CONQUERING CANCERS CHANGING LIVES

MID-YEAR REPORT - MICHAEL CUCCIONE FOUNDATION
FEBRUARY 2023

THANK YOU

Thank you, Michael Cuccione Foundation, for your steadfast advocacy for child health, tireless leadership and exceptional generosity in support of world-leading childhood cancer research in the Michael Cuccione Childhood Cancer Research Program at BC Children's Hospital.

Thanks to your dedication and generosity, children battling hard-to-cure cancers in British Columbia are able to access novel immune therapies. Because of you, innovative research focused on CAR T-cell therapy is happening right here in BC in the Michael Cuccione Childhood Cancer Research Program. You are changing and saving lives. For this we are so grateful.

We are pleased to provide you with an update on research initiatives focused on CAR T-cell therapy, supported by your donations.

THE FIRST PHASE - ACCESS TO CAR T-CELL THERAPY

Thanks to the incredible support of the Michael Cuccione Foundation, BC Children's Hospital is one of the founding members of the CureWorks network, and the only member centre in Canada. CureWorks is the only pediatric-focused CAR T-cell research network in North America and has offered the most advanced CAR T-cell therapies to children and adolescents in BC. As a result of this partnership, to date, eleven children with acute lymphocytic leukemia (ALL) have been treated with CAR T-cell therapy.

CAR T-cell therapy has not been successfully established for any pediatric cancers besides ALL and lymphoma of the B-cell type. This was where you, the Michael Cuccione Foundation, stepped in with yet another extraordinary commitment. Thanks to you, the next phase of CAR T-cell research is underway in the Michael Cuccione Childhood Cancer Research Program at BC Children's.

THE NEXT PHASE OF CAR T-CELL RESEARCH

In this second phase, BC Children's is developing CAR-based capacity and research targeting pediatric cancers that are currently not treated by CAR T-cell therapy - especially solid pediatric cancers.

PROGRESS UPDATE - YEAR 1-2

Development of Radio Conjugates - Partnering with TRIUMF

CAR T-cell therapy has already been tried for several pediatric and adult cancers with little success. Unlike blood cancer such as ALL, most solid cancers have a well-developed population of cells located in the cancer tumour called the tumour microenvironment.The tumour microenvironment is a complex subsystem of immune cells that instead of attacking the cancer cells suppress anti-cancer killer cells.These suppressive tumour microenvironment immune cells stop CAR T-cells from penetrating the tumour, or render CAR T-cells unable to eradicate the cancer cells once inside. One approach by researchers in the US has been to try to further modify CAR T-cells to see if they can overcome the tumour suppression effects, but this approach has not been very successful.Another is to attempt to remove the suppressive tumour microenvironment which then allows killer cells, such as CAR T-cells, to successfully attack the cancer cells and eradicate the tumour cells.

In BC, we have the exceptional opportunity to develop an approach to disrupt and possibly destroy the tumour immune-suppressive microenvironment by using radio conjugates.

This approach using radio conjugates uses a tumour specific antibody linked to a radioisotope that only penetrates at a microscopic level, and avoiding irradiation of normal tissues.These radioisotopes are called alpha and beta -emitters as compared to gamma emitters usually used for CT scans or conventional irradiation therapy.TRIUMF is one of only a few places in North America that can make these alpha and beta -emitter radio conjugates to be used to damage the tumour microenvironment that then allows CAR T-cell therapy to eradicate cancer cells.In partnership with TRIUMF, the team has selected 2 antibodies to target two sets of cancers.IL-1RAP that can target Ewing's sarcoma as well as acute myeloid leukemia (AML) and GD-2 that can target neuroblastoma.

In the first two years, the following goals have successfully been accomplished:

- Creation of optimized radio conjugated anti-IL-1RAP and GD-2 radio conjugates (completed in December 2022, TRIUMF - Schaffer).
- Initiation of animal experiments to evaluate the effect of these radio conjugates in Ewing's sarcoma in a human immune suppressed mouse model that will enable the evaluation of the effect of these radio conjugate's ability to kill tumours without an effective human immune microenvironment (started in January 2023, BCCA - Sorensen).
- Initiation of experiments to evaluate the effect of an anti-GD-2 radio conjugate (Alpha and beta emitter) on the tumour immune microenvironment with a mouse neuroblastoma and mouse immune environment (started in January 2023, BCCHR - Reid). In both models, the teams will also evaluate the biodistribution of the radio conjugates in all normal organs to ensure that they will be safe for later human clinical trials. It is anticipated that these experiments will be completed in the next year.

YEAR 3 GOALS

Development of CAR T-cells for Eventual use in Clinical Trials

The development of CAR T-cells has focused on two tumour specific targets, IL-1RAP and GD-2. To combine the targeted radio conjugates and CAR T-cells, the development of optimized CAR T-cells is also needed.This has involved a two-pronged approach.

The first is to develop an optimized genetic construct which can then be inserted or transfected into T cells isolated from the patient with cancer. This is being done in partnership with BC Cancer Agency (BCCA) and Dr. Kevin Hay, who has already developed an ALL CAR T-cell that is now being evaluated in a national clinical trial for adults.
Dr. Hay joined the team in the second year of the project and has begun development of an initial first-generation CAR T-cell construct for IL-1RAP which will require further adjustments and modifications before it will be ready for evaluation in a preclinical mouse model, and eventually in clinical application.

The second approach to optimize the CAR T-cells is to metabolically optimize the CAR T-cells so that they stay in the body longer in order to maintain a remission.This is needed as the successful CAR T-cells for ALL are only effective in 50% of patients for a long-term cure, as a result of CAR T-cells disappearing after a period of time. Metabolic optimization has been able to improve the success of CAR T-cells by developing longer-term T-cell memory. This approach is being developed for both IL-1RAP and GD-2 CAR T-cells at BC Children's by Dr. Ramon Klein Geltink. The goal is to have initial experiments completed by the end of year 3 (March 2024).

Evaluating CAR NK Cells

Currently, there is early evidence that natural killer (NK) cells – naturally occurring in the human body – are effective in killing cancer cells in adult solid cancers, as they are better at avoiding the tumour microenvironment. Drs. Geltink and Schultz, will be evaluating an approach to prime these NK cells, similarly to the approach taken in T-cells, and optimizing a CAR NK construct. If the results are promising, the team will further investigate using these cells in pre-clinical models in year four.

LOOKING AHEAD - YEAR 5 and BEYOND

Clinical Trials - IL-1RAP CAR T-Cells and Radio Conjugate Therapy

Both the radio conjugates and CAR T-cells that are developed will require testing in individual clinical trials before they can be combined.

The strategy is to test an IL-1RAP CAR T-cell alone in an early phase trial against AML. The rationale for this is that the microenvironment of AML is, like ALL, not well developed. Using it initially in AML will meet a great need, as current therapies only result in a cure rate of about 60% in children with AML and about 50% of these children receive a Blood and Marrow Transplant (BMT) as part of their therapy.

If successful, CAR T-cell therapy of AML may either replace the need for BMT or, will further improve the cure rate of BMT for children with AML. The team envisions this trial can occur in 2-3 years' time, as a collaboration between BC Children's and BCCA.

Early phase trials will also take place for the IL-1RAP radio conjugate in Ewing's sarcoma patients to evaluate the efficacy in children without receiving CAR T-cells. The next phase will be based on the safety of IL-1RAP radio conjugates, followed by CAR T-cells.

THANK YOU MICHAEL CUCCIONE FOUNDATION

We are truly grateful for your outstanding commitment and remarkable generosity.

If you have any questions or would like additional information, please do not hesitate to contact me.

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