POLICY AND EDUCATION

Training Translators for Smart Drug Discovery

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To achieve advances in clinical medicine, we need investigators with a sophisticated understanding of medicine and pharmacology who are capable of projecting their preclinical research across the translational divide. Such expertise in translational medicine and therapeutics has become scant in academia, industry, and regulatory bodies. Here we discuss strategies for addressing this deficit in human capital.

DRUG DISCOVERY: BEING OR NOTHINGNESS

Despite a marked escalation in investment in drug discovery and development and in the attributed cost of bringing a new drug to market, the rate of approval of small-molecule therapeutics has remained essentially constant since 1950 (*1*). Furthermore, political pressures to contain health care costs have accelerated a shift toward generics—which presently account for ~60% of drug prescriptions in the United States—and the assessment of comparative effectiveness as a basis for reimbursement of drug costs by governments (*2*–*4*). This latter movement may target, in particular, the growing numbers of biopharmaceuticals newly approved for the treatment of cancers, for which premium pricing often confers marginal benefit as assessed by such measures as quality of life years (*5*). Recent experience with the H1N1 flu vaccine (*6*) and the promotion of Gardisil [a human papillomavirus quadrivalent recombinant vaccine (types 6, 11, 16, and 18)] (*7*) also highlights the challenges of distribution and adoption peculiar to vaccines (such as their common administration to healthy individuals with a consequent low tolerability of adverse effects), a therapeutic modality some hope will compensate for the static nature of small-molecule drug approvals.

This collection of policy and financial issues has presented an existential challenge to the pharmaceutical and biotechnology industries. Clearly the present business model is unsustainable for large pharmaceutical companies (big Pharma), which comprises costs that are escalating at a log-linear rate to deliver a constant number of products to market (*1*), while the viability of the biotechnology industry is threatened by the increasing conservatism of investment strategies by venture capital. Although recognition of these problems is pervasive, the response to the challenge has so far been fragmented and partial, essentially consisting of minor modifications of the existing business model. There has been a proliferation of rather traditional partnerships with academia (*8*) mostly focused on drug discovery, a wave of mergers and acquisitions (*9*), some modest initiatives to expand the precompetitive space (*10*), and some structural reorganization within big Pharma, all in an attempt to integrate the creativity of the particulate with the power of scale (*11*).

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THE DEFICIT IN HUMAN CAPITAL

Although the gap between investment in drug discovery and development on the one hand and approval of new medical entities on the other cannot be sustained, the failure is one of drug development, not target identification. Investment has permitted an ongoing revolution in drug target discovery. Presently, we have more rationally selected drug targets than can be pursued through development. High-throughput screening approaches and cheminformatics (*12*, *13*) are likely to combine increasingly with our ability to inform biological networks with genomic information (*14*), resulting in novel drug/target combinations. Imaginative strategies will be deployed to suggest the repurposing of existing drugs (*15*). However, to realize this potential in the form of actual therapeutics, we need investigators with a sophisticated understanding of the principles of human medicine and expertise in both basic and human pharmacology, who are capable of projecting their preclinical work across the translational divide. Such expertise in translational medicine and therapeutics has become scant in academia, industry, and the regulatory bodies.

A particular problem has been the erosion of expertise in human pharmacology with the demise of clinical pharmacology as an academic discipline (*16*) and its limitation, increasingly, to an industry-based pursuit focused on early studies of drug exposure and tolerability. There have been attempts to rectify this situation within industry. It has been periodically fashionable for Pharma to establish clusters of physician-scientists charged with exploring mechanisms to attenuate the risk of late-stage failure and to speed the efficiency of drug development. However, these groups are usually small, transient, unempowered, underfunded, and dispersed across a conventional organizational structure. They are poorly positioned to argue against the pressures exerted by marketing or venture capital to accelerate progress from initial evidence of human drug tolerability into large-scale trials. Arguably, the much-discussed problems associated with COX-2 inhibitors (*17*), gene therapy (*18*), and biological therapeutics (such as antibodies) (*19*) might have been avoided if the developmental strategies had been informed sufficiently by expertise in human pharmacology. We also pay a price for this deficit in the practice of medicine. Most doctors in the United States, like most patients, now acquire knowledge about the drugs they prescribe from direct-to-consumer advertising (*20*).

REMEMBRANCE OF THINGS PAST

How does one recover lost expertise? Indeed, the decay of clinical pharmacology as a brand captures only one element of the collective expertise now needed to reenergize the drug development process. To facilitate the translation of more personalized therapeutics, we require investigators facile with model systems, informatics, principles of drug action, quantitative signatures of drug exposure, and both mechanism-based and unbiased readouts of drug effects (*21*). How can we develop such expertise as a way of bridging the translational divide?

Brand a discipline. Although the stakeholders are diverse, they should agree on a name for the discipline. The rapidly developing network of institutes supported by the Clinical and Translational Science Awards (CTSAs) (*22*, *23*), with their emphasis on education and infrastructure, can be highly supportive of this endeavor. However, the term CTS is too broad for a focus on bridging the translational divide in the quest to develop new therapeutics. CTS includes many established disciplines, from the basic sciences through to health services research. "Clinical pharmacology" is too limited and

outmoded a term to attract recruits to a modern drug-discovery paradigm, whereas "T1" translational research—an aseptic phrase used to cover the translation of discoveries from proof of concept in cells and model systems to the exploration of mechanisms in humans—is unlikely to set pulses racing. In contrast, translational medicine and therapeutics (TMAT) places the discipline at the heart of medicine and captures the focus on translation and the ultimate goal of novel therapeutics. Here, the National Institutes of Health (NIH) and Wellcome Trust, together with academic and industry partners, might play a catalytic role in popularizing the brand. Successful branding, from the Walkman to the iPhone, can capture the imagination, project a lifestyle, and deliver a product, while creative rebranding—think Burberry bikinis—can breathe fresh life into a moribund enterprise.

Establish career structures. An attraction of a brand is that one can build around it the funding that supports initial training and subsequent career, program, and infrastructural awards. This funding is also a statement of how much value society places on the endeavor, which in itself can enhance recruitment with the promise of a stable career path. Presently, science and society have made a statement about the value of clinical and translational research and the importance of translation per se. We need now to name and nurture the orphan stepchild of this process, so-called T1 translational research.

Use flexible, interdisciplinary, and diversified approaches to education. Ideally, one might enter the TMAT discipline with any primary science–based doctorate. Thus, the flexibility of a Master's degree makes it an ideal introductory degree. Such a program might include didactic material from many presently segregated disciplines; rotations in industry, the NIH Clinical Center, and the Food and Drug Administration (FDA); and engagement in translational science projects. One could then build on that experience with postdoctoral studies prior to faculty appointment. Segments of such a Master's program might be offered as freestanding options to facilitate pursuit of TMAT in interdisciplinary teams. Undergraduate courses might be linked to preferential entry to Master's programs. Sabbaticals and the ability of trainees to move across centers, such as exist within the CTSAs or the U.K. Biomedical Research Center consortia, might further broaden the interdisciplinary capabilities of such a program.

Establish appropriate funding and promotional cycles. A particular challenge of TMAT is the prolonged research cycles intrinsic to work that is projected across the translational divide. In particular, the regulatory burden imposed on mechanistic studies in humans often delays study initiation by well more than a year from time of concept. Extended funding cycles—maybe to 8 years

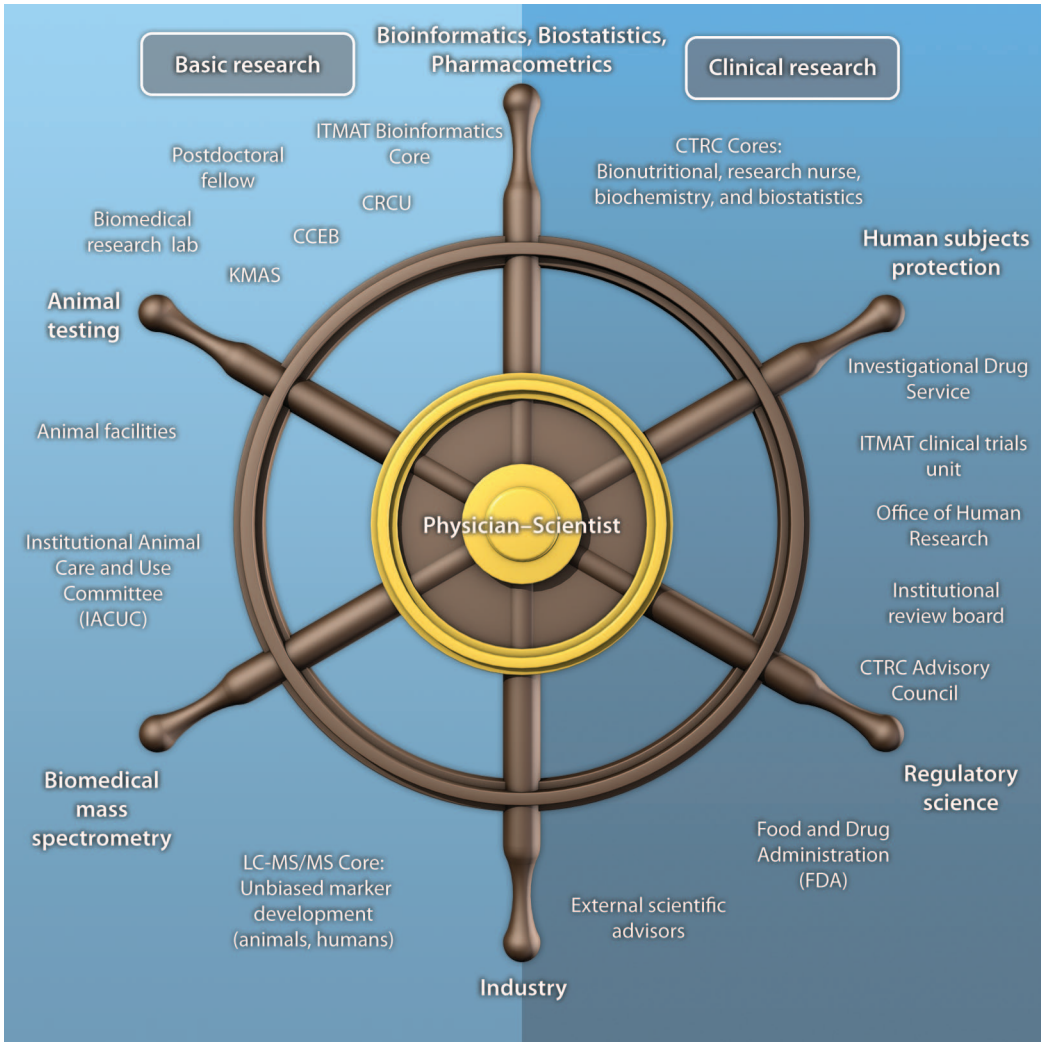

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Fig. 1. Physician-scientists at the helm. This case study demonstrates the scope of interactions involved in the pursuit of two mechanistic investigator-initiated protocols (clinicaltrials.gov identifiers NCT00682318 and NCT00780325). The physician-scientist (center) navigates resources situated in the clinical (right) and basic (left) research domains. In this case, initiation of the clinical research plan required a multiplicity of interactions, mainly with resources of the Clinical Translational Research Center (CTRC), regulatory bodies (institutional review board, FDA), and industry to ensure a protected environment for research participants. Resources from the basic research enterprise provided development and validation of unbiased markers in animals. Collectively, approximately 65 colleagues ensured mostly service-oriented requests, with a smaller number participating in intensive interdisciplinary project-oriented collaborations (for example, in the domain of biometrics). ITMAT, Institute for Translational Medicine and Therapeutics; CRCU, Clinical Research Computing Unit; CCEB, Center for Clinical Epidemiology and Biostatistics; KMAS, kinetics, modeling, and simulation core; LC-MS/MS, tandem liquid chromatography mass spectrometry.

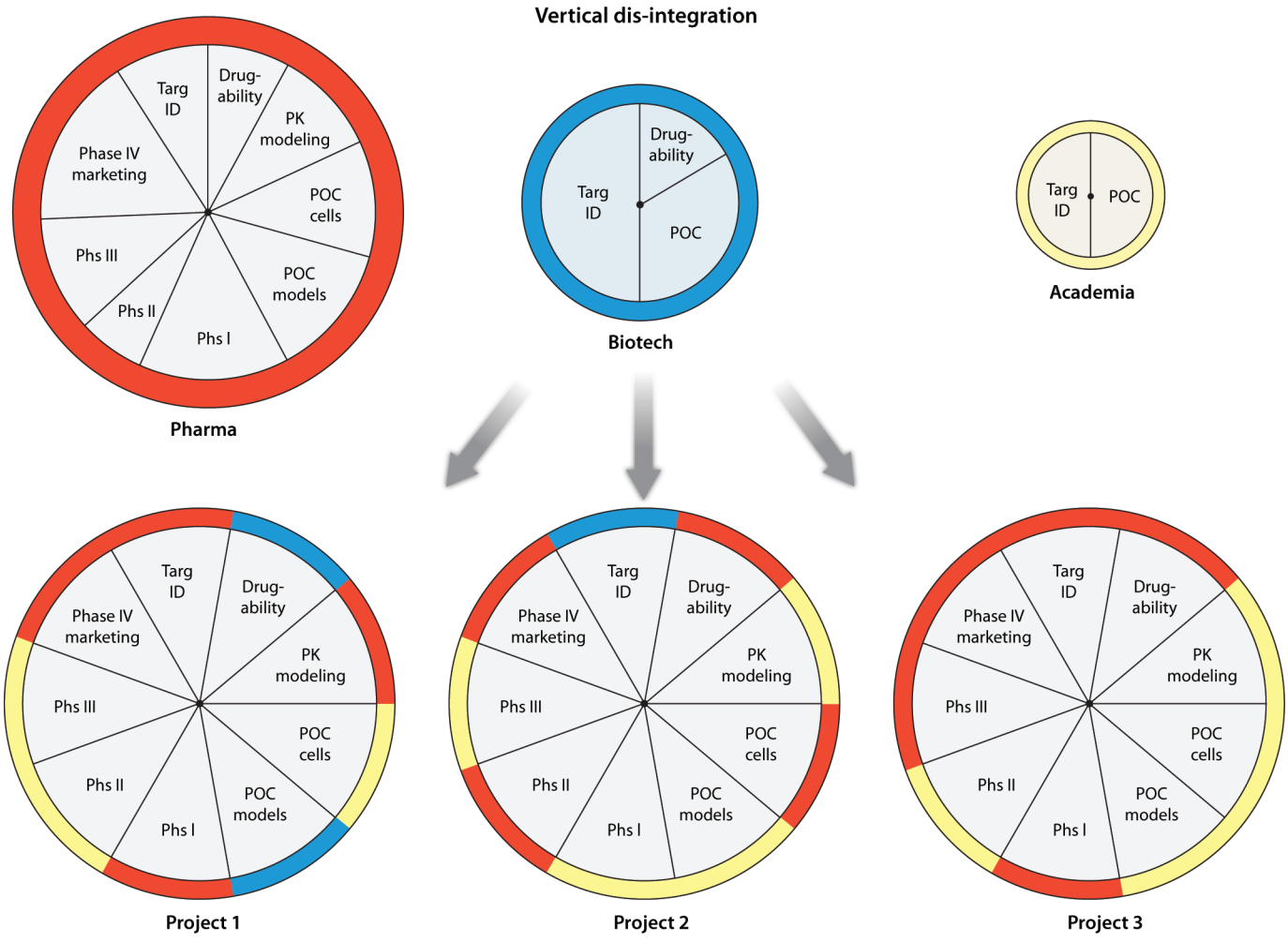

Fig. 2. Modular, dis-integrated models of drug discovery and development. (Upper panel) Traditionally, the vertically integrated large pharmaceutical company retained expertise in target identification, medicinal chemistry, and clarification of the drugability of the target; pharmacokinetics and modeling; proof of concept (POC) in cells and model systems; and all phases of clinical development. Biotechnology traditionally focused on target identification, medicinal chemistry, and drugability and POC studies, whereas the smaller contributions from academia focused on target identification and limited POC studies. (Lower panel) As the capacity of academia to engage in TMAT pursuits increases, we are likely to move to a more segmented approach that crosses sectorial and geographic boundaries. Precisely what sector supports which segment may vary with each project. Examples of this approach are presently extant in the not-for-profit sector; examples include the Medicines for Malaria Venture (MMV), TB Alliance, and Institute for OneWorld Health.

rather than 5—are necessary to support this research, particularly if it has a preclinical element, although consideration for promotion might be based on nearer-term milestones. Pursuit of TMAT by teams of scientists presents distinct challenges for promotional recognition.

Establish a strategic approach to reviving human pharmacology. Rather than the occasional recruitment of a single faculty member with an interest in drug action, Academic Medical Centers (AMCs) might adopt an integrated strategy for rebuilding expertise in human pharmacology across all clinical departments, using a common divisional nomenclature. The resulting recruits from such an integrated endeavor might become members of a transdepartmental structure focused on TMAT and have their clinical appointments anchored by secondary appointments in pharmacology.

Manage unintended consequences. The very interdisciplinary nature of education in TMAT reinforces the need for a well-endowed career structure and a prominent academic home. One unintended consequence of developing an infrastructure to facilitate TMAT at the University of Pennsylvania (www.itmat.upenn.edu) has been the multiplicity of interactions now available to the trainee to pursue merely the clinical domain of such research (Fig. 1). Initiatives to navigate such emerging resources will prove as important as their creation.

Reward the pursuit. Any nascent discipline benefits from visible role models. Again, it is a statement of societal attribution of value if these individuals are celebrated in ways visible to potential recruits.

ENDGAME

The translational process is perhaps the most pivotal in the continuum of drug development (*24*). Given the diversity of stakeholders, the cultural and structural adjustments and funding required, the challenge of engaging recruits, and the cost of failure, it seems timely to develop an international and

strategic approach to addressing the human capital deficit in TMAT. Doing so promises to impact favorably the development, approval, and distribution of first-in-class therapeutic entities and will be crucial to pursuing strategies that move progressively toward more personalized forms of therapeutics.

Academia should be the main engine of education and the hub of this emergent discipline. Indeed, AMCs in developed countries perform conventional large-scale clinical trials inefficiently as compared to clinical research organizations or consortia of medical practitioners. A more credible option for AMCs is to move up the value chain by pursuing the more intense phenotyping that is intrinsic to TMAT (*25*). Development of a critical mass of knowledge in a TMAT structure can allow it to function as an incubator or mother ship for this expertise, permitting graduates to populate other departments in an AMC or to pursue careers in industry and regulatory bodies pertinent to the development of novel therapeutics.

The Wellcome Trust has recently funded several academic centers in the United Kingdom to establish TMAT programs (*26*), and enhancement of T1 research has been identified as a strategic goal of the CTSA consortium (*22*). As we witness the dis-integration of the conventional business model of drug development within large vertically integrated pharmaceutical companies, transition to a more segmented model that transcends sectors and national boundaries (Fig. 2) depends on the emergence of TMAT capabilities in our AMCs.

"We have not the time to take our time."

—Eugene Ionesco

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