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FINAL REPORT

Project / Program Title		Identification of Children with Type 1 Diabetes Suitable for Antigen-specific Tolerising Immunotherapy: T-cell response to Pro-insulin
Name		Dr Yassmin Musthaffa
Award Received		2019 New Zealand Research Development Scholarship
Report Date		27 April 2019
Chief Investigator / Supervisor		Mark Harris
Administering Institution		University of Queensland
Funding Period	Start Date:	1 January 2019
	Finish Date:	1 January 2020

PROJECT SUMMARY

Type 1 Diabetes affects several thousands of Australasian children. The burden on these children and their families is significant. Children with Type 1 Diabetes have to do multiple blood glucose checks and injections of insulin, day and night for the rest of their lives. At the moment, our only option for these kids is limited to simply replacing insulin through things like injections. But this is not a cure.

Type 1 Diabetes occurs because there is an imbalance in the regulation of our immune system. This means that insulin-making cells are mistakenly thought to be 'bad'. The immune cells go 'rogue' and start destroying the cells that make insulin.

What we need is an intervention that can save these insulin making cells. If we can change immune cells from being destroyers into protectors of insulin making cells, then we can cure Type 1 Diabetes.

Immunotherapy aims to intervene at the beginning of the rogue immune process and restore balance and regulation to the immune system. Immunotherapy can change the way immune cells behave in T1D and teach them to be 'good' or protective towards our insulin-making cells.

My PhD focuses on two aspects that are important to understand in order for immunotherapy to succeed.

First, we need to identify these rogue immune cells in people with diabetes and those who are at high risk of developing diabetes. I have developed just such a test based on a simple blood collection, that can identify these rogue immune cells. We can use this test to monitor patients before and after immunotherapy, to carefully track the immune response.

Secondly, we need to find the best patients for immunotherapy. We know that not everyone with Type 1 Diabetes is going to respond to immunotherapy, so it is important to carefully select the

patients that we should be treating, and the window of opportunity in which immunotherapy may be more likely to succeed.

With this knowledge we can use immunotherapy to turn cell destroyers into cell protectors, with the goal of curing and one day preventing Type 1 Diabetes.

PROJECT AIMS / OBJECTIVES

BACKGROUND: Type 1 diabetes (T1D) is an autoimmune disorder caused by autoreactive T-cell mediated destruction of β-cells. In T1D, pro-insulin and neoantigens derived from insulin peptides (hybrid insulin peptides, HIPs) are important targets of autoreactive T-cells. A critical issue is a lack of sensitive and reproducible methods to analyse antigen-specific T-cell responses, despite various attempts.

OBJECTIVE 1: To refine an assay that enables robust, reproducible measurement of antigen-specific T cell responses.

OBJECTIVE 2: To assess the proliferative response of CD4+T-cells from children with T1D and those at risk of T1D to islet autoantigenic epitopes

SIGNIFICANCE AND OUTCOMES

CONCLUSION:

Optimisation of a number of key elements in the CFSE proliferation assay can enable robust, reproducible application to longitudinal cohort studies or clinical trial samples in which antigen-specific T-cell responses are relevant, and adaptation to other autoimmune diseases.

CD4+T-cell proliferative responses to multiple proinsulin-containing auto-antigens is common in children with pre-diabetes and T1D ≤ 3 months. The likelihood of autoantigen-specific proliferative responses decreases with increasing disease duration. CD4+T-cell responses to proinsulin33-63 are most frequent and most robust across all groups tested.

PUBLICATIONS / PRESENTATIONS

Y Musthaffa, E Hamilton-Williams, M Harris, R Thomas. Antigen-specific T cell responses in Type 1 diabetes

Recipient of Emerging Investigator Award and Travel Award: Australasian Paediatric Endocrine Group conference, Sept 2019

Best Poster Runner up: Translational Research Institute Symposium, August 2019

Best Poster finalist, Oral presentation and Travel Award: Royal Australasian College of Physicians Congress, May 2019

Best Poster finalist: Princess Alexandra Hospital Health Symposium Research Excellence Awards, July 2019

Poster presentation: Brisbane Immunology Group Conference, September 2018.

Best Oral Presentation Award: Clinical and Public Health Symposium, November 2018