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Regulatory Science Innovation: A Rate-Limiting Step in Translation

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Sustained funding for academic regulatory science will drive innovation and implementation, forge a viable career path, and build an educated workforce.

An essential part of the translation process, regulatory science is underfunded, undervalued, and in need of innovation. The Burroughs Wellcome Fund (BWF) has a history of jumpstarting scientific fields with targeted funding. In keeping with this tradition, BWF announces an initiative to support regulatory science. The goal of the new program is to fund academic research on innovative approaches and technologies for assessing the safety and efficacy of new therapies, and as a result, to promote regulatory policy decisions based on state-of-the-art science. Here, we describe BWF’s new focus on innovation in regulatory science as a natural extension of our interest in fostering translational research.

For scientific research to drive advances in human health, basic biomedical discoveries must be translated from preclinical studies in cell-based in vitro systems and animal disease models to testing in human subjects, and ultimately to incorporation into medical practice, with subsequent assessment of the resulting health outcomes. Since the mid-1990s, much has been written about the obstacles that block the path between basic and clinical science (1). Major initiatives have been launched with the intention of addressing this “bench-to-bedside” gap and speeding the translation process (2).

In 1997, BWF began to dedicate substantial resources to the then-emerging field of “T-1” translational research; this investment of more than $72 million in 97 midcareer clinical investigators—who spanned myriad medical subspecialties—produced work that has helped to define the field (3, 4). For example, BWF grant recipient Brian Druker helped to develop the first molecularly targeted treatment for chronic myelogenous leukemia; another grant recipient, Jane Koehler, combined clinical insight with basic microbiological expertise to determine that the cause of a devastating skin lesion appearing in AIDS patients was a zoonotic bacteria and then went on to discover a new bacterial species.

In the last decade, translational science has enjoyed growing and substantial public and private investment, which has yielded vast new knowledge and attracted talented investigators to build careers in the field. However, the costs and time required to gain regulatory approval, and thus turn promising but complex concepts and technologies into safe, effective diagnostics and therapies, have grown to the point that the implementation of medical innovations has stalled (5). Delivery of the desired outcome of translation—new, effective therapies—depends on a correspondingly innovative system for regulating the testing and approval of new therapies. But just as the field of translational research was poorly defined and underfunded in the 1990s, the field of regulatory science remains underappreciated now (6). The inadequate commitment of human, institutional, and financial resources afforded to this field has made it a rate-limiting step in the movement of biomedical discoveries from the bench to the bedside (5, 7).

According to U.S. Food and Drug Administration (FDA) Commissioner Margaret Hamburg, regulatory science underlies the development and application of new tools, standards, and approaches for the assessment of medical product safety, efficacy, and quality. The field comprises an array of scientific disciplines and approaches that include laboratory-based biomedical and engineering research, computational modeling, bioinformatics, and statistical analysis and method development (8). In its Strategic Plan for Advancing Regulatory Science, the FDA outlines priority areas that require innovation (9). Successful implementation of this plan depends on new sources of funding and collaborative engagement of regulatory agencies with academia, the nonprofit community, policy-makers, and industry.

IF YOU FUND IT, THEY WILL COME

Fifteen years ago, BWF came to the conclusion that innovative advances in clinical medicine would best be realized by supporting investigators who were working in the T-1 gap (1) in translation—ideally, those scientists who, prompted by clinical insight, had begun to decipher mechanisms of physiology and pathophysiology and were poised to initiate small-scale studies in human subjects that, if successful, could attract the industry funding needed to move into large multicenter clinical trials and, ultimately, develop new therapeutic products.

A growing innovation gap, which corresponds to the T-1 gap, now exists in the regulatory science field (5–8). Emerging
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technologies such as cell-based, gene, and antisense therapies and engineering of tissues, materials, and nanotechnologies have led to the development of potential therapies whose complexity requires new evaluative tools. Thus, modern regulatory science research offers significant intellectual challenges as well as the potential to serve society by promoting human health.

BWF believes that it is time to harness the expertise, creativity, and drive of research scientists in academic medical centers and in schools of engineering and computational biology to address the regulatory innovation gap. Our plan is to attract talent to the field of regulatory science by providing research funding for projects in a wide array of subdisciplines. This support system should, over time, form an interconnected community of regulatory science innovators—biomedical researchers, mathematicians, engineers, physicists, and biostatisticians—that will include scientists funded by BWF and other sources as well as those working within regulatory agencies. Through the development of new methods, technologies, and model systems, this innovation community is expected to advance the multidisciplinary scientific knowledge that forms the basis of modern regulatory decisions. Such a body of work has the potential to define the regulatory science field and raise its profile.

The availability of sustained funding is crucial, because it provides an incentive for academic investigators to take the risk of turning their attention toward new research questions that will have an impact on regulatory science. Just as BWF supported T-1 research by making new awards for 11 years, until it was no longer an underfunded area, we are committing $5 million in 2013 to funding regulatory science and expect to continue making awards through this program until this subfield becomes established and better funded.

THOROUGHLY MODERN METHODS

BWF intends to fund projects that develop new in vitro models and natural animal models of disease, as well as in silico “virtual human” models that will generate new hypotheses about the molecular mechanisms behind idiosyncratic severe adverse reactions to therapies. The design and application of such models will require scientists who are able to synthesize diverse sources of genomic, physiological, pathophysiological, chemical, structural, pharmacodynamic, and imaging data and knowledge. Such advances in predictive toxicology can reduce the large numbers of animals and human subjects and extensive preclinical and clinical testing that would otherwise be required to assess a product’s potential toxicity and drug-interaction profile—all of which make for a costly approval process in terms of both time and money.

Regulatory decision-making also depends on meaningful analytical measures of clinical status, some of which may be developed with as-yet-unvalidated reagents and technologies (for example, genomics-based diagnostics, imaging agents, nanoparticle drug-delivery systems, and in vivo sensors). Projects that develop new biomarkers, surrogate markers, and clinical study end points are needed to improve the accuracy and reliability with which these new technologies measure clinical status and outcomes.

BWF is also interested in the application of biostatistics and epidemiology to clinical trial design. Innovation in statistical approaches will not eliminate the need for appropriately powered clinical trials and long-term follow-up studies to validate efficacy, safety, and surrogate end points; it can, however, strengthen confidence in interpretations of diverse sources of data as bases for decision-making. Incorporation of Bayesian methods, assessing of multiple end points, and development of new methodologies for postmarket surveillance, in the context of vast amounts of data from multiple clinical trials, can improve and accelerate our knowledge about the safety profiles of new therapies.

BWF expects that its awardees will represent many scientific disciplines but will be connected by a focus on research designed to have an impact on regulatory decision-making.

FASHION THE WORKFORCE, CREATE CAREER PATHS

Although BWF recognizes that the education of scientists is a critical part of building any new field, we have decided to target academic research—the context in which scientific education occurs—because the regulatory science field needs concrete examples of research excellence and demonstrations of viable career paths. This strategy was effective in the translational research arena: The 97 investigators supported by BWF’s Clinical Scientist Awards in Translational Research program have mentored several hundred students and postdoctoral fellows. Fostering innovation in and transforming the field of regulatory science will require, and help to create, a cadre of appropriately trained scientists within and beyond regulatory agencies.

Academic programs in regulatory science exist, but at this time most focus on educating students about regulatory affairs, rather than on the development of new regulatory science, and thus steer participants toward career paths in regulatory compliance. A consensus on core competencies for regulatory science is beginning to take shape as a subset of the array of skills needed for translational research; however, deep training in an existing scientific discipline—biostatistics, clinical pharmacology, engineering, genetics, among many others—is an essential starting point from which to shape research questions that will advance the science of regulation (8, 9).

One barrier to regulatory science innovation is a bias on the part of academic scientists toward basic biomedical research priorities and a cultural bias against considering regulatory science to be a field that can enhance academic careers by yielding high-impact publications and continuous funding, which are required for promotions in the current academic reward structure (9, 10). BWF expects that its targeted funding will add momentum to the work of investigators already working in the regulatory science arena and help to create a well-funded career path in academia that draws new players with specialized talents and fresh insights. For more information on the new initiative, we invite interested scientists to refer to http://www.bwfund.org.

REFERENCES AND NOTES


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