2022 Community Dissemination Report

BioCanRx-Cancer Stakeholder Alliance Learning Institute

A Summary of Current Immunotherapy Research discussed at the 2022 BioCanRx Summit for Cancer Immunotherapy

Written by: Participating Learning Institute 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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January 2022

Welcome

From BioCanRx

We are proud to share this publicly available Community Dissemination Report written by the participants of the 2022 BioCanRx-Cancer Stakeholder Alliance Learning Institute. We are very happy to have hosted the Learning Institute in-person for the first time since 2019 at the 2022 Summit for Cancer Immunotherapy (Summit4CI) from November 19th – 21st, in Montréal, Québec. 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 at the next Summit in October 2023. You can learn more about the Summit4CI at 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

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

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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.

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.

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.

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

This year's Learning Institute was designed by the 2022 BioCanRx-CSA Learning Institute Working Group and BioCanRx staff using the feedback obtained from last year's initiative.

Table 1: Members of the 2022 BioCanRx-CSA Learning Institute Working Group

Members:
Paul O'Connell, Co-Chair The Leukemia & Lymphoma Society of Canada (LLSC) **Patrick Sullivan, Co-Chair** Team Finn **Jeanette Boudreau** Dalhousie University **Kim Badovinac** Canadian Cancer Research Alliance (CCRA) **Vera Samarkina** Patient Scholar Advisor **Frederic St-Denis-Bissonnette** Academic Scholar Advisor
BioCanRx Staff:
Stéphanie Michaud President and CEO, BioCanRx **Megan Mahoney** Director, Scientific Affairs and Training Programs, BioCanRx **Mackenzie Huckvale** Knowledge Mobilization Intern, BioCanRx

2022 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 represent a diverse range of research and life experiences.

Figure 1: 2022 BioCanRx-CSA Learning Institute participants

Together, they participated in a series of interactive and collaborative “Knowledge Exchange sessions” that enabled then 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 2022 Learning Institute

Patient Leaders/Caregivers who participated as "Patient Scholars":	
Adam Auer **Louise Bird** **Melissa Coombs** **Sarah Hunt**	**Angus Pratt** **Chantale Thurston** **Don Wood**
BioCanRx Trainees who participated as "Academic Scholars":	
Sabrina Guettouche **Victoria Hoskin** **Omar Kassas** **Celine Laumont**	**Lorenzo Lindo** **Laura Mah** **Alex Shepherd** **Shannon Snelling**
CSA Learning Institute Working Group members who participated as "mentors":	
Paul O'Connell, Co-Chair The Leukemia & Lymphoma Society of Canada (LLSC) **Kim Badovinac** Canadian Cancer Research Alliance (CCRA)	**Vera Samarkina** Patient Scholar Advisor **Frederic St-Denis-Bissonnette** Academic Scholar Advisor
BioCanRx Staff who participated as a "facilitator":	
Mackenzie Huckvale Knowledge Mobilization Intern	

Dissemination Report Details

The Learning Institute key take-away messages and group reflections from select plenary session at the 2022 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 November 19 – 21, 2022 in Montréal, Québec. 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 2022 Learning Institute experience from a Patient and Academic Scholar in the BioCanRx January 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.

We would also like to extend a big thank you to Canadian Institutes of Health Research for being a proud supporter of this initiative.

Public Forum: Cancer Immunotherapies: New Therapies on the Horizon and Future Patient Access

Notes contributed by: Don Wood and Alex Shepherd

Lay Summary of Public Forum: In this virtual forum, we heard from a clinical trial 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. Key themes covered:

- What's new and on the horizon for cancer immunotherapy
- How does the cancer immunotherapy treatment available in Canada rank against other countries
- Barriers for Canadian research – getting basic science to Clinical Trials
- The need to help government pinpoint the actions and approvals needed to focus their efforts and dollars
- What are the barriers and how can we improve Canadian patient access to cancer immunotherapy treatments & clinical trials

Click here to view a recording of the 2022 Public Forum

Learning Institute Perspective: Cancer immunotherapy and targeted cell therapies have been proven to be extremely effective, especially in the case of relapsed cancer patients, such as patient speaker Stefany Dupont who began the forum. While Canada is not lacking in research and innovation, we lack the infrastructure and expertise to fully develop and produce 'in Canada' treatment, forcing patients to have to travel to the United States to receive treatments and in some cases, survive.

To fully support Canadian patients and reduce the annual 26.1 billion dollars spent on cancer treatment annually, we must invest into the facilities necessary to create these treatments and the personnel required to staff them. BioCanRx has taken the first step with CanPRIME; a program that trains students for biomanufacturing. Additionally, the forum presented the need for patient advocate engagement alongside research and development. Researchers and the patient community each have their own perspectives on what needs to change such as cost and quality of life, as well as what needs to be improved. Ultimately, the forum highlighted Canada's need to create and develop made-in-Canada solutions, moving away from general therapies (chemo, radiation etc.) and more towards targeted therapies for better patient survivability and quality of life.

Plenary Session 1: Applications of Synthetic Biology and Next Generation Engineering Strategies

Notes contributed by: Adam Auer and Omar Kassas (Talks 1 & 4), Louise Bird and Victoria Hoskin (Talks 2 & 3)

Lay Summary of Plenary 1:
The cancer immunotherapy field is a relatively new and evolving realm of study in the overall picture of cancer treatment. There are various immunotherapy platforms that are currently being developed, and that have been talked about at the BioCanRx Summit4CI. However, all of them revolve around the same idea: allowing the patients' own immune system to recognize the cancer cells in their body and initiate a specific and strong attack against them. Over the last couple of decades, a lot of advancements in technology and science, like the ability to sequence the human genome, have made it possible for scientists and clinicians to design these treatments. In the first plenary session of this conference, we heard about CAR-T Cell therapy from Dr. Robert Holt, the co-director of BC Cancer immunotherapy program and Professor at the University of British Columbia and Simon Fraser University. After that Dr. Ying Tam, the Chief Scientific Officer at Acuitas Therapeutics, gave a talk on mRNA Lipid Nanoparticles and their application on cancer therapy. Later, we heard from Dr. Risini Weeratna from the National Research Council Canada about Nano-CARS. Finally, Shea Komant, PhD candidate at the University of Alberta, gave a talk on her thesis project where she is engineering an oncolytic virus to target Melanoma.

1. Robert Holt's Talk: CAR-T Treatment as Systemic Gene Therapy

Focus of Talk: Chimeric Antigen Receptor T-Cell therapy or CAR-T therapy is an evolving immunotherapy platform that involves the use of the patient's own immune cells. The patients' immune cells are extracted from their blood, engineered in a laboratory and reprogrammed to improve their ability to recognize and kill the patients' cancer, and then infused back into the patient after they have received a chemotherapy treatment.

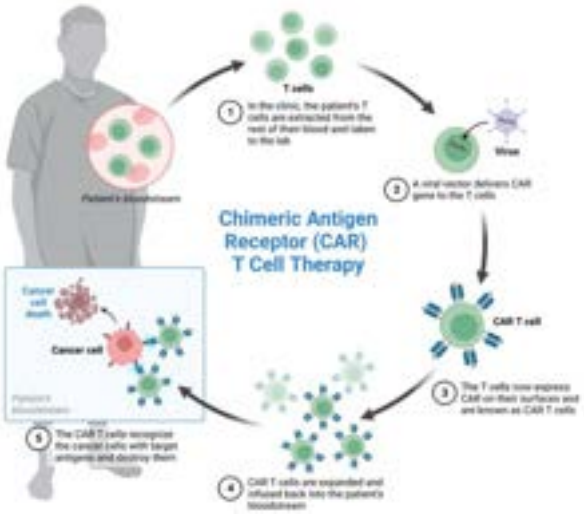

Figure 3. Schematic showcasing steps involved in CAR-T therapy. *Omar Kassas, created with BioRender.com*

Key Takeaways: Dr. Holt spoke about the first Clinical trial for CAR-T cell therapy in Canada, the CLIC-01 trial. This project has been a huge collaborative effort between scientists and clinicians nationwide with the hope of making this treatment more affordable and allow for more equitable access.

As promising as this therapy platform is, there are some downsides that come with it, both from the biomanufacturing side and from the clinical side.

- Currently in Canada, the viral vectors being used in the CAR-T cell clinical trial, CLIC-01, are being produced only in the Biotherapeutics Manufacturing Centre (BMC) of the Ottawa Hospital Research Institute. To allow more access nationwide, there needs to be more manufacturing facilities.
- As of now, CAR-T cell therapy is only applicable for certain blood cancers, meaning only a limited group of patients are eligible to receive this treatment.
- Patients still require chemotherapy treatment before the newly programmed immune cells are infused back into their body.

Final Thoughts: Although CAR-T cell therapy is moving forward and showing promising results, we must streamline more efficient manufacturing protocols. Moreover, we need to find ways to improve CAR-T therapy to target a wider range of cancers.

2. Ying Tam's (Acuitas) Talk: mRNA lipid nanoparticle therapeutics for cancer therapy

Focus of Talk: Lipid nanoparticles are a novel and safe platform for delivering various molecules that can be used to treat/prevent diseases. They are based on fat molecules and are easy to manufacture.

Key Takeaways:
Onpattro: 1st approved RNA product – lipid nanoparticle formulation for BioNTech's COVID-19 vaccine

QUESTION: can these lipid nanoparticles be used as a form of cancer immunotherapy?

- Can deliver molecules that act as therapies
- Can target these nanoparticles to specific immune cells to deliver the "therapy" in a targeted fashion

Example: targeted delivery of mRNA molecules to produce CAR T cells within cells

3. Risini Weeranta's Talk: Made in Canada NanoCARs

Focus of Talk: How is the NRC improving existing CAR-T and CAR-NK development?

Key Takeaways: One proposed solution is using single domain antibodies, or nanobodies to improve existing immunotherapies.

It turns out camels and llamas form very small antibodies (nanobodies) that are very similar to human antibodies and are quite stable. Nanobodies are cheaper, accessible, and easy to make. Their small size allows for them to be modifiable (e.g., target lipid nanoparticles with nanobodies and direct them to specific immune cells.

The National Research Council (NRC) has developed a workflow for screening for novel CARs using llama nanobodies

- Their approach involves immunizing llamas and screening for the best candidate nanobodies with high affinity to a particular protein (ex. the CD22 cell surface receptor). These can then be used as the basis for novel CARs - nanoCARS
- So far CAR-T therapies are better suited for blood cancers. For solid tumours, there still needs to be a lot of research done/optimization to reduce toxicity

4. Shea Komant's Talk: Genetically Engineered Vaccinia Virus Expression MHC-1 as a Precision Medicine Melanoma Vaccine.

Focus of Talk: Oncolytic viruses are cancer-killing viruses that specifically grow and replicate in cancer cells, leaving normal tissues unharmed. The idea behind this immunotherapy platform stems from the fact that cancer cells have accumulated permanent genetic changes, or mutations, in order to grow uncontrollably. To do that, cancer cells let go of certain characteristics or mechanisms found in normal, healthy cells. One of these characteristics is the ability to fight off viruses. Here, Shea Komant is designing a virus, known as Vaccinia virus, and is going the extra mile by enhancing this virus' cancer killing abilities using a protein called MHC-1.

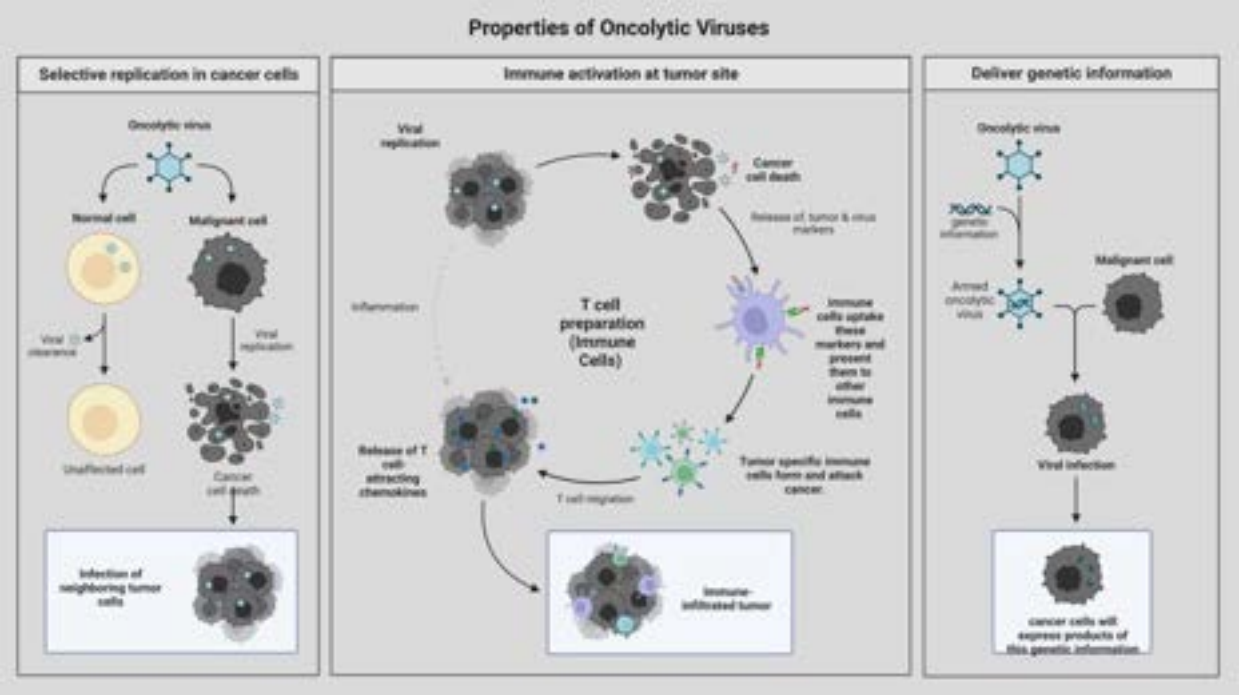

Figure 4. Schematic showcasing functions of oncolytic viruses as discussed by Shea Komant. *Omar Kassas, created with BioRender.com*

Key Takeaways:

Key points about Vaccinia virus:

1. It is a safe virus as it has been used to eradicate smallpox.
2. It is well characterised and studied.
3. It is able to be manipulated genetically to replicate in cancer cells **ONLY.**
4. **It can also be used as a delivery system and a cancer killing agent, like a trojan horse.**

Point four made above is the key message of Shea's talk. She is using this virus to deliver a protein called MHC-1 to the cancer cells being infected.

What is MHC-1?:

MHC-1 is a protein that all cells in the body, aside from red blood cells, express on their surface. Its function is to present protein fragments found in the cell to the body's immune cells. Through this action, immune cells can then recognize which cells are acting abnormally and kill them.

However, interestingly, cancer cells can sometimes hide from the immune system by downregulating MHC-1, basically shutting off MHC-1. This way, the immune cells will not recognize if there are abnormalities going on in the cell.

Why is Shea designing a virus that produces MHC-1?:

Her hypothesis is that if she can infect the cancer cells with the Vaccinia virus, the virus will replicate in those cells and produce the protein, MHC-1. This will then prevent the cancer cell from hiding, as MHC-1 will present the abnormal protein fragments to immune cells. The hope is

that the immune system will recognize that there are cancerous cells growing, and initiate a systemic antitumor attack.

Plenary Session 2: Cancer Immunotherapy and the Microbiome

Notes contributed by: Angus Pratt and Laura Mah (Talks 1 & 3), Sarah Hunt and Shannon Snelling (Talks 2 & 4)

Lay Summary of Plenary 2:
The world around us can be identified by the bacteria that are present. For example, we would be able to identify trees by the bacteria that are present. The same is true for various parts of the human body. Humans and some microorganisms (for example "gut bacteria'') have evolved together to become balanced in a way that benefits both the host (the human body) and the microbe.

The role of the microbiome in modulating the bodies' activities it is a relatively new one. The immune system also plays a key role in maintaining the healthy activities of the human-microbiome relationship. If this balance goes awry, the immune system can become dysfunctional, and the result can be that the microbiome can impact cancer initiation, progression, and response to treatments. Research on these interactions is having profound effects on cancer treatments. Most of the research is focusing on the gut microbiome. There are other areas that need exploration. The plenary session will speak to these interactions between the microbiome and the immune system, and will discuss the relationship between the microbiome, cancer, and immunotherapy.

The microbiome interacts with and is influenced by the following factors:

- Geographical location
- Host genetics
- Exercise
- Stress
- Antibiotics
- Age
- Gastric motility
- Antimicrobial peptides and IgA
- Gastric secretion
- Diet
- Mode of delivery

Summarized from handout provided in Orientation: Gut Reactions, Breaking Down Xenobiotic - Microbiome Interactions - Pharmacol. Rev. 2019 Apr, 77(2): 198 – 224

1. Kathy McCoy's Talk: Identifying Microbes and Metabolites That Enhance Immunotherapy

Focus of Talk: The microbiome is the community of microorganisms (e.g., bacteria, viruses, fungi) that live within the body. They are commonly found on mucosal surfaces, such as the gut. The microbiome is heavily influenced by the environment, although genetics can play a role. It can influence immune disorders and diseases through small molecules called metabolites. These metabolites pass through small spaces and reach important immune organs (e.g., bone marrow, thymus). In turn, these organs can affect the immune system and its function. An example of this action is the maternal microbiome producing certain metabolites. They are captured by immune molecules called immunoglobulin G (IgG) antibodies and these can be passed to the foetus and confer protection.

One central focus of Dr. McCoy's work is identifying key metabolites involved in this microbiome-immune crosstalk in the context of immunotherapies for cancer. One of these immunotherapies is immune checkpoint inhibitors (ICIs), which are molecules that can block the "brakes" of the immune system and provide a "go" signal for immune cells to kill cancer cells. Her studies demonstrated that ICI therapy in mouse models of cancer that lacked a microbiome did not work, meaning that a microbiome is important for this therapy to have an effect. Further, this effect can also be found by transplanting parts of the microbiome from mice that respond well to ICI therapy to mice that previously did not respond well. The previously non-responding mice then respond to ICI therapy after receiving this new microbiome. Upon further investigation, Dr. McCoy and her research group discovered a specific metabolite produced by bacteria in the microbiome of responding mice that was contributing to the effectiveness of ICI therapy.

Key takeaways:

1. The microbiome is a complex ecosystem of microorganisms that live inside us.
2. The microbiome can impact our immune system, especially, immune diseases and immunotherapies.
3. Key metabolites produced by the microorganisms in the microbiome can impact the efficacy of ICI therapy.
4. This could be used as a prognostic tool to identify which patients would benefit from ICI therapy based on their microbiome.
5. Alternatively, this could open the door for new combinatorial therapies where ICI therapy is administered with these key metabolites for increased efficacy.

2. Meriem Messaoudene's Talk: Microbiome In Immuno-Oncology

Focus of Talk: We need to develop strategies for taking what we know about the relationship between the gut microbiome and immunotherapy response and translating it into treatment plans to help Canadians living with cancer. Small particles released by bacteria in the gut can improve the response to PD-L1 immune checkpoint blockade therapy for people who have melanoma and non-small cell lung cancer. These good bacterial derivatives are lost when a person is treated with antibiotics. Although antibiotics kill bacteria that could improve cancer immunotherapy response, some patients waiting to get immunotherapy require antibiotics. Therefore, we need a way of preventing useful antibiotics from harming the good bacteria in our gut. The group with whom Dr. Messaoudene works, has developed a protective coating for antibiotic pills that prevents the release of antibiotics until the medicine has passed the gut and is in the blood where it is needed. This type of innovation is one example of how people living with cancer receiving immunotherapy are better off because of gut microbiome research.

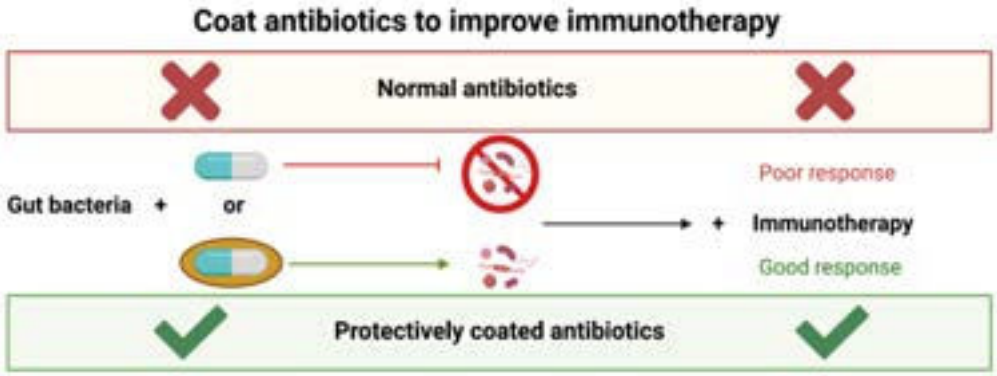

Figure 5: Diagram depicting use of protective coating in antibiotic deliver for immunotherapy patients. *Sarah Hunt and Shannon Snelling, created with BioRender.com*

Key Takeaways:

- Everyone has a different gut microbiome and some microbiomes allow our immune system to fight cancer
- Immune checkpoint inhibitor therapy (ICI) works better for people with specific gut microbiomes
- Bacterial derivatives can improve response to ICI therapy
- Patients who don't receive antibiotics respond better to ICI therapy because the bacteria that produce derivatives are not killed
- Antibiotics can be made with a protective coating that protects good bacteria and allows patients who need to take them while receiving ICI therapy

3. Manuela Santos' Talk: The Gut Microbiome in Colon Carcinogenesis and Intestinal Healing: Friend or Foe?

Focus of Talk: As we have seen in previous talks, there is a role for gut microbiome in cancers. Another example to demonstrate this is in colorectal cancer where certain types of microorganisms in the microbiome (microbiota) are more prevalent and associated with a better

prognosis. However, some types are the opposite and can be harmful by helping the tumour grow. Not only does the microbiome affect tumour progression, but it can also have impacts on outcomes of treatment, like surgery.

In colorectal cancer, it is common to get surgical anastomosis where a section of the colon that is tumorous is removed and the two ends are joined together to reconnect the pathway. A problem that can occur from this surgery is an anastomotic leak, which is when the reconnected intestine is not completely closed and contents from the intestine can leak out. This is one of the most serious complications that can happen after anastomosis and can be fatal. The group found a link between cytokine production - proteins released by immune cells to communicate with other cells - and low-grade inflammation related to the gut microbiome. One question of interest is how the microbiome affects aspects of anastomotic leaks, such as tissue regeneration and resolution of inflammation from the surgery. In her study of 70 patients, 9 developed anastomotic leaks. Dr. Manuela Santos and her research group investigated this problem using mouse models and faecal transplants from the patients with leaks. They found that gut microbiota can influence the surgical outcomes of anastomosis. The group identified one type of bacteria that improved healing and one type that was implicated in poorer outcomes. Further work demonstrated that adjusting the microbiome improved tissue repair and healing in mouse models.

Key takeaways:

- Gut microbiota can influence tissue repair and improve outcomes of surgical treatments for cancer.
- Future therapies can harness the positive effects of the microbiome to enhance its outcomes.

4. Saman Maleki's Talk: Microbiome-Based Strategies to Enhance Anti-Tumor Immunity and Response To Immunotherapy

Focus of Talk: The gut microbiome modulates response to cancer immunotherapy and our microbiome can be altered by fecal matter transplant (FMT). Bacteria from one person's gut microbiome can be processed into pills which can be taken by cancer patients who want to alter their gut microbiome to make them better immunotherapy responders. Following taking FMT pills, patients can acquire the healthy gut microbiome of the donor over the course of several weeks. These FMT pills have been shown to be safe and have improved the therapy outcomes of people living with melanoma. One of the ways you can measure the success of FMT pills is by looking at the bacteria metabolites in our blood that originated in the gut and are dependent on the type of microbiome one has. This new screening method will help us understand the potential of FMT therapy for people living with cancer and receiving immunotherapy.

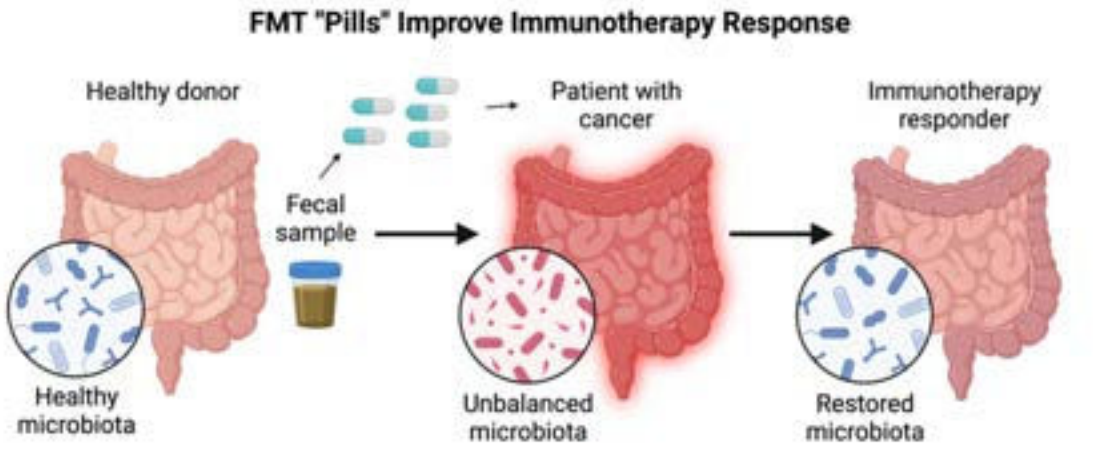

Figure 6: Diagram depicting process of FMT pill creation and use in restoring unbalanced microbiota in cancer patients. *Sarah Hunt and Shannon Snelling, created with BioRender.com*

Key Takeaways:

- Some gut microbiomes allow patients to respond better to cancer immunotherapy
- You can change your microbiome with fecal matter transplant (FMT)
- Patients who undergo FMT acquire the microbiome of the donor over time
- Patients with melanoma treated with an immune checkpoint inhibitor who responded well had a unique microbiome
- Healthy donor fecal matter was made into pills for checkpoint inhibitor melanoma patients to allow them to acquire a good microbiome

Plenary Session 4: Adoptive Cell Immunotherapy: Current State and Future Directions

Notes contributed by: Melissa Coombs and Lorenzo Lindo

Lay Summary of Plenary 4:

This plenary session began with a brief review of current trials and approved cell therapies for hematological and solid malignancies. Then, novel ways to target solid cancers were discussed: Dr. Eric Tran shared his thoughts on tumour infiltrating lymphocytes (TIL) vs t-cell receptor therapy for gastrointestinal cancers. Chris Helsen shared early data on the first cell therapy trial targeting HER-2 new cancers. Julie Nielsen then presented on the CAR-T therapy manufacturing considerations for the made-in-Canada CAR-T by the Canadian-Led Immunotherapies in Cancer (CLIC) group. This plenary served as an excellent segue to the next and closing plenary 5, focusing on how to improve access to cell therapy in Canada.

1. Isabelle Fleury ‘s Talk: CAR-T Research and Clinical Implementation in Hematological Malignancies - Full Speed Ahead

Focus of Talk:

- CAR-T cells (chimeric antigen receptor T-cells) are a type of immunotherapy (which harnesses the body’s immune system) that can target T-cells to a cancer cell
- CAR-T cells have a “synthetic protein” on their cell surface that allows a T-cell to seek out a tumour cell and destroy it using the T-cells machinery

Key Takeaways:

- There are 6 FDA (United States) approved CAR-T cells for various blood cancers after very promising results from clinical trials
- Unfortunately, despite Health Canada approvals for some of these products, access and funding is limited to certain provinces (however, CAR-T cells may be accessed via clinical trials in some provinces)
- CAR-T cells with deeper remissions and lower cost may be needed to improve the case for funding in Canada

Final Thoughts:

- CAR-T Cell therapy is that has been proven but not widely available in Canada only via clinical trials
- It would be great to see it widely available in Canada
- In the future with cost reductions and proven efficacy CAR-T may become a standard of care and not just a clinical trial

2. Simon Turcotte‘s Talk: Cell Immunotherapy for Solid Cancer - An Update

Focus of Talk:

- TIL (tumour-infiltrating lymphocyte) therapy relies on using the body’s T-cells that are able to respond to a tumour
- TIL therapy involves removing a piece of the tumour, taking out the T-cells in the tumour, and expanding those T-cells
- The idea behind TIL therapy is that the T-cells in the tumour have the correct T-cell receptors (TCRs) to attack a tumour, but they are just not numerous enough - so by expanding them in a lab and giving them back to a patient

Key Takeaways:

- One of the challenges with TIL therapy is that we do not know the actual target of the T-cells - the therapy is based on the assumption that the T-cells present in the tumour are somehow reactive against the tumour cells
- TIL therapy typically includes “non-myeloablative chemotherapy” prior to the infusion of the TIL therapy product, and it is followed by support with IL-2 (which is a molecule that promotes the growth and activation of T-cells)

- Long-term follow-up studies for metastatic melanoma have shown good overall response rate with long term remissions (among the 22% of patients who achieved a complete response, 96% of whom are alive 10-years after receiving therapy)
- In a randomised controlled trial in metastatic melanoma, TIL therapy had superior median progression-free survival over a standard-of-care immunotherapy called ipilimumab (which is an immune checkpoint inhibitor)

Final Thoughts:

- TIL therapy shows great promise for metastatic melanoma. 96% of responding patients are alive after 10 years
- May have better outcomes than traditional chemotherapies
- This is an exciting new therapy that works better and has 96% survival rate

3. Eric Tran's Talk: Cell Transfer Therapy Targeting Mutated Neoantigens in Epithelial Cancer

Focus of Talk:

- Despite the impressive responses to TIL therapy seen in metastatic melanoma, it is not effective for a majority of patients (it is currently a minority of patients who respond)
- This is due to various problems that can relate to the T-cell infusion product itself (e.g., T-cells may be exhausted, the binding of the T-cell to the tumour target may not be optimal), surgical resection is required to isolate T-cells (not all patients have a resectable tumour), and manufacturing failures

Key Takeaways:

- The answer to the challenges with TIL therapy may be something called TCR-T which stands for "T-cell receptor engineered T-cells"
- TCR-T overcomes many of the limitations to TIL therapy:
  - Doesn't require surgery
  - Can "select for" optimal T-cells
  - Shorter manufacturing time
  - TCRs with optimal characteristics can be used

Dr. Tran then presented two case studies - to highlight the "story" of T-cell immunotherapy; how he used a relapse after TIL therapy to inform the design of a TCR-T therapy

- A 50-year-old woman with colorectal cancer with lung metastases received TIL therapy (which included many cells reactive against "KRAS-G12D" which is overexpressed by the patient's tumour cells)

    - They found a dominant T-cell receptor in her TIL therapy product, which they then used to develop a TCR-T product - this was an HLA-C*08:02-restricted TIL population reactive against the tumour's KRAS-G12D mutation
- A 71-year-old woman with pancreatic ductal adenocarcinoma (with lung metastases) progressed after a TIL therapy, and then received a TCR-T; she also previously received several rounds of chemotherapy and surgical resection (Whipple procedure)
    - She had regression of her lung metastases after 1 month and achieved a partial response at 6 months after receiving TCR-T
    - While she unfortunately succumbed to her disease at the time of Dr. Tran's talk, she did have an on-going response at the time of publication of that case report
    - Despite the unfortunate outcome, this patient was able to gain a response (and almost another year of life) despite having a very aggressive and heavily pretreated disease

Final Thoughts:

- TCR-T is the next generation and can be used for solid tumour cancer
- Does not require surgery
- Another tool to use when TIL, chemo and immunotherapy fail

4. Christopher Helsen's Talk: TAC-T Cells in the Treatment of Solid Tumours - HER2 Clinical Update and Pre-Clinical Development of CLDN18.2 and GUCY2C in GI Cancers

Focus of Talk:

- Whereas CAR-T cells use a fully synthetic chimeric receptor that operates distinctly from the natural T-cell receptor, TAC T-cells is a novel platform that harnesses the natural T-cell receptor in cells
- TAC stands for "T-cell antigen coupler", and it consists of 3 components:
    - Ligand-binding domain (that allows the TAC to detect a cancer cell)
    - TCR-recruiting domain (that allows the TAC to interact with that T-cells natural TCR
    - CD4 co-receptor domain (that allows the TAC to help activate the T-cell)
- This platform may be safer

Key Takeaways:

- Clinical update from the TAC01-HER2 (TACTIC-2 Trial) for cancers that express the HER2+ protein
    - Shorter vein-to-vein time than most CAR-T cells
    - Progress so far showed favourable safety profile
    - They presented a case study of a 42y male with Stage 4b gastric adenocarcinoma who progressed after chemotherapy of a bispecific antibody (HER2xCD3); he was

treated at dose level 2 in the phase 1 portion of this trial and at 1 month, achieved a 36.5% reduction in tumour size by PET-CT - no severe adverse events or cytokine release syndrome/ICANS
    - Summary from this trial is that there is a good safety profile with promising clinical activity
- Novel targets for their TAC-T platform:
    - CLDN18.2 (optimal target for gastric cancer) - in vitro and in vivo (mouse) studies show good activity and long-term disease control
    - GUCY2C (very early development) - good potency with studies using in vitro and in vivo models

Final Thoughts:

- Early stages but results seem promising
- Another possible immunotherapy treatment that should be accessible and feasible for all Canadians

5. Julie Nielsen's Talk: Made-in-Canada - Manufacturing CAR-T Cells for the CLIC-1901 Clinical Trial

Focus of Talk:

- While CAR-T cells have revolutionised the treatment of blood cancers with many FDA and Health Canada approvals, access for Canadians is still limited
- This is in part due to the high costs of commercial CAR-T cells

Key Takeaways:

1. The CLIC-1901 (CLIC-01) trial is a publicly funded CAR-T cell trial that uses a construct within the public domain - which allows more accessible use with lower costs (as the products are made in Canada)
2. The manufacturing outcomes for the autologous CAR-T cell products show very high success rates that pass all release criteria - and they are able to make large number of CAR-T cells
3. They did some exploratory work based on phenotyping of the CAR-T cell products and found that high levels of CD28 on the starting T-cells collected from apheresis is correlated with increased viable cell yield at the end of manufacturing
4. They are still working to develop potency assays that will be utilised as part of the release criteria for the upcoming CLIC-02 trial (targeting CD22)
5. Summary - they were able to open a trial within 3.5 years of initial discussions and have achieved a 97% manufacturing success rate using the CliniMACS prodigy
    - Most cells are in the infusion product are T-central memory or T-effector memory cells
    - 58 patients have been treated to-date
    - They want to expand manufacturing to additional sites to improve access

Final Thoughts:

- Impressive that 58 patients have been treated with CLIC
- More are being invited to participate in the clinical trials
- This is exciting as it will allow more Canadians access in more centres at a lesser expense when it becomes mainstream
- CLIC will allow all those patients that require CAR-T the opportunity to do so and Canadians will not have to go the US and pay up to 10 times more for treatment

Final Discussion: A lot of great work is being done globally around the world in the field of immunotherapy. In particular, there is considerable ground-breaking research being done by Canadians to create the innovations for the next generation of immunotherapies. The advances made in Canada, particularly those by academic and public agencies, have the potential to offer more affordable and equitable cancer treatments throughout the country in hopes of improving outcomes for Canadians.

Plenary Session 5 Panel – What's the endgame for cancer immunotherapy in Canada?

Notes contributed by: Chantale Thurston, Sabrina Guettouche and Céline M. Laumont

Lay Summary of Plenary 5: The plenary was in a panel format. The panel's purpose was to ask: "what's next for cancer immunotherapy in Canada?" The panelists represented several different sectors and disciplines involved in the translational pipeline of a biotherapeutic drug product and addressed issues beyond proof of concept and into products. It addressed some of the pain points and barriers to treatment access: cost, time, time for approvals or lag in actual treatment access. Additionally, ultra-rare indications do not have any industry interest: what does their path look like from experimental to clinical trial and beyond?

1. Julie Douville's Talk: n-Lorem: A non-profit model for translating advanced therapeutics to nano-rare patients

Key takeaways:

- n-Lorem is a 100% non-profit organization based in the United States that provides individual therapy to patients with genetic diseases affecting < 30 patients worldwide (so-called "nano-rare diseases") since 2020.
- n-Lorem's therapy of choice, called antisense oligonucleotide therapy or ASO therapy, relies on the design of ASO molecules that can modulate the production of the disease-causing protein.
- n-Lorem uses ASO therapy because this well-established technology is:
    - rapid and efficient

    - versatile
    - validated and understood
    - cost effective
    - already approved by regulatory bodies in other contexts (e.g., Food and Drugs Administration)
- The process from diagnosis to treatment takes about 15 to 18 months and involves the following steps:
    - Apply for treatment: done through a webform by the patient's physician.
    - Review by Access to Treatment Committee: an expert panel reviews each application and makes recommendation to n-Lorem.
    - Treatment decision by n-Lorem: n-Lorem notifies the physician of treatment decision.
    - Drug discovery and development: n-Lorem and its partners design multiple ASO candidates that are then tested to select the most specific, safe, and effective ASO that will be used to treat the patient.
    - Manufacturing: a clinical batch of the selected ASO is produced using good manufacturing practices (GMP).
    - Patient administration: the patient receives their ASO therapy.
- Meaningful statistics about n-Lorem:
    - 156 applications to date, with ~50% accepted for treatment
    - 70 patients are currently in the pipeline
    - 3 patients received treatment

Final thoughts:
n-Lorem is a foundation that tries to address the need for treatment of "unconventional" patients, that is patients for whose no clinical trials can be done because their conditions are too rare.

2. Kathy Brodeur-Robb's (C17) Talk: Pediatric access to personalized medicine: the regulatory perspective on single patient studies

Key takeaways:

- Along the translational continuum, there are two valleys of death that slow down patient access to effective drugs:
    - Valley 1: between basic biomedical research (what happens at the bench) and clinical research (clinical trials)
    - Valley 2: between clinical research and the implementation in clinical practice

However, patients have no time to waste, they need to be treated NOW!

- Single Patient Studies (SPS) are single-patient clinical trials that allow clinicians to treat a single patient with a non-approved drug or a drug that has been approved for another indication.

- Setting up an SPS is a very difficult process that is not yet documented on the Health Canada website. SPS are considered to be regulated clinical trials, so they require a lot of documentation including a clinical trial application, ethics approval and informed consent, a plan for adverse event reporting and study monitoring, etc.

Final thoughts:
SPS can sometimes be the only option left to treat a patient. While the road is long and sinuous to get them approved, C17 can help interested clinicians get there. Hopefully, as more and more clinicians request SPS, Health Canada will develop a more streamlined process for them.

3. Karen Facey's Talk: Enabling access, whilst resolving uncertainties – What's feasible?

Key takeaways:
- In England, the National Health Services (NHS) in collaboration with National Institute for Health and Care Excellence review data from pharmaceutical companies to decide whether or not new cancer treatments should be routinely reimbursed. While the choice is obvious for some drugs (approval or not), some drugs might have promising clinical data that are not strong enough to back a firm decision.
- The Cancer Drug Fund was created as an interim funding solution so that patients can access, for a limited period of time, a newly recommended cancer drug. During this time, new data will be acquired to resolve uncertainties around its effectiveness.
- Dr Facey compared the English system to the Spanish and Italian ones.

Final thoughts:
The Cancer Drug Fund allows patients to access promising new cancer drugs, while giving more time for the NHS to acquire data that will inform its decision making around routine reimbursement.

4. Nicole Mittman's Talk: Health technology assessment in Canada

Key takeaways:
- CADTH is the Canadian organization that reviews drugs for approval in Canada and makes recommendations to the federal, provincial and territorial governments.
- They are involved with Project Orbis, which includes multiple countries, that aims to be a quicker pathway for drugs approval by partnering the review of cancer drugs.
- They use real world evidence to look at benefits of cancer drugs, as well as the short-term vs long term effects of the drugs.

Final thoughts:
By sharing the work of reviewing information can help increase the pace of having approvals, however there is an opportunity cost that if they fund one treatment it will take away from another treatment.

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.