Abe Abuchowski

As CEO of one of the first companies to make protein delivery into a profitable business, Abe Abuchowski knows what it takes to bring a new technology to market. Although his technology—PEGylation—is now considered an industry gold standard, its three-decade development history illustrates the often rocky path to commercial success for platforms.

Drug delivery is a dicey business, and Abe Abuchowski was one of the first to make it work. At the dawn of the biotech industry, proteins' promise as therapeutics was undisputed. But taken from animal or recombinant bacterial sources, their therapeutic potential was often undone by high immunogenicity. Short circulating life posed an additional problem—frequent doses were required to maintain therapeutic levels, again increasing the likelihood of an immune response.

As luck would have it, when Abuchowski began his doctoral research in biochemistry in 1971, his thesis advisor at Rutgers University, Frank Davis, put him to work on this very problem. A few years back, Davis had happened upon a paper suggesting that poly(ethylene glycol) (PEG), a polymer widely used in foods and cosmetics, could provide a solution. Initial studies indeed showed that "hanging a bit of PEG" onto a protein reduced immunogenicity and improved circulating life, recalls Davis, and along with two colleagues he patented a technique for PEG-protein delivery.

Within a few years Abuchowski and his colleagues hit the jackpot when looking for a general method for attaching PEG to a protein: a formulation of PEGylated bovine serum albumin. This was the first protein molecule created that was neither immunogenic nor antigenic. "It was a real Eureka moment," says Abuchowski. "Even after we did it we couldn't believe it, quite honestly." More importantly, the researchers went on to show in mice that a PEGylated protein could cure a previously untreatable enzyme deficiency.

At a time when researchers were just beginning to venture into the commercial side of discovery, Abuchowski was happy to take the leap. "I think Abe very quickly saw the business applications," says Davis, who is now retired. In 1982, the duo formed Enzon Corporation in New Jersey to bring PEG-based treatments to the clinic. In 1990 the company's first product, PEGylated adenosine deaminase enzyme (ADA), known as Adagen, gained US Food and Drug Administration (FDA) approval—making Enzon the fifth company to have a biotech drug approved. Inherited absence of ADA had recently been found to cause one type of severe combined immunodeficiency disorder. Without PEG, ADA has no therapeutic effect. Four years later, the company received approval for Oncaspar, PEGylated L-asparaginase for acute lymphoblastic leukemia. "A company doesn't exist to do research, but to get products on the market," says Abukowski.

The decision to go after two products with almost no market was a deliberate one. "I think Enzon was pretty smart," notes Roger Harrison, an associate at Plexus Ventures, a global pharma consultancy based in Maple Glen, Pennsylvania, and an independent consultant specializing in drug delivery. "There's an established belief that anything you do [to a protein] will create a problem with the FDA," he says. But both Adagen and Oncaspar minimized this added uncertainty because both were made possible by the technology, and both approval processes could be expedited by orphan drug status. Even with Enzon's irrefutable clinical data on Adagen, Abuchowsky notes, "up until the day of [FDA] approval, I probably had half of Enzon management betting against me." Ultimately, getting the two products out in quick succession essentially proved the technology.

Meanwhile, big pharma was beginning to appreciate PEG's potential. Enzon signed a deal with Schering-Plough to develop a PEGylated version of alpha-interferon (PegIntron) for treating hepatitis C. But as Enzon's management waited to see whether the project would succeed, resources dwindled, stock price fell and disagreement began to brew. A messy restructuring ensued, its outcome being a much-diminished R&D program and Abuchowski's departure—not just from Enzon but, for a time, from biotech.

PegIntron's approval in 2001 pushed Enzon into profitability, and also marked the first time that a second-generation protein superior to the first generation due to a biotech improvement. Within a year, it had captured about 65% of the market share of a protein that had already been on the market for over a decade. "Had Enzon had the ability to prepare their own proteins and chosen more of a therapeutics model than a drug delivery model, they could have done alpha-interferon on their own," notes Robert Shorr, who served as vice president of research and development from 1991 to 1997. Shorr is now CEO of Cornerstone Pharmaceuticals in New York. He also serves a scientific advisor to Abukowski's new company, Prolong Pharmaceuticals in Monmouth Junction, New Jersey.

By all indications, Abukowski is not about to make the same mistake twice. "Enzon was a company that developed the technology and introduced it," he says. "Prolong is a product company." Part of the plan is to realize some of the projects that languished in Enzon's deep-freezer. But with several biotech drugs coming off patent and manufacturing costs falling, Prolong is also looking to Asia. For Abukowski, one of the lessons of Enzon was that the sooner you get to revenue, the more freedom you have to decide where to go next. "There's an alignment in philosophy between Abe and many players in Asia," notes Gurinder Shahi, director of the Global Biobusiness Initiative at the University of Southern California in Los Angeles. Unlike in the United States, "in Asia there is no risk capital, so companies are forced to use a quick-to-revenue strategies and use that revenue to make a product." Because the technology is now well established, it creates a proprietary dimension to generics.

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In the five years since the technology's acceptance became official with the approval of PegIntron, about ten other PEG products have come to market, with several more in trials. Yet other technologies are emerging. Even for old products, notes Walter Blatter, CEO of ImmunoGen in Cambridge, Massachusetts, protein modifications other than PEG, such as the two additional N-glycosylation sites in Amgen's long-acting erythropoietin Aranesp, can increase the circulation life of a molecule. Whether PEG has the capacity to surpass its primary role as a second-generation modification remains to be seen, says Samuel Zalipsky, associate director of protein and linker chemistry at ALZA in Mountain View, California. He concludes: "It's still got some life in it, though it's not the only game in town as it was in the past."

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