As Technologies for Nucleotide Therapeutics Mature, Products Emerge

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The long path from initial research on oligonucleotide therapies to approval of antisense products is not unfamiliar. This lag resembles those encountered with monoclonal antibodies, gene therapies, and many biological targets and is consistent with studies of innovation showing that technology maturation is a critical determinant of product success. We previously described an analytical model for the maturation of biomedical research, demonstrating that the efficiency of targeted and biological development is connected to metrics of technology growth. The present work applies this model to characterize the advance of oligonucleotide therapeutics. We show that recent oligonucleotide product approvals incorporate technologies and targets that are past the established point of technology growth, as do most of the oligonucleotide products currently in phase 3. Less mature oligonucleotide technologies, such as miRNAs and some novel gene targets, have not passed the established point and have not yielded products. This analysis shows that oligonucleotide product development has followed largely predictable patterns of innovation. While technology maturation alone does not ensure success, these data show that many oligonucleotide technologies are sufficiently mature to be considered part of the arsenal for therapeutic development. These results demonstrate the importance of technology assessment in strategic management of biomedical technologies.

INTRODUCTION

With the recent approval of the antisense therapeutic nusinersen for the treatment of spinal muscular atrophy, jointly developed by Biogen and Ionis Pharmaceuticals, oligonucleotide technologies may have finally yielded a clinically and commercially successful biopharmaceutical product. This long-anticipated success was the subject of a series of recent review articles that have chronicled the difficult, 30-year path that led to this important milestone.1-4

The recent series of expert reviews chronicled a long series of insights, false starts, successes, and failures that mark the path from the initial discoveries of nucleotide therapeutics to the approval of nusinersen.1-4 Analogous expert reviews have been written for other technologies that experienced decades-long lags between an enabling scientific insight or invention and approval of a first-in-class therapeutic based on that advance. For example, the ability to make monoclonal antibodies, first described by Kohler and Milstein, only generated therapeutic products when their methods for producing murine antibodies was supplanted by methods for producing chimeric, humanized, and, finally, fully human monoclonal antibodies,5 while the discovery of TNF only led to anti-TNF therapeutics after the failure of TNF as a cancer therapy and recognition of the role played by TNF in arthritis and other inflammatory disorders.6-9 While this type of analysis by experts in a field can faithfully relate the complex, and often convoluted, path of translational science, such post hoc reflections have not produced a generalized explanation for the characteristic innovation lag between scientific insights and inventions and first approval of successful therapeutic products based on this science.6

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A 2011 RAND report highlighted the importance of such an understanding in concluding: “Despite their policy salience, little is known about time lags and how they should be managed. This lack of knowledge puts those responsible for enabling translational research at a disadvantage.”

Explanations for this characteristic lag have come from research on the process of innovation itself, including the roles of organizational behavior, strategy, social networks, and technology management and the dynamics of scientific, intellectual, human, and economic capital in the innovation ecosystem. One aspect of this research has focused on the temporal relationship between scientific and technological progress and successful product development, demonstrating that technological maturation or “readiness” is a critical determinant in the ability to develop successful products. A 1999 General Accounting Office report on the management of technologies noted, for example: “….no element is more important than having technology, advanced enough to meet requirements but also mature enough to be predictably managed, available at the start of the product development cycle. Maturing new technology before it is included on a product is perhaps the most important determinant of the success of the eventual product.” As a result, strategic technology management often uses tools such as technology roadmapping,10 technological forecasting,15,16 or technology readiness assessment15,17 to assess the maturation of critical path technologies and their ability to satisfy the performance specifications for innovative products over time.

While most of this research involves computers and communication technologies, mechanical engineering, aerospace engineering, or defense systems, we have applied these theories18–20 to develop analogous models for biopharmaceutical development. Specifically, we have asked whether the characteristic lag between biomedical discoveries and successful biopharmaceutical development is analogous to the lag related to technological maturation or readiness observed in other technology sectors.21–25 Studies have shown that many different technologies mature through a characteristic “S curve,”26,27 in which an initial insight or invention initiates a period of exponential, technological advance, which slows as the technology approaches its limits. Our initial studies suggested that there were qualitative parallels between patterns of innovation observed in other technology sectors and the accumulation of publications for monoclonal antibodies, nucleotide therapeutics, and gene therapies.21 We then described a bibliometric-based analytical model, the Technology Innovation Maturation Evaluation model (“TIME model”), which allows for a quantitative assessment of research maturation based on publication activity over time. Briefly, the model posits that peer-reviewed research papers embody a quantum of new knowledge related to a research area; some represent positive contributions, while others may represent insignificant, or even negative, contributions. Integrated over large numbers of published papers, the number of publications may be considered a metric for the advance of that technology. We have applied this model to more than 200 discrete drug targets along with technologies for monoclonal antibodies and gene therapies and have shown that the accumulation of publications for the large majority of technologies examined can be modeled as an exponentiated logistic function (“S curve”).22–24 This curve is characterized by a point of initiation (“Ti”) representing the point of maximum acceleration into a period of exponential growth, which slows as the technology passes an established point (“Te”), defined as the point of maximum slowing, and approaches a limit (Figure 1). The analytically defined point of initiation and the established point provide objective, quantitative metrics for asking whether successful development of biopharmaceutical products is linked to maturation of associated technologies, as observed in other technology sectors.

In studies of >400 new molecular entities (NMEs) using the TIME model, we have shown that few products discovered using targeted screening or biological products are approved before the associated technologies pass the established point,25 and that interval between the initiation point of a new research area and first approval of a drug based on this research is 36 years.24,25 In contrast, there was no association between metrics of technology growth and approval of product discovered through phenotypic methods.24,25 These observations are consistent with the expectation that targeted discovery is based on accumulated knowledge of potential drug targets and their relationship to disease processes, whereas phenotypic methods are not based on such knowledge.29

These studies suggest that the characteristic lag between the initiation of new areas of research and first approval of biopharmaceutical products based on this research is an intrinsic property of targeted and biologic strategies for drug discovery and development. In this report, we extend these studies to oligonucleotide therapeutics, asking whether quantitatively similar patterns are evident in this field. The results suggest that innovation of oligonucleotide therapeutics has followed largely predictable patterns, with successful products emerging only after research related to the specific oligonucleotide technology, component technologies, and the molecular targets past
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