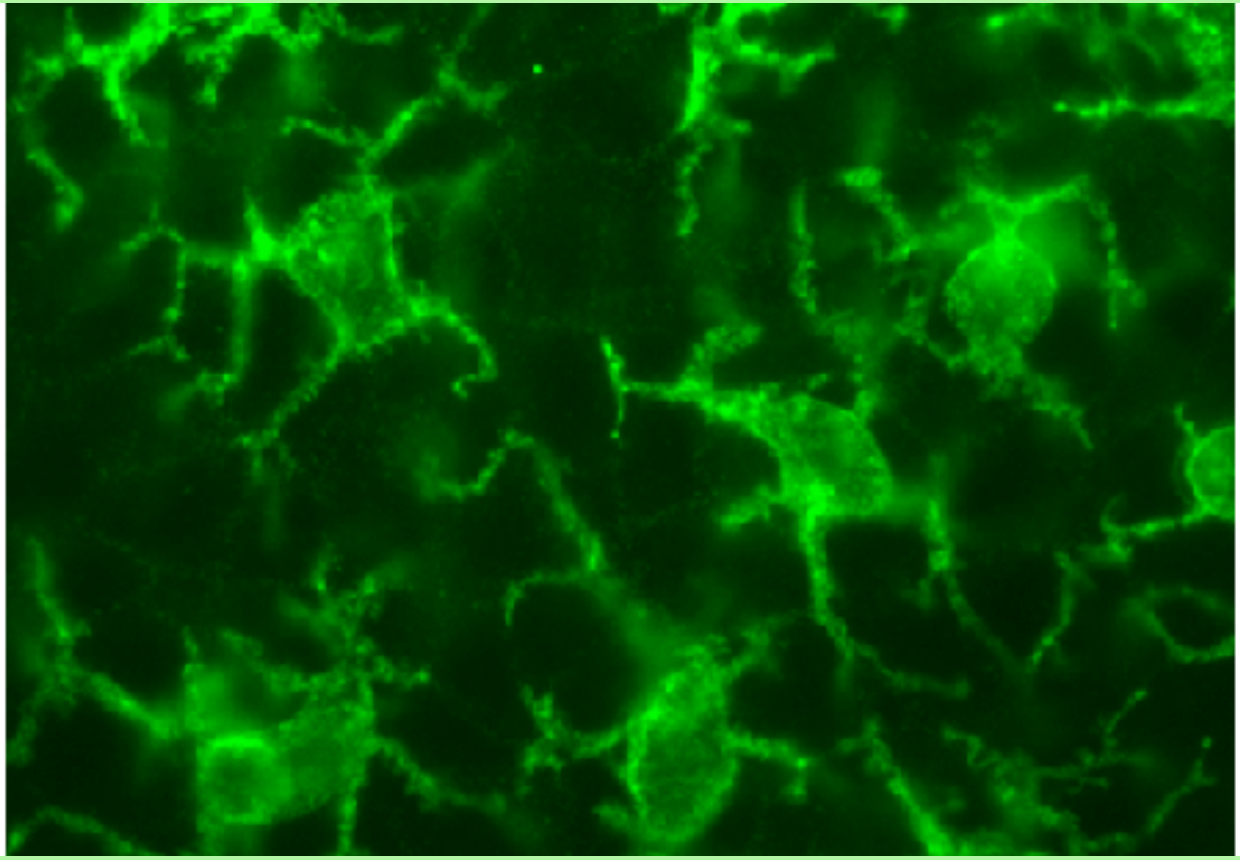
Designing Antigen-specific Immunotherapy for Treatment of Type 1 Diabetes.



Kristin V. Tarbell

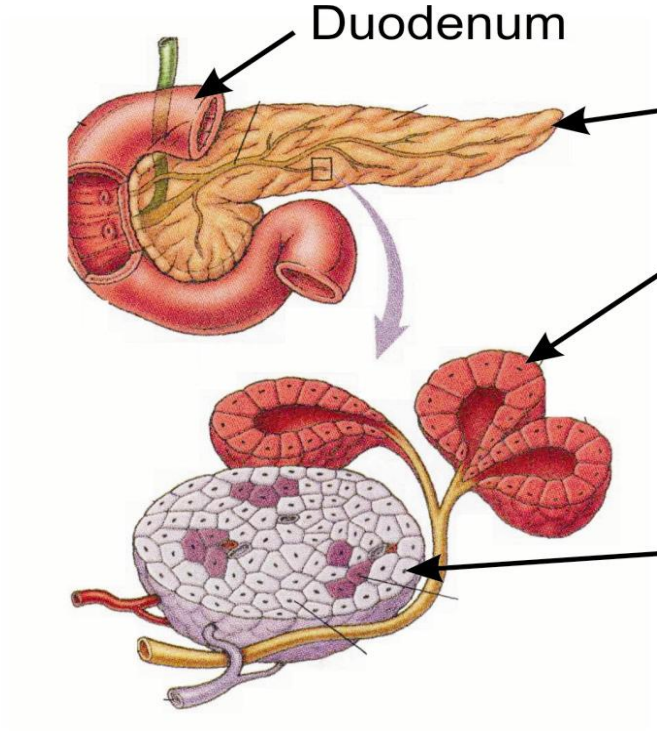
Immune Tolerance Unit,

Diabetes Endocrinology and Obesity Branch, NIDDK

Outline

- **Background on type 1 diabetes**
- **The role of dendritic cells in type 1 diabetes pathogenesis**
- **Current Immunotherapies: global immunosuppression (not antigen-specific)**
- **Our work in mouse models to develop antigen-specific immunotherapies using dendritic cells**

Islets of Langerhans within the Pancreas



In Type 1 diabetes the beta cells are the autoimmune target.

Clinical complications in Type 1 Diabetes Patients

Hyperglycemia (high blood sugar)

Acute effects: Diabetic Ketoacidosis: Low Insulin leads to a shift from carbohydrate to fat metabolism.

Chronic effects: increased risk for heart disease, neuropathy.

Can be minimized by tight blood glucose control.

HbA_{1c}: a measure of average blood glucose.

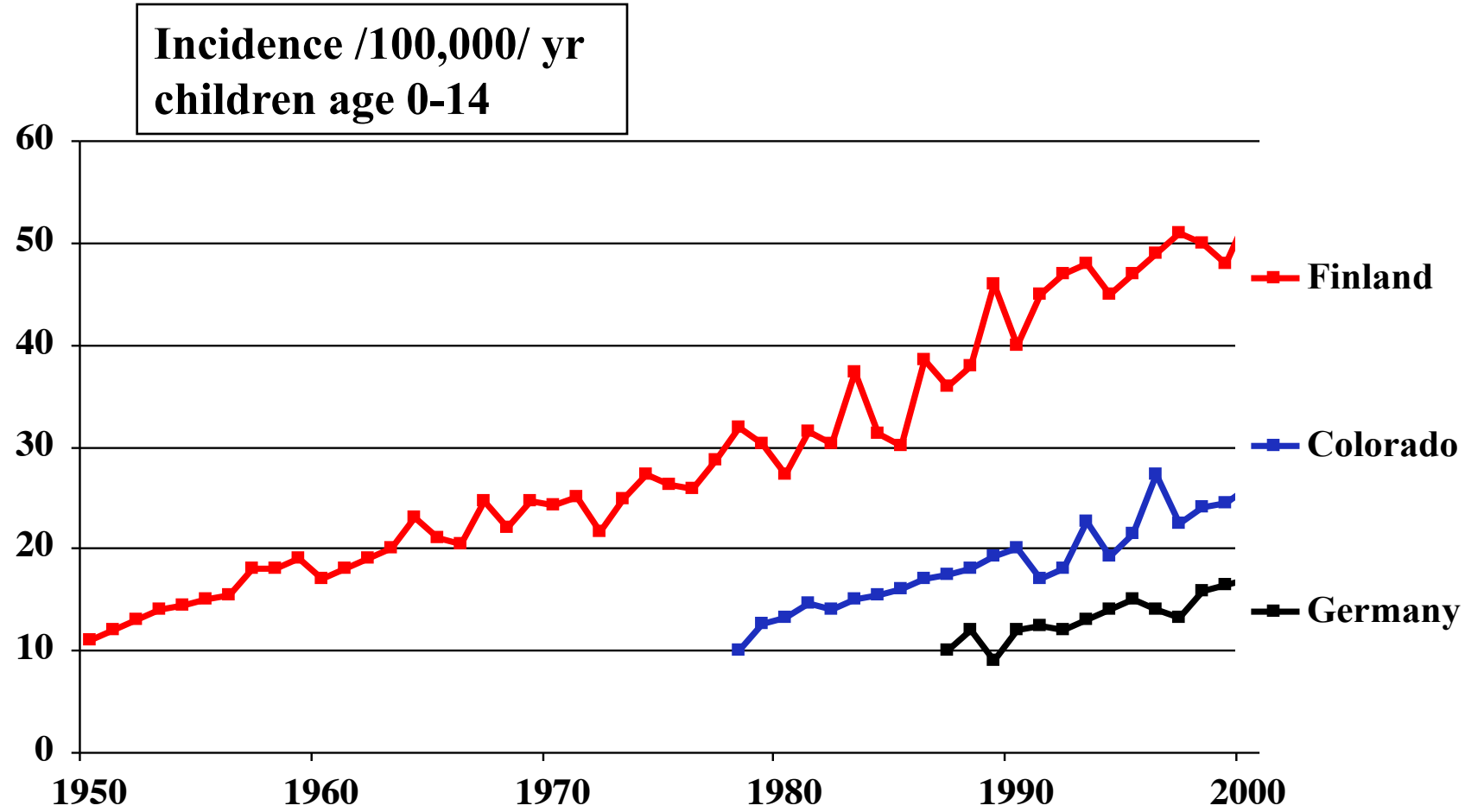
Normal is 5. For T1D, goal is usually <7.

Hypoglycemia

The brain is the most sensitive to low blood glucose.

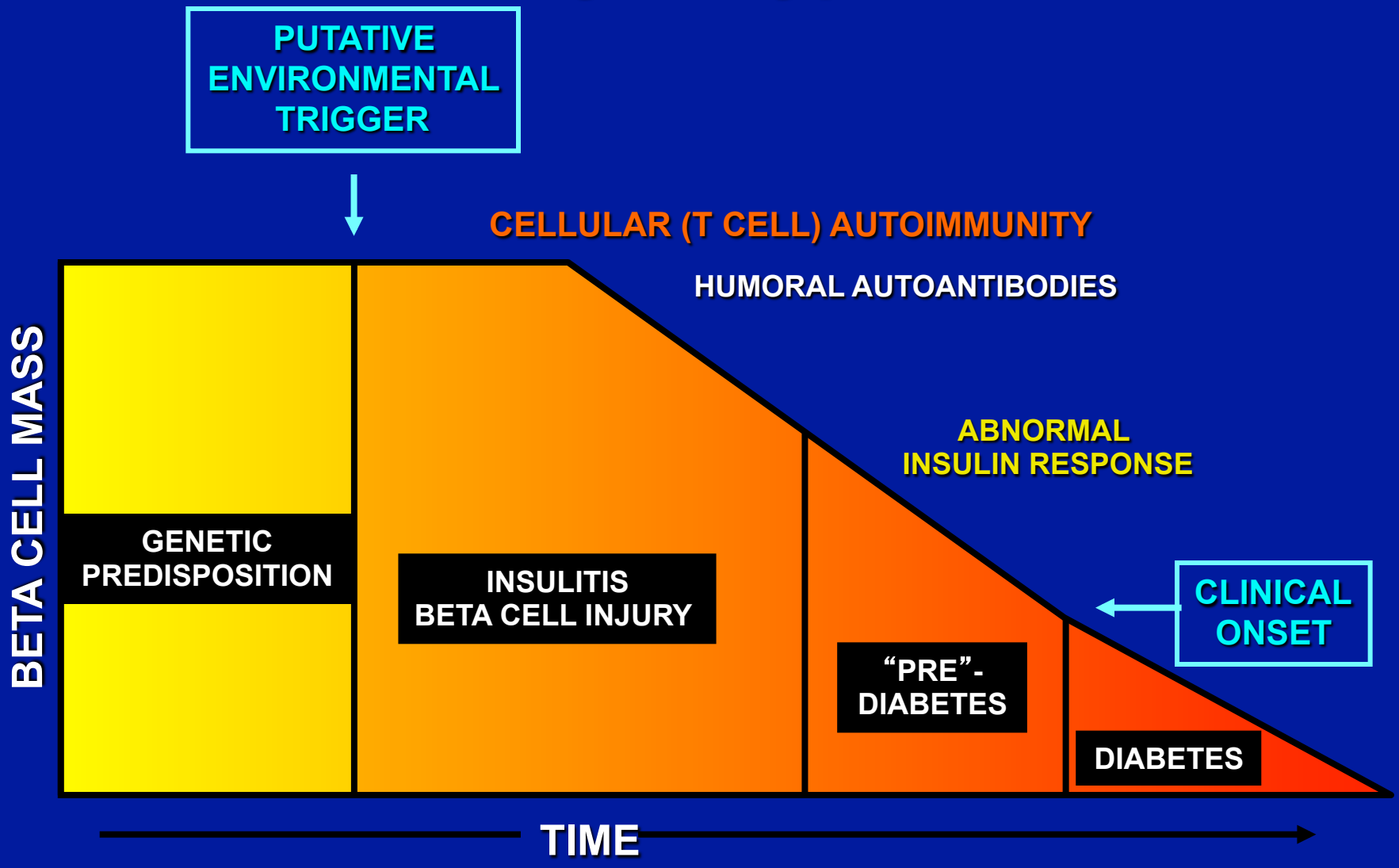
Some T1D patients are hypoglycemic unaware, and blood glucose is lowest at night. (increases mortality)

Type 1 Diabetes incidence is rising 3-5% /year



Rewers

Natural History of Type 1 Diabetes



Slide from Barbara Davis Center for Childhood Diabetes

Dendritic cells (DCs) are professional antigen presenting cells

Dendritic Cell

+ Antigen

+ costimulation or cytokine

TOLERANCE

Regulatory T cell expansion/ induction
Anergy or deletion

Imbalance of tolerance vs immunity = autoimmunity

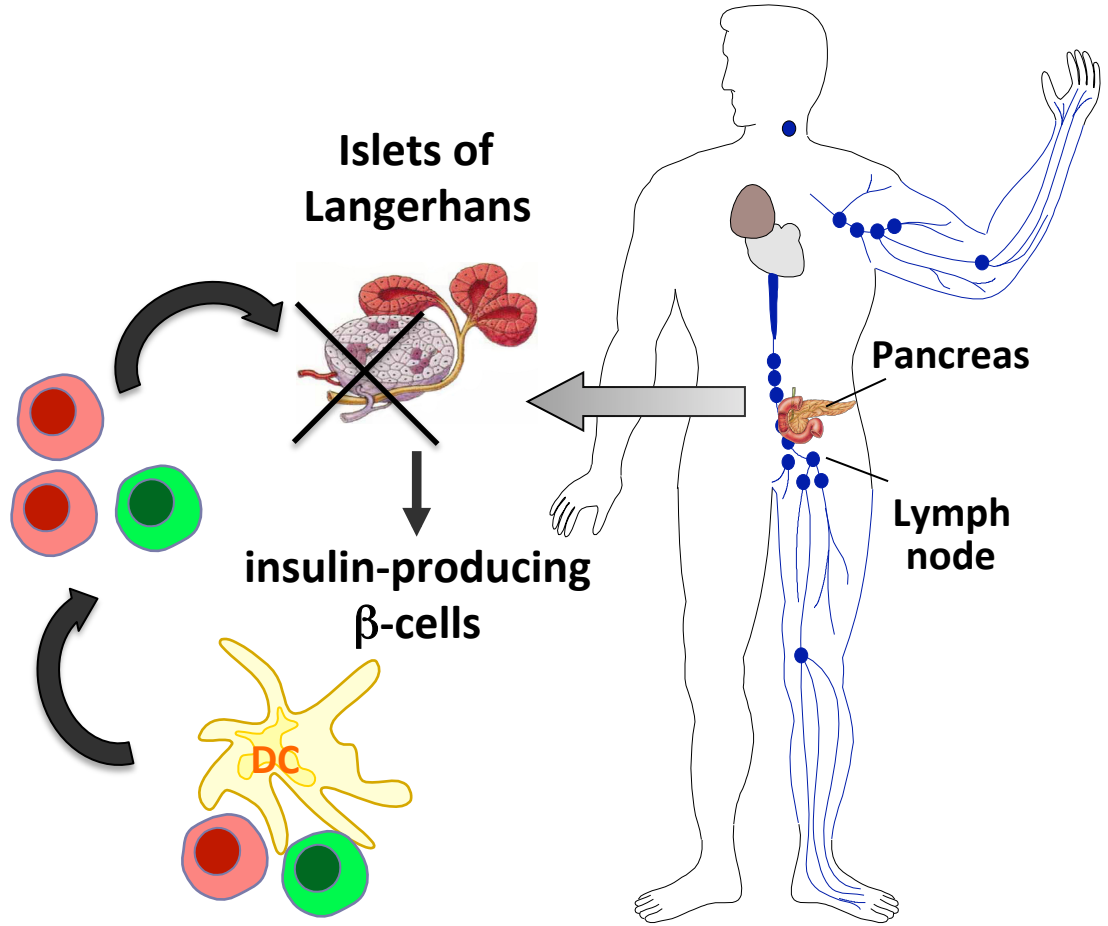
IMMUNITY

Effector T cell expansion and differentiation

- **Innate immunity – DCs respond to environmental signals such as pathogens.**
- **Adaptive immunity – DCs take up, process, and present antigen via peptide-MHC complexes to T cells.**

Goal: To use DCs to induce antigen-specific T cell tolerance for treatment of autoimmune diabetes.

Type 1 Diabetes Pathogenesis



Beta-cell-specific CD4+ and CD8+ Effector T cells (T_{eff})

Aberrant activation of self-specific T cells

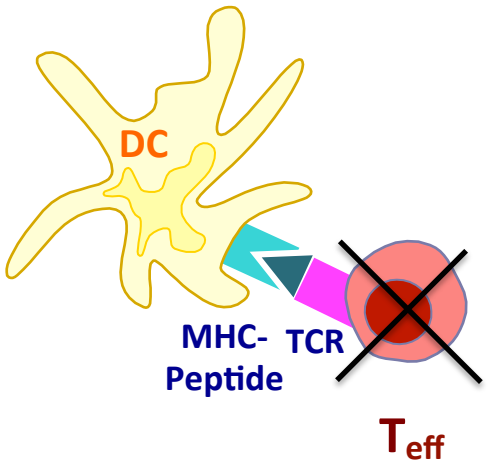
Failure of peripheral tolerance mechanisms

Non-Obese Diabetic (NOD) mice:
80% of females develop spontaneous autoimmune diabetes

Dendritic Cells are Important for Induction of Peripheral T cell Tolerance

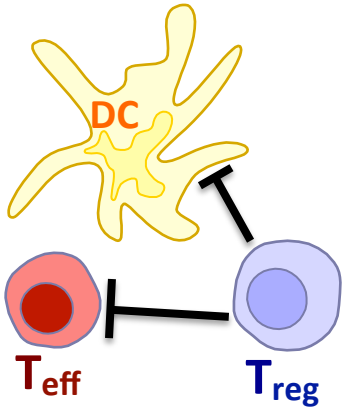
Anergy or Deletion

Pathogenic cells become unable to respond, or die after antigen exposure from DCs



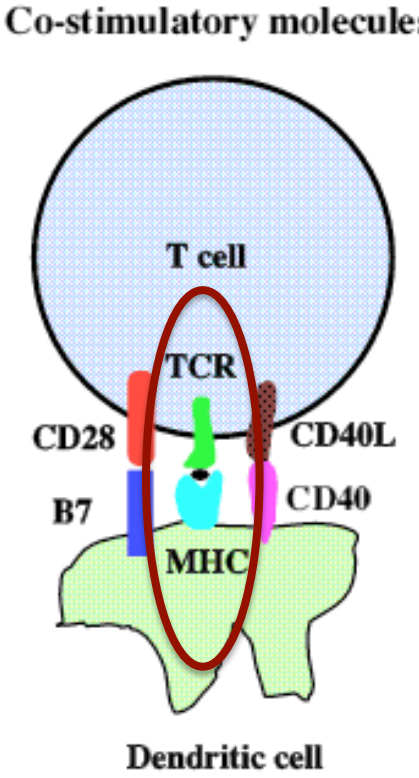
Regulatory T cells

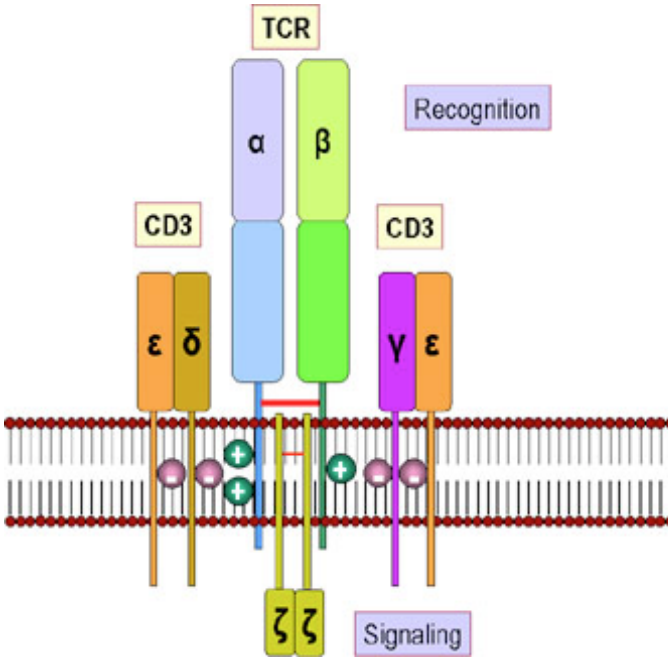
Regulatory T cells turn off pathogenic cells via effects on both dendritic cells and T cells.



DCs are important stimulators of Treg proliferation and activation

One approach to treating T1D is to alter T cell responses with antibodies specific for CD3 (anti-CD3)

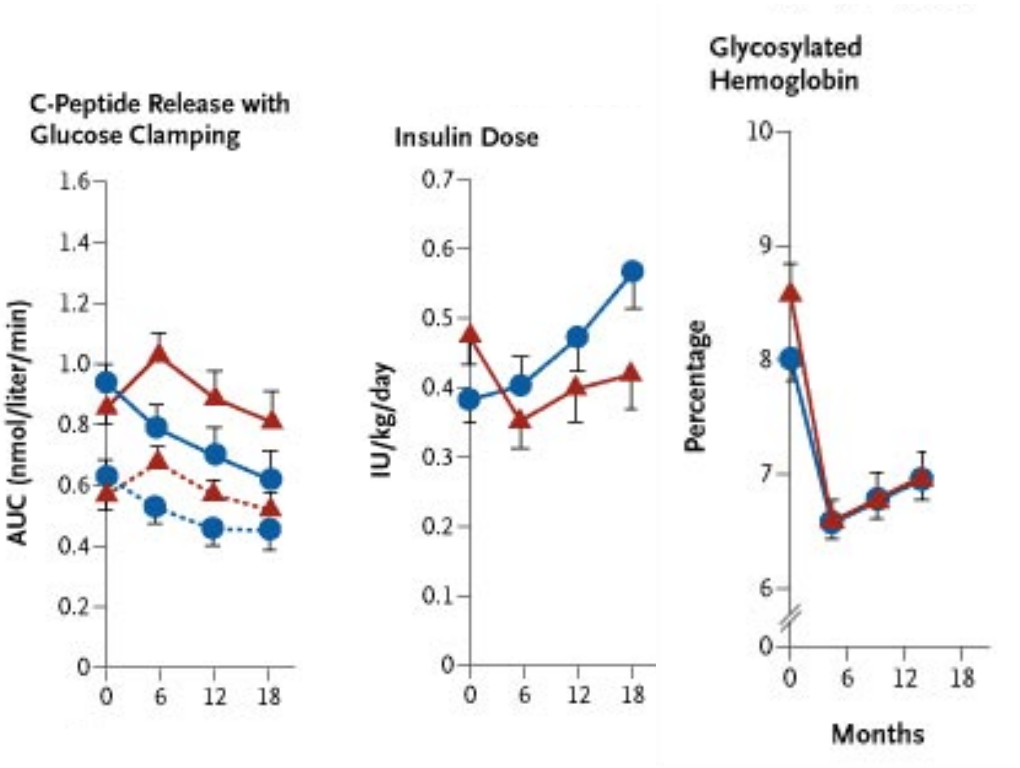




Anti-CD3 may work by inducing cell death in pathogenic T cells or increasing regulatory T cells

This treatment affects all T cells: not antigen-specific

Anti-CD3 slightly preserves insulin (C-peptide) release in new onset type 1 Diabetics



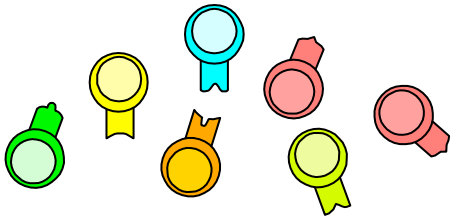
But average blood glucose levels are the same

Blue= placebo **Red=anti-CD3**

Keymeulen et al. 352 (25): 2598, NEJM 2005

A recent Phase 3 trial failed to show efficacy, but a much lower dose was used because of toxicity concerns.

Advantages of Antigen-Specific Therapy

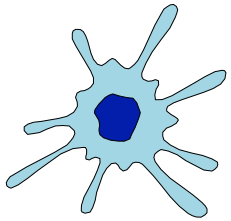


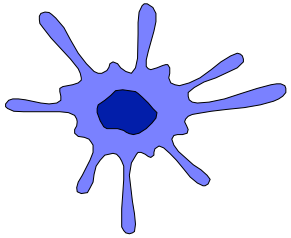
A vast lymphocyte repertoire = many clones, each specific e.g., for a microbial, tumor, self or environmental antigen

Valuable antibody - based therapies for autoimmunity e.g., anti-TNF, anti-CD3

But these therapies are antigen non-specific and can potentially dampen responses against microbial or tumor antigens as well.

Dendritic Cells Subsets: CD8+ and CD11b+ DCs



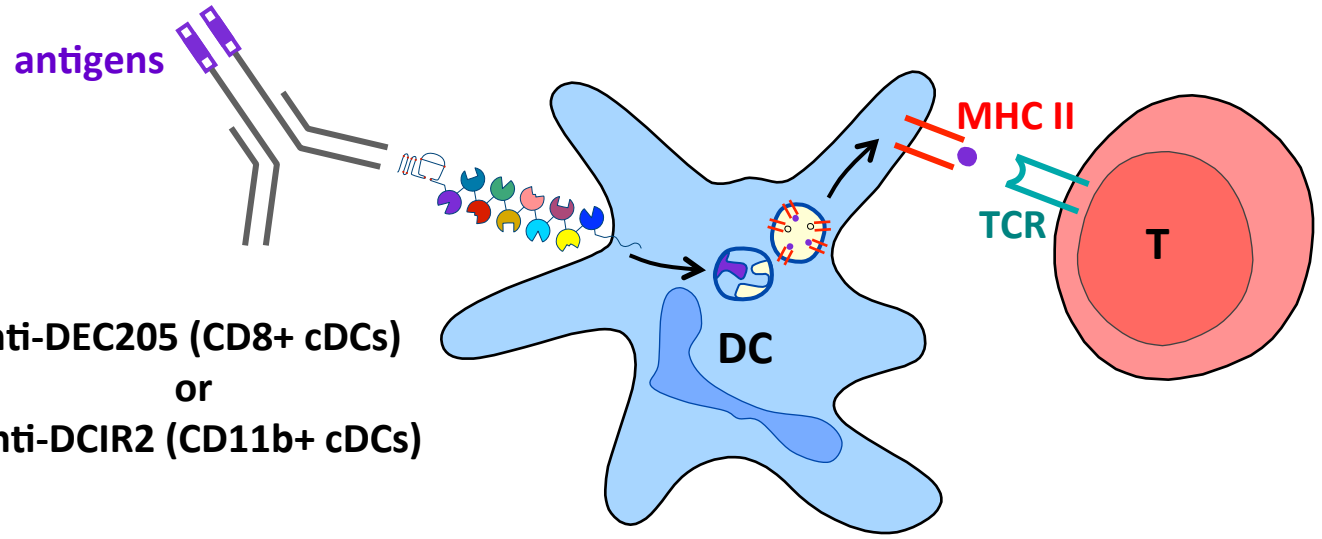


	CD8+ cDCs	CD11b+ cDCs
Other markers:	**DEC-205+**	**DCIR2+**
Immunogenic functions:	**Can cross-present extracellular antigens to CD8+ (cytotoxic) T cells**	**Strong stimulation of CD4+ (helper) T cells**
Tolerogenic functions:	**induces Tregs via TGFβ** **Uptake of apoptotic cells**	**and Tregs**

Both subsets can induce deletion or anergy to antigen presented absent inflammation

What pathogenic/ tolerogenic roles do these DC subsets have for autoimmune diabetes?

Targeting beta cell Autoantigens to Dendritic Cells in vivo



Immunity
(with other activating signals)

or

Tolerance
(antigen alone: steady-state)

Does steady-state targeting of beta cell antigens to DCs induce tolerance during chronic autoimmunity?

Can we create a tolerogenic vaccine to turn off the autoreactive T cell responses that induce pathology in T1D patients?

How do CD4 T cells respond to DC-targeted antigen in the context of autoimmune diabetes?

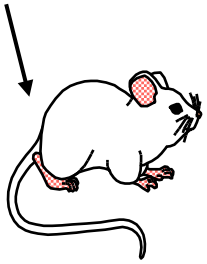
Use autoreactive CD4+ TCR transgenic T cells specific for a beta cell antigen.

Thy1.1+ beta cell-specific CD4+ T cells

Thy1.2 NOD

1 day

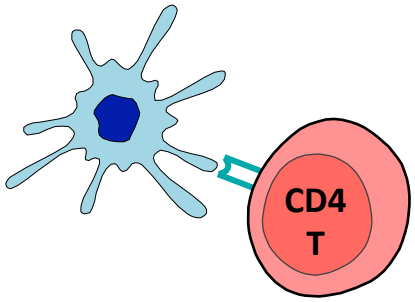
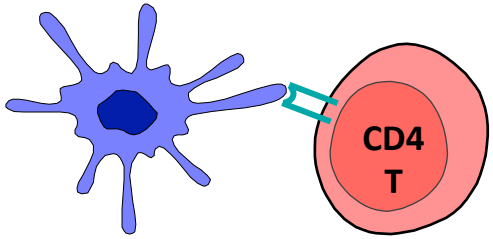
Anti-DEC205 or anti-DCIR2 conjugated to beta cell antigen



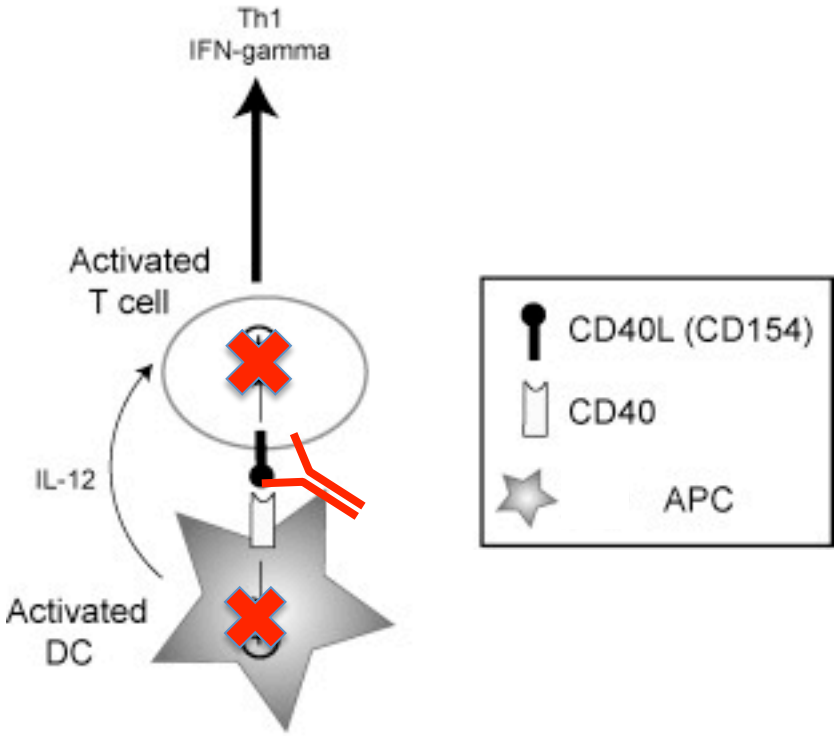
3-10 days

Harvest lymphoid tissue, measure T cell responses

T Cell Responses After Targeting Antigen to cDCs

	Self Antigen in autoimmune NOD mice	Model Antigen in wildtype mice
CD8+DEC-205+ 	No Tolerance: continued expansion and cytokine production	Tolerance: deletion, anergy, and/ or Treg induction
CD11b+DCIR2+ 	Tolerance: Some initial proliferation/ expansion followed by partial deletion, but almost no cytokine production.	Tolerance: deletion, anergy, and/ or Treg proliferation

Interactions between CD40L on activated T cells and CD40 on DCs enhances immunity

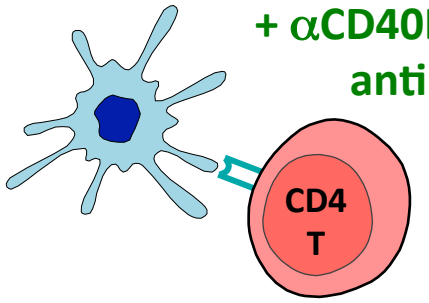


Would blocking this interaction help restore tolerance when given with DC-targeted antigen?

T Cell Responses After Targeting Antigen to cDCs

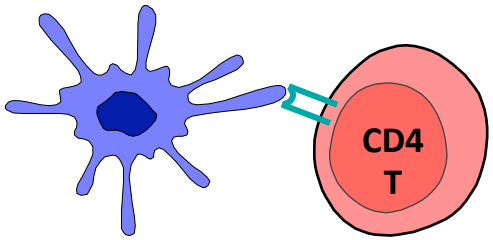
Self Antigen in autoimmune NOD mice

CD8+DEC-205+



Tolerance: initial proliferation followed by partial deletion, but without cytokine production.

CD11b+DCIR2+



Tolerance: Some initial proliferation/ expansion followed by partial deletion, but almost no cytokine production.

Acknowledgements

Next steps:

- **Test whether targeting beta cell antigens to either DC subset (with or without αCD40L) can alter diabetes development.**
- **Try inhibiting other proinflammatory signals.**
- **Find better ways to deliver inhibitory signal**

Current lab members

Jeff Price
Cosima Kretz

Alan Guerrero
Barret Zimmerman
Anjana Sinha

Former lab members

Annie Lau-Kilby
Grace Linder
Angel Li