# The For-Profit HIV Cure Research Crunch

How pharmaceutical and biotech companies are playing a major role in the search for an HIV cure.

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A common perception in the HIV community is that the for-profit sector, in particular pharmaceutical companies that make antiretrovirals (ARVs), will never pursue cure research because its ultimate goal is to keep people living with the virus on expensive and highly profitable drugs.

“I don’t think there are any sweeping statements you can make about that sector,” says Rowena Johnston, PhD, the vice president and director of research at amfAR, The Foundation for AIDS Research. “There are some companies that appear to have been motivated for as long as cure research has been prominent, like Merck and Gilead.”

At the International AIDS Society meeting in Washington, DC, in 2012, numerous commercial companies such as GlaxoSmithKline, Roche, Bristol-Myers Squibb, Tibotec, Gilead and Merck joined biotech groups and academics to form an industry collaboration group to promote cure research.

“The fact that there is such a group—and that people regularly turn up to these meetings—goes to show you that there are companies large and small who are interested in keeping up to date with this research and seeing how they can contribute their expertise,” Johnston says.

According to Anthony S. Fauci, MD, director of the National Institute of Allergy and Infectious Diseases (NIAID), a division of the National Institutes of Health (NIH), “We are still in the stage of discovery because we still don’t fully appreciate what we are talking about when we’re talking about a cure.”

Fauci and other researchers say that open collaboration between the commercial sector, academia and government groups is crucial to laying the proper groundwork. Researchers need to establish the basic science—for example, defining the nature of the HIV reservoir—so that industry can take the baton and turn those findings into effective therapies.

Of the current level of collaboration he observes in the HIV cure field, Fauci says, “I think it’s much

better now than it has been." This level of team playing, he feels, "is going to pay some significant dividends."

**Gene Therapy: Training the Body to Fight HIV**

California Institute of Technology professor and Nobel laureate David Baltimore, PhD, founded the for-profit biotech firm Calimmune in 2007 to pursue an HIV therapy based upon the academic research on stem cell technology he has conducted with Irvin Chen, PhD, of the University of California, Los Angeles.

Calimmune is in the midst of an early study of 12 HIV-positive participants to determine the safety, feasibility and tolerability of a stem cell modification treatment that knocks out the CCR5 receptors on CD4s (HIV latches onto these receptors in order to infect the cells). Baltimore's team takes a blood sample from each participant and draws out CD4 cells as well as stem cells that make CD4s in a process called leukapheresis. Then they use a deactivated version of HIV to serve as a carrier of genetic code, which the virus splices into the cells, ultimately eliminating the CCR5 receptors. Since not all strains of HIV use CCR5 in order to make contact with CD4s, the therapy also inserts instructions to create a facsimile of a fusion inhibitor.

About 1 percent out of people of European descent have a genetic abnormality that causes their immune systems to produce CD4s without the CCR5 receptor, making them naturally resistant to HIV, and without any known ill effects. The famed "Berlin Patient," an American named Timothy Brown, was functionally cured of HIV after his 2007 treatment for leukemia was conducted with a transplant of bone marrow taken from a donor who lacked the CCR5 gene.

The goal of Baltimore's research is to provide those who receive Calimmune's treatment with enough HIV-resistant CD4 cells that their immune systems can prevent the progression to AIDS, without the life-threatening nature of the treatment Brown received and by using an HIV-positive person's own cells, thus eliminating the need to find a suitable donor. The company is currently testing different doses of a drug called Busulfex (busulfan), which is given before the infusion of the study participants' gene-modified CD4s and stem cells in order to improve the efficacy of the transplant. This process knocks out cells of the bone marrow to make space for the new cells, but with much less extensive loss of cells when compared with a traditional bone marrow transplant, and with minimal side effects.

"I'm quite optimistic that this will provide a form of treatment for the disease that will be long lasting and will enable patients to take much less drugs, maybe no drugs, if it works very well," Baltimore says.

As for why he felt the biotech sector was the best arena for this research, Baltimore reflects, "Because the work that needed to be done after we developed this was largely technical work. It wasn't discovery work. And therefore it was not the kind of thing that you can expect NIH to support. So we felt that having gotten as far as we'd gotten in the university, that it was only in the context of a commercial operation that we would be able to carry it forward."

Another biotech firm pursuing similar genetic therapies targeting the CCR5 gene is Sangamo BioSciences, headquartered in Richmond, California. In addition to capital it raises from the sales of shares—the company went public in 2000—Sangamo funds its general operations from a variety of sources, including royalty and sublicensing revenue from business partnerships. For example, Sangamo partners with Dow AgroSciences, a division of Dow Chemical Company, in developing the Sangamo's technology for agricultural purposes. Along with research partners City of Hope National Medical Center in Duarte, CA, and the University of Southern California, the company also received a $14.5 million research grant from the California Institute for Regenerative Medicine to fund its research into stem cell therapies for HIV.

Calimmune, meanwhile, receives most of its funding from angel investors.

**HDAC Inhibitors: Using Cancer Drugs to Flush the HIV Reservoir**

Pharmaceutical giant Merck, which produces the ARVs Isentress (raltegravir) and Crixivan (indinavir) and which is still studying new HIV drugs, is also in the midst of pursuing multiple approaches to flushing HIV's latent reservoir. This is a still poorly understood collection of "resting" CD4 cells that, because they are not replicating, remain off limits to the effects of ARVs. It is because of the latent reservoir that ARVs cannot eradicate the virus from the body and that viral load will typically surge after stopping HIV treatment.

HIV cure investigators are eager to test drugs that have already been approved for other uses, allowing scientists to fast forward years in the research process. Merck is collaborating with academic researchers such as David Margolis, MD, of the University of North Carolina, and Sharon Lewin, PhD, of Monash University in Melbourne, Australia, to study anti-cancer drugs known as histone deacetylase (HDAC) inhibitors. Among other pursuits, Merck is conducting a small proof-of-principle study of how the HDAC inhibitor Vorinostat (suberoylanilide hydroxamic acid, or SAHA), which is already in the company's oncology portfolio, may cause HIV-infected cells to wake from their resting state.

In May, the Internet lit up with false rumors that an HIV cure was only months away—the consequence of an erroneous news report published by the United Kingdom's The Telegraph about a Danish group's still-unpublished HDAC inhibitor study. However, the Danish research is in its infancy—as are all potential avenues to widely replicable HIV cures. Scientists envision years or decades of hard work ahead of them.

Just as ARVs require a multidrug cocktail to effectively fight HIV replication, scientists theorize that successfully flushing and eliminating the reservoir will take a multi-pronged approach. Thus far, research has shown that HDAC inhibitors only activate a small fraction of HIV-infected cells. So both Merck and Gilead are trying to identify different drug compounds—be they commercially available, compounds the company has already looked at for other reasons, or as-yet-to-be-developed agents—that may attack the reservoir in multiple ways.

Another major avenue of research many companies are pursuing is an attempt to develop badly

needed standardized tests to measure the depletion of the reservoir.

Gilead is the world's leader in the HIV drug field, boasting a portfolio that includes Atripla (efavirenz/tenofovir/emtricitabine), Complera (emtricitabine/rilpivirine/tenofovir), Truvada (tenofovir/emtricitabine) and other major ARVs. It is currently researching an HDAC inhibitor called Istodax (romidepsin), which is owned by the oncology pharma company Celgene. Gilead scientists are partnering with the NIAID-sponsored AIDS Clinical Trials Group (ACTG) in preparing to study the effects of a single dose of the drug in HIV-positive study participants who are on ARVs and have a fully-suppressed viral load.

Gilead also partners with John Mellors, MD, at the University of Pittsburgh to research the drug's effect on latently infected cells in tissue cultures.

Daria Hazuda, PhD, vice president of early development and discovery sciences research for infectious disease at Merck, says that a collaborative effort between academics and the pharmaceutical industry is an ideal way to spur scientific progress. The university researchers, she says, are best suited to developing basic scientific understanding of cure approaches while the pharma groups have access to millions of potential drug compounds as well as their own team of scientists who specialize in drug development.

Through these partnerships, Hazuda says, pharma companies "can answer some of these fundamental questions much more quickly than if we were to do this on our own or if we were to rely solely on NIH-funded academic research."

On the flip side of the collaboration coin, Hazuda touts the benefits of competition between players as a driving force behind research progress in the HIV cure field.

"In principle," she says, "it's like evolution: It makes sure you get to the best solution over time."

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