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# Medicine man

*As director of the NIH's bold new translational research centre, Christopher Austin has to show that he can jump-start a tortuous drug-discovery process.*

**BY MEREDITH WADMAN**

In his last role two years ago with the Opera Vivente in Baltimore, Maryland, Christopher Austin played the Calvinist chaplain in Gaetano Donizetti's *Lucia di Lammermoor*. The story does not lack for drama: the heroine pulls out a knife in her wedding bed and stabs to death the husband who has been forced on her in place of her true love. On the heels of the murder, the chaplain "is the guy who is trying to bring order to chaos", says Austin, a bass-baritone who once considered a full-time career in opera.

Austin's most recent stage part has a certain resonance with his new day job. In September, he was appointed as director of the fledgling

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National Center for Advancing Translational Sciences (NCATS) at the US National Institutes of Health (NIH) in Bethesda, Maryland. In existence since December 2011, the centre has an ambitious — some say audacious — agenda that channels the central passion of both Austin and his boss, NIH director Francis Collins: to get more successful medicines into more patients, more quickly. That means forcing the agonizingly slow, failure-prone process of 'translational research' — the term of art for moving promising discoveries from the lab to the clinic — into a higher gear.

Passion runs high among the sceptics, too. Researchers both inside and outside the agency fear that NCATS — the first new centre at the NIH in more than a decade, funded at US$575 million last year — will encroach on a finite pot of money that they say would be better spent probing the mechanisms of basic biology and disease. Others question the scale of its mission. "With the available resources, how are you going to achieve this?" asks Thomas Caskey, a molecular geneticist at Baylor College of Medicine in Houston, Texas. "To me, you cannot just take this money and be another biotechnology company and you certainly don't have enough money to be a pharmaceutical company."

NCATS will be neither, Austin responds. What will set it apart, he says, is a focus on overcoming obstacles on the road to drug development, from inadequate toxicology methods to inefficient clinical-trial recruitment, rather than actually producing the drugs. In an era in which more than 95% of drug candidates fail, and a novel drug takes 13 years and more than $1 billion to develop, "NCATS has to be focused on logarithmic improvements in the process", says Austin. "You can't do this in a brute-force way. You have to do it differently. You have to drive the technology development."

Austin's fans say that if anyone has a shot at making this work, it is him. "This guy has got clinical training, industry training and scientific training. If you wanted me to pick a quarterback, this is the quarterback I'd pick," says Lee Nadler, director of Harvard Catalyst, the NCATS-funded clinical and translational science centre based at Harvard University in Boston, Massachusetts. But whether quarterback or maestro, Austin has now to give the performance of his career. The biggest risk he faces lies in "not delivering something concrete within 12–24 months", says Nadler. "Everybody is watching him."

## LOSING A LIFE

Austin learned early, and at first-hand, about the tragic shortcomings of medicine. One night in 1989, when he was a neurology resident on call at Massachusetts General Hospital in Boston, an ambulance brought in a middle-aged man with end-stage amyotrophic lateral sclerosis (ALS), a disease that slowly destroys muscle power but leaves brain function intact. Patients usually die when their breathing muscles give out.

The man had a 'do not resuscitate' order, but, because of a miscommunication, he had been revived by the paramedics. Furious that he had not been allowed to die at home, he demanded that his ventilator be turned off. Austin complied. Watched by his family and Austin, the man died slowly over three hours, in the end turning blue before his heart monitor flatlined. "It was like sitting through the crucifixion," Austin recalls. "And I just said: 'I can't do this. There has got to be a better way.'"

Convinced that he had to do more, Austin began a postdoc in the lab of Connie Cepko, a geneticist at Harvard Medical School in Boston. There, he dived into developmental neurology, using new tracing techniques to reveal the migration of neural progenitor cells in the budding mouse cortex (C. P. Austin and C. L. Cepko *Development* **110,** 713–732; 1990).

"He was just really driven. He absolutely loves research," says Cepko. She recalls the day that Austin's wife went into labour with the couple's first child at the Brigham and Women's Hospital, around the corner. "I went to the lab and there was Chris sitting as his bench, pipetting away. I said, 'Chris, aren't you supposed to be in the delivery room?' He said: 'It'll be a couple hours [yet].'"

Despite all the time he logged in the lab, Austin did not stop seeing patients; at one point, he did a stint as the lone doctor in a hospital in rural Swaziland. But the distance from the elegant experiments of Cepko's lab to the clinic increasingly bothered him. "That gulf was so wide," says Austin. In 1995, when Edward Scolnick, research chief for the pharmaceutical company Merck, visited Harvard and announced that his firm was launching a genetics-based research operation that would redefine how it developed therapeutics, Austin immediately applied.

He spent the next seven years at Merck Research Laboratories in West Point, Pennsylvania, using the sequence that was beginning to come out of the Human Genome Project to seek targets for treating schizophrenia, bipolar disorder and Alzheimer's disease. Austin's know-how in identifying drug targets was "revered" says Caskey, who was his boss at Merck, although he "never really did" the downstream drug development during which so many potential drugs founder. And Austin also learned up close the disappointments of drug development: the Merck compounds that arose from his considerable work on the Alzheimer's target γ-secretase were dropped by the company several years ago because of their side effects.

*"He's a guy with a sense of humour, which God knows to do that job you need."*

Eventually, Austin grew frustrated with the constraints of working for a huge drug company, where the need for profit made chasing cures for rare diseases such as ALS a non-starter.

He had already crossed paths with Collins, then the director of the NIH's National Human Genome Research Institute. In August 2002, after Austin gave a talk on the NIH campus, Collins asked him to "'come down here and help us figure out what to do with the genome'. Those were his exact words," Austin recalls. By November, Austin was in place as Collins's senior adviser for translational research.

## THINKING BIG

Austin's most prominent early project was the launch of the Molecular Libraries Program (MLP), a multi-centre effort to identify small molecules that academics could use to probe potential drug targets, and that sometimes formed the basis for drugs themselves. Many NIH officials envisioned a fairly modest effort for screening and tweaking molecules on the NIH campus. But Austin, with his commercial experience, thought on a different scale. He shopped high and low for the latest in high-throughput robotics systems and landed a deal with Kalypsys, a biotechnology firm based in San Diego, California. The company built him a one-of-a-kind, fully automated system that could, as an NIH YouTube video claimed, "boldly go where no robot had gone before". In the space of five days, it could screen seven concentrations each of 400,000 compounds to test their activity against genes, proteins or cellular pathways implicated in a panoply of diseases. Before long, the robot was hosting a steady string of industry visitors who wanted to understand Austin's technological leap.

In 2009, Austin launched a programme in which the NIH partners with companies, non-profit organizations and academics to try to move into clinical testing compounds that show promise against neglected diseases — including some from the MLP. The Therapeutics for Rare and Neglected Diseases programme, which is now part of NCATS, has already proved its worth, says Austin, with four compounds moving into clinical trials in the past 15 months. The trials include one launched

last month, which deploys cyclodextrin against a rare, fatal disorder of cholesterol metabolism, Niemann–Pick disease type C.

Austin's supporters say that he is no grey bureaucrat buried in the bowels of the NIH. He has proved, says Collins, "exceptionally effective" in building collaborations, whether with academics, industry veterans or earnest disease advocates. "He's a guy with a sense of humour, which God knows to do that job you need," adds Garret FitzGerald, director of the NCATS-supported Institute for Translational Medicine and Therapeutics at the University of Pennsylvania in Philadelphia. Last month, while speaking at the J.P. Morgan Healthcare Conference in San Francisco, California, Austin was asked whether it is true that he is an opera singer and whether, if so, he could sing a C for the audience.

"Yes, on both counts!" he sang loudly into the Colonial Room at the Westin St. Francis Hotel.

## ROUGH START

In December 2010, Collins, early in his second year as NIH director, announced his intention to form a translational-medicine centre from existing components of the NIH, and to do so within a year — a veritable burst of speed in the government world. The reorganization would mean the dissolution of the NIH's National Center for Research Resources, an entrenched institute with heavy investment in translational science and many constituents in basic research (see *Nature* **471,** 15–16; 2011).

The next month, *The New York Times* ran a front-page story declaring that NIH officials "have decided to start a billion-dollar government drug development center to help create medicines" and that to do so Collins was willing to "cannibalize" other parts of the NIH. The reaction was fierce. Congressional Republicans, drug-industry executives and NIH-funded basic researchers blasted the agency for treading on private-sector prerogatives, for neglecting its basic-research mandate and for presuming that it could succeed where industry had been failing.

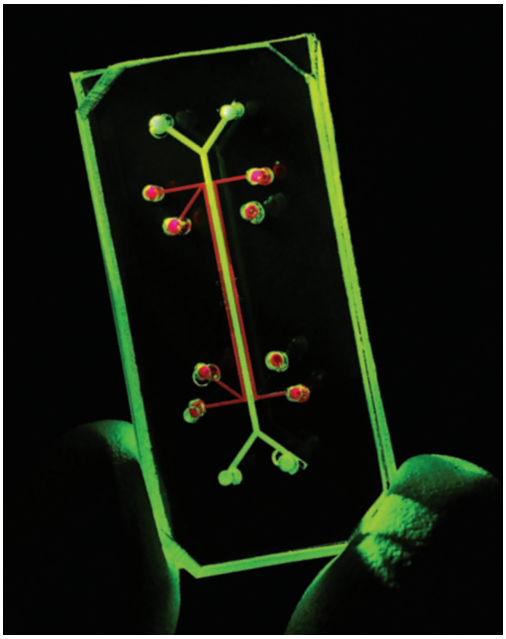
Perhaps the most damaging jab came from Roy Vagelos, former chief executive of Merck, at a congressional hearing last March. "Does anyone in the audience believe that there is something that NCATS is going to do that the industry thinks is critical and that they are not doing?" he asked. "That is incredible to think that. If you believe that, you believe in fairies."

Collins rushed to defend the nascent centre's mission. NCATS, he explained, would "complement and not compete with" industry, by taking on thorny problems in the technology of drug development to smooth the road to the clinic for all concerned. And, he assured his constituents, NCATS would not eat into the NIH's basic-science dollars. Congress, at least, set aside its doubts, and funded NCATS in the dying days of 2011. The search for a director took nine months, and at least one other candidate was offered the job. But Austin, who had created many of the programmes that comprised NCATS, was a natural fit to head the centre. Besides, says Nadler, "Francis loves this guy".

During a recent interview, Austin spontaneously countered the now-famous "fairies" criticism. On the NCATS to-do list, "are there things pharma hasn't thought of doing? Maybe, but for the most part, no," he says. However, he adds: "That's not the right question. The right question is: what can they do within the confines of … a profit-making organization? There's a lot of things you just can't do even if you want to."

To underscore what sets NCATS apart from industry, Austin has been showcasing the centre's first new programme, which makes available to NIH-funded scientists 58 drugs tested in humans but abandoned by big drug firms for business reasons or because they didn't work against the conditions that the companies had tested them on. The goal is to put those candidates to other uses. The programme has become a useful flagship for NCATS not least because it — unlike others in the opaque field of translational research — is easily explained to the public.

Austin also likes to talk about NCATS's bid to overcome one of the biggest hurdles in the quest for new drugs: the discovery of harmful side effects when a compound is well into development. "This is a classic problem for NCATS to work on," he says.



WYSS INSTITUTE

**NCATS is helping to develop chips that mimic human tissues to screen for toxic effects of drugs.**

His solution, in part, is a programme in which NCATS is working with the Defense Advanced Research Projects Agency and the US Food and Drug Administration to put ten human tissues, from heart to brain and gut, on a chip that could then be used to screen potential drugs rapidly and efficiently for toxic effects. Another attack on toxicity can be found in the Tox21 programme, a collaboration between NCATS, the National Toxicology Program at the NIH's National Institute of Environmental Health Sciences and the Environmental Protection Agency. It began in December 2011 to screen 10,000 environmental chemicals and approved drugs against every known human signalling pathway, to identify which molecules might have toxic effects.

In the longer term, one of Austin's major goals is to find a better way to use NCATS's biggest programme: the $461-million Clinical and Translational Science Awards (CTSAs), which fund around 60 translational-medicine centres, each operating independently. The awards aim to train the next generation of translational researchers and to improve the full spectrum of that research, from discovering drug targets to answering health-delivery questions such as: do asymptomatic women really need routine manual pelvic exams? Since September, Austin has visited nine of the CTSA centres — he has planned six more visits — to talk to principal investigators and other staff members. While praising the centres' work, he says that they have so far mostly operated "without particular encouragement or direction from the NIH, and thus in a disjointed and uncoordinated fashion". Austin wants to see a "CTSA 2.0" that will apply the consortium collectively to problems including clinical-trial recruitment, the development of better biomarkers and the rational use of electronic medical records in research. This can best be done "across a nationwide network focused on solving systematic problems", says Austin.

Austin has not sung in an opera since the launch of NCATS. It is a fact of his current life that he regrets. "When I got this job," he says, "I got more than one congratulatory note saying: 'Now you really need to do the music. Because this is the only way that you're gonna maintain your sanity.'"

Working out how to make that happen may be easier said than done; Opera Vivente folded during the economic meltdown, and Austin is logging 12–15-hour workdays. But he still sees the pursuit as intimately related to his chosen career.

"If you look at what NCATS is trying to do, and why I got into medicine in the first place — you are trying to understand the human condition. Fundamentally, that's what opera does, that's what it tries to explore. What makes people tick? And then, sometimes, how do you fix it?" ■

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