IMPACT ON transformation

2011 ANNUAL REPORT

Tufts

CTSI

Tufts Clinical and
Translational
Science Institute

A collaboration of
organizations, founded
by Tufts Medical Center
& Tufts University.

Translating research into better health

TUFTS CTSI ANNUAL REPORT 2011
May 1, 2010 – April 30, 2011

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TUFTS CTSI LEADERSHIP

Harry P. Selker, MD, MSPH

Dr. Selker is Dean of the Tufts University-wide Clinical and Translational Science Institute (Tufts CTSI) and Principal Investigator of the NIH Clinical and Translational Science Award (CTSA) that supports it. He is Professor of Medicine at the Tufts University School of Medicine and Executive Director for the Institute for Clinical Research and Health Policy Studies at Tufts Medical Center, where he is also Chief of the Division of Clinical Care Research in the Department of Medicine and Director of the Center for Cardiovascular Health Services Research. He has served on boards and as an officer for a variety of professional and educational organizations, including in 2011-2012 as President of the Society of General Internal Medicine, 2010-2011 as President of the Society for Clinical and Translational Science and 2003-2004 as President of the Association for Clinical Research Training. He has been an active advisor in the design of Clinical Research graduate and training programs in the United States and internationally, and he is an active advocate and advisor in Washington in support of clinical research, research training, and for improvements in the healthcare delivery system. He maintains his medical practice at the Pratt Diagnostic Clinic at Tufts Medical Center.

June S. Wasser, MA

Ms. Wasser is the Executive Director for Tufts CTSI and has a faculty appointment in the Tufts University School of Medicine as an Instructor of Medicine and Clinical and Translational Science. She is responsible for implementing and maintaining all infrastructure and management processes as well as strategic planning; and actively develops Tufts CTSI programming initiatives including public outreach and utilizing technology for distance learning and communications. Her career has spanned both the non-profit and for-profit worlds. Prior to joining Tufts CTSI, Ms. Wasser worked as a contractor to the Department of Defense, educating health professionals in the military. She also held senior level management positions at the American College of Cardiology Foundation, WebMD, and the American Association of Neurological Surgeons directing continuing medical education initiatives.

Her academic career began at Northwestern University Medical School and the University of Chicago Comptrollers' Office. Her professional experience includes operations, finance, research administration, business development, strategic planning, and medical education programming. She has participated in numerous professional society activities and national conferences related to the topics of continuing medical education and distance learning. Ms. Wasser earned a Bachelor of Arts at the State University of New York at Buffalo and a Master of Arts at the University of California at Los Angeles. She also completed two additional years of advanced graduate studies at the University of Chicago.

Laurel K. Leslie, MD, MPH

Dr. Leslie is an Associate Professor at Tufts University School of Medicine, with a primary appointment in the Department of Medicine and holds a secondary appointment in Pediatrics. She is an active faculty member in the Sackler School of Graduate Biomedical Sciences. She is also the Director of the Program for Aligning Researchers and Communities for Health within Tufts CTSI. Dr. Leslie received her BA from Harvard University and her MD from the University of North Carolina at Chapel Hill. She completed her residency training in Primary Care Pediatrics and fellowship training in Developmental-Behavioral Pediatrics at the University of California, San Francisco, where she also served as Chief Medical Resident. Subsequently, she served as a Research Scientist at the Child and Adolescent Services Research Center (CASRC) at Rady Children's Hospital and Health Center in San Diego. While at CASRC, Dr. Leslie received a Masters of Public Health in Epidemiology and Biostatistics at San Diego State University.

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MESSAGE FROM THE DEAN

In our many visits around campus and with our partners we are often asked what is a Clinical and Translational Science Award (CTSA) and what does our Clinical and Translational Science Institute do? We respond with a consistent message about our mission to impact health and the many programs and services we provide to support our mission. This annual report provides you with a glimpse of the breadth of these activities in year 3 of our grant and how these activities have transformed the way people work. We attempted to capture vignettes that highlight not only what is novel, but also what is at the heart of our daily life.

We cross many disciplines, schools, hospitals and partners. We also cross the translational spectrum in most things we do, from bench to bedside, bedside to practice, and practice to policy. But even in telling this narrative we fall short of an explanation of all we do and seek to do. Partly this flaw seems to lie in communications. Not that we don't produce enough communications material or hesitate to reach out with our message, but the conceptual nature of what translational science stands for is vague in most people's minds, and especially to the public, our largest group of stakeholders.

According to Wikipedia, "The word *translation* derives from the Latin *translatio* (which itself comes from *trans-* and *fero*, the *supine* form of which is latum, together meaning 'to carry across' or 'to bring across')." Here we might imagine crossing the finish line to a miracle drug, a clinical trial breakthrough, or comprehensive healthcare reform. In each case, crossing the finish line means a major shift on how we do something, hopefully with an impact on health. It does not mean doing the same thing or maintaining the status quo.

As with all things, the CTSA as a national Consortium of 60 prestigious academic medical centers is undergoing evolution. What began as a vague notion of changing biomedical research—to bring it across the finish line—is actually quite focused on building institutional capacity for change. In other words, transforming organizations and structures of how people work, before we can actually change the output, the science itself.

Before science itself can change, the people carrying out the science and the institutions that support them must embrace change. It is not for those who are risk averse or cannot adapt quickly to a new process or model. The ideal new model that will support major cultural and scientific transformation is a team approach, based on solid operational processes, individual and team accountability, sound project management, trust and resource investment in the unknown, and a belief that the unknown can hold a better future. We want to express our fondest gratitude to those individuals who have come along with us on this exhilarating ride. We hope to look back with you in ten years and say, "Yes, it was good."

Sincerely,

Harry P. Selker, MD, MSPH, Dean, Tufts CTSI

> “The pilot award really provided new validation of our hypothesis and allowed us to initiate the animal model that will be so critical for testing it.”

Transforming Pilot Studies

In 2011, Tufts CTSI renewed its commitment to advancing translational research from bench to bedside, bedside to practice and practice to policy. We expanded our Pilots Studies Program by adding another category for funding: four new Methods Development grants were awarded to develop specific methods that will advance research across the translational spectrum. Eight very deserving investigators also received Catalyst awards to develop sufficient preliminary data to secure extramural funding. In addition, one Planning grant award was provided to support a collaboration to develop initial hypotheses and study questions relating to gender disparities and pulmonary arterial hypertension.

Five of these transformational pilot awards follow.

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Transforming "Untreatable" Brain Cancers

Imagine a disease that has a median survival rate of just 14 months and does not have any telltale symptoms until too late. Then imagine that this disease, even when aggressively treated, commonly recurs and when it does, is untreatable. Such is the case with glioblastoma (GBM), the most common adult brain tumor. The current treatment options of surgery, aggressive radiation, and chemotherapies have done little to alter this prognosis. Yet, this may change shortly. Daniel Jay, PhD, recipient of a Tufts CTSI Catalyst Pilot Award, is investigating a new pathway to treat GBM by inhibiting Neuropilin-1 (NP1), a protein receptor in brain cells that recent data suggests leads to tumor growth and dispersal.

Inhibiting NP1 could be a major advancement from the current treatment of GBM. That treatment usually involves Avastin, a chemotherapy that prevents new blood vessels reaching the tumor and hence gains GBM patients about a month survival before more invasive and inoperable tumors recur. Dr. Jay, who is a Professor of Molecular Physiology and Pharmacology at Tufts University School of Medicine, hypothesizes in his research that a therapy able to block NP1 with Avastin could result in an improved chance of survival in comparison to Avastin alone. Using *in vitro* cell models developed to mirror GBM invasion, he's already discovered two antibodies shown to significantly inhibit GBM invasion by blocking NP1.

Although Dr. Jay is pleased that these antibodies have been discovered, he says that "they function only at high concentrations. More research must be done." Such research will certainly be helped by the animal model that was developed by a Co-Investigator on the project, Jann Sarkaria, MD, a radiation oncologist researcher at the Mayo Clinic. Dr. Sarkaria's animal model has precisely replicated the manner in which GBM tumors form, not as solid masses, but more like a spider web of tumors. "Using this model, the GBM cells maintain their in vivo-ness," explains Dr. Jay. "Dr. Sarkaria's model has been immensely helpful in advancing our research." Two Tufts Medical Center Co-Investigators are also on the project—Julian Wu, MD, Professor of Neurosurgery at Tufts University School of Medicine and Associate Chairman of Neurosurgery at Tufts Medical Center, and Rolf Pfanni, MD, Assistant Professor at Tufts University School of Medicine and Director of Neuropathology at Tufts Medical Center. Both have provided critical input into the neuroscience aspects of the research.

According to Dr. Jay, the pilot grant support he received from Tufts CTSI "really provided new validation of our hypothesis and allowed us to initiate the animal model that will be so critical for testing it." Asked why he chose GBM for his research, he is quick to point to the severity of the disease, the need to develop something to help these patients, and that his origins were in neuroscience. "With this research, I'm returning to my roots."

Daniel Jay, PhD, Professor of Molecular Physiology and Pharmacology, Tufts University School of Medicine

For Janet Forrester, PhD, Associate Professor at Tufts School of Medicine, collaboration was and is the defining word for her career. After finishing her doctorate in epidemiology and biostatistics, Dr. Forrester was first attracted to Tufts Medical School because of its collaborative pairing of infectious diseases and nutrition in a single unit within public health and community medicine. “That was unheard of then,” she explains. Fifteen years and several studies later, Dr. Forrester has completed her first pilot award from Tufts CTSI for a project whose success depended on close collaboration between her unit—Tufts Medical School’s Nutrition/Infection Unit—and the Vascular Function Study Unit and the Division of Radiology at Tufts Medical Center.

The pilot project focused on the collection of preliminary data to examine the association between liver fat and surrogate markers of cardiovascular disease (CVD) in relation to apolipoprotein C3 (APOC3) genetic variability and serum lipids in an HIV-infected population. Fatty liver disease is an overabundance of fat in the liver of a non-alcoholic patient. APOC3 is a gene that affects triglyceride metabolism. A recent study in a non-HIV population demonstrated that persons carrying APOC3 allele (DNA coding) variants had both higher triglycerides and more liver fat compared to wild-type or “normal” allele controls.

Dr. Forrester’s interest in fatty liver disease was piqued when she heard the story about the marathon runner, Nick Giordano, who has liver disease, and whose grandfather died of liver cirrhosis. Nothing about Nick’s physical status on the surface seemed to have caused this: he was in his forties and was physically fit. However, on closer examination he was found to have a fatty liver. Dr. Forrester’s interest was further sparked in March 2010 when the *New England Journal of Medicine* published an article regarding a New Haven study that found a genetic variance of APOC3 was associated with fatty liver. The timing could not have been better: the Tufts CTSI pilot applications were due a month later and Dr. Forrester had an idea for further research on this disease. Was the genetic variance of APOC3 also associated with fatty liver in individuals with HIV, a population at risk for premature CVD, a risk that is not explained by traditional risk factors?

Pulling the pilot team together was not difficult. For years, Dr. Forrester had worked in the Nutrition/Infection Unit alongside Alexandra Mangili, MD, MPH, who conducted genetic studies related to CVD in an HIV cohort. Similarly, Dr. Forrester had been collaborating with Hoon Ji, MD, PhD, Assistant Professor, Tufts University School of Medicine, and Chief of Body MRI in the Division of Radiology. Finally, both Jeffrey Kuvin, MD, Director of the Vascular Function Study Group within the Cardiovascular Center at Tufts Medical Center, and Kevin Heffernan, PhD, a Post-Doc at the time, joined the team to provide the vascular function assessment of the study participants that the proposed project needed.

With the Nutrition/Infection Unit providing all of the participant scheduling, Dr. Ji and his staff performed the MRIs, which provided invaluable fatty liver information non-invasively. Juggling the study-related MRI appointments in between the already tight 24/7 clinical MRI schedule was a challenge. “Both research and clinical demand for MRIs has increased,” says Dr. Ji. “Our Radiology Division is very supportive of our research work but we had to find ways to balance both.” The pilot allowed Dr. Forrester’s

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scheduling team to figure out the best strategy for how to do that. As Dr. Forrester points out, “Pilots show you everything you didn’t take into consideration when you developed the idea for the study. It gives you time to smooth out the details.” Additional participant scheduling was needed for Dr. Heffernan to conduct the brachial reactivity tests within the Vascular Function Study Group. Such tests are a non-invasive way to assess for CVD. “Dr. Forrester’s scheduling team was at the top of their game,” says Dr. Heffernan. “There were very few speed bumps, which is unusual for this type of complex study.”

“This was a true collaborative effort,” adds Dr. Kuvin. “It symbolizes the essence of what we do so well at Tufts at all levels, from developing the project together, utilizing the special expertise each of the investigators brought to the table, making sure the nuts and bolts of the daily scheduling were right, having the patients fully informed every step of the way, and then analyzing the data together.”

The collaboration has not ended with this pilot either. So far three RO1 grant applications have been submitted using what was learned in the pilot.

“The key is to understand how genetic variants manifest against different backgrounds and/or other factors such as diet, exercise and medication, in the HIV population, as well as the general population,” says Dr. Forrester. “We will continue to use the data in studies to explore the relationship between genetics and liver fat disease. Dr. Ji has developed a very unique, robust protocol for non-invasively measuring fatty liver and that combined with our nutrition, cardiovascular, and genetic experts really places Tufts at the forefront of research in this field.”

Janet Forrester, PhD, Associate Professor,
Tufts University School of Medicine

Transforming Environmental Health in Family Childcare Facilities

A genuine example of how Tufts CTSI cultivates ongoing relationships with our community partners is the recent research path of Elizabeth Tanefis, Bridget Hickson, and Mary White. All three women work with Health Resources in Action (HRIA) in Dorchester, Massachusetts as part of the Boston Healthy Homes and Schools Collaborative (BHHSC). The women are also past fellows of Tufts CTSI's *Building Your Capacity and Advancing Research through Community Engagement Program* (see page 31). Soon after graduating from the program, the three then collaborated with Dr. Doug Brugge from Tufts Medical School on a successful application to Tufts CTSI's Pilot Program Studies.

"The BYC Program taught us how to design a community study both practically and scientifically," explains Ms. Tanefis, a Program Manager at HRIA. Incorporating their newly learned community-based participatory research approach, the trio proposed in the Tufts CTSI pilot application to examine the extent to which environmental health hazards exist in family childcare facilities (FCFs). They were particularly interested in factors causing or triggering asthma and lead poisoning. Both health issues have been a priority for prevention at HRIA for several years. "Because I have a child with asthma, I was especially interested in asthma triggers," adds Ms. Hickson.

The team hypothesized that the same FCFs containing lead hazards would show up as also having asthma triggers. Ultimately, these community researchers hoped the pilot data

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would position them for the possibility of submitting a federal grant application for a larger research project.

With Ms. Tanefis managing the project, Ms. Hickson and Ms. White completed the data collection at 50 FCFs. Surveys were largely completed on-site within each Dorchester childcare facility itself. A local childcare provider helped out by giving them a list of all local family childcare facilities in the area.

"We know the people in these neighborhoods and they know us," explains Ms. Hickson. "That helped to persuade some of the providers to allow us to come in and ask them our questions." According to Ms. Tanefis something else also helped them reach their pilot sample size goal. "HRIA already had a well-known program with lead poisoning prevention education in the community and we were able to build the relationship on that as well in the pilot."

One of the challenges of the pilot was dealing with the ethical consideration of whether the FCFs could potentially get into trouble with their answers. Ms. Tanefis says that "most of the things we asked weren't related to violations of regulations and we assured them that their answers would be kept confidential and all results would be tabulated together."

What did those results suggest? According to Tanefis, "They reinforced that healthy childcare homes is a significant public health issue and that our assumption that FCFs containing lead hazards also would show up as having asthma triggers as well was correct." For example, 48 percent of those responding present potential lead triggers and an equal number have asthma triggers.

The formidable community-based trio is not finished with the issue either. In October 2011, the Boston Healthy Homes and Schools Collaborative (BHHSC) held a meeting for a new working group of family childcare stakeholders, including the Greater Boston Regional Director at the MA Department of Early Education and Care, three family childcare providers, and representatives from childcare resource and referral agencies. At the meeting, Tanefis, White and Hickson presented their pilot data and according to Tanefis, the members were "both dismayed, yet at the same time not surprised." The group will have bi-monthly meetings and will develop policy recommendations regarding regulatory policies that will make FCFs more environmental health-friendly. "The pilot," says Ms. Hickson, "allowed us to get the data we needed." Ms. White adds, "We were able to move ahead using the evidence we've gathered, assess the information, and hopefully now it will result in a quality improvement in our state."

Transforming How We Design Community Health Interventions for Puerto Ricans

The overarching goal of the Tufts CTSI Pilot Studies Program is to provide researchers with critical planning and preliminary study support so that they may apply for funding of a full-scale research project. A shining example of the success of this program is Katherine Tucker, PhD, Professor within the Nutritional Epidemiology Program at Tufts University's Gerald J. and Dorothy R. Friedman School of Nutrition Science and Policy. Dr. Tucker parlayed her pilot results into a successful competitive renewal of a P50 grant from the National Heart, Lung, and Blood Institute (NHLBI). That renewal expands the originally funded *Boston Puerto Rican Health Study, Center for Population Health and Health Disparities (CPHHD)*, by including a culturally-appropriate community intervention for the prevention and control of CVD risk factors in Puerto Rican adults, an intervention that was at the center of the pilot.

At the time of her 2009 Tufts CTSI Pilot application, Dr. Tucker was a Senior Scientist within the Dietary Assessment and Epidemiology Research Program at the Human Nutrition Research Center of Aging at Tufts University. After completing the pilot, she went to Northeastern University, a Tufts CTSI affiliated partner, where she is Chair of the Department of Health Sciences, Professor of Nutritional Epidemiology, and Director of the Center for Population Health and Health Disparities. With support from the Tufts CTSI Pilot, eight focus groups with Puerto Rican adults were conducted to inform the design of a multi-level, culturally appropriate, community intervention that addresses social, behavioral, and environmental contributors to CVD at the individual and community level.

Puerto Ricans are the second largest Hispanic subgroup in the United States, and the largest Hispanic subgroup in Massachusetts, with a majority living in dense urban environments such as the Boston metro area. As a group, they present several inequalities in social and behavioral measures, such as low income and education and low physical activity, in comparison to other ethnic groups in the US. They also have significant disparities for metabolic conditions and for cardiovascular disease (CVD) and its risk factors. Few interventions on CVD risk factors have been targeted previously to this population.

Because recruiting for focus groups in the community can be challenging, Dr. Tucker collaborated with La Alianza Hispana, one of Tufts CTSI's original affiliated partners, for recruitment and conducting of the focus groups. Each of the eight groups included between eight and ten Puerto Rican adults. La Alianza's proven expertise and rapport within the Boston Puerto Rican community resulted in highly informative qualitative data. When transportation was perceived as an obstacle to participation in the focus groups, La Alianza was able to host the groups at community programs located in the neighborhoods. "Through the pilot, we learned the benefit of being decentralized," Dr. Tucker says. "We also found out very quickly during the focus group discussions that participants felt very strongly that any intervention to prevent and control CVD risk factors must allow them to bring a friend to take part in the intervention with them. They did not want to be involved in an intervention with only strangers. That was incredibly useful for our refinement of the intervention design."

Other helpful information gleaned from the focus groups included their very vocal interest in and willingness to participate in a corollary dietary intervention. "This was new because in prior studies we found that most of the Puerto Rican adults were not interested in ways to modify their diets to be healthier," says Dr. Tucker. "Early interactions in our prior interventions through the Center had focused on 'don't touch our diet, just tell us about exercise.'" This was an important change with implications for the intervention design given that 40 percent of Puerto Ricans, aged 45-75 years had diabetes in the original *Boston Puerto Rican Health Study* sample of 1500, and that one of the primary strategies for reducing both CVD and diabetes is through nutrition and exercise.

The focus groups also revealed that Puerto Rican adults may not be as resistant to change as Dr. Tucker had found in her prior research and that they were more willing to understand that health interventions, like the one her Center is developing, could make a difference. In addition, the participants reinforced previous findings that they felt socially isolated and that such isolation was stressful and detrimental to their health. Their isolation may be partly due to English being their second language coupled with the generally low-income status of this community. Data from the *2005-2007 American Community Survey* indicates that 21.8% of Puerto Rican families are living in poverty as compared to 8.4% of non-Hispanic families. "A sense of community was very important to them," adds Dr. Tucker. "Whatever health prevention intervention we design for them had to take all of these results into consideration. We added an additional component on stress and social networking because of it."

With such substantial focus group data, Dr. Tucker along with her Co-Investigators on the Tufts CTSI Pilot (Luis Falcon, PhD, Professor of Sociology, Northeastern University; Jose Ordovas, PhD, Professor, Nutrition and Genetics, at Tufts University's Gerald J. and Dorothy R. Friedman School of Nutrition Science and Policy; and Carmen Sceppa, PhD, Associate Professor, Northeastern University) was able to develop a more relevant intervention that has a greater chance of success within the Puerto Rican population. Moreover, the expanded CPHHD program now includes interaction with nine other population and health disparity centers throughout the country, where they are sharing their experiences with interventions in diverse populations.

"We redesigned our large center study based on the pilot," says Dr. Tucker. "We're incredibly thankful to Tufts CTSI for that."

Katherine Tucker, PhD, Professor, Nutritional Epidemiology Program, Tufts University's Gerald J. and Dorothy R. Friedman School of Nutrition Science and Policy

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Transforming Quality of Life for Dialysis Patients

Although hemodialysis extends lives, it is extraordinarily demanding on patients, time-wise and physically. Used primarily to treat end-stage renal failure, about 25 percent of all patients receiving hemodialysis die each year and more than 345,000 people undergo hemodialysis regularly. Most are elderly. Most are quite sick. And most have a high mortality rate and a low referral rate to hospice. To address these issues, Lewis Cohen, MD, applied for and received a Tufts CTSI Pilot Catalyst Grant.

As Director of the Renal Palliative Care Initiative at Baystate Medical Center and a Professor of Psychiatry at Tufts University School of Medicine, Dr. Cohen was concerned about the psychological and physical toll on those dialysis patients at greatest risk of dying within a six month period. A practicing psychiatrist, he saw how few patients received end-of-life counseling and hospice referral. "About 20 years ago I stumbled across how the issues concerning dialysis had changed: it was no longer about who were the precious few who would be permitted to have dialysis and who would not. Now, it's more about the question of whether we are offering it for too long of a time. Are there considerations we should think about in terms of quality of life for their end of life rather than just to keep providing dialysis? Are we keeping patients on dialysis too long?"

Consequently, several years ago, Dr. Cohen and his Baystate colleague, Nephrologist and Director of Baystate's Transplantation, Michael Germain, MD, developed a prognostic tool as part of a grant funded by the Diabetes and Digestive and Kidney Diseases (NIDDK). The tool identifies dialysis patients who are likely to die within six months. Physicians can refer patients with six month prognoses to hospice and it will be paid for by Medicare.

However, developing the tool was not enough. Dr. Cohen's pilot grant from Tufts CTSI is to establish the feasibility of the Renal Supportive Care (RSC) intervention, a communication intervention that pairs the use of Dr. Cohen's prognostic tool with a team approach towards communicating both the prognosis and possible terminal care options to such patients. The pilot project also involves obtaining formal support for using the RSC in 18 different dialysis clinics via three clinical and translational science centers: Baystate Medical Center as part of Tufts CTSI, University of Pittsburgh, and Stanford University.

The RSC teams include the attending nephrologist and a social worker. During the team meeting with the patient and his/her family, the nephrologist usually takes the lead in delivering information about the medical prognosis. Knowing that every dialysis clinic has a Medicaid mandated social worker, Dr. Cohen believed that patients would be better served by social workers talking with them about end of life issues. "Social workers are often much more comfortable than physicians discussing these issues with patients and loved ones," according to Dr. Cohen.

All of the social workers in the RSC must complete a Post-Masters certificate program at Smith College School for Social Work in Northampton, Massachusetts that provides advanced training on end of life issues. Yet, nothing prepared them for one of the surprises of the pilot. "One of the outcomes so far was learning that some patients don't

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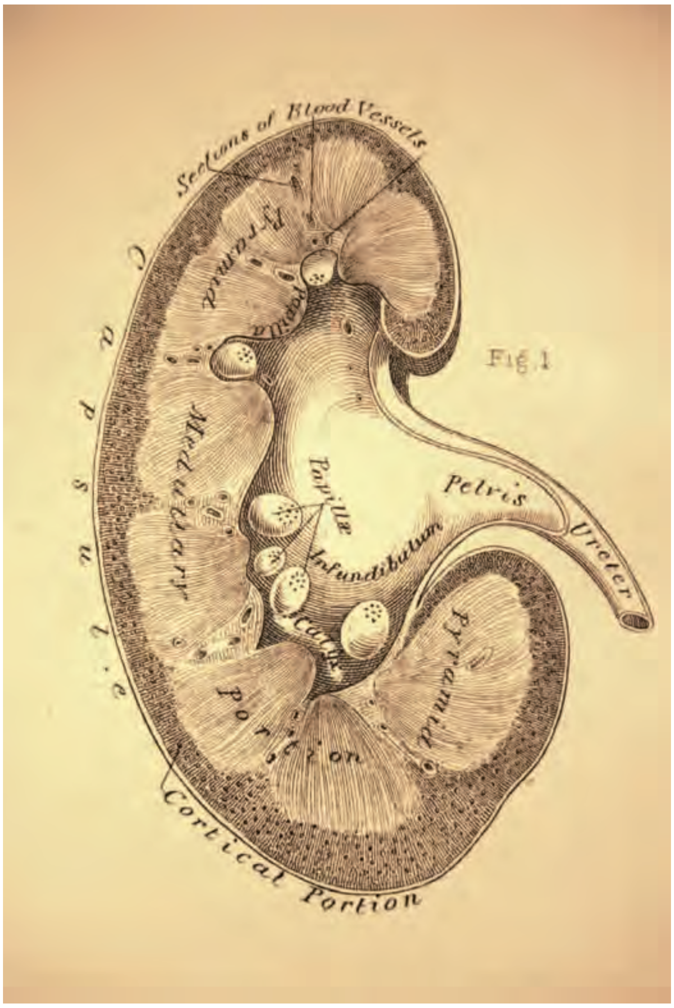
want to know their prognosis, but they want their families to know," explains Dr. Cohen. "We may need to change the intervention to accommodate that. It seems out of step with the literature and will be important in adjusting our study protocol."

This as well as other lessons learned during the pilot will help Drs. Cohen and Germain to further improve a larger U34 grant application involving the RSC to be resubmitted in the coming months. One of the reasons why Dr. Cohen applied for the Tufts CTSI Pilot was because the reviewers had pointed out the lack of pilot data in the original U34 application.

"The pilot could mean the difference between the proposal being accepted and rejected," says Dr. Cohen. "I can't underscore enough the importance of the pilot. It had all been theoretical up until that point and it has been an eye opener to try the intervention out, go through the logistics, and actually put it into practice. The intervention has now been used at Baystate and Berkshire Medical Center, and we hope to also gain some experience from a Pittsburgh dialysis clinic. The CTSI Pilot will demonstrate that our intervention is applicable in a variety of settings and well worth the investment of substantial NIH funds."



> "The CTSI Pilot will demonstrate that our intervention is applicable in a variety of settings and well worth the investment of substantial NIH funds."

CLINICAL STUDIES

Transforming Clinical Study Research

Through our Clinical and Translational Research Center (CTRC) and Core Laboratory, we offer a full spectrum of support for clinical trials involving inpatient and outpatient adult, pediatric or neonatal participants. In addition to our team of specialized nurses and study coordinators, the CTRC provides assistance with all aspects of protocol development and regulatory submissions. The Core Laboratory offers specimen processing and storage, assays, trace element testing, and DNA analyses.

Here are a few highlights of the clinical trials conducted in 2011.

Transforming Lives, One Life at a Time

We often hear about large-scale, legendary clinical trials that have changed how we historically treat a specific disease. But what if a clinical trial only changes the life of one patient? If as Voltaire put it, "History consists of a series of accumulated imaginative inventions," then surely a creative trial that saves even one life should be considered of historical importance. Such is the case with a clinical trial conducted by Robert Martell, MD, PhD, Director of the Neely Center for Clinical Cancer Research.

In 2010, Dr. Martell, a renowned medical oncologist, began to work with CTRC staff to conduct a study that examined the effect of a receptor tyrosine kinase inhibitor on liver tumors. Tyrosine kinases are a group of enzymes that influence signaling between cells, especially as it relates to cell growth and death. Existing in the surface of a cell, they essentially catalyze the transfer of phosphate from one site into protein at another site. However, such signaling can be altered when the normal gene governing such activity mutates or has increased expression, morphing into a type of proto-ocogene, called c-Met. Abnormal c-Met activation results in "a cascade of events," Dr. Martell says, "leading to abnormal growth in cells, resulting in tumors." One of the patients in Dr. Martell's study had previously developed several tumors in her liver which were not amenable to surgery. Since it is known that multiple signaling pathways are involved in cancer, Dr. Martell's trial involved combining this novel kinease inhibitor drug with another targeted anticancer agent.

Nurses in the CTRC had to constantly perform a variety of blood draws and testing, EKGs, and other medical evaluations that monitored the patient's drug reactions and progress. "To launch a space shuttle there is an incredible amount of work that gets done before the actual launch," explains Dr. Martell. "The CTRC staff had to complete a tremendous number of tasks related to the protocol within a strict timeline. And they did, from the beginning to its successful end."

After several months, the patient's tumors had completely disappeared, and remain so more than a year after she enrolled in the study. Now, planning is underway for larger clinical trials of this new drug. Perhaps, Voltaire wasn't totally correct. Perhaps history is defined by a *single* imaginative invention transforming one life at a time.

Robert Martell, MD, PhD, Associate Professor,
Tufts University School of Medicine

Transforming Treatment of Heart Attacks

Against many odds, the IMMEDIATE Trial completed its enrollment in 2011, nine years after it began. Funded by the National Heart, Lung, and Blood Institute at the National Institutes of Health (NIH), this trial tested whether early intervention of intravenous (IV) Glucose, Insulin and Potassium ("GIK") could improve outcomes of patients in the community having symptoms of heart attack. Preliminary studies had shown that immediate GIK treatment could protect the heart when it is not receiving sufficient blood flow because of a clot in a coronary artery and could minimize heart muscle damage that might otherwise lead to death or to long-term heart failure. Based on this trial, the IMMEDIATE Trial investigators will be able to provide an answer to whether this commonly-available treatment could have as dramatic an impact on patients as initial animal studies suggested.

The IMMEDIATE Trial's completion is a testament to the perseverance and unwavering belief of its investigators that this translational trial had to be conducted. From start to finish, the Trial's research team faced seemingly insurmountable obstacles, ranging from years of seeking funding, to a controversial debate stemming from another study's contrasting results—in spite of dissimilarities in the studies' locations and the timing and delivery of the GIK—and the challenge of the study design itself, which involved a high level of complexity. IMMEDIATE was an EMS-based, randomized, placebo-controlled, clinical effectiveness trial conducted in 13 cities across the US. It enrolled 911 patients, aged 30 years and older, with chest pain or other symptoms suggesting acute coronary syndrome (ACS). All patients were treated in the community by paramedics who performed an electrocardiogram (ECG) to evaluate their symptoms following a 9-1-1 call. The electrocardiographs used by the paramedics included decision support, and the paramedics also completed an electrocardiograph ACI-TIPI (Acute Cardiac Ischemia Time-Sensitive Predictive Instrument, created by IMMEDIATE's Principal Investigator, Harry Selker, MD, MSPH, and his team in the Center for

"This has been over thirty years in the making. Saving lives is what I dreamed of when I started med school. The IMMEDIATE Trial and other trials like it, that's what makes us researchers happy that we plug along and don't give up."

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Cardiovascular Health Services Research). If the ACI-TIPI predicted a greater than 75% probability that a patient was having ACS, the paramedics administered IV GIK or placebo.

The Tufts CTSI Core Laboratory conducted several tests for the IMMEDIATE trial, including those measuring each participant's insulin B-type natriuretic peptide (BNP). The function of natriuretic peptides, such as BNP, is to regulate blood pressure, electrolyte balance and fluid volume. BNP is produced primarily by the ventricle in response to pressure and functions to counteract increasing blood pressure, a sign of possible cardiovascular constriction. BNP measurements have been found to correlate well with ventricular functional status.

Such a novel design required national paramedic training and a heightened degree of community participation and engagement. For example, Dr. Selker in conjunction with federal agencies, had to obtain emergency exception to human subject consent because these patients were not in a position to give informed consent while they were experiencing ACS and were being treated by emergency medical personnel. All participating communities also were pre-surveyed by an outside vendor to obtain support for the study before being implemented in each city. Then, the research team had to use the collected survey data to convince city government officials to allow their EMS teams and residents to participate.

Despite the challenge in this, and in training paramedics in 13 cities, the IMMEDIATE team persisted. "We knew this was a very important study," says Dr. Selker. "If we could show that administering GIK in the first hour of someone having ACS resulted in *any* reduction of cardiac arrest and mortality, that would be significant, especially given that every year 1.2 million people have heart attacks in this country and GIK is so inexpensive and easy to administer."

The results will be released within weeks, hopefully with results that will cause IMMEDIATE to significantly change the way ACS is treated. IMMEDIATE also has provided new methods for how to get communities on board for research involving new EMS procedures and how to ensure protection of human subjects in such studies, which should help further research in this field.

However, research involving GIK is not new. Starting in 1980, scientists began administering GIK to laboratory animals to examine its metabolic stabilizing effect on the heart during coronary thrombosis. From those early bench days, initial Phase 1 studies were done on humans. Now, after this large clinical trial, this translational study could be on the brink of changing public health policy throughout the country.

"This has been over thirty years in the making," Dr. Selker notes. "Saving lives is what I dreamed of when I started med school. The IMMEDIATE Trial and other trials like it, that's what makes us researchers happy that we plug along and don't give up."

CLINICAL STUDIES

Transforming the Tissue Repository for Research

One strategy to speed up the delivery of new drugs, diagnostics and medical devices to patients is to consolidate our core resources. In 2011, Tufts CTSI was asked to assist the Tufts Medical Center Cancer Center in the development of a new, consolidated tissue repository. The Director of the Cancer Center and Chief of the Division of Hematology/Oncology, Richard Van Etten, MD, PhD, and Andreas Klein, MD, Clinical Director of the Lymphoma and Myeloma Services and an Assistant Director of the Adult Bone Marrow Transplantation Program, have been leading this much needed project that will be of great benefit to all investigators throughout Tufts CTSI. The expected launch date is spring of 2012.

Work on the new Tissue Repository was started two years ago by Ira Wilson, MD, who is now at Brown University but at the time was a Tufts faculty member and a CTSI Portal Director. The immediate goal was to create a searchable catalog or database of tissue samples presently archived in the Department of Pathology at Tufts Medical Center. According to Dr. Van Etten, Tufts Medical Center currently has 300,000 formalin-fixed paraffin-embedded (FFPE) tissue blocks, dating back 20 years. About 3,000 of those specimens are also available as frozen tissue samples, which allow for extraction and analysis of macromolecules, including protein, DNA, and RNA. Over the years, the tissue repository has always been available to researchers, but investigators had to mine several locations for the samples, with limited search functionality and equally limiting sample information. The samples had been originally collected for clinical purposes, but not for research.

The development of the new Tissue Repository has been a joint collaboration between Tufts Medical Center's Cancer Center and Department of Pathology together with Tufts CTSI staff. Basic parameters for the design of the underlying database system were set by the Tissue Repository Oversight Committee and Drs. Van Etten and Klein, who worked with John Griffith, PhD, then Director of Tufts CTSI's Research Design Center, and Tufts CTSI Senior Software Engineer Sam Yang, PhD, on ensuring that the new database meets all requirements for the Cancer Center and satisfies federal regulations concerning the security of Protected Health Information. Under Dr. Klein's direction, Dr. Yang also programmed the database, stripped all identifiers buried in the repository data, and completed system debugging.

The team looked to one of Tufts CTSI's most active affiliates, Maine Medical Center, for guidance. "Maine Medical Center has had a very advanced tissue bank for years," explains Dr. Van Etten. "We were very fortunate to be able to use them as a model for our new system. They have a proven, easy-to-use system for investigators."

Investigators within the Tufts community will no longer need to go through the tedious process of submitting paperwork to multiple locations storing samples. "This is a very interactive system that will essentially cut the middle man out for investigators looking for tissue samples," says Dr. Klein. "They will very easily search one database which will tell them everything they need to know for their possible study tissues. Researchers will simply identify the type of tissue samples they need and the results will display the contents of the available tissue and the formats the tissues are in, FFPE or frozen." The team also is now developing forms for investigators to make the submissions to the IRB and the Tissue Repository Oversight Committee easier and those forms will eventually be in the same location of the database. "In part, we're also trying to make it more rapid for clinical research to occur not only within Tufts, but also between our affiliates," says Dr. Van Etten.

"There has been tremendous progress with the new Tissue Repository database," adds Dr. Van Etten. "But there is more to do. The National Cancer Institute has begun an effort called *caBIG*, which aims to have all CTSA tissue repositories linked so that we can all share the samples we have for research and speed up clinical trials even more. In the coming months we have to show we're *caBIG* ready. Our new Tissue Repository database is an important first step in getting us there."

> "Maine Medical Center has had a very advanced tissue bank for years. We were very fortunate to be able to use them as a model for our new system. They have a proven, easy-to-use system for investigators."

EDUCATION

Transforming Education

In 2011, Tufts CTSI's Education Program began several new initiatives that advanced our program. First, we launched I LEARN, an online learning platform that allows users to access courses whenever they want and wherever they are in the world. Our first course that utilized both in-person lectures as well as I LEARN access, and which focused on Comparative Effectiveness Research (CER), was attended by 154 individuals. Together with our Graduate Program in Clinical and Translational Science, these educational advancements have positioned Tufts CTSI as one of the premier providers of translational science education.

Our students continue to inspire us to constantly refine and reenergize our Educational Program. Whether we provide them with internationally renowned Graduate Program courses or with scholar fellowships, our steadfast hope is that our students may achieve their career goal of becoming independent and *influential* translational scientists. It is not enough to simply graduate with a degree; we want them to change the very course of medicine in years to come.

MENTORED RESEARCH

In 2011, the Graduate Program in Clinical and Translational Science within the Sackler School of Biomedical Sciences provided students with rigorous training in methods related to three Concentrations: Evidence-Based Clinical Effectiveness Research, Clinical Investigation, and Health Services and Outcomes Research. In addition to graduate fellowships within specific clinical departments, there are two Tufts CTSI K Career Development scholarships. The KL2 provides highly-qualified junior faculty with 75 percent support to conduct multidisciplinary clinical/patient-oriented research for a period of two years. This program is specifically designed to further the goals of Tufts CTSI, linking across Tufts affiliated hospitals/campuses and across disciplines. The KM1 in Comparative Effectiveness Research (CER) provides similar support for the conduct of comparative effectiveness research for a period of two years.

Here are several students who are transforming their fields of research at the same time as obtaining higher academic degrees in clinical and translational research.

Transforming Perinatal Care

More often than not, K awardees tailor their research based on their clinical experience. Not so for Sarah Goff, MD, recipient of a KL2 award. Dr. Goff's K-related research is an examination of maternal healthcare associated infections (HAI) related to labor and delivery in hospitals across the country, and how such infections can be prevented. And yet, Dr. Goff is not a trained obstetrician, nor has she ever delivered a baby. Prior to the K, her research focused on obesity prevention and management in children. A health service trained internist and pediatrician at Baystate Medical Center, one of Tufts CTSI's affiliated partners, Dr. Goff became personally interested in the maternal-child health aspect of obstetric HAI when she became a parent and began to read the limited body of evidence about delivery-related complications, including HAI.

"Prior studies have estimated that more than 6 percent of deliveries—approximately 240,000 cases—every year are complicated by infections, yet so little is known about how infections can be prevented," says Dr. Goff. "There is an enormous potential for health impact if we can reduce the causes of these infections."

Dr. Goff's K research has several goals. First, using highly detailed claims data from Premier's Perspective Comparative Database on 355 hospitals with 100 or more deliveries annually, she and her colleagues are calculating risk-adjusted obstetric HAI rates. In the second phase of the study, the research team will apply observational epidemiologic methods to examine the association between HAI rates and selected modifiable clinical practices and hospital characteristics in a retrospective cohort. Such characteristics include nursing staff ratios, the number of beds, and teaching status.

"We're interested in not just those hospitals which have high rates of obstetric HAI to see what they may be doing that may be modified," explains Dr. Goff. "We're also interested in hospitals with low rates of HAI, looking at their culture of safety and what strategies and procedures they're using that are resulting in such low rates." An outgrowth of the study could be the development of an intervention to reduce hospital-based obstetric HAI in the future.

"The K award has given me an amazing opportunity. It's given me protected time to complete this research. More importantly, it's provided me with resources through my coursework at the Graduate Program in Clinical and Translational Science, resources which I wouldn't ordinarily have had. I can receive advice from faculty like Dr. David Kent (Program Director, Clinical and Translational Science Graduate Program) and that advice makes the study 50 times better. This is in addition to my mentorship at Baystate Medical Center with Dr. Peter K. Lindenauer and Dr. Errol Norwitz, Chair of the Department of OB-Gyn at Tufts. Prior to receiving the K, I wouldn't have had the chance to have such immediate contact with these incredible experts."

Transforming Pediatric Disability Screening

Research has shown that as many as 20 percent of children have a developmental and/or behavioral disability. Despite evidence for the importance of early detection, fewer than one-third of children with disabilities are diagnosed before school age. Why? One reason is that pediatricians often lack the time and expertise to identify young children with developmental and behavioral problems. Consequently, pediatricians are increasingly using screening instruments—parent questionnaires that allow information about child behaviors to be gathered quickly and reliably. However, according to KM1 recipient Chris Sheldrick, PhD, we don't have enough research to determine which of the many available screening instruments is best. Dr. Sheldrick's KM1 award is specifically for the purpose of providing rigorous didactic training, mentorship, and support to highly-qualified junior faculty to conduct comparative effectiveness research for a period of two years.

Dr. Sheldrick's interest in clinical psychology and how we treat children for behavioral and developmental issues dates back seventeen years ago when he worked at a shelter for adolescent boys and was a research assistant on a family relationships project in the Department of Psychiatry at Brown University. After obtaining his PhD in clinical psychology and then being on the Tufts Pediatrics Faculty for six years, he realized how little was known about whether one developmental/behavioral screening instrument was better than another.

Currently, there are a range of instruments physicians and parents can choose from, including general developmental questionnaires, general social/emotional screeners, and specific questionnaires for autism. Unfortunately, screening research has tended to focus on each of these domains in isolation, despite the fact that behavior and development are intricately intertwined, and that problems in one area often co-occur with problems in the other. Moreover, evidence supporting screening instruments' accuracy varies widely—too widely to allow for direct comparisons based on existing research.

The need to know which screening instrument is the most effective was further heightened in 2006 when it became mandatory for all child health providers in Massachusetts to administer a behavioral health screening instrument to the parents of all children receiving Medicaid at every pediatric health supervision visit from birth to age 21. Instituted in response to Rosie D. v. Romney, a lawsuit filed on behalf of eight families who believed the state was failing in its obligation to screen and treat Medicaid-eligible children for mental health disorders, this requirement put the screening issue front and center in every Massachusetts health clinic that treats children, including the Floating Hospital at Tufts Medical Center.

The KM1 award has allowed Dr. Sheldrick to begin to address the paucity of research on these screening instruments. Working with Ellen Perrin, MD, Director of Research, Center for Children with Special Needs at the Floating Hospital for Children at Tufts Medical Center, Dr. Sheldrick is developing and testing the comparative effectiveness of a screening instrument called The Survey of Wellbeing of Young Children (SWYC) (pronounced SWIK). The SWYC includes assessments of (1) a child's developmental progress, (2) a child's behavioral health, and (3) a child's family context. The entire SWYC takes no more than 10 minutes to complete. A preliminary validation study was conducted with a sample of 906 parents. Dr. Sheldrick and his colleagues are submitting a R01 grant application in early 2012 to conduct a larger comparative effectiveness trial of the SWYC and other screening instruments.

In addition to affording Dr. Sheldrick the time to complete the SWYC and its validation, the KM1 award has also allowed him to receive unique training in advanced statistics and research methods that are necessary to properly conduct comparative effectiveness research. In particular, he has welcomed the opportunity to work with Laurel Leslie, MD, MPH, to apply decision analysis to developmental-behavioral research in pediatrics.

"Decision analysis is rare at best in pediatrics and even rarer in developmental-behavioral pediatrics," says Dr. Sheldrick. "But it is a particular strength of the research team here at Tufts, which is incredibly fortunate. Decision analysis has the wonderful potential for offering new ways of understanding problems in pediatric screening, including finding ways to make sure that screening results are relevant to primary care pediatricians and the families they treat. Ultimately, we will be better able to diagnose developmental disabilities in kids and that, at the end of the day, is what we are all striving for."

Christopher Sheldrick, PhD, KM1 Scholar

Transforming How We Treat Chronic Obstructive Pulmonary Disease

For an internist, like Mihaela Stefan, MD, who is interested in conducting studies of treatment effectiveness among hospitalized patients, the KM1 program is exactly what she needed to advance her career.

"I was a hospitalist with a great deal of clinical experience," explains Dr. Stefan, Assistant Professor of Medicine, Tufts University School of Medicine, and Director of the Medical Consultation Program at Baystate Medical Center, an affiliated partner of Tufts CTSI. "I began to notice that there were large gaps in healthcare quality with wide variations in how patients are treated in part due to lack of evidence of which interventions work best."

At first, in order to address these issues, Dr. Stefan contributed 25 percent of her time building a Quality Improvement training track for Baystate's medical residents. Through this program, she started to work with Peter Lindenauer, MD, MSc, Director of Baystate's Center for Quality of Care Research. "Peter Lindenauer is the mentor you want to have. He has guided my career and supported me throughout my training and research projects, enabling me to embark on the path of becoming a successful independent investigator."

The two researchers connected on several mutual research interests, such as comparing interventions to improve the outcomes of patients with chronic obstructive pulmonary disease (COPD). Subsequently, Dr. Stefan applied for and was awarded the Tufts CTSI KM1 scholarship. Using the Perspective Database®, a highly detailed patient-level, multi-hospital database developed for measuring quality and healthcare use in hospitalized patients, Dr. Stefan examined

Mihaela Stefan, MD, Assistant Professor of Medicine, Tufts University School of Medicine, KMI Scholar the safety and effectiveness of beta-blockers in patients admitted with acute exacerbations of COPD who have underlying coronary artery disease or heart failure. In 2009 the Perspective Database® included data on approximately 15% of all US hospitalizations, and currently contains the records of more than 45 million total inpatient encounters. Despite its scope, however, Perspective has limitations, which Dr. Stefan had to address. For example, the database lacks patient-level details used in clinical decision-making, such as direct physiologic measurements or overall measures of health status. “To limit the threat of these confounding, I employed powerful statistical analytical methods focusing on understanding the results of a series of models in a coordinated manner,” explains Dr. Stefan. The perspective database also has information for many treatments and diagnostic tests which she will use as potential proxies for disease severity.

Recently, she and Dr. Lindenauer co-authored a paper published in *Chest*, which reported the findings of a large observational study of the *Worcester Heart Attack Study* which found that patients with Acute Myocardial Infarction (AMI) and COPD were less likely to receive evidence-based therapies during hospitalizations and they had a higher risk of dying during hospitalization and at 30-days after discharge. In that article, Dr. Stefan and her co-authors argued that, “...it is essential to educate providers to consider cardiovascular comorbidities in patients with COPD and not focus on pulmonary disease in isolation.” To accomplish that goal, she believes that physicians must be shown the evidence that there is a gap in medical care between patients with AMI with and without COPD. Physicians will need to understand that COPD is a complex disease and consider the associated multiple comorbidities.

While the robust training offered by the Clinical and Translational Science Graduate Program did not surprise Dr. Stefan, “discovering how supportive everyone was in the K scholar program did. I was amazed. The faculty researchers make time for you. They want you to succeed. Dr. David Kent, in his role as the Director of the CTSI Graduate Program, was instrumental in facilitating my access to an exceptional research support infrastructure.”

In order to see that faculty, however, Dr. Stefan had to drive to the Boston Tufts Campus, some 90 miles away from her Baystate office as initially the Graduate Program did not have a good distance learning option for its students who did not live in the Boston area. “But, Tufts CTSI has really improved its distance learning program and implemented a great videoconferencing system, so I really didn’t have to be in the classroom this last year. Although, sometimes I would drive all that way anyway just to spend time with the other fellows and the faculty,” admits Dr. Stefan.

> “...it is essential to educate providers to consider cardiovascular comorbidities in patients with COPD and not focus on pulmonary disease in isolation.”

Transforming Treatment for Children with Leukemia

Leukemia is the most common cancer in children accounting for approximately 30 percent of all childhood cancer and it generally has a high cure rate. However, approximately one percent of all childhood cancer patients have acute myeloid leukemia (AML), which is characterized by unfavorable chromosome abnormalities. Children with poor risk AML have the poorest survival outcomes of any other childhood leukemia patients. Yet, little research has been done regarding this disease because of the comparatively few children battling AML. "These kids are usually the smallest subgroup in any cancer-related research and so haven't received a lot of attention, but they do deserve further investigation," says KM1 scholar Michael Kelly, MD, MPH.

Dr. Kelly's current research is comparing the effectiveness of hematopoietic stem cell transplant (HSCT) versus chemotherapy for children with poor risk AML. The current recommendation is to transplant all poor risk patients in the first remission. Typically, kids with AML who have a transplant start with two or three cycles of a cytarabine-based therapy and then have the transplant (usually bone marrow). Cytarabine is a chemotherapy agent used mainly in the treatment of cancers of white blood cells such as AML. It destroys cancer cells by interfering with how they multiply. Unfortunately, it also has significant side effects ranging from GI disturbances to kidney damage, to peripheral neuropathies, causing the patients to get very sick. After two or three treatments, the AML patient then will have a transplant, if there is a match from a sibling or someone from the National Marrow Donor Program, a national registry. The children have to stay in the hospital for two months, there is a high risk of kidney failure, infertility may occur many years later, and there is a five to ten percent mortality rate. If they don't have a transplant, then usually they have five cycles of Cytarabine.

Comparing the effectiveness of treating with and without transplant will enable Dr. Kelly to determine whether the current recommendation to transplant all poor risk patients in the first remission should be reconsidered. In order to do so, he is examining retrospective cohorts for both transplant and non-transplant data from two international cooperative groups, the Children's Oncology Group and the Center for International Bone Marrow Transplant Research.

His comparative effectiveness work is not limited to AML patients though. Another study involves a literature review and a meta-analysis looking at whether kids with T-cell immunophenotype acute lymphoblastic leukemia (ALL) and lymphoma should receive prophylactic cranial irradiation or not. Collaborating with two faculty from the Tufts School of Medicine, Assistant Professor Thomas Trikalinos, MD, PhD, and Professor Susan Parsons, MD, MRP, Dr. Kelly hopes to answer the underlying question of whether ALL patients' survival rates ultimately benefit from such radiation or not.

"I knew I wanted to take care of the sicker kids with cancer," Dr. Kelly explains. "The K award is allowing me an incredible opportunity to compare how we treat such kids. If you have an idea of what you want to explore, what you want to research, someone here can help you. Tufts is well known for research methods and great access to expert methodologists."

> “I knew I wanted to take care of the sicker kids with cancer. The K award is allowing me an incredible opportunity to compare how we treat such kids. If you have an idea of what you want to explore, what you want to research, someone here can help you. Tufts is well known for research methods and great access to expert methodologists.”

MENTORED RESEARCH

Michael Kelly, MD, MPH, KM1 Scholar

Transforming Diabetes Prevention

Graduate fellow Joanna Mitri, MD, already had prior experience conducting research in the field of diabetes when she enrolled in the Clinical and Translational Science Graduate Program. “I wanted to learn how to be more critical of research I was doing. How to approach research in a systematic way,” Dr. Mitri says. “I was also interested in continuing my work in diabetes prevention and I was already engaged in research with Dr. Pittas.” Anastassios Pittas, MD, MS, Dr. Mitri’s mentor, is a faculty member of the Graduate Program and the Program Director of the Tufts Clinical and Translational Research Center. He is also a foremost expert on type 2 diabetes and the ways the disease can be affected by lifestyle-based interventions.

Dr. Mitri’s graduate fellowship research is examining whether vitamin D status is associated with cardiometabolic disease. Specifically, her work is focused on the metabolic syndrome, which is a constellation of risk factors that increases the risk for cardiovascular disease and type 2 diabetes. Such risk factors include central adiposity, insulin resistance, hyperlipidemia, and hypertension.

Her study uses data from the Diabetes Prevention Program, a major multicenter research study whose original aims were to test whether modest weight loss through dietary changes and increased physical activity or treatment with the oral diabetes drug metformin delayed the onset of type 2 diabetes in persons at high risk for diabetes. The Diabetes Prevention Program found that even a modest amount of weight loss significantly reduced the chances of developing diabetes.

“Obesity is paramount to type 2 diabetes,” explains Dr. Mitri. “But weight loss is very hard to maintain long-term.” Under the mentorship of Dr. Pittas, Dr. Mitri began to look for alternative ways of preventing diabetes, such as whether vitamin D status has a role in prevention of diabetes and metabolic syndrome. “Vitamin D is safe, easy to administer in its pill form, and it’s relatively easy to diagnose vitamin D deficiency,” Dr Mitri says. In an another study, Drs. Mitri and Pittas reported that vitamin D status is inversely associated with progression of diabetes. In a short-term randomized trial, whose results were published recently with Dr. Mitri as first author, vitamin D supplementation slowed down the progression of glucose intolerance in persons at risk for diabetes. If these results are confirmed in large intervention studies of vitamin D that she is currently designing, they will have “great implications for the possible prevention of diabetes,” says Dr. Mitri.

Joanna Mitri, MD, Graduate Fellow

Transforming the Community

For over four years, Tufts CTSI's community engagement program delivered by the Center for Aligning Researchers and Communities for Health (ARCH) has forged collaborations with community-based organizations and community-based researchers. True to its mission of empowering community organizations to conduct excellent, effective research, ARCH continued in 2011 its popular training initiative called *Building Your Capacity and Advancing Research through Community Engagement* (the BYC Program). With its goal being the building of capacity in community-based organizations so that they can participate fully in community engaged research, this landmark program, which was established in 2009, is now serving as a national model for other CTSA community empowerment training programs. Tufts CTSI staff provide relevant, interactive training sessions that utilize local examples and expert community researchers. Fellows are selected from community-based organizations through a competitive process and are mentored through a research project. To date, there have been 30 Fellows, representing 20 community organizations. See page 10 for one BYC success story.

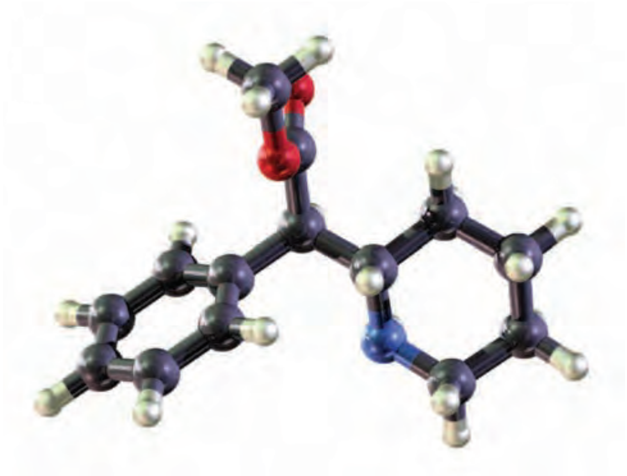
COMMUNITY

COMMUNITY

Transforming Drug Prescribing for Foster Children

One of our most influential reports throughout communities this past year was a report from a multi-state study on psychotropic medication oversight in foster care. Led by ARCH Director Laurel K. Leslie, MD, MPH, Christopher Bellonci, MD, at Tufts Medical Center, and Justeen Hyde, PhD, at Cambridge Health Alliance, the study examined state policies and practices in 47 states, including Massachusetts, and the District of Columbia regarding the use of medication for treating behavioral and mental health problems in foster care children and adolescents ages 2 to 21 years.

The Tufts CTSI multi-state report concluded that while oversight of psychotropic medication is a high priority of the state child welfare agencies, there is also great variability among the state policies and practices governing such oversight. The Study Report called for a national approach and resources for medication oversight for youth in foster care. A more detailed national look at which state policies and practices are the most effective for improving the mental health of these youth is also needed. Without a national approach, crossing a state border could mean the difference between a youth in foster care being over or under treated with medications. The report also stressed the need for youth-serving organizations and state agencies to work together, and for more informed decision-making and appropriate medication monitoring for youth in foster care, especially given that the majority of states in the multi-state study reported an increasing trend in the use of psychotropic medications among youth in foster care.



Molecule of Ritalin

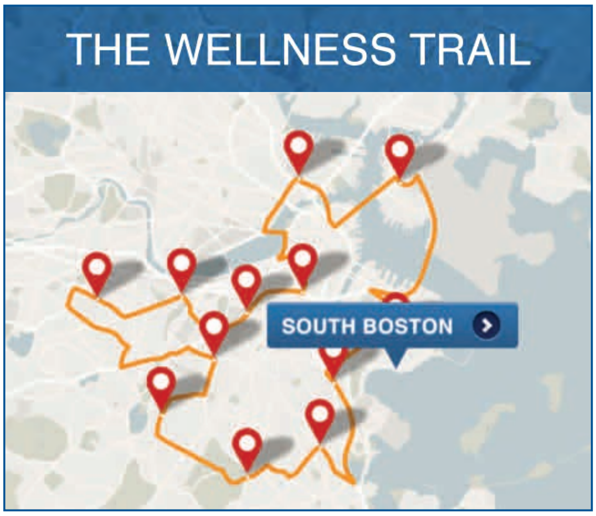
Funded by the Charles H. Hood Foundation and the National Institute of Mental Health-funded Child and Adolescent Services Research Center in San Diego, the study involved interviews with state child welfare agency key staff as well as a review of existing policies and guidelines available on state public websites or provided by staff. The Study Report and specific tools developed by states are available online at http://www.tuftsctsi.org/About-Us/CTSI-Components/Community-Engagement.aspx. The Study Report was funded by the William T. Grant Foundation and Tufts CTSI.

Transforming Health Disparities

The Wellness Trail

Tufts CTSI staff developed and launched in 2011 a new innovative health disparities application, called the Wellness Trail, patterning it on Boston's famous Freedom Trail. This mobile app (http://wellnesstrail.tuftsctsi.org/) provides easy-to-understand health information for 12 Boston neighborhoods along the MBTA Boston subway green line. Moreover, the intent of the application is to uniquely address not just disease rate differences, but also more upstream factors for health disparities such as lack of neighborhood parks to exercise in, or neighborhood food options for healthy eating, or community air quality.
For each neighborhood, the Wellness Trail offers users three interrelated areas of current information:

1. Based on annual data from the Boston Public Health Commission, **"Disease Rates"** details rates of various health conditions (asthma, obesity, high blood pressure and heart disease) and compares them to other Boston neighborhoods and the greater Boston area.
2. **"Community Resources"** offers links to maps of local parks and open spaces, grocery stores, farmers markets and community gardens, and information about each neighborhood's safety and proximity to highway pollutants.
3. **"Take Action"** raises the health disparity discussion up a notch by providing resources and information on how to better your community by contacting legislators and encouraging them to lobby for the development of additional parks and the creation of violence protection programs; or whom to contact for starting a farmers market in your neighborhood.



This exciting application has been cited by multiple sources as an innovative way to present community health data, including Health Leads, a national program mobilizing college volunteers for connecting patients and their families with the basic resources they need to be healthy.

The Race Exhibit at the Museum of Science, Boston

In celebration of Martin Luther King Jr. Day 2011, Tufts CTSI participated in the launch of the Boston Museum of Science's traveling exhibit "Race: Are We So Different?". The Boston Museum of Science is a Tufts CTSI affiliate partner. Through interactive components, historical artifacts, compelling photographs and multimedia presentations, this exhibit uncovered the impact of race and ethnicity on society from biological, cultural and historical viewpoints. It explored how differences among people become the basis for discrimination, reveals the reality and unreality of race and also encouraged attendees to engage in an open discussion about the everyday experience of living with race.

Many racial and ethnic minorities experience severe health disparities, which are higher than usual rates of illness and death from certain health conditions. In response to this, Tufts CTSI launched a new health disparities mobile application, The Wellness Trail and Tufts CTSI investigators and community partners presented findings from two research projects aimed at combating health disparities and improving overall community health.

The first presentation was by Christine Rioux, PhD, Research Assistant Professor in the Department of Public Health and Community Medicine. Dr. Rioux presented the *Community Assessment of Freeway Exposure and Health* study with which she is affiliated. The study examines examines the effects of highway pollution on the cardiovascular health of residents in Somerville, Dorchester and Chinatown. The team organized an interactive exhibit and discussed the health effects of traffic pollution on vulnerable populations.

The CAFEH study also had on display a specially-equipped, air monitoring van that measures ultrafine particulates and other pollutants while also measuring certain health parameters in local residents.

The second project team, led by Flavia Perea, PhD, Assistant Professor in the Department of Public Health & Community Medicine at Tufts University School of Medicine, and Linda Martinez, PhD, Assistant Director of the Community Health Program at Tufts University, and including youth researchers, discussed findings from a Lawrence-based research project, *Improving our Opportunities for Recreation and Physical Activity: Engaging Youth in Research and Local Policy Advocacy*. Its goal is to engage local youth in examining the quality, condition and utilization of parks and playgrounds in the city of Lawrence with the hope of reducing obesity. This project is a collaboration between Tufts University's Department of Public Health and Community Medicine, the Community Development Department, and Groundwork Lawrence.

The Living Lab

Research has shown that the idea of race is fluid among adults. But what about among children? Last year, Sam Sommers, PhD, Associate Professor in the Psychology Department within Tufts University's School of Arts and Sciences, joined with Sarah Gaither, a 3rd year PhD student, and a few research assistants to begin an innovative project that would start to answer that question. Moreover, they set up the research itself within the highly trafficked Living Lab at the Museum of Science Boston.

The Living Lab is an educational, on-site research program where scientists conduct research studies within the museum exhibits, educate visitors about their research topics, and work with museum educators to introduce the public to science. In 2010 Tufts CTSI began to participate in the Living Lab with three studies: in addition to Dr. Sommers study, there was *Factors Associated With Childhood Asthma* led by Public Health and Community Medicine Professor, Douglas Brugge, PhD, and a third study, Professor of Psychology, Nalini Ambady's *How Do We Make Social and Moral Judgments About Our Own and Other Groups?*

The Sommers and Gaither study, *Children's Racial Perceptions and Categorizations*, examined children's abilities for remembering racially ambiguous Black/White faces in comparison to White (racial ingroup) and Black (racial outgroup) faces. Past research has shown that people tend to remember faces from their racial ingroup better than faces from their racial outgroup, but this had not yet been studied regarding racially ambiguous or racially mixed faces for children.

"We don't share a comfort level discussing race," says Dr. Sommers. "I've always been fascinated as a scientist and a citizen at seeing how differently we shape how we interact with others based on how we perceive identities. There is a disconnect between how we believe we perceive other people and how we actually perceive other people." Such research has profound implications for how patients are treated in a healthcare system.

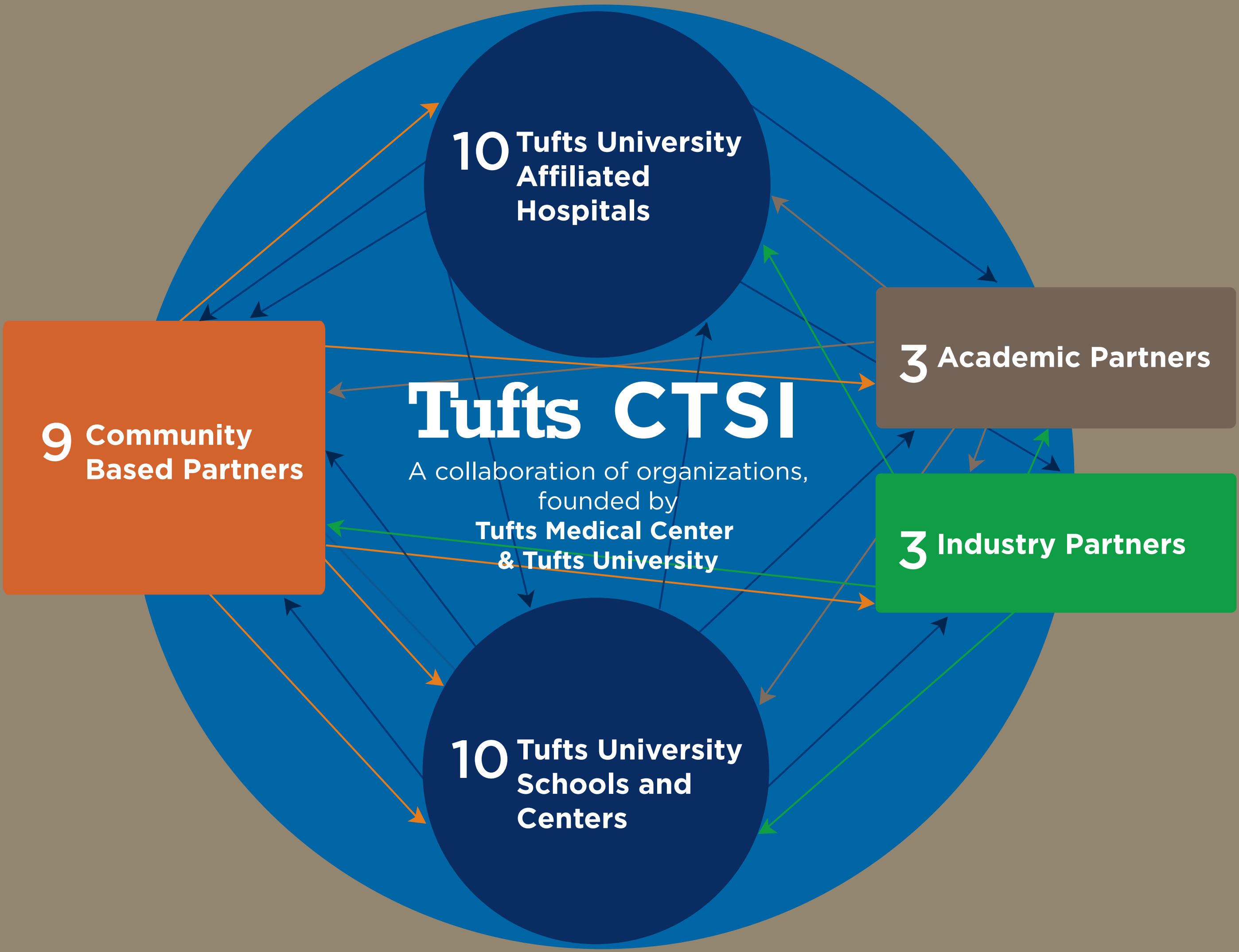
The research team conducted the study once a week during a three hour time block at the Living Lab. Children between the ages of 3 and 8 years of age were recruited through visiting parents. Participating children were shown adult male and female White, Black and racially-ambiguous Black/White faces. The children were asked to remember the faces. All faces were shown in a randomized order and were shown for five seconds each. Then the children were asked about their weekend plans as a distracter before the recognition portion of the study began. They were shown two faces (of the same race and gender) side-by-side on the computer and were asked to tell the researcher which face they recognized. They also told the researcher how sure they were with their choices.

Subsequently, the children completed a racial constancy measure to measure whether children understand that race stays constant across the lifespan. They were shown a picture of a child who was the same gender as the participant and were asked "when this child grows up, will they look more like this adult or that adult?" One adult option was White and one was Black. Then participants were asked, "If this child wanted to change their skin color to look like this adult (the adult of the opposite race) could they do that? Why or why not?" Their answers were recorded and if they got both questions correct and gave a plausible/realistic answer for their racial reasoning they were deemed as having gained an understanding of racial constancy.

A large benefit of including the study in the Living Lab was that unlike school-based studies where researchers eventually run out of children to recruit, the Museum of Science brings in new families each week. Gaither thinks The Living Lab is also "a good first step in making short and easy research experiences readily available to the general public, since without this option many families wouldn't have an opportunity to be exposed to academic research practices. Parents also get to complete the research project with their child, so they often have the chance to learn about their children as well, which also does not happen when we test in schools."

Returning to our original question—Is race fluid for children?—overall, the study team found that children without the ability to know that race stays constant across the lifespan remembered White, Black and racially ambiguous faces the same (i.e., no significant differences in facial memory). But, those children who had achieved racial constancy and understood more about racial categories and the fact that race stays permanent over time, demonstrated a significant increase in their memory for White or racial ingroup faces in comparison to both Black and racially ambiguous faces. After learning more about race, children view racially ambiguous faces as outgroup faces, replicating the findings found previously with adults.

"Increasingly, researchers and clinicians are going to need to focus on multi-racial, multi-ethnic participants in their work," Dr. Sommers says. "And in order to do that they must be aware of the intersection of identities and how that may impact outcomes such as health behaviors. Race is not an either or issue. It's much more fluid than that. The more we understand that, the better our research will be."



10 Tufts University Affiliated Hospitals

9 Community Based Partners

Tufts CTSI

A collaboration of organizations, founded by **Tufts Medical Center & Tufts University**

3 Academic Partners

3 Industry Partners

10 Tufts University Schools and Centers

Translating research into better health

TUFTS CLINICAL AND TRANSLATIONAL SCIENCE INSTITUTE

CONNECTIONS

Our Affiliated Partners include:

Tufts Schools and Centers

Center for the Study of Drug Development
Cummings School of Veterinary Medicine
Friedman School of Nutrition Science and Policy
Jean Mayer USDA Human Nutrition Research Center on Aging
Sackler School of Graduate Biomedical Sciences
School of Arts and Sciences
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School of Engineering
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RAND Corporation

Industry/Non-Profit Partners

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Community Based Partners

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Boston Chinatown Neighborhood Center
Boston Museum of Science
Boston Public Health Commission
Center for Community Health Education, Research and Service
Codman Square Health Center/Dorchester House Multi-Service Center
Immigrant Service Providers Group/Health
Latin American Health Institute
New England Quality Care Alliance

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CONNECTIONS

Transforming Social Networking for Researchers

In 2011 Tufts CTSI began development of the Tufts CTSI Profiles research networking system and expertise mining website. In addition to providing researchers with traditional directory information about faculty researchers, Tufts CTSI Profiles is a gateway to connect to others in the broad research community. Tufts researchers can easily connect with possible collaborators on future research and publications. In addition to "passive" research community networks for users—Tufts CTSI Profiles automatically establishes these when faculty share common traits such as being in the same department, working in the same building, co-authoring the same paper, or researching the same topics—Tufts CTSI Profiles also offers users the capability of establishing "active" research community networks themselves, i.e. users can mark other faculty profiles as collaborators, advisors, or advisees. Importantly, Tufts CTSI automatically updates all PubMed data and National Institutes of Health grants within each user profile.

Transforming Clinical Patient Databases

Tufts CTSI's biomedical informatics team also made significant progress in developing a clinical patient database for identifying study cohorts. i2b2 (Informatics for Integrating Biology and the Bedside) is an NIH-funded National Center for Biomedical Computing. Its primary purpose is to facilitate the development of a scalable informatics framework that will enable Tufts clinical and translational researchers to use existing clinical data for discovery research and, when combined with IRB-approved protocols, will facilitate observational studies and clinical trials.

Working in partnership with Recombinant Data Corp., Tufts CTSI has successfully deployed a clinical research data warehouse that includes an i2b2 data mart for patient cohort selection and hypothesis generation. The mart contains de-identified patient data from the following Tufts clinical systems: Soarian, Logican, Invision, IDX, Tracemaster and DrFirst. This data includes patient demographics, vitals, medications, diagnosis (ICD-9), ECG, lab test results, drug allergies, vaccinations and patient visit histories.
In addition to the i2b2 mart, the data warehouse has been successfully integrated with a local installation of REDCap (See page 39), a browser based, metadata driven application for developing clinical and translational research databases, i.e. registries.

A RANGE OF TRANSFORMATION

Highlights of other Tufts CTSI transformational achievements in 2011 are as follows.

■ Transforming Protocol and Proposal Development

Our statistical and programming staff supported the development of over 254 protocols and grants in 2011 and also developed 16 research databases, assisting investigators with the full range of study services, from proposal and protocol development to data management, to data analysis and publication.

■ Transforming Genetics and Genomics

Services at our state-of-the-science genomics facility were significantly expanded in 2011 with an advanced and reliable liquid handling robotic system for precision assay processing.

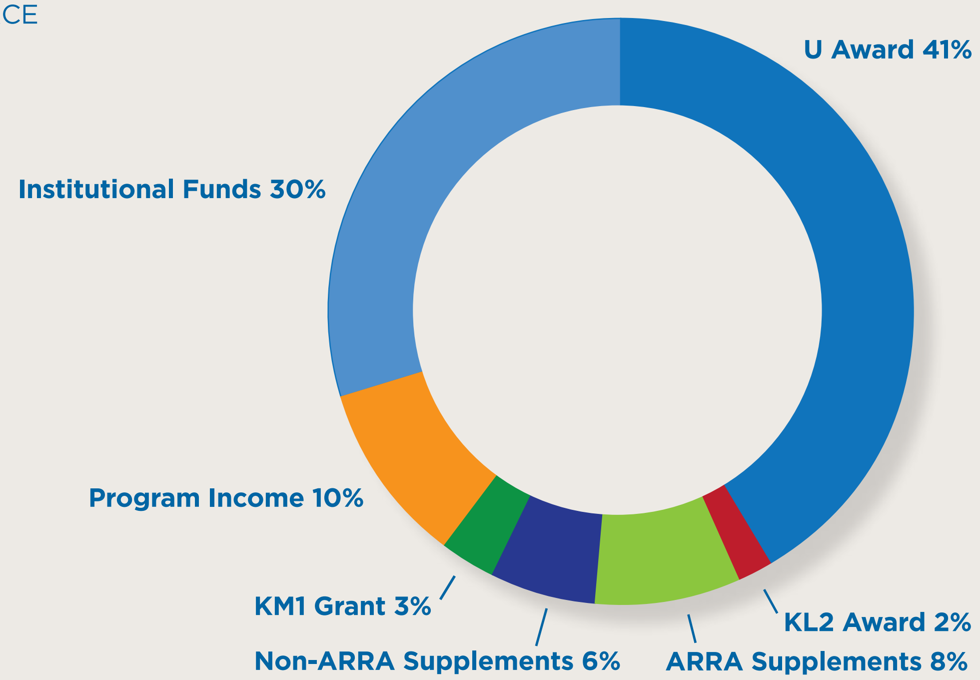
■ Transforming Study Design and Analysis

Our statistical and design staff also continued to expand our seminars and workshops in study design and analysis and grants writing. In 2011 staff led 122 such seminars and workshops.

In addition, in 2011 the RDC began to offer REDCap to investigators. REDCap provides free, web-based electronic data capture tools to support clinical and research studies, and is now available to all Tufts CTSI partners. Designed at Vanderbilt University, REDCap (Research Electronic Data Capture) and REDCap Survey are secure web applications for building and managing online databases and surveys. Using REDCap's streamlined process for rapidly developing projects, researchers may create and design databases, surveys, or a mixture of both whether online or offline. REDCap provides audit trails for tracking data manipulation and user activity, as well as automated export procedures for seamless data downloads to Excel, PDF, and common statistical packages (SPSS, SAS, Stata, R).

INSTITUTE RESOURCES

YEAR 3 REVENUE BY SOURCE
(TOTAL = $7,737,785)



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