
■ Breast Cancer Think Tank Receives Unexpected Boost

A research group studying molecular and genetic markers of breast cancer is bolstered by a novel immunological approach.



In 2003, the Molecular and Genetic Markers in Breast Cancer (MGM) working group “was launched as a way to synergistically apply the latest research findings to discover better ways to treat and eradicate breast cancer,” according to **Joseph Crowe, MD**, Chair, Breast Services, Ob/Gyn & Women’s Health Institute.

The group’s title implies that the anticipated “latest research findings” would come in the form of molecular discoveries, gene expression analyses and insights on how altered genetic expression induces disease.

In fact, research within this multi-institutional Cleveland Clinic think tank contributes in many important ways along this path. From the Lerner Research Institute alone, **George Stark, PhD**, Molecular Genetics, has contributed novel findings regarding resistance to taxane, a drug class used to treat breast cancer; **Hisashi Tanaka, MD, PhD**, also of Molecular Genetics, brings his expertise in studying how unstable DNA sequence patterns form in and contribute to breast cancer; and **Ofer Reizes, PhD**, Cell Biology, has molecular evidence for a connection between obesity and breast cancer.

However, the group expanded in 2009 to include an unsuspected technique that fit the mission perfectly.

This is when **Vincent Tuohy, PhD**, Immunology, approached Dr. Crowe and **G. Thomas Budd, MD**, a staff physician in the Taussig Cancer Institute. Dr. Tuohy showed that at the laboratory level, he could vaccinate three different mouse breast tumor models with astonishing results affecting the tumor. He wanted to know if the MGM group members were interested in collaborating to pursue this research clinically. He proposed developing a vaccine that would not only treat established breast cancer, but also safely prevent this disease.

What followed was an expansion of the MGM group to include an immunologic approach: the MGM’s Breast Cancer Vaccine Team. Momentum

increased with the online publication of Dr. Tuohy’s research in the highly respected journal *Nature Medicine* in May 2010.

Drs. Budd, Crowe and Tuohy have since submitted grants together, and Dr. Crowe accompanied Dr. Tuohy to Washington, DC, to lobby Congress to support the clinical phase of preventive breast cancer vaccination. Interaction continues via weekly team meetings, where Dr. Tuohy leads the discussion “by throwing out ideas and fielding responses: It’s an open, Socratic process,” he states. Funding the clinical trial component involves many more resources than funding laboratory science, but the team agrees that there is a need for this research to move forward, and this is what Cleveland Clinic is all about.

Dr. Tuohy foresees a day when breast cancer will be a disease of the past, much like polio or smallpox—through safe and effective preventive vaccination.

Dr. Tuohy is no stranger to translational research, which directly brings laboratory-based studies to clinically relevant problems. Originally recruited to Cleveland Clinic in 1989 for his work in the multiple sclerosis (MS) field (he developed a mouse model of MS that is still commonly used experimentally), Dr. Tuohy has also contributed to clinical programs related to hearing loss, infertility, bladder inflammation and heart failure, with high-impact publications.

Having focused on translational research from his graduate education onward, Dr. Tuohy is convinced that “collaborations form because researchers and clinicians bring distinct strengths to the table. Collaborations work best when clinicians and researchers are willing to roll up their sleeves and work together, side by side, so to speak, against a common problem.”

**Pictured (left to right):
G. Thomas Budd, MD,
Vincent Tuohy, PhD, and
Joseph Crowe, MD**

Outwitting Kidney Cancer

Pulling out all the stops to defeat tumor resistance

The body holds many mysteries, as does disease — for example, why do some initially effective treatments suddenly stop working? The ability of tumors to develop resistance to treatment is the frustration of many who deal with cancer, whether as patients or as physicians. It is also what motivates biomedical research.

Recent years have seen the development of the drug sunitinib, which has shown distinct activity against kidney cancer. It is currently first-line therapy for localized and metastatic renal cell carcinoma, the most common type of kidney cancer.

Although sunitinib shows remarkable anti-tumor activity, all patients eventually develop resistance, rendering the drug ineffective. What's worse is that the disease is then free to progress—and resuming treatment provides no benefit. This challenge is the focus of a collaboration between **James Finke, PhD**, Immunology, and **Brian Rini, MD**, Solid Tumor Oncology.

Together, Drs. Finke and Rini have been working on identifying ways to make sunitinib work better. But with the drawbacks noted above, what makes this treatment worth pursuing?

To answer that, it helps to understand a little about what a tumor needs. For starters, increased blood flow is essential for tumor progression. Tumor growth is associated with increased levels of vascular endothelial growth factor (VEGF), a protein that induces angiogenesis (the development of new blood vessels). In fact, sunitinib was designed to prevent tumor progression by blocking the process through which angiogenesis occurs.

But increased blood flow is not all that a tumor requires—it must also avoid the body's natural defense: the immune system. When a tumor forms,

the body recognizes it as an invader and sends out immune cells called T cells to destroy it.

However, this response is cut short by an even larger counter-attack *from the tumor*, which involves proteins that increase the number of cells that suppress T-cell immune responses.

Yet another mechanism also targets T cells. VEGF has been linked to an increase in a special cell type called myeloid-derived suppressor cells (MDSCs), which promote angiogenesis and inhibit T-cell function.

Because two important aspects of renal cell carcinoma are angiogenesis and immune dysfunction, important aspects of therapy against the tumor are to inhibit angiogenesis and block MDSC formation.

In 2008, Drs. Finke and Rini showed for the first time that in addition to inhibiting angiogenesis, sunitinib also reversed the immune suppression seen in metastatic renal cell carcinoma, and did so by inhibiting MDSC accumulation (*Clinical Cancer Research* 2008 and 2009 publications).

Although a number of drugs inhibit angiogenesis, sunitinib is the only one shown to date to also reverse immune deficits. And this is what gives sunitinib treatment such promise: It can attack the tumor on two independent fronts.

But what about the drug resistance problem? In a 2010 publication in *Cancer Research*, Drs. Finke and Rini and colleagues found that although sunitinib blocked angiogenesis and decreased MDSC accumulation in general, MDSCs continued to thrive if they were located in the tumor's immediate surroundings, or "microenvironment." The authors further discovered a potential molecular mechanism responsible for this, which involves a specific growth factor called granulocyte macrophage



Pictured (left to right): James Finke, PhD, and Brian Rini, MD

colony-stimulating factor (GM-CSF). Current efforts are investigating ways to eliminate these critical pockets of resistance and enhance the potency of sunitinib.

Together with colleagues from Cleveland Clinic, University of Pittsburgh and the Mayo Clinic, Drs. Finke and Rini have most recently used a mouse model to test a new strategy. This approach involves using sunitinib in combination with a vaccine designed to recondition the tumor microenvironment to promote the anti-tumor action of functional T cells. With promising results, they hope to extend this study to clinical trial in the near future.

“The explosion of new therapy in renal cell carcinoma recently is tempered by the development of resistance to these drugs. Working with Dr. Finke to utilize our clinical volume and expertise with his immunology expertise has resulted in new insights

into the mechanisms of response and resistance to agents such as sunitinib. These advances will hopefully soon translate into treatment advances for renal cell carcinoma patients,” says Dr. Rini.

Dr. Finke adds, “The oncologists and urologists here [at Cleveland Clinic] are very talented. I enjoy interacting with them to see what the clinical problems are so that I can then develop an appropriate laboratory model with which to probe for answers. I am also excited by the fact that much of what we have learned regarding renal cell carcinoma is helping to promote our understanding of melanoma and brain tumors, as part of additional physician-researcher interactions with Borden [Ernest Borden, MD, Taussig Cancer Institute] and Vogelbaum [Michael Vogelbaum, MD, PhD, Neurological Institute]. This is very gratifying for me.”

■ Hearts Set on Heart Health

Combined expertise formulates early detection strategies for cardiovascular diseases.



W. H. Wilson Tang, MD, Research Director, Section of Heart Failure and Cardiac Transplantation Medicine, and staff, Cell Biology, is determined to find strategies to halt the growing epidemic of heart failure and cardiomyopathy.

For the past decade, Dr. Tang, a heart failure specialist and transplant cardiologist, has been immersed in an environment of successful clinicians, talented researchers, abundant clinical questions and leading-edge technological tools. He and a mentor and colleague, **Stanley L. Hazen, MD, PhD**, Co-Section Head, Preventive Cardiology and Rehabilitation; Director, Center for Cardiovascular Diagnostics and Prevention; and staff, Cell Biology, are probing the mechanisms underlying a wide variety of cardiovascular diseases, from atherosclerosis to heart failure.

A major problem with heart failure is that patients are not all alike, and it is difficult to determine who is at risk of clinical deterioration. Dr. Tang explains it like this, “Say two people have heart attacks, even at similar locations in the heart; in one, heart function remains relatively preserved, while in the other, it deteriorates over time. We hope to discover why—so that we can personalize therapy and treat each patient accordingly.”

Dr. Hazen says, “We envision that in the future, a patient’s blood test results will help individualize targeted therapies for their personal optimal health.”

One molecule that interests Drs. Hazen and Tang is nitric oxide, a key signaling molecule that regulates cardiovascular function and health. Their research teams in the Center for Cardiovascular Diagnostics and Prevention within the Lerner Research Institute have developed sophisticated measurements of different oxidative and metabolic pathways related to nitric oxide. By defining the relationship between altered nitric oxide levels and cardiovascular function—changes that can be detected only by the latest biochemical tests and cardiac imaging

techniques—they hope to examine an exciting hypothesis: that early alterations in cellular processes affecting nitric oxide are linked to heart failure, even before clinical symptoms emerge.

On another front, Dr. Hazen’s laboratory has recently discovered a variety of oxidative processes that can affect the function of high-density lipoprotein (HDL). Dr. Tang is currently applying these findings to explore how they influence disease mechanisms leading to the development of heart failure. Together, they led a group that was the first to report that decreased activity of paraoxonase-1 (PON-1), a protein associated with HDL, has a connection to heart failure. In a recent publication in *Circulation Heart Failure*, they show results of a simple blood test for PON-1 activity that indicate its important role in cardiac function and that it can serve as a predictor of impending heart failure development. Their studies also suggest that PON-1 may serve as an innovative therapeutic target to thwart the progression of heart disease—a research area they are further pursuing.

Launching the Cleveland Heart and Metabolic Prevention Study (CHAMPS), Drs. Hazen and Tang hope to identify additional pathways that contribute to early development of heart failure and serve as diagnostic markers and therapeutic targets of novel preventive strategies.

“We are dealing with a dire problem,” says Dr. Tang. “I derive much pleasure from taking care of my patients and their families. When one succumbs to heart failure, it spurs me to work all that much harder to find a solution. Bringing together basic and clinical research infrastructure and expertise to the bedside is the only way we can translate scientific innovations to improve clinical care. With the talent here at Cleveland Clinic and our collaborations elsewhere, we are gaining insight into this growing clinical healthcare problem at an increasing pace.”

**Pictured (left to right):
W. H. Wilson Tang, MD, and
Stanley L. Hazen, MD, PhD**



Research at the Heart of the Matter

There's more to the best treatment than the latest techniques and devices.

Cleveland Clinic is often associated with heart care, and its heart program has been ranked No.1 in the nation according to *U.S. News & World Report* for each of the past 17 years. But there is more to this reputation than the latest treatment techniques and devices. Research is critical when even these innovations do not provide satisfactory answers.

Take, for example, a cardiac condition called atrial fibrillation (a-fib), which is characterized by rapid, chaotic electrical activation of the atria (two of the heart's four chambers). In a-fib, the heart loses its ability to effectively pump blood.

A-fib affects over 2.3 million people in the United States and brings with it a 5- to 7-fold increased risk of stroke. Following cardiac surgery, 20-50 percent of patients will have a-fib. Yet after decades of research, how a-fib develops and how best to treat it are still unanswered questions.

Mina Chung, MD, a cardiologist in the Robert and Suzanne Tomsich Department of Cardiovascular Medicine, set out to find some answers. Based on intriguing observations, Dr. Chung pursued studies into a possible genetic component of the disease.

Building on a long-term productive collaboration with researcher **David Van Wagoner, PhD**, Molecular Cardiology, Dr. Chung brought together the Atrial Fibrillation Genetics Group—an interdisciplinary cadre of hand-picked specialists from the Lerner Research Institute.

“Cleveland Clinic is a great place to conduct this research, as we can pair state-of-the-art clinical technology with internationally respected researchers to really focus on solving a medical problem,” states Dr. Chung.

The initial team included Dr. Van Wagoner, an expert in electrical activity of the heart at the cellular level; **Jonathan Smith, PhD**, Cell Biology, who specializes in molecular genetics; and **John Barnard, PhD**, Quantitative Health Sciences, whose command of statistics is essential for interpreting the complex genetic and genomic data. Together, the group developed a strategy for identifying genetic risk factors for a-fib. With several years invested in planning, data gathering and developing further collaborations with other institutes around the globe, new findings and publications are emerging.

Last year alone, the group's research contributed to three major findings (two published in *Nature Genetics* and one in *Circulation*), all of which expanded the study's scope. Two more research areas were added to the team: **David Serre, PhD**, an expert in genomics, a field that studies the consequences of how genes interact, and **Angela Ting, PhD**, who

specializes in epigenetics, the study of how genetic function is modified. Both are with the Genomic Medicine Institute.

The essence of the first phase of the group's research was to compare DNA sequences from a-fib patients to those from people not affected by a-fib. Genetic differences then serve as clues for new ways to predict, prevent, diagnose and treat a-fib. This research included collection and extensive use of DNA from patients with a-fib.

Among the important findings so far is identification of a region on chromosome 4q25 that is strongly associated with a-fib. The nearest gene, *PITX2*, helps to direct formation of the heart—including the pulmonary veins, where triggers of a-fib are often found. This clue, that a-fib may be related to an alteration in the *PITX2* gene, is an exciting new area of study.

While participating in an international consortium of investigators, the group confirmed the importance of the 4q25 region and discovered another significant genetic variation in patients with “lone a-fib,” a type of a-fib that occurs in the absence of significant heart disease. This research identified a link between lone a-fib and changes in the *KCNV3* gene, which encodes a potassium channel involved in atrial electrical activity.

The group is currently completing a massive study expected to identify even more genetic factors that could lead to the discovery of novel pathways and targets for intervention in a-fib.

The second phase of the group's research efforts is learning what these genetic discoveries mean. Now that several genetic risk factors have been identified, the next step is to study the relationship between genetic variation and gene expression directly in human atrial tissues. In the first results from this approach, Dr. Smith led the team in identifying an altered gene site that controls the expression of connexin 40, a protein that is critical for maintaining normal electrical activity in the atria. These findings were recently published in *Circulation: Arrhythmia and Electrophysiology*.

To further establish the relevance of the genetic variations to a-fib, the group will use a many-sided approach employing the latest in molecular biological techniques, such as microarray technology, next-generation DNA and RNA sequencing, and epigenetic analyses. Together, these findings will add significantly to a field that historically viewed a-fib simply as an electrical problem within the heart. With this new information, the capacity to better define the problem may lead to identifying new targets for a-fib diagnosis, treatment and prevention.



MS Tissue Holds Secrets of the Disease

Research collaboration recognizes critical value of MS tissue.

Multiple sclerosis (MS) is a prevalent disease of the central nervous system, affecting more than 2.5 million people worldwide. For young adults of North America and Europe, it is the primary cause of non-traumatic neurological disability.

This progressive, debilitating, and incurable disease is not fully understood, though it has long been thought to result from the deterioration of an “insulation”-like covering called myelin, encasing the axonal portion of the nerve cell (neuron). Axons are responsible for conducting electrical impulses throughout the body’s nervous system—without myelin, the axon’s transmission of these signals gradually slows down, leading to impaired movement and even compromised cognitive processes.

Bruce Trapp, PhD, Chair, Neurosciences, a long-standing leader in MS research whose entire career has focused on myelination, recently made a fundamental discovery. While examining lesions from MS patients, his laboratory found that transected (damaged) axons were *11,000 times* more plentiful than in comparable healthy tissue. Whereas demyelination is often reversible, axonal loss is not. These results pointed to a new understanding in MS research:

Axonal loss, not demyelination, was revealed as the underlying cause of irreversible and progressive neurological decline in MS patients.

This landmark finding, which opens up new research avenues, would not have been possible without MS tissue acquisition through a program established by Dr. Trapp and colleagues of Cleveland Clinic’s Mellen Center for Multiple Sclerosis Treatment and Research. Directed by **Richard Rudick, MD**, the Mellen Center is among the largest clinical MS centers in the world. “We could not be at the leading edge of discovering aspects about MS and its treatments without these tissues and the skills of the basic scientists,” says Dr. Rudick.

“When I was a postdoc and junior faculty member,” says Dr. Trapp, “I was trained to apply basic science observations to relevant gaps in understanding human disease mechanisms—I also learned the importance of collaborating with clinicians who could identify problematic disease questions that needed scientific insight.” This and prior experience with tissue procurement for other diseases of the central nervous system facilitated the establishment of the current program for MS research, launched about 15



Pictured (left to right): Cynthia Schwanger, RN, BSN, MSCN, CCRP, Robert Fox, MD, Micheal Phillips, MD, Susan Staugaitis, MD, PhD, Bruce Trapp, PhD, Richard Ransohoff, MD, Richard Rudick, MD, and Elizabeth Fisher, PhD

years ago. The program is a joint effort of Drs. Trapp and Rudick, **Susan Staugaitis, MD, PhD**, a board-certified neuropathologist in Neurosciences and Anatomic Pathology; **Richard Ransohoff, MD**, Neurosciences and Mellen Center; and **Elizabeth Fisher, PhD**, Biomedical Engineering. The group has grown to include numerous members and support personnel, including **Robert Fox, MD**, Mellen Center, the front-end leader of the tissue procurement program, and **Micheal Phillips, MD**, Neuroradiology, an imaging specialist.

This team works around-the-clock, bound by a common interest in advancing MS patient care. In fact, one scientist associated with Dr. Trapp's laboratory, an MS patient himself, draws on his personal experience with the disease as an impetus for discovery.

Examining tissue from MS patients is critical for advancing the development of potential treatment options. This model of MS can be used to show the number of damaged axons, the extent of demyelination, markers of disease progression, and genetic indicators. The model is also important for developing imaging techniques that can detect disease stage or monitor cognitive impairment in living patients.

As a model of neurodegenerative diseases in general, research relying on MS tissue helps identify neurodegenerative processes that may play a part in other

diseases such as Alzheimer's, for which comparable tissue is too compromised to be a reliable resource.

In keeping with the traditional notion that demyelination is the basis of MS, it has largely been considered a disease of the brain's white matter, as this is where the bulk of myelinated axons are located. The brain also has gray matter, where the bulk of neuron cells are located and message processing occurs. However, gray matter has not been strongly associated with MS—largely because it has been difficult to study. With the MS research program at the Lerner Research Institute, new insights into the involvement of the brain's gray matter are now possible, providing striking revelations that challenge prior assumptions and inform further investigations. Recent findings link MS lesions in the brain's gray matter to fatigue, the most common MS symptom, and cognitive loss, which is experienced by approximately half of MS patients.

"The collaboration of patients, pathologists, MS physicians and researchers, nurse coordinators, and specialists in imaging and cognitive testing has been an amazing effort with far-reaching implications. This research fuels new directions of discovery that are closely linked to application in clinical trials," says Dr. Trapp. "We are devoted to finding the causes of neurological diseases and developing treatments that stop or delay their progression."



‘So What are *My* Chances, Doc?’

An entirely new dimension in *personalized* healthcare

There are times when knowing you’re “at risk” just isn’t enough.

Michael Kattan, MBA, PhD, found himself in that very spot after receiving 16 chemotherapy treatments for Hodgkin’s lymphoma. The question became whether to go through radiation therapy directed at his chest in the midst of conflicting test results, some suggesting active cancer in his chest and others indicating that he was cancer-free. The risk of not going through radiation therapy, should he have active cancer, needed consideration in light of the risk radiation posed for his heart—a risk that could bring a whole different set of potentially fatal complications. Kind of a “Catch 22.”

Faced with only generalized predictions, Dr. Kattan, then in his first year of graduate school, concluded that the best predicted outcomes for an individual do not come from information based on the general public. He realized that, in fact, generalized information might even be as bad as no prediction at all. In the end, he decided to go with chemotherapy and embarked on a career dedicated to developing medical risk calculation.

Today, Dr. Kattan is Chair of the Department of Quantitative Health Sciences at Cleveland Clinic’s Lerner Research Institute. His risk calculators have been applied to medical decision-making related to many diseases, including coronary artery disease, an array of cancers, type 2 diabetes and total joint replacements. Each calculator, designed for a particular disease or condition, contains a spreadsheet for entering patient-specific information—information (including test results) known to affect prognosis.

Wael Barsoum, MD, Chair of Surgical Operations and Vice-Chair of Orthopaedic Surgery at Cleveland Clinic, is familiar with these calculators. He has incorporated the concept into his medical practice after growing increasingly dissatisfied with how

subjectively total joint arthroplasty patients are guided regarding decisions affecting successful and cost-effective recovery. Upon identifying a variety of factors that contribute to a patient’s recovery, whether it is the number of stairs in the house (or to the bathroom), the patient’s body mass index (BMI), or the consistency of care the patient receives at home, Dr. Barsoum worked with Dr. Kattan’s group to create and validate a risk calculator based on approximately 400 case histories.

The result is that the surgical/research collaborators have now managed to decrease length of stay by an entire day and increase patient satisfaction by enabling patients to plan ahead for optimal individualized care. “It is incomprehensible that we didn’t used to make these arrangements in advance like we do now; but then—without the calculator, we couldn’t,” comments Dr. Barsoum. The impact on his clinical practice has prompted Dr. Barsoum to work with Dr. Kattan on two additional upcoming risk calculators—one assessing complications following total joint replacement and another predicting length of stay, mortality and discharge site for ICU patients.

Perhaps the power of such calculators, in terms of both health and economics, is catching on: Dr. Kattan has been awarded a \$1.2 million grant from the National Institutes of Health to further refine and enhance his Web-based medical risk calculator system. These second-generation calculators will not only generate the percent risk of a given treatment option, but also feature a side-by-side comparison of the pros and cons of the different treatment options, listing the probabilities of harmful outcomes. Overall, these new tools add an entirely new dimension to “personalized healthcare” and “educated consumer,” bringing with them the potential to revolutionize medical practice.

**Pictured (left to right):
Wael Barsoum, MD, and
Michael Kattan, MBA, PhD**



■ Carpal Tunnel Syndrome Gets a Fresh Look

An innovative approach to this common malady is under way.

Carpal tunnel syndrome (CTS), first identified by Cleveland Clinic, is a condition characterized by numbness, tingling, and pain in the hands and fingers. CTS is widespread yet not fully understood, although there are 500,000 CTS surgeries per year in the US alone, at an estimated cost of \$2 billion.

The culprit? Increased pressure on a nerve—the median nerve—that runs down the forearm into the hand, innervating all digits except the pinky finger. As this nerve goes through the wrist, it passes through a “tunnel” of bony structures on one side and a sheet-like transverse carpal ligament (TCL) on the other. In CTS, the median nerve becomes aggravated. As for the root problem, is it the fibrosis of the tendon sheath, inflammation of the median nerve itself, or thickening of the TCL? Or is it an anatomical problem where the space for the nerve is simply too small in some people? Although the answers could be a mix of the above, our understanding of this disorder is limited, and its management awaits improvement.

Optimal treatment is also highly debatable. No one likes the idea of going to surgery. Yet surgically cutting the TCL to provide more space for the median nerve is a common and effective treatment for CTS. Surgery does have drawbacks, though, such as the potential for damaging the median nerve or limiting finger strength.

In light of the conundrum posed by this syndrome, **Zong-Ming Li, PhD**, Biomedical Engineering, was recently recruited to establish a hand research program here. Dr. Li has been researching hand biomechanics for nearly a decade and is the former Director of the Hand Research Laboratory at the University of Pittsburgh. In 2007, he received the prestigious Frank E. Raymond Memorial Orthopaedic Research and Education Foundation (OREF) Research Grant with the top score among applications submitted throughout the US. He has gone on to receive NIH funding that has generated even more testable ideas regarding CTS.

Dr. Li is one of the few researchers in the world devoted to hand biomechanics and its clinical applications. Upon his arrival at Cleveland Clinic, Dr. Li formed a research team including **Peter J. Evans, MD, PhD, FRCSC**, hand surgeon and Director, Cleveland Clinic Upper Extremity Center, and **Guang H. Yue, PhD**, also of Biomedical Engineering, an expert on neuromuscular control.

Dr. Li’s most recently funded NIH award, for nearly \$1.5 million over four years, is for the first time addressing novel ways of measuring median nerve function to develop new strategies for managing CTS patient care. The study involves 60 CTS patients who will participate in six different noninvasive, experimentally derived tests, as well as other conventional tests, to define the neural and functional deficits in CTS. A computer model developed as part of this study will be used to establish improved diagnostic criteria.



“This study marks a strong partnership between our research and clinical skills. Working together, we are in a great position to support each other’s pursuits for better science and clinical management of orthopaedic problems,” says **Joseph P. Iannotti, MD, PhD**, Chair, Orthopaedic & Rheumatologic Institute. Over the years, the research of Dr. Li has attracted enthusiastic attention of Dr. Evans. “Through our collaboration and with the knowledge gained from this grant, we will be able to design and apply future interventions to optimize the care of carpal tunnel patients,” states Dr. Evans. “Cleveland Clinic is an excellent environment for this approach,” adds Dr. Li.

“Carpal tunnel syndrome is so common and disabling, yet the mechanisms of this condition are poorly understood,” says **Frederick S. Frost, MD**, Executive Director, Cleveland Clinic Rehabilitation and Sports Therapy and Interim Chair, Physical Medicine and Rehabilitation. “Dr. Li’s research approaches the problem from a fresh perspective.”

■ **Education:**
Cleveland Clinic's
Third Pillar



FORESIGHT FOR EDUCATION

Cleveland Clinic's founders recognized patient care, research and education as the three pillars upon which they built. Realizing that investment in education is a critical driving force for the future of healthcare, Cleveland Clinic has made education a core of its mission for 90 years. In the past decade, several landmark advances in education have helped carry that vision forward into the 21st century. These

INNOVATIVE MEDICAL SCHOOL

In 2004, the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University (made possible by a generous gift from **Al and Norma Lerner**) enrolled its inaugural class, which graduated in 2009. The Lerner College of Medicine's unprecedented program is one of the most innovative in the country. Lectures and exams are things of the past—as are grades. Instead, students compile an extensive academic portfolio comprising self, peer, and research and clinical faculty assessments. The curriculum extends

INNOVATIVE GRADUATE SCHOOL

In 2007, a corollary program was launched for students interested in using laboratory research to address clinical questions. Under the leadership of **Martha Cathcart, PhD**, Cell Biology, this one-of-a-kind PhD program in Molecular Medicine received initial funding from the Howard Hughes Medical Institute (HHMI) "Med into Grad" initiative, with additional HHMI support awarded in 2010. Fitting HHMI's goal, "to develop a cadre of PhD researchers who understand pathobiology and are committed to working at the interface of the basic sciences and clinical medicine," the Molecular Medicine PhD Program is an exciting advance in graduate education, which Director **Jonathan Smith, PhD**, Cell Biology, carries into 2011 and beyond.

include the establishment of two highly innovative educational programs—a medical school with a strong research component and a graduate school with a strong medical component. Both programs fit the Centers of Research design, in which clinical and laboratory research perspectives are integrated through a common disease focus.

beyond traditional clinical studies to include a significant emphasis on research. Within the five-year program, with one full year devoted to research, Lerner College of Medicine students are specifically trained to be physician-scientists and graduate with a medical degree and specialization in biomedical research. The Lerner Research Institute faculty members serve as program instructors, research advisors, and problem-based learning facilitators.

The Molecular Medicine PhD Program's core curriculum includes both basic science and clinical principles that integrate medical knowledge into graduate education. The curriculum has been carefully designed to train students to think translationally—that is, to translate scientific observations into clinical answers. This state-of-the-art approach to training biomedical researchers pairs each student with both a research advisor and a clinical mentor. The result is that graduates of the Molecular Medicine PhD Program are uniquely qualified to approach relevant clinical problems with the tools of molecular and cellular biology to improve patient care.

Image depicts the Education wing of the Lerner Research Institute, viewed from a research laboratory.

Education: Cleveland Clinic's Third Pillar

With the increasing number of research trainees, the Research Education Office (REO) was established in 2002 under the direction of **Marcia Jarrett, PhD**. The office orchestrates educational opportunities available within research at Cleveland Clinic—for undergraduates, graduate students and postdoctoral fellows. A large responsibility of REO is administering the Molecular Medicine PhD Program and its initiatives, including admissions.

In addition, REO supervises the Molecular Medicine PhD Program Peer Mentoring Group, a student-driven means of enhancing a first-year student's experience while providing second- and third-year students with mentoring experience—a lifelong skill in a science career. The Diversity Initiative Group (DIG) also is overseen

by REO. Organized by Molecular Medicine PhD students, DIG is designed to support other minority graduate students currently pursuing careers in research, as well as younger students in the Cleveland Metropolitan School District who might be interested in exploring a future in science. In addition, REO is committed to the Molecular Medicine PhD Program's annual retreat, where students share their findings through both poster and oral presentations following a stimulating address by an invited keynote speaker.

Altogether, REO provides academic services for approximately 250 postdoctoral fellows, more than 175 graduate students and 150 summer research students, as well as reciprocal support for about 190 research investigators.

“Our number one goal is to support the research programs of the LRI through our services. We do this by providing knowledgeable, efficient and courteous administrative support and by developing programs that provide meaningful education for research training and career development for all LRI research trainees.”
-Marcia Jarrett, Director, REO

Responsive to the training and career needs of research trainees, the REO upholds the academic mission of LRI to provide excellent research training and professional development.



■ New Staff

The Lerner Research Institute welcomes eight new staff members recruited for or appointed to their positions in 2010. Each individual brings significant skills, talents, and credentials that fit well within the Centers of Research framework, and each is making important contributions to biomedical research.

COMBINING COMPUTERS, ENGINEERING, BIOLOGY, AND DISEASE



Ahmet Erdemir, PhD, Biomedical Engineering, was appointed to Assistant Staff in 2010. Dr. Erdemir earned his PhD in Kinesiology, the study of human movement, from Pennsylvania State University. He has been with the Lerner Research Institute since 2002. In 2007, he

became Director of the Computational Biomodeling (CoBi) Core, the only known core facility of its kind, which he continues to lead. Through modeling biological systems, Dr. Erdemir uses computers to facilitate research in assessing therapeutic interventions and surgical techniques in rehabilitation and diagnostics, and in providing virtual prototyping for medical device design. This computational approach to simulating and evaluating normal and diseased conditions is the focus of the CoBi Core, which provides numerical analysis, research support, and translational investigations in a cost-effective manner to all Cleveland Clinic researchers, as well as outside clients. Particular areas of interest for Dr. Erdemir include knee joint function and the effects of aging and osteoarthritis on a person's mobility.

NEUROSCIENCE APPROACH TO MOTOR FUNCTION DISORDERS AND PSYCHIATRIC DISORDERS



John T. Gale, PhD, Neurosciences, studies the basal ganglia, a specific cluster of nerve cells located at the base of the forebrain that are involved in motor control, motivation, and learning. This work provides a basis for understanding dysfunctions of the basal

ganglia, thought to underlie a wide range of human diseases, from motor disorders, such as Parkinson's disease and dystonia, to psychiatric disorders, such as major depression and addiction. During Dr. Gale's previous training, which included a focus on deep brain stimulation, he mastered complex behavioral, electrophysiological, and computational techniques, providing his research with a solid interdisciplinary platform. For Dr. Gale, clinical input is essential for prompting the right questions, which can then be tested in the laboratory setting. Dr. Gale comes to Cleveland Clinic from Massachusetts General Hospital/Harvard Medical School, although he is not entirely new. It was here that he started as a technician and discovered his passion for neurosciences—and in 2004, he was the first to obtain his graduate degree from the Kent State University/Cleveland Clinic Collaborative Doctoral Program in Biomedical Sciences.

New Staff

PLASTIC SURGERY, IMMUNE SYSTEM, AND CANCER



Brian Gastman, MD, comes to Cleveland Clinic from the University of Maryland, where he was Assistant Professor in the Departments of Surgery (Plastic Surgery) and Otolaryngology, with joint appointments in the Department of Surgery at Johns Hopkins and as a

plastic surgeon in the Department of Surgery (and Head of the Section of Head and Neck Plastic Surgery) at the Baltimore VA Medical Center. Dr. Gastman's interest in research began during his undergraduate experience in molecular and cellular biology at the University of Michigan, Ann Arbor. Today, he sees patients through the Department of Plastic Surgery in the Dermatology and Plastic Surgery Institute, while he conducts research in Lerner Research Institute's Department of Immunology. Dr. Gastman is interested in what causes the destruction of T cells (a type of white blood cell responsible for maintaining our immune system) in the vicinity of tumors. Specifically, he aims to understand how tumors evade the immune system and also how other proteins in our bodies can prevent this evasion. These studies will contribute to the development of new mechanisms to thwart cancer resistance to current treatments.

STEM CELLS, BRAIN TUMORS, AND SONIC HEDGEHOG



Dolores Hambarzumyan, PhD, Stem Cell Biology and Regenerative Medicine, is interested in primary brain tumors. Specifically, her research focus is on gliomas, tumors derived from glial cells—special cells that support and protect neurons.

Astrocytes are a particular glial cell type that reside in stem cell niches and along the tumor's border. Dr. Hambarzumyan's research has shown a link between glioma formation and the activation of the "sonic hedgehog" signaling pathway in astrocytes. She is studying this to determine how the tumor's surroundings impact tumor growth—and how to stop it. This information is needed to develop new treatments for this devastating disease, which currently has no cure. Dr. Hambarzumyan comes to Cleveland Clinic from Memorial Sloan-Kettering Cancer Center in New York.



GENOMIC INSTABILITY, INFECTION, AND FRUIT FLIES



Michelle Longworth, PhD, has recently joined the Department of Molecular Genetics, coming here from Massachusetts General Hospital (MGH), Charlestown. A native of Pittsburgh, her family relocated to Northeast Ohio while she was still in high

school, where she had her first taste of research—at Cleveland Clinic, shadowing a researcher for two months. She went on to complete her undergraduate education at Miami University in Oxford, Ohio, then earned her PhD at Northwestern University in Illinois. Dr. Longworth's research identifies genes, proteins, and processes of interest using a *Drosophila* (fruit fly) model, which is much simpler than other organisms. She then extrapolates the information to human systems for improved understanding of how things function. During her postdoctoral fellowship at MGH, Dr. Longworth discovered a protein interaction involved in a mechanism that contributes to genomic instability, which characterizes many tumors. Most recently, she has found that these same proteins play an important role in regulating the body's response to infection. Dr. Longworth's overall goal is to identify the genetic basis of cancer development and infection.

BLOOD CLOTTING AND NEW BLOOD VESSEL FORMATION



Keith McCrae, MD, sees patients through the Department of Hematologic Oncology and Blood Disorders of the Taussig Cancer Institute and conducts research in Lerner Research Institute's Department of Cell Biology. Originally from Maine, Dr.

McCrae earned his undergraduate degree from Dartmouth College and his MD from Duke University. After his residency in Internal Medicine at Duke, Dr. McCrae completed his fellowship in Hematology/Oncology at the University of Pennsylvania. While there, he began studying antiphospholipid syndrome, a clinical disorder characterized by blood clotting and recurrent fetal loss. Today, his laboratory also studies kininogen, a protein involved in the pathway that controls blood clotting. Kininogen also plays a role in regulating angiogenesis, the process of new blood vessel formation. His research focuses not only on factors involved in blood biology, but also on the cells that line blood vessels. Dr. McCrae comes to Cleveland Clinic from Case Western Reserve University.



New Staff

ABDOMINAL AORTIC ANEURYSMS AND TISSUE MODELING



Anand Ramamurthi, PhD, Biomedical Engineering, is interested in developing treatments for abdominal aortic aneurysms (AAAs) that lead to viable repair and regression. AAAs typically are characterized by thinning and weakening of the wall of the aorta, leading to catastrophic

rupture. Current treatments only slow further deterioration but do not actually reverse the condition. Dr. Ramamurthi aims to develop ways to induce and assemble the elastic matrix that constitutes the aorta's wall, thereby helping not only to fix the AAA, but actually to reverse the disease. One challenge is inducing diseased adult cells to produce the protein elastin, which, as its name implies, makes the vessel wall stretchy. Although elastin is an essential component of this elastic matrix, it is typically produced only neonatally (during development). In addition to promoting the formation of elastic fibers, other challenges include orienting these fibers as they would be in a healthy aorta and stabilizing these structures against further breakdown at the site of the aneurysm. Dr. Ramamurthi has several exciting working models to overcome these challenges. He received his initial training here at the Lerner Research Institute and returns from Clemson University, where he was a tenured Associate Professor of Bioengineering.

LIVER DEVELOPMENT, LIVER REGENERATION, AND ZEBRAFISH



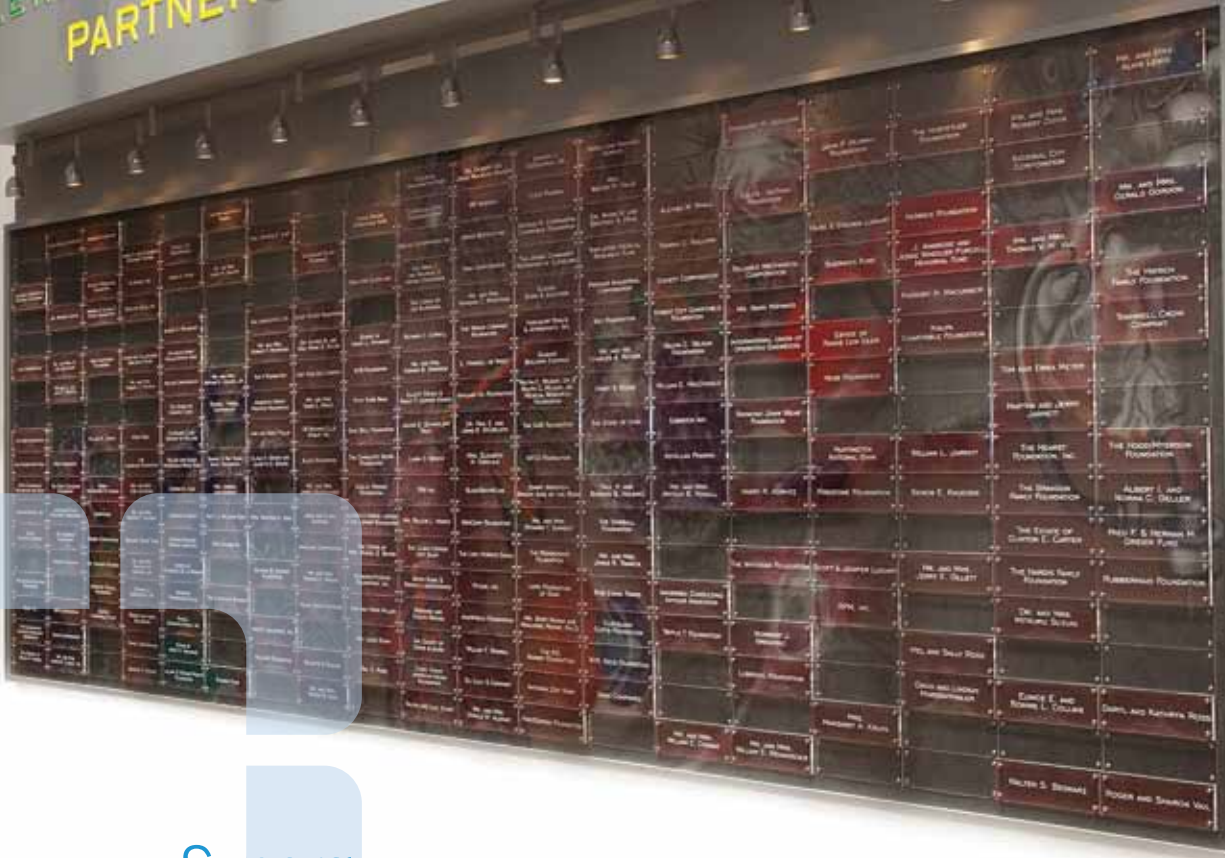
Takuya Sakaguchi, PhD, Stem Cell Biology and Regenerative Medicine, is interested in liver development and regeneration, using the zebrafish model for his studies. Zebrafish embryos are transparent, making them an ideal model for studying organ

development, including that of the liver. Dr. Sakaguchi's studies involve identifying different genes that play critical roles in organ development, thereby contributing to understanding the molecular mechanisms underlying liver development and regeneration. His overarching goal is to find new treatments for human liver disorders based on insights gained from this model system. In his previous work, Dr. Sakaguchi identified novel roles for vascular endothelial cells in liver development, especially that of the liver's bile duct system, which transports bile to the gut to aid in digestion. Dr. Sakaguchi comes to Cleveland Clinic from the University of California, San Francisco.

A hallmark of the Lerner Research Institute is its focus on disease-oriented research. The approach blends research across several departments and disciplines to address major clinical areas.



LERNER RESEARCH INSTITUTE PARTNERS IN RESEARCH



Synergy

**There is incredible power in joint efforts.
The whole is greater than the sum of its parts.**

When scientists and clinicians come together to pool their talents and abilities, they accomplish far more than each of them could have achieved individually. Lerner Research Institute provides a research environment that stimulates such synergy, as seen in our Centers of Research.

What makes Cleveland Clinic one of the foremost medical facilities in the world is its combined strength, which draws on expertise from many areas.

The stories conveyed in this issue illustrate how joint efforts help uncover new ways to prevent and better treat debilitating and life-threatening diseases; how better ways of evaluating patient information lead to improved patient care; and how the scientist-clinician collaboration is being carried forward to the next generation through strategic educational programs.

Friends and supporters of Lerner Research Institute are part of this synergistic process, since philanthropic funds provide the solid foundation from which new ideas and discoveries can spring forward.

There are many ways in which an individual or family can contribute and make a difference to the important biomedical research that unravels the mysteries of disease and finds the key to new methods of prevention, therapies, and cures.

Please consider the Fund Development staff as your philanthropic advisors who can provide you with information on research areas that are most closely aligned with your interests and values. We can also help identify ways in which you can make a significant impact on the work at Lerner Research Institute and still meet your personal and financial objectives.

Making a meaningful gift to help advance research is often easier than many people think, and we welcome support at all levels. Please join us in the powerful synergy at Lerner Research Institute and help accelerate discoveries that will change the future of medicine.

Susan Sasvari

Susan Sasvari, MBA
Director of Fund Development
Lerner Research Institute



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page 10: June O'Neil, *Deep Space Nebula*

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