




## *Highlights of Medical Research*

Across the UVa Health System, an exceptional community of biomedical researchers works toward new treatments, preventions, and cures for some of the world's most threatening diseases. They are making tremendous progress on many fronts, fueled, in part, by the human genome project and other major scientific breakthroughs of the past five years. These efforts reflect a growing interest in medical research at the national level and across the University of Virginia.

Recently, a University of Virginia commission released a far-reaching report, "Virginia 2020: Agenda for the Third Century," which targeted "science and technology" as a key growth area for UVa. Other areas include public service, international programs, and the arts. The commission recommended an aggressive expansion of UVa's biomedical facilities and major initiatives in faculty recruitment – an expansion that will in large measure depend upon private philanthropy. With the help of alumni and friends, the University can continue to foster the innovative research rapidly becoming a hallmark of the Health System. Already, five of UVa's basic science and clinical departments rank among the top 30 in the nation in funding received from the National Institutes of Health.

The following summaries represent promising areas of research currently underway.


### **ALZHEIMER'S AND PARKINSON'S DISEASES**

**Discovery of the underlying causes of Alzheimer's, Parkinson's, and other "sporadic" neurological diseases.** UVa researchers led by Davis Parker Jr., M.D., have identified genetic defects that appear to cause Alzheimer's and Parkinson's diseases and possibly schizophrenia and ALS (Lou Gehrig's Disease). Their findings suggest that these diseases may actually be inherited, though not in the way we typically think about inheritance. The genetic defect they have found is not in any of the 46 chromosomes, but in tiny organisms called mitochondria, which are present in every cell of the body, enable the body to process oxygen, and are passed on only by the mother. Scientists now have a starting point for developing drugs that prevent or slow the progression of these diseases rather than simply treat the symptoms. Compounds that inhibit genetic mutations responsible for sporadic neurological disorders are showing promise. One, R(+) pramipexole, has received FDA approval for initial clinical trials in ALS. Subsequent trials in Alzheimer's and Parkinson's are planned. These insights may hold the key to stopping the progression of a host of perplexing and devastating diseases.  *Science & Technology*

## ASTHMA


**Helping millions to breathe normally.** Between 10 and 20 million Americans are believed to suffer from asthma, a chronic lung disease characterized by swelling of the airways and spasms of the muscles surrounding the walls of the airways. It is the leading cause of hospitalization for children. Benjamin Gaston, M.D., an associate professor of pediatrics at the School of Medicine, and a team of investigators from UVa and two other institutions have discovered a link between a deficiency of S-nitrosothiol (SNO), a chemical that dilates the bronchial tubes, and severe asthma in children. A second study headed by Gaston found that an inappropriately low pH level within the lung might contribute to the disease. His team has now discovered specific, potentially treatable reasons for this imbalance, opening new areas of asthma research that are likely to lead to the development of new therapies. These discoveries may also have critical implications for the treatment of other diseases, such as cystic fibrosis and tuberculosis.

## BIOMEDICAL ENGINEERING

**Engineering solutions to heart and blood vessel diseases.** Part of UVa's emphasis on nanotechnology, UVa biomedical engineers are working hard to find new methods of preventing, diagnosing, and treating cardiovascular diseases. Klaus Ley, M.D., studies adhesion molecules and their role in the development of atherosclerosis, a potentially dangerous buildup of plaque in the arteries. His work may lead to the development of a new class of adhesion-molecule-based anti-inflammatory and anti-atherogenic therapies for patients. His colleague, Thomas Skalak, Ph.D., hopes to gain a better understanding of how arterioles (minute arteries) compensate for environmental changes that cause the flow of blood to slow down or the body's blood pressure to increase. With such knowledge, new drug therapies can be developed for heart disease, stroke, diabetes, wound healing, post-surgery recovery, and other diseases and conditions involving the body's circulatory system.  *Science & Technology*

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## CANCER

**In search of cancer vaccines.** UVa researchers are homing in on ways to harness the body's own immune system to destroy cancer cells. At the Cancer Center – ranked 22<sup>nd</sup> in the nation by the *U.S. News and World Report* – one team, led by Craig Slingluff, M.D., has already taken great strides toward developing a vaccine against melanoma, a serious form of skin cancer. UVa is participating in exclusive clinical trials of a FDA-approved, NIH-funded melanoma vaccine program. If their work continues to progress, these researchers could develop a wide range of immunotherapies to fight other cancers, including ovarian cancer. They seek support to expand immunotherapy research in ovarian cancer and to establish the Center for Human Immune Therapy.  *Science & Technology*

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**Understanding cell movement.** In normally functioning organisms, the migration of cells is highly controlled by signals that tell cells when to move and where to go. In cancer, the signaling process becomes deregulated, and cells begin to migrate, or metastasize, at will to places where they don't belong, with catastrophic consequences to the invaded tissues. To prevent tumor cells from metastasizing, Tom Parsons, Ph.D., chair of UVa's microbiology department, Rick Horowitz, Ph.D., and other researchers are trying to better understand how cells move. Research

shows that when a certain enzyme increases activity in a cell, there is a parallel increase in the cell's ability to migrate in response to a signal. Scientists are working to identify and characterize molecules to block this enzyme and halt unwanted cell movement. Ultimately, cancer patients won't be the only ones to benefit from this work. Since the ability of cells to move from one position of the body to another is central to many functions – from the development of limbs in an embryo to the activation of a health immune response in a sick adult – the potential for this research to expand to other therapeutic targets is enormous. The NIH has awarded a \$38 million, five-year, prestigious “glue” grant for research being led by Parsons and Horowitz and involving a consortium of 11 leading academic medical centers across the nation.

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**New ways to detect, prevent, and cure prostate cancer.** By studying the basic cellular differences between normal and cancerous prostate cells, UVa scientists are identifying targets that can be used for diagnosis, therapy, and prevention of prostate cancer, the nation's most frequently occurring cancer in men. What they discover could lead to breakthroughs in the treatment of other cancers as well. In August 2000, the estate of Paul Mellon awarded \$20 million to the University of Virginia School of Medicine to establish the **Mellon Prostate Cancer Research Institute**. The Mellon Institute's goal is to understand how and why the disease strikes some men and not others, to determine who is likely to have cancers that need aggressive treatment, and to design therapies to prevent the onset or progression of the disease. As part of the institute, a functional genomics program will be created to identify the genes involved in prostate cancer and to determine their function and relationship to clinical outcomes.

### **Tumor Angiogenesis**

Researchers led by Dan Theodorescu, M.D., Ph.D., are targeting genes that allow a prostate tumor to recruit surrounding blood vessels into helping it grow, or tumor angiogenesis. The team has discovered several of the key genes involved in this process. They hope to use their growing knowledge to design treatments that would cut off a latent tumor's blood flow and effectively starve it to death. These researchers have also developed a blood test to find residual prostate cancer after surgery. The test is more accurate and may also be quicker, less painful, and less costly than the current practice of removing and examining tissue samples. **VIRGINIA2020**, *Science & Technology*

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### **Keeping Slow-Growing Tumors from Switching into High Gear**

UVa microbiologists Sally Parsons, Ph.D., and Cancer Center Director Michael Weber, Ph.D., are working to understand the basic events that enable a prostate cancer cell to grow, even when the normal growth signals, such as testosterone, are absent. Initially, prostate cancer cells require the presence of the male hormone, testosterone, to develop. By cutting off the supply of testosterone, tumor growth can be slowed. Eventually, however, prostate cancer cells develop the ability to grow and spread independent of hormone levels. This progression makes the cancer resistant to most effective anti-hormone therapies. In 1999, the National Cancer Institute awarded \$4.2 million over five years to support Weber's team in this research. **VIRGINIA2020**, *Science & Technology*


## CARDIOVASCULAR DISEASE

**Preventing erratic heartbeats.** Close to 2 million Americans suffer from atrial fibrillation (AF or “irregular heartbeats”). Normally, a group of specialized cells – called the sinus node – trigger the heart to beat. Erratic heartbeats occur either when a signal originates from an abnormal point or when the signal travels in multiple chaotic circles, causing rapid heartbeats. In the Heart Center at UVa, cardiologists can now treat patients who have irregular heartbeats with two new procedures. Focal AF ablation maps the heart and locates the problem. Then a catheter carrying an electrical charge can find and destroy the problem cells. The second procedure, called multiple electrode catheter ablation, also uses a catheter to destroy tissue in a long line, creating a firewall against chaotic electric pulses. UVa researchers are working to refine these procedures with the aim of curing atrial fibrillation, which can cause blood clots and stroke.

**Prevention through detection.** You can’t prevent what you can’t detect. That’s why multidisciplinary teams of UVa cardiologists, radiologists, and biomedical engineers are honing imaging tools to see the heart and blood vessels more clearly and diagnose disease more accurately. Magnetic resonance imaging (MRI) is among the new generation of cardiac imaging techniques under investigation. Christopher Kramer, M.D., explores the use of MRI to detect developing plaque in coronary arteries and predict future attacks. He has discovered that MRI can be effective in determining the extent of damage to the heart’s small blood vessels and the amount of functional reserve remaining in the damaged heart muscle following a heart attack. These assessments can help physicians predict how much the heart muscle is likely to recover.

Clear images of structures within the body’s organs are elusive because of the lack of tissue to reflect imaging signals. Sanjiv Kaul, M.D., has pioneered a technique using microbubbles and ultrasound to detect early heart disease and assess inflammation, which plays a role in many diseases. The microbubbles, made of insoluble, encapsulated, high-molecular weight gases, produce a signal that can be detected and measured by ultrasound. Called myocardial contrast echocardiography (MCE), this technique can be used for greater accuracy in diagnosing heart disease and, possibly, in the delivery of drugs to sites of heart disease and inflammation.

## CONTRACEPTION & POPULATION CONTROL

**Pursuing a contraceptive vaccine.** UVa researcher John Herr, Ph.D., leads the nation’s most comprehensive effort to develop a vaccine that would use a woman’s own natural antibodies to prevent fertilization. An important component of Virginia 2020’s biodifferentiation initiative, the Center for Recombinant Gamete Contraceptive Vaccines has published 95 papers, received 13 patents, and started the process of seeking government approval for one element of a possible vaccine. His interdisciplinary team has isolated a human sperm antigen – CD52 – which may lead to certain types of immune-induced infertility. Information from the study may lead to development of an antibody-based birth control method. Private support is sought to aid in discovering new vaccine components, providing international training in immuno-contraception and conducting human trials.  *Science & Technology, International*

## DIABETES

**Beating type I and type II diabetes.** Diabetes – a chronic disease that causes the body to produce inadequate amounts of insulin – is the third leading cause of heart disease in the United States. Since type I diabetes destroys insulin-producing beta cells, people with this form of diabetes must inject insulin four or five times a day. In advanced stages, diabetes can lead to kidney failure and death. Jerry Nadler, M.D., of UVa, is leading an attack on diabetes across several fronts. One investigation looks at ways to arrest the disease in the early stages by employing ribozymes, which act as molecular scissors that cut off bad genes, in this case ones that are destroying beta cells. Another approach looks to reverse the disease by replacing damaged cells through transplantation. Nadler’s researchers have succeeded in showing that this approach could work to transplant new genes into beta cells. Both of these approaches may control type I and II diabetes; the former most prevalent in children while the latter typically develops after 45 and is the most common form of diabetes.


## DIGESTIVE DISEASE

**Targeting the Cause of Crohn’s.** UVa researchers are gaining ground on understanding Crohn’s disease, an autoimmune disorder causing inflammation of the intestines and affecting an estimated 1 million Americans. Working with a \$5.1 million grant from the National Institute of Diabetes and Digestive and Kidney Disease, Fabio Cominelli, M.D., Ph.D., director of UVa’s Digestive Health Research Center, and his colleagues recently established a colony of mice that spontaneously developed mild to moderate intestinal inflammation. The mice exhibited inflammatory lesions in the small intestine similar to human Crohn’s disease. Because the development is spontaneous, researchers can characterize the mechanisms that moderate the disease as they occur – providing a model to use in studying the disease in humans. They have discovered that TH1-type cells from the mice can transfer the disease and that these pathogenic T-cells directly mediate the resulting ileitis. This model is a significant tool for pursuing the cause, and eventual cure, for Crohn’s disease.


## GENETICS & MOLECULAR BIOLOGY

**Evidence of a second genetic code.** Sequencing and mapping the human genome was the first scientific step toward locating genes for diseases like cancer. Yet how do different types of cells – all containing the same DNA – selectively turn on or off those genes? UVa researchers, collaborating with scientists at the NIH, may have found the answer in an area outside the DNA that suggests the existence of another type of genetic code. UVa molecular and cell biologist David Allis, Ph.D., has co-authored recent articles in the journal *Science* that hypothesize how changes in proteins called histones, which coil around the DNA and form a structure called chromatin, provide sites where additional genetic coding takes place apart from the DNA. This series of chemical reactions within the chromatin is a new phenomenon of inherited change, or “epigenetics,” that cannot be accounted for by DNA alone. As researchers learn more about the histone code, they may be able to identify highly targeted therapies for disease control through gene regulation. And if this histone code can be used as a “master switch” to control which genes can be turned on or off, then scientists could reduce disease risk and turn off genes that promote tumor growth to help prevent cancer development, or conversely, turn on other genes to suppress tumors. VIRGINIA2020, *Science & Technology*


## GLOBAL HEALTH


**Extending health care and education around the world.** UVa's Center for Global Health involves world-class faculty committed to excellence in research, training, and education in international health. Their goal is to develop fellowship and scholarship programs designed to build sustained collaboration efforts between the University and health care professionals in developing countries. The center's scope extends beyond the School of Medicine to draw upon the resources of other UVa departments, including education, business, ethics, anthropology, and political science. The mission of the CGH is simple: to better understand how to alleviate the diseases of poverty. Diseases of poverty demand the attention of the entire world community. Our common humanity requires that our resources be directed at preserving and enhancing life wherever it is endangered, and poverty increases the frequency and severity of disease. The overall goal of the CGH is to build a comprehensive, international program of medical mentoring that provides specialized, life-saving care to developing nations.  *International*

## HEARING LOSS

**The potential to cure nerve deafness.** One out of four Americans over the age of 65 suffers significant hearing loss, which is most frequently caused by a loss of the tiny hair cells that transmit signals to the nerves of the ear. Until recently, any loss of hair cells was believed to be permanent and irreversible. However, studies by UVa researcher Jeffrey Corwin, Ph.D., and others have proven otherwise. Internationally recognized for his findings, Corwin is now focusing on ways to accelerate the regeneration of hair cells and restore hearing for millions of people.  *Science & Technology*  
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## INFECTIOUS DISEASES

**Harnessing the immune system to battle Hepatitis C.** UVa scientists are trying to determine what allows the hepatitis C virus (HCV) to evade or suppress the body's immune system, many times damaging or destroying a patient's liver, before it is discovered they suffer from the disease. Young Hahn, Ph.D., and a team of researchers in the Beirne B. Carter Center for Immunology Research are trying to uncover the "accomplice" in the human body that protects the virus from detection. The team has developed a model to study the role of HCV gene product on immune regulation, discovering that the core protein of HCV modulates the immune response in hepatitis C. This work could lead to new vaccines and drugs for preventing and treating HCV infection by blocking the action of the new HCV core protein.  *Science & Technology*

**Working toward a vaccine for the parasitic infection that causes dysentery.** Amebiasis, the second leading cause of death by protozoan parasites, primarily afflicts children in developing nations. Basic and clinical investigations by William Petri, M.D., and Barbara Mann, M.D., have resulted in a molecular understanding of how amoebas kill human cells and have led to new FDA-licensed diagnostic tests. The team is now developing a prototype vaccine to prevent amebiasis.  *Science & Technology, International*

**A revolutionary approach to clearing the body of viruses and other pathogens.** Biochemist Ronald Taylor, Ph.D., has established that a receptor called CR1 on the surface of red blood cells plays a key role in removing pathogens, and has developed a heteropolymer that connects to both the CR1 receptor and to antigenic sites on pathogens. Taylor has shown that in rhesus and cynomolgus monkeys, the technique cleared from the circulation in minutes substantial quantities of a model virus. Imaging studies indicated the virus was cleared to the liver, where it was destroyed and eliminated from the body. This research holds significant implications for investigations into and ultimately the treatment of autoimmune diseases, bacterial and viral infections, including HIV. Support is sought to establish proof of principle in studies involving E-coli bacterial strains, the Dengue virus, Marburg and Ebola virus, and autoimmune antibodies.

## **ORGANOGENESIS**

**Growing replacement organs.** Ariel Gomez, M.D., a UVa professor of pediatrics, is conducting research aimed at using a patient's own tissue cells to grow blood vessels, skin, kidneys, and other organs. As part of Virginia's renewed commitment to biodifferentiation, Gomez and his colleagues are currently working to understand how organs develop at the genetic and cellular level. They want to decipher the program that tells an undifferentiated cell to become, for instance, a kidney cell. Already, they have succeeded in growing the specialized cells that make up the basic kidney structures in a petri dish. If they continue to progress, Gomez and fellow scientists could develop techniques to allow a patient to have cells "harvested" for later use should an organ be irreparably damaged. A patient's body should be less likely to reject an organ made from its own cells, making organogenesis superior to traditional transplants.

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