CAROLINAS HEALTHCARE SYSTEM

Research Highlights
2012

Carolinas HealthCare System

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LETTER FROM THE CHIEF ACADEMIC OFFICER

JAMES T. McDEAVITT, MD
Chief Academic Officer

2012 was another year of great accomplishments as well as a year of change for research at Carolinas HealthCare System. The System has tremendous assets to position it as a leader in world-class research, such as a large patient population and a large network of experts to comprehensively address patient-centered issues.

New System resources in 2012 included an Ion Proton™ in the molecular biology and microarray core facilities, which is the latest generation of genome deep sequencer machines and is a first in the state of North Carolina. Also new are the imaging/histology and immune-monitoring cores to provide in-house capabilities to support the targeted discovery work led by clinicians and scientists from different disciplines. Also, strategic alliances with regional partners, such as UNC Charlotte and the NC Biotechnology campus in Kannapolis, will provide access to synergistic capabilities in the areas of bioinformatics, bioengineering, metabolomics, advanced imaging technology and more.

A large NIH grant, major scientific awards and publications in leading peer-reviewed journals constitute a few signs of our success. This highlight of research provides a detailed review of such accomplishments. The successes and resources described in the pages that follow stand to show that prospects for the System are bright, particularly with the collaboration and support from our many partners in the Charlotte area and throughout North and South Carolina.

Regards,

James T. McDeavitt, MD
Chief Academic Officer

BEHAVIORAL HEALTH

William (not his actual name), a patient at Carolinas Medical Center-Randolph, is a 62-year-old man with a long history of paranoid schizophrenia. He has been treated with a conventional long-acting injectable antipsychotic for more than two decades. Although this pharmacologic agent provided him with adequate control of psychotic symptoms, such as auditory hallucinations and paranoid thoughts, William was getting progressively concerned about his weight gain and feelings that his current medicine were slowing him down physically and mentally. To address his concerns, William decided to participate in a 52-week clinical study examining the long-term effect of mGlu2/3 receptor agonist LY2140023 conducted at the Behavioral Health Center (BHC)-Research. The results exceeded everyone's expectations. William was able to achieve significant and clinically meaningful effects on the primary symptoms of his illness as well as his cognition and functional symptoms. He lost weight, got married* and entered vocational rehabilitation.

Schizophrenia is a devastating neurodegenerative disorder affecting approximately 24 million people worldwide. It is characterized by a wide spectrum of symptoms, including auditory and visual hallucinations, delusional beliefs, paranoid ideation and difficulties with motivation, social isolation and cognition. Since the introduction of the first-generation of antipsychotics in the 1950s, the pharmacological approach has become the most widely accepted therapeutic modality for the treatment of schizophrenia.

The great advances in basic neuroscience and major new insights into brain circuitry and function have made it possible to produce a number of new antipsychotic agents during the past two decades, broadening the armamentarium available to clinicians. Although conventional and more recently developed antipsychotics have been shown to be efficacious in treating some of the symptoms of this condition, collectively they do not adequately address core domains of symptomatology and, over the longer term, will effectively treat only about half of patients. Therefore, significant unmet needs still exist. In this light, the neurotransmission mediated by glutamate is of interest to the psychopharmacology of schizophrenia due to its complex interaction with major brain neurotransmitters, dopamine in particular, and its role in brain development and neurotoxicity.

However, in recent years, discovery and development of newer, more effective and safe pharmacological treatments for major psychiatric disorders, particularly those medicines with distinctly novel mechanisms of action, were hampered by a high rate of failure. Compounding the lack of progress has been the unprecedented pullback by the pharmaceutical industry from drug development in this therapeutic area.

In 2012, in the rapidly changing and competitive business environment, BHC-Research, which is spearheaded by Oleg Tcheremissine, MD, continued to provide real-world patients from community mental health centers with access to novel and innovative treatment options. We maintain our focus on undoubtedly the most difficult areas in CNS drug development, such as schizophrenia and treatment-resistant depression. We conduct our research in the context of our daily clinical practice. This bidirectional reciprocity allows us to align the process of drug development with information derived from direct clinical care and also to provide an opportunity to further bridge the "efficacy-effectiveness" gap, commonly defined as the differences between two populations of patients, those enrolled in clinical trials and those who will be treated in real clinical settings.

**Results not guaranteed.*

CARDIOVASCULAR SURGERY

It is every parent's nightmare. A previously healthy 13-year-old boy suffers cardiac arrest at home and is transferred to Levine Children's Hospital barely alive. He is in cardiogenic shock due to idiopathic dilated cardiomyopathy. Standard medical therapy will not save this child. He will inevitably need a heart transplant if he is to survive, but he is too sick to wait for a heart to become available. Pediatric cardiac surgeons Ben Peeler, MD, and Tom Maxey, MD, turn to Sanger Heart & Vascular Institute clinical research to facilitate a solution. They implant the HeartMate II®, an investigational pediatric left ventricular assist device, and the child's condition stabilizes. He recovers, is discharged home and is back to school, awaiting a definitive transplant.

Sanger Heart & Vascular Institute Clinical Research continues to grow and enhance our larger clinical and academic mission. Sanger Heart & Vascular Institute clinical research manages more than 40 clinical trials with more than 1,600 patients under management. More than 140 publications, abstracts and national presentations were contributed over the last year. While most research work is conducted at Carolinas Medical Center, research activity is now integrated over all four greater Charlotte hub facilities in a coordinated program.

Sanger Heart & Vascular Institute clinical research continues to facilitate the development of new technology and expertise. The Sanger Heart & Vascular Institute valve center is a leader in percutaneous valve therapy, contributing to a national database on transcatheter aortic valve replacement (TAVR), and is a national leader in percutaneous mitral valve repair, with the MitraClip through the REALISM and COAPT trials for high-surgical-risk patients.

Atrial fibrillation (AF) is a growing public health burden and an area of active study for Sanger Heart & Vascular Institute, through both the National Institutes of Health-sponsored CABANA trial, evaluating AF ablation, and several studies of percutaneous left atrial appendage occlusion with the Watchman™ device for stroke prevention.

The number of patients living with heart failure continues to grow. Sanjeev Gulati, MD, and colleagues study strategies to prevent readmission rates with the Heart Failure Success program, which has led to several presentations at national meetings, and through the study of new implantable devices to predict and prevent acute congestive heart failure episodes in outpatients.

Another area of leadership for Sanger Heart & Vascular Institute is in the study of anti-platelet therapy for the prevention of stent thrombosis. The multi-center international ADAPT-DES registry, with Michael Rinaldi, MD, as national co-principal investigator, and data management coordinated through the Dickson Advanced Analytics Group at Carolinas HealthCare System, presented one-year outcomes at the Transcatheter Cardiovascular Therapeutics (TCT) conference. It showed platelet hyporesponsiveness is a powerful predictor of both stent thrombosis and bleeding. These results may allow more selective use of more powerful anti-platelet agents to higher-risk cohorts. It also showed, for the first time, that routine use of intravascular imaging, an area of Sanger Heart & Vascular Institute expertise, can reduce stent thrombosis.

Quality improvement research is an active area of Sanger Heart & Vascular Institute research. The FOCUS initiative, led by Tom Johnson, MD, involved the institution of a system-wide quality improvement program, which led to marked improvement in appropriate utilization of echocardiography and stress testing. This has led to abstracts, papers and national recognition with Sanger Heart & Vascular Institute now represented on the American College of Cardiology (ACC) national committee for promoting appropriate use of cardiovascular imaging.

Sanger Heart & Vascular Institute has been a national and world leader in expedient, coordinated systems of heart attack care with numerous presentations over the last year at national meetings including the ACC and TCT, as a top 10 center for door-to-balloon times to open blocked arteries to the heart.

CHARLES BRIDGES, MD, ScD
Cardiothoracic Surgeon; Department Chair

THOMAS MAXEY, MD
Pediatric Cardiac Surgeon

MICHAEL RINALDI, MD, FACC, FSCAI
Interventional Cardiologist

Hadley Wilson, MD, is now a faculty member for 2012–14 for the American Heart Association's Mission Lifeline Project STEMI Systems Accelerator to bring these rapid transport heart attack models to 20 other cities in the United States, serving more than 20 million people.

Basic science and translational research are also active at Sanger Heart & Vascular Institute, led by Charles Bridges, MD, ScD, and his team. They have developed a technique called molecular cardiac surgery in which a viral vector is used to efficiently insert specific genes into cardiac myocytes to improve cardiac contractility in heart failure models.

Through participation in some of the most important clinical trials active in the country and through active original research from bench to bedside, Sanger Heart & Vascular Institute clinical research continues to advance the greater Sanger Heart & Vascular Institute and Carolinas HealthCare System mission.

CARDIOTHORACIC RESEARCH

Modern heart failure therapy is symptom oriented and employs pharmacological, percutaneous coronary interventional, electrophysiological and surgical principles. Despite extensive research and progress in reducing overall mortality rates, these therapeutic options do not deal with the key underlying intracellular signal transduction abnormalities that cause the development and progression of cardiac failure. Novel technologies are needed to further optimize the care of patients with heart failure. DNA delivery to the heart with gene transfer is now considered to be one of the most promising options. Several gene therapy clinical trials including patients with heart failure have been initiated in the United States. However, many hurdles are still present in this field. A major disappointment is that none of the randomized controlled phase II/III cardiovascular gene therapy trials have shown clinically relevant positive effects. A sophisticated and efficient delivery method for cardiovascular applications is still lacking, and very low concentrations of the gene product are produced in the target tissue. Systemic leakage of the gene solution is a problem that is not yet possible to solve in the clinical setting. According to modern concepts, to achieve a successful therapeutic effect with gene therapy, scientists must create technology that connects four factors: genetic strategy, appropriate vector, delivery method and target for intervention.

Delivery method. Dr. Bridges and his colleagues constructed the first "closed-loop" recirculating system, which they called molecular cardiac surgery with recirculating delivery (MCARD). Using this technology, they were able to achieve adeno-associated virus-mediated gene overexpression in a majority of myocytes and improve cardiac contractility and energy utilization efficiency in a preclinical large animal model. This system results in a

100-fold increase in gene expression and a 100-fold reduction in extracardiac gene expression compared to intracoronary delivery, or a 10,000-fold increase in (delivery efficiency) × (organ-specificity).

The molecular target. Over the last decade, there has been a significant evolution in the understanding of the molecular and cellular pathophysiologic mechanisms of heart failure. New evidence was found that, in heart failure, calcium cycling and excitation contraction coupling are severely disturbed at different levels. This leads to an overall decreased sarcoplasmic reticulum (SR) calcium (Ca^{2+}) uptake, which contributes to diastolic dysfunction. Additionally, calcium extrusion from the cytosol is enhanced by increased expression of the membranous sodium–calcium exchanger. This amplifies the overall diminishment of calcium transients, contributing to systolic dysfunction. Therefore, the restoration of normal calcium handling in heart failure should be one of the major targets of genetic intervention.
Roger Hajjar, MD (Dr. Bridges' collaborator from Mount Sinai Medical Center, NY), first reported that SERCA2a activity is decreased regardless of the etiology of the heart failure. It is known that SERCA2a is the major isoform of SR Ca^{2+}-ATPases in the adult heart; it accounts for 40 percent of the total SR proteins. SERCA2a is responsible for SR Ca^{2+} uptake in diastole, and its activity is tightly regulated by the small protein phospholamban. The observed association between decreased SERCA2a expression levels and reduced SR Ca^{2+} uptake in heart failure has prompted the selection of SERCA2a as a promising target for failing cardiac myocytes. This observation led the Bridges lab to investigate utilizing the highly efficient and organ-specific MCARD delivery platform for vector-mediated SERCA2a delivery.

Delivery vector. Choosing the right vector for cardiac applications is one of the most critical issues in gene therapy. Dr. Bridges and his colleagues have used adeno-associated virus (AAV), serotypes 1, 6 and 9. These vectors were chosen because of their cardiomyocyte-cell tropism, long-term expression and absence of a significant immune response.

Dr. Bridges' cardiac surgery research group, which includes Michael Katz, MD, PhD, Anthony Fargnoli, MS, and Richard Williams, BS, invented the MCARD procedure and was the first to combine genetic strategy (overexpression), delivery vector (AAV1), gene delivery method (MCARD) and molecular targets (SERCA2a) and achieved very promising results with the potential for early clinical translation. The main goal of their pilot study was to determine whether MCARD-mediated delivery of AAV/SERCA2a in a large animal model of ischemic heart failure would result in robust overexpression in the myocardium and long-term beneficial cardiac mechanoenergetic effects. Furthermore, this work aims to study the effect of gene transfer on the degree of apoptosis, the activation of different proteolytic caspases and the development of myocardial hypertrophy in the infarct/border zone. In this study, it was demonstrated that SERCA2a gene transfer significantly enhanced global and regional left ventricular function.

Moreover, this effect has a positive correlation with the level of gene expression. It was discovered that MCARD/SERCA2a gene therapy led to statistically significant silmultaneous reductions in the degree of apoptosis affecting the death receptor (extrinsic) pathway and the mitochondrial (intrinsic) pathway simultaneously. This leads to considerable and statistically significant improvements in the area of fibrosis and a diminution of myocardial hypertrophy as assessed by myocyte size.

Clinically, the MCARD/SERCA2a approach could be applicable to patients with ischemic heart failure, initially in those who would undergo cardiac surgery for coronary artery bypass procedures, valve repair, etc.

THROUGH PARTICIPATION IN SOME OF THE MOST IMPORTANT CLINICAL TRIALS ACTIVE IN THE COUNTRY AND THROUGH ACTIVE ORIGINAL RESEARCH FROM BENCH TO BEDSIDE, SANGER HEART & VASCULAR INSTITUTE CLINICAL RESEARCH CONTINUES TO ADVANCE THE GREATER … CAROLINAS HEALTHCARE SYSTEM MISSION.

CAROLINAS REHABILITATION

Following a long day at work, 24-year-old Todd (not his actual name) joined friends for a game of flag football. Running full speed toward the goal line, Todd was looking for the quarterback's pass. His friend on the opposing team was looking to intercept when they collided. Todd's body and head immediately stopped their forward momentum and he was thrown back to the ground. Although he did not lose consciousness or even hit his head directly, he experienced an intense headache. Additional symptoms included balance difficulties and sensitivity to light. During his visit to the emergency department (ED), Todd's diagnostic imaging came back negative. However, the ED physicians explained to Todd that he had a mild traumatic brain injury (mTBI), commonly referred to as a concussion, due to the violent movement of his brain in his skull at the time of injury. Todd enrolled in the Mild TBI Registry, a study that aims to identify biological and behavioral markers that can assist with prognosis and treatment prescription following a mTBI. This study is a collaboration among several departments and facilities in Carolinas HealthCare System, including the Carolinas Medical Center ED and Physical Medicine and Rehabilitation. Lori Grafton, MD, a study co-principal investigator who works in Physical Medicine and Rehabilitation, meets with subjects one and three weeks following injury to assess unresolved cognitive, behavioral and balance issues. Todd, who consented to be a subject in the study, also had the option to provide a blood sample to eventually test for TBI biomarkers.

Although many people who have experienced a mTBI recover without lasting problems, a small percentage have ongoing difficulties, such as short-term memory problems, irritability, headaches and other symptoms. These may last six to 12 months post-injury, sometimes longer. Currently, no reliable method exists for predicting who will experience long-term problems following mTBI. Initiation of therapeutic interventions can thus be delayed or impeded.

Physical Medicine and Rehabilitation and Carolinas Rehabilitation investigators are incorporating participatory action research approaches to their research efforts to improve acute patient education about mTBI. Participatory action research engages the assistance and contributions of persons with disabilities, their family members and the community in designing research projects and potential products. In addition, Physical Medicine and Rehabilitation has long taken the lead in investigating the effects of neurological injuries, such as TBI, spinal cord injury, stroke and Parkinson's disease, on the lives of people who have sustained these injuries and illnesses. As part of a National Institute on Disability and Rehabilitation Research (NIDRR) TBI Model System site and Follow-Up site, Carolinas Rehabilitation researchers will collect data on subjects 15 years following their TBI. This data has helped and will continue to help shape best practices when providing post-injury interventions that may improve such common and disruptive symptoms as irritability.

In late 2012, Janet Niemeier, PhD, ABPP, joined the Physical Medicine and Rehabilitation research team as the research group director. She has more than 20 years of experience providing clinical and neuropsychological services for people with disabilities and their family members. Dr. Niemeier has also been an active investigator of ways to improve the mental and physical health and quality of life for people with disabilities. She is author of more than 50 journal articles, books and treatment materials. Her research has been funded by NIDRR, National Institutes of Health and the National Alliance for Research on Schizophrenia and Depression. Dr. Niemeier brought with her to Physical Medicine and Rehabilitation her NIH/Eunice Kennedy Shriver National Institute of Child Health and Human Development-funded R01 randomized clinical trial testing the effectiveness of a manualized, acute neurobehavioral and cognitive intervention for people with moderate and severe TBI. These studies are a few examples of how Physical Medicine and Rehabilitation and Carolinas Rehabilitation investigators are improving the lives of people with neurological and other disabilities through participatory action and other leading-edge research methods.

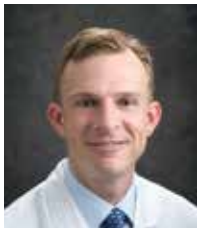
EMERGENCY MEDICINE

Charles (not his actual name) was mowing his lawn on a sunny afternoon, when he began to feel ill. Lightheaded and sweating profusely, he was able to yell out to his wife before he collapsed. She hurried to her husband and found him unresponsive and not breathing. She immediately dialed 911, and minutes later emergency medical services arrived and found the patient in cardiac arrest. Chest compressions were promptly started, and a breathing tube was placed. For the next hour, Charles received continuous chest compressions, numerous electrical shocks and multiple rounds of cardiac medications in an attempt to restart his heart. After an hour, circulation was finally restored. Charles was rushed to the cardiac catheterization lab, noted to have a blocked coronary artery and a coronary stent was placed to keep the vessel open. He was cooled to 33 degrees Celsius for 24 hours in an attempt to preserve brain function and was admitted to the intensive care unit.

Weeks later, Charles walked out of the hospital with a good neurological outcome. He doesn't recall the events that happened but, with a smile, he offered warm regards to the entire team that cared for him. "Thank you for saving my papa," whispered his 6-year-old granddaughter next to him. In North Carolina, there are more than 5,500 cardiac arrests annually, approximately 16 arrests daily. Historically, the survival rate in the United States has been an abysmal 6 to 8 percent.

In 2007, Carolinas Medical Center instituted a specialized resuscitative protocol for cardiac arrest patients known as Code Cool™. By cooling patients after a cardiac arrest, brain damage is lessened and survival improved. Resuscitation of the shock state that ensues requires aggressive hemodynamic support, ventilatory support and other critical care measures. This comprehensive protocol has been implemented more than 350 times at Carolinas Medical Center since its inception and is followed by a network of 25 regional hospitals that transfer patients to Carolinas Medical Center for continued cardiac arrest care. In a recent article published in the *American Heart Journal*, Alan Heffner, MD, and David Pearson, MD, studied the effects on outcome after implementation of Carolinas Medical Center's regionalized system of cardiac arrest care. Overall, 43 percent of patients survived with good neurologic function to hospital discharge. Even at one year, 93 percent were still alive. Thus, as with other high-acuity diseases such as STEMI, trauma and stroke, a regionalized approach to post-cardiac arrest care based on a referral cardiac resuscitation center is both feasible and effective.

As one of the largest cardiac arrest referral centers in the nation, Carolinas Medical Center has the large team of pre-hospital personnel, nurses, and physicians—including emergency physicians, cardiologists, neurologists and intensivists—that is necessary to be successful. Additionally, coordination among regional facilities to aggressively resuscitate, initiate the cooling process and coordinate timely transfer is paramount. This collaborative effort is what resulted in Charles' incredible outcome, bringing a man, who was without a pulse for an entire hour, back to life.



ALAN HEFFNER, MD
Emergency Medicine Physician

DAVID PEARSON, MD
Pediatric Cardiac Surgeon

FAMILY MEDICINE

MICHAEL DULIN, MD, PHD
Department Chair; Director of Research and Evidence-Based Medicine

Lakeyta (not her actual name) is a 52-year-old female who has had asthma for most of her life. She recently relocated to North Carolina and became part of the shared decision-making initiative begun at Carolinas Medical Center's Biddlepoint Family Medicine in 2011. Shared decision-making is one approach to patient-centered care. In this approach, both patient and provider are involved in the decision-making process: They share information with each other and participate in the decision process by expressing treatment preferences and agreeing on the treatment to implement. Lakeyta explained that for many years she had very poor control of her asthma despite being prescribed a lot of asthma medications. She was very confused by all the medications and frequently mixed up which medications to take when, resulting in almost weekly asthma attacks and leading to missed work and frequent hospitalizations.

During her shared decision-making visit, she and her provider worked together to prioritize her goals for asthma management. They jointly made a lot of decisions about her medications and, to her great relief, were able to reduce the total number she was taking. In conjunction with decisions about the medications, Lakeyta was also engaged in a simple, effective medication education strategy. Within weeks, she reported having the best control of her asthma that she could remember from her entire adult life.

Asthma is a chronic disease that is difficult to manage. Disadvantaged populations often have higher rates of disease, poor medical compliance and worse outcomes. This translates to higher healthcare costs. Failure to consider individual patient circumstances and goals may contribute to nonadherence with treatment programs. Patient-centered care is an innovative approach to the delivery of healthcare in which patients are encouraged and enabled to participate in the management of their health issues.

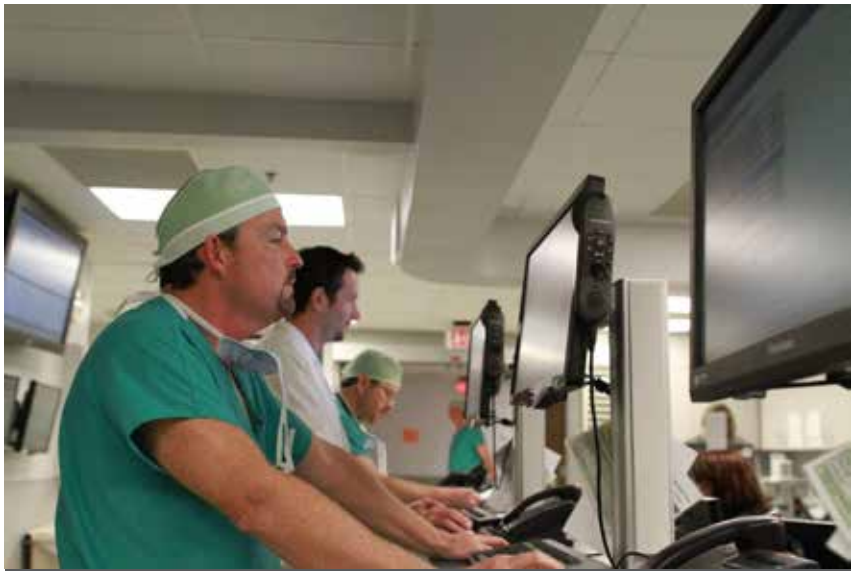
Working in partnership with six community care clinics, Michael Dulin, MD, PhD, and his team of researchers in the Department of Family Medicine have implemented shared decision-making for asthma management, and close to 200 patients have benefited from an understanding of their disease and decision-making associated with their treatment.

“ASTHMA IS A CHRONIC DISEASE THAT IS DIFFICULT TO MANAGE. ... PATIENT-CENTERED CARE IS AN INNOVATIVE APPROACH TO THE DELIVERY OF HEALTHCARE IN WHICH PATIENTS ARE ENCOURAGED AND ENABLED TO PARTICIPATE IN THE MANAGEMENT OF THEIR HEALTH ISSUES.”

DICKSON ADVANCED ANALYTICS GROUP

The Dickson Advanced Analytics Group (DA^2) provides data management and analytics for studies across Carolinas HealthCare System. One example is the Asthma Comparative Effectiveness (ACE) study in the Department of Family Medicine. The shared decision-making study includes sending a survey to patients with asthma and asking them to report on their quality of life and level of control. Data and other metrics from the study are imported into the ACE Research (ACER) database. The ACER database is maintained and managed by DA^2. The variables that comprise the database are patient demographics, ED visits, hospitalizations and Medicaid/Medicare and Cerner data. This data is instrumental in helping determine the health outcomes of our patients. Patients who self-report a poor quality of life will be contacted by a clinical research nurse to encourage them to see their primary care providers. The shared decision-making intervention of the study has shown that patients who attend an asthma half-day seminar at one of our six ambulatory clinics have fewer hospitalizations and ED visits, which, in turn, lowers costs for the System. By being able to associate and link individual patient data and report it in aggregate form, DA^2 is able to show the valuable impact of the ACE study on a system-wide level. When ED and inpatient costs associated with the shared decision-making asthma intervention were evaluated, we found that patients who participated in shared decision-making experienced a decline in average cost. Findings suggest that involving patients in the decision-making process reduces the financial burden for both patients and hospitals.

Nearly 9 million children in the United States have asthma. Children have smaller airways than adults, which makes asthma especially serious for them. Our school-based intervention has school nurses send Cerner messages to providers who work at one of the six ambulatory clinics involved with the study. School nurses are currently receiving information about students who have been hospitalized at Levine Children's Hospital. School nurses obtain parental consent from those students who were hospitalized to access and message providers with vital



information, such as the student's availability and use of medications at school, whether correct technique was used, last hospitalization, Asthma Control Test score, peak flow reading, activity tolerance, unmet needs and school nurse contact information, thus closing the loop of communication. Ultimately, this provides case management for the students at school and providers are notified in a more timely manner of the health status of their patients.

GENERAL SURGERY

B. TODD HENIFORD, MD
Chief, Division of Gastrointestinal and Minimally Invasive Surgery

DIMITRIOS STEFANIDIS, MD, PhD, FACS, FASMBS
Bariatric Surgeon; Medical Director, Carolinas Simulation Center

Alex (not his actual name) had part of his intestine removed at Carolinas Medical Center due to a precancerous polyp. Surgery was uneventful, but on the second night of his hospital stay, he felt short of breath. His nurse examined him, placed him on oxygen, which immediately improved his breathing, and called the on-call resident. Janice Sumner, MD (not her actual name), responded promptly to the call to evaluate him. The nurse provided her with a succinct assessment of Alex's symptoms and relayed to her the urgency of the situation. Dr. Sumner was at the bedside in no time and, after a brief and focused evaluation and consultation with the attending physician, a well-outlined plan for Alex's care was established. The patient was transferred to the intensive care unit. Blood tests and imaging studies revealed that Alex had a small clot in his lungs. With appropriate treatment and a few more days in the hospital, he was discharged home in excellent condition. Alex was impressed by the care he received and was most appreciative of the efforts of the medical and nursing staff and their ability to work so well together as a team.

The great care provided to Alex was not by chance. Besides having well-qualified personnel caring for him, his providers had undergone intense training on simulators at the Carolinas Simulation Center (CSC). Simulation-based education is a new teaching technique used at Carolinas HealthCare System to improve learning of healthcare providers and patient care. Dr. Sumner had practiced the exact same patient scenario she encountered with Alex a couple of weeks before at the CSC using one of the sophisticated, high-tech mannequins available. She had received detailed feedback on her performance by her attending surgeon after the scenario and was better prepared, more confident and ready to act when she was called to see Alex. The same was true for the nurse, who also trained using simulation-based education at the CSC and was ready to treat a patient like Alex. Importantly, both healthcare providers had also received simulation-based training on teamwork and effective communication to prevent any ambiguity or misunderstandings from interfering with patient care. They had never received this type of training before during their conventional professional training and both were very happy and appreciative to have the resource of the CSC available to them at Carolinas HealthCare System.

The CSC is the only education institute in the region accredited both by the American College of Surgeons and the Society for Simulation in Healthcare. This is an important distinction that highlights the quality of work done at the center. Among other criteria, both accreditations require that the center demonstrate excellence in simulation-based research. In 2012, under the leadership of Dimitrios Stefanidis, MD, PhD, a minimally invasive surgeon who serves as the medical director for the center, the CSC has added several important publications to the simulation literature. In 2012, Dr. Stefanidis led a multi-institutional project aimed at establishing national performance benchmarks for surgery residents in an effort to standardize surgical training across the United States. This study was the product of the first collaborative grant award of the Association for Surgical Education and the Association of Program Directors in Surgery and was presented at the plenary session of the 2012 Surgical Education Week. This year, Dr. Stefanidis also published the results of a grant-funded study that demonstrated emphatically the value of using a secondary task that assesses the spare attention capacity of trainees for performance assessment on simulators in the *Annals of Surgery*. This study allowed Dr. Stefanidis and his collaborator Marc Scerbo, MD, a human factor psychologist from Old Dominion University, to secure an Agency for Healthcare Research and Quality grant, currently ongoing, to further investigate the value of a newer and better version of the secondary task.

Research projects such as these help improve teaching methods, with visible results on improved skill acquisition and learning of our trainees, and pave the way for improved patient care and outcomes. It is not by chance, but by design, that Alex received excellent care at Carolinas Medical Center.

GASTROINTESTINAL AND MINIMALLY INVASIVE SURGERY

Since its introduction at the International Hernia Congress in March 2012, the Carolinas Equation for Quality of Life (CeQOL) mobile app has

been downloaded thousands of times in more than 40 countries. The app was developed to help patients and clinicians discuss quality of life after an inguinal hernia repair, the most common surgery performed in the world. While the vast majority of patients experience an uneventful recovery, more than 30 percent can suffer from chronic symptoms that can be severe enough to cause disability. Previously, these complications were rarely discussed by physicians and almost unknown to patients prior to surgery.

As modern hernia repair techniques have dramatically improved traditional outcomes measures (hernia recurrence, infection, operative time, etc.), focus has shifted to a strong emphasis on postoperative quality of life. B. Todd Heniford, MD, along with the Division of Gastrointestinal and Minimally Invasive Surgery's research team, led this innovative movement with the development of the Carolinas Comfort Scale™ (CCS), a validated, hernia-specific quality of life assessment tool. Since its development in 2006, the adoption of the CCS has been extraordinary, now translated into more than 25 languages. Large administrative outcomes databases, such as the International Hernia Mesh Registry (IHMR), the French and British governmental health agencies and others have employed the CCS to track and monitor quality of life following hernia repair with mesh in an effort to continually improve surgical procedural outcomes.

The IHMR, of which Dr. Heniford is the chair, is a multi-national, prospectively collected database with more than 40 participating sites in the United States, Europe, Canada and Australia. The Division of Gastrointestinal and Minimally Invasive Surgery research team, including Amy Lincourt, PhD, MBA, Paul Colavita, MD, Igor Belyansky, MD, Amanda Walters and Kristian Dacey obtained 3.5 million data points from more than 1,700 prospective IHMR inguinal hernia repairs. From this data, a complex, predictive, three-page mathematical equation was developed to predict a patient's chance of having chronic discomfort following inguinal hernia repair surgery. The equation, while too complex for a clinical setting, serves as the engine for the CeQOL app. The app uses a series of 18 questions regarding age, hernia details and pre-operative quality of life symptom assessment to calculate the patient-specific risk. CeQOL is a powerful tool in pre-operative discussions, in the consent process between surgeons and patients and as part of our continued research as well as that of several centers in Europe, Asia and Australia.

CeQOL, the first medical or surgical predictive app in the world, has been recognized as a major healthcare innovation worldwide. It was named best research project of 2012 by international hernia societies in North and South America, Europe and Asia. CeQOL has also been highlighted nationally in two articles in the *Wall Street Journal*, locally in the *Charlotte Observer*, and in numerous articles in healthcare publications such as *General Surgery News*.

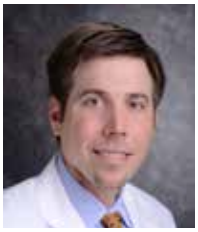
CeQOL, a culmination of combined talents within the Division of Gastrointestinal and Minimally Invasive Surgery, is the first of a number of apps being developed to allow physicians and surgeons to better care for patients. One such application will focus on predicting wound complications, like infections, and cost associated with more complex abdominal surgeries. The data for this application will originate from the Division's database, consisting of more than 1,000 prospectively consented patients. Risk factors for postoperative complications along with the impact of modifiable risk factors, such as obesity, smoking and diabetes, will play a significant role in allowing us to foresee problems, and the cost of such, prior to an operation. With the changes in healthcare that we now face, modeling such as this will be remarkably important for patients and the physicians and hospitals caring for them.

The Carolinas Comfort Scale, the Carolinas Equation for Quality of Life app and our future developments have shown and will continue to demonstrate to our patients, our community and the world Carolinas HealthCare System's dedication to the quality of life of those for whom we care.

INTERNAL MEDICINE

HERBERT BONKOVSKY, MD
Gastroenterologist

MARC JOHNSON, MD
Medical Director; Infectious Disease Clinic-CMC



PAUL SCHMELTZER, MD
Transplant Hepatologist

PHILIPPE ZAMOR, MD, MPH
Transplant Hepatologist

Several members of the Department of Internal Medicine, including Mark Russo, MD, MPH, Philippe Zamor, MD, MPH, Marc Johnson, MD, Paul Schmeltzer, MD, and Herbert Bonkovsky, MD, are leading the way in the fight to cure hepatitis C viral infection. The United States Centers for Disease Control and Prevention is now recommending that all "baby boomers" (everyone born from 1945 to 1965) get a blood test for hepatitis C. This recommendation calls for one-time testing of baby boomers and, it is estimated, will result in the discovery of 800,000 previously undiagnosed patients with chronic hepatitis C in the United States. Early detection and treatment can save lives by preventing liver damage, cirrhosis and possibly liver cancer.
In 2012, the Liver-Biliary-Pancreatic Center participated in 14 industry-sponsored clinical trials for the treatment of hepatitis C as well as several investigator-initiated studies.
Dr. Russo conducted a study using intravenous interferon for the treatment of chronic hepatitis C virus (HCV) during the anhepatic phase of liver transplantation. Dr. Bonkovsky and his PhD candidate, Shahin Sendi, MD, are currently aiming to determine predictive indicators of anti-viral treatment response in patients with hepatitis C. Weihong Hou, PhD, research scientist, and Dr. Bonkovsky have discovered striking anti-viral effects of heme and zinc protoporphyrin, the latter of which has striking effects on the NS5A protein of HCV, which is essential for viral replication. The Liver-Biliary-Pancreatic Center also conducts numerous studies in the field of drug-induced liver injury, porphyrias, hepatocellular carcinoma and pancreatic cancer. The expert help of Gale Groseclose, RN, and the clinical research staff of the center, are essential components of these efforts.

Access to clinical trials has positively impacted the hepatitis C patient population by giving patients other treatment options in addition to the standard of care, as well as potentially changing the standard treatment. The Liver-Biliary-Pancreatic Center is participating in clinical trials that are adding additional medications to current treatments (protease and polymerase inhibitors, direct anti-viral agents) or eliminating treatment medications (non-interferon trials), changing dosage requirements and treating populations that have not been previously recommended (post-liver transplant patients and those with HIV co-infection, being studied particularly by Drs. Johnson and Zamor). Clinical trials with triple therapy have led to an increase in the cure of hepatitis C from around 40 percent to 75 percent, and, for many patients, it has decreased the length of therapy from 48 to 24 weeks.

One such success story is that of Mary (not her actual name), a 64-year-old diagnosed with chronic hepatitis C and advanced hepatic fibrosis. She was enrolled in an industry-sponsored clinical trial and was treated with pegylated interferon, ribavirin and a protease inhibitor not currently approved by the FDA. She was on treatment for six weeks, at which time she developed pancreatitis and was admitted to the hospital. At the time of admission, her HCV RNA level (the HCV viral load) was undetectable. A liver biopsy done in the hospital showed the progression to cirrhosis. Due to the hospitalization, she had to be discontinued from the trial. She is currently in follow-up and at 36 weeks post-treatment, the virus remains undetectable. Standard rule is if the virus remains undetected after completion of 24 weeks of treatment and 24 weeks' follow-up, the patient is considered cured. Mary only had six weeks of this triple therapy regimen, and the virus was undetectable 24 weeks after the treatment was stopped.

Kathy (not her real name) is a young single mother who did not have health insurance and was struggling to take care of herself and her child. She received treatment for her hepatitis C in a clinical trial at the Liver-Biliary-Pancreatic Center and was cured with 24 weeks of triple therapy. She is otherwise young and healthy, has minimal liver damage and is able to work productively to provide for her family.

NEUROSCIENCES

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is an incurable progressive neurodegenerative disease characterized by muscle weakness and wasting resulting from the combined loss of upper and lower motor neurons. The incidence of ALS in the United States is one to three cases per 100,000 each year, typically affecting men and women in their 50s. The causes of ALS are poorly understood, and genome-wide association studies have identified genetic determinants (single nucleotide polymorphisms, deletions, copy number variations) with limited penetrance. Significant advances in gene expression studies in whole blood, peripheral blood mononuclear cells (PBMCs) and peripheral blood lymphocytes (PBLs) have been made recently. These studies have identified specific alterations that may permit longitudinal assessment of potential biomarkers with respect to treatment effects in prospective clinical trials.

At Carolinas Neuromuscular/ALS-MDA Center, ALS Research Laboratory (directed by Benjamin Rix Brooks, MD), Jean-Luc Mougeot, PhD, who leads the ALS biomarker discovery program, has conducted microarray analyses on PBLs from ALS patients and healthy controls to identify molecular signatures relevant to ALS pathogenesis. For the first time, Dr. Mougeot has shown the perturbation of the Kyoto Encyclopedia of Genes and Genomes (KEGG) ALS pathway of motor neuron degeneration in lymphocytes from ALS patients.

In summer 2012, within the frame of the Cannon Summer Scholar Program, Dr. Mougeot updated the KEGG ALS pathway map to be used as a template for future data-mining studies. He developed a novel systems biology method to identify ALS pathway-related drug targets. In collaboration with UNC-Charlotte Department of Bioinformatics and Genomics, Dr. Mougeot also confirmed differential expression of TARDBP and is pursuing further pathway analyses. Thus, these studies have indicated that the peripheral blood compartment, in particular the PBL and PBMC components, may partially replicate pathophysiological changes occurring in the central nervous system.

JEAN-LUC MOUGEOT, PHD
Director, Scientific Development

ORAL MEDICINE

MICHAEL BRENNAN, DDS, MHS
Associate Department Chair

PETER LOCKHART, DDS
Department Chair

Bill (not his actual name) was referred to the Carolinas Medical Center Dental Clinic for evaluation of a painful lesion on his tongue that had been present for four months. The referring dentist had done a brush biopsy, which was reported as benign. The lesion continued to expand, and it became increasingly painful. A biopsy confirmed the clinical concern for squamous cell carcinoma. The patient was treated with surgical removal of the cancer, followed by radiation therapy. Ten months later, he returned for evaluation of tooth pain and jaw swelling. A carious tooth was removed, but the surgical site failed to heal, and he developed a large area of exposed and necrotic bone and a fractured jaw. This was determined to be osteoradionecrosis (ORN), which was managed over the course of several months with multiple surgical procedures, including a resection of a large portion of his mandible (lower jaw).

Each year, 40,000 Americans develop head and neck cancer, and many require high-dose radiation therapy, often in combination with surgery and/or chemotherapy. An unavoidable side effect of radiation therapy is damage to the oral and maxillofacial tissues, some of which persists for the lifetime of the patient. This side effect includes a permanent decrease in saliva production (hyposalivation), as the major salivary glands are often included in the areas treated with radiation therapy. Hyposalivation has a major impact on patients' overall quality of life and significantly increases the risk of tooth decay and loss. Radiation can also impair bone healing, leading to a lifelong risk of infection of the bone surrounding the teeth, referred to as osteoradionecrosis, which can lead to an increased risk of jaw fracture and severe pain, requiring extensive medical and surgical therapy. It is believed that approximately 50 percent of all ORN cases are associated with dental extractions following radiation therapy. These patients are often caught in a vicious cycle as they are at a high risk of needing dental extractions.

In 2012, Michael Brennan, DDS, MHS, associate department chair, was awarded an $8.15 million grant from the National Institutes of Health National Institute of Dental and Craniofacial Research to study the dental and oral medicine outcomes of patients who have received high-dose radiation therapy to the head and neck region. The results of this five-year, multi-center study will lead to a better understanding of the oral and dental sequelae experienced by head and neck cancer patients. This, in turn, will guide decision-making and standard of care protocols for the dental management of patients in the pre- and post-radiation period. Dr. Brennan will work closely with his co-principal investigator from the University of Connecticut, Raj Lalla, DDS, PhD, and the site investigators at Harvard University, University of Pennsylvania and New York University. The University of Minnesota will serve as the data coordinating center for this study, which also includes a collaborative effort from co-investigators and researchers from the Department of Oral Medicine and Dickson Advanced Analytics Group at Carolinas HealthCare System.

Another major area of research in the Department of Oral Medicine is the role of oral diseases in cases of infective endocarditis (infection of a heart valve) and as a contributor to cardiovascular disease. Peter Lockhart, DDS, department chair, co-chaired a writing committee for the American Heart Association that included pediatric and adult cardiologists, infectious diseases specialists and other researchers in this field. This group was charged with conducting a systematic review to determine the existence or nature of a possible association between periodontal and cardiovascular diseases. This four-year effort culminated in May 2013 with the publication of an AHA Statement in *Circulation: The Journal of the American Heart Association*. The researchers reported an association between periodontal and cardiovascular diseases but found insufficient evidence to suggest a causative role for periodontal disease. This publication has had a major impact on our understanding of the controversy concerning the potential for dental diseases to contribute to cardiovascular disease, and the way this well-publicized issue is viewed by clinicians, patients and the press.

ORTHOPEDICS

The Major Extremity Trauma Research Consortium (METRC) was funded by the Department of Defense to conduct critical "gap" extremity trauma research, focused on the improvement of outcomes to the nation's wounded warriors. The Consortium staffs a coordinating center in the Johns Hopkins School of Public Health and has engaged more than 30 civilian and four military trauma centers. Ellen MacKenzie, PhD, is the METRC principal investigator. Michael J. Bosse, MD, serves as METRC's co-principal investigator and the clinical chair of the Consortium. At present, more than $70 million is targeted to support 15 different research topics. Two of the projects are now funded by the National Institutes of Health (NIH). One of the NIH projects will test the new Patient Reported Outcomes Measurement Information System computer adaptive testing algorithms to assess patient outcomes in trauma patients.

The Department of Orthopedic Surgery at Carolinas Medical Center has a primary role in METRC. Carolinas Medical Center is participating in 10 of the studies. The efforts at Carolinas Medical Center are coordinated through the Orthopedic Clinical Research office. Rachel Seymour, PhD, serves as METRC site coordinator and is a co-investigator on many of the studies. James Kellam, MD, Steve Sims, MD, and Madhav Karunakar, MD, actively participate as site co-investigators. At present, Carolinas Medical Center is the leading patient contributor to METRC.

METRC's studies are currently focused on the prevention or treatment of trauma-related infections and the predictive value of objective and subjective patient findings on the diagnosis of compartment syndrome and fracture repair in the face of bone defects. The most significant project, however, is a patient-focused recovery program targeted at the reduction of complications, post-traumatic stress disorder and disability. Carolinas Medical Center will serve as one of six active treatment sites for the study and began enrolling patients into a new post-trauma recovery paradigm in spring 2013.

For more information on METRC's research agenda and for a detailed description of all studies, visit **metrc.org.**

MICHAEL J. BOSSE, MD
Director, Orthopaedic Clinical Research

PEDIATRICS

AMINA AHMED, MD
Pediatric Infectious Diseases

ANDREW GILMAN, MD
Pediatric Hematologist-Oncologist

THOMAS GRIFFIN, MD, PHD
Pediatric Rheumatologist

SUSAN SPARKS, MD, PHD
Clinical Geneticist

The Center for Pediatric Research (CPR) at Levine Children's Hospital continues to expand its breadth and depth of clinical trials to allow patients access to innovative diagnostic methodology and therapeutic interventions. A major accomplishment in 2012 has been the establishment of the Pediatric Research Fund by the Division of Neonatology. The fund will provide financial support for future research endeavors conducted by residents and faculty of the Department of Pediatrics.

BEHAVIOR AND DEVELOPMENT

As part of the emerging field of epigenetics, the Center for Neurodevelopmental Research is interested in how a wide range of common prenatal conditions, including maternal drug use, depression, anxiety and medication use during pregnancy, affect the "wiring" of the infant's developing nervous system. A major component of the research of Philip Zeskind, PhD, is developing leading-edge methods by which the health of the infant's nervous system can be assessed in the absence of any routine abnormal signs. These measures of the infant's cry sounds are not only predictive of such problems as sudden infant death syndrome, attention deficits, regulatory disorders and behavioral problems, but also of such developmental outcomes as lower intelligence and physical child abuse. Future work will explore the possible detection of problems leading to autism.

PEDIATRIC INFECTIOUS DISEASE AND IMMUNOLOGY

A multi-center Centers for Disease Control and Prevention study has recently been launched to evaluate the diagnosis of latent tuberculosis infection (LTBI). With the decline of tuberculosis disease in the United States, it is now imperative to treat LTBI to prevent future tuberculosis cases with the ultimate goal of tuberculosis elimination. As a member of the National Institutes of Health (NIH)-funded Collaborative Antiviral Study Group, Amina Ahmed, MD, will begin enrollment in four clinical trials evaluating maternal and congenital viral infections.

Niraj Patel, MD, is currently participating in a national registry to enhance early diagnosis and treatment strategies for children with primary immunodeficiency diseases (PIDDs). Although generally considered rare, PIDDs may be unrecognized and, therefore, not diagnosed in a timely manner. Dr. Patel will also be spearheading a multi-center evaluation of the safety and efficacy of a new subcutaneous immunoglobulin product for the treatment of primary immunodeficiency diseases.

PEDIATRIC NEPHROLOGY

Pediatric Nephrology is involved in several multi-center clinical trials through the Midwest Pediatric Nephrology Consortium, evaluating the therapeutic management of nephrotic syndrome, cardiovascular complications in renal transplant recipients and genetic markers of nephrotic syndrome. Jack Weaver, MD, recently completed a retrospective study examining the risk of cardiovascular disease in pediatric renal transplant recipients on immunosuppression protocols that minimize steroid exposure. Compared with patients on standard immunosuppression regimens, patients on steroid minimization demonstrated improved blood pressure control, lower rates of obesity and improved serum lipid profiles. The patients also demonstrated less left ventricular hypertrophy, a known risk factor for future cardiovascular events. As cardiovascular disease is the leading cause of death in these patients, this research will hopefully lead to improvements in the long-term mortality of these patients.

PEDIATRIC RHEUMATOLOGY

The Division of Rheumatology has completed its participation in an NIH-funded genetics repository for patients with juvenile idiopathic arthritis (JIA), recruiting nearly 100 children with JIA. Ongoing studies include contributions to an NIH-funded P01 program project that is investigating the ability of gene expression in white blood cells to predict and assess response to medications in JIA, involvement in a nationwide pediatric rheumatology registry that is supported by the Childhood Arthritis & Rheumatology Research Alliance (CARRA), and participation in a pharmaceutical company-sponsored phase II/III trial of a novel anti-TNF biologic response modifier, certolizumab pegol, that is coordinated by the national Pediatric

Rheumatology Collaborative Study Group (PRCSG). Affiliation of the Division with CARRA and PRCSG will provide future opportunities to participate in additional studies benefiting children with rheumatic disease.

Madeline (not her actual name) is a 9-year-old research participant who is enrolled in a JIA study being conducted by Thomas Griffin, MD, PhD. As part of the study, she receives injections of an investigational medication every two weeks. Madeline and her family are required to make frequent trips to see Dr. Griffin, principal investigator for the study, but she says being in a research study is "fun." When asked if there is anything she can do today that she couldn't do before starting the investigational therapy, Madeline excitedly said, "I can almost do my back walkover [in gymnastics] now!"

BLOOD AND MARROW TRANSPLANTATION

The primary research focus for Blood and Marrow Transplantation is the use of T-cell depletion to allow every child who needs a bone marrow or blood stem cell transplant to have a donor. Many patients don't have a tissue-matched family member. Although there are more than 10 million volunteer donors who have registered to donate bone marrow or stem cells, there are patients for whom matched unrelated donors can't be found. Carolinas HealthCare System's team has been able to use mismatched family members to successfully perform stem cell transplantation for 19 children.

The department is able to perform transplants from mismatched donors by using a machine to remove T cells. T cells are usually given as part of the bone marrow or stem cell transplant. T cells cause the most common complication of transplant by attacking the patient's body. This attack can be fatal when the donor and patient aren't matched for tissue types.

Andrew Gilman, MD, has been participating in clinical trials of T-cell depletion for more than a decade. A report of his work in collaboration with researchers at the University of California-San Francisco has recently been accepted for publication. His current clinical trial builds on this work. Our studies aim to decrease leukemia relapse and infections after transplant.

John (not his actual name) is a 6-year-old boy from Puerto Rico who was diagnosed with acute lymphoblastic leukemia in August 2010. John was referred to Levine Children's Hospital for a stem cell transplant. He has benefited from two research studies at Levine Children's Hospital. John did well with chemotherapy for 10 months. Then his leukemia returned, and he needed even stronger chemotherapy, which resulted in severe damage to his liver. When John recovered, he needed a stem cell transplant urgently to prevent his leukemia from recurring. John's brothers were not matches, and doctors were unable to find a matched unrelated donor for him. His doctors was able to use his mother, who was only a half match with him, as his donor in Levine Children's Hospital research study. Levine Children's Hospital is one of the few hospitals in the country that can perform this type of transplant. John tolerated the transplant well despite his prior liver disease. His mother's bone marrow grew well in John's body and he remains free of leukemia one year after transplant.

John's transplant was complicated by an infection due to a virus called CMV, which can cause disease ranging from pneumonia to brain infection. John had the virus in his body prior

JACK WEAVER, MD
Pediatric Nephrologist

PHILIP ZESKIND, PHD
Research Group Director

to transplant. His mother had not had CMV before and therefore her blood cells could not control the CMV in John's body after transplant. The CMV in John's body multiplied rapidly despite standard anti-viral drugs and was likely to cause serious disease. The team was able to use a drug in development, CMX001, in a research study to treat John. The drug helped control the CMV and prevented disease. The research was performed as a compassionate use study in collaboration with the company that manufactures CMX001.

ALTHOUGH THERE ARE MORE THAN 10 MILLION VOLUNTEER DONORS WHO HAVE REGISTERED … THERE ARE PATIENTS FOR WHOM MATCHED UNRELATED DONORS CAN'T BE FOUND … CAROLINAS HEALTHCARE SYSTEM'S TEAM IS ABLE TO PERFORM TRANSPLANTS FROM MISMATCHED DONORS BY USING A MACHINE TO REMOVE T CELLS.

CLINICAL GENETICS

The Department of Clinical Genetics has significantly expanded research activities since the arrival of Susan Sparks, MD, PhD, in 2009. Dr. Sparks' particular interest is in neuromuscular disorders with a biochemical basis, and she oversees several research projects. She is the current director of the Pediatric Muscular Dystrophy Laboratory at Cannon Research Center, which focuses on glycosylation defects and neuromuscular disease. She is also the principal investigator on a research project called Molecular Diagnostics and Cell Banking as part of the Center of Research Translation: Systemic Exon-Skipping in Muscular Dystrophy, with Eric Hoffman, PhD, from the Center for Genetic Medicine Research, Children's National Medical Center. In addition to general and metabolic genetics expertise, she is also site principal investigator of the Cooperative International Neuromuscular Research Group (CINRG; **cinrgresearch.org**). Dr. Sparks also participates in the weekly multi-disciplinary Muscular Dystrophy Association clinic at Carolinas Medical Center.

TRAUMA

The Carolinas Trauma Network (CTN) Research Center of Excellence (COE) was funded through an internal competitive grant opportunity to unify Carolinas HealthCare System's trauma research efforts under one umbrella and to establish a robust clinical platform to attract external funding. As the second-largest not-for-profit healthcare organization in the United States, Carolinas HealthCare System is uniquely poised to leverage its organization, the large population served and its trauma-related programs into a model trauma service delivery research platform. The CTN Research COE will be able to respond to the demands for safer, more efficient and more effective care and conduct the required associated Comparative Effectiveness and Outcomes Research. Michael Bosse, MD, and Rachel Seymour, PhD, from the Department of Orthopedic Surgery, are the co-directors of the COE and are collaborating with faculty from the departments of Orthopedic Surgery, Emergency Medicine, General Surgery-Trauma, Physical Medicine and Rehabilitation and Neurosciences, as well as the Dickson Advanced Analytics Group (DA^2). Currently, the COE's research efforts are focused on geriatric trauma and mild traumatic brain injury (mTBI).

During the first year, the Geriatric Trauma Workgroup initiated several clinical and translational research studies, including:

1. A translational study on falls prevention (principal investigator: Richard Peindl, PhD; co-investigators: James Kellam, MD, Rachel Seymour, PhD, Mark Hirsch, PhD, and Christine Churchill, Carolinas HealthCare System's Healthy@Home, and Nigel Zheng, PhD, and Eric Wickstrom, PhD, from University of North Carolina-Charlotte)

2. Evaluation of the implementation of the Fragility Fracture Program (co-principal investigators: James Kellam, MD, and Joshua Patt, MD)

3. Assessment of anticoagulation therapy in the older trauma patient (co-investigators: Joshua Patt, MD, Rachel Seymour, PhD, David Jacobs, MD, David Miller, MD, Michael Gibbs, MD, Jeffrey Kline, MD, and Lindsay Fairfax, MD)

4. Development and validation of a geriatric trauma triage score (co-investigators: Madhav Karunakar, MD, David Jacobs, MD, Rachel Seymour, PhD, Sanjit Konda, MD, Elizabeth Freeman, RN, Jill Scott, RN, Matthew Wilson, MD, and Sam Ross, MD)
A prospective epidemiological study to examine incidence and outcomes in the geriatric trauma population is also under way.

The mTBI Workgroup initiated three clinical research studies, including:

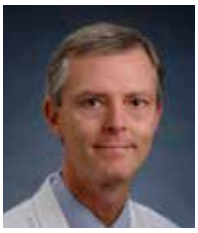
1. mTBI Transfer Guidelines Retrospective Study (co-investigators: Ron Sing, DO, Tuan Huynh, MD, and Erin Hanna, MD)

2. mTBI Longitudinal Biomarker Registry (co-principal investigators: Michael Gibbs, MD, Lori Grafton, MD, and Michael Runyon, MD)

3. A participatory action research study with mTBI treatment needs emphasis (principal investigator: Mark Hirsch, PhD; co-investigators: Lori Grafton, MD, Tami Guerrier, Rachel Seymour, PhD, and Molly Zmuda, MHA)

The COE Coordinating Center, DA^2 and staff from the CTN have been working together closely to establish data capture systems that will meet our common needs. Specifically, we currently have two projects critical to the success of the COE: a minimal data set for trauma and a map of all available Carolinas HealthCare System data sources.

WOMEN'S HEALTH



DAVID TAIT, MD
Associate Director, Gynecologic Oncology

Beth (not her actual name) was diagnosed with and underwent surgery for a stage IIIC ovarian cancer in August 2006, and then volunteered to participate in a chemotherapy trial on Gynecologic Oncology Group (GOG) 218. She did well until August 2009, when she was diagnosed with a recurrence. Knowing the importance of research, she again agreed to consider one of the team's clinical protocols, which was built on the knowledge gained from the previous trial in which she had participated. The new study was GOG 213, which incorporated two standard chemotherapies with bevacizumab as a maintenance regimen. Now, some three years later (and more than six years from her original diagnosis), Patsy continues on this regimen, will soon receive her 60th cycle of bevacizumab and is disease-free.

2012 has been a very exciting and productive year for research in the Department of Obstetrics and Gynecology. Among the research projects in 2012 that have received particular attention are studies in the areas of gynecologic oncology and reproductive endocrinology.

The Department of Gynecologic Oncology continued to participate in numerous studies in 2012 in both basic science research and clinical trials.

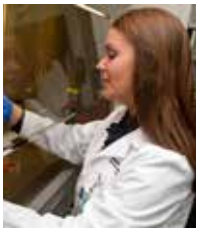
This past year, Carolinas Medical Center/Levine Cancer Institute was honored to become a full member and primary site of the Gynecologic Oncology Group (GOG), which is the research arm of the National Cancer Institute. There are fewer than 50 primary sites in the United States.

This affiliation affords patients the opportunity to be a part of important clinical research, giving them access to the latest chemotherapy regimens. Ovarian cancer is the most lethal of the gynecologic malignancies that physicians like David Tait, MD, treat, taking some 15,000 lives annually. The research conducted at Levine Cancer Institute is making a difference in women's lives.

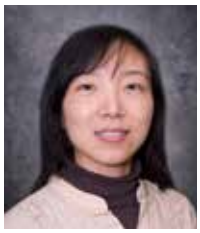
What is so great about Beth's story is how she lives her life with cancer. Since her diagnosis, she has been very proactive not only for herself, but for the health of many other women. She has been an active participant in the annual fundraiser "Stiletto Sprint," and she works with the Integrative Medicine group at Carolinas Medical Center-Northeast. One of the most innovative projects she has undertaken is in the education of medical students. Having been a patient herself, and having interfaced with many nervous third-year students, acting interns and residents, she saw a real need to educate them on the patient's perspective. She wanted them to understand how a woman with a potentially terminal disease viewed life and the interactions with the students and physicians responsible for her care. Through her efforts, she organized a teaching module that she and some of her fellow survivors present to our students and residents, and then allow "her students" to ask questions. This has been an amazing learning experience for all … giving a tiny perspective of the idea of "walking a mile in my shoes."

> CAROLINAS MEDICAL CENTER/LEVINE CANCER INSTITUTE WAS HONORED TO BECOME A FULL MEMBER AND PRIMARY SITE OF THE GYNECOLOGIC ONCOLOGY GROUP … THIS AFFILIATION AFFORDS OUR PATIENTS THE OPPORTUNITY TO BE A PART OF IMPORTANT CLINICAL RESEARCH, GIVING THEM ACCESS TO THE LATEST CHEMOTHERAPY REGIMENS.

PRE-CLINICAL LABORATORY GROUPS



ASHLEY LAKNER EHEIM, PHD
Post-Doctoral Fellow



TING LI, PHD
Research Scientist

QI LONG LU, MD, PHD
Research Group Director

LAURA SCHRUM, PHD
Research Group Director; Interim Director, Imaging Core Facility

MCCOLL-LOCKWOOD LABORATORY FOR MUSCULAR DYSTROPHY

Muscular dystrophies are mainly genetic disorders impacting between 50,000 and 100,000 individuals in the United States. The diseases are characterized by skeletal muscle weakness and wasting (dystrophy). There are more than 30 types of muscular dystrophies, and two of the most common types, limb-girdle muscular dystrophy type 2I (LGMD2I) and Duchenne muscular dystrophy (DMD), are caused by mutations in the FKRP gene and DMD gene, respectively. Currently, no cure or effective treatment for LGMD2I or DMD exists. Scientists in the McColl-Lockwood Laboratory for Muscular Dystrophy have one goal: to develop novel therapeutic approaches for the treatment of these diseases.

Under the leadership of Qi Long Lu, MD, PhD, the laboratory has reached significant milestones on the journey toward achieving their goal. Several research programs critical to developing experimental therapeutics have been developed. First, unique animal models with genetic defects the same as those in patients have been created to support research relevant to LGMD2I. Additionally, the laboratory has developed a drug-screening system aimed at identifying potential drug candidates that will enhance glycosylation of alpha-dystroglycan, a key element for muscle integrity. Last year, the National Institutes of Health (NIH)-sponsored drug-screening program concluded and served as the initial foundation for an in-house drug screen, which has identified several dozen compounds capable of enhancing glycosylation as demonstrated in a cell culture system. The laboratory has also developed a drug-testing program and gene therapy targeting patients with LGMD2I. Initial adeno-associated virus-mediated gene therapy has demonstrated therapeutic potential for patients with LGMD2I. Drug testing in the animal models has identified a few unique drugs capable of improving dystrophic pathology. Also important in the translational research of DMD, the McColl-Lockwood Laboratory has kept its front-line role in developing antisense oligonucleotide therapy for DMD. It has recently identified more effective antisense oligonucleotides capable of removing several dystrophin exons, by which defective DMD genes can be corrected. These antisense oligonucleotides will be the candidates for further drug development. This is especially exciting because initial clinical trials have demonstrated efficacy in DMD patients. However, this therapy is a personalized medicine, with each drug being applicable only to a portion of DMD patients. The laboratory is actively engaged in collaboration with a pharmaceutical company to extend the successful clinical trials to a wider DMD population.

The McColl-Lockwood Laboratory continues to collaborate with Susan Sparks, MD, PhD, clinical geneticist, in the Department of Pediatrics, and James Dollar, MD, of the Carolinas Pathology Group, to conduct molecular diagnosis of muscular dystrophies and to establish an infrastructure for future clinical trials. The quality of research conducted in the laboratory is continuously recognized by new publications and the award of NIH grants. A U54 grant was awarded to Dr. Lu as part of a consortium by NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development for preclinical drug development of exon skipping.

LIVER PATHOBIOLOGY LABORATORY

Chronic liver disease/cirrhosis is the 12th-leading cause of death in the United States, and total costs in the country have been estimated at $10 billion a year. Cirrhosis is a long-term, progressive disease initiated by many factors, including chronic alcoholism and exposure to hepatitis B and C viruses (HBV and HCV) and, if left untreated, will advance to end-stage liver disease. Hepatic fibrosis is an exacerbation of the generic wound-healing response resulting in excess deposition of collagen by activated hepatic stellate cells (HSCs), the main effector cell of fibrosis. Unresolved fibrosis may proceed to cirrhosis, which affects millions of people worldwide and is a substantial economic burden. Currently, there are no established FDA-approved treatments for fibrosis/cirrhosis, and liver transplant remains the only cure for cirrhosis. Therefore, establishing treatments for fibrosis/cirrhosis will decrease yearly deaths and United States economic burden.

During development of fibrosis, there are critical changes in microRNAs (miR), small non-coding RNAs, which regulate wound-healing transcripts, and therapeutic modulation of miRs by inhibiting or increasing miR expression holds great promise to restore delicate genetic programs vital to normal organ function. In the Liver Pathobiology Laboratory, directed by Laura Schrum, PhD, researchers have identified miR19b as an important mediator for hepatic fibrosis development. Studies from the work of Ashley Lakner Eheim, PhD, in collaboration with Mark Russo, MD, MPH, medical director of Liver Transplantation, and colleagues, demonstrated that miR19b is decreased in fibrotic liver impeding profibrogenic signaling in the HSC by decreasing transforming growth factor receptor II expression. To demonstrate the clinical relevance of miR19b in fibrosis, similar results have been concluded in human livers. miR19b was reduced significantly (80 percent reduction) in fibrotic human liver compared with normal/control livers. The studies also revealed increased levels of miR19b in serum of fibrotic patients compared with tissue, suggesting miR19b is released from fibrotic livers into circulation and can be employed as a non-invasive diagnostic marker for fibrosis. Future studies will test miR19b as a therapy for fibrosis, which will be initiated in animal models. Additionally, miR profiles will be established in HCV-induced fibrotic patients to help develop personalized treatment strategies. These studies will be conducted by a team of dedicated researchers composed of bench scientists, hepatologists and surgeons. Overall, these studies propose that miR19b may serve as a therapy and non-invasive diagnostic biomarker for liver fibrosis.

Approximately 160 million people are chronically infected with HCV worldwide and more than 5 million are infected in the United States. Twenty to 30 percent of patients with chronic HCV will develop cirrhosis over a 20- to 30-year period. The let7 miR plays an important role in human liver diseases, such as hepatocellular carcinoma, hepatic fibrosis and viral hepatitis—diseases known to be accelerated by increased oxidative stress. Studies by Weihong Hou, PhD, research scientist, and colleagues, demonstrated that let7 miR attenuates oxidant injury in human hepatocytes and may represent a therapeutic approach for protection against oxidative stress-induced injury observed in chronic liver diseases.

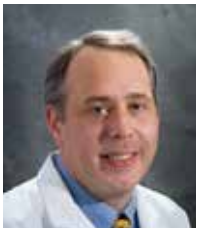
> OUR TEAM IS ACTIVELY INVOLVED IN RESEARCH AND CONTINUOUSLY CONTRIBUTES TO THE SCIENTIFIC INFORMATION BASIS FOR THE TREATMENT OF ORTHOPEDIC CONDITIONS, WHICH BRINGS THE MOST ADVANCED CARE TO THOSE WE SERVE.
>
> —Edward Hanley, MD, Chair, Orthopaedic Surgery

For fibrosis to initiate, HSCs undergo an activation/transdifferentiation process. Ting Li, PhD, research scientist, has identified nuclear receptor Rev-erb as a key regulator in this process. Studies conducted by Dr. Li showed suppressive effects on HSC activation when cells were exposed to a Rev-erb ligand/agonist, S6452, resulting in a decreased fibrogenic response (i.e., fibrotic gene expression). These data, in addition to other data, suggest a functional role for Rev-erb in maintaining/promoting the nonfibrogenic HSC phenotype while suppressing fibrogenic gene expression (e.g., smooth muscle actin, connective tissue growth factor and desmin). Future studies will test this ligand in a fibrotic animal model with the expectation that Rev-erb can serve as a therapeutic target for the treatment of hepatic fibrosis and related pathologies.

Overall, the Liver Pathobiology Laboratory will continue their efforts to bring bench research to the bedside, to unfold cellular and molecular mechanisms of several liver diseases with the expectation of identifying biomarkers and developing novel therapeutic strategies. These research endeavors are aimed at providing improved and high-quality patient care and superior personalized medicine.

ORTHOPAEDIC RESEARCH BIOLOGY

The Department of Orthopedic Surgery at Carolinas Medical Center is a nationally recognized program of excellence in clinical care, education and research. In 2011–12, it was once again recognized as an outstanding orthopedics center by *U.S. News & World*



IAIN McKILLOP, PhD
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Report. In 2012, *Becker's Hospital Review* named it as one of the 101 great orthopedic programs with recognized leadership in orthopedic treatment and research. Orthopedic Research Biology has forward-thinking research teams conducting cellular, molecular and tissue engineering research.

The intervertebral disk degeneration and low back pain research program directed by Helen Gruber, PhD, Edward Hanley, MD, and the research staff of Gretchen Hoelscher, Darla Morton, Jane Ingram, Natalia Zinchenko, Synthia Bethea and staff assistant Khristina Gellar studies the relationship between disk degeneration and low back pain. Recently published findings detail the utility of microarray analyses in identification of pain-, neurotrophin- and nerve-related genes in the disk and point to the importance of future work exploring functional interactions between nerve and disk cells in vitro. Notable publications from the disk research team focused on features of the adipose-derived mesenchymal stem cell population, genome-wide analysis of genes involved in low back pain and the deleterious effects of diskography radiocontrast solution on human disk cells in vitro. For outstanding contributions in spine-related basic science research Helen Gruber, PhD, received the 2012 Henry Farfan Award from the North American Spine Society.

In addition, the department's osteoarthritis research program, which includes the efforts of Yubo Sun, PhD, Andrea Roberts, PhD, David Mauerhan, MD, and Edward Hanley, MD, studies osteoarthritis, a form of arthritis that features the breakdown and eventual loss of the cartilage of one or more joints. Among the more than 100 different types of arthritis conditions, osteoarthritis is the most common, affecting more than 25 million people in the United States. Osteoarthritis occurs more frequently with advanced age and most commonly affects the hands, feet, spine and large weight-bearing joints, such as the hips and knees. There is no cure for this disease and the overall goal of treatment is early elimination of risk factors, early diagnosis and surveillance of the disease, with appropriate treatment of pain. Current research focuses on collagen and proteoglycan changes in the meniscus and the biologic effects of phosphate on cells in the synovial fluid. The goal for the research team is to understand the disease process to develop novel structure-modifying drugs for osteoarthritis therapy.

GENERAL SURGERY RESEARCH

2012 was a successful year for the Research Division in the Department of General Surgery as they continued to support physicians in their studies to address clinically relevant problems through translational research. These efforts resulted in the publication of 18 peer-reviewed manuscripts and the presentation of more than 20 peer-reviewed abstracts at local, national and international societies and meetings. These efforts encompassed a broad spectrum of research interests addressing disease pathology and etiology from the molecular and cellular level to tissues and organs, utilizing a diverse range of techniques and experimental models. In doing so, the Department of General Surgery continues to be at the forefront of innovation and research, providing an outstanding teaching and learning environment for current and future clinicians, academics and researchers.

LIVER CANCER RESEARCH

Iain McKillop, PhD, and his research team continued their collaboration with Ahmed El Ghannam, PhD, from the Department of Mechanical Engineering, University of North Carolina-Charlotte, and David Iannitti, MD, chief of hepatopancreaticobiliary (HPB) surgery, to develop a bioceramic nanoscaffold drug delivery system to treat hepatocellular carcinoma. These complex 3-D structures provide a large surface area-to-volume ratio onto which a wide range of chemotherapeutics can be bound. Upon insertion into a tumor mass, they act as drug reservoirs, generating toxic levels of chemotherapy within the tumor while avoiding systemic toxicity side effects. This work is supported by an external multi-center grant from the North Carolina Biotechnology Center and was presented at the European Association for the Study of the Liver (Barcelona, Spain) and the American Association for the Study of Liver Disease (Boston, MA) this year.

At the bench, Dr. McKillop's group continues to study the cellular and molecular mechanisms by which alcohol consumption affects liver disease, and the development and progression of hepatocellular carcinoma. In doing so, these studies address changes in signal transduction fidelity and the effect of unbalancing divergent signaling pathways on the regulation of both normal and abnormal (cancer) cell growth within the liver.

From a translational perspective, Dr. McKillop and his scientists, Eugene Sokolov, PhD, David Foureau, PhD, and Jacob Swet, MS, have continued their collaborations with physician scientists from the HPB surgery group. David Iannitti, MD, John Martinie, MD, David Sindram, MD, PhD, and Ryan Swan, MD, develop and evaluate improved microwave ablation devices that are used clinically to destroy liver tumors in situ. These studies have involved collaborations with InnerOptic (Hillsborogh, NC) and Microsulis (Hants, UK) to develop a 3-D magnetic image guidance system to allow more accurate antenna placement within the tumor. The phase I clinical trial of this system was completed at Carolinas Medical Center this year.

The successes of these projects are a direct result of the continued efforts of physicians working in tandem with bench research scientists. These efforts will be further aided by the recent addition of Valentina Zuckerman, PhD, who joined the group from The Hebrew University Hadassah Medical School, Jerusalem, Israel, this year. Dr. Zuckerman brings with her a strong background and knowledge in cellular and molecular biology, flow cytometry and protein biochemistry.

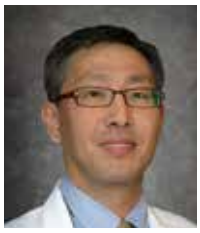
TRAUMA RESEARCH

Physician scientists from the F.H. Sammy Ross Jr. Trauma Center continued their research efforts to understand the clinical problems associated with systemic shock caused by infection or hemorrhage. While these initial insults are different in nature, they appear to share many common molecular and cellular responses that can lead to progressive, multiple organ failure. These studies, directed by Toan Huynh, MD, and Susan Evans, MD, focus on providing a greater degree of understanding as to how cellular stress and changes in organ blood flow combine to initiate a "protective response"; a process that has evolved to minimize subsequent organ damage, but that paradoxically compromises the functional capacity of the organ being protected. In doing so, additional organs are placed under stress and, if uncorrected, can fail leading to devastating systemic consequences. By understanding these pathways at a fundamental cellular and molecular level, the long-term aims of these studies is to target and develop novel means of intervention with which to slow or arrest these potentially catastrophic events while organ function is restored. The group was assisted in these endeavors by Rebecca Powell, PhD, who joined the team this year from Wake Forest Medical Center.

SURGICAL ONCOLOGY RESEARCH

David Foureau, PhD, and Kendall Carpenter, working with Richard White, MD, and Jonathan Salo, MD, from Levine Cancer Institute, continued their work studying immunotherapy for melanoma. Unlike melanomas that are detected early during the disease pathology, late-stage melanoma, in which the tumor metastasizes to other sites, is notoriously difficult to treat. The only current FDA-approved therapy is interleukin (IL)-2 immunotherapy. However, few patients successfully respond to IL-2 and, even in those that respond, the side effects can be so severe as to prevent continued therapy. Previous work from this group utilized novel animal models of melanoma with which to identify specific subsets of immune cells that act as potential "markers" of likely responsiveness to IL-2 therapy. This work led the research team to expand these studies to analyze serum from patients, both before and during immunotherapy, and their new data from this analysis suggest similar immune cell subsets exist in melanoma patients. By performing these critical translational studies, it is anticipated that "responsive patients" will be able to be identified earlier. In addition, these studies raise the possibility that for those patients for whom a positive response is not predicted, immune system manipulation may be possible to convert them to a "responsive" phenotype. These studies were sponsored by a research grant from the Purple Promise Foundation and were presented at a prestigious Keystone Symposia conference held in Dublin, Ireland, this year.

The successes for the Division in 2012 arose as a direct result of physician–scientist collaborations whereby clinically relevant problems are addressed at the bench and translated directly back to the bedside. In 2013, the group continues to strive toward the goal of bench-to-bedside research and anticipates continued growth through the opening of Levine Cancer Institute and the continued support provided by Medical Education, the Carolinas HealthCare Foundation and Carolinas HealthCare System.



SUNIL HWANG, PhD
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PROTEOMICS AND METABOLOMICS TRANSLATIONAL RESEARCH

Sunil Hwang, PhD, director of the Proteomics and Metabolomics Translational Research Laboratory, along with his team, utilizes in vitro and in vivo techniques to identify markers of disease in pancreatic cancer and pulmonary embolism. Pancreatic cancer is an aggressive disease with nearly equal yearly rates of diagnosis and death. Current therapies have failed to improve outcomes due to rapid disease progression and late stage at presentation. Recently, pathways involved in progression and metastasis have been elucidated; however, new knowledge has not generated more effective therapies. In one study, the protein profiles from a subcellular level were compared between pancreatic cancer cells derived from patients with metastatic and non-metastatic disease. Specific proteins of interest, which may play a role in the rapid progression and metastasis of this disease, were identified. These proteins will be further studied to determine whether they can be used as prognostic indicators or developed as targets of new therapeutic drugs. The advancement of this type of knowledge is key to improving outcomes for pancreatic cancer patients.
In another study, the group enriched blood samples for microvesicles known as exosomes. These small extracellular packages contain proteins and other biological molecules that can be identified using mass spectrometry techniques. During this study, the group collaborated with Emergency Medicine Research to identify proteins involved in the pathophysiology of pulmonary embolism in an animal model. This knowledge can be used to better understand this disorder and might be employed to aid in earlier detection and more successful patient treatment strategies. Future studies will apply these insightful techniques to the further study of pancreatic cancer as well as traumatic brain injury, stroke, rheumatoid arthritis and multiple sclerosis.

> WITH THESE TOOLS, PHYSICIANS WILL CONSIDER DETAILED INFORMATION ABOUT A PATIENT'S GENOTYPE, ALONG WITH CLINICAL DATA, ENABLING THEM TO PRECISELY IDENTIFY A PATIENT'S CONDITION OR RISK EXPOSURE, AND THEN SELECT A MEDICATION, THERAPY OR PREVENTIVE MEASURE UNIQUELY SUITED FOR THAT INDIVIDUAL PATIENT.

CLINICAL TRANSLATIONAL MOLECULAR BIOLOGY RESEARCH LABORATORY

Under the direction of Nury Steuerwald, PhD, the Clinical Translational Molecular Biology Research Laboratory has been engaged in a variety of projects aimed at investigating the molecular mechanisms underlying a variety of human diseases. In particular, the lab is examining the role of microRNAs (miRNAs) in the pathogenesis of various disease processes. miRNAs are members of a class of small RNAs whose function is to regulate gene expression in organisms as diverse as animals, plants and fungi. Many miRNAs are evolutionarily conserved and believed to play a role in controlling a variety of biological functions, including developmental patterning, cell differentiation, cell proliferation, genome rearrangements and transcription regulation. In collaboration with Mark Clemens, PhD, in the Biology Department at University of North Carolina-Charlotte, the lab is investigating the role of miRNAs in altered hepatic blood flow regulation during experimental sepsis. Together with Herbert Bonkovsky, MD, the team is delineating miRNA profiles in drug-induced liver injury to determine if a characteristic signature exists. The lab has also teamed with David Sindram, MD, PhD, and William Ahrens, MD, to examine global changes in miRNA expression in archival malignant pancreatic tissue samples. This fall, the lab acquired a high-capacity next-generation sequencing instrument, providing the capability to perform unbiased whole transcriptome, exome and genome analyses. This technology will used to profile miRNAs and discover novel species expressed under pathological conditions.

Carolinas HealthCare System is the first institution in North Carolina to acquire the latest genome-sequencing instrument. Managed in the Molecular Biology Core Laboratory by Dr. Steuerwald and her team, this equipment gives Carolinas HealthCare System the capability to sequence the entire human genome in less than a day.

Personalized medicine—including genome sequencing—is a medical model that proposes customization in healthcare, as decisions and practices are tailored to the individual patient, based on genetic or other unique information. The goal is to solve some of the problems that have limited the effectiveness of current treatments.

Genomic and proteomic tools are rapidly changing the way medicine is practiced, as genetic fingerprinting of individuals is fused with research in creating targeted therapies. With these tools, physicians will consider detailed information about a patient's genotype, along with clinical data, enabling them to precisely identify a patient's condition or risk exposure, and then select a medication, therapy or preventive measure uniquely suited for that individual patient. The benefits of this approach are accuracy, efficacy, safety and speed. Both prevention and clinical outcomes will be significantly enhanced.

More specifically, genome sequencing in cancer cells will deliver remarkable insight into the complexity of cancer and identify new genes and biological pathways implicated in tumor initiation, progression and metastasis. Our new genome technology will dramatically enhance therapeutic innovation and transform healthcare in our community.

EMERGENCY MEDICINE RESEARCH

The Emergency Medicine Research Laboratory, directed by John Watts, PhD, is currently studying pulmonary embolism, a condition in which blood clot material breaks free, producing an embolism that travels through the heart to lodge in the arteries of the lungs. The presently approved treatments only address the clot material in the lungs. The group's experimental models show that excessive inflammation contributes strongly to the dysfunction of the right ventricle following pulmonary embolism. A clinical trial is presently being conducted in Madrid, Spain, to examine whether anti-inflammatory treatments reduce right ventricular injury in human pulmonary embolism. The laboratory's experimental studies, completed in collaboration with Bayer AG, also identified a treatment that dilates pulmonary arteries not blocked by the embolism. This treatment enhances blood flow through the lungs, improves gas exchange and also protects the right ventricle from damage. The results of these studies were presented by Dr. Watts at the European Respiratory Society Congress in Vienna, Austria, and the Society for Academic Emergency Medicine in Chicago, IL. Ongoing studies will compare three different approaches to dilating the nonoccluded arteries in the lungs during experimental pulmonary embolism to determine the best pharmacological approach for actively managing this condition.

ORTHOPEDIC ENGINEERING RESEARCH

Richard Peindl, PhD, and his colleagues in the Orthopedic Engineering Research Laboratory collaborate with clinicians and researchers from Carolinas Medical Center's Orthopedics, Physical Medicine and Rehabilitation and Neurology departments, faculty and students from the Departments of Mechanical Engineering and Kinesiology at the University of North Carolina-Charlotte, in addition to significant contributions from physical therapists and patients from Carolinas HealthCare System's Healthy@Home to study falls prevention. The goal of the Falls Prevention Technology Development Project is to apply the same inertial guidance and control technology used in modern aircraft and robotic vehicles to monitor the movements of individuals during activities of daily living.

In early tests, miniature sensor packages worn by study subjects are now providing data that can be used to determine not only the types of gait- or balance-affecting activities that are being performed but also the speed and relative stability of the subject while performing the activities. The long-term goals include using the technology to provide ongoing falls risk assessments, monitoring patients in community settings, providing extended reports on patient motor functions (e.g., as a Holter monitor is used in cardiac patients) and eventually to provide real-time biofeedback to the patient regarding the kinematic stability of his or her activities. The technology has numerous applications in addition to falls prevention. Examples include providing quantitative assessments as to how aging, brain injury and orthopedic/neuromuscular diseases affect an individual's ability to perform common motor functions. It also can be used to assess the efficacy of pharmacologic, therapeutic or surgical interventions in treating these conditions.

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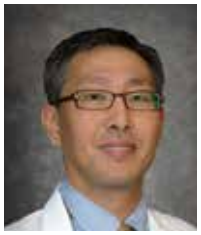

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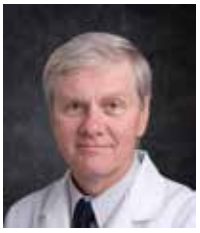

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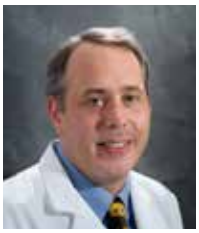

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FACULTY AND STAFF PATENTS AND TRADEMARKS

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