2021 Community Dissemination Report

BioCanRx-Cancer Stakeholder Alliance Learning Institute

Cancer Immunotherapy Research:

An outline of current work discussed at Summit4CI 2021 written by participating patients and caregivers, in collaboration with early-career researchers working in the field.

BioCanRx
Canada's Immunotherapy Network
Le réseau canadien d'immunothérapie

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December 2021

Welcome Messages

From BioCanRx

We are very proud to share this publicly available **Community Dissemination Report** written by the participants of the 2021 BioCanRx-Cancer Stakeholder Alliance Learning Institute and we're very happy to host the Learning Institute this year after a one-year hiatus due to the global COVID-19 pandemic. The Learning Institute was held at the 2021 Summit for Cancer Immunotherapy (Summit4CI) from November 21 to November 22, virtually. We would like to thank the BioCanRx staff and the CSA-LI Working Group for planning a virtual event. And we would like to congratulate the Learning Institute participants for completing this program during these unique times.

The Learning Institute piloted at the 2017 Summit for Cancer Immunotherapy and has since become a permanent component of the annual Summit. This initiative was developed in partnership with the Cancer Stakeholder Alliance through the members of its working group. We are deeply grateful for this partnership and for the invaluable time and focus that participants have committed to developing this important patient engagement initiative.

This Dissemination Report serves to highlight and share the key research take-away messages presented at the Summit4CI as well as group reflections of the Learning Institute. The report is targeted toward the boarder oncology patient and researcher community, BioCanRx network, the Cancer Stakeholder Alliance, and the general public.

We look forward to hosting another successful event at the next Summit in November 2022. You can learn more about the Summit4CI at cancersummit.ca.

We hope you will find this informative report as enlightening as we do.

John C. Bell, Ph.D.
Scientific Director
BioCanRx

Stéphanie Michaud, Ph.D. President and CEO BioCanRx

From the Cancer Stakeholder Alliance

In 2017, on the advice of the Cancer Stakeholder Alliance and with inspiration from the Community AIDS Treatment Information Exchange (CATIE) – Canadians Association for HIV Research (CAHR) Learning Institute, BioCanRx created the Learning Institute. The Learning Institute was built with the following objectives in mind:

- To create a model of learning that encourages, supports and creates the integration of patient leaders into the scientific conference,
- Integrate the patient/caregiver perspective to ensure that cancer research is well informed by the patient voice and lived experience and,
- Ensure that scientific research presented at the conference is accessible so that patients can be advocates to their communities.

As part of the Learning Institute, trainees working in cancer immunotherapy research are paired with patient advocates. Together, they attend the annual BioCanRx Summit for Cancer Immunotherapy and learn from each other through a bi-directional exchange of information during the conference.

Trainees are able to guide patient advocates through the conference and help them to better understand the scientific knowledge and general scientific process, as well as to practice their knowledge-translation skills. Patient advocates are able to help trainees understand the real-world implications and importance of their work while passing on their own lived experience both within and outside of the cancer landscape.

I believe we have created the start of something very valuable for patients and researchers alike. It is important to remember that patients have a lot to teach others about the cancer landscape and this initiative helps the patient voice be heard.

I want to thank and commend BioCanRx for being so committed to patient engagement in cancer research even in these unprecedented times. And I would like to give special acknowledgement to the patient advocates and trainees for participating in the virtual Learning Institute this year.

Louise Binder
Chair of the Cancer Stakeholder Alliance Working Group
Health Policy Consultant, Save Your Skin Foundation

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The Learning Institute

What is the Learning Institute?

The BioCanRx-Cancer Stakeholder Alliance Learning Institute brings together leaders from oncology patient communities (patient scholars) and BioCanRx Trainees (academic scholars) from the immunotherapy research community to engage in interactive, collaborative, and bidirectional knowledge exchange activities at the annual Summit for Cancer Immunotherapy. The overall aim of the Learning Institute is to ensure that novel cancer immunotherapy research is accessible to the cancer patient community.

Goals

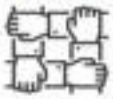
- ☑ Create a model of learning that encourages, supports and creates the integration of patient leaders into the scientific conference
- ☑ Integrate the patient/caregiver perspective to ensure cancer research is well-informed by the patient voice and lived experience
- ☑ Ensure that cancer immunotherapy research is accessible so that patients can be advocates to their community
- ☑ Bridge the knowledge gap between patients and researchers through bi-directional learning
- ☑ Connect patients and caregivers with researchers to facilitate patient involvement in cancer research projects

The Five Main Components of the Learning Institute

PRE-SUMMIT TRAINING

Familiarization of basic cancer biology and immunotherapy concepts in advance of the Summit for Cancer Immunotherapy.

BUDDY SYSTEM



The buddy system involves pairing a technical expert (academic scholar) with people with lived cancer experience (patient scholars) for sharing of their respective expertise.

KNOWLEDGE EXCHANGE SYSTEM

Buddy groups get together and discuss the research they have heard. After discussion, buddy groups present to the group and explain the key take-aways of the research.

DISSEMINATION REPORT

Co-authorship of a community dissemination report outlining key takeaways from the Summit. The report is available to the public and is written in lay language to make it accessible.

PATIENT-RESEARCHER ROUNDTABLE

Learning Institute participants and BioCanRx funded investigators connect over lunch to discuss ongoing research projects.

Interested in Participating?

For more information, please visit the BioCanRx website at biocanrx.com or email us at info@biocanrx.com

Development

The Learning Institute was inspired by the Community AIDS Treatment Information Exchange (CATIE) – Canadians Association for HIV Research (CAHR) Learning Institute. In 2016, the Cancer Stakeholder Alliance (CSA) and BioCanRx identified the Learning Institute as a joint priority and made it part of their Joint Action Plan. Members of the 2017 CSA Working Group partnered with BioCanRx staff and Highly Qualified Personnel to develop the inaugural Learning Institute, which was piloted at the 2017 Summit4CI. This year's Learning Institute was designed by the BioCanRx-CSA Learning Institute Working Group and BioCanRx staff using the feedback obtained from last year's initiative.

Table 1 Members of the 2021 BioCanRx-CSA Learning Institute Working Group.

Members:
Patrick Sullivan President, Team Finn and a Founder & Chairman of Ac2orn **Jeanette Boudreau** Dalhousie University **Kim Badovinac** Canadian Cancer Research Alliance (CCRA) **Paul O'Connell** The Leukemia & Lymphoma Society of Canada (LLSC)
BioCanRx Trainee(s):
Etienne Melese PhD candidate, University of British Columbia
BioCanRx Staff:
Stéphanie Michaud President and CEO, BioCanRx **Megan Mahoney** Director, Scientific Affairs and Training Programs, BioCanRx **Rida Gill** Data & Knowledge Mobilization Intern, BioCanRx

Thank You

BioCanRx and the members of the BioCanRx-CSA Learning Institute Working Group wish to thank the CATIE-CAHR Learning Institute for the inspiration and for setting the bar of excellence.

BioCanRx wishes to give a special thank you to the Learning Institute Working Group and mentors for their dedication of their time, energy, focus and work in making the Learning Institute a great success.

We would also like to extend a big thank you to Notch Therapeutics for being a proud supporter of this initiative.

2021 Learning Institute

This year's initiative brought together three members from the cancer patient/caregiver community, in the role of patient scholars, four members of the BioCanRx trainee community, in the role of academic scholars, two members from the Learning Institute Working Group as mentors, and a BioCanRx staff as a facilitator (Figure 1). Trainees are defined as all individuals responsible for the translation of promising cancer biotherapeutics. They include undergraduate and graduate students, post-doctoral fellows, and research and clinical staff.

Figure 1: 2021 BioCanRx-CSA Learning Institute participants.

Together, they participated in a series of interactive and collaborative "Knowledge Exchange sessions" that served to guide the process of knowledge synthesis, dissemination, and exchange. Participants discussed the plenary sessions from the day each evening. These high-energy sessions included small group discussions followed by a brief presentation to the group highlighting key take-aways, scientific content, personal thoughts, and overall accessibility of the talks. They also attended webinars to prepare for the summit (Figure 2).

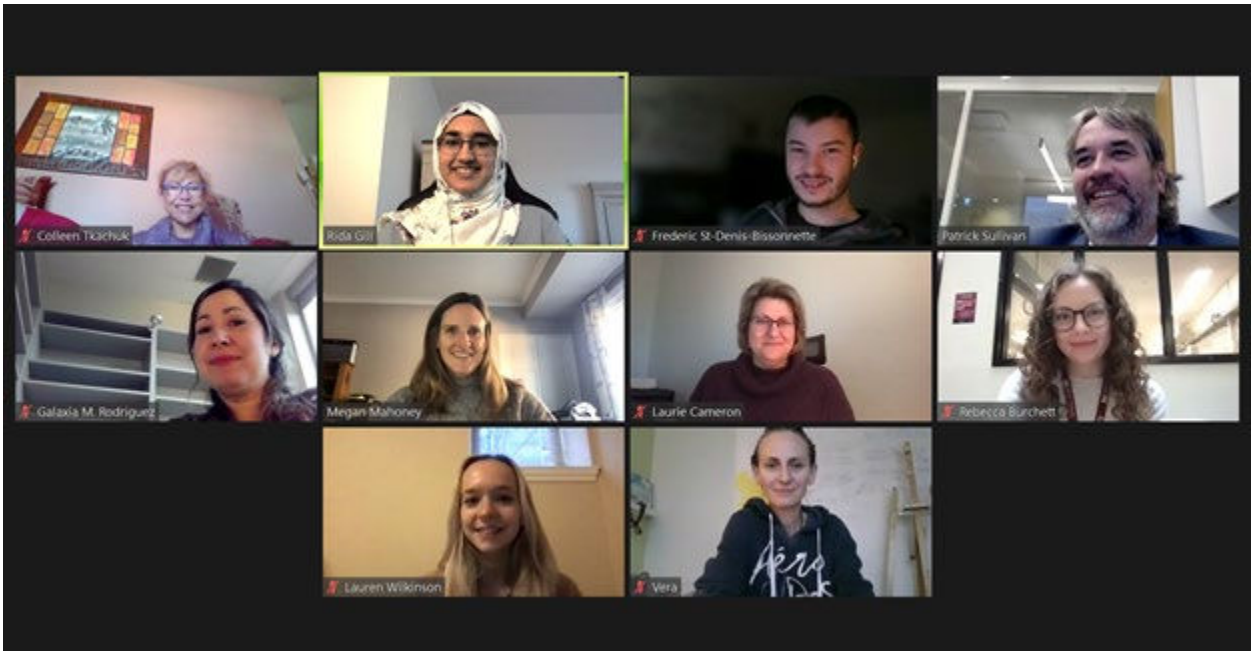


Figure 2: A webinar to prepare the participants for the Patient-Researcher Roundtable in which patients and their buddies would discuss the project of one researcher and provide their unique perspectives and researchers would inform the patients on new immunotherapies.

Table 2 Full List of the participants in the 2021 Learning Institute.

Patient Leaders/Caregivers who participated as "patient scholars":	
Catherine Wilhelmy Centre Hopitalier Universitaire de Sherbrooke (CHUS) **Colleen Tkachuk** Ovarian Cancer Canada **Vera Samarkina**	
BioCanRx Trainees who participated as "academic scholars":	
Galaxia Rodriguez Postdoctoral Fellow, Dr. Barbara Vanderhyden's Lab, Ottawa Hospital Research Institute **Frédéric St-Denis Bissonnette** Master's Student, Dr. Jessie R. Lavoie and Dr. Lisheng Wang's Lab, University of Ottawa	**Lauren Wilkinson** Undergraduate Student, University of Western Ontario **Rebecca Burchett** PhD Candidate, Dr. Jonathan Bramson's lab, McMaster University
CSA Working Group members who participated as "mentors":	
Etienne Melese PhD candidate, University of British Columbia **Patrick Sullivan (Co-Chair)** President, Team Finn, and a Founder & Chairman of Ac2orn	
BioCanRx Staff who participated as a "facilitator":	
Rida Gill Data and Knowledge Mobilization Intern	

Dissemination Report Details

The Learning Institute key take-away messages and group reflections from select plenary session at the 2021 Summit4CI can be found below.

This conference was held from November 21st to November 22nd, 2021, virtually. A general overview of the program agenda is provided below.

Sunday, November 21 (Day 1)	• Plenary Session 1: Advances in Cellular Immunotherapy • Plenary Session 2: Approaches to Making Cold Tumors Hot
Monday, November 22 (Day 2)	• Plenary Session 3: Advances in Pediatric Immunotherapy • Oxford-style Debate: Who is driving the CAR: NK cells vs T cells

To learn more about the Summit and to view the full program, please visit http://www.cancersummit.ca/.

SATURDAY, NOVEMBER 20, 2021

Public Forum: Understanding Cancer Immunotherapy Clinical Trials in Canada: Are they Needed Now More than Ever?

Lay Abstract of Public Forum

A clinical trials doctor, a patient partner who has participated in a clinical trial and a scientist who spoke about the latest developments in immunotherapy cancer research and treatments. They discussed the value of clinical trials in making effective therapies available to patients, how cancer patients access clinical trials, how clinical trials have pivoted during COVID-19 and what the impacts for future care are, and conversations you can have with your physician.

Notes by Colleen Tkachuk and Galaxia Rodriguez

Talk title: Patient Advocate Perspective on Clinical Trials by David McMullen

- David McMullen is a patient partner advocate and clinical trial participant. He was a professional engineer for 37 years, working in several management positions for Ontario Power Generation. He was diagnosed in 2012 with multiple myeloma, an incurable hematologic cancer. David has been treated with two stem cell transplants and numerous other treatments including participation in a phase one clinical trial. He was treated this summer with an immunotherapeutic approach called "bi-specific antibody" with encouraging results so far. He is actively involved in many organizations representing patients and particularly Myeloma Canada, a national patient-based organization, and a charity. He founded the National Myeloma Canada Advisory Council. He is a patient representative for a national organization called CADTH which makes recommendations to provinces about funding treatments based partly on clinical trial's results.

Key takeaways:

- He is extremely grateful to be still alive with this incurable disease thanks to the life-saving treatments and the care of his wife.
- Clinical trials take place after treatment has been tested in a dish as well as some animals, and if deemed safe it enters a clinical trial with a small number of patients. If it seems to be safe, it moves to stage 2 where it is tested in patients to see effectiveness and safety, and then a third clinical trial with a broader range of patients.
- Participating in a clinical trial not only is beneficial for the patient but also contributes to the future of treatments for fellow patients and saves many lives.
- His advice for patients:

    - Don't be shy, talk to your doctor about clinical trials and if your doctor knows that you are interested in clinical trials and are open to the concept, then your doctor is more likely to take the time to discuss it.
    - Be more educated to be able to get better treatment. Patients should become better advocates for themselves, and the first step is to educate themselves.
    - Do your own research, become more knowledgeable to be able to politely and respectfully advocate for yourself.
    - Based on his experience, he has noticed that people more educated are able to get more access to clinical trials, and he acknowledged there are health inequities and some lack social determinants of health which may result in less access to clinical trials.
- By participating in clinical trials, patients get access to treatments otherwise not available to the public.
    - It takes time to be an active participant.
- Some inconveniences:
    - Need some time off if you are working.
    - Access to big cities to have treatment.
    - Some out-of-pocket costs
- Benefits outweigh the inconveniences involved. He has observed more success with immunotherapy and less side effects.

Final thoughts:

- We are also thankful for the volunteers who participate in clinical trials.
- No-one entering a clinical trial knows what the outcome will be.
- To be eligible for a clinical trial: Safety first for patients.
- Doctors need to have the means to give information about clinical trials, but it is a patient's responsibility to get informed about clinical trials by asking their doctor.
- The government needs to increase visibility about clinical trials, so the accessibility is more anticipated.
- Donate to cancer research (2 in 5 Canadians are expected to develop cancer during their lifetime).
- Inform politicians about the need for funding.

Talk title: CRAFT: Remote Access to Clinical Trials – Health Sciences North and Abroad by Dr. Lacey Pitre, Northeast Cancer Centre; Northern Ontario School of Medicine

- Dr. Lacey Pitre is a medical oncologist from Sudbury, Ontario [Northeast Cancer Centre (NECC)]. Dr. Pitre is a lung cancer expert and a strong advocate for equitable access to cancer clinical trials, leading clinical trials involving breast, lung and head and neck

cancers. She is also an assistant professor at the Northern Ontario School of Medicine and leads the Ontario Health Cancer Care systemic therapy for the northeast Ontario region.

Key takeaways:

- Dr. Pitre is in charge of the NECC- Clinical trials to make sure all cancer patients in Northeastern Ontario get the best care possible
    - Phase IV trials: clinical research conducted after a drug has been approved.
    - Sudbury is the main cancer center for treatment but in this region, there are 12 satellite places to cover the region (hub and spoke model).
        - Patients can get their treatment as close to home as possible.
        - 1 out of every 3 patients are followed-up virtually (virtual care established even before the COVID19 pandemic).
    - Big struggles:
        - Operating clinical trials- currently they have about 20 clinical trials opened.
        - Delays in getting access to the drug due to distance and paperwork involved
        - There is still a lack of research clinical trials involving Aboriginal Communities.
- **What benefit is there for patients to participate in clinical trials?**
    - You will be given the best standard cancer treatment available even if you aren't in the new treatment group.
    - You will be followed up closely during and after the clinical trial.
    - You may be one of the first people to benefit from the treatment.
    - You have the chance to help others and improve the treatment of cancer.
- In order to increase accessibility/benefit to clinical trials for patients living in rural areas, the Canadian Cancer Clinical Trials Network (established in 2014), patients, administrations, and doctors, including Dr. Pitre, created the CRAFT Project.
    - 3CTN: **CRAFT Project** (Canadian Remote Access Framework for Clinical Trials) brings new opportunities for cancer patients residing in rural and remote communities.
        - Pan-Canadian initiative to promote equity in the cancer system, to improve opportunities for clinical trial participation for all eligible Canadian patients.
        - Includes industry, patient representatives, researchers, oncologists, trial coordinators, and administrators.
        - Goal: to address many of the regulatory, ethical, legal, and practical barriers that can impede the conduct of clinical trials in rural and remote communities.

        - 3 Satellites sites across Canada: St. John's (NL), Sudbury (ON), Prince George (BC).
            - Based at Timmins and District Hospital: Pilot CRAFT current clinical trial for lung cancer: Skyscraper-03 (immunotherapy) for unresectable, stage III NSCLC.

Final thoughts:

- What happens to patients in placebo groups? These group of patients still receive the best current standard of care whether that patient is in the placebo group or not, they still get the recommended treatment plan. There are several groups or "arms" in a clinical trial, and a patient may belong in the treatment group, or the placebo group. Clinical trials take place because experts believe that new treatments could be better than the standard treatment, but we don't know at that moment. Sometimes, during a clinical trial, the patient will know to which arm they belong but also, other times neither the patient nor the doctor know this information, and this depends on the type of clinical trial you are engaged in (the latter is called "blind" clinical trial).
    - "Blind" clinical trials are done to avoid experts being biased in their interpretation when following up the disease, for the entire duration of the trial.
        - If tumor progression is seen or the patient is very sick/adverse side effects, the study is "unblind" to help experts to determine possible causes and how to improve future studies.
    - Regardless of the arm a patient belongs to, the patient is contributing to the knowledge and at the same time, getting very good care.
    - Placebo is related to standard treatment and is harmless medication that has no therapeutic effects and is used as a control to see the effects of the new treatment.
- Clinical trials are very costly. Academic clinical trials are very important, they are created by universities and run by the CCTG and need a lot of funding. These trials create more knowledge for future research, independently of industry.
- Based on the feasibility of clinical trial access in remote areas (CRAFT project), more satellite sites could be developed in future, but first the most important is to consolidate the safety for patients.

Talk title: Developing Cancer Therapeutics: A Long Winding Road by Dr. John Bell, BioCanRx; The Ottawa Hospital; University of Ottawa

- Dr. John Bell is a Senior Scientist, Cancer Therapeutics Program (Ottawa Hospital Research Institute, Ottawa, ON) and professor of Medicine and Biochemistry, Microbiology, and Immunology at the University of Ottawa. Dr. Bell is a leader in oncolytic virus research and development and the scientific director of BioCanRx, Canada's immunotherapy

network. Dr. Bell was the winner of the inaugural public and patient engagement award from the European society of gene and cell therapy in 2019, showing his strong dedication to patient involvement and engagement in research.

Key takeaways:

- Standard treatment for cancer Chemotherapy: <u>not specific with a very narrow therapeutic window.</u>
    - Also suppresses the immune system, and "attacks" the normal tissue.
- **Immunotherapy**: more <u>targeted</u> therapy, attacks only cancer cells leaving normal tissue unscathed.
- We have learned over the last 40 years that cancer arises in normal healthy tissues. Cancer cells were normal cells that acquired mutations over the lifetime of a person. If those mutations arise in important genes that control the growth of the cell, ultimately the cell becomes malignant and a dangerous tumor that can spread throughout the body. These mutations allow cancer cells to acquire the ability to be stealth and hide from our immune system.
- Each patient's cancer is genetically unique: we need to create regimes or treatments that allow a therapy to be personalized to an individual patient.
    - We can use each person's immune system to tailor an immune response that's specific for their therapy.
- The era of the living drug.
    - Dr. David Barlett used viruses to treat a cancer patient with advanced disease and observed that in the biopsies of regressing tumors, there were a lot of immune cells but not viruses remaining. The viruses kill tumors, but the immune system avoid cancer cells from coming back.
    - Viruses are an essential part of CAR-T (Chimeric Antigen Receptor) manufacturing. This is an approach to engineer a person's immune system to recognize their cancer as foreign. Immune cells are taken out of the patient and engineered with a virus in the lab, so they now express a new protein on their surface so they can bind to cancer cells specifically and then these cells are put back in the patient. These CAR-T cells will recognize and destroy cancer cells.
        - Ex: First pediatric patient to be treated: Emily Whitehead was treated with CAR technology to treat recurrence of acute lymphoblastic leukemia in 2012. Today she is cancer free (first child enrolled)

Final thoughts:

- Immunotherapy is now commonly used as chemotherapy for almost every type of cancer at this time.
    - Side effects are more under control (ON/OFF) (steroids, long term treatment ex: Tocilizumab, originally designed for rheumatoid arthritis), stop treatment.

- The effect is very fast: important to always talk and follow up with oncologist to avoid collateral damage

SUNDAY, NOVEMBER 21, 2021 (DAY 1)

Plenary Session 1: Advances in Cellular Immunotherapy

Lay Abstract of Plenary Session 1

Using immune cells that are manipulated outside the body before being injected as living drugs, is among the most promising new avenues to treat cancer. This session will feature leading ideas in this field which require deep knowledge of immune cells, expertise to manipulate T cells in the laboratory to enhance their performance against cancer cells (processes collectively known as cellular engineering) and the conduct of innovative clinical trials. Our first speaker, Dr. Stephanie Goff, will discuss how T cells found within the tumor can be manipulated in the laboratory and used as cancer treatment. The second speaker, Dr. Aude Chapuis, will describe her innovative research program, which includes strategies to engineer immune cells so that they recognize blood cancer cells more efficiently after bone marrow transplant. Her integrated work from the laboratory to the patient is a model for those who wish to bring innovations rapidly into the clinic. To complete the session, Dr. Étienne Gagnon, will show how understanding the way immune cells get activated can help in the development of cellular engineering methods capable to improve immune cell function when targeting cancer cells. Our three speakers will discuss three forms of therapies using immune cells and will therefore provide a fairly complete survey of current anti-cancer cellular therapies.

Notes by Vera Samarkina, Lauren Wilkinson, and Rebecca Burchett

Talk Title: The Curative Potential of Tumor Infiltrating Lymphocytes for solid cancer by Dr. Stephanie L. Goff, National Cancer Institute (NIH)

- **Focus of talk**: making tumour infiltrating lymphocyte (TIL) therapy more effective in the treatment of resistant solid tumours by enriching for highly tumour-specific cells ("selected TIL") during manufacturing
- TIL therapy is a form of adoptive cell therapy that uses immune cells found in a patient's own tumour after it has been surgically removed
    - Tumor Infiltrating Lymphocytes, or TILs, are cells that already know how to find the tumour and potentially kill it, but growing them outside of the body for a while helps them to "recharge" and become better cancer killers

Key takeaways:

- TIL therapy has been very successful in the treatment of melanoma

    - It has the potential to become a frontline therapy for treatment-refractory metastatic melanoma
- But most epithelial solid tumours have proven to be much more resistant
    - This is thought to be due to fewer mutations that the immune system can see on the cancer cells when compared to melanoma, which is highly mutated
- Dr. Goff's group has identified one step of the TIL manufacturing protocol as being a major obstacle to successful TIL therapy: identification of tumour-specific TIL after rapid expansion protocol
    - *Rapid expansion protocol* refers to the period of time when the patient's cells are stimulated to grow and divide rapidly in a dish after they've been taken out of the body
    - After this growth period, the scientists need to make sure that the cells they've grown are tumour-specific - this is done by stimulating the cells with tumour antigen in a dish and looking for markers of immune cell activation
    - But, in the case of many epithelial cancers, we don't know which tumour antigens are important for a strong antitumor immune response
- To tackle this, Dr. Goff explained an *unbiased screening approach*, or a way to identify important cancer antigens without knowing exactly what they're looking for
- The way this approach works is by taking a patient's cancer cells, taking out the DNA (the cellular instructions) and comparing this to DNA from the same patient's healthy cells to identify mutations
- The mutations they found were then shown to the patient's immune cells to see which pieces of the "cancer code" could induce a response
- The researchers found that by using this strategy, they were able to generate more tumour-specific TIL and these "selected TIL" were better at inducing long-term tumour-regression in patients with resistant epithelial tumours

Final thoughts:

- This new strategy allows for identification of cancer-specific immune cells from a patient's own tumour that might otherwise not be found
- This might also lead to discovery of new tumour markers that can be targeted using gene-engineered T cell approaches (ex. TCR-T and CAR-T cell therapies)
- Outstanding questions: Is this strategy clinically feasible? Will it be too expensive to analyze each patient's tumour and personalize the manufacturing process? What technology needs to be developed to make this method accessible to patients and health care providers?

Talk title: Learning from Past Experience: Furthering T cell Receptor Gene Therapy by Dr. Aude Chapuis, Fred Hutchinson Cancer Research Centre

- **Focus of talk**: Improving T cell receptor (TCR)-engineered T cell therapies. The T cell receptor, or TCR, is a natural surface protein on a subset of immune cells, called T cells, that allows them to recognize and distinguish unhealthy cells from healthy cells.
- The body doesn't produce many T cells with TCRs that can recognize cancer cells, but you need a lot of cancer-specific cells to get rid of a tumour.
- To increase the number of T cells that have a tumour specific TCR, a new TCR targeting some cancer antigen can be genetically engineered into the T cells in a patient's blood
- This is similar to the process of making CAR-T cells, but may be safer and allow for targeting of a broader range of tumour antigens because the TCR is a natural receptor (vs. a CAR, which is a synthetic/non-natural receptor)

Key takeaways:

Dr. Chapuis broke her talk down into three stories:

Story 1: Choose your target wisely

- Wilm's tumour antigen 1 (WT1) is a marker found on high-grade leukemias
- WT1 can be targeted with a TCR engineered into T cells from healthy donors
    - This kind of T cell product is known as *allogeneic* (not a patient's own cells)
    - This treatment worked to prevent relapse in acute myeloid leukemia (AML) patients who had received a stem cell transplant (*prophylactic* use), but was not effective in treating patients who had already relapsed (*therapeutic* use)
- The Chapuis group found that the tumour cells were outsmarting the T cells by changing the way WT1 was processed and presented, leading to limited T cell persistence
    - T cells only see a small piece of a tumour marker, known as an *epitope*
    - Epitopes are made when proteins go through a cellular shredder, known as a *proteasome,* to generate small fragments that the immune system can recognize
    - The leukemia cells that did not respond to T cell therapy were getting rid of this cellular shredder to prevent the targeted WT1 epitope from being made
    - They found that a different WT1 epitope (a different fragment of the protein) could be made without this cellular shredder - therefore it is a better target for T cell therapy
        - This is where the title of the story comes from - choosing a target wisely means selecting a target that the tumour cannot easily get rid of

Story 2: Targeting Merkel Cell PolyomaVirus (MCPyV)

- Merkel Cell Carcinoma (MCC) is a very aggressive skin cancer with a high mortality rate
- Merkel cell polyomavirus infection causes 80% of cases
    - This works well for immunotherapy because the virus puts its own markers (*viral antigens*) on the infected cancer cells, which can be targeted by T cells

    - One viral antigen in particular, known as T-ag, is <u>required</u> for MCC tumour to survive and proliferate
        - Therefore, the tumour cells cannot get rid of it to avoid being killed by the T cells and is therefore persistently expressed, making it a perfect target
- Dr. Chapuis' group found a TCR that was specific for T-ag expressed on MCC cells
- However, the tumour was still able to outsmart the T cells expressing this TCR
    - Instead of getting rid of T-ag, the tumour got rid of the antigen presentation machinery
    - T cells cannot see the antigen on its own, it must be "presented" on proteins called HLA (*human leukocyte antigen*)
        - Think of the antigen as a piece of art and HLA as the pedestal that the art sits on for viewing
        - The T cells cannot see the art if it's not on the pedestal (i.e. cannot see the antigen if it's not on HLA)
        - So, the tumour cells got rid of HLA to prevent the T cells from recognizing it
- The scientists found that they could overcome this by giving another molecule, called *interferon gamma* (IFNγ), alongside the T cells
    - IFNγ is a cytokine, or immune signaling molecule, that tells cells to express HLA
    - Therefore, the tumour cells were forced to put the tumour antigen on the "molecular pedestal" for the T cells to see again
    - Once the T cells see this, they can start killing the tumour cells

Story 3: The challenge of the tumour microenvironment

- A challenge with TCR-T cell therapies is that the T cells are able to get into the tumour but, once they get there, they aren't strong enough to kill the tumour cells
    - This is because tumour cells have ways of turning the T cells "off" before they can do enough damage
- There are two main types of T cells, called CD8 T cells (killer T cells) and CD4 T cells (helper T cells)
    - Usually, adoptive T cell therapies focus on transferring the killer CD8 T cells, because they are the ones that can kill cancer cells
    - But the helper CD4 T cells to help the CD8 T cells survive, grow, and become effective killers
- Dr. Chapuis explained that by engaging CD4 TCR-T cells alongside the CD8 TCR-T cells, tumour cell killing and persistence of the engineered CD8 T cells in patients can be improved
- Therefore, both the killer and the helper T cells are beneficial in TCR-T cell therapies

Final thoughts:

- Dr. Chapuis' three stories showed how tumours are able change themselves to avoid being killed by TCR-T cells and how these changes can be overcome by modifying the therapy
- Learning how tumours are able to avoid being killed by the immune system will allow us to develop better immunotherapies

Talk title: Chimeric Antigen Receptors: More than the Sum of Their Parts by Dr. Etienne Gagnon, Institute for Research in Immunology and Cancer; Université de Montréal

- **Focus of the talk**: Modifying Chimeric Antigen Receptors (CARs)
- CARs are *receptors* (molecules that allow cells to receive a signal) that have been designed in the lab from different pieces of natural proteins found in the body
    - A "Frankenstein protein"

Key takeaways:

- CARs are modular - each part has a different function
    - The part of the CAR that sits outside of the cell is the antigen-binding domain - this is what binds markers on cancer cells and usually comes from an antibody
    - The signaling domains sit inside of the cell - these tell the immune cell to turn on when the antigen-binding domain binds to a tumour cell
        - A CD3ζ signaling domain is taken from the natural T cell receptor (TCR) to turn the T cell on (signal 1)
        - Costimulatory signaling domains provide a second signal to confirm that the T cell should turn on (signal 2)
- T cells naturally get signal 1 and signal 2 through multiple different receptors, but CARs deliver both signals at the same time
    - Sometimes the combined signal is too strong and causes the T cells to become overstimulated and lose their function (T cell *exhaustion*)
    - Since the CARs are not natural proteins, they are not regulated by natural processes in the cell - this can also lead to uncontrolled "on" signals and T cell exhaustion
- Dr. Gagnon described an alternative approach to designing CARs
    - Instead of sticking many different proteins together to make a single receptor, it can be broken down into different parts that can be naturally regulated by the T cell
- Modular antigen receptor complex (MARC) - a new synthetic tumour antigen receptor that separates the receptor (antigen-binding) domain from the signaling domain
    - The receptor domain is produced as one protein and the signaling domain is produced as a separate protein

    - The two domains interact with each other at the cell membrane to create a functional receptor complex (similar to the natural T cell receptor)
    - MARC receptors are customizable
        - Additional signals can be added to change the message (or the strength of the message) that the T cell receives
- T cells expressing a MARC become activated when they encounter target tumour cells
    - But the MARC does not tell the T cell to turn on when there is no tumour antigen
        - CARs are so active that they can turn themselves on even when there is no tumour antigen - this leads to T cell exhaustion
        - Therefore, MARC signaling is more tightly regulated
- The Gagnon group found that the T cells interpret the "on" signal from the MARC in a way that is similar to an "on" signal through the TCR
    - MARCs induce more natural T cell activation than CARs
- T cells expressing a MARC can respond to repeated tumour stimulation without becoming exhausted
    - This suggests that they may remain functional for a longer period of time, giving them a better opportunity to kill tumour cells

Final thoughts:

- We have a lot to learn from the way immune cells naturally function
- A better understanding of how T cells receive, interpret, and regulate signals through natural receptors will help us build better synthetic receptors
- Outstanding questions:
    - How do you see MARC-T cells fitting into the current cellular immunotherapy landscape?
        - Do you think MARC-T cells would be better for some cancers and CAR-T cells for others?
    - Do you see MARC-T cells as potentially having fewer side effects compared to CAR-T cells?

Plenary Session 2: Approaches to Making Cold Tumors Hot

Lay Abstract of Plenary Session 2

Across an array of tumors, it is now understood that infiltration of a tumor by immune cells is associated with good prognosis, but not a guarantee of treatment success. This idea underlies the terms "hot" and "cold" tumors, which represent tumors infiltrated or not, respectively, with immune cells. Recent research aims at understanding how the infiltration of immune cells into a tumor and their locations within them matter for therapy. Dr. Jeanette Boudreau will discuss how

infiltration and co-infiltration of different immune cells to the tumors and their surrounding regions predict outcomes for patients with cancer, using assessment of tumor spatial biology and natural killer cells to discuss the potential role and function of cells in the tumor environment. Dr. Alexandre Reuben will discuss the immune cells present in lung cancers, the accumulation of the "right" versus "wrong" immune cells and their impact on patient outcomes. The sole presence of large numbers of immune cells ("hot tumor") is insufficient to ensure optimal clinical responses, rather it is essential to recruit the immune cells which are best calibrated to destroy tumors in order to maximize their therapeutic efficacy. Dr. Douglas Mahoney will discuss how anticancer immunity can be influenced by "oncolytic viruses", through infections of cancer and non-cancer cells in the tumor micro- and macro-environment".

Notes by Catherine Wilhelmy and Frédéric St-Denis Bissonnette

Talk title: Identifying Mechanisms of Resistance Through Analysis of the T cell Repertoire by Dr. Alexandre Reuben, MD Anderson Cancer Centre

- T cells have anti-tumour properties and can be «educated» to improve their superpower.
- TILs: tumour infiltrating lymphocytes. Includes T cells, B cells, NK cells, macrophages, etc. Any immune cell retrieved from a tumour.
- Cold tumour: low TILs infiltration & hot tumour: high TILs infiltration.
- T cell response varies depending on heterogenous genomics (T cell receptor [TCR] specificity).
- In summary, figuring out the different resistance mechanisms in adoptive T cell therapy could improve the way T cells use their superpower on cancer.

Key takeaways:

- Dr. Reuben research focuses on characterizing the repertoire of T cells in NSCLC.
- Dr. Reuben provided mainly three mechanisms to explain T cell resistance in NSCLC.
    - ***Mechanism 1***: T cell subset : neoantigen pool ratios in untreated patients
        - Increased clonality (reactivity of the T cells) in uninvolved lung.
        - Majority have unique clonality (about 80%).
        - Correlation was found between T cell clonality and frequency of neoantigen (a new protein found in cancer cells).
        - Patients with high T cell clonality (and neoantigen frequency) have a shorter disease-free survival (measure of time after treatment during which no sign of cancer is found) since it is more challenging to eradicate the tumour.
        - About 10% of those TILs (in this case T cells inside the tumour) recognize tumour antigens. His group found that T cells in uninvolved lung (non-cancerous tissue) are more reactive than these TILs.

        - Therefore, it is important to generate a T cell product that is specifically tumour focused. Those are more cytotoxic which is desired from a clinical point of view.
        - All of the previous points are shifted around in TREATED patients.
            - Namely T cells in tumours are more reactive than those outside the tumour.
            - Thus, the therapy ultimately affects T cells ratio.
    - ***Mechanism 2***: Viral antigens distracts T cells and makes them less efficient
        - T cells are decoyed by viral antigen; cross-reactivity. These T cells were termed by-standard T cells.
        - Patients with T cells that were increasingly susceptible to these viral antigens exhibited the worst clinical outcome (overall survival and recurrence). Varies across patients.
    - ***Mechanism 3***: product expansion ex-vivo (outside the body) insufficient
        - The common method was unable to yield large scale expansion of cellular products for adoptive cell therapy.
        - Leveraging the new T cell expansion protocol titled "T cell 3.0 expansion" yields improved expansion (faster production, greater number of cells yielded, greater diversity) with increased TCR diversity & specificity for tumour specific antigen or neoantigen.
        - Makes use of the three TCR activation signals (#1: TCR act.; #2: co-stim act.; #3: cytokines act.) which allows for high proliferation & expansion of desired product.

Final thoughts:

- Finding a way to focus T cells away from viral antigen could improve clinical outcome.
- Upcoming step is to assess TILs in clinical trials for NSCLC.

Talk title: Non-Cancer Cell Infections Drive Anticancer Immunity After Oncolytic Virus Therapy by Dr. Douglas Mahoney, University of Calgary

- Dr. Mahoney discussed utilizing oncolytic viruses (OV) to turn solid tumours from cold to hot. In other words, can OV increase the infiltration of immune cells into solid tumours.
    - OV are viruses that prefer to infect tumours and kill them in that process.
    - However, some tumours show highly variable infection rates, and the degree of infection does not predict the clinical outcome
- His research focuses on OV that infects non-cancer cells that are close enough to tumours, thereby causing the recruitment of immune cells to the tumour site.

Key takeaways:

- OV infections were found to be present in the lymph nodes, spleen, and tumour perivascular cells.
    - Infection in non-cancerous cells contributes to the anti-tumour immunity.
- Dr. Mahoney used an OV example (vesicular stomatitis virus**;** VSV) that targets perivascular cells. Perivascular cells were prominently found in tumour vasculature.
    - The OV-VSV effect at the target cell's location allows for the recruitment of immune cells (by secreting chemokines) which now are in very close proximity with the tumour.
    - This virus also targets human pericytes but not mice pericytes. Therefore, mice are less responsive to VSV therapy.
    - Analogy: using a flare gun to designate nearby tumour location.
- In vivo work using mice confirmed in vitro results EXCEPT for the replication of the OV in the perivascular cells.
- These OV can improve CAR-mediated therapy via immunogenic cell death.
- In a way, OV can "jump start" the immune system to upregulate the anti-tumour immunity which is characterized by increased cytokines secretion which recruits immune cells to the tumour location.

Final thoughts:

- Next step is to further engineer the OV-VSV to target mice pericytes to preserve the close tumoural proximity, warming up the tumour (increased TILs count).

Talk title: Natural Killer Cell Diversity Predicts the Immune Contexture and Outcomes for Patients with Ovarian Cancer by Dr. Jeanette Boudreau, Dalhousie University

- NK cells are an incredible cellular Swiss pocketknife, however, not all NK cells are the same. In fact, we know a lot less about the different subtypes of NK cells comparatively to T cells. More work is to be done in that aspect and Dr. Boudreau's work investigates CD16 and CD73 expression NK cells.

Key takeaways:

- High-grade serous carcinoma (HGSC) accounts for 80% of ovarian cancer.
- The presence of NK cells in tumours is a good prognostic sign. These cells have innate ability against cancer, so there is no need to educate them against cancer.
- Part of the research from her lab is to investigate whether CD16 (a cell surface tag/marker) can predict the outcome of adoptive NK cell therapy in HGSC.
    - CD16 is a marker involved in NK-mediated antibody-dependent cell-mediated cytotoxicity (ADCC). High CD16 expression was found to indicate a better prognosis. Dr. Boudreau explained that NK cells are able to infiltrate solid tumours using different patterns of infiltration.

    - Non-infiltrated, intrastromal infiltration and intraepithelial infiltrated; the latter two accounts for 95% infiltration success.
- CD16+ and CD16- NK cells have opposing impacts in HGSC prognosis.
    - T cells and macrophages co-infiltrated the tumours alongside CD16+ NK cells.
    - CD16- NK cells do not co-infiltrate with other TILs.
- CD16+ NK cells were also found to be CD73-, inverted pattern of expression.
    - This cell surface tag/marker presence on NK cells is detrimental for the anti-tumour immunity since it reduces the NK cells activity.
    - CD73's role is to limit excessive immune response and has been associated with poor prognosis.

Final thoughts:

- NK cells phenotypes and infiltration patterns can predict the clinical outcome for patients with HGSC, but the subset needs to be considered.
    - Dr. Bordeau proposes CD16+/CD73- NK cells as a biomarker for improved prognosis and CD16-/CD73+ as a biomarker for reduced NK cells activity since it aids in establishing an immunosuppressive microenvironment.

MONDAY, NOVEMBER 22, 2021 (DAY 2)

Plenary Session 3: Advances in Pediatric Immunotherapy

Lay Abstract of Plenary Session 3

While over 80% of childhood cancers are manageable with conventional chemotherapy, radiation and/or surgery, for many kids these treatments create debilitating life-long side-effects and for others still they simply do not work. In 2018, Health Canada's approval of the first Chimeric Antigen Receptor (CAR) T cell therapy for a form relapsed or refractory acute lymphoblastic leukemia (ALL) ushered in a new era for treating pediatric cancer in Canada, using immunotherapy. In this plenary, our speakers and moderators will discuss the successes, failures and unique challenges associated with developing immune-based therapies for children with cancer. Dr. Joerg Kruger will open the session by providing an update on the Canadian experience with CD19-CAR T cell therapy for pediatric blood cancer and advances in CD19-CAR T cell research. Dr. Michel Duval will then discuss innovative research of a different form of cellular immunotherapy for pediatric cancer, using plasmacytoid dendritic cells (pDC) to condition tumours for anticancer immunity. And finally, Dr. Laura Donovan will present new research on the prospects and unique challenges associated with developing cellular immunotherapy for pediatric brain cancer.

Notes by Vera Samarkina, Lauren Wilkinson, and Rebecca Burchett

Talk title: Therapeutic Inducers of NK cell Killing (ThINKK): New Weapons Against Childhood Cancers by Dr. Michel Duval, Université de Montréal; CHU Sainte-Justine

- **Focus of the talk**: Inducing NK-cell mediated tumor killing following stem cell transplantation
- Some people with leukemia will undergo a stem cell transplantation
    - Stem cells are cells found in the bone marrow and the bloodstream that develop into various types of cells that have different jobs
    - A stem cell transplantation is used to replace the healthy blood-forming stem cells that have been destroyed by high doses of chemotherapy

Key takeaways:

- Following a stem cell transplant, the transplanted T cells and natural killer (NK)-cells in particular mediate anti-tumor effects
    - NK cells are the assassins of the innate immune system
    - They are very good at finding and killing unhealthy cells
    - They are a little different from T cells, which are part of the adaptive immune system
        - T cells see "sick" cells when they express very specific markers
            - These markers are different between different individuals and different diseases
        - NK cells see "sick" cells based on more general markers of cell health
            - From person to person, these markers are mostly the same
- However, leukemia cells evade early graft vs. leukemia (GvL) effect due to their resistance to NK cell killing
    - GvL is an important phenomenon where the donor stem cells have the ability to produce an immune response against the recipient leukemia cells
- To decrease the rate of relapse of acute lymphoblastic leukemia (ALL) following a stem cell transplant, the NK cells need to be able to kill the leukemia cells
- Dr. Duval found that *plasmacytoid dendritic cells* (pDCs) help overcome ALL resistance to NK cell mediated tumor killing
    - pDCs are a special subset of innate immune cells that circulate in the blood and can be found in tissues like the spleen and lymph nodes
- However, pDCs make up a very small proportion of the blood (they are rare)
    - Instead of taking these cells directly from the blood, the scientists took hematopoietic stem cells (the stem cells that create all blood cells)
    - The stem cells were given specific growth factors and immune signaling molecules in a dish to force them to become pDCs
        - This was successful and made it easier to get enough pDCs for the experiments

- Stem-cell derived pDC analogs are cytokine producers (interferon alpha), not antigen presenters
    - This means that they mainly provide "help" to the T cells by producing immune signaling molecules that regulate their growth and differentiation, instead of showing them tumour proteins and activating them
    - They also do not exacerbate graft vs. host disease (GVHD) in mice
        - GVHD occurs when transferred cells from a stem cell donor begin to attack the recipient's healthy tissues
        - This is because the donor's cells see the recipient's tissue as foreign and begin to mount an immune response
        - This is a large obstacle to stem cell transplant because recipients have to take drugs that suppress the immune response in order to avoid GVHD - but this also suppresses the anti-tumour immune response
- Overall: Adoptive transfer of human pDC analogs controls ALL after hematopoietic transplantation in mice
- Next steps: Conduct a clinical trial

Final thoughts:

- The adoptive transfer of human *plasmacytoid dendritic cells* (pDCs) has the potential to strengthen NK cell mediated tumor killing and decrease Acute Lymphoblastic Leukemia relapse following stem cell transplant

Talk title: Locoregional Delivery of CAR T cells as an Effective Treatment Against Recurrent Medulloblastoma and Ependymoma by Dr. Laura Donovan, UCL Great Ormond Street Institute of Child Health

- Novel approach to treat pediatric brain tumors (Group 3 medulloblastomas and PFA ependymomas)
    - Posterior fossa A (PFA) ependymomas are lethal malignancies of the back of the brain that commonly occur in young children
    - Group 3 medulloblastomas are highly malignant brain tumors that are commonly seen in pediatric patients
- Brain tumors are difficult to treat, as therapies have to cross the blood brain barrier
    - The blood brain barrier is a semipermeable barrier that protects the brain
- Focus of the talk: Using CAR-T cells to circumvent inter-patient and intra-patient variability and successfully bypass the blood brain barrier to target medulloblastomas and ependymomas

Key takeaways:

- There are specific proteins that are consistently expressed across medulloblastomas and ependymomas
    - These proteins can be targeted using CAR-T cells
    - In pediatric Group 3 medulloblastomas, EPH receptor A2 (EPHA2) is consistently expressed. EPHA2 is a receptor that has been implicated in mediating developmental events, particularly in the central nervous system
    - In ependymomas, three targets are consistently expressed
        - IL-13Rα, HER2, and EPHA2
- Dr. Donovan therefore made CAR-T cells targeting EPHA2 to treat pediatric Group 3 medulloblastomas, and TRI-CAR T cells that target three different antigens to treat pediatric PFA ependymomas
- Delivery of CAR-T cells directly into cerebrospinal fluid, a liquid found in the brain and spinal cord, increases exposure of CAR-T cells to pediatric PFA ependymomas and Group 3 medulloblastomas
    - Better than intravenous administration, which is the common mode of CAR-T cell administration
- Repeat administration of CAR-T cells targeting proteins expressed on pediatric PFA ependymomas and Group 3 medulloblastomas increases the efficacy of the CAR-T cell therapy
- Co-administration of Azacitidine, a cytotoxic chemotherapy drug, and CAR-T cells, for the treatment of pediatric PFA ependymomas and Group 3 medulloblastomas, results in synergistic effects
    - This mechanism is the focus on future experiments in Dr. Donovan's lab

Final thoughts:

- Current treatments for pediatric PFA ependymomas and Group 3 medulloblastomas, such as chemotherapy and radiation, impact pediatric brain development
- This technology has the potential to improve cure rates and as well as improve the quality of life for surviving patients by reducing these impacts on normal child brain development

Talk title: Locoregional Delivery of CAR T cells as an Effective Treatment Against Recurrent Medulloblastoma and Ependymoma by Dr. Laura Donovan, UCL Great Ormond Street Institute of Child Health:

- Acute lymphoblastic leukemia (ALL) is the most common malignancy in children
    - It is a type of cancer of the blood and bone marrow
    - Once it has relapsed it becomes very hard to treat
- CD19 Chimeric antigen receptor (CAR) T cell therapy has achieved great clinical efficacy in the treatment of relapsed ALL

- CD19 CAR-T cell therapy is an immunotherapy that involves the adoptive transfer of T cells that have been genetically modified with a chimeric antigen receptor to target cancer cells expressing CD19
- CD19 is a protein marker commonly expressed on B cells. It is also marker of B-cell malignancies, as the majority of B cell malignancies express normal to high levels of CD19

Key takeaways:

- CD19 CAR-T cell therapy has been very successful in the treatment of relapsed pediatric Acute Lymphoblastic Leukemia (ALL), with remission rates of 81%
- Due to the success of CAR-T cell therapy, fewer children are receiving transplants.
    - Instead, CAR-T cell therapy is being used earlier, thus decreasing the occurrence of chronic health conditions caused by radiation and high-dose chemotherapy in children
- CD19 CAR-T is also safe and efficacious for use in hard-to-treat populations, such as children with Down Syndrome who have relapsed or/and refractory ALL
- There are challenges associated with the use of CD19 CAR-T cells in children:
    - First of all, obtaining CAR-T cells remains a challenge for some patients.
        - CAR-T cell manufacturing sometimes fails and bridging chemotherapy – which helps to prevent rapid disease progression prior to CAR-T cell infusion, doesn't always work.
    - Second of all, CD19 negative and positive relapse sometimes occurs following CAR-T cell therapy
        - CD19 negative relapse results when tumor cells downregulate the CD19 target to evade the CAR-T cells
        - CD19-positive relapse is associated with a failure of the CAR-T cells to persist in the body following infusion
- Solutions to the aforementioned challenges
    - To overcome difficulties in CAR-T cell manufacturing, off-the shelf allogeneic CARs could be used.
        - Allogeneic, or universal, cell therapies rely on a single cell source, usually a master cell bank, to treat patients
        - When this was tested in human patients, increased toxicity was observed.
        - However, this off-the-shelf allogeneic CAR-T cell therapy remained effective, achieving an 82% complete remission rate upon co-administration with alemtuzumab
            - Alemtuzumab is a monoclonal antibody, another type of immunotherapy that helps the immune system attack cancer cells

        - A very immunosuppressive environment does need to be created to facilitate allogeneic CAR-T cell expansion
    - To overcome the issue of CD19 negative relapse, which occurs in ⅔ of the relapse cases, bi-specific CAR-T cells may be used instead of the single target CD19 CAR-T cells
        - Bispecific CAR-T cells target two tumor antigens at once
    - To overcome CD19 positive relapse, which sometimes occurs following CAR-T cell therapy when the CAR-T cells fail to persist, multiple solutions have been proposed
        - A) Simple re-infusion of CAR-T cells
        - B) Use of another type of therapy (as long as the tumor is not refractory to other treatments)
        - B) Use of low affinity CARs instead of the current CD19 CAR-T cells
            - Low affinity CARs have been found to exhibit better proliferation and improved CAR-T cells persistence

Final thoughts:

- Children are not little adults and therefore what works in adults is not guaranteed to work in children
- More work needs to be done to learn about how children respond differently to CAR-T cell therapies so that these therapies can be modified with pediatric patients in mind

Oxford-Style Debate: Who is Driving the CAR: NK cells vs T cells

Lay Abstract of Oxford-Style Debate

Adoptive T-cell therapy, also known as CAR T cells, have become a standard of care in certain types of blood cancers because of their impressive clinical activity. CAR stands for chimeric antigen receptor, meaning it is receptor, engineered by man, which allows the cell to target a specific protein (called ab antigen) present on a cancer cell and they are chimeric because this receptor is linked to a protein inside the cell that activates the killing function of the cell. This makes the T cell a highly effective killer against any cell that expresses the cancer-specific antigen. Currently this treatment involves taking T cells from a patient, engineering them with the CAR receptor, expanding the T cells to increase their number, and then infusing them back into the patient. While the therapy has unprecedented success in the clinic, it can be associated with significant toxicity, including a life-threatening complication called cytokine release syndrome (CRS). Natural Killer Cells (also called NK cells) are a slightly different kind of killer cell of the immune system that can also be engineered with a CAR. It has not been as well studied as the CAR T cell, but some scientists and clinicians believe it has real advantages over the current standard CAR T cell standard. Which CAR cell is better for adoptive immunotherapy and why will be fiercely debated in this session.

Motion: Be it resolved that: When it comes to driving the CAR, T cells are better than NK cells

Notes by Catherine Wilhelmy, Frédéric St-Denis Bissonnette, Colleen Tkachuk and Galaxia Rodriguez

Talk title: FOR (CAR T cells) by Dr. Jean-Sébastien Delisle, Hopital Maisonneuve-Rosemont - CIUSSS-EMTL

- Dr. Delisle makes the comparison that T cells are like a 2021 Ferrari and that NK cells are like T-Ford 1920.
- Numerous possibilities for CAR-T cell improvement.

Key takeaways:

- CAR-T cells have a proven track record with practical experience in the manufacturing and administration to patient.
- Dr. Delisle makes the point that the actual driver of CAR-mediated therapy field is going to be T cells.
    - He acknowledges the roles of NK cells or other immune cells in CAR therapy.
- Dr. Delisle mentions the advantageous leverage of the TCR and the vast selection of T cell subtypes with the possibility of various differentiation suggesting many variables to work and improve upon.
- T cells (cells used to make the CAR-T cell product) are abundant and obtainable from various sources. They also are relatively easy to expand compared to NK cells.
- CAR-T cells are associated with some serious and dangerous toxicities, although manageable. Work is currently on-going to address these shortfalls.

Final thoughts:

- Argument: better to start with the Cadillac of immune cells and there is a lot of room to play with in order to improve CAR-T cell therapy.

Talks: AGAINST (NK cells) by Dr. Michele Ardolino, Ottawa Hospital Research Institute; University of Ottawa

- NK cells are Natural Born Killer cells of the immune system that can also be educated following genetic engineering.
- Recent developments and most promising immune cell mediated CAR therapeutic.

Key takeaways:

- Dr. Ardolino makes the point that scientists have the responsibility to look for innovation and future advances.
- Dr. Ardolino acknowledged the incredible track-record of CAR-T cells.
- Three main problems with CAR-T cells that are not shared with CAR-NK cells.
    - Safety issue, not off-the-shelf and antigenic escape.

- Dr. Ardolino also acknowledges that CAR-T cells have been dominating the field for now and he makes the point that CAR-NK cells are still in their infancy, although this field has been exploding in popularity over the past few years.
- In regard to solid tumours, CAR-NK cells have shown more promising results comparatively to CAR-T cells.
- If you had to pick one, why CAR-NK cells?
    - Better safety profile.
        - No indication of CRS in pre-clinical trial models or clinical trials.
            - CRS (Cytokine Release Syndrome) is a serious side-effect too often associated with CAR-T cells therapy.
        - No indication of neurotoxicity (ICANS; Immune effector cell-associated neurotoxicity syndrome), even after intracranial injection.
        - NK cells have limited lifespan (which might be desired) and have a much lower risk of causing graft-versus-host disease (GVDH).
        - In short. increased safety = saves more life and money.
    - Off-the-shelf option.
        - Allogeneic product (the same product can be administered to various patients).
        - Various sources: PBMCs, cell line (predominantly NK92), cord blood and iPSC (induced pluripotent stem cell).
    - Versatile killing abilities.
        - Naturally expresses killer proteins that do not require the “CAR”.
        - Natural cytotoxicity against cancer cells.
        - The collection of all the various killer proteins outweighs the TCR.
- Dr. Ardolino acknowledged the current limitation with CAR-NK.
    - Mainly CAR introduction (various means), expansion protocols (they don't proliferate as much as T cells) and persistence in vivo (last 1-2 weeks; short therapeutic window).

Final thoughts:

- We know a lot more about T cells at the moment, but the NK field is catching up and it is believed that we will be able to generate a superior CAR product using NK cells
- Exciting innovations are upcoming in the CAR-NK field.

Helpful Websites

BioCanRx Cancer Stakeholder Alliance
https://biocanrx.com/about/governance/cancer- stakeholder-alliance

BioCanRx-Cancer Stakeholder Alliance Learning Institute
https://biocanrx.com/about/governance/cancer-stakeholder-alliance/biocanrx-cancer-stakeholder-alliance-learning-institute

BioCanRx's Patient Section
https://biocanrx.com/patients/about-biotherapeutics

Canadian Cancer Society
http://www.cancer.ca/en/research-horizons/e/c/9/immunotherapy-promising-new-field-treatment/

Clinical Trials http://www.canadiancancertrials.ca/
and https://www.cancer.gov/aboutcancer/treatment/clinical-trials/advanced-search

Leukemia and Lymphoma Society of Canada
http://www.llscanada.org/treatment/types-of-treatment/immunotherapy

NCRI Consumer Forum
https://www.ncri.org.uk/

Society for Immunotherapy of Cancer patient glossary:
http://www.sitcancer.org/patient/glossary

Society for Immunotherapy of Cancer patient resource:
http://www.sitcancer.org/patient/resources

US American Cancer Society
https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/what-is-immunotherapy.html

US Cancer Research Institute
https://www.cancerresearch.org/immunotherapy/what-is immunotherapy

US Cancer Support Community
https://www.cancersupportcommunity.org/immunotherapy-cancer-it-right-you