Diabetologia
https://doi.org/10.1007/s00125-017-4530-x

REVIEW

Hope vs hype: where are we in type 1 diabetes?

Jay S. Skyler[1]

Received: 7 August 2017 / Accepted: 9 November 2017
© Springer-Verlag GmbH Germany, part of Springer Nature 2017

Abstract

Much progress has been made in type 1 diabetes research. Biological replacement of islet function has been achieved with pancreas transplantation and with islet transplantation. In the future, human embryonic stem cells and/or induced pluripotent stem cells may offer a potentially unlimited source of cells for islet replacement. Another potential strategy is to induce robust beta cell replication so that regeneration of islets can be achieved. Immune interventions are being studied with the hope of arresting the type 1 diabetes disease process to either prevent the disease or help preserve beta cell function. Mechanical replacement of islet cell function involves the use of glucose sensor-controlled insulin infusion systems. As all of these avenues are pursued, headlines often overstate the case, thus hyping any given advance, which provides enormous hope for patients and families seeking a cure for type 1 diabetes. Often, however, it is an animal study or a pilot trial that is being described. The reality is that translation to successful trials in human beings may not be readily achievable. This article discusses both the hype and the hopes in type 1 diabetes research.

Keywords Automated insulin delivery · Immune intervention · Islet regeneration · Islet replacement therapy · Review · Stem cells · Type 1 diabetes

Abbreviations

AEP	Artificial endocrine pancreas
BB rat	BioBreeding rat
GLP-1RA	Glucagon-like peptide-1 receptor agonists
hESC	Human embryonic stem cell
INGAP	Islet neogenesis-associated protein
iPSC	Induced pluripotent stem cell
TRIGR	Trial to Reduce IDDM in the Genetically at Risk

Introduction

'Hope' and 'hype' differ by one letter. Announcements of scientific advances offer hope of new approaches to type 1 diabetes. Unfortunately, headlines may hype such advances more than is warranted. The fact is that science moves slowly, and the exciting 'breakthroughs' cited in headlines require confirmation, refinement and further development, which may stretch over years. Sometimes the scientific underpinnings are weak. Sometimes the initial reports may even need to be retracted. Sometimes observations in animal models do not translate to similar findings in human beings. Sometimes developments that appear to work on a small scale on a benchtop cannot be made and manufactured on a commercial scale. Even then, potentially attractive interventions may not be affordable by patients or the healthcare system. For all these reasons, not all advances result in outcomes that improve health for people with type 1 diabetes. This article reviews the studies that were hyped and that led to hope, and the outcomes that resulted in disappointment. The areas that are included are islet replacement therapy, immune intervention and automated insulin delivery. Over the years it has been proposed that advances in these areas will alter the face of type 1 diabetes [1]. However, journalists and scientists must be careful not to overly hype the advances, but rather recognise and project the long time needed for fruition of the hopes. For example, I wrote a chapter entitled 'Diabetes in 2021: one hundred years after insulin' for a book published in 1984 [2]. The themes are the same. Indeed, Fig. 1 depicts headlines heralding advances. The sobering thing is that these headlines are derived

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00125-017-4530-x) contains a slideset of the figures for download, which is available to authorised users.

✉ Jay S. Skyler
jskyler@miami.edu

[1] Diabetes Research Institute, University of Miami Miller School of Medicine, 1450 NW 10th Avenue - Suite 3054, Miami, FL 33136, USA

Published online: 23 December 2017

Fig. 1 News headlines (derived from a slide from 1975) heralding diabetes advances. This figure is available as part of a downloadable slideset

from a slide from a presentation by Daniel Mintz at the American Diabetes Association Postgraduate Course in 1975.

The issue of hope vs hype is not unique to type 1 diabetes. In a search of PubMed conducted for the purposes of this article, there were 427 articles identified when the search term was 'hope and hype', and this number was reduced to 24 for the search term 'hope and hype and diabetes'. Several discussed 'hope or hype' or 'hype and hope', while others addressed going 'from hype to hope', and at least one talked of 'hype, hope and reality'. The point is that the scientific community needs to be cautious about how provocative findings are communicated. Journals, too, need to be cautious when issuing press releases about articles that are appearing in them. This applies also to academic institutions and research organisations that issue press releases.

Figure 2 indicates the ideal therapeutic goals in type 1 diabetes. This article discusses attempts to achieve these goals, and the hype, hopes and reality concerning the progress in achieving them.

Headline: transplants offer hope for diabetes

Islet replacement therapy: reality

Pancreas transplantation The modern era of pancreas transplantation began with a report from the University of Minnesota in 1967 [3]. The field expanded such that 15 years later it was touted as an important approach to type 1 diabetes that resulted in durable control of blood glucose [4]. This was further enhanced by the demonstration that pancreas transplantation reduced the recurrence of renal disease in patients also receiving kidney transplants [5]. Moreover, the 10 year patient and kidney graft survival rates were higher in individuals having a kidney transplant together with a pancreas transplant than in those having a kidney transplant alone, regardless of whether the kidney donor was deceased or living [6].

A problem with pancreas transplantation is the associated morbidity, including acute rejection, graft thrombosis resulting in the need for allograft pancreatectomy, the need for chronic immunosuppression, infectious complications and the relatively high rates of haematological cancers [7]. Nonetheless, as surgical techniques have been refined, accompanied by better immunosuppression, there have been improved pancreas graft survival rates and lower acute rejection rates [7]. An unexpected but important finding has been the recurrence of autoimmunity without evidence of rejection in the setting of chronic immunosuppressive therapy [8].

Organ procurement has been a limiting factor, as there are only a limited number of organ donors and not all have a pancreas suitable for transplantation. Initially, this was a major problem. Somewhat surprisingly, however, in the USA there has been a progressive decline in pancreas transplantation over the past 10–15 years [9]. This is somewhat of a paradox in that pancreas transplantation is a definitive therapy with improving success rates over time but one that is applied less often. Moreover, the continued limited number of organ donors means some patients barely surviving the waiting list for a transplant. Intriguingly, it is also now possible to perform pancreas

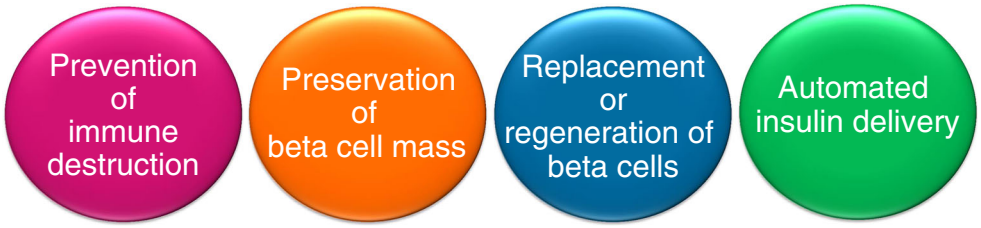

Fig. 2 Ideal therapeutic goals in type 1 diabetes. This figure is available as part of a downloadable slideset

transplantation using a laparoscopic robotic approach [10]. One criticism is the lack of randomised clinical trials to establish the actual risk, benefit and cost effectiveness of pancreas transplantation [11].

Islet transplantation Transplantation of islets, rather than whole pancreas, was first reported in rodents in 1972 [12], and in human beings in 1977 [13]. Progress in the field was markedly facilitated by improvements in islet isolation and purification, including the development of the Ricordi chamber, reported in 1989 [14]. Using the Edmonton protocol, involving a glucocorticoid-free immunosuppressive regimen, insulin independence was achieved in most patients, giving great hope to the field [15]. However, an international trial using that protocol did not have equivalent success [16], perhaps related to differences in sites in experience both with the complex preparation of human islets for transplantation and clinical experience in the routine management of immunosuppressive therapies [17]. Nonetheless, there has been a progressive improvement in outcomes [18], and the Clinical Islet Transplantation Consortium has completed a Phase III trial of transplantation of human islets in type 1 diabetes complicated by severe hypoglycaemia [19]. Compared with pancreas transplantation, the procedure is less invasive and is associated with less morbidity, but the requirement for chronic immunosuppression remains. Another problem is that islets often fail to continue to produce insulin, requiring a second islet transplant or a return to insulin therapy. According to the most recent report from the Collaborative Islet Transplant Registry, between 1999 and 2013, worldwide a total of 1011 individuals received islet transplantation, 25–30% of whom were insulin independent after 5 years and 40–55% had significant C-peptide production [20]. Interestingly, at least 40 islet transplant recipients have had to undergo pancreas transplant after the islets failed [21]. Moreover, even if the procedure were highly successful, the limitation of cadaveric organ donors would preclude wide-scale use. Ideally, being an organ donor should be the default position, with individuals having to opt out of organ donation rather than having to opt in.

Headline: stem cells can cure diabetes

Stem cells

There has been enormous progress in our understanding of the development of islets [22], thus permitting the generation of islets from human embryonic stem cells (hESCs) [23]. The hope has been that this would provide an unlimited source of islets suitable for replacement therapy. Indeed, formal clinical trials were initiated with encapsulated hESCs, the capsules designed to obviate the need for immunosuppression [24]. Unfortunately, there was inadequate vascularisation and a foreign body reaction that has led to a new trial with a modified encapsulation device but the need for immunosuppression [25]. A limitation of the preclinical programme for these trials was that they were conducted in immunodeficient rodents [24, 25], since it was known that the original encapsulation device would not stop a xenograft reaction and the embryonic stem cells were human in origin.

Encapsulation devices have been under development for many years [26]. Recent improvements in approaches to encapsulation may yet eliminate the need for immunosuppression [27, 28]. Unfortunately, this has not yet proved to be the case in human beings. Another approach for production of cells is to differentiate human induced pluripotent stem cells (iPSCs) into insulin-secreting beta cells [29, 30]. If allogenic iPSCs are used, these, too, will require encapsulation and/or immunomodulation, as is the case for hESCs. Alternatively, autologous iPSCs could be used, which would be given to the same individual from which they were derived, which would obviate rejection but not necessarily recurrent autoimmunity [31]. A similar approach, known as transdifferentiation, has been used in which liver cells are obtained by biopsy and differentiated in vitro into beta cells and re-implanted in the individual from whom the cells were obtained [32]. However, any autologous approach would require the site at which the procedure was performed to have a specialised laboratory for differentiating the cells, rather than a single manufacturing site making allogenic cells.

Another issue that needs to be considered is that pure beta cells might not be the answer, as one of the benefits of islet transplantation has been the prevention of severe

hypoglycaemia, which involves improvement of alpha cell function and effective paracrine interactions within the islet [33].

Headline: peptide can make new beta cells

Regeneration

A potentially exciting approach to recovering islet function is in vivo treatment with a substance that causes islets or beta cells to regenerate or reawaken. In rodent islets, glucagon-like peptide-1 receptor agonists (GLP-1RA) were found to increase both neogenesis and proliferation of beta cells while inhibiting beta cell apoptosis [34]. In contrast, in human islets, GLP-1RA inhibits beta cell apoptosis, but only stimulates beta cell proliferation in very young islets [35]. An interesting experiment in human type 2 diabetes was to test whether exenatide, a GLP-1RA, could increase beta cell mass [36]. Although beta cell function was improved, the improvement was not sustained after withdrawal of exenatide. The interpretation was that beta cell mass was thus not increased. Another interpretation could be that beta cell function is improved with exposure to a GLP-1RA, and that the drug must be continued indefinitely in an attempt to maintain increased beta cell function. The use of a GLP-1RA could also be studied in type 1 diabetes.

Many other substances, including small molecules, growth factors, hormones and nutrients, have been found to induce robust beta cell replication in rodent or other eukaryotic models [37]. Some have been widely claimed to be of potential importance, such as islet neogenesis-associated protein (INGAP) [38] (or its human counterpart, human proislet peptide [39]), gastrin [40] and betatrophin [41]. INGAP failed in clinical trials [42]. In the case of betatrophin, the experiments could not be reproduced [43, 44], and the initial paper was subsequently retracted [45]. Again, much of the problem in regeneration is that success in animal models does not translate into success in human beings.

Headline: new approach prevents type 1 diabetes

Immune intervention

Prevention of type 1 diabetes There have been literally hundreds of treatments that prevent autoimmune diabetes in animal models such as the NOD mouse [46] and the BioBreeding (BB) rat [47]. However, to date, none of several tested interventions has been successful in preventing type 1 diabetes in human beings [48, 49]. Most of the studies have been conducted in relatives of people with type 1 diabetes, who have an increased risk of the disease. The participants in trials for secondary prevention are recruited from screening programmes that identify individuals with beta cell autoimmunity. Yet, this requires screening tens of thousands of individuals, since 95% of relatives will not have antibodies. Moreover, most tested interventions have focused on antigen-based immune deviation using various forms of insulin or GAD, or benign substances such as the vitamin nicotinamide [50]. It may very well be that antigen-based immune deviation needs to be initiated prior to the development of antibodies if it is to be successful. This may require population-based genetic screening to select an appropriate cohort for testing primary prevention of disease. One study in primary prevention, the Trial to Reduce IDDM in the Genetically at Risk (TRIGR), is evaluating whether an infant formula that uses casein hydrolysate rather than cow's milk could delay or prevent the development of type 1 diabetes [51]. A pilot study from Finland suggested that such a formula could delay the appearance of diabetes antibodies [52], but this was not confirmed in the larger TRIGR trial [51]. Screening the general population for high genetic risk of type 1 diabetes may be feasible [53]. The question is: what intervention should be tested?

Preservation of beta cell function in type 1 diabetes Many immune intervention studies have been conducted in recent-onset type 1 diabetes [49]. Some have shown no effect. Some have looked promising and have demonstrated a slower decline of beta cell function than the control group. Unfortunately, in most of the latter circumstances, after a transient apparent benefit, there has been a subsequent progressive decline in beta cell function which parallels that in the control group. At least four interventions (the anti-CD3 monoclonal antibodies teplizumab and otelixizumab, a GAD vaccine, and DiaPep277) have actually entered into Phase III trials, all of which failed to meet their primary endpoint [49]. The reasons for failure have been discussed elsewhere [49]. A resulting problem is that public enthusiasm for such trials has waned as apparent failures accumulate. Yet, almost all of the approaches investigated to date have used single agents directed at one or another component of the immune response. However, because some have demonstrated at least a transient response, this suggests their potential for use in a combination therapy approach and/or the potential for consideration for additional course(s) of treatment. It may well be that a different approach is needed, such as blocking innate immunity (inflammation) while inhibiting adaptive immunity (the T-lymphocyte response) and stimulating regulatory immunity, and simultaneously providing a treatment that may improve beta cell health [49]. This may seem radical, but two such

trials are listed in ClinicalTrials.gov and should soon be recruiting participants (NCT02586831, NCT03182426). Alternatively, success may require a better understanding of the heterogeneity in disease progression, and the possible need for precision medicine in selection of interventions for different individuals.

Immune tolerance One potential problem with some of the immune intervention studies that have been conducted is that there was only transient exposure to the intervention early after enrolment. The hope was that an immune tolerant state would emerge so that the immune system of the person treated would no longer mount an anti-beta cell response. One trial that suggested this was feasible was an early study with otelixizumab in which the treatment lasted only 6 days, and preserved beta cell function was demonstrated 18 months later [54]. Moreover, at 4 years after initial treatment, although beta cell function was not measured, the otelixizumab group required much less insulin than the control group in order to maintain a similar HbA_{1c} [55]. This suggested that the benefit of a 6 day course of treatment could be maintained 4 years later, but there was insufficient data and follow-up to establish tolerance. Yet, immune tolerance may have been too high a bar for autoimmune disease (or organ transplantation), despite the efforts of the Immune Tolerance Network [56]. Tolerance has been achieved in allergy, and can be at least partly or transiently achieved by bone marrow transplantation. However, documented tolerance has yet to be demonstrated in autoimmune diseases, including type 1 diabetes.

Headline: artificial pancreas makes debut

Automated insulin delivery

Closed loop systems An artificial endocrine pancreas (AEP), or closed loop insulin delivery, or more precisely, a glucose-controlled insulin delivery system, has been a holy grail of type 1 diabetes since the initial reports of development of such systems in the early 1970s [57–59]. The initial systems involved a bulky bedside apparatus and required intravenous access both for glucose measurement and for insulin delivery. Nonetheless, commercial versions of such systems were introduced and used for research studies and for inpatient management of diabetic ketoacidosis or control of blood glucose during surgery [60]. Later, a glucose-controlled insulin delivery system that used an intravascular glucose sensor and intraperitoneal insulin delivery was tested in clinical trials [61].

External systems More recently, external glucose-controlled insulin delivery systems have been tested with much fanfare [62, 63]. These involve conventional insulin pumps that are controlled by an algorithm (via computer or smart phone) to deliver insulin, and sometimes glucagon, based on the prevailing level and rate of change of interstitial glucose measured by a glucose sensor [64]. Sensor accuracy and performance, which were previously limiting factors in the development of systems, has dramatically improved over the past decade, thus allowing rapid advancement of the field [65]. Overnight control of basal glucose has readily been achieved, but control of meal-related glucose excursions has been a bigger challenge. Thus, a 'hybrid' system has been made commercially available—one that can control overnight glucose but still requires user intervention to control meal excursions [66].

Onset of insulin action Part of the reason for difficulty in controlling meal glucose excursions may be that the current generation of 'rapid-acting' insulin analogues may be too slow to respond to abrupt increases in glucose following a meal. Newer more rapid analogues are being developed to overcome this issue [67]. Also, refinement of the algorithms controlling insulin delivery may overcome the problem. Control of mealtime glucose was not a problem with intravenous or intraperitoneal insulin delivery, as the pharmacokinetics of insulin produced much quicker insulin excursions.

'Smart' insulins One potential approach for achieving glucose control is an insulin that can be administered but released in response to prevailing level of glucose, so-called 'smart' insulin [68]. The concept dates back to the late 1970s [69]. More recently, several groups have attempted to develop such an insulin [68], but no clinical trial results have yet been reported.

Conclusions

There are many exciting areas of research addressing type 1 diabetes. Much progress has been made, but this progress has evolved over decades. Sometimes hype of progress in news reports has raised hope and expectations on the part of diabetic individuals and their families, who interpret such headlines as indicative of forthcoming success. Hype and hope are not mutually exclusive, however, the public would be better served by more tempered reports (see Text box). In all cases, clinical investigators must remember to seek equipoise and work to do no harm. Science is advancing, but instantaneous success is highly unlikely. Reports need to clearly distinguish studies in animals, as these may or may not translate to success in human beings. The optimistic view is that all of the scientific directions discussed in this review will come to fruition. The biggest difficulty is predicting when.

Issues faced when conducting and reporting studies in type 1 diabetes

- Success of studies in rodents poorly translates to success in human beings
- Incomplete understanding of the pathogenesis of type 1 diabetes in human beings
- The disease may be uniform in rodent models but heterogeneous in human beings
- Need for appropriate expectations for both scientific community and people with type 1 diabetes
- Importance of rigorous application of the scientific method
- Limitations of interpretation of small pilot studies that are under-powered
- Progress is often slower than desired
- There are often new unanticipated issues that need to be solved on the road to success
- Inherent conflict in wanting to report success while acknowledging limitations
- The entire scientific enterprise (investigators, funders, journals) needs to take responsibility for tempered and realistic reporting

Funding The author is supported by the Diabetes Research Institute Foundation.

Duality of interest The author has acted as an advisor to: Adocia, Abvance, AstraZeneca, BD Technologies, Boehringer Ingelheim, Dance Biopharm, Diavacs, Elcelyx Therapeutics, Eli Lilly and Company, Ideal Life, Immunomolecular Therapeutics, Intrexon, Merck, Orgenesis, Sanofi, Servier, Tolerion, vTv Therapeutics, Valeritas LLC and Viacyte. He has had research funding from: NIH, JDRF, Mesoblast and Viacyte. He is a member of the board of directors of: Dexcom Inc., Intarcia Therapeutics and Moerae Matrix. He has equity in: Dance BioPharma, Dexcom Inc., Ideal Life, Intarcia Therapeutics, Intexon, Moerae Matrix and VasoPrep Surgical.

Contribution statement The author was the sole contributor to this paper.

References

1. Skyler JS (2003) A view of the future. In: Raz I, Skyler JS, Shafrir E (eds) Diabetes: from research to diagnosis and treatment. Martin Dunitz, London, pp 547–558
2. Skyler JS (1984) Diabetes in 2021 - One hundred years after insulin. In: Baba S, Gould M, Zimmet P (eds) Diabetes – recent knowledge on aetiology, complications and treatment. Academic Press, Sydney, pp 237–252
3. Kelly WD, Lillehei RC, Merkel FK, Idezuki Y, Goetz FC (1967) Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. Surgery 61:827–837
4. Sutherland DE, Goetz FC, Najarian JS (1982) Pancreas transplantation. Clin Endocrinol Metab 11:549–578
5. Bilous RW, Mauer SM, Sutherland DE, Najarian JS, Goetz FC, Steffes MW (1989) The effects of pancreas transplantation on the glomerular structure of renal allografts in patients with insulin-dependent diabetes. N Engl J Med 321:80–85
6. Lindahl JP, Hartmann A, Horneland R et al (2013) Improved patient survival with simultaneous pancreas and kidney transplantation in recipients with diabetic end-stage renal disease. Diabetologia 56: 1364–1371
7. Gruessner RW, Gruessner AC (2013) The current state of pancreas transplantation. Nat Rev Endocrinol 9:555–562
8. Vendrame F, Pileggi A, Laughlin E et al (2010) Recurrence of type 1 diabetes after simultaneous pancreas-kidney transplantation, despite immunosuppression, is associated with autoantibodies and pathogenic autoreactive CD4 T cells. Diabetes 59:947–957
9. Gruessner AC, Gruessner RWG (2014) Declining numbers of pancreas transplantations but significant improvements in outcome. Transplant Proc 46:1936–1937
10. Boggi U, Signori S, Vistoli F et al (2012) Laparoscopic robot-assisted pancreas transplantation: first world experience. Transplantation 93:201–206
11. Dean PG, Kukla A, Stegall MD, Kudva YC (2017) Pancreas transplantation. BMJ 357:j1321
12. Ballinger WF, Lacy PE (1972) Transplantation of intact pancreatic islets in rats. Surgery 72:175–186
13. Najarian JS, Sutherland DE, Matas AJ, Steffes MW, Simmons RL, Goetz FC (1977) Human islet transplantation: A preliminary report. Transplant Proc 9:233–236
14. Ricordi C, Lacy PE, Scharp DW (1989) Automated islet isolation from human pancreas. Diabetes 38:140–142
15. Shapiro AM, Lakey JR, Ryan EA et al (2000) Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med 343:230–238
16. Shapiro AM, Ricordi C, Hering BJ et al (2006) International trial of the Edmonton protocol for islet transplantation. N Engl J Med 355: 1318–1330
17. McCall M, Shapiro AJM (2012) Update on islet transplantation. Cold Spring Harb Perspect Med 2:a007823
18. Barton FB, Rickels MR, Alejandro R et al (2012) Improvement in outcomes of clinical islet transplantation: 1999-2010. Diabetes Care 35:1436–1445
19. Hering BJ, Clarke WR, Bridges ND et al (2016) Phase 3 trial of transplantation of human islets in type 1 diabetes complicated by severe hypoglycemia. Diabetes Care 39:1230–1240
20. Collaborative Islet Transplant Registry (2017) Collaborative Islet Transplant Registry Ninth Annual Report. Available from https://citregistry.org/system/files/9AR_Report.pdf. Accessed 2 October 2017
21. Gruessner RW, Gruessner AC (2016) Pancreas after islet transplantation: a first report of the International Pancreas Transplant Registry. Am J Transplant 16:688–693
22. Kim SK, Hebrok M (2001) Intercellular signals regulating pancreas development and function. Genes Dev 15:111–127
23. D'Amour KA, Bang AG, Eliazer S et al (2006) Production of pancreatic hormone-expressing endocrine cells from human embryonic stem cells. Nat Biotechnol 24:1392–1401

24. Agulnick AD, Ambruzs DM, Moorman MA et al (2015) Insulin-producing endocrine cells differentiated in vitro from human embryonic stem cells function in macroencapsulation devices in vivo. Stem Cells Transl Med 4:1214–1222
25. JDRF and ViaCyte announce support for development of pec-direct cell replacement therapy for type 1 diabetes. Press Release 22 May 2017. http://viacyte.com/press-releases/jdrf-and-viacyte-announce-support-for-development-of-pec-direct-cell-replacement-therapy-for-type-1-diabetes/. Accessed 2 October 2017
26. Lanza RP, Hayes JL, Chick WL (1996) Encapsulated cell technology. Nat Biotechnol 14:1107–1111
27. Tomei AA, Manzoli V, Fraker CA et al (2014) Device design and materials optimization of conformal coating for islets of Langerhans. Proc Natl Acad Sci 111:10514–10519
28. Desai T, Shea LD (2017) Advances in islet encapsulation technologies. Nat Rev Drug Discov 16:338–350
29. Nair G, Hebrok M (2015) Islet formation in mice and men: lessons for the generation of functional insulin-producing β-cells from human pluripotent stem cells. Curr Opin Genet Dev 32:171–180
30. Pagliuca FW, Millman JR, Gürtler M et al (2014) Generation of functional human pancreatic β cells in vitro. Cell 159:428–439
31. Millman JR, Xie C, Van Dervort A, Gürtler M, Pagliuca FW, Melton DA (2016) Generation of stem cell-derived β-cells from patients with type 1 diabetes. Nat Commun 7:11463
32. Meivar-Levy I, Ferber S (2015) Reprogramming of liver cells into insulin-producing cells. Best Pract Res Clin Endocrinol Metab 29: 873–882
33. Alejandro R, Barton FB, Hering BJ, Wease S (2008) Collaborative Islet Transplant Registry Investigators. 2008 Update from the Collaborative Islet Transplant Registry. Transplantation 86:1783–1788
34. Baggio LL, Drucker DJ (2006) Therapeutic approaches to preserve islet mass in type 2 diabetes. Annu Rev Med 57:265–281
35. Dai C, Hang Y, Shostak A et al (2017) Age-dependent human beta cell proliferation induced by glucagon-like peptide 1 and calcineurin signalling. J Clin Invest 127:3835–3844
36. Bunck MC, Diamant M, Cornér A et al (2009) One-year treatment with exenatide improves beta-cell function, compared with insulin glargine, in metformin-treated type 2 diabetic patients: a randomized, controlled trial. Diabetes Care 32:762–768
37. Wang P, Fiaschi-Taesch NM, Vasavada RC, Scott DK, García-Ocaña A, Stewart AF (2015) Diabetes mellitus—advances and challenges in human β-cell proliferation. Nat Rev Endocrinol 11: 201–212
38. Pittenger GL, Taylor-Fishwick D, Vinik AI (2009) The role of islet neogeneis-associated protein (INGAP) in pancreatic islet neogenesis. Curr Protein Pept Sci 10:37–45
39. Levetan CS, Upham LV, Deng S et al (2008) Discovery of a human peptide sequence signaling islet neogenesis. Endocr Pract 14:1075–1083
40. Tellez N, Joanny G, Escoriza J, Vilaseca M, Montanya E (2011) Gastrin treatment stimulates beta-cell regeneration and improves glucose tolerance in 95% pancreatectomized rats. Endocrinology 152:2580–2588
41. Yi P, Park JS, Melton DA (2013) Betatrophin: a hormone that controls pancreatic β cell proliferation. Cell 153:747–758
42. Fleming A, Rosenberg L (2007) Prospects and challenges for islet regeneration as a treatment for diabetes: a review of islet neogenesis associated protein. J Diabetes Sci Technol 1:231–244
43. Cox AR, Lam CJ, Bonnyman CW, Chavez J, Rios JS, Kushner JA (2015) Angiopoietin-like protein 8 (ANGPTL8)/betatrophin overexpression does not increase beta cell proliferation in mice. Diabetologia 58:1523–1531
44. Cox AR, Barrandon O, Cai EP et al (2016) Resolving discrepant findings on ANGPTL8 in β-cell proliferation: a collaborative approach to resolving the betatrophin controversy. PLoS One 11: e0159276
45. Yi P, Park JS, Melton DA (2017) Retraction Notice to: Betatrophin: a hormone that controls pancreatic β cell proliferation. Cell 168: 326
46. Shoda LK, Young DL, Ramanujan S et al (2005) A comprehensive review of interventions in the NOD mouse and implications for translation. Immunity 23:115–126
47. Greiner DL, Rossini AA, Mordes JP (2001) Translating data from animal models into methods for preventing human autoimmune diabetes mellitus: caveat emptor and primum non nocere. Clin Immunol 100:134–143
48. Skyler JS (2013) Primary and secondary prevention of type 1 diabetes. Diabet Med 30:161–169
49. Skyler JS (2015) The prevention and reversal of type 1 diabetes—past challenges and future opportunities. Diabetes Care 38:997–1007
50. European Nicotinamide Diabetes Intervention Trial (ENDIT) Group (2004) European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomized controlled trial of intervention before the onset of type 1 diabetes. Lancet 363:925–931
51. Knip M, Åkerblom HK, Becker D et al (2014) Hydrolyzed infant formula and early β-cell autoimmunity: a randomized clinical trial. JAMA 311:2279–2287
52. Knip M, Virtanen SM, Seppä K et al (2010) Dietary intervention in infancy and later signs of beta-cell autoimmunity. N Engl J Med 363:1900–1908
53. Hagopian WA, Erlich H, Lernmark A et al (2011) The Environmental Determinants of Diabetes in the Young (TEDDY): genetic criteria and international diabetes risk screening of 421 000 infants. Pediatr Diabetes 12:733–743
54. Keymeulen B, Vandemeulebroucke E, Ziegler AG et al (2005) Insulin needs after CD3-antibody therapy in new-onset type 1 diabetes. N Engl J Med 352:2598–2608
55. Keymeulen B, Walter M, Mathieu C et al (2010) Four-year metabolic outcome of a randomised controlled CD3-antibody trial in recent-onset type 1 diabetic patients depends on their age and baseline residual beta cell mass. Diabetologia 53:614–623
56. Bluestone JA, Auchincloss H, Nepom GT, Rotrosen D, St Clair EW, Turka LA (2010) The Immune Tolerance Network at 10 years: tolerance research at the bedside. Nat Rev Immunol 10:797–803
57. Albisser AM, Leibel BS, Ewart TG et al (1974) Clinical control of diabetes by the artificial pancreas. Diabetes 23:397–404
58. Albisser AM, Leibel BS, Ewart TG, Davidovac Z, Botz CK, Zingg W (1974) An artificial endocrine pancreas. Diabetes 23:389–396
59. Pfeiffer EF, Thum C, Clemens AH (1974) The artificial beta cell. A continuous control of blood sugar by external regulation of insulin infusion (glucose controlled insulin infusion system). Horm Metab Res 6:339–342
60. Clemens AH, Chang PH, Myers RW (1977) The development of Biostator, a Glucose Controlled Insulin Infusion System (GCIIS). Horm Metab Res Suppl 7:23–33
61. Renard E (2002) Implantable closed-loop glucose-sensing and insulin delivery: the future for insulin pump therapy. Curr Opin Pharmacol 2:708–716
62. Russell SJ, El-Khatib FH, Sinha M et al (2014) Outpatient glycemic control with a bionic pancreas in type 1 diabetes. N Engl J Med 371: 313–325
63. Brown SA, Breton MD, Anderson SM et al (2017) Overnight closed loop control improves glycemic control in a multicenter study of adults with type 1 diabetes. J Clin Endocrinol Metab
64. Peyser T, Dassau E, Breton M, Skyler JS (2014) The artificial pancreas: current status and future prospects in the management of diabetes. Ann N Y Acad Sci 1311:102–123

65. Rodbard D (2017) Continuous glucose monitoring: a review of recent studies demonstrating improved glycemic outcomes. Diabetes Technol Ther 19(Suppl 3):S25–S37
66. Garg SK, Weinzimer SA, Tamborlane WV et al (2017) Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. Diabetes Technol Ther 19:155–163
67. Mathieu C, Gillard P, Benhalima K (2017) Insulin analogues in type 1 diabetes mellitus: getting better all the time. Nat Rev Endocrinol 13:385–399
68. Rege NK, Phillips NFB, Weiss MA (2017) Development of glucose-responsive 'smart' insulin systems. Curr Opin Endocrinol Diabetes Obes 24:267–278
69. Brownlee M, Cerami A (1979) A glucose-controlled insulin-delivery system: semisynthetic insulin bound to lectin. Science 206: 1190–1191