POLICY

Herding CATS

Gregory A. Petsko

The U.S. National Institutes of Health's new National Center for Advancing Translational Sciences (NCATS) should be refocused to spur innovation and renamed in a way that doesn't further polarize the scientific community. This Commentary offers some suggestions for both types of transformations.

The solution of every problem is another problem.

–Goethe

The Naming of Cats is a difficult matter, It isn't just one of your holiday games.

–T.S. Eliot

"Beware," said my father, who was trained as an economist and hated the term "social sciences," "of anything that has to call itself a science. There's a good chance it isn't."

I can hear him say it every time I think about the National Center for Advancing Translational Sciences (NCATS). It is one of the reasons I am worried about NCATS (although as you will see it is not the only one) (Fig. 1).

As I have said before (*1*), I hate the term "translational research," and "translational science" is no better. I should point out that I'm an equal-opportunity hater: I also hate the term "basic research." In my view, these are artificial distinctions between parts of a continuum. By treating them as different, we set up a competition for resources and influence that confuses the public and is detrimental to finding cures. We should talk about biomedical research, period. Every time Francis Collins, director of the U.S. National Institutes of Health (NIH), uses the term translational science when describing his vision for NCATS (*2*), I cringe. Someone in his position, in particular, needs to fight this tendency to Balkanize biomedical research, not contribute to it.

"NEVER TRY TO OUTSTUBBORN A CAT" (LAZARUS LONG)

Of course, the reason Collins is doing it is that he is beset by people—in the U.S. Congress and from patient advocacy groups—who keep asking him, "Where are all the cures you promised us?" The "you" here is a collective pronoun that encompasses all scientists and science administrators—from the Nixonian "War on Cancer" of 40 years ago, to the Human Genome Initiative of the 1990s, to the doubling of the NIH budget and beyond—who have implied that rapid benefits would result from sharp increases in public funding of biomedical research. And now, as Collins explains in his recent Commentary in *Science Translational Medicine* (*2*), the situation has reached the point at which the pharmaceutical and biotechnology industries are not delivering new medicines fast enough to meet expectations—and take the heat off NIH. Collins's response is the creation of NCATS and the promulgation of translational science. He presents a closely reasoned argument for why this is necessary and what he hopes it will achieve (*2*). I find some of his arguments persuasive but not all of them, and I have concerns about both the practical aspects of NCATS and the philosophy that underlies its establishment.

Before I discuss those concerns, however, I should make it clear that I am not wholly opposed to the creation of a new center at NIH that is not disease-specific. For one thing, programs that cut across the numerous islands at NIH are not numerous. For another, NIH directors do not control much money, unlike the heads of the institutes and centers, and if the price of getting good people to serve in that job is letting them start some new initiatives—even if those initiatives will be run by others—that might not be too high a price to pay. As Harold Varmus, who served as NIH director during the budget doubling and then returned there last year to head the National Cancer Institute, said recently, "When I was the NIH director, I often expressed envy of institute directors: They had the money and ran the scientific programs. I was right—this job is more interesting." (*3*)

I should also make it clear that I do not think the primary product of NCATS is intended to be new products. In the vision Collins sets forth, drug companies will make drugs, and the other Institutes and Centers will continue to perform translational research. The purpose of NCATS, Collins says, is to change the processes by which potential products move down the pipeline—hence the term "reengineering." The question is, given that goal and the money available, are the suggested means of achieving the goal optimal—and realistic?

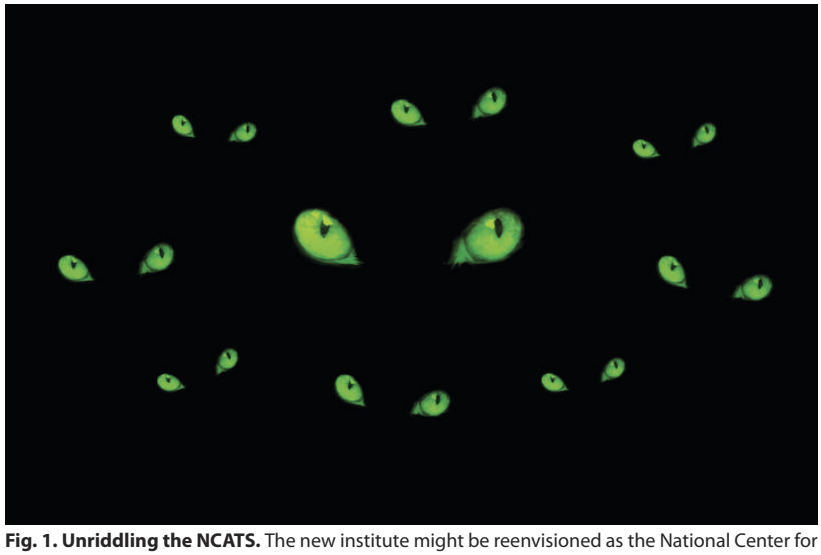

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Fig. 1. Unriddling the NCATS. The new institute might be reenvisioned as the National Center for Advancing TherapeuticS, with education of the public about the process of biomedical research as a key goal (*20*).

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"CATS … TEACH US THAT NOT EVERYTHING IN NATURE HAS A FUNCTION" (GARRISON KEILLOR)

Speaking of money, the budget is one of the practical aspects of NCATS that worries me. Among the ongoing activities that will be folded into NCATS is the Clinical Translational Science Awards (CTSAs), which establish a consortium of ~60 institutions across the United States that carry out support functions for translational science—primarily, although not exclusively, with the aim of facilitating clinical trials. The annual budget for the CTSA program is almost $500 million, which is more than half of NCATS's proposed budget. Added to this are the Molecular Libraries Program, which provides compounds for high-throughput screening and carries out some of those screens in another set of centers, with an annual cost of more than $100 million, and the proposed Cures Acceleration Network, a yet-to-be-funded $500 million authorization from Congress that is slated to receive $100 million in U.S. President Barack Obama's 2012 federal budget.

If the budget for NCATS is estimated to be around $1 billion per year, these fixed costs don't leave a lot of money for funding the research that Collins outlines at any sort of level that would make an impact on the problems he describes. To make that impact, I think NCATS either will need to select at most two cross-discipline areas of research focus (which raises the thorny matter of who will do the choosing), or it will have to lobby for considerable additional funds. Because I suspect the latter is more likely than the former, we may end up with an institute that claims to be advancing cures engaged in a fight for more money during a time when money will be very hard to come by—with serious consequences, you may imagine, for the rest of the biomedical research establishment. Of course, NCATS could also primarily function to catalyze research that will actually be carried out in the disease-specific institutes. As others have pointed out, these institutes already do a large amount of the sort of work that Collins talks about, so a CATalytic role for NCATS (I know; I apologize) is a plausible scenario, although how that would work in practice is unclear.

My other concerns about the practical details of NCATS are primarily directed at its stated areas of focus. I am disturbed by the emphasis in Collins's article, and in public discussion of the NCATS mission, on following up the genome-wide association studies (GWASs). In my view, GWASs were a mistake from the beginning, like going fishing in a dry lake. I believe the money spent on continuing such studies and on pursuing the dubious leads they have turned up thus far would be better spent elsewhere (see below). I think one of the unfortunate consequences of the Human Genome Project, which is correctly touted as an example of the success of such initiatives, is that it has led many people to think that all "genome-enabled" big-science projects will be similarly successful. That simply is not true.

Another area of focus that I find troubling is the emphasis on high-throughput screening of "diverse" molecular libraries. Thoughtful pharmaceutical researchers are moving away from this shotgun approach, which has very low rates of return, and back to structure-guided and natural products–based strategies. Chemistry is not NIH's strong suit, and an overemphasis on screening is already threatening to turn a number of first-rate biology research programs into fourth-rate drug discovery efforts.

Are there focuses that are appropriate for the new NIH center? Well, yes, I think there might be. The biggest problems at NIH at the moment are an excessive conservatism in what receives funding and the disease-oriented silos in research—the latter abetted by specific territories staked out by the existing institutes and centers. A new center could undertake a number of activities that are difficult to do in the current culture:

(i) ***Funding research that explores connections among diseases.*** Did you know that most cancer patients have a significantly reduced risk of Alzheimer's, Parkinson's, and Huntington's diseases and that the reverse is also true (*4*)? I know of very few traits that connect virtually all forms of cancer, but this fact does. [The fascinating exception is melanoma, in which the risk of Parkinson's disease is greatly elevated, and vice versa (*5*).] Did you know that diabetes is more common in people with schizophrenia than in the general population [almost one-fifth of schizophrenics have type II diabetes; the general prevalence is less than 1 in 10 (*6*)], but schizophrenics are reported to have lower rates of many cancers, despite poor diets and a high incidence of smoking (*7*)? Did you know that Gaucher disease patients are at an elevated risk for the rare cancer multiple myeloma (*8*)? Do these sound like the bases for potentially illuminating research projects to you? They do to me.

(ii) ***Making better disease models.*** A high number of promising drug candidates fail in phase II and III clinical trials, which means they fail for efficacy. That suggests to me that our animal models for toxicity are not too bad (these compounds passed phase I safety evaluation) but that our models for disease are not very good. [In some fields, such as neurodegenerative diseases, nearly all of the rodent models have significant deficiencies (*9*).] A systematic effort to make better models would likely save time and funding in the future.

(iii) ***Understanding why most biopharmaceuticals are immunogenic, even though they are human (or humanized) proteins.*** My own guess is that it is largely because misfolded proteins break tolerance (*10*); if that is true, research on improving the folding and stability of expressed proteins would be worthwhile.

(iv) ***Investigating the connection between being a carrier for a recessive metabolic disorder and the risk for a completely unrelated disease.*** It is in these connections, not in the common variants beloved by the GWAS program, that I believe the most important risk factors for major diseases will be found. By definition, the mutations that make one a carrier for a recessive metabolic disorder must affect the function of the protein in question. Most of the GWAS mutations probably do nothing. Haploinsufficiency is a sensible place to hunt for physiological affects. Want proof? Gaucher disease carriers are at significantly increased risk for Parkinson's disease (*11*), and 1 in 100 in the general population is a carrier. Such "rare" variants are often not as rare as you would think, and I'll bet that they account for a substantial number of cases of many different diseases. This kind of investigation is what researchers should have been doing all along, not the GWAS fishing expedition. Cirulli and Goldstein have given a detailed—and possibly more balanced—discussion of this point (*12*).

(v) ***Having a policy of funding people, not projects, once a track record is established.*** I do not mean that projects should count for nothing, but I do mean that funding could be longer-term and less predicated on the details of procedures and that riskier things could be funded when a person has a history of delivering. Past performance may be no guarantee of future outcome in the stock market, but it is a very good indicator in science. Many researchers believe that this kind of funding model would help alleviate the excessive conservatism that seems to bedevil federal funding of biomedical re-

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search and would lead to greater innovation (*13*). Here is a chance to test this hypothesis.

Please note that none of these ideas depend on—or have any real connection to—the CTSAs, the Molecular Libraries Program, or GWASs, even though those activities are major points of emphasis in NCATS. Collins's article alludes to endeavors that are similar to a couple of my suggestions, and that is encouraging, but once again—given the amount of money that will need to be spent on the CTSAs and other things destined for inclusion in NCATS—how much of an impact could realistically be made on any of these components?

"ANYONE WHO CONSIDERS PROTOCOL UNIMPORTANT HAS NEVER DEALT WITH A CAT" (ROBERT A. HEINLEIN)

One of the stated purposes of NCATS is to help the pharmaceutical industry increase the number of new drugs that are approved each year. Although this may be a laudable goal in principle, the devil, as always, is in the details. And looking at the details, I am not sanguine that most of the NCATS activities will make much of an impact on that problem—primarily because I do not believe that they address the major causes of the problem. I think the problems faced by the drug industry are as much cultural as scientific:

(i) ***Merger mania.*** The recent spate of pharmaceutical company mergers has too often resulted in bloated entities that are so busy managing the problems caused by the merger that they have forgotten how to make drugs (there are exceptions, but I would argue that the trend as a whole has been unhealthy). These mergers frequently look to be driven by short-term financial considerations, are often against the public good, and have almost wrecked one of the United States' best industries. There is no evidence that a single megapharmaceutical company will always make more drugs than two or three smaller ones—and considerable evidence that it will probably make fewer. The long-term financial benefit to shareholders of having drug companies that are good at making drugs would also, I argue, outweigh any short-term bump in share price that mergers might create.

(ii) ***Questionable priorities.*** I believe that it is important for pharmaceutical companies to keep the science in mind when making decisions (*14*). I worry that some companies are so occupied with constant reorganization and short-term profits that the science is forgotten. I respectfully suggest that some big pharma executives would benefit from reading Bob Lutz's new book, *Car Guys vs. Bean Counters: The Battle for the Soul of American Business*, a scary description of how process-oriented, cost-cutting management can stifle product-knowledgeable creativity and run a great company into the ground (*15*).

(iii) ***Hoarding.*** I wish pharmaceutical companies would get their phase II and III failures out into the academic community to be tested in every disease model around. What good are those erstwhile drugs doing sitting on the shelves? A few companies are starting to do some of this in a limited way. They call it "repurposing," and it may be the next fad in big pharma—to which I say, what took you so long? Collins implies that NCATS could act as a broker to facilitate this process; if it really did that, it would be a very good thing.

(iv) ***Cutbacks.*** The pharmaceutical industry has traditionally spent 15 to 20% of its sales revenue on research and development (R&D) (Bristol-Myers Squibb, with one of the strongest pipelines in the industry, spends 18%), but at some companies this figure is now slated to decline to ~10%. Again, such decisions seem to be made to please investors and analysts in the short run. True, it is essential that the money spent on R&D be spent wisely, and this has not always been the case. But the cure is wiser, science-based decisions about spending, not slashing the research budget in what is by definition a research-oriented business. Happily, some chief executive officers seem to agree, such as John Lechleiter of Eli Lilly (*16*) and Ken Frazier of Merck (*17*).

In fact, one of my worries about NCATS is that its very existence may make a halt to cutbacks less likely. Why should pharmaceutical companies increase their R&D spending if the government is putting its own money into solving the industry's problems? The fact that, as I've tried to indicate, NCATS is probably not going to solve the real problems is beside the point: A bottom line–oriented management would be happy to have another excuse to cut expenditures.

"CATS KNOW HOW WE FEEL—THEY DON'T CARE, BUT THEY KNOW" (UNKNOWN)

Now, about my philosophical concerns—I have three major ones. The first is that this increased emphasis on particular types of biomedical research is coming "from the top down," that is, the change is being driven by policy-makers at NIH rather than by the research community. The great strength of U.S. science has always been that its directions were set by open competition among investigator-initiated proposals. Money slotted for particular areas narrows that competition, often to an unhealthy degree, and establishes "priorities" that we do not seem to be able to rid ourselves of even when they have outlived their usefulness [such as the Protein Structure Initiative (*18*)]. I am not saying that there is no room for programs initiated by bureaucrats or in response to clamor from the public. But such policy decisions need to be made carefully and with due regard for their consequences, intended and unintended. In an era of flat funding, such programs can only grow at the expense of the individual, curiosity-driven "little science" from which nearly all breakthroughs originate. If NIH is serious about fostering innovation—and I believe it is—the center needs to fund more small science, not less, and it needs to let most ideas well up from the bottom.

My second concern is that NCATS is soaking up all of NIH leadership's energy and attention at a time when these should be directed to the type of rethinking that, for example, Rosbash suggested in a recent *Science* editorial (*19*). Like many others, I worry that we may not have the sense of urgency and focus needed from the NIH leadership to mitigate the coming disaster from the new world of flat NIH budgets.

The final overarching concern I have, and perhaps the most serious, is that in establishing NCATS we are trying to solve a problem by doing more of what caused the problem in the first place. As I outlined above, NCATS is a response to the demand of Congress and the public for the cures we promised them. Deliberately or not, we exaggerated the immediate benefits of increased funding for biomedical research: I vividly recall one meeting during the initiation of the Protein Structure Initiative when, in response to a warning that this program sounded as though it was being oversold, one of its advocates said, "It is impossible to oversell this program." That was either astonishingly naïve or blatantly self-serving, and a similar attitude has helped raise unrealistic expectations about everything from the War on Cancer to the GWAS project. Given our past experiences, does it make any sense now to promise still more? Especially because, as I've tried to point out, the amount of resources available to NCATS is unlikely to be sufficient for it to deliver on

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its multiple promises in the kind of time scale that is implied. What is needed from all levels of science, but especially from its chief administrators, is to communicate to the lay public a realistic perspective on what biomedical research is and how long it takes to go from discovery to application. If that were part of the NCATS mission and message, I would be much happier, but there is no indication that it is.

"THE WORST ENEMY OF A CAT IS A CLOSED DOOR" (OLD PROVERB)

If none of my other suggestions are adopted, let me offer a final one that I pray will be. If we are going to have this new center, please, can we call it something that will not further polarize the scientific community? How about the National Center for Advancing TherapeuticS (Fig. 1)? You could keep the same acronym, so you would not have to get new stationery printed; there would still be a CAT in there; and it just might be something that would be easier for the rest of us to get behind. If my father were still alive, I would like to think that he would approve.

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