# 2023 Community Dissemination Report

## BioCanRx-Cancer Stakeholder Alliance Learning Institute

*A Summary of Current Immunotherapy Research discussed at the 2023 BioCanRx Summit for Cancer Immunotherapy*

*Written by: Participating Learning Institute Patients and Caregivers, in Collaboration with Early Career Researchers*

# Table of Contents

December 2023

# Welcome

## From BioCanRx

We are proud to share this publicly available Community Dissemination Report written by the participants of the 2023 BioCanRx-Cancer Stakeholder Alliance Learning Institute. We are very happy to have hosted the Learning Institute at the 2023 Summit for Cancer Immunotherapy (Summit4CI) from October 1st – 4th, in Ottawa, Ontario. We would like to thank the BioCanRx staff and the CSA-LI Working Group for planning and facilitating an amazing event. We would also like to congratulate the Learning Institute participants for bringing such enthusiasm and commitment in completing this program.

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-aways 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, Cancer Stakeholder Alliance, and general public.

We look forward to hosting another successful event in the future. You can learn more about the Summit4CI at www.cancersummit.ca.

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

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

**Stéphanie Michaud, Ph.D.**
President and CEO,
BioCanRx

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

## From the BioCanRx 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:

- Create a model of learning that encourages, supports, and facilitates the integration of patient leaders into the annual BioCanRx Summit for Cancer Immunotherapy (Summit4CI);
- Integrate the patient/caregiver perspective to ensure that cancer research is well informed by the patient voice and lived experience;
- 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 Summit4CI and learn from each other through a bi-directional exchange of information during the conference.

Trainees 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 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 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 through initiatives like the Learning Institute.

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

# 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 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.

## Development of the Learning Institute

This year's Learning Institute was designed by the 2023 BioCanRx-CSA Learning Institute Working Group and BioCanRx staff using the feedback obtained from last year's initiative.

*Table 1: Members of the 2023 BioCanRx-CSA Learning Institute Working Group*

| **Members:** |
| --- |
| **Paul O'Connell, Co-Chair**<br>The Leukemia & Lymphoma Society of Canada (LLSC)<br><br>**Patrick Sullivan, Co-Chair**<br>Team Finn<br><br>**Catherine Wilhelmy**<br>University of Sherbrooke, CIUSSSE-CHUS, Patient Scholar Advisor<br><br>**Chantale Thurston**<br>AYA Can, Patient Scholar Advisor<br><br>**Lorenzo Lindo**<br>BC Cancer Research Centre, Academic Scholar Advisor<br><br>**Sarah Hunt**<br>Hunt4cure, Patient Scholar Advisor<br><br>**Shannon Snelling**<br>University of Calgary, Academic Scholar Advisor |
| **BioCanRx Staff:** |
| **Laurie Cameron**<br>Manager, Knowledge Mobilization and Training Programs, BioCanRx<br><br>**Megan Mahoney**<br>Director, Scientific Affairs and Training Programs, BioCanRx<br><br>**Sasha Patacairk**<br>Knowledge Mobilization Intern, BioCanRx |

# Interested in Participating?

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

## 2023 Learning Institute

This year's initiative brought together seven Patient Scholars from the cancer patient/caregiver community, and eight Academic Scholars from the BioCanRx trainee community. Participants came to the Learning Institute from coast to coast across Canada and beyond to represent a diverse range of research and life experiences.

*Figure 1: 2023 BioCanRx-CSA Learning Institute participants*

Together, Learning Institute participants participated in a series of interactive and collaborative "Knowledge Exchange sessions" that enabled them to process and share knowledge based on research being presented at the conference. These high-energy sessions included small group discussions followed by group presentations highlighting the accessibility, science, and key takeaways from the talks.

*Figure 2: A collage of photos from the Learning Institute Knowledge Exchange Sessions*

*Table 2: Full List of the participants in the 2023 Learning Institute*

| **Patient Leaders/Caregivers who participated as "Patient Scholars":** | |
|---|---|
| **Dan Albas**<br>**Melinda Bachini**<br>**Amy Clark**<br>**Thomas Flannery**<br>**Nadine Frisk** | **Lucie Lacombe**<br>**Camille Leahy**<br>**Peggy Pickett**<br>**Randy Thompson** |
| **BioCanRx Trainees who participated as "Academic Scholars":** | |
| **Nawal Amhis**<br>**Farah Alam**<br>**Victoria Gilchrist**<br>**Bryan Marr**<br>**Allyson Moore** | **Lauralie Short**<br>**Kesia Titosky**<br>**Sydney Vallati**<br>**Tian Zhao** |
| **CSA Learning Institute Working Group members who participated as "mentors":** | |
| **Paul O'Connell, Co-Chair**<br>The Leukemia & Lymphoma Society of Canada (LLSC)<br>**Sarah Hunt**<br>Patient Scholar Advisor<br>**Lorenzo Lindo**<br>Academic scholar Advisor | **Shannon Snelling**<br>Academic Scholar Advisor<br>**Chantale Thurston**<br>Patient Scholar Advisor<br>**Catherine Wilhelmy**<br>Patient Scholar Advisor |
| **BioCanRx Staff who participated as a "facilitator":** | |
| **Sasha Patacairk**<br>Knowledge Mobilization Intern | |

## Dissemination Report Details

The Learning Institute key take-away messages and group reflections from select plenary session at the 2023 Summit4CI can be found below.

This report also includes takeaways from the pre-Summit Public Forum, which occurs annually in advance of the Summit4CI.

This conference was held from October 1st – 4th in Ottawa, Ontario. An overview of the plenaries that will be covered in this report can be found below:

To learn more about the Summit and to view the full program, please visit http://www.cancersummit.ca/. You can also learn more about the 2023 Learning Institute experience from a Patient and Academic Scholar in the BioCanRx December newsletter.

## 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.

CIHR IRSC Institute of Cancer Research Institut du cancer

We would also like to extend a big thank you to Canadian Institutes of Health Research's' Institute of Cancer Research for being a proud supporter of the Learning Institute initiative.

## Plenary Session 1: Extracellular Vesicles – An Emerging Nanoplatform for Cancer Diagnosis and Therapeutics

*Notes contributed by: Amy Clark and Tian Zhao*

**Lay Summary of Plenary 1:**
Imagine millions of tiny bubbles zipping around your bloodstream, carrying crucial messages from cell to cell. These mini messengers, known as extracellular vesicles, are small bubble-like structures released by cells. They work like our body's postal system, transporting proteins and genetic information that help cells function and communicate. These extracellular vesicles are found all over the body, playing crucial roles in maintaining health, but they can also be implicated in spreading diseases, including cancer. Scientists have realized that if these vesicles can transport harmful materials, perhaps they can be harnessed to transport beneficial ones as well, such as tools to detect and treat diseases like cancer.

Researchers are now not only studying these naturally occurring vesicles, but they are also creating artificial ones - imagine small, synthetic bubbles that can be programmed with specific missions, such as destroying cancer cells or alerting the immune system to fight off a disease. In this plenary session, we will explore how these extracellular vesicles can be loaded up with therapeutic drugs and dispatched as mini medical delivery vans. This novel approach could revolutionize the way we treat cancer and other diseases. Join us to discover more about this exciting field.

**Focus of the Plenary:**
The opening plenary was an introduction to the use of extracellular vesicles (EVs), “lipid bobbles” naturally derived from cells, to enhance the immune system and restrict tumor growth and metastasis.

Traditional cancer therapies of chemotherapy, radiotherapy, and surgical intervention have been mainstay approaches to cancer treatment for years. It's only recently with much focused research that different avenues, such as EV-based therapies, are showing promise.

EV-based therapies address the challenges to deliver cancer-fighting compounds to cancer cells and have the potential to one day offer low-toxic treatment options to cancer patients, who are deeply concerned with quality of life issues after conventional treatments.

## 1. Raghu Kalluri's Talk: Novel Approaches to Treatment of Pancreatic Cancer

**Key Takeaways:**
The human body has a system of delivering proteins, lipids, and genetic materials to various areas within itself using microcarriers called EVs, which are lipid membrane-bound vesicles that are secreted by cells. Exosomes are one form of EVs: they travel through blood and can be taken up by cells in other organs.

There are significant challenges in the treatment of pancreatic cancers. From late-stage diagnosis to real challenges in treating the tumor, these issues have resulted in a very high mortality rate for this cancer.Fortunately, recent studies in animals showed that exosomes can be used to treat pancreatic cancer. There is evidence that the exosomes can pass into cancer cells and deliver an anti-tumor "payload" into tumors in the pancreasIn one series of studies, exosomes were manipulated to carry cancer-fighting agents to pancreas cancer cells.

Exosomes can carry engineered RNA molecules, which silence genes (e.g. KRAS and G12D) crucial for the replication and survival of cancer cells, making exosomes a new avenue of targeted cancer therapy. Animal studies found that exosomes carrying RNA molecules targeting KRAS and G12D accumulate in pancreas tumors and reduce their growth.

On the other hand, exosomes can deliver immune-strengthening agents, such as STING agonists or IL-12, to stimulate anti-tumor immune response in the tumor.

A similar approach to this is to create artificial lipid vesicles that resemble exosomes to deliver bio-active agents, these artificial vesicles are chemically modified to release content only in tumors to enhance specificity and lower toxicity.

This emerging therapeutic strategy will be under investigation for its efficiency and safety in humans.

## 2. Enzo Baracuhy's Talk: Elucidating the Role of Non-replicating Particles in Bovine Herpesvirus-1 Immunotherapy

**Key Takeaways:**
Oncolytic viruses (OVs) are viruses that selectively infect the tumor and then subsequently kill cancer cells. Because of this ability, they have emerged as a viable cancer therapeutic option.

Bovine herpesvirus-1 (BHV-1) is one such OV: introducing this therapeutic virus into the body causes tumor infection and thus allows the immune system to locate and kill cancer cells.

The study found that BHV-1, even when inactivated can suppress cancer cell growth as much as live BHV-1 can. This finding suggests that it may be possible to use an inactivated oncolytic virus to treat cancer, which improves safety.

While this research is now in vivo (being studied at the cellular level), the results look promising. Injecting inactivated BHV-1 resulted in the remission of the tumor in one of the experimental

mice. A promising result indicates that inactivated BHV-1 may be a viable approach to treat cancer.

However, this is a new area of research and further research is needed to confirm the efficacy of the therapy.

## 3. Janusz Rak's Talk: Impact of Oncogenes on Blood Vessel Regulating Cancer Nanosphere

**Key Takeaways:**
The genes that regulate and control the growth and replication of cells can become mutated. These mutated genes are referred to as oncogenes and are instrumental in the creation of tumor cells and ultimately cancers.

Oncogenes can be transferred between cells via EVs and the transfer of oncogenes into cells renders the cells cancer-like. These oncogenes carried by EVs are termed extracellular oncogenes.

One of the extracellular oncogenes is EGFR-VIII. Not only does the transfer of EGFR-VIII induce cancer, but it also stimulates the growth of blood vessels in the tumor, which feed tumor cells and suppress the anti-tumor immune response. However, the molecular mechanism behind this is still not understood.

Interestingly, EGFR-VIII-induced blood vessel growth can be inhibited by Dacomitinib (DAC). Therefore, this drug may be used to suppress the vascular network required for tumor growth.

This is an emerging field of discovery, but understanding the extracellular oncogenes can help develop targeted therapies for cancer treatment.

**Final Thoughts on Plenary 1:**
It was very exciting to hear about the emerging areas of research. Traditional cancer treatments like chemotherapies are very toxic to the patients, leaving with them a myriad of post-treatment issues that can severely hamper the quality of life. New treatment options with low toxicity and better quality of life are required.

Research shows that there are many forms of intervention possible. The actual delivery of tumor-fighting and immune-enhancing agents can be engineered and optimized to offer treatments for many cancers.

Traditional treatments like chemotherapy, while initially effective, are limited by their high toxicity and tumor resistance. These EV-based therapies offer the hope for an enhanced delivery of the required (and newly discovered) compounds with a low impact on patients' quality of life.

The hope for the reduction of the toxicity of cancer treatments is what patients desperately need. Any improvement that brings a better quality of life for surviving patients is a hope for others who follow a similar patient journey.

The hope is on the horizon!

## Plenary Session 2: Novel Targets and Immunotherapy Approaches

*Notes contributed by: Thomas Flannery and Farah Alam, Dan Albas and Victoria Gilchrist*

**Lay Summary of Plenary 2:**
Cancer cells acquire the ability to replicate, spread, and resist being killed. Many of the molecular changes in cancer cells can, however, be detected by immune cells and further targeted by immunotherapies. This plenary session will explore some of the ways T cells (immune cells) can recognize cancer cells and how immunotherapies can enhance cancer visibility to the immune system. During the session, the speakers will talk about a kind of treatment called oncolytic viruses (OVs). These good, therapeutic viruses can use the weaknesses in cancer cells to target and destroy them, which is a type of immunotherapy. OV infection exposes both virus and tumour components to the immune system, and both virus-specific and cancer-specific T cells are stimulated by therapy. Understanding how this happens will help us design novel strategies that preferentially direct the immune response toward the tumour rather than the virus.

In addition to reporting new research on OVs, this plenary session will explore how T-cells can recognize different types of cancer cell-specific alterations including 1) neoantigens, which are altered proteins originated from mutated genes (aka neoantigens), and 2) glycans, which are cell surface carbohydrate (sugar) molecules that can change form and increase dramatically in abundance on cancer cells. Glycans interact in a very specific (lock and key) manner with other proteins call lectins. Identifying lectins on immune cells that can interact specifically with cancer cell glycans, can help us to design better cancer immunotherapies. Finally, we will learn about new ways that we can use synthetic receptors called chimeric antigen receptors (CARs) and vaccines to create stronger immune cells.

**Focus of the Plenary:**
The NIH has defined cancer as – “a disease in which some of the body’s cells grow uncontrollably and spread to other parts of the body”. Cancer cells have unique abilities to grow and evade the body’s immune system, from developing their own blood supply (angiogenesis), to evading immune cells, to evading check point inhibitors. They by and large grow uncontrollably and are immune from the body’s natural defense mechanisms unless we can develop treatments to overcome these tumour defenses.

Plenary Session 2: Novel Targets and Immunotherapy Approaches, through the use of oncolytic viruses as a vaccine for the treatment of pancreatic cancers, looking at oncolytic viruses and CAR T cell therapy to examine heterogeneity and how to extend the effectiveness of CAR T cell therapy. Examining the role that cell communication imparts into the effectiveness of the immune system. How the use of TIL's (tumour infiltrating lymphocytes) can enhance the immune response and how engineered CAR-T therapy can increase the effectiveness and spectrum of treatment against melanoma.

1. **Dmitriy Zamarin's Talk: Overcoming Adaptive Immune Response Heterogeneity with Oncolytic Viruses**

**Key Takeaways:**
The session began with a talk by Dr. Dmitriy Zamarin from the Tisch Cancer Institute, Mount Sinai, discussing heterogeneity in ovarian cancer and the use of oncolytic viruses and CAR T therapy. Heterogeneity can be likened to a jar of M&Ms, where the chocolates come in various colours, each subtly distinct but still identified as M&Ms. Now, imagine cancer cells of the same type, but distant from the original mass, akin to the diverse colors of M&Ms, these cells are slightly different (mutated) but are the same underlying cell type. Through the use of oncolytic viruses and using CAR T cells, they demonstrated that they could affect an enhanced immune response not just against the original cancer site, but also at the site of the metastasis. One treatment to recognize the heterogeneity of these ovarian cancer cells and to be effective against each.

2. **Matthew Macauley's Talk: Immunomodulatory siglecs: Fundamental Roles in Immunity and Therapeutic Opportunities**

**Key Takeaways:**
The talk by Dr. Macauley, University of Alberta discussed SIGLECs and how these function as receptors on immune cells and contribute to the selective nature of cell to facilitate or supress these immune cells response to tumours. SIGLECs can facilitate receptors for both pathogens and immune cells. Understanding how a small change with respect to SIGLECs and their receptors could have a huge impact on the effectiveness of how the immune system recognizes cancer cells and its ability to attack these cells.

3. **Rebecca Burchett's Talk: Evaluating a Paired Universal Synthetic Receptor-Rhabdovirus Vaccine System to Boost Adoptive T-cell Therapies for Cancer**

**Key Takeaways:**
Rebecca Burchett, Doctoral student from McMaster University, discussed the challenges that adoptive cell therapies like tumour-infiltrating lymphocyte (TIL) therapy face in being able to persist within a tumour because of a lack of survival signals and dealing with an immune inhibitory environment.
Through using a rhabdovirus, which have small easily manipulated genomes that can stably express engineered proteins (antigens), they created a booster vaccine encoding an antigen that can be recognized by a matching chimeric antigen receptor (CAR). A patient's own tumour-

specific T cells could be genetically engineered with this boosting CAR, allowing them to be turned on by the vaccine after it is delivered.
This boosting vaccine could be used to overcome the lack of persistence by telling the T cells to "go" after they are transferred to the patient and in turn promote an immune response that bolsters the ability of T cells to expand and persist within tumours.
From a patient's perspective, this demonstrates the complexity in the application of CAR-T, immune response and that further investigation is required.

## 4. Cristina Puig-Saus's Talk: Engineering a potent T-cell Response Against Solid Tumours

**Key Takeaways:**
Dr. Puig-Saus's work on melanoma to broaden the effectiveness of treatment across a broad spectrum of patients. Initial work demonstrated the effectiveness of the CAR T cell therapy but only to a small subset of patients. Through the application of CAR T cells optimized for specific shared antigens, the response rate was significantly improved, thus making this therapy more broadly effective to a wider patient population. The issue of costs was discussed and that while this investigation/application showed great promise, there were still technical and financial challenges to overcome before this became SOC (standard of care).

**Final Thoughts on Plenary 2**:
In the second plenary called "Novel Targets and Immunotherapy Approaches" we learned why some forms of cancer exhibit substantial immune heterogeneity, even within the same patient, as the reason why most current immunotherapy treatments largely do not apply to ovarian, breast and prostate cancers, among others. This is not for a lack of trying. There are some promising technologies, such as Oncolytic viruses (OVs), which target and destroy cancer cells by exploiting their weaknesses, the use of siglecs to better target and recognize cancer cell through cell specific alterations, or the use of synthetic receptors called chimeric antigen receptors (CARs) and vaccines. There is significant potential in all of these methods, however more research is needed.

The final takeaway I would like to leave, is that this conference was highly informative, thought provoking and exciting. It provided a real stretch for myself and my fellow Patient Scholars. For those of you at the conference, I left everyone there with the importance of immunotherapy for patients with solid tumours specifically but also for blood cancers, as this is the Holy Grail for cancer therapy and hope for us. Let us not be the 99% of the 550,000 as Dr Rosenberg stated.

I left the conference with hope. Hope that for those of us with cancer that we might see the Holy Grail. I reported at an advocacy meeting shortly afterwards that I thought immunotherapy would be a viable option for us (the advocacy group) with the next 5 years. I Hope that that hope comes to fruition and that these scientists, researchers, and governments can bring immunotherapy to the mainstream of cancer therapy.

## Plenary Session 3: RNA Strategies and Lipid Nanoparticles for Cancer Immunotherapies

*Notes contributed by: Melinda Bachini and Allyson Moore*

**Lay Summary of Plenary 3:**
mRNA and lipid nanoparticle (LNP) technology are being explored for cancer treatment. mRNA carries instructions from DNA to produce proteins in cells. LNPs, made of fats, protect and deliver mRNA to specific cells. In cancer, mRNA can be used to instruct cells to produce proteins that help the immune system recognize and attack cancer cells. This approach aims to use the body's immune system to fight cancer. mRNA technology is flexible, allowing for customization to target different cancers or individual patient needs. In this plenary session, the speakers will discuss experimental and clinical data regarding different ways they are using mRNA technology to develop therapies for cancer treatment. Dr. Darrell Irvine is a researcher who will talk about engineering strategies for genetically modified self-replicating RNA and its role for cancer immunotherapeutic development. Self-replicating RNA contains special instructions to make copies of itself. Dr. Irvine is creating a special type of self-replicating RNA that carries instructions to produce proteins that can target and kill cancer cells. Dr. Vinod Balachandran is a surgical oncologist who will talk about RNA vaccines for pancreatic cancer, and will highlight clinical trial data results from his team's personalized mRNA cancer-treatment vaccine therapeutic. Lauralie Short is a PhD student who will present her doctoral research on a strategy for making CD19-targeting chimeric antigen receptor (CAR) T cells in vivo (in the person's body) using LNP-mRNA delivery in Non-Hodgkin's Lymphoma.

### 1. Dr. Darrel Irvine's Talk: Emerging Self-replicating RNA for Cancer Immunotherapy

**Focus of Talk:**

- Using self-replicating RNA as a synthetic oncolytic virus for cancer immunotherapy
    - Self-replicating RNA contains special instructions to make copies of itself
- Use of engineering strategies to create self-replicating RNA that can carry therapeutic payloads and regulatable circuits to generate more potent anti-tumour responses

**Key Takeaways:**

- These LNP replicons can be engineered to carry therapeutic payloads
    - The inhibitory tumour microenvironment can be remodeled by having these LNP-replicons encode the pro-inflammatory cytokine, IL-12
- LNP replicons can induce an abscopal effect regressing distal untreated tumours
    - abscopal effects- when local treatment not only shrinks the targeted tumour, but also leads to regression of the untreated tumour at secondary site
- LNP replicons have high-level expression and are long-lasting

- They can be made to be toxic to cancer cells

**Final Thoughts:**

- LNPs can be designed for more functionality than just RNA delivery to achieve complex therapeutic goals.

## 2. Dr. Vinod Balachandran's Talk: Pancreatic Cancer- Exceptional Survivors to RNA Vaccines

**Focus of Talk/Background:**

- PDAC is a cold tumor with few mutations and is immunotherapy-resistant
- 9% of PDAC tumours are hot, which contributes to long-term survival
    - These 'hot' tumours have immunogenic neoantigens
- Neoantigens of high quality, not quantity, predicts survival in PDAC
    - High quality neoantigen-specific T cells persist long-term in pancreatic cancer
- Using mRNA vaccines encoding patient-specific neoantigens to generate tumour-specific T cells
- Clinical trial- Individualized mRNA neoantigen vaccines in pancreatic cancer

**Key Takeaways:**

- Tumours were resected from patients and sent for sequencing to computationally predict neoantigens for personalized mRNA vaccine development
- Polyclonal expansion of vaccine-expanded T cell clones
- T cell responses were observed in 50% of patients
- Vaccine-expanded T cells reached up to 10% of all blood T cells
- T cell responses were durable – neoantigen-specific T cells found 2 years later
- Responders had delayed tumour recurrence
- Vaccine non-responders had a higher rate of splenectomy
    - Common in surgical management of PDAC

**Take Home Message:**

- Individualized mRNA neoantigen vaccines create durable T cell responses in 50% of PDAC patients and delay tumour recurrence

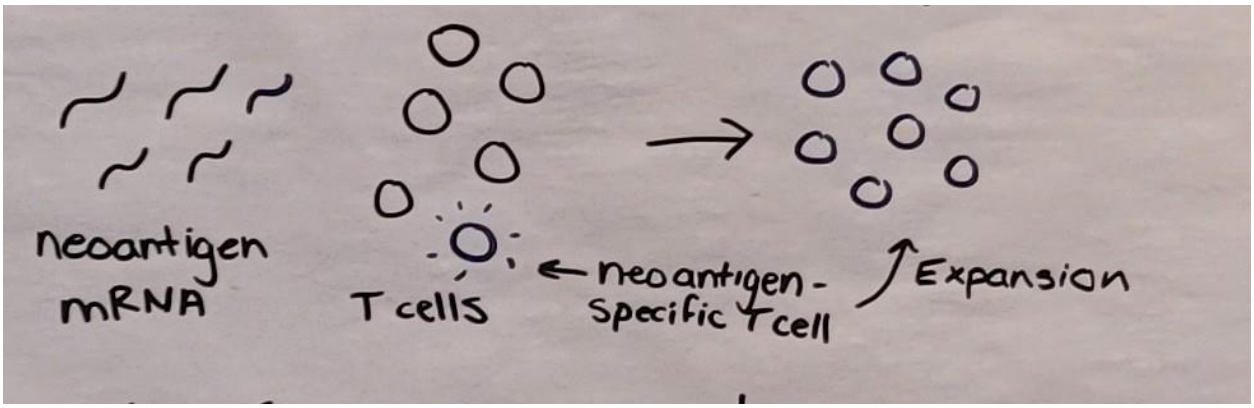


*Figure 1*

## 3. Lauralie Short: *In Vivo* Generation of CD19-CAR Cells by Lipid Nanoparticle Mediated mRNA Delivery for Non-hodgkin Lymphoma

**Focus of Talk/Background:**

- CD19 CAR T therapy is very effective in treating B cell malignancies, but CAR T manufacturing is expensive, time-consuming, and arduous
- *In vivo* generation of CAR-engineered cells could decrease cost, decrease time, and increase access
- CAR-engineered cells can be made *in vivo* using lipid nanoparticles (LNP) carrying mRNA that encodes for a CD19-CAR

**Key Takeaways:**

- A modified LNP, called long-circulating LNP (lcLNP), can transfect a variety of immune cells *in vivo*
- CD8 T-cells and macrophages in the blood take up and express CD19 CAR mRNA
- The lcLNP is preferentially taken up by macrophages
- Memory T cells have higher uptake of the lcLNP than other T cell populations
- Uptake of the lcLNP in the lymph nodes and blood

**Take Home Message:**

- LNPs can be used to deliver mRNA for in vivo production of CAR-engineered immune cells to generate an anti-tumour response

## 4. Dr. Christine Allen: Cancer Nanomedicine, Beyond Treatment of Locoregional Disease

**Focus of Talk:**

- Challenges with nanoparticles
    - Poor tumor penetration, limited drug release, variability in uptake within tumors
- Using mild hyperthermia as a way to control drug release from nanoparticles

**Key Takeaways:**

- Thermosensitive liposomes can be used to deliver therapeutic payloads at the site of interest using mild hyperthermia
- Increased drug concentration at site of interest
- ThermoDox (thermosensitive liposome) was evaluated in clinical trials but did not prove to be effective overall
- Ongoing efforts to improve the parameters for mild hyperthermia
- Mild hyperthermia improved the efficacy of anti-PD1 checkpoint therapy in a mouse model

**Final Thoughts:**

- Thermosensitive liposomes can be used for targeted delivery of therapeutics in combination with mild hyperthermia
- Mild hyperthermia can enhance the effect of existing immunotherapies

## Plenary Session 4: Clinical Application of Immune Cell-based Therapies

*Notes contributed by: Randy Thompson and Nawal Amhis, Camille Leahy and Bryan Marr*

**Lay Summary of Plenary 4:**
In this plenary session, four speakers will present insights into the clinical applications of immune cell-based therapies for cancer treatment, showcasing recent advancements, research findings, and practical assessment methods for such therapies. First, Dr. Marco Ruella from the University of Pennsylvania will discuss the role of the microbiome's role chimeric antigen receptor T cell (CART) relapse. Dr. Özcan Met from the National Center for Cancer Immune Therapy in Denmark, will present on using information and methodologies shared by the Canadian Canadian-Led Immunotherapies in Cancer (CLIC) platform, led by Dr. Natasha Kekre, to initiate their CAR T clinical trial. CLIC is the overarching term for a program developing made-in-Canada CAR T cell therapies (e.g., targeting CD19 and CD22). The HQP speaker, Tyler Dyer, a Research Associate from the BC Cancer Agency, will talk about potency assays for clinical CD19 CAR-T cell products. Potency assays are specific biological tests that measures how strong and effective a cellular therapy is (e.g., CAR T cell therapy). Finally, Drs. John Haanen and Valesca Retèl from the Immunotherapy Group at the Netherlands Cancer Institute will discuss correlative analyses and the economic evaluation data from their Phase III, publicly funded clinical trial examining TILs in advanced melanoma. In a clinical trial setting, correlative analyses mean looking closely at different kinds of information, like patient details, test results, and how treatments work. This helps clinician scientists figure out if there are any connections between these factors and how well the treatment works or if there are any side effects. E.g. using biomarkers to predict success of a specific treatment.

### 1. Marco Ruella's Talk: The role of the microbiome in CART Therapy

**Focus of the Talk**:
The microbiome is a vast community of tiny microorganisms, including bacteria, viruses, and fungi, living in and on our bodies. It plays a crucial role in maintaining our health and when disrupted, can play a role in disease. Antibiotics, frequently employed to fight infections, are known to impact the balance of the gut microbiome.

CAR-T cells are created by extracting a patient's T lymphocytes, a type of immune cell, from their blood. These cells are then genetically modified and activated in the laboratory before being reintroduced into the same patient. Once inside the patient's body, CAR-T cells function as a living

drug, seeking out and destroying cancer cells, offering a highly targeted and potentially curative approach to cancer treatment.

Marco Ruella's research links the microbiome to CAR-T cell therapy outcomes. In a retrospective analysis, they discovered that patients who had previously taken certain antibiotics before undergoing CAR-T cell therapy experienced lower survival rates and an increased risk of neurotoxicity. By examining patient stool samples, the researchers analyzed the composition of the gut microbiome. Their experiments revealed differences in the species of bacteria inhabiting the gut microbiome of CAR-T cell recipients compared to that of healthy individuals. Notably, they identified particular types of bacteria in the patients' guts that correlated with improved treatment responses. This research underscores the impact of the gut microbiome on how patients respond to CAR-T cell therapy.

**Key Takeaway:**

The microorganisms living inside patients' gut may influence CAR-T cell therapy outcomes. Taking certain antibiotics before CAR-T cell therapy may limit treatment success and increase side effects.

### 2. Tyler Dyer's Talk: Potency assays for clinical CD19 CAR-T cell products

**Focus of Talk:**

Confirming the successful conversion of a patient's T cells into functional CAR-T cells is a critical step. Given the complex manufacturing process and natural variability in T cells isolated from one patient to another, it's imperative to account for potential inconsistencies in CAR-T cell batches.

To advance the Canadian CLIC-01 clinical trial, Tyler Dyer is developing laboratory tests aiming to guarantee successful CAR-T cell manufacturing and to assess the cancer killing abilities CAR-T cells prior to treatment. In the next stage of the CLIC-01 trial, each CAR-T cell batch will be analyzed using these tests. Eventually, by linking the laboratory test data with clinical results, researchers may uncover which metrics reliably predict treatment outcomes. This potency assay is fundamental to advancing the CLIC-01 trial and making CAR-T therapy accessible to Canadians.

**Key Takeaways:**

To advance the Canadian CLIC-01 clinical trial, tests are being developed that ensure each patient's CAR-T cells are made successfully and demonstrate cancer killing ability. In the future, linking these tests with patient data will help researchers understand what properties of CAR-T cells predict how well they will treat patients.

### 3. John Haanen and Valesca Retèl's Talk: The effectiveness and cost-effectiveness of TIL compared to ipilimumab in advanced melanoma

**Focus of the Talk:**

Despite many advances in the field, advanced melanoma remains a deadly disease. This talk centered on a trial using tumor infiltrating lymphocytes (TILs) for melanoma treatment. TILs are made by harvesting immune cells from surgically resected tumors, growing, and activating them in a lab, and re-administering them back into the same patient where they will fight cancer.

In the first half of the talk, John Haanen discussed their clinical trial comparing TIL therapy against a drug called ipilimumab which boosts the immune response against cancer. Their research found that melanoma patients who received TIL therapy had better treatment outcomes with a longer period of time in which the disease did not worsen and prolonged survival.

In the second half of the talk, Valesca Retèl compared the cost-effectiveness of this TILs to ipilimumab. Their results showed that TIL was expected to give patients a better quality and quantity of life at a lower cost compared to ipilimumab. In other words, TIL was a more cost-effective option. This information will help doctors and healthcare systems make informed decisions about which treatment to use.

**Key Takeaways:**
Tumour infiltrating lymphocytes (TILs) are immune cells isolated from a patient's tumour, grown to large numbers in a lab, and then reinfused back into the patient to help destroy cancer cells. The presenters' research showed how TIL therapy is both more effective and cost-friendly for treating advanced melanoma compared to current treatment.

### 4. Natasha Kekre's Talk (Presenting for Özcan Met): DAN-CART 1901, CAR-T Cell Therapy Across the Atlantic

**Focus of the Talk**:
In the presentation, Natasha Kekre shared insights into the collaborative efforts of the Canadian CLIC-01 trial investigators and the National Center for Cancer Immune Therapy in Denmark, who are jointly working on the DAN-CAR-T cell trial (DAN-CART 1901). The CLIC-01 team has been instrumental in this partnership, contributing their valuable expertise, CAR construct, and manufacturing framework. This cooperative effort is aimed at utilizing CLIC-01 CAR-T cells for the treatment of Acute Lymphocytic Leukemia and Non-Hodgkin Lymphoma within the Danish trial. Natasha Kekre noted that the Danish trial is still in its early stages, with only five patients having undergone treatment thus far.

**Key Takeaways:**
Dr. Natasha Kekre discussed the collaborative effort between Canadian investigators and Denmark's National Center for Cancer Immune Therapy on the DAN-CAR-T cell trial. Still in early stages, this CAR-T cell trial aims to advance CAR-T cell treatment for leukemia and lymphoma patients in Denmark.

## Plenary Session 5: International and Alternative Models for Access to Immunotherapies, and Prospects for the Canadian Healthcare

*Notes contributed by: Lucie Lacombe and Kesia Titosky (Talks 1&2), Peggy Pickett and Sydney Vallati (Talks 3 &4)*

**Lay Summary of Plenary 5:**
Potential new treatments for cancer that harness the power of the patient's own immune system are an exciting scientific development. For patients to access them, however, we need to move these innovative treatments out of the laboratory and into clinical settings. To do that, we need to know which patients will benefit from the treatments, in what setting they should be delivered, how they should be regulated, and whether they are valuable. In this plenary session, we will be looking to other international jurisdictions to see how they have evaluated and implemented immunotherapy in cancer care so that we can start to design a 'made in Canada' solution for Canadian patients. We will be focusing the discussion on chimeric antigen receptor (CAR)-T cell and tumour-infiltrating lymphocyte (TIL) therapies, and Canadian regulatory response to some international examples. However, the pathway to patient access that we define may be applicable to other new cancer treatments, and we recognise that patient access goes beyond regulatory approval to include Health Technology Assessment (HTA), payers and patient perspectives (which we hope to address in the Q&A).

### 1. Manel Juan's Talk: Driving Academic CAR-T Products to Authorization: Barcelona's Model

**Key takeaways:**

- Manuel Juan presented various methods for gathering funding and building collaborative relationships to deliver second-generation CAR-T cell constructs to patients within the European healthcare system.
- The presented strategy provided CAR-T cell therapy to patients through the hospital network rather than traditional regulatory and pharmaceutical pathways.
- Currently, to get a new drug approved, new treatments in Europe undergo a 3-year-long approval process through the European Medicines Agency (EMA). This process is time-consuming and delays patient access to new treatments.
- Manuel proposes using existing hospital networks to expedite CAR-T cell therapy availability without compromising treatment quality. The approach is outlined in the following phases:
    1. Receiving a PRIME designation. This allows researchers to take the CAR-T cell trials from pre-clinical studies directly to centralized authorization.
    2. Through the regulatory agency, AEMPS (Spanish Agency of Medicines and Medical Devices), the drug candidate can receive a hospital exemption, allowing it to be made available to a wider range of clinicians and patients.

3. To work with university labs near the Barcelona Hospital to build clinical-grade CAR T products, instead of manufacturing them with pharmaceutical companies. These laboratories can provide patients/clinicians with quick access to CAR-T cell therapies while reducing costs.

**Final Thoughts:**
Manufacturing autologous CAR-T cells is laborious, time-consuming, and expensive. It was promising to hear that patients can receive affordable and accessible CAR-T therapy in Barcelona, and it could be a great model for the Canadian healthcare system to emulate. He finished his presentation confirming that oncology is indeed an expensive business!

## 2. Rimas Orentas' Talk: CAR-T Therapy: Challenging Targets and Real-World Implementation

Caring Cross co-founder, Dr. Rimas Orentas, presented a wide range of challenges to accessing innovative health technologies, in particular, the challenges around CAR-T cell therapy. He shared novel solutions such as Point of Care manufacturing, and hospital exemption processes.

**Key takeaways:**

- A critical challenge to CAR T cell therapy is the high cost, and Rimas noted the importance of increasing the affordability and access of this treatment.
- Some of the high costs associated with CAR-T cell therapy include air and ground travel of the patient samples to, and, from hospitals and GMP-grade labs.
- Caring Cross is supporting a sustainable and decentralized point-of-care manufacturing model to overcome this financial barrier.
- CAR-T cell products could be manufactured on-site at the hospitals using a certified GMP-grade mobile laboratory, such as those designed by the company Germ Free. It would reduce the amount of vein-to-vein time (the amount of time from collecting T cells to administering the CAR T cells back to the patient).
- Rimas noted that product safety, quality, and consistency are important when developing protocols for this alternative solution.
- Collaboration is a vital aspect of this alternative design because labs across the country might have resources and knowledge that can improve CAR-T therapy and its delivery to patients.
- Hospital exemption pathways can also streamline the approval process for patients to have faster access to care. Here the regulatory body provides access during approval.


*Figures 2& 3: GermFree mobile laboratories that are GMP-grade to produce CAR-T cell therapies. Source:* ***https://www.germfree.com/facilities/mobile-cgmp-cleanrooms/***

**Final Thoughts:**
Designing now for future manufacturing, once you begin clinical trials, can expedite patient access and delivery while reducing costs. The planning process could involve building a team of scientists, including regulatory scientists, and patient partners. Patient partners are particularly vital because they might give you an important perspective on the regulatory barriers to accessing treatment options.

## 3. Dr. Inge Jedema's talk: Treatment with TILs- Moving from Academic Setting Towards Marketing Authorization

**Key Takeaways:**
The Netherlands group developed a clinical treatment using tumour infiltrating lymphocytes (TIL) therapy for metastatic melanoma patients who have failed first-line treatment. Their group showed an increase in progression-free survival with TIL therapy over the standard of care treatment which at the time of study beginning was an immune checkpoint therapy, Ipilimumab. Importantly, they showed that there was also a cost benefit of TIL therapy compared to Ipilimumab.

Dr. Jedema joined the group as a regulatory expert and upon review of the project, defined their primary challenge of bringing this TIL therapy to market today as: **There had been no**

**consideration of applying for market authorization when the trial started in 2014. The group is now challenged by having to work backwards to compile everything needed to submit the application for market authorization.**

Hospital exemption is a system in Europe that allows access to treatments that have been proven to be safe and effective but are still in the process of getting market approval. After a risk benefit analysis, it is limited to a set number of patients at specific, approved centres. Under hospital exemption in the Netherlands, these treatments are covered by the national health insurance system. In the Netherlands as of January 15, 2023, TIL therapy using the protocol established in the clinical trial under academic production can be accessed by up to 50 patients per year under hospital exemption.

While the hospital exemption ensures access to patients to this treatment within the Netherlands, it is meant to be a stop gap measure while waiting for approval. Therefore, it is important to receive market approval, as there is a limit on the number of patients per year that can be treated under the hospital exemption and the hospital exemption could be revoked should a commercial party receive market approval for a TIL product for the same indication. The goal of this group was to ensure that patients still have access to TIL treatment at a fair price, making it important for them to achieve market approval first. Dr. Jedema said that for efficacy and a streamlined process, it is important that at the very beginning of planning the clinical trial, you must plan for the end point – which in this case was manufacture and distribution of the product, not just the end of the trial, but beyond. Her hindsight considerations are that you need to include, from the very beginning:

- inviting regulatory experts onto the team
- product development process needs to ensure enough structure is in place for the transition to market authorization
- cost of the product
- product characteristics.

**Final Thoughts:**
Dr. Fedema determined that preloading the planning team and process leads to streamlining the movement of the product being tested through to market authorization. Consider the end goal right at the very beginning.

## 4. Dr. Michael Rosu-Myles' Talk: Health Canada Perspective- Regulatory Pathways to Enable Access for Innovative Health Technologies

**Key Takeaways:**
Dr. Michael Rosu-Myles of Health Canada, outlined the current and future pathways that therapeutics, including immunotherapies, can use to receive approval from Health Canada for marketing and use in Canada. Four Divisions (1A, 2, 4, and 8) within the *Food and Drug Regulations (FDR), Part C* are involved in traditional drugs and therapies gaining access to the market in Canada.

*Division 1A: Requirements for Establishment Licensing* relates to the requirement of having an Establishment License for sites involved in any part of the drug fabrication, packaging and labeling, importation, and distribution of the therapeutic product; and the requirements must be met in order for sites to receive an Establishment License.

*Division 2: Good Manufacturing Practice (GMP) Requirements* relates to the GMP requirements, which are then harmonized with international standards.

*Division 4: Schedule D Drugs (Biologics)* relates to the specific requirements for biologics. Many immunotherapies, including cell therapies and oncolytic viruses, are consider Schedule D Drugs (Biologics) under the FDR, and are thus subject to the specific requirements outlined by *Division 4. Division 4* is currently being modified to remove product-specific language and introduce more risk-based flexible approaches.

*Division 8: Requirements for Authorization of a New Drug* relates to the information and materials that are required for Health Canada to assess the safety and efficacy of drug products applying for approval. The review process takes approximately 300 days, after which the sponsors of the application will receive a Notice of Compliance (NC) that allows for the sale and importation of the new drug product in Canada.

For clinical trials in Canada, they must meet the requirements under the *Food and Drug Regulations Part C: Division 5* and will receive a No Objection Letter (NOL) once the criteria is met for the clinical trial within a 30 days after submission of the application.

Beyond the traditional pathway outlined under *Division 8* of the FDR, there are two additional pathways by which early access for sale and importation in Canada can occur:

1. Priority Review Policy
    a. has a timeline of 180 days;
    b. can only be used for products that treat a serious, life-threatening, or severely debilitating disease/condition;
    c. and ***there must be substantial evidence*** that the drug provides effective treatment or prevention for a disease that currently does not have any available treatments in Canada, **or** that the drug shows significantly greater efficacy such that its overall benefit/risk profile is improved compared to existing therapies available in Canada.
2. NOC with Conditions Policy.
    a. can only be used for products that treat, prevent, or diagnose life-threatening or severely debilitating disease.
    b. the product ***only need show promising evidence of clinical effectiveness*** with the condition to show substantial evidence of clinical effectiveness at a later date.
    c. intended for products that would be a first line treatment or have potential to significantly improve the benefit/risk profile compared to existing products.

Access to drugs and products not authorized for market use outside of clinical trials for individual patients can occur through two avenues:

1. Special Access Program (SAP)

a. allows for healthcare professionals to request access to drugs that are currently not for sale in Canada for a patient that they are treating for whom conventional treatments have failed, is unsuitable for, or unavailable in Canada.

2. Early Open Label Individual Patient studies (OLIP).
    a. provides access to non-marketed drugs where this is no clinical trial available and is considered too investigational for SAP due to not clear knowledge on the risks or effectiveness.
    b. intended for compassionate use for patients with no remaining clinical options.

Many cancer immunotherapies and other emerging therapies are too complex, posing challenges for the traditional regulatory system, resulting in barriers for these therapies becoming accessible to Canadians. Some of these classes of products include gene and cell therapies manufactured at point of care, fecal microbiota therapy, phage therapy, islet therapy, and 3D Bio-printing.
Examples of the challenges these therapies pose include regulations designed for large-scale facilitates not being appropriate for point of care manufacturing and having to treat each phage as a single drug, making traditional licensing impractical. These products are now grouped under the label Advanced Therapeutic Products (ATP) Framework due to changes in the *Food and Drugs Act (FDA)*, allowing Health Canada to create legislative pathways to authorize these products.

*Schedule G*
This **new** schedule allows for Health Canada to adjust the requirements to address the unique challenges individual ATPs pose while maintaining the high standards for market approval. This process requires continuous collaboration and communication between a wide variety of stakeholders. There are plans for new regulations to be introduced once more experience of regulating different ATPs is acquired to transition this class of products out of a tailored pathway and into a more traditional framework for market authorization.

**Final Thoughts on Plenary 5:**
Early advice mechanisms for those seeking to conduct clinical trials in Canada to help develop their programs and create clinical development strategies to support market authorization can occur through pre-submission meetings and opportunities to schedule meetings with Health Canada scientific teams. Creation of a "Concierge Service" will support stakeholders in navigating the regulatory environment for ATPs, complex products that challenge the traditional pathways.

***Some audience feedback:***

- The concierge idea found favour
    - a patient concierge process was asked for as well
- Challenged Health Canada to include patient partners
- Challenged Health Canada to include not just stakeholders at the review table, but constituency who have no agenda other than a better health care experience
- A strong voice advocating for Hospital Exemption in Canada was heard:
    - Health Canada response was we didn't need one – that our patchwork system was working well. The Combination of the
        - Priority review (doesn't allow for stop gap measure)

        - Notice of Compliance with Conditions (less than a year turn around time)
    - **The audience strongly disagreed with this assessment.**

**Final discussion:**

- The future of cancer treatment is personalized medicine, that is when each patient gets treated with therapeutic tailored specifically to their disease.
- However, it takes a long time to get patients the personalized treatments they need (e.g., 15 o 18 months for an ASO therapy), and this needs to be improved
- As we are moving towards personalized medicine, Canada has to loosen their policies to reimburse drugs that are supported by a smaller body of data than previously required, which should help the approval on personalized treatments.
- Canada needs to simplify applications for the compassionate use of drugs and treatments.

## Plenary 7: Non-Traditional and Emerging Cell Therapies

*Notes contributed by: Nadine Frisk and Lauralie Short*

**Lay Summary of Plenary 7:**

This plenary session on non-traditional and emerging cell therapies will focus on cutting-edge, cell-based ways create better immunotherapies. Dr. Nicholas Arpaia from Columbia University Medical Centre will discuss his work microbial neoantigen vectors for cancer Immunotherapy. Microbial neoantigens are molecules produced by microorganisms (e.g., bacteria and viruses) that are not normally found in our body. Dr. Arpaia has developed microbial neoantigen vectors that carry special codes for attacking tumors. Dr. Elie Haddad from Université de Montreal will discuss his groups' work on CAR-NK cells and CAR-HPSCs. CAR NK cells are genetically engineered Natural Killer (NK) cells with Chimeric Antigen Receptors (CAR) to make them more effective at targeting and destroying cancer cells. Similarly, CAR-hemopoietic stem cells (HPSCs) are genetically engineered HSPCs with CARs. Though these two therapeutic approaches sound similar, they are each offer different advantages and disadvantages that Dr. Haddad will discuss in his talk. Dr. Saif Sikdar, a Postdoctoral Fellow from the University of Calgary, will talk about the potentially beneficial role of small molecules produced by microorganisms that live in our body on helping us have immunity against tumours. Finally, Dr. Emily Titus from Notch Therapeutics will talk about Notch's approach of using special cells called induced pluripotent stem cells (iPSCs) to create T cells for treating cancers.

### 1. Dr. Nicolas Arpaia's Talk: Microbial Neoantigen Vectors for Cancer Immunotherapy

**Focus of the Talk:**
Antigens are markers on the surface of cells and pathogens that can trigger an immune response in the body if they are foreign to the system. Microorganisms such as bacteria and viruses will lead to an immune response in most cases as they are recognized as being "non-self." Neoantigens, are new antigens which can be made by tumor cells and thus can be recognized by the immune system as foreign due to their novelty. However, cancer cells will often evade the immune system by not expressing any neoantigens. To get cancer cells to express neoantigens, Dr. Arpaia and his group utilized microbial vectors. These microbial vectors can deliver molecules, that are produced by bacteria to enable cancer cells to be recognized by the immune system. These tumor-specific antigens that are completely unique to the cancer cells, so targeting neoantigens for immunotherapy comes with a lower risk of accidentally harming healthy cells as well. Since neoantigens trigger strong immune responses and are only present in cancer cells, neoantigens have become a preferred targeted therapy of immunotherapy.

**Key Takeaways:**
- Finding neoantigens in solid tumors is very difficult because cancer cells are:
    - Immune suppressive
    - Evasive
    - Do everything possible not to be recognized
- Vaccinations using an engineered bacterial vector like E. coli Nissle, can deliver neoantigens to the site of the tumors
    - Since bacteria naturally accumulate at the site of the tumor, this will enhance the anti-tumor response

**Final Thoughts:**
- Bacteria encoding neoantigens can act as a vaccine for your cancer
    - This bacteria vaccine helps to activate your immune system and directs the immune response against the neoantigens

## 2. Dr. Saif Sikdar's Talk: Microbiome-derived hydroxyphenyl propanoates enhance antitumor immunity

**Focus of the Talk:**
The potentially beneficial role of small molecules produced by microorganisms that live in our body and help us have immunity against tumors.

**Key Takeaways:**
- Your microbiome (gut health) regulates tumor immune surveillance by influencing immune cell activity in the tumor microenvironment (TME) through the production of specific immunomodulatory metabolites, hydroxyphenyl propanoate (HPP).
- Immunomodulatory metabolites are molecules produced in the microorganisms in the gut that can help regulate the immune system by shaping the activity of the immune cells.

- HPP and ICB is better together
    - HPP is a novel class of microbiome-derived metabolites that can enhance antitumor immunity and improve the efficacy of ICB therapy
        - 3 natural HPP molecules are produced in the animal and human microbiome
            - Can impact gene expression
        - Immune checkpoint blockade (ICB) is a type of cancer immunotherapy that uses antibodies to block the signals from tumor cells that that tumor cells use to suppress the immune cell activity
        - By combining HPPs and ICB they achieved a complete regression of tumors in 40% of the mice
        - Advanced melanoma patients received ICB therapy and were found that patients who responded to ICB had higher levels of HPPs and higher abundance of HPP-producing bacteria than patients who did not respond to ICB

**Final Thoughts:**

- The microbiome has a significant impact on immune health and the response to cancer immunotherapy.
    - HPPs produced by certain gut bacteria enhance antitumor immunity in mice and humans
        - Having more HPP metabolites can improve the efficacy of ICB
        - HPP molecules creates the potential key cancer immune signaling pathways
        - This has the potential to improve anti-PD1 and anti-PDL1 therapy

## 3. Dr. Elie Haddad's Talk: CAR NK cells and CAR in Hematopoietic Stem Cells

**Focus of the Talk:**

CAR NK cells are more effective at targeting and destroying cancer cells than endogenous NK cells. Endogenous NK cells are white blood cells produced naturally by the body and are part of the innate immune system to act as the first line of defense against killing cancer cells. CAR NK cell research has demonstrated NK cells as a potential candidate to mitigate some of the current challenges faced with CAR T cells. CAR are synthetic proteins which engineer cells to enable them to recognize and kill cancer cells. Whereas, HPSCs are genetically engineered HSPCs with CARs. CAR HPSCs are also immune cells engineered to recognize and destroy cancer cells. Each of these two therapeutic approaches offer different advantages.

**Key Takeaways:**

- How CAR NK cells mitigate CAR T cell challenges
    - Safety
        - No cytokine release syndrome (CRS); where your immune system responds too aggressively after immunotherapy

        - No graft vs host disease or GVHD; where the new cells attack the recipient's body
        - No neurotoxicity; where the nervous system becomes damaged from the immunotherapy
    - Efficacy in solid tumors
        - intrinsic ability to kill tumor cells
    - NK cells have properties that make them 'off the shelf' potential
        - Larger production
        - Lower price
        - May allow for more sophisticated engineering
- Benefits of using HSCs stem cells to generate the CARs
    - These alternatives are aiming to improve on the hurdles currently faced by CAR T cells
        - Enhanced persistence of the cells in the system and HPSCs have been shown to improve this
        - Manufacturing advantages; reduced cost and accessibility improvements using allogeneic cells, cells harvested from a donor, rather than each patient undergoing individual manufacturing

**Final Thoughts:**

- Genetically engineered CAR NK cells are a more effective alternative treatment for targeting and destroying cancer cells while mitigating some of the challenges of CAR T cells
- CAR HPSCs have the potential to improve the accessibility to CAR based therapies through the use of allogeneic cells and hold the potential to build a more complex and durable CAR response by utilizing not only CAR T cells but also CAR NK cells
- Both of these alternatives mitigate some of the current challenges faced by CAR T cells and there is still more work that needs to be done but they hold the potential to help more patients and expand the scope of diseases which could be treated with this precision therapy

## 4. Dr. Emily Titus's Talk: Delivering on the promise of iPSC-derived T cell therapy

**Focus of the Talk:**

Notch Therapeutics is a biotech company that manufactures special cells called induced pluripotent stem cells (iPSC) to eventually create CAR T cells from an allogeneic cell bank for treating cancers. iPSCs are a type of stem cell that can be generated from adult mature cells, such as a skin cell and reprogrammed back to a stem cell. This process involves introducing specific genes into the adult cells, which causes them to revert to an undifferentiated state. An undifferentiated state consists of cells that have not become any specific cell type yet (i.e., T cell, etc.) before they are generated into T cells and then manipulated to become CAR T cells.

**Key Takeaways:**

- Manufacturing steps
    - Donor selection
    - Cell collection
    - Cell bank
    - Engineer and clone
    - Analyze
    - Educate the cells to create CAR T cells
- iPSC derived T cells solve many key bottlenecks for adoptive cell therapy
    - Unlimited supply of consistent starting material from the master cell bank with the selected edits
    - More off the shelf
        - Quicker productive (days vs months)
        - Larger production
        - Increased accessibility
- Benefits of iPSCs as a starting product
    - Prevents GVHD; where the new cells attack the recipient's body because iPSCs aren't seen by the immune system as not being their own, or as an invader
    - Cytokine support; the use of interventions to help balance the protein levels in the body; which leads to improved cell fitness, proliferation and persistence
    - Kill switch; the cell will kill itself if problematic to the system
    - Cost-effectiveness
    - Less toxicity

**Final Thoughts:**

- The Notch manufactured T cells are working
    - Still killing cancer cells after multiple threats
    - Now trying in vivo; tested in animal models
    - Scaling up to supply larger clinical trials in 50 L batches
    - Getting closer, but more work is still needed

**Final Discussion:**

In Plenary 7 the presenters talked about alternatives to improve cancer immunotherapies as we have seen success, but more work needs to be done to overcome the hurdles currently being faced. Dr. Arpaia demonstrated the potential of using bacterial vectors to teach the immune cells to recognize the cancer cells specifically. Dr. Saif Sikdar shared the potentially beneficial role of small molecules produced by microorganisms that live in our body and help us build an immune response against tumors. Drs. Haddad and Titus highlighted the need to change the manufacturing of CAR T cells to improve accessibility by moving away from autologous products, cells from a patient and sourcing cells from healthy donors. We are excited to see future developments in these projects that aim to improve the health and quality of life of more Canadian cancer patients, by overcoming hurdles faced by current cancer immunotherapies.