MEETING THE CHALLENGES FACING TRANSLATIONAL RESEARCH

by Dave Hart

photos by Bruce DeBoer
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ROBERT M. CALIFF, director of the Duke Translational Medicine Institute and vice chancellor for clinical and translational research
We know more about the human body today than we did yesterday, and tomorrow we’ll know even more—a lot more. In the last two decades, advances in human genome sequencing, molecular imaging, and other areas have sparked a research revolution that reveals ever more detailed and precise information about how our bodies work. Every day brings new discoveries, many of which may hold the potential to improve human health in meaningful ways.

But the pace at which those discoveries lead to improved health has been frustratingly slow. Yes, new drugs and new therapies do reach patients, and when they do, they often make a tremendous difference. But relative to the number of research projects conducted, papers published, and trials run, it is clear that new health care advances have lagged behind the vast amounts of data generated by the explosion in biomedical discovery.

Duke is playing a lead role among academic medical institutions working to change that. On multiple fronts, and in collaboration with partners within the university and nationwide, Duke researchers and clinicians are exploring ways to increase the speed and efficiency with which research discoveries are translated into advances in patient care.

Last October, the National Institutes of Health awarded the Duke Translational Medicine Institute a five-year, $47 million grant to help fuel that effort. The Clinical and Translational Science Award (CTSA) provides wide-ranging resources for clinical researchers at Duke and an infrastructure that supports sharing developments across a consortium of more than 60 other research institutions nationwide. The award represents a renewal of the grant that Duke received in the initial round of CTSA funding in 2006.

“Our vision is to create a research environment at Duke that links discovery science with a creative engine that can accelerate the development of new technologies based on scientific merit and societal need to improve public health,” says cardiologist Robert M. Califf, MD, T’73, MD’78, HS’78, ’80-’83, the Donald F. Fortin, MD, Professor of Cardiology, director of the Duke Translational Medicine Institute and vice chancellor of clinical and translational research.

There are many challenges to closing the gap between new knowledge and new therapies, says Califf.

“If you look at drug development, the failure rate is over 95 percent. So an enormous amount of money is being spent nationwide on things that don’t work. We have to get better at predicting what will be successful.”

ROBERT M. CALIFF

Califf says there may be something else at work too: the questions researchers are trying to answer have gotten harder.

“Look at how many advances in medicine we’ve had in the past century,” he says. “There has been a 40-year increase in life expectancy. That’s remarkable, but we see that rate of progress slowing down. It may be that the easier problems have been dealt with, and what we’re tackling now are the much more difficult ones, where progress is much more incremental.”

The process of translating laboratory discovery into patient care—often referred to as a “bench to bedside” process—is more complex and more varied than it might first appear. At Duke, researchers are approaching translational research from various angles and coming up with innovative ways to overcome the many challenges.

TEAM SCIENCE: BENCH TO BEDSIDE

When Bruce Sullenger, PhD, began working to try to develop a new anticoagulant drug made with the ubiquitous molecule ribonucleic acid (RNA) to prevent dangerous blood clots in patients during cardiac or vascular surgery, he quickly learned that he was only addressing half the problem.

“Some of the cardiologists pointed out that the challenge wasn’t inhibiting blood clotting,” says Sullenger, the Joseph W. and Dorothy W. Beard Professor of Surgery and director of the Duke Translational Research Institute. “The challenge is that when you inhibit blood clotting you also create the safety risk of excess bleeding. It’s like one of those angry emails you send out and then wish you could pull back: you give a patient an anticoagulant, and then they start bleeding and you need to quickly pull it back. It’s a fine line.”

Using RNA’s innate capability to act as a sort of molecular switching mechanism, Sullenger managed to walk that line. He found a way to make
both a novel blood thinner and its own antidote: a companion molecule that would bind to the first and very quickly produce the opposite effect.

“With this new discovery, we not only could give a drug to inhibit clotting, but if the patient started to bleed we could give a second drug, also made of nucleic acid, to reverse it rapidly,” Sullenger says.

Sullenger founded a company, Regado Biosciences, to raise the capital to continue development and trials of the new drug, called REG1. REG1 is currently in a phase 3 clinical trial of more than 13,000 patients, and the company went public last fall—one of four Duke biomedical spinoff companies to do so last year. In early March 2014 the Food and Drug Administration (FDA) designated REG1 as a “Fast Track” development program with the goal of making it available for use in patients sooner.

It’s a classic example of bench-to-bedside research—but the journey, like most similar ones, has been anything but fast and inexpensive. Sullenger began work on the project well over a decade ago. Data suggests that taking just one discovery from the lab to development and delivery to patients costs millions if not billions of dollars.

Among the things he has learned is that it takes a lot more than just scientists to shepherd a novel therapy along the translational path. You can’t just focus on molecules, physiology, and potential clinical applications. You also have to think—and this may not come naturally to a lot of scientists—about venture capital.

“The drug has worked as well as you could hope, but it’s taken longer than I would have thought, because you have to raise money,” says Sullenger. “There’s a whole business side of it. It costs so much money that you have to go outside the university. You need a critical mass of innovators and...
entrepreneurs to move these things forward. Translation is team science. It’s fundamentally different than being a scientist working alone in an ivory tower lab. Collaboration is critical.”

The Duke Translational Research Institute that Sullenger directs is designed to support and facilitate translational research. The institute, established with the initial CTSA grant, awards pilot grants and helps researchers move projects through the pipeline, identify potential funding sources, negotiate the regulatory maze, and tap the expertise and collaboration of project leaders in many fields.

That last part is one of the things Duke does best, Sullenger says. “Duke is leading in the area of putting teams together,” he says. “We try to find the best people from the private sector who know the culture of pharma or business or biotech and bring them here. They come back to Duke because they believe in this mission: We’re discovering all this stuff, now we have to figure out how to use it to help people. A lot of other institutions are struggling with that. We’ve changed the culture that way, and it’s really helping us.”

That’s not to say it’s going to be easy, or quick. But Sullenger is optimistic. “There is a recognition nationally that this is a need,” he says. “CTSA is the biggest program in the NIH, and it was federally mandated by Congress because taxpayers said, ‘We’re putting billions of dollars into biomedical research, and what is the outflow?’”

“I think one thing people are learning is that biology is much more complicated than they may have thought. The idea that because we can sequence the genome we should suddenly know how to cure all these diseases is pretty naïve. There’s not going to be a short-term fix. It’ll be a long process, and it’s going to take a sustained effort. But I think we’re going to get there.”

RESEARCH THAT MAKES A DIFFERENCE: CLINICAL TRIALS

Newborn babies who develop potentially fatal intra-abdominal infections are often treated with an antibiotic called meropenem. Until recently, though, no one really knew what the most effective dose was for infants less than three months old, or even whether it was truly safe to treat them with the antibiotic: in adults, similar compounds have been linked to seizures.

Thanks to the Pediatric Trials Network (PTN), a $95 million National Institutes of Health initiative headed by Danny Benjamin, MD, PhD, MPH, HS’98-’01, professor of pediatrics and faculty director of trials at the Duke Clinical Research Institute, we now have answers to those questions. And we are gaining answers to similar questions about many other drugs used in children.

The NIH tapped Benjamin to lead the PTN, a nationwide initiative designed to close a critical loophole in drug regulations: the lack of pediatric dosing and safety standards for off-patent, or generic, drugs.

In the absence of such standards, pediatricians have to rely on their experience and expertise to prescribe these medications. Empirically tested and approved dosing guidelines would lead to safer, more consistent, and more efficient use of such drugs in children.

“Twenty years ago, in pediatrics we simply took the adult dose of a drug, divided by 70, and gave it on a milligram-per-kilogram basis,” Benjamin says. “Now that seems laughable. But it’s still the case with a lot of these off-patent drugs. We’re fixing that.”

Under Benjamin’s leadership, the PTN is in various stages of generating data to guide the pediatric use of more than two dozen drugs. In the case of meropenem, Duke’s Michael Cohen-Wolkowiez, MD, HS’09, associate professor of pediatrics, and P. Brian Smith, MD, MPH, MHS’06, HS’01-’07, associate professor of pediatrics, led a study of 200 young infants. Among the questions the investigators wanted to answer: What is the safest and most effective dose? Does the drug increase the risk of seizures or other serious side effects? And does it reach the brain?

“In babies, infections in the blood go to their brain,” says Benjamin. “If you use a molecule that’s only good in the blood but doesn’t reach the brain, you’re going to have a baby that might look better but really has that bug still in the brain, as meningitis. And you do not want that.”

The trial’s findings? Meropenem is safe to use in very young infants, some babies should get a higher dose than had been customarily prescribed, there is no statistical correlation between the drug and seizures, and, yes, it does work in the brain. The FDA is in the final stages of requiring re-labeling to reflect the findings.

“This will change the way people dose the molecule, and it changes the safety profile,” Benjamin says. “This is research that is going to make a difference.”

That, in essence, is the definition of translational research. Clinical trials are one of the stepping-stones in the translational path. And, as every medical researcher knows, trials are not easy, quick, or cheap.

“Taking molecules through clinical testing takes so much planning and infrastructure and thoughtfulness and
finances that it can seem daunting,” says Benjamin. “But if it were easy, everyone would do it, right? Despite the shortcomings, we’re headed in the right direction.”

Clinical testing involving newborns is especially difficult, and Benjamin and his team encountered a lot of skepticism about their chances of designing trials for very young infants that would produce sufficient reliable data.

“People said, ‘You can’t draw enough blood from neonates because they’re so small,’” says Benjamin. “So we did a lot of technical work to develop viable microsamples. Then people said, ‘You can’t find enough moms who will consent to having blood drawn from their babies so much.’ So we worked it out so that we only draw blood when the babies are giving blood anyway for glucose or other checks, and the moms started consenting. Then people said, ‘You won’t be able to interpret the data correctly.’ So we developed mathematical models to interpret the data correctly. Then they said, ‘Well, you can’t upscale it.’ So we showed we could do it across several dozen molecules, and for each molecule we did it across several hundred babies.”

On and on it went. For every apparent hurdle, Benjamin and the other researchers came up with a solution.

“We get ‘You can’t’ a lot,” says Benjamin. “We’re good with ‘You can’t.’ Because yes, you can. And not only can you do it, but we’ve done it.”

The procedures Benjamin and the investigators developed for conducting trials with newborns were so successful that the FDA recently asked him to bring a team of researchers to Washington, D.C., to share their trial template and the lessons they’ve drawn.

The investigators told the FDA’s anti-infectives unit how they designed their trials for newborns and offered advice that might help guide future trials. They also shared their findings about which drugs tested in adult and older pediatric studies for various indications could safely be extrapolated for use in infants, and which could not.

“We showed the FDA, ‘Here’s how we did it with various molecules,’” says Benjamin. “It’s up to the FDA to decide what to do with that in terms of requirements and enforcement. The drug companies may tell them, ‘We can’t do that.’ But it seems to me that if a couple of guys from Duke can do it, so can a major pharmaceutical company.”

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EBONY BOULWARE, chief of the Division of General Internal Medicine
interventions actually reach and benefit the people who need them, and do interventions that work in a controlled research environment work in a real world setting? There’s a lot of great research being done in academic settings, but if it doesn’t get out into the community and to the patients it’s designed to help, it’s not helping anyone.”

The test of meaningful translation, Boulware says, depends on successfully navigating that final step. “This is the last mile on the translational research spectrum,” she says. “Our ultimate goal in health care is for the things we learn in our research to be practically applied in communities in ways that matter to patients. That really is the last mile of the journey.”

It’s a particularly challenging step. The potential barriers between promising treatments and the people who could benefit from them, especially those in underserved populations, are legion. Bridging the last mile requires, among other things, access to services, effective communication between patients and health care workers, mutual trust, coordination of care, commitment by policy makers, and mechanisms to ensure sustainability over time.

Every one of those issues presents its own challenges, says Boulware. “We have a lot of research showing various interventions to be in one way or another efficacious, meaning it works in an ideal research setting,” she says. “We have much less effectiveness research, meaning, ‘Does it work when you take it out of that ideal setting and into the real world?’”

Boulware, who earned her medical degree at Duke in 1995, returned to join the faculty in October 2013 from the Johns Hopkins University School of Medicine. In Baltimore, she conducted several NIH-funded studies of ways to improve the effectiveness of health care for patients, including a study exploring the real-world effectiveness of home blood pressure monitoring for African-American patients with hypertension. At Duke, she joins an institution that is one of two leading the Southeastern Diabetes Initiative, a $10 million Health Care Innovation program that collaborates with community partners to use geospatial mapping, electronic records, and a specially trained workforce to reduce death and disability from type-2 diabetes among at-risk populations.

Boulware says one lesson from effectiveness research stands out above all the others: the importance of ongoing community engagement in biomedical research. That engagement, she says, should start before research actually begins and continue after it is complete. “Traditionally we, as academic researchers, decide what the priorities for research are,” she says. “We decide what diseases to study, and we say, ‘OK, what are the biomedical questions we need to answer to cure this disease?’ But we rarely go into the community first to find out what health care needs they want addressed.

“Communities are familiar with researchers coming and gathering people up for studies and then saying, ‘OK, thanks very much, we have our results and we’ll go ahead and publish those,’ and then the researchers are gone. We need to engage with communities throughout the research process, from identifying health care needs to participating in the research and then in the dissemination of research findings. Can ideas be jointly generated so the research answers the questions the community needs answered? And can results not just be published in a biomedical journal but also put into lay language and shared with the people who helped generate it and will ultimately use it? Thinking about research this way takes the focus away from just the researchers and shifts it more toward a partnership with communities.”

With the changes accompanying the Affordable Care Act, Boulware says she has arrived at Duke at the perfect time to tackle the challenges of the last mile. “It’s a very dynamic time right now in health care, so it’s a very dynamic time for research,” she says. “As the health system adapts to accommodate these policy changes, it’s a good time to examine how we can provide the types of care that provide the greatest benefits to patients, families, and their communities. And, really, that’s what we’re here for.”