

COUNTDOWN

TO A CURE

ONLINE



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The Progression of Anti-CD3 Trials

One of the latest success stories in diabetes research has been at least a decade in the making.

A major breakthrough in the treatment of new-onset type 1 diabetes is the use of drugs known as anti-CD3 monoclonal antibodies to slow the progression of the disease. Anti-CD3 antibodies, which block immune cells from destroying the insulin-producing beta cells, were first used to suppress the immune system during transplants. In just the past few years, phase III trials of these drugs in a modified form (there are decreased side effects from the originals) have begun, in which they modulate, rather than suppress, the immune system. These trials—the last phase before FDA approval of a drug—mark the culmination of years of research progress with these compounds, a significant portion of which was funded by JDRF.

By the late 1990s, JDRF researchers had launched the first human trial testing one of the antibodies, and results in 2002 showed it had the potential to be effective at stopping the progress of diabetes in people who had recently been diagnosed, by preserving beta cell function. In 2005, researchers found that short-term treatment with the anti-CD3 antibody preserved beta cell function for up to 18 months, significantly reduced insulin requirements, and helped to maintain good blood sugar control. While these results were encouraging, more studies were necessary to provide the FDA with enough information to approve routine use of anti-CD3 drugs in people with new-onset type 1 diabetes.

To fill this gap and foster the commercial development of anti-CD3 therapy, JDRF's Industry Discovery and Development Program (IDDP) partnered with two biotechnology companies, MacroGenics in Maryland and

Tolerx in Massachusetts, which are testing anti-CD3 drugs (each company is testing a different antibody that targets the same molecule). Both companies were able to demonstrate proof of principle that anti-CD3 drugs could effectively slow diabetes from progressing in the newly diagnosed. It is believed by many leaders in the field that slowing of type 1 diabetes progression by preservation of beta cell function has the potential to decrease the risk for future complications of this disease.

As a result of these findings, Tolerx formed a partnership with GlaxoSmithKline (GSK), and MacroGenics formed a partnership with Eli Lilly & Company. Such partnerships as these, with major pharmaceutical companies, allow advancement to large phase III clinical trials necessary for a therapy to be approved by the FDA for use in clinical practice. The IDDP program was designed to do just that—provide proof of principle data and allow major pharmaceutical companies to evaluate partnership opportunities.

Tolerx

In a study of new-onset type 1 diabetes patients published in 2005, with a six-day course of therapy, the anti-CD3 monoclonal antibody oteelixumab preserved the function of insulin-producing beta cells in the pancreas and reduced the amount of administered insulin needed to control blood sugar levels for at least 18 months. The study was extended to 48 months, and the additional data demonstrated sustained effect after one course of treatment.

JDRF's IDDP partner Tolerx is currently enrolling people who have recently been diagnosed with type 1 diabetes in a phase III trial of oteelixumab called DEFEND (Durable Response Therapy Evaluation for Early or New Onset Type 1 Diabetes). The goal of the trial is to verify that an eight-day course of anti-CD3 treatment developed by Tolerx and its partner GlaxoSmithKline, preserves beta cell

function (as measured by c-peptide) and leads to greater insulin production (reducing the amount of insulin patients need to take to control blood sugar levels), as suggested by previous trials (to see how Tolerx believes the science behind this treatment works in type 1 diabetes, click here: <http://www.tolerx.com/index.php?page=featdetail&cid=156>). If successful, the results will be submitted to the FDA for approval of the treatment.

MacroGenics

In a series of phase III trials known as the Protégé trials, MacroGenics is testing whether two courses of treatment with a different anti-CD3 monoclonal antibody called teplizumab may preserve some insulin production in the newly diagnosed. Previous trials showed that it promoted stabilization or improvement in C-peptide levels if given within six weeks of diagnosis of type 1 diabetes.

MacroGenics and Eli Lilly are evaluating the safety and efficacy of three dosing regimens administered at the start of the studies and again at six months in people within 12 weeks of showing symptoms of type 1 diabetes. All regimens will be administered as an addition to insulin and other standard of care treatments. If effective, patients may be able to take less insulin while maintaining relatively normal blood sugar levels.

Enrollment for the Protégé Encore trial is open (Protégé enrollment is complete). Additional information can be found at www.protegediabetes.org.

For clinical trial information on the DEFEND or Protégé trials, go to http://www.jdrf.org/index.cfm?page_id=101984.

If you want more information about clinical trials, please consider registering for the JDRF Type 1 Clinical Trials Connection at www.trials.jdrf.org.

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