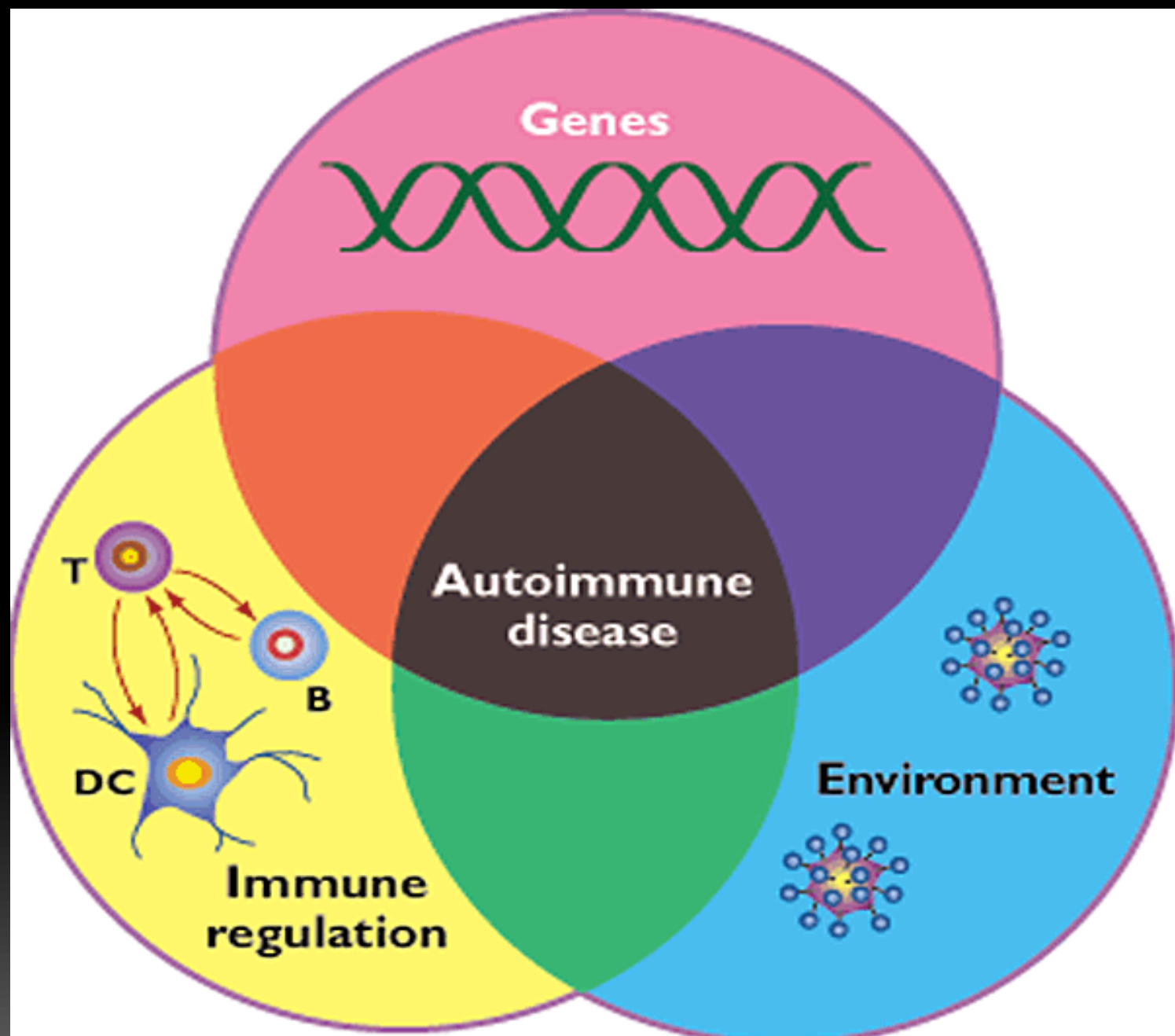


Prevention of autoimmune diseases

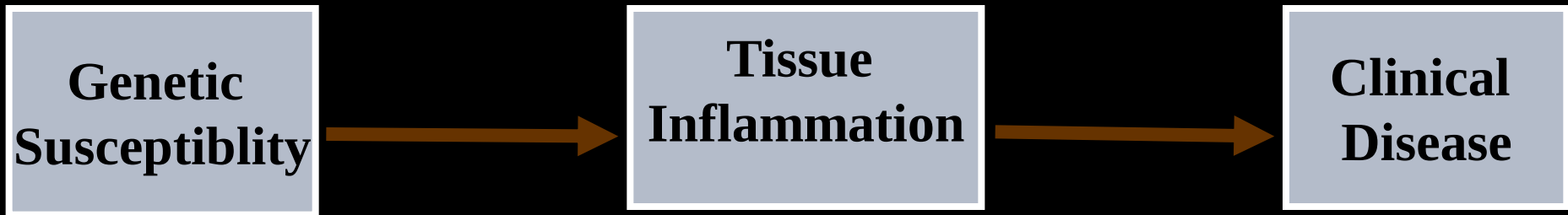
Professor David Leslie

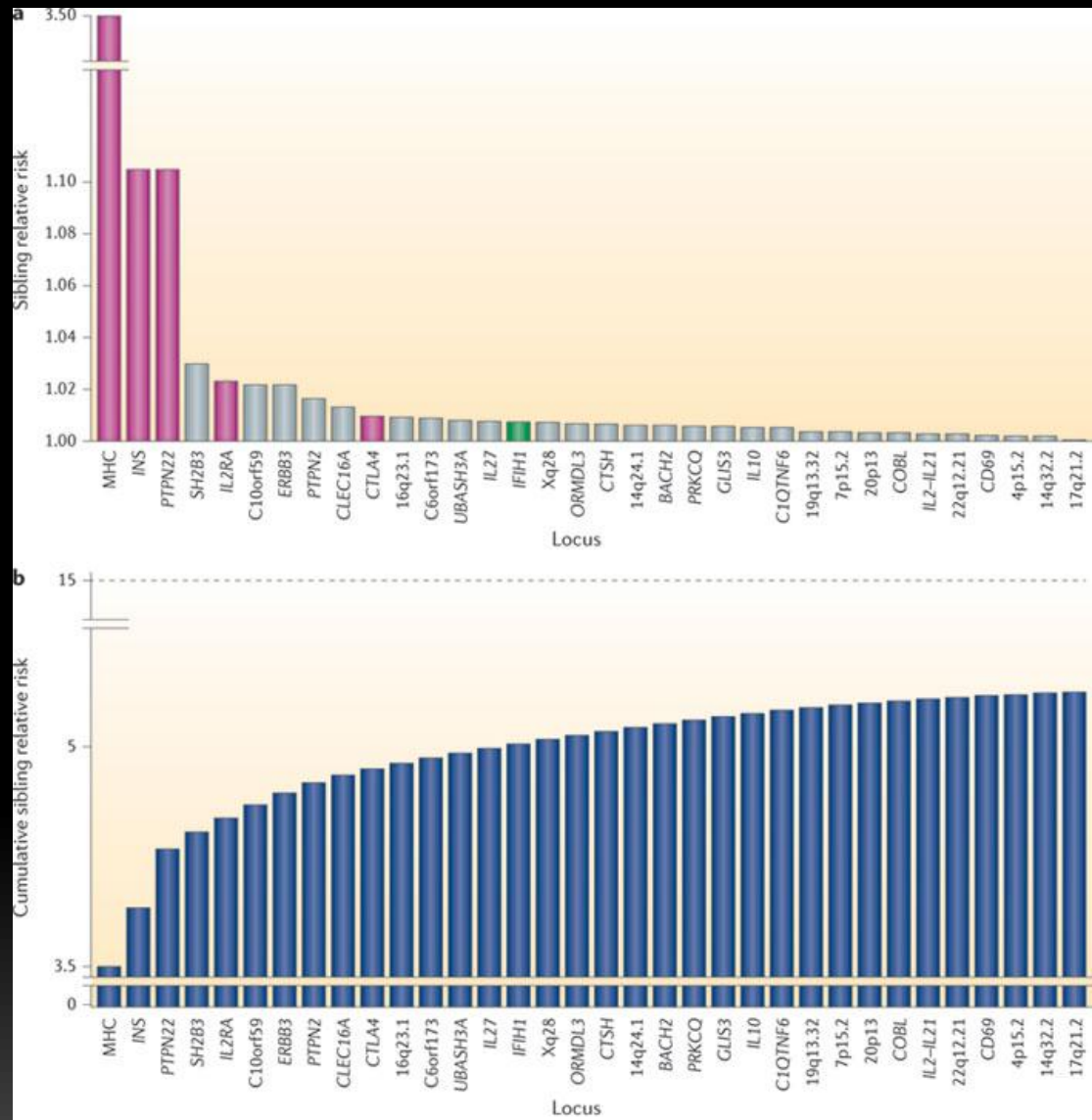
Blizard Institute, University of London
and St Bartholomews Hospital

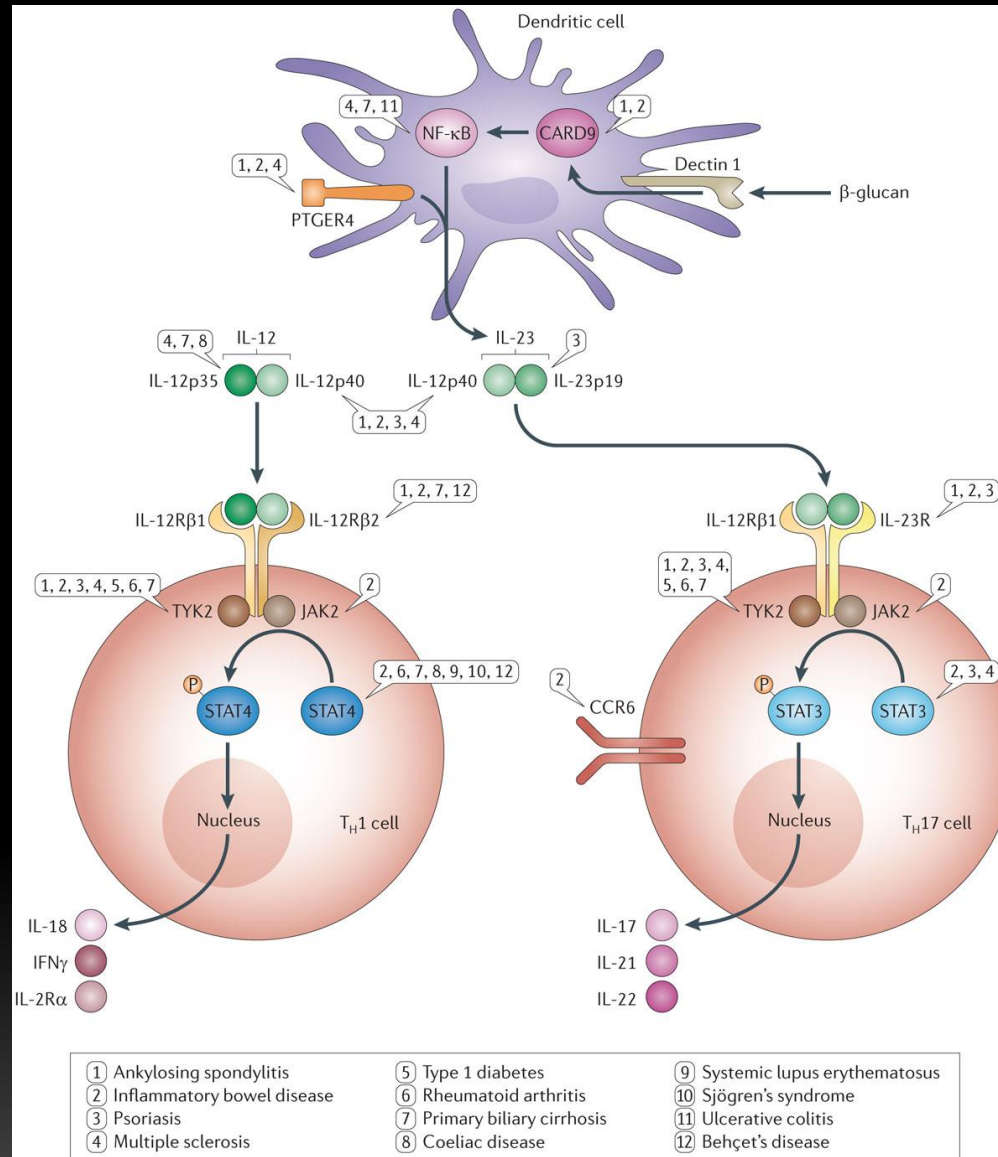
Disclosures: Advisory Board Diamyd, Andromeda



Autoimmune Disease- a minimal model







Pathogenesis of autoimmune diseases

- Induction
- Activation
- Homing
- Destruction



Pathogenesis of autoimmune diseases

- Early
- Immune Response
- Chronic/Persistent



From: **Seroconversion to Multiple Islet Autoantibodies and Risk of Progression to Diabetes in Children**

JAMA. 2013;309(23):2473-2479. doi:10.1001/jama.2013.6285

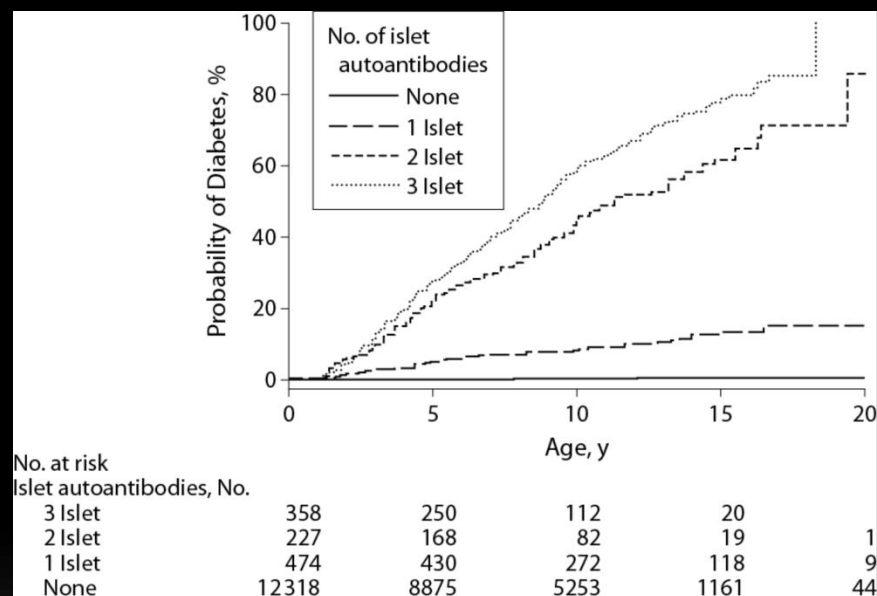
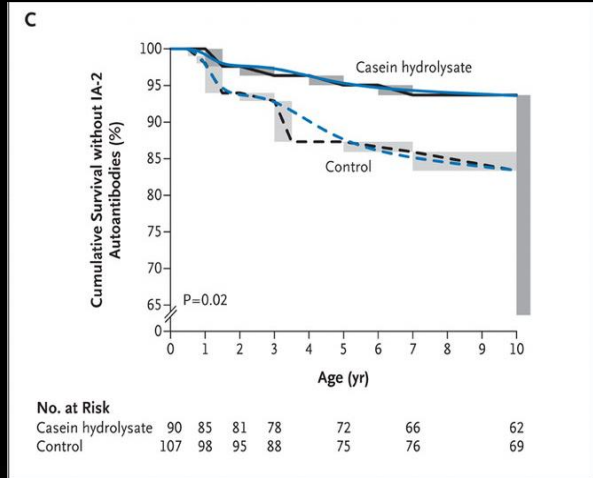
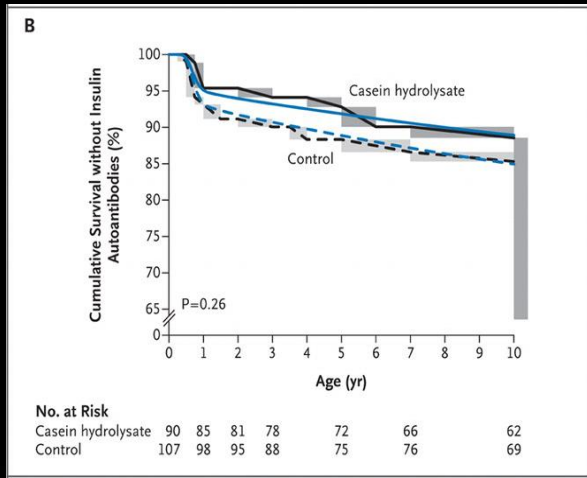
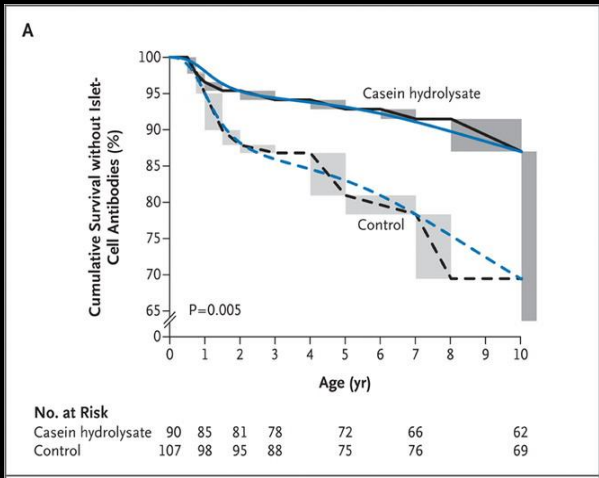


Figure Legend:

The numbers at risk represent the children receiving follow-up at age 0, 5, 10, 15, and 20 years.

Cumulative Incidence of Islet-Cell Antibodies According to Casein or Cows Milk Exposure



Knip M et al. *N Engl J Med* 2010;363:1900-1908.

Pathogenesis of autoimmune diseases

- Early
- Immune Response
- Chronic/Persistent

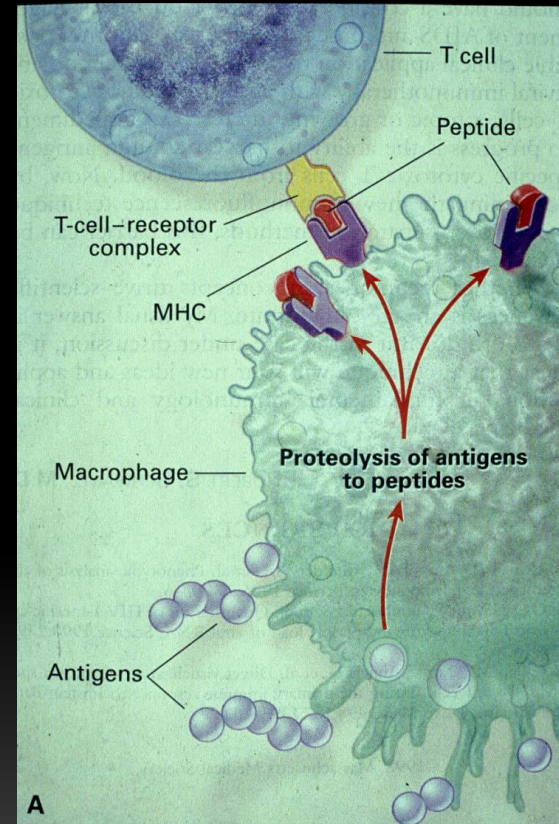


Pathogenesis of autoimmune diseases

- Induction
- Activation
- Homing
- Destruction

Immune Response

- Innate Immunity
 - Macrophage
- Adaptive Immunity
 - T cells
 - B cells



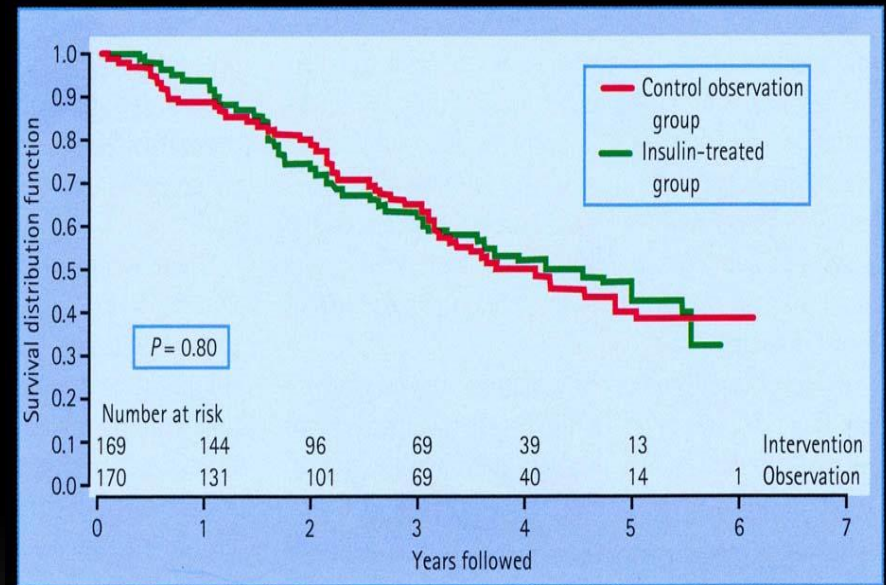
DPT-1 Study Design

- Double-blind randomized placebo controlled
- First degree relatives of children with type 1 diabetes
- Risk defined as 5 year risk of type 1 diabetes > 50%

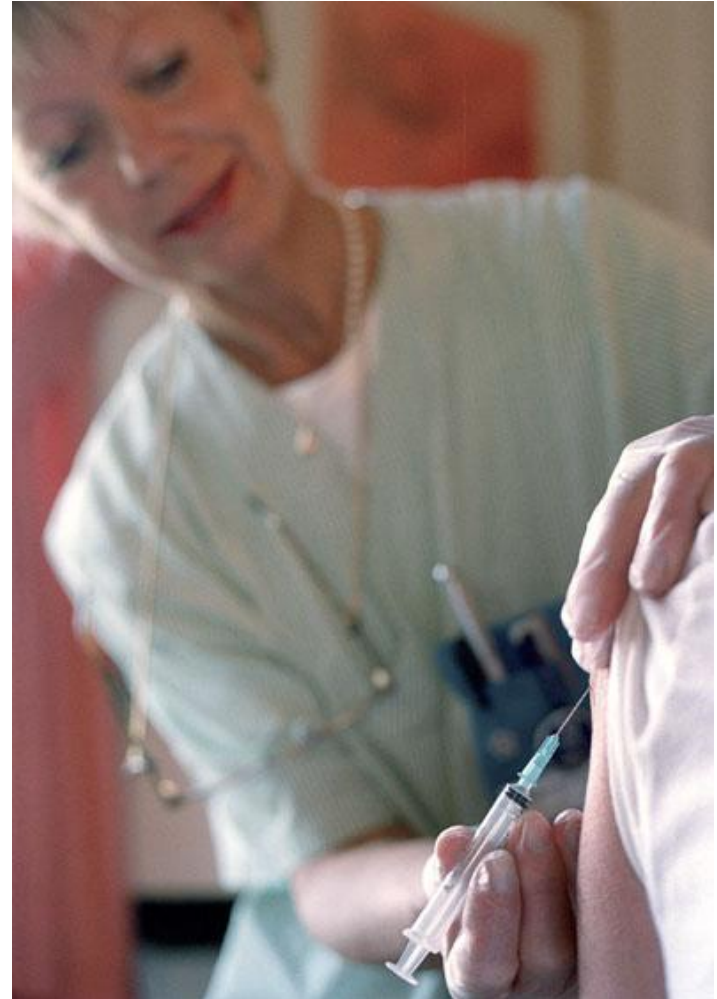
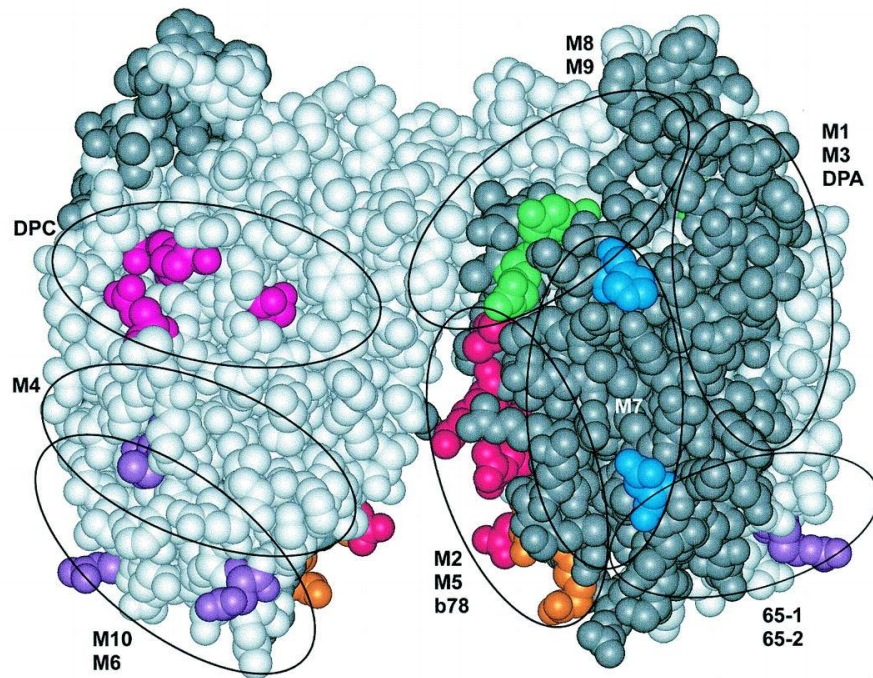


Prevention of Type 1 Diabetes

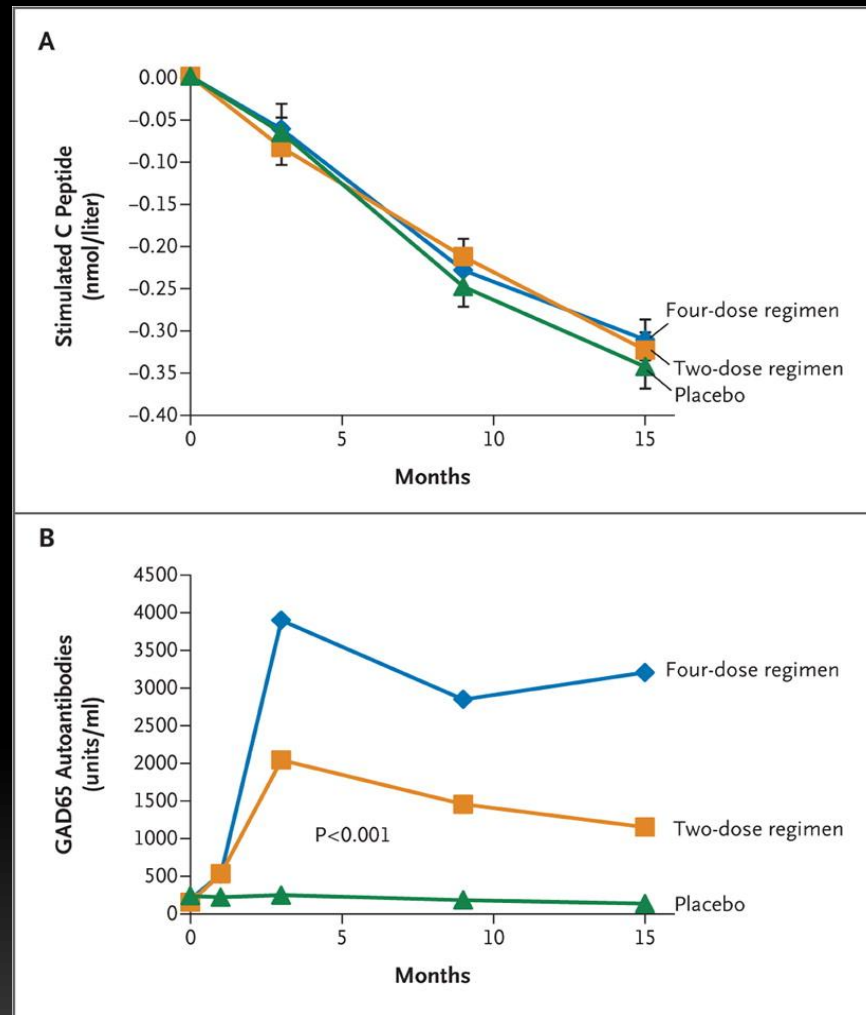
- progression as predicted
- no effect of insulin using this regime



A Phase II Clinical Trial With Alum-Formulated rhGAD65

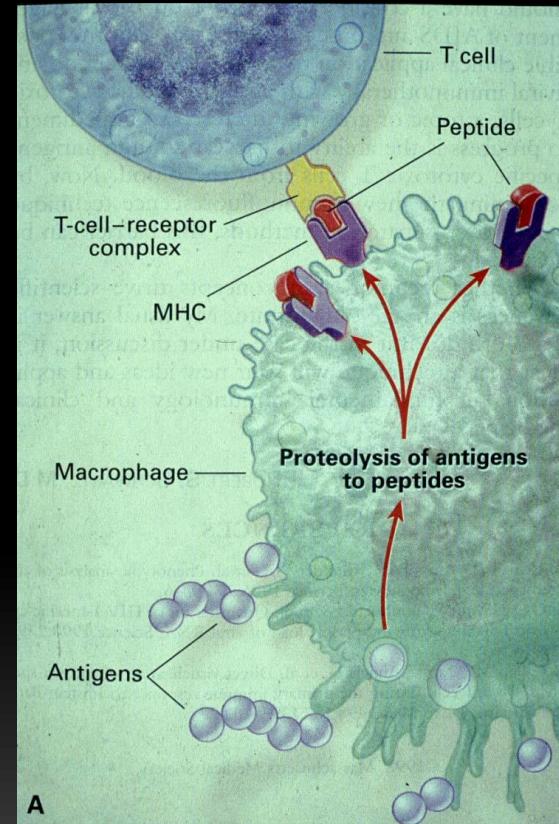


C-Peptide and GAD65 Autoantibody levels, According to Study Group



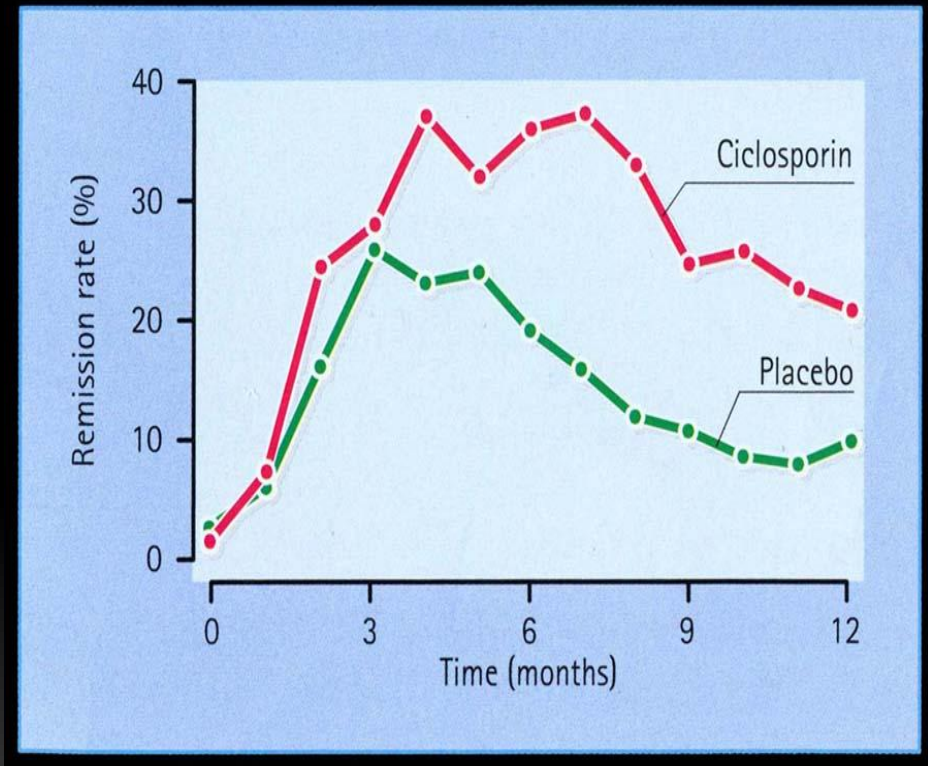
Immune Response

- Innate Immunity
 - Macrophage
- Adaptive Immunity
 - T cells
 - B cells

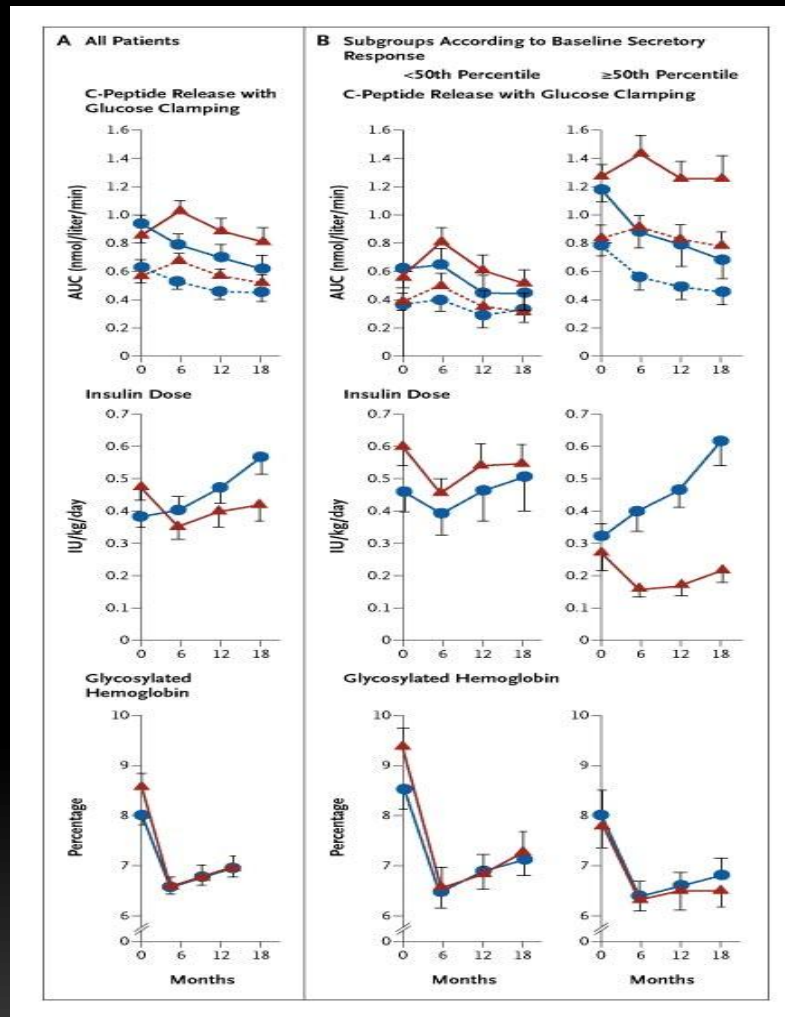


Phase 2 Cyclosporin Trial

- Newly-diagnosed type 1 diabetes
- Cyclosporin orally
- Follow-up



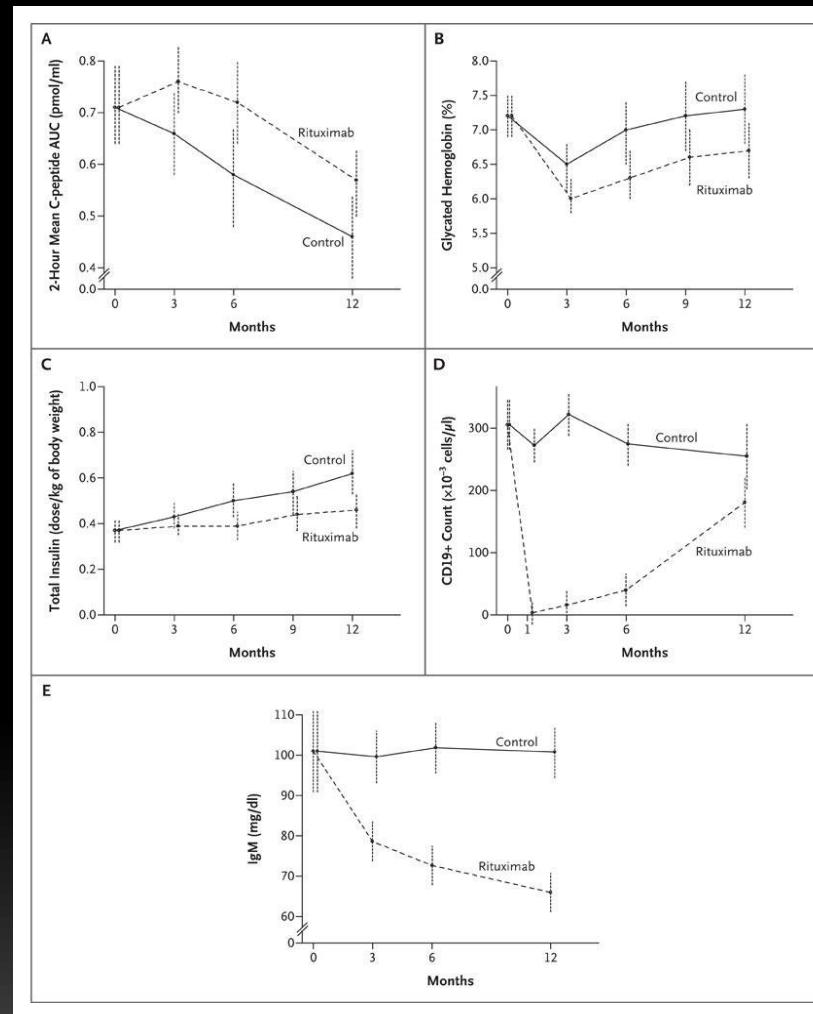
Phase 2 Anti-CD3 Trial



■ Anti-CD₃

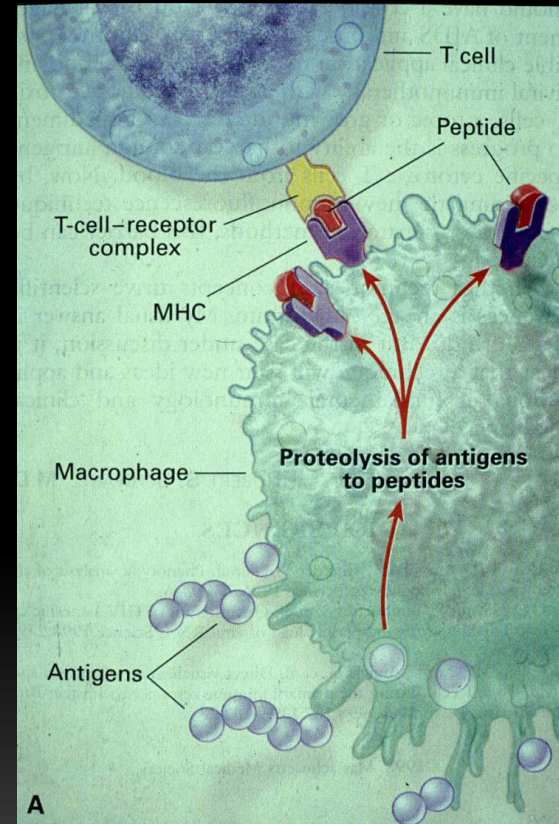
■ Control

Effects of Rituximab on C-Peptide Level, Glycated Hemoglobin Level, Insulin Dose Required, CD19+ Cell Counts and IgM Level

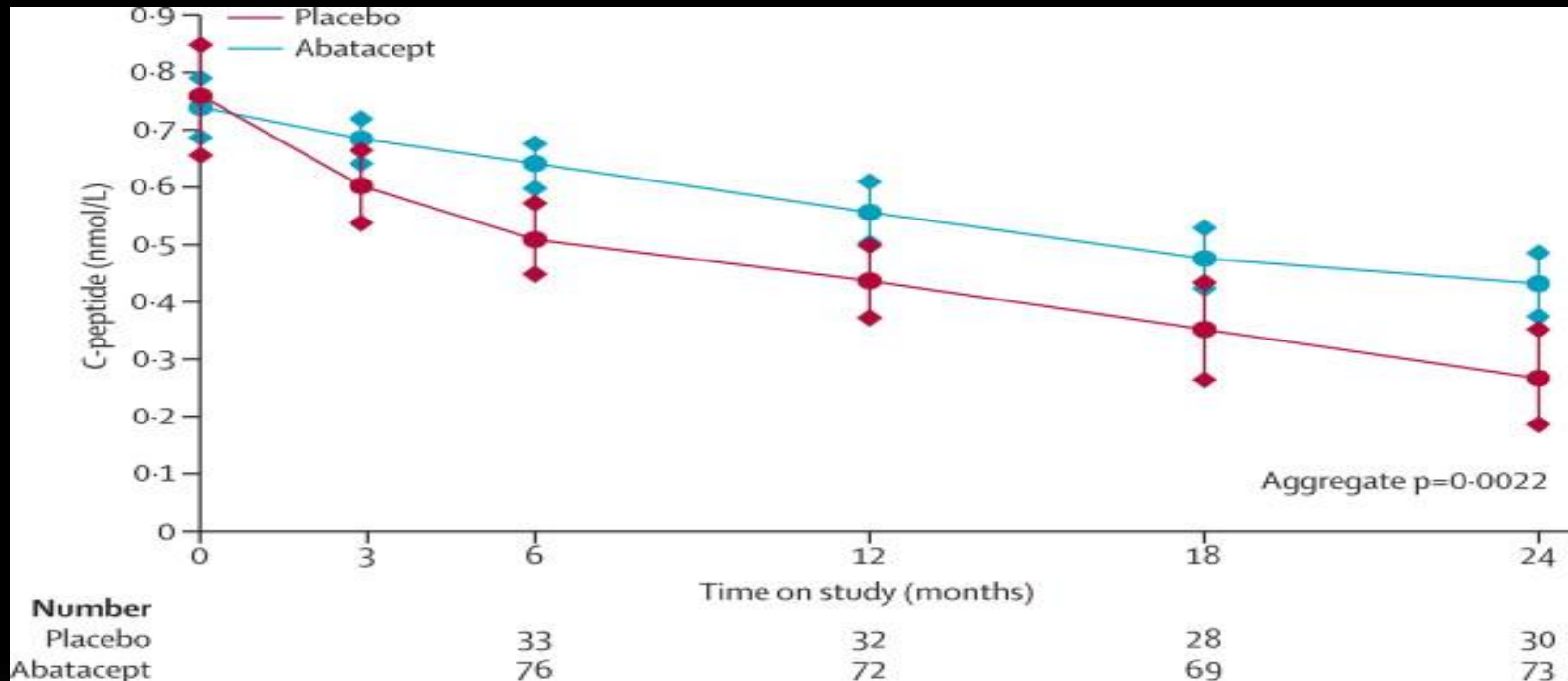


Immune Response

- Innate Immunity
 - Macrophage
- Adaptive Immunity
 - T cells
 - B cells



Phase 2 Anti-CTLA4 Results



Tihamer Orban , Brian Bundy , Dorothy J Becker , Linda A DiMeglio , Stephen E Gitelman , Robin Goland , Peter A G...

Co-stimulation modulation with abatacept in patients with recent-onset type 1 diabetes: a randomised, double-blind, placebo-controlled trial

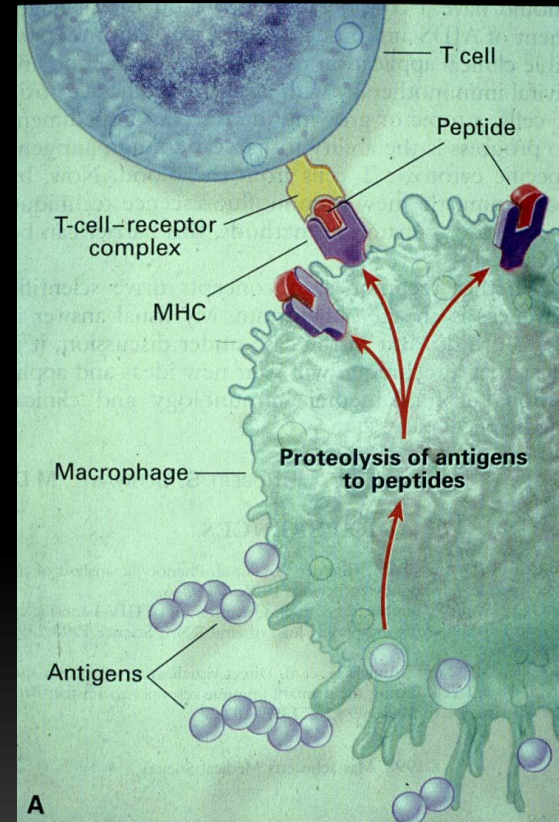
The Lancet Volume 378, Issue 9789 2011 412 - 419

[http://dx.doi.org/10.1016/S0140-6736\(11\)60886-6](http://dx.doi.org/10.1016/S0140-6736(11)60886-6)

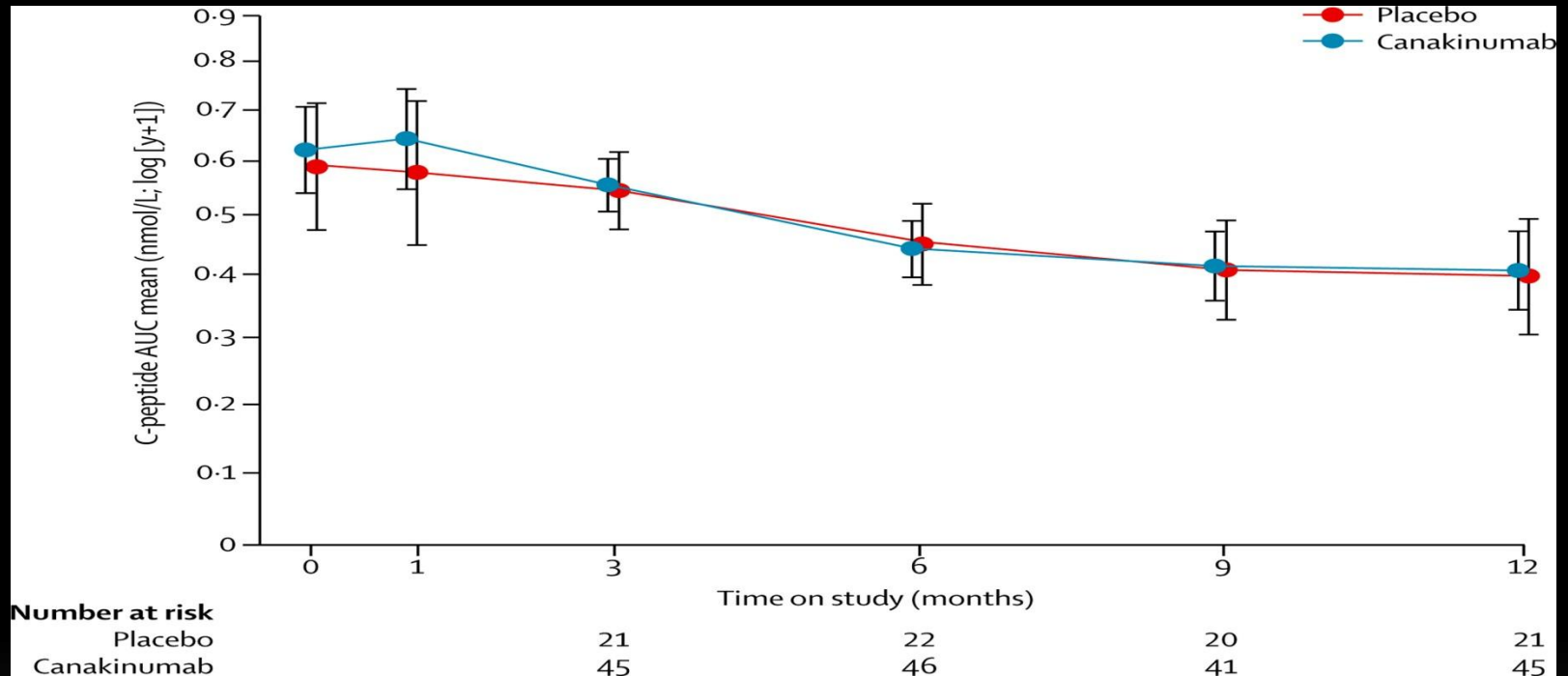
Immune Response

*Anti-Interleukin 1 (IL-1)
Heat shock protein 277
analogue (Diapep)*

- Innate Immunity
 - Macrophage
- Adaptive Immunity
 - T cells
 - B cells



Phase 2 Anti-IL1 Results



Antoinette Moran , Brian Bundy , Dorothy J Becker , Linda A DiMeglio , Stephen E Gitelman , Robin Goland , Carla J...

Interleukin-1 antagonism in type 1 diabetes of recent onset: two multicentre, randomised, double-blind, placebo-controlled trials

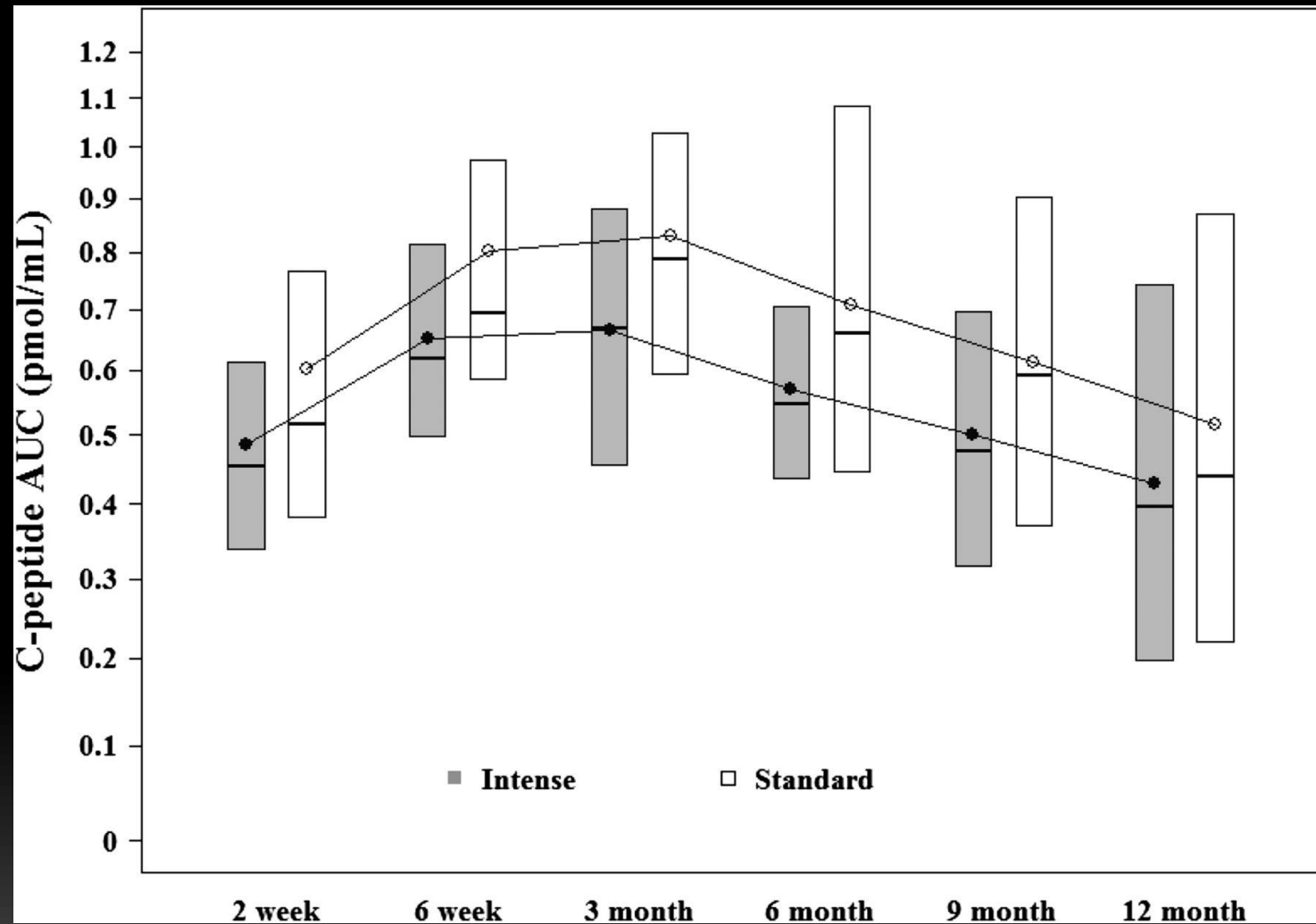
The Lancet Volume 381, Issue 9881 2013 1905 - 1915

[http://dx.doi.org/10.1016/S0140-6736\(13\)60023-9](http://dx.doi.org/10.1016/S0140-6736(13)60023-9)

Pathogenesis of autoimmune diseases

- Induction
- Activation
- Homing
- Destruction

Beta Cell Rest: Intensive Early Therapy



Buckingham B et al. Dia Care 2013;36:4030-4035

Beta Cell Stimulation: DPP4 Inhibitor

