Attrition and Translation

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The recently published NIH Roadmap proposes that public-sector science should place increased emphasis on the development of new therapeutics and diagnostics based on the fruits of fundamental research. Such "translational research" activities, traditionally the province of the private sector, have long been compromised by high rates of attrition (failure during the course of preclinical or clinical development of therapeutics). Attrition has led to growing financial costs, as well as opportunity costs. The new focus offers a way to reverse these trends, especially if the scientific community can improve on its ability to reconcile molecular genetic research with integrative organ- and organism-based research.

Translational research, particularly the discovery and development of therapeutics and diagnostics, has been the traditional province of the private sector. The National Human Genome Research Institute's vision (*1*) for the future of genomics research, as well as the NIH director's (*2*) recently proposed grand challenge for the U.S. life sciences research community, emphasize increasing support for the enablement and execution of translational research activities. In addition, a number of not-for-profit organizations that underwrite basic research, such as the Gates Foundation (*3*) and the Cystic Fibrosis Foundation (*4*), are also promoting translational research initiatives to encourage the discovery and development of therapeutics for medical disorders largely ignored by the pharmaceutical and biotechnology industries. The anticipated rebalancing of the funding portfolio is a welcome attempt to broaden the scope of the academic research enterprise. This will result in an increased awareness of the challenges and opportunities associated with therapeutic discovery and development, as well as diversifying and deepening the talent pool engaged in such activities.

The emerging interest in translational activities is not surprising, given the success of the Human Genome Project (HGP). The scientific community's confidence in its ability to develop, access, implement, and integrate new technologies and capabilities has only been enhanced by this track record of success. There is also an element of pragmatism reflected in choosing this strategic option. In the wake of the HGP, it is evident that the time required for completion of what until recently were considered heroic projects (e.g., positional cloning, genome sequencing, etc.) has been substantially shortened and that an increasing number of the traditional tasks of molecular genetics have become trivialized. On the basis of these trends, there is recognition of the necessity for redefinition of what constitutes technical progress or demonstrates legitimate scholarship. In this context, it is not surprising that there is interest in expanding the depth and breadth of activities as well as know-how expected of life scientists, and that these changes should also be reflected in their research programs. Another driver for translational research is the acknowledgment that the essential component of the funding thesis for the HGP has been the promise of its direct and tangible impact on human health, and it logically follows that promoting such activities should lend additional credibility to the ongoing effort.

An expansion of the public effort directed toward translational research should not simply replicate the existing paradigm. There is a tremendous opportunity for innovation that is afforded by a lack of commercial constraints, as well as by the absence of systems and processes often found in large, established, bureaucratic "top-down" organizations. The decentralized, independent nature of the academic system, in contrast to the highly concentrated and integrated research organizations favored by industry, offers another dimension to translational research efforts. The proposed investments in translational research are also well timed, as research and development organizations within biotechnology and pharmaceutical companies begin to confront the distractions and uncertainties that have accompanied the economic downturn and other pressures challenging their sector. The frequent mergers that have plagued the industry over the last several years are part of a trend toward consolidation that has become the default pathway for sustaining desirable compound annualized growth rates within the industry, in the absence of expanding pipelines based on internal investments in research and development. The resulting downsizings and restructurings accompanying these mergers, as well as the shifts in priorities favoring the acquisition of marketed products and later stage clinical candidates, come at the expense of more speculative investments in innovation and in earlier stage research and discovery programs.

As the academic community begins to plot its course in the area of translational research, there are two important questions to ask: What are the central issues confronting therapeutic discovery and development today? What types of investments will have the greatest impact on the process? The short answer to the first question is attrition, and the short answer to the second question is the enhancement of "predictability" premised on the reconciliation or unification of genetics and physiology.

The Problem and Impact of Attrition

A recent report from Tufts University (*5*) suggests that the fully loaded cost for the development of a single novel therapeutic with anticipated "blockbuster potential" exceeds $800 million. A fundamental driver for this expenditure is the cost of failure (i.e., the attrition rate) of drug development programs (*6*–*9*). Furthermore, the number of drugs exiting the pipeline to the market continues to shrink, which, when combined with the rising costs, suggests that the drug development process requires rethinking. Ironically, any drug candidate that enters clinical development will have demonstrated evidence of safety and efficacy in preclinical models, yet still faces a >90% chance of failure because of either a lack of clinical efficacy or

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the presence of intolerable side effects (*6–10*). As a consequence, sustaining a commercially viable pipeline of therapeutics under the current model requires a massive enterprise supporting multiple programs moving forward in parallel, so as to ensure the survival of at least a few product candidates in the face of this Darwinian-like selection process.

The cost structure underlying the development of drugs, especially given the requirement for a reasonable return on investment, places substantial constraints on the choices that are made by drug developers, ultimately limiting the breadth, access, and innovation of emerging therapeutics. Less common disorders and diseases of the developing world that do not promise the commercial return necessary to support investment are often excluded from the process. This cost-and-risk equation compels companies to balance their portfolios by including in their pipelines "fast follow-on" programs or "me too" products [e.g., multiple 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, selective serotonin reuptake inhibitors, Cox-2 inhibitors, PDE5 inhibitors, etc.] at the expense of developing novel or highly differentiated candidate products. Furthermore, the dream of "personalized medicine"—a cornerstone of the promise of the HGP—cannot be promoted or realized if it only results in diminishing the size of a potential market without contributing to an associated improvement in the overall attrition rate. In addition, the industry is reluctant to explore and develop de novo disease-preventive agents because of the considerable technical, development, and commercial risks. Other practices within the industry that are often targets for critics, such as direct marketing to patients and providers or focused efforts to extend periods of exclusivity, are good business tactics as well as symbols of the difficulty of refilling the product pipeline.

The implication of the "attrition problem" is far-reaching because both public and private investment in basic research is predicated on the promise of a future impact on public health, and both sectors are investing in translation. Failure to meet these goals in a cost-effective and consistent manner undermines not only our credibility, but also the public's trust and enthusiasm for the overall enterprise.

In Search of Predictability: Reconciling Physiology and Genetics

The villain in this story is the inherent lack of predictability of our available models for complex biological processes and the inability of our current life science paradigm to provide an effective road map for improvement. Today, we have successfully deciphered the human genome, defining to a first approximation the objects of biology (i.e., genomes, genes, gene products, and their variants), as well as basic aspects of their behavior (*11*). Increasingly, we are developing an understanding of the connections among these objects, as elaborated in the descriptions of pathways and networks, and in many cases we can even provide a three-dimensional picture of a biological object on its own or as part of a larger molecular machine. The boundaries between the many "classical" fields of life sciences research are disappearing as a result of a shared intellectual and experimental framework, as well as the common vocabulary that has arisen from molecular biology and genomics. Our work, dedicated largely to the further description of these objects, has developed a remarkable sameness, an almost ritualistic "bottom-up" effort that leads to a foreseeable set of experiments designed with the pretense of establishing molecular mechanisms.

Yet, more often than not, we generate correlations and teleological explanations that are more operational than they are mechanistic. The picture *du jour* often seems to promote "biology" as nothing more than the sum of its "hierarchical clusters," and that picture is less than satisfying. Our current paradigm, often confusing technical success with progress, fails as we attempt to incorporate physiology into the schemes that have been unified under the umbrella of molecular biology. We must acknowledge that we are falling woefully short of defining clear chains of causality that would effectively "link genetics to physiology" in a manner that could form the basis for robust, reliable models of complex biological processes. It is ultimately the deficits in this domain that deny translational research—despite its appearance of rationality and technological sophistication—a legacy of cost-effectiveness, reliability, and consistent success.

Genetics and physiology are two of the pillars of basic medical research. Although they are often viewed and practiced as unique disciplines, the hope of a more "predictable" translational research model requires that they are reconciled in the 21st century. A continuous experimental and/or theoretical path that links or promotes the interconnection between microscopic and macroscopic phenomena is a fundamental challenge for all basic sciences. Whether we ultimately succeed in developing a grand unified theory is less important than being committed to transcending the current status quo.

Pathways to Progress

Where do we go from here? Acknowledging the problem and embracing the necessity for change is a first step, but there are a number of short-term strategic investments or policy decisions that can be made that will promote the emergence of a more "predictable" biology. The knowledge base and experimental foundations and methodologies of physiology and pharmacology (i.e., integrative, whole-organism, or organ system biology) need to be part of the training for all life scientists. In addition, we need to encourage and support more people to enter these fields as a primary discipline. A recent report by the Life Sciences Research Office (*12*), sponsored by the American Physiological Society and the American Society for Experimental Pharmacology and Therapeutics, suggests that in the wake of the ascendance of more reductionist disciplines of molecular biology and genomics, there has been a marked decline in the number of trainees and experienced professionals in these areas, and this fact is reflected in the reduction of relative published output of this sector in high-impact peer-reviewed journals. This is a trend that needs to be reversed. An area of particular interest would be comparative physiology, especially as it relates to the development and characterization of animal models of disease and drug response.

As a community, we have placed a high priority on defining molecular mechanisms of disease initiation and progression with the aim of improving diagnosis, disease monitoring, and treatment. However, effort or investment has not been focused on systematic and comprehensive approaches to understanding the mechanism of action of drugs, as well as the biology of xenobiotic responses (i.e., absorption, distribution, metabolism, and excretion of drug-like substances). A major contributor to the rate of attrition is the failure of preclinical models to predict these behaviors in human subjects. To a first approximation, half of all failures during the course of preclinical and clinical development across all therapeutic areas can be attributed to failure to resolve these issues. Optimizing the pharmacologic properties of candidate therapeutics is often rate-limiting in early discovery programs. Improvement in our understanding of this area, linked to the development of new tools to help guide drug development, would be one of the highest impact investments that could be made by the emerging effort in the public sector.

Research in human subjects remains the cornerstone of our efforts to link genetics to physiology. We need to invest in clinical researchers and clinical research centers in order to both drive and support translational research. This includes not only clinical and epidemiological research, but experimental medicine as well. Investments in training and technology, particularly in the areas of noninvasive testing and functional imaging, will be key drivers. Like physiological and pharmacological research, experimental medicine efforts have lagged in investment and prominence during the emergence of molecular genetics and genomics, and this is another trend that needs to be reversed. Expansion of such efforts also requires a concurrent investment in the ongoing development of the necessary legal and ethical safeguards, as well as monitoring systems to ensure both public safety and access to these categories of research.

Prospective population-based and family-based resources, inclusive of biological, clinical, genetic, and environmental information, are essential tools for genetic and epidemiology re-

search and are another foundation resource for translational research. These ascertainment efforts and the knowledge extracted from them are key drivers for translational research, yet this type of resource remains largely under the direct control of the principal investigators. Although it will be difficult to make retroactive changes, we need to explore how future resources can be established on an "open-source model," improving access, enhancing utility, and reducing unnecessary duplication of effort and cost. Establishment of such community-based standards, in the form of the "Bermuda Guidelines," was an important factor in the overall success of the large-scale genome sequencing efforts and remains an important legacy of the HGP (*11*). The success of these guidelines has been an important factor in recent efforts directed toward expanding the scope of primary and derived data sets that operate under such principles (*13*). Bringing preclinical research and development data as well as clinical trial and postapproval trial methods, rationales, materials, and data—regardless of the outcome of these efforts in the marketplace of ideas—would also be of tremendous benefit and would generate substantial goodwill.

Along these lines, the scientific community also needs to be supportive of the proposals recently outlined by the commissioner of the Food and Drug Administration (FDA) to facilitate the introduction of the emerging tools of molecular medicine into the clinical trial environment (*14*). The anticipated success of such efforts may benefit patients and will also provide mechanisms to explore and review new ideas. This support needs go beyond "lip service" and will require the provision of enhanced resources directly to the FDA, as well as the possibility of allocating research dollars/efforts from other agencies in support of these initiatives. Adapting open-source practices to experimental medicine, clinical trials, and epidemiological research will also require investment in the development and implementation of information storage, retrieval, representation, and management systems of the scale and complexity required to enable the type of access for this class of data that we have become accustomed to with respect to DNA sequence–based data.

The emerging emphasis by the public sector on translational research, coupled with the increasing need and desire on the part of the private sector to access the output of academic research, will help the relationship between the public and private sectors to evolve. The guiding principles governing costs for access to information, tools, and resources, as well as freedom to operate, are generally defined by the community's consensus regarding the boundary between precompetitive research and competitive research. Competitive research activities are often encumbered by mechanisms that promote exclusivity and regulate access. Traditionally, concern over "freedom to operate" has only drawn the attention of the private sector. However, as the public sector contemplates a broader role in translational research, it will increasingly need to focus on such issues in a manner that does not create unnecessary limitations on the eventual development of the fruits of such research. The recent challenges to the "research exemption" (i.e., the expectation that intellectual property rights will not be asserted in the case of academic research activities) are clear wake-up calls to tribulations that may lie in front of us (*15*). It would appear that the interests of the public and private sectors may become more closely aligned in these matters, and together they will need to develop a consensus on the boundary between precompetitive and competitive research activities (as well as licensing and intellectual property policies) that preserves the necessary exclusivity required for commercialization and rewards innovation, and does not unduly burden or inhibit the underlying translational research activities (*16, 17*).

In summary, an emerging challenge for life science research is to unify the fields of genetics and physiology, resulting in a more comprehensive and predictable picture of biology while enhancing the translational research process. The current lack of predictability not only represents a deficit in our knowledge base, but results in substantial opportunity cost, increased financial cost for therapeutic development, and limits on the potential impact of our basic research enterprise on public health. Therapeutic development will likely remain a highly empirical, attrition-driven process. To the extent that advances in research and development paradigms will enable us to fail earlier at a less costly juncture of the process, as well as "fail better" by ensuring a better understanding of the deficits in our understanding, we will eventually bring ourselves to fail less often.

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18. The opinions stated in this article are those of the author and not necessarily the opinions of Exelixis Inc. or its partners.

VIEWPOINT

Molecular Imaging: Looking at Problems, Seeing Solutions

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Noninvasive molecular-imaging technologies are providing researchers with exciting new opportunities to study small-animal models of human disease. With continued improvements in instrumentation, identification of better imaging targets by genome-based approaches, and design of better imaging probes by innovative chemistry, these technologies promise to play increasingly important roles in disease diagnosis and therapy.

Most biologists associate "imaging" with microscopic, cell-based studies. Our familiarity with noninvasive imaging procedures is primarily personal; we think in terms of our dental x-rays, the magnetic resonance imaging (MRI) necessitated by our overzealous passion for tennis, or the diagnostic positron emission tomography (PET) scan for a family member threatened with a devastating disease. This limited view may soon be a thing of the past, however. A new set of technologies, collectively termed "molecular imaging" (*1–4*), is providing biologists with exciting new opportunities to study noninvasively and repetitively the mechanisms un-