



415 Lane Road
MRS Bldg., Rm. 1010
Box 801394
Charlottesville, VA 22908

Tel: 434.924.5500
Fax: 434.924.2828

cvrc@virginia.edu

www.healthsystem.
virginia.edu/internet/cvrc

Center Staff

Dr. Klaus Ley
Director

Evelyn Gorman
Business Manager

Eileen Gallagher
Education and Events
Coordinator

Sandra Saxe
Research Administrator

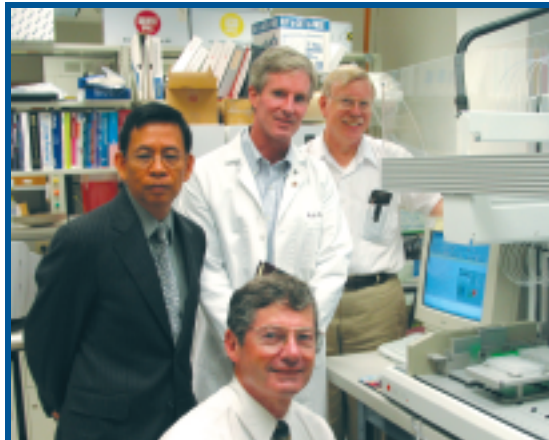
Jackie Jarrell
Assistant to Drs. Linden
and Hedrick

Teresa Morris
Assistant to Drs. Schwartz
and Leitinger

Barbara Spangler
Administrative Assistant

NHLBI Funds Felder, Carey Hypertension Grant

CVRC members Dr. Robin Felder and Dr. Robert Carey's PPG application recently received an overall excellent/outstanding rating from the National Heart, Lung and Blood Institute. As a result, the doctors have been



Drs. Robert Carey (front), Pedro Jose, Robin Felder
and Core Lab Director Theodore Mifflin

awarded a \$10.2 million dollar grant for the study entitled, "Dopamine and Angiotensin

Receptor Interactions in Genetic Hypertension."

Joining Dr. Felder and Dr. Carey on the project is Dr. Pedro Jose, Vice Chair and Professor of Pediatrics, Physiology and Biophysics at Georgetown University. Dr. Jose is Felder's former graduate studies mentor at Georgetown.

The PPG will study the interaction between two renal sodium regulatory pathways with key roles in blood pressure regulation. The hypertension group will investigate how dopamine D1, and angiotensin AT1 receptors regulate blood pressure and renal sodium transport through shared and independent second messenger pathways.

"Through these grant funds, we wish to stimulate research in the area of hypertension and especially salt sensitivity, because these diseases account for more disability and death than all other disease combined [NHLBI]," says Dr. Felder, PI for the project.

Working together, Dr. Felder and Dr. Jose
cont. pg. 4

Scientific Obituary for Andrew P. Somlyo, M.D.

By Richard A. Murphy, Ph.D. (April 12, 2004)

Andrew P. Somlyo, M.D., died unexpectedly on January 14, 2004. Dr. Somlyo was Chair and Charles Slaughter Professor of Molecular Physiology and Biological Physics, Professor of Internal Medicine (Cardiology), and a member of the Cardiovascular Research Center at the University of Virginia. He is internationally recognized for his many contributions to our current understanding of smooth muscle function among several other areas.

Dr. Somlyo was born in Budapest, the son of a cardiologist, and was educated in Jesuit schools. After the premature death of his father, he emigrated with his mother to the United States to escape the communist occupation in 1948. Subsequently he earned a B.S. (1954), M.S. (Pathology, 1956) and M.D. (1956) at the University of Illinois. Dr. Somlyo was an intern and resident in Cardiology at Philadelphia General Hospital before moving to New York for advanced clinical training at Mount Sinai Hospital, Bellevue

Hospital and Columbia Presbyterian Medical Center between 1956 and 1961. At this junct-



Andrew P. Somlyo, M.D.
(1930-2004)

ture he focused on research, first earning an M.S. at Drexel University of Technology in Bioengineering in 1963.

Dr. Somlyo was appointed assistant Professor (1963), Associate Professor (1967) and Professor (1971) of Pathology and
cont. pg. 2

The National Institutes of Health is funding a major new Program Project Grant (PPG) in the Cardiovascular Research Center, beginning in August 2004. The PPG, led by Dr. Joel Linden (Cardiology/CVRC), is entitled "Role of Inflammation in Pulmonary Injury," and seeks to better understand molecular and cellular mechanisms responsible for pathological inflammation of the lung and consequent myocardial dysfunction.

Project one, led by Dr. Linden, explores "Molecular and Cellular Targets of Adenosine in Lung," project two, headed by Dr. Klaus Ley (BME/CVRC), focuses on "Neutrophil

Trafficking to Normal and Inflamed Lung," and the third project, led by Dr. Brent French (BME), investigates "Cardiopulmonary Response to Lung Injury." The PPG will bring in about \$8.2 million over five years.

The program is well-integrated, focusing on common themes of pulmonary inflammation and mechanisms of lung protection by adenosine. The studies will provide new insights into the cells and cytokines that control lung and heart inflammation and injury and are likely to lead to new therapies. A feature article will follow in the next issue of CVRC News. ■

Scientific Obituary (cont.)

Physiology at the University of Pennsylvania. At Penn he was a member of the Graduate Group in Cell Physiology and served as Director of the Pennsylvania Muscle Institute and Director of the Biomedical Instrumentation Group, as well as the Principal Investigator of an NIH Program Project for muscle studies.

In 1988 Andrew Somlyo was recruited as Chair and Charles Slaughter Professor of Molecular Physiology and Biological Physics at Virginia by Dean Robert M. Carey. This was a key time in the growth of the School of Medicine. The basic science departments had a primary teaching role up to the mid 1960's when then Dean Kenneth Crispell initiated a major expansion program with the aid of a large Health Sciences Development Award from NIH and construction of Jordan Hall. Dr. Crispell recruited new chairs in all departments who subsequently attracted a relatively youthful, research oriented faculty. The second expansion of basic sciences under Dean Carey saw construction of MR4, the Jordan addition and MR5, plus recruitment of a new cadre of chairs. Dr. Somlyo was the first of this group, and he played a key role in setting standards of research excellence, faculty recruitment, and the establishment of research centers and facilities that have garnered international recognition.

Dr. Somlyo developed the Dept. of Molecular Physiology and Biological Physics into a center of excellence for structural biology. A variety of innovative techniques are applied to elucidating protein structure with a particular emphasis on membrane proteins associated with cell signaling and cell homeostasis with special relevance to cardiovascular

diseases and cancer. Dr. Somlyo was awarded a Program Project by the National Institutes of Health that supports and coordinates many of these research initiatives. The Department now consistently ranks among the five leading physiology departments in the United States.

Dr. Somlyo's research contributions are voluminous. Most of this research was a close collaboration with his wife, Dr. Avril V. Somlyo. The Somlyo laboratory is notable for the application of new technologies to smooth muscle and other cell types. Pharmacological and electrophysiological investigations of vascular smooth muscle predominated during the 1960s. In 1968 and 1970 the Somlyos published two exhaustive reviews on smooth muscle. Up to that point the field was balkanized, with research fragmented among specialists in the various organ systems. The reviews provided an authoritative source of information that attracted new investigators and integrated their findings. In important respects these reviews marked the beginning of smooth muscle as an active growth area at the cellular level. They established the Somlyos as leaders in the field. It is easy to forget the magnitude of this effort in these days of searchable databases and bibliographic citation software. Dr. Somlyo's remarkable mastery of the literature and synthesis skills continued to advance his field through many influential reviews throughout his career.

The ultrastructure of smooth muscle continues to frustrate efforts to synthesize structural and functional information analogous to the synthesis represented by the sliding filament/crossbridge paradigm in striated

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Scientific Obituary (cont.)

muscle. Nevertheless in the 1970s the Somlyo lab applied electron microscopy to smooth muscle, demonstrating the existence of arrays of thick and thin filaments with the polarities necessary for a sliding filament mechanism. This led to investigations of the membrane systems regulating Ca^{2+} and activation-contraction coupling in smooth muscle.

In the late 70s, the Somlyos applied high resolution scanning electron probe X-ray microanalysis in studies of Ca^{2+} mobilization and the distribution of Mg^{2+} and other ions in smooth muscle and other cell types. In collaboration with physicist, Henry Shuman, this technology was enhanced and combined with X-ray mapping and electron energy-loss spectroscopy. Techniques to permeabilize smooth muscles with toxins to allow clamping of small ion concentrations were developed in the 1980s. When coupled with laser-flash photolysis of caged compounds concentrations of Ca^{2+} and other second messengers such as inositol 1,4,5-trisphosphate could be changed instantaneously. The Somlyos initiated a series of ongoing influential studies on signal transduction.

Permeabilized smooth muscle preparations were developed in the 1990s to show the dependence of force on Ca^{2+} and cross-bridge phosphorylation could be modified. Regulation of myosin (light chain) phosphatase activity was implicated as responsible for modulation of the Ca^{2+} -sensitivity of contraction. Subsequently the Somlyo lab showed G-protein coupled receptors and the Rho A/Rho kinase pathway participated in regulation of myosin phosphatase activity. This period also brought extensive application of laser confocal scanning microscopy and cryo-atomic force microscopy to various unresolved structural problems in smooth muscle and other tissues.

Even a brief overview illustrates the breadth of Dr.

Somlyo's impact on the current understanding of smooth muscle cell function. It has resulted in approximately 250 peer-reviewed research papers, 70 invited chapters, and the editing of 5 books. The legacy is the product of a formidable intellect, insistence on excellence, a workaholic approach to his laboratory, quirky humor and an ability to laugh at himself, as well as the collaboration of Avril Somlyo who shares these qualities. These accomplishments have been recognized in numerous awards including his election as Fellow of the American Association for the Advancement of Science and Fellow of the Biophysical Society, service on the editorial boards of 15 journals and many advisory committees, and numerous invited lectures. Another important contribution to the field that is hard to quantify are the scientists trained in the Somlyo laboratory: Some 58 individuals at the pre- and postdoctoral levels, plus visiting professors, enrich the field internationally.

Andrew Somlyo also excelled in non-scientific pursuits. His knowledge of fine arts and many traditional crafts matched his mastery of the scientific literature. He and Avril Somlyo have assembled internationally preeminent collections of Japanese porcelains and Tibetan art.

Sir Andrew Huxley, recipient of a Nobel prize for his work on nerve and skeletal muscle, tells the story of how he found his dissertation research topic. One of his advisors, Lord Adrian, offered several bits of advice. One of these emphasized "don't mess with smooth muscle." Then and for many decades afterwards smooth muscle was scientifically in disrepute as a diverse and complex tissue unsuited for the elucidation of basic biological principles. In my judgment, Andrew Somlyo made smooth muscle respectable for the rest of us.

He will be missed. ■

CVRC Labs To Benefit From More Cord Tissue

The BME/CVRC Endothelial Cell Isolation Shared Facility is now receiving increased supplies of human umbilical cord tissue specimens from UVa and Martha Jefferson Hospitals.

This higher yield will expand the capabilities of the shared facility and allow researchers in BME and the CVRC access to primary human endothelial cells from both artery and venous vessels.

The new arrangement will also prove cost-effective, as cells are very expensive to purchase from companies that supply such material.

"We are all very thankful to the CVRC Executive Committee and the IRB Committee at Martha Jefferson Hospital for their dedication to biomedical research in the Charlottesville community," says Dr. Brett Blackman, Assistant Professor of BME, who runs the shared facility.

Dr. Blackman's interest in this area began during a postdoctoral fellowship at Harvard Medical School, where he was

trained to isolate human cells from the umbilical cord. The cord is a rich source of both arterial and venous endothelial cells, which Dr. Blackman's lab uses in its research.

"When I arrived at UVa two years ago, I was the only researcher harvesting these cells from this tissue," adds Dr. Blackman. "Many other investigators in BME and the CVRC had a great interest in using these cells, and I thought it would be a good idea to share these resources with our immediate community."

The tissue is available to all interested investigators to assist in vital cardiovascular research, such as the study of endothelial cell structure being carried out by Dr. Ley and Dr. Helmke. Interested parties should contact Dr. Blackman at bblackman@virginia.edu for more information. ■

discovered that GRK4 gene variants, alone or via their interactions with the renin-angiotensin system play a crucial role in the pathogenesis of human genetic hypertension.

A Professor in the Department of Pathology, Dr. Felder came to UVA in 1984 and was appointed the Director of the Medical Automation Research Center in 2000. His primary areas of research include hypertension and the biochemical mechanisms associated with blood pressure regulation.

Dr. Carey adds value to the team with his research focus on the renin angiotensin system, and the dopaminergic system and their function in human physiology. He is a David A. Harrison III Distinguished Professor and Dean emeritus of the School of Medicine at UVA.

Dr. Jose brings to the project expertise in adrenergic mechanisms involved in blood pres-

sure control as well as genetic polymorphisms that play a role in the etiology of hypertension and salt sensitivity.

Administrative, analytical and mouse breeding support will come from Margaret Margin, Amy Thompson, Theodore Mifflin, Ph.D., at UVA and John Jones, Ph.D. of Georgetown University.

With a contribution from the Cardiovascular Research Center, the PPG will purchase a confocal, real-time, two-color fluorescent microscope, to be made available as a shared facility to investigators throughout UVA. The hypertension study will use the equipment to collect images of protein trafficking in cells that maintain their polarized nature in culture, similar to the orientation in vivo.

“We are on the verge of understanding the basis for this elusive disease,” says Dr. Jose. ■

Ley & Helmke Receive Four Year R01 Funding

CVRC members Dr. Klaus Ley and Dr. Brian P. Helmke have received funding for their four year, renewable NHLBI R01 grant entitled, “Micro-Viscometric Studies of the ESL in Microvessels.” Helmke and Ley are co-investigators on the project with Dr. Edward R. Damiano, of the University of Illinois at Urbana-Champaign (UIUC).

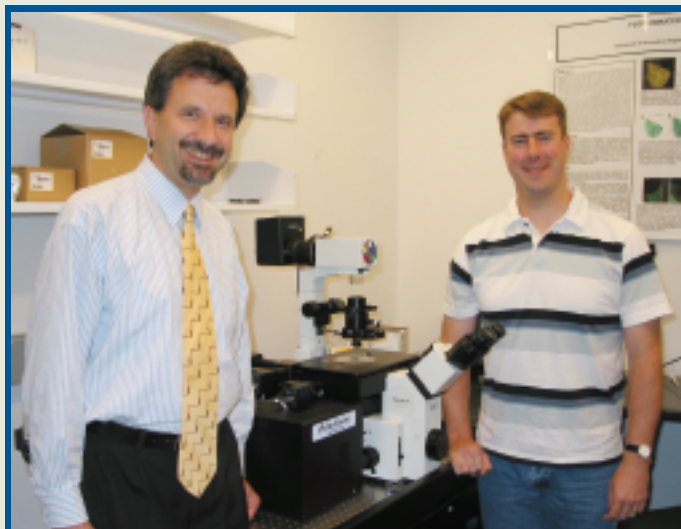
The study represents a first in the measurement of spatial and temporal relationships between mechanical interactions in the cytoskeleton and locations involved in initiation of mechanotransduction. It will study the influence of the vascular endothelial surface layer (ESL), originally discovered by Dr. Brian Duling, on microvascular hemodynamics in venules and arterioles, how ESL is expressed in cultured cells, and its role as a barrier to spontaneous rolling of leukocytes from the free stream in venules.

The project’s goal is to establish the extent to which the glycocalyx surface layer on vascular endothelium extends into the plasma-rich zones of venules and pre-capillary arterioles, and the implication that structure has on the transmission of fluid stress to the vascular endothelium in vivo.

“This model...is changing how we think about cell sensing,” says Dr. Helmke.

Dr. Helmke, Assistant Professor of BME,

works with flow chambers and utilizes deconvolution microscopy, which allows the retrieval of very fine detail from tissue, even inside the cells. Dr. Ley will contribute expertise in inflammatory cell recruitment and the development of micro-viscometric technique. Dr. Damiano, a theoretician and modeling expert, will analyze the data produced by Helmke and Ley.



Drs. Klaus Ley and Brian Helmke

“Measurement of cell layers has been largely ignored elsewhere,” says Dr. Ley. “Now UVA is leading the way in developing these measurement techniques.” ■

Dr. William H. Guilford was recently named a recipient of the 2003-04 All-University Teaching Awards. His award is one of five honors given to outstanding faculty members teaching students in various disciplines at UVA. Dr. Guilford is an Assistant Professor of Biomedical Engineering.

"I can't think of any teacher more deserving than Will, particularly as he has reached out and inspired students across three schools of UVA: the School of Medicine, SEAS, and Arts and Sciences, at undergraduate, graduate and medical student levels," says Dr. Klaus Ley, Director of the CVRC.

Dr. Guilford's love of teaching was born during his under-



Dr. William H. Guilford

graduate years while substitute teaching for his chemistry professor. Years later, he believes in a "do as I do" approach to teaching.

"It is truly an honor to be recognized by my students and colleagues for something I so enjoy doing. My own teachers and professors instilled in me the love of learning, and made clear the responsibility of educators to teach well. I look forward to a long career of the same joyful responsibility."

The awards were presented at the annual "In Celebration of Teaching" banquet held on April 28 in the Rotunda. ■

Li to Coordinate Research in Progress Series

Dr. Guohong Li has been named host of the CVRC's RIP Seminar Series for the 2004-2005 academic year. As Assistant Professor of Research in Cardiovascular Medicine, Li has a great desire to foster the sharing of cardiovascular research, the overall goal of the series.

Born and educated in China, Dr. Li pursued postdoctoral studies in Vascular Biology at the University of Alabama in Birmingham. He came to UVA in 2003 and has become a valued member of the CVRC community, contributing his knowledge and expertise to the cellular and molecular mechanisms underlying inflammation response.

The RIP Seminar Series plays an important role in the CVRC by bringing together students and faculty each month to present their ideas and engage in discussion.

Dr. Li takes over for the outgoing coordinator, Dr. Yuqing Huo, who is now Assistant Professor at the University of Minnesota. RIP Seminars are held regularly on the third Thursday of the month in MR5 seminar room 1005. Dr. Li may be reached at (434)924-2614 or by e-mail at gl6a@virginia.edu. ■

UVA Shows Well at Toronto Conference

CVRC representation was strong at the XIIIth International Vascular Biology Meeting held in Toronto, Canada, June 1-5, 2004. Seven faculty members from the center made presentations over the four-day event.

Drs. Klaus Ley, Brett Blackman, Martin Schwartz, Gary Owens and Brian Helmke as well as graduate student Elizabeth Browning and staff member Andrew Pryor shared their research

findings with other leading investigators from the international vascular biology community.

Through a series of workshops, plenary sessions, poster sessions and a keynote address, meeting attendees were informed of emerging approaches to the study of the origin, function and therapeutic manipulation of vascular cells and tissues. ■

Dr. Guohong Li, Research Assistant Professor in the Cardiovascular Research Center and the Department of Medicine, has been awarded a Partners' Fund Award in the amount of \$25,000 for his proposal, "The Role of Periostin in the Response to Vascular Injury."

This proposal will test the general hypothesis that periostin, a novel adhesion molecule, is overexpressed after vascular injury and plays a role in neointima formation after carotid injury using gene-targeted mice deficient in expression of periostin on an atherogenic background and will explore underlying mechanisms.

Dr. Li's previous study demonstrated that periostin dramatically increases after vascular

injury in both rat and mouse carotid injury models, with negligible expression in uninjured control vessels. This suggests a role of periostin in the response to vascular injury, but the exact role it plays is unknown. An improved understanding of periostin's role may open new avenues for the development of potential therapeutic strategies to treat vasculoproliferative disease.

The Partners' Fund Award is made possible by the generous support of the Heart Center Board members and other friends of cardiovascular research. If the past is an indicator of the future, this award will likely generate data that will allow Dr. Li to submit an R01 application to the NIH. ■

Lindner Receives Two R01s

Jonathan R. Lindner, M.D., CVRC member and Associate Professor of Internal Medicine, Division of Cardiovascular Medicine, has had an exciting summer: he was awarded two NIH R01s. The first, "Contrast-enhanced Ultrasound Assessment of Angiogenesis," started July 1, and the second, "Targeted CEU Imaging of Atherosclerosis and Angiogenesis," will kick off in late September.

"I feel like Sally Field," Lindner said, poking fun at his recent success. "No, actually, it is very encouraging that grants like this that bridge fields—vascular biology, imaging, chemistry—are being received in a positive light."

The first grant will investigate the relationship between angiogenesis and inflammation. Lindner will use molecular imaging with targeted contrast ultrasound to assess the spatial and temporal relation between integrin expression, leukocyte recruitment, growth-factor

receptor expression and neovessel formation in models of limb ischemia. The second grant will use molecular imaging of selectins, VCAM-1, and alpha-v integrins to temporally characterize the inflammatory response in atherosclerosis in mice.

Together with his collaborators, Drs. Klaus Ley, Sasha Klibanov, and Sanjiv Kaul, Lindner has worked for 5-6 years developing and validating methods for molecular and cellular imaging of vascular phenotype in inflammation, angiogenesis, and tumor growth. These projects represent the next step, namely to use these techniques in animal models of disease to better characterize pathophysiologic processes and how they can be interrupted.

It is likely that molecular imaging with methods such as targeted contrast ultrasound will provide an effective tool to study new therapies, and possibly to diagnose disease in patients at a very early stage. ■

NIH Awards Shi RO1

The National Institutes of Health National Heart, Lung, and Blood Institute has funded an RO1 proposal from CVRC member Weibin Shi, Ph.D., entitled "QTL Analysis of Carotid Atherosclerosis." The four-year project began July 1, 2004.

This grant will investigate genetic factors contributing to the development of carotid atherosclerosis. Family history is a major risk factor for stroke and a significant fraction of ischemic stroke cases are caused by carotid atherosclerosis, which results in stenosis of the vessels and blocks the blood flow to the brain.

Stroke is the third leading cause of mortality and the leading cause of disability in the United States.

"Funding of this project," says Dr. Shi, "enables us to continue our effort toward the goal of eradicating one of America's major health problems." ■

NIH Awards Okusa RO1

Mark Okusa, M.D., CVRC member and Professor of Medicine and Director of Research, Division of Nephrology, began work on his new NIH RO1 July 1, 2004. The new four-year project, "Lysophosphatidic Acid and Acute Renal Failure," will investigate the critical role of lysophosphatidic acid (LPA) receptors in renal tubule cell survival and injury.

With a mortality reaching up to 80-90%, acute renal failure is an important clinical problem that demands novel therapeutic modalities for treatment or prevention.

The simple phospholipid, lysophosphatidic acid (LPA) is an autacid that can be generated by many cell types and binds to a family of G-protein coupled receptors (LPA1, LPA2 and LPA3). LPA has heterogeneous functional effects including cellular proliferation, alterations in differentiation, cell survival, suppression of apoptosis and platelet aggregation. In addition to these effects, LPA is similar to other inflammatory lipid mediators (platelet activating factor, prostaglandins, thromboxane) and has the capacity to evoke an immune response by attracting and activating immune cells and

regulating leukocyte endothelial cell interaction. These multiple divergent responses are likely mediated by specific LPA receptors that have distinct signaling mechanisms.

Dr. Okusa's research indicates that a selective LPA3 antagonist markedly reduces ischemia reperfusion injury in mouse kidneys. The dramatic response by this compound underscores the critical role that LPA receptors play in renal tubule cell survival and injury, and this study will help determine their potential as therapeutic targets.

Studies supported by this award are a culmination of years of collaboration with Drs. Kevin Lynch and Tim Macdonald that incorporate synthetic chemistry, molecular pharmacology and animal models of renal injury. ■

Duling Receives Malpighi Award

Dr. Brian Duling has been selected to receive the prestigious Malpighi Award, the highest award presented by the European Society for Microcirculation.

The biennial award recognizes the lifetime achievement of researchers known for outstanding publications and scientific contributions, by their service to the entire field, and by their promotion of younger scientists. Dr. Duling is invited to give the Malpighi Lecture at the 23rd ESM Conference in Lisbon, September 8-10, 2004. ■

Wamhoff Receives APS Award

At the 2004 Experimental Biology Conference, held this spring in Washington, DC, the American Physiological Society Cardiovascular Research Section awarded Brian R. Wamhoff, Ph.D., a Research Associate in the Owens lab, with the 2004 Recognition Award for Meritorious Research by a Young Investigator. ■

Mark Your Calendars...

2004 Berne Lecture • Tuesday, October 12 • Jordan Hall Auditorium

This year's speaker, Dr. Enrico Stefani, Professor of Anesthesiology and Physiology, is Director of the Division of Molecular Medicine of the Department of Anesthesiology at UCLA. Look for a full article in the next CVRC News.



415 Lane Road
MR5 Bldg., Rm. 1010
Box 801394
Charlottesville, VA 22908

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Fax: 434.924.2828

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www.healthsystem.virginia.edu/internet/cvrc

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