



Environmental factors and type 1 diabetes

The interplay between *diets, gut flora and intestinal permeability*

Dr. Jeroen T.J. Visser

Department of Cell Biology,
Immunology section,
University Medical Center Groningen,
University of Groningen,
the Netherlands

Introduction

- Type 1 diabetes is the result of the autoimmune destruction of the β -cells
- Prevalence:
 - In the Netherlands: 74.000: =0.46%

Factors involved in type 1 diabetes development

- Genetic (immunological):
 - HLA-type (I.E. Class II: HLA-DP, DQ and DR)
 - Increased levels of autoreactive T cells
 - Reduced regulatory potential
- Environmental
 - Viruses
 - Chemicals/toxins
 - Diet
 - Bacteria (gut Flora)

**In order to induce the autoimmune response
leading to T1D,
diabetogenic triggers from the food and gut flora
must be able to pass the
intestinal barrier!!!**

Intestinal barrier

The integrity of the intestinal barrier is maintained by Tight Junctions

Tight junctions are not always closed, but are regulated by complex signal transduction processes.

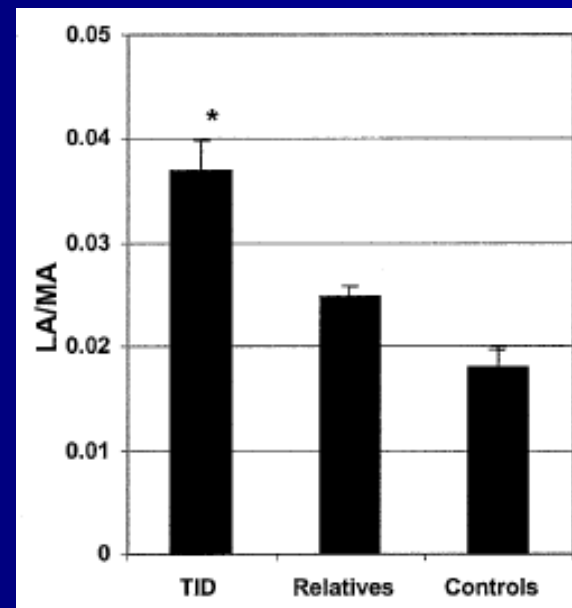
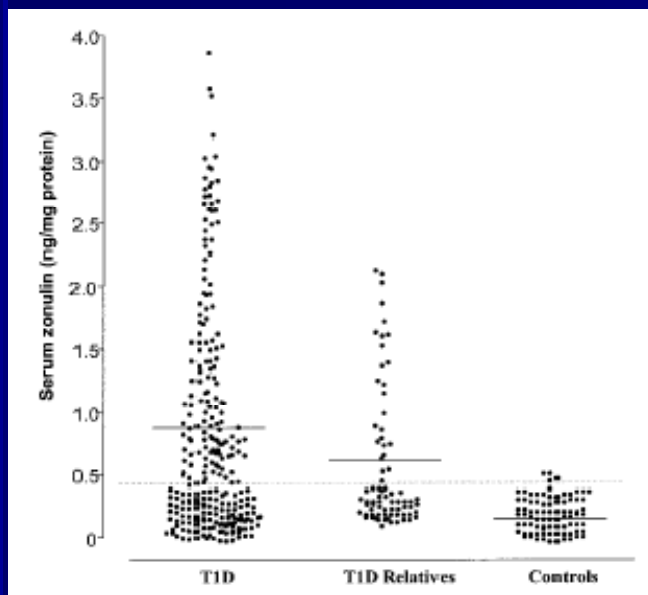
Tight junctions can be regulated by the protein Zonulin, that by binding to its receptor activate a signaling cascade that leads to opening of the tight junctions.

Zonulin is produced by enterocytes upon stimulation with bacterial compounds and food components like gliadin.

Function: Innate immune response against bacterial/parasitical infection

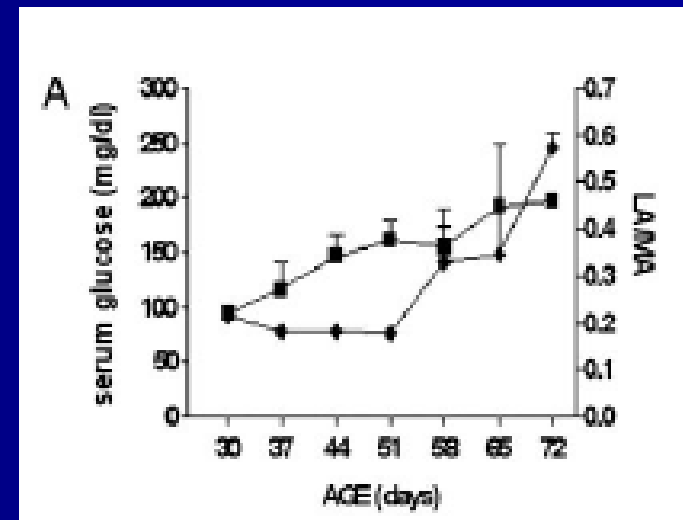
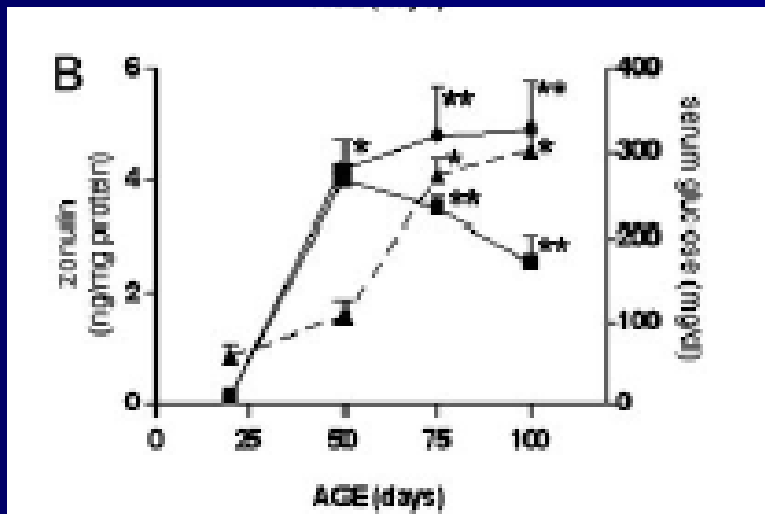
T1D patients and diabetes prone BB rats show impaired intestinal permeability that precedes the onset of T1D

- T1D patients have impaired gastrointestinal permeability:
 - Increased serum zonulin levels
 - Increased LA/MA ratio



T1D patients and diabetes prone (DP) BB rats show impaired intestinal permeability that precedes onset of T1D

- DP-BB rats have impaired gastrointestinal permeability:
 - Increased serum zonulin levels
 - Increased LA/MA ratio
 - Decreased TEER of the ileum



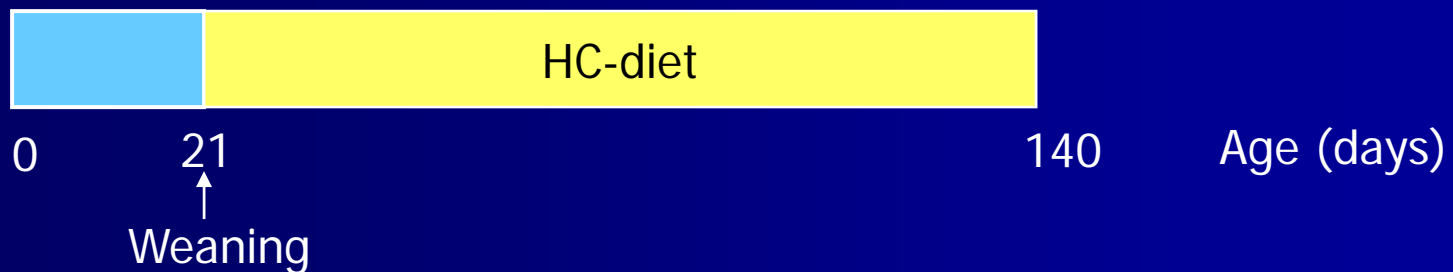
Aim

- Investigate the interplay between diets, gut flora and the intestinal permeability in the development of T1D.
- Is restoration of the impaired intestinal permeability a mechanism in the prevention of T1D by dietary interventions.

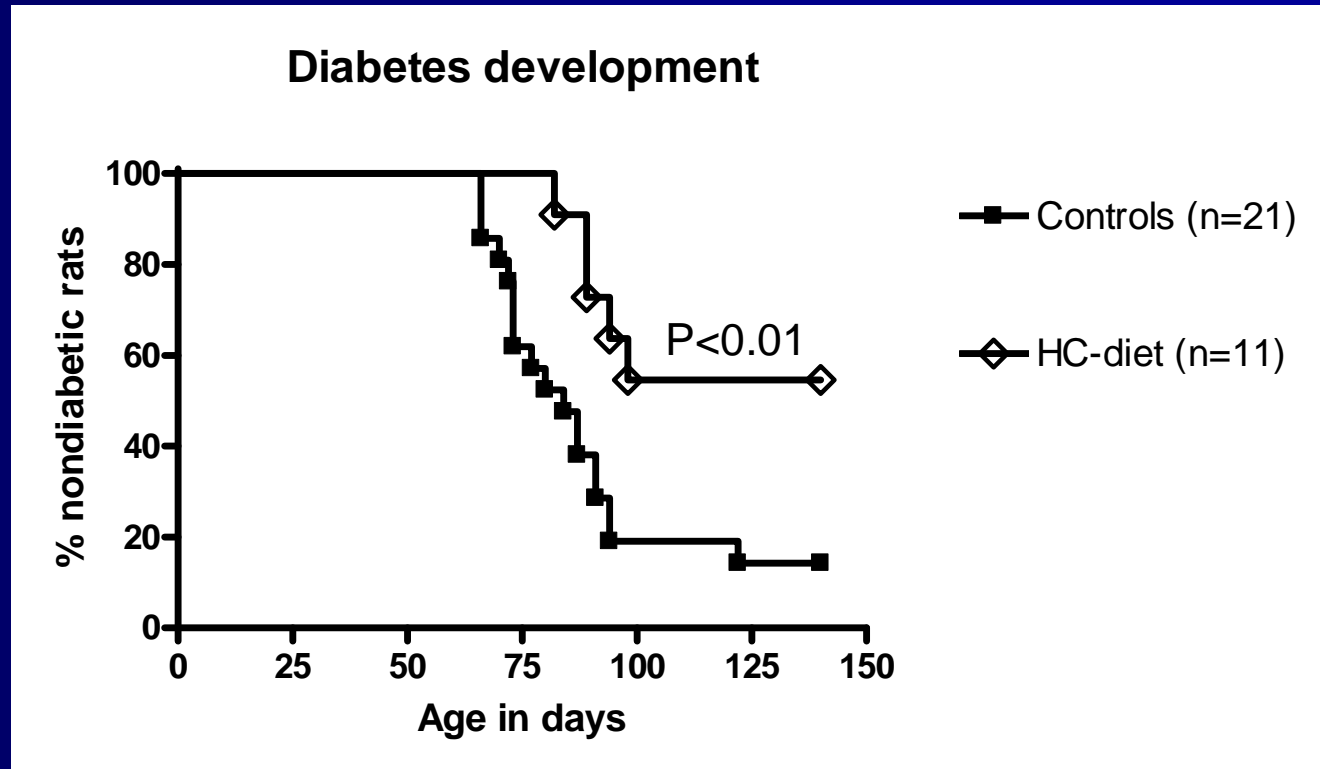
Use BB-rat model to study the role of environmental factors in Type 1 diabetes development

- Hydrolysed Casein (HC)-diet
 - Protein source (casein) is hydrolysed to small peptide fragments. Also known as hypo-allergic diet.

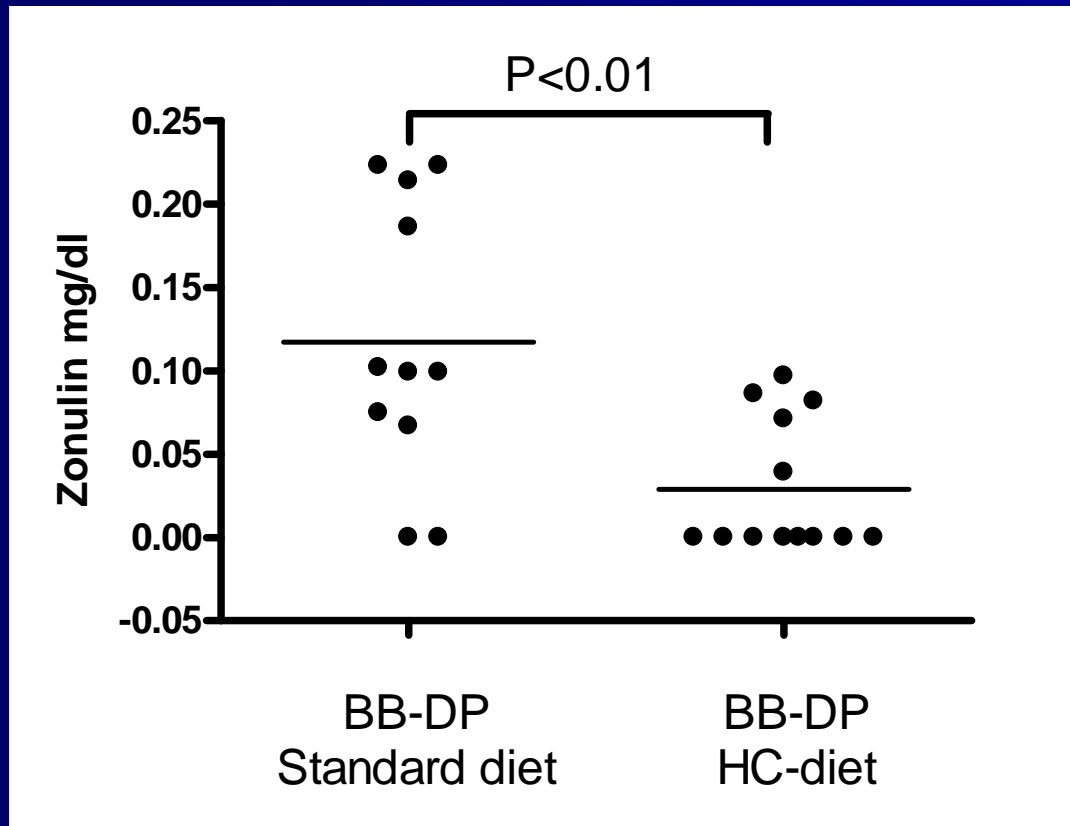
Intervention:



Effect of the Hydrolysed Casein diet on T1D development.

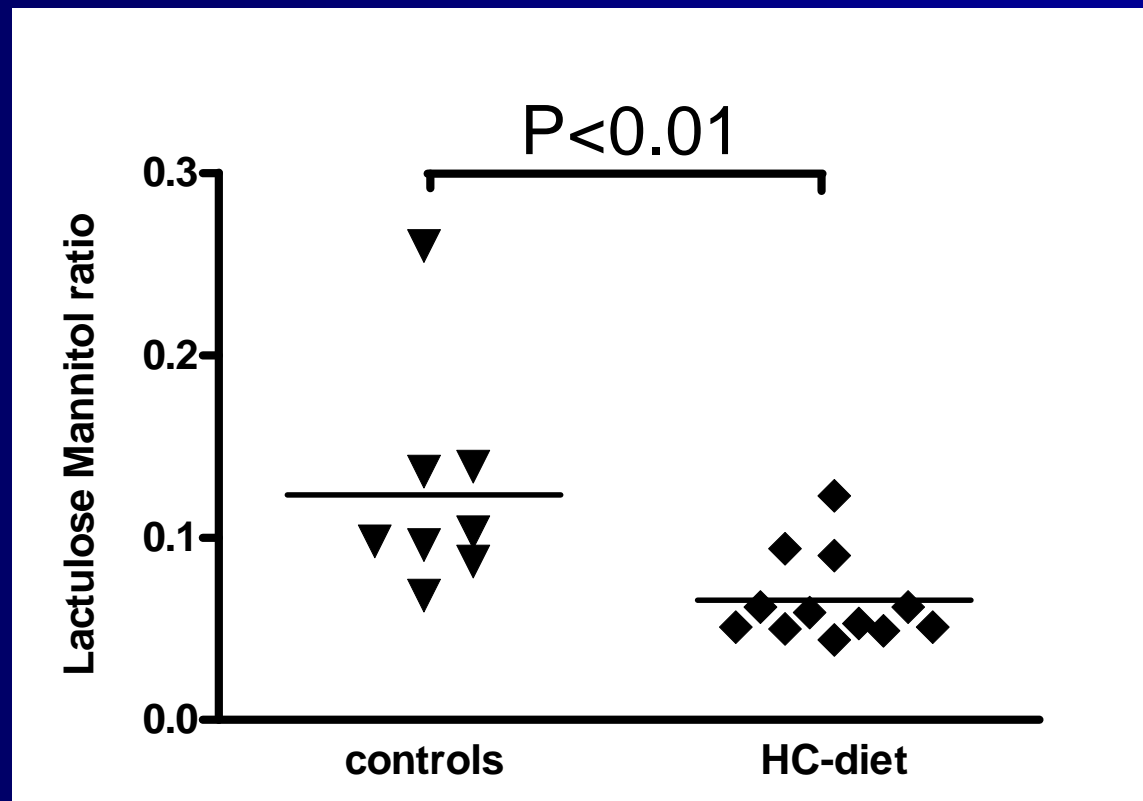


Lower zonulin levels in Diabetes prone (DP) BB rats that received the hydrolysed casein diet



The hydrolysed casein diet improves the impaired intestinal permeability in BB-DP rats.

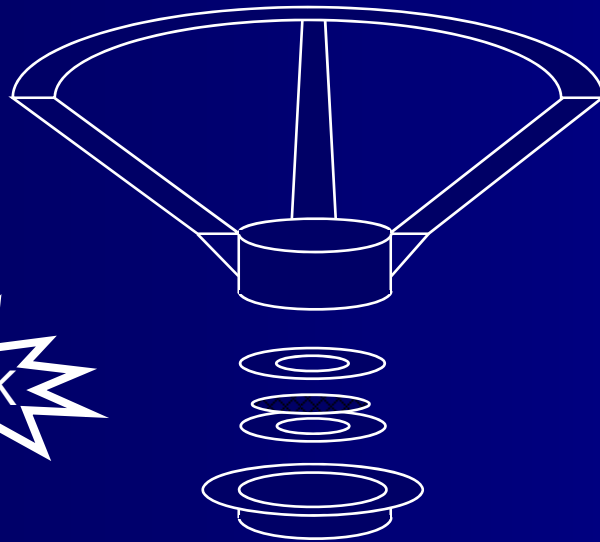
Lactulose Mannitol Ratio (LA/MA)



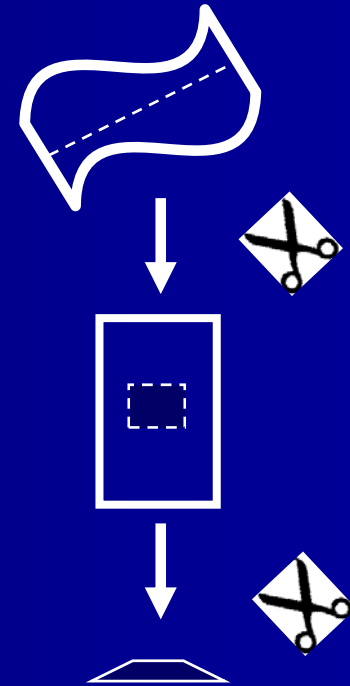
Snapwell Setup



Snapwell



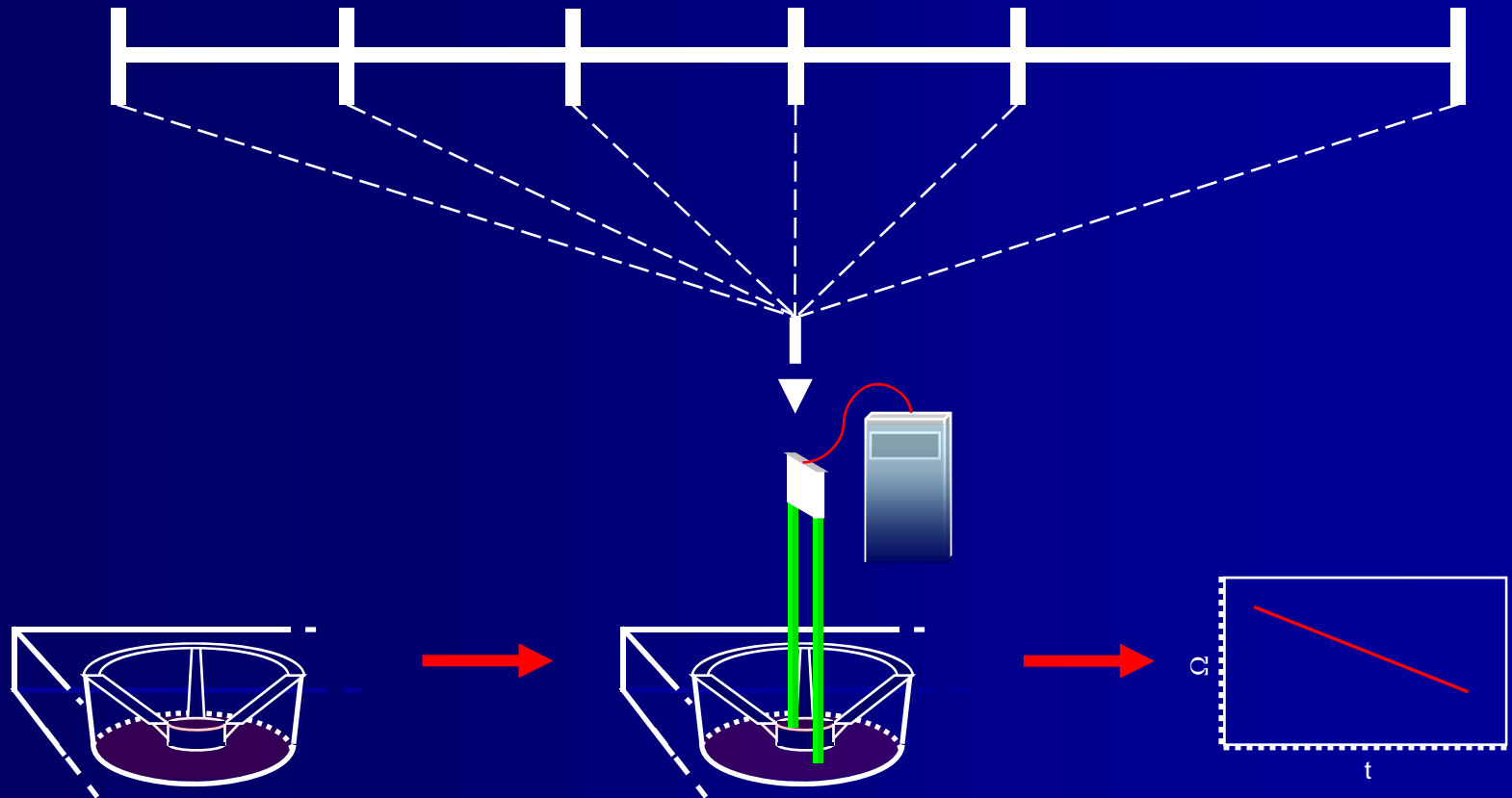
Ileum



Snapwell Setup

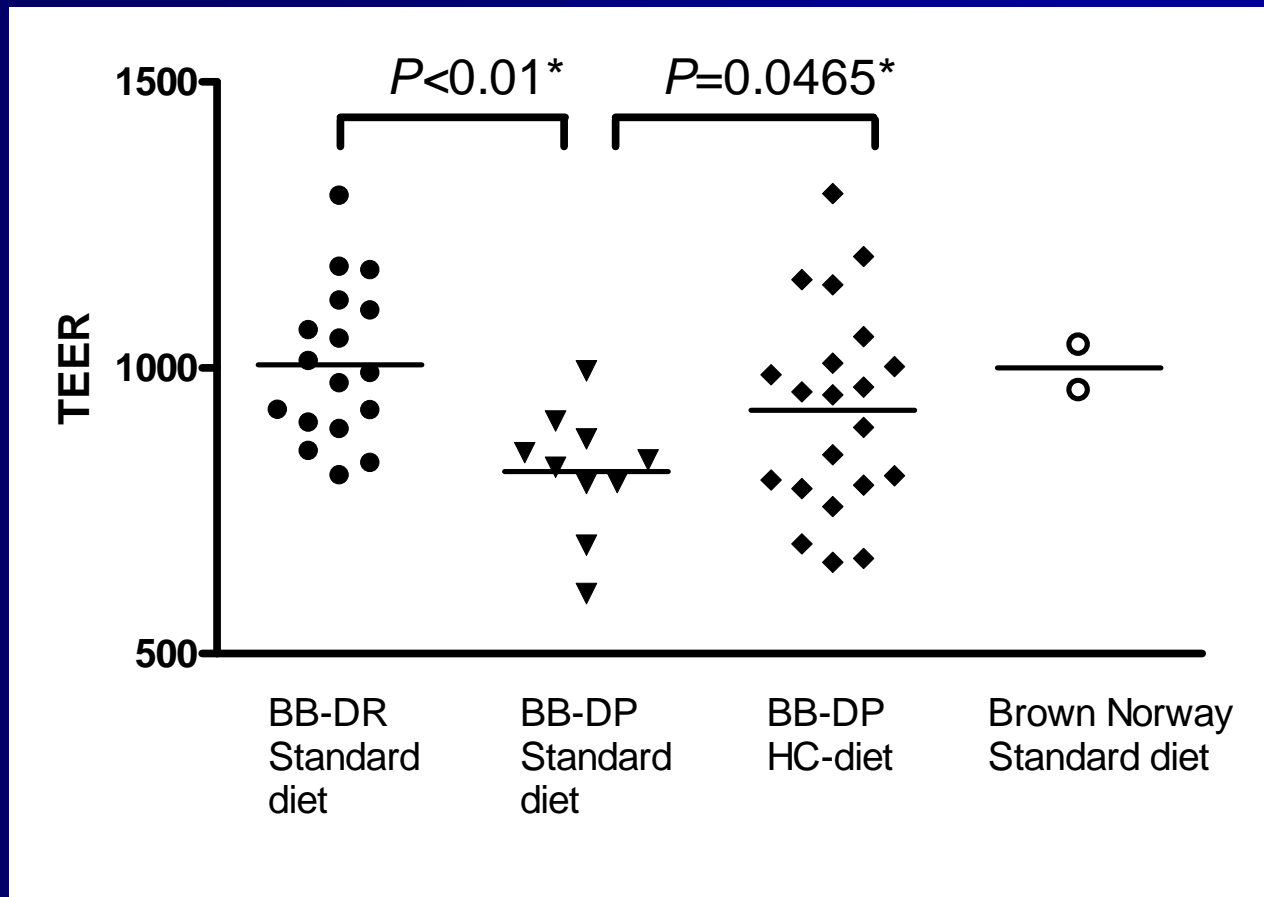


t (min) 0 30 60 90 120 180

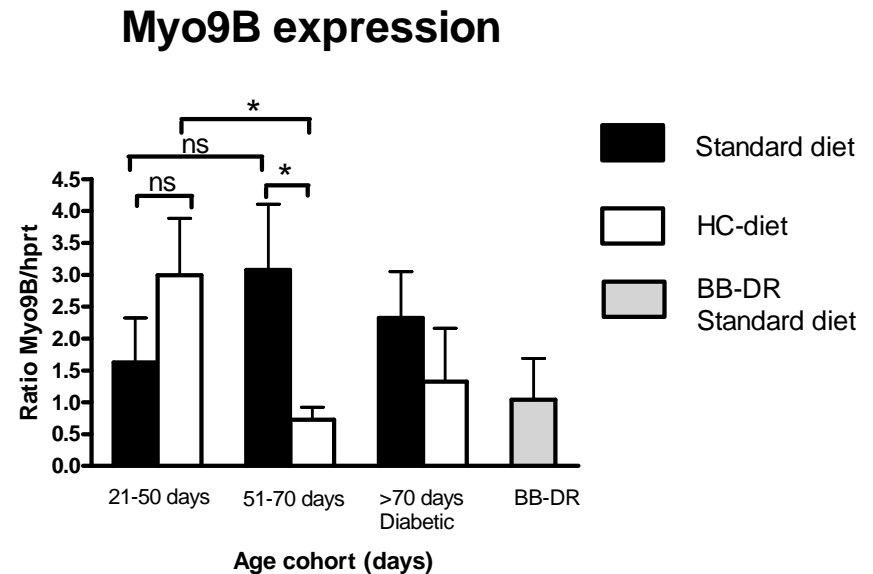
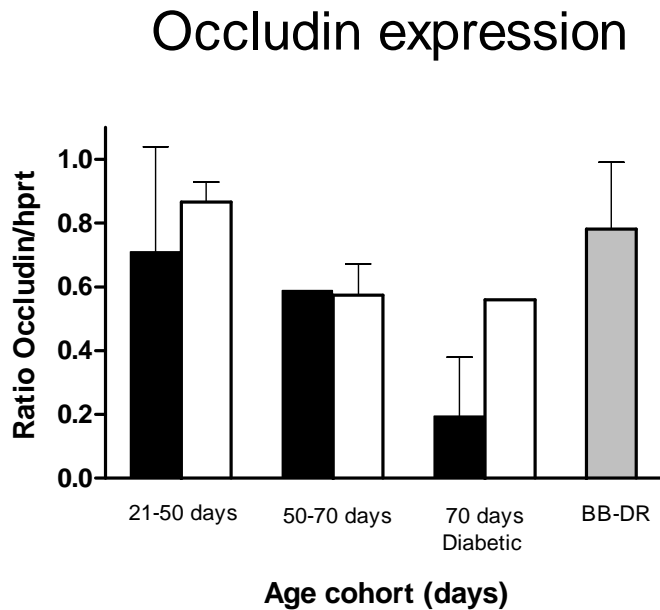


The hydrolysed casein diet improves the impaired intestinal permeability in BB-DP rats.

Trans Electrical Epithelial Resistance (TEER)

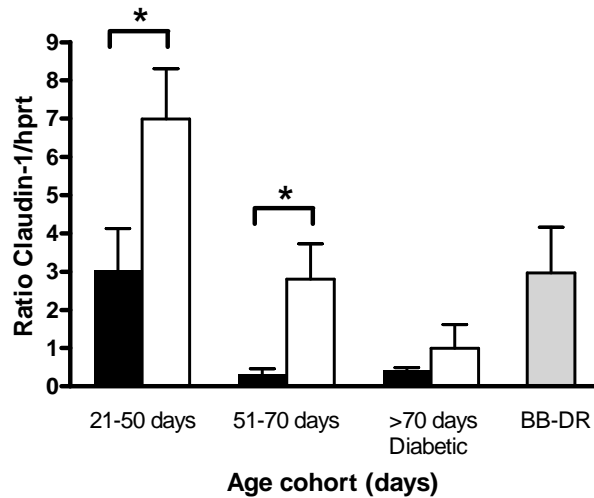


The hydrolysed casein diet changes the expression of tight junction related proteins

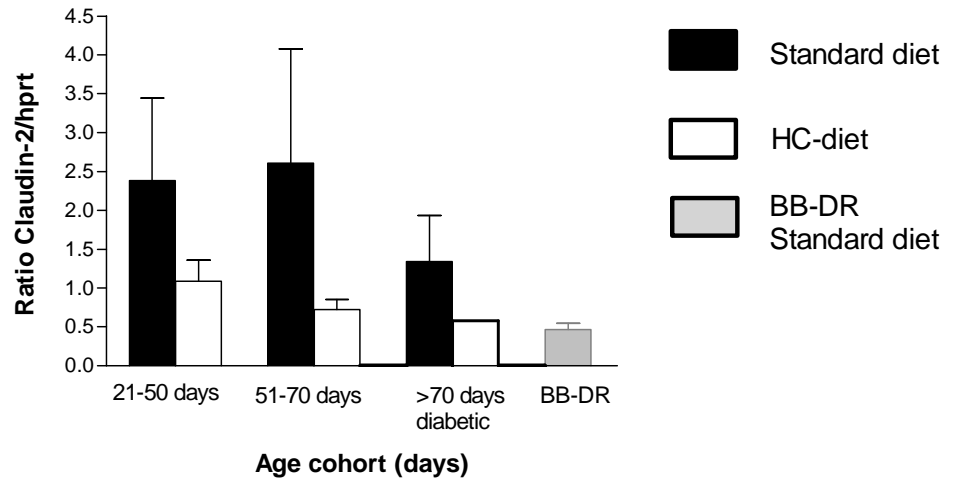


The hydrolysed casein diet changes the expression of tight junction related proteins

Claudin-1 expression

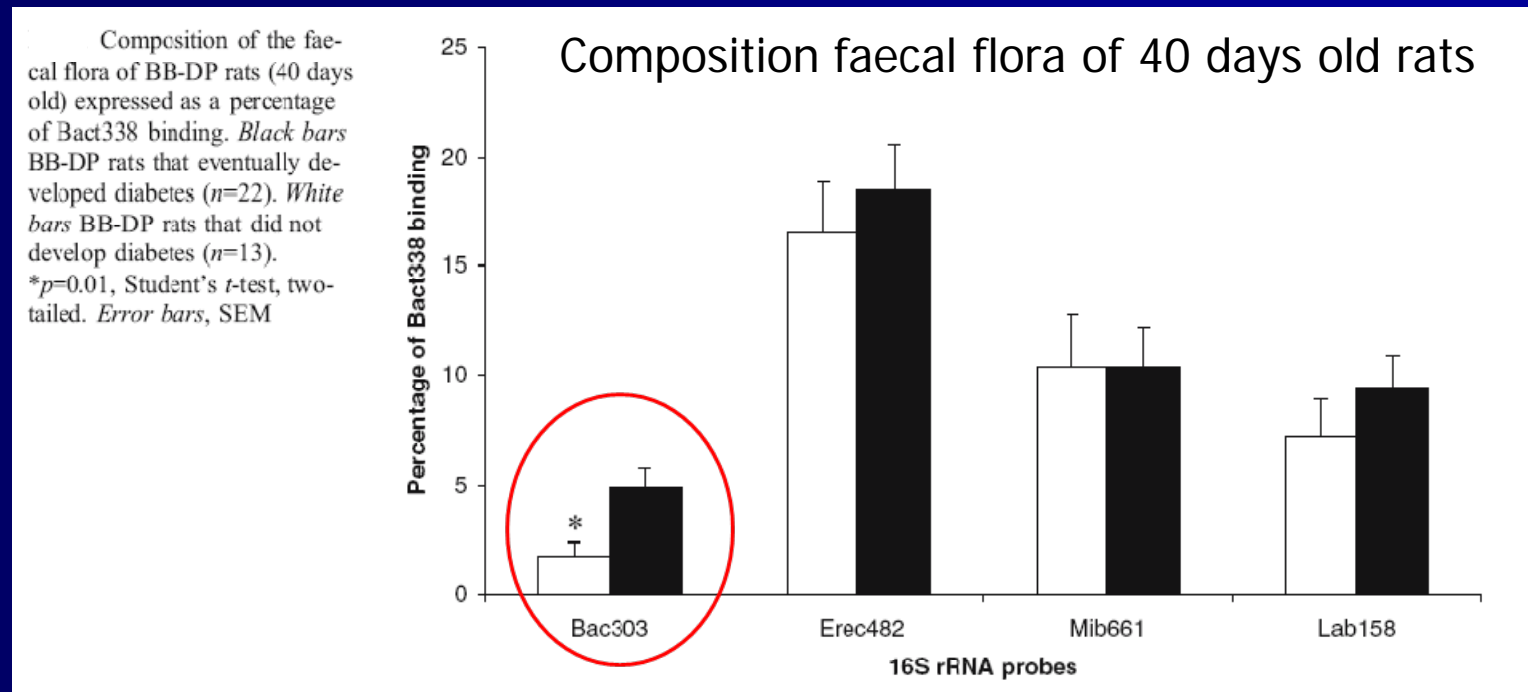


Claudin-2 expression



Relation between gut microflora and Type 1 diabetes development

Composition of microflora predicts the outcome of diabetes development in the BB-DP rat.

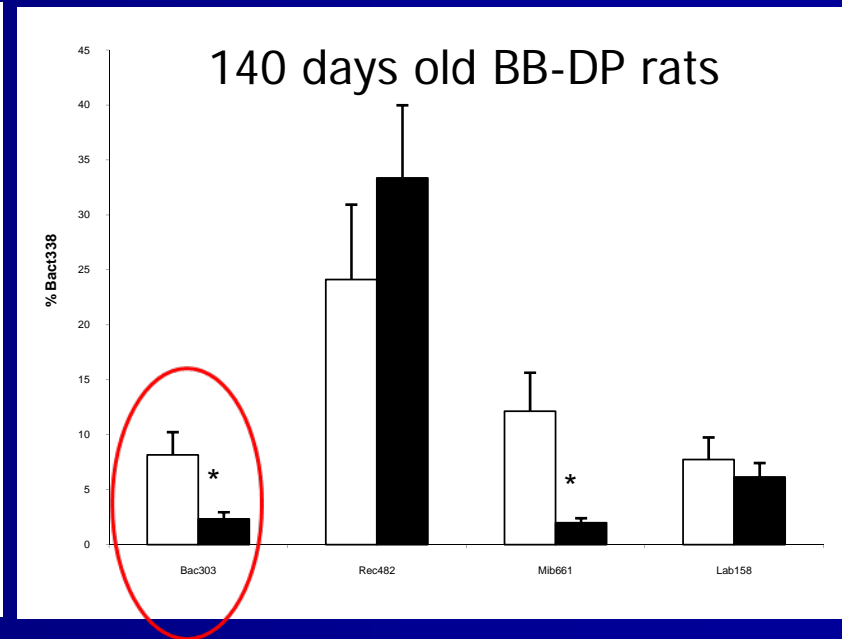
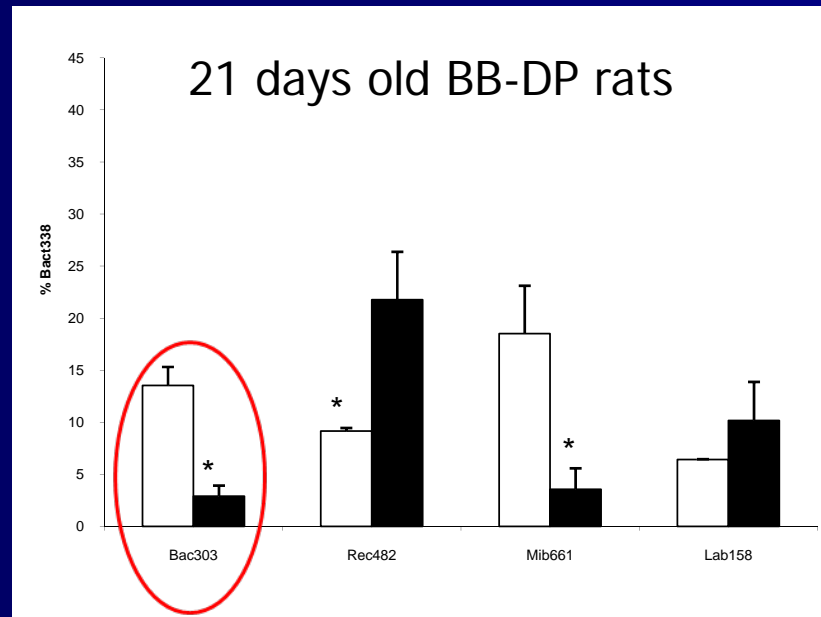


Brugman S, Klatter FA, Visser JT, et al.,
Diabetologia. 2006 49: 2105-2108.

■ Developed diabetes
□ Did not develop diabetes

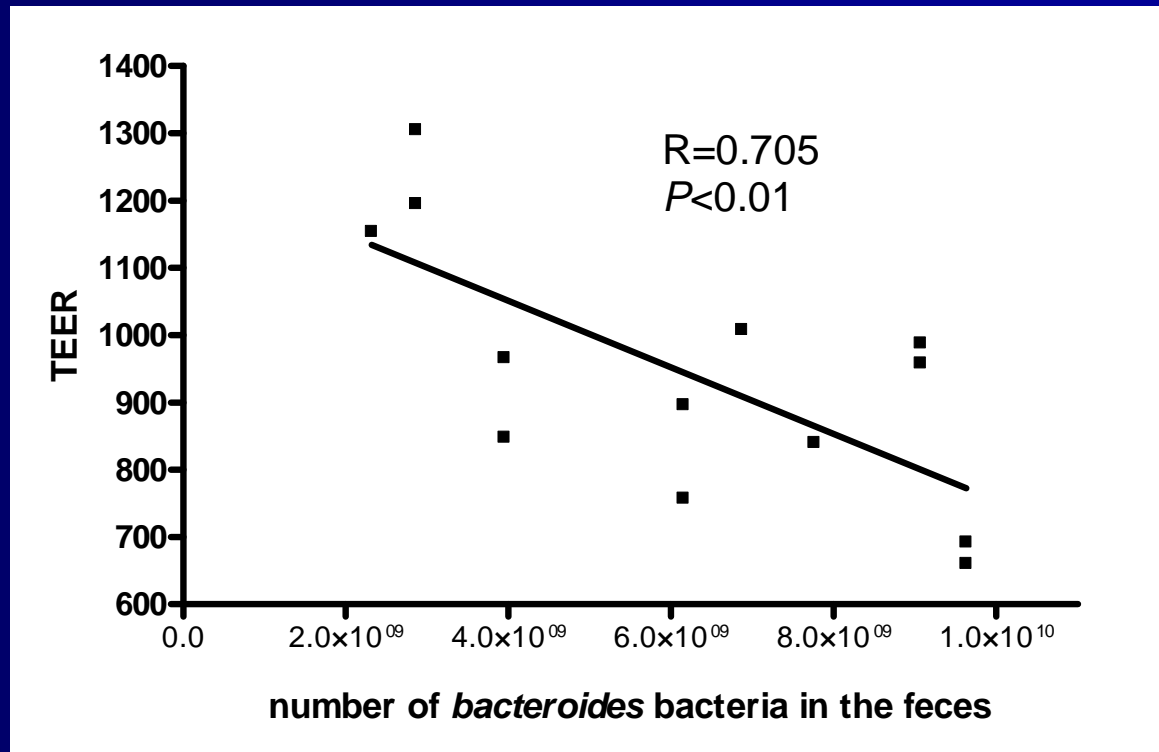
Relation between gut microflora and Type 1 diabetes development

HC diet changes the composition of the microflora in the BB-DP rat.

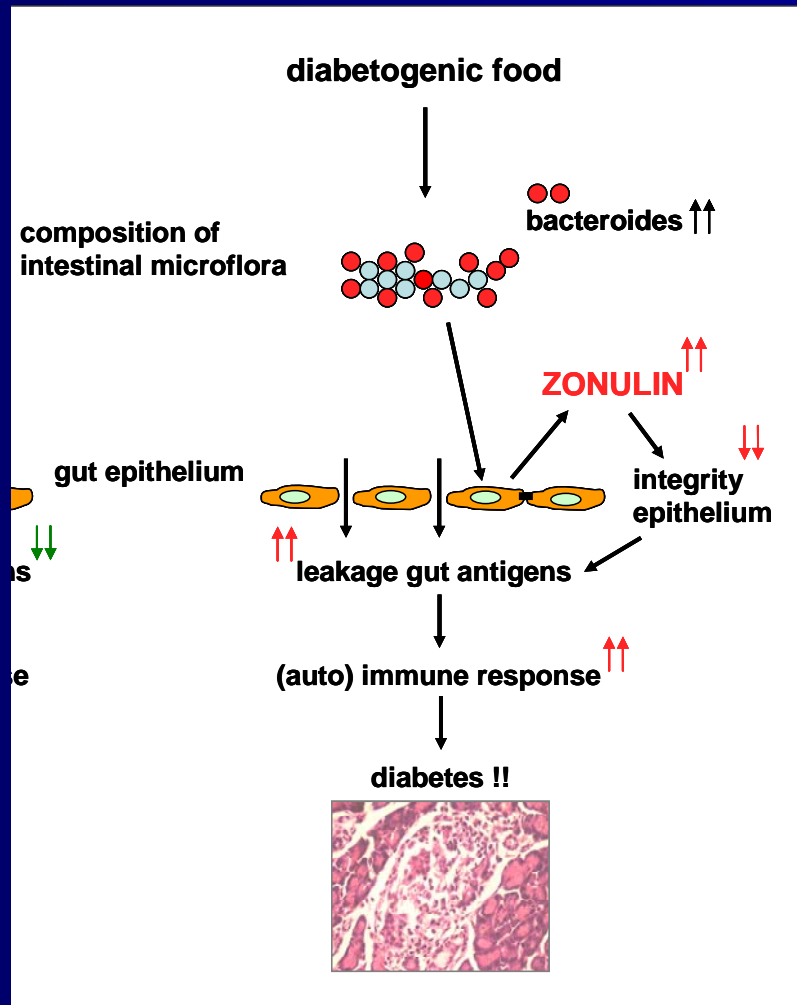


 HC-diet
 Standard diet

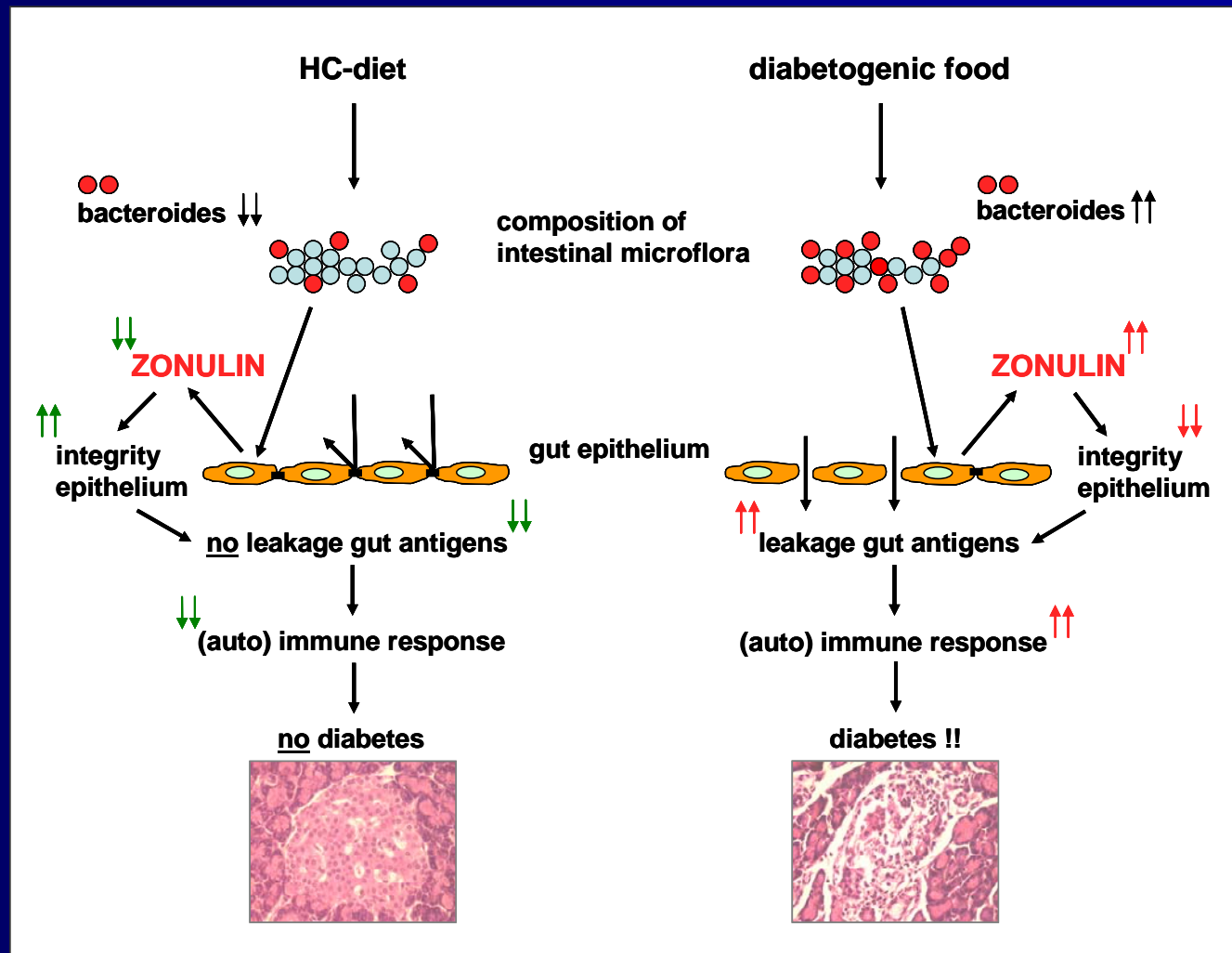
Correlation between *bacteroides* levels and intestinal permeability



Proposed mechanism in how the HC-diet prevents type 1 diabetes development



Proposed mechanism in how the HC-diet prevents type 1 diabetes development



People involved

- **Department of Cell Biology, Immunology section, University Medical Center Groningen, University of Groningen**
 - Jan Rozing
 - Jeroen Visser
 - Jan-Luuk Hillebrands
 - Sylvia Brugman
 - Nico Bos
 - Arjan Hoogendijk
 - Mark Walther Boer
 - Frans Stellaard

- **Department of Medical Microbiology, University Medical Center Groningen, University of Groningen**
 - Hermie Harmsen
 - Gjalt Welling

- **University of Massachusetts, Worcester, USA**
 - Dale Greiner

- **Mucosal Biology Research Center, University of Maryland, Baltimore, USA**
 - Alessio Fasano
 - Karen Lammers