COMMENTARY

Biotechnology and Translational Medicine

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INTRODUCTION

A significant proportion of innovative proof-of-concept clinical science is performed in biotechnology companies. They can benefit from the many lessons learned by large pharma companies, and they should in turn contribute their lessons learned to the literature.

COMMENTARY

The process of translating a basic scientific discovery into a novel therapeutic that improves public health is immensely gratifying. A particularly exciting time in the translation process is the early clinical testing to assess—for the first time—whether a novel molecule is efficacious in humans. This “proof-of-concept” (POC) stage of translation has a high risk of failure and must be carefully tested, but a positive POC is scientifically—and often financially—rewarding. This is particularly true for small biotech companies where a positive POC is a “value inflection point,” leading to enhanced market valuation or strategic partnerships or even acquisition.

How much of the industry-sponsored POC science is done by small biotech companies? It is hard to say. There are over 3,500 industry-sponsored, open, interventional phase II studies currently listed at clinicaltrials.gov without any way of knowing which are definitive POC trials. However, if we examine the 86 New Molecular Entity and New Therapeutic Biological product approvals by the US Food and Drug Administration (FDA) over the past 2 years (2014–2015), we see that a significant percent of the POC science done for these recently approved molecules was conducted by small companies. For 26 of the 86 approvals, the approval was granted to a small company, and for another nine approvals the POC science was conducted by a small company, although the eventual approval was attributed to a large company. For example, the POC science for lesinurad, a URAT1 inhibitor for the treatment of gout (whose approval was granted to AstraZeneca) was conducted by Ardea BioScience prior to the AstraZeneca acquisition; the POC science for blinatumomab, a bispecific anti-CD3/anti-CD19 for the treatment of acute lymphoblastic lymphoma (ALL) (whose approval was granted to Amgen) was done by Micromet prior to the Amgen acquisition; and idelalisib, a PI3K inhibitor for treatment of chronic lymphocytic leukemia (CLL) and other related malignancies (whose approval was granted to Gilead) was already in phase II studies conducted by Calistoga at the time of the Gilead acquisition. In addition, a number of large pharmaceutical companies create separate subsidiaries from the small biotech companies that they acquire and the POC science is conducted by scientists from the acquired company (e.g., the Imclone subsidiary of Lilly and the Millennium subsidiary of Takeda). Thus, it would appear that upwards of 40% of the POC science done for recently approved products is done by small companies. Indeed, it is the demonstration of efficacy in humans—the POC result—that has led to many acquisitions. If one or more of these small companies had erred in designing or conducting their POC trials, yielding a false-negative result, we may never have benefited from their breakthrough. Given that ~500 biotech companies were started over the period 2011 to 2015, and that there were 175 biotech Initial Public Offerings (IPOs) over that same period, it is reasonable to believe that small biotech companies continue to contribute significantly to POC science.

Given the high stakes related to POC trials, a number of groups have conducted retrospective analyses of their successes and failures in hopes of deriving general principles than can enhance the probability of POC success. Morgan et al. performed an analysis of 44 programs that reached a decision point during phase II clinical development at Pfizer between 2005 and 2009. Of these 44 programs, 32% achieved a positive readout in their clinical POC study. These authors determined that the presence of three fundamental pharmacologic elements (which they termed the “Three Pillars”; Box 1) were important in determining phase II success:

1. Drug exposure at the target site of action
2. Binding of the drug to the pharmacologic target
3. Evidence of functional modulation of the target resulting in alterations in downstream pharmacology

In this analysis, if none of the three fundamental pharmacologic elements were evident, all 12 programs failed to test their novel mechanism, whereas when all three elements were evident, all 14 programs tested their novel mechanism with 12 achieving POC and 8 advancing to phase III.
Box 1. The three pillars of survival

PILLAR 1: Drug exposure at the target site of action is necessary to elicit a pharmacological effect over a desired time period.
PILLAR 2: Target occupancy is a prerequisite for expression of pharmacology and target modulation.
PILLAR 3: Functional modulation of the target is a prerequisite for expression of pharmacological activity to test the mechanism.

From Morgan et al. ⁶

Cook et al. ⁷ performed a similar lessons-learned analysis of 142 drug discovery and development projects that had been active at AstraZeneca between 2005 and 2010. They identified five technical factors associated with project success that they termed “the 5 R’s” (Box 2): right target (having a high level of confidence in the biological role of the target in human disease), right tissue (demonstrating drug exposure and pharmacological activity in the target organ), right safety (having an appropriate safety profile), right patient (testing the drugs in the correct patient population during phase II), and right commercial (confidence that a project would deliver a medically differentiated and commercially viable product). Cook et al. note the similarity of their “right tissue” to the Three Pillars of Morgan et al.

Box 2. The 5 R framework

RIGHT TARGET
• Strong link between target and disease
• Differentiated efficacy
• Available and predictive biomarkers

RIGHT TISSUE
• Adequate bioavailability and tissue exposure
• Definition of pharmacodynamic (PD) biomarkers
• Clear understanding of preclinical and clinical pharmacokinetic and pharmacodynamics
• Understanding of drug–drug interactions

RIGHT SAFETY
• Differentiated and clear safety margins
• Understanding of secondary pharmacologic risk
• Understanding of reactive metabolites, genotoxicity, drug–drug interactions
• Understanding of target liability

RIGHT PATIENTS
• Identification of the most responsive patient population
• Definition of risk–benefit for a given population

RIGHT COMMERCIAL POTENTIAL
• Differentiated value proposition against future standard of care
• Focus on market access, payer, and provider
• Personalized healthcare strategy, including diagnostic and biomarkers

What are the implications of the analyses of Morgan et al. and Cook et al. for biotech companies? They need translational scientists! It is imperative that biotech companies have people who can develop and validate assays for the new chemical or biological entity itself (and its metabolites), as well as assays for the assessment of downstream pharmacology. As we saw in the analysis of Morgan et al., even in a large company like Pfizer these assays were not always in place at the time of the POC trial. It would be prudent for small biotechnology companies to consult with experts either in academia or in larger companies as they develop their translational plans, and to be sure to have validated assays in place when their molecules enter the clinic.

The retrospective analyses by Morgan et al. and Cook et al. highlight important pharmacologic principles, but are perhaps most remarkable for their candor and willingness to share both their successes and their failures. More such analyses will continue to advance the science of translational medicine. Nonetheless, there are notable limitations in the analyses of Morgan et al. and Cook et al. First, the programs they reviewed are almost entirely small-molecule programs. A similar analysis of a large portfolio of biologic programs would be most welcome. Second, as we move into novel modes of therapeutics—such as cell therapies, nanotechnologies, oncolytic viruses, RNA therapies, gene therapies, and regenerative therapies—we do not have a large portfolio of programs to analyze. These novel therapeutics are largely developed in small biotech companies with a limited number of programs. While many of the principles articulated by Morgan et al. and Cook et al. will surely apply to all translational programs—especially early evidence of anticipated pharmacologic activity in the target organ, appropriate safety, and testing the drug in the right patients—we can also anticipate that additional factors may be determinative in the success of novel therapeutic modalities. For example, chemistry, manufacturing, and controls (CMC) of small molecules is a well-established enterprise and will rarely contribute to POC success. However, in the case of cell therapies, oncolytic viruses, and gene therapies CMC quality may be crucial in ensuring adequate testing of novel mechanisms and novel therapeutic modalities.

Large pharmaceutical companies have the resources (time, people, and money) and a large portfolio of successful and failed projects to undertake the type of retrospective review conducted by Morgan et al. and Cook et al. Small biotech companies do not. Indeed, especially with a failed POC trial, small biotech companies will often lay off large numbers of employees as they seek to control costs. While understandable from a business perspective, the rapid loss of knowledge and insights that accompanies the layoffs...
means the potential loss of important lessons learned regarding novel science. Small companies are encouraged to take the time to deeply analyze the root cause of their failures, and to publish their results. This journal invites such important manuscripts.

It is also important to note that the transition of a research program from a small biotech company to a large biopharmaceutical company through acquisition is an important time to reassess the principles articulated by Morgan et al. and Cook et al. Programs are increasingly acquired at the “IND ready” stage. A small biotech may have been intensely focused on simply getting their molecule into the clinic—the minimum requirements for IND submission being met—without developing the necessary tools for assessing the three Pillars, for example. It behooves the acquirer to take the time to ensure that the acquired program has met the criteria of Morgan et al. and Cook et al. in order to optimize the probability of success.

In summary, the field of translational science is exploding with novel therapeutics, many of which are being developed in small biotech companies with limited resources. The future of these companies—and the future of therapeutics—rests on the quality of translational science conducted in these small companies. Let’s hope the management of these companies embrace the learnings of their large company peers—and add to our knowledge by sharing their science in the peer-reviewed literature.

Conflict of Interest
The author declared no conflict of interest.

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