Nationally, the ecosystems that support getting scientific discoveries into the clinic have been pretty fragile. A few years ago, the NIH stepped in to help.

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SURVIVAL OF THE FUNDED

BACK FROM THE BRINK OF EXTINCTION

BY ELAINE VITONE

It begins with a good idea. With a little luck and a lot of sweat, this idea grows into a fully realized and hard-won laboratory discovery. Then, with more luck and, yes, more sweat, that good idea in basic science could develop to become a human trial and gestate for a while, experimentally, in the clinic. And, with time, effort, resources, and sweat, sweat, sweat, it could prove its worth—improve patients' lives—and gain acceptance in the medical community. Eventually, our brave young idea could mature into an advancement that improves human health on a grand scale.

This is translational science—a bit of a buzz term, really. Simply put, it's the process by which researchers work to bring new science to the clinic. One key group of researchers on whom we've relied to do this—physician-scientists, the MDs who

both treat patients and study their ailments—are a vanishing breed. And with their staple food—federal research funding—in such short supply, it's no wonder.

Not only that, but medical research has become extremely complex. This has made it more difficult to learn all the skills needed "on the job," as Elias Zerhouni, former National Institutes of Health (NIH) director, notes in a 2005 *New England Journal of Medicine* op-ed. Increasingly, translational and clinical research relies on technology and on specialization in multiple areas. Thus, game-changing discoveries in medicine often emerge from novel partnerships—people from disparate disciplines coming together to dream up entirely new approaches to old problems.

Of course, the business of getting hatchlings out of the lab and into the clinic requires money to support the professionals who undertake years of study and training. It requires money to staff and sustain labs. Money to recruit patient volunteers; collect samples from them; and crunch, troubleshoot, and interpret the data. Biomedical and behavioral research eats funding as insatiably as a round-the-clock noshing newborn.

But what's even more costly? Scientific inertia. Good ideas stuck forever in the nest.

The stakes are high. Zerhouni notes in his 2005 op-ed that this country's medical and public health practices "must undergo a profound transformation in the coming decades if we are to succeed in providing access to care for all Americans at reasonable costs."

In 2006, the NIH created a special set of funds to support the delicate ecosystem that scientists who do this work need to thrive. Among their longest-running awardees is the University of Pittsburgh–based Clinical and Translational Science Institute (CTSI). Pitt and its local partners have received some $150 million for its CTSI since 2006. Today, CTSI supports hundreds of researchers by funding pilot studies, core laboratories, statistical support, regulatory assistance, study-volunteer recruitment, education for researchers at all stages of their careers, and more.

In addition to doing its level best to incubate physician-scientists and their partners, CTSI has helped make Pitt a hospitable environment for getting great ideas into the clinic.

Robert Arnold, the Leo H. Criep Professor of Patient Care and professor of medicine, says CTSI resources have been invaluable in supporting his own translational science efforts. And, more importantly, the institute's education programs (18) deserve credit for Pitt's success in attracting a number of stellar junior faculty and fellows to his department.

"To go someplace that has a fabulous group that has organized mentoring and meetings every month, where people get to present their research, where they have grant reviews and they urge people to involve statisticians early in their project? That's a great way to make sure the project is structured so that it's most useful and most likely to get good results.

"There are few places in the country that have that. It's so hard to get funded. These are the things that help people succeed."

Throughout the last six years, CTSI has provided crucial support in such discoveries as the possible gene-regulation role of usRNAs (small strands of RNA once dismissed as molecular junk) and the part polyomavirus plays in Merkel cell carcinoma.

A few years ago, CTSI helped a team of researchers try an experimental treatment for paralysis—a brain-computer-interface device, in its first-ever human test drivers (patients with epilepsy who volunteered to have their neurological signaling studied during hospital stays for seizure-mapping). CTSI seed money and regulatory support helped the researchers land an NIH grant, and, long story short, the researchers' hard work culminated in October in an exciting moment: A man with paralysis moved a robotic arm with his thoughts, reaching out to his girlfriend's hand for the first time in seven years. (See our Investigations story in the Spring 2012 issue.)

And the good ideas keep germinating. Here are just a few examples of translational science research coming of age here at Pitt.

Finally Airborne

Twenty years ago, Don DeFranco and Selma Witchel (MD '78, Fel '83) began their translational science journey at, of all places, a little league game in Churchill, Pa. They were sitting on the sideline—each had a son in the game that they were pretending to watch.

"We were taking turns to see who was at bat," admits Witchel.

"We were both reading articles," says DeFranco, "and I looked over, and her article had words that I recognized."

Ever since, DeFranco, a molecular endocrinologist and professor and vice chair of education in Pitt's Department of Pharmacology and Chemical Biology, and Witchel, associate professor of pediatrics and director of the pediatric endocrinology fellowship program at Children's Hospital of Pittsburgh of UPMC, have wanted to collaborate on their common ground—glucocorticoids and steroid physiology.

Often, in response to sepsis and traumatic brain injury, blood levels of free cortisol—a steroidal hormone that (among other functions) keeps inflammation in check—increase. For good reason: Inflammation can be a critically ill patient's undoing. But some patients have much lower total cortisol levels than others. So, in the 1970s, researchers tried administering drugs related to cortisol (synthetic glucocorticoids) to patients with lower levels of the hormone; the researchers found that some improved. But in the coming years, other studies showed that there were too many complications, including infections and high blood sugar. The practice has been debated in the literature ever since, its favor swinging back and forth like a pendulum.

Today, glucocorticoids are again used in these critically ill patients, albeit in smaller doses than they were 40 years ago. Yet the debate has hardly been put to rest. "Some patients it helps, some patients it doesn't," says DeFranco. "There's still no consensus about how to best evaluate for adrenal insufficiency during clinical illness."

DeFranco and Witchel thought: Rather than the amount of total cortisol in the bloodstream, wouldn't it be more helpful to know how cortisol interacts with these patients' immune cells—how well it's doing its job, at the molecular level?

Interdisciplinary collaborations are among the hardest to get off the ground. To win a federal grant, you need pilot data to prove your idea has wings, and that takes money. Ideally, you have a larger effort to draw on—a big, preexisting, funded study that dovetails into a little spinoff study. First-of-their-kind, fledgling ideas generally aren't so lucky.

Such was the case with DeFranco's and Witchel's brainstorming. Then they heard about a CTSI pilot fund for investigations exploring new territory and promoting new research partnerships. Right around the same time, Cristina Candido-Vitto (Fel '09), then a fellow, expressed interest in doing the legwork for such a project. The team applied for and received their award in 2008 and, after years of talking about it, finally got to work.

The researchers studied white blood cells taken from pediatric critical-care patients (using very small samples, collected while

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What's more costly than the business of moving breakthroughs from the lab into the clinic? Scientific inertia. Good ideas stuck forever in the nest.

other blood draws were already being taken, so as not to interfere with care). They looked at what was actually going on within the cell: Were glucocorticoid receptors in the right places, in adequate numbers? Was cortisol binding to them in the cytoplasm, then moving to the nucleus—all-important steps that enable a molecule to give the cell its marching orders?

They found that the glucocorticoid receptor protein maintained some function—it was indeed binding to the hormone and moving from the cytoplasm to the nucleus. However, in these critically ill patients, the level of receptors and their ability to bind were decreased in the early stages of illness.

"It looks like these kids don't have the capacity to respond to glucocorticoid therapy," says DeFranco.

"The physiologic significance of the decreased number of receptors is unclear. ..." says Witchel. "[Still] they're missing part of the effector mechanism they need to get a response."

The team has written a review article on the topic. They hope their findings might eventually contribute to a better blood test and take

the guesswork out of who stands to benefit from anti-inflammatory hormones, what dosage is beneficial, and how long patients should continue the therapy.

Before CTSI's pilot-funding program and others like it across the country, there were no federal mechanisms to bring good ideas like DeFranco and Witchel's to fruition. Apart from a few very targeted grants, there was virtually no way to fund a mini-proof-of-concept project to demonstrate whether a study was worthy of funding. It was classic chicken and egg.

"Without CTSI," says DeFranco, "this would have been just another dinner conversation."

Different Feathers

Say you are unlucky enough to have a bad fall, or a run-in with a piece of construction equipment, or any of the other cringe-worthy scenarios that could eventually land you in recovery from orthopaedic surgery, waking up with what arguably amounts to the worst of the worst of post-op pain. The good news is that you live in a time when there are drugs available to keep you comfortable. For most people, opioids are very good at lulling a profoundly traumatized body.

But for some people, they're so good that the body neglects one all-important function: breathing.

At that point, an alarm sounds—a signal that your blood-oxygen level is too low. The team of nurses caring for you leaps into action. They'll lift your chin and draw your jaw uncomfortably forward—to open your airway and, more importantly, to annoy your groggy body into breathing again. If they have to, they'll put an endotracheal tube down your throat.

If all else fails, you'll receive what's called an opioid rescue. Naloxone, a common option, will nix that whole not-breathing thing for a full hour. Problem is, it will also get rid of what you, on that most unlucky day, want most: pain relief.

Genetic and other factors that contribute to how well opioids manage individuals' pain have been widely studied—but not the risk factors for respiratory depression. Which means we have absolutely no way of knowing who is in for a particularly rude awakening after surgery.

"I did the math," says Will Lariviere, assistant professor of anesthesiology and neurobiology in the School of Medicine, "and it turns out there's a quarter-million Americans getting a naloxone rescue for profound respiratory depression each year—and that's based on conservative estimates."

Lariviere is an expert in the responses to pain and analgesia and the interactions between stress and pain systems—in animal models. But how respiratory depression looks in the clinic never really came to life for him until a few years ago, when a colleague introduced him to nurse anesthetist Rich Henker, a professor and international education coordinator for acute and tertiary care in the School of Nursing. They got to discussing recovery in the postoperative environment.

"Every time we met," says Lariviere, "I would realize, *Oh my gosh, the nurses are running around like crazy trying to keep people breathing.*"

"Will brings new perspective to my clinical [experience]," says Henker. "I don't think about it. I'm like, *Well, no, that's just what we do.*"

The problem with opioid-induced respiratory depression has been cited numerous times in nursing literature. And now, thanks to a 2009 CTSI pilot grant, this unlikely pairing of a bench scientist and a nurse anesthetist is finally confronting a problem that peer-reviewed literature aimed at MDs has yet to address: A side effect of analgesia, respiratory depression, is actually dictating the quality of care that some patients receive.

Lariviere is hunting for relevant genetic targets in animals; Henker is testing for those targets in humans—orthopaedic-surgery patients with lower-limb fractures, to be precise. So far, they have identified several distinct genotypes that respond uniquely to opioids, either in terms of analgesia, respiratory depression, or both. They have presented their findings nationally and published twice in *Biological Research for Nursing*. Their work is ongoing while they apply for larger grants from the NIH.

The goal, says Henker, is to tailor analgesia for optimal effects. Who needs more opioid, who needs less? And whom can they flag, based on genetic risk factors, as a patient who would fare much better on a nonopioid medication?

"The goal is to try to get rid of pain for these people."

Eagle Eye

Melanoma is unique among cancers in that it's right there where you can see it—a new mark on your skin, a visual reminder that you've got to get it checked out. The rub is in the getting-it-checked-out part. Most often, you'll see a primary care doc, who then has to decide whether to call a dermatologist. Who will then decide whether you need a biopsy. Which will take time to process in pathology. And all the while, the clock is ticking.

"Melanoma can grow from a curable lesion to an incurable one while you're waiting for an appointment," says Laura Ferris, an MD assistant professor of dermatology.

False-alarm biopsies cause patients undue expense, not to mention discomfort and worry, and that thought weighs heavily on the mind of your front-line clinician. But what if there were a virtual second opinion available, a tool to aid in the determination of whether to biopsy you right then and there?

Ferris is working with Mahadev Satyanarayanan, professor of computer science at Carnegie Mellon University, on a new use for his Web-based application, dubbed Diamond. The application can take any image you give it, compare it to others in a database, and display the ones it most closely resembles. Diamond has already been deployed in a number of ways, from clarifying mammogram results to spotting terrorists in video-surveillance footage.

Ferris has uploaded some 1,000 images of UPMC patients' skin lesions with known biopsy results (with patient identities removed). Funding from CTSI's Novel Technologies Core—which supports new biotech efforts—allowed the researchers to hire a programmer to harness this resource for melanoma screening. Once complete, this latest iteration of Diamond will be able to find the image best resembling a new lesion's unique features—shape, color, pigment patterns, blood vessels, and so on. In addition to its great potential as a diagnostic aid for both primary docs and dermatologists, it's a promising dermatological teaching tool.

And yet it almost didn't happen.

Ferris and Satyanarayanan began the project at a privately funded laboratory. That arrangement fell through when it became clear that their mission—to make Diamond open-sourced, for anyone to use and benefit from—didn't jibe with that of their sponsor.

CTSI's Novel Core was uniquely suited to the project, says Ferris. "There's really not a lot of funding to help you sit down and build something like this from scratch." ■

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Since its establishment six years ago, CTSI has enabled investigators to conduct 5,200 studies.

CTSI: A BIRD'S EYE VIEW

The University's Clinical and Translational Science Institute (CTSI), a National Institutes of Health (NIH)–funded effort, helps get clever ideas off the ground. With its support, Pitt has become an incubator of physician-scientists and others engaged in bringing promising discoveries to the clinic, where they can help patients. Here are a few ways CTSI is feeding the flock.

• CTSI's Institute for Clinical Research Education has grown into one of the premier clinical and translational research training programs in the country, now offering 18 academic career-development programs for grad students, med students, residents, fellows, postdocs, and faculty in all phases of their careers. For example, in 2011, CTSI's PhD Program in Clinical and Translational Science graduated its first three students. Another 11 are in the queue. (The Institute has even engaged more than 9,000 high school students. CTSI runs a mobile science lab—it's a truckload of fun.)

• In the past six years, CTSI programs enabled 2,100 investigators to conduct 5,200 studies.

• Last fiscal year, CTSI-funded facilities provided quantitative analysis of more than 6,000 clinical samples, bioinformatics analysis for 43 studies, and assistance with regulatory compliance for 69 investigators.

• Each year, CTSI fills more than 150 requests for assistance with study design, biostatistics, and epidemiology support.

• ProDy, a free and open-source molecular-systems-modeling software package (developed by Pitt's Ivet Bahar with CTSI support), has been downloaded more than 10,000 times in the past two years.

• At last count, there were more than 34,000 people enrolled in the CTSI Research Participant Registry. *—EV*