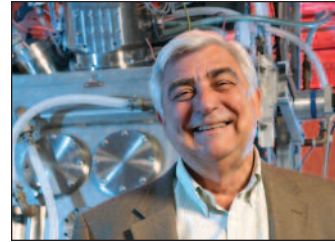
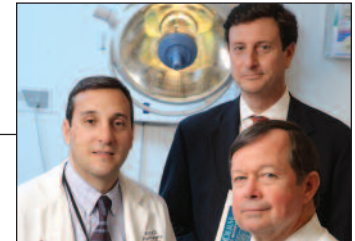


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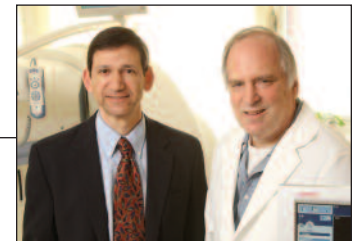
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Spring 2009

Research Highlights from the University of Virginia: Translating Discovery to Application

To Our Readers

Translational research is anything but a linear process. Basic research can suggest solutions that the “real world” never dreamed of. The application of basic knowledge can produce unexpected innovations and open new avenues of discovery. Some stunning developments in medical treatment come not from classical hypothesis-driven investigations, but from the computationally intensive integration of existing information. In many fields, these nonlinear and iterative relationships involve collaborations among investigators from different disciplines and different kinds of institutions. Intellectual property developed by one investigator can have great value to another, and it can have financial value for the University and our partners as well. The dissemination of knowledge is a core mission of the University, and no creative act is greater than the act of bringing knowledge to society.

Here we highlight the distinctive character and potential of a comprehensive university research community: no other research organization includes the range and diversity of research interests and tools, and no other research organization has the capacity to perform the iterative and collaborative processes illustrated here. At the University of Virginia we now are developing a comprehensive plan for research that is based on the lessons of

projects such as these. In so doing, we aim to establish a new model for research and a new foundation for teaching and learning as well.



Thomas C. Skalak

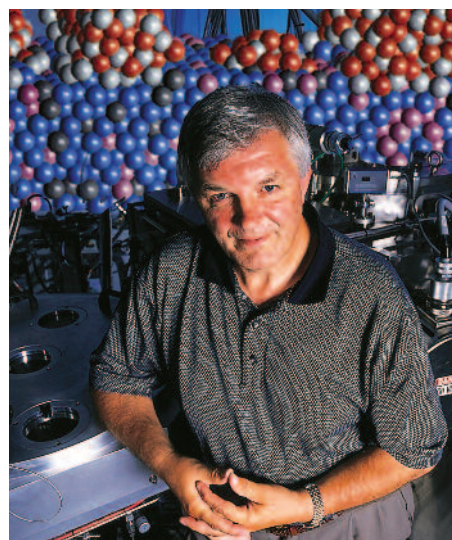
Thomas C. Skalak
Vice President for Research

Applying Perfect Coatings

To say that directed vapor deposition is a bit like spray painting barely hints at the power of this revolutionary new technology. It coats materials with a higher degree of control and efficiency than any other process. It can be used to apply coatings composed of exotic molecules and to produce layers that are not only extremely fine but also have novel properties because of the way the molecules are placed on the surface. Equally impressive, the vapor can be directed exclusively at the target and not the surrounding area, even coating surfaces that are outside the line of sight.

For more than a decade, research teams led by Haydn Wadley, University Professor and the Edgar Starke Research Professor of Materials Science and Engineering, have been world leaders in developing techniques that greatly expand the potential of this technology. Among other projects, Wadley has created coatings that protect materials from heat and produced thin films for lithium ion battery systems.

In directed vapor deposition, materials are vaporized using electron-beam guns similar to



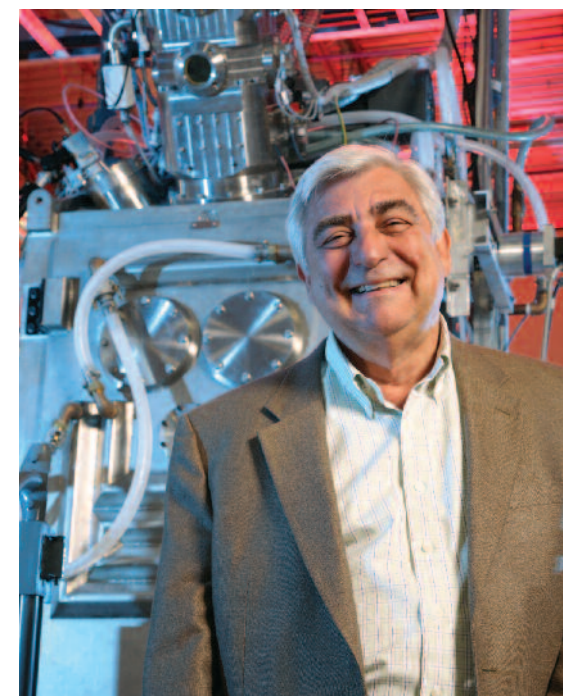
Haydn Wadley, University Professor and the Edgar Starke Research Professor of Materials Science and Engineering

those used to create semiconductors a microscopic layer at a time. These guns, however, have been specially modified to permit their operation in a low vacuum environment, making it possible to envelop the evaporated materials in a jet of carrier gas. By manipulating this gas, operators can control the evaporants with unequaled precision. “We set up the specific conditions required for the assembly of molecules on a surface,” Wadley explains. “We can control the direction from which they arrive, their energy and motion on the surface, and other conditions that determine their properties.”

Wadley sees himself engaged in the interrelated activities of training students and doing basic research at the frontiers of materials science and physics. While his focus is on fundamental research, there are occasions when his work has led to patentable discoveries. Wadley believes that having U.Va. intellectual property available to be licensed by start-up companies is an important way to further economic development. He cites Stanford University as an academic institution that has had a profound impact on the economy in the surrounding region, and he stresses that the decline in industrial research and development makes the role of universities even more critical.

In 2000, Directed Vapor Technologies International (DVTI) was formed to capitalize on Wadley’s patents associated with creating and controlling the assembly of materials from vapor. “As it turns out, directed vapor deposition is an economical way to coat materials and make thin films,” Wadley says.

“AT DVTI, our job is to take basic research and explore its application for a variety of purposes,” says Harry Burns, CEO and president of DVTI. “When you have a technology that is as powerful and flexible as directed vapor deposition, that’s a big job.” DVTI is working with government and industry partners to develop coatings that protect surfaces from heat, wear, and corrosion. When used in airplane engines, for instance, DVTI’s thermal barrier coatings can reduce fuel consumption or increase engine thrust. DVTI is also working on coatings that could pave the way to



Harry Burns, CEO and president of DVTI

longer superconductive cables and to improve the efficiency of solid oxide fuel cells and batteries.

Currently, DVTI is working with its partners to optimize the technology and developing prototypes for specific applications, a process that entails conducting extensive testing. “Testing is particularly important with conservative industries like aircraft manufacturing that are extremely careful about adopting new technologies,” Burns notes. As part of this effort, DVTI has built a production-scale coating machine at its Charlottesville facility.

At the same time, Wadley follows the development of the company with interest. “The work done at DVTI sometimes points to areas where there is a lack of fundamental knowledge,” he says. “It serves to help us see our research in a different context and suggests directions for future inquiries.” ■

Treating Burns and Wounds

One of the first challenges a physician faces when patients are brought into the emergency room is cleansing their wounds of debris, a process made more painful by the products that are available for the task. Many of them, like hexachlorophene and iodine, are even toxic. They destroy healthy cells along with bacteria.

As director of U.Va.'s Wound Healing Research Laboratory, George Rodeheaver was determined to find a biocompatible, water-soluble solution that could be used to clean wounds without doing more damage. "The goal of our lab is to apply science to maximize the healing process," he says.

Rodeheaver set his sights on finding a surfactant, a wetting agent essential for cleaning agents, that was non-ionizing and that would not destroy healthy tissue. After extensive research, he developed a base formulation that was commercialized as Shur-Cleans®. "I discovered a correlation between chemical structure and toxicity that led me to this surfactant," he says. As a wound cleaning agent, Shur-Cleans is ideal. A physician can use it to flush debris out of a patient's eyes without causing pain or harming tissue.

Rodeheaver soon realized that his cleansing formula might have other applications. The products used by surgeons to treat burns and chronic wounds like bedsores also have their drawbacks. Because they are not truly water soluble, they form a residue that interferes with the delivery of healing agents. This residue must be removed each time a dressing is changed, a process that causes additional pain and destroys new tissue.

Rodeheaver modified the formula for Shur-Cleans to produce a stable gel. Not only is this gel water soluble, but it also thickens at body temperature, making it the perfect vehicle for coating wounds and burns and delivering a variety of agents, including antibiotics. Rodeheaver patented it as PluroGel™. For the past 15 years, physicians at the University Hospital have used PluroGel to carry antibiotics to burns and chronic wounds, dramatically reducing the incidence of infection among their patients and augmenting the healing process. In 2008, Rodeheaver was named the Edlich-Henderson Inventor of the Year by the University of Virginia Patent Foundation for this work.

Because PluroGel as a carrier for antibiotics has not been approved by the FDA, it can only be used at the University. When Dr. Adam Katz joined the Department of Plastic Surgery as the director of the Chronic Wound Care Clinic, he was so impressed by PluroGel's value that he partnered with Rodeheaver to start a company, PluroGen Therapeutics, Inc. PluroGen's initial

goal is to secure FDA approval for a topical antibiotic product based on PluroGel and make it widely available. They enlisted Neal Koller, a former pharmaceutical company executive, to serve as president and CEO.

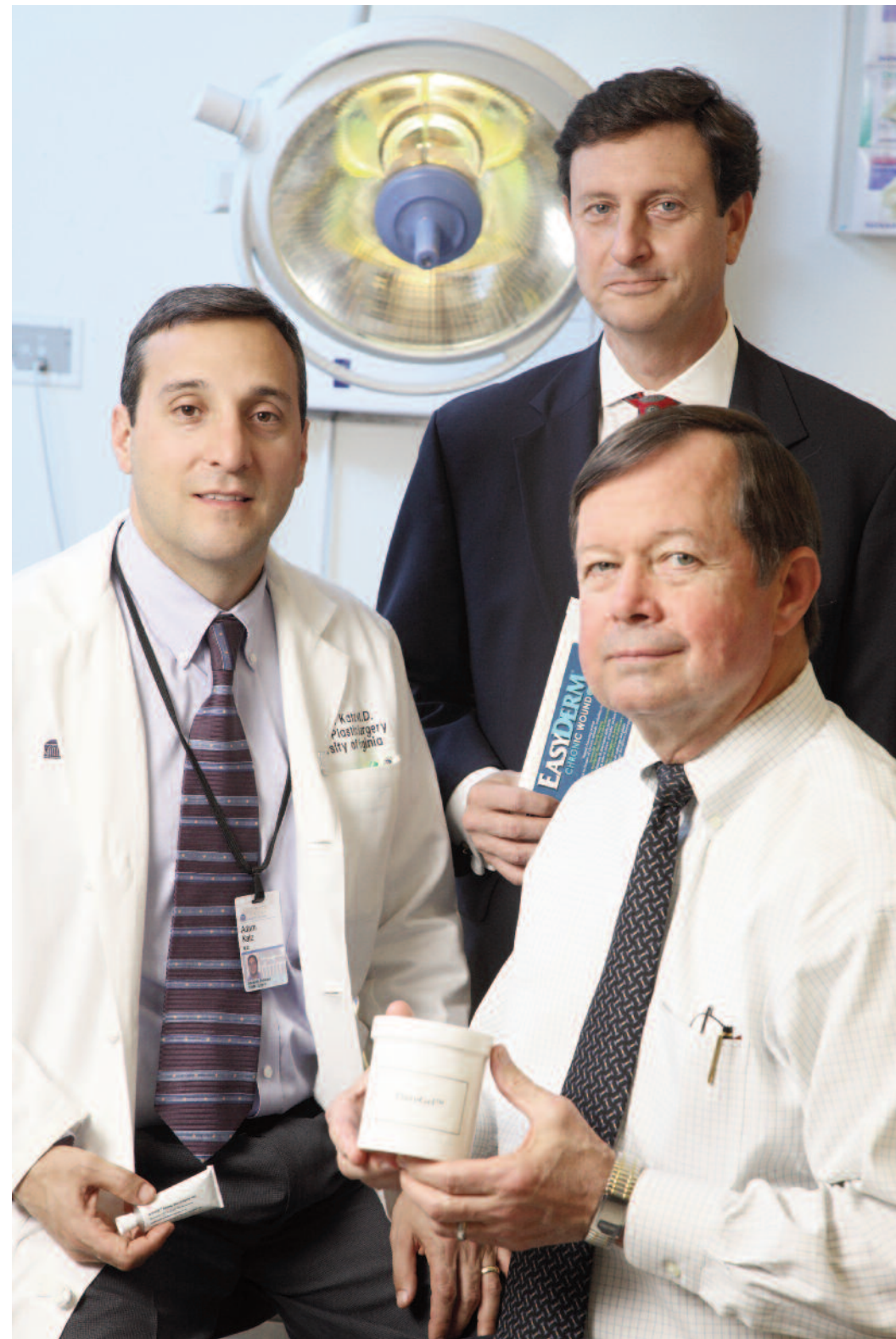
In creating the company, Katz and Rodeheaver tapped into the T100 Alumni Mentoring Program, an initiative in the Office of the Vice President for Research that matches alumni business experts with emerging companies. Through T100, PluroGen received mentoring and financial support to refine its business plan and build its network of relationships. Guidance from T100 was helpful in bringing Koller on board.

One result of starting a company like PluroGen is that it stimulates additional research. New companies actively seek out products that diversify their portfolio and increase their chance of success. At the same time, researchers see in these start-ups a vehicle to realize the full potential of their discoveries. This has certainly been the case with PluroGen. Rodeheaver has been collaborating with former faculty member Dr. Cato Laurencin and his team to find new applications for PluroGel. They are combining PluroGel with nanocrystalline silver, an important antimicrobial; and with chitosan, a naturally occurring biocompatible material that makes PluroGel dressings last even longer. At the same time, Katz is working with PluroGel to deliver fat-derived stem cells to wounds to promote healing.

In the meantime, Koller focuses on keeping the company afloat by promoting the use of PluroGel for a variety of products that do not require FDA submission. For example, one of PluroGen's commercial partners has already introduced a line of skin and wound cleansing wipes that include PluroGel. PluroGen is working with a number of other companies to develop products for additional new markets, including the retail, cosmetic, and dermatology markets. Who knows? The next generation of skin cream may have a PluroGel base. ■

"The goal of our lab is to apply science to maximize the healing process."

—George Rodeheaver



Clockwise from left: Adam Katz, director of U.Va.'s Chronic Wound Care Clinic; Neal Koller, CEO of PluroGen Therapeutics; and George Rodeheaver, director of U.Va.'s Wound Healing Research Laboratory

Treating Alcoholism like a Disease

Historically, the United States has shown itself to be as poorly equipped to deal with the consequences of alcoholism as some individuals are to deal with the effects of alcohol itself. Temperance advocates saw alcohol dependence as a moral failure, urging alcoholics to sign pledges to reform. The 18th Amendment to the Constitution made alcohol illegal, prohibiting its sale, manufacture, and transportation, only to be repealed 13 years later. More recently, society has viewed alcohol abuse as a behavioral disorder to be treated with therapy and 12-step programs.

In each case, there has been only limited success in reducing the social costs and preventing the personal tragedies caused by alcohol dependence. Today, there are approximately 14 million people in the United States who abuse alcohol, and the financial repercussions of alcohol abuse—ranging from medical costs and lost productivity to harm to others—have been estimated to be \$185 billion annually.

“Most people assume that addiction reflects a lack of moral willpower,” says Professor Bankole Johnson, M.D., chair of the U.Va. Department of Psychiatry and Neurobehavioral Sciences. “However, there is a biological component of alcoholism—just as there is with diabetes or high blood pressure. Alcoholism is a disease of the brain.”

While the idea of alcoholism as a disease gained currency in recent years, it was a metaphor in search of a factual basis. Johnson was instrumental in changing that. He is a world leader in researching the biological mechanisms of addiction and testing treatments that might interrupt them. For his achievements, Johnson was honored with the Distinguished Psychiatrist Award, one of the highest honors bestowed by the American Psychiatric Association. He founded ADial Pharmaceuticals to translate his discoveries into treatments that are effective in helping people with alcohol dependence.

Alcoholism is now understood as an abnormality in the regulation of certain brain chemicals, especially dopamine. Dopamine is modulated by more than a hundred neurotransmitters—and Johnson and his colleagues Dr. Nassima Ait-Daoud and Ming D. Li have focused on the role of one of them: serotonin. They have discovered that people with a particular variant of the serotonin transporter gene have a propensity for heavy drinking, and that ondansetron, a drug used to

prevent chemotherapy-induced nausea and vomiting, is particularly helpful in treating these people.

For Michael Torok, chief operating officer of ADial, this combination of discoveries is particularly exciting. “People have talked about the promise of personalized medicine,” he says. “ADial has the means to deliver it.” ADial is seeking FDA approval for using ondansetron to treat alcoholism and is developing an inexpensive test to identify individuals who would particularly benefit from it.

ADial is also pursuing the introduction of a series of combination medications using ondansetron and two other drugs used to treat

alcohol dependency, topiramate and naltrexone. Along with Ait-Daoud, Johnson conducted a series of pioneering studies that showed that topiramate—a drug currently used to treat seizures and migraine headaches—was highly effective in curbing alcohol consumption. ADial’s first dual medication, which combines topiramate with ondansetron, is expected to enter Phase III clinical trials in 2010, at which point it will be tested against standard treatments.

The treatments that Johnson and his colleagues have developed are not merely more effective than existing treatments; they are more likely to be adopted by heavy drinkers. “One of the chief advantages of the treatments that ADial is devel-

oping is that individuals don’t have to stop drinking to use them, as they do with current medications,” Torok says. “Our treatments can help people stop or manage their drinking more effectively, not just keep them from drinking once they’ve stopped.”

ADial’s goal is to provide people with other choices besides complete abstinence or complete failure, improving their ability to function in society. “One of the reasons I conduct my research is that as a physician and a scientist, I want to reduce suffering,” Johnson says. “ADial is part of that vision.” ■



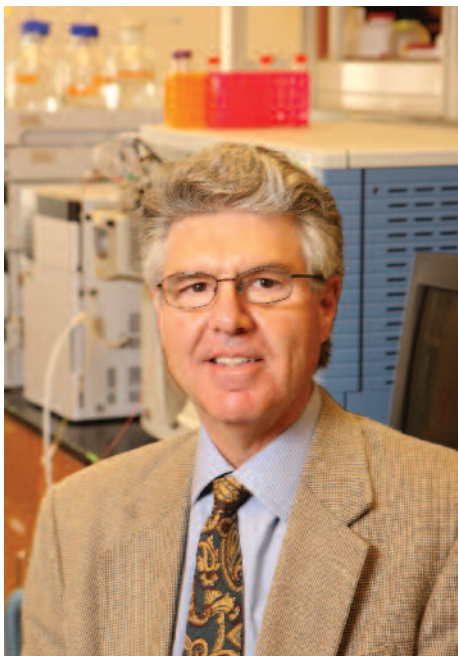
From left: **Nassima Ait-Daoud**, director of the U.Va. Center for Addiction Research and Education, and **Bankole Johnson**, Alumni Professor and chair of the Department of Psychiatry and Neurobehavioral Sciences

Controlling Inflammation

Power plants produce energy by burning coal. Human beings burn a compound called adenosine triphosphate (ATP). And while power companies struggle to find ways to deal with the byproducts of combustion, evolution solved that problem for humans long ago. The human body not only recycles the byproducts of ATP, it has found other uses for them as well.

One of these molecules—adenosine—is produced when cells under stress burn lots of ATP. Accordingly, it has been adapted by the body as a cell signaling agent, to help the body deal with inflammation and injury. Because receptors for adenosine are found on virtually every cell type in the body, its therapeutic potential for treating diseases like diabetes, atherosclerosis, and arthritis is vast.

For more than 40 years, researchers at the University of Virginia have been world leaders in uncovering adenosine's role in cell signaling and in synthesizing molecules similar to adenosine. Realizing that this research had the potential to significantly improve human health, Joel Linden, a professor of cardiovascular medicine; and Timothy Macdonald, professor of chemistry, joined forces with business executive Robert Capon to build a company that licensed U.Va. patents in this area. Their work has shown such promise that their company, Adenosine Therapeutics, was bought in 2008 by Clinical Data, a global pharmaceutical company, in one of the largest deals of its type ever done with



Timothy Macdonald, professor of chemistry

University technology.

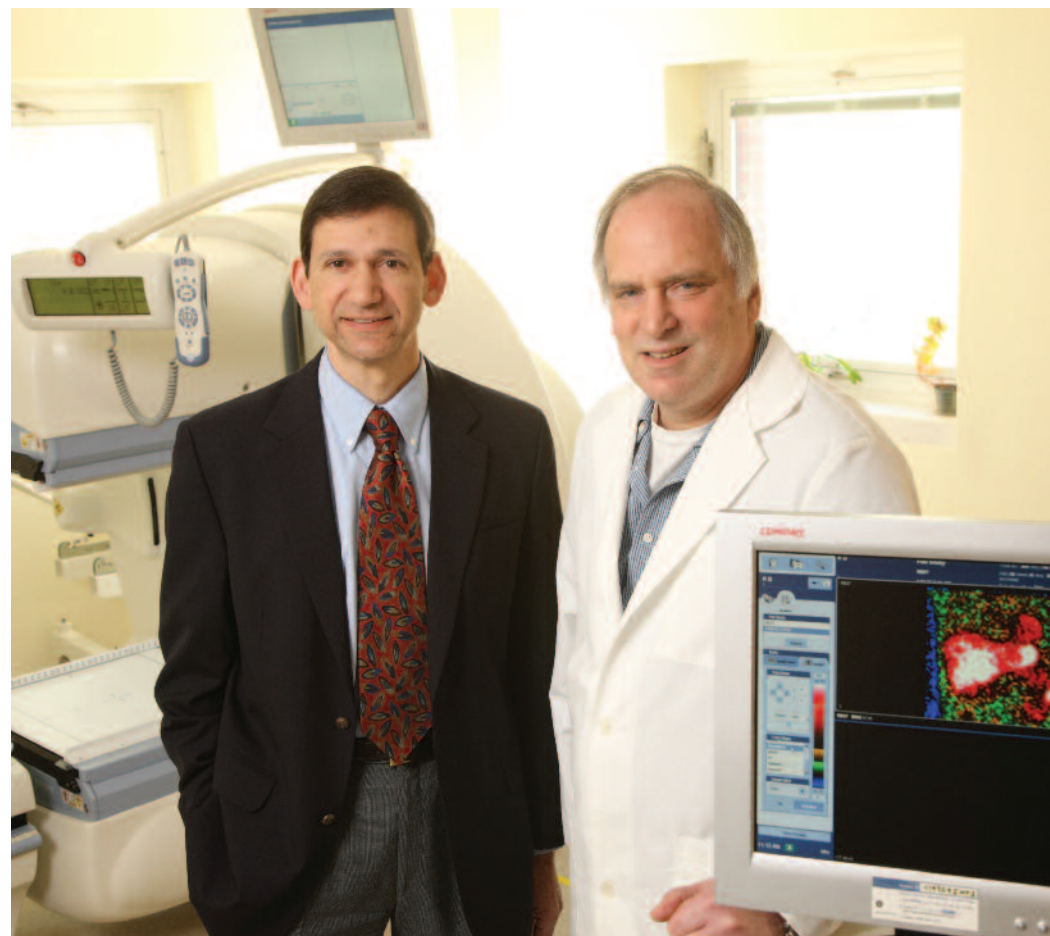
The key to harnessing adenosine has been the identification of the four adenosine receptors, each of which sets in motion a specific cascade of events within the cell when adenosine docks with it. Linden played a prominent role in identifying these receptors, and his collaboration with Macdonald enabled him to elucidate the functions of each one. Macdonald synthesized adenosine-like molecules that would dock with a specific adenosine receptor, either mimicking the action of adenosine or blocking it.

In effect, these molecules allowed Linden to turn the receptors on and off, the key to enabling him to discover their function. "When you're doing biological research, the University's tradition of medicinal chemistry is wonderful," Linden says. "You can walk across campus and find people who can help you develop the research tools you need as well as create potentially therapeutic drug candidates."

Linden found that one of the four receptors is responsible for dilating coronary arteries. The ability to dilate these arteries at will is particularly useful for imaging coronary arteries in the hearts of people who are not healthy enough to undergo traditional treadmill stress testing. Although there are other pharmacological stress agents on the market, Macdonald's synthetic vasodilator potentially causes fewer side effects, is fast acting, and disappears from the system quickly. Adenosine Therapeutics has shepherded this compound, named Stedivaze™, through development. It will enter Phase III clinical trials later this year, where it will be evaluated against existing treatments. Additional compounds are in development to treat a variety of inflammatory diseases. Both Linden and Macdonald have received the Edlich-Henderson Inventor of the Year Award from the University of Virginia Patent Foundation for their discoveries.

Adenosine Therapeutics served to amplify the consequences of Linden's and Macdonald's work in other ways. Researchers in fields like nephrology, infectious disease, and transplantation who were intrigued by adenosine's ability to control inflammation partnered with Adenosine Therapeutics to secure Small Business Innovation Research grants from the federal government. These grants are meant to help commercialize research discoveries, and the company's role was to supply the specialized molecules these researchers needed. "This process brought in tens of millions of dollars in research funding to the University," Linden notes. "In the process, researchers could assemble the preliminary findings they needed to apply for traditional NIH grants for more basic research."

The result of this work has been more than a



From left: **Rob Capon**, CEO of Adenosine Therapeutics, and **Joel Linden**, professor of cardiovascular medicine

score of patents held by the University for uses of adenosine-related compounds. Many of these patents were paid for, licensed, improved, and commercialized by Adenosine Therapeutics. "All this activity benefits the University because it adds to the stock of intellectual property it holds and creates value by developing its patents into commercial products," notes Capon. By raising private equity capital and through its relationships with larger pharmaceutical companies, Adenosine Therapeutics secured the funding needed to finance clinical trials, moving these inventions closer to commercialization, where they can potentially bring benefits to patients by fulfilling important unmet medical needs. "This is a great tribute to the University," Capon added.

"The benefits of a company like Adenosine Therapeutics are broader and deeper than most people realize," says Linden. "A company is an engine that expands the research and development capability of the whole institution.

Research at the company and research at the University are synergistic. As long as U.Va. maintains its prominence in medicinal chemistry there will be opportunities for new start-up companies like Adenosine Therapeutics." ■

"The benefits of a company like Adenosine Therapeutics are broader and deeper than most people realize."

—Joel Linden

Making Cancer Manageable

Until recently, treatment for cancer—though quite sophisticated in practice—has been limited to three basic approaches: killing cancer cells by removing them surgically, blasting them with radiation, or poisoning them with chemotherapy. The goal is to destroy all malignant cells, curing the cancer and preventing remission. Even when these three approaches are used in combination and treatment is administered repeatedly, some cancer cells survive, and the disease can and does recur.

In a way, the flaw in this line of attack has been its ambition. In the last few years, a number of treatments have been approved with the more modest goal of simply holding cancer in check. They do this by blocking the cellular pathways that enable cancer cells to grow and flourish. Tau Therapeutics, based on intellectual property patented at the University by Timothy Macdonald, a medicinal chemist, and former faculty member Dr. Lloyd Gray, a pathologist, specializes in developing cancer-fighting drugs that control the calcium T-channel in cells. Calcium T-channels are tiny, transient openings in the cell membrane that allow calcium, which is necessary for cell proliferation, to enter the cell. “If we can stop the tumor cells from dividing, we can provide a meaningful increase in lifespan,” Macdonald says.

“Tau’s method represents an advance over other treatments to halt the growth of cancer,” says Tau’s president and CEO Andrew Krouse. “That’s because all pathways for tumor cell proliferation—for tumor growth as well as for the new blood vessels needed for tumor growth—converge at the point of the calcium T-channel, CaV3.2, that Tau has patented.” Tau’s vision is to block CaV3.2, thus allowing cancer to be managed as a chronic disease like diabetes or heart disease.

Tau’s initial focus is to reposition existing calcium-channel blockers that have already been

approved for other conditions, a tactic that can decrease the time to bring the new cancer medications to market. For instance, it will be sponsoring a Phase Ib/IIa clinical trial to test the efficacy of mibefradil, a calcium-channel blocker that had been approved for the treatment of hypertension and chronic angina. Tau envisions mibefradil being used in combination with other medications to treat a wide range of cancers.

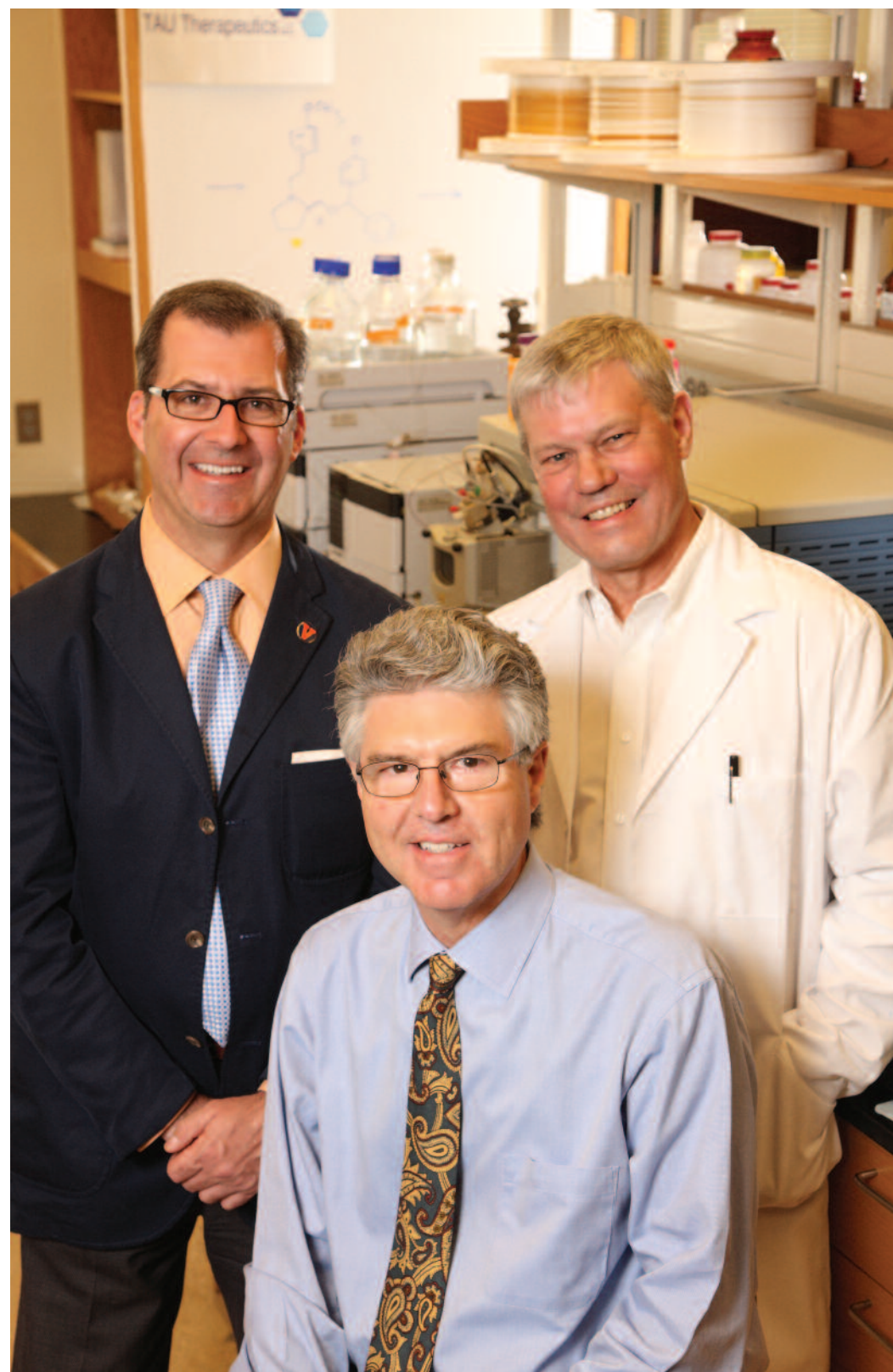
Tau’s longer-term strategy involves building libraries of small molecules that could control calcium-channel processes. It has patented two libraries, synthesized and tested more than 400 compounds, and has identified several viable substances for development. The first of these, TTL 1177—a drug targeted at colon cancer—is undergoing laboratory testing, and Tau could file an investigational new drug application with the FDA within the next 18 months.

Tau’s approach could have several advantages. Unlike conventional cancer treatments, Tau’s medications will not destroy healthy tissue. Because calcium T-channels only appear during adulthood as part of a pathological condition like cancer, T-channel blockers focus only on cancer cells. In addition, molecules in Tau’s pipeline can be administered orally, an improvement over drugs like Avastin that must be injected.

Ultimately, Tau’s goal is to be the world leader in producing calcium T-channel drugs for the personalized treatment of cancer. “We envision combining early detection through diagnostic screening of the calcium T-channel, biopsies for the particular expression of the target, and the prescription of complementary drugs based on the molecules in our library,” says Krouse. “In this way, we hope to treat cancer like any other chronic disease, extending both the length and quality of life of people with cancer.” ■

“If we can stop the tumor cells from dividing, we can provide a meaningful increase in lifespan.”

—Timothy Macdonald



From left: **Andrew Krouse**, CEO of Tau Therapeutics; **Timothy Macdonald**, professor of chemistry; and **Lloyd Gray**, pathologist