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COMMENTARY **OPEN**

Conveying the pathogenesis of type 1 diabetes to the blind, low-vision and diverse needs communities through sensory stimulation

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Abstract

To educate members of the blind, low-vision and diverse needs communities on the pathogenesis of the chronic autoimmune disease, type 1 diabetes, members of our team with research expertise in immune-mediated diseases, participated in the 2023 Monash Sensory Science (MSS) Exhibition. Using QR code linked audio commentary, participants were guided through tactile displays demonstrating normal insulin action in the regulation of blood glucose levels and its vital role in providing energy to tissues, followed by displays describing the various stages of the immune system's aberrant attack and the eventual complete destruction of the insulin producing beta-cells of the pancreatic islets in type 1 diabetes. These models conveyed to the participants the huge effect that this autoimmune-mediated disease has on the quality of life of affected individuals including the subsequent lifelong reliance on insulin injections to maintain glucose homeostasis. This MSS Exhibition provided a unique opportunity for our researchers to engage with under-represented members of the community and to raise awareness about such a debilitating and common autoimmune disease.

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INTRODUCTION

Approximately 130 000 Australians (~8.7 million people worldwide) are living with the chronic autoimmune disease type 1 diabetes (T1D), with about 3000 Australians newly diagnosed every year. Type 1 diabetes has serious effects on the quality of life and increases the mortality of affected individuals.[1–4] Indeed, in Australia ~12 000 people (~3 million people worldwide) with type 1 diabetes should still be alive today but for complications associated with the disease.[1] A significant disease burden is also evident for type 1 diabetics, with an estimated 19 years of healthy life lost per person.[1] There is a strong genetic association with susceptibility to type 1 diabetes, predominantly via the inheritance of certain alleles of the human leukocyte antigen (*HLA*) Class II loci, particularly *HLA-DRB1* and *HLA-DQB1*.[5] The strongest genetic risk for type 1 diabetes is observed for the haplotypes *HLA-DR3-DQ2* (odds ratio (OR) ~3.64) and *HLA-DR4-DQ8* (OR ~ 11.37). Hence, given that the strongest genetic association is with certain HLA Class II haplotypes, an autoimmune mechanism in disease pathogenesis is evident. Although the etiology of type 1 diabetes is unknown, abundant evidence suggests there is a breakdown of immune tolerance to one or more self-antigens produced in pancreatic beta-cells, including preproinsulin, glutamic acid decarboxylase 65 (GAD65), insulinoma antigen-2 (IA-2), islet-specific glucose-6-phosphatase catalytic subunit related protein (IGRP), heat shock protein (HSP), zinc transporter 8 (ZnT8), chromogranin A (ChgA) and islet amyloid polypeptide (IAPP).[6] This is proposed to occur via a process of molecular mimicry, whereby microbial infection leads to T cell cross-reactivity to self-antigens leading to an autoimmune response mounted against pancreatic beta-cells, ultimately leading to their destruction.[7] Another theory is that central tolerance to self-antigens is broken via the emergence of "neoantigens" that are the product of post-translational modification of self-peptides in the pancreas.[7–9]

Given the participants in the MSS Exhibition had varying degrees of visual impairment and differed widely

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in age as well as level of education in science, the tactile displays and accompanying guided commentary were specifically designed to provide greater accessibility to these participants in gaining a fundamental understanding of the processes involved in the development of type 1 diabetes. This started with a description of the normal action of insulin followed by the autoimmune-mediated pathogenic events culminating in the complete destruction of the insulin producing beta-cells of the pancreatic islets.

T1D DISPLAY 1: CHARACTERISTICS OF TYPE 1 DIABETES

Members of the team initially introduced participants to the subject of type 1 diabetes by providing a tactile display accompanied commentaries outlining the facets of type 1 diabetes (Figure 1): (i) average age of onset, represented by a raised figure of a young person, popsicle sticks spelling out "age less than 30"; (ii) signs and symptoms, with high blood glucose shown by clusters of jellybeans, weight loss shown as a tactile stick-figure, increased hunger shown by toy food items and cutlery, increased thirst shown by toy models of drink containers; (iii) potential causes including genetic susceptibility and viral infection shown by twisted pipe-cleaner DNA strand and spikey ball virus; and (iv) complications for people living with type 1 diabetes represented as a material anatomical cut-out with various parts raised including eyes, heart, kidneys, feet to indicate associated pathology including blindness, heart disease and stroke, kidney failure, nerve damage and vascular disease.

Displays 2–4 (Figures 2–4) were all accompanied by a QR code linked pre-recorded guided commentary for the participants, read by a team member. The audio commentary could be paused at any stage so that the participants could ask for clarification from a team member on any aspect of the display/commentary they did not understand, before resumption of the recording. Where possible, in the descriptions of Displays 2–4, the materials/shapes used to depict the various components of the figures are indicated in brackets immediately after the name. Display 2 (Figure 2) also had a push button activated audio describing healthy versus type 1 diabetes affected pancreas that assisted with spatial awareness of the tactile models.

T1D DISPLAY 2: MECHANISM OF INSULIN ACTION: MAINTAINING BLOOD GLUCOSE HOMEOSTASIS

Participants were then engaged in a display describing the mechanisms of insulin action and what happens when there is a breakdown in the production of insulin from the pancreas.

The participants were first shown the difference between glucose levels in the blood of healthy versus diabetics after consuming a meal (Figure 2). On the top left of the display, the healthy pancreas was depicted as a plastic model decorated on the surface with popcorn kernels representing the insulin secreting islet beta-cells. The blood vessel located

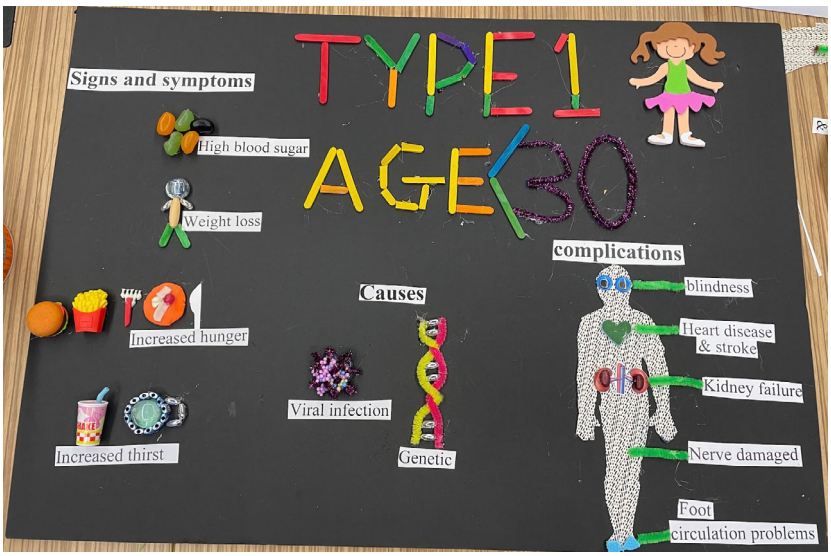

Figure 1. List of type 1 diabetes-disease related symptoms, complications and possible causes.

Figure 2. Tactile models of insulin-mediated glucose homeostasis in health and breakdown of glucose homeostasis in autoimmune type 1 diabetes.

below the pancreas (horizontal line of modeling clay) had insulin (small beans) secreted from beta-cells released into the bloodstream when there are high levels of blood glucose (jellybeans), after consuming a meal. Insulin was shown to engage cell surface insulin receptors (popsicle stick "Y"), which subsequently signaled for the opening of the transmembrane glucose transporter (vertical corkscrew pasta with a gap), and the uptake of glucose (jellybeans) from the blood through the glucose transporter channels into muscle cells (cardboard). Thus, the participants were shown how the healthy body manages homeostasis of blood glucose, the body's main energy source, via active uptake in tissues following a meal.

Next, participants were directed to the top right of the display which showed the effect of the autoimmune response in type 1 diabetics on the regulation of their blood glucose level. T cell receptors (TCR) (wooden "H") on the surface of cytotoxic $CD8^+$ T cells (glass balls with facets) detect and delineate self- from non-self-peptide antigens produced by the pancreatic beta-cells. In the display, we showed that instead of tolerating self-peptides presented by HLA Class I molecules, the T cells are activated and release their cytotoxic cargo (crystal beads) including perforin that creates pores in the target beta-cell and granzymes that enter the cell through these pores, thus initiating cell death leading to their destruction. Fragments of the dead beta-cells (loose broken popcorn kernels) were shown surrounding the same pancreas model used in the upper left-hand corner but now with a mostly smooth surface with only a few popcorn kernels remaining, depicting the few surviving beta-cells. Beta-cell death leads to a lack of insulin production and a subsequent chronic increase in blood glucose (large cluster of jellybeans). The connection between the lack of insulin production and subsequent accumulation of blood glucose was demonstrated with muscle cell (cardboard) surface insulin receptors (popsicle stick "Y") without bound insulin (beans) leading to a failure to activate and open the glucose transporter (vertical corkscrew pasta with no gap between them). Thus, the participants were provided with a broad overview of how the destruction of the insulin producing pancreatic beta-cells leads to the pathology of type 1 diabetes in the absence of treatment with exogenous insulin.

T1D DISPLAY 3: THE DESTRUCTION OF INSULIN SECRETING BETA-CELLS OF THE PANCREAS BY THE IMMUNE SYSTEM 1

Next, participants were led through a tactile display describing, in more detail, the mechanisms associated with the autoimmune attack directed at the beta-cells of pancreatic islets and their destruction.

On the top left of Display 3 (Figure 3), the healthy pancreas was again depicted as a plastic model covered in insulin secreting islet beta-cells (popcorn kernels). Just below this, a cross-section of the pancreas was depicted to reveal the Islets of Langerhans containing the three main protein hormone producing cell types: glucagon secreting alpha cells (soft balls), somatostatin secreting delta cells (soft pieces of polystyrene) and insulin secreting beta-cells (popcorn kernels). To the right of the model of the pancreas, the three chains (i.e. A, B and C) of pro-insulin were shown as a contiguous string of balls arranged in a spiral shape with each ball representing a single amino acid. Two strings of soft balls, one above and one below represented

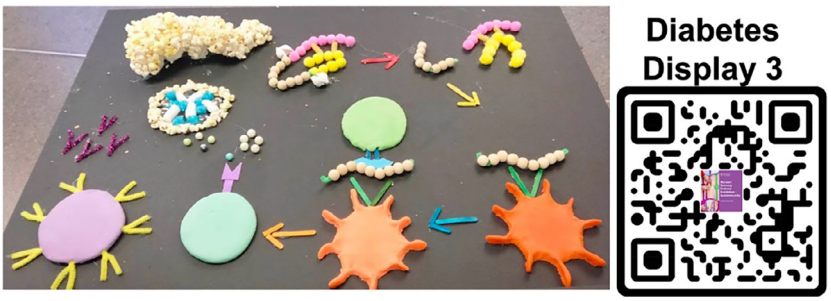

Figure 3. A tactile model of immune-mediated destruction of pancreatic beta-cells in type 1 diabetes.

the insulin B- and A-chains, respectively. The A- and B-chains were connected by two inter-chain disulphide bonds (corkscrew pasta). The C-peptide (wooden balls) connected the A- and B-chains. The beta-cell proteases (sea-shell shapes) responsible for removal of the C-peptide to produce the mature active insulin protein were positioned at the beginning and the end of the C-peptide at the sites of enzymatic attack. An arrow was used to direct participants to the right to show the A- and B-chains of the mature active insulin protein and the cleaved C-peptide.

Moving to the bottom right of the display, we showed how a self-peptide can be mistakenly recognized as a non-self/foreign antigen, leading to an autoimmune response. We depicted HLA Class II (two sticks in a V-shape) on the surface of an antigen presenting cell (APC; pancake shaped with filopodia in modeling clay) with C-peptide bound in the antigen binding cleft. Moving to the left with the wooden arrow, we depicted antigen recognition by $CD4^+$ T helper cells (pancake-shape in modeling clay) with a cell surface TCR (crescent of cardboard connected to the surface of the T cell by two sticks) engaging the APC with HLA-Class II C-peptide complex directly below it. Moving to the left via another wooden arrow, we then showed that the act of antigen recognition triggers the $CD4^+$ T helper cell to proliferate and secrete cytokines. This then leads to the autoimmune response in the pancreas including (moving left again) (i) the activation and recruitment of cytotoxic $CD8^+$ T cells (modeling clay pancaked shape with cardboard HLA Class I on the surface) secreting cytotoxic cargo (beads) directed towards killing the islet beta-cells and (ii) B-cell (far left, modeling clay pancaked shape with "Y" shaped pipe-cleaner on the surface to represent B cell receptor) activation and subsequent pathogenic anti-insulin antibody (cluster of "Y" shaped pipe cleaner) production by plasma cells (not shown), ultimately leading to the destruction of the insulin secreting cells and type 1 diabetes.

T1D DISPLAY 4: SCHEMATIC OF PANCREATIC ISLET CELLS AND THE STAGED PROGRESSION OF ISLET BETA-CELL KILLING BY CYTOTOXIC $CD8^+$ T CELLS IN TYPE 1 DIABETES

For Display 4 (Figure 4), a more in-depth description of how cytotoxic $CD8^+$ T cells of the immune system mistakenly destroy the insulin-producing pancreatic beta-cells was provided, with reference to the role of neighboring pancreatic alpha and delta-cells in health.

On the bottom left of Display 4 (Figure 4), the participants were directed to examine three cell types of the pancreatic Islets of Langerhans discussed in Display 2 (Figure 2). An alpha cell (left, glass beads), beta-cell (middle, popcorn kernels) and delta cell (right, velvet material) all have a cell surface HLA Class I molecule (modeling clay and plastic punctate cylinders) on their surface presenting self-peptides that they produce (a string of beads). Above this on the top left were depicted glucagon (round beads), insulin (small beans) and somatostatin (long beads) protein hormones produced by the alpha-, beta- and delta-cells, respectively. The effects of each hormone were also briefly described in the commentary. Moving to the right, $CD8^+$ T cell (pancake) surface TCR (twin punctate plastic cylinders) antigen recognition of the HLA-Class I bound insulin self-peptide presented by beta-cells but not alpha- or delta-cells (because they do synthesize insulin) in type 1 diabetes was depicted. Again, moving to the right, the effect of $CD8^+$ T cell recognition of insulin self-peptide on beta-cells is demonstrated by a lack of insulin whereas glucagon (round beads) and somatostatin (long beads) remain in abundance and below this, there is a destruction of the beta-cell (fewer and broken popcorn kernels) whilst

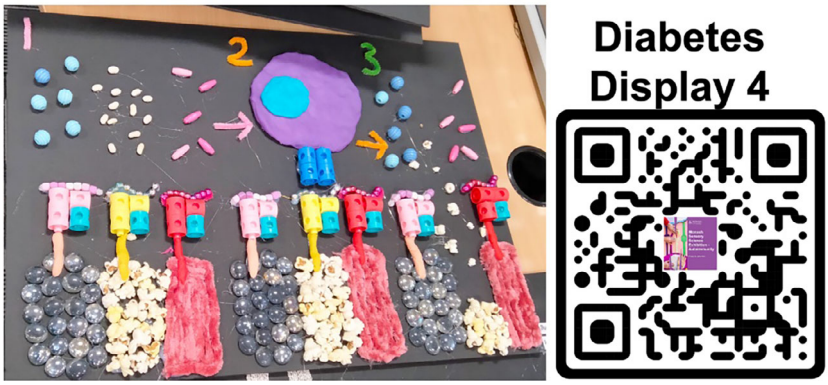

Figure 4. Schematic of pancreatic islet cells and the staged progression of islet beta-cell killing by cytotoxic $CD8^+$ T cells in type 1 diabetes.

the alpha- and delta-cell on either side remain healthy. Thus, the display helped to explain in detail the cytotoxic $CD8^+$ T cell arm of the autoimmune attack on pancreatic islet beta-cells in type 1 diabetes and their subsequent destruction leading to a lifelong dependence on insulin for type 1 diabetes patients.

EXHIBITION OUTCOMES

The MSS Exhibition highlighted the benefits to the team in participating in inclusive science education. The design of the tactile displays and the content of the audio commentaries greatly assisted in the team's ability to effectively convey the scientific principles we aimed to deliver to the blind, low-vision and diverse needs communities. By being on hand to interact directly with participants, who had different levels of science education, we were able to answer their questions regarding concepts they were not initially able to understand. This greatly assisted participants in following the whole type 1 diabetes presentation and was a highly rewarding experience for our team. Given the concepts involved – particularly the multiple cell types and molecules as well as the complex interplay of these components in insulin action and the autoimmune response against the pancreatic islet beta-cells – it was not surprising that there were, indeed, many questions. For example, many participants wanted to know the difference between type 1 and type 2 diabetes, whilst a few struggled to understand insulin processing as described in Figure 3 as well as the concept of antigen presentation on HLA molecules on the surface of antigen presenting cells described in Figures 3 and 4. These, and other questions, as well as feedback from the members of the blind, low-vision, and diverse needs communities about the overall experience, will form the basis to improve both the tactile displays and the associated commentary in the future. Such improvements may include the use of movable blocks/items to convey antigen presentation on HLA molecules, as well as a better script for the presenters and QR code linked commentaries that simplifies the technical information and limits the use of scientific jargon, so it is more accessible to a lay audience. Describing highly technical scientific concepts so that they are understandable to a lay audience without diminishing the key message is a delicate balancing act.

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AUTHOR CONTRIBUTIONS

Mai T Tran: Conceptualization; data curation; investigation; methodology; project administration; visualization; writing – original draft; writing – review and editing. **Laura Ciacchi:** Conceptualization; data curation; investigation; methodology; project administration; visualization; writing – original draft; writing – review and editing. **Lisa Ciacchi:** Conceptualization; data curation; investigation; methodology; project administration; visualization; writing – original draft;

writing – review and editing. **Hugh H Reid:** Supervision; writing – original draft; writing – review and editing.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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