes," concludes Dr. McGarrity.

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