University of Rochester Medical Center Receives $100,000 Grand Challenges Explorations Grant for Innovative Global Health

The University of Rochester Medical Center today announced that it has received a Grand Challenges Explorations grant from the Bill & Melinda Gates Foundation.It is one of 105 grants, each of $100,000 and designed to help scientists "explore bold, new solutions for health challenges in developing countries." The grants represent the first round in the foundation's five-year, $100 million initiative.

To receive funding, researchers had to show in a two-page application how their ideas fell outside current scientific paradigms and could lead to significant advances in global health if successful. This initial set of grants, provided to scientists in 22 countries, was chosen to inject fresh perspective into research seeking to prevent or cure infectious diseases such as HIV/AIDS and tuberculosis.

One focus of the initiative is to support work seeking to limit the emergence of viral resistance to drug treatments. Antibiotics and anti-viral therapies have been the centerpiece of efforts to control diseases like AIDS, but their effectiveness has been compromised by disease-causing organisms, which evolve so quickly that drugs are rendered obsolete. HIV, for instance, has been become resistant to every antiviral drug prescribed today.

Harold C. Smith, Ph.D., professor in the Department of Biochemistry and Biophysics at the Medical Center, has received the institution's first individual grant from the Gates Foundation to pursue an unorthodox approach to the dire problem of viral resistance to current AIDS drugs.

"While AIDS is no longer an immediate death sentence, those living with it long term struggle terribly in part due to drug resistance," Smith said. "Patients must regularly switch medications as their infection becomes resistant and take treatment breaks as side effects become too punishing, which only further encourages viral resistance. We are grateful to the Gates Foundation for supporting new approaches, especially because many traditional funding sources are not comfortable with supporting broadly innovative leaps."

"I congratulate each individual who took the initiative to share their idea with us to help fight the world's most serious diseases," said **Tachi Yamada**, **M.D.,** president of the Gates Foundation's Global Health Program. "The number of creative approaches we received exceeded our highest aspirations. Projects from this initial pool of grants have the potential to transform health in developing countries, and I will be rooting for their success."

Study Details

Most antiviral drugs today are designed to be the right shape to fit precisely into and shut down proteins produced by viruses and needed by them to reproduce. Thus, the drugs start to lose their effectiveness as their viral protein targets mutate and change shape.

The core of novelty in Smith's approach is that it envisions new drugs that encourage the action of a protein expressed in human cells, instead of a viral protein, that has the ability to destroy HIV, but that is often rendered inactive. To evolve around such a mechanism, a virus cannot make a small structural change, but must instead fundamentally alter its nature.

In recent years, Smith's work extended the seminal finding of Ann Sheehy in Michael Malim's laboratory (formerly at the University of Pennsylvania) by showing that patients with higher than normal levels of the

protein called APOBEC-3G (A3G) in their white blood cells were better able to resist HIV.

It also became clear that A3G is used by human cells to "edit" the HIV genetic code every time the virus copies itself, corrupting the code until the virus can no longer reproduce.

Past structural studies carried out jointly by the Smith lab and structural biologist **Joseph E. Wedekind, Ph.D**., confirmed the finding by Warner Greene (Gladstone Laboratories) that A3G has two forms. One is active, and the other, an inactive form wrapped up in complexes with ribonucleic acids (RNAs). When RNA switches off the enzymatic activity of A3G, the primary defense of the human cell against HIV is shut down.

HIV is devastating because it infects the same cells that are charged with destroying it, namely the T lymphocytes, one kind of white blood cell. When infected by HIV, a great many T cells self-destruct in an attempt to take the virus with them, which leaves the body open to opportunistic infections (AIDS).A few T cells, however, survive to preserve the body's memory of HIV, so that the system can respond more fiercely to a second infection. In the age-old battle between HIV and the ancestors of human cells, however, HIV has also evolved to take advantage of memory T cells, using them as long-term reservoirs in which the virus can hide from the immune system.

With this long-term haven in place, the virus is free to continue reproducing, which provides more opportunity for it to become resistant. Should infected, resting T cells get activated again by another exposure to any invader, and they most likely will, the T cells then proliferate into an army of clones specifically selected to attack the invader at hand. Ironically, this same process, T cell proliferation, has been shown to deactivate A3G, which enables HIV infection to spread.

For one T cell to proliferate into an army of T cells, each cell must bring down the barriers that surround their DNA so that it can be copied and transferred to their daughter cells during many rounds of cell division. Smith's team is working with the theory that proliferating T cells, as they divide, mistakenly conclude that A3G has gained access to their genome, and could make unwanted changes to their briefly exposed DNA. Thus, T cells switch off A3G by wrapping it up in RNA complexes just when they most need it to protect themselves against HIV. Smith's lab, however, discovered that A3G is anchored in the cytoplasm of the T cell and cannot access the genome. Given this new information, Smith proposed to the Gates foundation that A3G activators should represent a safe and novel way to treat HIV infection.

Efforts funded by the Gates grant will focus on liberating the parts of A3G that RNAs seek to attach to in proliferating T cells. Specifically, the grant will support the design of a rapid screening test to be used in the search for compounds that interfere with the ability of RNA to switch off the catalytic activity of A3G. Such compounds could briefly turn on the A3G already in place in T cells, giving them greater ability to fight back as the virus attempts to infect and replicate. In the first phase of work, the team will seek to demonstrate proof of principle for the screening assay, which is designed to emit fluorescent light when a compound is capable of keeping A3G and RNA apart.

Secondly, they hope to put the screening assay through its first paces in the next few months, screening through 10,000-25,000 compounds from libraries available at the University of Rochester to make a first list of drug candidates. Should the team win phase II funding (up to $1 million) from the foundation, they will move the best candidates into the next phase of validation and preclinical testing.

While Smith received the Medical Center's first individual grant from the Gates Foundation, two researchers**, Xia Jin, M.D., Ph.D**., and **Jacob Schlesinger, M.D.,** in 2004-2005 both received consortium funding through the Pediatric Dengue Vaccine Initiative (PDVI). The PDVI is an effort, funded by the Gates Foundation, the Rockefeller Foundation and the Korean government, to design an effective vaccine for dengue, a virus spread by mosquito bite that caused joint pain in hundreds of thousands and 200 deaths in a recent outbreak in Latin America.

About Grand Challenges Explorations

Grand Challenges Explorations is a five-year $100 million initiative of the Gates Foundation to promote innovation in global health.The program uses an agile, streamlined grant process – applications are limited to two pages, and preliminary data are not required.Proposals are reviewed and selected by a committee of foundation staff and external experts, and grant decisions are made within approximately three months of the close of the funding round.

Applications for the second round of Grand Challenges Explorations are being accepted through November 2, 2008, and topics for the third round will be announced in early 2009.Grant application instructions, including the list of topic areas in which proposals are currently being accepted, are available at www.gcgh.org/explorations. A list of the projects funded along with Smith's in the current round is available at the same address.

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