Supported by

sanofi

Summary of proceedings:

T1Decade of Research Progress – Past & Future

24–25 July 2023, Sydney, Australia

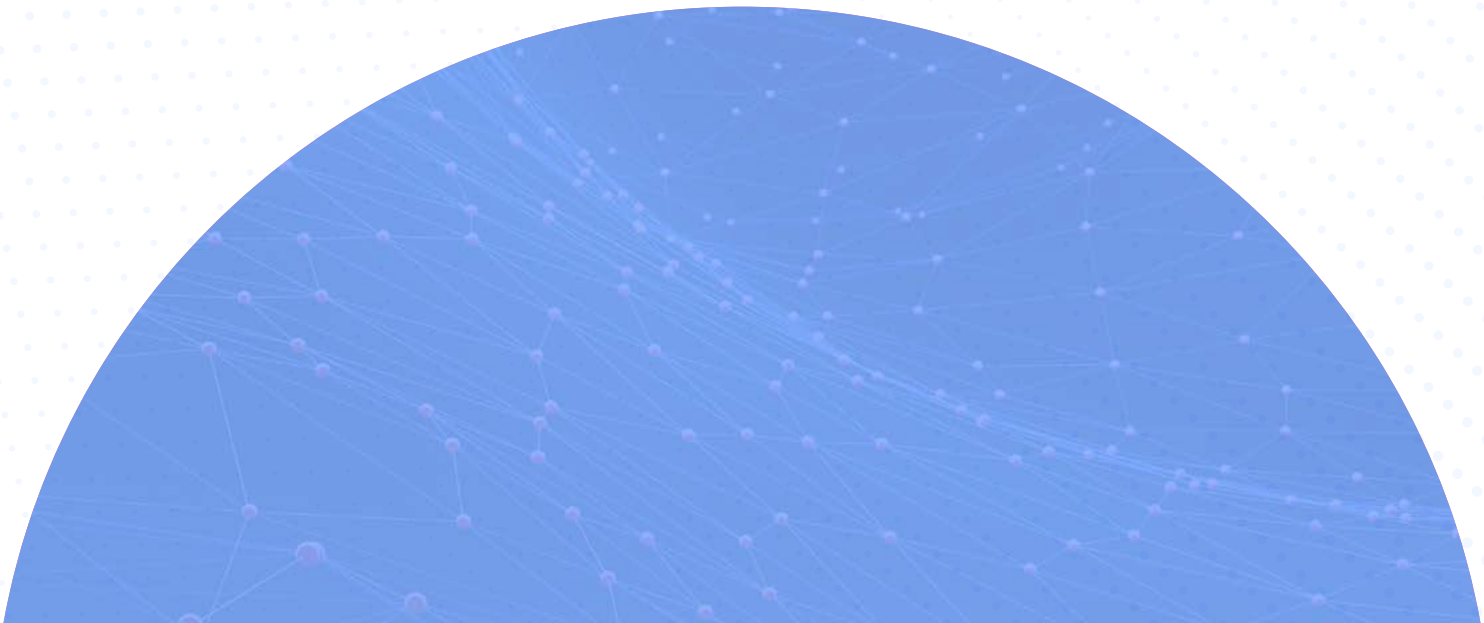
A JDRF T1D Clinical Research Network Symposium

PROGRAM

Australian Type 1 Diabetes Clinical Research Network

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

Contents



Introduction

On 24th and 25th July 2023, JDRF Australia hosted a two-day face to face symposium in Sydney Australia, to commemorate over a decade of achievements of the Type 1 Diabetes Clinical Research Network (T1DCRN), JDRF Australia's primary vehicle for T1D research funding.

The Symposium brought together over 170 multi-disciplinary attendees from the type 1 diabetes (T1D) research ecosystem, from basic researchers to clinician-researchers, patients, funders and pharmaceutical companies. It was opened by the Hon Mark Butler MP, Minister for Health and Aged Care and featured a multitude of people living with T1D about what research advances have meant for them.

The Symposium was based around four sessions which represent the most cutting-edge research in T1D. These were:

- **Session 1:** Progress towards early diagnosis and primary prevention
- **Session 2:** Intercepting and delaying the course of T1D development - disease modifying therapies
- **Session 3:** Beta cell replacement and regeneration
- **Session 4:** Technologies, adjunct therapies, adoption and policy.

A summary of the entire Symposium is provided below along with the program found in **Appendix A**. Each session summary contains: 1) Key take home messages from the presentations and panel discussions 2) Future research and policy directions for the next decade.

Summaries of each presentation and panel discussion are found in **Appendices B to E**.

Recordings of the day can be freely accessed on JDRF Australia's website.

JDRF Australia would like to thank Sanofi for its support of the Symposium.

DAY 1: 24th JULY 2023

Welcome and opening

Dr Dorota Pawlak, Chief Scientific Officer of JDRF Australia provided a comprehensive history of the T1DCRN within the backdrop of the scarcity of treatments for T1D since the discovery of insulin over a century ago. Dr Pawlak noted the urgent need for acceleration in the discovery of new therapies and the way that JDRF is able to do this by 1) bringing together various players in the T1D research ecosystem and 2) having a patient-centric approach. Dr Pawlak also launched the T1DCRN research impact report: **'Type 1 Diabetes Clinical Research Network: a decade of impact'** which celebrates the significant impact that the T1DCRN has achieved since its inception in 2010.

Professor Mark Atkinson gave his positive impression of the T1DCRN and JDRF in light of T1D research in Australia and internationally and noted that its model "speeds up the progress of discovery, leading to more rapid impact on public health care".

SESSION 1:

Progress towards early diagnosis and primary prevention

The first session focused on the research developments in identifying triggers of T1D initiation and progression, to be used as a basis for primary prevention strategies.

We heard two keynote speakers: **Professors Jennifer Couper** and **Marian Rewers**, followed by four short presentations from **Professor John Wentworth**, **Dr Kristine Bell**, **A/Professor Emma Hamilton-Williams** and **Dr Ki Wook Kim**. The session was completed by a multidisciplinary panel discussion on primary prevention, collaborative solutions and future directions. Summaries of the presentations are found in **Appendix B**. A summary of the entire session is as follows.

Key Messages of session- Early diagnosis and primary prevention

The main messages from the presentations as well as the panel discussion were:

- **The genetic basis of T1D:** In recent years the advancements in genetic and 'omics' research have identified HLA and non-HLA loci which together concur 80% of heritability of T1D. Single Nucleotide Polymorphisms (SNPs) from these loci have formed the basis of the Genetic Risk Score (GRS), a potential tool to identify individuals at the highest risk of developing T1D. However, having an increased genetic risk alone is not sufficient to drive T1D development, with environment triggers needed to initiate islet autoimmunity.
- **Postnatal triggers:** The analysis of several long-running cohorts have identified the most likely postnatal triggers of T1D development including viral infections (in particular, enterovirus and respiratory infections), an abnormal microbiome profile and rapid infant weight gain. These have been shown to bestow the highest risk of developing T1D across multiple cohorts.
- **Prenatal Triggers:** The Environmental Determinants of Islet Autoimmunity (ENDIA) cohort was established in Australia as the first study in the world aimed at identifying prenatal triggers leading to T1D. While the study is still ongoing, it has demonstrated that a more proinflammatory microbiome profile in mothers and babies, a reduced pancreatic size and exocrine function in infancy were present in children who later developed T1D. The study also supports earlier results from prior cohorts showing that early

weight gain in a baby increases the risk of T1D.

- **Primary Prevention:** Findings from prior and ongoing cohorts are driving current investigations in T1D primary prevention strategies. The results of the clinical studies testing oral insulin (POInt) and oral probiotics (SINT1A) administered to infants with high GRS are estimated to be released in 2024 and 2026 respectively. The potential for viral vaccination to reduce the risk of T1D has been extensively studied in pre-clinical models and the PRV-101 coxsackievirus vaccine has been now tried in a first in human safety study.
- **Screening of the general population:** Screening for asymptomatic T1D in the general population as well as in familial cases is being tested in several countries including Australia with the aim of adoption into routine public health programs. It has been demonstrated that 90% of cases of diabetic ketoacidosis (DKA) at diagnosis can be prevented with early screening, monitoring, and education programs.
- **A robust R&D pipeline of therapies:** The FDA approval of the first immunotherapy for T1D, Teplizumab, in November 2022 underscores the importance of screening programs that identify individuals in the early stage of T1D who could benefit from such therapies. In addition, more therapies are being investigated and showing promise in preserving beta cell function, including the calcium channel blocker Verapamil and JAK inhibitor Baricitinib, with a clinical trial completed in Australia in 2023.
- **Policy implications of research:** There was a consensus that discoveries in understanding T1D aetiology are bringing change on how T1D should be diagnosed and treated, with over 100 international clinicians developing guidelines for clinical care of pre-symptomatic diabetes. This change will require strategic investment in education, training, effectiveness of clinical care models and regulatory approaches.

Where we need to go next - Early diagnosis and primary prevention

Based on the Session 1 presentations and panel discussion, the areas of future focus for the next decade of T1D research and policy action should be:

- **Acceptance of general population screening:** Collaborating globally and acting locally to identify and reduce implementation barriers to whole population screening for T1D. Currently there remain implementation challenges around general population screening, including the best screening approach, costs structures and societal/ethical considerations.
- **Investigate prenatal factors increasing the risk of T1D:** Further elucidate the aetiology of T1D especially in the earliest stages in at-risk populations before the immune process becomes irreversible.
- **Explore the variability in T1D development and presentation:** Elucidate variability in triggers and disease progression through global collaborative studies using precision analytics. This should include broadening the ethnicity of the population studied and include vulnerable population such as First Nations where the pattern of diabetes development is atypical.
- **Progress the development of guidelines** towards safe options for primary prevention such as pro and prebiotics, timing of gluten introduction, vitamin E and D levels as new research is undertaken.

SESSION 2:

Intercepting and delaying the course of T1D development- disease modifying therapies

The second session focused on the inroads made in disease modifying therapies (DMTs) to delay the initiation and progression ofT1D.

Keynote presentations were heard from **Professors Colin Dayan, Thomas Kay** and **Dr Leni Ramos**. These were followed by four short presentations from **Professor Ranjeny Thomas, Dr Irina Buckle, Professor Helen Thomas** and **Dr Andrew Sutherland**. A panel discussion finished off the session. Summaries of the presentations and panels are found in **Appendix C**. A summary of the entire session is found below.

Key Messages of session - Disease modifying therapies

Research and clinical trials aimed at using DMTs to alter the course of T1D by addressing the underlying autoimmune mechanisms offer a paradigm shift from traditional insulin treatment. Such intense research efforts led to the approval of Teplizumab, the first immunotherapy approved for people with T1D in late 2022. However, T1D prevention remains a challenging goal, largely due to the diversity in T1D onset and progression.

The main messages conveyed by the presentations and panel discussion in Session 2 are listed below:

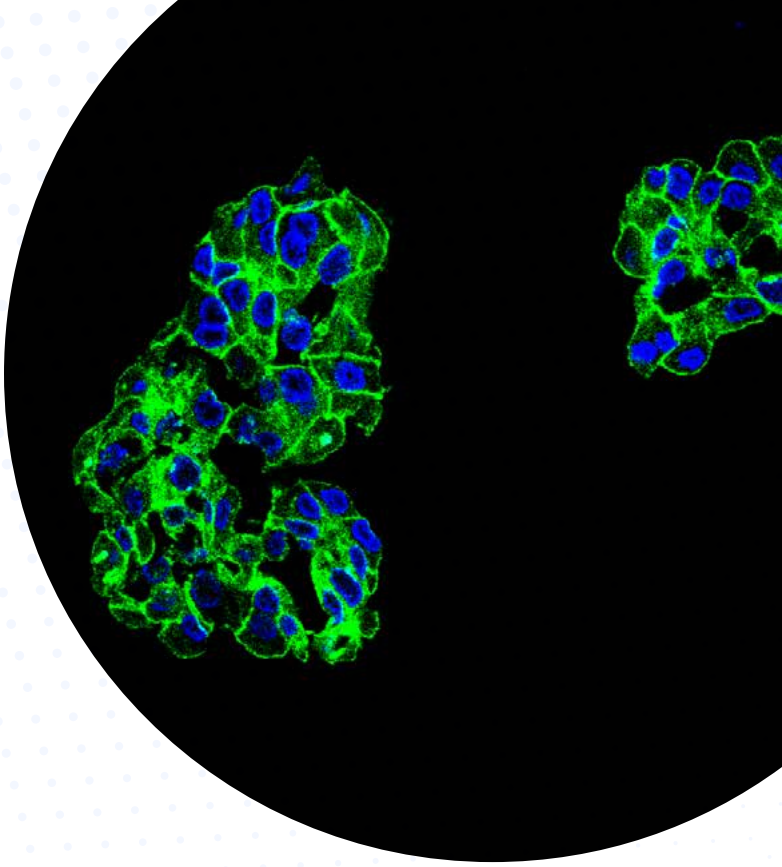
- **Intense research in immune modifying T1D research:** Globally, there is a plethora of potentially impactful immune modulators being tested for their application in T1D. These include: Baricitinib, Iscalimab, Ladarixin and Anti Thymocyte Globulin (ATG), Interleukin-2 (IL-2)/anti-Tumour Necrosis Factor (TNF), Golimumab/Glucagon-like Peptide-1 (GLP-1) and T cell immune modulators such as ATG/Granulocyte-Colony Stimulating Factor (G-CSF), Abatacept, T-Regulatory Cell (TREG) vaccine, Alefacept and TREGs/Il-2. Importantly, there is ongoing discovery into preclinical models of other targeted approaches and combination therapies.

- **Baricitinib breakthrough findings:** A study of the JAK inhibitor Baricitinib, undertaken within the Australasian Type 1 Diabetes Immunotherapy Collaborative (ATIC) at St Vincent's Institute showed that in newly diagnosed patients, Barictinib administration leads to: 1) sustained C-peptide production, and therefore suppression of T1D progression 2) reduced blood glucose variation 3) improved time in range and 4) lower insulin requirements. Baricitinib is well-tolerated, with few side-effects.

- **The Australasian Type 1 Diabetes Immunotherapy Collaborative (ATIC)** is now internationally recognised as a successful, well-connected T1D clinical trial platform. Of critical importance for Baricitinib is now progression to regulatory approval with potentially a phase III clinical trial, research into Baricitinib's mechanism of action, the identification of the phenotype of the immune cells affected by treatment and differences between responders and non-responders. This work will illuminate aspects of T1D immune pathogenesis and will allow for better stratification of patients to understand who could benefits best from this therapy.

- **The challenges with DMT trial outcomes:** Although Teplizumab and Baricitinib represent considerable steps forward in the field, neither cure T1D. For DMT trial participants with new-onset T1D, the challenges include difficulty demonstrating the effect of treatment on HbA1c as a validated endpoint for glucose control; acceptance of C-peptide values as a measure of beta cell function but not as a surrogate end point by regulators and severe hypoglycemia events (although rare in new-onset of T1D).

- **Ways to accelerate DMT progress:** We need sensitive outcome markers for Stage 1 of the condition, measures of disease activity, innovative and more efficient trial designs to test drug combinations, a global platform and adequate investment. Of particular importance is to learn from other immunological diseases (e.g. Rheumatoid Arthritis) and tap into opportunities to gain insights of how the immune system can become dysregulated and how and when to treat these conditions for best outcomes.
- **Screening programs and prevention through DMTs:** An increasing number of DMTs means future opportunities for combination therapy with anti-CD3, which would simultaneously act across different pathways to prevent the condition at any stage of development. Linking screening and intervention programs such as the General Population Screen (GPS) will identify and recruit individuals at risk for T1D, build and expand efficient trial platforms and conduct research into biomarker discovery to enable precision immunology.
- **Inclusion of DMTs in clinical management:** A paradigm shift will need to occur to introduce research evidence into clinical management. This includes innovative strategies starting with presentations and dissemination of new information about DMTs, structured conversations about the barriers to adoption of new therapies with practitioners and people with T1D, and workforce preparation. Roadmaps and pathways towards adoption of DMTs in the clinic will need engagement and action. To succeed, collaboration amongst philanthropy, industry and government is needed to ensure that any clinical trial opportunity, national or international, meets with adequate financial support.



Where we need to go next – Disease modifying therapies

Based on the Session 2 presentations and panel discussion, the areas of future focus for the next decade of T1D research and policy action should be:

Support research innovation and build a stronger portfolio of T1D therapies in Australia that encompasses:

- **Clinical trials (CTs):** 1. deliver innovative and affordable CTs focused on targeted approaches; 2. for maximal therapeutic benefit in different populations, test combinations of immune therapies, prioritising the most promising mono-therapies; 3. include both immune and beta cell-survival and beta cell regenerative therapies wherever potential synergies in therapeutic effect are plausible.
- **Immuno-pathogenesis:** 1. support research that leads to better understanding of T1D immune pathogenesis, leveraging knowledge from and in partnerships with other immunological disease areas; 2. continue to engage with other autoimmune fields and pharmaceutical partners to understand their drug development and approval strategies.
- **Biomarkers:** 1. enable precision prevention and treatment, continue support of immune biomarker-related research, inclusive of all 'omics', link existing population registries and

databases (ENDIA, the Australasian Diabetes Data Network, Generation Victoria and others), support a skilled workforce, cutting edge technologies and sophisticated data integration and machine learning; 2. enhance Australia's leadership in the field and the establishment of much needed validated immune biomarkers and fit-for-purpose assays to establish patient stratification tools and facilitate efficient clinical testing of candidate immune therapies in T1D.

Determine a path forward to bring approved DMTs to the clinic including:

- **Fill the evidence gap to accelerate approval pathways of DMTs:** 1. Conduct follow up trials to strengthen evidence of the benefit of DMTs on beta cell survival, clinical outcomes and insulin free period; 2. Conduct research to understand DMTs' mechanisms of action and conduct secondary analysis to elucidate the optimal response period of DMTs.
- **Invest in comprehensive precision approaches to understand differential responses to DMTs** through inclusion of ethnically diverse individuals to drive personalised medicine in T1D, especially in emerging markets.
- **Implement educational and awareness strategies** to optimise recruitment of Australians at-risk or diagnosed with T1D into available clinical trials.

- **Optimise islet survival and increase the insulin-free period via CTs that test combination DMTs** to delay the onset and/or the progress of T1D. Identify the best combination approach to build the evidence and to secure approval for the use of DMTs to treat patients. Wherever possible, the trials should focus on those immediately after diagnosis to ensure a higher baseline C-peptide and focus on younger children. We should also conduct larger trials with longer treatment duration so that DMTs are combined with other agents such as Verapamil, tolerising agents or/and other DMTs and use the established clinical trial platform to test other JAK inhibitors which may be cheaper and better tolerated.
- **Implement precision prediction and prevention:** Utilise outcomes of genomics research, sophisticated 'omics' techniques and machine learning, and real-time metabolic monitoring disease pathogenesis; determine predictors of response to treatment through mono-therapy and combined immunomodulatory trials.
- **Improve the clinical care of T1D:** The goal over the next decade will be to progressively change the diagnosis and treatment of T1D based on immunological markers and interception of the disease before symptoms appear. This will require significant shift within the health system with widespread changes in education, pathology, Medicare reimbursement and clinical targets.

DAY 2: 25th JULY 2023

SESSION 3:

Beta cell replacement and regeneration

The third session focused on advances and barriers to beta cell replacement and regeneration, a topic of great importance as it has the potential for clinical reversal of T1D. Leading the discussion were keynote speakers **Professors Mark Atkinson, Natasha Rogers** and **Shane Grey**. Insights were also presented by **Dr Jacqueline Schiesser, Professors Peter Thorn, Assam El-Osta, Anand Hardikar** and **Toby Coates**. A multidisciplinary panel discussed future directions and challenges of beta cell replacement and regeneration, particularly those which were relevant to the Australian context. A summary of each presentation and panel discussion is found in **Appendix D**. A summary of directions for future research and support environment needed in this field area are outlined below.

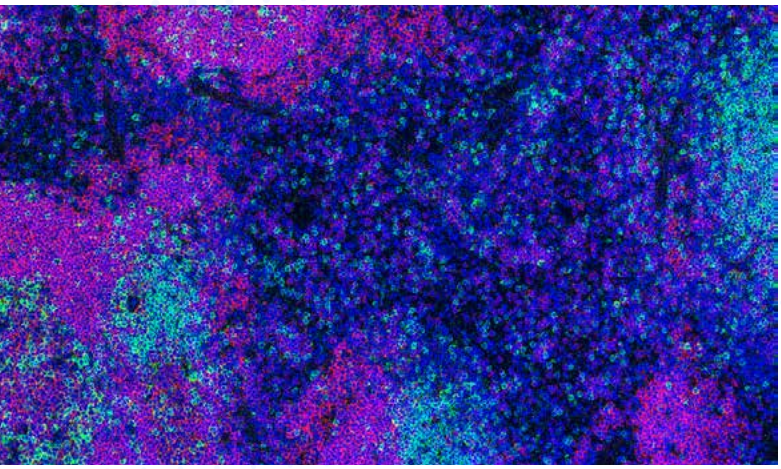
Key Messages of session - Beta cell replacement and regeneration

From the presentations and the panel discussion several key insights emerged:

- **Transplantation as a therapeutic intervention:** Islet transplantation can provide improved glycaemic control, relief from recurrent severe hypoglycaemia, sometimes independence form insulin and vastly improves quality of life. However, there are considerable challenges to its widespread application as follows:
  - **A significant scarcity of donor islets:** This limitation is a major bottleneck, as the number of patients requiring transplants far exceeds the available supply. This scarcity is compounded by the fact that not all harvested islets are suitable for transplantation. A substantial number of islets are lost during the isolation process. Islets are extremely delicate and can be damaged by the mechanical and enzymatic procedures used to extract them from the donor pancreas. This loss further reduces the already limited supply of viable islets for transplantation.
  - **The host environment:** Even after successful transplantation, islets face challenges. They can suffer from the hostile environment in the transplantation site leading to further cell death. This issue often necessitates transplanting a higher number of islets than what might be ideally required.
  - **Immunosuppressive drugs post-transplantation:** Recipients of islet transplants must take immunosuppressive drugs to prevent their immune system from rejecting the transplanted tissue. These drugs can have significant side effects and increase the risk of infections and other health issues like certain cancers. The entire process, from islet isolation to the transplantation procedure and post-operative care, including lifelong immunosuppression, is costly. These costs can be prohibitive and limit the treatment's accessibility.
- **Further transplantation research required:** There is a need for more research to improve each step of the process; from efficient and less damaging islet isolation techniques and improving islet survival and function post-transplantation, to developing less toxic immunosuppressive regimens. Research is crucial for addressing limitations and making islet transplantation a more feasible option for a larger number of patients with T1D. Addressing these challenges requires a multi-faceted approach, combining medical research, technological advancements, improvements in healthcare policies, donor management programs and alternative sources of insulin-producing cells.
- **Biological superiority of transplantation in glycaemic control:** An important topic of the panel discussion was the comparison of islet transplantation with the use of continuous glucose monitors and pump technology (artificial

pancreas) for glucose management and quality of life. Historically glycaemic control through islet transplantation has outperformed that of technology. However, with rapid advances in device technology, some clinicians feel that fewer people may be recommended for islet transplantation. The question has now become: Have technological advances diminished the need and demand for islet transplantation?

- **Undiscovered territories in T1D biology:** Despite significant advances in our understanding of T1D, there remains a considerable knowledge gap regarding the biology of islets and the pancreas, particularly the importance of the microenvironment. The islets of Langerhans, home to insulin-producing beta cells, are complex structures, and their functionality and communication, especially under the stress of an autoimmune attack, are not fully comprehended. The islet microenvironment, including surrounding cells, vascularisation, and the extracellular matrix, is critical for islet health and function. In T1D, alterations to this microenvironment can impact islet survival and effectiveness. Additionally, the dynamics of the autoimmune response involving immune cells, beta cells, and the pancreatic environment are intricate and pivotal to the onset and progression of T1D. This complexity is also evident in islet transplantation, where islets are removed from their native environment, which can affect their survival and functionality. Research is urgently needed to understand how the transplant environment affects islet survival, addressing issues like the immediate post-transplant blood supply and interactions with the new extracellular matrix. Enhancing our knowledge in these areas is crucial for improving the success rates of islet transplantation and developing more effective treatments for T1D.



- **Innovative pursuits where Australian researchers are making valuable contributions include:**
  - Genetic engineering and gene therapy approaches to evade the host immune response after transplantation of beta cells.
  - Using induced pluripotent stem cells (iPSCs) and epigenetic modifications to progenitor cells to regenerate beta cells.
  - Exploring xenotransplantation using pigs' islets as an alternative source of beta cells.
  - Developing ways to evade the host immune system post-transplantation.
  - Further understanding beta cell decline in T1D progression. This includes investigating donor pancreases and using molecular signatures and biomarkers to predict a decline in beta cell mass.

- **Barriers in the field of beta cell replacement and regeneration include:**
  - Limited collaborative efforts that facilitate a multi-disciplinary approach to the development of beta cell therapies.
  - Lack of infrastructure to manufacture and scale up the production of stem cells and other alternative sources of beta cells.
  - Complexities in acquiring regulatory approval for cell and gene therapies in Australia.
  - Insufficient support for utilising surplus human islets from transplantation procedures for translational research.

Where we need to go next- Beta cell replacement and regeneration

Based on the Session 3 presentations and panel discussion, the areas of future focus for the next decade of T1D research and policy action should be to:

- **Form globally-connected collaborative networks:** Establish and strengthen robust collaborative platforms that foster interdisciplinary efforts in beta cell replacement and regeneration. The next decade should see us breaking down silos and accelerating global partnerships which will expedite the exchange of knowledge and resources.
- **Strategise expansion of beta cell infrastructure:** Establish state-of-the-art facilities dedicated to stem cell research, beta cell regeneration, and xenotransplantation. The next ten years will be pivotal in bridging infrastructural gaps, especially where we might be lagging at an international level.
- **Accelerate regulatory approval:** Commit to working closely with regulatory bodies to simplify and streamline the approval processes for innovative cell and gene therapies, always keeping patient safety in mind. The next decade should mark a shift towards a more efficient, yet patient-safe, regulatory pathway for these therapies.
- **Optimise public and private funding:** Explore and optimise funding options with government grants, private sector investments, philanthropic initiatives, and public fundraising campaigns. The next decade should see a surge in funding for regenerative therapies in T1D, accelerating groundbreaking research and clinical trials.

- **Educate and engage the public:** To introduce/amplify public awareness campaigns around T1D and islet transplantation. We expect that encouraging community understanding and support will lead to increased donor numbers and foster a supportive environment for clinical trials and therapies.
- **Adopt a patient-centric approach:** Re-evaluate transplantation guidelines regularly, considering the ever-evolving technological landscape. Keeping the patients' needs, safety, and improved quality of life at the heart of all advancements will ensure that research remains relevant.
- **Expand translational research scope:** Encourage efforts in harnessing surplus human islets, ensuring they're put to good use in translational research, thereby enhancing the real-world application of our scientific endeavours.
- **Continual technological integration:** Recognise the critical interplay between islet transplantation and technological advancements. A decade-long strategy should involve extensive interactions with clinicians to harmonise these domains. We should pursue a balanced approach, harnessing the best of both worlds so that people living with T1D can expect tailored and efficient treatments.

SESSION 4:

Technologies, adjunct therapies, adoption, and policy

The last session focused on the translation of research into the real world through improvements in technologies and therapies to treat T1D, as well as regulatory approval and changes to government policy and clinical care guidelines.

We heard from seven key notes speakers which include: **Professors Jeffrey Braithwaite, Mark Cooper, A/Professor Sybil McAuley, Professors Tim Jones, Louise Maple-Brown, Joshua Byrnes** and **Jane Speight**. This was followed by an expert panel discussion on embedding new therapies and new technologies across T1D patients of all ages.

A summary of all presentations and panel discussion are found in **Appendix E**. A summary of the session and next stages are found below.

Summary of session - Technologies, adjunct therapies, adoption and policy

The main messages from the presentations as well as the panel discussion were that:

- **Technological advances:** The last decade has witnessed significant technological advancements, especially hybrid closed loop systems. But we must now ensure equity of access to this technology and therapies, especially in disadvantaged communities, older populations and in rural areas. In Australia, at the policy level, great progress has been achieved with continuous glucose monitoring (CGM) subsidies through the federal government but we need to ensure a clear pathway for approval for AI enhanced insulin delivery systems.
- **Transdisciplinary research and networks:** Current T1D clinical care needs to adapt to the new diagnostic staging of T1D and shift towards DMTs as they become available. Transdisciplinary research and networks are essential to ensure bench-to-bedside translation of research. Networks should include industry, governments, clinical services, consumers/patients, researchers, stakeholder groups, funders and professional groups.
- **Improving therapeutic approval and subsidy processes:** There needs to be a faster and more streamlined regulatory approval and PBS listing processes for therapies, especially adjunct therapies used in the management of type 2 diabetes, frequently used off-label in T1D. Currently only pramlintide (USA), metformin (France) and ipragliflozin (Japan) are currently licensed for use as adjunct therapy in T1D. The robust pipeline of repurposed therapies currently in CTs will add additional pressure to establish effective regulatory approval frameworks.
- **Assessing efficacy and economics of new therapies:** It is important to undertake economic assessments which integrate health outcomes as well as patient-reported outcome measures (PROMs) and compare them to the burden and cost of T1D. This is because health expenditure is under increasing pressure. Economic modelling of therapies and technologies which demonstrates cost effectiveness and improvement in Quality of Life (QoL) measures are critical to advocate for policy change.
- **The voice of the T1D patient and the T1D community:** This is essential to deliver real world outcomes from research. Co-design models applied to research and policy development are imperative. However, often funding for co-design is lacking. Implementation plans of research are also essential from the outset as we aim for patient-centric models of care.

- **Inclusiveness in T1D research:** There is not enough inclusion of diverse populations across ages and ethnicities in T1D research. For example, Indigenous communities often exhibit heterogeneous T1D phenotypes, with a mix of T1D/T2D presentation. Social determinants of health in these communities are leading to greater disparity in access, clinical care and outcomes. Novel approaches including partnership research are essential to deliver culturally-appropriate and effective clinical care within these groups.
- **The need to join international clinical trial (CT) networks:** Globally, it is a challenge to conduct highly statistically powered CTs especially when focusing on the earlier stages of T1D. Therefore, we

need to increase CT participation and boost patient numbers. Enabling Australia to join international CT networks will help increase T1D patients enrolled and allow trials to proceed.

Where we need to go next - Technologies, adjunct therapies, adoption and policy

Based on the Session 4 presentations and panel discussion, the areas of future focus for the next decade of T1D research and policy action should be to:

- **Diagnose T1D and treat early:** A sector-endorsed roadmap will be essential to embed T1D screening programs into routine care with early care offered at pre-symptomatic stages of T1D. DMT treatment of T1D is now feasible with potential therapies such as Teplizumab, Verapamil and Baricitinib offering a pragmatic choice for patients. The sectoral change and support for this novel approach to T1D care is a target in the next decade.
- **Accelerate adoption of T1D research:** Research should be co-designed, have implementation plans from the outset and adequate translational funding provided to accelerate uptake into policy and clinical care. We need to build or enhance transdisciplinary networks (including industry, patients, government, clinicians, funders). The voice of the patient/T1D community should be central to the co-design model with a focus on diversity and culturally appropriate advisory groups as critical partners. We need clear, purpose-built pathways for approval of T1D therapies and technologies and to ensure equitable and affordable access. We need to work with the sector to accelerate regulatory approval of therapies in Australia, in particular those approved internationally but currently used off-label for T1D in Australia.
- **International coalition for CTs:** We need to build a globally connected CT network to increase T1D patient participation which would allow not only increased access to trials by Australian patients but also accelerate research progress. CT should be designed to allow access by individuals at all stages of T1D, with varying geographical distribution and ethnic background.

Monday 24 July 2023

7.00 – 8.00am	**REGISTRATIONS OPEN**
8:00 – 8:45am	**WELCOME AND OPENING** • Mr Mike Wilson OAM, Chief Executive Officer JDRF Australia – Acknowledgement of Country and welcome • The Hon Mark Butler, Minister for Health and Aged Care – Opening Address (Virtual) • Young T1D research advocates • Dr Dorota Pawlak, Chief Scientific Officer JDRF Australia – Overview of the Type 1 Diabetes Clinical Research Network • Prof Mark Atkinson – Director, University of Florida Diabetes Institute
8:45 – 9:15am **9:15 – 9:55am**	**PROGRESS TOWARDS EARLY DIAGNOSIS AND PRIMARY PREVENTION – Then and now** ***Moderator: Dr Megan Penno*** **KEYNOTE SPEAKERS** • Patient voice • Prof Jennifer Couper – The first 1000 days • Prof Marian Rewers – Paradigm shifts in prevention and treatment of T1D
9:55 – 10:00am **10:00 – 10:05am** **10:05 – 10:10am** **10:10 – 10:15am**	**RAPID FIRE presentations** • Prof John Wentworth – An overview of the Type1Screen program since its inception in 2019 • Dr Kirstine Bell – Paving the way towards a national screening program for type 1 diabetes of all Australian children • A/Prof Emma Hamilton–Williams – Targeting the gut microbiota to prevent type 1 diabetes • Dr Ki Wook Kim – Antiviral vaccines for primary prevention of type 1 diabetes
10:30 – 10:50am	**MORNING TEA AND NETWORKING BREAK**
10:50 – 11:05am	**PANEL DISCUSSION – PRIMARY PREVENTION IN T1D, COLLABORATIVE SOLUTIONS AND FUTURE DIRECTIONS** ***Moderator: Dr Kirstine Bell*** **EXPERT PANEL –** Prof Marian Rewers, Prof Jennifer Couper, Prof Edwin Kirk AO, Prof Jane Holmes–Walker, Prof Maria Craig, Ms Melanie Cullen, Ms Renza Scibilia, Dr Gina Agiostratidou
11:50 – 12:20pm	**RECAP OF MORNING SESSION** ***Presenter: A/Prof Emma Hamilton–Williams*** Highlights, learnings, barriers and where to next in early diagnosis and prevention
12:20 – 12:50pm	**LUNCH AND NETWORKING BREAK**

Monday 24 July 2023

12:50 – 1:30pm 1:30 – 2:00pm 2:00 – 2:30pm	**INTERCEPTING AND DELAYING THE COURSE OF T1D DEVELOPMENT – DISEASE MODIFYING THERAPIES** ***Moderator: Dr Stuart Mannering*** **KEYNOTE SPEAKERS** • Patient voice • Prof Colin Dayan – Moving towards insulin–free T1D...what is stopping us? • Prof Thomas Kay – The BANDIT trial – where to next? • Dr Leni (Eleanor) Ramos – Disease Modifying Therapies: Teplizumab
2:30 – 2:45pm 2:45 – 3:00pm 3:00 – 3:15pm 3:15 – 3:30pm	**HOT TOPIC PRESENTATIONS** • Prof Ranjeny Thomas AM – New therapies/learnings from other autoimmune diseases • Dr Irina Buckle – RAGE targeted therapies for T1D prevention • Prof Helen Thomas – JAK inhibitors/target validation/BANDIT • Dr Andrew Sutherland – Contemporary immunology of T1D: exploring new frontiers and opportunities
3:30 – 3:45pm	**AFTERNOON TEA AND NETWORKING BREAK**
3:45 – 4:45pm	**PANEL DISCUSSION – OPPORTUNITIES AND BARRIERS OF EXPANDING THE NUMBER OF DISEASE MODIFYING THERAPIES TO T1D PATIENTS AT ALL DISEASE STAGES** ***Moderator: Prof Josephine Forbes*** **EXPERT PANEL –** Prof Thomas Kay, Prof Colin Dayan, Prof Kim Donaghue, Prof Simon Barry, Prof Fabienne Mackay, Christine Garberg, Dr Leni (Eleanor) Ramos, Dr Sanjoy Dutta, Dr Katja Beitat
4:45 – 5:00pm	**RECAP OF AFTERNOON SESSION** ***Presenter: A/Prof Tony Huynh*** Highlights, learnings, barriers and new directions in intercepting and delaying the course of T1D development
5:00 – 7:00pm	**WELCOME & NETWORKING FUNCTION (including Symposium Cocktail function and Awards)** ***Presented by the JDRF Australia Research Committee***

Tuesday 25 July 2023

8:00 – 8:30am	**MEETING THE EXPERTS AND FUNDING PARTNERS – Breakfast for early career researchers** ***Moderator: Dr Dorota Pawlak*** **EXPERT PANEL** – Prof Colin Dayan, Prof Marian Rewers, Prof Jennifer Couper, Prof Thomas Kay, Dr Leni (Eleanor) Ramos, Prof Natasha Rogers, Prof Philip O'Connell, Prof Timothy Jones, Prof Shane Grey, Dr Sanjoy Dutta, Prof Louise Maple–Brown, Prof Fabienne Mackay, Prof Peter Thorn, Dr Gina Agiostratidou
8:40 – 8:45am	**MORNING WELCOME** ***Dr Dorota Pawlak*** **BETA CELL REPLACEMENT AND REGENERATION** ***Moderator: Dr Aveni Haynes***
	KEYNOTE SPEAKERS
	• Patient voice
8:45 – 9:05am	• Prof Mark Atkinson – Lessons from nPOD and the Human Islet Network
9:05 – 9:25am	• Prof Natasha Rogers – Tailoring the success of islet transplantation
9:25 – 9:45am	• Prof Shane Grey – From the silk road to human trial – gene therapy for type 1 diabetes?
	PECHAKUCHA STYLE PRESENTATIONS
9:45 – 9:55 am	• Dr Jacqueline Schiesser – Stem Cell–Derived Beta Cells: The State of Play
9:55 – 10:05am	• Prof Peter Thorn – How to improve beta cell function within an implant
10:05 – 10:15am	• Prof Sam El–Osta – EZH2 inhibition influences pancreatic progenitor capacity
10:15 – 10:25am	• Prof Anandwardhan A. Hardikar – Markers of beta cell decline
10:25 – 10:35am	• Prof Toby Coates – CAR–Tregs as a therapy for autoimmune–driven T1D
10:35 – 11:00am	**MORNING TEA AND NETWORKING BREAK**
11:00 – 12:00pm	**PANEL DISCUSSION – BETA CELL REPLACEMENT AND REGENERATION, FUTURE DIRECTIONS AND CHALLENGES** ***Moderator: Prof Toby Coates*** **EXPERT PANEL –** Prof Philip O'Connell, Prof Stephen Alexander, Prof Shane Grey, A/Prof Jane Holmes–Walker, Prof Peter Thorn, Prof Sof Andrikopoulos, Dr John Males, Prof Wayne Hawthorne, Mr John Waszczuk
12:00 – 12:30pm	**RECAP OF MORNING SESSION** ***Presenter: Prof Natasha Rogers*** Highlights, learnings, barriers and future directions in beta cell replacement and regeneration
12:30 – 1.00pm	**LUNCH AND NETWORKING BREAK**

Tuesday 25 July 2023

	TECHNOLOGIES, ADJUNCT THERAPIES, ADOPTION AND POLICY ***Moderator: Dr Mary Abraham*** **KEYNOTE SPEAKERS**
1:00 – 1:20pm	• Patient voice
1:20 – 1:40pm	• Prof Jeffrey Braithwaite – Implementation, adoption and policy in the health system of 2030 • Prof Mark Cooper AO – Adjunct therapies
1:40 – 2:00pm	• A/Prof Sybil McAuley – Improving health with diabetes therapeutic technology
2:00 – 2:20pm	• Prof Timothy Jones – Translation in the real world
2:20 – 2:40pm	• Prof Louise Maple–Brown – Challenges of T1D care/disadvantaged and remote populations
2:40 – 3:00pm	• Prof Joshua Byrnes – Applied Health Economics
3:00 – 3:20pm	• Prof Jane Speight – Quality of life matters in the use of glycaemic technologies
3:20 – 3:35pm	**AFTERNOON TEA AND NETWORKING BREAK**
3:35 – 4:35pm	**PANEL DISCUSSION – EMBEDDING NEW THERAPIES AND NEW TECHNOLOGIES ACROSS T1D PATIENTS OF ALL AGES** ***Moderator: Prof Elif Ekinci*** • Screening • Replacement therapies • Repurposed drugs • Adjunct therapies • Advanced technologies **EXPERT PANEL –** Prof Jeffrey Braithwaite , Prof Mark Cooper AO, A/Prof Sybil McAuley, Prof Timothy Jones, Prof Joshua Byrnes, Prof Jane Speight, Mr Jonathan Salmon, Prof Fergus Cameron, Prof Louise Maple–Brown, Dr Laura Knecht, Dr Benjamin Nash
4:35 – 5:00pm	**RECAP of all themes** ***Presenter: Prof Liz Davis*** Highlights, learnings, barriers and where to next in implementation of outcomes in T1D – advanced technologies, adjunct therapies, adoption, and policy
5:00pm	**CLOSING** ***Dr Dorota Pawlak***

SESSION 1:

Progress towards early diagnosis and primary prevention

Professor Jennifer Couper

Keynote 1: The first 1000 days-

Professor Couper presented her keynote 'The first 1000 days' where she outlined the possible early environmental origins of T1D, the research work being undertaken by the Environmental Determinants of Islet Autoimmunity (ENDIA) study and the potential role of its findings in the primary prevention of T1D.

ENDIA has recruited 1,500 Australian children with a first-degree relative with T1D and is following them up from pregnancy to 10 years to determine which environmental factors interact via the 'omes' to increase penetrance of T1D risk genes, leading to islet autoimmunity. As of May 2023, over 165,000 bio samples have been collected and visit follow up is 70-75% complete. 115 (9%) of ENDIA children have developed persistent islet autoimmunity or T1D (n=22) of whom only 1 developed mild DKA.

Some findings of ENDIA so far:

- Analysis of autoantibody development in the 115 children displays age-dependent appearance with IAA being the most common first-appearing autoantibody before 7 years of age and ZnT8A being the most common after 7.
- An analysis of pregnant mothers with T1D showed no increased risk in the development of islet autoimmunity in babies.

Professor Couper then discussed when endocrine and exocrine functions declined in T1D development, with data from the ENDIA study suggesting that both endocrine and exocrine functions may be altered even at the persistent multiple antibody stage (i.e., before a T1D diagnosis).

Professor Couper finished by outlining the current efforts being undertaken for primary prevention of T1D, including the role of maternal protection, vaccines, and changes to the microbiome. In terms of the microbiome, ENDIA work has shown that the gut microbiome is distinct in pregnant women with T1D and this may be a protective mechanism for babies. The following studies are being undertaken in the primary prevention space and Professor Couper emphasised the importance of understanding and potentially reintroducing protective factors to combat the increasing incidence of T1D.

- POInt- first trial to test if high dose oral insulin in children 4 months to 3 years can induce immune tolerance and prevent initiation of islet autoimmunity
- SINT1A- Supplementation at 6-12 months with the probiotic *Bifidobacterium Infantis* sub-species of *B. longum* to reduce development of multiple antibodies in at-risk children
- Understanding how maternal to infant transmission of the gut microbiome occurs and what elements are important
- How the gut microbiome in pregnant mothers can be modulated with changes in diet as a form of intervention
- Development of enterovirus vaccine against T1D: multivalent human Coxsackie B vaccine (PRV-101) in at-risk children
- Early life weight gain and increased risk of T1D

Professor Couper finally suggested we could learn from other autoimmune and inflammatory diseases in terms of immune therapy (e.g. JAK inhibitors) for young children.

Professor Marian Rewers

Keynote 2: Paradigm shifts in prevention and treatment of T1D

Professor Rewers presented a keynote on how our understanding of T1D has shifted over time by discussing 6 paradigm shifts which have evolved as research has progressed.

There has been a paradigm shift away from T1D being a childhood disease towards a recognition of it also as an adult disease (in the US over half of diagnoses are in adults over 30 years). Many of these adults have slowly progressing islet autoimmunity (IA). In fact, latent autoimmune diabetes in adults (LADA) is often misdiagnosed as type 2 diabetes in adults. Seroconversion peaks at 1-4 years of age, with very few seroconversions in adult age. It is thus hypothesised that autoimmunity commences very early on in childhood but that it remains latent until adulthood (thus often called 'delayed diabetes').

The second paradigm shift is around primary prevention, with work underway on addressing environmental triggers of IA (e.g. enteroviral vaccines, infant diet modification such as oral insulin and probiotics). It was noted that based on seroconversion peaking at 1-4yrs, primary prevention must start very early on, perhaps at 2 months of age for children with high genetic risk. There is evidence that persistent presence of enterovirus in the stool is a predictor of development of autoimmunity. This is backed up by studies conducted by nPOD using autopsy samples provided by UK investigators. There is currently a Phase 1 trial using Coxsackie virus B vaccine developed by Proventionbio (PRV-101). There have been positive interim results, and it is likely to now move to Phase 2.

The third paradigm shift is the use of screening to prevent DKA at diagnosis. In the US, there has been an increase in the incidence of DKA at diagnosis which has life-long sequelae such as higher HbA1c and brain oedema. It is estimated that 90% of DKA at diagnosis is preventable through screening, followed by education and monitoring for dysglycaemia. There are a number of screening studies being undertaken (DAISY, TEDDY, DIPP, Fr1da, ASK, Type1Screen). It has been shown that screening not only reduces DKA rates but also results in decreased HbA1c and increased C-peptide levels (increased functional beta cell mass) at diagnosis.

The fourth paradigm shift has been the ability to delay clinical T1D diagnosis through the first immunotherapy approved for T1D, Teplizumab and potentially preserve beta cell function in those newly diagnosed with drugs such as Verapamil (calcium channel blocker) and Baricitnib (JAK inhibitor). Teplizumab is already FDA approved and can delay insulin dependence by >3yrs in individuals with Stage 2 T1D. The first patient to receive Teplizumab as part of their medical care in the US was a 15-year-old boy in April 2023. This promising development paves the way for other DMTs which are at various stages of the R&D pipeline.

The fifth paradigm shift has been the widespread and affordable access to technologies to monitor glucose and administer insulin which have been proven to improve quality of life and health outcomes. The evidence is clear that the use of CGM and AID systems have both short- and long-term clinical benefits (especially a decrease in long-term complications).

The last paradigm shift was around islet transplantation. Islet replacement may soon become feasible as we overcome hurdles such as limited sources of beta cells, and their long-term survival once transplanted. Allogenic stem cell-derived islets are a promising area of research especially if removing the need for immunosuppression post-transplant. Companies such as Vertex and ViaCyte are undertaking phase 1/2 clinical trials using stem-cell islet transplantation. ViaCyte (which has now been taken over by Vertex) is also using encapsulation techniques and gene editing technologies to prevent an immune attack on transplanted cells. They are also trialing direct vascularisation versus passive diffusion techniques. Autologous stem cell transplantation is also promising as it removes the need for immunosuppression but challenges remain such as the scale up and costs of such a model.

Lastly it was mentioned that implementing paradigm shifts in diabetes care can come with added costs, and it's important to consider the economic aspects of these changes.

Rapid fire presentations

There were four rapid fire presentations covering "hot topics" in T1D research from CRN-funded researchers, including progress in screening, the gut microbiome, and viral triggers, with a focus on T1D screening and prevention.

1) Professor John Wentworth

Prof Wentworth discussed the Type1Screen program, funded by JDRF.

Type1Screen detects the presence of islet autoantibodies in family members of those with T1D. The screening program commenced in 2019 as standard blood serum collection but more recently transitioned to in-home collection using PCR-based antibody assays on blood spots with good results. Program participation in Australia has increased as a result of this transition and following the US approval of Teplizumab. Currently, the program has an average 5% positive screen rate, with most positive samples detecting two or more autoantibodies. Most individuals identified are in stage 1 T1D. The challenge the program faces is scale up due to resource shortages and the need for increased awareness of its existence amongst health care professionals and the T1D community. The goals of the program in the short term are to increase screening activity, accredit the blood spot assay with the National Association of Testing Authorities (NATA) and improve the health monitoring of individuals with positive screens.

2) Dr Kristine Bell

Dr Bell outlined the Australian Type 1 National Screening Pilot's vision for a routine, publicly funded national T1D screening program for all children.

The aim of Dr Bell's work is to undertake a T1D screening pilot program that is feasible, scalable, sustainable, equitable, and cost-effective. Dr Bell's team are testing 3 different T1D screening models, including genetic risk stratification and antibody testing and targeting different age groups. As of July 2023, there were 5,330 children registered to be screened. The second part of the pilot is a health technology assessment and economic modelling. The third part is stakeholder engagement and this will consider the preferences, the barriers and the opportunities of a screening program at all levels. The pilot has received positive responses from the community and they now plan to evaluate the preferences and barriers to stakeholders.

3) Associate Professor Emma Hamilton-Williams

A/Prof Hamilton Williams discussed the role of the gut microbiome and in turn the production of metabolites called short chain fatty acids in preventing T1D.

Previous work had shown that supplementation with a prebiotic fibre supplement (HAMSAB) prevented T1D progression in NOD mice. A/Prof Hamilton-Williams conducted a pilot study using HAMSAB as 6 week supplementation on 21 adults with T1D. Her team saw that HAMSAB supplementation changed gut microbiota and increased the key metabolites acetate and butyrate. They saw that those who had higher butyrate had better glucose control and their immune cells had higher markers of immune tolerance. Th team also conducted a human microbiota stool transfer model in NOD mice, suggesting a causal link between HAMSAB associated microbiota changes and T1D protection.

4) Dr Ki Wook Kim

Dr Kim presented research on the role of enteroviruses in T1D within the context of antiviral vaccines for primary prevention , and his work within the ENDIA team.

Dr Kim discussed the strong association between

enteroviruses (especially EV-B species such as coxsackievirus B) detection, autoimmunity and T1D development. Dr Kim discussed that clinical trials are underway to develop vaccines against enteroviruses, however there are concerns that we are being biased by solely focusing on these. Therefore, Dr Kim is undertaking comprehensive virome sequencing (gut, respiratory and plasma) to investigate the viral landscape in individuals within the ENDIA study to see if there is an association between viral presence and T1D development.

Panel discussion: Primary prevention in T1D, collaborative solutions and future directions

Panel members: Prof Marian Rewers, Prof Jennifer Couper, Prof Edwin Kirk, A/Prof John Wentworth, Prof Maria Craig, Prof William Rawlinson, Ms Melanie Cullen, Ms Renza Scibilia, Dr Gina Agiostratidou

Moderator: Dr Kristine Bell

The panel discussed the **advances in global approaches towards general population screening for T1D risk in the last 10 years**, with many noting that it was not even a consideration before this time. The panel noted however the **ethical concerns around screening without a widely available preventive treatment for T1D**. That is, is it justifiable to introduce a screening program without a widely-accessible treatment that slows or prevents T1D? Some panel members suggested that the role of screening in easing patients and their families into the world of T1D and avoiding a traumatic T1D diagnosis was reason enough to introduce T1D national screening programs.

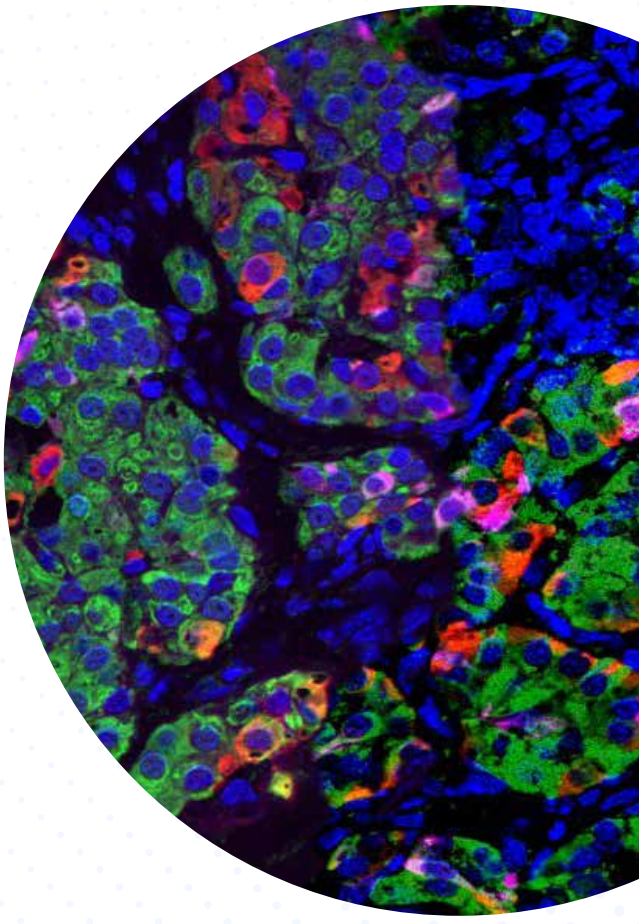
The issue of what **carers do with the information** that their child has a higher risk for T1D development was explored. One member suggested that the **medico-legal element requires consideration**, as legal challenges may result from incorrect results, and this can affect the viability of a screening program.

The panel agreed that the **anxiety generated from a positive result** is an important issue that needs consideration. This is especially the case in situations when a child tests positive but doesn't go on to develop T1D in the near future. **Structured monitoring and evidence-based education programs are key** to alleviating this anxiety. It was also discussed that other screening programs such as bowel cancer also screen for markers of the disease not disease itself therefore there is a precedent set for T1D.

Messaging of the results needs to be clear, with clear answers to questions such as: will I/my child definitely get diabetes? How confident are you? Educational programs associated with the results should be an integral part of the screening process. Members suggested that positive cost effectiveness as a result of reduced hospitalisation will be key for policy take up.

The panel then discussed what was needed to **accelerate primary prevention of T1D**. The presence of an effective preventive therapy is needed, but the panel felt that we're still too far away from this with results of the current interventions pending. Other members stated that industry partners need to be more strongly involved in **development of vaccines**, noting that the aetiology of T1D will not be the same for everyone. Indeed, the panel noted that since the underlying mechanisms and pathogenesis of T1D and the role of viruses is still not well understood and may be diverse, the **evidence is not sufficient to proceed with a whole population vaccination program** to ensure T1D prevention.

The panel finished by discussing the **stigma and misinformation** prevalent amongst the community about T1D. One area of misunderstanding is the link between lifestyle factors and T1D development. A suggestion was raised around changing the name of T1D to differentiate it from T2D. But would this help?



SESSION 2:

Intercepting and delaying the course of T1D development - disease modifying therapies

Professor Colin Dayan

Keynote 1: Moving towards insulin-free T1D....what is stopping us?

Professor Dayan presented current thinking around extending the period during which individuals with T1D can manage their condition without insulin- "Insulin-free T1D".

Professor Dayan explained this approach could be life changing because it could significantly improve the quality of life for people with T1D, particularly for teenagers, those with mental health problems and those from disadvantaged backgrounds. The focus of the talk was the impact of immunotherapies in delaying clinical onset of T1D, which could eventually lead to significant insulin-free periods in T1D. The aim would be to progressively "push out" clinical onset in someone's lifetime, to the point where T1D is no longer diagnosed.

The journey towards insulin-free T1D would commence with the early identification of at-risk individuals, with a particular focus on those in the prediabetic stage. The overarching goal is to delay the initiation of insulin therapy or entirely circumvent it, thus extending the period during which patients can manage their condition without insulin. The other or ideally concurrent option is to focus on the residual beta cells post T1D diagnosis and use therapies that result in regeneration of beta cells.

To realise this two-pronged vision, several immunotherapeutic interventions are currently under investigation, each with its unique mechanism of action and outcomes. Professor Dayan discussed immunotherapies such as teplizumab, abatacept, anti-TNF treatments, and verapamil. These interventions aim to modulate the immune system, impede the destruction of insulin-producing beta cells, and preserve endogenous insulin production for as long as possible. Professor Dayan also discussed using therapies to regenerate lost beta cells, in order to once again produce insulin.

Professor Dayan explained that what was needed to accelerate progress of DMTs was rapidly sensitive outcome markers; trial designs that test combination therapies; more efficient trial designs; a global platform (introduced T1D-Plus platform from INNODIA); and investment. In terms of markers, while C-peptide remains a valuable marker, relying solely on it may not provide a comprehensive assessment of disease progression, especially in the pre-diabetes stages. The use of combination treatments has been successful in other diseases like HIV and we should aim to mimic this. Finally, to accelerate progress in this area we also need to link screening with intervention programs so that we can achieve primary prevention of T1D.

Professor Thomas Kay

Keynote 2: The BANDIT trial - where to next?

Professor Kay gave a presentation on the findings of the BANDIT (Baricitinib in New Onset Type 1 Diabetes trial). The trial recently completed recruitment and the intervention period. The results of the trial were presented but under embargo at the time of the Symposium.

BANDIT tested baricitinib, a JAK inhibitor which is currently approved for rheumatoid arthritis. The trial enrolled people aged 10-30 years who were newly diagnosed with T1D in the previous 100 days. 60 people were provided with oral, once-daily baricitinib for 48 weeks and 31 were provided placebo. The primary endpoint was C-peptide production at 48 weeks. Secondary endpoints were insulin use, HbA1c, glycaemic variability and adverse events.

Dr Leni Ramos

Keynote 3: Disease modifying therapies - Teplizumab

Dr Ramos provided a comprehensive overview of the R&D and journey towards the FDA approval of teplizumab, a groundbreaking DMT for T1D.

The journey spanned three decades and was long and challenging. It began in the 1990s and culminated in the drug's US FDA approval in November 2022 as the first DMT for T1D. Teplizumab is an anti-CD3 monoclonal antibody that modulates T cell function by: inhibiting pathogenic autoreactive T cells, converting autoreactive T cells to exhausted T cells and increasing regulatory T cell function.

Dr Ramos highlighted early studies, such as "Study 1" and "AbATE," which yielded promising results regarding beta cell preservation measured by C-peptide targeting Stage 3 T1D. Macrogenics' acquisition of teplizumab in 2005 led to collaborations with Eli Lilly for pivotal phase three studies, "Protege" and "Encore" which also targeted Stage 3 T1D. Although these studies missed the primary endpoint based on a composite of HbA1C and insulin use, they confirmed beta cell function preservation. Despite setbacks, the academic community's persistence played a crucial role in advancing teplizumab's development. These included studies testing teplizumab in Stage 2 T1D ("TN-10" and extensions).

Dr. Ramos discussed ProventionBio's role in advancing teplizumab's development. The acquisition of the molecule in 2018 was followed by the initiation of the "PROTECT" study, a phase 3 trial targeting younger patients (children and adolescents aged 8 to 17) diagnosed within six weeks and with measurable residual beta cell function. An extension study, "PROTECT Extension," was established to follow patients for up to 5 years after the initial study.

The presentation highlighted the FDA's approval of teplizumab for Stage 2 T1D, based on results from the "TN10" trial and supportive data from previous Stage 3 T1D studies. Additionally, two post-marketing requirements were introduced, including long-term patient follow-up in a registry for a minimum of 10 years to collect vital safety data. Another requirement involved the "PETITE" study, focusing on patients under 8 years of age. This will be completed in 2026.

Hot topic presentations

There were four hot topic presentations presenting research on DMTs which focus on the dysregulation of the immune system in T1D development.

1) Professor Ranjeny Thomas

Professor Thomas presented on antigen-specific tolerising immunotherapy for T1D and what could be learned from rheumatoid arthritis.

Prof Thomas drew important similarities between rheumatoid arthritis and T1D, emphasising their autoimmune nature, the lack of cure, the significance of early diagnosis, and the need for disease-modifying drugs, especially in the early stages of the disease. The presentation highlighted the importance of sustaining remission and discussed innovative antigen-specific immunotherapy as a strategy to prolong remission in autoimmune diseases. By exploring shared T cell biology and the importance of regulatory T cells, this approach offers hope for newly diagnosed patients and the potential to reduce dependence on traditional disease-modifying drugs, while also underscoring the value of biomarkers to predict remission and monitor disease in the context of T1D.

2) Dr Irina Buckle

Dr Buckle presented on research focusing on therapies against RAGE (Receptor for Advanced Glycation end Products).

Dr Buckle elucidated the role of RAGE in binding various ligands, contributing to inflammation and oxidative stress, thereby exacerbating damage to pancreatic beta cells in T1D. RAGE is increased in autoantibody positive people and its expression is associated with progression to T1D. Dr. Buckle explored methods to curtail T1D progression by preventing downstream signaling from RAGE receptor directly or through competitive binding of RAGE ligands (sRAGE). Dr Buckle demonstrated that administering sRAGE in NOD mice delayed T1D onset. Subsequent work also demonstrated a delay when using an oral RAGE antagonist. Dr Buckle showed how oral RAGE treatment may be working on immune cells to improve beta cell function and reducing insulitis in NOD mice.

3) Professor Helen Thomas

Professor Thomas discussed the preclinical work on JAK (Janus kinase) inhibitors as a potential treatment for T1D, especially in combination therapies.

Professor Thomas presented evidence that these inhibitors, such as baricitinib, effectively halted the progressive loss of insulin production in NOD mice. Professor Thomas explained that JAK inhibitors work by blocking the JAK-STAT signalling pathway, which reduces T cell expansion, leading to decreased antigen recognition, T cell activation, and insulitis. Professor Thomas finished by outlining how combining anti-CD3 therapy with JAK inhibitors in mouse models can delay T1D onset.

4) Dr Andrew Sutherland

Dr Sutherland highlighted the importance of understanding key immune pathways involved in the autoimmune process behind T1D so that we may be able to intercept them with therapies.

Dr Sutherland emphasised that identifying these pathways, especially those related to Tregs and T cells, is crucial for developing effective immune interventions. Dr. Sutherland's research focused on Th17 cells, IL-17 cytokines, specifically IL-17F, and their role in T1D pathogenesis. His work revealed that IL-17F had similar pathogenic functions as IL-17A in islet inflammation and beta cell function. However, genetic knockout experiments in IL-17RA and IL-17RC deficient NOD mice showed divergent outcomes. These findings shed new light on the functions of these molecules in T1D and provide valuable insights for future research and clinical trials.

Panel discussion: Opportunities and barriers to expanding the number of disease-modifying therapies to T1D patients at all disease stages

Panel members: Prof Tom Kay, Prof Colin Dayan, Prof Ranjeny Thomas, Prof Kim Donaghue, Prof Simon Barry, Prof Fabienne Mackay, Ms Christine Garberg, Dr Elanor Ramos, Dr Sanjoy Dutta, Dr Katja Beitat

Moderator: Prof Josephine Forbes

The panel commenced by discussing the biggest challenge that DMTs for T1D face. Members commented that **limited awareness and education issues within broader segments of health care providers** was a significant barrier. For example, one panel member noted there is resistance amongst endocrinologists (especially adult endocrinologists) to move away from insulin and hybrid closed loop technology to alternative therapies. There is a persistent view that "insulin is safe but DMTs aren't". It was Important to note that this sentiment may not be shared by the T1D community.

Similarly, another member noted that it takes **medical education**, especially in the areas of nutrition and exercise which have been shown to be positive in T1D management but have not been taken up by the medical community. Medical education was also noted as a barrier in endocrinologists, stating that there is an aversion amongst adult endocrinologists to understand T1D from an immunological angle, with interventions coming in too late in the T1D disease pathway. A **paradigm shift in education** and change management on how clinical care in T1D is delivered is critically needed.

It was also noted that there is a need for **health economics to demonstrate return on investment** for DMTs and to include the patient during the design of DMT trials (i.e. "bring the patient to the trial rather than the trial to the patient").

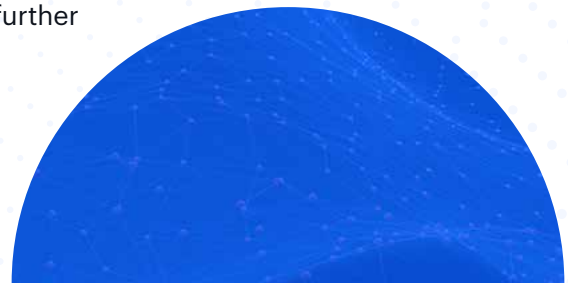
The theme of **education was further extended to all parts of the research and translation ecosystem.** One of the barriers stated was that all parts of the system had **different understanding of each other's roles** and that specifically there was a need for the education of researchers to understand the unmet needs of various partners (patients, industry, buyers etc)- i.e. to 'have the end in mind'.

The panel was then posed the question **if we had enough targets.** One response was that we do not, as preclinical models haven't been effective and we have been more focused on technological solutions at the expense of finding cures. Another response was that we still don't know enough about T1D aetiology to progress with new targets, but that the 'omics' will provide answers, especially to personalised medicine.

On **how to bring all the voices together to drive DMT development and adoption**, the panel heard about the positive way JDRF establishes consortia, engages with regulatory bodies (e.g. writing the policy for FDA), and selectively invests in research areas (e.g. JDRF has actively reduced its investment in the artificial pancreas as there is healthy competition in the area). Historically industry investment into DMT in T1D hasn't been very good but strategic approaches to de-risk this area and recent progress has seen significant shift as demonstrated by Sanofi acquiring ProventionBio and the Tzield licence.

The panel discussed whether **heterogeneity of T1D may affect the response to DMTs.** Panel members suggested that heterogeneity may not be an issue and that in other autoimmune diseases, heterogeneity is addressed by combination therapies and that as research progressed, the ideal therapy is elucidated, especially in the post marketing phase. It was noted however that personalisation comes with a trade-off, especially at the beginning of drug development where "slicing the pie" too early on means we're working with very small populations and that has implications for both research findings and industry interest. There was agreement that we could **learn from other diseases on how they deal with personalised treatments**. There was also agreement on the need for further understanding of patients at the molecular level, to understand diversity in disease presentation. That is **the path to personalised medicine in T1D is through more knowledge**.

The panel ended the discussion by focusing on **sources of funding and the role of government, industry, and philanthropy.** There was discussion on an over reliance on JDRF funding and the need to look outside of traditional funding bodies, and towards industry and philanthropy. There was also a comment on the need to generate funds for the next generation of researchers. A discussion was had around improved efficiencies in research funding, with researchers needing to join networks, collaboratives and learn from similar projects to make funding dollars go further



SESSION 3:
Beta cell replacement and regeneration

Professor Mark Atkinson

Keynote 1: Lessons from nPOD and the Human Islet Network

Professor Atkinson shed light on learnings from the Network for Pancreatic Organ Donors with Diabetes (nPOD) and the HPAP portion of the Human Islet Research Network (HIRN).

One of the key takeaways from these programs is the revision of long-standing dogmas regarding T1D development. For example, it was revealed that T1D doesn't always occur when beta cell destruction reaches 85-90%. Instead, there is wide variability (50-95%) of beta cell loss among individuals. There is also variability within individuals regarding the architecture of beta cell loss in the pancreas, with some islets being destroyed in someone with T1D and some being spared. Similarly, the widely held belief that all beta cells are lost within a few years of T1D onset has been challenged, as post-mortem studies on individuals who had T1D for decades still showed residual beta cells, hinting at an incomplete loss. Importantly, Prof Atkinson noted that histology of pancreases from those with T1D showed wide variability, indicating that T1D may not be a singular disease, but a collective of distinct disorders with commonalities of insulinopenia and loss of beta cells.

Prof Atkinson also highlighted that insulitis, a chronic feature believed to be a hallmark of T1D is challenging to visualise in the prediabetic stage, even when studying the entire pancreas and is variable amongst individuals. Lastly the dogma that T1D affects only beta cells and islets has been challenged with evidence suggesting that T1D affects the whole pancreas.

Prof Atkinson explained that whole suite of new visualisation techniques have been introduced to understand the anatomy and presentation of T1D in individuals (e.g. Spatial Mass Spec, IMC, CODEX). This has shown that insulitis is a 'mixed' bag with many different types of immune cells at the site and which can persevere for decades post T1D onset. There is heterogeneity in insulitis by age of onset (younger onset vs older onset) hinting at endotypes of T1D. The newer visualisation techniques have allowed us to confirm the identity of autoantibodies used in peripheral blood as markers of autoimmunity and see insulitis in 3D and in 'real-time' in nPOD specimens.

Prof Atkinson also raised the potential role of beta cells themselves in T1D development compared to that of the immune system (that is, the 'homicide or suicide' theory of beta cells).

Prof Atkinson discussed the use of modern techniques such as tissue multiplex cytometry (CyTOF) to analyse the interaction of islet endocrine cells and immune cells in the progression of T1D (use 90 antibodies on one tissue slice). Through this his team has been able to demonstrate that islets from people at different stages of T1D development exhibit different biomarkers (normal, vs late stage vs established T1D). Beta cell and islet aberrations are present in T1D and this has implications for the staging model that we use. There may be a stage before stage 1 with islet and beta cell aberrations (stage 0.5?).

Professor Atkinson also delved into the role of the exocrine pancreas in T1D. Contrary to traditional beliefs that it plays no part in the disease, research findings have shown that individuals with T1D have smaller pancreases compared to age and BMI-matched controls. This raises questions about how exocrine changes may influence insulitis and the immune system's response. Prof Atkinson emphasised the importance of incorporating AI and multi-dimensional analyses to advance our understanding of T1D and highlighted the shift towards biomarker and clinical development in the nPOD and HPAP studies.

Professor Natasha Rogers

Keynote 2: Tailoring the success of islet transplantation

Professor Rogers presented an overview of Australia's islet transplant program and associated research.

Professor Rogers discussed the prominent issue of severe hypoglycaemia in T1D, emphasising its associated mortality risk. Islet transplantation has been offered in Australia since 2002, providing near-normoglycemia, protection from severe hypoglycaemia, and insulin independence in some cases. Prof Rogers discussed that islet transplantation is complex and demanding, with a significant number of isolations not proceeding to transplantation (3:1 ratio of islets discarded vs transplanted).

The presentation showcased preliminary data from the National Islet Transplant Consortium, illustrating positive outcomes in terms of hypoglycaemia scores (especially after 3rd transplantation) and glycaemic control (HbA1c and glycaemic variation) after transplantation. Insulin independence is achieved in around 40% of people.

Prof Rogers discussed immunosuppression protocols highlighting the challenges associated with calcenurin inhibitors in terms of nephropathy and the potential of alternative options Belatacept and Sirolimus.

Prof Rogers discussed the current challenges in islet transplantations: severe shortage of donor islets, islets not functioning optimally post-transplantation, and the need for immunosuppressants.

Professor Rogers then presented on the potential of CD47 as a promising avenue for understanding how islets function optimally. Professor Rogers shared findings on CD47 knockout mice, indicating improved glycaemic profiles and insulin expression. The CD47 receptor's potential role in diabetes development was also explored, with increased expression of CD47 as T1D progresses in NOD mice and the administration of anti-CD47 antibody resulting in improved glycaemic profiles. Finally, Prof Rogers presented results from islet transplantation studies, showing marked euglycemia when using CD47 knockout islets, suggesting its significance in transplantation outcomes.

Professor Shane Grey

Keynote 3: From the silk road to human trial – gene therapy for type 1 diabetes?

Professor Grey presented on the development of his team's A20 vector which holds promise to improve post-transplantation survival of islets by decreasing islet inflammation during the peri-operative stage of transplantation. It does this via modulating NF-KB activity.

Professor Grey's work commenced with the discovery that the gene TNFAIP3 (which encodes A20 protein) is essential for inflammation. This was discovered through the investigation of A20 haploinsufficiency in Behcet's disease (an autoinflammatory disease). A20 is essential and functions to limit inflammation. Prof Grey's work on mouse models showed that A20 is a 'tuneable' switch for the regulation of NF-kB. Increased A20 function leads to decreased inflammation.

Prof Grey then explained that islet transplant outcomes are worse compared to solid organ transplants (i.e., shorter post- transplant survival) because of the immune response to the graft. Therefore, mouse work was undertaken to applying the knowledge on the role of A20 in islet transplantation.

In animal models, A20 depletion of donor islets resulted in early death of grafts. In contrast, overexpression of A20 in donor islets (via genetic engineering and use of the A20 vector) suppressed inflammation and led to increased islet graft survival.

Prof Grey ended by outlining that an A20 clinical trial will commence soon in Royal Adelaide Hospital using the Biodegradable Temporizing Matrix skin graft method developed by Professors Toby Coates John Greenwood.

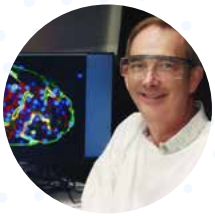
Pechakucha presentations

Five Pechakucha-style presentations were featured, which focused on how beta cells can be replaced or regenerated in those with T1D.

1) Dr Jacqueline Schiesser

Dr Schiesser presented on the use of stem cell-derived beta cells for both beta cell replacement therapies and modelling T1D in a laboratory setting.

Dr Schiesser began by introducing the two types of stem cells, embryonic stem cells and induced pluripotent stem cells (iPSCs), which can be reprogrammed from somatic cells. The aim of her work is: 1) for beta cell replacement in T1D 2) for generating diverse immune cells to model cell interactions in T1D ('T1D in a dish'). Dr Schiesser presented work which showed that iPSCs in the lab can be made into beta cell avatars that produce insulin. Dr Schiesser then presented data on immune cells lines derived from iPSCs from T1D human donors to understand immune cell interactions in T1D.



2) Professor Peter Thorn

Professor Thorn presented on the importance of the local environment in beta cell transplants to improve their survival rates.

Prof Thorn began by emphasising the promising results of islet transplantation in stabilising glucose control for those with T1D, which prompted the exploration of stem cells as an infinite source of islets/beta cells. However, stem cells lack the ability to respond to normal glucose levels or secrete sufficient insulin. The current model of stem cell research in T1D is looking at single beta cells. But we know that beta cells are strongly influenced by the local environment. Professor Thorn's team is therefore focusing on how the environment influences beta cell behaviour. He highlighted the importance of capillary contact for beta cells in an islet, showcasing that laminin (basement membrane protein) and liprin were closely aligned with capillaries and needed for insulin secretion. Upon islet isolation, there is a loss of laminin integrity and insulin secretion. The islet-capillary interface is therefore crucial and Professor Thorn's lab is investigating the machinery that ensures insulin granule fusion and insulin release from beta cells. The primary message was that it wasn't necessary to replicate islet behaviour exactly in stem cells, but rather to recreate the cues presented to cells to improve their survival and response during isolation and implantation.

3) Professor Sam El-Osta

Professor El-Osta presented on the role of DNA methylation and epigenetics in T1D, with a focus on how EZH2 can influence pancreatic progenitor capacity.

Prof El-Osta highlighted that there are parallels in DNA methylation patterns between mouse and humans but that they are not identical. The presentation discussed the master regulator EZH2, showing results that a small molecule inhibitor, GSK126, reduces H3K27 methylation in humans but not in mouse pancreas, with distinct effects observed in non-human primates. The results also suggested that pancreatic ductal cells can be primed to behave like beta cells by reducing EZH2 activity, leading to the re-expression of progenitor and beta cell markers in response to this inhibition. Some of these cells were also able to express the insulin gene and produce insulin.

4) Professor Anand Hardikar

Professor Anand Hardikar presented on markers of beta cell functional decline during the progression to T1D and how these could be used to predict decline before clinical diagnosis.

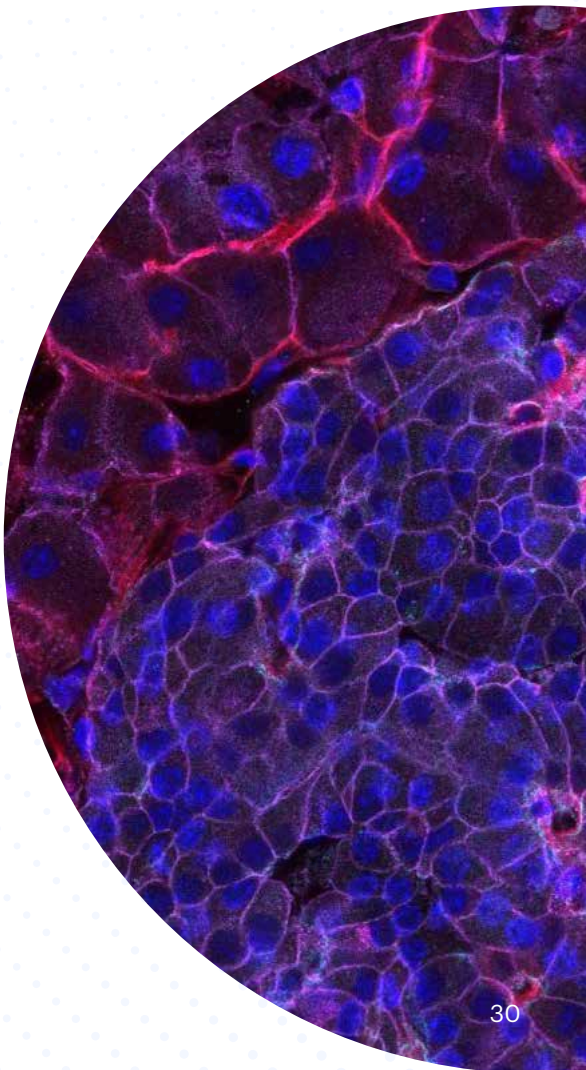
Prof Hardikar discussed how a combination of genetic predisposition, triggering environmental events, and functional decline leads to the clinical onset of T1D. Prof Hardikar emphasised that genetic risk, as measured by a genetic risk score (GRS), doesn't accurately predict development T1D as it is a static measure and many external mechanisms

trigger T1D development. He stressed the need for more dynamic markers beyond GRS to predict functional decline. Prof Hardikar presented options for biomarkers including autoantibodies, dysglycaemia before autoantibody seroconversion, and miRNAs as surrogate markers for beta cell dysfunction. Prof Hardikar's discussed his team's ongoing work to use miRNAs to develop a molecular signature to predict risk for progression to autoimmunity (microRNA Risk Score- mRS), using multiethnic cohorts. Prof Hardikar's current research focuses on developing an mRS for Stage 1 and 2 T1D using samples from the ENDIA study (nested case control) as well as heel blood spot samples from the Australian Type 1 Diabetes National Screening Pilot.

5) Professor Toby Coates

Professor Coates presented research on chimeric antigen receptor T regulatory cells (CAR Tregs) and the importance of Tregs in understanding the pathogenesis of T1D.

Treg depletion and/or reduced FOXP3 expression (a transcription factor critical for maintaining Treg phenotype) can induce diabetes in NOD mice. Tregs isolated from T1D patients have reduced suppressive activity linked to decreased FOXP3 expression and IL-2 signalling. The presentation introduced the concept of using CAR on Tregs for T1D, which could potentially enhance their immunosuppressive capabilities. Prof Coates provided an overview of CAR Treg technology, showing that it could be customised for various antigens, making it a flexible tool for immunotherapy in T1D. He presented preliminary results demonstrating successful CAR expression in human T regs targeting GAD65 autoantibodies, their suppressive capabilities, and their phenotype, which indicated the maintenance of essential Treg markers. Prof Coates outlined work testing the leukapheresis stage of this technology on five T1D volunteers. Prof Coates outlined the potential for this therapy in the future for 1) early prevention/treatment of autoimmunity or 2) treatment of recurrent autoimmunity after islet or pancreas transplantation.



Panel discussion: Beta cell replacement and regeneration, future directions, and challenges

Panel members: Prof Philip O'Connell, Prof Wayne Hawthorne, Prof Stephen Alexander, Prof Shane Grey, A/Prof Jane Holmes-Walker, Prof Peter Thorn, Prof Sof Andrikopoulos, Dr John Males, Mr John Waszczuk

Moderator: Prof Toby Coates

The audience heard from the panel that **whole pancreas transplant is still the best option for glycaemic control** but that it is risky in terms of mortality. This means that **islet transplantation is currently the next best option**.

The panel was asked what the greatest achievement in the last decade has been regarding beta cell replacement. One member of the panel stated that the **progress of transplantation has been difficult in the last decade because, despite initial enthusiasm, there have been regulatory challenges**. The next stage in transplantation science will be the **use of gene editing technology** (CRISPR/Cas9) with stem cells which Vertex is investing into. A panel member who has received transplantation said that it was "the best thing in life". It allowed him to restore some level of spontaneity, especially in regard to meal choices, and drastically **improve his quality of life**. Other panel members stated that the biggest advancement in the last decade has been auto-islet transplantation for chronic pancreatitis.

The panel then discussed in which direction this area needs to progress. The area of **gene modification was identified as one area in need of advancement**, with a focus on a multifactorial approach where different genes/proteins are targeted to derive a layered response. The **area of xenotransplantation was also an area that needed focus**, especially since Australia is a leader in this field. It was noted that we have the expertise and capacity to **build large transgenic pig and non-human primate facilities** but need government funding for infrastructure (piggeries and other facilities to mass produce xenotransplants). We also need **TGA movement** on this front. The panel noted there is growing interest in this area, with the WHO re-writing international guidelines this year and also a large meeting in San Diego in October going ahead.

One panel member noted that one of the barriers in the area is that because insulin and other technologies are currently so effective, that a very good safety profile in transplantation is needed to make it acceptable. So the **risk/benefit ratio for transplantation has changed with the mass introduction of technology**. Other panel members disagreed, saying that for a large number of people, an alternative will always be sought because **"biology is better than technology"**. This is especially the case for those with a very poor quality of life or those who are likely to develop many complications because of T1D despite the use of technology. Even with advanced technology, people with T1D still get better glycaemic variability with a transplant compared to technology. Several panel members agreed that the burden associated with T1D - even with technological advancements- is significant, and that transplantation provides a solution to this.

The panel was asked what we are doing in Australia to support stem cell research. The panel members indicated that **Australia is lagging behind in stem cell development** and that we need to **develop better infrastructure**. It is unclear where the new source of funding for this will come from (beyond JDRF support which has been substantial).

Other comments noted that in Australia, we focus on mouse models, but we need human models. One panel member suggested we need infrastructure similar to nPOD as mouse and human anatomy can be very different. Another panel member suggested **we need better support of islet biology research** with a national islet biology research program.

A better pathway for cell replacement therapies is needed with regulators (e.g. FDA) and the risk/benefit ratio or criteria needs to be crystalised. JDRF has been pushing for a wider group of adults with T1D to be able to access these therapies (i.e., not just restricted to severe hypoglycaemia unawareness).

There was discussion around the **"race between pigs and stem cells" in providing a sustainable, long-term source of islets**.

One important issue raised was how we **address the immune system post transplantation**. That is, is it better to alter the recipient's immune system or alter the islets themselves to make them less immunogenic?

On what Australia can offer the world in terms of transplantation, panel members stated that Australia is a great place to do research because we have a great platform for transplantation already. There are however **challenges to be faced with the TGA to get approval**.

The panel then discussed what the next decade of transplantation may bring. We have the clinical capacity to transplant islets and get internationally comparable results and have a T1D community that are keen to participate in trials and receive transplants. But one challenge is working with the regulatory authorities to get approval. One panel member discussed the progress in terms of regulatory approval around the world with the 'Chagsha Communique' and several white papers being developed and considered by regulators around the word (e.g. in Europe and FDA). What **we need at this stage is the infrastructure to mass generate islets** (e.g. from pigs) even if we were successful in getting regulatory approval to proceed.

These infrastructure facilities are 'big ticket items' that require extensive funding (e.g. MRFF, NCRIS) and economic modelling of the costs of T1D and other costing data. JDRF's work has been invaluable in this regard.

One panel member stated that in terms of scaling up to have a continuous source of islets, manufacturing for **autologous transplantation** does not make economic, manufacturing sense because you need to manufacture stem cells for every single person.

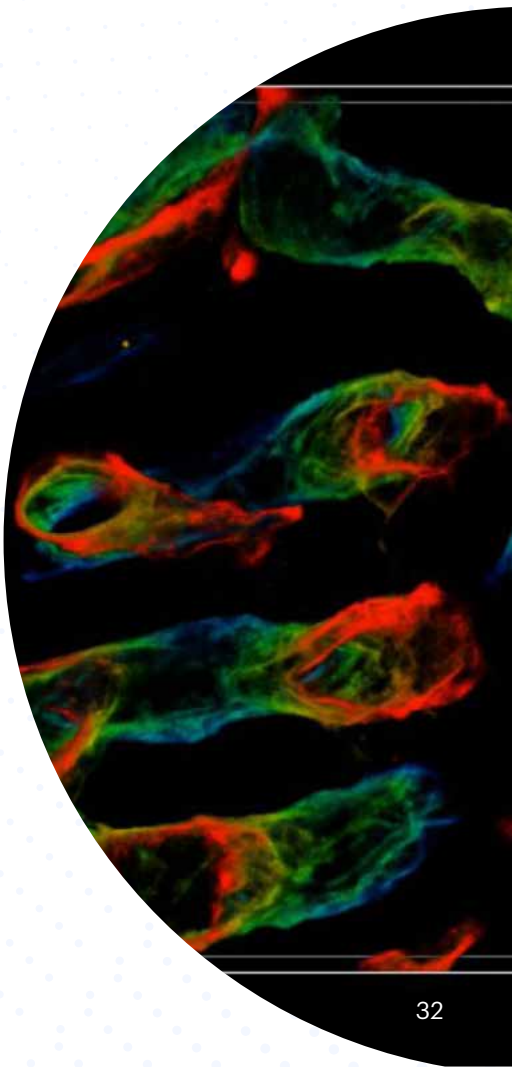
In terms of what patients require next, it was stated that **what patients want is a cure**, something that allows more freedom, no need for immunosuppressive drugs nor ongoing care.

The panel discussed **funding models and demonstrating return on investment for transplantation** and when that should be started. It was suggested that estimating cost-benefit ratios should start already, from the outset of transplantation programs. Some members stated they are already undertaking this task (e.g. cost benefit ratio for all technology for islet transplants).

In terms of progressing advancements in this area, it was agreed that large pharma needed to come on board to progress this area but also to be able to reach patients once a solution is found. And if researchers don't have reaching pharma as one of their objectives, they are not going to be able to impact patient care.

However, it was also noted that Australia had a different funding structure to other countries, without a strong philanthropic culture or large pharma presence (unlike in the US).

The panel finished the session by discussing how we can bridge the divide between what patients want and what clinicians are willing to do. That is **how do we improve access to transplantations, especially since we have the clinical ability to do them?** It was noted that there is a general reticence amongst endocrinologists to refer patients for transplantation even when they fit the criteria for transplantation of hypoglycaemia unawareness, adverse psychological outcomes, and poor quality of life. The main thing that is hampering us is supply issues, but we should be making transplantation more accessible for people. There is a role for JDRF and the community to play in pushing this agenda forward.



SESSION 4:
Technologies, adjunct therapies, adoption and policy

Professor Jeffrey Braithwaite

Keynote 1: Implementation, adoption and policy in the health system of 2030

Professor Braithwaite addressed the critical challenges of translating scientific research into clinical practice and enhancing healthcare systems.

Prof Braithwaite highlighted the persistent gap between scientific research and its practical application in healthcare, underscoring the importance of building a robust field of implementation science to bridge this divide.

Prof Braithwaite stressed that addressing this gap requires forming networks and coalitions among researchers, clinicians, and stakeholders. These alliances should work collectively to streamline the transformation of research findings into practical improvements. Additionally, he examined the concept of adoption, questioning whether healthcare providers are merely pushing new practices into the system or if the healthcare system is ready to be receptive to these changes.

Looking ahead to 2030, Prof Braithwaite discussed significant trends in healthcare, such as sustainability, genomics, and emerging technologies. He also emphasised critical initiatives to enhance healthcare delivery, including service integration, patient-cantered care, universal healthcare, and technology adoption.

Professor Mark Cooper

Keynote 2: Adjunct therapies

Professor Mark Cooper presented on adjunct treatments for T1D, additional therapies used alongside insulin to reduce long-term complications associated with the condition.

Prof Cooper emphasised that many individuals with T1D manage the condition effectively, leading to a normal or extended lifespan for those without complications. Although insulin is the main therapeutic, there is an increasing number of patients that use adjunct therapies to help control their T1D (even if off label) and for their organ protective effects by reducing complications.

The discussion revolved around adjunct treatments, including metformin, DPP-4 inhibitors, SGLT2 inhibitors (e.g. dapagliflozin and sotagliflozin), GLP-1 receptor agonists (e.g. Ozempic), and pramlintide which are often considered for individuals with T1D who are already using insulin. The use of SLGT2 inhibitors reduces HbA1c, basal insulin requirements, and aids weight loss. However, they are associated with an increased risk of DKA (2 to 4-fold). This could be circumvented by ketone monitoring and using ultra-low-dose formulations. Ipragliflozin is currently licensed for use as adjunct therapy in T1D in Japan.

The presentation also touched on the use of GLP-1 receptor agonists especially in those with T1D who have residual insulin production. T1D trials have shown that the use of GLP-1 receptor agonists (liraglutide) reduces HbA1c, insulin dose (basal and bolus) and leads to weight loss. The use of liraglutide leads to increased DKA and gastrointestinal side effects.

DPP4 inhibitors have a very good safety profile but have little effect for use in T1D.

Pramlintide is a derivative of amylin and is the only FDA approved adjunct therapy for T1D. Its use in T1D results in reduction of HbA1c, and insulin use, but has

gastrointestinal side effects that ease over time. It is not available in Australia and in the US the use has not been widespread.

Metformin use in T1D has had mixed results in trials looking at glucose control, insulin requirements and cardiovascular disease. However, Metformin remains approved for use in T1D in France.

Prof Cooper finished by comparing an ideal T1D adjunct therapy to current therapies and noted that some have only modest effects. There is much research being undertaken in these therapies for T2D, and it is likely that through this, we may learn about how they work and their potential application for T1D.

Associate Professor Sybil McAuley

Keynote 3: Improved health with diabetes therapeutic technology

Associate Professor McAuley discussed the advancements in diabetes technology, particularly in Australia, and their role in improving health outcomes for those with T1D.

A/Prof McAuley noted the last decade was a 'big' decade in terms of diabetes technology research, and we are now reaping the fruits of that labour. The presentation covered key advancements in this technology, such as CGMs and insulin pumps. The presentation covered: insulin pump basal delivery, the use of tech in exercise and automated insulin delivery (AID).

A/Prof McAuley presented on findings which showed that changes in basal insulin through pumps took time to be reflected in circulating insulin levels (i.e. delayed onset of changes). The presentation then covered the impact of technology on basal insulin delivery within the challenging context of exercise where insulin requirements vary greatly and unpredictably. A/Prof McAuley presented studies showing how glucose levels change depending on type of exercise, and how this knowledge can be used by patients to adjust insulin requirements to avoid hyper or hypoglycaemia.

A/Prof McAuley showed data from CRN funded Hybrid closed loop/AID RCT trials in 2017 in Australia showing improved TiR and less hypoglycaemia with use of AID in T1D patients. This was extended to the use of AID in those with T1D undertaking different types of exercise. Results showed that using pump announcements and, where needed, carb loading ensured safe exercise (high TiR and low hypoglycaemic rates).

The presentation also focused on the use of AID for older adults with T1D. This subgroup have greater risk of severe hypoglycaemia and may have additional clinical challenges. The ORACL study showed that in older adults (>60 yrs) with T1D, using AID increased TiR and reduced hypoglycaemia. Further studies investigating perceptions of AID use in older patients demonstrated satisfaction with AID systems, particularly improved sleep from better glucose levels, but had concerns with disruptive alarm functions.

A/Prof McAuley then provided an overview of the AID systems currently in the Australian market (3 commercial systems) and emphasised there is no one size fits all approach for patients choosing an AID system.

Real world evidence data two years post AID in Australia suggests that AID use results in reductions in HbA1C, increased in TiR that is sustained and no increase in hypoglycaemia or insulin dose.

The presentation concluded by highlighting the future prospects of diabetes technology, including advanced sensors, faster insulins, implantable glucose sensors, and the need for reliable automation and outcomes beyond glucose (psychosocial). Additionally, it mentioned the importance of considering health economics and equity in technology development.

Professor Tim Jones

Keynote 4: Translation in the real world

Professor Jones' presentation centred on his perspectives as a clinician of the translation of T1D research into the 'real world'.

Prof Jones highlighted the significant advancements in diabetes care and management over the past few decades, showing data on the significant decrease in mean HbA1C levels (halved since 1980s) and the reduction in severe hypoglycaemics events, both as a result of therapies and education. However, we have learned that multiple interventions and approaches were needed to achieve these results. These included changes in models of care delivery, increased knowledge and education, innovations in insulin and delivery methods and glucose monitoring. It was noted that no single intervention could achieve these results in isolation.

Prof Jones also noted that translation of research can be slow and there remains some challenges which halt research from reaching the real world. One is the lack of involvement of consumers/patients in research and decision-making processes which is now being increasingly addressed. Another is the challenge of ensuring equitable access to new diabetes technologies, as disparities often exist based on socioeconomic status and geography. Professor Jones provided an example of slow research translation with the low uptake of hybrid closed loop systems for hypoglycaemic unaware patients. The reasons for this were likely different in each jurisdiction.

Prof Jones then addressed the key question of how research translation can be accelerated with a particular focus on clinical trials. The presentation recommended designing trials with translation/implementation in mind, co-designing interventions with patients, reducing bureaucracy, and considering equity from the outset. On equity, Prof Jones explained that health disparities are established very early on in the course of T1D in young people. He presented data showing that by 12 months post T1D diagnosis, mean HbA1c was higher in Hispanic or black youth compared to white youth in the US. Likewise he presented data showing that pump and CGM use decreases with disadvantage and this is associated with increased HbA1c levels.

Prof Jones finished by discussing that we live within complex social determinants of health and so T1D research translation needs to take these elements into account if it is to be successful.

Professor Louise Maple-Brown

Keynote 5: Challenges of T1D care-disadvantaged and remote populations

Professor Maple-Brown presented on the complexities of living with T1D in Aboriginal and Torres Strait Islander youth and the challenges of T1D care in disadvantaged and remote populations.

Prof Maple-Brown pointed out the heterogeneity of youth-onset diabetes among NT Aboriginal and Torres Strait Islander people: the rarity of classic T1D, the growing prevalence of youth-onset type 2 diabetes and the mixed type 1 and type 2 phenotype which are relatively common (lean, antibody negative, borderline/low C-peptide and low levels of DKA).

Prof Maple-Brown discussed that extreme poverty and disadvantage significantly affect the lives and health of these young individuals, as demonstrated by case studies illustrating the challenges of managing diabetes under such circumstances.

The presentation highlighted the critical role of social determinants of health, especially food insecurity, as major barriers to managing diabetes in these communities. Additionally, she discussed the intricate challenges related to healthcare access and the impact of health staff turnover in remote primary care settings.

Collaborative efforts and partnerships aimed at breaking the cycle of type 2 diabetes among Aboriginal and Torres Strait Islander communities were presented, focusing on community engagement, capacity building, and improving care models.

Qualitative research involving individuals living with diabetes is used to better understand their experiences, facilitators, and obstacles to care.

Professor Maple-Brown's recommendations for improved partnerships include increasing awareness of youth-onset diabetes, addressing social determinants of health, and enhancing access to high-quality, culturally appropriate healthcare.

Professor Joshua Byrnes

Keynote 5: Applied Health Economics

Professor Byrnes presented on the importance of applied health economics to measure and demonstrate value in T1D care. He emphasised the critical role of economics in healthcare and the necessity of economic evaluation to secure funding and access to healthcare.

Professor Byrnes outlined the need for economics in policy setting because limited health budgets do not permit all people to access all available health care, and so there is a need to identify health care solutions which maximise benefit:cost ratios. Prof Byrnes also outlined the starting principles for health economics: that resources are limited, there are unlimited uses of these resources and that health care is an economic good.

Prof Byrnes explained the complex healthcare funding system in Australia, emphasising the substantial societal cost and the limited government coverage, leaving patients and families to bear a significant burden. He discussed the different perspectives and costs associated with healthcare stakeholders, such as patients, insurers, and providers.

Prof Byrnes then presented on how we measure 'value' in health economics, centred on maximising benefits relative to costs and using quality-adjusted life years (QALYs) to measure health outcomes. QALY captures the length of time lived (life expectancy) as well as the quality of that life. Prof Byrnes discussed the use of economic models to predict long-term outcomes and benefits of new health interventions while acknowledging the challenges and limitations of these models, especially in the context of T1D.

The presentation concluded with a discussion of the impact of uncertainty on healthcare decisions and the trade-offs between price, population, and time in the context of healthcare technologies. Prof Byrnes illustrated these trade-offs by presenting data on the economic benefits of reducing complications, prevention, and delaying treatments in diabetes care

Professor Jane Speight

Keynote 6: Quality of life matters in the use of glycaemic technologies

Professor Speight presented on the importance of recognising QoL as a vital component of diabetes management especially in the context of glycaemic technologies.

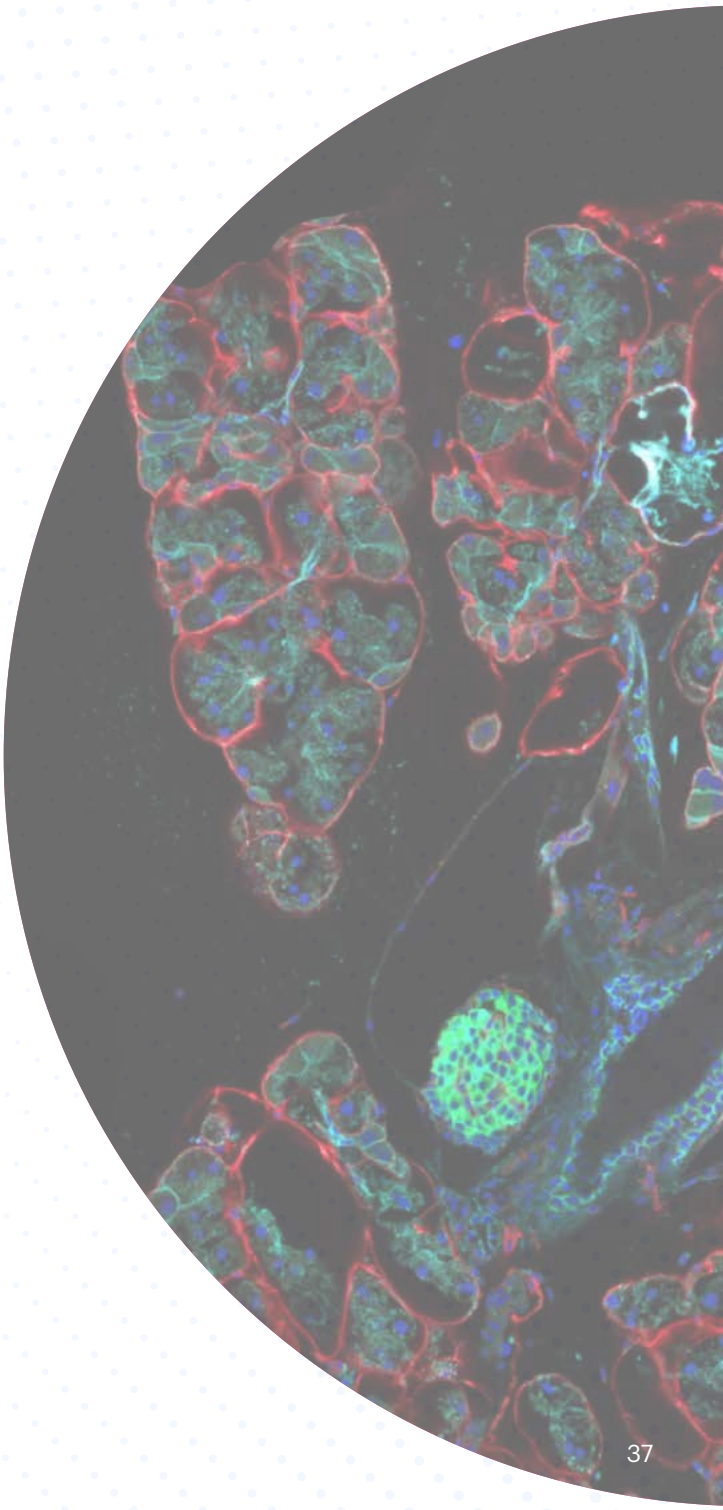
Prof Speight emphasised that people with T1D often had concerns beyond their health and discussed the significance of balancing health and QoL in everyday life. These concerns encompassed various aspects of daily life, such as work, family, social interactions, independence, and personal freedom. People often think in the present and discount future health issues such as long-term complications associated with T1D. The last 25 years of research have taught us that QoL is multidimensional, subjective, and dynamic. The question remains how to capture these QoL metrics within T1D research.

Prof Speight also highlighted the challenges associated with diabetes technologies. While these innovations offered health benefits, they introduced additional complexities and burdens, which in turn affect QoL. For instance, users have to navigate device adjustments, device costs, skin reactions, technical failures and sleep disruptions due to alarms. Prof Speight discussed that often these were not included in economic QoL metrics which has impacts on economic assessments of technologies. Prof Speight noted that to ensure people get the most benefit from these technologies, managing

expectations is crucial. She addressed the issue of stigma surrounding the use of these technologies in public, which could influence individuals' choice to continue using them. There is still research work to be undertaken on the impacts of stigma in technology uptake and continuation.

Prof Speight called for a more holistic approach to addressing the benefits of T1D technologies, advocating for new outcome measures which go beyond health and encompass QoL metrics.

Prof Speigh also recommended we move away from treating technology as a magic bullet and towards thinking about it as a complex behavioural intervention. Prof Speight recommended that we should value all forms of evidence (including qualitative studies), and not rely just on randomised controlled trials as the 'gold standard'.



Panel discussion: Embedding new therapies and new technologies across T1D patients of all ages

Panel members: Prof Jeffrey Braithwaite, Prof Mark Cooper, A/Prof Sybil McAuley, Prof Timothy Jones, Prof Louise Maple-Brown, Prof Joshua Byrnes, Prof Jane Speight, Mr Jonathan Salmon, Prof Fergus Cameron, Dr Laura Knecht, Dr Ben Nash

Moderator: Prof Elif Ekinci

The panel commenced by discussing how we can **increase the participation of people with T1D in clinical trials** and implement new therapies. We heard that education is key, with emphasis on what complications are and can be within T1D. We also heard that we have a very engaged community that is very interested in the research, but that undertaking trials in people with T1D is more technically difficult (presence of DKA and hypos) and also not as commercially interesting for industry to engage with.

The panel heard that engagement with people with a lived experience of T1D from the outset of a trial and using **a co-design approach is essential to success**. For remote and regional participants there are additional barriers to trial participation, but the ENDIA model has been successful in engaging with participants.

For all clinical trials, **the key is building international networks to increase patient numbers**, in particular partnering up with European networks. There was agreement that we need to partner up to increase clinical trials and access for individuals at all stages of T1D which T1DCRN has been supporting in the last decade.

The panel then discussed **how to improve access to insulin pumps** for those with T1D, in particular for adults where the evidence of clinical benefit is strong. We heard that with the introduction of hybrid closed loop systems, the positive data is already available to justify funded access to insulin pumps.

We heard that everyone's priority should be to advocate for pumps and put a case together, including **collecting health economic data early on**. We heard that with pumps, a particular barrier is not being able to **identify which pathway it should take for subsidy listing** (easier for pharmaceuticals or treatments under the PBS/MBS). Currently insulin pumps are under the prosthesis/implantable devices listing and this is a very complex pathway to navigate. We need to identify who we need to talk to and ask what cost-effectiveness evidence they require for funding to go ahead. The panel heard there is a **disparity in access to pumps** in terms of age, socioeconomic status and remoteness, particularly since only 50% of people have access to private health insurance which is required for pump access.

The panel was then asked who should be at the table during government approval processes and what the role of the patient should be. Most panel members agreed that T1D community representation is important, especially in regards to diversity (remote, Indigenous etc). It is important to have the voice of the people who are affected represented, front and centre and from the start.

Involving people with T1D in research design is also important. One panel member pointed out that we don't appreciate the burden that clinical trial involvement brings, so engaging people with T1D is imperative to trial design. But funding currently does not cover the costs of co-design (e.g. steering group to co-design). We need to advocate for funding for consultation and piloting so that co-design can take place and increase the collection of patient-reported outcome measures (PROMs) during the course of CTs.

The panel then moved onto discussing how **QoL measures are included in government approval and economic estimates**. QoL measures are essential and readily used by government and industry. We heard there are many measures of QoL, including disease specific ones but not yet one for diabetes, although work is underway in the UK. Other UK work is also looking at developing a new measure of hypoglycaemia on QoL for use in health econometrics. The panel heard it is important to note that there are always questions around sensitivity, specificity, how well we measure and the value of QoL measures.

Australian Type 1 Diabetes
Clinical Research Network

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

jdrf.org.au @jdrfaus @jdrfoz @jdrfaus