Immune responses to gut bacteria associated with time to diagnosis and clinical response to T-cell directed therapy for type 1 diabetes prevention

Quin Yuhui Xie[1,2], Sean Oh[2], Anthony Wong[2], Christopher Yau[2,3], Kevan Herold[4], Jayne Danska[1,2,3]

[1]Dept of Medical Biophysics, University of Toronto, ON, Canada [2]Hospital for Sick Children Research Institute, Toronto, ON, Canada [3]Dept of Immunology, University of Toronto, ON, Canada [4] Yale School of Medicine, New Haven, CT, USA

Background

Type 1 Diabetes (T1D) is mediated by T cells that destroy insulin-secreting β cells in the pancreatic islets. In TN10, the first human T1D prevention trial, a single treatment course with teplizumab delayed disease onset in participants at high risk for T1D[1]. However, heterogeneity in therapeutic responses in TN-10 identify gaps in understanding disease progression and treatment responses.

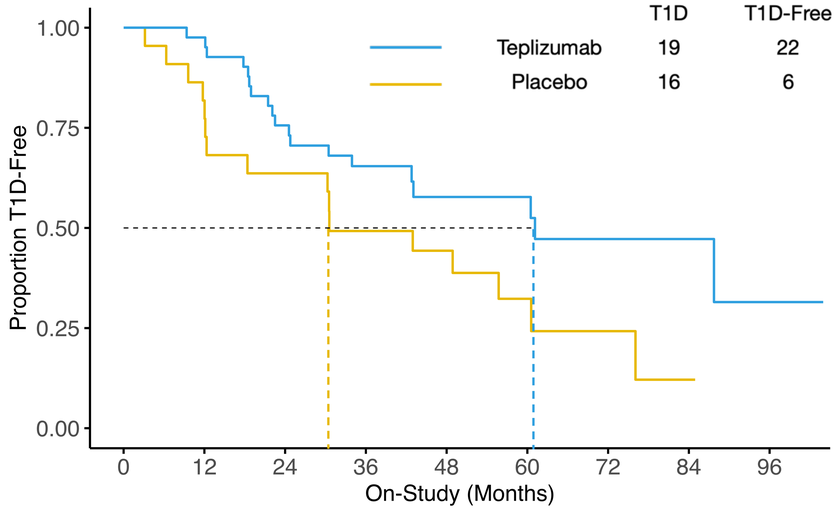

Figure 1. Teplizumab association with delayed T1D progression

Hypothesis

We previously found anti-commensal responses (ACAb) displayed interaction with *HLA-DR,* which accounts for the majority of T1D genetic risk, in its association to future T1D diagnosis. Therefore, we hypothesize that immune reactivities to gut bacteria are associated with progression to T1D and with teplizumab treatment responses.

Methods - ACAb Assay

Serially diluted serum sample were incubated with cultured, live-stained commensal intestinal bacterial species. Anti-isotype secondary Ab were added to the serum-incubated bacteria and evaluated by flow cytometry to quantify the percentage of serum-Ab-bound bacteria.

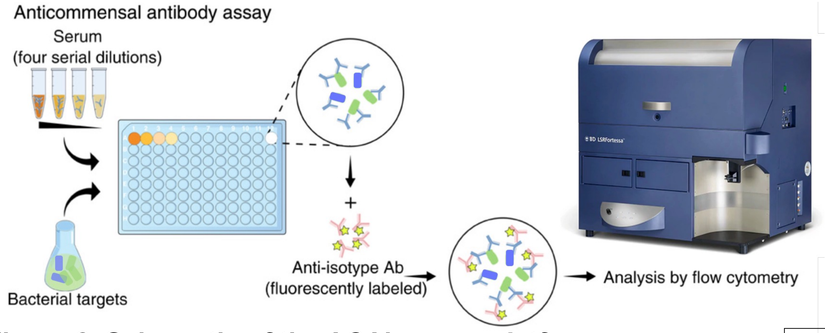

Figure 2. Schematic of the ACAb assay platform

Results

IgG2 responses to 3 bacterial species at baseline (before treatment) were associated with time to T1D diagnosis: Bifidobacterium longum (*B.longum*), Enterococcus faecalis (*E.faecalis*) and Dialister invisus (*D. invisus*).

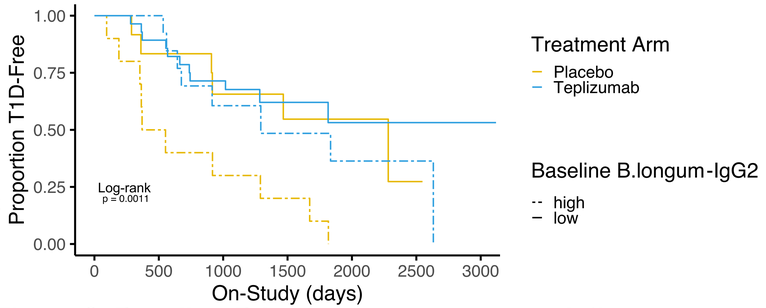

Figure 3. Baseline *B.longum* response association with time to T1D

Baseline ACAb responses, in addition to known T1D risk factors, such as treatment arm, age, *HLA-DR4*, and C – peptide level, improved performance of Cox models in predicting T1D diagnosis.

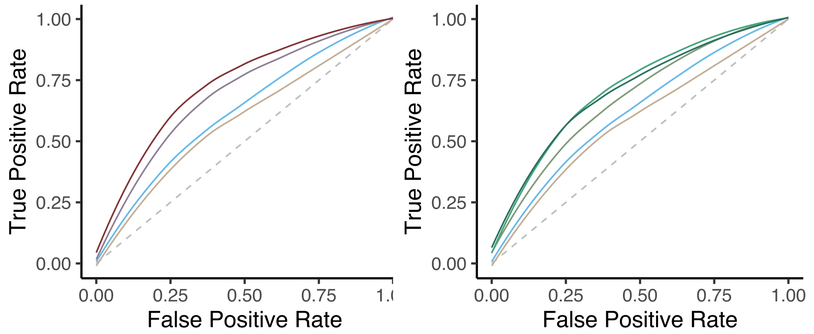

Figure 4. ROC curves for predicted T1D 550 days post-randomization

	Predictors	Integrated AUC	AIC	P value
Model1	Treatment.Arm	0.59	238.51	-
Model2	Age+Treatment.Arm	0.63	237.42	(vs model1) 0.0318
Model3	Treatment.Arm*DR4+Age	0.70	232.61	(vs Model2) 0.01
Model4	Treatment.Arm*DR4+Age+Di.IgG2*DR4	0.73	231.15	(vs Model3) 0.04
Model5	Treatment.Arm+Age+BMI+mu_cpep	0.68	234.61	(vs Model2) 0.009
Model6	Treatment.Arm+Age+BMI+mu_cpep+Ef.IgG2	0.72	230.84	(vs Model5) 0.009
Model7	Treatment.Arm+Age+BMI+mu_cpep+Bl.IgG2	0.71	231.23	(vs Model5) 0.02

Table 1. Predictors and performance metrics of Cox models

References

1. Herold, K. C., et al An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes. New England Journal of Medicine 381, 603–613 (2019).