Photo: Creative Services

HIV research is housed in the Biomedical Research Laboratory, headquarters of the National Center for Biodefense and Infectious Diseases, on the Prince William Campus. While many labs and scientists look at ways to kill pathogens, BRL researchers investigate the host-pathogen relationship to study how hosts respond to infectious diseases.

HIV Research:

Routing Out HIV that Hides and Halting Its Use of a Cell's Internal Machinery

Developed in the mid-1990s, highly active antiretroviral therapy (HAART) revolutionized HIV treatment so that the virus ceased being an automatic death sentence for the newly diagnosed. Since the advent of HAART, researchers have set their sights on the ultimate challenge: finding a cure for HIV, a global pandemic that continues to infect—and in some cases, kill—millions around the world each year.

HIV research at George Mason University began in earnest in 2003 when Yuntao Wu was recruited to the National Center for Biodefense and Infectious Diseases (NCBID) from the National Institutes of Health (NIH) in Bethesda, Maryland. Seven years later, researcher Fatah Kashanchi arrived at the center and set up a second lab devoted to HIV and other retroviruses.

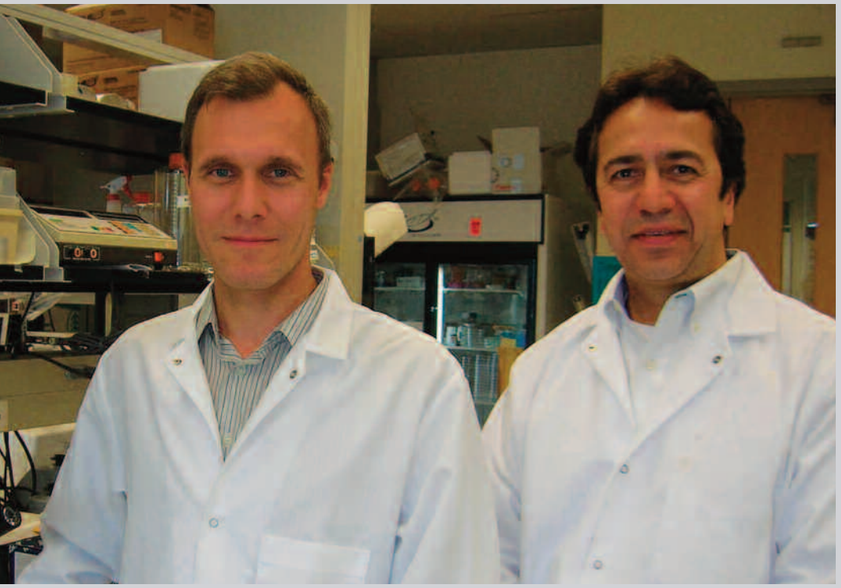


Photo: Archana Pyati

Sergey Iordanskiy, Fatah Kashanchi

The Human Immunodeficiency Virus, or HIV, attacks the immune system, destroying a person's natural disease-fighting capabilities. If left untreated, HIV leads to AIDS, or Acquired Immunodeficiency Deficiency Syndrome, the final stage of HIV infection where immune cell counts are so low that opportunistic infections cause a person to die. HIV is transmitted through the exchange of bodily fluids, like blood, semen, and breast milk.

Kashanchi and Wu belong to the vanguard of viral researchers attempting to pin down how HIV interacts with a host cell once HIV infects it. Understanding how HIV hijacks a cell's internal mechanisms to replicate itself can lead to better drugs and, ultimately, a cure or a vaccine. AIDS research is a hypercompetitive field and both Wu and Kashanchi have distinguished themselves, publishing papers in prestigious journals like *Cell* and *PLOS Pathogens*, *Journal of Virology* and receiving multiyear NIH grants to support their research. Here is a closer look at their work:

Kashanchi Lab: A New Approach to "Shock and Kill"

A vexing problem long-term HIV survivors face is viral reservoirs, areas in the body where HIV is alive but in a dormant state. The virus goes into hiding by integrating its own genetic material into a host cell's DNA, lingering in patients for decades. HAART won't work on these latent cells since the virus isn't actively replicating itself. Yet these latent cells are a "big time threat," says Kashanchi, since they "can allow low levels of virus population to take place once in a while." Latent cells, along with HIV, have to be eradicated. But how can this be done safely without destroying an HIV patient's healthy, uninfected cells?

> "Understanding how HIV hijacks a cell's internal mechanisms to replicate itself can lead to better drugs and, ultimately, a cure or a vaccine. AIDS research is a hypercompetitive field and both Wu and Kashanchi have distinguished themselves."

Over the years, HIV researchers realized that the only way to get at these viral reservoirs is to turn the inactive virus "on," treat it with HAART and destroy the latent cells so they're no longer hospitable to the virus. This approach, known as "shock and kill," is problematic because it doesn't explain how not to kill the body's uninfected cell population at the same time.

Kashanchi and NCBID researcher Sergey Iordanskiy think they may have an answer. Giving patients low doses of X-ray radiation activates HIV proteins while triggering latent cells to self-destruct. Once the virus is shocked into replicating itself, it can be treated with HAART, which Kashanchi and Iordanskiy demonstrated in humanized mouse models — mice with human immune cells embedded in them.

Radiation treatments are tricky because they usually damage the DNA of healthy, uninfected cells, which potentially leads to cancer. Kashanchi and Iordanskiy say the radiation level they propose is low enough to be safe and to trigger a healthy cell's own DNA repair process through the p53 pathway, a protein-based chain reaction that protects the cell from genetic mutations.

Kashanchi, who has trained dozens of postdocs and graduate and undergraduate students during his twenty-year career studying HIV, says he and Iordanskiy may have found a safe approach to "shock and kill," which might one day eradicate HIV in a patient who receives the treatment. He and Iordanskiy are hopeful as they wait to hear from NIH and other funding agencies on grants they've submitted to support their research.

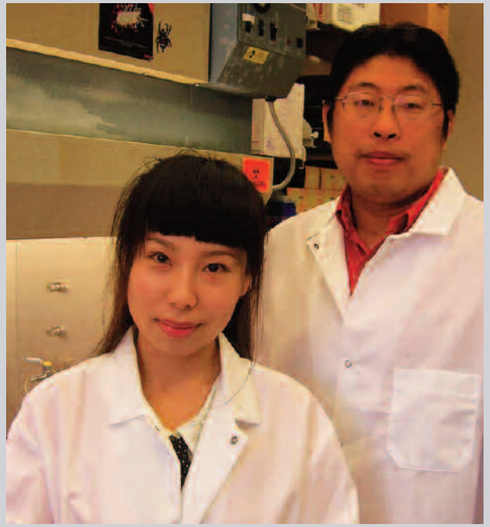


Photo: Archana Pyati

Jia Gua, Yuntao Wu

Wu Lab: HIV on the Cytoskeleton Treadmill

Meanwhile, Wu and Jia Guo are examining how HIV is able to exploit an immune cell's internal machinery to gain access to the nucleus, the place where HIV makes copies of its own DNA. So far, antiretrovirals haven't been able to stop HIV at this phase of its life cycle, known as transcription. Wu and Guo are particularly interested in treatments that disrupt HIV's use of cellular machinery even when the virus mutates. HIV is a notoriously unstable virus that is constantly mutating.

To enter a cell, HIV has to bind to several proteins dotting the cell's surface. First, HIV attaches itself to the CD4 receptor, then to one of two coreceptors, CCR5 or CXCR4. The coreceptor chosen to gain entry into the cell depends on the type of HIV a patient has been infected with. CCR5 is used by a more common and less lethal form known as M-tropic HIV; CXCR4, meanwhile, is used by T-tropic HIV, a deadlier form researchers speculate is a mutation of the earlier M-tropic version.

When these coreceptors are activated, the cell knows that something is wrong. Its natural immune response kicks in, causing the cell to physically migrate toward the source of the infection. The cell is propelled forward by a treadmilling process created when a protein called cofilin starts breaking up cytoskeleton fibers in the cell. Over a six-year period, Wu

continued on page 16

HIV Research, *from page 3*

discovered that when HIV uses the CXCR4 coreceptor, it hitches a ride on this treadmill so that it can enter the nucleus and begin transcription. In 2008, he published his results in a well-received and widely cited paper in *Cell*.

Wu and Guo, who began in Wu's lab as a postdoctoral researcher before her current position as a research assistant professor, are now trying to determine if the same treadmilling process occurs when HIV, in its M-tropic strain, binds to the CCR5 coreceptor. They're also exploring how genistein, a compound found in soybeans, can slow down treadmilling, depriving HIV the necessary machinery to cross into the nucleus. Published in the June issue of *Retrovirology*, their findings suggest it can, based on low doses of genistein given to rhesus monkeys with SIV (simian immunodeficiency virus), a disease similar to HIV.

Now, Wu and Guo are taking their work a step further by collaborating with Shenyang-based China Medical University, where 800 HIV-positive patients will participate in two different studies: one that more closely examines the role of cofilin during the HIV life cycle and another to determine if genistein can reduce the viral load of HIV and increase the number of healthy immune cells in human beings.

Previous AIDS research focused heavily on HIV proteins, and Wu was looking for "new and unknown territory," he says. In studying how HIV exploits cellular machinery to reproduce, Wu seems to have found his niche. His results can't seem to come fast enough: "HIV is a big problem not only for this country, but for the whole human race."

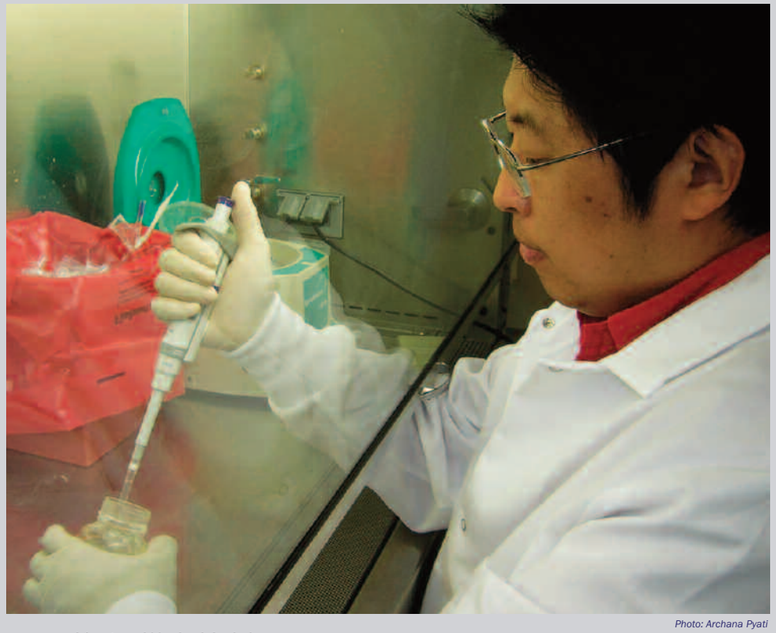


Photo: Archana Pyati

Yuntao Wu in his lab

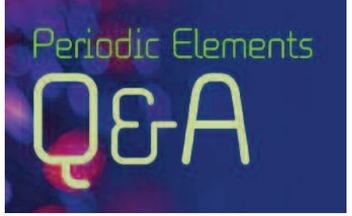
COS Fall Lineup

Total Students:	3,435
Full-time:	2,341
Part-time:	1,094
Female:	1,890
Male:	1,541
Gender Not Reported:	4
Undergraduate:	2,373
Graduate:	1,062

NanoNotes, *from page 7*

"The impact of IL28B genotype on the gene expression profile of patients with chronic hepatitis C treated with pegylated interferon alpha and ribavirin," published by scientists in the **Center for the Study of Chronic Metabolic Diseases** in the School of Systems Biology, has received the distinction of "highly accessed status" in BioMed Central (BMC). The paper was published in the *Journal of Translational Medicine*, one of a group of open access, peer-reviewed, research-only journals in BMC. This is the third paper published by the center to received this status, a hallmark of future citation rates. The paper has been accessed more than 3,800 times since publication.

Faculty, staff, students, and alumni are encouraged to send their NanoNotes *to cosnews@gmu.edu.*



Peggy Agouris was appointed acting dean of COS in June when Vikas Chandhoke, former dean, was selected as Mason's vice president for research and economic development. Agouris joined Mason from the University of Maine in 2007 and was named chair of the Department of Geography and Geoinformation Science and director of the Center for Earth Observing and Space Research the following year.

PE: Both the new facilities and the search for a new dean are huge transitional changes for COS. Your appointment appears to be a perfect fit because you have such history with the college and your colleagues and a passion for science at Mason. What do you see as your primary role in this important phase of the college's growth and development?
Agouris: I see my role as an exciting opportunity to facilitate the transition of the college to the next phase of evolution. While maintaining our strengths and our legacy, we need to look at who we are, where we are, who we want to be, and how to get there. Through this process, we will carve a new path, discover new strengths, and move to a higher level of interdisciplinary relationships and collaboration. At the same time, we can take advantage of and benefit from the direction being forged by new university leadership.

PE: What differences and similarities are you finding between your former position as a department chair and your current position as acting dean?
Agouris: Both positions are about connecting with people and allowing them to do what they do best. They both require vision and an obligation to take a holistic view and consider the common good. The most striking difference is in scope. A chair's role unfolds in a homogenous environment, but a dean must navigate a complex, multidisciplinary profile. Fortunately, the skills transfer between positions.

PE: You've watched COS transform over the past seven years into a thriving center of learning and community. What are some of the more significant changes you've personally noted?
Agouris: COS is one of the fastest growing academic units at Mason, so the most significant and obvious change is rapid growth. Under the leadership of (former dean) Vikas Chandhoke, we came together as a cohesive unit, which is never easy for a new organization. Now we better understand our identity, strengths, and direction.

Dean's Message

Photo: Creative Services

Peggy Agouris
Acting Dean, College of Science

It is an honor to be serving as acting dean of this dynamic College of Science (COS) and working alongside colleagues and friends. I am extremely proud of the level of new research happening at both the Fairfax and Prince William campuses, the quality of students filling our classrooms, and the excitement in science and research we share with our supporters, alumni, and the greater community.

This is an exciting time for students, faculty, and staff in the college as we showcase our new state-of-the-art science facility — Exploratory Hall. We are all working together to figure out just where the light switches and outlets are, and we are also taking some time to stretch out our legs and make ourselves at home. This issue of *Periodic Elements* offers a look inside our new surroundings, and I invite you to visit us and see science in action at the Fairfax Campus.

Periodic Elements

Read past issues of Periodic Elements at cos.gmu.edu

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