In the Lab

Lying in Wait
The elusive HIV

HIV, THE VIRUS THAT CAUSES AIDS, kills with deadly efficiency by disabling the human immune response, leaving people vulnerable to infection and other diseases. Since 1983, when researchers discovered the virus, at least 25 million people have died from AIDS or AIDS-related diseases and millions more have become infected with HIV.

One reason for HIV's success is that the virus has several ways of eluding the immune system's attempts to kill it. First, it targets and destroys CD4+ T cells — the cells that trigger the immune system to attack invading pathogens. Then, it mutates rapidly to stay one step ahead of a targeted immune response.

Recently, scientists have learned the virus has another trick up its sleeve. It can make itself invisible to the immune system by going into a latent state where its viral genes are inactive and no new virus is produced.

Researchers at Johns Hopkins Medical School found the first reservoir for latent HIV within resting CD4+ T cells. Now, U-M scientists have discovered a second hiding place for the virus in immature human bone marrow cells. Latent viral genes can lurk undetected within the DNA of these cells for long periods of time — waiting until conditions are right for a comeback.

HIV's ability to go dormant and hide inside infected cells explains why powerful anti-HIV drugs cannot completely remove the virus from the body, says Kathleen Collins, M.D., Ph.D., associate professor of internal medicine and of microbiology and immunology, who led the U-M study.

"Current drug therapies prevent active virus from spreading to other cells, but the drugs have no effect on latently infected cells. Once drug therapy stops, the virus comes back," says Collins. "To cure the disease, we have to find all the reservoirs and eradicate them."

Christoph Carter, a student in the Medical School's M.D./Ph.D. program, was a member of the research team that studied bone marrow samples from Health System patients who were taking anti-HIV drugs. He created a gene promoter that caused green fluorescent protein to glow in a small number of bone marrow cells infected with latent HIV. The glowing cells were hematopoietic progenitor cells — primitive bone marrow cells that give rise to red blood cells, white blood cells and immune system cells.

Postdoctoral fellow Adewunmi Onafuwa-Nuga (Ph.D. 2007) and graduate student Lucy McNamara analyzed the bone marrow samples to determine the number of cells that contained the virus. Some samples had as few as one out of 10,000 cells with latent HIV.

"In people on drug therapy, this very small number of latently infected cells may be the only virus that's left in the body," says Collins. "Unfortunately, it doesn't take many latent cells to rekindle active infection."

In future research, Collins hopes to find drugs capable of eliminating HIV from latently infected cells. She says her ultimate goal is to develop a "short-course therapy to cure the disease. That would have a global impact."

—SALLY POBOJEWSKI

Kathleen Collins and Adewunmi Onafuwa-Nuga

SCOTT SODERBERG, U-M PHOTO SERVICES

David Canter to Lead NCRC

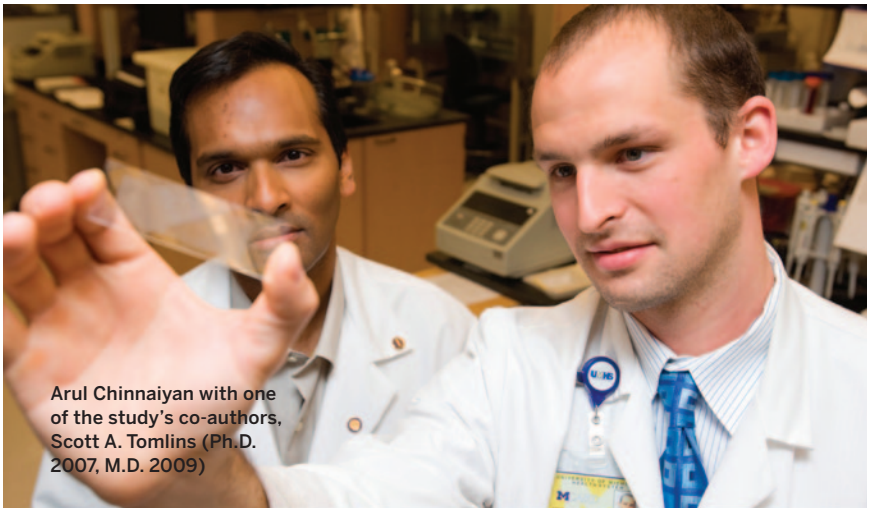
DAVID CANTER, M.D., THE PHYSICIAN-scientist who formerly led Pfizer's pharmaceutical research and development facility in Ann Arbor, is the first executive director of the U-M North Campus Research Complex (NCRC). Canter will develop and implement a university-wide strategy for use of the 30 buildings and 174 acres of land that make up the former Pfizer facility. U-M became the property's new owner on June 16, 2009.

"I'm honored to be chosen as the first executive leader of the NCRC team," says Canter. "It was a bold move by the U-M to purchase the Pfizer site and using it to its fullest potential will bring many challenges and opportunities."

Canter has 25 years of experience in the pharmaceutical industry. He came to Michigan in 1986 as a vice president for Warner-Lambert/Parke-Davis, which was purchased in 2000 by Pfizer. Canter served for eight years as a senior vice president for Pfizer Global Research and Development until the company closed its Ann Arbor research operation in 2008 — ending 50 years of pharmaceutical research and development on the site.

Canter began his appointment at the NCRC on July 19. He reports to Ora Hirsch Pescovitz, M.D., U-M's executive vice president for medical affairs and CEO of the U-M Health System. —SP

MORE ON THE WEB



Arul Chinnaiyan with one of the study's co-authors, Scott A. Tomlins (Ph.D. 2007, M.D. 2009)

Targeting the Trigger

IN 2005, A TEAM OF SCIENTISTS LED BY ARUL CHINNAIYAN (M.D. AND PH.D. 1999), the S.P. Hicks Endowed Professor of Pathology, discovered what triggers at least half of all prostate cancers. It was the abnormal fusion of two genes, one active only in prostate cells and the second an oncogene — a gene that causes cancer. Unfortunately, there was no way to target this gene fusion with existing pharmaceutical drugs.

Now, Chinnaiyan's team has found a new gene fusion that is present in about 2 percent of prostate cancers. The oncogenes involved in this fusion are RAF1 and BRAF — members of a signaling pathway known to be involved in aggressive forms of melanoma and gastric cancer. Until this study, no one knew the RAF pathway was involved in prostate cancer, also.

The good news is that four "anti-RAF" drugs have been developed and are being tested now in clinical trials in patients with advanced melanoma. The U-M discovery suggests the same RAF-inhibiting drugs could be an effective treatment for the 2 percent of men whose aggressive prostate cancer is caused by RAF-pathway gene fusions. About 192,000 American men are diagnosed with prostate cancer every year. Researchers estimate that 3,600 of these tumors could be RAF-driven.

Chinnaiyan suspects RAF gene fusions could play a role in other types of cancer. If this is true, it means more people with aggressive cancers might benefit from treatment with RAF-inhibiting drugs.

"Rather than treating these cancers as just a 'prostate tumor' or a 'gastric tumor,' we need to think of it as a 'RAF-mutant tumor,'" says Chinnaiyan. "We need to think more about the driving molecular basis for each patient's tumor and what oncologists can do about it." —SP

MORE ON THE WEB

LEFT: SCOTT SODERBERG, U-M PHOTO SERVICES
RIGHT: MARTIN VLOET, U-M PHOTO SERVICES

In the School

Curbing Maternal Mortality

U-M delegation witnesses impact of health mission in Ghana

A mother and her baby boy, only 11 hours old, leave the University of Ghana Korle-Bu Teaching Hospital in Accra, Ghana.

WHEN A COLLEAGUE WAS UNABLE to attend a Continuing Medical Education session in Ghana in 1986, Timothy R.B. Johnson, M.D. (Residency 1979), now chair of obstetrics and gynecology, took his place, making his first trip to Africa. That simple, serendipitous event sparked more than two decades of partnerships between Ghana and the University of Michigan, starting with a residency program in ob/gyn funded by the Carnegie Corporation — which continues with Ghanaian government support today.

In May, a nine-member U-M delegation, which included members of the Board of Regents, faculty, alumni and friends, visited Ghana to witness firsthand the breadth and depth of the U-M's work there, and to explore new partnership opportunities. Led by Joseph C. Kolars, M.D. (Fellowship 1989), professor of internal medicine and senior associate dean for education and global initiatives, the delegation visited Ghanaian teaching hospitals and government agencies and met with students, residents, postgraduates and faculty.

Carnegie's goal in funding the U-M and other programs in Ghana in the 1980s was to build international medical capacity and improve maternal medicine. Key to that effort is raising Ghanaian educational standards and implementing an improved system of teaching.

"Medicine in Ghana, even though it's very different, is still good medicine," says Johnson, the Bates Professor of the Diseases of Women and Children and a member of the visiting delegation. "However, their education system needs to catch up to ours."

Johnson would know: Since that first trip, he's visited Ghana more than 30 times, spearheading a physician education effort that now includes specialty training at the University of Ghana Medical School and the Kwame Nkrumah University of Science and Technology, both of which the delegation visited. More than 60 Ghanaian students have been trained in Ghana, with nearly all of them opting to remain in the country after completing their residencies.

High maternal mortality rates are the reason the U-M Health System became engaged in a health initiative in Ghana. According to UNICEF, the annual maternal mortality ratio in Ghana in 2008 was 450 deaths per 100,000 live births, compared to eight in the U.S. Rates are declining but remain unacceptably high. While the Health System's involvement is growing in many other disciplines — emergency and family medicine, oncology, physical medicine and rehabilitation — its main goal still lies squarely in reducing maternal deaths, according to Johnson.

Members of the group stressed Michigan's strong relations with its funding and donor communities, which have reduced the U-M's reliance on state funding. They hope that more members of the Board of Regents, faculty and friends of the University will visit Ghana in the future. University of Ghana Vice Chancellor, C.N.B. Tagoe, noted that U-G's relationship with the U-M is one of the most significant with a foreign university in the field of health sciences.

Says Tim Johnson, "The lesson for me was: Never hesitate to pick up the phone to see if someone might be interested in supporting some wild idea." —MARGARITA BAUZA AND RICK KRUPINSKI

JENNIFER EDWARDS

Depression Increases During Internship

A STUDY CONDUCTED BY ASSISTANT Professor of Psychiatry Srijan Sen (M.D. and Ph.D. 2005) and published in the June issue of *Archives of General Psychiatry*, indicates that depression among clinicians increases markedly during the period of medical internship. While studies have shown that rates of depression are higher among medical interns than the general population, few have looked at specific factors responsible. Sen and colleagues found that increased work hours, medical errors, genetic predisposition and receiving a medical education in the U.S appear to be associated with depressive symptoms. The study involved 740 interns who began residencies in 13 U.S. hospitals in 2007 or 2008. —RK

MORE ON THE WEB

Student's Leadership Honored

THIRD-YEAR MEDICAL STUDENT Brandon M. Wojcik was one of only 20 students nationwide to receive the 2010 Leadership Award from the American Medical Association Foundation. Wojcik, from Saranac, Michigan, was honored for outstanding non-clinical leadership skills in advocacy, community service and education. The award was presented, in association with Pfizer, Inc., at the AMA National Advocacy Conference, which provides training to students, residents, fellows and early-career physicians to prepare future leaders in medicine and community affairs. —RK

New Leadership for Psychiatry

THE DEPARTMENT OF PSYCHIATRY HAS A NEW CHAIR WITH THE appointment of Gregory Dalack, M.D., who has been serving as interim chair since John Greden, M.D., stepped down from the role in 2007 after 22 years to direct the U-M Depression Center. Dalack, an associate professor of psychiatry, leads a department comprised of 182 faculty members, 54 residents and fellows, and 364 administrative, research, nursing and clinical support staff.

Dalack earned his M.D. at Columbia University and completed his residency and a clinical research fellowship at the New York State Psychiatric Institute. Upon joining the Medical School in 1992, he headed the Mental Health Clinic at the VA Ann Arbor Healthcare System until 1999. From 2006 until his appointment as interim chair, Dalack also served as vice chair of the department. —RK

Former Dean Dies at 79

FORMER U-M MEDICAL SCHOOL DEAN JOSEPH EGGLESTON JOHNSON III, M.D., died April 19, 2010, in Jacksonville, Florida, at the age of 79.

Johnson served as dean of the U-M Medical School from 1985-90. During his tenure as dean, the Medical School curriculum was revised to emphasize preventive care, critical thought and independent learning. He oversaw the opening of the new University Hospital, the A. Alfred Taubman Health Care Center, and the Medical Science Research Building I — all in 1986 — as well as MSRB II in 1989. Johnson recruited eight new department chairs, and research funding from external sources more than doubled during his deanship. After completing his service as dean, he remained on the faculty as a professor of internal medicine until he retired in 2003.

Johnson received his bachelor's and medical degrees from Vanderbilt University and completed a residency at the Johns Hopkins Hospital. He served in the U.S. Navy as a medical officer aboard a nuclear submarine for two years, then returned to Hopkins to complete a fellowship in infectious diseases and immunology. Before coming to the U-M, Johnson held faculty and administrative positions at Hopkins, the University of Florida and Wake Forest University. —MF

In the Clinic

Changing the Practice of Medicine

The Southwest Oncology Group

Laurence Baker

IT TAKES A LOT OF MONEY TO design, conduct and analyze results from large-scale clinical trials of experimental cancer treatments and prevention regimens. Laurence Baker, D.O., professor of internal medicine and pharmacology, wants to make sure it's money well-spent. So every year, he asks the clinical researchers who attend Southwest Oncology Group meetings the same question: "Is the public getting $45 million worth of work out of you?"

Baker chairs the Southwest Oncology Group, or SWOG — the largest cancer clinical research cooperative in the United States. With an annual budget of $45 million, SWOG has more than 500 institutions and nearly 5,000 research investigators in its cancer trials network. Much of its research funding comes from the National Cancer Institute.

Evidently, the federal government believes it's getting its money's worth, because NCI just renewed SWOG's funding for the next six years with a package of grants expected to exceed $120 million. The principal grant totals more than $63 million and will be administered through the U-M Medical School where SWOG's administrative offices have been located since 2005 when Baker became chair. It is the largest single research grant ever awarded to the Medical School.

"SWOG conducts phase III trials involving hundreds or thousands of patients," explains Baker. "It's the evidence from phase III trials that changes the practice of medicine."

Baker has been an investigator with the Southwest Oncology Group since 1970. Over the years, he has seen many SWOG-tested experimental treatments become accepted as the standard of care for adult cancers. More recently, SWOG has begun a new initiative in comparative effectiveness research — studies designed to help physicians select the most effective therapy by determining which patients actually benefit from a test or treatment and which patients do not.

"We've been funded by NIH to evaluate a genetic test called Oncotype DX in women with node-positive breast cancer," says Baker. "The study's goal is to determine if this genetic test predicts whether chemotherapy improves cure rates in women with breast cancer. SWOG investigators also have just been funded for a study to determine whether cancer patients actually benefit from widely used drugs that stimulate the body's bone marrow to make more white blood cells."

There are about 1,500 Michigan patients currently enrolled in SWOG trials at 41 hospitals and medical centers in the state, including the U-M Comprehensive Cancer Center. About 70 Medical School faculty members are active SWOG investigators and 10 serve in leadership positions within the group.

—SALLY POBOJEWSKI

LIN JONES, U-M PHOTO SERVICES

The Gift of Speech

FOR THE FIRST THREE AND ONE-HALF YEARS OF HER LIFE, AYONNA GREEN never said a word. She was born prematurely with a damaged airway, and surgeons had to insert a tracheotomy tube in her neck so she could breathe. The surgery saved her life, but left her unable to speak and facing a lifetime of limitations, daily tracheotomy care and future medical complications.

But then her mother, Ra'mona Russell, brought Ayonna to U-M's C.S. Mott Children's Hospital where surgeons had developed a new procedure to reconstruct the airway and close tracheotomies in children.

"We pioneered a way to get the tracheotomy tube out and allow children to breathe and talk normally," says Glenn E. Green (M.D. 1991), an assistant professor of otolaryngology who performed Ayonna's airway reconstruction surgery. "For these children and their families, this is life-changing."

In the two-part procedure, called a cricotracheal resection with a hilar release, surgeons remove the damaged sections of the airway and then move the lower trachea up from inside the chest to connect it to the voice box. So far, the procedure has been 100 percent successful.

Today Ayonna's an active, engaging 6-year-old who's looking forward to first grade, loves to swim and is extremely fond of Dr. Green.

Like all the children who underwent the procedure, it took awhile for Ayonna to learn how to talk afterwards. Her voice is soft and still a bit raspy, but she's taking voice lessons and singing in her church choir. After all those years of silence, Ayonna Green has a lot to say. —SP

MORE ON THE WEB

Ayonna Green and Glenn Green

SCOTT SODERBERG, U-M PHOTO SERVICES

Health Briefs

The U-M's new C.S. Mott Chidren's Hospital and Von Voigtlander Women's Hospital will open for business in the fall of 2011 — one year ahead of schedule. Located adjacent to the current University Hospital, the state-of-the-art complex includes a nine-story tower for clinic space and a 12-story tower devoted to inpatient care, diagnostic, procedural and treatment services. Planning is under way for the big move and a grand opening celebration.

MORE ON THE WEB

Reusing pacemakers may be a safe and effective way to provide these life-saving medical devices to people in Third World countries who cannot afford them. A study by U-M Cardiovascular Center researchers found that implantable pacemakers can be removed prior to burial or cremation, sterilized and reused with no significant increase in complications. A large prospective clinical trial is being planned.

MORE ON THE WEB

Black men with chronic pain have a higher risk of depression and disability than white men with chronic pain, according to a new study by U-M researchers. The comprehensive study, which included 1,600 men, was the first to examine the impact of chronic pain on the overall health of black men. —SP

MORE ON THE WEB

In the Clinic

Statins for Cancer?

MORE THAN 25 MILLION PEOPLE take cholesterol-lowering drugs called statins to reduce their risk of cardiovascular disease. In 2005, U-M researchers found that taking statins also can cut the risk of colorectal cancer by as much as 50 percent.

The catch is that statins work much better for some people than others — both to lower cholesterol and to prevent colorectal cancer — and doctors had no way of knowing which patients should receive statin therapy. Now an international team of scientists, including researchers at the U-M Comprehensive Cancer Center, have discovered that a genetic test can predict who is most likely to benefit from long-term use of statins.

The study compared 2,138 people in northern Israel who were diagnosed with colon cancer and 2,049 similar people without colon cancer. Blood samples from study participants were analyzed to detect small individual variations in the genetic code for an enzyme called HMGCR — the same enzyme that controls how fast the body synthesizes cholesterol.

Some people have a long version of the enzyme; some people have a short version. The study found that people with the long version of HMGCR benefited the most from taking statins to reduce the risk of colorectal cancer and cardiovascular disease.

"The test by itself cannot predict whether you have an increased risk of colon cancer; but it can predict whether taking statins will reduce the risk," says Stephen Gruber, M.D., Ph.D., the H. Marvin Pollard Professor of Internal Medicine and a co-leader of the study.

Currently, there is no commercially available genetic test for HMGCR variants, and statins are not approved by the U.S. Food and Drug Administration for colorectal cancer prevention. The researchers hope the study's results will encourage pharmaceutical companies to develop a test and conduct the clinical trials required for FDA approval, so physicians can prescribe statins for patients at risk for colorectal cancer. —SP

Stephen Gruber

SCOTT SODERBERG, U-M PHOTO SERVICES

MORE ON THE WEB

Planning Ahead

IF YOU WANT TO DECIDE WHAT kind of medical care you'll receive at the end of your life, write it down and tell your family now. Because when the time comes, they may have to decide for you. A U-M study found that more than one in four elderly Americans lacked the capacity to make their own medical care decisions at the end of life. Those with advance directives — including living wills or durable powers of attorney for health care — were more likely to receive the care they wanted. —SP

MORE ON THE WEB

Partners in Caring

NEARLY 40 PERCENT OF chronically ill older Americans live alone, relying on family and friends to help manage their health care, according to a new U-M study. Adult children and other family members want to help, but they often live far away and may not have the information needed to make a difference, says Ann-Marie Rosland, M.D., a clinical lecturer in internal medicine. To help solve this problem, U-M physicians developed a telephone monitoring system, CarePartners, that uses e-mail alerts and automated phone calls to involve family members in the care of a chronically ill relative. The program is now being tested in clinical trials. —SP

MORE ON THE WEB