

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 answering many of the basic questions that have plagued investigators for years: why disease starts, how it spreads, and how to cure it. What's more, they're taking these discoveries in the lab and turning them into promising treatments that offer patients new options and new hope.

UVA investigators are making tremendous progress on many fronts, fueled, in part, by public support and an increased emphasis on the role of scientific discovery. To keep pace with these efforts and speed new knowledge for patient care, the UVA Health System has embarked upon an aggressive expansion of biomedical facilities and major initiatives in faculty recruitment—both of which will 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. The following summaries represent promising areas of research currently underway at UVA.

ADDICTION

Halting addiction at its source. Drug, alcohol, and other substance addictions rank among the nation's greatest health threats. Today, scientists are looking beyond the strength of will power to the chemical and biological forces that drive addiction. At the forefront of this new addiction science is Bankole Johnson, D.Sc., M.D., Ph.D., M.Phil., chair of UVA's Department of Psychiatry and Neurobehavioral Sciences. Johnson has created a unique program at UVA that combines basic neuroscience with addiction treatment clinics. The program fosters translational research that helps speed laboratory discoveries into new lifesaving treatments and cures. Johnson is mapping the fundamental underpinnings of drug-seeking behavior to determine whether some addicts have functional or structural abnormalities at the molecular level in the brain. Already his approach has proven fundamentally innovative for identifying alcoholism as a major brain disease and demonstrating that medicines targeted toward the underlying disease can make a difference.

ALZHEIMER'S AND PARKINSON'S DISEASE

Detecting early biomarkers for Alzheimer's disease. Steven T. DeKosky, M.D., vice president and dean of the UVA School of Medicine, is an international leader in the field of Alzheimer's disease research. His basic neuroscience laboratory studies the early pathological and chemical alterations in the brain associated with the development of Alzheimer's as well as the neurochemistry of brain trauma and how it relates to Alzheimer's. DeKosky is currently leading a 3,000-person National Institutes of Health-funded trial on the ability of Ginkgo biloba to prevent or delay the development of Alzheimer's disease. He also is directing a program for developing biomarkers to track the effectiveness of Alzheimer's treatment and prevention therapies.

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 the team 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.

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 from other institutions have discovered a link between a deficiency of S-nitrosothiol, 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 the 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 build-up 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.

CANCER

In search of cancer vaccines. UVA researchers are honing in on ways to harness the body's own immune system to destroy cancer cells. The Human Immune Therapy Center (HITC) at the UVA Cancer Center has identified several peptide antigens for the immune response to melanoma, and has pioneered the development of cancer vaccines using complex mixtures of these synthetic peptide antigens. They have developed and led multi-institutional, investigator-

initiated clinical trials of melanoma vaccines since 1996, enrolling almost 500 patients in these trials. The HITC was initially designed to focus on melanoma, but has since expanded to provide investigators with the infrastructure to develop and implement clinical trials for other cancers, including colon, ovarian, and breast. The center has had good success at inducing immune responses to the vaccines in 80-100 percent of patients. Investigators have observed actual tumor shrinkage in some patients, and stabilization of tumor growth in other patients.

Accelerating clinical trials for lung cancer. David Jones, M.D., chief of thoracic surgery at UVA, and his team are identifying ways to make chemotherapy more effective for lung cancer patients. Jones is one of a few investigators anywhere who has been able to translate his research findings into clinical trials for patients with lung cancer. He has discovered that inhibiting a protein found in lung cancer cells actually increases the sensitivity of cancer cells to chemotherapy. He has also investigated why lung cancers tend to metastasize (or spread) more than many other cancers. The major reason patients die from lung cancer is metastatic disease. Jones' team has identified a metastasis suppressor gene called BRMS1 that is lost early in the development of lung cancer. Loss of this gene appears to result from specific tobacco carcinogens and the ensuing inflammatory response in the lungs.

Maximizing chemotherapy's effectiveness. The incredible biological diversity of cancer makes it an especially difficult disease to treat. The same type of breast cancer in two different women, for instance, will have unique molecular aspects that could mean one of the women will respond well to a particular drug while the other will not. For decades, chemotherapy's effectiveness varied widely from patient to patient. Now Dan Theodorescu, M.D., Ph.D., a surgeon scientist, and Jae Lee, Ph.D., a biostatistician, have found a way to identify the best possible targeted therapy for an individual patient's cancer. The Coexpression Extrapolation (COXEN) system uses complex mathematical formulas to match the unique molecular and genetic signatures of a patient's cancer against the known cancer-killing properties of an array of chemotherapeutic drugs and other targeted agents. The best matches then become the front-line agents in the patient's treatment.

Amazonian plant could halt breast cancer. Deborah Lannigan, Ph.D., led a team at UVA that made a startling discovery—a compound, derived from a rare South American plant, that may stop the growth of human breast cancer cells in lab cultures. The compound, called SL0101, works like a key in a molecular lock, inhibiting the action of a cancer-linked protein called RSK, which the researchers discovered is important for controlling the growth of breast cancer cells. Interestingly, SL0101 does not alter the growth of normal breast cells. Now, Lannigan is working with Ian Macara, Ph.D., and David Brenin, M.D., to grow “organoids” from human tissue to track cancer growth at the cellular level. By adding cancer cells to the tissue, the team can see how cancer develops in human tissue rather than in mice. This breakthrough will be used to test the effectiveness of several therapies, including the Amazonian compound.

Understanding the biology of pancreatic cancer. The five-year survival rate for pancreatic cancer patients is a dismal five percent. Diagnosing pancreatic cancer early, preventing its spread to other organs, and understanding the genetic profile of each patient's individual tumor can greatly improve treatment options and outcomes. Todd Bauer, M.D., and his team are working to identify new molecular targets and novel therapies for pancreatic cancer. They

recently demonstrated that blocking a particular protein, uPAR, decreased growth of human pancreatic cancers in mice and prevented tumors from invading nearby tissues. Bauer is also teaming up with biomedical engineer Kim Kelly, Ph.D., who recently received a \$1 million grant from the NIH to identify early biomarkers that could make pre-cancerous cells visible via MRI and PET scans. UVA teams are also evaluating signaling pathways in individual tumors in order to develop patient-specific targeted therapies.

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 become deregulated, and cells begin to metastasize at will to places where they don't belong, with catastrophic consequences. 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 healthy immune response in a sick adult—the potential for this research to expand to other therapeutic targets is enormous.

Fighting leukemia, lymphoma, and myeloma. The Hematological Malignancy Team at the UVA Cancer Center provides state-of-the-art care to patients with all forms of hematologic malignancy and offers cutting-edge therapies that can maximize disease response and cure. Dramatic advances have been made in recent years for many of these disorders, arising from new insights into their molecular biology and the application of novel targeted therapies that complement or replace traditional chemotherapeutic and radiotherapy approaches. Led by Michael E. Williams, M.D., UVA's clinical research program on hematologic malignancies is focused on the development of new targeted therapies. The goal of these new approaches is to improve survival and increase the number of patients cured, with fewer of the toxicities associated with traditional chemotherapy. These new treatments will be increasingly "customized" for individual patients and will ultimately be more effective.

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 2000, the estate of Paul Mellon awarded \$20 million to the UVA 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.

Bringing the next generation of prostate cancer care to the Commonwealth. UVA is a leader in the use of robotic prostatectomy to shorten recovery time and reduce damage to healthy tissue and nerves. The da Vinci Surgical System in use at UVA enables the surgeon to operate using very small incisions in the abdomen through which a camera and surgical instruments are inserted. This technology allows the surgeon to remove the cancer with great precision, thus reducing the likelihood of infection or other complications. In addition to providing outstanding care today, physicians at UVA are conducting research to improve the treatments of tomorrow. William Steers, M.D., chair of the Department of Urology, is exploring how to make cancer cells glow and use an imaging technique, called confocal microscopy, in order to increase surgical accuracy and reduce damage to healthy tissue and nerves.

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 the 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.

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.

A promise of better brain cancer treatments. Statistics are grim for brain cancer patients, especially those diagnosed with a malignant glioma. Half of patients battling high-grade gliomas survive less than a year after their diagnosis. Pioneering research at UVA brings hope to these patients, and holds the promise of transforming the management of malignant brain tumors. Benjamin W. Purow, M.D., is testing a novel treatment strategy he hopes will stop glioma in its tracks. His work focuses on a molecule called microRNA-7 that is suppressed in glioma cells. When re-introduced to these cancerous cells, microRNA-7 inhibits key cancer pathways and appears to shut down the growth of glioma cells. Moving forward, Purow wants to know how microRNA7 stops certain cancer-related genes, and whether some tumors might be more sensitive to it. Meanwhile, Jason Papin, Ph.D., and James Mandell, M.D., Ph.D., are in the early stages of developing a computational tool that will help doctors more quickly diagnose and effectively treat gliomas. Mandell and his research team analyze sections of tumor biopsies to determine where particular antibodies are binding to their targets and try to determine the state of the switches that turn cell pathways on and off. These biomarkers form a tumor's "signature" and can be used to identify and differentiate tumor types and grades.

Leading the fight against adenoid cystic carcinoma. Adenoid cystic carcinoma (ACC) is a rare form of cancer that most often develops in the salivary and lacrimal glands. A very slow

progressing disease, it is unrelenting and often metastasizes to the lungs and liver. To date, there is no known effective drug treatment for ACC, and it is unresponsive to radiation therapy. UVA physicians Henry Frierson, M.D., and Christopher Moskaluk, M.D., Ph.D., have made important discoveries about a genetic abnormality that may be the underlying cause of ACC— and a possible target for future treatments. They are researching this gene in the hunt for a cure for ACC and are also engaged in work that may have a more immediate impact on people with the disease. Recent technological advances enable chemotherapeutic compounds to be screened for efficacy against specific cancer types based on the cancer’s unique molecular composition. Drs. Frierson and Moskaluk are applying this technology to ACC to determine if any of the existing chemotherapy drugs might be effective in combating the disease.

CARDIOVASCULAR DISEASE

Preventing erratic heartbeats. Close to two 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 hearts. In the Heart and Vascular 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 to 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.

New treatments for heart rhythm disorders. During 2008, UVA became a leading provider of epicardial ablations, a new minimally-invasive treatment for ventricular fibrillation, or V-fib, a condition in which the heart’s lower chambers beat erratically. UVA’s nationally-recognized expert in epicardial ablations is Srijoy Mahapatra, M.D., a cardiac electrophysiologist. In addition to performing 61 epicardial ablations in 2008—one of the largest volumes in the U.S.—Mahapatra began developing new specialized tools and launched a research program to make the treatment more effective. Working in collaboration with cardiothoracic surgeon Gorov Ailawadi, M.D., he performed UVA’s first surgical ablations (which are also known as mini-maze procedures) on 10 patients last year.

DIABETES

Freeing diabetics from daily injections. Under the direction of Kenneth L. Brayman, M.D., the Center for Cellular Transplantation and Therapeutics has performed seven islet cell transplants since the center’s inception in 2004—with the last five transplants using islets processed completely in our own islet facility. Over the last three years, our results and productivity have been equivalent to, and in some cases better than, that of long-established islet transplant programs nationally and internationally. UVA was one of the first teams to identify the role of the development of donor-specific sensitivity and allo-antibody formation as important factors in early islet loss, and the return to hyperglycemia following islet infusion. The team also reported that using incompatible islet tissue (not matched to the corresponding ABO blood type) was possible in human transplantation. During the next three years, the center plans to expand on this success by building our programs in islet transplantation, with the goal of obtaining a license from the FDA to become an approved site for human islet manufacture.

Obtaining a biologic license from the FDA to produce and transplant human islet tissue is of paramount importance. In so doing, UVA will remain a prominent player on the national islet transplant stage.

Groundbreaking work on the artificial pancreas. UVA is the only institution in the world that has developed both islet transplant and artificial pancreas research programs. Working in conjunction, the two approaches should allow for improved metabolic control at times of glucose stress (meals, exercise, etc.), which is extremely challenging for the artificial pancreas, while the closed-loop system provides insulin at times of reduced glucose stress, freeing the transplanted islet mass from metabolic stress and exhaustion. In February 2009, the largest clinical trial to date of the artificial pancreas was completed at UVA, with 20 individuals with type 1 diabetes testing the closed-loop system. Led by Boris Kovatchev, Ph.D., the trial's initial results have been very promising, with improved overnight glucose control and a five-fold reduction in hypoglycemic episodes. The success of the two approaches has led to the development at UVA of a modular design concept, allowing for sequential testing, regulatory approval, and deployment of the bio-artificial pancreas system. Within three years, the team plans to run the first clinical trial of islet transplantation and the bio-artificial pancreas.

The genetics of diabetes. Investigators at UVA's Center for Public Health Genomics, led by Steve Rich, Ph.D., are working to translate findings from the Human Genome Project into usable science and treatments to benefit type 1 diabetics. His team is identifying potential genetic biomarkers that can be useful in assessing risk for developing the disease and its complications. A world leader in the fields of molecular epidemiology and genetics, Rich also heads the NIH Type I Diabetes Genetics Consortium, an international effort to understand the genes that underlie diabetes and its complications.

GLOBAL HEALTH

Extending healthcare and education around the world. UVA's Center for Global Health (CGH) brings together 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 healthcare 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. 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.

HEARING LOSS

The potential to cure nerve deafness. One out of every 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. Internally recognized for his findings, Corwin is now focusing on ways to accelerate the regeneration of hair cells and restore hearing for millions of people.

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 Han, 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.

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 amebas kill human cells and have led to new FDA-licensed diagnostic tests. The team is now developing a prototype vaccine to prevent amebiasis.

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. Using rhesus and cynomolgus monkeys as subjects, Taylor has shown the technique cleared substantial quantities of a model virus from circulation in minutes. 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, as well as bacterial and viral infections, including HIV.

MYOTONIC MUSCULAR DYSTROPHY

Reversing a debilitating disease. Myotonic muscular dystrophy (MMD) is a genetic disease that causes the progressive wasting of muscle, and damages the heart, brain, and other organs and tissues. No existing treatments stop or reverse this debilitating and life-threatening disease. The University of Virginia's Mani Mahadevan, M.D., is recognized as one of the world's foremost experts in MMD. In 1992, he was a member of the research team that discovered the gene mutation that causes MMD, and he has dedicated his life to finding a cure for the disease. Mahadevan and his UVA research team were able to reverse MMD in animal models by "turning off" the defective RNA. Remarkably, their experiments showed that the disease not only ceased in its progression but that previously damaged muscles and organs actually healed.

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.

STROKE

Envisioning the next generation of stroke care. UVA is committed to developing new and better treatments for stroke, as well as innovative tools for predicting and preventing it. Our research ranges from basic laboratory studies on fundamental cellular mechanisms and genetics to national, NIH-sponsored, multi-center clinical trials of new and promising drugs. UVA researchers explore varied and diverse approaches for preventing, treating or controlling strokes. One research team studies and tests new drug compounds that could improve recovery outcomes. Other research is aimed at ways to extend the window of time in which drugs can be administered effectively. Yet another team of investigators looks to genetics to help predict who is at the greatest risk for stroke. This knowledge could lead to more “individualized medicine,” using genetic information, along with other patient characteristics, to choose specific therapies for each patient.