



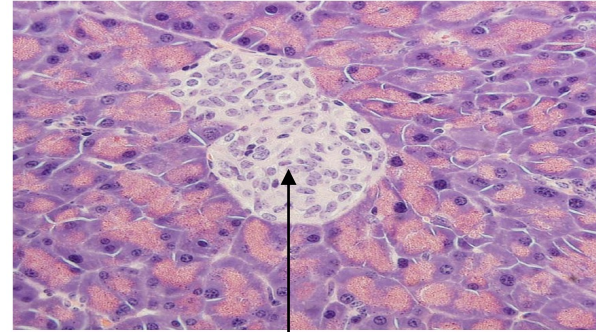
The Influence of IL-4 On T Cell Development And Type One Diabetes

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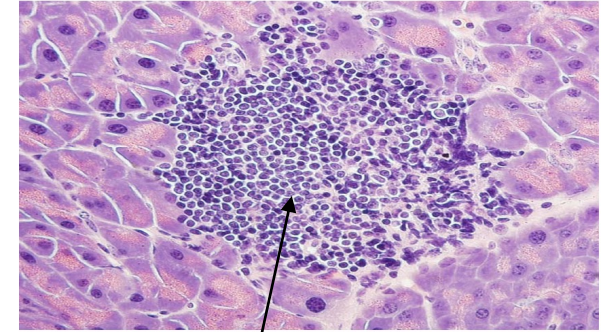
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Background

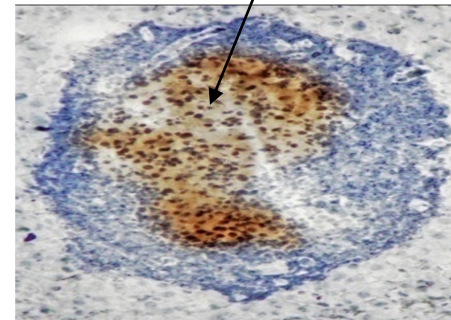
- Type One Diabetes (T1D) is an autoimmune disease in which healthy pancreatic islets are infiltrated by cells of the immune system leading to destruction of the insulin producing pancreatic islets; patients are dependent on insulin for life.
- 1.6 million people in the United States suffer from T1D with 64,000 new cases every year.
- T lymphocytes of the immune system become aggressive and attack the beta cells.



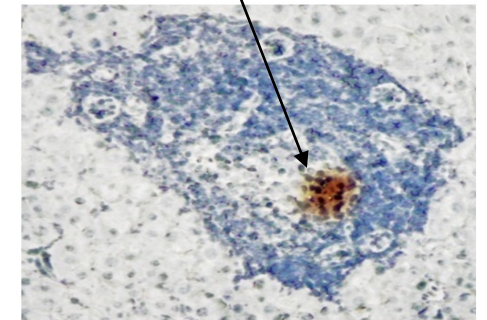
Healthy Intact Islet



Attack Of Islet By The Immune System



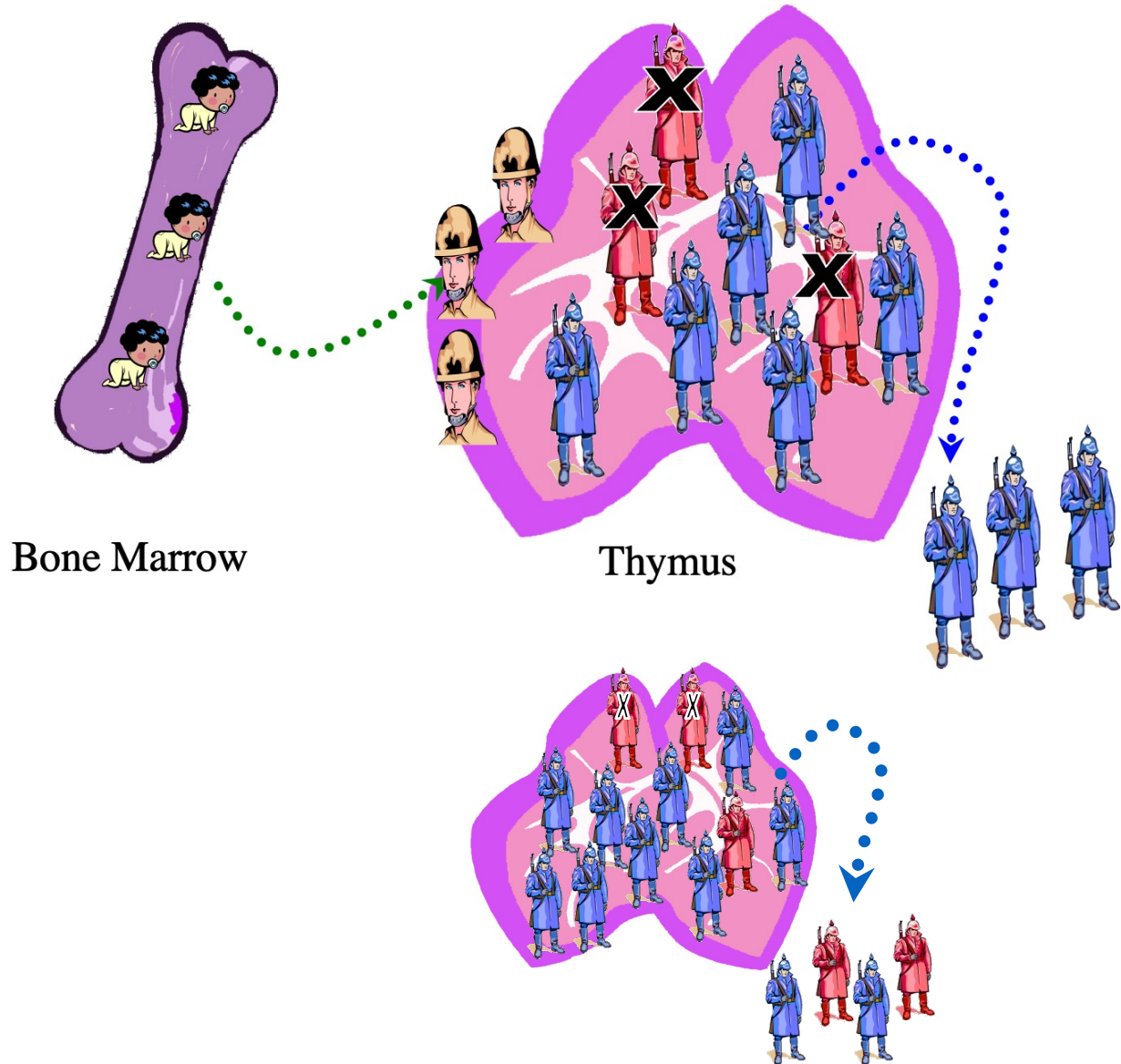
Normal Insulin (Brown Stain)



Diminished Insulin (Smaller Brown Stain)

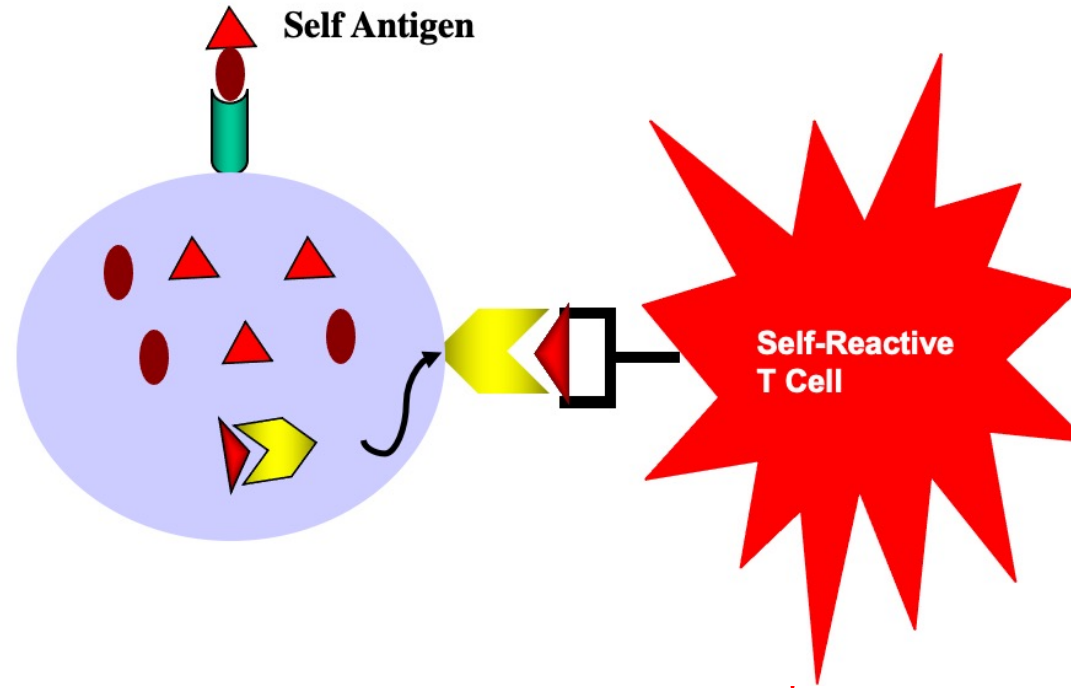
My study investigates the role IL-4 cytokine plays in the development and modulation of aggressive T cells to prevent Type One Diabetes.

T Cell Development



- Stem cell precursors migrate from the bone marrow to the thymus and become Early Thymic Progenitors (ETPs).
- A large portion of ETPs mature into T cells most of which are specific for foreign antigens (**blue soldiers**), and a small number are reactive with self-antigens (**red soldiers**).
- Dendritic cells in the thymus serve as a monitoring system that eliminates self reactive T cells (**negative selection**) but allows T cells specific for foreign antigens (**blue soldiers**) to migrate to the periphery and participate in immune surveillance.
- The monitoring system is imperfect, and some self-reactive T cells (**red soldiers**) can escape **negative selection** and migrate to the periphery with potential to cause autoimmune diseases such as T1D.

Thymic negative selection

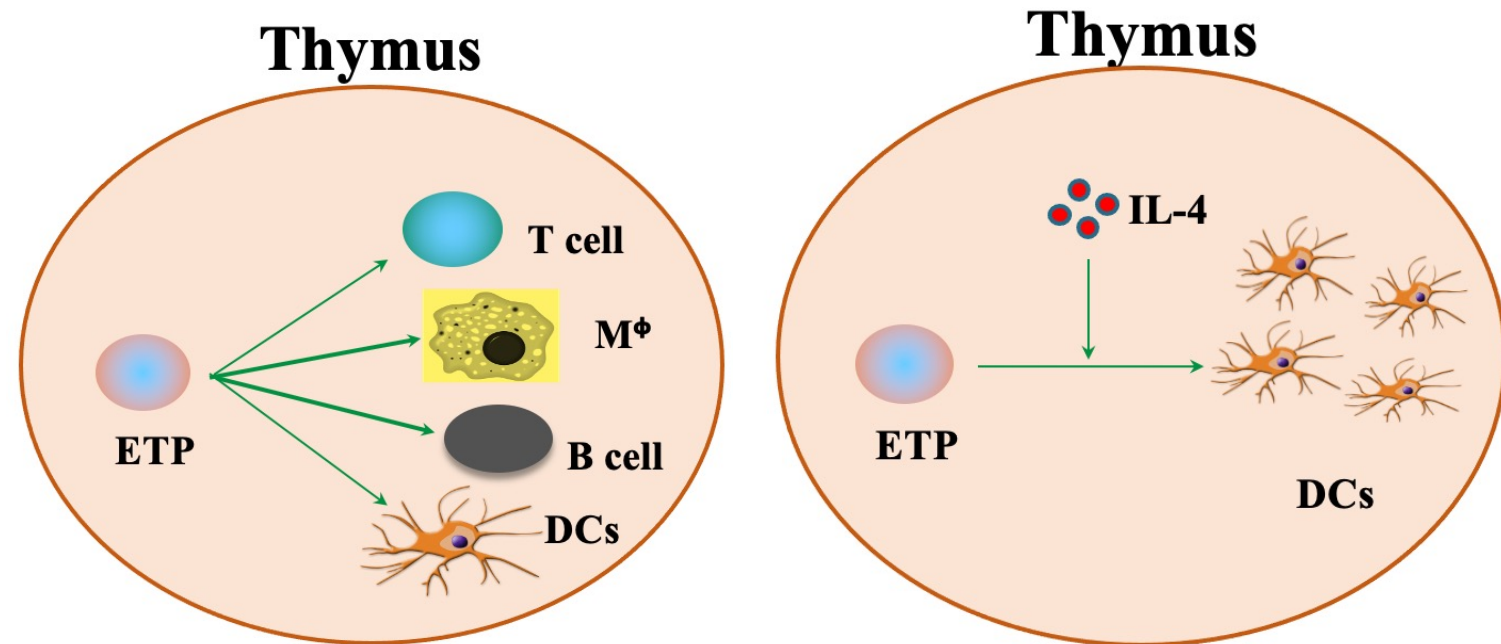


- Dendritic Cells in the thymus present self antigens to T cells.
- Strong recognition of self antigen triggers death of self-reactive T cells.

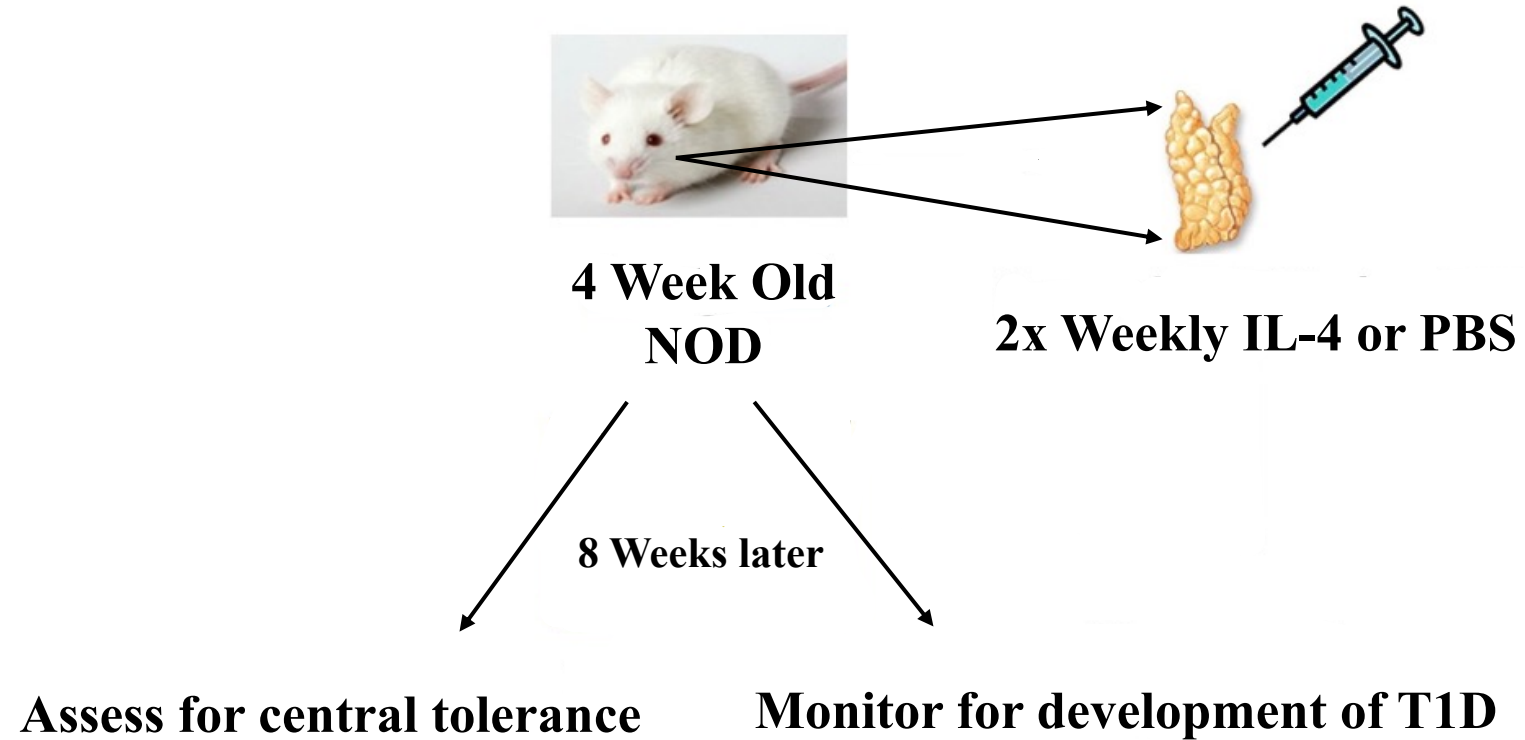
Hypothesis: Intrathymic injection of IL-4 cytokine tightens central tolerance and protects against T1D.

Rationale

- ETPs mature into a variety of cells including T cells, B cells, Macrophages, and Dendritic cells
- IL-4 guides ETPs to mature to Dendritic cells
- ETP derived Dendritic cells enhance central tolerance leading to protection against T1D

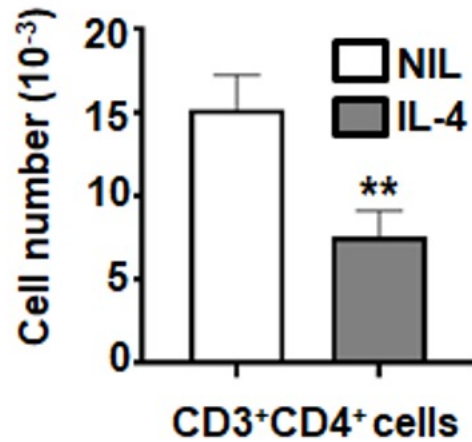


Experimental Procedures

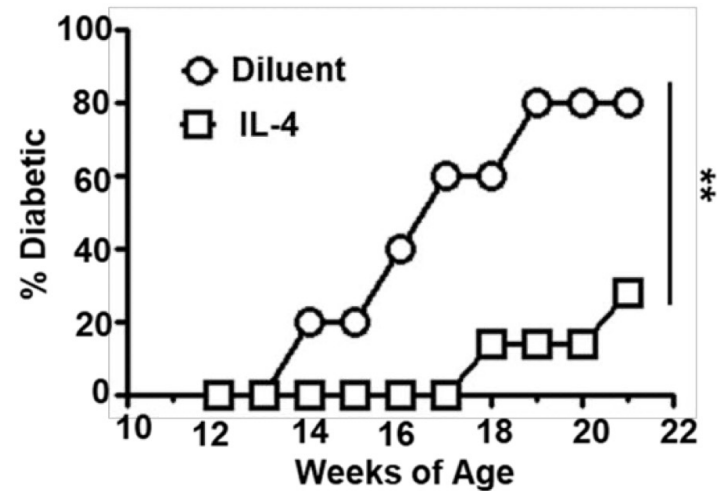


Results

A: IT IL-4 induces central tolerance leading to reduced thymic output of CD4 T cells to the periphery



B: IT IL-4 induces central tolerance leading to protection against T1D



Summary

- IL-4 cytokine given intrathymically guide ETP maturation towards dendritic cells able to enhance negative selection of self-reactive T lymphocytes during development
- The end result is prevention of the onset of T1D
- Currently we are investigating the effect intrathymic IL-4 would have on negative selection of potentially diabetogenic T lymphocytes
- These findings provide support to theories of the hygiene hypothesis, suggesting that microbial infection that trigger IL-4 production in the micro-environment would counter autoimmunity such as T1D

Acknowledgements

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- This study is preformed under the mentorship of my Principal Investigator Dr. Habib Zaghoulani
- My work is carried out under the supervision of former graduate student Alexis N Cattin-Roy and current PhD candidate Caitlyn E Guldenpfennig