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UCONN School of Medicine Dean's Newsletter, Winter 2010

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UConn School of Medicine
Dean's Newsletter
Winter 2010

A Workhorse and a Thoroughbred

Next-Gen Sequencing

Dean's Message

Momentum Is Strong

Talk about progress: a massive effort that took 10 years to complete just a decade ago can now be accomplished in a matter of days. I'm talking about the sequencing of RNA expression and the speed and precision of "next generation" technologies like our powerhouse, the Illumina® Genome Analyzer. As you will see in our lead story, next generation technologies recently helped researchers publish two major papers in *RNA* and *Cell*.

This is a source of great pride for the UConn School of Medicine and a powerful reminder of how fortunate we are to be educators during a time of such profound growth and discovery.

Every day, the momentum and energy of our school, our students and our faculty is felt in Connecticut and beyond. In this issue, you will also learn about achievements of our faculty across a broad range of medical specialties from angiogenesis and gene therapy to novel approaches to prevent high blood pressure and advocacy for cancer survivors.

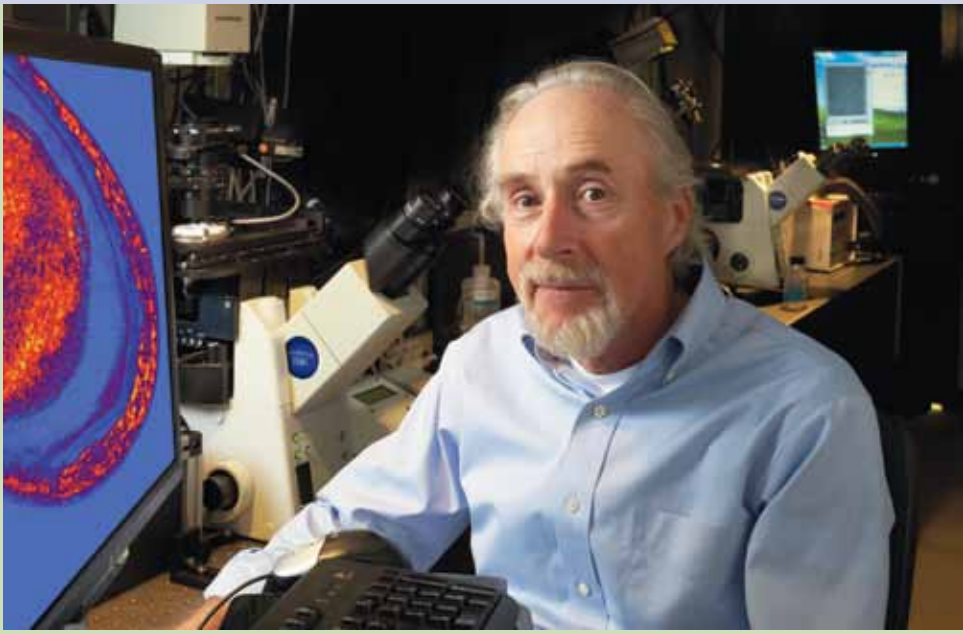
As always, please do not hesitate to share your thoughts about medical education with me at laurencin@uchc.edu or by calling 860-679-2594.

Sincerely,

Cato T. Laurencin, M.D., Ph.D.
Vice President for Health Affairs
Dean, UConn School of Medicine

Grants

Health Center Researcher Awarded Multimillion Dollar Department of Defense Grant



Peter Setlow, professor in the Department of Molecular, Microbial and Structural Biology

Bacterial spores can be nasty. Just ask Peter Setlow, Ph.D., a professor in the Department of Molecular, Microbial and Structural Biology, who has been studying them for over 40 years. He'll tell you that spores, such as those of *Bacillus anthracis*, can cause anthrax. Other bacterial spores are to blame for deadly cases of food poisoning, botulism, and life-threatening infections that are especially hazardous to hospitalized patients. Setlow heads a team of researchers who have been awarded a multimillion dollar grant from the Department of Defense to uncover some of the secrets of spores and potentially make them less dangerous.

"The vegetative organisms cause the disease but it's the spores that transmit the disease," explains Setlow. "When they are dormant, they're very resistant and can survive all kinds of harsh chemical treatments, extremes of temperature and low-nutrient environments. However, once the spores germinate, they are easy to kill. Our research goal is to better understand the mechanisms that spur them to come out of their dormant phase and spring back to life."

The award is for $1.25 million per year for a total of five years and is a Multidisciplinary University Research Initiative (MURI) grant designed to support basic science and/or engineering research at U.S. institutions of higher education that are of critical importance to national defense.

Along with focusing on the mechanisms of spore germination, Setlow and his team are studying their heterogeneity. "It turns

Vitamin D Low, Blood Pressure High?

William B. White, M.D., and Pooja Luthra, M.D.

Vitamin D is known to be important to bone health, but what about heart health? UConn Health Center physician-scientists are looking into a possible link between vitamin D deficiency and high blood pressure.

"Often patients don't realize they have a vitamin D deficiency, or are unaware of its relationship with health problems other than bone disorders," says the study's principal investigator William B. White, M.D., professor of medicine and hypertension expert in the Pat and Jim Calhoun Cardiology Center.

White and Pooja Luthra, M.D., assistant professor of medicine and an endocrinologist in the New England Musculoskeletal Institute, are recruiting patients with a diagnosis of treated or untreated high blood pressure and a low vitamin D level.

In the 14-week, double-blind, randomized trial, participants will receive either vitamin D supplements or an enzyme blocker that targets renin, which is produced in the kidney. They then will get both medications in combination. Their blood pressure will be monitored both in the office setting and out of the office using a 24-hour ambulatory blood pressure monitor.

The UConn Health Center study is supported by an independent $480,000 investigator-initiated grant from Novartis Pharmaceuticals, Inc., in East Hanover, N.J., over the next three years.

out that even though spores may be genetically identical… they don't all behave identically," says Setlow. During germination, spore number one may come back to life in 5 minutes but spores two, three and four may take their time and not germinate for 30 minutes, 24 hours or up to a month. Setlow says that's where the problem arises. For example, if you're being treated for anthrax, how long should you take antibiotics – for a week? Then the spore that germinates in two weeks might kill you.

"It turns out that even though spores may be genetically identical...they don't all behave identically."

Setlow believes if his team can figure out why there is this heterogeneity - why one spore germinates faster than another - they might be able to figure out a way to get the spores to all germinate at the same time. An instrument developed by Ji Yu, Ph.D., in the Center for Cell Analysis and Modeling is crucial to this research. Instead of studying whole spore populations, Yu's apparatus will allow them to look at one spore at a time, how it germinates differently from other spores and perhaps how it differs from other spores in the population.

"If we can better understand this process, maybe we can figure out ways to subvert it, figure out a better way to kill the spores," adds Setlow. "Then there would be big savings in terms of food quality, energy costs, etc., and medical treatments for bacterial diseases could be more effective and potentially life-saving."

Health Center Researchers Find Combination Gene Therapy Effective in Healing Hearts

Researchers in the Molecular Cardiology and Angiogenesis Laboratory have found that damaged diabetic hearts can be repaired using combination gene therapy.

Nilanjana Maulik, Ph.D., professor in the Department of Surgery, found in preclinical studies that adenoviral VEGF (vascular endothelial growth factor) and Ang-1 (angiopoietin-1) increased blood flow and the heart's ability to pump more effectively. The study is published in *Diabetes*, a journal of the American Diabetes Association.

"In diabetes, there is impairment of myocardial angiogenesis – decreased vessel formation in the heart which leads to decreased blood flow and eventually to heart failure," explains Maulik. The decrease in blood vessel formation is mainly due to the imbalance in growth factors such as VEGF and Ang-1.

Scientists have long studied ways in which gene therapy could be used to repair the damaged diabetic heart. Most of the studies have focused on using a single gene as the therapeutic agent. Maulik decided to focus on a combination gene therapy which proved to be the key.

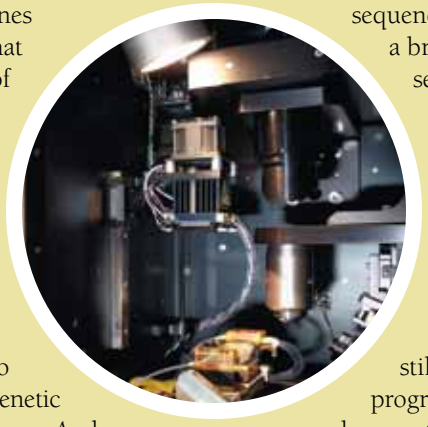
In animal studies, diabetic hearts damaged by myocardial infarctions were injected with a mixture of VEGF and Ang-1. Thirty days later, heart function was measured using an echocardiogram. The hearts subjected to this therapy performed better than the untreated hearts. "We observed reduced fibrosis and increased capillary and arteriolar density in the treated diabetic hearts compared to the diabetic hearts that were not treated with the combination therapy," explains Maulik. The next step is a clinical trial to test the therapy's effectiveness in humans with diabetic heart failure.

Brenton Graveley, Ph.D., associate professor of genetics and developmental biology

Next-Generation Sequencer

At first glance it appears to be just another laboratory slide, a millimeter-thick rectangle 1.5 centimeters wide by 6.5 centimeters long. But when it's examined against a light source, a series of whispery parallel lines becomes apparent. They are internal walls that separate the slide into eight chambers each of which is as narrow as angel hair pasta.

When Brenton Graveley, Ph.D., associate professor of genetics and developmental biology, inserts the slide into a squat device called a cluster station, clear liquid is injected through the almost imperceptibly small holes at the ends of the chambers. The slide is instantaneously transformed into a library of information. The liquid injected into the eight tiny chambers contains samples of genetic material, chemically extracted from organic tissue. And with the help of the Health Center's powerful Illumina® Genome Analyzer, Graveley will soon know the precise sequence of genes in each sample.



"Soon" is the key word. In the Health Center's Translational Genomics Core, a center that provides a host of esoteric services for monitoring gene and microRNA expression, the sequencer is both a workhorse and a thoroughbred, a brute for work and incredibly fast. While sequencing technology has been around for almost a quarter of a century, "next generation sequencers" like this one are emphatically 21st century. To understand how rapidly – and dramatically – they have revolutionized genetic research, it is worth considering how they would have impacted the Human Genome Project.

Launched in 1990, when Graveley was still a graduate student, that celebrated research program occupied an army of researchers worldwide who spent a full decade determining the sequence of chemical base pairs that make up human DNA. For the record, there are about three billion base pairs containing the 20,000 to 25,000 distinct genes that make up the 23-chromosome human genome.

The project resulted in a working draft of the genome in 2000 and a more complete draft three years later. At that point, next generation sequencers were still a couple years in the future and, as the adage goes, timing is everything. "Our sequencer can process more than twice the number of bases in the genome," says Graveley, matter-of-factly, "in about five days." In fact, armed with the Illumina sequencer, which the Health Center acquired in the spring of 2008, Graveley's team has already generated over 125 billion bases of sequence, more than 40 times the size of the human genome. And, he notes, "The output is increasing exponentially."

Some of those data are included in two papers co-authored by Graveley and recently accepted for publication in the prominent journals *RNA* and *Cell*. The *RNA* paper is about a family of small RNAs that are expressed in planarians (flatworms) and required for the worms' well-known ability to regenerate and for their stem cells to function. The *Cell* paper focuses on small RNAs in bacteria that function to defend the bacteria against invading viruses. They are the first two papers containing data generated by the Illumina sequencer. But they are only the vanguard.

The Mysteries of Alternative Splicing

Part of what has made the new sequencers so popular are scientific breakthroughs in the study of microRNAs and alternative splicing that have significantly changed the research picture in the nine years since the Human Genome Project was completed. "As recently as the late 1990s, it was thought that most human genes encoded only a single messenger RNA (mRNA) isoform," says Graveley. "Now we know that alternative splicing is the rule, not the exception. In fact, 95 percent of human genes encode at least two isoforms and most known alternative-splicing events are regulated."

Graveley and his team are currently hard at work on one line of related research. They are one of six teams at major universities all over the U.S. participating in a project called modENCODE, funded by the National Human Genome Research Institute, part of the National Institutes of Health. Researchers in the modENCODE project are trying to identify the myriad alternative splicing pathways in the genomes of ***Drosophila melanogaster***, the common fruit fly, and ***Caenorhabditis elegans***, a tiny roundworm. The project is less about those organisms than it is about the process of unraveling the mysteries of their sequence-based functional elements.

Graveley's team is working on the fruit fly, an insect that has captivated his scientific imagination for years. "The Drosophila's genome is very compact and only about one-tenth the size of the human genome," he says. "That makes it very useful for this research."

Even so, completing the project – which involves studying which genes are turned on and off at some 30 points over the course of the fly's short, two to three week lifespan – is expected to take about four years, so complex are the twists and turns of the fly's genetic sequencing. Graveley's team is about halfway through. "When the project is complete, researchers expect to know much more about how to tackle studying the much more complex human genome. That task is expected to be wrapped up by 2012." ⚛

Fast Fact

471 **Number of scientists actively involved in biomedical research at the UConn Health Center.**

Dental Researchers Study Potential Treatment for Common Chemotherapy Side Effect

Douglas Peterson, D.M.D., Ph.D., is leading a team of researchers who are studying treatments to prevent oral mucositis in patients undergoing high-dose cancer therapy. Peterson is a professor of oral medicine in the Department of Oral Health and Diagnostic Sciences in the School of Dental Medicine and is also the chair of the Head and Neck/Oral Oncology Program in the Neag Comprehensive Cancer Center. Peterson and his team authored a paper that was recently published in the *Journal of Clinical Oncology*. The study evaluated the safety and efficacy of a topical oral spray for the prevention and treatment of chemotherapy-induced oral mucositis.

Oncology patients may develop mouth problems during and following cancer treatment, including painful mouth ulcers, infection, taste changes and/or dryness. Relative to the clinical trial, a sore, ulcerated mouth is a frequent side effect of high-dose chemotherapy and/or head and neck radiation. The mouth, as well as the remainder of the digestive tract, contains lining cells (mucosa) that are sensitive to several types of cancer therapies. Injury to these lining cells in the mouth results in oral mucositis, which can appear as redness (inflammation) and sores (ulcerations). The condition can lead to pain that may cause hospitalization and/or cancer treatment interruptions if sufficiently severe.

In the phase II, randomized, double-blind, placebo-controlled study, Peterson and his colleagues tested an oral spray containing recombinant human intestinal trefoil factor (rhITF) administered for approximately two weeks during the period of highest risk development of oral mucositis. They found the spray to be safe and highly effective when used for the reduction of chemotherapy-associated oral mucositis in patients with colorectal cancer. Future clinical study is planned to develop this drug for use in oral mucositis management in patients undergoing high-dose cancer therapies. ⚛

Advocating for Advances in Cancer Research and Care

Carolyn D. Runowicz, M.D., Director of the Neag Comprehensive Cancer Center continues to be a national voice for a range of cancer-related issues, from increased awareness about cancer survivorship to advocacy for more robust activity in clinical research.

Since 2004, she has served on the National Cancer Advisory Board (NCAB), and has held the role of chair since 2006. She is the first gynecologic oncologist to hold this position. The role of the NCAB is to advise the secretary of the U.S. Department of Health and Human Services and the Director of the National Cancer Institute with regard to its activities, including the review and recommendation of support grants and cooperative agreements. There are 18 members of the advisory board which include leading representatives from health and science disciplines; all are appointed by the president of the U.S.

In addition, Runowicz also serves as Chair of the Clinical Research Committee for the American Society of Clinical Oncology (ASCO), the world leading professional organization representing physicians who treat people with cancer.

"Working with national organizations is a tremendous opportunity to help all of us achieve strategic objectives related to improvements in the prevention, early detection and treatment of cancers," said Runowicz who previously served as President of the American Cancer Society.

Fast Fact

22 Years UConn medical students have been providing primary care and counseling to Hartford's homeless at the South Park Inn Medical Clinic.

Dr. Faryal Mirza Recognized for Osteoporosis Research

The American Society for Bone and Mineral Research has presented the 2009 ASBMR Award for Most Outstanding Research in the Pathophysiology of Osteoporosis to Faryal Mirza, M.D., an endocrinologist with the New England Musculoskeletal Institute.

Mirza was recognized for her abstract of her study on the role of sclerostin, a hormone believed to inhibit bone formation, in the development of postmenopausal osteoporosis.

Dr. Philip P. Smith Honored by American Geriatrics Society

Philip P. Smith, M.D., head of the Center for Continence and Voiding Disorders is the recipient of a Dennis W. Jahnigen Career Development Scholars Award from the American Geriatrics Society.

The Jahnigen Career Development Scholars Awards Program provides two-year grants of $200,000, including an institutional match, to assist young faculty as they initiate and ultimately sustain a career in research and education in the geriatrics aspects of their discipline. Smith is the only 2009 Jahnigen scholar from Connecticut and one of seven nationwide. The grant will support his research in the area of lower urinary tract function in old age under the mentorship of Peter Albertsen, M.D., chief of the UConn Division of Urology, and George A. Kuchel, M.D., director of the UConn Center on Aging.

An abstract of Smith's winning proposal is available at http://www.americangeriatrics.org/hartford/2009_Jahnigen_Career_Development_Scholars.shtml#smith.

Cato T. Laurencin, M.D., Ph.D., in his research lab with a group of scientists for whom he serves as mentor

Mentoring, Mother's Professional Influence Leads to Laurencin's Lifetime of Success

His career has taken him to the forefront of musculoskeletal care and research, recognition by the White House, national prominence in his field, and the helm of the UConn Health Center as the vice president for health affairs. However, the inspiration that started Cato T. Laurencin, M.D., Ph.D., down the road of medicine was provided by his mother, who operated a clinical practice and research laboratory on the first floor of the family's row house in North Philadelphia.

It is in her name and honor that Laurencin and his wife, Cynthia, have now created a fellowship for UConn School of Medicine students. The Helen I. Moorehead-Laurencin, M.D. Research Fellowship Fund supports students who have demonstrated academic achievement and are involved in conducting summer research projects. He says the emphasis on research perfectly matches his mother's passion for understanding the science of medicine.

The fellowship addresses the other area of focus of Moorehead-Laurencin's life: ensuring that young people have a mentor. Recipients must provide mentorship to an inner city high school student in the Hartford region. Laurencin says that his mother sought out and assisted young people in their neighborhood, encouraged them to pursue careers in medicine and science, and counseled those around her.

In addition to contributing a major gift to create the fund, Laurencin will also utilize an additional $10,000 presented to him as a recipient of the 2009 Presidential Awards for Excellence for supporting student research experiences.

Department of Dermatology Highlights Fundraising Efforts

Located in a new, larger facility, and fresh from recruiting a new research expert through the support of private giving, the Department of Dermatology is also celebrating two major gifts.

A pledge of $100,000 from Jane M. Grant-Kels, M.D., chair of the department, and her husband, Barry D. Kels, J.D., M.D., executive director of risk management has been matched dollar-for-dollar by an anonymous donor, a grateful patient of Grant-Kels.

"The support shown by Jane and Barry, as well as our grateful patients at the Health Center, is a testament to the generosity and commitment of those most personally connected to the UConn Health Center," says Cato T. Laurencin, M.D., Ph.D., vice president for health affairs.

The gifts are part of an upcoming sustained fundraising effort for the department, which includes the preliminary goal of a $3-million distinguished endowed department head chair in melanoma and cutaneous oncology or psoriasis.

In addition, the department recently recruited a leading researcher to the cutaneous oncology program, partially supported through funds raised by the *(2007) Imagine gala*.

Soheil Sam Dadras, M.D., Ph.D., a specialist in cutaneous melanoma, has joined the research team at the Health Center. Grant-Kels says that his addition shows the power that private giving can have in elevating research efforts at the University.

Jane M. Grant-Kels, M.D., chair of the Department of Dermatology

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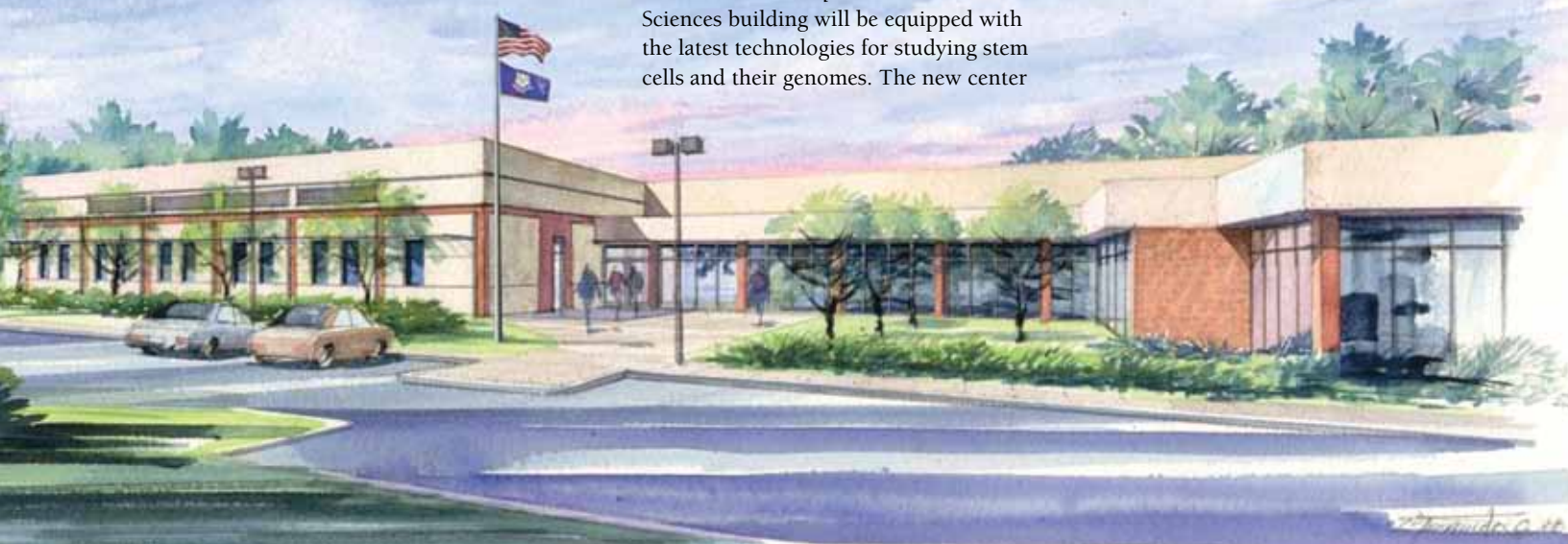
The University of Connecticut is establishing a center of innovation that will include its world-renowned Stem Cell Institute and Center for Cell Analysis and Modeling as well as cutting edge genetics and genomics research. The $52 million, 117,000 sq. ft. Cell and Genome Sciences building will be equipped with the latest technologies for studying stem cells and their genomes. The new center will unite UConn scientists in a cross-disciplinary, collaborative setting to enhance Connecticut's role as a leader in biomedical research and accelerate discoveries that ultimately could lead to therapies treating a broad range of diseases and disorders. Situated on 24 acres of land near the Health Center campus, the renovation is expected to be completed by the summer of 2010.