Retuning the immune system: the future of type 1 diabetes therapy?

Strategies that restore immune tolerance are attracting growing interest in their potential to advance the treatment of type 1 diabetes beyond lifelong insulin therapy. Dan Jones investigates.

In June, Bayhill Therapeutics and Genentech announced a collaboration to develop BHT-3021, a novel therapy to treat juvenile or type 1 diabetes (T1D). This autoimmune disease affects approximately 3 million people in the United States and there are 30,000 newly diagnosed cases a year — a figure that is rising by ~4% annually. “The numbers are increasing in epidemic proportions,” says Richard Insel, Executive Vice President of Research at the Juvenile Diabetes Research Foundation (JDRF), based in New York, which funded part of the early development of BHT-3021, a DNA plasmid that encodes proinsulin.

Current treatment of T1D is centred upon the lifelong administration of the hormone insulin (by injection or pump), which patients are unable to produce in sufficient quantities because their immune system has destroyed the insulin-producing β-cells of their pancreas. Normally, insulin regulates blood sugar levels and metabolism, and lack of insulin leads to various complications over time, including eye disease and blindness, cardiovascular disease, and disorders of the kidneys and nervous system.

Although insulin is life-saving, it is not a cure and cannot prevent the long-term complications. “We need to address the underlying immune response that caused the disease in the first place, and to restore β-cell function, to create a cure,” says Insel. However, “There is no approved way of stopping the autoimmune attack against the pancreatic β-cell in T1D thus far,” says Lawrence Steinman, Chair of the Interdepartmental Program in Immunology at the Beckman Center for Molecular Medicine, Stanford University, and co-founder of Bayhill.

To address this issue, companies such as Bayhill have been developing therapies that use the immune system’s own mechanisms to ‘tolerize’ the autoreactive immune cells (BOX 1). “Tolerogenic drugs re-establish tolerance to autoantigens by suppressing or inactivating pathogenic autoreactive T cells,” says Andrew Glasebrook, Senior Research Fellow at Lily. “In a sense, these drugs re-establish the equilibrium between autoreactive T cells and T regulatory cells that has become disrupted.”

For example, it is thought that BHT-3021 works in the following way: the proinsulin that is encoded by the DNA plasmid is processed by antigen-presenting cells of the immune system. They present the proinsulin to effector T cells as an antigen without the co-stimulatory signal that would ordinarily activate the effector cells to respond to the antigen. Instead, the lack of the co-stimulatory signal causes the effector T cells to become inactive against insulin, so that they no longer attack the insulin-producing pancreatic β-cells.

Data on 50 patients with T1D who were treated with BHT-3021 in a Phase I–II trial show that it stabilizes C-peptide levels (a by-product of processing proinsulin to insulin) and decreases levels of glycosylated haemoglobin, which reflect blood sugar concentration over time (measurement of which is the main accepted surrogate end point of clinical trials for antidiabetic therapies). “We’ve shown we’re able to impact two very important parameters of the disease through this tolerogenic approach,” says Steinman.

The new licensing deal between Bayhill and Genentech — in which Bayhill will receive an upfront payment of US$25 million and possible milestone payments of up to $325 million — will produce more detailed insights into the tolerogenic benefits of BHT-3021. “As we continue this trial and launch the more advanced trials, we’ll have a much better idea of the longevity of the effect and its potency,” says Steinman.

BHT-3021 is not the only therapy in the T1D drug pipeline that aims to promote immune tolerance. The monoclonal antibodies (mAbs) otelizumab (Tolerx/GlaxoSmithKline) and teplizumab (MacroGenics/Lilly), which target CD3 (a protein complex expressed by all T cells), are being evaluated in Phase III trials in T1D — and, as for BHT-3021, both received some early development funding from JDRF.

“A tremendous amount of preclinical research evaluating anti-CD3 mAbs in the NOD [non-obese diabetic] mouse — a model of type 1 diabetes — demonstrates disease remission with a single course of treatment,” says Glasebrook.

Human trials with CD3-specific mAbs are also showing promise, according to Doug Ringler, Chief Executive Officer of Tolerx, based in Cambridge, Massachusetts, which is the company co-developing otelizumab with GlaxoSmithKline. “We’ve dosed well over 100 subjects to identify the most efficacious and safe dosing regimen to be used in the Phase III trial, which is ongoing,” says Ringler.

Treatment causes a dramatic increase in the number and function of T regulatory cells, which control the effector arm of the immune system and suppress autoimmune attack on pancreatic β-cells, says Ringler, adding that these suppressive effects persist long after dosing has stopped and the drug has been fully metabolized.

If the treatment is, as Ringler thinks, durable — lasting years, perhaps — it could dramatically reduce the severity of the disease, decrease reliance on administered insulin, improve metabolic control and preserve endogenous insulin production from any residual β-cells that are saved from destruction. “We think that ultimately this will result in a decrease in the incidence of vascular and other complications later in life,” says Ringler.

However, there are some concerns about mAbs that target CD3. “They are highly specific, but they may hit an underlying molecule that has a broad effect,” says Steinman. CD3 is expressed by all T cells, he says, and so targeting this molecule can compromise the normal function of the immune system. “A published clinical trial [N. Engl. J. Med. 352, 2598–2608; 2005] of otelizumab has shown re-activation of Epstein–Barr virus in recipients,” notes Steinman.

Ringler acknowledges that immune-modulatory mAbs can cause serious side effects — as shown for the approved CD3-specific mAb muromonab (Orthoclone OKT3; Ortho Biotech) when used in transplantation therapy, and for the integrin-specific mAb natalizumab (Tysabri; Biogen Idec/Elian) when used to treat multiple sclerosis and Crohn’s disease.

Nevertheless, Ringler says such safety concerns can be addressed through tailoring the dosage: “We can dose the antibody without any appreciable side effects.
**Box 1 | Immune tolerance and its therapeutic potential**

Normally, during development, processes of central tolerance (which take place in the thymus) eliminate T cells that have high affinity for antigens that are created within the body (known as self antigens or autoantigens) so that the immune system recognizes only foreign antigens — typically indicating viral, bacterial or parasitic infections.

Some potentially autoreactive T cells escape this central control mechanism. These T cells are kept in check by the process of peripheral tolerance, in which the cells are exposed to tissue antigens under non-inflammatory conditions, resulting in a tolerant state, or are actively suppressed by T regulatory cells.

However, immune tolerance can go awry, particularly in the presence of stimuli that provide ‘danger’ signals, such as infection and tissue damage, leading to the activation of destructive autoreactive effector T cells. In the case of type 1 diabetes, this leads to the destruction of insulin-producing pancreatic β-cells.

Therapies currently in development that aim to promote immune tolerance in T1D can be divided into two broad categories. The first exposes potentially autoreactive T cells to specific tissue autoantigens to which they should not respond (for example, with BHT-3021 the proinsulin is presented to the T cells) in the absence of a co-stimulatory signal. The second uses monoclonal antibodies (mAbs) that target CD3 (for example, otezolizumab and teplizumab), a protein complex expressed by all T cells that associates with the T cell receptor (TCR). It is postulated that when CD3-specific mAbs bind to CD3, in the short term, the antigen-specific pathogenic T cells undergo apoptosis or become anergic. In the long term, the numbers of adaptive regulatory T cells increase after treatment, which can control the pathogenic effector T cells (Nature Rev. Immunol. 7, 622–632; 2007).

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Chair of The Sanford Project, a recently launched philanthropic initiative at Sanford Health and the Sanford School of Medicine, The University of South Dakota, that is focused on T1D. Glucagon-like peptide 1 (GLP1) and gastrin both stimulate β-cell proliferation, and a GLP1 analogue, exenatide (Byetta; Amylin/Lilly), has already been approved for use in late-onset or type 2 diabetes. “Our translational R&D efforts include the design and execution of clinical trials that evaluate the combination of antigen-specific, tolerogenic approaches with GLP1- and gastrin-based regenerative approaches,” says Burn.

Such an approach could boost endogenous insulin production in those with some residual β-cell function, and restore insulin production in those who have lost most of their β-cells (who would still require suppression of their autoimmune response to prevent destruction of regenerated β-cells). “Combining these approaches is the key to effectively treating both newly diagnosed and established T1D patients,” says Burn. “This is the future of T1D therapies and the first step on the path towards a cure.”

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Epstein-Barr virus activation or cytokine release, and still be effective.” Although these Phase II dosing data have not yet been made public, they will be presented at the 20th World Diabetes Congress in Vienna, Austria, in October, says Ringler.

Some experts think that both CD3-specific mAbs and drugs such as BHT-3021 could have a role in the clinic, and combination therapies might prove particularly beneficial for patients who are newly diagnosed with T1D and still have some residual β-cell function (20–30% of normal). In these patients, shutting down the autoimmune response would preserve the remaining endogenous insulin production, which would ameliorate later complications of T1D. Insel suggests a possible scenario in which CD3-specific mAbs are used when T1D is diagnosed to rapidly knock down the aberrant immune response that is destroying the β-cells, which could then be followed by BHT-3021 to achieve long-term immune tolerance.

These immune-modulating approaches could, in turn, be combined with ways of restoring β-cell function, says Paul Burn, Broin Chair of The Sanford Project, a recently launched philanthropic initiative at Sanford Health and the Sanford School of Medicine, The University of South Dakota, that is focused on T1D. Glucagon-like peptide 1 (GLP1) and gastrin both stimulate β-cell proliferation, and a GLP1 analogue, exenatide (Byetta; Amylin/Lilly), has already been approved for use in late-onset or type 2 diabetes. “Our translational R&D efforts include the design and execution of clinical trials that evaluate the combination of antigen-specific, tolerogenic approaches with GLP1- and gastrin-based regenerative approaches,” says Burn.

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