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Novel T cell receptor-based solid tumor therapies

3T Biosciences has developed an immune response-guided approach for identifying pharmacologically active T cell receptors and their targets in solid tumors. With a pipeline of therapeutics targeting novel tumor antigens, 3T is seeking partners to advance these programs.

The explosive development of novel cancer immunotherapies over recent years has disrupted the oncology space by opening unprecedented therapeutic opportunities that have reshaped R&D priorities. The initial clinical success in certain cancer types continues to fuel investment and partnering activity, but several bottlenecks, including a need for exquisitely tumor-specific targets, will have to be addressed to ensure further progress.

South San Francisco-based 3T Biosciences, an immunotherapy company focused on the discovery of novel targets for the treatment of solid tumors, is tackling the issue by harnessing its proprietary screening platform and computational technology to identify the most prevalent and tumor-specific T cell receptor (TCR) targets in cancer patients responding to immunotherapy treatment. This is in order to advance effective therapies that exhibit minimal normal tissue toxicities often associated with existing high-potency therapeutic modalities (Fig. 1).

The 3T technology not only provides the foundation for the development of TCR-T cell therapies but also enables the development of high-potency therapeutic modalities such as antibody–drug conjugates (ADCs), bispecific antibodies and CAR-T cells that selectively target tumors while sparing normal tissues. In addition, the approach can be applied to other T cell-mediated disease areas such as autoimmunity, allergy and infectious diseases.

"Our technology consists of an end-to-end target and therapeutic discovery pipeline that allows us to streamline the development of novel and unique therapies for solid tumors," said Hans-Peter Gerber, CEO and CSO of 3T. "Our expertise in immunology, synthetic biology, computation and drug development uniquely positions us to develop the next generation of therapies for broad patient populations."

With a deep preclinical pipeline of therapeutics targeting different classes of antigens, including novel, tumor-specific cancer testis (CT) antigens, as well as a known CT antigen established in the field, 3T is seeking partners interested in driving the development of these programs to the clinic.

Immune response-guided targets
The vast majority of antigens targeted by existing immunotherapies for cancer are cell surface antigens that are highly expressed across tumors. Unfortunately, most of them are also expressed on normal tissues, resulting in on-target, off-tumor toxicities that can cause severe side effects and even fatalities.

To circumvent this problem, 3T has built an engine for the discovery of effective and widely applicable cancer target antigens by using, as a starting point,

Start with the end in mind — TCRs and targets from patients responding to CPI therapy
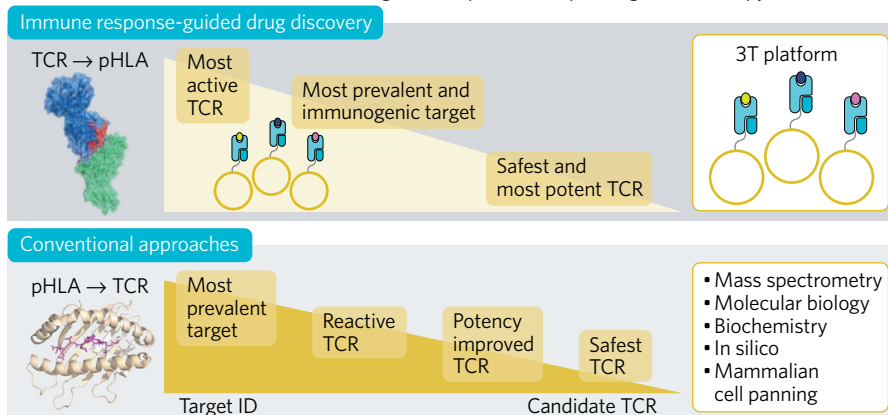
Fig. 1 | 3T Biosciences' immune response-guided platform. 3T identifies pharmacologically active T cell receptors (TCRs) and their antigens in cancer patients in remission to identify target antigens that have already demonstrated utility in immunomodulating cancer. CPI, checkpoint inhibitor; PBMC, peripheral blood mononuclear cell; pHLA, peptide–human leukocyte antigen complexes; TI, therapeutic index.

the TCR repertoire of cancer patients in remission following treatment with immune checkpoint inhibitors[1,2]. Clinical studies have shown that CD8^{+} T cells bind, via their TCRs, to tumor-specific intracellular targets that elicit deep and durable responses in solid tumors and without normal tissue toxicity. To maximize the therapeutic potential of its compounds, 3T samples a broad and genetically diverse patient population to ensure that resulting therapeutics will be applicable to a majority of cancer patients.

Patient tumor samples are first processed and sequenced to identify tumor-infiltrating lymphocytes and their TCRs. Next, 3T's proprietary yeast display technology enables the identification of relevant targets for their corresponding TCRs. Machine learning algorithms are then used to identify TCR specificities and off-target cross-reactivities. Positive hits are further validated via antigen processing, T cell activation and tumor cell killing.

According to Gerber, "the potential of our immune response-guided target identification strategy to be a game-changer for immunotherapies goes beyond oncology and could benefit areas such as autoimmune and infectious disease."

Enabling multiple therapeutic modalities
The 3T platform addresses the key challenge for high-potency modalities in oncology: normal tissue toxicity. To avoid cross-reactivity with normal tissues, 3T's TCRs and TCR-mimics are screened against the company's highly diverse peptide–human leukocyte antigen (pHLA) libraries, providing comprehensive specificity maps for potential

therapeutic compounds. The resulting TCRs and TCR-mimics exhibit improved therapeutic indices, efficacies and safety profiles. 3T is focusing on a few therapeutic modalities for targeting the novel antigens that include adoptive T cell therapies (TCR-T cells), TCR-mimic compounds and peptides—including mimotopes—for cancer vaccines (Fig. 1).

The company's platform has utility in other T cell-driven disease indications such as autoimmune diseases—diabetes, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and atopic dermatitis, and infectious diseases—HIV and other viral diseases such as COVID-19.

"The versatility of our platform offers unique opportunities for collaboration with biopharma," said Gerber. "The 3T platform is the tool of choice for partners seeking to identify novel targets in oncology and immunology to develop first-in-class and best-in-class pHLA-targeting immunotherapeutics."

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2. Gee, M. H. et al. Antigen identification for orphan T cell receptors expressed on tumor-infiltrating lymphocytes. *Cell* **172**, 549–563 (2018). https://doi.org/10.1016/j.cell.2017.11.043

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