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