THE MIRACLE OF SYNTHETIC INSULIN

A biopharmaceutical success story

Insulin research and production have been at the center of developments in the biopharmaceutical industry.

Leonard Thompson was 14, and he was dying. Just 65 pounds, the young teen faced the fate of all diabetic children in 1922: he would soon become comatose and die.

At the time that Thompson lay dying at the Toronto General Hospital, Type I diabetes was always lethal.

Frederick Banting, Charles Best and their colleagues at the University of Toronto had already demonstrated that a canine pancreatic extract of insulin could treat diabetes in dogs, and they had hopes that an extract purified from ox pancreas would work in humans. Unfortunately, Thompson had a severe allergic reaction to the bovine extract, and the emergency clinical trial had to be postponed. The team worked diligently to improve the purification process and, when they tried again 12 days later, the experiment worked: the child's blood sugar levels dropped and his symptoms improved dramatically. Six more diabetics were successfully treated the following month and insulin's status as a miracle medicine was on its way to being cemented, ensuring Banting the Nobel Prize in Medicine in 1923.

Insulin research and production have been at the center of developments in the biopharmaceutical industry since then. Banting and Best sold the patent for insulin to the University of Toronto for 50 cents. The university, unable to produce the necessary quantities of the drug, entered into an agreement with Eli Lilly & Co., and in less than 2 years tens of thousands of patients in North America were being treated. Mass production required large amounts of slaughterhouse pigs, cows and horses, with as much as 2 tons of pig needed to produce only 8 ounces of insulin. The drug was produced in the same manner into the 1980s.

Along the way, researchers and industry collaborated on a number of firsts. Insulin was the first protein to have its amino acid sequence determined, in 1951-52 by Frederick Sanger, for which he received the Nobel Prize in Chemistry (1958). In 1978, Genentech used recombinant DNA technology to synthesize the human insulin gene. These recombinant DNA sequences—one for each chain of the insulin molecule—were inserted into plasmid DNA, then used to transform *E. coli*. Bacteria were induced to synthesize either one or the other of the two protein chains that when joined together formed insulin. In 1982, human insulin manufactured by Eli Lilly became the first genetically engineered pharmaceutical protein approved by the FDA. This form had the benefit of mitigating the allergic reactions diabetics experienced from porcine and bovine versions of the hormone.

Currently, recombinant DNA technology is used to manufacture tons of insulin, using either *E. coli* or the yeast *S. cerevisiae*. As well, researchers have taken the naturally occurring gene and molecule and modified it slightly to create synthetic versions of human insulin that have enhanced properties. These insulin analogs—examples include Humalog® (Eli Lilly), Levemir® (Novo Nordisk), and Lantus® (Sanofi)—have altered amino acid sequences that differ from naturally occurring insulin. These synthetic forms serve two purposes: they can improve the efficacy of insulin, rendering it longer acting or slower acting than the natural versions; and they allow a company to obtain a new patent and "evergreen" its product, thus staving off competition from the introduction of lower-cost generic alternatives (which cannot be produced until the patent expires).

The first long-acting synthetic insulin got FDA approval in 2000.

Evergreening was the focus of a recent article in the *New England Journal of Medicine*, which outlines the reasons that there are no generic insulin alternatives yet on the market. The authors worry that some of the 6 million diabetics in the US cannot afford the out-of-pocket expense of insulin, which can be $120-$400 per month. Industry insiders point out that patents offer incentives to biopharmaceutical companies to improve medicines like insulin. It will not take long to see how this plays out, as the patent on one long-acting synthetic insulin expired almost a year ago and a biosimilar version has been approved in Europe.

We have progressed from a time when one life was saved through groundbreaking research—with regular injections, Leonard Thompson lived to be 27 before succumbing to pneumonia—through a half-century of insulin production requiring massive amounts of animal material, to a highly efficient means of purifying synthetic insulin. Hand in hand, it is scientific research combined with the mass production and distribution capabilities of the biopharmaceutical industry that has improved the lives of diabetics worldwide.