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 advances in molecular engineering and other major scientific breakthroughs of the past ten years. These efforts reflect a growing interest in medical research at the national level and across the University of Virginia.

Leaders at the University of Virginia are committed to 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, lifesaving research rapidly becoming a hallmark of the UVa 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. But more importantly, the search for better treatments and cures to life-threatening diseases provide hope and healing for countless individuals.

The following summaries represent promising areas of research currently underway at UVa.

CANCER

Searching for cancer vaccines. UVa researchers are developing ways to harness the body's own immune system to destroy cancer cells. The Human Immune Therapy Center (HITC), led by Craig Slingluff, M.D., is conducting clinical trials of a melanoma vaccine that has shown remarkable promise in extending the lives of patients participating in UVa's clinical trials. Now Slingluff has expanded the vaccine program to clinical trials in ovarian, colon, and breast cancer. Researchers expect the vaccine used in the breast cancer trials to be relevant to patients afflicted with lung or pancreatic cancer. HITC researchers are also testing the delivery of cancer vaccines through a "patch" on the skin. Not only would the patch reduce side effects from injections, it would also open up the possibility of sending vaccines by mail to patients across the country.

Using nature to fight breast cancer. After five years of painstaking tests, scientists at UVa have discovered that a compound, derived from a rare South American plant, stops the growth of human breast cancer cells in laboratory cultures. Deborah Lannigan, Ph.D., and Jeffrey Smith, Ph.D., hope their discovery will translate into a successful drug for the treatment of breast cancer. The team has discovered that their compound works like a key in a molecular lock. It inhibits the action of a cancer-linked protein that the researchers discovered is important for controlling the growth of breast cancer cells.

Discovering new ways to detect, prevent, and cure prostate cancer. Two teams of researchers at UVa are conducting high-impact laboratory research projects that have great potential to improve treatment for men with advanced prostate cancer. Michael Weber, Ph.D., director of the UVa Cancer Center, and John Chirgwin, Ph.D., have laid the groundwork for future clinical trials of new diagnostic tests and therapies. Weber's lab is working to identify the molecular "targets" that drive the growth, metastasis, and survival of cancer.

The development of bone metastases is a painful and often debilitating effect of progressive prostate cancer. In a different project, Chirgwin and his colleague Theresa Guise, M.D., are studying the

interactions among different proteins produced by prostate cancer cells in an attempt to determine whether bone metastases can be treated and/or prevented. By learning more about the presence and interactions of certain biological targets, the researchers ultimately will aid research into drugs that can help to treat or prevent advanced prostate cancer.

Finding more effective treatments for lung cancer. Making chemotherapy treatment for non-small cell lung cancer more effective and less toxic may eventually be possible. David R. Jones, M.D., and his team are currently investigating a protein that had been shown to promote tumor cell survival even after the tumor had been exposed to chemotherapy. In fact, Jones discovered that common chemotherapy agents used to treat non-small cell lung cancer actually activate the protein, allowing tumor cells to survive instead of die after treatment. Now the team has identified a way of inhibiting the protein and enhancing chemotherapy's ability to kill lung cancer cells, meaning that lower doses of chemotherapy can be used to treat tumors, allowing patients to suffer fewer toxic side effects.

Creating highly accurate tests for bladder cancer. Bladder cancer is often difficult to diagnose. Diagnostic tests have been created based on the increasing knowledge of molecular changes that occur as this cancer progresses, but none of these tests have the optimal sensitivity and specificity to detect the cancer. Now, Dan Theodorescu, M.D., Ph.D., and his team have created a test that is not only more accurate but may also be quicker, less painful, and less costly than the current practice of removing and examining tissue samples. The test will also help doctors determine how the cancer will behave and how best to treat it.

Expanding clinical trials in pancreatic cancer. When Virginia State Senator Emily Couric came to UVa for treatment of pancreatic cancer, her doctor, Michael Williams, M.D., designed a new regimen of chemotherapy for her. Even though pancreatic cancer is rapidly fatal when diagnosed in advanced stages, Couric lived far longer than expected, and her regimen has shown dramatic results in other patients. Now investigators are refining the process and studying the response to the treatment in other patients diagnosed with advanced pancreatic cancer.

Creating new therapies to fight brain cancer. Meningiomas, the most common brain tumors, are curable surgically when the location and the shape of the tumor allow complete removal. Tumors that cannot be completely removed are devastating. Due to what medical scientists call the blood/brain barrier, chemotherapy is not an effective treatment for brain cancers. David Schiff, M.D., and his team are working to change the chemistry of an existing chemotherapy agent so that it bypasses the blood/brain barrier and, it is hoped, block tumor growth and starve the tumor of the blood flow it needs in order to survive.

CARDIOVASCULAR DISEASE

Preventing erratic heartbeats. Close to two million Americans suffer from atrial fibrillation, or irregular heartbeats. 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 and Vascular Center at UVa, cardiologists can treat patients who have irregular heartbeats with two new procedures. Now UVa researchers are working to refine these procedures with the aim of curing atrial fibrillation, which can cause blood clots and stroke.

Studying the role of inflammation. In 1963, Robert M. Berne, M.D., hypothesized that the chemical adenosine helped to regulate coronary blood flow to the heart. Today adenosine is well recognized for its importance in regulating cardiac blood flow and heart rhythms. As the basis for treatment for conditions including cardiac arrhythmias, or irregular heartbeats, it has saved thousands of lives. Now

one of Berne's students, Joel Linden, Ph.D., is the principal investigator for a $7.4 million grant from the National Institutes of Health to study the role of inflammation in lung injury—a condition that also impacts heart function.

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.

Studying the cause of atherosclerosis. Atherosclerosis happens gradually as deposits of fat, cholesterol, calcium, and waste products build up in the inner lining of the arteries. Sometimes called the hardening of the arteries, this disease can cause heart attack, stroke, difficulty walking, gangrene, or the loss of a limb. No one can say for sure what causes atherosclerosis at the cellular level, though it's well known that high cholesterol, cigarette smoking, high blood pressure, diabetes, and obesity can contribute to it. Now cardiovascular researchers at UVa have discovered evidence that lymphoid structures may be contributing to the development of atherosclerosis because they attract a response from the body's immune system. Klaus Ley, M.D., and Elena Galkina, Ph.D., are continuing their research in order to one day possibly manipulate the immune system to block the disease's progression.

CONTRACEPTION & POPULATION CONTROL

Pursing 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. UVa's Center for Recombinant Gamete Contraceptive Vaccines has started the process of seeking government approval for one element of a possible vaccine that may lead to the development of an antibody-induced infertility. Information from the study may lead to development of an antibody-based birth control method.

DIABETES

Reversing type 1 diabetes. Researchers at UVa have discovered that a combination of lisofylline and exendin-4 reversed the course of type 1 diabetes in mice. Jerry Nadler, M.D., director of the Diabetes and Hormone Center of Excellence, and his colleagues theorized that simultaneously blocking a biological pathway that damages beta cells in the pancreas, while adding a growth-promoting stimulus for beta cells, might provide the critical ability to reverse type 1 diabetes. This exciting finding may one day lead to restoring insulin-producing cells in people with type 1 diabetes without the need for toxic anti-rejection medications.

Freeing diabetics from daily injections. UVa surgeon Kenneth Brayman, M.D., Ph.D., is one of the few surgeons in the U.S. to perform islet cell transplants, an experimental procedure designed to free type 1 diabetics from daily insulin injections. Islets are cells within the pancreas that secrete insulin. With type 1 diabetes, the body's immune system destroys islets, forcing patients to take daily injections to survive. Islet transplants can help diabetics begin to produce insulin again on their own.

Uncovering the link between diabetes and heart disease. Statistics from the Centers of Disease Control and Prevention reveal that people who are insulin-resistant have an increased risk of heart disease and that 65 percent of people with full-blown diabetes will die of heart disease and stroke. Jerry

Nadler, M.D., and his colleagues at UVa believe they know why. Nadler has identified an inflammation-inducing enzyme in blood vessels that is activated when exposed to high levels of sugar seen in diabetes. Inflammation can lead to the formation of fatty plaque and hardening of the arteries, the precursor to heart disease. In pre-clinical experiments, Nadler has used a novel anti-inflammatory agent called lisofylline to block this inflammatory response. His discovery could ultimately lead to treatments that protect diabetics from heart disease.

Envisioning a new way to cure type 1 diabetes. Adult stem cell research offers the possibility to defeat type 1 diabetes at the genetic level. Raghu Mirmira, M.D., Ph.D., is studying the complex system of genetic switches that cause certain cells to begin producing insulin for the body. He believes that by understanding how these switches work he may be able to induce different kinds of cells to produce insulin. Mirmira's team plans to utilize technology pioneered at UVa to deliver these genetic "master switches," called transcription factors, to specific stem cells already in a patient's body.

Changing the way we treat diabetes patients. In the course of their work, UVa scientists often generate insights and develop new techniques that have the potential to radically change the way we treat diabetes. For instance, Susan Kirk's, M.D., work on diabetes during pregnancy shows that a hormone secreted by pregnant women acts similarly to another, which is commonly associated with diabetic eye and kidney disease. If Kirk can find a way to block this hormonal reaction, she may be able to control symptoms in all diabetics, not just pregnant women.

Imaging diabetes. People with diabetes experience elevated levels of blood sugar, which can cause damage to the body's organs and vascular systems because their muscles cannot store sugar efficiently due to insufficient insulin or insulin resistance. Eugene Barrett, M.D., is leading a scientific investigation to determine how insulin works within the muscle to enable it to store sugar. Barrett and his team are developing new imaging techniques to trace the movement of insulin from the bloodstream to muscle tissue. Their findings could lead to new ways of designing drugs that can restore a diabetic patient's ability to utilize sugar.

DIGESTIVE DISEASE

Targeting Crohn's disease. UVa researchers are gaining ground on understanding Crohn's disease, an autoimmune disorder causing inflammation of the intestines and affecting an estimated one 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 Center of Excellence, has identified a key protein that plays an important role in the development of inflammatory bowel disease, or IBD. His findings may give researchers a new target for future therapies for Crohn's disease.

"Seeing" Crohn's disease. Inflammatory bowel disease, the general term for Crohn's and ulcerative colitis, can be notoriously tough for doctors to diagnose and monitor. But now doctors at UVa have successfully tested in animals a new, painless, non-invasive technique to catch IBD early. The technique uses tiny microbubbles developed at UVa to measure the severity and extent of inflammation in the intestine. The technology has the potential to be used in a clinical setting to non-invasively detect intestinal inflammation, as well as monitor disease severity during the course and treatment of IBD.

GLOBAL HEALTH

Extending health care and education around the world. UVa's Center for Global Health (CGH) involves world-class faculty committed to excellence in research, training, and education in international health. 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. Since 2001, over 200 UVa students have been selected to conduct projects in Asia, Africa, and Latin America. And the program has developed sustained, NIH-supported UVa collaborations with top universities in Brazil, Ghana, China, the Philippines, and South Africa. 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 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.

Restoring hearing loss. Scientists at UVa have discovered a new protein that could one day show them how to restore hearing loss due to genetic causes, the reason for half the cases of hearing loss in children. Profound, early-onset deafness is present in thousands of children and is traced to genetic causes in at least half of cases. Jeffrey Holt, Ph.D., and his colleagues have identified a protein that allows the sensory cell in the ear to convert sound stimulus into an electrical response that can be transmitted to the brain so that sound can be perceived. Identification of this protein and the gene that encodes it could bring future treatments for deafness.

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. Their work could lead to new vaccines and drugs for preventing and treating HCV infection.

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. Now, with a $4.2 million grant from the National Institutes of Health, the team will develop a vaccine against the world-wide killer.

A revolutionary approach to clearing the body of viruses and other pathogens. Biochemist Ronald Taylor, Ph.D., has identified a key receptor on the surface of red blood cells that plays a key role in removing pathogens. This research holds significant implications for investigations into and ultimately the treatment of autoimmune diseases, bacterial and viral infections, including HIV.

NEUROSCIENCES

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 in tiny organisms called mitochondria, which are present in every cell of the body and are passed on only by the mother. These findings will help produce simple diagnostic tests for these diseases and open up new avenues 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 combination has received FDA approval for initial clinical trials in ALS. Subsequent trials in Alzheimer's and Parkinson's are planned.

Uncovering the mechanisms responsible for premature nerve cell death. Jim Bennett, M.D., Ph.D., is searching for a way to block premature nerve cell death in chronic brain diseases such as Alzheimer's and Parkinson's—the first step in developing treatments to stop disease progression. His team has developed novel technologies that allow manipulations and replacement of mitochondrial genome inside living cells, opening up a completely new therapeutic approach to treatment. Now the team is investigating natural plant-derived antioxidants as treatments.

Discovering one key to Parkinson's disease. Research by neuroscientists at UVa shows that oxygen-free radicals are damaging proteins in mitochondria, the tiny cellular "batteries" of brain cells. This damage may be one main cause of Parkinson's disease, the chronic movement disorder that affects at least one million Americans. Researchers at UVa believe the damage is taking place in a large protein structure called complex 1, the first stop in the electron transport chain, which produces an electrical charge inside mitochondria. Parkinson's patients may one day benefit from drugs that can slow the damage from free radicals.

Finding a new treatment for cocaine dependence. Researchers from UVa have found that ondansetron, a serotonin antagonist drug, has shown promise in battling cocaine and its addictive qualities. Despite almost two decades of scientific effort, no medication has been approved by the Food and Drug Administration for the treatment of cocaine dependence. Bankole Johnson, M.D., Ph.D., chief of UVa's Department of Psychiatric Medicine, and his team found that individuals treated with the highest dose of ondansetron had low dropout rates and a greater rate of improvement than those who were not treated with the new drug. Cocaine dependence and its psychiatric, social, and economic consequences add up to a major public health problem in the U.S.

WORKING ACROSS GROUNDS / PAN-UNIVERSITY INITIATIVES

BIOMEDICAL ENGINEERING

Engineering solutions to heart and blood vessel diseases. As part of UVa's emphasis on nanotechnology, 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 and anti-inflammatory 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.

HUMAN GENOME PROJECT

Advancing our knowledge of the human genome project. One of the many exciting recent developments in science is the sequencing of the human genome. Scientists at UVa are going beyond the DNA sequence and are looking at the science of epigenetic signaling and regulation of gene

expression. Epigenetic signals can change gene expression without altering the DNA sequence, by "switching" genes on or off. Determining how these signals work is expected to dramatically advance our understanding of many human diseases that are not purely genetic in nature, but are products of changes in gene expression, including cancer progression. The findings of Sepideh Khorasanizadeh, Ph.D., and other UVa structural biologists may have direct implications for the large-scale human epigenome project that is expected to pave the way for breakthroughs in understanding both normal and disease states.

ORGANOGENESIS/REGENERATIVE MEDICINE

Adult stem cell research at UVa. Theoretically, stem cell research holds the key to curing any disease in the body. Adult stem cells, which persist even after we are born, serve as a back up—if a particular kind of cell needs replacing, these adult stem cells can differentiate and form those cells. However, adult stem cells lack the potential of embryonic stem cells and can only form a limited number of cell types. Researchers at UVa, led by Adam Katz, M.D., are working to harness adult stem cells to fight a variety of diseases. For example, stem cells could be nudged to become heart muscle to treat patients after a heart attack, while bone cells could be used to heal complex fractures or to treat osteoporosis. Stem cells can also be used to create new insulin-producing islet cells that are then transplanted into patients with type 1 diabetes. Adult stem cell research at UVa offers great hope and promise to countless individuals.

Growing replacement organs. Ariel Gomez, M.D., 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, trying to decipher the program that tells an undifferentiated cell to become, for instance, a kidney cell. The team has 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.