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Commentaries

It's Time for Gene Therapy to Get Disruptive!

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Soon after my arrival at the University of Pennsylvania, a colleague at the Wharton School warned me that our research in gene therapy may be viewed as disruptive to the biopharmaceutical industry. My initial reaction was astonishment since I had never considered gene therapy in such negative terms.

My colleague was referring to the work of Harvard economist Clayton Christensen, who studies innovations that disrupt existing markets and value networks, thereby replacing earlier technologies (Bower and Christensen, 1995). Examples include steam ships replacing sailing ships, downloadable digital media replacing CDs and DVDs, and ultrasound replacing traditional X-ray imaging. He further refined the concept to recognize the fact that the disruptive nature of innovation is not in the actual technology but rather in the new business model it creates (Christensen and Raynor, 2003). Without question, gene therapy now qualifies as a disruptive technology, as it has been shown to be successful in pilot human clinical trials. Gene therapy will not replace the use of small-molecule drugs or traditional biotherapeutics; however, it is a platform that will have applications across most specialties of medicine.

Early clinical applications of gene therapy have been reserved for severe diseases with limited therapeutic options and substantial morbidity and mortality. Examples include bone marrow gene therapy for several inherited diseases such as X-linked severe combined immune deficiency (SCID) (Hacein-Bey-Abina *et al.*, 2010) and adrenoleukodystrophy (Cartier *et al.*, 2009); in both cases the only viable treatment is allogeneic bone marrow transplantation with a matched donor. Another example is the reconstitution of vision following adeno-associated virus (AAV) gene therapy in patients with congenital blindness due to a rare form of Leber's congenital amaurosis for which no existing therapy is available (Bainbridge *et al.*, 2008; Maguire *et al.*, 2008; Cideciyan *et al.*, 2009). These applications are innovative but are hardly disruptive in that there are no commercial markets to displace.

Bone marrow gene therapy for another form of SCID, due to a deficiency of adenosine deaminase (ADA), is one of the first examples of a potential disruption to an existing market, that is, an ADA enzyme replacement product called Adagen (pegademase bovine; Gaspar *et al.*, 2011). Little has been written about the impact of bone marrow gene therapy on Adagen, possibly because the disruptive technology is cumbersome and associated with significant risks, and because of the limited size of the Adagen market, which yielded only $32 million in annual sales in 2009 (Enzon Pharmaceuticals, 2009). This all changed, however, with the phase 1 study of AAV gene therapy for hemophilia B, which is a genetic disease that is normally treated by recurrent protein replacement infusions to limit and/or treat bleeding episodes (Nathwani *et al.*, 2011). A single injection of vector either eliminated or substantially reduced the patient's need for protein replacement. A similar approach is being developed for the more common form of this disease, called hemophilia A. The successful commercialization of gene therapy for hemophilia A and B would clearly threaten large commercial markets of protein replacement products, which are estimated to yield $6.5 billion in annual revenues (Aarkstore, 2010). Gene therapy as a way to deliver therapeutic proteins has the potential to disrupt many other businesses based on enzyme/protein replacement therapies.

It is important to emphasize that the hemophilia B study was a phase 1 trial; more clinical data are needed before commercial sales and distribution can be considered. For this to happen, however, we need the participation of the biopharmaceutical industry. Christensen's research suggests there may be impediments to this happening, based on what he calls the "Innovator's Dilemma," (Christensen, 1997) which is best described by the following question: "How [can] executives…simultaneously do what is right for the near-term health of their established businesses, while focusing adequate resources on the disruptive technologies that ultimately could lead to their downfall?"

In understanding the forces that influence this dilemma (Christensen, 1997), Christensen describes the rationale for favoring investment in *sustaining technologies*, which improve the performance of established products leading to increased market share and higher margins, as opposed to investing in *disruptive technologies*, which lack virtually any relevant market research but have a huge upside if successful. Sound management decisions are based on an understanding of regulatory issues, market definition, and financial projections, which are difficult to apply to disruptive technologies because relevant data do not exist. In addition, most

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disruptive technologies are rolled out in niche markets, which in the case of gene therapy include orphan diseases that are likely to provide lower revenues due to small markets. Finally, traditional business models often do not easily accommodate the commercialization of disruptive innovations.

Principles relevant to the Innovator's Dilemma accurately reflect the state of biopharmaceutical development of gene therapy, with hemophilia providing a useful case study. Virtually all current pharmaceutical research in hemophilia can be classified as sustaining technologies. These include attempts to modify the protein used in standard hemophilia replacement products, such as to increase its half-life and/or increase its activity. In contrast, the development of the disruptive technology of gene therapy for hemophilia has had little, if any, commercial funding, with virtually all support coming from foundations and the public sector. Uncertainty regarding the business model of gene therapy for a disease such as hemophilia is a deterrent to commercial investment and development. Insurance companies currently reimburse for each service/infusion using existing protein replacement products, which in the aggregate cost up to $300,000/patient/year for prophylactic dosing (Manco-Johnson *et al.*, 2007). An obvious question concerns how to charge for gene therapy in which one injection of vector confers stable expression for an extended period of time, which, for purposes of argument, I will say is 10 years. I have heard this kind of therapy referred to as "one and done" with the very legitimate question asked: "How do you price a cure?" It is unlikely that reimbursement for the one-time injection of vector will be equivalent to the costs of treating a hemophiliac with 10 years of protein (i.e., $10 \times \$300{,}000 = \$3$ million). Unfortunately, there are no data available to answer these pricing questions with any certainty.

The critical path to the development of gene therapy for diseases like hemophilia may reside in the creation of new business models that reimburse for the long-term efficacy afforded by a single gene therapy injection/treatment. One approach is to charge the insurance company an annual fee for gene therapy as long as it continues to work. This may be difficult to implement in countries in which health care is covered by private insurance companies and patients frequently change their health insurance affiliations. For example, it is unlikely that insurance company A will continue to pay the annual fee if the patient moves to insurance company B, which, in the United States, occurs quite frequently. This leaves one to conclude that reimbursement for a gene therapy product may be substantially less than that provided under current protein replacement therapies, leaving companies with traditional franchises in these diseases little incentive to invest in gene therapy. Those who lead in this scenario are often new to the business area and not concerned about compromising competing internal programs. The other important point to consider is that many early candidates for gene therapy are associated with significant disability and early mortality and, unlike hemophilia, have no effective treatments. Truly effective therapies in these disorders will likely be rewarded in terms of reimbursement in proportion to the value that they bring, which may be enormous if they address a substantial unmet need.

A key issue in assessing investment in biopharmaceutical products is the requisite regulatory influence of agencies like the U.S. Food and Drug Administration (FDA) in determining the suitability of products for the marketplace. The limited regulatory track record for gene therapy (i.e., no gene therapy product has been approved in Europe or the United States) creates significant concern with the investment and pharmaceutical communities that stymies investment. Anticipating activity in this new therapeutic area, the Center for Biologics Evaluation and Research of the FDA created an office dedicated to research and evaluation of gene therapy products. This group is knowledgeable, accessible, and supportive of our efforts. I concede, however, that we are in uncharted territory although the early focus of gene therapy on severe diseases with little to no therapeutic options provides some important advantages in facilitating regulatory processes. Janet Woodcock, Director of the Center for Drug Evaluation and Research at the FDA, summarized the agency's efforts to promote the development of novel therapeutics for severe and untreatable diseases during her testimony to Congress regarding the 2012 reauthorization of the Prescription Drug User Fee Act (Woodcock, 2011). Under the Act, the FDA has agreed to review novel drugs more quickly if they "represent the truly innovative medicines generally targeted at severe illnesses with few or no available therapeutic options." Another way the FDA can facilitate the approval of novel therapeutics for this category of diseases is through the use of surrogate end points, even if not fully validated, as long as the sponsor agrees to participate in postmarketing studies.

The time for addressing issues of gene therapy commercialization is now! Technical feasibility has been established in multiple diseases and with different technology platforms. Patients suffering from diseases that are treatable by these technologies deserve access to them. It seems prudent for stakeholders in gene therapy to learn how other industries have successfully commercialized disruptive technologies. Christensen describes the challenges of nurturing a disruptive technology within large successful companies despite the existence of necessary talent and financial resources; many companies have tried and virtually all fail (Christensen, 1997). An alternative approach is to establish venture capital-financed biotechnology companies where there are fewer limitations and relevant value networks can be created. While this may have been the case in the past, the current focus of the venture community on technical feasibility, short timelines, and clear paths to liquidity creates significant challenges.

Christensen has pointed to lessons learned from the computer industry, which I believe may be useful in charting a path forward for gene therapy (Christensen, 1997). Two computer giants, IBM and Digital Equipment Corporation (DEC), had become industry leaders in the 1980s based on mainframe and microcomputers and both were threatened by the emergence of desktop personal computers (PCs). DEC attempted on several occasions to develop PC products within its parent organization with no success; the company eventually faltered and sold its assets in the 1990s. This is in contrast to IBM, which established an incredibly successful PC business via an independent and geographically distinct business unit. The first personal computer that emerged from this new venture was named *Time Magazine*'s "man of the year" (Friedrich, 1983) and its PC business dominated the marketplace; IBM PCs and associated clones composed 98% of the marketplace in 2005, representing the sale of

approximately 212 million computers in that year (Gartner, 2006). The ability to leverage resources of the larger IBM organization while establishing within the independent business unit managing principles of the disruptive technology of PCs provided elements of success. Translation of the IBM/personal computer model to gene therapy could be the creation of biotechnology companies that are spun out of, or substantively partnered with, the pharmaceutical industry. The early participation of venture capital may occur with gene therapy platform technologies that have shown success in the clinic and in candidate diseases that can be evaluated in small trials using easily measured end points.

In conclusion, lessons learned from the rollout of disruptive technologies provide important context for the commercial development of gene therapy. The strategic focus of gene therapy on severe diseases with unmet need in niche markets is exactly what is prescribed by the work of Christensen (1997). Features of the initial commercial targets of gene therapy such as small markets and limited vector treatments per patient provide business challenges in the context of traditional reimbursement mechanisms. However, our society has demonstrated a willingness to provide appropriate compensation for therapies that improve the lives of people afflicted with severe diseases. My prediction is that 2012 will usher in an era of commercial development of gene therapy that, although likely to begin slowly, will quickly gather momentum.

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