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EMERGING COMPANY PROFILE

PIGGYBACK CAR RIDE

By Michael J. Haas, Associate Editor

The disappointing durability of CAR T cells in the clinic has been attributed to the cells' too-mature phenotype, and the immunogenicity and low stability of the chimeric antigen receptors (CARs) themselves. Poseida Therapeutics Inc. is using its virus-free gene delivery technology to load up T cells with modifications that address all three problems and provide long-lasting responses.

The company is pursuing allogeneic and autologous CAR T therapies, in addition to NK cell therapies.

According to President and COO Nishan de Silva, a core component of Poseida's technology is the piggyBac transposon system, a non-viral vector method of gene delivery that results in more stable, longer and higher expression of inserted genes than viral vectors allow. In addition, piggyBac can carry upwards of 300 kb cargo — about 20-30 times more than viral vectors — and that capacity lets Poseida engineer its CAR T cells with safety switches, plus two major modifications aimed at improving durability.

The first shifts the CAR T cells away from the predominantly mature effector phenotype that is needed to kill cancer cells but thought to lead to premature exhaustion, and towards a younger stem-cell memory phenotype. Those cells create a pool of cells that yield a steady crop of mature effectors over time. "With piggyBac, we can engineer about 70-80% of the CAR T cells to have this younger phenotype," compared with 15-20% for virus-based delivery systems, de Silva said.

The second modification involves centyrins, a class of human fibronectin type III domain-based molecules exclusively licensed for immuno-oncology applications from the Janssen Biotech unit of Johnson & Johnson. Poseida use centyrins to construct its CARs, which avoids several problems caused by the single-chain variable fragments (scFvs) used in most CARs.

"Antibody fragments used in current CAR T cells are rodent-derived, and so there may be an immune response to them" that wipes out the cells, de Silva said. Moreover, centyrins are more thermally stable than scFvs and "we see no tonic signaling in our CAR T cells indicative of T cell exhaustion."

POSEIDA THERAPEUTICS INC., San Diego, Calif.
Technology: CAR T cell therapies engineered for durability using the piggyBac non-viral gene delivery platform
Disease focus: Gene/cell therapy, Cancer
Clinical status: Preclinical
Founded: 2015 by Transposagen Biopharmaceuticals Inc.
University collaborators: None
Corporate partners: Johnson & Johnson
Number of employees: 34
Funds raised: $33 million
Investors: Malin Corp. plc, other undisclosed parties
CEO: Eric Ostertag
Patents: More than 30 issued covering piggyBac and proprietary CRISPR and TALEN gene editing platforms

Poseida's lead product, P-BCMA-101, is a CAR T cell therapy targeting B cell development protein BCMA. In a xenograft mouse model of aggressive multiple myeloma (MM), a single injection of the product eliminated tumors in all 37 mice and extended survival through day 57, whereas all 10 vehicle-treated mice died by day 29. Also in the treated animals, there were multiple instances of tumor relapse and re-elimination in response to the single injection, suggesting the cells had the desired durability.

Poseida plans to submit an IND for P-BCMA-101 to treat relapsed/refractory MM in 2Q17 and begin a Phase I/II trial by year-end.

Kite Pharma Inc., Novartis AG, bluebird bio Inc. and Celgene Corp. have CAR T cells targeting BCMA in preclinical or Phase I testing for MM.

Poseida raised $33 million in a series A round in 2015, and is now looking to raise $40-$60 million in series B, to close this half, that will fund the trial and Poseida's earlier programs.

In addition to piggyBac, Poseida has gene editing technology it obtained when it was spun out of Transposagen Biopharmaceuticals Inc. Its CRISPR platform relies on a nuclease other than Cas9 and requires two components to bind the same point in the genome to allow gene editing. It also has a TALEN platform with "a unique architecture" that is different from that used by Cellectis S.A., de Silva said.

COMPANIES AND INSTITUTIONS MENTIONED

bluebird bio Inc. (NASDAQ:BLUE), Cambridge, Mass.
Celgene Corp. (NASDAQ: CELG), Summit, N.J.
Cellectis S.A. (Euronext:ALCLS; NASDAQ:CLLS), Paris, France
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Kite Pharma Inc. (NASDAQ: KITE), Santa Monica, Calif.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Poseida Therapeutics Inc., San Diego, Calif.
Transposagen Biopharmaceuticals Inc., Lexington, Ky.

TARGETS

Cas9 - CRISPR-associated protein 9
BCMA (TNFRSF17; CD269) - Tumor necrosis factor receptor superfamily member 17

REFERENCES

Hermanson, D., et al. "A novel BCMA-specific, Centyrin™-based CAR-T product for the treatment of multiple myeloma." *Presented at the Annual Meeting of the American Society of Hematology* **(2016)**

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