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UPDATE

Advances in insulin therapy from discovery to β-cell replacement

One hundred and one years have passed since Frederick Banting and Charles Best[1] demonstrated that injections of extract of pancreas lowered blood glucose levels in depancreatized dogs (Table 1). In 1922, Eli Lilly and Company succeeded in formulating insulin extracted from porcine pancreas (Figure 1), making it possible to save many lives from the incurable disease of diabetes. However, insulin at that time contained many impurities that irritated the injection site, and required a large volume using a relatively thick needle. The isolation of crystalline insulin in 1926[2,3] corrected these issues, but the increased purity of the substance shortened the duration of its action, resulting in the need for 3–4 injections per day. In 1936, Hagedorn[4] found that the addition of protamine isolated from trout sperm to insulin resulted in microscopic clumping that slowed its absorption rate, allowing continuous and prolonged action. Despite these advances, antibodies against porcine or bovine insulin posed problems. In 1955, Sanger[5] determined the amino acid sequences in the two chains of the insulin molecule and their linkage[5], enabling chemical synthesis of human insulin by several groups independently. However, the synthesizing process involved multiple steps, and the drug proved prohibitively expensive to market. Alternatively, the production of human insulin by enzymatic replacement of the amino acids in porcine or bovine insulin was reported[6]. Opening a new path to the production of an unlimited amount of insulin by using bacteria and yeast, Graeme Bell and his associates[7] sequenced human insulin complementary deoxyribonucleic acid in 1979. Soon after, David Goeddel and his associates at Genentech Inc. (San Francisco, CA, USA) succeeded in expressing human insulin in *Escherichia coli*; Genentech and Lilly then agreed to commercialize recombinant insulin, which was marketed in 1982 as Humulin® R (rapid-acting) and N (intermediate-acting). By genetic and chemical engineering, insulin preparations with various characteristics have been developed, and newer insulin preparations such as once-weekly basal insulin, icodec and basal insulin fc are now under development.

Among these newly developed insulin preparations, fixed-ratio combination (FRC) basal insulin together with glucagon-like peptide-1 receptor agonist (GLP-1RA) has recently been gaining attention as a simplified insulin regimen for people with type 2 diabetes. GLP-1RAs can be subdivided into two groups: long-acting (e.g., liraglutide, dulaglutide, and semaglutide) and short-acting (e.g., exenatide and lixisenatide). Long-acting GLP-1RAs enhance insulin secretion and suppress glucagon secretion glucose-dependently, thereby ameliorating both pre- and postprandial glucose excursions[8]. Short-acting GLP-1RAs delay gastric emptying, thereby ameliorating postprandial glucose excursions[8]. It was reported that the HbA1c-lowering effect of long-acting GLP-1RAs is dependent on the remaining pancreatic β-cells[9,10]; it is now clear that both long- and short-acting GLP-1RAs require some residual β-cell function to reach target HbA1c levels[10–12]. The addition of basal insulin to GLP-1RA to replenish insulin insufficiency is therefore a reasonable strategy for patients with diminished β-cell function. Basal-supported GLP-1RA therapy is also attractive as a substitute for multiple daily insulin injections, and exerts comparable HbA1c-lowering effects with reduced hypoglycemia risk and body weight gain[13]. In addition, recent advances in insulin preparations have enabled the generation of FRC basal insulin to be used in combination with GLP-1RA. To date, there are two once daily FRCs of basal insulin and GLP-1RA on the market (iGlarLixi and iDegLira); once weekly FRC is under development. Accumulating evidence suggests that iGlarLixi and iDegLira are especially effective in Asian patients with type 2 diabetes[14–16].

Thus, advances in insulin delivery and glucose monitoring have rendered insulin therapy remarkably safer and more effective. Sensor-augmented pumps with a hybrid closed loop system (e.g., MiniMed™ 770G) can effectively increase the duration of glucose control in the ideal range and reduce the incidence of both hyper- and hypoglycemia in patients with type 1 diabetes[17], but they are not used widely in clinical practice due to their high cost. Continuous glucose monitoring (CGM), both real-time CGM and intermittently scanned CGM (isCGM), permits visualization of glucose fluctuations, allowing a more precise dose titration of insulin. In Japan, the benefit of isCGM FreeStyle Libre™ has been demonstrated in type 2 diabetes patients receiving basal-supported insulin therapy[18]; it is now covered by insurance for type 2 diabetes patients who receive insulin therapy as well as for those with type 1 diabetes. While it is important to scan adequately to make full use of the isCGM FreeStlye Libre™[19], its usefulness is evident, and its dissemination at a reasonable price is a worthy goal in Asia. Smart insulin pens also represent an avenue to improved insulin therapy today; the technology has evolved over the past decade to include features such as smart

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Table 1 | Historical highlights and Nobel Prizes

1921	Discovery of insulin by Frederick Banting and his assistant Charles Best
1922	First human administration of purified insulin extract for treatment of diabetes
1923	Launch of the world's first clinical insulin preparation, Iretin
	Frederick Banting and John Macleod, Banting's laboratory director win the Nobel Prize for the discovery of insulin
1936	Hans Christian Hagedorn demonstrates that addition of protamine slows the rapid absorption of purified insulin
1950	Launch of the first clinical intermediate-acting insulin, Neutral Protamine Hagedorn (NPH)
1958	Frederick Sanger wins the Nobel Prize for determining the amino acid sequence of insulin
1964	Dorothy Hodgkin wins the Nobel Prize for the x-ray diffraction method later used to determine the molecular structure of insulin
1977	Rosalyn Yarrow wins the Nobel Prize for developing radio immunoassays to quantify peptide hormones including insulin
1983	Launch of the first recombinant insulin for clinical use, Humulin® R and N
1996	Launch of the first fast-acting insulin analog for clinical use, Humalog®
2000	Launch of the first long-acting insulin analog for clinical use, Lantus®

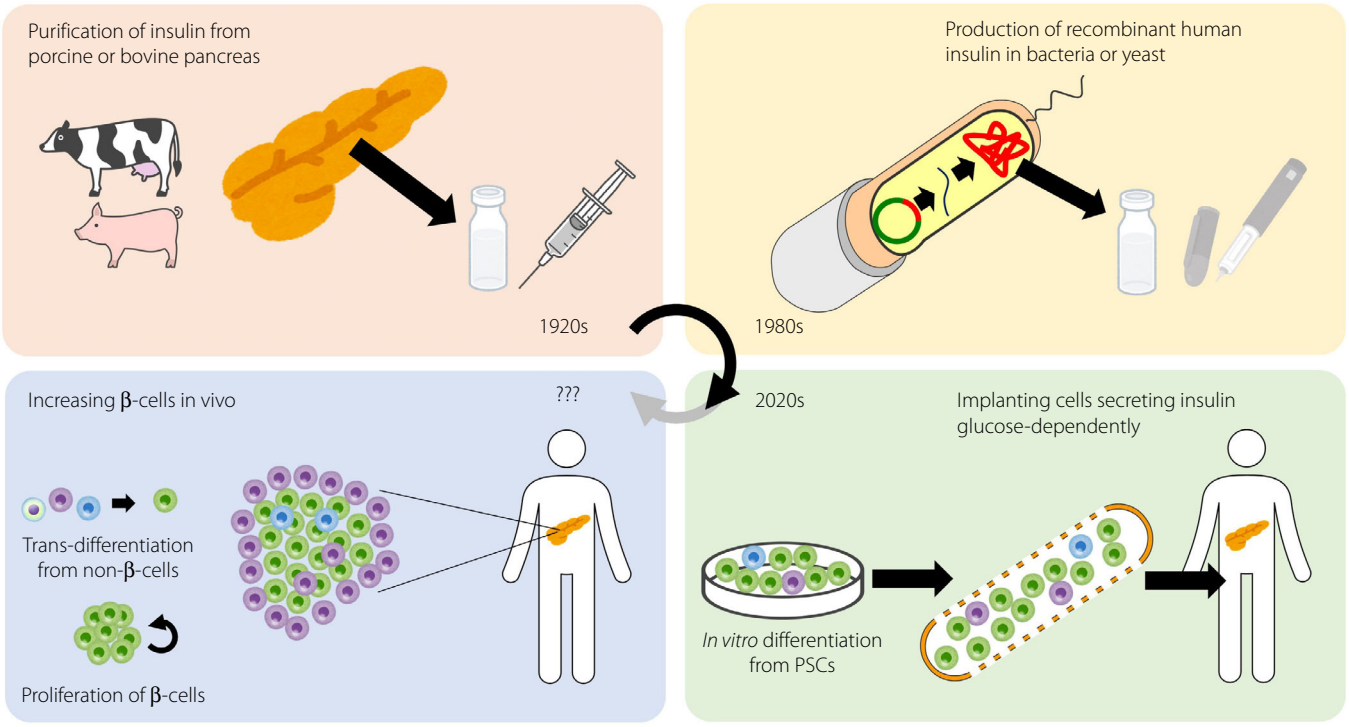

Figure 1 | From purified insulin to β-cell replacement therapy. Insulin therapy using insulin purified from porcine or bovine pancreas revolutionized diabetes therapy in the 1920s. A series of advances including cloning human insulin complementary deoxyribonucleic acid in 1979 enabled the development of recombinant human insulin with improved features. In 2021, Timothy Kieffer and his associates[24] reported that implantation of pancreatic endoderm from pluripotent stem cells (PSCs) can detect meal-induced C-peptide secretion in people with type 1 diabetes. Thus, insulin treatment for diabetes may well be upended by β-cell replacement therapy in the coming decades.

phone connectivity and integration with mobile health apps and continuous glucose monitors[20]. Although the benefit of smart insulin pens needs to be established in well-designed clinical trials of adequate sample size, they emphasize the relationships between insulin dosage, dietary intake, and physical activity, and encourage optimization of insulin use among people with diabetes.

The next advance in diabetes treatment may well be β-cell replacement therapy, which could upend insulin therapy in the coming decades. The transplantation of donor human islets can virtually cure diabetes by eliminating the need for insulin injections. *In vitro* differentiation of both human embryonic stem cells and induced pluripotent stem cells is being actively pursued as an islet cell replacement source[21,22]. It also has been reported that the pancreatic β-cell mass can be expanded *in vivo* and *in vitro* by *MYCL*-mediated reprogramming[23].

Macro-encapsulation devices for islet cells are being developed that contain and protect the cells from immune attack[21,22]. Importantly, Timothy Kieffer and his associates[24] have reported that the implantation of pluripotent stem-cell-derived pancreatic endoderm can detect meal-induced C-peptide secretion in people with type 1 diabetes. Although numerous barriers must be overcome to establish β-cell replacement therapy for diabetes treatment clinically, the virtual cure of the disease now appears to be a practicable goal.

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