Leading Edge
Commentary

Cell

Communication in Drug Development: "Translating" Scientific Discovery

Jeff Settleman[1,*] and Robert L. Cohen[1]
[1]Calico Life Sciences, 1170 Veterans Boulevard, South San Francisco, CA 94080, USA
*Correspondence: settleman@calicolabs.com
http://dx.doi.org/10.1016/j.cell.2016.02.050

The discovery and development of new medicines that promote human health and potentially extend natural life remains a remarkably challenging endeavor. In this Commentary, we identify key elements of communication required to successfully translate promising biological findings to novel approved drug therapies and discuss the attendant challenges and opportunities.

While the successful development of numerous drugs to manage a wide variety of maladies has improved the quality and length of life for countless people, there remains a large unmet need for therapeutics for especially challenging diseases, including various cancers, cardiovascular disease, metabolic disorders, neurodegenerative diseases, psychiatric disorders, infectious diseases, and numerous genetic syndromes. What are the key factors that limit our ability to tackle these diseases with novel medicines? For one, disease biology is immensely complex, and despite an ever-increasing understanding of both basic and disease biology, our ability to identify the most relevant therapeutic targets and to discover drugs that selectively, effectively, and safely modulate those targets to produce clinical benefit remains frustratingly limited. Furthermore, recent advances in the various "omic" technologies that enable precise molecular characterization of diseased tissue have revealed substantial inter-patient heterogeneity, prompting efforts to "personalize" drug treatment. This new paradigm presents both an opportunity to match patients with the right medicines as well as the challenge to develop a sufficiently diverse arsenal of drugs to benefit the growing number of subsets of biomarker-stratified patients.

There is also the challenge of the drug discovery and development process itself—a byzantine and expensive undertaking that fails far more often than it succeeds. A typical program, culminating with regulatory approval, involves dozens to hundreds of workers, requires 10–15 years, and costs hundreds of millions of dollars (DiMasi et al., 2016). Several recent trends have converged to highlight the role of effective, forthright communication among the many participants in this process as an important element of success.

While the discovery and development of currently approved drugs has proceeded through various paths, a somewhat standard approach underlies most successful programs (Figure 1). Typically, a drug discovery campaign begins with a biological observation and an associated therapeutic hypothesis. In most cases, the identification of such targets reflects the cumulative findings of multiple investigators whose independent efforts eventually converge. However, even a single especially provocative discovery can prompt efforts to prosecute a target for therapeutic development. Initial findings are usually reported by academic researchers in peer-reviewed publications, and the especially promising reports prompt efforts to further validate the target and the therapeutic hypothesis.

Once a promising target is deemed "validated," it is often prosecuted for drug discovery. The development of high-throughput screening approaches and improvements in medicinal chemistry and antibody engineering methods in the 1980s and 1990s have revolutionized the pharmaceutical industry, greatly enabling the discovery of candidate therapeutic molecules. The underlying technology has moved beyond pharmaceutical companies, and screening is also now conducted (usually on a smaller scale) in many academic research institutions, with academic laboratories pursuing efforts to discover drugs—or at least "tool compounds" to serve as potential starting points for drug development. Such efforts have yielded numerous tantalizing publications as well as many licensing agreements between academic institutions and biopharmaceutical companies.

Unfortunately, many of the published claims regarding candidate therapeutic targets and "lead compounds" prove problematic. In a revealing study, Amgen scientists described their efforts to replicate results from dozens of landmark cancer research publications (Begley and Ellis, 2012). The result was disappointing—findings could be replicated in only six of 53 cases. While this was surprising to many, our experience as industry scientists and that of many of our colleagues has been similar. A number of root causes and contributing factors have been suggested, and they continue to be widely discussed. In any event, a basic failure of scientific communication was made plain by this experiment.

The ensuing discussion of these issues has been generally productive. While some changes in the manuscript review process have been implemented, it is too early to assess the impact. One approach, implemented by some journals, is a checklist for authors of life sciences articles intended to document the rigor with which experiments were conducted, including statistical methods and measures taken to address potential bias (Nature Editors, 2013; see also checklist available at: http://www.nature.com/authors/policies/checklist.pdf). The editors of some journals have also indicated a willingness to commission statisticians as consultants for certain manuscripts—noting that the training of young biologists is often inadequate with regard

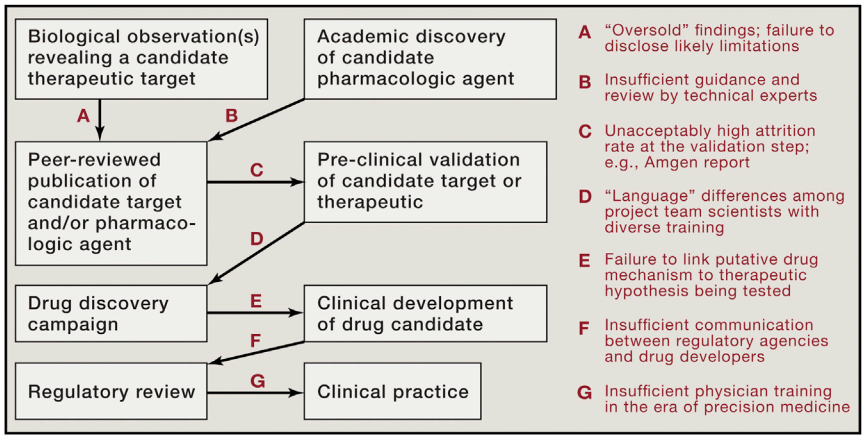

Figure 1. Communication Challenges Associated with the Process of Drug Development
On the left, the various steps involved in a typical drug development program are described, beginning with the early discovery and reporting of candidate therapeutic targets or pharmacologic agents and culminating with regulatory drug approval and clinical implementation. On the right, some of the key challenges associated with each step in this process are briefly described.

to statistics and quantitative analysis, potentially resulting in invalid conclusions.

In the context of drug discovery reports, especially those coming from academic biologists, many of whom underestimate the rigorous evaluation required to adequately credential a novel pharmacologic agent, journal editors should routinely engage industry-based scientists with relevant technical expertise to review such studies. This would be analogous to the aforementioned enhanced use of statisticians as consultants in the review process. One reason why industry reviewers are particularly attentive to robustness is their recognition of the cost of all-too-frequent clinical development failures.

Prior to publication, even at the early stages of a drug discovery project, academic biologists should be encouraged to seek guidance from technical experts. While soliciting consultation from industry scientists is likely to be challenging, many experts with relevant knowledge are in fact embedded within most academic biomedical research institutions these days. Notably, academic technology transfer departments within these institutions have a clear incentive to foster such interactions, considering their interest in developing and licensing intellectual property resulting from drug discovery projects. In our experience, industry reviewers of such licensing opportunities often uncover flaws that were perhaps missed by journal reviewers and the investigators themselves.

More fundamentally, communicating information regarding novel candidate targets and therapeutics in journal articles can be problematic because many claims are simply "oversold," with authors failing to note potential caveats, or other limitations of their analysis. Contributing factors include a peer-review journal publication process that sometimes favors luster over rigor, the evolving NIH mission that increasingly emphasizes translational potential, as well as the occasionally blind optimism that characterizes human nature. However, considering the importance of these target and drug discoveries in the future development of medicines to address important human diseases, additional scrutiny is appropriate before such claims are published. We also suggest that published claims regarding novel targets or inhibitors should include specific communication regarding potential caveats. Journal editors should consider mandating that the Discussion section of such reports includes an honest and complete listing of these limitations. Such "disclaimers" should not preclude publication (unless the limitations are substantial), but rather, they should set a realistic foundation for the next important steps in the process of adequately credentialing and validating a candidate target or molecule. In short, the benefit of an enhanced process for manuscript review and publication to improve communication of genuine biomedical advances with the potential to provide a foundation for eventual drug development seems clear.

The drug discovery paradigm itself introduces a variety of communication challenges. Typically, once a target is validated, a project team is formed within a biotechnology or pharmaceutical company to initiate the laborious process of discovering and evaluating candidate molecules with therapeutic potential. Teams include biologists, medicinal chemists, biochemists, structural biologists, pharmacologists, safety toxicologists, clinicians, and marketing professionals. This group is charged with oversight of a carefully orchestrated effort involving various technical functions. Although they share a common goal, each of the experts on the team is, in some measure, a "specialist," having trained for many years to develop competence in an arcane discipline. The biologists talk of "membrane blebs" and "mitotic catastrophe," chemists describe "chiral centers" and "rotational bonds," structural biologists refer to "steric hindrance" and "NMR spectroscopy," biochemists speak of "Hill coefficients" and "non-competitive inhibition," pharmacologists relate to "bioequivalence" and "hepatic clearance," toxicologists make note of "exposure limits" and "genotoxicity," and clinicians describe "marrow suppression" and "edema." In short, the various team members each speak a different "language," and unlike at a United Nations meeting, there is usually no interpreter at the table.

Given the high level of specialization among the participants, the drug discovery paradigm faces an inherent communication challenge, operating against a backdrop of the innumerable decisions required of project teams. We suggest that team experts make a concerted effort to describe vital information using language that is readily understandable to everyone on the team. A conscious effort should be made to avoid jargon. It is neither necessary nor practical that everyone on the team understands all the technical nuances of each discipline, and use of jargon often bundles assumptions in a "short-hand" that can obscure the essential points for others. The most effective project teams use their shared