Rapa Therapeutics
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RAPAtherapeutics

Rapa's epigenetic reprogramming creates T cell therapies for solid tumors and neurodegeneration

The biotech firm's polyclonal anti-cancer therapy is based on an ex vivo approach and avoids the use of toxic immune-depleting chemotherapy.

Rapa Therapeutics (Rapa) is bringing the power of epigenetically reprogrammed T cells to the treatment of solid tumors. Building on almost 20 years of work at the United States National Institutes of Health (NIH), the Rockville, Maryland, biotech's new polyclonal Th1/Tc1 cell therapy has shown promise in producing remissions in multiple solid tumor types, positioning it to start several phase 2b cancer studies while working with Harvard Medical School/Massachusetts General Hospital (MGH) and NIH, utilizing grant funding to develop a hybrid T_{reg}/Th2 cell therapy for people living with amyotrophic lateral sclerosis (ALS).

CAR-T cell therapies trigger deep responses in hematological malignancies but investigations in solid tumors, which comprise 90% of all cancers, have been constrained by high toxicity rates and low efficacy rates. Rapa's polyclonal Th1/Tc1 cell therapy offers advantages relative to other cell therapies, namely: increased feasibility due to epigenetic modulation (no need for viral vectors); increased safety due to natural T cell receptor (TCR) signaling, which eliminates cytokine release syndrome (CRS); and increased efficacy due to an unbiased, TCR-driven clonal expansion.

Daniel Fowler, MD, Rapa's chief medical and scientific officer, was a translational researcher at the NIH National Cancer Institute for 27 years prior to co-founding Rapa. After an introduction in 2016, Fowler teamed up with experienced business leader Brian Radecki, to spin his polyclonal reprogrammed T cell therapy science out of the NIH to create Rapa. Radecki has worked with many public and private companies over his 30-year career, and currently serves as CEO and co-founder of the biotech.

Optimizing T cells for solid tumors

Rapa creates its therapies by harvesting T cells from the patient, applying its epigenetic reprogramming approach ex vivo, based upon mTOR (mechanistic target of rapamycin) inhibition, and infusing the RAPA-T cells back into the patient. This reprogramming, which promotes autophagy and cellular de-differentiation towards central and stem memory, sets Rapa apart from competing T cell therapies that typically promote T cell differentiation and effector memory that associates with immune checkpoints.

Rapa's approach yields a T cell product with a phenotype with anti-cancer effects, including: promotion of Th1/Tc1 cytokine secretion while eliminating regulatory T cells; elimination of multiple immune checkpoint receptors for a period of time, which provides a window of opportunity for safely achieving in vivo T cell clonal expansion; and increased responsivity to the homeostatic cytokines IL-7 and IL-15, which facilitates RAPA-T cell therapy of cancer without the use of toxic immune-depleting chemotherapy.

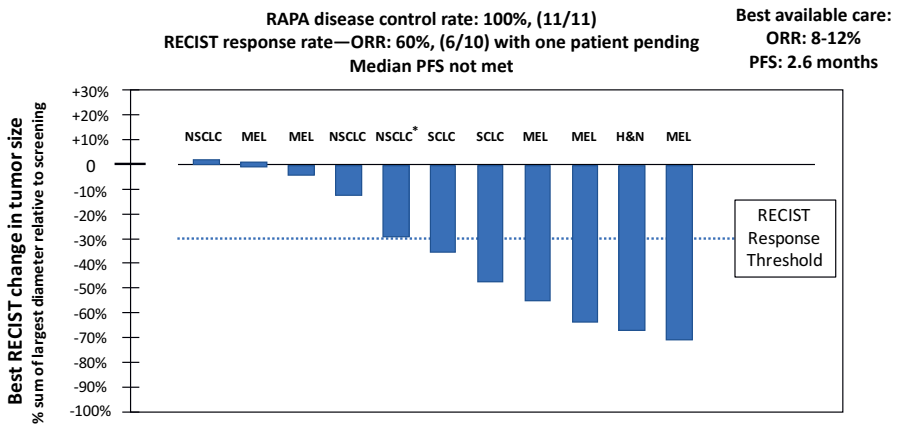

Fig. 1 | Solid tumors shown to shrink using RAPA-201 cells in phase 1/2 trials. RAPA-201 is safe and effective after PD(L)-1 therapy. *Indicates patient to receive additional RAPA-201. H&N, head and neck cancer (squamous); MEL, malignant melanoma; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; SCLC, small cell lung cancer.

Rapa has begun to validate its reprogrammed Th1/Tc1 cell therapy (RAPA-201) in a phase 1/2 trial (NCT05144698) that has ten evaluable patients. RAPA-201 has safely achieved, exclusively through outpatient therapy, a 60% overall response rate (ORR) and 100% disease control rate in solid tumor patients with advanced, metastatic disease after anti-PD(L)-1 therapy (Fig. 1). Clinical remissions by iRECIST criteria have been observed in RAPA-201 recipients with end-stage melanoma, small cell lung cancer, and head and neck cancer, thereby paving the path for dedicated phase 2b trials in these cancer types, with more indications being tested. Given zero CRS toxicity treating patients in an outpatient setting, and substantial single-agent activity, Rapa is well-poised to collaborate with the pharmaceutical industry to evaluate RAPA-201 in combination with targeted agents such as bi-specific monoclonals or antibody–drug conjugates.

The path to market

Rapa is developing its RAPA-201 cancer product in parallel to RAPA-501, which is an ALS cell therapy product that has a United States Food and Drug Administration fast track designation. To make RAPA-501, the team uses mTORC1/mTORC2 inhibition to reprogram the patient's pathogenic inflammatory cells to create induced regulatory T (T_{reg}) cells with a hybrid Th2 phenotype. Rapa's ALS program was recently awarded a $29 million NIH grant over three years to work with MGH, the teaching hospital of Harvard Medical School, to run a phase 2b clinical trial of RAPA-501 in patients living with ALS.

The NIH grant covers the cost of this pivotal trial, thereby positioning Rapa to demonstrate RAPA-501 clinical benefit in ALS, which will, in turn, drive future efforts to use its novel T_{reg}/Th2 platform for the therapy of other neurodegenerative and autoimmune diseases.

Rapa is also beginning to raise capital to fund several planned phase 2b solid tumor clinical trials. New investor capital will be utilized to fund the solid tumor program, which is Rapa's primary focus, while advancement of the neurodegenerative program in ALS funded by the NIH grant represents a 'free call option' that the company expects to become another key driver of shareholder value as this program evolves.

With Rapa set to start phase 2b trials in solid tumors and an NIH-funded ALS pivotal clinical trial starting in 2024, it is de-risked and positioned for success. Designed with more than 20 years of research on mTOR-focused reprogrammed T cell therapies, the RAPA-T cell platform aims to be a safe and effective T cell therapy for solid tumors and ALS, as Rapa strives towards its goal of developing breakthrough cell therapies.

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