The College of Medicine brings together best of bench, bedside worlds

Among those furthering the potential of translational research are College of Medicine Dean Dimitri Azar (third from left) and recently recruited department heads (from left) Mary D. Stephenson, obstetrics and gynecology; Rohit Varma, ophthalmology and visual sciences; Thomas Royston, bioengineering; Patricia W. Finn, medicine; and John Hickner, family medicine.
UY WEINBERG, MD, developed a lipid emulsion treatment to resuscitate patients who present with toxicity to local anesthetics and overdoses of a variety of drugs. Mary Jo LaDu, PhD, followed the link between the gene apoE and Alzheimer’s disease, and her work has made a major impact on research around the globe. Victor Gordeuk, MD, director of the College of Medicine’s Sickle Cell Center, leads a team that has built an airtight feedback loop of basic research and clinical observations.

These are just a few examples of how translational research continues to transform the College of Medicine into a home for the integration of basic and clinical research. To bolster its existing talented leadership, the college has strategically recruited five new department heads with experience promoting this tight bench-to-bedside connection and providing mentorship support to NIH-funded researchers (see sidebar profiles, page 24). Their work will help to foster the university’s strengths in developing technological innovations for clinical applications and fuel the college’s ability to address unmet medical needs.

The college also has undertaken a strategy to enhance the research environment and infrastructure for translational science through its partnership with the federally funded Center for Clinical and Translational Science (CCTS). Many of the college’s investigators have relied on support services such as study design, regulatory support, biomedical informatics, community engagement and a clinical research facility provided by the CCTS, which serves as home for the concept and a nexus for multidisciplinary collaboration.

For example, the center awards pilot and just-in-time grants that provide stimulus to investigators with novel ideas at the forefront of translational science, enabling preliminary research that will help prepare them for externally funded research grant proposals, says CCTS co-director Robin Mermelstein, PhD. Just-in-time grants increase the responsiveness and competitiveness of proposals by, for example, helping investigators bolster preliminary data sections.

“We emphasize collaborations among faculty and across departments, certainly throughout the College of Medicine,” Mermelstein says. “They bring together different perspectives on approaching a problem, and that creates new linkages, particularly in bringing basic scientists in contact with clinical scientists in a feedback loop, which is critical.”

Serving a dual role as director of the CCTS and dean of the College of Medicine, Dimitri T. Azar, MD, MBA, has a unique perspective on the integral role of translational science in today’s research landscape.

“There has always been patient- and community-centered research here, along with a well-established and respected infrastructure in basic research,” he says. “We have the opportunity to enhance the impact of our research through collaboration. A structured approach, through translational science, will make the whole greater than the sum of the parts. It will enhance the effectiveness of our institution across the clinical and basic research spectrum. Ultimately, our collaborations will break down the traditional barriers that have developed over the years and will help us solve more health-related problems.”

UIC is one of 60 institutions funded by the Clinical and Translational Science Awards program, administered by the National Center for Advancing Translational Science, created at the National Institutes of Health in 2012.

The purpose of NCATS is to help “enhance the development, testing and implementation of diagnostics and therapeutics across a wide range of human diseases and conditions. By improving the process through which diagnostics and therapeutics are developed, NCATS aims to make translational science more efficient, less expensive and less risky,” according to the NCATS website.

HEN WEINBERG LEFT HIS POSITION as a basic researcher at the National Institutes of Health nearly 30 years ago, he never expected to be back in the laboratory. Instead, his career has dovetailed anew with the bench at the College of Medicine, jump-started initially by his desire to understand why a patient with carnitine deficiency almost died from a very small dose of local anesthetic. That question led to animal studies of the mitochondrial effects of local anesthetics, which confirmed Weinberg’s suspicion that they inhibit normal mitochondrial metabolism of fatty acids.

Building on this result, Weinberg and his team did studies in 2000 to replicate the metabolic effects of carnitine deficiency—which led to the unexpected observation that pre-treating an animal with an intravenous lipid emulsion rendered it very resistant to local anesthetic toxicity. The follow-up experiments identified intravenous lipid emulsion infusion as a very effective method for reversing an otherwise fatal local anesthetic overdose and toxicity.

“That has now led back to the bedside and has saved lives in operating and emergency rooms across the globe,” Weinberg says.
Recently recruited department heads spearhead translational research

**Rohit Varma:**
**Clearer Vision**

**John Hickner:**
**Breathing Easier**

**Patricia W. Finn:**
**Safer Patients**

**Mary D. Stephenson:**
**Saving Pregnancies**

**FOR ROHIT VARMA, MD, MPH, head of ophthalmology and visual sciences, translational research has provided methods to assess the risk factors of developing blinding eye diseases, the impact those diseases have, and the issue of access and barriers to care.**

When it comes to risk factors, “There is a very straightforward translational component,” says Varma, principal investigator on three NIH-funded, community-based studies to examine prevalence of and socioeconomic burdens caused by vision impairment. “We look at the factors that cause disease that are modifiable.” Diabetic eye disease, for example, is strongly related to levels of hemoglobin a1c, while cataracts are closely associated with cigarette smoking.

Examining the impacts of people’s vision loss on everyday activities like driving or watching television also has an obvious translational aspect, says Varma, who is associate dean for strategic planning. “The amount of change in vision is directly associated with the difficulty in performing these tasks,” he says. “If you can reduce vision loss, you can improve the person’s ability to perform them.”

Perhaps even clearer are the effects of barriers to care, says Varma, whose research focuses primarily on epidemiology in minority and disadvantaged populations. “If you can potentially reduce the barriers and have greater access to care, you can reduce the potential for losing your vision and going blind,” he says.

**DEPARTMENT OF MEDICINE head Patricia W. Finn, MD, is excited that the College of Medicine has taken such a proactive stance in encouraging translational research. “The basic scientist working on the bench has a lot to offer the clinician,” she says. “It’s possible that those analyses and discoveries can lead to a better treatment, or at the very least a better understanding of disease.”**

With a clinical and research focus on immune mediated pulmonary diseases, including transplantation, lung injury and asthma, Finn sees her work drawing from these connections in a number of ways. In treating asthma, for example, translational research can lead to not only new drug discovery but also greater analyses of immune system responses that trigger attacks. “It requires a discussion about, ‘How do you avoid those triggers?’” she says.

As the most common cause for mortality among those admitted to an intensive care unit, lung injury is ripe for exploration through translational research, says Finn, an NIH-funded researcher who is also Earl M. Bane Professor of Medicine. “Who goes on to have lung injury? Why does that happen?” she says. “These are questions that are incredibly exciting and have to do with how you identify the data and intervene.”

Transplantation is another area where translational research could provide answers, Finn believes. “Why do certain populations have better outcomes? Is it due to immune response, related to the microbes that live on you?” she asks. “There are so many unanswered questions and so many ways to analyze the data.”

**DEPARTMENT HEAD and professor of family clinical medicine John Hickner, MD, MPH, figures his specialty takes the final step in bringing translational research to the front lines of care at the bedside. “How do we take the work of specialists and apply it to the run-of-the-mill patient who walks into the clinic?” he says. “That’s where we tend to get interested and focused … at the far end of translation.”**

The application of translational research to patient safety, particularly regarding safe use of medication, has been Hickner’s own focus. “In primary care, we’ve studied errors and how to do something about that in physicians’ offices, not hospitals,” he says. “A lot of my, quote, ‘research’ has really been supporting others and supporting networks of doctors working together to improve care.”

Hickner has started four such networks to bring research into practice, in addition to being the founding director of the American Academy of Family Physicians. He’s also worked on general health systems improvement, mostly focused on medication management, “reducing the costs of care and hopefully improving efficiency,” he says. “There’s a widespread belief that we do 30 percent to 40 percent more tests and procedures than are really needed to improve outcomes.”

Given the underserved nature of the patient population at the University of Illinois Hospital & Health Sciences System, Hickner says it’s important to apply the lessons of such translational research to that profile. “Our work is going to focus on pragmatic issues: management of common illnesses, appropriate testing, appropriate use of medication, and frankly, whatever else is of interest to our researchers.”

**AN INTERNATIONALLY renowned expert in recurrent pregnancy loss and head of the college’s department of obstetrics and gynecology, Mary D. Stephenson, MD, conducts randomized, controlled trials to assess treatments and optimal drug dosing strategies.**

“Studying pharmacokinetics of medications in pregnancy is paramount because absorption, bioavailability and elimination of medications change in the first, second and third trimesters,” she says. “It’s extremely important to determine whether there is a significant benefit to taking medication during pregnancy.”

Often, recurrent pregnancy loss patients are prescribed multiple medications, Stephenson says. “But what is the net effect of multiple medications?” She adds, “Such translational research, from bench to bedside, impacts patient care; with recurrent pregnancy loss, this means improving the likelihood of having a successful pregnancy outcome.”

For example, Stephenson was co-investigator of a multicenter trial in which women were injected with “white blood cells” from their reproductive partners. “This treatment had been given for over a decade, despite little evidence to support doing so,” she says. “The trial showed that this treatment was not effective; in fact, there were more miscarriages.”

Stephenson is presently focusing her research on genetic factors associated with recurrent pregnancy loss. “Looking to the future, couples with a history of recurrent pregnancy loss may be screened for miscarriage genes,” she says. “If identified, there may be a role for preimplantation genetic testing to select embryos which are not affected, which should lead to a high likelihood of success.”
Thomas Royston: Acoustical Diagnoses

THE RESEARCH of Thomas Royston, PhD, focuses heavily on how various diseases and injuries can be diagnosed by measuring the stiffness and damping of tissues through optical or magnetic resonance elastography.

“The objective, technically, is to get a map of the mechanical properties,” says Royston, head of the newly merged department of bioengineering in the College of Medicine and College of Engineering.

He’s using optical elastography to map the stiffness of the cornea, which can change in response to disease and then again in response to treatment. His use of magnetic resonance elastography, more applicable to internal organs, includes preliminary study of the brain and heart and a more in-depth look at the lungs, the latter of which Royston has a federal NIH R01 grant to study.

The lung study is part of a broader effort called the “audible human project” to develop an acoustic model of sound and vibration transmission inside and throughout the body, Royston says.

“You’re measuring vibratory wave motion. Sometimes, it’s easy to correlate that with stiffness properties,” he says, as in the liver, because it’s a large and relatively homogenous organ. “But with more complicated geometries like the heart wall or lungs, it’s extremely difficult to interpret what you’re measuring. The R01 project will develop a comprehensive computer model that will simulate how these organs vibrate.”

He’s used animal models so far, but Royston anticipates translational applications. “We’re looking at developing diagnostic methods that we intend to translate into human subject studies, and ultimately the clinic,” he says.

[Lipid rescue] is now included in the guidelines and practice advisories of a number of professional societies.”

The clinical crossover was accelerated in 2006 when New York anesthesiologist Meg Rosenblatt, MD, who was familiar with Weinberg’s publications, intervened in an unsuccessful resuscitation attempt with the recommended lipid emulsion and saved the patient.

In another case, lipid emulsion saved a patient from an extreme buproprion overdose, demonstrating for the first time that the technique also worked in cases of non-anesthetic toxicity. In that case, Archie Sirianni, MD, an anesthesiologist in Media, Pa., resuscitated a 17-year-old girl who overdosed on the drug in a suicide attempt. She went into cardiovascular collapse and had aggressive CPR for 50 minutes with her family in the room.

Finally, Sirianni asked the hospital pharmacy to deliver the lipid emulsion to the ICU. The patient was so close to death the hospital was poised to harvest her organs. She survived and recovered after the lipid emulsion was given.

“This is a great example of translational science. Guy had postulated and written about it,” Sirianni says. “I started to call toxicologists and said they had to get the information out because it had the potential to help a lot of people. In my mind it has a broader application, including petrochemicals, agriculture chemicals, pesticides and pharmacological toxicities.”

A new paper in the American Journal of Cardiology reports that lipid emulsion is effective in treating severe cocaine toxicity, which will help physicians handle the approximately 400,000 emergency room visits per year for cocaine overdose.

Weinberg notes that LipidRescue™ is used in combination with the primary elements of good Basic Life Support: oxygenation,

Guy Weinberg, MD, has come full circle to the bench 30 years after leaving his position as a basic researcher at the National Institutes of Health, prompted by the near-death of a carnitine-deficit patient from a very small dose of a local anesthetic. He has discovered a lipid emulsion treatment that reverses the toxic effects and is now bedside saving lives.
ventilation and, when needed, high-quality chest compressions. And it’s now considered a standard procedure within ACLS treatment of certain drug overdoses.

The most interesting finding related to lipid emulsion may be that the beneficial effects extend beyond the emulsion acting as a sponge to absorb the toxic drug and “likely involve the important contributions of a variety of other effects inside cells, at the cell membrane and in the plasma,” Weinberg writes on the LipidRescue website (see resource box on page 28 for URL).

LaDu, an associate professor of anatomy and cell biology, and her lab team developed an antibody and series of tests that allow identification of the earliest accumulations of one specific form of amyloid beta, oligomeric Abeta, believed to be one of the keys to the specific brain damage characteristic of Alzheimer’s. They recently reported the second part of their six-year study in the Journal of Biological Chemistry.

Further, LaDu developed a test to measure the amount of apoE bound to amyloid beta, which showed transgenic mice with apoE4 exhibit an increase in the oligomeric form of amyloid beta and lower levels of apoE bound to Abeta, compared with mice carrying the other, more benign variants of apoE.

LaDu and her colleagues validated this data in human brain tissue and cerebral spinal fluid from Alzheimer’s patients as compared with controls. Levels of oligomeric Abeta increased and apoE bound to Abeta decreased in Alzheimer’s cases and further with apoE4.

In doing so, LaDu has established biomarkers and an animal model that track progression of the disease and could revolutionize the development of candidate drugs to prevent or treat Alzheimer’s in its earliest phases. Labs around the world are currently using her mice to test promising therapeutics.

“We think the measures we’ve developed to characterize this mouse are going to carry over in humans and could possibly become

**“Translational science builds on observations**

in patients that give you insights into what you should be working out at the basic level,” says Victor Gordeuk, MD, shown administering chronic pain treatment to a patient. He has led a team of researchers at the college’s Sickle Cell Center in investigating remedies for the disease’s often chronic pain and sometimes fatal symptoms.
Biochemist Mary Jo LaDu, PhD, has spent two decades researching the risk factors for Alzheimer’s disease—most particularly the reasons why apoE4, one of three variants of the apoE gene, is the disease’s most significant genetic risk factor, making a patient 15 times more likely to contract Alzheimer’s. She has developed biomarkers and an animal model that could revolutionize drug development.

very good markers for progression of the disease,” she says. “Translational science has always been part of what we do, in that if you don’t go back and ground your observations [from animals] to what’s going on in humans, what are you chasing?”

LaDu’s approach also illustrates that academic translational research can attract young researchers who might otherwise prefer industry. For example, postdoctoral fellow Leon Tai, who has a background in drug discovery, joined LaDu’s team, enticed by the potential that her research “will ultimately identify the mechanisms underlying apoE4-induced Alzheimer’s risk.”

Gregory Thatcher, PhD, professor of medicinal chemistry and pharmacology at the College of Pharmacy, is using LaDu’s transgenic mice in his research that tests therapeutic agents targeting Alzheimer’s. “The real advantage of [her] model is that it incorporates apoE4, the major genetic risk factor for Alzheimer’s disease, associated with 50 percent of patients over 85 years,” he says. “In addition, apoE4 patients often display a differential response to therapeutic treatments.”

Sickle Cell Center researchers, for example, are studying how the disease affects the cardiovascular system and leads to often deadly pulmonary hypertension. They also are investigating the way patients perceive pain and the pathways of the excruciating, sometimes days-long bouts of pain they suffer.

“There’s research done in the laboratory at the cell culture level looking at pathways in cells, research done at the genetic level looking at expression of genes and the association of genes with symptoms and complications,” Gordeuk says. “That’s basic science intersecting with clinical problems the patients have. Likewise, the problems patients have are what are driving animal models in cell biology.”

Gordeuk is the principal investigator of a clinical study involving an agent that may prove useful for treatment of acute pain crisis in sickle cell disease, and the center is involved in multisite studies, some supported by the NIH, some by small drug companies like Emmaus, Glycoimetics and HemaQuest, to develop treatments to prevent sickle cell’s many complications, such as chronic pain and organ damage.

As part of the college’s section of hematology and oncology, the Sickle Cell Center stresses collaboration with numerous faculty members. “We have a really broad approach to treatment of the disease,” Gordeuk says. “We’d like to make real contributions to solving the problems of sickle cell disease.”

Patients like Gloria Johnson, 56, heap enthusiastic praise on the Sickle Cell Center. “I don’t know what I would do without the
Sickle Cell Center,” she says. “Patients have found out more about their health because there is a better understanding of how sickle cell works and how to minimize symptoms.”

Damiano Rondelli, MD, the director of the section’s stem cell transplantation program, has directed his research toward sickle cell disease, with dramatic results: Four of the center’s most complicated patients with sickle cell anemia essentially have been cured with stem-cell transplants. Rondelli and his team have radically reduced their risk of death from the procedure by employing a regimen that changes the immune response and improves patients’ tolerance of the transplant.

Joseph DeSimone, PhD, has capitalized on the clinical observation that sickle cell patients with higher levels of fetal hemoglobin (Hb F) that persist into adulthood have milder courses of sickle cell disease and live longer. In the lab, he has been studying the regulation of Hb F at the molecular and cellular level as well as the effects of the drug decitabine on increasing hemoglobin F synthesis.

His research with Donald Lavelle, PhD, is now being translated to human patients, who are being treated with decitabine to increase hemoglobin F in the red blood cells, thereby reducing sickling of the cells and preventing complications such as acute chest syndrome, a type of respiratory failure particular to sickle cell.

One out of every 500 African-Americans has sickle cell disease, while one of every 12 is a carrier. Given the population Illinois Medicine largely serves, the Sickle Cell Center is also a prime example of the college’s emphasis on addressing health care disparities, a concept that the CCTS also stresses in multidepartment and cross-college collaborations across the Chicago campus.

“Creating the [CCTS] made a big difference on this campus, but we’re not done,” says Larry Tobacman, MD, senior associate dean for research and CCTS co-director. “When the first discussions took place, people would stand up and say that UIUC research occurs in many separate silos. Investigators were unable to connect productively with each other. But now, such views are the exception rather than the rule. Furthermore, even basic scientists know the importance of translational application of their discoveries. The CCTS has very wide support.”

WHAT IS THE CCTS?

Center builds infrastructure for bench-to-bedside connections

THE UIUC CENTER FOR CLINICAL AND TRANSLATIONAL SCIENCE has three overarching mandates: education, research support and the facilitation of novel and collaborative approaches to clinical and translational research.

The CCTS includes five research service cores: Design and Analysis; Clinical Interface; Biomedical Informatics; Regulatory Support, Advocacy and Bioethics Core; and Community Engagement. Researchers around the College of Medicine and across the Chicago campus, who enter into multidepartment and inter-college collaborations, rely on support services such as study design, regulatory support, biomedical informatics and community engagement.

The CCTS also provides clinical research facilities and sponsors a pilot grant program, a distinguished lecture series and daylong transdisciplinary seminars to stimulate innovation and collaboration. These goals allow for clinical translational research at the University of Illinois to benefit patients, our investigators and the entire university.

Pictured above is the hard-working CCTS team that helps to bring the bench and bedside closer together across the Chicago campus.