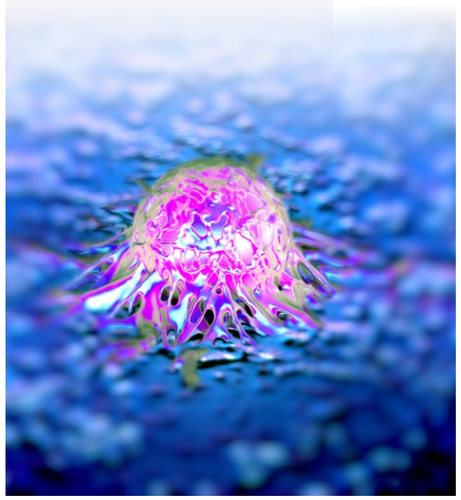
Next-generation cancer therapies based on T cell receptors

Treating tumours requires developing therapies that target specific molecules that are found on cancer cells. Identifying ideal targets is challenging. Dr Hans-Peter Gerber, CSO of 3T Biosciences, works with his team on developing next-generation therapies for oncology, autoimmune and infectious disease patients. Their innovative approach, which harnesses the company's proprietary screening platform and computational technology, eliminates two major challenges in advancing T cell receptor-based therapeutics. 3T Biosciences is currently seeking partners to collaborate in the development of TCR-based therapies.



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Once in a while, mutations occur in our cells. While most of these changes in the DNA are minor, they sometimes lead a cell to keep growing and divide out of control. This is how a cell becomes cancerous and how a tumour starts.

Our immune system, whose main function is to protect us from diseases, can detect and destroy abnormal cells, and therefore prevent or slow down cancer growth. However, cancer cells sometimes find ways to avoid destruction; genetic changes can make them less visible to the immune system or can allow them to 'turn off' immune cells. Cancer then gets the upper hand over the immune system. That is when therapies are necessary.

One of the main reasons why tumours are so difficult to treat is that each cancer is different: there are various mutations which can turn a healthy cell into a cancer cell. Finding the right treatment to target and destroy cancer cells without affecting healthy cells is challenging.

IMMUNOTHERAPY

Immunotherapy is one of the strategies that can be used to treat cancer. Other strategies include surgery, radiation therapy, chemotherapy and targeted therapy. Immunotherapy helps the immune system to fight cancer with different types of treatment such as monoclonal antibodies, immune checkpoint inhibitors and adoptive cell therapy.

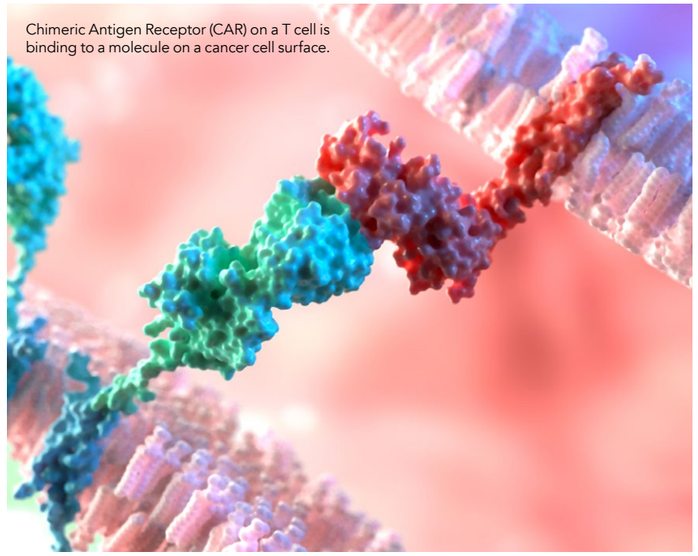
Monoclonal antibodies are immune proteins created in the lab, designed to bind to specific targets (also called antigens) on cancer cells. Antibodies then act as little flags that signal the presence of cancer cells to immune cells, thus facilitating their detection and destruction by the immune system.

Immune checkpoint inhibitors are drugs that block, as their name suggests, immune checkpoints. These checkpoints are a normal part of the immune system whose role is to keep immune responses from being too strong. By blocking them, these drugs allow immune cells to respond more strongly to cancer.

Adoptive cell therapy is a type of immunotherapy which boosts the natural ability of T cells to fight cancer. In this treatment, immune cells are taken from the patient, modified in the lab to better attack cancer cells, grown in large batches, and injected back into the patient's body.

CHALLENGES

The ideal cancer target antigen is expressed on tumour cells and absent on normal tissues so that, when a therapy targets this antigen, cancer cells are destroyed and healthy cells remain intact. However, such ideal targets are difficult to find. The lack of antigens that are uniquely expressed on tumours, but not on normal tissues, has limited the progress of medical research. The presence of targeted antigens on healthy cells triggers off-tumour toxicities that can cause severe side effects and even fatalities. To successfully treat solid tumours, it is therefore critical to identify novel, truly tumour-specific targets.



Chimeric Antigen Receptor (CAR) on a T cell is binding to a molecule on a cancer cell surface.

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ADVANTAGE OF INTRACELLULAR ANTIGENS

The vast majority of antigens targeted by existing immunotherapies for cancer are cell surface antigens (proteins on the surface of cancer cells) that are highly expressed across tumours. Unfortunately, most, if not all, of them are also expressed on normal tissues. But there is another way.

Inside the cell, intracellular proteins are broken down into peptides. The peptides are brought to the surface of the cell by a complex named human leukocyte antigen (HLA). Peptide-HLA (pHLA) complexes then act as a proof of identity. Identity check is performed by some T cells which, by means of their T cell receptors (TCRs), interact with HLA and examine the peptide. If the T cell recognises the peptide as foreign or mutated (each type of T cell targets specific antigens), it initiates the destruction of the cell.

This mechanism is involved in the fight against cancer: in patients with solid tumours, T cells can mediate effective antitumour responses by targeting peptide-HLA complexes presented on tumour cells. Therefore, peptide-HLA complexes could represent the ideal targets needed for the development of new therapies.

TCR-T THERAPIES

Once targets are identified, they can be used for T cell receptor-engineered T cell (TCR-T) therapy, a form of adoptive cell therapy in which genetically modified T cells are used as direct anti-cancer therapeutics. More specifically, T cells are modified to be directed toward the target antigen.

Identifying the TCR-peptide-HLA targets that mediate complete responses in ICI-treated solid tumours has proven to be a challenge.
3T Biosciences, an immunotherapy company based in South San Francisco, aims to do just that through a process called response-guided target identification, in order to develop next-generation therapies for the treatment of solid tumours. Their experience makes them a leader in T-cell receptor targeting and therapeutic discovery.

The company's proprietary screening platform and computational technology allows them to identify the most prevalent and pharmacologically active TCRs and the pHLA targets to which they recognise in cancer patients who are in remission, and to screen TCR-based therapeutics to assess the risk of off-tumour toxicities.

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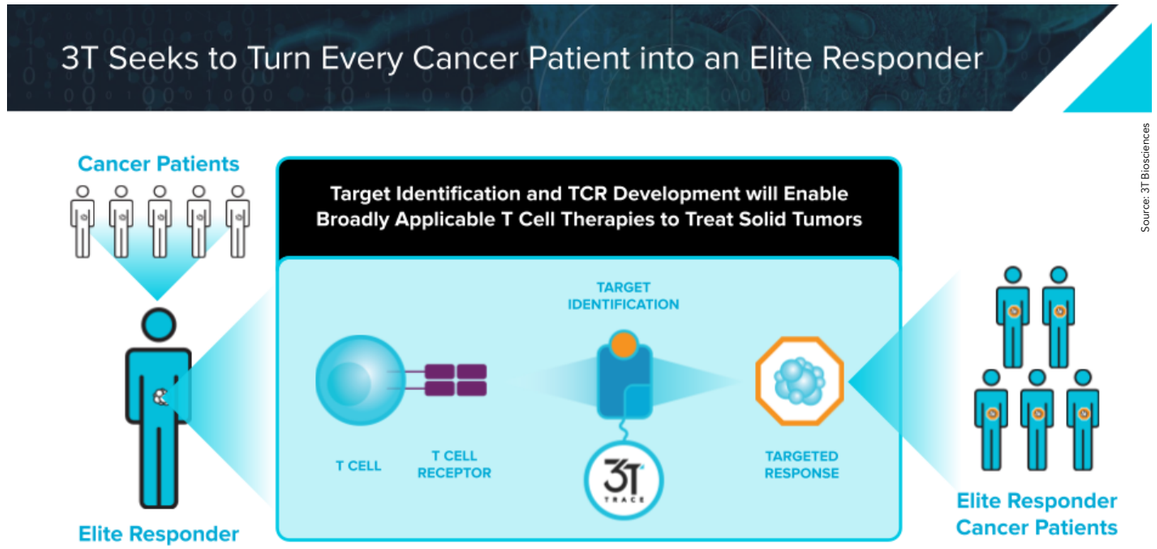
IDENTIFYING NOVEL TARGETS

To identify novel targets in solid tumours, 3T Biosciences employs the most sensitive detectors of pHLA targets, the T cell receptors expressed on cytotoxic T cells. The tissues source for such pHLA probes are tumour biopsies and/or blood samples containing cytotoxic T cells from patients who are in remission after being treated with immune checkpoint inhibitors. A broad and genetically diverse patient population is sampled to ensure that resulting therapeutics will be applicable to a majority of cancer patients.

Tumour samples are processed and sequenced in order to identify tumour-infiltrating lymphocytes and their TCRs. Tumour-infiltrating lymphocytes, or TILs, are immune cells found in and around tumours. Their presence is a sign that the immune system is responding to the tumour; people whose tumours contain TILs often have a better prognosis than people whose tumours do not contain them.

Once TILs and their TCRs are identified, the peptide-HLA complexes that the TCRs specifically target are determined thanks to the company's yeast display technology. These peptide-HLA complexes are the targets that could be used to develop new therapies.



Source: 3T Biosciences

Through a process called response-guided target identification, 3T Biosciences aims to develop next-generation therapies for the treatment of solid tumours.

MONITORING OFF-TUMOUR TOXICITY

Previous attempts with engineered, patient-derived lymphocytes expressing TCRs that were engineered to bind to cancer targets had limited success in the clinic because of off-tumour toxicity: therapeutic TCRs reacted to peptides other than the one intended, resulting in the destruction of healthy cells. These attempts revealed a need for technology improvement to monitor off-tumour reactivities of TCRs before clinical testing.

3T Biosciences addresses this issue. To avoid cross-reactivity with normal tissues, their platform, 3T-TRACE, uses machine learning algorithms to identify peptides on healthy tissues that are likely to be targeted by TCRs. The 3T-TRACE technology consists of screening TCRs against the company's highly diverse peptide-HLA libraries, to check that TCRs do not react to antigens other than the one that is intended.

Selected TCRs are then validated by tests assessing their ability to process antigens, activate T cells, and kill tumour cells.

ENABLING MULTIPLE THERAPEUTIC MODALITIES

The 3T-TRACE technology provides the foundation for the development of TCR-T cell therapies, but also enables the development of high-potency therapeutic modalities that selectively target tumours while sparing normal tissues; the selected targets could be used to develop antibody-drug conjugates (ADCs), bispecific antibodies, and chimeric antigen receptors cell therapies (CAR-T). CAR-T is a type of immunotherapy similar to TCR-T, except that CAR-T relies on the recognition of peptide antigens via a non-TCR molecule, such as antibodies or other scaffolds, to initiate an immune response. ADCs are a class of biopharmaceutical drugs designed to target and kill tumour cells by delivery of toxic payload to tumours, while sparing healthy cells. Bispecific antibodies, as the name suggests, simultaneously target a tumour antigen and cell surface antigen exclusively present on immune cells, to initiate an anti-tumour immune response.

While the aim of 3T Biosciences is to develop novel therapies to treat solid tumours, their platform can also be useful to treat autoimmune and infectious diseases.

TREATING DISEASES OTHER THAN CANCER

While the primary aim of 3T Biosciences is to develop novel therapies to treat solid tumours, their platform can also be useful to treat other diseases in which T cells are involved, such as autoimmune diseases (including diabetes, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and atopic dermatitis), and infectious diseases (including HIV and other viral diseases such as COVID-19).

LOOKING FOR PARTNERS

The 3T platform is a tool of choice to identify novel targets in oncology and immunology to develop first-in-class and best-in-class peptide-HLA-targeting immunotherapeutics. Potential targets and possibilities are so numerous that 3T Biosciences is currently seeking partners to collaborate in the development of TCR-based therapies.

Behind the Research

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Research Objectives

3T Biosciences develops next-generation therapies for oncology, autoimmune and infectious disease patients. Recently, the team around Dr Gerber has developed a novel tumour therapy.

Detail

Bio

Dr Hans-Peter Gerber has over 25 years of research and development experience in oncology, including antibody-drug conjugates (ADCs), redirected T-cell targeting compounds and adoptive T-cell therapies. He is currently CSO at 3T Biosciences, an immunotherapy company located in South San Francisco, where he is overseeing platform- and therapeutic program development of TCR-T and Bispecific therapeutics.

Dr Gerber is a recognised leader in oncology drug development, with strong expertise in target identification and validation, development of novel therapeutic modalities and companion diagnostics, regulatory filings and translational support for early clinical development. He has a proven track record in making initial contacts and to successfully execute external collaborations and licensing deals with academia and corporate partners.

References

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3T BIOSCIENCES

Personal Response

What inspired you to conduct this research?

"The most important decision teams make when developing targeted therapeutics in Oncology is the selection of the target. Despite the success in the development of high-potency modalities like ADCs, CAR-T cells or bispecifics over the past 10 years, most of them are still directed at cell surface targets that were identified over 25 years ago. The 3T-TRACE technology provides access to a much larger and cleaner target antigen space compared to cell surface antigens which will fuel the development of highly tumour specific, high potency therapeutics that overcome the current limitations caused by surface antigens for solid tumour targeting.

What are the next steps?

We identified a portfolio of novel, previously unknown pHLA targets that are expressed across a variety of solid tumour indications. We are now matching these targets with the optimal therapeutic modality, including bispecifics, TCR-T-, CAR-T cells and ADCs by taking into account differences in pHLA expression levels, differential sensitivities between tumour indications towards these modalities, immunogenicity of the targets, pHLA internalisation rates and their levels of normal tissues expression. The final test before advancing any of our novel therapeutics toward clinical trial is a comprehensive screen to eliminate any potential cross-reactivities to avoid normal tissue toxicity in phase 1 trials."