NCATS two years later

By C. Simone Fishburn, Senior Editor

The **National Center for Advancing Translational Sciences** (NCATS) was founded at the **NIH** a little over two years ago, in the wake of increasing concern over the slow pace of converting scientific discoveries into new therapies. "*BioCentury This Week*" television sat down with NCATS director Christopher Austin to discuss how NCATS is delivering on its promise to overcome the roadblocks and accelerate the translational process.

Austin thinks that NCATS's biggest advantage is its ability to collaborate with different players in the field to fill gaps left underdeveloped by industry and academia. Examples include the Tissue Chip for Drug Screening program and the New Therapeutic Uses program.

The former is a collaboration between the NIH, **FDA** and **Defense Advanced Research Projects Agency** (DARPA) that aims to develop 3D human tissue chips that model human organs for use in predicting toxic effects of candidate therapeutics, as discussed by DARPA's Jay Schnitzer on "*BioCentury This Week*."

The New Therapeutic Uses program provides a channel between pharmas and the biomedical research community to help repurpose compounds not pursued for their original indication for scientific or commercial reasons.[1]

Austin also pointed to new interventions in Parkinson's disease (PD) that might arise from a joint genomewide siRNA screen performed by NCATS scientists and researchers from the **National Institute of Neurological Disorders and Stroke** and the **NIH Center for Regenerative Medicine**.

Results of the screen, which were published in *Nature*, identified proteins that regulate the accumulation of parkin (PARK2) in mitochondria, a process that has recently come to the forefront of PD research.[2]

NCATS also wants to play a role in areas in which the private sector sees too much risk. For example, the Therapeutics for Rare and Neglected Diseases (TRND) program at NCATS brings not-for-profit organizations together with academic and industry partners to enable preclinical testing of compounds for under-served diseases.

Edited excerpts from the *BioCentury This Week* television (BCTV) interview with Austin follow.

BCTV: NCATS's mission is to re-engineer the way basic research is translated into medicine. Supporters say NCATS will solve problems academics and industry can't tackle on their own, but skeptics inside academia and industry and even at NIH say it diverts funds from NIH's core research mission and is taking on tasks that should be left to drug companies.

Let's start with target validation, which is one of the things that NCATS is looking to improve. That's what many drug companies exist to do. So why do we need NCATS to do it?

Christopher Austin: Right. Thanks to the Genome Project, among other things, there are many more targets than we can possibly deal with. For example, there are about 6,000 rare diseases, and we now know, from the Genome Project and other advances, the genetic basis of about 4,000 of them. That's up from 50 about 15 or 20 years ago.

So although there are thousands of putative targets that could be investigated, we don't have very good ways of sifting through the data to identify the targets that are the most tractable.

We believe the solution lies in one of the core principles of NCATS, which is that translation is a team sport.

Early on in the science process, it can be a fairly solitary exercise. That's how I got my start in fundamental genetics research, but translation requires multiple players with distinct expertise from multiple disciplines and multiple organizations. Every project NCATS does is a collaboration with somebody in the public sector or the private sector, so we are not doing this alone.

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—Christopher Austin, National Center for Advancing Translational Sciences

BCTV: And can you give examples of outcomes or of how NCATS can deliver real results?

CA: The NCATS RNAi program is focused on the general principles that underlie using RNAi as a target validation tool. We started by using genomewide RNAi to knock out every gene one by one and find every gene involved in disease or a cellular process—and thereby identify targets.

But the RNAi technology initially was not usable for that use, so our people developed new technologies to allow that to happen.

There was no public database, so researchers around the world had no access to the data. And so we developed new screening, informatics and analysis technologies to fix that.

We developed the first public database for these data in collaboration with **Life Technologies Corp.**, and we've done a number of projects now on very important diseases to identify novel targets for intervention. One example is the paper we published last month in *Nature* on Parkinson's disease.

BCTV: Another area NCATS is working on is improving the process of getting drugs and new therapies to people who need them—not simply getting them approved, but actually getting them disseminated. Many biotech and pharma companies and academics don't seem to focus much on that. What are you doing there?

CA: This is a very important problem, as part of NCATS's mission is to improve health. Getting a drug approved can be very important, but we haven't actually improved health there.

It currently takes between 10 and 15 years to get new medicines approved by FDA to all the patients that need them. And this is a problem that includes reimbursement, patient access to medicine, heterogeneity in the population—genetically and environmentally—and heterogeneity of disease.

BCTV: So again—why is this something that NIH needs to do? A drug company has a fantastic incentive to get new drugs used as widely as possible as quickly as possible.

CA: We should do it because NCATS is focused on areas where we think we can do things better. As an example, it's well known that most patients who were prescribed a medicine either never fill the prescription or they only take it one month and then they stop.

And so this is an issue of physician behavior, prescribing behavior and patient behavior. And this is an issue of implementation science, which is quite different from the fundamental preclinical work that NCATS does.

Through our CTSA program, the Clinical Translational Science Award program, which is a network of 62 academic medical centers all over the country—it's actually NIH's biggest single program—we have really pushed the idea of patient engagement and community engagement from the very beginning of projects.

One of the reasons that patients do not take the medicines that might be prescribed them is they don't feel that they're partners with their prescribers in understanding what these medicines can do for them. And so they're not invested, and they don't take them.

It's an interesting development that patient groups are becoming much more active in the development and utilization of medicines for diseases. And we think this is a transformational development, and I've actually challenged NCATS to have our people and our grantees and our internal scientists involve patients in every project we do from the very beginning.

BCTV: Can you give us some other examples of the way that you've tried to use your funding to meet your goal of transforming medicine—and at $10 million a year that funding is a lot less than the half-a-billion dollars originally envisioned?

CA: We are using the money well; for example, for the Tissue Chip program—a body on a chip to do toxicology—which, if successful, will transform how we identify the safety and efficacy of novel therapeutics.

Another example is in a collaboration we have called New Therapeutic Uses with eight pharmaceutical companies, which addresses the problem that because of a very high failure rate of drug development, for every drug that gets approved for human use by the FDA, there are about 10 which have been in people and then fail, often for efficacy reasons or for business reasons.

We teamed up with these companies and proposed reaching out to the academic community to see if there are other ideas for diseases that these drugs might be used for. By advancing the repurposing of these compounds, there are actually compounds for nine different diseases that are in patients right now in collaboration between NCATS and academic organizations and the pharmaceutical companies who made the drugs and have all the data on them.

I would say it will take about a year to get some results. Some of them are actually getting animal studies done on them, so we'll know a little bit earlier than that.

But I should say that this whole program was about $13 million, which is a very small amount of money that could catalyze nine new drugs.

BCTV: Going back to rare diseases, tell us about the TRND project, which is trying to find new therapies for really rare diseases. What are you working on there, and again why is it something that the private sector, which has invested a lot in rare diseases, wouldn't do on its own?

CA: There are many rare diseases that are not sufficiently de-risked for a company to make a business case to adopt them. And the purpose of TRND is to be the starting point of proto-drug development up to a point where a company is willing to adopt them. So it's really an adapter or a chaperone for those projects.

Sickle cell disease is a very important public health disease that affects about 100,000 people in this country. It was the first genetic disease [for which the cause was identified], in 1949. We still have no treatment for that disease based on that genetic discovery.

AesRx LLC, a little biotech in Boston, came to us with an unconventional molecule. It's an unconventional mechanism. There have been regulatory issues of getting drugs for sickle cell approved, and there are clinical trial issues in that particular disease, which have bedeviled that disease from the beginning.

No company would adopt that project because of all those risks, despite the very important public health implications. So we adopted that project, working very closely with AesRx, having a joint project team that decided where the funding that NCATS put into it would go. And the company put their own resources into it. And within a year, we went from starting that collaboration to being in people.

So this is what I want to emphasize, is that rapid advances in translation are possible. They weren't possible when I was in training 40 years ago. They are possible now. It's a matter of will and having the science and operational systems to do it.

BCTV: Thank you very much.

Fishburn, C.S. *SciBX* 7(4); doi:10.1038/scibx.2014.106
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2. Hasson, S.A. *et al. Nature* **504**, 291–295 (2013)

COMPANIES AND INSTITUTIONS MENTIONED

AesRx LLC, Newton, Mass.
Defense Advanced Research Projects Agency, Arlington, Va.
Food and Drug Administration, Silver Spring, Md.
Life Technologies Corp. (NASDAQ:LIFE), Carlsbad, Calif.
National Center for Advancing Translational Sciences, Bethesda, Md.
National Institute of Neurological Disorders and Stroke, Bethesda, Md.
National Institutes of Health, Bethesda, Md.
NIH Center for Regenerative Medicine, Bethesda, Md.