

OPINION

The NIH's role in accelerating translational sciences

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The NIH's proposed initiatives in translational science deserve solid financial backing from legislators and vocal support from the biomedical community.

As the election year dawns, a spending bill covering the US National Institutes of Health (NIH) and its proposed National Center for Advancing Translational Sciences (NCATS) initiative is in the balance. Clearly, if the life sciences and medical research communities want the US Congress to sustain NIH's budget at a time of reduced resources, we who depend on NIH funding must show unequivocally our commitment to accelerating the practical translation of basic research toward improved therapies, diagnostics and preventive strategies that reduce disease burden, increase the efficiency of healthcare delivery and drive economic development. We believe NCATS is an important step in that direction, not because NCATS necessarily means that NIH will commit more funding to translational research at this time, but because the creation of this new center demonstrates that NIH is making a long-term commitment to the goal of more efficient translation of basic research into clinical benefits.

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The proposed plan for NCATS, which was devised with input from a broad spectrum of knowledgeable stakeholders¹, aims to solidify and expand NIH's commitment to improving the efficiency with which its investment in basic research is translated into improvements in human health. Nearly all of the programs slated to move into NCATS are already funded by NIH², through the NIH Center for Research Resources, the NIH Common Fund or the Office of the Director. Importantly, much of what NCATS will support provides a basic infrastructure for America's nonprofit life sciences research community to enable translation of basic research into clinical impact, including such programs as the (i) Clinical and Translational Science Awards (CTSA; <https://www.ctsacentral.org/>), which provide a broad spectrum of services and organizational capabilities for fostering translational and clinical research at 60 of the nation's medical schools; (ii) the Molecular Libraries Program (MLP), which provides essential infrastructure for small-molecule drug discovery, making sophisticated services available in assay development, high-throughput screening, large chemical libraries, cheminformatics and medicinal chemistry (<http://mli.nih.gov/mli/>); and (iii) Therapeutics for Rare & Neglected Diseases, devoted to nurturing promising therapies for rare and neglected diseases through pre-clinical development and into clinical testing (<http://trnd.nih.gov/>). Here we describe what we see as the feasibility, opportunities, possible pitfalls and potential impact of NCATS.

The need

Why is NCATS needed? Many have argued that the for-profit biopharmaceutical industry is solely responsible for translating basic science discoveries into new medicines, diagnostics and devices. Although ultimately few products will reach patients (consumers) without a for-profit company involved, it is

also clear that the world has changed greatly in terms of what investments companies are willing to make in pursuit of new healthcare products. In the 1990s, venture capitalists frequently backed early-stage biotech companies with nothing more than a good idea and a few drug targets, funding target validation and drug discovery research. Since the turn of the century, however, the valuations that biotech companies receive from the investment community have changed drastically, such that most venture capital funding is now directed at clinical-stage assets, where most product opportunities must have already completed phase 1 testing to garner investor support. This trend has created a widening gap between the traditional juncture where NIH funding subsides and where venture capital and biotech company funding begins—the so-called 'valley of death,' about which much has been written^{3,4}. NCATS is aimed in part at addressing the valley-of-death problem, without providing a comprehensive solution. With no efforts to resolve this problem, the slow pace of clinically relevant progress will become increasingly frustrating, despite remarkable progress in basic life sciences research—including (and particularly) completion of the human genome and the exponential decline in the costs of DNA sequencing—that is currently transforming the field of personalized oncology and promises to affect other areas of disease in the future.

Programs aligned under NCATS at least get us part of the way across the chasm. For example, the MLP helps academic scientists at least get from target to proof-of-concept compounds, demonstrating chemical tractability of targets and thus establishing feasibility (as well as eliminating targets that aren't destined to yield to a traditional small-molecule approach). That said, at the moment there is no infrastructure solution for those attempting to develop protein-based therapeutics (e.g., monoclonal antibodies) or nucleic acid-based drugs (e.g., antisense oligonucleotides). Also, the CTSA program at least provides an infrastructure for patient-oriented research that can generate genomic-based stratifications of patients for clinical trials of experimental therapeutics and that can support physician-sponsored investigational new drug applications (IND; e.g., novel drug repurposing opportunities).

Importantly, according to the NIH leadership, the driving mission of NCATS is to develop innovative methods and technologies that address the fundamental problem of the currently high failure rates in drug development⁵. Clearly, present models for commer-

cial drug development are unsustainable, with an average new chemical entity costing over \$1 billion and taking 13 years to reach US Food and Drug Administration (FDA) approval. For example, NCATS proposes to promote discovery of more predictive methods of preclinical toxicology, a notion entirely consistent with recent advances in induced pluripotent stem cell technologies that finally permit facile production of human (not animal) neurons, cardiomyocytes and other types of cells traditionally difficult to access. The joint program of NIH, FDA and the Defense Advanced Research Projects Agency (Washington, DC) to create 'body on chip' technologies for toxicity screening is precisely the sort of visionary initiatives needed at this time. Laudatory new strategies for creating innovative clinical trial designs (e.g., adaptive trial designs) are also touted by NIH leadership as a central mission of NCATS. Even so, where the funding resides within the NCATS' budget for most these programs aimed at eliminating roadblocks to drug development is still unclear from inspection of the NIH's proposed FY12 budget.

In our view, NCATS is needed not only to contribute to more efficient methods for developing drugs, but also to address areas of medicine that are largely neglected by the pharmaceutical industry. Consider, for example, the problem of antibiotic resistance, which claims an estimated 14,000 lives annually in the United States alone. In the past 40 years, only 4 classes of new antibiotics have been introduced. Large pharmaceutical companies have abandoned antibiotic drug discovery for commercial reasons. Far larger profits can be made developing medicines that treat chronic conditions, such as high cholesterol, where patients are dependent on the drug for many years, if not their entire lives. Antibiotics, on the other hand, are relatively inexpensive and consumed only for a short time. Thus, the pharmaceutical industry has little incentive to invest in developing these types of drugs, even if they would benefit millions of people.

The pharmaceutical industry also leaves many other diseases to the public sector. For example, the few small companies working towards therapeutics for traumatic brain injury and post-traumatic stress disorder, leading causes of death and long-term disability among military personnel serving in combat, are mostly funded by the government (especially the US Department of Defense), not by investors. Thanks to the MLP (an NCATS program), the nation's research community now has an infrastruc-

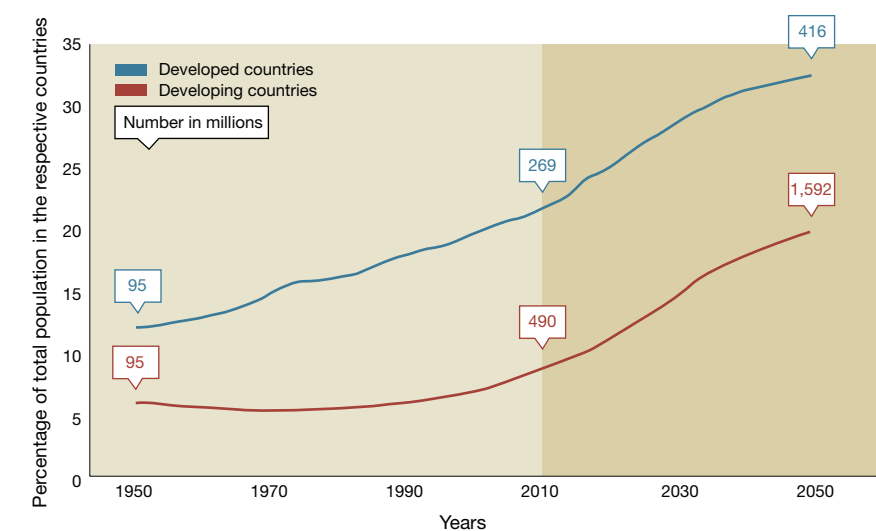


Figure 1 Public health in the United States and elsewhere faces unprecedented challenges in terms of the burden of chronic, aging-related disease in the coming decades. The NCATS initiative is one way in which the NIH can address these challenges. Source: World Population Prospects, United Nations, 2009. [AU: Figure OK or would you prefer to substitute with another?]

ture for initiating drug discovery efforts aimed at such neglected classes of targets. In fact, with respect to the examples cited above, drug discovery projects addressing microbial resistance and neuroprotection are already underway through the NIH's MLP initiative, with promising results. Moreover, several other academic and nonprofit research centers have established programs to address these and other under-resourced, yet critical, biomedical problems.

Let's also not forget the mounting concern over healthcare costs, which presently consume 16% of the gross domestic product of the United States. As Americans become more aged (Fig. 1), these costs will continue to rise, unless we find ways to deliver healthcare more efficiently. Enter the promise of personalized medicine, where genomic, epigenomic, proteomic and metabolomic signatures could be employed to take some of the guesswork out of patient management, ensuring that the right patients get the right medicine at the right dose. Without CTSA (another NCATS program), the basic infrastructure for conducting clinical biomarker trials will be severely jeopardized. The return on investment for diagnostic tests just doesn't justify R&D spending by for-profit companies to do biomarker discovery research. Once a biomarker is identified and validated, plenty of diagnostic companies will be eager to commercialize test kits, but the for-profit sector is not conducting the essential discovery research needed to make personalized medicine a reality. NCATS programs (particularly the CTSA) provide the foundation

for genomic medicine and thus have the potential to be a big contributor to driving more efficient healthcare delivery. Moreover, the nation's CTSA could and should join together to set national standards (in collaboration with NIH, healthcare providers and payers) for clinical informatics, including data formatting standards, data warehousing, data sharing and data mining. With 60 medical schools across America aligned under the CTSA program, the nation could finally press forward with a unified system for electronic medical records poised to embrace the opportunities implicit in the current drive to produce genome sequences for under \$1,000 (likely to occur within the next 5 years). A CTSA network could also serve as an organizational structure for rapidly conducting genomics-based clinical trials.

Why now?

Another reason why NCATS makes sense is because the academic research community is ready for it. Unlike the siloed approaches of the past, the nonprofit research community has embraced collaborative, multidisciplinary research more than ever in its history. Whereas the idea of teams of university-based scientists and physicians operating toward a common goal was a rare exception as recently as a decade ago, it is commonplace today. Now, biologists and physicians routinely work hand in hand with chemists, physicists, computer scientists and engineers towards practical deliverables. NCATS programs that illustrate the ability of the academic community to undertake

complex collaborations toward common translational science goals are found in the MLP, which created a national network of drug discovery centers that combine their complementary expertise, share projects and work with ‘assay providers’ across the nation to produce proof-of concept chemical probes for diverse targets. Moreover, the vast majority of the targets being pursued by the MLP drug discovery centers are truly novel, not worked-over classes of targets (e.g., G-protein coupled receptors (GPCRs), nuclear receptors and ion-channels), but exciting new biology, cellular pathways and pathophysiological processes that blaze new trails in drug discovery—trails that pharma will likely follow once the way is illuminated by government-funded discovery campaigns.

The research community is also ready for NCATS because more and more, nonprofit research organizations are repatriating experts from the biopharmaceutical industry with extensive drug discovery experience, thus increasing the core competencies of academia in drug discovery and development, while retaining academia’s innovation and creativity. The blended workforces emerging within the world of nonprofit biomedical research, where academics are married with industry-trained professionals, are a very exciting trend that bodes well for the success of NCATS.

The opportunity

With NCATS bringing various translational science programs under one roof, enormous opportunities exist to establish increasingly coordinated translational research programs that complement and enhance each other, rather than operating in isolation or competition. For example, when developing an innovative new medicine, having pharmacodynamic biomarkers that provide information about the proper dosing and verify *in vivo* modulation of the desired target by compounds is enormously useful. CTSAs-based programs in biomarker research could be coupled with MLP programs in drug discovery so that complementary biomarker assays are ready to go when experimental therapeutics advance into the clinic. The existing programs could also be focused more sharply on delivering healthcare outcomes. The MLP program for instance might set more stringent criteria for target selection to increase the probability of clinical translation, yet hold true to its commitment to explore new classes of targets and novel biology. This program might also add *in vivo* pharmacology as a routine part of its objectives, so that the chemical probes that emerge are optimized

sufficiently for undertaking proof-of-concept studies in animal models of disease—not just cell culture experiments. The NIH’s small-molecule library could also be improved by expanding the representation of drugs already approved by regulatory authorities (e.g., FDA and the European Medicines Agency in London) and that have already passed safety hurdles but that failed for reasons of efficacy. Comprehensively including in the library these ‘safe’ compounds with demonstrated bioactivity in humans would maximize drug-repurposing opportunities, shaving years and hundreds of millions of dollars off the development process. A more robust drug repurposing effort is particularly needed for rare and neglected diseases, where the return on investment doesn’t warrant billion-dollar investments in development⁶.

An element of the NCATS strategy is to not only publicize successes but also openly share information about failures so that the entire community can learn, refine strategies and constantly improve. At present, pharma companies tend to keep many of their failures quiet (**AU: YOU MIGHT WANT TO QUALIFY THAT THEY ALSO ONLY DISCLOSE THEIR FAILURES, SUCH AS CHEMICAL SERIES THAT END UP IN MED CHEM JOURNALS; E.G. ‘and predominantly publish only failed lead chemical series in the literature’**) and consequently the same mistakes are sometimes unnecessarily repeated. This open-access model promises to move the science of drug discovery and drug development science forward. In this regard, an underutilized resource is the PubChem database into which MLP screening centers have been depositing high-throughput screening data for nearly 8 years. Improved informatics tools are needed that correlate compound structures with their bioactivities across hundreds (eventually thousands) of assays, which will aid future selection of chemical leads for development by avoiding pharmacophores with unwanted (off-target) activities and thus reducing failure rates due to nonmechanism-based toxicity.

However, NIH leadership could do far more to integrate its various activities into coherent programs that drive translational efficiency. For example, the NIH’s \$200 million program to help provide researchers with high-quality animal models and specialized animal research facilities (Comparative Medicine Program) is slated for alignment under the Director’s Office, rather than NCATS. Generating more predictive animal models of disease is critically needed for testing new diagnostics and therapeu-

tics before embarking on expensive clinical development. Efforts in the CTSAs to discover and validate biomarkers could also be better integrated so that therapeutic lead candidates arising from NCATS programs are supported by companion diagnostics that take the guesswork out of finding the proper dosing schedule or selecting the right patients for trials⁷. Also, too many of the NIH’s 26 institutes duplicate infrastructure or fail to share resources. For example, the National Cancer Institute (NCI) has a natural product collection of ~140,000 extracts that could be applied for therapeutic indications beyond oncology, especially when attempting to tackle challenging targets such as protein-protein interactions.

Even the earliest of steps in translation (target discovery and validation) could be better organized by NIH to fund high priority areas. Take kinases as a highly tractable target class, for instance. Of the 727 kinases encoded in the human genome, fewer than 10% are well studied and nothing (or almost nothing) is known about approximately one-third. Thus, much of the kinome remains unexplored. Why doesn’t NIH create funding opportunities for laboratories and scientific teams that are willing to ‘deorphanize’ the entire kinome within the context of the various therapeutic areas represented by the 26 institutes that NIH comprises? The same could be said for orphan GPCRs and nuclear receptors, highly tractable classes of targets for which several orphans still remain.

Finally, we applaud NIH leadership’s proposal to make NCATS a catalyst for organizing more public-private partnerships, where government, academia and industry collaborate to solve problems in ‘precompetitive’ spaces, such as biomarker discovery and validation, thus leveraging financial resources during this time of dwindling public support for medical research.

The pitfalls

Given the challenges inherent in translating basic research into clinical benefits, NCATS-based programs are not immune to failure. Clearly, resources must be deployed cautiously when projects reach the clinic due to the high costs associated with clinical trials. The NIH’s description of NCATS suggests that clinical-stage projects will be limited to demonstration projects that seek to validate new technologies or methods for improving the efficiency of developing diagnostics and therapeutics, which we believe is wise. In general, all efforts should be made to partner clinical-stage projects with the biopharmaceutical industry at the earliest opportunity,

relying more on for-profit company dollars than taxpayer dollars to push drug candidates and other types of product opportunities toward FDA approval. [AU: WORTH EMPHASIZING AFTER ALL, THIS IS TRULY WHERE THE EXPERTISE OF INDUSTRY LIES]. One exception may be drug-repurposing trials, where a new indication for an existing drug has been discovered. For those drug-repurposing circumstances that do not require modification of existing formulations, clinical testing might be readily organized through close coordination with the CTSA's. However, NIH's efforts to accelerate drug and diagnostic development through NCATS will only be successful if FDA reciprocally modernizes its positions on regulation of healthcare product development. The NIH's plans to forge a deeper partnership with FDA on regulatory science issues are a critical component of the overall NCATS effort. But, developing innovative new technologies for predicting toxicity won't speed drug development if FDA merely uses these advances to add more tasks to their list of requirements, rather than replacing some of the existing ones. Eventually, much more will be needed to make FDA more of a partner and less of an adversary in accelerating drug development, including far more use of NIH-style peer-review mechanisms for evaluating risk-benefit ratios for new drugs and giving more consideration to the views of patients—at least for life-ending diseases where the risk-benefit equation is entirely different from that for chronic diseases.

The consequences of not addressing FDA reform in parallel with NIH's evolving posture towards translational science are huge, not only in terms of potential lost opportunities to affect human health but also with respect to the barrier to economic development that FDA all too often represents as the government entity responsible for regulating goods and services that account for >20% of the entire US economy. The same political voices that stepped up to support NCATS should next address FDA and begin exploring how to evolve FDA to complement what NIH is doing.

Lastly, at the risk of sounding self-serving, we caution NIH leaders against building the NCATS infrastructure in house. The last thing America's politicians want currently is programs that add to the headcount of the federal government. Extramural grants and contracts provide a far more effective means of retaining accountability for performance,

reducing long-term costs associated with benefits for federal government employees and realizing cost-sharing opportunities (e.g., leveraging philanthropy-based investments made by universities to create or maintain research capabilities).

Conclusions

Although the current programs moving into NCATS account for only 2% of the overall NIH budget, perhaps more than any other component of NIH, this new center has the potential to greatly magnify the clinical impact of NIH-sponsored research by serving as a unifying catalyst for translational research. Importantly, NCATS is also charged by NIH leadership with advancing the science of drug discovery and development, with the goal of reducing the unacceptably high failure rate of experimental therapeutics during clinical development.

Moreover, the impact of NCATS will be measured not only in the clinic, but also in the market place because nurturing the translational research enterprise stands to also promote economic development. Catalyzed by NCATS, new product opportunities emerging from NIH-sponsored research will attract more investment capital, thus creating more high-quality jobs and generating taxable revenue streams that will more than repay the government for its wise investment. At a time of global recession, the economic impact of this new center at NIH should neither be overlooked nor underestimated.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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