TRANSLATIONAL SCIENCE

NCATS: Getting Insights Through the Risky "Middle Zone" to Drug Development

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WHEN ASKED WHY DRUG prices are so high, manufacturers offer some version of the same answer: the cost of research and development. Although there is debate over how much it actually costs to bring new therapies to market, a 2016 study by Tufts University put the price tag at $2.56 billion (in 2013 dollars), and researchers found costs were rising 8.5% a year.[1] Failure rates of drugs also contribute to their high prices. A 2018 paper coauthored by Andrew Lo, PhD, of the Massachusetts Institute of Technology found that the probability of success in clinical trials was 13.8%, but the success rate within just oncology was 3.4%.[2]

Why do so many promising findings fizzle out before they become cures? What can be done to boost success rates—and perhaps, over time, slow the rise in drug development costs? A lot, it turns out, because for a long time improving the process of taking basic science from the laboratory to the point of affecting public health—the task of science translation—took a back seat. However, since 2012, this has been the mission of the youngest branch of the National Institutes of Health (NIH), the National Center for Advancing Translational Sciences (NCATS).[3]

NCATS plays a different role than its fellow institutes, which typically focus on an organ system or a group of related diseases. As Christopher P. Austin, MD, director of NCATS, explained in an interview with *Evidence-Based Oncology*™, "Our 'disease' is the translational process—that is, getting from a fundamental insight to an intervention that is available to all the people who need it."

That means NCATS doesn't stop once a new scientific process or therapy is developed; its mission calls for bringing change "all the way out to the public health level," Austin said.

NCATS' researchers look for ways to speed up the translational process, to devise new methods to make the critical leap from the basic insights about disease to the premarket clinical trials that have, for good reason, historically been the work of private industry. This "middle zone"—as NIH Director Francis Collins, MD, described it in a 2011 commentary that laid out the vision for NCATS[4]—is where "attrition rates for candidate products are horrendously high," yet the methods of translation had not seen the same level of innovation found in other scientific realms.

When projects fail at this stage, Austin said, "about half the time they fail because of hard science reasons; perhaps the new drug has a toxicity that wasn't expected. But projects fail about half the time not because of hard science reasons, but because of soft science (sociological issues, finance, IP [intellectual property]),," all things that are part of the translational effort that NCATS is designed to address.

Thus, a major purpose of NCATS is to provide support at the preclinical and early clinical stages; another is to create platforms to launch many types of research that would otherwise fail, sometimes because the level of uncertainty in the early stages is simply too high to attract investment, especially if the therapy would treat very few patients. NCATS has a division that focuses on rare disease and another that forms strategic partnerships. At its outset, the agency was given control of the Cures Acceleration Network, and in 2016, the 21st Century Cures Act empowered NCATS to support clinical trials through phase 2 for all diseases and through phase 3 for rare diseases.[5]

Although NCATS' mission is not expressly tied to the cost of drugs, Austin said the current focus on cost, which has "always been simmering in the background," has brought the plight of patients with cancer and rare disease to the forefront in a dramatic way.

"There are many successes and many more drugs," he said. "But what hasn't changed is the cost of production, which is inexactly related to pricing." Drug prices necessarily fold in multiple other factors, "only one of which is the cost of production."

The predictability of developing a therapy, and the fact that the cost of developing a therapy is driven largely by failure, has remained largely the same, Austin said. "Our ability to predict the overall success of a translational project has changed very little, and although financing has become easier at both NIH and in the private sector, it still remains an example of extreme risk. The only way to make therapeutic development more attractive, is to make the cost of capital lower by making it more predictable, and that means understanding the general principles that drive success in the process."

The following are some examples of NCATS programs and projects:

Getting From Preclinical to Clinical Trials. The BrIDGs Operational Model (for Bridging Interventional Developmental Gaps) makes NCATS staff available to collaborate with researchers who need help making the jump to the clinical trial stage and meeting investigational new drug application requirements to file with the FDA.[6]

Repurposing Existing Molecules. In 2018, NCATS funded 3 academic–industry partnerships that will examine new uses for existing molecules. In one partnership, Duke University and the National Cancer Institute will test a new strategy to prevent graft-versus-host disease in patients who receive stem cell transplants, using AZD9668, an AstraZeneca compound that blocks neutrophil elastase. The project will involve a series of preclinical and clinical trials.[7]

Using High Throughput Screening. A 6-year collaboration between NCATS and Charles Serhan, PhD, DSc, of Brigham and Women's Center for Experimental Therapeutics and Reperfusion Injury, came to fruition with the publication of a paper in *Cell Chemical Biology*.[8] Back in 2002, Serhan and his team discovered resolvins, which are byproducts of omega-3 fatty acids, and developed knowledge of how they reduce inflammation. They knew resolvin D1 reduced inflammation in the nervous system through a specific protein, GPR32, but sought help from NCATS to find other molecules that were more stable and could do the same thing. NCATS scientists used high throughput screening to sort through 48,000 compounds for candidates able to activate human GPR32 receptor. They found 2 known molecules and 2 novel chemical structures, which could lead to new drug development possibilities for patients who have suffered spinal injury or stroke.

Modernizing translational science under the umbrella of NCATS means that much of what is discovered can be used by everyone in the pharmaceutical industry, Austin said. But NCATS is unique in the degree to which it collaborates with industry, and the institute has systems in place—some based on work that predate NCATS—that spell out how intellectual property issues are managed. "We have programs where half the collaborators are companies and half are from academia," he said.

Because NCATS is focused on finding solutions rather than seeking an immediate return on investment, its researchers can take on larger problems that span across many diseases. The agency can therefore ask scientific questions that industry knows are worth exploring, but can't justify spending investor money pursuing. And the answers belong to everyone, Austin said.

"We are a force multiplier," he said. ◆

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