Unlocking the Mysteries of AIDS

By Kate Rix, UC Newsroom

In the battle to end the AIDS epidemic, scientists are grappling with a central mystery: What mechanisms allow the HIV virus to stay hidden inside the body, even in the face of powerful antiretroviral medications?

Antiretroviral drugs are effective at suppressing HIV, but they are unable to completely eradicate it. Reservoirs of the virus remain hidden and dormant inside cells, even in patients on effective medication.

Unlocking the mystery of these reservoirs has become an important fight in the battle against AIDS.

The California HIV/AIDS Research Program, funds some of the most pioneering work in this area. It supports novel, groundbreaking studies providing seed funding to novel approaches aimed at unraveling the biological mystery of how HIV hides and persists. For example, could a single gene hold the key to eradicating HIV from the human body?

The gene – called "Nef" for negative factor – appears to play a key role in helping the virus infect healthy cells and then hide from the body's natural defenses.

"The Nef research could have stalled out, but the CHRP funding gave it the bridge it needed to get to a much further point," says Dr. John Guatelli, whose lab at UC San Diego School of Medicine studies the Nef gene. "This exemplifies what CHRP does: Support young trainees with post- and pre-doctoral support that is hard to come by elsewhere."

More than 30 years after the first cases of AIDS appeared in the United States, the virus can be suppressed with anti-retroviral drugs. This approach puts normal life within reach for people living with HIV and protects public health as well – the virus cannot be transmitted so long as medication is taken.

"It has become very obvious from a grant-making perspective that the secret is to understand the cellular and molecular biology at work," says Anwer

Mujeeb, a biomedical program officer with the University of California who oversees research grants for the Cure Initiative.

“How does HIV hide itself? What mechanisms of cells does it hijack? And most importantly, how can we expose and kill it?”

The Cure Initiative

All pathogens that cause disease are able to circumvent the body's immune system. But HIV, which creates persistent infection, has sophisticated ways of getting around natural defenses. Eradicating a virus this pernicious requires more resources than any one agency could ever muster.

Last year, President Obama announced an initiative to allocate $100 million through the National Institutes for Health (NIH) in pursuit of a cure. In this big picture, CHRP's role is to advance the best early-stage possibilities.

“This approach makes the most impact for our investment: Equip the state’s most meritorious researchers to try out new ideas,” says Mujeeb.

While the NIH funds large research projects for which some initial testing has occurred, labs across the state need funds to get good ideas off the ground.

“There is a valley that science has to cross to reach the point of an NIH grant. We come in there,” Mujeeb says.

Since 1983, CHRP has invested more than $250 million to support roughly 2,000 California HIV/AIDS research projects that span the gamut from community education and new models of patient care, to leading edge science.

It's Cure Initiative, however, focuses entirely on research aimed at eradicating HIV. About 100 California-based researchers apply for funding each year. A panel of peer reviewers from the University of Pennsylvania, Harvard University and other medical centers make the grant decisions. About 20 percent of applicants receive awards.

More than 110,000 Californians living with HIV/AIDS will benefit from a successful cure strategy — along with millions more around the world.

A cure hasn't happened yet, for one reason: A long list of "reservoir" cells maintain the virus in a dormant state. Anti-retroviral treatments can't touch the virus where it hides, but ongoing research strives to decode how HIV infects and replicates in healthy cells.

Dr. Melanie Ott, a senior investigator at the Gladstone Institutes affiliated with UC San Francisco, used a CHRP grant several years ago to initiate her look at how HIV interacts with host cells.

"The preliminary results I generated flowed into the next grant," says Ott. "Now, the majority of the HIV work in my lab is focused on latency research."

One of Dr. Ott's students recently received a CHRP post-doctoral fellowship grant for research into an aspect of HIV latency.

"CHRP helps attract new talent to the field," says Ott. "It is a smaller community, so the chances to get funding are better."

Support for Untested Ideas

Understandably, multi-year federal research grants from the NIH require not only ample preliminary data but also that the applying researcher has a track record.

With a national applicant pool and competing needs for its resources, the NIH has to be highly selective. Of a dozen excellent hypotheses on the same subject, the agency may pick only one. Rejection is the rule and funding the exception.

Senior investigators like Dr. Paula Cannon have an edge over others in the HIV research field nationwide. They can hatch their untested ideas with CHRP and, if given funding, develop an idea toward a later federal grant.

"Knowing that the CHRP funding mechanism is there and that I've been successful in the past getting grants, I am more likely to get excited about risky ideas," says Cannon, an associate professor at University of Southern

California's Keck School of Medicine. "It changes how I think about research. Otherwise, my second thought would be, 'I'll never get the funding, so why bother?'"

Cannon received her first CHRP grant in 2003 and six more since then. The most significant came in 2007 for work developing a technique called ZIinc-Finger Nuclease Stem Cell Therapy – essentially using an engineered protein to knock out a cellular gene HIV needs in order to replicate.

The approach has since become mainstream and has been tested in clinical trials on HIV positive patients at the University of Pennsylvania. But when Cannon first began work on it, she could get no funding.

"I was laughed out of the room at NIH," she recalls. "But then I was able to get CHRP funding. With the preliminary data I developed, I was able to turn it into two big grants to develop the idea further."

Today, Cannon is a co-investigator on a related $14.5 million study funded by the California Institute for Regenerative Medicine.

"CHRP is a unique and valuable mechanism," she says. "There are other charities and foundations for AIDS research, but they don't exclusively target the fabulous scientists in California."

Training Next Generation Scientists

California has about 14 percent of all AIDS cases in the U.S. This translates into a medical and fiscal burden that is larger than anywhere except New York.

The counterweight to this challenge is that many of the most meritorious young investigators looking for a cure to HIV work in California. With support from CHRP, a graduate student in John Guatelli's lab at UC San Diego drilled down into Nef's molecular structure to see how it does its dirty work.

Three years later a post-doctoral research trainee in the same lab streamlined techniques to analyze the gene *in vitro*. Then, like a chemical reaction, another lab took note and offered to help make the proteins visible in an entirely new way.

“If you crystallize the proteins like salt and shine X-rays through them, you get this 3D picture,” Guatelli says. “Now we know all the atomic details of the cellular process. As consequence, we can try to find inhibitors, which would thwart the virus's ability to co-opt cellular mechanisms.”
Awards from CHRP help senior investigators like Guatelli, Cannon and Ott to continue the mission of teaching and advising young scientists.

Even applicants who don't receive CHRP grants benefit in another way: Peer reviewers write a 10-page memo explaining how applications could improve and encourage reapplication.

“This is not just money going into a black hole,” says Cannon. “We use these funds for our teaching mission: to hire graduate students and train post-doctoral fellows. Even as a full-time researcher, a large part of my job is mentoring and training the next generation of scientists to work in the state’s biotech industry.”