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An NIH National Center for Advancing Translational Sciences: is a focus on drug discovery the best option?

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In a recent interview Francis Collins, the Director of the US National Institutes of Health (NIH), described why translational medicine was one of his top priorities (An audience with… Francis Collins. *Nature Rev. Drug Discov.* **10**, 14 (2011))[1]. He noted that one potential solution to the current productivity problems in drug research and development (R&D) and the recent cutbacks in R&D by pharmaceutical companies would be for the NIH to become more engaged in drug discovery. Shortly after, he proposed the formation of a 'National Center for Advancing Translational Sciences' (NCATS)[2]. This centre would be assembled primarily from existing programmes focused on clinical research and drug discovery within the NIH, with the goal of conducting translational research that is needed to bring new ideas and materials to the attention of industry by demonstrating their value.

However, some critics of Collins' proposal fail to see why such a centre should be more successful at early-stage drug R&D than the pharmaceutical industry. In addition, low productivity has forced the industry to rethink the model of a research-based pharmaceutical company, in which most of its products come from in-house pipelines, and it has already started to invest heavily in academic collaborations with the same goals that have been proposed for the NCATS. For example, in November 2010, Pfizer announced the creation of its 'Centers for Therapeutic Innovation', a network of partnerships that also aims to accelerate the translation of biomedical research into medicines. It committed up to US$85 million over 5 years to its first centre at the University of California, San Francisco, USA, for the development of new biologic-based medications[3]. Other recent academic research collaborations have also been announced by Novartis, GlaxoSmithKline, Roche and AstraZeneca[4].

Given this, although it may have made sense in the past for the NIH to create the NCATS to support translational research targeting new drug discovery, it may now be better for the NCATS to have a different translational science focus. One attractive possibility that also benefits from greater molecular understanding of diseases and has the potential to greatly improve medical care — but importantly, that currently lacks major commercial incentives for industry — is advancing personalized medicine for established drugs.

Indeed, just as many are unhappy with the number of new drug approvals, others are unhappy with the slow advancement of personalized medicine. Following the publication of the sequence of the human genome a decade ago, and major advances in molecular biomarker technologies since then, many — including Francis Collins — predicted that patients would soon see substantial benefits from the promise of personalized medicine: the right drug, at the right time, at the right dose, for the right patient[5]. With the advent of targeted drugs for patients with cancer, and efficient molecular characterization of their tumours, this promise of personalized medicine is becoming a reality in oncology, in which medical need and commercial incentives favour rapid acceptance of new drugs[6]. However, this is not the case for patients with common chronic diseases in which, as in the past, recent approvals were almost always based on average efficacy and safety in the broad population of patients. Indeed, most marketed drugs for common diseases only have optimal benefit in a subpopulation of patients. For example, biologics targeting tumour necrosis factor are the gold standard for treating patients with progressive rheumatoid arthritis, but 29–54% of patients do not experience clinically significant responses[7].

There are now many hypotheses for greater personalization of the use of established drugs, which are supported by molecular biomarker associations with disease, clinical outcomes and drug response data, and by a better understanding of the molecular basis of disease, a few of which are shown in TABLE 1. The lack of translation of hypotheses such as these into accepted personalized medicine treatment paradigms is primarily due to the lack of commercial and regulatory incentives to create the necessary infrastructure, and to conduct hypothesis-generating association studies

Table 1 | **Examples of personalized medicine treatment paradigm hypotheses**

Disease indication	Drug or drug class	Biomarker (or biomarkers)	Clinical benefit	Refs
Congestive heart failure	Beta blockers	SNP of *ADRB1* gene (at position176) and deletion (at positions 322–325) of *ADRA2C* genes	Selects patients who are most likely to benefit	10,11
Type 2 diabetes	Oral hypoglycaemic agents (for example, sulfonylureas, metformin and thiazolidinediones)	Multiple candidate genes, including *OCT1*, *PPARG*, *KCNJ11*, *TCF7L2* and *CDKAL1*	Selects patients who are more likely to respond for initial therapy choice	12
Rheumatoid arthritis	Tocilizumab (monoclonal IL-6 receptor-specific antibody)	SNP at position –174 of the *IL6* gene (promoter)	Selects patients who are most likely to benefit	13,14
Asthma	Albuterol	SNP of *ADRB2* gene coding for amino acid at position 16	Predicts long-term response (G/G genotype) or lack of response (R/R genotype)	15

ADRA2C, α2C adrenergic receptor gene; *ADRB1*, β1 adrenergic receptor gene; IL-6, interleukin-6; *KCNJ11*, ATP-sensitive inward rectifier potassium channel 11 gene; *OCT1*, organic cation transporter 1 gene; *PPARG*, peroxisome proliferator-activated receptor-γ gene; SNP, single nucleotide polymorphism; *TCF7L2*, transcription factor 7-like 2 gene.

and biomarker-qualifying large retrospective and prospective clinical studies.

Clinical databases that are linked to samples could be used to create new and test existing hypotheses on the effectiveness and safety of already approved drugs in stratified populations of patients, based on molecular biomarkers. Advances in whole-genome scanning efficiency and its reduced costs have set the stage for rapidly advancing our molecular knowledge of disease and identifying more opportunities for personalized therapeutic interventions[8]. The availability of NCATS funding would be an incentive to create biorepositories at institutions (perhaps managed care organizations) with electronic medical records and could enable the creation and testing of many new hypotheses that would advance personalized medicine. NCATS funding for prospective clinical validation studies to qualify biomarkers predicting drug responsiveness in disease subpopulations could lead to drug label changes that would rapidly influence medical and reimbursement practices. Grants for these types of projects could be reviewed jointly by the NCATS and the US Food and Drug Administration to ensure agreement on biomarker qualification criteria for drug label changes, should the project be successful. These investments could greatly accelerate the adoption of personalized medicine treatment paradigms as the standard of care for many common diseases.

There is much low-hanging fruit in this area, but no one has the incentive to pay for the harvest. It therefore makes more sense for this to be the primary mission of the NCATS, rather than mimicking the investments of industry in early-stage drug discovery. This is also in line with the recommendations of the September 2008 report on 'Priorities for Personalized Medicine' published by The President's Council on Science and Technology. The Council recommended that "the Federal government should make critical investments in the enabling tools and resources essential to moving beyond genomic discoveries to personalized medicine products and services of patient and public benefit"[9]. If personalized medicine is only pursued by developing new drugs with companion diagnostics, it will be a long time before this approach becomes the standard of care for most common medical conditions. However, if patient stratification can improve the safety and efficacy of many drugs that are already approved, then the potential of personalized medicine will be realized much sooner.

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Competing interests statement

The author declares no competing financial interests.