POLICY

# NIH revamp rushes ahead

*Translational-science centre remains on the fast track, despite concerns about upheaval.*

BY MEREDITH WADMAN

Jeremy Berg was fighting rush-hour traffic on his way home from the US National Institutes of Health (NIH) in Bethesda, Maryland, on 8 February when he took an unexpected call. On the line was a senior NIH official who was helping to plan the dismantling of the agency's National Center for Research Resources (NCRR) to make way for a translational-medicine centre strongly backed by Francis Collins, director of the NIH.

The caller asked Berg, who is head of the US$2-billion National Institute of General Medical Sciences (NIGMS) at the NIH, to consider whether his institute could absorb the Institutional Development Award (IDeA), an NCRR programme that builds research infrastucture in states with historically limited success at winning NIH grants. He wanted an answer by the following day.

"I was given *approximately 24 hours* to decide whether NIGMS should take on a large (>$200M), complicated program not closely related to our core mission," Berg wrote on 22 February in an open letter to the Scientific Management Review Board, which advises Collins on structural changes at the NIH. Berg agreed to absorb the programme, but "with very little comfort that this was a sound decision". He went on to urge the board to fight the hasty dissolution of the NCRR.

Berg's complaint is one of a deluge facing Collins and his staff as they rush to launch the National Center for Advancing Translational Sciences (NCATS) by the start of the US government's 2012 budget year on 1 October. Most critics do not disagree with the reasoning for the proposed centre — Collins wants the NIH to become more strategically engaged in turning promising compounds into clinically approved drugs, a process that often stalls for lack of resources and know-how. Rather, many are challenging the speed at which NCATS is being established — and the even greater speed with which Collins decided in December to dissolve the NCRR, transfer a significant portion of it to the new centre and scatter the rest across the NIH (see graphic). It will be the first such break-up in the NIH's 81 years.

***Critics fear that the changes will put at risk programmes that they say are working extremely well.***

Sixteen US senators wrote to Collins on 14 February, supporting IDeA and urging him to slow the pace of the reorganization to gauge its impact. Other critics fear that the changes will put at risk NCRR programmes that they say are working extremely well. "Why are we fixing what isn't broken?" asks Brad Bolon, director of GEMpath, a biopharmaceutical consultancy in Longmont, Colorado. (see page 36).

Collins, who has made translational research one of five priorities for his tenure at the NIH, sees NCATS as removing the risk from early-stage therapeutic compounds by bringing them through the first phases of drug development, to the point at which companies are willing to license them. The centre would consolidate several existing NIH projects — most prominently the Clinical and Translational Science Awards, which at $490 million in 2010, is the largest NCRR programme. And if congressional spending committees agree to a White House request for a 10% budget boost for the NIH Office of the Director, which is responsible for organizing programmes across the agency, Collins plans to channel $100 million of that money to NCATS to fund the Cures Acceleration Network, a grant programme supporting 'high need' drug-development projects.

Collins' decision to push ahead quickly with NCATS means that the rest of the $1.3-billion NCRR — which supports a diverse collection of infrastructure and training programmes, from primate-research centres to high-end instrumentation grants — cannot simply be left intact. This is because of a 2006 law that caps the number of NIH institutes and centres at 27; the dissolution of the NCRR creates the needed opening for NCATS. Lawrence Tabak, principal deputy director of the NIH and co-chairman of the NCRR Task Force, a working group deciding what to do with the remaining pieces of the centre, says that, "given the opportunity to think this through", the group had decided that the remaining NCRR programmes would thrive better if strategically ▶

## CHANGE AT THE US NATIONAL INSTITUTES OF HEALTH

The proposed dissolution of the National Center for Research Resources and creation of the National Center for Advancing Translational Sciences will lead to some programme relocations (figures are for fiscal year 2010).

### AS OF MARCH 2011

| National Center for Research Resouces |
|---|
| Clinical and Translational Science Awards (US$490 million) |
| Shared and High-End Instrumentation ($65 million) |
| Division of Comparative Medicine ($197 million) |
| Extramural Construction ($1 billion, 2009–10) |
| Institutional Development Award ($229 million) |
| Research Centers in Minority Institutions ($59 million) |
| Biomedical Technology Research Resources ($150 million) |

| Office of the Director |
|---|
| Rapid Access to Intervention Development ($5.8 million) |
| Molecular Libraries Program ($113 million) |

| National Human Genome Reseach Institute |
|---|
| Therapeutics for Rare and Neglected Diseases ($24 million) |

* Proposed by President Barack Obama for fiscal year 2012

### BY OCTOBER 2011

| National Center for Advancing Translational Sciences |
|---|
| Clinical and Translational Science Awards |
| Therapeutics for Rare and Neglected Diseases |
| Cures Acceleration Network ($100 million)* |
| Rapid Access to Intervention Development |
| Molecular Libraries Program |

| Office of the Director: Infrastructure Entity |
|---|
| Shared and High-End Instrumentation |
| Division of Comparative Medicine |
| Extramural Construction |

| National Institute of Biomedical Imaging and Bioengineering |
|---|
| Imaging and Point-of-Care Biomedical Technology Research Centers grants |
| Imaging and Point-of-Care research grants for Technology Research and Development |

| National Institute of General Medical Sciences |
|---|
| Institutional Development Award |
| All other Biomedical Technology Research Centers grants |
| All other research grants for Technology Research and Development |

| National Institute on Minority Health and Health Disparities |
|---|
| Research Centers in Minority Institutions |

placed in other NIH institutes and in the Office of the Director.

Many constituents of the NCRR fear for the futures of their programmes in institutes that didn't sign up for them and may not share the NCRR's commitment. "Dr Tabak and Francis Collins say this is going to be budget neutral," says one member of the NCRR's external advisory council. "But when you take a programme from one institute and hand it to another, perhaps without their agreement, you know that within five years or so that orphan programme could be budgeted out of existence."

That concern was especially evident in mid-January, when Tabak's group proposed a 'straw' model — designed to generate discussion — for the dissolution of the NCRR that showed much of its portfolio in an 'interim infrastructure unit'. Some critics were mollified when Tabak issued a revised plan last week, calling the infrastructure entity permanent and placing it in the Office of the Director. The latest plan includes other adjustments: for example, the straw model had divided the NCRR's primate and non-primate animal-model resources, but the revised model keeps them together under the director's office.

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EMORY UNIV.

**Stuart Zola's research centre is slated to become the responsibility of the NIH Office of the Director.**

Stuart Zola, director of the Yerkes National Primate Research Center in Atlanta, Georgia, which is currently funded by the NCRR, is one of those whose fears were soothed by the adjustments. "Given that we were going to be moved, it makes sense to be moved into another broad-based environment" rather than a disease-specific institute, he says.

"The willingness to listen to the stakeholders is very clearly evident in the new document," says William Talman, president of the Federation of American Societies for Experimental Biology in Bethesda, Maryland, who praises Collins for making a "bold stroke" in launching NCATS. Still, he says: "I don't think I will be comfortable until the test of time determines exactly what the outcome is."

Those seeking to challenge the dismantling of the NCRR will have another opportunity to voice concern at a meeting for stakeholders on 14 March. However, the window of opportunity to stop the process is narrowing. Collins plans to deliver a detailed budget for the new centre to Congress in the coming weeks, and last week he told reporters that he is preparing to search for the future director of NCATS. ■

GENE THERAPY

# Targeted gene editing enters clinic

*Patients with HIV first to receive experimental gene therapy.*

**BY HEIDI LEDFORD**

A gene-therapy method that specifically disrupts a single gene may have had its first success in the clinic, potentially boosting immune-cell counts in a small number of patients with HIV. The results, presented on 28 February at the Conference on Retroviruses and Opportunistic Infections in Boston, Massachusetts, mark an important therapeutic test for enzymes known as zinc finger nucleases — small proteins that can be designed to bind to and edit specific DNA sequences by virtue of their zinc-bearing structures.

The study, a phase I safety trial, tested a zinc finger enzyme developed by Sangamo BioSciences in Richmond, California. It included six men with HIV who were already taking the standard regimen of antiretroviral drugs. The drugs had kept the virus at bay, but their immune-cell counts remained abnormally low. Researchers removed a sample of $CD4^+$ T cells, the type of immune cells affected by HIV, from each man and used Sangamo's enzyme to disrupt the *CCR5* gene, which encodes a protein that HIV uses to enter $CD4^+$ cells. The engineered cells were then infused back into the patients. Immune-cell counts subsequently rose for five of the six patients who received the therapy.

"It's very exciting," says John Rossi, a molecular biologist at the City of Hope's Beckman Research Institute in Duarte, California. "If they did this several times in a given patient, you could establish a high percentage of resistant cells."

The inspiration for targeting the *CCR5* gene comes from the small percentage of people who, thanks to a natural mutation in the gene, are resistant to most types of HIV infection. At the meeting on Monday, Jacob Lalezari of Quest Clinical Research in San Francisco, California, reported that the engineered cells migrated throughout the body and thrived in the gut mucosa — a key reservoir of HIV. No serious side effects were seen.

The zinc finger nuclease technique is promising for the treatment of many diseases beyond HIV, says Patrick Aubourg, who studies gene therapy at France's national biomedical agency INSERM in Paris. The method could replace the more common technique of inserting modified genes into the genome, in which researchers have less control over the gene in question. But he cautions that the technique still has a relatively low efficiency and might have off-target effects.

Meanwhile, Rossi, who is himself embarking on an HIV study that will use Sangamo's zinc finger nucleases, says that it is not yet clear whether the patients' $CD4^+$ cell count rose because of the *CCR5* disruption or because the extracted cells were activated as part of the protocol for growing them outside the body. And because levels of HIV were already below the threshold of detection in these patients, it is too early to say what effect the therapy could have on patients that have more of the virus. Researchers do not yet know what fraction of a person's $CD4^+$ cells would need to be HIV-resistant to significantly rein in the virus's spread and liberate patients from a lifetime of antiretroviral drugs.

***"If they did this several times in a given patient, you could establish a high percentage of resistant cells."***

"It's going to take a while to put all of those pieces together," says Carl June, who studies T cells at the University of Pennsylvania in Philadelphia, and is an investigator on another HIV trial involving Sangamo's nuclease. "But it's at least conceivable now." ■