A Hundred Years of Insulin Innovation: When Science Meets Technology

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The story of insulin development is a remarkable example of what can be accomplished in medicine when academic science meets translational biotechnology. The foundation was laid 100 years ago this year with the discovery of insulin in Toronto in 1921, prompting a Nobel Prize in 1923.

The discovery made by Banting and Best (1) was so spectacular and of such importance for many people that it immediately led to collaboration with industry partners, most notably Eli Lilly in the U.S. and what became Novo Nordisk in Europe. One of the founding fathers of Novo Nordisk, Dr. August Krogh, was himself a Nobel Prize laureate. Krogh understood the scientific significance of the insulin discovery and partnered with people skilled in medicine as well as in technological development and upscaling. In the following decades, academic discoveries such as insulin crystallization (2) and binding of zinc (3) and protamine (4) immediately translated to benefits on insulin product characteristics that are of importance even today. Seminal discoveries in academia in the 1950s and 1960s unraveled the amino acid sequence as well as the secondary, tertiary, and quaternary insulin structures. These academic endeavors were led by Nobel Laureates Sanger (5) and Hodgkin (6), respectively. Another major milestone was Don Steiner's discovery that human insulin is produced as a single-chain proinsulin (7). The immunological characterization of proinsulin provided the technological background that allowed the pharmaceutical industry to refine the purification of insulin to obtain monocomponent insulin; this breakthrough lowered the risk of inducing an immune response in patients treated with insulin. The characterization of proinsulin and the realization that it could be converted into mature two-chain insulin by enzymatical treatment with trypsin and carboxypeptidase B led the way for industrial production of recombinant human insulin. Furthermore, in the 1990s, the first-generation long-acting basal insulin analog, insulin glargine (8), was designed by Hoechst, probably inspired by the proinsulin structure that carries the two arginine residues characteristic for glargine.

Alongside the breakthroughs in genetic engineering taking place through the 1970s involving both academia, biotech (Genentech, ZymoGenetics, Chiron Corporation), and industry (Eli Lilly, Hoechst AG and Company, and Novo Nordisk A/S), the fascinating structural elucidation of the insulin hormone both inspired and facilitated recombinant production of human insulin (9,10). Multiple tons of insulin are required yearly for treatment of people with diabetes, which simply would not be possible to supply without recombinant production. Identification of the insulin receptor (11) and the mapping of receptor binding surfaces (12) in the 1970s and 1980s were additional examples of academic discoveries of fundamental importance for future drug design.

Thus, at the time we joined the scientific insulin journey, the insulin molecule was structurally and pharmaceutically well characterized. At the same time, however, it was realized that human insulin in its native form was not perfectly suited for subcutaneous injection. Moreover, it was during the 1990s that the Diabetes Control and Complications Trial (DCCT) (13) and UK Prospective Diabetes Study (UKPDS) (14) provided evidence for the significance of intensive glucose control in reducing the risk of microvascular complications in people with both type 1 and type 2 diabetes, underscoring the clinical need for better insulin preparations to improve long-term patient outcomes.

It was hypothesized and later demonstrated that rational application of genetic engineering on the basis of structural insights would offer a possibility to tailor insulin analogs with optimized pharmacokinetic profiles. The first article on a rapid-acting insulin analog was a copublication between industrial and academic scientists, who had been contributing to resolving the X-ray structure of the insulin hexamer (15). There were long-standing and close contacts between scientists—industrial as well as

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academic—with the common aim of improving insulin therapy. Hence, throughout the 1990s, the scientific environment was vibrant, collaborative, and competitive at the same time. However, it was the fatty acid acylation technology (16) that led to the next generations of basal insulin analogs and also proved to have the most far-reaching consequences beyond insulin into other areas of peptide drug delivery. This technology was inspired by the knowledge that albumin functions as an abundant carrier protein with immense capacity for fatty acids and drugs and that reversible acylation is used in nature for governing subcellular trafficking.

The fatty acid acylation technology provides an example of how scientific insights from the academic setting were applied to insulin discovery, prolonging the action profile for both daily (17) and weekly (18) administration. Intriguingly, a unique mechanistic dimension enabled by fatty acid acylation was applied to engineer insulin degludec, which is an ultra-long-acting insulin due to formation of multihexamers at the site of injection. Furthermore, the fatty acid acylation technology has provided a general approach to molecular engineering and pharmacokinetic protraction applicable to protraction of peptide drugs (19,20) and even to facilitation of oral peptide delivery (21–24). Thus, this principle was successfully utilized in the field of glucagon-like peptide 1 receptor agonists to design, for example, liraglutide, semaglutide, and tirzepatide and across other areas of protein-based therapy exemplified by the growth hormone analog somapacitan. The acylation technology is thus a recent example of a technology with a broad scope, first developed for insulin.

Taken together, we have been privileged to be part of a vibrant period of insulin innovation that illustrates the importance and strength of both academic and translational science, and we have seen that combined efforts have led to improved quality of life and life expectancy for people with diabetes.

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