CellCAN
Regenerative Medicine and Cell Therapy Network

CELL & GENE THERAPY REVOLUTION

Time to gown up!

in partnership with

CCRM Commercializing Living Therapies

C3i Center for Commercialisation of Cancer IMMUNOTHERAPY

CellCAN's Second pan-Canadian Strategic Forum on Cell & Gene Therapy

From Translation to Commercialization

March 13 to 15, 2019
Toronto

EVENT REPORT
WWW.CELLCAN.COM/FORUM2019

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2019 STRATEGIC FORUM - SCIENTIFIC ORGANIZING COMMITTEE

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OVERVIEW

There were tremendous advances since our last forum two years ago. The Canadian experience and comfort with cell production have grown exponentially, and we are making remarkable progress every year to treat a growing number of diseases and develop safer and more efficient treatments. We cannot slow down! We must intensify our efforts because it is only a matter of time before Canadians have broad access to the most innovative and safe therapies available. This is one of the major conclusions of the second **CellCAN pan-Canadian Strategic Forum, Cell & Gene Therapy Revolution: Time to Gown Up!**

Organized in partnership with the Center for Commercialisation of Cancer Immunotherapy (C3i) and the Centre for Commercialization of Regenerative Medicine (CCRM), the 2019 edition spoke to the practical experiences here and abroad. How can manufacturing, characterization and delivery of cell therapies be better optimized and made affordable? The 3-day conference revealed that things are definitely coming to fruition in Canada, and that through collaboration, we have the ability to mold the future.

The preconference, hosted by C3i, covered the role of biomarkers in supporting GMP manufacturing, how to characterize the response to CAR-Ts and other cellular therapies, and the importance of companion testing and patient stratification in the era of personalized medicine.

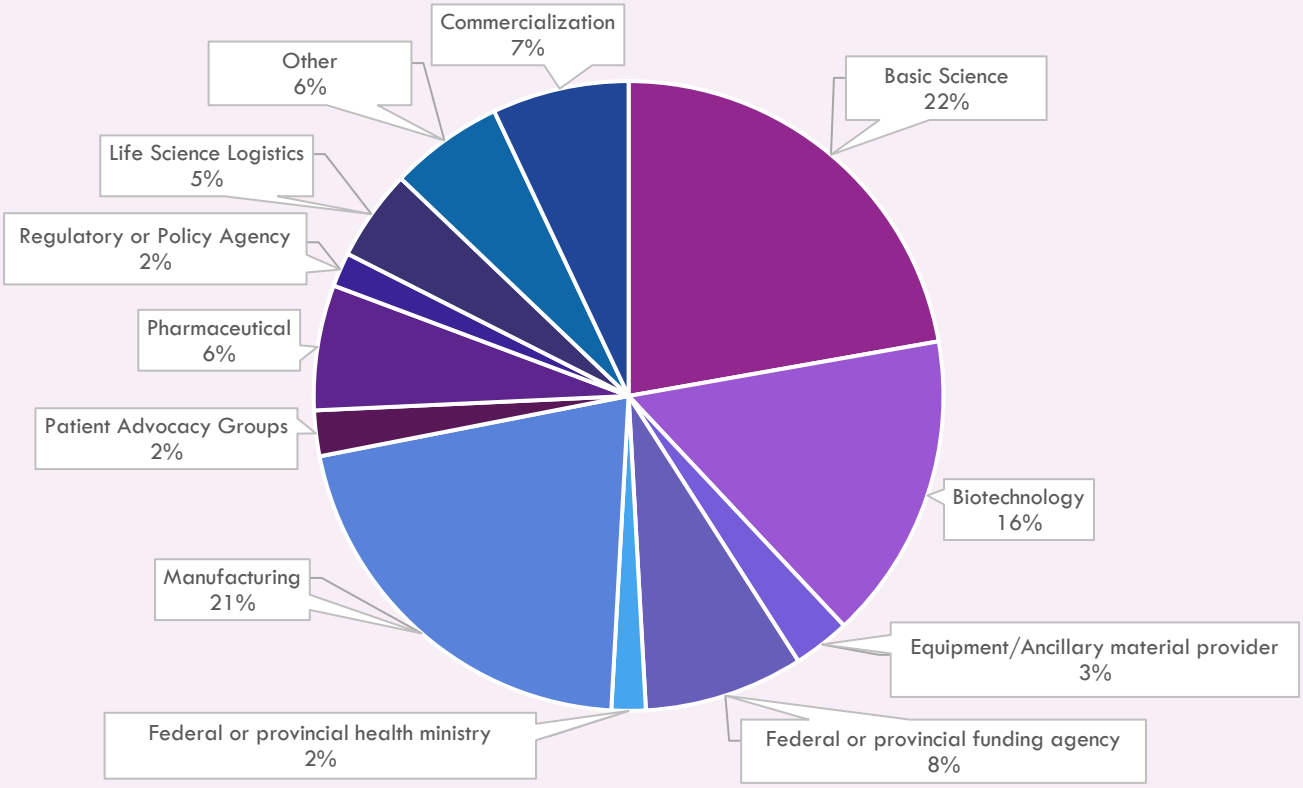
The main program covered some fascinating innovations (off-the-shelf therapies, FailSafe™ kill switch, and others), the evolution of cancer immunotherapy and regenerative medicine clinical trials, addressed various strategies such as techniques to reduce the cost of goods, and demystified the agile framework behind our evolving regulations. It also identified ways to facilitate and accelerate access to cell and gene therapies for patients in Canada and abroad.

We know these innovative therapies are within our reach, as the first commercial therapies that have received approval in Canada. This report provides a summary from the plenary talks and panel discussions, and identifies key messages and key questions to move forward.

On behalf of the CellCAN Board of directors, CellCAN's management team and the entire scientific organizing committee, we would like to thank our speakers, our invaluable partners and sponsors, and all the participants for making this event a success!

STRATEGIC FORUM AT A GLANCE

180 participants from across Canada and abroad representing:



The Forum created a space for strategic discussions about the future of cell and gene therapy in Canada and for direct interactions between stakeholders: patients, clinicians, researchers, representatives from industry and structuring networks, policy makers, regulators, government representatives, and members of the media.

- 15 sponsors
- 9 exhibitors
- A very high participant satisfaction rate:
  - **92% overall satisfaction rate**
  - 92% of the respondents said the event met their expectations
  - **95 % would participate again**
- More than 30 speakers on four strategic themes

Social Media Reach

13 086 views

255 998 impressions

STRATEGIC FORUM AT A GLANCE

Quotes from participants

"Great networking and learning opportunities."

"My presentation at the 2019 Forum led to my contribution to a proposal with another participant met there, and this has now resulted in my participation in a major new National Research Council Project. It also resulted in a proposal to NSERC with a company partner met at this Forum, with great potential for a fruitful long-term collaboration. This was an extraordinarily useful meeting for me to attend, perhaps the most ever!"

"It was a very, very good experience, hope to be there in 2021!"

Michel Rochon: Renowned moderator to facilitate rich discussions

- Seasoned scientific communicator and speaker
- More than 30 years of experience as a scientific and medical journalist
- Book author: *Le cerveau et la musique*
- His passion and energy allowed panelists and participants to engage in rich discussions

"Outstanding moderation by Michel Rochon. Great meeting! Enjoyed all presentations."

FORUM HIGHLIGHTS

- A complete pre-conference day focused on biomarkers.
- Dr. Daisuke Doi came all the way from Japan to present the first human trial of iPSC-derived cells for Parkinson's disease.
- Presentation of the National Research Council of Canada's Health Challenge Program by Dr. Kelley Parato, the newly appointed Program Director.
- Invited stakeholders had a productive lunch meeting in the presence of Health Canada's Biologics and Genetic Therapies Director General, Dr. Celia Lourenco, to discuss the ongoing regulatory reform for drugs and devices.
- Four patients shared their incredible journeys and the impact of cell therapies on their lives. **Listen to Kevin Bolusi's interview, recipient of self-assembling skin substitute for 3rd degree burns:**

Pre-conference – March 13, 2019
Theme 1: The role of biomarkers in supporting GMP manufacturing

The objective for theme 1 was to discuss the analytical and regulatory requirements to characterize products in the era of cell and gene therapy. The opening lecture by **Donna Rill** from Triumvira Immunologics, highlighted the importance of quality control and the development of practical workflows to assess product attributes during the cell isolation, manipulation and expansion process with respect to Triumvira's CAR-T therapeutic candidate, TAC01-CD19 engineered T-cell.

How to develop a framework to define key biological parameters/benchmarks for a cell therapy product outside of which the efficacy of the clinical product may be compromised?

A workflow should be created to assess the quality of the starting materials, the manufacturing process and the final drug product. A strategy to work backwards from the final drug product was proposed to identify potential risk to process parameters. Critically, one should realize the importance of being able to broadly characterize the product from the initial stages of development.

Along the same lines, **Dr. Martin Giroux** from the CETC insists that early planning and wide collaboration will ensure successful manufacture. Analytical tests must be kept at the forefront of any translational and development programs to ensure safety and quality of the product and the process. Complexity of production and complexity and intrinsic heterogeneity of the final product in cell and gene therapy necessitate a deep investment in the analytical testing necessary for its characterization.

In response to the need of analytical technologies with the ability to define the product identity, purity, safety and potency of highly complex and heterogeneous biologics manufacturing, **Dr. James Piret** from the Michael Smith Laboratories spoke to the value of Raman spectroscopy. This technology allows the characterization of various cell products and the monitoring of multiple analytes, which provides rich information in a reagent-less, label-free and non-invasive manner. It is an orthogonal technique that can be used in concert with other functional or immunological assays to identify unexpected cell type deviations over the course of cell product manufacturing. **Raman spectroscopy is a technology that can be easily incorporated to cell manufacturing workflows and can provide valuable information regarding product consistency and quality.**

While cell therapies are believed to have specific advantages with respect to therapeutic benefit and extended duration of effect, hurdles remain with respect to consistency of manufacturing, patient material and final product variability, and the potential for both short-term and long-term adverse events. Beyond the challenges of manufacturing and quality control, as compared to their small molecule counterparts, cell therapy products or biologics require additional attention from the perspective of regulatory oversight and approval of product release. To highlight their inherent complexity in the consistency of manufacturing, the variability of patient material, the variability of the final product and the potential for both short-term and long-term adverse events, **Dr. Dino Petrin** from Health Canada referenced a quote from Scott Gottlieb, the former commissioner of the Food and Drug Administration:

"**A lot of the complexity with gene therapy is in product related issues, not the clinical issues.** With normal drugs, I'd say 80% is the clinical portion and 20% is the CMC and product portion of the review. I think with gene therapy and cell-based regenerative medicine, it is completely inverted. We're having to think very differently about the regulatory issues with these."

The path to market authorization in the context of the regulatory expectations have been defined by Health Canada. Interestingly, Dino Petrin noted that **50% of the clinical trial applications for gene therapy originate in academic centres, not large biopharmaceutical companies**. As such, a lack of familiarity with Health Canada's regulatory road map can pose a challenge for individuals/sponsors not attune to regulatory expectations. He echoed some of the statements that had been made in previous discussions including the necessity of knowing your product, and building in quality and good documentation processes as early as possible. The principles of good manufacturing processes should be initiated early on and manufacturing changes kept to a minimum, since generally speaking, it is easier to make changes in product development early rather than later. Similarly, the end goal of the product should be identified as soon as possible and you should work backwards from this point. Lastly you should also be aware of what will happen to the product post-manufacturing with respect to traceability, shipping, and storage at clinical locations.

Pre-conference
Theme 2: Clinical response to CAR-Ts and other cellular therapies

The objective of theme 2 was to learn about ongoing trials with promising cell and gene therapy strategies and how these impact the immune system and clinical response.

While emerging techniques such as Raman spectroscopy have the potential to characterize specific analytes in cell products, immunophenotyping by flow cytometry remains the gold standard in cellular characterization. **Dr. Jean Sebastien Delisle**, from the Maisonneuve-Rosemont Hospital, spoke to his institute's experience with respect to immune-phenotyping of cell therapy trials using their integrated platform for cellular analysis.

The methodologies employed here include a combination of flow and mass cytometry coupled with functional assays and cytokine arrays, allowing the group to qualify products, monitor the cells post-infusion and assess systemic effects in patients. In addition, genomic techniques are also used to track and characterize T-cell clones.

Critical attributes of a successful immunophenotyping platform were highlighted, such as the availability of adequate personnel prepared to accept and process samples unexpectedly. In addition, the importance of distinguishing between the implementation of required versus exploratory elements of the protocol is essential. If possible, over complicating the workflow with unnecessary assays and measurements should be avoided.

Dr. Andreas Bader, from Triumvira Immunologics, presented his company's novel T-Cell Antigen Coupler (TAC) technology which includes both the chimeric antigen receptor (CAR) and the engineered T cell receptor (TCR) therapies. The TAC technology platform offers competitive advantages over standard CAR-T cells therapy through moderate cytokine release and low off-tumor sensitivity, rather than high and uncontrolled activation by CAR-T cells. TAC-T cells low toxicity and robust therapeutic efficacy have been shown in both liquid and solid tumors using different human tumor xenograft models. A promising TAC

product candidate pipeline was presented with a focus on TAC01-CD19 that is anticipated to enter phase I/II clinical trials in 2019 in patients with diffuse large B cell lymphoma (DLBCL). Furthermore, Dr. Bader spoke about using focused scientific questions to define the biomarker strategy, read-outs and endpoints of interest.

While CD19-targeted CAR-T cell have shown promising results in relapsed/refractory acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphoma (NHL), treatment failure occurs, and development of resistance represents an ongoing challenge. What are the factors that contribute to the CAR-T treatment failure? What are the mechanisms of resistance? **Dr. Joerg Krueger**, from the Hospital of Sick Children, discussed the determinants and mechanisms of treatment failure in CAR-T cell therapy and suggested some possible solutions.

Reasons and determinants for treatment failure	What can we do?
The quality of the apheresis and CAR-T product (T cell fitness)	Pre-collection assessment Product assessment Earlier collection for high risk patients?
Successful bridging chemotherapy	Low intensity chemotherapy regimen for a balance of disease control vs toxicity
Early CAR-T cell loss	Re-infusion and use of checkpoint inhibitors
Target antigen loss (mutation)	–
Target down regulation	Targeting dual pathways
Receptor masking	–
Lineage switch	Role of the cytokine release syndrome in lineage switch?

While CD19-targeted CAR-T (CTL019) cells have shown to be very potent in clinical trials to treat hematologic malignancies, its efficacy for long-term complete remission in chronic lymphocytic leukemia (CLL) has only been shown in a subset of patients. Here, **Dr. Jan Joseph Melenhorst**, from the University of Pennsylvania, discussed how a comprehensive assessment of patient-derived CAR-T cells allowed his group to identify the mechanisms of therapeutic success and failure in CLL. By genomic, phenotypic and functional studies, his group demonstrated that the T-cell memory function is the key component of therapeutic efficacy of CTL019 in CLL. Dr. Melenhorst also discussed how manipulation of important cellular pathways or regulators of the T-cell memory function (such as glycolysis, IL6/STAT3 signaling and TET2) can affect CTL019 cell expansion and therefore the maintenance of a durable antitumor effect. These findings support that intrinsic T-cell mechanisms and their key components constitute potential biomarkers to predict response to CTL019 therapy.

Pre-conference
Theme 3: Companion tests and patient stratification in the era of personalized medicine

The objective of the last theme was to understand the underlying of the development and implementation of biomarkers as companion diagnostics for cell and gene therapy.

Monoclonal antibody checkpoint inhibitors have been shown to have impressive clinical activities in subsets of both solid and hematological malignancies. Unfortunately, only subsets of patients respond to treatment. **Raffi Tonikian**, from Merck Canada, highlighted the importance to identify biomarkers that report on which patients are most likely to respond to checkpoint inhibition. Biomarkers are defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention".

PREDICTIVE	PROGNOSTIC	DIAGNOSTIC
Used to identify patients who will benefit from a particular drug therapy.	Used to determine how aggressive the disease process is and/or how a patient may expect to fare regardless of therapy.	Used to diagnose a disease potentially before it is detectable by conventional methods.

In the realm of checkpoint inhibitors and immunotherapy, a number of emerging biomarkers are currently being tested and further validated in clinical trials and from samples on standard of care treatment. In cancers where interventions targeting the PD-1/PD-L1 interaction are used, the evaluation of PD-L1 expression by immunohistochemical staining has emerged as a potentially important predictive biomarker. PD-L1 testing has been FDA approved for histological analysis of a number of solid tumours, though the criteria of PD-L1 expression and cut offs vary.

Tumour mutational burden (TMB) is also a potential predictive biomarker of response to checkpoint inhibition. Certain tumours with elevated levels of mutated genes have been shown to display favourable response to PD-1 blockade. The rationale for this observation is that mutated genes have the potential to encode for abnormal proteins with increased numbers of neoantigens leading to enhanced activation of the immune system. To evade the activated immune system, these cancers are reliant on the overexpression of inhibitory receptors, such as PD-L1, rendering them highly susceptible to checkpoint inhibitors. However, the correlation between mutational burden and response to checkpoint inhibitors does not hold for all tumour types and different biomarkers should be identified for these cases. This analysis shows that TMB and inflammatory biomarkers (such as PD-L1 expression) can jointly stratify human cancers into groups with different clinical responses to the treatment and identify patterns of underlying, targetable biology related to these groups.

Biomarker discovery and development is an active area of scientific research with great promise. Diagnostic tests used as a companion to a therapeutic drug to determine its applicability to a

specific person, are going to be increasingly present in the clinical setting. However, the integration of companion tests in the healthcare system represent some challenges, as underlined by **Dr. Lambert Busque**, from C3i. Identifying biomarkers of response early in the process of the drug or cell and gene therapy development is ideal but can be difficult for academically driven projects or small biotechs. Moreover, clinical laboratories have to be ready with companion tests upon approval/reimbursement of drug. "**But the system is not built that way. In Canada, laboratory systems are not linked to drug development**" said **Dr. Busque**. There is still a lot of work to be done to integrate these novel techniques into the system. This pre-conference was a definitive first step in understanding and preparing our healthcare system.

Main Conference – March 14 & 15, 2019

The program of the main conference was carefully crafted to address the emerging issues that cell and gene therapy stakeholders are facing. The first Cell and Gene Therapy Revolution Strategic Forum, hosted in 2017, put forth a very strong and clear message and brought together key stakeholders to discuss what it meant for Canada: it's coming. A mere 24 months later, this message is no longer relevant: it's here. We're there. The cell and gene therapy revolution is now happening in Canada - the first commercial therapies were approved by Health Canada. It's time to gown up!

With that, new challenges arise and this program allowed stakeholders to dive deep into practical clinical experiences here in Canada and abroad. How can the manufacturing and delivery of cell and gene therapy products be optimized?

While the pre-conference presented by C3i opened a discussion about the optimization of cell therapy delivery through the use of biomarkers, the Strategic Forum was built around 4 themes:

- Innovation in allogeneic cellular therapies: game changer in regenerative medicine
- The next generation of clinical trials
- Regulatory reform & reimbursement
- Innovations in cell & gene therapy manufacturing

Below you will find a summary of the presentations and panel discussions that were held around each of those themes. We hope this provides you insightful information and piques your interest in joining us at our next Strategic Forum in 2021!

Main Conference – Theme 1: Innovation in allogeneic cellular therapies: game changer in regenerative medicine

Allogeneic cellular therapies using human pluripotent embryonic stem cells (ESC) or induced pluripotent stem cells (iPSCs) that can differentiate into many different cell types, hold considerable promise as an unlimited source for cell replacement in autoimmune and neurodegenerative diseases.

While differentiated pluripotent stem cells hold tremendous therapeutic potential, several important questions still need to be addressed:

- What is the nature of the optimal cell preparation?
- How to protect cells from an immune attack?
- How to control the cells proliferation and differentiation?
- Where should cells be implanted?

Exciting progress has been made into bringing more efficacious, less immunogenic and safer allogeneic cell therapies. Each speaker showcased innovative technologies developed to bring these therapies to patients.

Dr. Tim Kieffer, from the University of British Columbia, presented an innovative cell therapy option for the treatment of type 1 diabetes using pancreatic progenitor cells, derived from embryonic stems cells (ESC), as engineered insulin-producing pancreatic islets for transplantation. The patients receiving this treatment would be given back tight glycemic control and would no longer require insulin injections, potentially avoid debilitating and sometimes life-threatening complications. This is currently under clinical trial and addresses an unmet need for type 1 diabetics.

The feasibility of this therapy is shown by the Viacyte's product VC-01, consisting of human ESC-derived pancreatic progenitor cells, encapsulated in the ViaCyte's Encaptra device. This macro-encapsulation device has a semipermeable membrane that is designed to allow oxygen, nutrients, and proteins (e.g. insulin) to freely transport across, while protecting the cells within from the patient's immune system.

As underlined by **Dr. Andras Nagy**, from the Lunenfeld-Tanenbaum Research Institute, the use of pluripotent stem cells in allogeneic cell-based therapy not only brings concerns with rejection by the immune system, but also with the difficulty to control their propagation and differentiation — which poses a risk of uncontrolled cell proliferation and stem cell induced tumour formation.

To tackle this safety issue, the research team developed the FailSafe™ kill switch system, which consists of a drug-inducible suicide capacity linked to the cell division. Upon treatment of the recipient with the suicide-inducing drug, the FailSafe™ system can selectively eliminate proliferating cells following transplantation. Only well differentiated and mitotically arrested (or slowly proliferating) cells remain.

What is Failsafe™?

It's a technology that stops an unwanted proliferation of cells following an allogeneic cell-based therapy. As one of the risks with these therapies is the occurrence of stem cell induced tumours, this drug induced technology acts as a call to suicide for the unwanted proliferating cells.

Another major hurdle of allogeneic cell therapy is the necessity of acute and chronic immune suppression of the patient, which can result in potentially deadly complications. Dr. Nagy presented their newly developed induced allogeneic cell tolerance (iACT) system that addresses this problem. In their studies, by combining the FailSafe™ and the iACT systems, long-term allograft tolerance without the need for systemic immune suppression of the recipient has been achieved.

One of the greatest recent advances in the field of regenerative medicine is that the first in human clinical trial using iPSC-derived cells for Parkinson's disease treatment is being conducting! This very exciting development for allogeneic cell therapies was presented by **Dr. Daisuke Doi**, from Kyoto University. The methodology developed by Dr. Doi and his team utilizes iPSCs to generate dopaminergic progenitors for transplantation into patients suffering from Parkinson's disease. Once transplanted into the patient, these cells have the ability to reconstitute damaged dopaminergic neurons and potentially resolve some of the symptoms of the disease. The researchers showed that clinical grade iPSC-derived dopaminergic progenitors can be produced and demonstrated safety and efficacy in preclinical rodent and primate models. Importantly, a substantive dopaminergic receptor characterization protocol has been developed to ensure the reproducibility and quality of the cells. Currently, the clinical development plan includes administering these cells to seven patients and following them for two years to ascertain efficacy and safety.

These advances have the potential to change the lives of millions worldwide, in addition to potentially reducing the cost of disease management for the healthcare system.

Panelist discussion: Allogeneic vs autologous sourced donor cells: the strategic advantages

From left to right

Moderator: Heidi Elmoazzen, Director, Stem Cells, Canadian Blood Services

Andras Nagy, Canada Research Chair in Stem Cells and Regeneration

Daisuke Doi, Research Associate, Department of Clinical Application, Center for iPS Cell Research and Application, Kyoto University, Japan

Lucie Germain, professor Université Laval, CHU de Québec-Université Laval

Duncan Stewart, President, OHRI, CEO, OIRM

Concepts explored in this panel discussion:

- Moving away from autologous therapies to off-the-shelf products
- Whether or not there is an advantage for particular therapies to be produced under a "universal donor" strategy
- Situations where autologous cells make the most sense
- If the severity of the disease dictates the urgency for timely and optimal manufacturing
- Benefits and risks to recipients
- Site of implantation or infusion risks based on cell source
- Regulatory concerns with autologous or allogeneic cells

Theme 2: The next generation of clinical trials

The evolution of cancer immunotherapy and regenerative medicine clinical trials was explored with a forward-looking approach to the implementation of changes that will facilitate the launch of novel cell and

gene therapies in Canada. Speakers and panelists guided the participants through strategies that have worked both in Canada and other jurisdictions for cell and gene therapies and identify areas that require further development.

To start, **Dr. Donna Wall**, from The Hospital for Sick Children, illustrated the therapeutic potential of gene therapy with the diseases of thalassemia and sickle cell anemia. Through decades of fundamental biology and clinical studies, we now have the understanding of both diseases to design novel and creative gene therapy strategies. Leveraging experience from bone marrow transplantation and new gene-editing tool of CRISPR/Cas9, Dr. Wall's group started a phase I/II study in the fall of 2018 to test the safety and efficacy of CTX001, a CRISPR-Cas9 genetically modified hematopoietic stem and progenitor cell (hHSPCs) autologous treatment for Thalassemia patients.

Key factors impacting the outcome of a gene therapy:

- Haematopoietic stem cell (HSC) number and quality
- Ex vivo manipulation
- Delivery method of the modified cells
- Pre-infusion conditioning
- Patient age and disease

Dr. Wall also emphasized the importance of engaging the patient community in building the clinical research agenda.

Another cell and gene therapy that attracts a lot of attention lately in Canada is certainly CAR-T therapy with the major question being:

Can we produce a therapeutically effective CAR-T therapy entirely within the Canadian academic hospital setting?

Dr. Rob Holt, from the British Columbia Cancer Agency, discussed the Canadian-led manufacturing and delivery of CAR-T therapy as a healthcare implementation research project. Following the discovery and pre-clinical studies, CAR-T clinical development and testing is a complex process with multiple steps:

- Seeking Regulatory & REB approval
- Vector GMP manufacturing & release testing
- CAR-T GMP manufacturing & release testing
- Clinical testing & monitoring
- Correlative studies

Ideal characteristics of a CAR-T product:

- Lower toxicity
- Fine-tuned control (a Boolean control logic)
- Effective stop mechanisms
- Novel antigens
- Positive results treating other cancers (such as solid tumours)
- A growing "engineered cell therapy" bio-economy
- Sustainability

The production of Canadian CAR-T has enabled a collaborative studies program from coast to coast, involving different experts and multiple sites to cover all of the clinical aspects of its development. Cell production methods and study approaches have been shared and discussed with the goal of producing the best CAR-T product.

The first CAR-T product and cell therapy to be approved in Canada (fall 2018) is KYMRIAH™ (tisagenlecleucel) and is manufactured by Novartis. **Marta Majdan**, Medical Advisor from Novartis, gave industry insights as to how Novartis plans to approach access to CAR-T therapy in the Canadian landscape. The focus of the presentation was drawn to the logistics and challenges of manufacturing and delivering an engineered cell product.

To streamline manufacturing and delivery, the company intends to build a Canadian support and logistics centre that will liaise with local healthcare providers using an e-platform for product request. Following the apheresis protocol, cryopreservation, shipping, manufacturing and infusion steps are initiated as per the master protocol. Going forward, additional activities in the CD19 CAR-T portfolio include clinical trials testing combination strategies with other targeted agents including BiTEs, checkpoint inhibitors and BTK inhibitors. Trials utilizing CAR-T cells targeting other antigens including BCMA, CD22, CD123, EGFRv3 are planned for 2019.

Panelist Discussion: Vision of clinical trials for the next 5-10 years

From left to right
Moderator: Janet Dancey, Director, Canadian Cancer Trials Group
Marta Majdan, Medical Advisor, Cell and Gene Therapy, Novartis Canada
Denis Claude Roy, CEO, CellCAN
Donna Wall, Blood and Marrow Transplant/Cellular Therapy Program, The Hospital for Sick Children/University of Toronto

Concepts explored in this panel discussion:

- Resources needed for novel cell & gene therapies are unlike traditional small molecule-based clinical trials
- Logistical concerns for manufacturing and delivering CGT to patients
- Some centres have tried an alpha-clinic approach: will this be the way to move forward?
- Improved integration of various hospital departments (e.g. ICU, pharmacy, specialized nursing units, etc.)
- What has worked for experienced Canadian centres?
- Is it too early to implement cost-saving strategies?
- Can Canadian centres learn from other jurisdictions?
- Are the regulatory authorities working well enough with HTAs?
- What areas must be streamlined before widespread clinical trials are initiated
- Will this be the same for commercialized products?

Theme 3: Regulatory Reform and Reimbursement

The Canadian regulatory framework is evolving in the face of novel technological advancements in cell and gene therapy treatments. This new and forward-looking approach to regulate these therapies will be responsive and adaptive to the evolving field while looking to the horizon for next generation of therapies that will soon be in the clinic. Participants learned how advanced technology health products fit within newly crafted regulations from Health Canada to enable an adaptive and modern framework. Indeed, health technology assessment and the evaluation of reimbursement strategies are evolving in parallel. Participants learned about the impacts of bringing these novel therapies to the healthcare system and how patient care is impacted. New paradigms in reimbursement were discussed and featured.

Cell and gene therapies are regulated by Health Canada under the Food and Drugs Act for safety, quality and efficacy. **Dr. Celia Lourenco**, Director General of the Biologics and Genetic Therapies Directorate of Health Products and Food Branch, presented how Heath Canada is addressing the current challenges of advanced therapeutics regulation by modernizing the existing framework through the creation of agile regulations in order to provide flexibility to enable product innovation.

"Regulation has to be agile and adaptive enough to address the ways that innovative companies will continuously re-write the rules of competition, ensuring sufficient oversight to protect public interest without posing obstacles to innovation"

Investing in a Resilient Canadian Economy, Advisory Council on Economic Growth, 2017

Through the Regulatory Review of Drugs and Devices (R2D2) initiative and Cell Therapy Stakeholder Group Bilateral meetings, Health Canada is working to create an agile regulatory system that supports better access to therapeutic products based on healthcare system needs. Health Canada is also working closely with international partners to align where appropriate and to share lessons learned and best practices as we develop the best approach for Canada.

Following Health Canada's approval, novel cell and gene therapies review process is followed by a health technology assessment (by CADTH and INESSS) for the value of the treatment, price negotiations (by pCPA) and provincially led decisions on funding and reimbursement. In its current operating format, the average number of days between regulatory body approval and agency reimbursement decisions in Canada is 213 days. **Alexandra Chambers**, director of pCODR at CADTH, presented a pilot study focusing on initiatives to better align the workflows of Health Canada and the bodies responsible for health technology assessment to allow for real time discussions, a greater ability to share information and reduce the possibility of duplication of efforts. Taken together, this should create a more efficient regulatory process. In June 2018, this pilot study was operationalized, formally introducing the aligned review process between Health Canada, CADTH and INESSS. Once the drug company provides a consent letter, this will allow the bodies to share documentation, discuss review status and observe meetings. Going forward, the plan is to collect and analyze data to assess the impact of the aligned review process and generate a pipeline for information sharing.

Different approaches to the access and the reimbursement of high-value and high-cost therapies have also been discussed. **Dr. Kathleen Reape**, Chief Medical Officer for Spark Therapeutics shared her experience with the retinal dystrophy treatment with the gene therapy of Voretigene, Neparvovec-rzyl. Gene therapy for genetic diseases that underscores the need for genetic diagnosis may require different approaches from the medical/payer community. Spark has worked with healthcare providers and payers to develop alternative distribution and payment methods:

- Innovative Contracting Model (ICM)
- Direct sale to payer or specialty pharmacy as an alternative to traditional "buy and bill" model
- Reduces financial burden and risk to the institution as well as mark-up to the payer
- Coverage to label; expedited benefits processing; patient out-of-pocket cap
- ICM + outcomes-based rebate arrangement
- Outcomes-based rebate arrangement with both:
    - An initial efficacy (30-90 days) measure
    - A longer-term durability (30 months) measure
- On-going discussions with Centers for Medicare & Medicaid Services (CMS)
- Potential to enable Spark to offer outcomes-based installment payments focused on initial efficacy and long-term durability

Regulatory and reimbursement challenges for cell and gene therapies have been discussed, but what about the impact on the healthcare system where the treatment will be provided? **Dr Lambert Busque**, medical coordinator of the Cancer Program at Maisonneuve-Rosemont Hospital explained how the hospital prepared itself for the implementation of Novartis' KYMRIAH CAR-T therapy. First, inspection and certification of the GMP facility by Novartis was required since CAR-T therapy involves GMP production. Novartis also provided safety training for the management of potential side effects of the treatment to all related personnel (hematologists, intensive care physicians, neurologists and emergency personnel). Mobilisation of the institution's executives, other departments and personnel, as well as the medical-legal team for contracts requires a streamline governance. It is also important to note that the evaluation of costs has to take into account both the costs related to the CAR-T cells and to the patients. CAR-T delivery marks the beginning of a new era. The process has to be simple and streamlined to allow a rapid patient access to novel technology and care.

Panel: Reimbursement for regenerative therapies: can we demonstrate value?

Moderator: Sowmya Viswanathan, University Health Network
Lesley Dunfield, Director of HTA and Program Development for Medical Devices and Clinical Interventions portfolio, CADTH
Michèle de Guise, Director of Health Services and Technology Assessment, INESSS *(left on the picture)*
Siofradh McMahon, Senior Manager, Clinical Translation and Regulatory Affairs, CCRM *(right on the picture)*
Lambert Busque, Hematologist, Maisonneuve-Rosemont Hospital, Medical Director, C3i

Concepts explored in this panel discussion:

- Value proposition may be the limiting factor in making novel cell & gene therapies broadly available to Canadians
- Budget impact issues – Public payers, private payers, healthcare systems
- Payment by installments
- Single course therapies vs. multiple doses over patient's lifetime
- Should private payers be involved?

Theme 4: Optimizing cell and gene therapy manufacturing

Innovative technologies for cell, gene and tissue manufacturing are revolutionizing the sector. This session guided participants through strategies for cost of goods reduction, 3D bioprinted human tissue, closed system manufacturing, scale-up and scale-out, and late phase to commercialization manufacturing strategies. Centralized and decentralized manufacturing were also discussed to demonstrate where each approach provides the best fit.

Spiro Getsios, from Aspect Biosystems, gave a fascinating talk on producing cellular therapies through 3D bioprinting. Bioprinters could eventually be used to quickly build replacement organs by precisely placing cells within 3D structures to respond to the serious shortage of donor organs that is failing to meet the demand of patients.

Aspect Biosystems' RX1™ Bioprinter uses microfluidic printheads to print core-shell fibres, a fibre that is surrounded by a sheath fluid, which protects cells from damage seen with other bioprinting systems, such as extrusion-based units. The feature of a protective sheath fluid is particularly important for labile cells that are sensitive and easily damaged by shear stress (i.e. human iPSCs). Dr. Getsios talked about the results from Dr. Stephanie Willerth's lab showing that the microfluidic printhead decreased the shear stress on cells, increasing their overall viability. After printing, the iPSC-derived neural progenitor cells were also able to differentiate into neurons. In another study, Dr. Timothy Kieffer used bioprinting to encapsulate insulin-producing engineered islets. Eventually, these encapsulated cells could be printed within more complex tissue patches to provide a treatment for diabetes.

Overall, 3D bioprinting is a promising manufacturing method that combines cell therapy products with biomaterials. This technology may eventually produce transplantable organs to address the gap in supply and demand for organs.

Dr. Gary M. Pigeau, from the Centre for Advanced Therapeutic Cell Technologies at CCRM, spoke about scale-up, cost reduction and data considerations for cell manufacturing optimization. Referring to his experience with pluripotent stem cell manufacturing, Dr. Pigeau shared their process flow to scale-up from a static culture into a 200 mL process controlled stirred tank reactor, and even further into a 10 L Xcellerex stirred tank bioreactor before building a high-density cell bank. Scale-up expansion process moves the manufacturing process into a closed and automated system and represents many advantages. Cost reduction is realized in labor, monitoring and quality release testing. Moreover, therapeutic relevance has

also been demonstrated with an increase of more functionally differentiated cells derived from the large-scale culture of pluripotent stem cells.

Data considerations are also very important when optimizing cell and gene therapies manufacturing. While sample-based data generation represents several risks during sampling such as contamination, loss of therapeutic cells and the need of highly trained labor and its associated cost, continuous bioprocess data offers many advantages. Example of benefits have been given:

- First step in eliminating paper records,
- Data backed up and easy to access,
- Streamlined regulatory reporting and optimized manufacturing efficiency and,
- Automatically order consumables and invoice customers.

Continuous bioprocess data allows full data interrogation, looks for potential control points and process correlations and allows the development of sensor-based growth modeling. Moreover, it can be leveraged to develop:

- Control charts,
- Statistical process control,
- Sample free operation and harvest prediction, DSP and patient scheduling.

Finally, **Donna Rill** from Triumvira presented strategies for the commercialization of cell and gene therapy products. She highlighted the importance of an integrated systems approach and covered specifically the aspects of product and process development.

Donna Rill reinforced the importance of knowing your product. Establishing a Target Product Profile (TPP) that states the goals for the drug product and estimates the net value during the product development plays a major role in the Strategic Program Management (SPM). It is important to understand the expectations and needs at the different stages of drug development.

What characteristics contribute to product success?
What characteristics contribute to product failure in early trials?

Critical quality attributes, critical process paraments, and critical material attributes include:

- Well defined process flow,
- Establishing acceptance criteria for seed material, drug substance (in-process) and final drug product,
- Establishing quality and performance indicators for critical steps and in-process and release testing,
- Understand how raw materials and critical consumables influence the final product.

Innovation at every stage of the process development is crucial. Scale-out parameters should be determined to ensure a production that is optimized for cost, reliability and consistency. During the implementation of automation, Donna Rill highlighted the necessity to balance between the turnaround time (TAT), labor utilization, throughput, cost and space utilization. Determining realistic strategy for migration to commercialization with a Strategic Commercial Manufacturing Plan is suggested for the planning for success in the commercialization of cell and therapy products.

Panel Discussion: Centralized vs. decentralized manufacturing – opportunities and challenges

Moderator: Michael May, CEO, CCRM
Behnam Baghbadernai, Global Head, Process Development & Emerging Technologies - Cell & Gene Therapy, Lonza
Mayo Pujols, VP and Global Head of Cell & Gene Technical Development & Manufacturing, Novartis
Nuala Trainor, Director of Biological Programs, Octane

Concepts explored in this panel discussion:

- Can adequate quality control be enforced with multiple sites of manufacture
- Reduction of COGs
- Incorporation of closed systems in manufacturing
- Automation opportunities
- Considerations for manufacturing capacity

Conclusion

Participants had the chance to discover the most recent innovations that will improve the safety, quality and efficacy of cell and gene therapies. They explored numerous ways to develop more efficient therapies, according to the context of various diseases and depending on the profile of the patients, by discussing the advantages of selecting different treatment paradigms. The future of clinical trials was also on the menu, since they are becoming increasingly complex and require greater transparency, while also requiring greater efforts to gather post-approval data on the real-world evidence of long-term efficacy.

The Strategic Forum was also an opportunity to better understand the current cell and gene therapy ecosystem, its legal framework, and how to collaborate with the regulatory authorities to facilitate the approval process. Finally, participants had very constructive debates about how we can find innovative solutions to finance and reimburse novel cell and gene therapies to the benefit of more patients, and learned on the various strategies and innovations that can help optimize the manufacturing of therapies in the future. Moving forward, the next major challenge our sector will face includes overcoming the dearth of adequately trained highly qualified personnel capable of producing these advanced therapies to create a thriving environment for our technologies to flourish and ensure patients are treated close to home. The stage is set for another great edition of the Cell and Gene Therapy Revolution. It’s time to gown up!

Don’t miss the next edition of CellCAN’s pan-Canadian Strategic Forum in Ottawa, from March 13-15, 2021!

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