BIOCENTURY
Innovations
FROM IDEA TO IND

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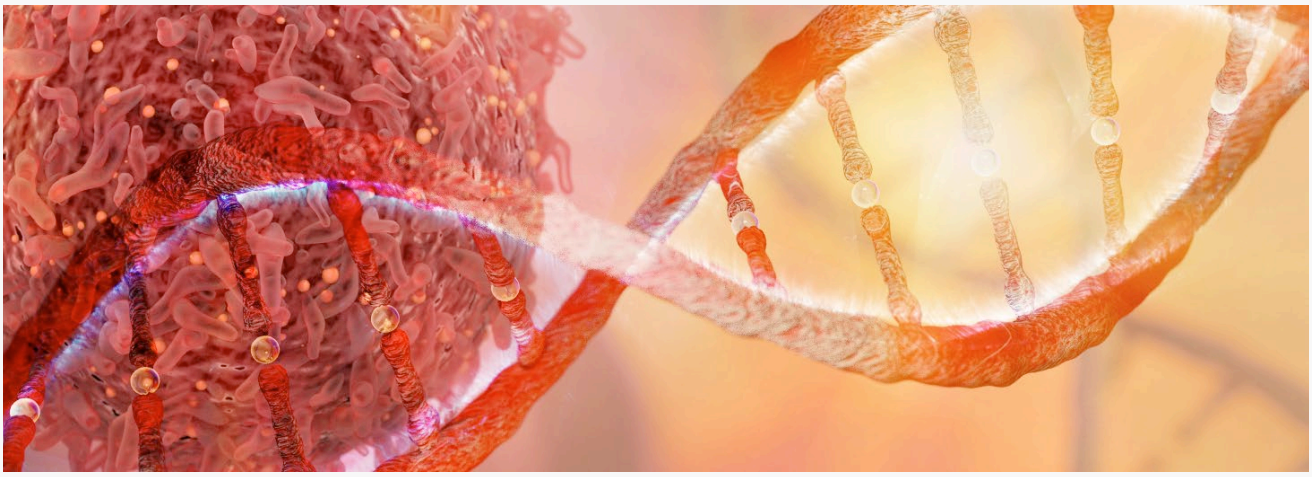

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PRODUCT R&D

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,

UNIQUE MAGNETISM

Pact Pharma Inc. is isolating rare neoantigen-specific CD8⁺ T cells from patient blood using a magnetic nanoparticle-based high avidity capture approach developed at the **California Institute of Technology**.

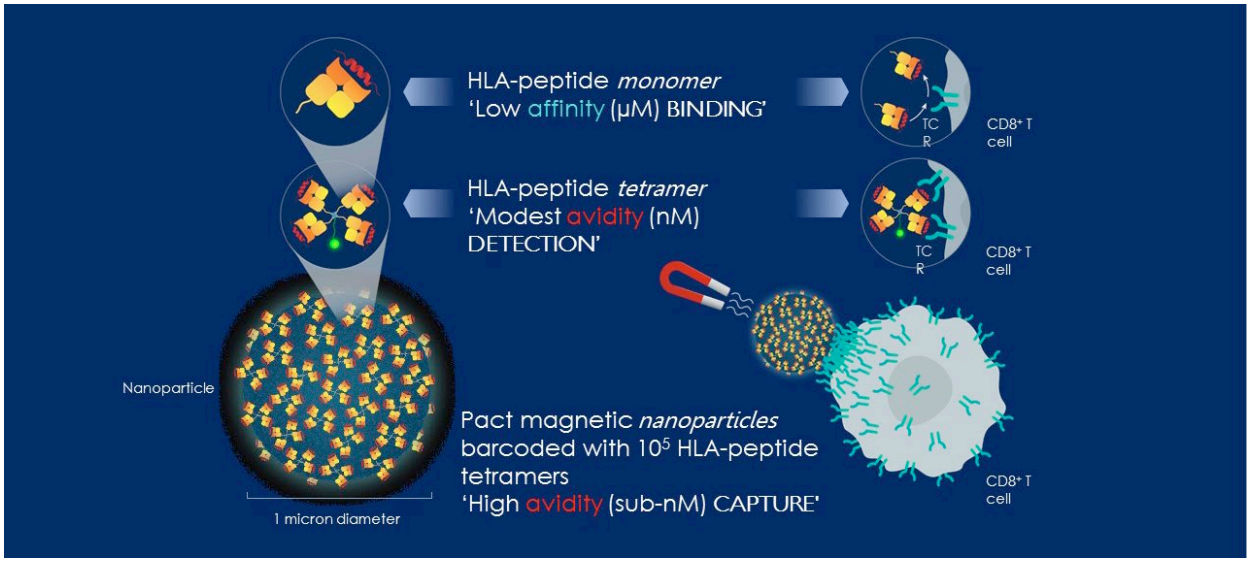
Top. A single HLA molecule (**orange**) loaded with a peptide antigen (**red**) exhibits low affinity monomeric binding to a cognate TCR on a T cell surface. K_d values for the monomeric binding interaction are in the μM range.

Middle. An HLA-peptide tetramer complex exhibits modest avidity binding to cognate TCRs on a T cell surface. K_d values for the tetrameric binding interaction are in the nM range. HLA-peptide tetramers are frequently used to detect cognate TCRs, and are thus often labeled with a fluorescent reporter (**green**).

Bottom. A nanoparticle coated with 100,000 HLA-peptide tetramer complexes exhibits high avidity binding to cognate TCRs on a T cell surface. K_d values for the nanoparticle binding interaction are in the sub-nM range. Pact mixes patient CD8⁺ T cells with nanoparticles coated in tetramers of patient HLA molecules and patient neoantigen peptides. The mixture is exposed to a magnetic force, which enables capture and isolation of neoantigen-specific T cells.

HLA - human leukocyte antigen; TCR - T cell receptor

Source: Pact Pharma Inc.



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.

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.

> "One critical success factor is an attitude that informatics is a critical enabling tool and not just an afterthought."
>
> Nina Kjellson, Canaan Partners

"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.

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.

BIOCENTURY PRODUCT PROFILE

BIOCENTURY PRODUCT PROFILE	
INNOVATION STAGE	
Product	Personalized neoantigen-specific T cell therapy
Concept	Autologous T cell therapy engineered to express neoantigen-specific T cell receptors (TCRs) isolated from patient blood
Disease	Cancer
Competition	Therapies based on tumor-infiltrating lymphocytes (TILs)
Differentiation	Does not require harvesting functional T cells from tumor samples; neoantigen specificity added to T cells with desired functional phenotype
Administration	IV
Risks	Complex manufacturing process for each patient; possibility of selecting wrong T cell
Development status	Preclinical
Patents	Patented; patent applications filed
Company; lead investigator	Pact Pharma Inc.; James Heath

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.

DOWNLOADING UPDATES

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.

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>
> Blake Byers, GV

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.

Byers said another risk is that while "there is an abundance of literature" supporting the role of neoantigen-specific T cells in immunotherapy, whether Pact's method can reliably find T cells that drive potent antitumor immunity in patients is still unproven.

"Where Pact may fail is if we are unable to identify the most therapeutically relevant T cells. We could do everything right, but if we choose the wrong TCRs, nothing else will matter," he said.

Byers thinks that because Pact's technology requires making a series of real-time decisions for each patient, the company is well-poised to improve its neoantigen- and TCR-selection algorithms over time.

"It brings up the opportunity to learn from every patient in a way that drug development hasn't ever really done before," said Byers. "If we can systematize that information, we have the ability to improve every time we treat someone."

He acknowledged the company would have to work with FDA to define what could be updated, and how. "At worst, it would be another approval process, but we'll be happy to undertake that as a company for additional information that we know is going to improve the product."

Byers thinks the concept of products getting better over time, a given in the software industry, could be a model for drug development. "We're still in the very early days of all that, but it's going to be a really interesting time as software best practices merge with scientific best practices."

Down the line, he said innovative access models will be required to reach the biggest possible market. Byers said Pact needs to start thinking now about "navigating significant cost improvements, coordinating with clinical care centers so the patient experience can be improved, and changing the clinical course of care so that patients can be treated in the community."

"We need to be thinking about the future if we want to have the impact we dream of and remain an independent company over the long term," he said.

COMPANIES AND INSTITUTIONS MENTIONED

23andMe Inc., Mountain View, Calif.
Alphabet Inc. (NASDAQ:GOOG), Mountain View, Calif.
California Institute of Technology, Pasadena, Calif.
DNAnexus Inc., Mountain View, Calif.
Editas Medicine Inc. (NASDAQ:EDIT), Cambridge, Mass.
Foundation Medicine Inc. (NASDAQ:FMI), Cambridge, Mass.
Freenome Inc., South San Francisco, Calif.
Grail Inc., Menlo Park, Calif.
Gritstone Oncology Inc., Emeryville, Calif.
Immune Design Corp. (NASDAQ:IMDZ), Seattle, Wash.
Institute for Systems Biology, Seattle, Wash.
LifeMine Therapeutics Inc., Cambridge, Mass.
Neon Therapeutics Inc. (NASDAQ:NTGN), Cambridge, Mass.
Owkin Inc., New York, N.Y.
Pact Pharma Inc., Hayward, Calif.
Tango Therapeutics Inc., Cambridge, Mass.
University of California Los Angeles, Los Angeles, Calif.

TARGETS

HLA - Human leukocyte antigen
TCR - T cell receptor
T cell receptor α chain (TCRA)
T cell receptor β chain (TCRB)

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