



Tom Price, Swoop

FROM THE ANALYST'S COUCH

Type 1 diabetes

Paul Burn

Type 1 diabetes (T1D), also termed juvenile-onset or insulin-dependent diabetes, is an autoimmune disease and a metabolic disorder characterized by T-cell-mediated destruction of pancreatic β cells, resulting in insulin deficiency and hyperglycaemia. In 2007, it was reported that 437,500 children were affected by T1D worldwide¹. About 70,000 children aged under 14 years are developing T1D per year¹, with a reported annual global increase of about 3%, particularly in younger children².

The aetiology of T1D is largely unknown, but it is thought that a genetic predisposition, environmental factors and distinctive metabolic changes are involved in the initiation, development and progression of the disease. Insulin deficiency in T1D leads to increased gluconeogenesis and lipolysis, elevated metabolism of free fatty acids, and the generation of ketone bodies, resulting in diabetic ketoacidosis. The primary clinical signs of T1D are ketoacidosis — which can lead to coma and death — and chronic hyperglycaemia. Chronic hyperglycaemia is the primary cause of several macrovascular and microvascular diabetic complications, including cardiovascular disease, renal disease, diabetic retinopathy and peripheral neuropathy.

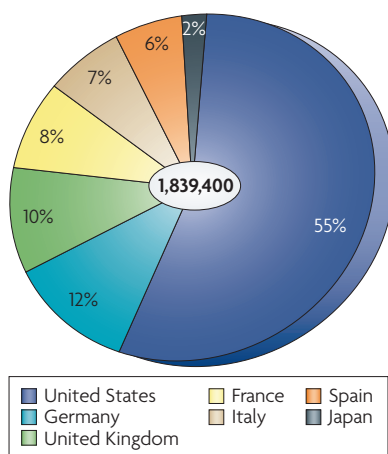


Figure 1 | **Diagnosed and drug-treated cases of type 1 diabetes (all age groups) in the major pharmaceutical markets by 2017.** Numbers are projected for the seven major pharmaceutical markets (US, Germany, UK, France, Italy, Spain and Japan). Data adapted from REF. 8.

Therapy and unmet medical needs

Insulin-replacement therapy is the life-saving first-line treatment for T1D, and the pharmaceutical industry's focus has traditionally been on developing novel insulins with improved pharmacokinetic profiles, more convenient formulations and alternative delivery methods. For the seven major pharmaceutical markets, the number of diagnosed and drug-treated cases of T1D is estimated at around 1.84 million (FIG. 1), resulting in an approximate market size for insulin sales of US\$2 billion for the T1D indication (FIG. 2).

However, although intensive insulin therapy for T1D is life-saving, it is not a cure. It can result in hypoglycaemic incidents and cannot prevent the development of long-term complications. So, the development of disease-modifying therapies remains a major unmet medical need. Therapies for patients with newly diagnosed (recent-onset) as well as established T1D are needed.

Immunological approaches. At present, the most advanced disease-modifying strategies are aimed at halting the further progression of T1D by inducing immune tolerance or by modulating the autoimmune and/or secondary immune and inflammatory responses.

Antigen-specific, vaccine-based approaches using β -cell-specific autoantigens to induce immune tolerance are under development and include glutamate decarboxylase 65 kDa isoform (GAD65; also known as GAD2) and BHT-3021 (TABLE 1). Non-antigen-specific immunomodulators (TABLE 1), such as the CD3-specific monoclonal antibodies oteplizumab and teplizumab are also in development. However, owing to their mechanism of action, these agents might be more prone to compromising the normal function of the immune system. In addition, various non-antigen-specific, FDA-approved immunomodulators are being explored in clinical research settings for their utility in T1D by TrialNet, the Immune Tolerance Network and academic institutions.

Although such strategies could delay or halt the further decline of β -cell function, patients with T1D typically only retain about

10–20% of functional β -cell mass at the time of disease diagnosis. Thus, vaccine-based, tolerogenic approaches have the potential to be most effective in non-diabetics who are at risk of developing T1D. Such approaches may be less effective in patients with recent-onset or established T1D who have lost most of their β -cell mass already and so require insulin-replacement therapy to maintain glycaemic control. Similarly, non-antigen-specific immunomodulators may be most effective when given early in the disease process, before the onset of clinical overt diabetes.

Overall, based on safety considerations of non-antigen-specific therapies and/or the limited patient population who may benefit from any particular approach, the market size of any of these potential immunological products for T1D is likely to be limited (FIG. 2).

Regenerative approaches. β -Cell mass expands in response to increased metabolic demand such as in pregnancy and obesity. It also has been established that β cells can replicate, differentiate or trans-differentiate from various endocrine or non-endocrine cells, thus providing hope that reduced β -cell mass can eventually be restored endogenously³. More specifically, it has been shown that certain peptides and growth factors such as gastrin and glucagon-like peptide 1 (GLP1) can increase β -cell mass and restore normoglycaemia in animal models of T1D in the absence of immunosuppressants⁴. Two FDA-approved drugs, a dipeptidyl peptidase 4 (DPP4) inhibitor and a proton-pump inhibitor, can elevate circulating levels of GLP1 and gastrin in diabetic NOD mice⁵, thereby providing the rationale for testing these approaches in humans.

Cellular approaches including stem cell, progenitor cell, dendritic cell and xenotransplantation are also providing scientifically exciting opportunities, although most are at an exploratory stage. Moreover, in addition to the scientific and technical challenges, there are considerable regulatory hurdles associated with cell-based therapies that need to be addressed before commercially viable products move towards the market⁶. ▶

TYPE 1 DIABETES | MARKET INDICATORS

► **Combination therapies.** Although an attractive approach for treating patients with recent-onset or established T1D, any regenerative therapy by itself may be hampered by the uncontrolled, ongoing autoimmune response. So, combining safe, antigen-specific tolerogenic therapies with emerging, regenerative therapies seems to be the logical next step in the research and development of novel disease-modifying medicines.

Pregnancy is associated with a mild suppression of the maternal immune system to tolerate the developing fetus, and the expression and action of factors that stimulate growth and regeneration. A recent study reported that women with long-term T1D show a pregnancy-induced improved β -cell function and an associated improvement in glycaemic control⁷. This provides support to the idea that mimicking nature by combining safe tolerogenic agents with regenerative therapies might have the potential to become an important strategy for developing disease-modifying treatment regimens for T1D.

Market evolution

On the basis of the current T1D development pipeline, insulin-replacement therapies will dominate the market for T1D over the next decade (FIG. 2). In the long term, the growing, but early, pipeline of novel tolerogenic, antigen-specific and β -cell-specific regenerative agents could provide a promising platform for the development of disease-modifying therapies. Although single-agent therapies are likely to reach the market first, combination therapies could be most effective in delivering the long-sought cure.

Paul Burn is the Todd & Linda Broin Chair of the The Sanford Project at Sanford Health, Sanford School of Medicine of The University of South Dakota, 900 West Delaware Street, Sioux Falls, South Dakota 57104, USA.
e-mail: burnp@sanfordhealth.org
doi:10.1038/nrd3097

- International Diabetes Federation. *Diabetes Atlas* 3rd edn (IDF, Brussels, 2007).
- Dabelea, D. The accelerating epidemic of childhood diabetes. *Lancet* **373**, 1999–2000 (2009).
- Pittenger, G. L. *et al.* A role for islet neogenesis in curing diabetes. *Diabetologia* **52**, 735–738 (2009).
- Suarez-Pinzon, W. L. *et al.* Combination therapy with glucagon-like peptide-1 and gastrin restores normoglycemia in diabetic NOD mice. *Diabetes* **57**, 3281–3288 (2008).
- Suarez-Pinzon, W. L. *et al.* Combination therapy with a dipeptidyl peptidase-4 inhibitor and a proton pump inhibitor restores normoglycaemia in non-obese diabetic mice. *Diabetologia* **52**, 1680–1682 (2009).

- Fleming, A. What will it take to get therapies approved for type 1 diabetes? *Immunology of diabetes V. Ann. N.Y. Acad. Sci.* **1150**, 25–31 (2008).
- Ringholm Nielson, L. *et al.* Pregnancy-induced rise in serum C-peptide concentration in women with type 1 diabetes. *Diabetes Care* **32**, 1052–1057 (2009).
- Gates, C., Wong, D. & Dreyfus, J. *Type 1 Diabetes* 1–147 (Decision Resources, Waltham, Massachusetts, 2008).

Competing interests statement

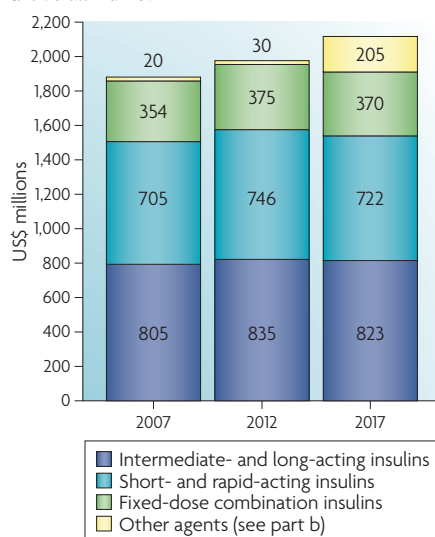
The author declares no competing financial interests.

Table 1 | Selected agents in development for type 1 diabetes

Drug	Company	Properties	Patient population	Trial phase
Teplizumab	MacroGenics/Eli Lilly	CD3-specific mAb	Newly diagnosed	III
Otelixizumab	Tolerx/ GlaxoSmithKline	CD3-specific mAb	Newly diagnosed	III
Alum-formulated GAD	Diamyd Medical AB	GAD65-based vaccine	Newly diagnosed	III
DiaPep277	Andromeda Biotech	HSP60-derived peptide	Newly diagnosed	III
BHT-3021	Bayhill Therapeutics/ Genentech	DNA plasmid encoding pro-insulin	Newly diagnosed	I/II
TT-223 and GLP1	Transition Therapeutics/Eli Lilly	Gastrin and GLP1	Newly diagnosed	I/II
Prochymal	Osiris Therapeutics/ Genzyme	Mesenchymal stem cells	Newly diagnosed	I/II
INGAP peptide	Exsulim Corporation	15 amino-acid sequence in INGAP	Established	I/II

GAD65, glutamate decarboxylase 65 kDa isoform (also known as GAD2); GLP1, glucagon-like peptide 1; HSP60, heat-shock protein 60; INGAP, islet neogenesis associated protein; mAb, monoclonal antibody.

a Overall market



b Other agents

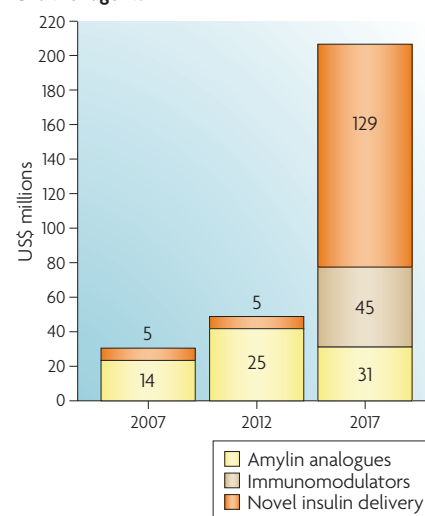


Figure 2 | **Market for type 1 diabetes (T1D): 2007–2017.** Data are estimates for the seven major pharmaceutical markets (US, Germany, UK, France, Italy, Spain and Japan). Estimated insulin sales do not include any additional sales for type 2 diabetes (T2D) (a). By 2017, the T1D market is predicted to grow modestly, which reflects increasing disease incidence and minimal population growth. Insulin sales will dominate, and sales of immunomodulators (b) will be limited owing to the current stage of development, safety issues and the small patient population (recent-onset T1D). To date, β -cell regenerative therapies that would serve a broader patient population (recent-onset and established T1D, and T2D) are small in number and at an early development stage, and so are not anticipated to claim a significant market share within the next decade. Data adapted from REF. 8.