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## **$\beta$ -cell preservation and regeneration for diabetes treatment: where are we now?**

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### **SUMMARY**

Over the last decade, our knowledge of  $\beta$ -cell biology has expanded with the use of new scientific techniques and strategies. Growth factors, hormones and small molecules have been shown to enhance  $\beta$ -cell proliferation and function. Stem cell technology and research into the developmental biology of the pancreas have yielded new methods for *in vivo* and *in vitro* regeneration of  $\beta$  cells from stem cells and endogenous progenitors as well as transdifferentiation of non- $\beta$  cells. Novel pharmacological approaches have been developed to preserve and enhance  $\beta$ -cell function. Strategies to increase expression of insulin gene transcription factors in dysfunctional and immature  $\beta$  cells have ameliorated these impairments. Hence, we suggest that strategies to minimize  $\beta$ -cell loss and to increase their function and regeneration will ultimately lead to therapy for both Type 1 and 2 diabetes.

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Diabetes is a major health issue with more than 200 million people affected worldwide [1]. According to the latest statistics, approximately 439 million people will be suffering from diabetes and its complications by 2030 [1,2]. Insulin secretion from pancreatic  $\beta$  cells is integral to the regulation of blood glucose levels, and the loss of functional  $\beta$  cells is seminal in the development of both Type 1 diabetes (T1D) and Type 2 diabetes (T2D). T1D results from autoimmune destruction of  $\beta$  cells, while T2D results from a combined loss of  $\beta$ -cell mass and  $\beta$ -cell function, where the loss of  $\beta$ -cell mass could result from  $\beta$ -cell dysfunction [3–5]. Much progress has been made in recent years towards finding ways to prevent the reduction of  $\beta$ -cell mass, preserve function of remaining  $\beta$  cells and develop approaches to regenerate them [6–9]. This article will briefly summarize our current understanding of these therapeutic strategies and highlight some of the recent advances in the field.

### **Strategies for preserving & restoring $\beta$ -cell mass in T1D**

Long after the onset of T1D, a significant number of patients retain a limited number of  $\beta$  cells [4,10,11]. The examination of pancreases from the Joslin Medalist Cohort, which included individuals who have suffered with T1D for 50 years or more, showed that all the pancreases had some scattered single or small clusters of insulin-expressing cells and some contained a range from a few to many insulin cells [12]. More than two-thirds of medalists

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had detectable random C-peptide, a measure of endogenous insulin secretion in serum, suggesting that remaining  $\beta$  cells retain some function [12]. The quantity of remaining  $\beta$  cells in T1D patients is not sufficient to control blood glucose, and hence we need to develop ways to prevent the destruction of  $\beta$  cells and replenish functional  $\beta$  cells.

Several excellent reviews have summarized the etiological and immunological base for the development of T1D, and have discussed prevention and intervention strategies to avert  $\beta$ -cell loss in T1D patients [4,11,13–15]. The prevention approaches target high-risk individuals prior to the development of diabetes, while intervention strategies are used for newly diagnosed T1D. As the destruction of  $\beta$  cells in T1D is an autoimmune event, antigen-specific and antigen-nonspecific immunotherapies have been used in both prevention and intervention trials [11,13,14,16,17]. Antigen-nonspecific approaches include the use of cyclosporine, BCG, anti-thymoglobulin, anti-CD3, anti-CD20, IL-1 antagonists and TNF- $\alpha$  blockade [11,15,18]. Similarly, trials assessing the capacity of antigen-specific therapies to induce regulatory T (Treg) cells and/or delete pathogenic T cells used antigens including insulin, GAD65, HSP60 and their peptides [14,16]. Despite promising results from clinical trials, there is yet to be an immune therapy that completely stops autoimmune destruction and works successfully in humans [17]. Ultimately, a potential therapeutic strategy for T1D may require a combination of inducing nonspecific immunosuppression and antigen-specific induction of Treg to achieve a long-term silencing of autoimmunity without losing the protective immune response [11,16]. Advances in high-throughput screening strategies (e.g., to identify molecules that suppress cytokine-mediated  $\beta$ -cell apoptosis [19]) could provide new approaches for T1D treatment. However, even with an effective immunotherapy, a true  $\beta$ -cell-based cure for T1D will require the replacement of lost  $\beta$  cells with functional  $\beta$  cells.

## Replenishing $\beta$ cells generated from *in vitro* differentiation strategies

Successful suppression of autoimmunity and  $\beta$ -cell replacement are key components for developing a successful therapy for T1D. Over the last decade, significant advances have been made towards generating insulin-producing cells from stem cells, induced pluripotent stem (iPS) cells and from rare adult pancreatic progenitors, duct cells and nonpancreatic cell types [9,20–22]. A biotechnology company, ViaCyte (San Diego, CA, USA) have developed a differentiation protocol for human embryonic stem cells (hESCs) based on the current understanding of pancreatic development. They generated a stepwise differentiation protocol to convert hESCs first into definitive endoderm, then into the primitive gut tube, posterior foregut and pancreatic endoderm [23,24]. However, the formation of mature glucose-responsive  $\beta$  cells required the transplantation of hESC-derived pancreatic endoderm in nude mice [24]. A similar stepwise differentiation strategy was used to derive insulin-producing islet-like clusters from hESCs [25,26]. Even iPS cells derived from human somatic cells in control and T1D subjects were differentiated into insulin-producing cells using similar strategies [27].

Despite the successful *in vitro* differentiation of stem cells and progenitor cells into insulin-producing cells, the process is still inefficient and the differentiated cells are immature, have limited insulin content and lack glucose-stimulated insulin secretion (GSIS). High-throughput screening has been used to enhance the efficiency of this differentiation process by identifying a series of small molecules capable of sequentially differentiating stem and progenitor cells into  $\beta$  cells. Recently, two small molecules, IDE-1 and -2, were identified as being capable of efficiently converting mouse and human embryonic stem cells into definitive endoderm [28]. Similarly, indolactam V was identified as a compound that enhanced the differentiation of hESC-derived endodermal cells into Pdx1-expressing pancreatic progenitors [29], and was used in the differentiation of human iPS cells into

insulin-producing cells [30,31]. Recently, an approach has combined small molecules and stepwise differentiation strategies to convert hESCs into mature glucagon-secreting  $\alpha$ -cells [26]. Hence, it is likely that the high-throughput screening approach may increase the efficiency of stepwise differentiation protocol of converting hESCs into  $\alpha$ -,  $\beta$ - and other endocrine cells, as well as identify small molecules that can enhance the responsiveness of  $\beta$  cells to glucose.

## Strategies to preserve $\beta$ -cell function in T2D

T2D is characterized by impaired insulin secretion accompanied by insulin resistance in peripheral tissues [32–34]. The major cause of T2D development is decreased pancreatic  $\beta$ -cell mass and impaired  $\beta$ -cell function [3,35]. However, as the reduction in  $\beta$ -cell mass only correlated with the duration of diabetes, Henquin and colleagues argued that the reduction in  $\beta$ -cell mass could be a consequence of  $\beta$ -cell dysfunction, and not the cause of diabetes [5]. Interestingly, reducing insulin demand can delay the progression of disease from the insulin-resistant stage, to impaired glucose tolerance (IGT) and diabetes [36]. Approaches that have been used to preserve  $\beta$ -cell function include weight loss and increased physical activity to improve insulin sensitivity [36]. Pharmaceuticals, such as thiazolidinediones (TZDs) and metformin, improved insulin resistance in individuals with IGT and prevented their progression to T2D [37,38]. GLP-1 and GLP-1 analogs represent another class of drugs that prevent such progression from IGT to T2D by improving  $\beta$ -cell function and triggering weight loss [36,37,39–43]. Although one needs to be concerned about the side effects of therapeutics, such as TZDs, these observations suggest that a combination of diet and exercise along with therapeutics designed to reduce the insulin demand can be used to preserve  $\beta$ -cell function and prevent diabetes.

## Enhancing $\beta$ -cell mass & function: strategies with therapeutic potential for both T1D & T2D

Since the finding that T1D and T2D result from a reduction in functional  $\beta$ -cell mass, strategies that can enhance  $\beta$ -cell mass and function will benefit both forms of diabetes.  $\beta$ -cell number can be increased by enhancing proliferation of existing  $\beta$  cells or by *in vivo* regeneration of new  $\beta$  cells from non- $\beta$  cells (i.e., by neogenesis/transdifferentiation). However, consequences of such therapies should be carefully evaluated for enhanced risk for uncontrolled cell growth. In addition to enhancing  $\beta$ -cell proliferation, another therapeutic strategy for diabetes will be to increase the effectiveness of the remaining  $\beta$ -cell mass by enhancing their functional capacity. The next section will summarize recent advances in our understanding of different approaches used to enhance  $\beta$ -cell mass and function.

## Increasing $\beta$ -cell mass by enhancing $\beta$ -cell proliferation

Mice expressing constitutively active cell-cycle activators, such as CDK4R26C or lacking the expression of cell-cycle inhibitors, such as p16, p18 or p27 had greater  $\beta$ -cell mass, suggesting that cell-cycle regulators tightly control the proliferation of pancreatic  $\beta$  cells [44,45]. Furthermore, the increased levels of cell-cycle inhibitors with age accompanied the reduction in  $\beta$ -cell proliferation [44–48]. Although evidence suggests that the regulation of  $\beta$ -cell proliferation in humans and rodents is not identical, increased understanding of this process in humans and rodents will benefit our efforts to enhance the proliferation of human  $\beta$  cells [48–50]. A polycomb group of repressor protein EZH2 was identified in mice as an inhibitor of p16 expression in  $\beta$  cells during early stages of life [51]. A recent study demonstrated that PDGF regulates the expression of EZH2 and in turn the proliferation of both mouse and human pancreatic islets [52]. Several other growth factors are also

implicated in regulating  $\beta$ -cell proliferation. Increased expression of CTGF during embryonic development has been found to increase the proliferation of immature  $\beta$  cells [53]. *In vivo* overexpression of HGF in the  $\beta$  cells of transgenic mice increased  $\beta$ -cell mass, insulin production and glucose metabolism [54,55].

Similar to growth factors, several hormones have been implicated in regulating  $\beta$ -cell proliferation. The transgenic expression of PTHrP in  $\beta$  cells increased their mass and insulin secretion, and the mice became resistant to streptozotocin-induced diabetes [56]. Such an effect of PTHrP could be mediated by its N-terminal peptide, which was sufficient to increase the expression of cell-cycle regulators cyclin E and CDK2, and enhance proliferation of human  $\beta$  cells [57]. An examination of the mechanisms enhancing  $\beta$ -cell proliferation during pregnancy has led to the identification of several potential regulators of the *in vivo*  $\beta$ -cell mass. Placental lactogen and prolactin have been linked to the increased  $\beta$ -cell mass during pregnancy [58,59]. Further examination of how  $\beta$ -cell mass is enhanced during pregnancy and how this increase is rapidly normalized to nonpregnant levels after birth suggested a role of serotonin signaling in regulating this process. Serotonin was shown to signal through two distinct serotonin receptors: first through the HTR2b receptor to enhance  $\beta$ -cell proliferation during midgestation and then shortly before parturition through the HTR1d receptor to inhibit  $\beta$ -cell proliferation [60].

Gastric hormones represent another class of regulators implicated in  $\beta$ -cell proliferation and survival. Several studies in various mouse models of diabetes and obesity have found that GLP-1 and its analogs can cause  $\beta$ -cell regeneration and improve glucose tolerance [61,62]. GLP-1 has a short half-life in the body, and GLP-1 analogs with a longer half-life, such as exendin-4, improved both  $\beta$ -cell proliferation and neogenesis [61]. Similar long-acting DPP-IV-resistant GLP-1 analog, Liraglutide, increased  $\beta$ -cell mass and protected them against oxidative and ER stress in db/db mice [63]. Inhibitors of DPP-IV, an enzyme that inactivates GLP-1 and GIP-1, when given to patients with T2D markedly improved their  $\beta$ -cell function and HOMA-B [64]. Despite these promising findings, it is still unknown whether GLP-1 analogs and DPP-IV inhibitors can preserve and enhance the  $\beta$ -cell mass in human T2D patients [65].

Another gastric hormone, gastrin, has been implicated in regulating  $\beta$ -cell proliferation [66]. Gastrin is widely expressed during embryonic development in the pancreas but its expression decreases during postnatal development when  $\beta$ -cell proliferation is reduced [67]. However, gastrin alone was not sufficient to enhance  $\beta$ -cell proliferation, but when used in conjunction with other factors, such as EGF and GLP-1, increased  $\beta$ -cell mass [68–71]. While these data sound promising, the question remains as to whether gastrin by itself, or in combination with other factors, can preserve or regenerate  $\beta$ -cell mass in the human pancreas.

Although we discussed several growth factors and hormones that have the ability to regulate  $\beta$ -cell proliferation, glucose is still considered to be the major regulator of this process [72–75]. Recently, using novel animal models, such as mice with altered glucokinase levels in  $\beta$  cells and compounds, such as GKA, Porat and colleagues convincingly demonstrated that glucose-mediated  $\beta$ -cell replication *in vivo* reflects  $\beta$ -cell glucose metabolism [76]. They also demonstrated the importance of  $\beta$ -cell membrane depolarization in regulating  $\beta$ -cell proliferation [76]. Studies are being conducted to identify other small molecules that are capable of enhancing  $\beta$ -cell replication. TMEM27, a 46 kDa transmembrane protein and a major target of transcription factor TCF1 (*MODY3* gene), increased  $\beta$ -cell mass *in vivo* and augmented GSIS [77,78]. Recent work on characterizing how TMEM27 regulates this process resulted in the identification of BACE2, a protease that cleaves TMEM27 and inactivates its ability to enhance  $\beta$ -cell proliferation. By screening for a library of protease

inhibitors, a BACE2-specific inhibitor was identified that successfully increased  $\beta$ -cell mass and improved insulin secretion [79]. In another high throughput screen approximately 850,000 compounds were examined for their ability to induce proliferation of an immortalized mouse  $\beta$ -cell line (R7T1); a few regulators of the Wnt signaling pathway along with L-type calcium channel agonists were identified as potential stimulators of  $\beta$ -cell proliferation [80]. Taken together, these results indicate that several growth factors, hormones and small molecules have the capacity to enhance *in vivo* proliferation of  $\beta$  cells.

## Regeneration of $\beta$ cells via transdifferentiation & neogenesis

$\beta$ -cell proliferation is not identical in rodents and humans [48–50]. Furthermore, human  $\beta$  cells show relatively modest proliferative responses to maneuvers that more dramatically increase the  $\beta$ -cell mass in rodents [81–85]. Therefore, strategies to increase the *in vivo*  $\beta$ -cell mass, other than by enhancing  $\beta$ -cell proliferation, should also receive serious consideration. We define neogenesis of  $\beta$  cells as a process by which adult progenitors or facultative progenitors (e.g., pancreatic ductal cells) differentiate into  $\beta$  cells. Transdifferentiation is the conversion of a differentiated cell from one developmental lineage into a differentiated cell of another lineage without first reverting into a more primitive stem or progenitor cell type [86–88].

Lately, much attention has focused on developing new  $\beta$  cells after birth from  $\alpha$ -cells, ductal cells, acinar cells and other nonpancreatic cell types. The expression of endocrine transcription factors *in vivo* was shown to convert acinar cells and hepatic progenitors into  $\beta$  cells [89,90]. Interestingly, the suppression of transcription factor PFT1a in acinar cells of zebrafish was shown to trigger the conversion of acinar cells into insulin-positive endocrine cells [91]. These studies suggest that the balance between the acinar and endocrine fate can be perturbed *in vivo*. Other studies have successfully generated insulin-producing cells from other pancreatic and nonpancreatic cell types, including a recent study that demonstrated that the expression of transcription factors NGN3 and PDX1 in human mesenchymal stem cells could partially reprogram these cells into insulin-expressing cells [92]. Several recent reviews address the presence of stem cells/progenitor cells in the adult pancreas, the increased plasticity of adult pancreatic cell types to differentiate into  $\beta$  cells, the therapeutic potentials and limitations of neogenesis and transdifferentiation approaches in the treatment of diabetes [9,21,22,93–96]. In this section, we will highlight a few recent studies that provide hope for deciphering the mechanisms underlying transdifferentiation and neogenesis of  $\beta$  cells.

### Transdifferentiation

Diphtheria toxin-mediated ablation of the majority of  $\beta$  cells in transgenic mice has been shown to result in the formation of new  $\beta$  cells from the transdifferentiation of  $\alpha$ -cells [97]. Similarly, ablation of  $\beta$  cells using alloxan lead to the formation of new  $\beta$  cells, most likely from the conversion of  $\alpha$ -cells [98]. Transgenic expression of Pax4 in  $\alpha$ -cells, and the expression of Pdx1 in Ngn3+ cells and their progeny also triggered transdifferentiation of  $\alpha$ -cells into  $\beta$  cells [99,100]. Such conversion of  $\alpha$ -cells into  $\beta$  cells was also observed in  $\alpha$ -cell-specific *Men1* knock-out mice [101]. Further analyses of these different experimental systems should lead to the identification of mechanisms regulating transdifferentiation of endocrine cells. Interestingly, the deletion of DNMT1 in  $\beta$  cells caused derepression of a key  $\beta$ -cell regulator *Arx*, and converted  $\beta$  cells into  $\alpha$ -like cells, suggesting that chromatin reprogramming may regulate the transdifferentiation of endocrine cells [102]. Thus, these recent studies could identify key regulators and small molecules regulating *in vivo* transdifferentiation of  $\alpha$ -cells into  $\beta$  cells.

## Neogenesis

Recently, several studies have used a lineage-tracing approach to examine the role of pancreatic ductal cells in the neogenesis of  $\beta$  cells after birth. These include a study that identified NGN3+ multipotent islet progenitors near ducts in the pancreas following pancreatic ductal ligation in adult mice [103], and a study demonstrating that CAII-dependent lineage-marked duct cells gave rise to new islet and acinar cells after birth, supporting a role of ductal cells in postnatal neogenesis [104]. However, results from several other studies have suggested the lack of (or limited)  $\beta$ -cell neogenesis after birth [105–107]. No neogenesis of  $\beta$  cells or any other endocrine/acinar cells from late gestation and after birth was seen from HNF1+ duct cells [105]. Consistent with these results, mucin1-expressing duct cells did not differentiate into endocrine cells after birth [106]. During the early postnatal period, some progeny of Sox9+ cells expressed Ngn3 and differentiated into a small number of non- $\beta$  cells, but in adults Sox9+ cells did not form endocrine or acinar cells [107]. However, Furuyama and colleagues demonstrated some neogenesis of  $\beta$  cells from ducts labeled at P1, but not at P7 using a Sox9-based lineage-tracing approach [108]. Additionally, they showed that Sox9+ duct cells did differentiate into acinar cells after birth. These results demonstrate some disagreement between these excellent studies over the role of ductal cells in the neogenesis of  $\beta$  cells and acinar cells after birth. Hence, it is likely that in mice, neogenesis of  $\beta$  cells after birth is a very rare event with only a sub-population of ductal cells having the potential to give rise to  $\beta$  cells. Further examination of these possibilities would provide yet another way to enhance  $\beta$ -cell mass *in vivo*.

## Enhancing $\beta$ -cell function: a strategy to develop long-term insulin independence

The reduction in  $\beta$ -cell mass can be restored by enhancing the functional capacity of individual  $\beta$  cells. Several of the approaches described earlier in respect to enhancing  $\beta$ -cell proliferation and prevention of diabetes also enhance  $\beta$ -cell function. The use of incretin hormones represent one such therapy that has multiple physiological benefits that help ameliorate diabetes. GLP-1 analogs and DPP4 inhibitors enhance  $\beta$ -cell proliferation, survival and differentiation. They also increase insulin secretion, insulin gene expression and the expression of key  $\beta$ -cell transcription factors, such as Pdx1 [62,63,109–112]. Similar to incretins, GKAs regulate  $\beta$ -cell proliferation, inhibit apoptosis and enhance  $\beta$ -cell function [76,113]. Long-term administration of GKA in *Gck<sup>+/-</sup>* mice on a high-fat diet improved their glucose metabolism [114]. Similar chronic treatment with GKA71 enhanced GSIS, prevented  $\beta$ -cell exhaustion and upregulated important  $\beta$ -cell genes such as insulin, Pdx1, Glut2, IAPP and PC1 [115]. Furthermore, treating T2D patients with piragliatin, another GKA, lowered their plasma glucose in both fed and fasting states [116]. Efforts are also underway to identify novel regulators of  $\beta$ -cell function. One new class of regulators are miRNAs. A miRNA, *miR-375*, was shown to regulate insulin secretion, PDK1 and glucose response in  $\beta$  cells [117,118]. In addition, *miR-375* is required for the formation of normal endocrine  $\beta$ -cell masses during pancreatic development [119]. Taken together, these studies demonstrate the presence of novel molecules that regulate both  $\beta$ -cell mass and function, and consequently such regulators represent an important class of molecules for the treatment of diabetes.

## Enhancing $\beta$ -cell function via insulin gene transcription factors

Major insulin gene transcription factors, such as MafA, Pdx1 and NeuroD1, play a critical role in regulating glucose-responsive expression of the insulin gene. Reduced expression of these genes is associated with  $\beta$ -cell dysfunction and diabetes. Hence, strategies involved in

enhancing expression of these factors will improve  $\beta$ -cell function, prevent  $\beta$ -cell exhaustion and delay future deterioration of  $\beta$ -cell function.

MafA regulates glucose-stimulated insulin gene expression [120–123] and loss of its expression is linked with impaired  $\beta$ -cell function [124,125]. Consistent with this observation, enhancing the expression of MafA in the INS-1 cells enhanced both GSIS and the expression of genes implicated in controlling insulin synthesis and secretion [126]. Furthermore, overexpression of MafA in immature neonatal islets improved their GSIS by increasing both the proportion of cells secreting insulin and the amount of insulin secreted by the individual  $\beta$  cells [127]. These observations suggest that strategies to enhance MafA expression would lead to improved  $\beta$ -cell function.

Like MafA, transcription factor Pdx1 is critical for the formation and function of  $\beta$  cells [128–130]. Enhancing expression of Pdx1 in  $\beta$  cells in *IRS2*<sup>-/-</sup> mice successfully overcame their  $\beta$ -cell dysfunction [131]. Similarly, the loss of one *Pcif1* allele, a PDX1 C-terminal-interacting protein that regulates degradation of PDX1, was sufficient to improve glucose tolerance, and compensate for the reduction in Pdx1 expression in *Pdx1* heterozygous mice [132]. In addition to preventing protein degradation, other approaches have been developed to enhance the expression of key regulators of  $\beta$ -cell function. A small molecule, Isx, identified in a chemical library screening, was capable of activating expression of transcription factor NeuroD1. Treating insulin-producing cells with this activator led to increased GSIS as well as a modest increase in insulin content [133]. Hence, we suggest that identifying novel approaches to enhance expression and function of key  $\beta$ -cell transcription factors offers a tremendous opportunity for developing new therapies for diabetes.

## Conclusion & future perspective

Over the last decade, significant advances have been made in our understanding of  $\beta$ -cell biology, which provides many avenues to improve  $\beta$ -cell mass and function. Studies examining the effects of various growth factors, hormones and novel small molecules on  $\beta$ -cell growth offer hope for successfully enhancing the proliferation of remaining  $\beta$ -cells *in vivo*. Similarly, improved understanding of pancreatic development and differentiation of  $\beta$  cells will lead to new strategies for *in vivo* regeneration of  $\beta$  cells from endogenous progenitors and transdifferentiation from non- $\beta$  cells. Finally, new approaches to enhance the expression and function of key regulators of  $\beta$  cells will be critical to improve GSIS and replenish the  $\beta$ -cell store, a key to preventing the progressive decline in  $\beta$ -cell function evident in diabetes. Hence, we suggest that a combination of prevention, regeneration and functional enhancement, together with the strategies to protect new  $\beta$  cells, will be critical for the development of an ultimate cure for both forms of diabetes.

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### Practice Points

- Both Type 1 and 2 diabetes result from a loss of  $\beta$ -cell mass and function.
- Antigen-specific and antigen-nonspecific approaches offer a way to preserve and restore  $\beta$  cells in Type 1 diabetes.
- $\beta$ -cell replacement from stem cells, induced pluripotent cells and other sources can potentially yield insulin-producing cells.
- Diet, exercise and pharmacological intervention have been the main treatments for preserving  $\beta$  cells in Type 2 diabetes patients.
- Cell-cycle regulators, growth factors and hormones are avenues that can be used to stimulate  $\beta$ -cell proliferation.
- GLP-1/GIP and their analogs can direct  $\beta$ -cell proliferation and increase  $\beta$ -cell function.
- Neogenesis and transdifferentiation are two potential approaches for *in vivo*  $\beta$ -cell replenishment.
- Glucokinase activators and microRNA offer alternative pathways for  $\beta$ -cell enhancement.
- $\beta$ -cell function can be augmented by enhancing the expression of insulin gene transcription factors.