PRODUCT R&D

HIGHLY PERSONAL

By Karen Tkach Tuzman, Associate Editor

Pact Pharma Inc. has raised $120 million in venture financing to tackle one of the most complex forms of personalized medicine proposed to date: neoantigen-targeted T cells. Backed by Alphabet Inc’s GV, the company is using an informatics mindset to create hyperpersonalized therapies.

The challenge will be to turn the technology into scalable products that could treat many more patients than other cell-based treatments.

Neoantigen companies have primarily focused on using tumor-specific mutations to create cancer vaccines that stoke an immune response.

Pact's approach is more ambitious, aiming to use neoantigens as bait to fish out rare antitumor T cells from patient blood, then use information from those cells in blueprints for engineering autologous T cell therapies.

In May, Pact completed a $95.5 million series B round led by GV. Canaan Partners, AbbVie Ventures, Casdin Capital, DROIA, Foresite Capital, Invus, Pontifax, Taiho Ventures and Wu Capital also participated. The newco launched in 2016, and raised a $30 million series A led by GV in December of that year.

GV has made informatics-driven precision medicine a key theme in its portfolio; the firm has invested in genomics-based companies Foundation Medicine Inc., Grail Inc., Freenome Inc., LifeMine Therapeutics Inc. and 23andme Inc., patient data integrators Flatiron Health, DNAnexus Inc. and Owkin Inc., and neoantigen cancer vaccine company Gritstone Oncology Inc. GV has also put a stake in the ground for gene editing, joining the $120 million series B round for Editas Medicine in 2015.

Canaan, the second largest investor in the B round, was drawn by the degree to which Pact's technology is tailored to each individual patient, according to general partner Nina Kjellson, who is a Pact board member. The approach, she said, is “a nod to the conviction that this kind of super-hyperpersonalization is the way cancer is going to be treated.”

Most personalized medicine products contain one or two elements unique to the patient, such as targeting a specific mutation or using the patient's cells as starting material, but the rest of the process is standardized. Pact's process is tailored at almost every step of the path.

Pact performs personalized sequencing, bioinformatic analyses, immunoassays, gene engineering and cell manufacturing for each patient. That means the products will be precisely tailored to a patient's tumor and immune system.

However, it also raises questions about whether the company’s multimodal manufacturing process can scale with sustainable COGS.

Interim president and GV general partner Blake Byers thinks the rapid pace of innovation in cell therapy manufacturing has made it an achievable goal. In the last five years, he said,
improvements in the field have substantially cut the cost and time required to produce CAR T cells.

“We’ve traded what was a very manual, labor intensive process for a new cohort of companies using closed loop technologies to gain a lot of additional efficiency in the manufacturing process,” Byers told BioCentury. At least six companies are developing full or partially automated cell therapy manufacturing systems to sell to drug developers (see “Automation Navigation”).

Byers believes Pact’s ability to engineer T cells targeting tumor-specific mutations will expand the success achieved by CAR T cell therapies in hematological cancers to solid tumors. “In solid tumors, we really have to be better at differentiating between tumor cells and healthy cells, and really ask, what are the unique fingerprints of those tumor cells?”

Kjellson said her firm sat out the first round of T cell therapies while it waited for proof the technology could find workable regulatory paths and models for pricing, reimbursement and manufacturing. In the background, she said, “we were forming this thesis about what we believe the criteria for a next-generation, transformative cell therapy in cancer would look like.”

From a therapeutic perspective, those criteria included the ability to selectively kill solid tumors, using targets that were validated by immunoassays and deploying T cells that were minimally expanded and readily engrafted. But she said Canaan
also sought an “attitude and approach to manufacturing that would allow for a faster, lower cost production” of cell therapies.

“One critical success factor is an attitude that informatics is a critical enabling tool, and not just an afterthought,” she said. “Every portion of the discovery process needs to have strong data integration and appropriate machine learning applied in order to maximize the insights from every input.”

Pact plans to submit its first IND within the next year.

BUILD-A-TIL

Byers said Pact’s goal is to amplify, not outsmart, the immune system. He pointed to literature research on tumor infiltrating lymphocytes (TILs), including a June Nature Medicine study in chemorefractory metastatic breast cancer, that showed endogenous T cells targeting specific neoantigens can be potent antitumor therapeutics.

“Both TILs and checkpoint inhibitors show that you already have T cells in the patient that are capable of driving really dramatic results,” he said. “We’re trying to leverage what the immune system is already good at, pull out the best TCRs, and try to make a synthetic TIL.”

Therapies based on endogenous TILs involve expanding, screening and adoptively transferring a limited set of T cells from resected tumor tissues.

Pact’s technology creates synthetic TILs by incorporating neoantigen-specific TCRs into freshly isolated lymphocytes from patient blood. “The advantage you have in our approach is being able to make the exact cell type and cell quantity you want,” said Byers.

Unlike standard TIL therapy, Pact’s platform isolates neoantigen-specific T cells from blood rather than cultured tumor samples, which means its product could work for patients with relatively “cold” — T cell-poor — tumors, or for whom it would be difficult to obtain culturable samples.

The biotech’s approach is to “engineer and generalize” TIL-like responses for every patient, said scientific co-founder James Heath.

Heath, whose lab developed the company’s nanoparticle-based immunoassay at the California Institute of Technology, is now president and professor at Seattle’s Institute for Systems Biology.

The company’s other two scientific co-founders are Antoni Ribas, professor of medicine, surgery and molecular and medical pharmacology at the University of California Los Angeles, and David Baltimore, professor of biology and former president at Caltech. Ribas also co-founded cancer synthetic lethality company Tango Therapeutics Inc., and Baltimore helped found immunotherapy companies Immune Design Corp. and Calimmune Inc.

Byers said Heath’s magnetic nanoparticle technology, dubbed imPACT, is “the cornerstone that started the company” because it enables Pact to find and capture each patient’s neoantigen-specific T cells, which are typically concentrated in tumors but rare in blood. “What they figured out how to do was increase the avidity of a complex that could pull down T cells, so you could pull down really rare populations,” he said.

The nanoparticles are coated with protein complexes containing a potentially neoantigenic peptide displayed on an HLA molecule, and are labeled with DNA barcodes that identify the peptide being presented.

At least one other company, Neon Therapeutics Inc., is developing neoantigen-specific T cell therapies. Instead of magnetically isolating neoantigen-specific T cells, Neon’s
NEO-PTC-01 program involves an *ex vivo* co-culture process, dubbed "NEO-STIM," in which patient neoantigen-specific T cells are expanded via stimulation with peptides predicted to be neoantigens. On Tuesday, the company raised $100M through its NASDAQ IPO.

Pact and Neon declined to comment on each other’s technologies.

GONE FISHING
To generate a personalized cell therapy, Pact starts by sequencing DNA and RNA from a patient’s samples of tumor tissues, and uses bioinformatics to identify tumor mutations that encode mutant peptides. The company’s algorithms predict which of those mutant peptides are likely to be presented to CD8+ T cells on HLA I molecules.

Byers said that while Pact’s bioinformatics process is similar to that commonly used for neoantigen cancer vaccines, a major difference is that rather than making stringent predictions about which neoantigen will be the most immunogenic, Pact casts a wide net and delegates the neoantigen-finding process to its imPACT immunoassay.

“We don’t need to be quite as accurate in our algorithmic prediction,” he said. “We just need to know that all the real neoantigens are in that set.”

Pact synthesizes each patient’s predicted neoantigens, loads them onto recombinant versions of the patient’s HLA I molecules, and assembles the peptide-HLA complexes into tetramers. The company coats the DNA-barcoded magnetic nanoparticles with about 100,000 neoantigen-loaded tetramers, mixes them with CD8+ T cells from the patient’s blood and magnetically isolates the nanoparticle-bound, neoantigen-specific T cells (see “Figure: Unique Magnetism”).

The cells are then placed in a microfluidics system that traps individual T cells and enables identification of each one’s neoantigen through a fluorescent DNA-based barcode readout. The cells are flushed out of the microfluidics chip and sequenced for their TCRα and TCRβ chains, which are then engineered into Pact’s cell therapies.

“In a single stone’s throw, we get to confirm the existence of the neoantigen, and get a TCR that binds that neoantigen,” said Byers. He added that because those TCRs have been filtered for auto-reactivity by the thymus, they’re unlikely to have off-target activity.

The company also characterizes gene expression in the neoantigen-specific T cells, which can help inform which ones would make good templates for a cell therapy.

Byers said Pact uses the imPACT technology to screen about 100 predicted neoantigens, and thinks that as the company learns more about what makes a good neoantigen, it could bring that number down.

Having identified neoantigen-specific TCR sequences from CD8+ T cells, Pact engineers those sequences into CD4+ and CD8+ T cells from patient blood using an undisclosed process.

Byers said Pact “drops in” the neoantigen-specific TCR sequences a way that eliminates the T cells’ endogenous TCRs, with the goal of expressing the new TCR at physiological levels.

“We need to make a T cell that’s as similar to a normal T cell as possible – virally overexpressing the TCR is probably not going to be the most effective way,” he said.

The engineered cells are expanded in culture, and then re-infused into the patient.
According to Byers, Pact will likely enter the clinic first with cell therapies containing a single TCR, but it plans to rapidly move to three-TCR products.

The company hasn’t selected an indication. Because the occurrence of neoantigens is associated with greater tumor mutation burden, Pact probably won’t target very low mutation burden patients, said Byers, though he added that it will not target indications that are already well-served by existing immunotherapies.

Byers said Pact hopes to make its therapies accessible to a diverse range of patients by adapting its screening system so that it can be used with any human HLA I allele, rather than just the HLA-A02 allele, which is common in European populations and is the dominant target for engineered TCR therapies.

The company is now capable of making nanoparticles for every HLA type, though “there’s still a lot of work to do to make that robust enough for a full clinical process,” Byers said.

Kjellson said a key risk is whether Pact can “lock down” its manufacturing process into a protocol acceptable to FDA within the time frame for the IND, which will require bringing in the right people.

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