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**ORIGINAL ARTICLE**

# Why commercialization of gene therapy stalled; examining the life cycles of gene therapy technologies

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This report examines the commercialization of gene therapy in the context of innovation theories that posit a relationship between the maturation of a technology through its life cycle and prospects for successful product development. We show that the field of gene therapy has matured steadily since the 1980s, with the congruent accumulation of >35 000 papers, >16 000 US patents, >1800 clinical trials and >$4.3 billion in capital investment in gene therapy companies. Gene therapy technologies comprise a series of dissimilar approaches for gene delivery, each of which has introduced a distinct product architecture. Using bibliometric methods, we quantify the maturation of each technology through a characteristic life cycle S-curve, from a Nascent stage, through a Growing stage of exponential advance, toward an Established stage and projected limit. Capital investment in gene therapy is shown to have occurred predominantly in Nascent stage technologies and to be negatively correlated with maturity. Gene therapy technologies are now achieving the level of maturity that innovation research and biotechnology experience suggest may be requisite for efficient product development. Asynchrony between the maturation of gene therapy technologies and capital investment in development-focused business models may have stalled the commercialization of gene therapy.

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## INTRODUCTION

It has been 40 years since the emergence of recombinant DNA technologies led to consideration of engineering genetic material into therapeutic products.[1,2] Since then, the human genome has been sequenced, >35 000 research papers on gene therapy have been published in academic journals, >16 000 US patents addressing gene therapy have been issued and gene therapy technologies have been used to 'cure' hundreds of diseases in animal models. Gene therapies have also been investigated in almost 2000 clinical trials, producing both salient setbacks and successes.[3–5] Recently, dramatic successes in treating diseases such as hemophilia,[6] Leber Congenital Amaurosis[7–9] and X-linked Severe Combined Immunodeficiency[10] have been heralded as the long-awaited confirmation that gene therapy can be used to safely and effectively treat human disease.[11]

It has been 25 years since the first gene therapy companies were founded to commercialize gene therapy technologies.[12] Since then, >50 companies have been founded explicitly to develop gene therapies, and these companies have collectively attracted >$4.3 billion dollars in capital investment from private and public markets. By the end of 2012, however, there were no commercially available human gene therapy products in the US or EU. Several gene therapy products are in clinical use in China[13] (Gendicine and Oncorine) and Russia[14] (Neovasculogen), although these products have not been subjected to the clinical studies that are required for approval in the US or EU. One product, Glybera, originally developed by Amsterdam Molecular Therapeutics, received approval from the European Commission in November 2012[15] after clinical trials demonstrated its safety and efficacy for treating familial lipoprotein lipase deficiency.[16,17] The company, however, was insolvent before approval was granted, and as of mid-2013 Glybera had not yet been launched.

This report examines the protracted path toward commercialization of gene therapy in the context of innovation theories that posit a relationship between technological maturity and successful product development. These theories are based on the observation that science and technology mature through a characteristic life cycle, classically described as an S-curve.[18] The life cycle begins with a Precursor stage, during which there is an accumulation of ideas, materials and methods leading to an initiation event in the form of a discovery or invention. The initiation event introduces a Nascent stage of the life cycle, characterized by diffusion and rapid acceleration of research. This leads to a Growing stage, in which knowledge and technological capability advance exponentially. As the limits of the technology are encountered and progress slows, the technology enters an Established stage. In response, research turns to new, nascent ideas and inventions designed to overcome these limits. The sequential emergence of new, ordinal technologies, each progressing through a characteristic life cycle, produces the continuous, exponential progress commonly associated with Moore's Law.[19,20]

Extensive research in many fields, ranging from computer hardware and communications to new materials and heavy machinery, suggests that the position of a technology in its life cycle influences the quality of products that can be developed, the nature of value created by investments in that technology and the components of business models required for creating this value.[18,19,21–26] The essential observation is that commercial markets are dominated by products enabled by Established

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stage technologies. These markets are sustained by those innovations that can be incorporated into existing product architectures[23,26] and value networks,[26] and which can be effectively developed with the 'resources, processes, and values' extant in industry.[19]

Some innovations, however, introduce new dissimilar architectures. Research shows that in their Nascent stage, such technologies rarely generate products that can meet the standards of existing markets or compete effectively against established products.[18,19,26] Such innovations are often classified as disruptive. It is not until such technologies achieve a requisite level of maturity that they begin to generate a pipeline of successful products.[18,19,21]

### Technology life cycles in biotechnology

Our previous work considered the application of these innovation theories to biotechnology.[27] We examined three classes of biotherapeutics—monoclonal antibodies (MAbs), nucleotide therapeutics and gene therapy—using bibliometric methods to quantify the accumulation of knowledge and technological capability. This analysis showed that the maturation of these three biotechnologies followed a classic S-curve with the discrete stages described in other fields. Most importantly, we observed an association between the maturation of MAb technologies and the first successful development of MAb products.[27]

The emergence of MAb technologies in 1975 created enormous optimism that this nascent technology would provide a pipeline of therapeutic products. The early approval of Orthoclone in 1986 reinforced this optimism, but proved to be deceptive. Over the next decade, >200 different MAbs failed in clinical trials, and Orthoclone was eventually withdrawn from the market.[28] The first successful MAb products were not approved until 1994. Many successes followed. By 2012, there were 34 MAb products on the market and >50 in late-stage trials.[29,30] Our analysis of the MAb technology life cycle suggested that the decades of futility in clinical development corresponded to the Nascent and Growing stages of the life cycle. Consistent with observations in other fields, MAb technologies began to generate successful products only when the enabling technologies reached the Established stage.[27]

In this report, we examine the relationship between the commercialization of gene therapy and the progression of these technologies through their life cycle. Critical to understanding the maturation of gene therapy is the fact that gene therapy comprises a series of dissimilar, ordinal gene delivery technologies with different architectures. Using quantitative, bibliometric methods, we show that gene therapy has progressed steadily over the past 25 years, and that each of the ordinal gene therapy technologies has matured through an independent life cycle that can be modeled as an S-curve. We observe that capital investment and clinical investigation have been asynchronous with the maturation of these technologies. Both capital investment and clinical investigations have focused predominantly on technologies in their Nascent stage, where product development is classically problematic. We examine the implications of this asynchrony and how it may have contributed to the lag in commercialization of gene therapy technologies. This analysis suggests an optimistic future for gene therapy, as the leading gene therapy technologies are now achieving the levels of maturity that have been requisite for the development of successful products in other technology fields.

## RESULTS AND DISCUSSION

### The progression of gene therapy

Progress in the field of gene therapy was measured by the number of papers addressing gene therapy in PUBMED (Figure 1a), the number of issued US patents mentioning gene therapy (Figure 1a) and the number of clinical trials involving gene therapy (Figure 1b). All three metrics accelerated through the 1980s and 1990s and remained relatively stable thereafter.

Figure 2 shows the cumulative number of papers, US patents and clinical trials as a fraction of the total at the end of 2011. These three metrics are highly correlated ($R^2 = 0.99$, $P < 0.01$).

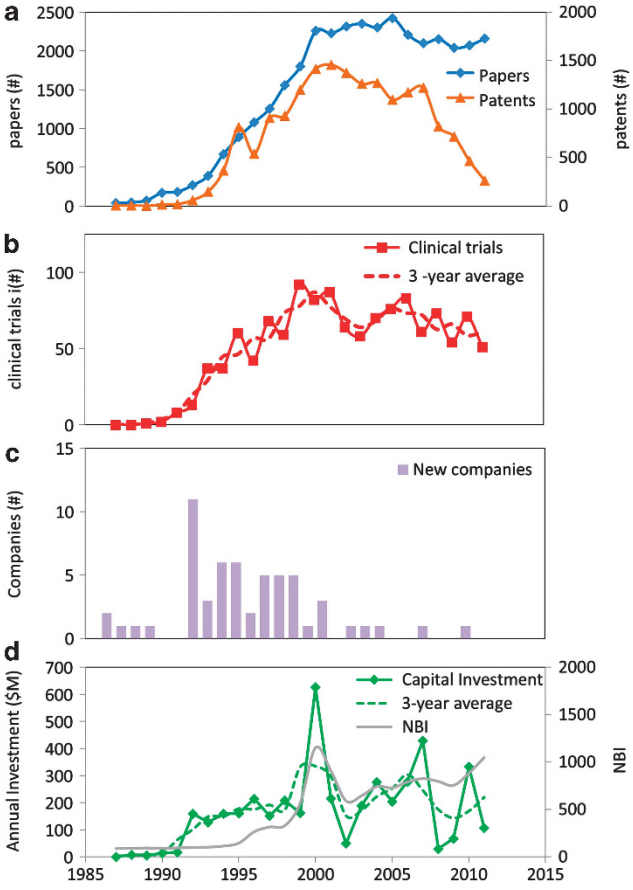


**Figure 1.** Metrics for the progression of gene therapy. (**a**) Annual publications in PUBMED (left axis) and issued US patents (right axis) addressing gene therapy. (**b**) Annual number of new clinical trials involving gene therapy. (**c**) Number of new companies founded to commercialize gene therapy. (**d**) Annual capital investments in gene therapy companies, 3-year average of capital investments in gene therapy companies and the NASDAQ Biotechnology Index (NBI, right axis).

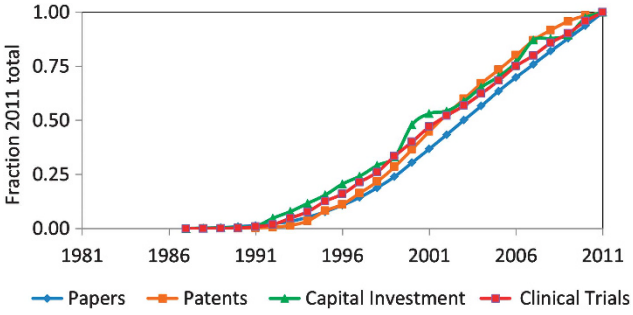


**Figure 2.** Congruent metrics for the progression of gene therapy. The cumulative number of publications in PUBMED, issued US patents, clinical trials and capital investment is shown as a fraction of the total at the end of 2011.

**Table 1.** Number of gene therapy companies, outcomes and financings included in study

| | *All* | *Viral* | | | | | *Nonviral* |
|---|---|---|---|---|---|---|---|
| | | *ALL* | *Retro* | *AAV* | *AAV* | *Lenti* | |
| Companies, *n* | 59 | 36 | 4 | 11 | 17 | 5 | 22 |
| Active at end of study, *n* | 30 | 21 | 1 | 9 | 7 | 4 | 9 |
| With capital financing, *n* | 50 | 29 | 3 | 8 | 14 | 4 | 21 |
| Number of financings, *n* | 260 | 185 | 36 | 48 | 75 | 26 | 75 |
| Total capital investment, $(M) | 4195 | 3128 | 272 | 874 | 1569 | 412 | 1067 |
| Constant 2011, $(M) | 5317 | 3937 | 426 | 1080 | 1947 | 484 | 1381 |

Abbreviations: AAV, adeno-associated virus; Lenti, lentivirus; Retro, retrovirus.

The first few companies explicitly focused on commercializing gene therapies emerged in the late 1980s (Figure 1c). We identified 59 gene therapy companies (Table 1). This number is less than that described by Crofts and Krimsky,[31] Martin[32] and Jain,[33] which included companies developing cell-based therapies, platform technologies or services, as well as companies not focused primarily on gene therapy.

We identified 260 separate capital financings between 1987 and the end of 2011 by 50/59 companies (Table 1). The first capital investments in gene therapy companies were made in the late 1980s, and by 2012 these investments totaled $4.2 billion ($5.3 billion in constant 2011 dollars). Annual investment in gene therapy increased through the early 1990s (Figure 1d) and was closely correlated with general market indices. The 3-year moving average of capital investment showed a significant correlation with NASDAQ ($R^2 = 0.84$, $P < 0.01$), NBI ($R^2 = 0.75$, $P < 0.01$) and the S&P 500 ($R^2 = 0.87$, $P < 0.01$). Cumulative capital investment in gene therapy between 1987 and 2011 significantly correlated with the cumulative number of papers, patents and clinical trials ($R^2 = 0.99$, $P \ll 0.01$) (Figure 2).

These data paint the picture of an apparently robust gene therapy sector that progressively expanded in scope through the 1990s, and has sustained a steady level of publication, patenting, clinical investigation and capital investment to the present day. Of note, these data suggest that the often-discussed, adverse events encountered in clinical trials between 1999 and 2002[5,34] had little, if any, long-term effect on any of these metrics. Although there was a substantial drop in capital investments in 2001–2002, and a similar drop in 2008, these drops correlated closely with general market conditions and rebounded with the markets in ensuing years.

The dominant influence of market conditions on capital investments in gene therapy is not surprising. It has been observed that early-stage venture capital investments, in general, correlate with market conditions.[14,35,36] What is striking in these data is the absence of a positive correlation between capital investment and progress in the field of gene therapy. Multivariate analysis, in fact, shows a significant negative correlation (inverse relationship) between capital investment in gene therapy and metrics of progress in their field of gene therapy (either the number of papers or number of patents) when market indices are included in the statistical model. Results of this multivariate analysis are shown in Supplementary Material.

## Modeling the maturation of gene therapy

Progress in gene therapy has been characterized by a series of ordinal innovations in gene delivery technologies, each designed to circumvent the limitations of earlier technologies. For example, the first viral technology, Retrovirus, was developed to circumvent the inefficient transfection technologies; Adeno circumvented the oncogenic potential and low titer of Retrorivus; AAV technologies circumvented the limited persistence of Adenovirus; and Lentivirus circumvented the limited carrying capacity of AAV. Of particular importance for this analysis is the fact that each of these ordinal innovations involved an alternative approach to gene therapy, rather than incrementally modifying earlier methods to improve performance. Furthermore, each of these technologies introduced a different architecture. For example, each method required a distinct set of materials and methods for engineering and manufacturing the product, modes of administration, clinical applications, pricing constraints and potential toxicities. As such, each ordinal technology represented an architectural, or disruptive, innovation and would be expected to mature through a separate S-curve and life cycle.[26]

The sequential emergence of these ordinal technologies is evident in the annual number of papers (Figure 3a), US patents (Figure 3b), clinical trials (Figure 3c) and capital investment (Figure 3d) in companies focused on each technology. The S-curve of the technology life cycle for each technology was modeled from the cumulative number of papers related to each technology as a logistic regression (Figure 4a). For each technology, the best fit logistic regression exhibited an $R^2 > 0.98$. The limit (L) that provided for the best-fit logistic regression represents the maximum number of papers that would be expected if progress continued along the best-fit, logistic curve. From this limit, the maturity index of each technology over time was calculated as the ratio of the cumulative number of papers ($y^*$) divided by the projected limit (Figure 4b). As of the end of 2011, Retro technologies had a maturity index of 0.93, and would be characterized as Established. The maturity index of the other ordinal technologies (AAV = 0.73, Adeno = 0.83, Lenti = 0.48, nonviral = 0.72) would be classified as Growing.

## Capital investment and maturity of gene therapy

To examine the relationship between capital investments in gene therapy technologies and the maturation of these technologies through their life cycle, we determined the maturity index at the time of each investment based on the technology focus of the company in which the investment was made. Over time, the number of capital investments (Figure 5a, left) and the total capital investment (Figure 5b, left) in gene therapy, viral gene therapy companies or nonviral gene therapy companies exhibit the pattern of early growth and subsequent stability observed generally for the field of gene therapy as a whole. The same data considered as a function of the maturity index exhibit a significant negative correlation (inverse relationship) between maturation and either the number of capital investments (Figure 5a, right) or the total capital investment (Figure 5b, right). The majority of all investments in gene therapy ($5.3 billion in constant 2011 dollars) has been invested in companies with technologies that have a maturity index of $< 0.3$, and investment has waned as these technologies have matured. It should be noted that this analysis likely underestimates the extent of the

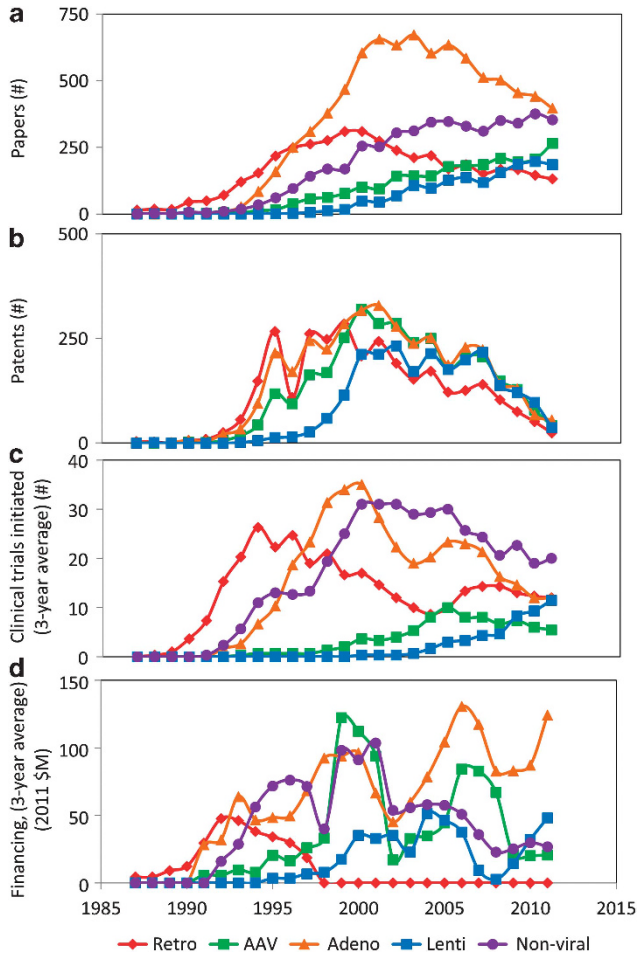


**Figure 3.** Metrics for the progression of ordinal gene therapy technologies. (**a**) Annual papers in PUBMED addressing specific technology. (**b**) Annual issued US patents addressing specific technology. (**c**) Annual clinical trials involving specific technology (3-year moving average). (**d**) Annual capital investment in companies based on their primary technology focus (constant 2011 dollars, three-year moving average).

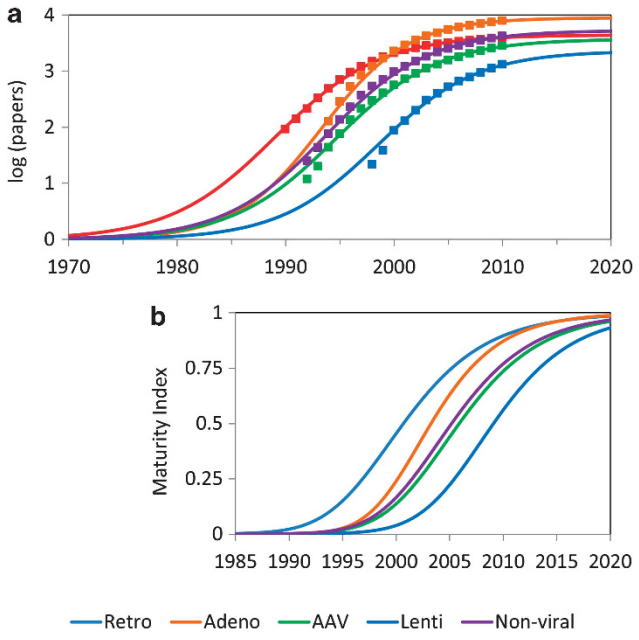


**Figure 4.** Analytical model for technology life cycles of ordinal, gene therapy technologies. (**a**) The S-curve of the technology life cycle is modeled from the log of the cumulative number of publications (symbols) as a logistic regression (solid lines). (**b**) The maturity index is calculated from the analytical model as the ratio of the cumulative number of papers at any point in time divided by the projected maximum number of papers calculated from the limit of the logistic regression shown in **a**.

asynchrony, as the data on early-stage private investments and on investments made prior to 1995 are incomplete.

Capital investment in gene therapy companies represents that largest source of funding for applied gene therapy research and development over the past 25 years. The scope of government grants to academic institutions and small businesses as well as nonprofit involvement in gene therapy research is small compared with the magnitude of capital investment. Moreover, it should also be noted that such investments are also traditionally focused on nascent, basic and pre-clinical science. Recent efforts by the government and nonprofit organizations to support translational research in gene therapy have been relatively smaller in scope. For example, the NHLBI Gene Therapy Resource Program promised $69 million in grants over a 10-year period;[37] the nonprofit Genethon BioProd facility for gene therapy is estimated to cost $37 million;[38] and the Alliance for Cancer Gene Therapy has contributed $23 million for translational research.[19]

Pharmaceutical alliances, which are normally the lifeblood of late-stage biotechnology development, have been notoriously absent for most of the recent history of gene therapy.[38] Of the major biopharmaceutical companies, Genzyme had the most substantial in-house program,[39] and this was funded in part through a special purpose entity, Neozyme, whose capital funding is included in the present analysis. The biotechnology consortia assembled by Rhone Poullenc Rorer (RPR Gencell) and Pfizer (PfizerGen) in the mid-1990s, which included gene therapy, totaled $<$$300 million, much of which comprised capital investments.[40] Although a more thorough analysis of all sources of gene therapy funding is warranted, we believe that this analysis of capital investments in gene therapy reflects the majority of resources available for the commercialization of gene therapies.

## Asynchrony between investment and technological maturation

There are several possible explanations for the observed asynchrony between investment and maturation of gene therapy technologies. First, it is possible that gene therapy simply does not work, and that the investments made in Nascent technologies led investors to conclude that further investment was not warranted. In fact, early clinical trials of gene therapy and efforts to develop commercial products with any of the ordinal technologies were largely disappointing and may have led investors to transition toward successive ordinal technologies.

This analysis suggests that clinical investigation followed a similar sequence. Although the annual number of clinical trials has been relatively stable (Figure 5c, left), a disproportionate number of trials have involved Nascent stage technologies (Figure 5c, right). This is significant, because research in many different technology sectors has shown that Nascent stage technologies commonly do not produce products that can meet the standards of existing markets.[18,19,26] In the case of medical therapeutics, these standards are embodied in the criteria for regulatory approval. This phenomenon is exemplified by the experience with MAb technologies, which did not generate successful products until reaching the Established stage of their life cycle. The first successful MAb products entered clinical trials only after MAb technologies had a maturity index of 0.28. Thus, the fact that

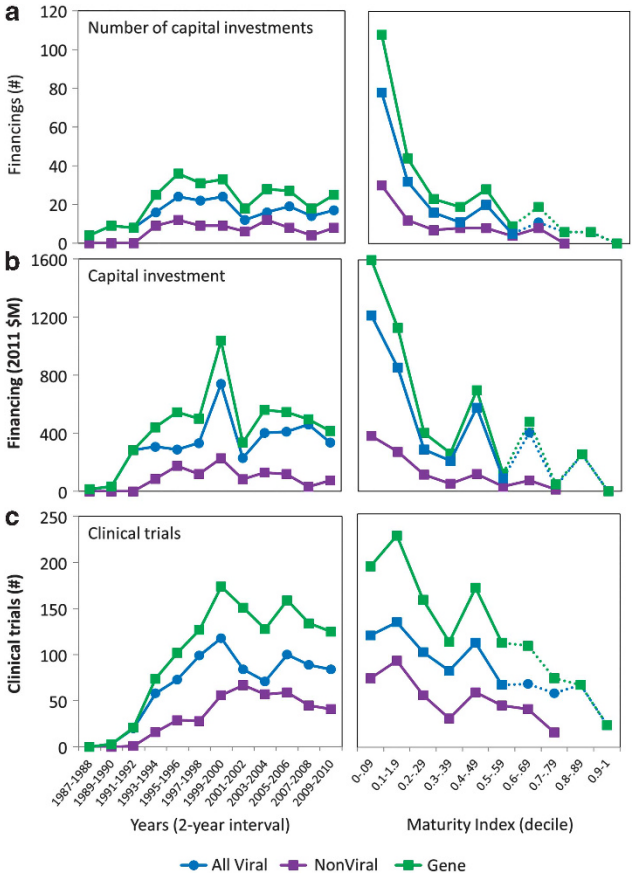


**Figure 5.** Asynchrony between investment and the progression of viral, nonviral, and all gene therapy technologies. The left panels show the progression of metrics over time, shown for 2-year intervals. The right panels show the same data as a function of the maturity index, shown for deciles. (**a**) Number of capital financings in gene therapy companies. (**b**) Total value of capital investments in gene therapy companies (constant 2011 dollars). (**c**) Number of clinical trials initiated. Note that not all of the ordinal technologies were mature as of the date of this analysis; hence, points with a maturity index $>0.5$ are shown as dotted lines.

clinical trials on gene therapies arising from Nascent stage gene therapy technologies have failed to demonstrate the performance or price required of a successful product is entirely consistent with innovation theories and experience with other technologies. So too, the recent clinical successes[11] with maturing technologies are consistent with recognized patterns of innovation.

While declining investment in ordinal technologies may have resulted from disappointment with the clinical results achieved with Nascent stage, this pattern may have also constrained the commercialization of these technologies as they matured. This is exemplified by the experience of Amsterdam Molecular Therapeutics, which was unable to raise capital and entered receivership even as its lead product, Glybera,[15] was undergoing the EMA review that resulted in approval.

Second, the asynchrony between investment and the maturation of gene therapy technologies reflects selective investment in business models that focus on Nascent technologies. The role of a business model has been described thus: 'The business model provides a coherent framework that takes technological characteristics and potentials as inputs, and converts them through customers and markets into economic outputs. The business model is thus conceived as a focusing device that mediates between technology development and economic value creation.'[21]

Although none of the companies in this study successfully commercialized a product for human gene therapy in the US or EU by the end of 2012, it is noteworthy that many created economic value for certain investors. Of the 59 companies in this study, 26 completed an IPO, providing liquidity and a step-up in valuation for early-stage, private investors. Other companies were acquired, although not all of these provided a positive return for investors. Significantly, as none of these companies in this study had positive earnings, product revenues or even therapeutic products in late-stage development, their determined value at the time of IPO or acquisition could not have been based on conventional financial metrics or present value calculations.

Pisano has described biotechnology as a 'science based business' that 'attempts not only to use existing science but to advance scientific knowledge and capture value from the knowledge it creates.'[41] Foster has observed that investments in Nascent stage technologies, before the exponential phase of the technology life cycle, have the greatest potential to generate new knowledge and generate such value. In contrast, investments in Growing or Established stage technologies are more likely to encounter the limits of the S-curve[18] and thus limited knowledge-based value. Thus, investments in science-based business models would be expected to focus predominantly on Nascent stage technologies and not on more established technologies. Most of the companies in this study, in fact, fit the description of science-based businesses, which were founded with Nascent stage technologies, and often generated considerable value for early-state investors as the technology matured.

It has been observed that 'a firm that has excellent capabilities to do scientific research may not succeed well in producing marketable innovations.'[13] This is due, at least in part, to the fact that business models focused on monetizing the value that accrues from the generation of new knowledge may differ significantly in their timeline, scope and strategy compared with business models optimized to develop products.[22] This is evident, for example, in strategies for clinical development of Nascent technologies. Although early clinical trials can generate considerable knowledge and value for science-based business models, such trials may not be optimal for achieving commercial success. Studies have shown that companies without product development experience are more likely to move candidate products into phase 2, and these products are more likely to fail.[42] Successful clinical development has also been shown to be influenced by the amount of capital raised,[43] and even companies that succeeded in generating value from the advance of Nascent technologies struggled to find sources of funding for late-stage clinical trials.[44] When these companies were able to attract investment from the pharmaceutical industry, this support tended to focus on complex diseases with competitive markets,[44] as opposed to low-end, disruptive markets where Nascent stage technologies are most likely to succeed.[19,22,26]

These classic patterns are evident in efforts to commercialize gene therapy. In 1995, the NIH review of gene therapy noted that clinical trials were being initiated to attract investment, writing 'The field is at risk to the extent that the premature initiation of clinical studies and overzealous, uncritical reports of clinical results are used by industry to promote investment…',[24] even though the technologies were immature. Moreover, the recent successes in gene therapy, including the approval of Glybera™ for rare, inherited disease,[11] are classic examples of the low-end, disruptive market introductions that are characteristic of disruptive innovations. So too is the use of gene therapy technologies in veterinary medicine, such as a GHRH gene therapy, LifeTide, approved for increasing litter size in pigs,[21] a cancer vaccine, Oncept, approved for treating canine melanoma,[19] a DNA vaccine, Apex-IHN, approved for preventing infectious hemorrhagic

necrosis in Salmon,[18] and DNA vaccines against West Nile virus.[26] In contrast, almost two out of three of all clinical trials of gene therapy have been in oncology,[45] a notoriously difficult clinical indication with a four-time higher failure rate for NMEs than the average of other indications.[23]

Future research needs to be directed at understanding how statistical measures of technological maturity correspond to specific technical milestones. For example, the maturation of MAbs involved the progressive humanization of MAb sequences to minimize adverse reactions, advances in methods for discovery and manufacture of MAb products and improved selection of appropriate targets and indications. Future research also needs to be directed at characterizing the components of the business models developed by these companies, including their R&D strategy, clinical and regulatory expertise, projected timelines, management, alliances, financing strategy and sources of financing, to understand how these components impacted their ability to move products forward towards commercialization. Importantly, this research must integrate not only a first-principle understanding of the scientific and technical aspects of gene therapy, including both their potential and technical challenges, but also a first-principle understanding of the business models required for scientific and technical innovations to succeed.

## CONCLUSION

More than 25 years after the first gene therapy companies were founded, there are no gene therapy products on the market in the US or EU. Many reasons have been proposed for this failure, including intrinsic limits on the efficiency of gene delivery into human cells, adverse events encountered in clinical trials, lack of interest and investment by large pharmaceutical companies, market preference for small-molecule drugs, regulatory hurdles, and concerns over market acceptance. Although it is beyond the scope of this report to critique each of these arguments and their relative contribution, our analysis suggests that the commercialization of gene therapy is following a path that is entirely consistent with established theories of innovation and the experience of many other technology sectors.

In this context, the present data suggest an optimistic outlook for the commercialization of gene therapy. Our analytical models of the technology life cycles for the major gene therapy technologies suggest that they are now achieving the level of maturity that has been requisite for product success in other technology sectors, including MAbs. Moreover, recent successes in treating rare inherited diseases represent the type of low-end, disruptive successes that classically enable maturing technologies to gain first entry into the market. It may be predicted that, as gene therapy technologies move through the Established stage of their life cycles, they will generate successful products.

The present observations reinforce the perspectives of Pisano[41] that, as science businesses, biotechnology companies that can effectively generate value from the advance of science may be inefficient in developing successful products and sustainable businesses. This inefficiency has an opportunity cost. In the case of gene therapy, $>$\$4.3 billion (\$5.4 billion in 2011 constant dollars) was invested in companies with Nascent technologies, which may have had little prospect of generating successful products. It cannot be determined how much of this investment went into unnecessary corporate infrastructures or premature clinical investigations, how the failures of these initiatives may have discouraged investment in gene therapy as the technologies matured, or how much faster the field may have progressed if clinical investigations and capital investments had been focused on more mature technologies. Such questions are relevant to many Nascent stage biotechnologies. We have shown, for example, that companies with Nascent stage technologies at the time of IPO are often overvalued and face unrealistic expectations for product development and financial value creation. As a result, many of these companies choose to pivot, abandoning their founding technologies in favor of Established stage technologies.[20] We would propose that translational science might be expedited by applying theories of innovation that recognize the predictive significance of the technology life cycle. This would enable better alignment of investment, business models and clinical development strategy to accelerate the maturation of technologies and the efficiency of clinical development.

## MATERIALS AND METHODS

### Data sources

Clinical trials of gene therapy were identified in the Wiley database on Gene Therapy Trials Worldwide.[45] Companies engaged in gene therapy were identified in the 'gene/cell therapy' category of BioCentury's BCIQ database, the biotechnology database described by Morgan and Abetti,[36] and in Jain.[33] Each company's technology was characterized from reports in BioCentury, press releases, company web sites or regulatory filings, as well as patents or publications citing the company as the 'institution.' Companies developing cell therapies, stem cells, nontherapeutic products (for example, platforms, devices, diagnostics) as well as companies that were developing other classes of products in addition to gene therapies were excluded from this analysis. Capital financings were identified in the BioCentury BCIQ database, the Moran and Abetti database,[36] or in CapitalIQ. This analysis did not include other forms of financing such as nonconvertible debt, noncapital investments by nonprofit or government organizations, grants, or revenues from contract research, products or services.

Technologies are defined by the composition of matter of the manufactured product. A nonviral technology is one in which the manufactured product is a formulated nucleic acid. This includes so-called 'naked' DNA as well as formulations of DNA with salts, lipids, proteins, polymers or particulate materials as well as the use of devices for physical gene delivery. A viral technology is one in which the manufactured product is a genetically engineered, attenuated virus. Viral technologies are further delineated based on the species of the virus. This analysis considered technologies based on murine retrovirus (Retro), adenovirus (Adeno), adeno-associated virus (AAV) and lentivirus (Lenti). Other technologies were excluded because of insufficient numbers of papers, patents or capital investments for statistical analysis.

### Bibliometric methods and modeling

The life cycle of gene therapy technologies was characterized using bibliometric methods described previously.[27,46–50] The principle of bibliometric methods is that each research publication contributes a quantum of new knowledge or technical capability that, integrated over thousands of papers, provides a relative, quantifiable measure of scientific or technological progress. Boolean search terms were used to identify relevant citations in the PUBMED database of the National Center for Biotechnology Information (NCBI). These terms are provided in Supplementary Material.

The S-curve of the technology life cycle was modeled as the best-fit logistic regression as described (Ledley *et al.*, submitted). The regression was calculated as:

$$Y^* = L/(1 + e \hat{} (-(mx + b)) ) \quad (1)$$

where $Y^*$ is the log of the cumulative number of papers ($y^*$), $x$ is years and $L$ is the limit of $Y^*$. $L$ represents the log of the predicted maximum number of papers if progress continues along a typical S-curve. The variables $L$, $m$ and $b$ are calculated from the linear form of the regression:

$$W^* = -\ln(L/y - 1) = mx + b \quad (2)$$

To determine $L$, regressions were performed with different values of $L$ to identify the value that produced the highest $R^2$. The maturity index is calculated as $MI = y_i^*/10^L$, where $y_i^*$ equals the number of papers estimated by the regression model at time $i$. Statistical analysis was performed in Microsoft Excel.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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