Arnie Charbonneau Cancer Institute
The Riddell Centre for Cancer Immunotherapy

University of Calgary | Alberta Health Services

Advancing CAR T-Cell Therapy: Overcoming Challenges in Glioblastoma with a Hematopoietic Stem Cell-Derived Approach

PROJECT TEAM

Dr. Douglas Mahoney (PI)

Dr. Jennifer Chan (Co-I)

TARGETED CANCERS

- Glioblastoma
- Cancer agnostic

RESEARCH PRIORITIES

- Discovery & Innovation

RESEARCH ENABLERS

- Preclinical modeling
- Synthetic immunology

Previous enablers:

- Vectorology

PROJECT SUMMARY

While CAR T-cell therapy has shown success in treating certain blood cancers, its application to solid tumours, such as glioblastoma, faces several challenges. In solid tumours, CAR T-cells often lose their effectiveness due to chronic antigen exposure and immune suppression within the environment surrounding the tumour. These factors lead to CAR T-cell exhaustion, which limits the longevity of the therapy and can result in treatment failure. Additionally, CAR T-cells are typically administered as a single large dose of pre-activated cells, which can cause the immune system to tire out quickly, making the treatment less effective.

To overcome these limitations, scientists at UCalgary, led by Dr. Douglas Mahoney, are developing a novel approach in which hematopoietic stem cells — specialized cells found in bone marrow that can develop into all types of blood cells, including T cells — are genetically engineered to produce a continuous supply of CAR T-cells directly within the patient's bone marrow. This approach would provide a sustained presence of CAR T-cells, enabling them to target cancers such as glioblastoma and reducing the risk of exhaustion.

Riddell Centre scientists, led by staff scientist Dr. Kris Ellestad, have successfully engineered hematopoietic stem cells that can generate CAR T-cells, and they are working on developing a system to control when the CAR is expressed during T cell maturation. The regulation of CAR expression in T cells is crucial, as its premature activation during T cell development can disrupt the proper maturation process. Therefore, it's important to control CAR expression so that it only activates when the T cells are fully mature and ready to fight the cancer.

To address this, the team has developed a new platform technology: a gated genetic switch that can be activated in a cell-type-specific manner. Once triggered by a single brief exposure to an inert drug, the gene remains permanently active in the targeted cells, eliminating the need for ongoing drug administration. This new platform ensures that CAR expression occurs only at the right stage of T cell development, bringing us closer to realizing the full potential of hematopoietic stem cell-derived CAR T-cells for cancer treatment.

OVERALL IMPACT

The overall goal of this project is to develop a continuous, controlled supply of CAR T-cells derived from hematopoietic stem cells to enhance the effectiveness and persistence of CAR T-cell therapy in treating solid tumours, such as glioblastoma, while minimizing immune exhaustion.

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