New NIH Center Broadens Scope of Translational Research

By Susan Jenks

Nearly 30 years after auranofin gained approval from the U.S. Food and Drug Administration to treat rheumatoid arthritis, researchers are repurposing the drug for a possible new use: chronic lymphocytic leukemia (CLL). Moreover, the arthritis drug could emerge as a model for accelerating patients’ access to other repurposed drugs or for rescuing drugs that the pharmaceutical industry has abandoned and now are languishing on companies’ shelves, researchers say.

“What we did was go from in vitro experiments directly into patients,” said Scott Weir, Pharm.D., Ph.D., director of the Institute for Advancing Medical Innovation at the University of Kansas Medical Center, one of several test sites nationwide, which soon will include the National Heart, Lung, and Blood Institute.

“We didn’t feel we needed to go through the traditional drug paradigm,” he said, given auranofin’s earlier testing for safety and efficacy.

As a result, less than 2 years after scientists discovered that auranofin could kill CLL cells in the lab, researchers began dosing the first relapsed CLL patient in a clinical trial. That compares with, on average, 8–10 years to reach a similar stage in drug development for a new drug, according to Weir, one of several authors of a recent commentary in Cancer Research about the pilot project.

The repurposing of older drugs such as auranofin, as well as second looks at unapproved agents stuck in the regulatory pipeline, is part of an intense systematic approach to translational research embodied in the first new center at the National Institutes of Health in more than a decade. The National Center for Advancing Translational Sciences (NCATS), which replaced the National Center for Research Resources earlier this year, incorporates many of the former center’s programs.

In particular, NCATS takes over the Clinical and Translational Science Awards, which funds a national consortium of 60 medical research institutions and still is at the heart of the NIH mission to turn research discoveries into new therapies for patients, said Thomas Insel, M.D., the center’s acting director and director of the...
National Institute of Mental Health. The consortium also receives $487 million of the $575 million budget that Congress approved for fiscal year 2012.

“Clearly, this is a new entity,” Insel said, describing the center’s essence as shifting programs and grants from across NIH’s 26 other institutes and centers. “We’re addressing areas of research that are not being addressed and attempting to find cures for diseases that are not being pursued.”

Among them is schistosomiasis, a chronic parasitic disease in the developing world, which Insel says is one of the center’s first big efforts, despite little expectation of financial reward.

Cautious Beginnings
In proposing NCATS’ creation in late 2010, NIH Director Francis Collins, M.D., Ph.D., met initial resistance from several scientists, including one member of NIH’s Scientific Management Review Board, Jeremy Berg, Ph.D., former director of the National Institute of General Medical Sciences, who suggested that the idea had been drawn up too hastily. Others, such as William Talman, M.D., a neuroscientist at the University of Iowa and former president of FASEB (the Federation of American Societies for Experimental Biology), warned that the result could be another bureaucratic layer, rather than smoothing the bridge between basic and clinical research.

Since then, however, with the center operating, and the dissolution of its predecessor complete, a wait-and-see attitude seems to prevail. A FASEB spokesperson said the federation would have no further comment, and Berg—now at the University of Pittsburgh as the first associate senior vice chancellor for science strategy and planning in the Schools of Health Sciences—also indicated through a spokesperson that he had nothing more to say.

But at congressional hearings in March on NIH’s proposed budget for the coming fiscal year, several earlier concerns resurfaced. Denny Rehberg (R-Mont.), chairman of the House Appropriations Committee’s subcommittee on labor, health and human services, and education, questioned whether the new center’s emphasis on translational research might overshadow NIH’s core mission of basic science.

“We do not want to wake up in the future to find an NIH director without a basic stable full of science available for translation because we took our eye off the ball of basic science,” Rehberg said in an opening statement.

And Roy Vagelos, M.D., chairman of Regeneron Pharmaceuticals and retired CEO and president of Merck, said he did not believe the new center could solve drug-development hurdles that the pharmaceutical industry—spending some $50 billion annually—already attempts to address. Money for NCATS would be better spent on support for young researchers in academia, which he said was flagging.

Not everyone agreed. Scott Koenig, M.D., Ph.D., president and CEO of Macrogenetics, a private biotechnology company, described NCATS as a unique opportunity to identify and validate new drug targets that industry has no financial incentive to pursue, as well as predict toxic effects for humans, among other stated goals.

Collins, for his part, assured congressional leaders, as he has before, that the center’s mission is complementary, not competitive, with private industry. And he said the biomedical research agency’s commitment to basic research has not changed in decades, nor will it.

Whatever reservations still dog the newest entity on the NIH campus, Insel’s appointment as acting NCATS director predates most of them. He was appointed in December, he said, several months after the hunt for new leadership began. A list of candidates for the center’s director is expected to reach Collins’ desk soon, but Insel’s name won’t be on it.

“I have a full-time day job, and I’m ready to go back to it,” Insel said.

Accelerating Drug Development
By centralizing the process by which basic research discoveries move from the lab to the patient’s bedside, NCATS seeks primarily to improve the success rate for new drug development, which Collins and others characterized as “dauntingly low.”

And some see that, over the past decade, that success rate has gotten worse. Not only are fewer new drugs coming through the pipeline, but blockbuster patents are also ending. This trend creates a crisis in the pharmaceutical industry, which is struggling, even as our understanding of the molecular basis of disease increases, said Lans Taylor, Ph.D., director of the Drug Discovery Institute at the University of Pittsburgh.

“Having a 90% failure rate is an unsustainable model,” he said, so new models are needed, creating an ideal opportunity for partnerships between academia, government, and industry.

Rather than focus exclusively on a target-centric approach, or “one gene, one target, one new chemical entity,” as has been done for many years now, Taylor said, a phenotypic approach holds greater promise for identifying how a drug affects cellular processes, such as cell division, across many different diseases.

“If we can do this, we can screen for modulation in these cellular processes,” Taylor said, with the goal of modulating one process, without damaging others.

Another widely recognized obstacle in drug development remains the gap between identifying a lead molecule and taking it through preclinical testing, where most failures occur.

At best, Taylor said, animal models—the present “gold standard” for screening new compounds—accurately predict human responses only 70% of the time, with rodents, the animals holding the worst track record, providing accuracy just half the time.

“The later you fail in the drug development process, the more expensive it is,” he said.
said, with industry putting the price tag for a single new drug at more than $1 billion. Just maintaining a mouse colony for translational research, Taylor said, is “brutally expensive.”

To cut such costs and in hope of increasing accuracy in predicting drug safety and efficacy far earlier, many academic centers, including Pittsburgh, are working on tissue chips composed of diverse human cells and tissues that mimic how cells and tissues in humans interact.

NIH is also working towards this goal through a partnership with the Defense Advanced Research Projects Agency and the FDA.

“The grants are in, and we hope by fiscal year 2013 to fund the first awards,” Insel said. “We’re putting $70 million into this effort.”

**New Therapies for Rare Diseases**

Meanwhile, Weir and others involved in the auranofin initiative offered insight into how well their project has worked so far.

In a recent NIH-sponsored webinar, Weir; Christopher Austin, M.D., director of NCATS’ division of preclinical innovation; and Louis DeGennaro, Ph.D., chief mission officer of the Leukemia and Lymphoma Society, discussed details of their collaboration—the Learning Cooperative—formed in June 2010.

The collaborators spent more than half the time before the dosing of the first patient...
on Oct. 7, 2011, Austin said, working out details of the organizational infrastructure—from defining how information would be shared to how to establish research teams and each team’s responsibilities.

“We’ve just kicked this process off,” Weir added, with talks around reimbursement issues and exclusivity still ongoing.

But he said the cooperative is always looking for other opportunities to partner with industry, other academic centers, and government to speed development of new drugs for neglected diseases. A similar collaboration to the one established for auranofin is in the works around sarcomas, he said.

That these earliest efforts stem largely from the quest for new therapies for rare diseases does not surprise Insel.

Whereas in the past clinicians might observe that a patient with both arthritis and leukemia could benefit from a drug such as auranofin, he said, it happened in a way that’s not predictable with limited application. In comparison, investigators today can screen patients’ leukemia cells against nearly 4,000 compounds in a single repository, which the NIH owns, for anticancer activity.

“We’re taking a process that, up until now, has been serendipitous and turning it into something organized and predictable,” Insel said.

And, with some 6,000 rare diseases, “increasingly, we recognize that even our common disorders or common cancers are made up of really rare ones,” he said.

© Oxford University Press 2012. DOI: 10.1093/jnci/djs247