# TRIDENT

# Annual General Meeting

# 2024 Report

## Table of Contents

# Overview

The first Translational Initiative to De-risk Neurotherapeutics (TRIDENT) Annual General Meeting (AGM) was held in London, Ontario on November 18 and 19, 2024. The event welcomed all members of the TRIDENT research teams, key institutional leadership representatives from participating research institutions, and external stakeholders from pharmaceutical industries, biotech companies, and charitable foundations to a two-day, hybrid-format event. The 2024 AGM engaged all these members in a series of dynamic research presentations, high-impact professional development sessions, and essential collaborative discussions to introduce and gather feedback on the TRIDENT platform.

## Aims

The 2024 TRIDENT AGM aimed to facilitate a bi-directional conversation to

- Provide an immersive engagement opportunity for all project stakeholders, with a focus on trainees;
- Collect expert opinions to calibrate the direction and prioritization of TRIDENT;
- Facilitate informative, program-wide research updates, lab tours, training; and
- Demonstrate to external stakeholders the value of the TRIDENT platform, i.e., how it transforms pre-clinical evaluation to maximize its predictive validity and result in higher translation to humans— resulting in a faster path for finding effective treatments and cures for neurodegenerative diseases in humans.

*86*

*In-person Attendees*

## Funding Acknowledgement

The TRanslational Initiative to DErisk NeuroTherapeutic (TRIDENT) draws upon research supported by the Government of Canada's New Frontiers in Research Fund (NFRF).
Le TRanslational Initiative to DErisk NeuroTherapeutic (TRIDENT) repose sur des recherches financées par le fonds Nouvelles frontières en recherche du gouvernement du Canada.

New Frontiers in Research Fund
Fonds Nouvelles frontières en recherche

Government of Canada
Gouvernement du Canada

# Committees

## Interdisciplinary Therapeutic Evaluation Panel (InTEP) Session

### Session Leaders

- Dr. Aled Edwards, CEO Structural Genomics Consortium & Dr. Jonathan Kimmelman, Associate Professor, Biomedical Ethics Unit/ Social Studies of Medicine, McGill University

### Committee Members

- Dr. Thomas Durcan, Dr. Liisa Galea, Dr. Richard Gold, Dr. Marco Prado, Dr. Jackie Sullivan & Dr. Dan Small

### Session Agenda

- Welcome
- Roundtable Introductions
- InTEP Purpose, Aims, Duties, Scope
- Wrap Up and Next Steps

### Session Summary

#### Overview

During the InTEP kick-off session, the members of the InTEP panel interacted with the TRIDENT research leads and external stakeholders, such as industry, foundation, and community partners, to outline the structure of InTEP and how this committee, working at arm's length from the TRIDENT leads, will facilitate decision-making at key junctures throughout the TRIDENT platform to maximize translation to humans.

#### TRIDENT Approach

TRIDENT integrates induced Pluripotent Stem Cells (iPSCs) and Organoids, Mouse, and Marmoset models in a one-stop shop to robustly evaluate new therapeutics for neurodegenerative diseases in a manner that is translatable to human trials. TRIDENT also leverages the Preclinical Approaches for Translation to Humans (PATH), a robust method for evaluating evidence of efficacy for therapeutics in a an unbiased and systematic manner. Therefore, TRIDENT is not only developing a unified platform but also standardizing practices for evaluating

## Session Leaders

Dr. Aled Edwards

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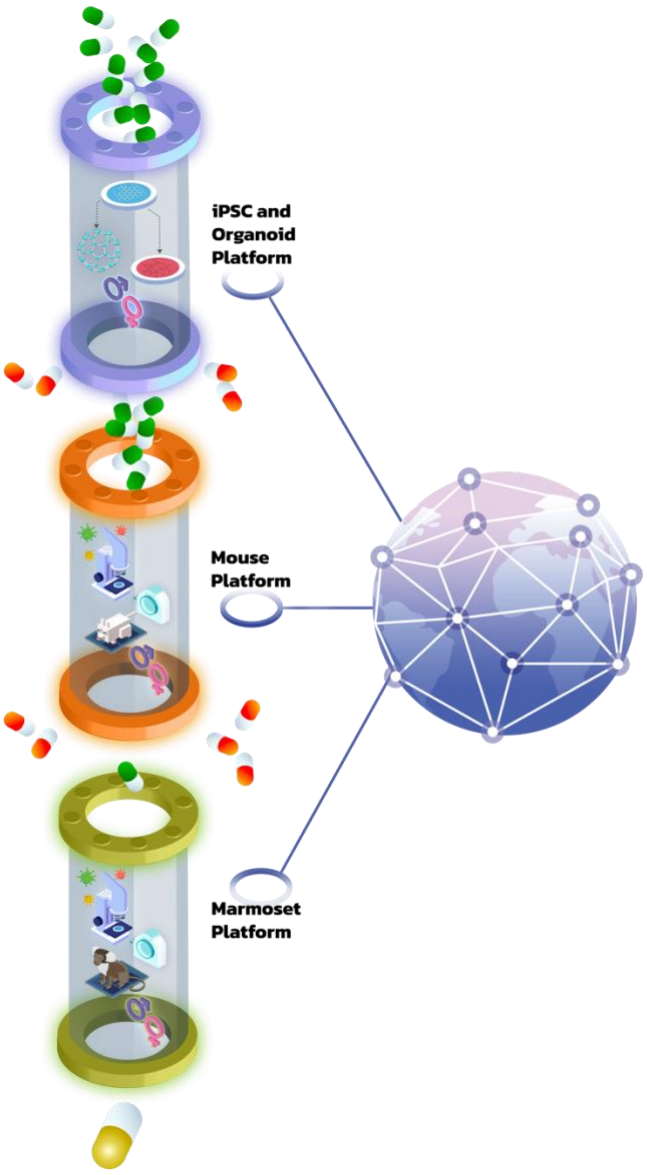
evidence to make go/no-go decisions at key junctures throughout the unified platform so that the predictive validity of the pre-clinical trials is maximized. This structured approach aims to ensure compounds are rigorously vetted before progressing further along the platform, and eventually to human trials.

The overarching goal of TRIDENT is to enhance predictive validity and reproducibility by aligning preclinical models closely with human disease conditions. Standardized protocols and assays, such as cognitive and imaging tests, including sex based based analysis throughout the platform, and incorporating multisite testing are being developed to ensure results are consistent and directly translatable to clinical scenarios.

*"Would you rather wait an extra year and save $2 billion, or rush into clinical trials and risk failure?"*

## The TRIDENT Pipeline



## Pipeline Objectives

A key objective is improving the pipeline's ability to predict translational success. The **PATH framework** was introduced as a systematic approach for evaluating evidence strength and translational relevance at each stage of the pipeline. The PATH framework emphasizes:

- **Construct Validity:** Ensuring models accurately represent the biological mechanisms and conditions of the target disease.
- **Predictive Validity:** Establishing that findings from preclinical models reliably translate to clinical outcomes.
- **Robustness:** Ensuring reproducibility through standardization and validation across multiple labs and conditions.

The use of common cognitive testing methods at TRIDENT across species—from mice to marmosets to humans—ensures consistency and comparability of results. Further, using imaging at the pre-clinical stage will help follow the pathology and efficacy closely while being mindful of the adverse effects of the treatments. A sex-based analysis is embedded throughout the platform to capture any differential effects of therapies. The pipeline incorporates multi-site validation to address variabilities in experimental conditions, such as differences in different labs, housing environments, and experimenters. This validation is crucial for reproducibility and can improve the predictive validity of the pre-clinical trials. TRIDENT, by addressing the key issues in current approaches of pre-clinical testing in neurodegenerative diseases, will help close the gap and transform the drug discovery process into a successful venture.

## Challenges and Risks Identified

- **Predictive Validity Challenges:**
    - Preclinical models often fail to fully replicate the complexity of human pathophysiology, leading to high rates of attrition in clinical trials.
    - There is a need to expand the pipeline's capability to predict adverse cognitive effects, including dementia, which are often overlooked in pre-clinical studies.

- **Resource Constraints:**
    - Limited throughput due to resource bottlenecks, including personnel availability and physical infrastructure, could hinder project scalability.
    - Delays in hiring and onboarding staff were noted as a potential bottleneck in expanding pipeline capacity.
- **Data Transparency and IP Concerns:**
    - Smaller companies expressed concerns about premature publication of preclinical data, which could impact competitive advantage and stock valuations.
    - Addressing these concerns requires clear data-sharing agreements and collaboration models with phased publications.
- **Standardization Versus Flexibility:**
    - While standardization improves reproducibility, it may limit the development of novel assays tailored to specific scientific questions.
    - Balancing these competing needs is a core challenge for pipeline development.

## Opportunities and Innovations

The meeting highlighted opportunities to address the identified challenges and optimize pipeline operations.

- **Validation Through Retrospective Analysis:**
    - Retrospective studies using compounds with known clinical outcomes could validate the pipeline's predictive capabilities and strengthen confidence in its models.
- **Predicting Adverse Cognitive Effects**:
    - The pipeline could be used to identify compounds causing cognitive impairments, regardless of therapeutic area. This application would expand its utility and address a critical gap in drug development.

- **Flexible Entry Points:**
    - Collaborators can engage with specific pipeline stages, such as iPSC screening or Marmoset models, based on their project's immediate needs and readiness.
- **Innovative Assays:**
    - Incorporating naturalistic environments and sex-specific disease models into testing paradigms could improve the ecological validity of preclinical findings.

## Conclusion

The meeting concluded with a strong emphasis on the importance of a structured, standardized approach to preclinical drug evaluation. Stakeholder engagement and collaboration are critical to refining the pipeline and ensuring its long-term success. Immediate next steps include securing funding beyond NFRF grant period, expanding capacity, validating predictive models, and working together with collaborators to find a balance between data transparency and IP protection.

By addressing these challenges and building on its strengths, the pipeline aims to become a robust, scalable, and reliable tool for accelerating drug discovery while maintaining scientific rigor and ethical standards. This collaborative and systematic approach has the potential to improve the translation of evidence from preclinical studies to clinical trials in neurodegenerative diseases and beyond.

## Next Steps

To address the challenges and capitalize on opportunities, the following steps were proposed:

- **Expand Capacity:**
    - Secure additional funding to hire personnel and expand physical infrastructure.
    - Transition to a service-based model to ensure scalability and sustainability.

- **Enhance Communication with Collaborators:**
    - Develop clear guidelines on IP protection and data transparency to alleviate concerns from smaller companies.
    - Host workshops and think tanks to gather stakeholder feedback and refine the open science policy when the platform transitions to a service-based platform.
- **Validate Predictive Models:**
    - Use retrospective validation to establish the pipeline's reliability and predictive power.
    - Include compounds known to cause cognitive decline as part of validation efforts.
- **Foster Innovation:**
    - Encourage the development of novel assays that address emerging scientific needs while maintaining core standardization.
    - Explore integrating machine learning tools for data analysis and predictive modeling.

# Trident Advisory Council (TAC) Meeting

## Session Leader

- Dr. Ravi Menon, TRIDENT Principal Investigator

## Committee Members

- Dr. Lynn Beattie, Dr. Samuel Chuang, Heather Innes, David Lee, Dr. Karen Lee, Dr. Ariel Louwrier, Dr. Mira Puri, Dr. Jane Rylett

## Session Agenda

- Welcome
- Roundtable Introductions and Feedback
- TAC Overview
- Discussion Point
- Wrap Up and Next Steps

### TAC Purpose and Goals

- **Strategic Input**
    - Provide insights on the direction of TRIDENT's research, outreach, and commercialization strategies.
    - Discuss long-term sustainability models and stakeholder engagement.
- **Initial Mandate**
    - Serve as an advisory body for the principal investigator and the core team.
    - Evaluate project outputs informally and suggest improvements to meet stakeholder needs and sustainability goals.
- **Sustainability and Future Planning**
    - Explore avenues for leveraging initial government funding for long-term impact and to secure funding for the future.
    - Develop strategies for transitioning into a self-sustaining entity post-grant.

## TAC Members

Dr. Lynn Beattie

Dr. Samuel Chuang

Heather Innes

David Lee

Dr. Karen Lee

Dr. Ariel Louwrier

Dr. Mira Puri

Dr. Jane Rylett

*"This initiative represents a culture shift in how therapeutics are being developed—bringing it back into academia and professionalizing the pipeline."*

## Key Discussion Themes

- **Sustainability Challenges**
    - Canada's research funding model requires significant industry collaboration and sustainability planning.
    - The need to balance academic integrity with practical considerations for commercialization.

- **Open Science and Intellectual Property**
    - Commitment to open science while recognizing industry's need for confidentiality and potential patenting.
    - Suggested compromises, such as limited embargo periods (e.g., 6 months) before data is released publicly.
    - Working with biotech and pharma partners to strike a balance between open science and their IP concerns.

- **Building Validation and Credibility**
    - Emphasizing the development of a validated pipeline for preclinical models to predict clinical outcomes. No model has been holistically validated for neurodegenerative diseases.
    - Leveraging existing academic and industry partnerships to test early-stage compounds**.**
    - It is important to include models that faithfully recapitulate symptoms as seen in humans for diseases such as Alzheimer's and Parkinson's.

- **Training and Human Resources Development**
    - Focusing on highly qualified personnel (HQP) as part of the project's sustainability and innovation strategy.

- Creating a collaborative framework for training across institutions to retain talent in Canada, and it provides scope for TRIDENT to extend beyond its current academic partners.

- **Balancing Academia and Commercialization**
  - A balance is needed between TRIDENT's academic mission and the practical needs of industry partners.
  - Hybrid models, such as fee-for-service structures for certain projects, were proposed to accommodate both academic and commercial stakeholders.
- **Ethical and Practical Considerations**
  - Ethical obligation to advance science transparently while addressing practical industry needs.
  - Balancing academic openness with the necessity for commercial viability in a highly competitive research environment.

## Conclusions

- **Regulatory and Commercial Strategy**
  - Develop clear communication around TRIDENT's open science commitments and flexibility for partners.
  - Present a regulatory strategy that incorporates innovative preclinical validation to attract industry support.
- **Stakeholder Engagement**
  - Identify and engage diverse partners, including biotech, pharma, patient organizations, and academic institutions.
  - Explore international collaborations and public-private partnerships for expanded funding opportunities.
- **Operational Planning**
  - Establish a clear timeline and metrics for achieving proof-of-concept and validation goals.

*"Ultimately, we aim to provide regulators and researchers with high-quality, predictive data that wasn't previously available."*

- Create a strategic roadmap for transitioning from grant funding to a sustainable model.

- **Focus Areas for Research**
  - Validating the TRIDENT platform is needed as evidence of predictive power in the preclinical space.
  - Testing compounds that have failed in clinical trials can serve as validation for failing compounds. How can TRIDENT prove a compound that has success in clinical trials?

## Next Steps

- Advisory members were encouraged to continue providing feedback and propose specific recommendations.
- Future meetings will incorporate updates on progress and address unresolved challenges in commercialization and sustainability.

# Industry-Regulatory Think Tank

## Session Agenda

- Introduction
- Initial Discussion Point
- Breakout Sessions
- Full Group Discussion
- Conclusions

## Session Summary

- The session aimed to engage key industry stakeholders in a bi-directional conversation that will gather feedback on what TRIDENT needs to do to prove its concept, gain insight about partner expectations, and collect ideas on how TRIDENT can help smoothen the path to regulatory affairs.
- Dr. Gold provided an introduction, acknowledging the funding from the New Frontiers in Research Fund (NFRF), which supports high-risk, high-reward academic projects in Canada. The primary goal of the AGM Think Tank was to engage participants in discussions about the TRIDENT project, which involves drug development, and to gather feedback on communication, timelines, and project outcomes.
- The specific focus of the Think Tank was on translating research into regulatory processes and exploring how industry partners, patient organizations, and government could benefit from these efforts. The research involves testing potential drug molecules using various models, including humanized models and sex-based analysis, with the aim of creating a robust, open, and data-driven platform for drug development.
- The meeting included breakout sessions where attendees discussed key topics such as validating the TRIDENT model, adapting it for the future, and contributing to the regulatory process. The session ended with a full discussion.
- Breakout groups were organized into different themes, with assigned leaders and reporters for each group.

*"Our goal is to identify potential molecules that could become drugs and validate them through humanized models, focusing on sex-based analysis and cognition measurement."*

*"We want to gain insights into what our partners—industry, patient organizations, philanthropy, and government—need from us."*

## Breakout Session 1: TRIDENT Now

- **Session Leader:** Dr. Ravi Menon
- **Reporter:** Dr. Liisa Galea
- **Coordinator**: Dr. Sriram Jayabal

### Discussion Points

- What is the extent of proof needed to validate TRIDENT's better translation to clinical success? E.g.: right model + touchscreen cognition + imaging on known failed drugs
- Will a one stop shop platform with iPSC organoid, mouse, and marmoset models be leveraged together?
- What different combinations of models or single model should be utilized?

### Session Summary and Key Comments

- **Platform Validation Challenges**
  - How to establish predictive validity for preclinical models.
  - Lack of validated models for neurodegenerative diseases like Alzheimer's and Parkinson's.
  - Benchmarks are needed to evaluate platform success.
- **Key Considerations for Validation**
  - Importance of replicability and reproducibility in preclinical studies.
  - Role of cognitive testing as a reliable metric compared to traditional methods.
  - Integrating multiple models and approaches (e.g., in vitro, animal models, and imaging).
- **Industry Expectations and Limitations**
  - Pharma's preference for faster timelines, even at the expense of deeper validation.
  - Focus on biomarker outcomes (e.g., amyloid reduction) rather than cognitive results.
  - Resistance to adopting slower, more rigorous validation methods due to time and cost constraints.

- **Recommendations for Improving the Platform**
  - Use failed clinical trials as proof points to validate predictive ability.
  - Incorporate cognitive and pathology measures into the pipeline for comprehensive evaluation.
  - Leverage computational models and advanced analytics for predictive insights.
- **Collaboration and Partnerships**
  - The need for business development efforts to engage industry partners.
  - Challenges of multi-institutional coordination for funding and implementation.
  - Opportunities to work with industry on next-generation drug testing.
- **Strategic Considerations**
  - Develop adaptable platforms to stay relevant with evolving scientific discoveries.
  - Focusing on combinations of approaches rather than single-model predictions.
  - Balancing academic and industry needs to align goals and expectations.
- **Broader Insights on Neurodegenerative Research**
  - Cognitive deficits as a critical yet underexplored aspect of many conditions.
  - Importance of integrating cognition, pathology, and imaging into drug validation.
  - Highlighting gaps in preclinical research, such as limited cognitive testing in models.

*"High-risk, high-reward academic research like this is essential for keeping Canada on the map for cutting-edge innovation."*

## Breakout Session 2: TRIDENT Future

- **Session Leader:** Dr. Tom Durcan
- **Reporter:** Dr. Joel Watts
- **Coordinator:** Shehrbano Khan

### Discussion Points

- How adaptable and scalable should TRIDENT be? To be your top choice to test a therapeutic, what should TRIDENT do?
- What would be an acceptable turn around time for TRIDENT therapeutic evaluation?
- Evaluation using a current TRIDENT model vs. developing a new model + evaluation.

### Session Summary and Key Comments

- **TRIDENT's Current Focus**

  TRIDENT's work revolves around creating advanced models, including iPSC-derived cells, organoids, and animal models like mice and marmosets, with an emphasis on Alzheimer's and Parkinson's diseases. These models aim to bridge gaps in understanding and testing potential therapies, offering a robust pipeline for research.

- **Opportunities for Growth**

  Participants explored ways to expand TRIDENT's scope beyond its current focus:

  - **Broader Applications:** Extending the pipeline to study conditions like ADHD, traumatic brain injuries, and other neurological disorders.
  - **Collaboration:** Strengthening partnerships with academic institutions, commercial entities, and patient advocacy groups to enhance resources and expertise.

- **Addressing Sustainability**

  A significant portion of the discussion revolved around what happens after the six-year grant ends. The group agreed on the importance of planning now to ensure TRIDENT's future:

  - **Diversified Funding:** Ideas ranged from seeking philanthropic donations and government grants to forming partnerships with biotech companies.

- **Defined Wins**: The team emphasized showcasing tangible successes—such as validated models, impactful collaborations, and published research—to attract continued investment.

## Building Trust and Credibility

Maintaining high standards for data quality and transparency was identified as crucial for long-term success. This includes adhering to certifications like ISO or GLP to ensure data reliability and reproducibility.

## Key Takeaways

- **Celebrating and Showcasing Wins**

  The group stressed the need to identify and communicate TRIDENT's successes:

  - Models validated as the "gold standard" for preclinical research.
  - Publications that highlight the program's contributions to science.
  - Collaborative projects that deliver meaningful results.

- **Sustaining Funding**

  To keep TRIDENT moving forward, participants proposed a multi-pronged funding strategy:

  - Engage philanthropic organizations to support the early stages of research.
  - Partner with biopharma companies for downstream development and testing.
  - Reach out to patient communities for advocacy-driven donations.

- **Smart Growth**

  Expanding the program without overextending was a key consideration:

  - Focus on diseases and models that align with TRIDENT's existing strengths.
  - Gradually increase capacity through partnerships and infrastructure development.

*"TRIDENT aims to create a robust, high-quality data management system comparable across fields, fostering collaboration and innovation."*

- **Strengthening Outreach**

  Effective communication is vital for attracting stakeholders. This includes:

  - Sharing TRIDENT's story through publications, conferences, and media.
  - Highlighting the real-world impact of its work, from training researchers to advancing therapies.

## Next Steps

- **Define and Achieve Wins:** Identify key milestones for the next several years, such as model validation and impactful partnerships.
- **Create a Business Plan:** Develop a clear roadmap for funding and operational sustainability post-grant.
- **Engage Stakeholders:** Strengthen relationships with funders, industry, and patient advocacy groups to build a supportive network.
- **Focus on Standards:** Work toward certifications and protocols that enhance TRIDENT's reputation and data reliability.

## Conclusion

The meeting underscored TRIDENT's incredible potential to reshape preclinical research. By focusing on defined successes, fostering collaboration, and planning for the future, TRIDENT can ensure its work continues to impact the field long after the initial grant concludes. It's clear that with the right support and strategy, TRIDENT is poised to become a cornerstone in the fight against neurodegenerative diseases.

## Breakout Session 3: TRIDENT Policy Appeal

- **Leader:** Dr. Jackie Sullivan
- **Reporter:** Kate Placide
- **Coordinator:** Sarah Brennan

### Discussion Points

- How can TRIDENT make itself relevant for regulatory affairs?
- What aspect of TRIDENT is appealing to the regulators? Discuss the economy of TRIDENT – savings, faster approval process etc.

### Session Summary and Key Comments

- The discussion centered on the TRIDENT pipeline, a framework for enhancing drug development, particularly focusing on preclinical to clinical transitions. The meeting covered challenges, opportunities, and strategies for integrating TRIDENT into regulatory and commercial frameworks.
- **Regulatory Integration and Relevance**
    - TRIDENT's focus on translational models (e.g., touchscreen tasks and multi-species cognitive assessments) is unique but not currently essential for regulatory approval. Regulatory standards prioritize safety and efficacy, with preclinical validation playing a supportive role.
- **Potential Influence**
    - TRIDENT could influence regulatory thinking by providing robust, translational data. Its inclusion of diversity (e.g., sex differences, hormonal impacts) aligns with growing regulatory emphasis on representation and precision medicine.
- **Challenges and Limitations: Negative Data Risks and Industry Skepticism**
    - A negative outcome through TRIDENT testing could harm a biotech company's prospects, especially for smaller firms. Public data sharing was identified as a sensitive issue due to commercial risk.

*"One key question is how our preclinical findings can translate into regulatory processes and influence existing paradigms?"*

- Smaller biotech companies may hesitate to engage if TRIDENT outcomes negatively impact valuation, emphasizing the need for clear predictive value and industry trust.

- **Commercial and Development Strategy: Biotech Perspective and Value Proposition**
  - Companies often aim for proof-of-concept milestones to attract investment or acquisition. TRIDENT's testing could add value by identifying promising candidates earlier in development.
  - TRIDENT could aid in clinical strategy by identifying biomarkers and refining eligibility criteria, improving trial success rates. However, it must balance rigorous validation with practical commercial timelines and costs.
- **Expanding Applications: Holistic Considerations and Rare Diseases**
  - Beyond cognition, TRIDENT could incorporate quality-of-life metrics, delivery mechanisms, and continuous-use designs, aligning with patient-centered goals.
  - The model could be adapted for rare diseases with small patient populations, offering rigorous preclinical validation where clinical trials are less feasible.
- **Future Directions: Collaborations, Open Data, and Pipeline Refinement**
  - Partnerships with regulators, industry stakeholders, and smaller biotechs are critical for scaling Trident's impact.
  - Managing data sharing (e.g., embargo periods or selective release) to align with both academic and commercial interests is a priority.
  - Tailoring the pipeline for specific disease mechanisms and broadening its application to other therapeutic areas.
  - TRIDENT holds promise for advancing drug discovery by bridging preclinical and clinical gaps, but successful integration will require careful navigation of regulatory, commercial, and scientific priorities
  - Stakeholder engagement, clear value demonstration, and iterative development are essential for its long-term impact.

## Think Tank Key Takeaways

- **Timelines and Flexibility:** TRIDENT must balance the need for rigorous validation with industry's demand for speed.
- **Proof Points:** Demonstrating the platform's success through small wins will attract partners and sustain funding.
- **Collaborative Approach:** Engage diverse stakeholders, maintain adaptability, and establish credibility through robust science

*"To sustain TRIDENT in the long term, we must prove our value to all constituencies while exploring adaptability to future scientific and regulatory needs."*

Session Leaders

Dr. Ann Ayinde

Dr. Meghan O'Hara

Session Leader

Dr. Samuel Chuang

# Trainee Events

## Life Design Seminar

### Session Leaders

- Dr. Ann Ayinde, Career Coach, Western University
- Dr. Meghan O'Hara, Program Specialist, Graduate Student Life, Western University

### Session Summary and Objectives

- Life Design harnesses design thinking methods to tackle key questions and major decisions surrounding key facets of a person's life, including education, career, and overall life's ambitions and purpose. Bill Burnett and Dave Evans originally introduced life Design at Stanford University's d.school (Design School) in Stanford, California, U.S.A. It became widespread with the publication of their book Designing Your Life in 2016.
- One of TRIDENT's mandates is to support and develop the next generation of neuroscientists. In line with this, the TRIDENT-Western University Life Design Seminar was organized during the AGM to introduce this creative and effective toolkit to the TRIDENT trainees.

## Career Exploration: Finding Your Path to Opportunities and Success Seminar

### Session Leader

- Dr. Samuel Chuang, Senior Director, Scientific Advisory Services, Charles River Laboratories

### Session Summary

- The session enabled Dr. Chuang to share his career journey of an industry expert that spanned academia, industry and contract research organization (CRO) careers.
- Dr. Chuang provided insight into the work life of different career areas than academia, in particular, industries and CROs.

- Dr. Chuang detailed how he found a career path that was fulfilling for him, and shared ways to do the same early on during graduate school
- Dr. Chuang also shared tips and strategies that helped him to successfully pursue a desired career

# Neuro Expert Mixer

## Session Leaders

- Dr. Shairaz Baksh, CEO, BioImmuno Designs
- Dr. Murali Gopalakrishnan, Global Head, Neuroscience & Evaluation, Abbvie
- Dr. Joseph Mancini, Vice-President of Research, adMare BioInnovations
- Dr. Viviane Poupon, President and CEO, Brain Canada
- Dr. Amyn Sayani, Head of Medical Evidence, AstraZeneca
- Dr. Marc Shenouda, Chief Executive Officer, Neuropeutics Inc.
- Dr. Tae Joon (TJ) Yi, Associate Director, Immunology, Krembil Foundation

## Session Coordinators

- Kate Placide, Western Research Partnership Development Manager, Neuroscience and Imaging
- Shehrbano Khan, TRIDENT Administrative Officer

## Session Summary

- A group round-table robin event structure with experts from industry and foundation partners enabled direct interaction of TRIDENT trainees with the experts.
- The session provided an opportunity for participants to learn about diverse career pathways in neuroscience.
- The discussions aimed to advance TRIDENT's mandate to support and develop the next generation of neuroscientists.

Session Leader

Dr. Jonathan Kimmelman

# PATH Lecture and Workshop

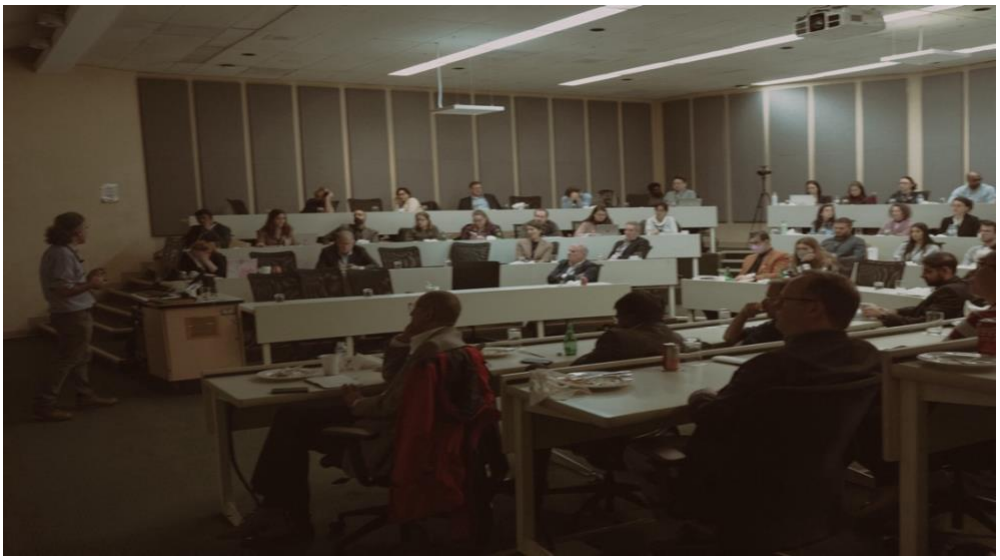
## Session Leader

- Dr. Jonathan Kimmelman, McGill University

## Session Summary

- The session provided an overview of an approach, Preclinical Assessment for Translation to Humans (PATH).
- A subsequent focused workshop session allowed attendees to experience and learn the application of the PATH approach to a drug being assessed for entry to the TRIDENT platform.

When launching early-phase clinical trials, researchers rely heavily on preclinical evidence to determine if a new treatment is ready for testing in humans. However, this evidence is often incomplete or inconsistent. Combined with the increasing reliance on smaller studies and mechanistic data, particularly in precision medicine, this creates challenges in deciding when and how to move forward. The PATH (Preclinical Assessment for Translation to Humans) framework was developed to tackle these issues by providing a clear, systematic way to evaluate evidence and make better-informed decisions.



## The Challenges

- **Reproducibility Problems**:
  - Many preclinical studies don't hold up under closer scrutiny. For instance, Amgen found that they could reproduce only 11% of published findings when testing potential new drugs.
  - A review of 17 high-impact cancer studies revealed that only half of the results could be replicated.
- **Gaps in Evidence**:
  - Many clinical trials are launched without solid preclinical support. In cancer phase II trials, nearly half lacked studies showing the drug worked for the condition being tested.
  - Protocols often fail to explain why specific models are used or how the findings translate to human outcomes.
- **The Problem with Narratives**:
  - Trial protocols often rely on compelling stories rather than objective analysis. While narratives are persuasive, they can obscure weak evidence. Studies show that systematic reviews lead to more cautious and accurate evaluations than narrative summaries.

## A Better Way: The PATH Framework

The PATH framework provides a structured way to assess evidence supporting early-phase trials. It ensures that decisions are based on solid science and clear reasoning, helping researchers and regulators avoid pitfalls caused by incomplete or poorly interpreted data.

PATH focuses on evaluating evidence across nine key steps, which span the process of drug development—from ensuring the drug engages its target to demonstrating it can produce meaningful clinical benefits in humans. The evidence is divided into two main types:

- **Vertical Evidence**: Direct findings from experiments, like whether the drug binds to its target or shrinks tumors in animal models.
- **Horizontal Evidence**: Evidence showing that findings in preclinical models are relevant to humans, such as similarities in mechanisms or proof the drug reaches the human target.

## Key Elements of PATH

- **Assessing Evidence Quality**:
  - Evaluate how well the study was designed: Was it blinded? Was the sample size adequate?
  - Look at the strength of the effect: How big was the observed change, and how precise is the estimate?
- **Checking for Relevance**:
  - Determine if the animal or lab models used reflect human biology (construct validity).
  - Ensure the drug behaves consistently across different models and conditions (external validity).
  - Address potential barriers like the drug's ability to cross the blood-brain barrier or issues with human metabolism.
- **Filling the Gaps**:
  - Identify missing steps or weak links in the evidence chain. The goal is to create at least one strong, well-supported path from preclinical data to expected outcomes in humans.

## Why PATH Matters

- **Improving Early-Phase Trials:**
  PATH ensures trials are backed by rigorous evidence, reducing the risk of investing in studies with weak foundations. It also encourages transparency, discouraging vague claims and fostering trust.
- **Learning from Failures**:
  By mapping out where evidence fell short, PATH can help researchers understand why a trial failed and how to improve future studies.
- **Streamlining Decisions**:
  Regulators, funders, and research teams can use PATH to structure evidence presentations, making it easier to evaluate the risks and benefits of moving forward with a trial.
- **Supporting Precision Medicine**:
  As we rely more on smaller, mechanism-driven studies, PATH provides a systematic way to evaluate the evidence needed to guide personalized treatments.

### Limitations

- While PATH is a powerful tool, it's not without challenges:
- It requires rethinking how evidence is presented in trial protocols and investigator brochures.
- Translating findings from models to humans (horizontal evidence) can be complex and subjective.
- PATH isn't quantitative—it doesn't predict exact probabilities of success—but instead provides a structured way to identify strengths and weaknesses in the evidence.

### Conclusion

The PATH framework represents a big step forward in making early-phase clinical trials more rigorous and transparent. By systematically evaluating evidence, it helps researchers and decision-makers identify gaps, address risks, and make more informed choices. While it won't guarantee success, PATH ensures trials are built on the strongest possible foundation, ultimately paving the way for safer, more effective treatments.

## PATH Workshop Overview

## Session Leader

- Dr. Jonathan Kimmelman, McGill University

## Agenda:

- Welcome
- Review of ALS protocol evaluated using the PATH approach
- Review and workshop of the proposed InTEP dry run therapeutic.

### Overview

The workshop explored how the PATH framework can be used to assess the quality of evidence supporting clinical trials, focusing on repurposing nilotinib, a cancer drug, for Parkinson's Disease (PD). Participants worked together to evaluate a real-world clinical trial protocol, identifying strengths, gaps, and lessons learned.

## Key Takeaways

### The Context

- **Drug in Focus**: Nilotinib, a cancer treatment approved for chronic myelogenous leukemia (CML), was hypothesized to help Parkinson's patients by targeting similar mechanisms at play in neurodegeneration.
- **Clinical Goal**: Test whether nilotinib could improve Parkinson's outcomes using the Unified Parkinson's Disease Rating Scale (UPDRS).
- **The Study**: A Phase II trial comparing nilotinib to placebo, based on early promising (but limited) preclinical and clinical evidence.
- **What is the PATH Framework?**

PATH (Preclinical Assessment for Translation to Humans) helps researchers systematically evaluate the evidence supporting clinical trials. It breaks the drug development process into steps:

- **Does the drug bind to its intended target?**
- **Does this binding produce the desired biological changes?**
- **Do these changes improve patient outcomes?**

## Workshop Insights: Evaluating Nilotinib's Trial

- **Step 1: Mapping the Evidence**

Participants reviewed the trial protocol and assigned evidence to different PATH steps:

- **Target Engagement**: Preclinical data showed that nilotinib binds to BCR-ABL, its intended target.
- **Biological Effects**: Animal studies suggested nilotinib reduced dopaminergic neuron loss, a hallmark of PD.
- **Clinical Outcomes**: Small open-label studies hinted at possible improvements in Parkinson's symptoms, but these studies lacked the rigor of placebo-controlled trials.

- **Step 2: Evaluating Evidence Strength**

When assessing the quality of evidence, participants found:

- **Inadequate Magnitude**: The reported effects were modest, particularly in early clinical trials.
- **Limited Precision**: Sample sizes were small, and statistical details were scarce in preclinical work.

- **High Risk of Bias**: Open-label studies (lacking blinding or placebo controls) made clinical results hard to trust.

- **Step 3: Translational Gaps**
  - **Model Limitations**: The preclinical studies used animal models that may not fully replicate human PD, making translation uncertain.
  - **Drug Delivery Issues**: The trial ultimately failed because the drug couldn't reach the brain in therapeutic levels.

## Post-Trial Reflections

### What Went Wrong?

- The trial failed to meet its primary goals, with nilotinib showing no significant benefit for Parkinson's patients.
- Post-trial analysis revealed that the drug didn't reach the central nervous system at sufficient levels, undermining its ability to work as hypothesized.

## Lessons Learned

- **Preclinical Evidence Needs Rigor**: It's critical to validate animal models and ensure they mimic human disease mechanisms.
- **Thorough Translational Justification is Key**: If a drug doesn't reliably reach its target, the trial is unlikely to succeed.
- **Clinical Studies Should Avoid Bias**: Open-label studies, while useful for exploration, can't substitute for well-designed, controlled trials when building a case for larger studies.

## Why This Matters

The workshop highlighted how the PATH framework can guide better decision-making in clinical trials, particularly for repurposed drugs. Nilotinib's trial underscores the need to address translational gaps before involving patients. Time and effort are valuable—for both researchers and participants—and should be justified by strong evidence.

## Future Applications

- Strengthening Evidence: By asking the right questions, PATH encourages researchers to present clear, comprehensive rationales for their studies
- Improving Ethics in Trials: Patients should only be asked to participate when trials are built on a solid foundation of evidence.
- Learning from Failures: The PATH framework can help analyze failed trials to identify gaps and prevent future missteps.

## Closing Thoughts

This workshop provided a thoughtful, hands-on experience with PATH, revealing its power to enhance the way trials are designed and evaluated. By using frameworks like PATH, the scientific community can create stronger, more ethical studies and improve the likelihood of successful therapies reaching patients.

# TRIDENT RESEARCH CORE UPDATES

## iPSC & Organoid Core

**Speaker:** Dr. Tom Durcan, iPSC & Organoid Core Lead, McGill University

**Title:** Midbrain Organoids: Moving from a Discovery to a Therapeutic Testing Platform

## Mouse Core

**Speaker:** Dr. Marco Prado, Mouse Core Lead, Western University

**Title:** Overview of the TRIDENT Mouse Core

**Speaker:** Aya Arrar, Graduate Student, Western University

**Title:** Translational Analysis of Cognition and Pathology Using Combined Humanized Mouse Models

**Speaker:** Cadence Emilee Opoka, Graduate Student, Western University

**Title:** Bridging Valleys Through Touchscreen-Based Cognitive Task Development

**Speakers:**

- Dr. Sara Touj, McGill University
- Janice Park, Graduate Student, McGill University

**Title:** Using MRI to Characterize Synucleinopathy Progression and Therapeutic Efficacy in Mice

## Marmoset Core

**Speaker:** Dr. Justine Clery, Marmoset Core Lead, McGill University

**Title:** Overview of the Marmoset Core

**Speaker:** Jiayue Yang, Graduate Student, McGill University

**Title:** McGill platform: Behavioral And Neuroimaging Marmoset Data

**Speaker:** Dr. Alessandro Zanini, Western University

**Title:** Western Platform: From The Behaviour To The Brain, A New Preclinical Model For Alphasynucleopathies

## Sex-Based Analysis + Core

**Speakers:**

- Dr. Liisa Galea, Sex-Based Analysis+ Core Lead, CAMH
- Dr. Laura Gravelsins, CAMH

**Title:** SBA+ Considerations for Translation Neuroscience: The Why and the How

## Data Management and Sharing Core

**Speaker:** Dr. Ali Khan, Data Management & Sharing Core Team Lead, Western University

**Title:** Toolkit for Light sheet Microscopy

**Speaker:** Dr. Mallar Chakravarty, Data Management & Sharing Core Team Lead, Imaging Biomarker Team Lead, McGill University

**Title:** Algorithmic Support for Streamlining Brain Imaging and Analysis

**Speaker:** David Roper, Research Associate, McGill University

**Title:** Mouse Open Data Capture (ODC) Platform

## Open Science, Practices and Partnerships Core

**Speaker:** Dr. Jie Fang, McGill University

**Title:** The Impact of Open Science and Academic Research on Drug Development

# TRIDENT Feedback Survey Summary

**Surveys Distributed:** 96 individuals
**Responses Received:** 41

**Respondent Profile:** A diverse mix of students, postdocs, professors, industry representatives, and advisory roles.

**Overall Satisfaction:**

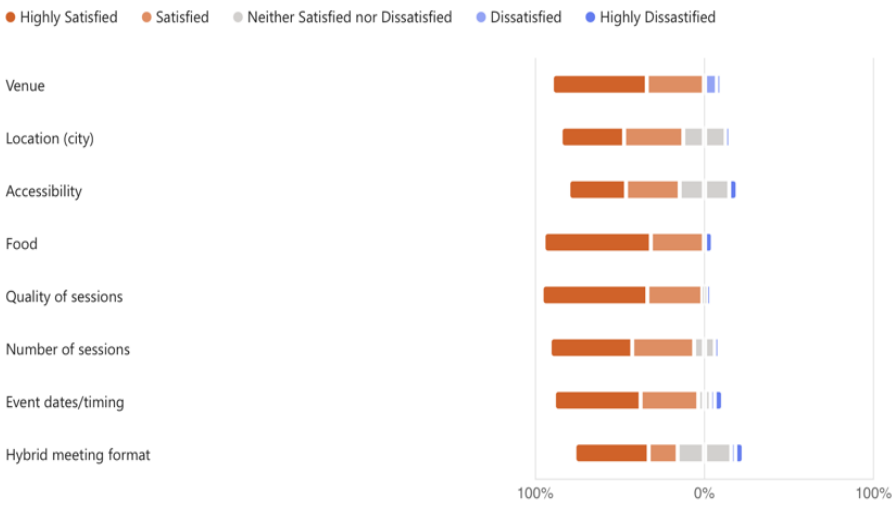
- **Rating:** 4.5/5 average satisfaction.
- **Majority:** 21 Highly Satisfied, 15 Satisfied.
- **Minority:** 4 Dissatisfied or Highly Dissatisfied.


*4.5*

*Average Approval Rating*

**Key Highlights:**

- **Venue & Accessibility:** Generally positive feedback was received, though some found the location challenging, particularly for attendees from Montreal. Future events could consider Toronto for better accessibility.
- **Food & Facilities:** Mostly positive feedback was received, but some suggested slight improvements in food quality and fewer, more meaningful tours.
- **Hybrid Format:** The hybrid format was valued but some technical issues were noted (e.g., screen overlays). More thorough technical checks were recommended for future events.

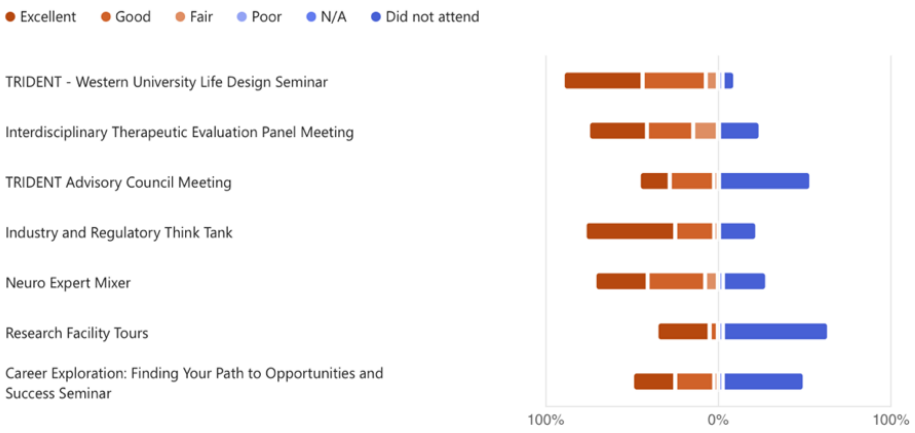


## Day 1:

- **Life Design Seminar:** The seminar was mostly well-received, but some attendees felt it could be better suited for HQPs rather than PIs. A few responses indicated dissatisfaction with the seminar.
- **InTEP Session & TAC Session**: Both sessions garnered generally positive feedback, though a few attendees rated them as "Fair." Participants suggested that the sessions could be more interactive.
- **Neuro Expert Mixer:** The mixer was a hit, but participants felt limited by the short time allocated for each rotation. Many were only able to ask one question before rotating. It was recommended we consider fewer experts or more time per rotation.
- **Think Tank Session:** Highly rated, with strong feedback for interactive discussions. Recommendation: More time for Q&A was recommended.

## Day 2:

- **iPSC & Organoid, Mouse Core, Marmoset Core Presentations:** These were the standout sessions, receiving mostly "Excellent" ratings. Attendees appreciated the depth of content, and the high-quality research presented.
- **SBA+ Analysis & PATH Lecture & Workshop:** The workshop was well-received overall, with a few areas for improvement. The PATH Lecture and Workshop received one "Poor" rating.
- **Open Science & Data Management:** Both sessions were well-received, but some feedback indicated that the topic of Open Science could be explored more deeply, particularly in terms of its application across the innovation pipeline.



## Suggestions for Future AGMs:

- **Session Timing & Structure**:
  - Extend Q&A and discussion periods to facilitate deeper engagement.
  - Consider mixing shorter and longer sessions to maintain attention and balance content delivery.
- **Trainee Involvement:**
  - Provide more opportunities for trainees and HQPs to present their work, either through dedicated sessions or as part of larger discussions, to enhance their visibility and involvement.
- **Networking Opportunities**:
  - Allocate more time for networking, especially between academia and industry.
  - Informal social sessions or dedicated breaks could help foster stronger connections.
- **Hybrid Format:**
  - Address technical issues with hybrid meetings (e.g., screen overlays)
  - Conduct more thorough technical checks to ensure smooth participation for remote attendees.
- **Refine Session Topics**:
  - Tailor session content to better meet participant interests and ensure relevance.
  - Avoid overcrowding sessions to maintain focus and engagement.
- **Venue & Logistics:**
  - Consider alternative locations (e.g., Toronto) for better accessibility, especially for attendees traveling from other regions.

## Preferred Communication Channels:

- Social media/website updates
- Tri-annual newsletters
- Reports/briefings
- Email updates and focus groups

## Suggested Partners:

- MJFF (Michael J. Fox Foundation)
- Alzheimer's Society
- Parkinson Canada
- CQDM
- adMare

## Conclusion:

The TRIDENT 2024 AGM was a highly successful event, with positive feedback regarding the quality of scientific content, networking opportunities, and overall organization. Key strengths included engaging sessions and insightful discussions. Areas for improvement include refining session formats, enhancing hybrid experiences, and providing more opportunities for trainee involvement. Future events could benefit from more interactive sessions, extended discussion time, and a focus on more streamlined networking opportunities. The overall experience was positive, with strong interest expressed by attendees to attend future TRIDENT events.

# Attendees

| | | | |
|---|---|---|---|
| Anoosha | Attaran | HQP | Western University |
| Erin | Azzopardi | Director of Strategic Partnerships | Western University |
| Shairaz | Baksh | CEO | BioImmuno Designs |
| Rob | Bartha | Vice Dean Research and Innovation | Western University |
| Ariel | Burrowes | HQP | Western University |
| Lynn | Beattie | President | CLEAR Foundation |
| Isabelle | Boileau | Associate Director & Senior Scientist | CAMH |
| Benoit | Boulet | AVP, innovation + Partnerships | McGill University |
| Alison | Brandt | HQP | McGill University |
| Sarah | Brennan | Director of Operations | Western University |
| Julie | Brown | Senior Advisor, Major Gifts and Planned giving | Douglas Foundation |
| Tim | Bussey | Mouse Core Lead | Western University |
| Benjamin | Carlisle | HQP | McGill University |
| Mallar | Chakravarty | Data Management & Sharing Core, & Mouse Core Lead | McGill University |
| Sam | Chuang | Senior Director, Scientific Advisory Services | Charles River |
| Justine | Clery | Marmoset Core Lead | McGill University |
| Tyler | Cook | HQP | McGill University |
| Adrienne | Crampton | Director, Neurosphere & Associate Director Business Development | McGill HBHL |
| Siobhan | Doherty | Executive Director, Principal Gifts | Western University |
| Constance | Dollet | HQP | McGill University |
| Andy | Donovan | Vice-President, Strategic Partnerships | Life Sciences Ontario |
| Tom | Durcan | iPSC/Organoid Team Lead & Non-voting InTEP member | McGill University |
| Aled | Edwards | InTEP Chair | University of Toronto |
| Amr | Eed | HQP | Western University |
| Czarina | Evangelista | HQP | Western University |
| Stefan | Everling | Marmoset Core Lead | Western University |
| Jie | Fang | HQP | McGill University |
| Caroline | Fernandes | HQP | Western University |
| Edward | Fon | iPSC/Organoid Team Lead | McGill University |
| Maeva | Gacoin | HQP | McGill University |
| Liisa | Galea | Sex Based Analysis+ Core Lead | CAMH |

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|---|---|---|---|
| Richard | Gold | Open Science, P&P Team Lead, InTEP Core Standing Member | McGill University |
| Murali | Gopalakrishnan | Global Head, Neuroscience Search & Evaluation | AbbVie |
| Laura | Gravelsins | HQP | CAMH |
| Kelly | Summers | HQP | Western University |
| Heather | Innes | Community Engagement Coordinator, North Region | Parkinson Society SW Ontario |
| Sriram | Jayabal | Research Program Director | Western University |
| Kruti | Joshi | HQP | Western University |
| Pamela | Kanellis | Chief Research and Program Officer | Brain Canada |
| Yi-Hsuan | Kao | HQP | Western University |
| Ali | Khan | Data Management & Sharing Core Lead | Western University |
| Shehrbano | Khan | Administrative Officer | Western University |
| Jonathan | Kimmelmann | InTEP Chair | McGill University |
| Natacha | Lachaine | Director, Major Gifts & Planned Giving | Douglas Foundation |
| Sam | Laxer | HQP | Western University |
| David | Lee | Chief Regulatory Officer | Health Canada |
| Karen | Lee | President & CEO | Parkinson Canada |
| Paula | Lepine | HQP | McGill University |
| Li Yao | Li | HQP | Unversity of Toronto |
| Ariel | Louwrier | President & CEO | StressMarq Biosciences |
| Wen | Luo | HQP | McGill University |
| Colin | Macauley | Business Development Manager | Western University (WORLDiscoveries) |
| Joseph | Mancini | Vice President Research | adMare BioInnovations |
| Jaipreet | Mattu | HQP | Western University |
| Surabhi | Mehra | HQP | University of Toronto |
| Ravi | Menon | TRIDENT Principal Investigator & Imaging Biomarker Team Lead | Western University |
| David | Muir | Associate Vice-President (Innovation & Strategic Partnerships) | Western University |
| Vikram | Nathan | HQP | McGill University |
| Emmanuelle | Nguyen | HQP | McGill University |
| Vladislav | Novikov | HQP | Western University |
| Kate | Onuska | HQP | Western University |
| Samina | Panjwani | HQP | Western University |
| Janice | Park | HQP | McGill University |
| Kate | Placide | WR Partnerships | Western University |
| Viviane | Poupon | President & CEO | Brain Canada |

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|---|---|---|---|
| Marco | Prado | Mouse Core Lead & InTEP Member | Western University |
| Vania | Prado | Mouse Core Lead | Western University |
| Mira | Puri | Manager, Science Initiatives | The Azrieli Foundation |
| Wolfgang | Reintsch | HQP | McGill University |
| Piero | Rodriguez | HQP | McGill University |
| Angela | Roedding | Research Commercialization Principal | CAMH |
| David | Roper | HQP | McGill University |
| Ashbeel | Roy | Director of Business Development | Ginkgo Bioworks |
| Jane | Rylett | Scientific Director | CIHR |
| Jesleen | Saini | HQP | Western University |
| Lisa | Saksida | Mouse Core Lead | Western University |
| Arash | Salahinejad | HQP | Western University |
| Rodrigo | Sandoval | HQP | Western University |
| Amyn | Sayani | Head, Medical Evidence | AstraZeneca |
| Marc | Shenouda | CEO | Neuropeutics |
| Lina | Sifi | HQP | McGill University |
| Nicholas | Silver | HQP | University of Toronto |
| Dan | Small | Senior Director, Business Development, Discovery | Charles River |
| Martin | Smith | Startup Advisor | Techalliance |
| Raphaella | So | HQP | University of Toronto |
| Jackie | Sullivan | Open Science, P&P Team Lead, Core Standing InTEP member | Western University |
| Latiyah | Timothy | HQP | Western University |
| Sara | Touj | HQP | McGill University |
| Maria | Trallero | HQP | McGill University |
| Stephanie | Tullo | HQP | McGill University |
| Esmin | Unaran | HQP | Western University |

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| Klara | Vichnevetski | Director, Industry Partnerships & Tech Services | CAMH |
| Joel | Watts | Mouse Core Lead | University of Toronto |
| Jiayue | Yang | HQP | McGill University |
| Tae Joon | Yi | Associate Director, Immunology | Krembil Foundation |
| Alessandro | Zanini | HQP | Western University |