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Drug Discovery 2012 and Beyond

David P. Rotella*

Margaret and Herman Sokol Professor of Chemistry, Department of Chemistry and Biochemistry, Sokol Institute for Pharmaceutical Life Sciences, Montclair State University, 1 Normal Avenue, Montclair, New Jersey 07043, United States

The first 11 years of this millennium have been tumultuous for the science of and scientists engaged in *drug discovery research*. At a fundamental level, the need to more clearly link drug−target interactions to the molecular/cellular pathways in a disease process, furnish preclinical models that more accurately reproduce the human disease, and identify useful markers to monitor therapeutic effect have stimulated a research in the field of translational medicine. These tools and the science associated with them are intended to provide greater confidence in targets selected for prosecution. Pharmaceutical companies of all sizes are in various stages of implementation of this strategy in an effort to increase the likelihood of clinical success for their drug candidates.

The beneficial impact of this revised discovery paradigm has yet to be fully felt in terms of improved rates of new drug approval. In pharmaceutical research, the influence has been dramatic in terms of new science that must be developed to support a given project. After approximately 6 years, this approach can also be evaluated for possible unforeseen or unanticipated negative effects to gain a more complete perspective on the net long-term value. For example, how much have these translational criteria contributed to several large pharmaceutical companies withdrawal from areas of research including CNS, hypertension, gastrointestinal diseases, osteoporosis, and asthma? A narrower spectrum of disease areas requires fewer scientists to conduct research. If one couples this with significant outsourcing of various components of the drug discovery process, a substantial headcount reduction in discovery organizations in both large and small companies has occurred. This hypothesis does not minimize the role that other well-publicized factors such as the increasing cost of drug discovery, revenue lost to generic competition, and increased emphasis on biologics play in the attempt to create leaner, more focused research organizations in companies of all sizes.

In spite of this substantial downsizing, long-term benefits to *drug discovery research* are likely to emerge. Many excellent scientists are now engaged in new venues that include virtual companies, research foundations, and academic drug discovery centers. Pharmaceutical companies of all sizes are actively engaging external organizations to take advantage of specific expertise and technology lacking in their portfolios. Industrial scientists now in the academic world are using their valuable skills and irreplaceable experience to develop their own research interests and train the next generation of drug discovery scientists. No longer bound by rigid productivity targets, research priorities and ever-changing philosophies, creative ideas flourish and develop. This increased freedom allows scientists to reinforce the meaning and value of research in the context of drug discovery. Research by definition is "an investigation or experimentation aimed at the discovery and interpretation of facts, revision of accepted theories or laws in the light of new facts, or practical application of such new or revised theories or laws to ***explore the unknown***."[1] Drug discovery in the pharmaceutical industry is and will remain a ***research***-based endeavor. Everyone recognizes that there is no guarantee of success, that is, regulatory agency approval of a drug candidate for human use. More importantly, even with a solid translational foundation, there is no clear path to improving the number of candidates that progress from discovery through the clinic, regardless of the criteria used to vet and evaluate programs.

One does not have to look far to recognize important contributions from academic *drug discovery research*. Professors Rick Silverman, Ted Taylor, Arun Ghosh, Dennis Liotta, and Robert Vince are well-known examples of academicians whose laboratories produced drugs. In each case, *drug discovery research* evolved from an ongoing program in the laboratory. Envoy Therapeutics, Aileron Therapeutics, Proteostasis Therapeutics, and FoldRx are just a few recent examples of companies based on research initiated in academic laboratories. Vanderbilt University recently established a drug discovery center focused on neuroscience targets, led by a group of experienced industrial scientists who also serve as faculty members. This group established multiple collaborations with pharmaceutical companies and advanced compounds into clinical testing. A number of other universities have drug discovery centers including the University of Pittsburgh, Temple University, University of North Carolina, Medical University of South Carolina, Yale, University of Illinois, Northeastern University, University of California at San Francisco, University of Kansas, University of Minnesota, and Montclair State University. Each center possesses unique attributes and capabilities, from specialized therapeutic/biology area interest (e.g., cancer, anti-infectives) to more diverse capabilities including medicinal chemistry, high-throughput screening, in vivo pharmacology, and pharmacokinetics. Many of these centers have ongoing collaborations based on a fit between the needs of an industrial partner and the capabilities and expertise of the academic group. Significant investments are being made in terms of modern research space, equipment, and personnel in an effort to strengthen these capabilities.

In a survey of academic drug discovery carried out by Frye and co-workers at the University of North Carolina,[2] three key obstacles to the ability of these centers to have an impact on drug discovery were identified as follows: funding, medicinal chemistry expertise, and lack of understanding of drug discovery in academia. Finances at these centers should be less of an obstacle in the future, assuming partnerships expand in number and value, and achieve milestones as specified in

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agreements. The influx of accomplished medicinal chemists and other drug discovery scientists into these academic centers will (and may have already begun to) address the latter two issues. However, the effect of these individuals will take time to be recognized and to impact existing perceptions by industrial partners. For example, experienced industrial scientists know that the activity of a novel compound in an animal model does not mean that one has an IND candidate in hand, regardless of how well this molecule performs relative to a positive control. Data on safety, pharmacokinetics, process chemistry, and even a more comprehensive structure−activity understanding are often lacking. Going forward, successful collaborations will be measured initially by the number of clinical candidates and much later by approvable NDAs, and it will be interesting to compare this portion of the industry's portfolio with internally derived programs.

An issue that the Frye report did not discuss (and may not have addressed) is centered on intellectual property and the value of technology and discoveries. There is a natural division of needs in this regard. University scientists, particularly untenured and research faculty, want to publish their work, and industrial scientists need to protect their discoveries. Resolution of this dichotomy exceeds the Wisdom of Solomon. From personal experience and based on discussions with colleagues at many companies, nearly every university believes its contribution is much more valuable than the industrial partner's initial offer. The industrial concern will assume the vast majority of the expense and effort, especially if the project or technology moves into the clinic. This often translates into single-digit royalty payments to the academic institution and/or investigator. Universities must recognize that project- or technology-based collaborations are considered components in a research portfolio by the industrial partner. The value of each collaborative agreement will vary depending on its scope and importance as viewed by the industrial concern. Each partner must protect itself and its contribution to the joint effort, and as individuals on each side become more accustomed to dealing with these issues, the process is likely to become more streamlined and straightforward.

The longer term benefits of industrial−academic collaboration in *drug discovery research* include the emergence of a new generation of scientists whose experience in an industrial−academic collaboration includes real-world exposure to science that impacts human health. Interactions between current and former industrial scientists, graduate students, and postdoctorals during these collaborations will furnish students with benefits beyond scientific learning to include teamwork, communication, and strategic-planning skills. It appears clear that the pharmaceutical industry will continue to expand its search for external partners to augment its strength, which lies in the later stages of the project. University-based drug discovery centers and faculties are increasing the number of former industrial scientists on their staff. The presence of former industrial scientists as a part of these collaborations should make corporate partners more comfortable when dealing with external partners because of their shared experiences (and scars). *Drug discovery research* will benefit as a direct result of the proliferation of the many new branches established outside the boundaries of industry. I look forward to the opportunities this will provide and to the continued evolution of our discipline.

AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

REFERENCES

(1) Adapted from the Merriam-Webster dictionary.
(2) Frye, S.; Crosby, M.; Edwards, T.; Juliano, R. US Academic Drug Discovery. *Nature Rev. Drug Discovery* **2011**, *10*, 409−410.