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DRUG DISCOVERY

Turning the Titanic

AT THE END OF THE 20TH CENTURY, BIG PHARMA AND ITS CUSTOMERS EXPERIENCED heady days. Translation of medicines such as cholesterol-lowering agents, HIV protease inhibitors, and the first molecularly targeted cancer drugs improved lives and enriched the pharmaceutical industry. The recipe for success appeared obvious: Tweeze apart biological pathways in model systems, and pinpoint molecular targets likely to be pivotal in a disease process. Use this information to develop high-throughput assays to screen for drug candidates. Test promising lead compounds in animal models of disease, and optimize the winners by using medicinal chemistry. Demonstrate safety and efficacy in clinical trials in order to satisfy the approval requirements of regulators, and deploy in the marketplace to benefit patients.

Expensive? Yes. But for a time, the formula was successful often enough to make medical and financial sense. More recently, costly failures in late-stage clinical trials have stalled the Titanic, and these leaks in the translational pipeline have produced a biomedical innovation gap: Most newly marketed drugs are close relatives of already approved, rather than first-in-class, entities (*1*).

Society's successes in the past century have transformed medicine—and revealed weaknesses in our approach to the treatment of patients and the development of medical products. No longer a collection of acute illnesses, the medical landscape now features chronic diseases, many of which are not well understood. This ignorance is expensive. It costs society in lives, dollars, and human contributions to the therapeutic development process. We need a new approach that redirects the research and development (R&D) engine toward deciphering the natural histories of human diseases and using this new understanding to identify therapeutic targets. Such a redesigned drug-development paradigm must begin with the patient.

PATIENTS AND FORTITUDE

There are obvious disadvantages to using people as model systems, but in one arena—human genetics—the information we glean is unmatched in its translational value. From the ongoing efforts of the human genome project, we have begun to reap a bountiful harvest. First with single-nucleotide polymorphisms; then with mutations unearthed through exome- and whole-genome sequencing; and now gene copy number variations, genetic deletions and insertions, and epigenomics, we have reliably defined the genetic landscape of simple diseases and are starting to do the same for complex ones. When it comes to insights into pathophysiology, robust genetic information does not lie. How genotype determines the phenotype may not be clear initially, but one can be certain that a link exists. Rich patient cohorts coupled with powerful research tools—systems biology, computational modeling, and theranostic imaging—can illuminate the genetic underpinning of molecular changes associated with human pathophysiology. Only after we lay the groundwork should drug targets be selected for further consideration.

Human tissue samples are crucial in the early validation of one's genetically derived hypothesis, and validation requires precise biopsy methods and serial tissue sampling over the course of the disease. Potent new analytical tools for obtaining and analyzing human materials can facilitate corroboration of ideas: single-cell analyses; clinical-grade liquid chromatography–mass spectrometry; three-dimensional (3D) and 4D cultures; multiplex tissue-based assays and readout capabilities; and next-generation bioinformatic, metabolomics, and proteomics methods.

Once one has used human genetics to identify a potential therapeutic target, evidence for disease-target validation (that is, proof of clinical mechanism) in humans should be gathered as early in the development process as possible. If one uses human genetics to identify a target, develops a high-throughput screening assay, and obtains a lead compound, then that compound must be used to show, in humans, proof of clinical mechanism and target engagement for validation. These data can include human pharmacological evidence of target engagement, surrogate biomarkers for early measures of efficacy, or proof of clinical mechanism in small clinical trials.

The R&D story of *PCSK9*, a gene that encodes a protease involved in cholesterol synthesis, illustrates the link between genetics and drug discovery. A genetic variant in *PCSK9* was discovered in patients with high cholesterol, and subsequent population studies revealed that *PCSK9* genetic variants can either reduce or raise serum cholesterol levels. Low-density lipoprotein (LDL)–cholesterol binds to liver LDL receptors (LDLRs), which internalize the lipid, thus removing it from the circulation. The wild-type *PCSK9* protein interacts with the LDLR and targets it and the LDL-cholesterol for degradation. Some *PCSK9* variants produce a version of the protein that does not bind LDLRs, which allows the receptor to return to the cell's membrane and further lower serum cholesterol. These individuals have a reduction in coronary heart disease relative to people with the wild-type gene. Other *PCSK9* variants produce a protein with increased protease activity, which depletes LDLR levels and blocks cholesterol uptake by the liver. One of these types of genetic variants was shown to be associated with familial hypercholesterolemia (FH) in 2003 (*2*). Sequence variation in *PCSK9* in the broad population was later found to associate with reduced LDL and reduced heart disease, generalizing the observation made in the rare FH group (*3*). This "target validation" in people led to the discovery and development of a *PCSK9* protease inhibitor that lowers serum cholesterol in nonhuman primates (*4*). PCSK9 protease inhibitor drugs are now in phase III clinical trials designed to measure the drug's ability to improve outcomes in patients with heart disease (*5, 6*).

DRUG DISCOVERY WILL GO ON

The movie *Titanic* has a powerful take-home message for Big Pharma: Turning an ocean liner requires a time-consuming and complex series of maneuvers that, if botched, can yield catastrophic consequences. Better to scrap the linear model of drug development in favor of a network of activities conducted by smaller maneuverable partnerships fueled by diverse stakeholders and a freer, bidirectional flow of scientific information. The ultimate goal of turning the Titanic is cost-effective innovation that enhances disease prevention, diagnosis, and treatment. Deciphering the complexity of human diseases and finding safe, cost-effective solutions that help people live healthier lives requires collaboration across scientific and medical communities throughout the health care ecosystem. Indeed, we must acknowledge that no single institution, company, university, country, or government has a monopoly on innovation.

And most importantly, if scientific innovation is to truly be innovative, we need to be more interested in the people our products will help and to ensure that their voices are heard.

In today's R&D world, partnerships with patient advocates and groups are necessary for defining treatment gaps, raising awareness about the benefits of participating in clinical trials, and accelerating the pace of research. For example, PatientsLikeMe has a clinical trial awareness tool to match patients with relevant clinical trials, and the nonprofit Center for Information and Study on Clinical Research Participation (CISCRP) provides educational materials to inform patients and their support networks about the clinical research process. The European Patients' Academy on Therapeutic Innovation (EUPATI) consortium—which comprises pan-European leaders in patient advocacy, academia, not-for-profit organizations, and companies that are members of the European Federation of Pharmaceutical Industries and Associations—works to help patients, patient groups, and the lay public to be effective advocates and advisers throughout the R&D process. EUPATI is funded by the Innovative Medicines Initiative Joint Undertaking and supported by the European Union (Seventh Framework Programme). This investment illustrates the critical and increasing importance of partnering with patient advocates for improving patient engagement in medical innovation.

Complementary to patient engagement efforts are innovative industry partnerships, such as Sanofi's Sunrise, that are built on new business models that move away from traditional in-licensing to an investor-partner model. Sunrise's first partnership, Warp Drive Bio (WDB), is a biotechnology company focusing on proprietary genomic technology to discover drugs of natural origin. Using a business model designed by Sanofi and Third Rock Ventures, WDB was founded as a fully independent company and retains strategic direction. This approach enables WDB to advance its programs in collaboration with Sanofi while also maintaining the ability to secure additional partnerships. Such nimble business models permit risk-sharing, efficient decision-making, expansion of the precompetitive space, and cost-effective, life-saving innovation.

– Elias A. Zerhouni

1. B. H. Munos, Pharmaceutical innovation gets a little help from new friends. *Sci. Transl. Med.* **5**, 168ed1 (2013).
2. M. Abifadel, M. Varret, J. P. Rabès, D. Allard, K. Ouguerram, M. Devillers, C. Cruaud, S. Benjannet, L. Wickham, D. Erlich, A. Derré, L. Villéger, M. Farnier, I. Beucler, E. Bruckert, J. Chambaz, B. Chanu, J. M. Lecerf, G. Luc, P. Moulin, J. Weissenbach, A. Prat, M. Krempf, C. Junien, N. G. Seidah, C. Boileau, Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia. *Nat. Genet.* **34**, 154–156 (2003).
3. J. C. Cohen, E. Boerwinkle, T. H. Mosley Jr., H. H. Hobbs, Sequence variations in *PCSK9*, low LDL, and protection against coronary heart disease. *N. Engl. J. Med.* **354**, 1264–1272 (2006).
4. M. Frank-Kamenetsky, A. Grefhorst, N. N. Anderson, T. S. Racie, B. Bramlage, A. Akinc, D. Butler, K. Charisse, R. Dorkin, Y. Fan, C. Gamba-Vitalo, P. Hadwiger, M. Jayaraman, M. John, K. N. Jayaprakash, M. Maier, L. Nechev, K. G. Rajeev, T. Read, I. Röhl, J. Soutschek, P. Tan, J. Wong, G. Wang, T. Zimmermann, A. de Fougerolles, H. P. Vornlocher, R. Langer, D. G. Anderson, M. Manoharan, V. Koteliansky, J. D. Horton, K. Fitzgerald, Therapeutic RNAi targeting *PCSK9* acutely lowers plasma cholesterol in rodents and LDL cholesterol in nonhuman primates. *Proc. Natl. Acad. Sci. U.S.A.* **105**, 11915–11920 (2008).
5. "Rare mutation ignites race for cholesterol drug," *New York Times*, 9 July 2013; www.nytimes.com/2013/07/10/health/rare-mutation-prompts-race-for-cholesterol-drug.html?pagewanted=all&_r=0.
6. K. N. Maxwell, J. L. Breslow, Antibodies to PCSK9: A superior way to lower LDL cholesterol? *Circ. Res.* **111**, 274–277 (2012).