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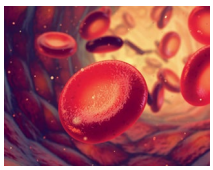

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Anti-CD3 drug keeps diabetes at bay

No drug has ever delayed islet cell destruction. Now that teplizumab has, the challenge turns to identifying eligible recipients for the treatment.

The first drug to ever slow the progression from pre-diabetes to clinical type 1 diabetes is one step closer to reaching the market.

On August 5, the US Food and Drug Administration (FDA) granted breakthrough therapy designation to teplizumab, a CD3-targeted antibody from Provention Bio, to prevent or delay type 1 diabetes onset among children and adults at high risk of developing the disease.

The regulatory distinction comes after a June report showing that teplizumab postponed the onset of symptomatic disease by a median of two years compared with placebo in patients who took the drug for 14 days (*N. Engl. J. Med.* **381**, 608–613, 2019). "It's a very prolonged effect after a single two-week course of the antibody," says Lucienne Chatenoud, an immunologist from the Necker Hospital for Sick Children in Paris who was not involved in the study. "This is, in view of all clinical diabetologists, a real measure of robustness... You are really delaying the onset of insulin therapy."

Although some researchers maintain that larger confirmatory trials are still needed to prove the benefit of teplizumab, especially in younger children, Provention Bio's chief executive Ashleigh Palmer says the company now intends to use the results of the 76-person study to support a marketing application for people who have autoantibodies against pancreatic islets or against insulin and are thus fated to develop type 1 diabetes. Provention also has an ongoing phase 3 trial evaluating the same drug in children and adolescents with newly diagnosed disease.

Type 1 diabetes is one of the most common chronic diseases of childhood. It is prompted by the autoimmune destruction of insulin-producing beta cells in pancreatic islets and leaves affected individuals dependent on daily insulin injections. Numerous approaches have attempted to prevent or stop islet cell destruction, but so far, all have failed. Teplizumab now ushers in the possibility of offering a drug to people who test positive for markers of beta cell autoimmunity but who do not yet have symptoms of disease.

"I seriously can't express enough what a landmark trial this is," says Carla Greenbaum, an endocrinologist at the Benaroya Research Institute in Seattle, Washington, who leads TrialNet, the academic consortium behind the prevention study. "I can assure you, if you talk to people who have diabetes, they would jump up and down" for two years free of their disease. But, she notes, identifying would-be drug recipients in that preventative setting remains a challenge.

Teplizumab traces its roots back more 30 years to the laboratory of Jeffrey Bluestone, an immunologist now at the University of California, San Francisco. In the late 1980s, Bluestone began working with Ortho Pharmaceutical to modify the company's OKT3, an agonistic CD3-directed murine monoclonal antibody that the FDA

Should a treatment to push back the age of type 1 diabetes onset become available, screening programs to identify children at a markedly elevated risk will be critical. One such European effort is the Global Platform for the Prevention of Autoimmune Diabetes, which has undertaken to screen 100,000 newborns for disease-associated variants, including polymorphisms in human leukocyte antigens (HLA) of the DR and DQ isotypes. Credit: KKStock / Alamy Stock Photo

Lung Biotechnology tags iBio for bioink production

Lung Biotechnology continues making inroads toward its goal of manufacturing 3D bioprinted lungs, with a newly announced partnership with iBio to scale up bioink production. The partnership follows a 2018 deal with the Israeli regenerative medicine company CollPlant to license and develop technology for creating organ scaffolds from bioink derived from recombinant human collagen. Lung Biotechnology, a public benefit corporation subsidiary of United Therapeutics, will use the scaffolds to create bioprintable lungs. iBio will use its FastPharma platform—an automated plant-based protein expression system combined with hydroponics and glycan engineering—to scale up production of CollPlant's bioink for fabricating lung scaffolds that can then be taken to clinical trials. Additional collaborations might be needed to optimize and expand the process for producing commercial quantities, iBio said.

Recombinant human collagen bioink is being used with various bioprinting technologies. CollPlant's bioink—extracted from the leaves of tobacco plants genetically engineered with five human genes to produce collagen—includes light-sensitive compounds that can modify the bioink to match natural tissue properties, ranging from cartilage to adipose tissue.

Other groups, like the biotech company Organovo, are using 3D bioprinting to generate a spectrum of tissues, including liver, kidney and intestine, mainly for lab-on-a-chip technologies. Bioprinting complex organs has remained out of reach, and few companies have attempted to produce lungs. But 3D bioprinted lungs took a step forward in May, with the publication of findings in *Science* from a Rice University team demonstrating a stereolithographic method of using photoactivated liquid resins to create hydrogels with vascular architectures that mimic lung air sacks. The researchers cofounded Volumetric last year to commercialize next-generation biofabrication materials and systems based on their findings.

At least one other company, 3DBio, is developing a collagen bioink for 3D bioprinters.

iBio declined to disclose financial terms of the deal.

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had approved a year earlier for reducing acute rejection of transplanted organs. He first mutated the Fc region of OKT3 to decrease binding of target receptors, thereby minimizing crosslinking of the T-cell receptor/CD3 complex that can trigger cytokine release. He then humanized the molecule to reduce its immunogenicity (*Transplantation* **57**, 1537–1543, 1994) and teplizumab was born.

After initial testing in kidney transplant recipients, Bluestone teamed up with Kevan Herold, a clinical immunologist now at the Yale School of Medicine in New Haven, Connecticut, to start evaluating teplizumab in patients with recent-onset type 1 diabetes in 1999. Within a year, a European group led by Chatenoud and Bart Keymeulen of the Free University of Brussels–VUB began its own study of otelixizumab, another humanized Fc-mutated immunoglobulin G1 antibody that, like teplizumab, targets the ε chain of the CD3 receptor. (The antibodies differ primarily in how they limit Fc receptor binding, with otelixizumab mutated specifically to avoid glycosylation.)

With either anti-CD3 agent, a short course of treatment started within a few months of diagnosis helped preserve C-peptide levels, a byproduct of insulin production that serves as an indirect measure of remaining beta cell function. The benefits also lasted for years and the therapies proved generally tolerable. At worst, teplizumab caused cytokine release syndrome–like toxicity in a minority of recipients, owing to the modest T-cell activation, and many otelixizumab recipients experienced transient symptoms of Epstein–Barr virus (EBV) mononucleosis owing to viral reactivation among patients with latent prior infections.

In the mid-2000s, MacroGenics secured the rights to teplizumab and Tolerx in-licensed otelixizumab. Both biotech companies then turned around and inked co-development deals with larger pharmaceutical partners—MacroGenics with Eli Lilly, Tolerx with GlaxoSmithKline—and launched phase 3 trials in new-onset patients. (The recently published study in at-risk individuals was not company-sponsored but run in parallel with funding from government and non-profit sources.)

The industry-backed studies for new-onset disease would both end in failure, but for different reasons. With otelixizumab, the drug's sponsors—seeking to avoid EBV reactivation—dropped the cumulative dose of the therapy more than 15-fold, from 48 milligrams in the academic phase 2 trial to 3.1 milligrams in the follow-up. No one in the low-dose otelixizumab study experienced symptoms of EBV-related disease, but neither did they do better than a placebo at preserving levels of C-peptide or other markers of diabetes control. After running one last dose-finding follow-up study in 30 individuals, GlaxoSmithKline eventually halted further development last year.

In the case of teplizumab, investigators ran a study that Eleanor Ramos, Provention's chief medical officer and chief operating officer, describes as "inherently flawed." For starters, the phase 3 Protégé trial enrolled a diverse global population, including patients from India who tended to have more advanced disease than those from North America, Europe and Israel—and that heterogeneity "seemed to dilute any effect" of the drug, Herold says. The study also had no minimum C-peptide requirement: patients only had to have detectable levels, an indicator of beta cell function but not necessarily a plentiful reserve of insulin-producing cells.

> "I can assure you, if you talk to people who have diabetes, they would jump up and down"

But perhaps the biggest problem with the trial was its primary outcome measure. MacroGenics came up with a composite measure defined by insulin usage and glycemic control as defined by hemoglobin A1c (HbA1c). It ultimately doomed the study. One year after treatment, using these criteria, a similar percentage of patients in the placebo and teplizumab arms of the Protégé study met the primary endpoint of low insulin usage and HbA1C levels in a healthy range.

C-peptide levels, however, were better preserved in teplizumab-treated patients, both one and two years out from treatment. And there were subgroups—younger patients, those who were recently diagnosed at the time of trial enrollment, participants from the United States—that experienced especially pronounced benefits.

After Provention acquired the asset from MacroGenics in May 2018, the company took the lessons of those post hoc analyses to heart and designed a 300-person study recruiting only US-based children aged 8–17 with C-peptide levels above a minimum threshold. Furthermore, the trial defined C-peptide responses at 18 months as the primary outcome measure. Herold, a site investigator who has consulted for Provention, describes the trial as a "new and improved Protégé."

In addition to better study design, researchers today also have an improved understanding of how teplizumab works on a molecular level. After an earlier phase 2 trial with teplizumab in

77 new-onset patients, a team led by Benaroya immunologists Alice Long and Peter Linsley probed gene expression profiles in the blood and identified a population of CD8-positive T cells, thought to be the cells that kill beta cells, with traits of exhaustion that increased in number among subjects who responded favorably to the therapy (*Sci. Immunol.* **1**, eaai7793, 2016).

For reasons that are not entirely clear, those T cells are more susceptible to teplizumab-induced activation than other immune subsets, Long explains. "Although [the antibody] hits all CD3 cells," she says, "what it modulates most are exhausted cells." The proliferation of those partially exhausted cells then creates a more tolerogenic immune landscape that safeguards beta cells from further attack.

Long thinks the same mechanism is likely operating in the pre-diagnosis setting as well—which would explain why teplizumab proved so efficacious in the recently published trial, where the median time to type 1 diabetes diagnosis was just over four years in the teplizumab group; in the placebo group, it was half that duration. Side effects were mild, without any EBV-related complications. "But," says Greenbaum, "we don't yet know whether there's something unique about this therapy as compared to other immune therapies."

Greenbaum and her fellow TrialNet investigators previously showed that oral insulin did not delay disease onset among autoantibody-positive relatives of people with type 1 diabetes. The group is now running prevention studies with two other immune-modulating drugs, the anti-malarial hydroxychloroquine and the cytotoxic T lymphocyte antigen 4 (CTLA-4) analog Orencia (abatacept), with plans to start two more trials—one involving anti-thymocyte globulin (a preparation of rabbit-derived anti-human T cell antibodies), the other with the CD20-targeted antibody rituximab and Orencia.

Janssen is also wrapping up a trial of its tumor necrosis factor-α blocker Simponi (golimumab), and several academic studies are looking at other putative beta cell–saving agents in at-risk individuals. These include a decades-old blood pressure medication called methyldopa, a concoction of probiotic bacterial strains, and the glucagon-like peptide-1 receptor agonist Victoza (liraglutide), commonly used to treat type 2 diabetes

Tiziana Life Sciences, headquartered in London, also has a fully human anti-CD3 antibody called foralumab that binds to the T cell receptor complex to modulate regulatory and effector T cells, and could be used in diabetes prevention. But according to CEO Kunwar Shailubhai, the company first plans to evaluate an oral formulation of foralumab in healthy volunteers before advancing the drug for non-alcoholic steatohepatitis, Crohn's disease and, if funding comes through from diabetes-focused non-profits, type 1 diabetes as well.

Any prophylaxis will ultimately only be as good as the screening effort used to find children positive for islet autoantibodies, though, and researchers are still "trying to figure out the best way to reach kids," says Kimber Simmons, a pediatric endocrinologist at the University of Colorado Barbara Davis Center for Diabetes in Aurora, who has helped screen over 20,000 children at doctors' offices, emergency rooms, urgent care centers, pop-up clinics and community health fairs over the past three years. And in Germany, a coalition of some 650 pediatricians from across Bavaria and Lower Saxony—led by Anette-Gabriele Ziegler, an endocrinologist at Helmholtz Zentrum München—have tested for autoantibodies in nearly 100,000 children over a similar time period.

Those kinds of population-wide screening efforts can help reduce life-threatening complications but ultimately falter because "we've never had [a preventative drug therapy] to actually offer kids," Simmons says. Should teplizumab enter the marketplace in 2021, as Provention hopes it will, "then we will be able to discuss screening more population-wide," says Helena Elding Larsson, a pediatric endocrinologist from Lund University in Sweden. ❐

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DTC pharmacogenomics testing under scrutiny

Since last October, the FDA has been signaling to patients and healthcare providers to exercise caution when applying the results of direct-to-consumer (DTC) pharmacogenomics testing to prescribing drugs. That signal got stronger in April when the FDA sent a warning letter to the genomics testing lab Inova, instructing it to modify labeling and marketing materials for several pharmacogenomics tests. Now some genomics companies, among them Color, Genomind and OneOme, as well as the NIH-sponsored All of Us Program, report that they are in discussions with the FDA and in some cases have already modified their informational materials. The tests at issue are mostly lab-developed tests, which typically are exempt from regulatory review so long as the testing lab is CLIA certified. However, FDA has the right to revoke that exemption in cases where public safety is at issue. With DTC marketing of pharmacogenomics tests, the fear is that individuals will modify their drug use on their own. Whereas companies profess that the FDA is not clear on which tests it considers dubious, the agency appears to be drawing the line at tests not described in drug labels. So far, 23andme is the only DTC genomics testing company that has an approved pharmacogenomics test: its Personal Genome Service Pharmacogenetic Report tests for multiple variants in eight genes that affect the metabolism of some 50 drugs. Further confusing the issue, United HealthCare in August announced that it will cover panels of genetic test for guiding the use of drugs for major depression and other depressive disorders, although the American Psychiatric Association's research council last year concluded that the evidence for testing in those indications is not conclusive.

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"If I tell you I wasn't disappointed, then I would be lying to you. But I'm also willing to accept that there are certain situations in which there are limitations to the technology." Huang Yu, who paid $35,000 to the Chinese company Sinogene to clone his dead cat Garlic. The cat clone, the first produced in China, was missing a black patch on its chin that Garlic had. (*The New York Times*, 4 September 2019)

"Although none of our companies are working on germline therapy, when I talk to people not involved in the biotechnology business, one of the first questions I get is: 'Aren't you worried about designer babies?' I am spending more time on this kind of question than at any point in my career." Jim Burns, CEO of Casebia and cochair of the Alliance for Regenerative Medicine task force on gene editing. The group put out a statement in August that germline gene editing is currently inappropriate. (*Financial Times*, 26 August 2019)

"In a world without any discrimination, understanding human behavior is a noble goal, but we don't live in that world," said Steven Reilly, researcher and member of the LGBTQ steering group at the Broad Institute. The publication of the largest genetic study of same-sex sexual behavior by the Broad Institute raised the hackles of LGBTQ community, even from within the Broad itself. (*The New York Times*, 29 August 2019)