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COMMENTARY

Fighting the uphill battle to cure type 1 diabetes

2021 marks the 100-year anniversary of the discovery of insulin, an historic breakthrough in the treatment of type 1 diabetes. Insulin has helped to save millions of lives. However, as Frederik G. Banting said, 'Insulin is not a cure for diabetes; it is a treatment'. Exogenous insulin cannot fully mimic physiologic regulation of endogenous insulin. While it can control the glucose level, it does so suboptimally. In addition, hypoglycemia, a life-threatening complication, can occur while regulating the blood glucose level.

There have been many efforts to cure type 1 diabetes, including immunotherapy, artificial pancreas, and beta cell replacement therapy (Figure 1).

Immunotherapy targets the pathogenesis of type 1 diabetes, with abatacept, anti-thymocyte globulin, golimumab, rituximab, and teplizumab having been shown to reduce C-peptide loss in patients with newly diagnosed type 1 diabetes[1]. However, since immunotherapy targets the autoimmune destruction of beta cells, its effects are bound to be limited in overt type 1 diabetes, wherein more than 90% of beta cells have already been destroyed. Therefore, early detection of individuals at risk of developing type 1 diabetes and the optimal timing of immunotherapy initiation are considerable challenges.

Recent technological advances have made the artificial pancreas a reality that may better represent a cure for type 1 diabetes compared with immunotherapy. An artificial pancreas, also known as a closed loop system, effectively increases the percentage of glucose control time in the range and reduces both hyper- and hypoglycemia[2]. While the system's use of artificial intelligence raises expectations for its efficacy, fundamental concerns related to the physiology of insulin and glucose remain. Exogenous insulin administered subcutaneously slows the effect onset compared with endogenous insulin delivered directly into the portal vein. Other issues include a persistent insulin effect even after lowering of blood sugar, decreased insulin action in the liver, and insulin resistance. The artificial pancreas adjusts the insulin dose based on the interstitial glucose level, which generally reflects blood glucose 5–15 min later. To address this time lapse, device makers are refining system algorithms to include patient-specific information such as glucose excursions and activity level, and in the future may incorporate glucose measurements taken at body sites such as the skin or eye versus the interstitial space.

If successful, beta cell replacement therapy can reverse diabetes. Pancreas and islet transplantation have been performed for decades, but the shortage of organ donors greatly limits this approach; therefore, alternative sources, such as xenogeneic or stem cells, have garnered attention. Of particular interest, the growing potential to generate functional beta-like cells from stem cells has fueled an expectation that type 1 diabetes might soon be curable. However, there are several challenges to this goal. Differentiated beta cells need to be as mature as human islets and need to be equally capable of secreting insulin in response to glucose. This differentiation protocol should be standardized, scalable, and expandable. The exact proportion of endocrine cells (α, β, δ, ε, and pancreatic polypeptide cells) and non-endocrine cells is not yet fully defined in differentiated beta-like cells. Cellular populations other than beta-like cells at the end of differentiation should be addressed. Additionally, the process must survive immune rejection for successful transplantation. Conventional immunomodulatory methods using immunosuppressants do not completely prevent host immune reactions and may alone adversely affect beta cells. Encapsulation of islets has been investigated as a means to avoiding immune response; however, it is difficult to overcome foreign body reaction and hypoxia using current techniques. We showed that xenogeneic transplantation (in mice) and allogeneic transplantation (in dogs) of encapsulated islets ameliorated diabetes for up to 1 year post-transplantation[3]. However, this was not reproduced in non-human primates in the xenogeneic transplantation setting. This suggests species-specific differences between rodents and primates. Therefore, other methods to overcome current limitations of encapsulation and immunity should be devised for study in higher-order animals.

Recently, Yoshihiro *et al.*[4] demonstrated that overexpression of programmed death-ligand 1 (PD-L1) helped human islet-like organoids (HILOs) avoid a host immune response in xenografts. Given that PD-L1 plays a crucial role in activating immune checkpoint pathways, this could be revolutionary in solving immune rejection. Like PD-L1, regulation presents a radically new vision of cancer treatment, it may be expected to open a new chapter in controlling immune rejection. However, as mentioned above, it is necessary to verify that PD-L1 overexpression produces similar immunomodulatory effects in higher animals, such as primates or humans. Another obstacle with PD-L1 overexpression is the concern about tumorigenicity. Many cancer cells overexpress immune checkpoint molecules for immune evasion, leading to the acquisition of malignant traits. Therefore, it is necessary to

*Correspondence author. Kun-Ho Yoon
Tel.: (+82)-2-2258-3589
Fax: (+82)-2-595-2534
E-mail address: yoonk@catholic.ac.kr
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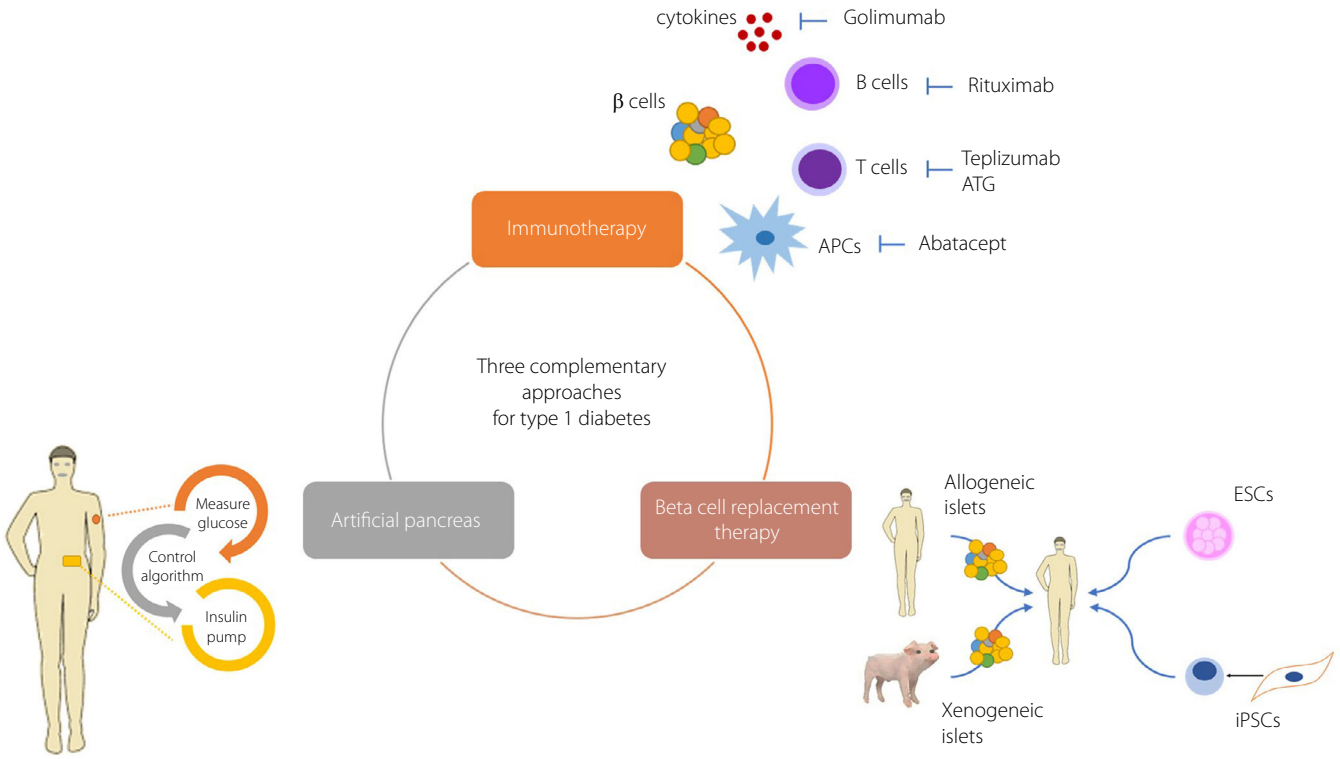

Figure 1 | Three complementary approaches for type 1 diabetes. Immunotherapy targets the pathogenic immune cells or inflammatory cytokines to revert type 1 diabetes. An artificial pancreas delivers insulin automatically using continuous glucose monitoring, a controlling algorithm, and an insulin pump. Beta cell replacement therapy varies depending on the cell sources: allogeneic, or xenogeneic islet; beta-like cells derived from ESCs or iPSCs. APCs, antigen presenting cells; ATG, anti-thymocyte globulin; ESCs, embryonic stem cells; iPSCs, induced pluripotent stem cells.

confirm whether increased PD-L1 expression stimulates tumorigenesis by conducting safety studies on teratoma formation over time. Consistent with this is the need to identify the cellular populations, except islets, in HILOs. In the report by Yoshihara *et al.*[4], the rate of beta cells was 50%–60%, which is lower than in previous studies[5]. Differentiation into more mature beta cells may alleviate some of the concerns for the unidentified cellular populations and tumorigenesis. In addition, it is necessary to: develop beta-like cells that function similarly to human islets; establish scalable and expandable protocols; resolve inhomogeneity, a fundamental problem of induced pluripotent stem cells; and evaluate cost-benefit.

From the discovery of insulin in 1921 to the present day, we have been waging an uphill battle to eradicate type 1 diabetes. While none of the therapies discussed here have resulted in a cure, they contribute to the arsenal of scientific knowledge and inquiry that drives the fight against this disease.

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DISCLOSURE

The authors declare no conflict of interest.

Eun Young Lee[1], Kun-Ho Yoon[1,2*]
[1]*Division of Endocrinology and Metabolism, Department of Internal Medicine, College of Medicine, Seoul St Mary's Hospital, The Catholic University of Korea, Seoul, Korea,* [2]*Institute of Catholic Ubiquitous Health Care, The Catholic University of Korea, Seoul, Korea*

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