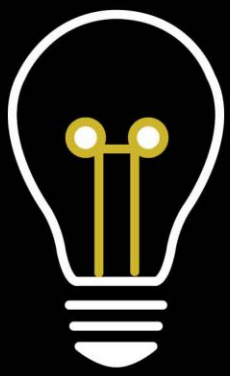


SICKKIDS INNOVATION SHOWCASE

Technology Pitch Book

May 19, 2021

SickKids® | Industry Partnerships & Commercialization

Ihor Boszko, MSc MBA
EXECUTIVE DIRECTOR

INDUSTRY PARTNERSHIPS & COMMERCIALIZATION

THE HOSPITAL FOR SICK CHILDREN

MESSAGE FROM IHOR

The COVID-19 pandemic has demonstrated the value of health science innovation and the need for investment in the brightest research minds driving breakthrough solutions to improve the health of people worldwide in key areas like *in vitro* diagnostics, vaccines, and therapeutics.

As Canada's most research-intensive hospital, SickKids has a long legacy of innovation that has improved the health outcomes of children and adults in Canada and beyond. Our office works closely with our top clinicians and researchers to support the development of technologies and products that are ripe to move from the lab and, with the help of partners, into the market – and to the patients who need them most.

That's why we created the SickKids Innovation Showcase, a new platform to highlight the incredible research at SickKids and the researchers behind it. I want to welcome you all to our inaugural event, this year profiling the top biopharma and diagnostics/tools technologies at SickKids.

I trust that our event will spur productive collaborations, and we look forward to celebrating the most advanced health and life sciences ideas from the labs of SickKids innovators.

ABOUT IP&C

The Industry Partnerships and Commercialization (IP&C) office at The Hospital for Sick Children (SickKids) champions the identification, development and commercialization of cutting-edge health research, technology and innovations developed by our scientists and clinicians.

SickKids innovators are on the front lines of health innovation. Our office brokers partnerships with industry and investors to spark research collaborations and help businesses tap into the robust innovation ecosystem at SickKids.

Contact us to find out about partnering with us on research and clinical technologies at SickKids through licensing, sponsored research, and start-up company creation.

BIOPHARMA PANELISTS

Jacki Jenuth, PhD
Partner
Lumira Ventures

With over 20 years of life science, IT and business development executive-level experience, Jacki is a key member of the senior investment team sourcing, conducting diligence on, structuring deals terms for and working closely at the board level with portfolio companies. Jacki has a strong reputation for providing the focus, clarity and cohesion required to drive projects from efficient inception to effective completion. Jacki also directs all aspects of Lumira Ventures' information technology initiatives having developed a world class venture capital analytics platform.

Prior to joining Lumira Ventures, Jacki worked at Base4 and Open Text Inc. where she developed, sold, and provided support for enterprise content management solutions targeted to the biotechnology and pharmaceutical industry in North America and Europe.

Deborah Palestrant, PhD, MBA
Partner, Head of 4:59
5AM Ventures

Deborah Palestrant, Ph.D., M.B.A joined 5AM Ventures in 2018 as Partner, Head of 4:59. Previously, Dr. Palestrant was Vice President of Corporate Development & Strategy at Relay Therapeutics, where she executed business strategy including alliances, partnerships, and other collaborations and led communications. She has over 15 years of life sciences industry experience including drug discovery, company creation, operations, business development, and strategy.

Dr. Palestrant holds a Ph.D. in biochemistry and molecular biophysics from Columbia University, an M.B.A from Northeastern University, and was Damon Runyon Cancer Research Foundation Postdoctoral Fellow at The Scripps Research Institute. She is based in the Boston, MA office.

Allyson Tighe, MBA
Co-Founder and Investor
Amplitude Ventures

Allyson Tighe is a Co-Founder and Investor at Amplitude Ventures, a capital catalyst for highly innovative companies at the point of value acceleration. Amplitude works with promising Canadian healthcare companies that share their vision of bringing ground-breaking technologies to patients with a focus on building world-class Canadian companies in precision medicine and next-generation medical devices.

Previously, Allyson was an investor at the BDC Healthcare Fund where their team managed $270 million in capital with investments in the drug, devices, diagnostics and digital health sectors.

Allyson holds a Bachelor in Science in Genetics and a Masters in Science in Physiology, both from Western University, and an MBA from the Richard Ivey School of Business.

DIAGNOSTICS & RESEARCH TOOLS PANELISTS

Matthew Clancey
Director, Corporate Development & Licensing
Labcorp

Matthew Clancey is a Director of Corporate Development and Licensing at Labcorp. In this role, he is responsible for leading diligence efforts around new technologies and testing opportunities, as well as executing on Labcorp's partnership strategies. His team manages deal flow for both diagnostics and CRO segments at Labcorp.

Prior to his current role, Matthew spent five years in Labcorp Research & Development, leading the development and evaluation of novel technologies.

Prior to LabCorp, Matthew received his B.S. in Genetics and Cell Biology and B.A. in English Literature from the University of Minnesota – Twin Cities.

Wouter Meuleman, PhD, MBA
Partner
Illumina Ventures

Wouter is a Partner at Illumina Ventures, a life sciences VC firm in the San Francisco Bay Area, investing in tools, diagnostics and therapeutics companies with a particular emphasis on genomics. Prior to Illumina Ventures, he worked at Illumina, Inc. in various roles including R&D, Product Development, and Corporate Development.

A physical chemist by training, he began his career in life sciences as a founding team member at the Oxford University spin-out Oxamer, co-founded by Prof. Sir Edwin Southern. Following the company's acquisition by Oxford Gene Technology, he continued working alongside Prof. Southern leading R&D programs in areas such as single cell gene expression analysis and novel applications for DNA microarrays.

He obtained his undergraduate and Master's degree in Chemistry from the University of Ghent, Belgium; a PhD in Chemical Engineering from the University of Newcastle, U.K; and an MBA from the University of Cambridge, U.K.

Shobha Parthasarathi, PhD
VP, External Innovation & New Ventures
Xontogeny

Shobha joined Xontogeny as Vice President, External Innovation & New Ventures. Shobha brings a combination of 20+ years of research, business development, strategic partnerships, and venture investing experience to development of new medicines and emerging healthcare technologies. Her career highlights include portfolio financings that have led to FDA drug approvals/marketed products, company acquisitions and IPO.

Prior to joining Xontogeny, she was Vice President, Strategic Alliances and Business Development at Harrington Discovery Institute, a unique international initiative created to translate scientific discoveries from academia to development of therapeutics.

Shobha obtained Ph.D. in Molecular Genetics and Microbiology from Rutgers University. She serves on advisory Boards of several academic institutions and life sciences accelerators.

AGENDA

1:00 pm Opening Remarks

- **Dr. Gabrielle Boulianne**
  - Chief of Research, SickKids Research Institute
- **Ihor Boszko**
  - Executive Director, Industry Partnerships & Commercialization at SickKids

1:15 pm Panelist introductions

- **Dr. Jacki Jenuth** | Partner, Lumira Ventures
- **Dr. Deborah Palestrant** | Partner, Head of 4:59, 5AM Ventures
- **Allyson Tighe** | Co-Founder, Investor, Amplitude Ventures

Biopharma pitches

- **Dr. Roman Melnyk**
- **Dr. P. Lynne Howell**
- **Dr. Martin Post**
- **Dr. Christopher Pearson**

2:20 pm Break

2:30 pm Remarks

2:40 pm Panelist introductions

- **Matthew Clancey** | Director, Corporate Development & Licensing, Labcorp
- **Dr. Wouter Meuleman** | Partner, Illumina Ventures
- **Dr. Shobha Parthasarathi** | VP, External Innovation & New Ventures, Xontogeny

Diagnostics & Research Tools pitches

- **Dr. Ryan Yuen**
- **Dr. Adam Shlien and Dr. Uri Tabori**
- **Dr. Robert Hamilton**
- **Dr. Jason Maynes**

3:45 pm Audience Choice Award
Closing Remarks

4:00 pm Q&A breakout rooms for each technology

4:30 pm Conclusion of event

TECHNOLOGY BRIEF

BIOPHARMA

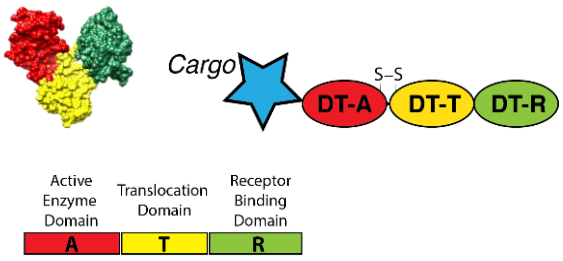
A novel cell-penetrant delivery platform applied to a pan-Ras targeting anti-cancer therapy

BACKGROUND

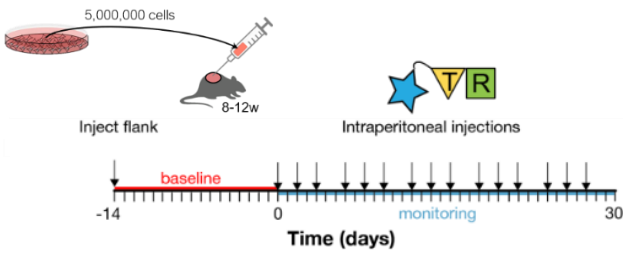
Ras proteins belong to a class of small GTPases that play a critical role in signal transduction, differentiation, cell growth, proliferation, and survival. Mutations in the *ras* gene lead to constitutively active signaling, causing unrestrained cell growth, division, and cancer. Mutations in *ras* are found in up to 30% of all human tumors and are present in 3 of the most lethal cancers (colon, lung, pancreatic), making this one of the most important oncogenes in humans. However, there are currently no effective inhibitory therapeutics targeting intracellular Ras proteins as the vast majority of biotherapeutics fail to penetrate the cell membrane. As a result, there is a growing need to develop protein carriers to traverse the plasma membrane barrier to target “undruggable” intracellular targets, such as mutant Ras.

DESCRIPTION OF THE INVENTION

Many bacteria secrete toxins that target and inactivate small GTPases, including Ras, as part of their strategy to disable the host immune system. Using these toxins as therapeutics, however, has not be possible since, until recently, none have been shown to be highly specific for Ras. Our team has discovered an effector enzyme (RRSP) that specifically targets and inactivates intracellular Ras in human cells. Ectopic expression of this enzyme was shown to cleave mutant Ras protein and inhibit cell growth. To deliver RRSP into cells, a chimera was generated with an intracellular protein delivery platform based on diphtheria toxin that has evolved a sophisticated mechanism for crossing the plasma membrane with high efficiency (RRSP-DTB). *In vitro* work has shown that RRSP-DTB can effectively degrade total Ras levels in colorectal cell lines (HCT-116).

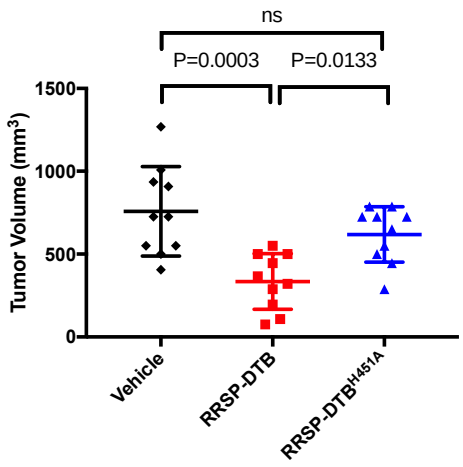


In addition, *in vivo* preclinical assessments have revealed that tumor growth and volume is significantly attenuated following RRSP-DTB administration in nu/nu immunodeficient mice who have receive either HCT 116 or breast cancer cell line (MDA-MB-436) injections.

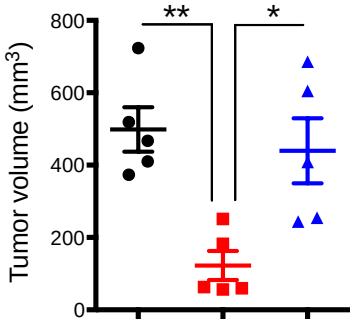


KEYWORDS
Cancer, RAS, diphtheria toxin, intracellular drug delivery

RRSP-DTB attenuates tumor growth in mice injected with HCT-116 cells



RRSP-DTB attenuates tumor growth in mice injected with MDA-MB-436 cells



COMMERCIAL APPLICATIONS & ADVANTAGES

This invention is a platform technology which permits the targeted delivery of a wide range of cargo into cells that have been previously unachievable.

- Ras proteins are implicated in one third of all cancers and mutated in 3 of 4 of the most lethal human malignancies (colon, lung and pancreatic cancers), making it a highly prized cancer drug target.
- There are two developing Ras inhibitors in clinical trial phases that target *KRAS G12C*. *KRAS* is a member of the Ras family, and the *KRAS G12C* mutation is present in 1-3% of colorectal and other solid tumors, and 13% of non-small cell lung cancer (NSCLC) patients.
- Unlike the two developing KRAS inhibitors, this invention targets all Ras mutants and isoforms.
- Versatility of the drug delivery platform will enable it to be easily redirected specifically to cancerous cells, and for additional applications (e.g. enzyme replacement therapy).
- Anticipate superior potency and safety over existing therapies (antibody-drug conjugates, immunotoxins) based on mechanism of action.

DEVELOPMENT STAGE

In vivo assessments of RRSP-DTB effects on tumor growth are completed.

PATENT STATUS

- US 2016/003053 A1 covers the enzyme (Satchell)
- US 10,597,663 (issued) covers the diphtheria toxin delivery system (Melnyk et al)
- US 2018/0080033 A1 covers the combination of enzyme and delivery platform (Melnyk et al)

IP&C intends to create a spin-off company and is seeking venture capital investment and/or a strategic partnership with a pharmaceutical company.

LEAD INVENTORS:
Dr. Roman Melnyk, PhD, Senior Scientist, Molecular Medicine, The Hospital for Sick Children
Dr. Karla Satchell, PhD, Department of Microbiology-Immunology, Northwestern University

LICENSING CONTACT:
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IP&C Ref. | RDLP 1171

SickKids
Industry Partnerships & Commercialization

TECHNOLOGY BRIEF

BIOPHARMA

Novel therapeutic compositions for degrading bacterial and fungal biofilms

BACKGROUND

Approximately 65-80% of all bacterial infections in humans are biofilm-related. Microbial biofilms, communities of adherent bacteria or fungi embedded in a matrix of exopolymeric substances, represent a significant medical challenge as they are highly resistant to antimicrobial agents, disinfectants and immune defenses. In fact, biofilm embedded microorganisms can tolerate antibiotic doses up to 1,000 times greater than doses that kill free-floating bacteria. Exopolysaccharides are a major component of the biofilm matrix, where they contribute to biofilm adhesion, architecture, and resistance. Biofilms can form on biotic surfaces, such as lung epithelial cells or other organs, and abiotic surfaces including, medical devices and implants, and they are responsible for biofouling in industrial and commercial settings.

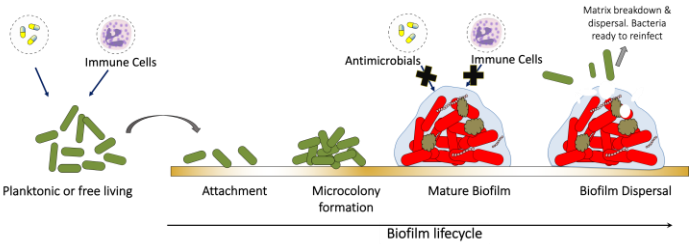

Fig 1: Biofilm formation and dispersal.

DESCRIPTION OF THE INVENTION

Our scientists have identified novel therapeutic enzymes for degrading and inhibiting production of bacterial and fungal biofilms. These compositions target and degrade the exopolysaccharides produced by a number of pathogenic species including, but not limited to; *Pseudomonas spp*, *Escherichia coli*, coagulase negative *Staphylococcus spp*, *Acinetobacter baumannii*, and *Aspergillus fumigatus*. Dispersing the biofilm and releasing the microbes into their free-floating state increases the efficacy of existing anti-infectives and immune defenses.

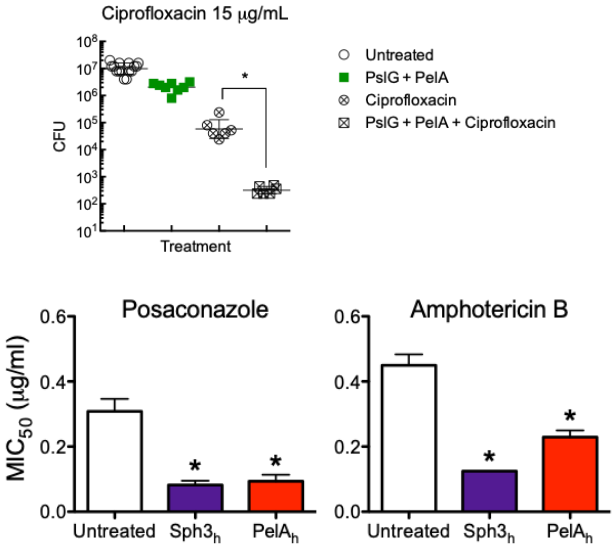

Fig 2: Antimicrobial potentiation using the enzymes PslG, PelA and Sph3

KEYWORDS
Anti-microbial, enzyme, biofilm degradation, therapeutic

The specificity of these novel enzymes allows for the selective dispersal of the pathogenic organism while eliminating off-target effects, including the disruption of host cells and the host microbiota.

In vitro data show that the hydrolases successfully potentiate the effect of antibiotics (Fig 2). We have also shown in an *in vivo* mouse burn wound model that these enzymes can increase the effectiveness of tobramycin treatment during wound infection (Fig 3).

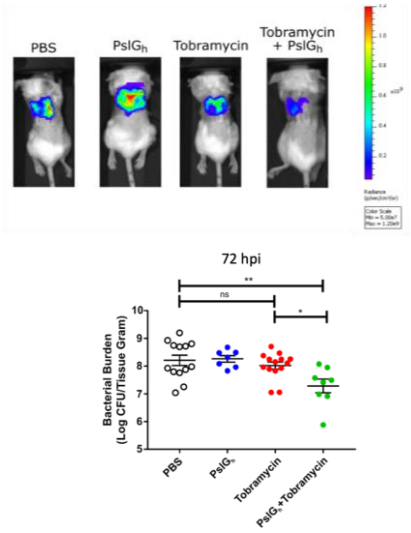

Fig 3: Effect of PslG on tobramycin treatment of burn wound infections

These enzymes can also be easily coated onto the surfaces of medical devices such as catheters to prevent biofilm formation (Fig 4). *In vitro* and *in vivo* proof of concept studies to prove the efficacy of a combination of these enzymes on multispecies biofilms are currently underway.

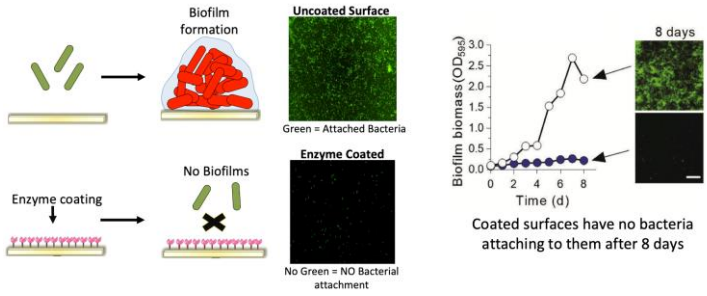

Fig 4: Efficacy of enzyme coating on abiotic surfaces

COMMERCIAL APPLICATIONS & ADVANTAGES

- Diverse applications:
  - Anti-infectives for lung diseases and wounds
  - Coatings for medical devices and implants
  - Disinfecting products
- Low (nanomolar) quantities of enzyme can prevent biofilm formation, protect lung epithelial cells from fungal damage prior to biofilm formation, or disperse existing biofilms in less than 1 hour. This high level of specificity for the biofilm matrix will lessen the likelihood of resistance.
- Enzymes synergize with standard antimicrobials and make them more effective.
- Enzymes are easy to produce, stable and non-toxic. High (milligram) quantities of enzymes are non-toxic to human lung fibroblast cells and preliminary toxicity studies in mice are promising.
- Enzyme coatings are active and stable for up to 8 days on surfaces.

DEVELOPMENT STAGE

Extensive *in vitro* data available; animal studies testing efficacy, toxicity and PK in bacterial and fungal models of pulmonary infection; porcine models of burn wound infection; and rat models of catheter infection are in progress.

The current findings point to a promising avenue for the development of these enzymes as novel therapeutics for the treatment of a wide variety of chronic infections, including pulmonary diseases (cystic fibrosis, invasive aspergillosis, and whooping cough), wound infections which affect 1-2% of the world's population and medical device associated infections.

PATENT STATUS

PCT national phase application (US 2017/0216410 A1) covering bacterial and fungal applications. First US patent allowed January 2021.

IP&C is seeking investment to advance the pre-clinical development of the lead therapeutic.

LEAD INVENTORS:
Dr. Lynne Howell, PhD, Senior Scientist, Molecular Medicine, The Hospital for Sick Children
Dr. Don Sheppard, MD, McGill University

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IP&C Ref. | RDLP 890, 892, 909-911, 1097-1100

SickKids
Industry Partnerships & Commercialization

TECHNOLOGY BRIEF

BIOPHARMA

Engineered human alveolar-like macrophages as a cell therapy for respiratory diseases

BACKGROUND

In recent years, directed differentiation of pluripotent stem cells (PSCs) has become a major focus of regenerative medicine to help address the shortcomings of pulmonary therapeutics or transplantation. Specific efforts have focused on endoderm-derived lung epithelium tissue regeneration, while mesoderm-derived tissues in the lungs, such as non-circulating hematopoietic lineages, have received minimal attention. This oversight in pulmonary stem cell regenerative medicine has led to a failure to appropriately address the importance of the innate immune system of the lungs, particularly its most abundant population of airway cells, the alveolar macrophage (AM). This cell type is an environmentally-adapted phagocytic macrophage, unlike those of other tissues.

Currently, there are inadequate therapeutic options for a variety of major respiratory diseases, including: bronchopulmonary dysplasia, RSV, COPD, and bacterial infections due to cystic fibrosis. Many of these diseases result from prolonged inflammatory states and compromised innate immunity leading to further tissue damage and infection. Bolstering the immune system could provide acute therapeutic relief and promote positive health outcomes in paediatric populations.

DESCRIPTION OF THE INVENTION

The Post lab has developed an *in vitro* differentiation protocol whereby human embryonic stem cells can be differentiated into human alveolar-like macrophages (hALMs) in xeno-free media (seeder/feeder independent). The protocol that was originally developed from murine PSCs (mPSC) has been successfully translated to human PSCs. AMs are highly phagocytic cells of the pulmonary innate immune system that represent the primary hematopoietic cells of the airways.

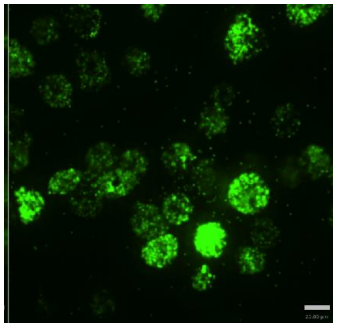

Fig 1: Internalization of GFP-expressing bacteria by hALMs

Their identity was phenotypically confirmed via co-expression of F4/80:CD11c:SIRPalpha and functionally characterized by their ability to phagocytose (Fig 1) and to remain functionally active in healthy, injured and injury-resolving mouse lungs without an obvious compromise in immune response. Furthermore, the mPSC-AM remained viable in

KEYWORDS
Pluripotent stem cells, alveolar macrophages, lung, cell therapy, respiratory diseases

culture for several months using expansion and maintenance media. Following xeno-transplant, hALMs did not appear outside the lungs after 2 weeks and did not elicit T-cell response, showing potential for allogenic and autologous transplants (Fig 2).

	Week 1	Week 2
Spleen	NS	NS
Thymus	NS	NS
Airways	ND	ND

Fig 2: CD4 and CD8 Tcell detection after 1 and 2 weeks following intratracheal hALM administration in mice.

COMMERCIAL APPLICATIONS & ADVANTAGES

This invention is a platform technology which permits the ex-vivo generation and transplant of hALMs that can be engineered to express several factors which become active in the lungs and has the potential to treat several respiratory illnesses.

- hPSC-AMs as a cell therapy tool: treatment with exogenous macrophage may mitigate the pathophysiological effects and/or progression of genetic or acquired lung diseases, including pulmonary alveolar proteinosis, cystic fibrosis, adenosine deaminase deficiency, infectious diseases, or chronic obstructive pulmonary disease (COPD).
- Robust model with human translation: mPSC-AMs have been extensively characterized phenotypically and functionally, *in vitro* and *in vivo*, and protocol has been successfully translated to human PSCs.

DEVELOPMENT STAGE

In vivo work evaluating hALMs therapeutic effect on RSV, BPD etc. are ongoing.

PATENT STATUS

- US 2017/0335282 A1: “Alveolar-like macrophages and method of generating same” – allowed in the US and Europe
- US Patent Application No. 62/825352: “Method of generating haemangioblasts” filed March 28, 2019

IP&C is seeking venture capital investment to create a company and/or a strategic partnership with a pharmaceutical company to complete the development and commercialization of the hALMs.

LEAD INVENTORS:
Dr. Martin Post, PhD, Senior Scientist, Translational Medicine, The Hospital for Sick Children

LICENSING CONTACT:
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IP&C Ref. | RDLP 1175

TECHNOLOGY BRIEF

BIOPHARMA

Methods of treating trinucleotide repeat expansion diseases

BACKGROUND

Genetic expansions of CAG/CTG trinucleotide repeat sequences in certain genes have been linked to at least 40 neurodegenerative, neurological, and neuromuscular diseases, including Huntington's disease (HD), fragile X syndrome, myotonic dystrophy, various spinocerebellar ataxias, and amyotrophic lateral sclerosis. These repeat expansions tend to get larger as they are inherited from one generation to the next, resulting in earlier age of onset, increased disease progression and severity. Importantly, the expansions grow in size as the individual ages, are believed to drive the disease onset, progression, and severity. A reduction of a few repeats could delay onset by years, and a method of arresting or reversing somatic CAG/CTG could be used to arrest or even reverse disease onset, progression, and severity (Fig 1).

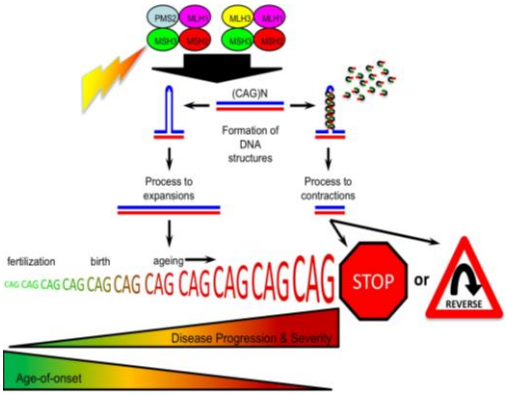

Fig 1. Targeting DNA repair proteins and/or Slipped-DNAs can modulate disease-causing expanded CAG tracts for therapeutic benefit

DESCRIPTION OF THE INVENTION

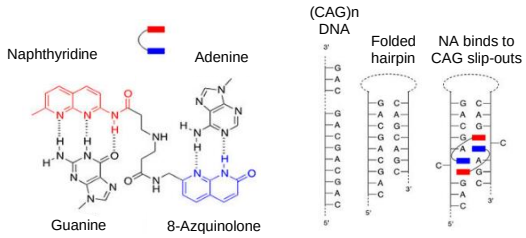

Fig 2: Naphthyridine-Azaquinolone (NA) compound and mechanism of action

The Pearson lab, in collaboration with colleagues at Osaka University, have discovered that a small molecule, Naphthyridine-Azaquinolone (NA), is useful in treating CAG/CTG repeats (Fig 2). NA not only arrests CAG/CTG expansions, but it induces contractions of expanded CAG repeats in HD patient cells and in a HD mouse model. Notably, NA acts specifically upon the mutant expanded repeat with no observed off-target effects (no effect on the non-expanded allele, and without damaging the rest of the genome).

Repeated administrations of NA have additive effects of inducing contractions of the CAG tract *in vivo* (Fig 3), leading to the reduction in the mutant HTT aggregates that are characteristic of HD in the disease mouse model.

KEYWORDS
Trinucleotide repeat, genetic expansions, small molecule, therapy

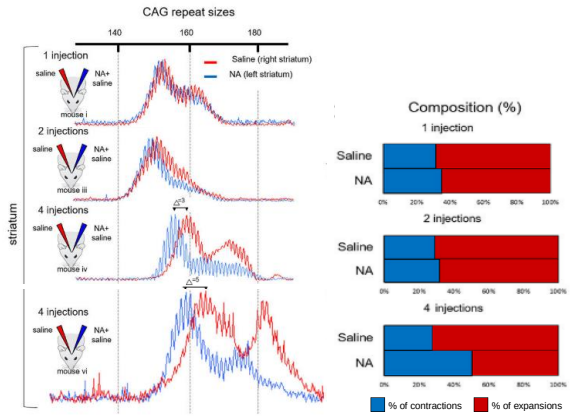

Fig 3: NA induces repeat contractions in vivo

COMMERCIAL APPLICATIONS & ADVANTAGES

This can be a transformative therapy for individuals with a range of neurodevelopment conditions, as there is currently no cure for rare trinucleotide repeat diseases.

DEVELOPMENT STAGE

Preclinical *in vitro* and *in vivo* data in a disease-specific brain region are promising. Next steps include medicinal chemistry, pharmacokinetic, animal efficacy, and toxicology studies.

The Pearson lab has developed a platform to discover chemical matter specific to other trinucleotide repeat diseases. Current work includes fragile X syndrome, amyotrophic lateral sclerosis, Friedreich's ataxia, and myotonic dystrophy.

PATENT STATUS

PCT national phase applications have been filed on the use of the small molecule in trinucleotide repeat diseases.

IP&C is seeking venture capital investment into the start-up company that will bring to market the lead compound NA.

LEAD INVENTORS:
Dr. Christopher Pearson, PhD, Senior Scientist, Genetics & Genome Biology, The Hospital for Sick Children

LICENSING CONTACT:
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IP&C Ref.| RDLP 1123

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TECHNOLOGY BRIEF

DIAGNOSTICS & RESEARCH TOOLS

Whole-genome detection and interpretation of repeat expansions in autism and related disorders

BACKGROUND

Advancements in genome analysis have greatly improved gene discovery and clinical diagnosis for many human diseases. As whole genome sequencing data have become available, this has enabled the identification of all classes of genetic variation.

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders resulting in social, behavioural, and communication challenges, and individuals with ASD may experience additional complications such as intellectual disability. There is an estimated heritability of up to 90%, and genomic analyses have indicated that individuals with ASD have 2-3-fold increase in rare copy number variations (CNVs) and *de novo* loss of function variants. There have been over 100 genes and loci identified that are associated with ASD, but these factors only attribute towards 20% of all ASD cases. While genome sequencing has become the gold standard technology for uncovering disease-causing variants, there remains difficulty in resolving complex variants, such as in repetitive areas.

The human genome is comprised of 6% tandem repetitive DNA, and certain repeat motifs have been associated with human diseases, such as the tandem repeat expansion of the CGG tract in fragile X syndrome, which is associated with ASD in 40% of cases. There are at least 50 other tandem repeat-related medical genetic disorders. Therefore, it is crucial to develop a method to resolve complex variants to identify novel genetic variants in ASD, other medical conditions, and likely several other disorders which are still to be discovered.

DESCRIPTION OF THE INVENTION

The Yuen and Scherer labs have developed a strategy to detect tandem repeats from whole genome sequence data to identify gene candidates involved in ASD for both clinical diagnosis and gene discovery. The tandem repeats detected are comprised of repeat motifs of 2-20bp, which span 150 bp or more.

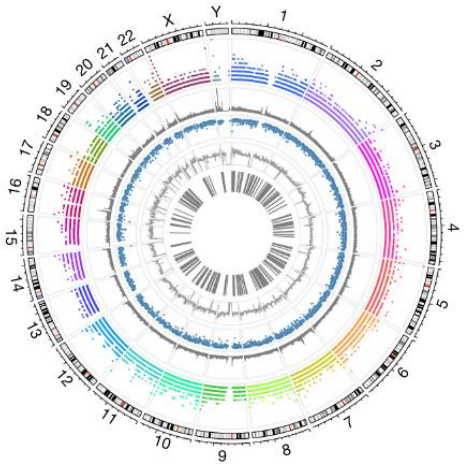

Fig 1. Genome analysis of tandem repeats.

KEYWORDS
Autism spectrum disorder, tandem DNA repeats, rare tandem repeat expansions, repeat motifs

From a sample pool of 17,231 which included individuals with ASD and a control population, more than 37,865 tandem repeat motifs were identified in 31,793 regions in the human genome (Fig 1). Comparison of rare tandem repeat expansions present in children with ASD versus children without ASD suggests that rare tandem repeat expansions contribute 2.6% to the genetic risk of developing ASD.

Individuals with the rare tandem repeat expansions also presented with lower IQ (Fig 2), further supporting the strength of this method in linking rare tandem repeat expansions to ASD-phenotypes.

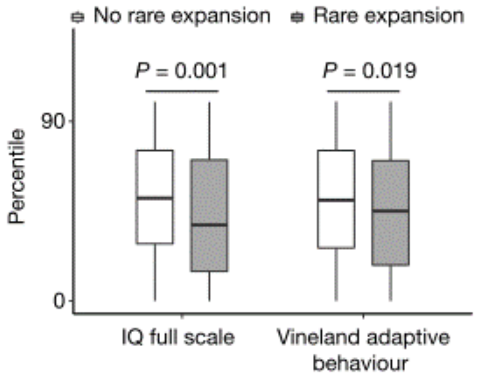

Fig 2. Clinical analysis of individuals with rare tandem repeat expansions.

COMMERCIAL APPLICATIONS & ADVANTAGES

- Identifying rare tandem repeat expansions in individuals with ASD or its related disorders that could not be resolved using standard genome annotation algorithms. Applications include:
  - Clinical diagnosis
  - Disease gene discovery
  - Assessing whole genome sequence data accompanying clinical trials
- Model application for other complex disorders with missing heritability

DEVELOPMENTAL STAGE

Clinical data from sample size of >17,000 and controls.

PATENT STATUS

PCT patent application has been filed.

IP&C is seeking investments and partnerships to complete the development of our three programs in diagnostic, target identification, and therapeutic development.

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IP&C Ref. | RDLP 1294

SickKids
Industry Partnerships & Commercialization

TECHNOLOGY BRIEF

DIAGNOSTICS & RESEARCH TOOLS

Machine learning-driven NGS-based diagnostic tests to optimize clinical response in oncology

BACKGROUND

Tumour cells circumvent normal DNA repair safeguards which allow for the accumulation of genetic mutations that drive tumour growth. Tumour Mutational Burden (TMB) is increasingly recognized as a potential prognostic biomarker for response to precision therapeutics such as immune checkpoint inhibitors (ICI). Existing methods (based on a universal TMB cut-off point of 10 mutations per megabase (hyperTMB)) to assess candidacy for, and relative response to, ICIs have improved treatment for some types of cancers, but are an imperfect indicator and fail to accurately identify the ideal target patient population across all cancers.

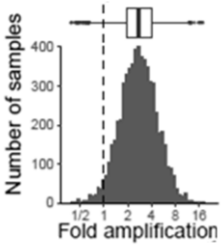

Fig 1: Histogram showing the transcriptional output of 6,095 cancers

RNA (transcriptional) content of rapidly proliferating tumour cells is greater than that in normal cells and suggests that cells which globally increase transcription have a growth advantage over those that cannot. Increased transcriptional output measured using RNA amplification by our researchers was determined to be an independent prognostic marker for disease outcomes across over 6,000 patient samples and 22 cancer types.

DESCRIPTION OF THE INVENTION

The Tabori and Shlien labs have developed the first direct method to quantify RNA output in tumour samples. Amplified RNA output detected and analyzed by their proprietary machine learning algorithm "RNAmp" determined that RNA amplification (hyperTX) measured by RNAmp is a precise, prognostic indicator of patient survival; patient groups with increased RNA levels have significantly worse survival.

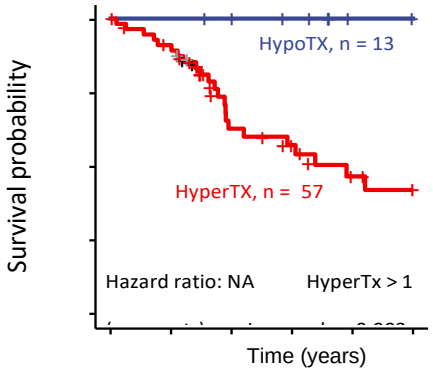

Fig 2: Survival differences based on RNAmp

Non-hyperTMB tumours, identified as hyperTX by this invention, express more mutations and were as responsive to immune checkpoint inhibitor (ICI) as hyperTMB patients (62% vs 68% respectively). As these non-hyper TMB patients are not regularly selected for ICI therapy, RNAmp biomarker analysis

KEYWORDS
Cancer, tumor, biomarker, diagnostic, prognostic, hypermutant, amplification

reveals a new segment of the tumour patient population for ICI therapy and improved patient outcomes.

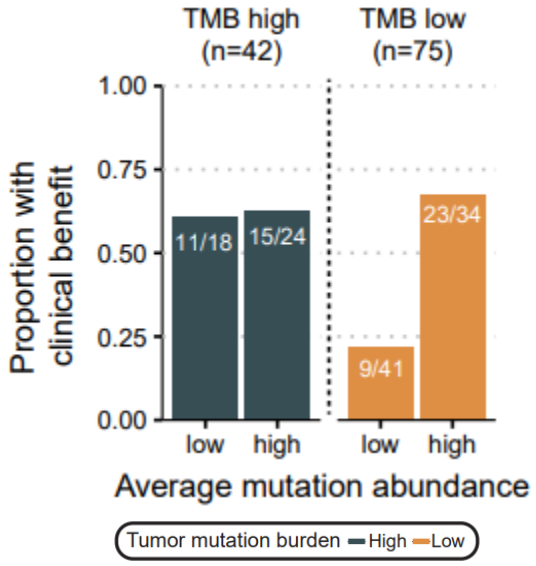

Fig 3: Clinical benefits differ for patients with different TMBs

COMMERCIAL APPLICATIONS & ADVANTAGES

While many companies and institutions perform cancer gene testing, the utility of these tests has limitations. In addition, the introduction of hyperTMB as a complex biomarker for tumour treatment has illustrated the need for more accurate methods within specific tumour types and subclasses. There remains a large unmet need to reliably determine patient responsiveness to treatments, as a large segment of cancer patients exhibit resistance toward immunotherapies. Our invention addresses this need and accurately identifies immune checkpoint inhibitor responders within low TMB tumour patient populations.

This first-in-class Tumour Profiling Test based on amplified RNA signatures developed by the Tabori and Shlien labs is unparalleled in the industry.

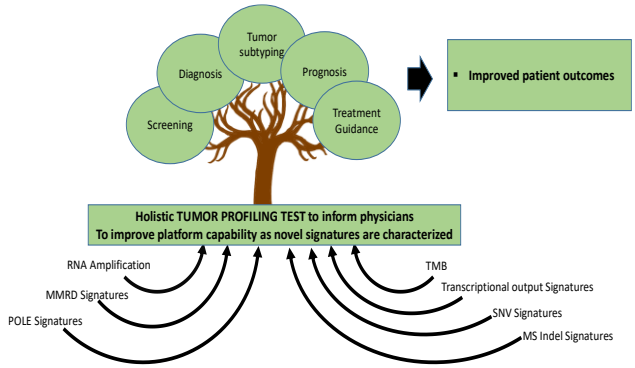

Fig 4: Clinical utility of RNAmp biomarker

Combining the lead asset of RNAmp with numerous diagnostic tests developed at SickKids, such as genomic hyper mutant analysis, MSI, SNV, MMRD and POLE signatures, provides a company creation/investment opportunity with a unique position in the industry providing:

- Novel assays for tumour subtyping and diagnosis
- Unparalleled prognostic biomarker accuracy
- Predictive patient responsiveness to cancer treatments

With a $400M diagnostic market for ICI therapy alone, this opportunity represents a chance to enter at the forefront of precision, complex biomarker analysis.

DEVELOPMENT STAGE

Prototypes developed.

PATENT STATUS

PCT and provisional patent applications filed.

IP&C intends to create a spin-off company and is seeking venture capital investment and/or a strategic partnership with a pharmaceutical company.

LEAD INVENTORS:
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SickKids
Industry Partnerships & Commercialization

TECHNOLOGY BRIEF

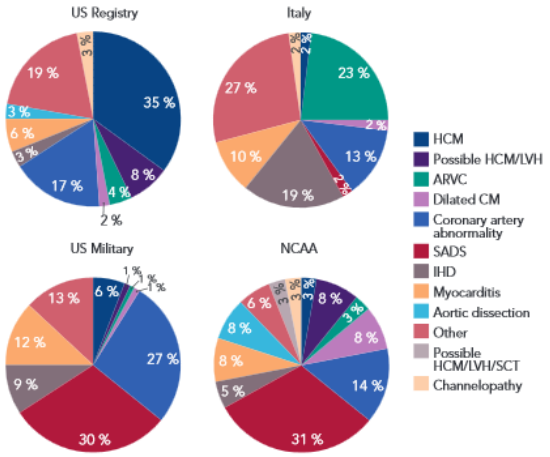
DIAGNOSTICS & RESEARCH TOOLS
Highly sensitive diagnostic tests for the prevention of sudden cardiac death

BACKGROUND

Sudden cardiac arrest (SCA) is the abrupt loss of heart function, breathing, and consciousness. SCA is usually caused by an electrical disturbance in the heart, which disrupts heart pumping and consequently the blood flow. In the case of a defect in electrical impulses or in the sinus node, SCA can lead to abnormal heart rhythm or arrhythmia. If not treated immediately, SCA can lead to Sudden Cardiac Death (SCD), which is the second largest cause of life-years lost in the US. Some SCD disorders are difficult to diagnose, including Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) and Brugada Syndrome (BrS).

ARVC is an inherited disease of the desmosomal proteins that hold together cardiomyocytes, and can result in sudden cardiac death. The prevalence of ARVC is as high as 1 in 1000 individuals, accounting for 11% of SCD in adults, 22% in athletes, and 25% in children. Currently, ARVC is diagnosed using a combination of imaging and electrocardiography in addition to genetic screening. However, 2/3 of ARVC patients are gene-elusive and go undiagnosed. Disease management includes exercise restriction and an implantable defibrillator for high risk cases.

BrS is a heritable disorder associated with an increased risk of SCD from ventricular arrhythmias and is characterized by a unique ECG pattern of coved "ST" segment elevation (>2mm) followed by a negative T wave in anterior chest leads (called the Type 1 Brugada Syndrome pattern). BrS causes 4-12% of SCD, where 20% of the patient hearts are structurally normal. The world prevalence is 1 in 2,000 persons, but it is much higher in those of southeast Asian descent. Once diagnosed, patient management includes alcohol avoidance and implantation of a defibrillator for high-risk cases.



ARVC = arrhythmogenic cardiomyopathy; CM = cardiomyopathy; HCM = hypertrophic cardiomyopathy; IHD = ischaemic heart disease; LVH = left ventricular hypertrophy; NCAA = National Collegiate Athletic Association; SADS = sudden arrhythmic death syndrome; SCT = sickle cell trait. Reproduced with permission from Harmon et al.[13] with data taken from Corrado et al.[7]

Fig 1: Comparison of causes of Sudden Cardiac Death

KEYWORDS
Arrhythmogenic right ventricular cardiomyopathy, sudden cardiac death, Brugada Syndrome, biomarker, autoantibody, diagnostic

DESCRIPTION OF THE INVENTIONS

ARVC: The Hamilton lab has discovered an anti-desmosome autoantibody that is present in the blood of subjects with ARVC but is absent in healthy individuals. Levels of antibody track with arrhythmia burden and specific epitopes targeted by the antibody have been identified. As an alternative to current diagnostic methods, a clinical ELISA has been developed as a simple, cost-effective test to identify the presence and severity of the ARVC condition, allowing for sensitive and specific diagnosis to inform treatment and prevent SCD.

BrS: The Hamilton lab has discovered a biomarker profile of autoantibodies against 4 cardiac proteins-alpha-cardiac actin, alpha-skeletal actin, keratin and connexin-43. These autoantibodies can be identified from sera of BrS patients, using a novel method that is highly sensitive, specific, and independent of the genetic cause of BrS.

COMMERCIAL APPLICATIONS & ADVANTAGES

ARVC: Currently, ARVC diagnosis involves genetic testing and clinical testing. These existing methods are unsatisfactory: genetic testing is only 33-50% sensitive, while clinical testing costs $1,000/year and provides only 70% sensitivity with false positives. The ARVC biomarker discovered by our researchers **identifies 98% of ARVC cases** with the following commercial opportunities:

- Development as a prognostic biomarker
- Poses as a potential companion biomarker
- Predictive testing of disease progression, which is in development

BrS: Genetic testing for SCN5A mutations is only performed in patients with a likelihood of developing BrS. However, mutations in SCN5A is only found in 11-28% of BrS patients. Clinical diagnosis is costly and is based on identification of the typical ECG pattern, which is often transient. Our researchers' profile of biomarkers **identifies 100% of probable cases that develop into BrS**, with possible commercial applications of:

- Development as a prognostic biomarker
- Predictive testing of disease progression, which is in development

DEVELOPMENT STAGE

In vitro diagnostic assays have been developed, and researchers are currently collaborating with all Canadian Inherited Arrhythmia Clinics and major US and European centres.

PATENT STATUS

ARVC - Patent applications filed in Canada, US, and Europe.

BrS - PCT/CA2020/050578 filed May 1, 2020.

IP&C is seeking an industry partner complete development, validate and commercialize these clinical diagnostic tests.

LEAD INVENTORS:
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IP&C Ref. | RDLP 1138 and RDLP 1238

TECHNOLOGY BRIEF

DIAGNOSTICS & RESEARCH TOOLS
MATCH: Machine learning algorithms for toxicity and cardiac health

BACKGROUND

Dysfunction of the heart due to unexpected toxicity can be related to problems with reduced contractility or adverse changes to cardiac rhythm. These complex actions make *in vitro* modeling of heart function challenging and preclinical animal models suboptimal, leading to significant problems in predicting the effect of pharmaceuticals on the heart. As a result, unexpected cardiac toxicity eliminates 30% of drug candidates from development pipelines and 16% of post-market drugs.

Current drug discovery and preclinical models of cardiac function do not accurately predict cardiac activity or toxicity, resulting in high rates of unexpected failure. To improve prediction and elimination of compounds with potential cardiotoxicity earlier in the drug discovery continuum, a test integrating multiple cardiac outputs with greater certainty and throughput is required.

DESCRIPTION OF THE INVENTION

Our cardiotoxicity platform incorporates multiple tests of cardiac function into a unified, multi-parametric system, providing predictive power. Our use of non-biased machine learning algorithms allows us to determine which metrics are most predictive of human cardiac activity, eliminating unnecessary tests and setting an industry standard for *in vitro* cardiac activity screening.

1. Multiple Electrode Array Analysis: determines the effect a compound may have on ion channel flux and cardiac electromechanical coupling, utilizing functional 2D monolayers of cooperatively beating iPSC-CM cardiac “tissue” (Fig 1) and analyzed using algorithms.

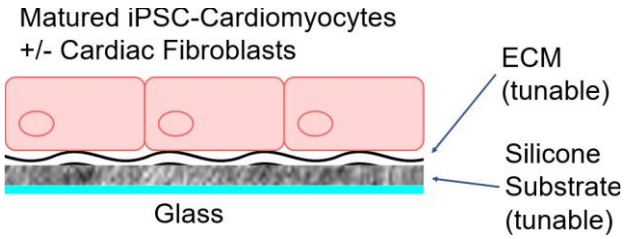

Fig 1: 2D monolayer of iPSC-CM cardiac tissue.

2. Beating and Contractility Analysis: determines how a compound alters tissue contractility and beating rate and rhythm using our carbon nanotube sensor device developed and patented for the purpose of determining drug effect on cardiac tissue composed of iPSC-CMs, which we have illustrated to be the first platform assay that recapitulates the *in vivo* effect of cardioactive drugs.

KEYWORDS
Cardiac, drug discovery, toxicity, platform, artificial intelligence, machine learning

3. Real-time Tissue Stiffness Analysis: determines how a compound alters tissue function in the context of a healthy (soft) and diseased (stiff) heart, using our advanced imaging and optical flow analysis to determine changes to cardiomyocyte function. This analysis is unique and illustrates how drug effect is dependent on the context of overall organ health.
The above three parameters are integrated through a proprietary cardiac activity machine-learning classifier against known drug classes (together called "MATCH") (Fig 3).

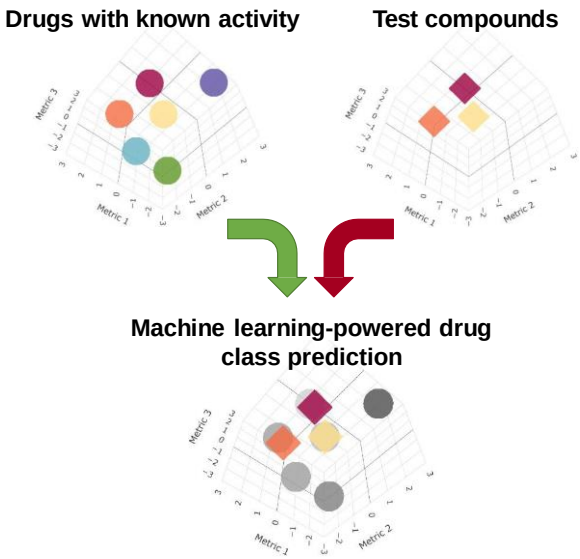

Fig 2: Our proprietary cardiac activity machine-learning algorithm called "MATCH"

MATCH identifies the cardiac activity/toxicity of the investigational drug(s) and generates a comprehensive report (Fig 3).

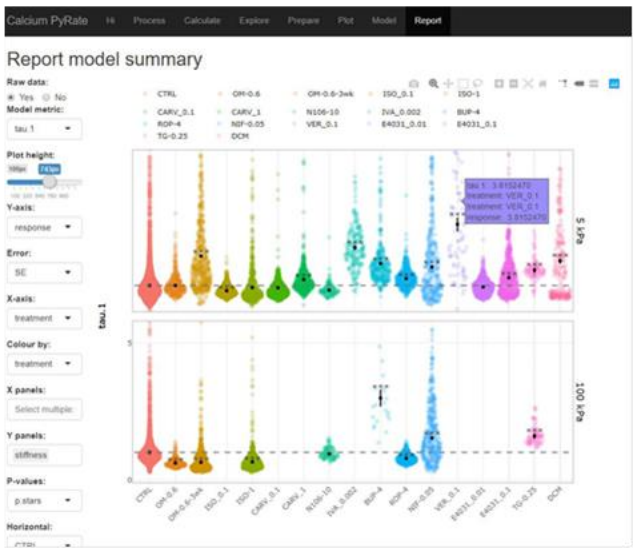

Fig 3: Comprehensive report generated by the MATCH platform

COMMERCIAL APPLICATIONS & ADVANTAGES

MATCH integrates multiple cardiotoxicity assays into a single a machine learning-based report designed to seamlessly integrate into contemporary preclinical drug discovery hit to lead validation. It provides a robust cardiotoxicity profile unparalleled in the industry translating to reduced cardiotoxicity of drug candidates, reducing failures and improving clinical trial success.

DEVELOPMENT STAGE

MATCH is a fully developed assay system validated through use in several drug discovery screens.

PATENT STATUS

PCT application filed.

IP&C is seeking an industry partner complete development, validate and commercialize this research tool.

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Dr. Yu Sun, PhD, Professor, Canada Research Chair in Micro and Nano Engineering Systems; Director, University of Toronto Robotics Institute

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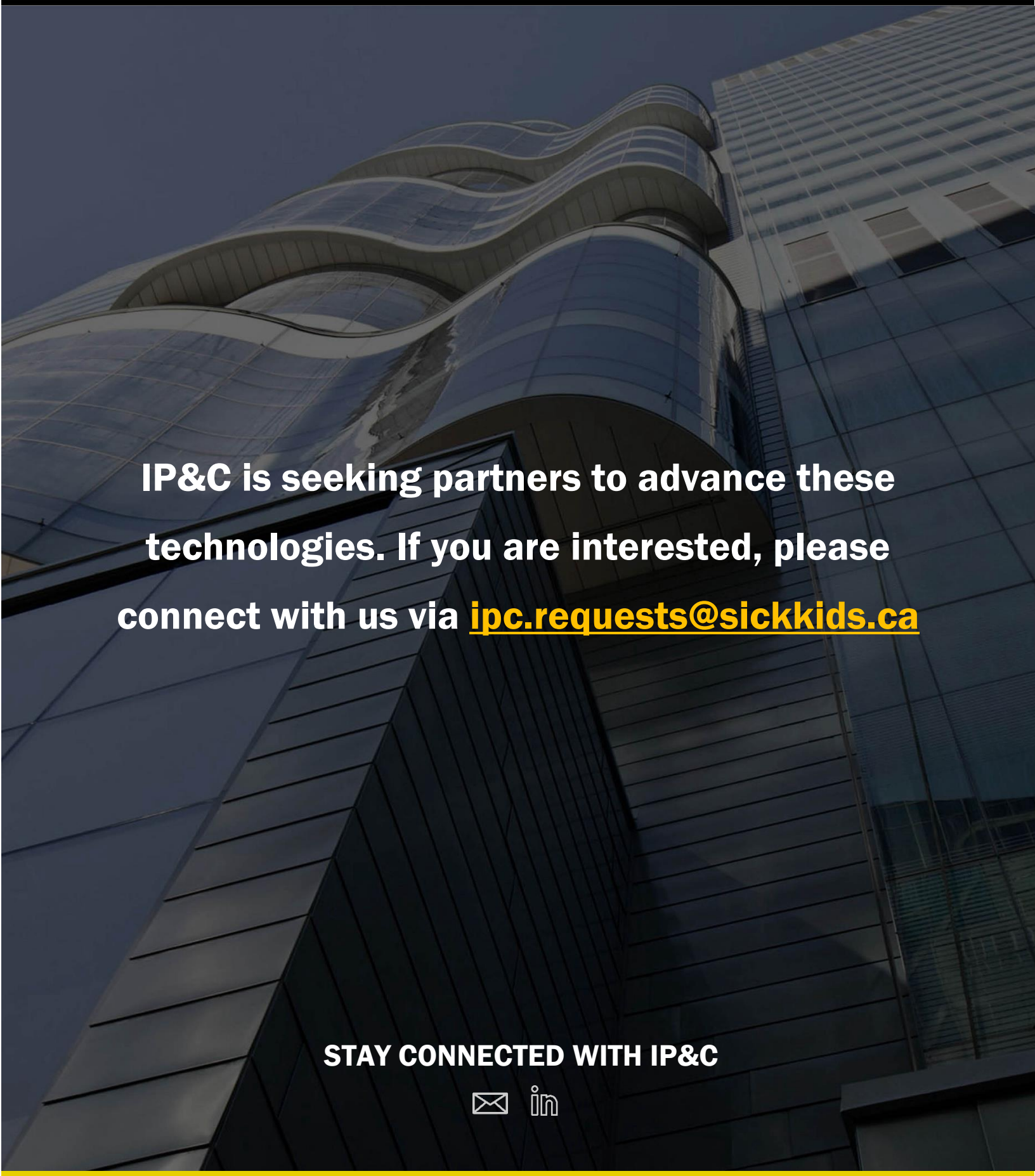

IP&C is seeking partners to advance these technologies. If you are interested, please connect with us via ipc.requests@sickkids.ca

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