

## Pact makes case for neoantigen-specific TCRs from patient blood

BY KAREN TKACH TUZMAN, ASSOCIATE EDITOR

Preclinical studies from Pact Pharma and UCLA suggest neoantigen-specific T cells in patient blood will be reliable blueprints for the company's personalized, engineered cell therapies. Recruitment is ongoing for a Phase I study of Pact's T cell therapy plus an anti-PD-1 therapy in solid tumors with a range of checkpoint inhibitor sensitivities.

In a pair of presentations Sunday, Pact Pharma Inc. (South San Francisco, Calif.) showed its platform identified neoantigen-specific CD8 T cells in blood from treatment-naïve patients with melanoma, ovarian or colorectal cancer, and neoantigen-specific T cell receptors (TCRs) isolated from the blood of a checkpoint inhibitor-treated melanoma patient enabled fresh CD4 and CD8 T cells to kill that patient's tumor cells in culture.

Results were presented at the American Association for Cancer Research's Special Conference on Immune Cell Therapies for Cancer.

Pact's platform uses bioinformatic analyses of patients' tumor and normal DNA and RNA to identify candidate neoantigen peptides that could drive antitumor T cell responses. These peptides are synthesized and presented on HLA molecules coating the surfaces of magnetic beads used to isolate neoantigen-specific CD8 T cells from patient blood; those cells' TCRs are then engineered into autologous CD4 and CD8 T cells that get re-infused back into patients (see "[Highly Personal](#)").

CEO Alex Franzusoff told BioCentury the company has found neoantigen-specific T cells in more than 90% of patients tested.

Study author Cristina Puig-Saus said, "Each patient already has the T cells, so you don't need to invent anything. You just have to find the cells that the patient already has that are able to target those mutations." Puig-Saus is an associate project scientist in hematology/oncology at University of California Los Angeles.

The case studies presented by Pact and UCLA researchers showed patients had endogenous T cell responses to multiple tumor

neoantigens, often with several different T cell clones against the same neoantigens.

Franzusoff told BioCentury the company selects TCRs against neoantigens that are "truncal" -- generated early in a tumor's evolution and therefore expressed across many, if not all, tumor subclones. The strategy is also being explored by Achilles Therapeutics Ltd. (see "[Targeting Cancer Evolution to Foil Drug Resistance](#)").

Pact's first clinical trial will test T cell therapies engineered to express a single TCR in combination with Opdivo nivolumab from Bristol-Myers Squibb Co. (NYSE:BMJ). The company uses an undisclosed, virus-free CRISPR-based approach to knock out T cells' endogenous TCRs and replace them with a neoantigen-specific receptor.

Next year, the company plans to test T cell therapies incorporating up to four TCRs.

The first-in-human trial will include solid tumors with high, medium and low sensitivity to checkpoint inhibitors -- melanoma and bladder cancer, microsatellite-stable colorectal and ovarian cancer, and prostate and hormone receptor-positive breast cancer, respectively. Testing combination therapies in cancers with low responses to checkpoint inhibitors can increase the chances of deducing whether a treatment provides benefit above that of PD-1 or PD-L1 inhibitors in single-arm trials (see "[Lessons from the ECHO Chamber](#)").

While most companies developing TCR-based therapies focus on receptors that interact with the HLA-A02 allele, which is most common in European populations, Franzusoff said Pact has extended its platform to nearly 100 HLA alleles, which covers 99% of patients.

Targets: HLA - Human leukocyte antigen; PD-1 (PDCD1; CD279) - Programmed cell death 1; PD-L1 (B7-H1; CD274) - Programmed cell death 1 ligand 1

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