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Development of the First Inhaled Antibiotic for the Treatment of Cystic Fibrosis

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Abstract

Tobramycin Inhalation Solution USP (TOBI), a therapy developed to treat lung infections associated with cystic fibrosis (CF), was presented as a demonstration case for collaborative pharmaceutical development at a Clinical and Translational Science Awards Industry Forum on "Promoting Efficient and Effective Collaborations Among Academia, Government, and Industry" held in February 2010. TOBI was developed by PathoGenesis Corporation (Seattle, WA) in collaboration with the academic inventors, the National Institutes of Health, the U.S. Food and Drug Administration, and the CF Foundation. The presenters, representing the academic, industry, and foundation partners, each reviewed the program from their perspectives and identified challenges that existed during the discovery, development, and commercialization of TOBI. The attendees were asked to consider other collaborative opportunities that might have further improved TOBI development, including the optimal roles of the academic researchers, foundations, and other agencies when industry drives development and commercialization decisions.

INTRODUCTION

Cystic fibrosis (CF)—an inherited condition that causes the body to produce abnormally thick mucus in the lungs and other mucus-secreting organs—is associated with breathing problems and lung infections. Tobramycin Inhalation Solution USP (TOBI) is an important component of the CF therapeutic arsenal used to treat such lung infections; it has been credited with significantly extending the life expectancy of CF patients. A breakout session on the topic of "Academic/Industry Issues and Barriers for Drug Development" was held at a Clinical and Translational Science Awards (CTSA) Industry Forum titled "Promoting Efficient and Effective Collaborations Among Academia, Government, and Industry," which took place in Bethesda, Maryland, in February 2010. This session was designed to explore the challenges associated with the development of this drug, as well as ways in which this process might have been improved.

The idea behind TOBI originated with A. Smith, an academic investigator at Seattle Children's Hospital and Research Institute ("Seattle Children's"), who hypothesized that administration of antibiotics by inhalation would deliver drug directly to the site of infection

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and thereby decrease the toxicity associated with intravenous administration. At the time Smith began his studies, intravenous tobramycin was standard care for CF-associated pulmonary exacerbations. High doses of intravenous drug were required to achieve minimally effective doses in the lungs and were associated with progressive renal disease and deafness. Smith discovered that the antibiotic formulation had profound effects on the delivery characteristics and that sputum (the mucus and other material generated in the lung) was antagonistic to the action of many antibiotics, requiring much higher levels of drug than originally imagined. These discoveries launched a series of studies designed to optimize delivery and evaluate dose-dependent killing of common CF-associated pathogens in sputum. In 1986, in collaboration with B. Ramsey, Smith initiated clinical studies under an investigator-sponsored investigational new drug (IND) application to the U.S. Food and Drug Administration (FDA). Their goal was to publish the results of the studies in a respected medical journal and to use the data to build consensus within the CF community on treatment guidelines for inhaled antibiotics. For their first study, high concentrations of the drug were achieved in the sputum with an ultrasonic nebulizer, a device used to convert the drug solution into a fine mist that is inhaled. Two additional Phase 2 studies showed that the delivered concentrations killed almost all bacteria, markedly improved lung function, and had few side effects. The data were published in the *New England Journal of Medicine* (1). The studies were funded by grants from the CF Foundation and the National Institutes of Health (NIH).

CHALLENGES AT THE “PROOF-OF-CONCEPT” STAGE

Despite the observed clinical efficacy, these early proof-of-concept studies did not stimulate widespread adoption of the treatment by other physicians treating CF nor interest from the pharmaceutical industry in commercialization of the product. Several important factors were cited for this early lack of uptake:

- i. The published data did not meet requirements for FDA approval; therefore, the product was not reimbursable by insurance.
- ii. The ultrasonic delivery system was inefficient and cost prohibitive, wasting 90% of the drug administered.
- iii. Investigators had no intellectual property (IP) protection for the antibiotic or the inhaled formulation.
- iv. Animal toxicology data were not available to support the safety of chronic inhalation of tobramycin.
- v. The estimated return on investment for a rare disease such as CF was below the acceptable threshold for many pharmaceutical companies.
- vi. There was a lack of precedent in the marketplace for a chronic inhaled antibiotic product, creating a sense of wariness within the investment and medical communities.

CHALLENGES DURING LATER STAGES OF DRUG DEVELOPMENT

Because of several factors (discussed below), one company did elect to pursue the commercialization of TOBI. PathoGenesis Corporation was a small start-up biopharmaceutical company with in-house development experience in both the CF indication and inhaled therapies. In addition, because of its lower operating expenses relative to those of larger pharmaceutical companies, the estimated return on investment for a chronic CF therapy was acceptable. Upon deciding to move forward with TOBI development, PathoGenesis Corporation negotiated with the CF Foundation and Seattle Children's Research Institute for nearly a year before reaching a simple 10-page agreement

with each organization. The structure of the agreement gave PathoGenesis an exclusive license for TOBI in exchange for royalties and a royalty advance. The contract required PathoGenesis to reach two milestones: (i) filing the sponsor-initiated IND application, which would allow them to conduct the required Phase 3 registration trials, and (ii) filing the new drug application, required for FDA approval of TOBI for sale and marketing. Factors affecting the time required for contract negotiation were discussed and included the following:

- i. Difficulty reaching agreement on the “value” of the IP and an acceptable royalty rate. Attendees suggested that universities may not appreciate the risks being taken by the company and the costs of development relative to the investments made in the university setting.
- ii. Fear on the part of the academic investigators that PathoGenesis would derail or stall the program in some unspecified manner.
- iii. General differences in the responsiveness and timeliness to contract negotiations. Attendees suggested that although academic institutions have a comprehensive portfolio to manage, they may not realize the cost of delay to the companies that are considering working with them.

ROLE OF THE ACADEMIC PARTNERS IN TOBI DEVELOPMENT

When PathoGenesis submitted their IND application, the FDA put the planned Phase 3 studies on clinical hold until inhalation toxicology studies were submitted and reviewed. The team quickly undertook the toxicology studies, along with manufacturing and stability studies with other corporate partners. In parallel, the company was able to conduct Phase 2 nebulizer studies under Smith’s IND, saving over a year in development time. This collaboration allowed a more efficient nebulizer to be selected in advance of the Phase 3 studies and the option of lowering the administered dose. The Phase 3 protocol was developed in collaboration with the original team at Seattle Children’s. Ramsey was the lead investigator for the Phase 3 clinical studies. She enrolled the first subjects, recruited and worked with sites, and supported use of the microbiology laboratory. She stayed involved through data review and publication (2) of the study results and several other publications resulted from this study.

ROLE OF FOUNDATIONS AND OTHER AGENCIES IN TOBI DEVELOPMENT

R. Beall from the CF Foundation presented the model of “venture philanthropy” used by Cystic Fibrosis Foundation Therapeutics, a nonprofit affiliate of the CF Foundation that supports activities related to drug discovery and development for CF. In this model, foundations play an active, investor-like role in drug discovery and development. For the TOBI project, the foundation sponsored the three Smith and Ramsey clinical trials and purchased the tobramycin for their studies. Beall also worked on their behalf to identify an industrial partner and was instrumental in bringing the project to the chief executive officer of PathoGenesis. He felt the company showed interest—in part because the foundation had reduced the company’s risk by financing the early work, in part because PathoGenesis would have immediate access to the expertise of Smith and Ramsey, and in part because of the access to patients and clinicians that the foundation provided. The CF Foundation has currently spent more than \$330 million on early-stage drug development for programs that came after the TOBI efforts.

The FDA Office of Orphan Products Development (OOPD)—whose mission is to promote the development of products for the diagnosis or treatment of rare diseases—was also instrumental in bringing TOBI to the market. As a result of an Orphan Product Designation,

PathoGenesis received 7 years of market exclusivity for the TOBI product (rather than the normal period of 5 years), an important factor for the company's financial interest. In addition, PathoGenesis received a grant from the OOPD for support of the Phase 3 clinical trials. The OOPD grant provided credibility to the investment community and enabled PathoGenesis to "go public" soon after the Phase 3 trials began in 1995, raising \$30 million in its initial public offering and another \$107 million during the following year and a half.

OPTIMIZING TOBI DEVELOPMENT

The session attendees discussed other collaborative opportunities that might have optimized TOBI development even further. Suggestions included the following ideas:

- i. Development of IP rights around the formulation. Although Smith did seek patent support, he was not successful in convincing his institution of the commercial viability of the product, partly because of lack of precedent for an inhaled antibiotic product for CF. It was thought that more business participation in the review of the IP might have positioned his application better within his institution. It was not until PathoGenesis sought to commercialize the product that IP rights were developed in partnership with Seattle Children's Research Institute. Although the "delay" model was preferable in hindsight, because it provided additional years of market exclusivity for TOBI and relieved Seattle Children's Research Institute of financial responsibility for defense of the patents, it did make the early-stage valuation more difficult and potentially lowered the upfront value of the program.
- ii. Earlier market analysis of an acceptable range for the cost of the drug to optimize the delivery requirements for administration at the preclinical stage.
- iii. Better and more open communication among the universities, the foundations, and the for-profit industries on the full cost of development to help the various stakeholders successfully negotiate with respect to acceptable royalty rates.

SUMMARY

The TOBI development story demonstrates the power of effective collaborative partnerships. The entire development program took only 4 years to go from a proposed project at PathoGenesis to FDA approval in 1997. This timeline would not have been possible without a strong multidisciplinary team that consolidated the complementary competencies from the various participants. The major themes from the breakout session were the following:

- i. Published proof-of-concept clinical studies were absolutely essential in obtaining corporate interest in this project. This was particularly true in the example of TOBI because it represented a new type of therapy (inhaled antibiotic) and addressed a new market, chronic treatment of CF pulmonary infections.
- ii. Venture philanthropy from foundations and public grant support were critical in filling the funding gap between basic research and proof-of-concept studies.
- iii. The business-science interface is often seen as a stumbling block in collaborations; with mutual respect of the needs and contributions of each party, this interface can instead drive the success of a project as it moves toward commercial development.

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