Reprogramming the immune system for personalised immunotherapy against cancer

For decades, researchers have strived to understand how the immune system recognises and fights cancer, ultimately aiming to exploit and augment these processes to create more effective cancer therapies. Dr Richard Koya, Associate Professor of Oncology, Associate Director of the Center for Immunotherapy, and Director of the Vector Development & Production Facility at Roswell Park Cancer Institute is a prominent researcher in this area. He leads an international team of researchers in developing cutting-edge technologies to use patients’ own immune systems to target and kill cancer cells.

Our immune system is not only critical in our defence against bacteria, viruses and other pathogens, but it also plays an instrumental role in preventing and fighting cancer. The immune response to cancer is complex, involving antibodies and a broad repertoire of white blood cell types, including lymphocytes and other leukocytes.

Cancer immunotherapy refers to any strategy that uses the immune system to fight cancer, and several breakthroughs have brought immunotherapy to the forefront of cancer treatment in recent years. Immunotherapy offers several advantages over conventional chemotherapy, including reduced side effects and the potential to suppress immune resistance mechanisms in cancer.

THE IMMUNE SYSTEM VS. CANCER
Continuous advances in the understanding of cancer immunology pave the way for significant clinical development of long-lasting immune responses.

RECEIVING THE CANCER SIGNAL – THE T CELL RECEPTOR
One class of white blood cells, known as T cells, has long been known to play an important role in the immune response to cancer. T cells harbour signalling proteins called T-cell receptors (TCR) on their surfaces, a feature that distinguishes them from other white blood cells. In a complex process, TCRs recognise pathogenic- or tumour-specific proteins (known as antigens) that are presented by other immune cells and also cancer cells.

While cancer vaccines represent an enticing strategy, the presence of immune resistance mechanisms in cancer cells can limit their long-term efficacy.

Several T cell subsets exist, each with their own unique TCR and specialised function. Cytotoxic T cells and T helper (Th) cells are characterised by the presence of a CD8 or CD4 receptor on their cell surfaces, respectively. Cytotoxic T cells become activated when they recognise pathogens or tumour cells via their TCR. This is followed by the release of enzymes and toxic proteins that trigger programmed cell death in target cells. Th cells, as their name suggests, help other immune cells by releasing important chemical messengers called cytokines, which refine and regulate immune responses.

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Dr Koya’s research uses genetic engineering to re-educate T cells to deliver a lethal hit on malignant cells.

NY-ESO1 TCR

Clinical grade (cGMP) production of the retrovirus vector and testing in human T cells

Phase I/IIa Clinical Trial for Advanced Stage NY-ESO1(+) Cancer (accruing patients)

Clinical Trial: Roswell Park Cancer Institute TGFβ blockade in TCR-engineered T cell cancer immunotherapy for advanced solid tumours

Research Objectives

Dr Koya’s research focuses on developing innovative ways to utilise the patients’ own immune system to target and kill cancer cells. His approach is based on genetic engineering of a subset of immune cells called T lymphocytes, by utilising viral vectors to re-programme these immune cells.

Funding

National Institutes of Health (NIH)

Collaborators

• Dr Kunle Odunsi, Deputy Director of Roswell Park Cancer Institute

Q&A

What has been the biggest technical challenge in your research to date?

The biggest challenge in my research was to select among many candidates the most efficient and more specific TCR to target a Tumour Associated Antigen that is in cancer but not in normal tissues.

Do you believe that future developments in immunotherapy will one day completely replace conventional chemotherapeutic approaches?

I would not say replace completely. Some chemo-agents are also useful to prime the cancer cells, making them more susceptible to immunotherapies.

Are there likely to be undesired effects or safety issues with widespread use of ACT?

There is no tumour type against which ACT will be ineffective; any solid or liquid tumour can be targeted by ACT. However, evidence is growing that ACT will be ineffective against solid or liquid tumours that evade the immune system.

Do you anticipate that patients can be re-treated by ACT after a relapse?

The answer to this is also a plan we are pursuing. The point is that in early trials the FDA recommends a trial with a single dose to check for side-effects, as safety is paramount.

Are there tumour types that ACT is unlikely to be effective against?

There is no tumour type against which ACT will be ineffective; any solid or liquid tumour can be targeted by ACT.