Docket #: S24-049

Engineering Spatially Targeted Cell Therapies via Metabolite Sensing GPCRs

Stanford researchers have discovered programmable mechanisms to mobilize T and Natural Killer (NK) cells to solid tumors. The therapeutic cells are engineered to detect bioactive molecules released by tumors, migrate along these tumor-derived biochemical gradients, and, in turn, achieve marked enhancement of tumor infiltration and therapeutic efficacy.

The invention addresses a critical barrier in cell therapies and immunotherapies, which have transformed cancer treatment but remain ineffective for many patients, in part due to insufficient immune recruitment and infiltration into solid tumors. While cell engineering efforts have primarily focused on protein-protein interactions, this invention has uncovered the untapped potential of bioactive metabolites and their cognate G protein-coupled receptors (GPCRs) as programmable levers for mobilizing immune cells to solid tumors.

Aberrant tumor metabolism is a well-established and prevalent cancer hallmark, which is already routinely used by oncologists for cancer detection and diagnosis. Using a tumor homing GPCR (thGPR), the invention enables the engineering of therapeutic cells to sense, migrate to, and target solid tumors based on their abnormal metabolic activity. Given the unique diffusion ranges, tissue partitioning, and clearance of small lipophilic metabolites, metabolite sensing GPCRs provide spatial information orthogonal to, and synergistic with, other axes, such as Chimeric Antigen Receptor (CAR) and T Cell Receptor (TCR) signaling, which recognize target cells upon contact. thGPRs can be expressed in therapeutic cells via ex vivo or in vivo genetic editing or targeted RNA/protein delivery and have already been shown by the investigators to significantly enhance the in vivo efficacy of NK, CAR NK, CAR T, and TCR-based therapies, leading to tumor control and elimination, as evidenced

by durable and complete responses in preclinical studies.

thGPRs were directly compared to dozens of genes with well-established roles in immune cell migration, including chemokine receptors, integrins, and proteases, and repeatedly outperformed these alternative strategies. Studies have thus far been performed in breast and ovarian cancer mouse models, where the thGPRs have been independently identified as top hits in NK CRISPR activation tumor infiltration screens, demonstrating a high degree of convergence and generalizability. Preclinical in vivo models are now being extended to additional cancer types. While the results obtained thus far, along with the well-established pan-cancer metabolic abnormalities, strongly suggest that the lead thGPRs will be relevant across a broad set of cancer types, the researchers are also testing metabolic biomarkers and developing rapid functional assays to determine the optimal thGPRs for a given cancer type or patient.

The invention creates modular mechanisms for spatially targeted cell therapies, where tumor-specific, tissue-specific, or pathology-specific metabolites serve as navigation cues to dynamically control immune cell location.

The work opens a new domain for the design and development of spatially targeted cell therapies and can provide a basis for a whole new class of therapies.

Stage of Development
Research - in vivo

Stage of Research
In vivo data from studies across therapeutic modalities, including xenograft models with human T cells and NK cells and immunocompetent syngeneic models with mouse T cells, have demonstrated a marked improvement in tumor infiltration and therapeutic efficacy.

Applications

- Spatially targeted cell therapies for solid tumors and potentially other indications, as described below:
    - **Navigation cue**: match tissue-derived metabolites to metabolite-sensing GPCRs to mobilize therapeutic cells to the target tissue/tumor.

- **Lead indications**: breast cancer, ovarian cancer, and other tumors with actionable metabolite or biochemical cues; potential non-oncology indications include autoimmunity and chronic inflammation.
- **Platform integration**: combine with CAR-T, CAR-NK, TCR-T, TIL, NK, and potentially myeloid or antigen-presenting cell therapies
- **Delivery**: ex vivo or in vivo genetic editing or targeted RNA/protein delivery.
- **Modularity**: identify the optimal thGPR for a given cancer type, disease, or patient via metabolic biomarkers, imaging scans, and/or ex vivo functional testing.

Advantages

- **More effective, targeted, and safer interventions** for solid tumors and other diseases.
- **Solves the central spatial barrier** in solid tumor cell therapy by actively mobilizing effector, tumor-reactive immune cells into the tumor.
- **Opens a new, untapped axis**: tumor-released bioactive metabolites and other non-antigen biochemical cues as programmable homing signals distinct from the protein-protein interactions that existing modalities rely and focus on (e.g., surface antigens, chemokines).
- **Complements rather than competes with antigen-directed therapies and existing pipelines**: metabolite gradients provide long-range guidance to the tumor, distinct from antigen recognition achieved via CARs and TCRs upon contact, so the two work synergistically.
- **Broad relevance and less prone to escape**: anchored to aberrant tumor metabolism, a deeply wired and prevalent cancer property that is harder for tumors to alter compared to a single surface antigen or chemokine.
- **Robust to tumor heterogeneity**: guided by aggregate metabolite gradients from the bulk tumor, tolerating non-uniform or partial production across cancer cells.
- **Modular across immune-cell platforms and delivery routes**, improving therapeutic index (and potentially safety and manufacturing cost) by concentrating immune activity at disease sites.

Publications

- Kim YM, et al. Jerby L. Engineering NK and T cells with metabolite-sensing receptors to target solid tumors. Nature Immunology (2026).
- Jerby L. Research Briefing: Engineering metabolite-sensing NK and T cells to target solid tumors. Nature Immunology (2026).
- Conger K. Immune cell 'bloodhounds' track cancer cells' unique metabolic signatures, eliminate tumors in mice. Stanford News (2026).

Patents

- Published Application: WO2025217175

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