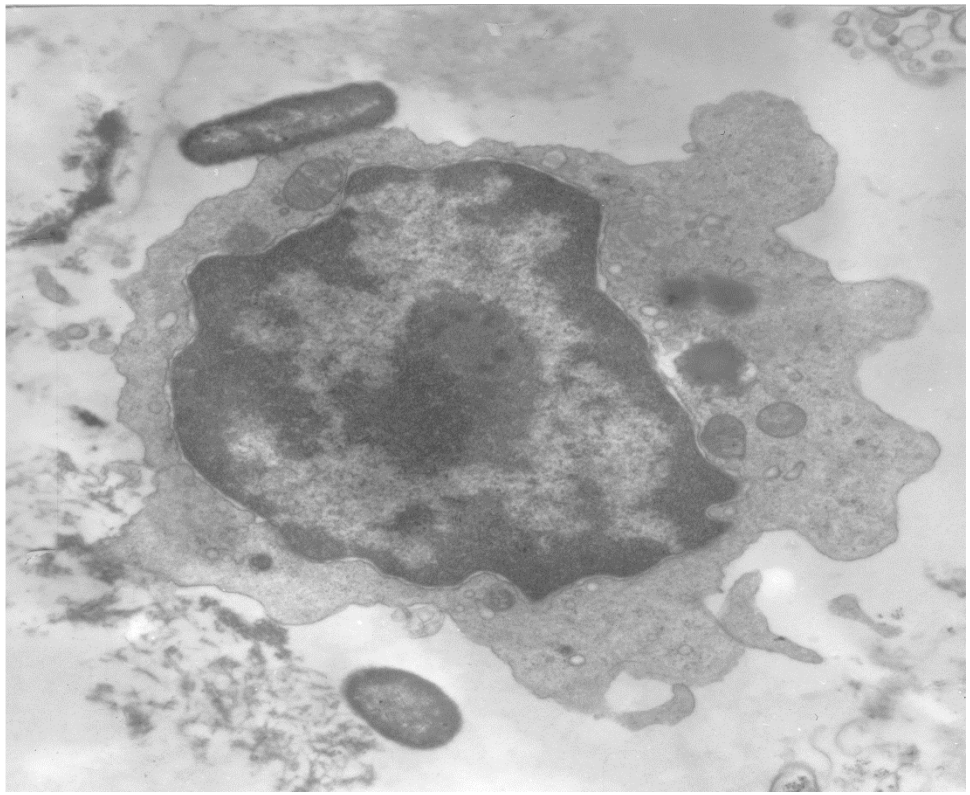
Probiotics and Immunoregulation: implication for health and disease

Claudio Nicoletti

Host Defence- GI Tract ISP

IFR



Probiotics

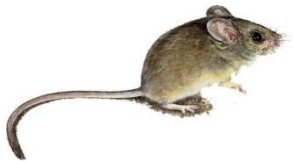
“ A live microbial feed supplement which beneficially affects the host by improving its intestinal microbial balance”

Do probiotics have immunoregulatory properties? Yes…

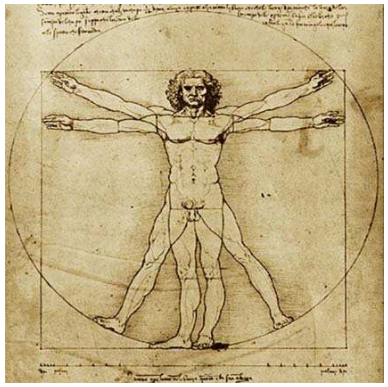
- Enterocytes: reduced signaling via NF-kB *(Kelly et al. 2004)*
- DCs: Promotes tolerogenic DC (IL-10 producing) *(Hart et al. 2004)*
- Effector T cells: T_H1 skewed response observed *(Veckman et al. 2004)*
- Treg: increased IL-10 and TGFb producing T cells *(Di Giacinto et al. 2005)*
- Monocytes: increased circulating monocytes *(Benyacoub et al. 2003)*
- Stem cells: increased bone marrow-derived CD34+ cells *(Mastrandrea et al. 2004)*
- B cell: increased local IgA production *(Prescott and Bjorksten 2007)*

…..and moving in the right direction

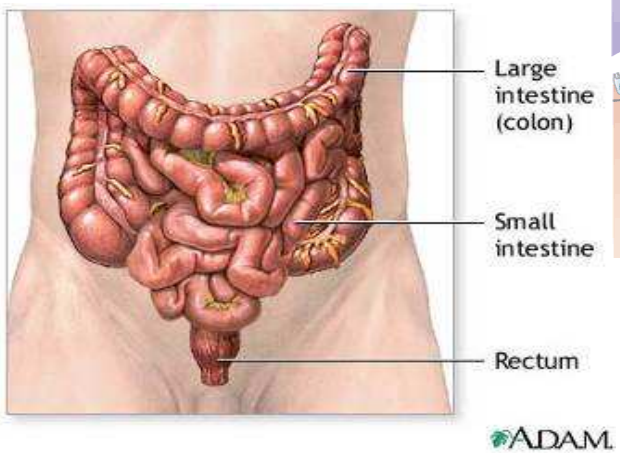
- *Kwon et al.* Generation of regulatory dendritic cells and CD4+Foxp3+ T cells by probiotics administration suppresses immune disorders. *Proc Natl Acad Sci* USA 107: 2159, 2010

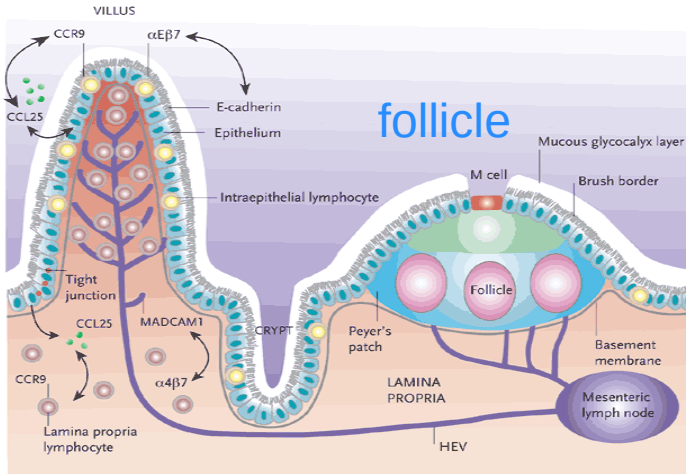


- *Van Baarlen et al*. Human mucosal *in vivo* transcriptome responses to three lactobacilli indicate how probiotics may modulate human cellular pathways. *Proc Natl Acad Sci* USA 108: 4562, 2011



Host-probiotics interaction: the gut immune system



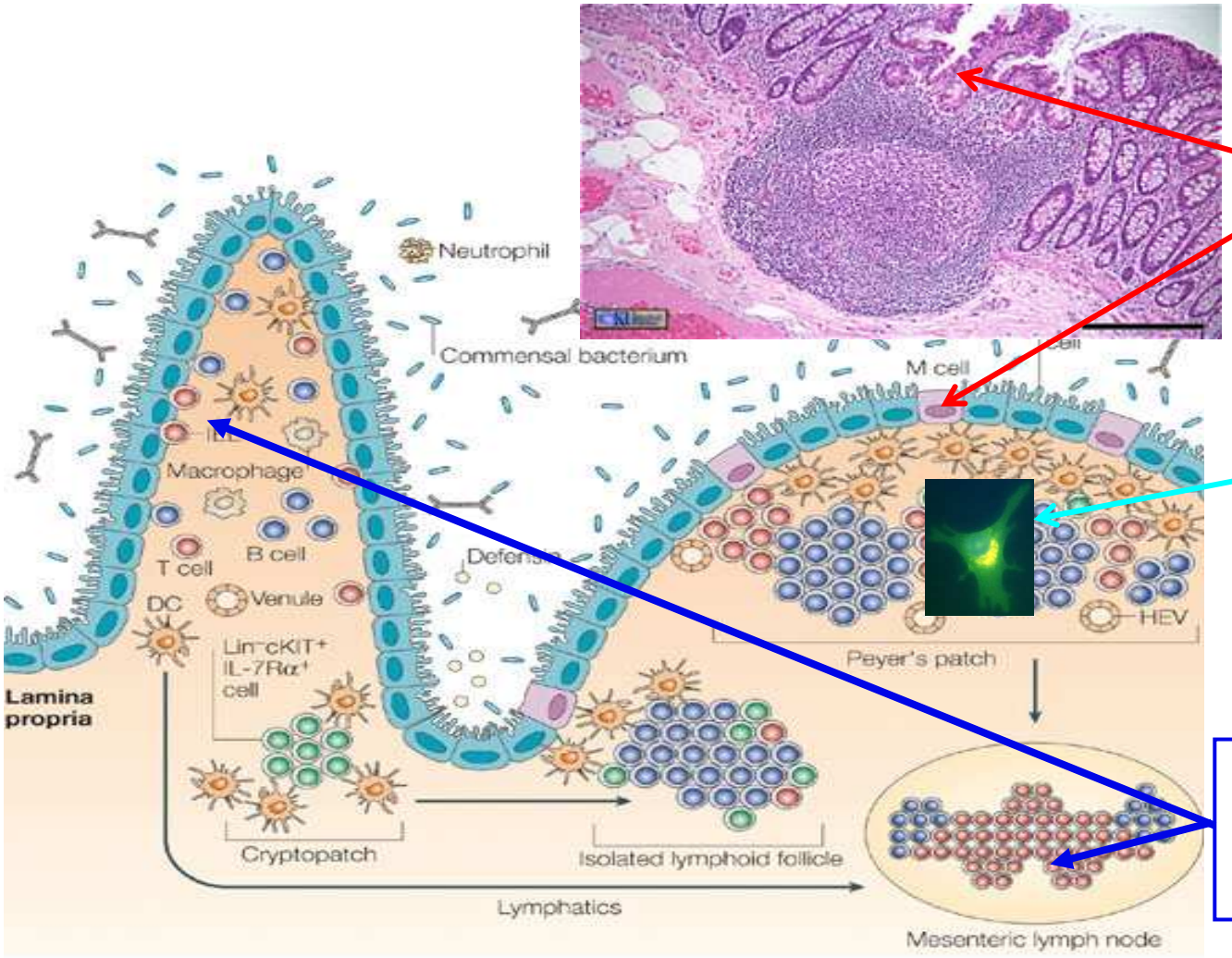


villus

follicle

Peyer's patch

Inductive and effector sites of the intestinal immune system

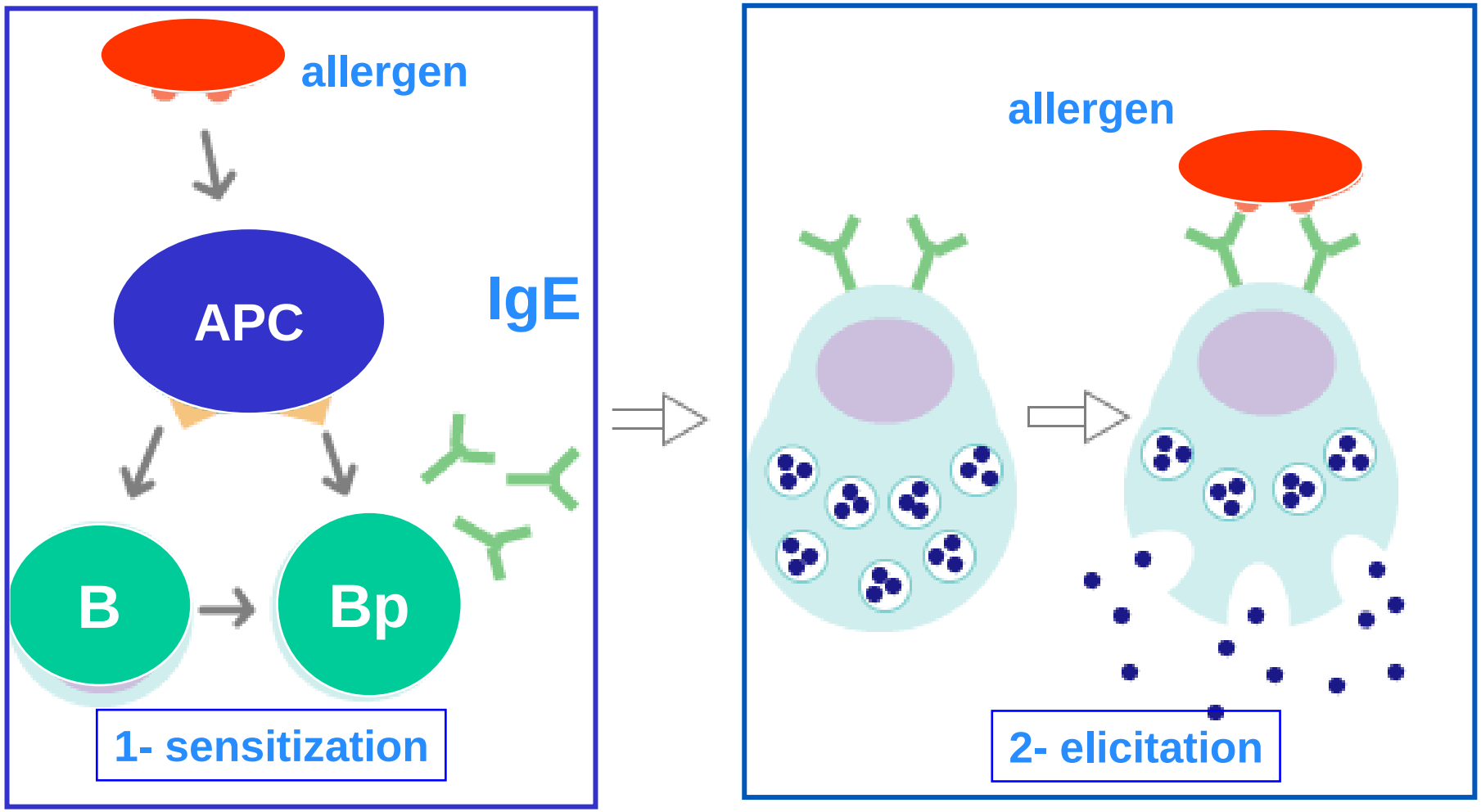


M-cells
transfer antigens
from the gut lumen
(sampling).

Ag-processing and
presentation by DCs to naïve
T cells. Generation of Ag
specific
T and B cells

T- and B-cell trafficking
conveys immunity
to other mucosal sites.

Improving vs. restoring: probiotics and allergy

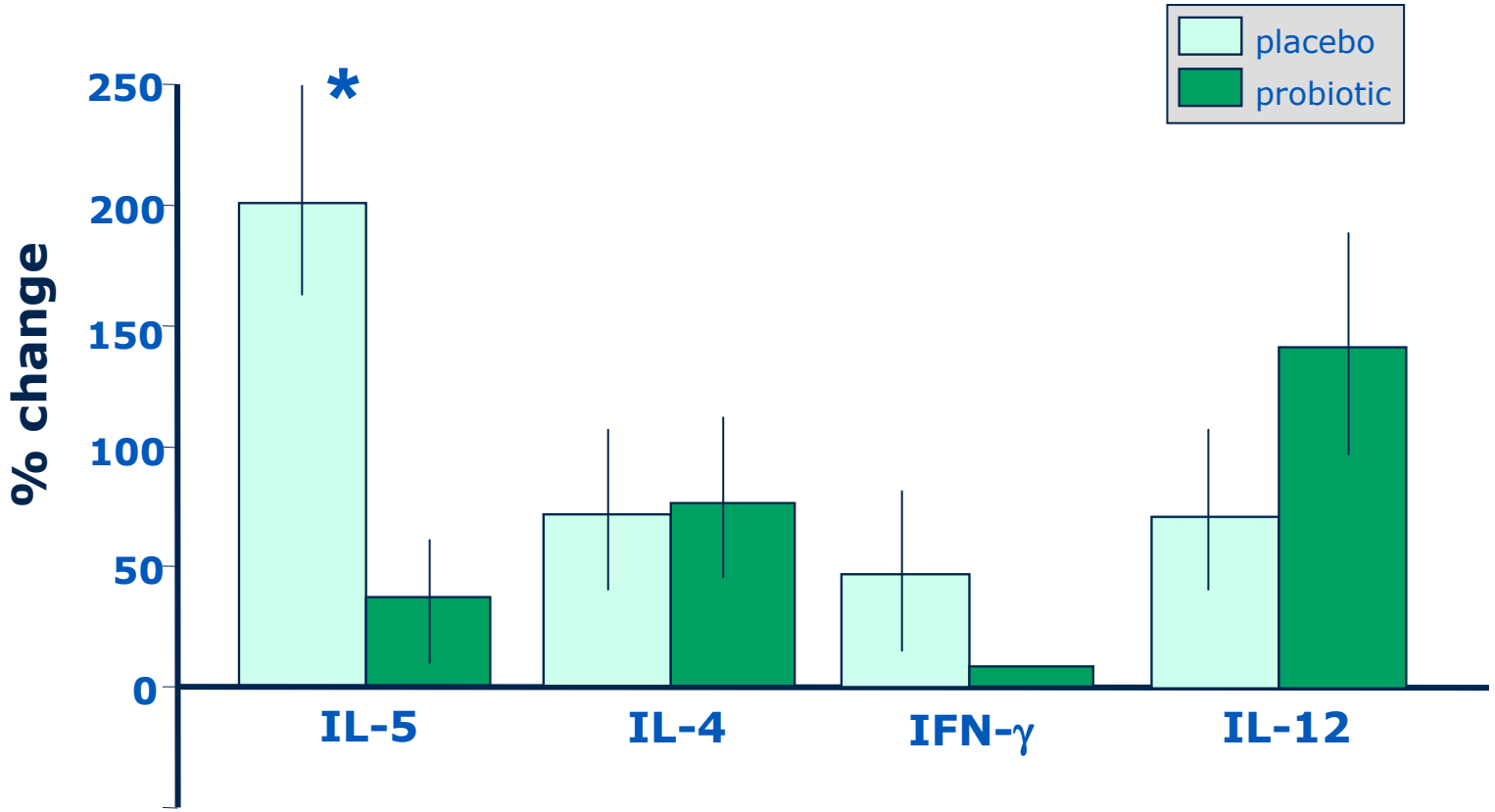


*Lactobacillus casei Shirota** in allergic rhinitis: a pilot human study

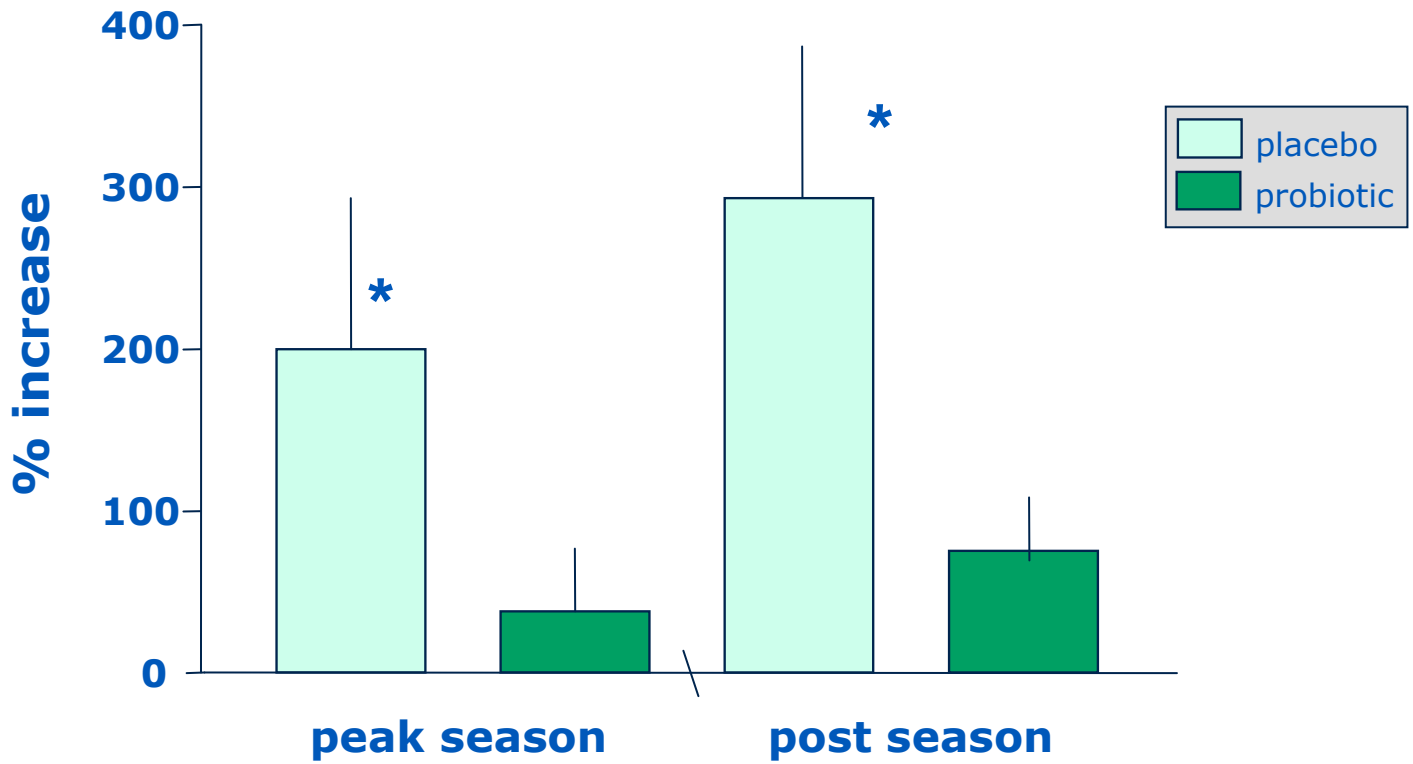
- DBPC study
- Daily supplementation of *Lc. Shirota* drink for 5 months
- Pre-season, peak- and post-season analysis of:

  - levels of serum early (GX1) and late (GX2) pollen-specific IgG and IgE
  - *In vitro* cytokine levels following in vitro recall challenge of MNC with GX1 and GX2

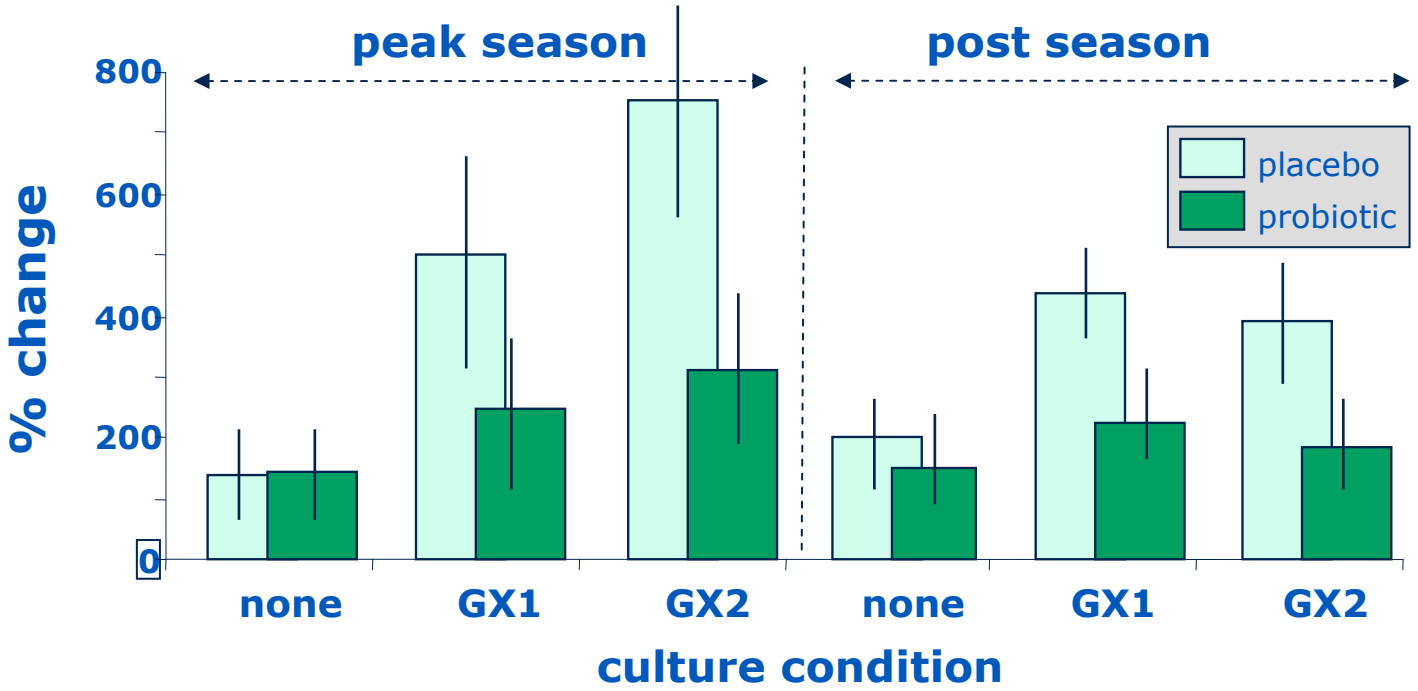
Change in cytokine secretion
(compared with pre-study responses)



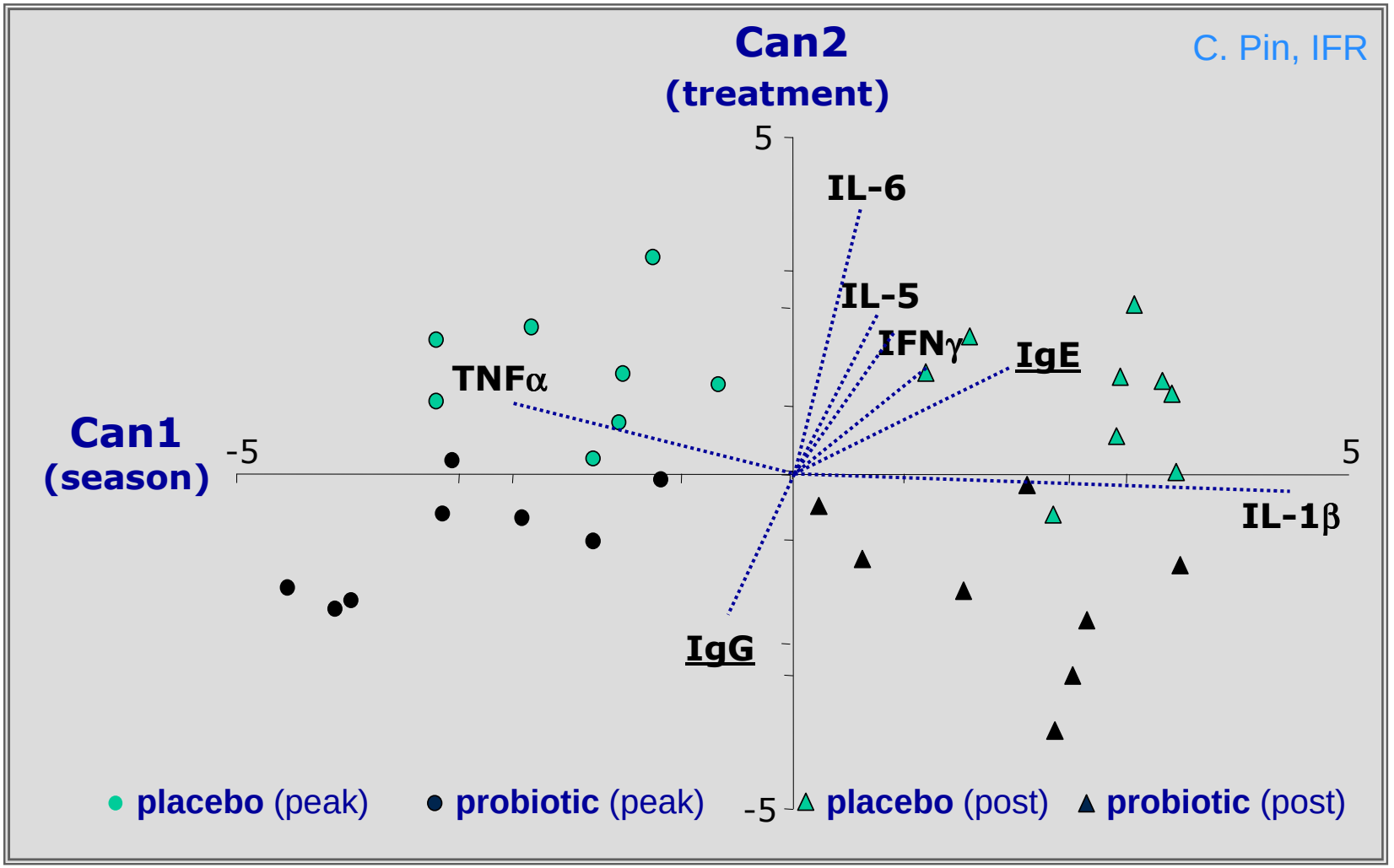
IL-5 levels
(compared with pre-season values)



IL-6 levels
(compared with pre-season values)



canonical discriminant analysis



Ivory et al. 2009

Work in progress: immunological and clinical study

Study design:

- Larger number (30/group) of individuals (Sept. 2010-Sept 2011)
- Daily supplementation *Lactobacillus casei* Shirota for 4 mos. followed by nasal allergen challenge

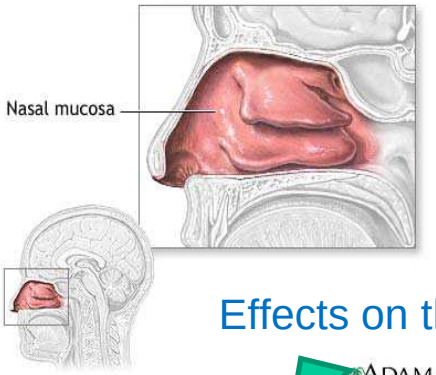
- **Endpoints**:
  - Total nasal symptoms score (TNSS)
  - Immunological parameters (Nasal lavage, PBMC)
  - AUC for nasal symptoms score (8, 24hrs)
  - AUC for peak nasal inspiratory flow (8, 24 hrs)
  - Nasal mucosae scraping: phenotype and regulatory features of EC and IEL

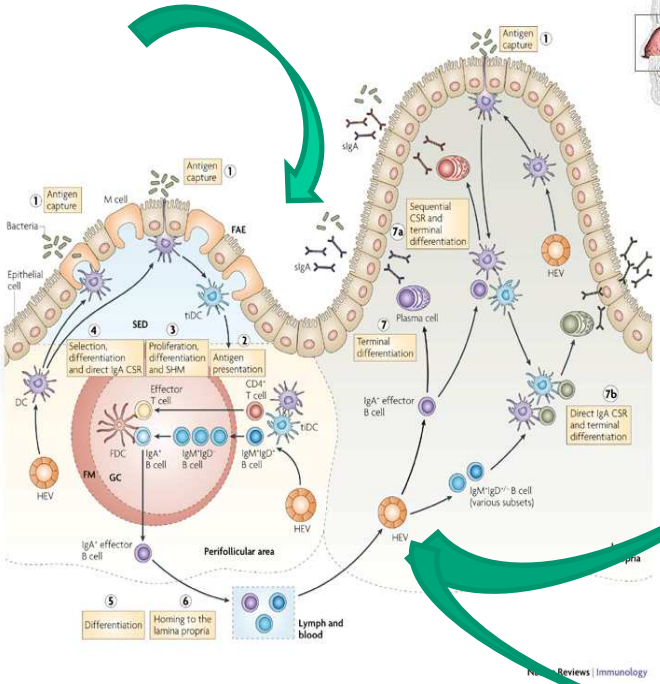
(coll. UEA-NNUH, Norwich)

ifr

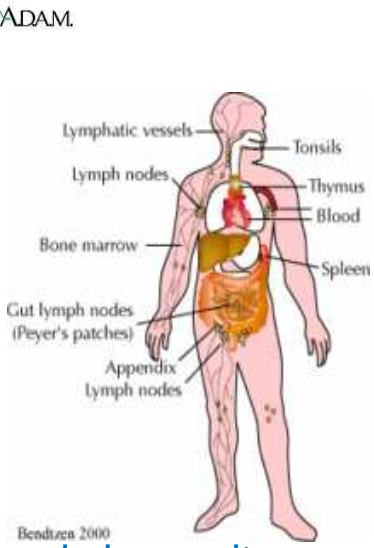
Via the gut to other mucosal sites

Oral delivery of probiotics



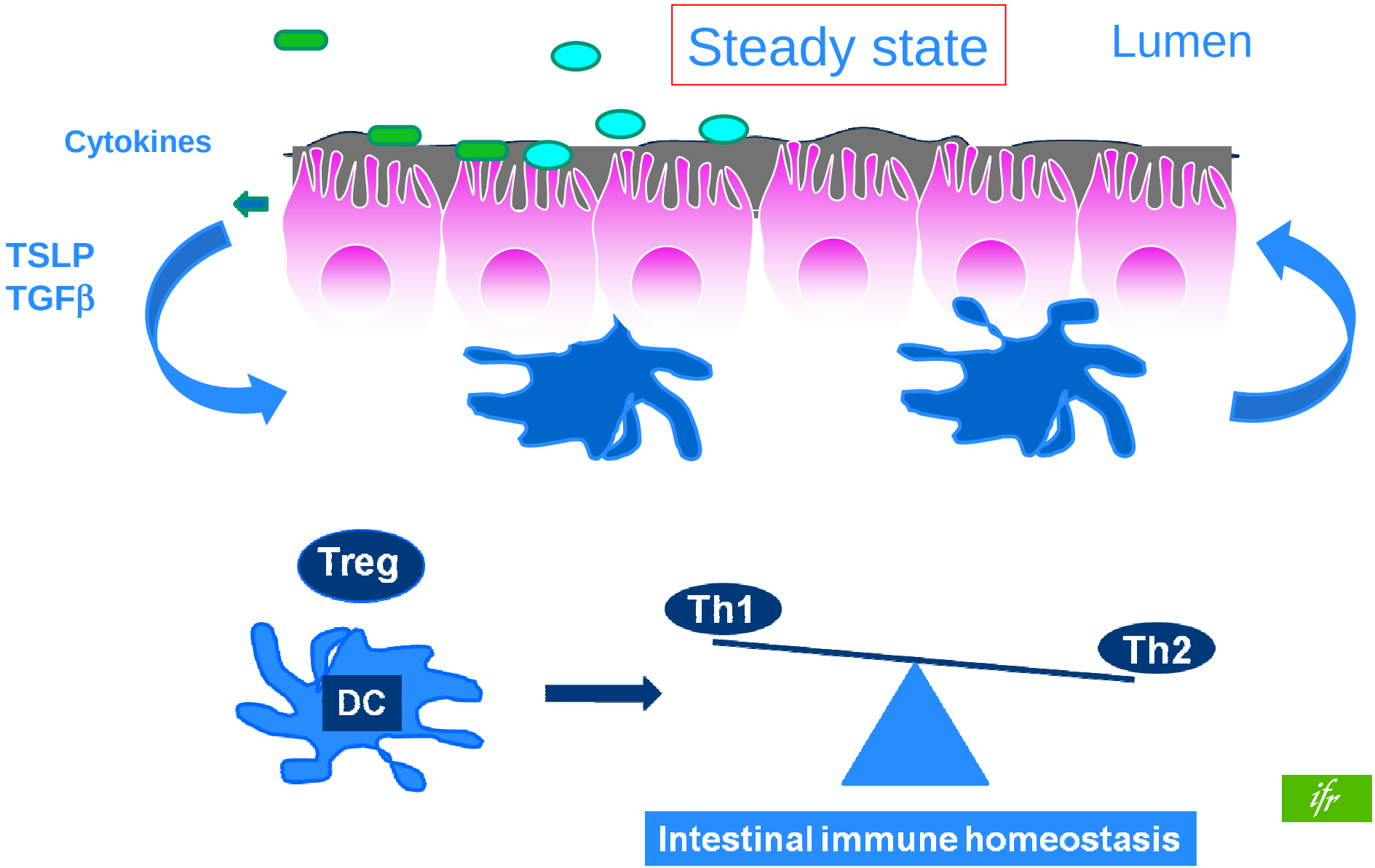


Effects on the nasal mucosa?

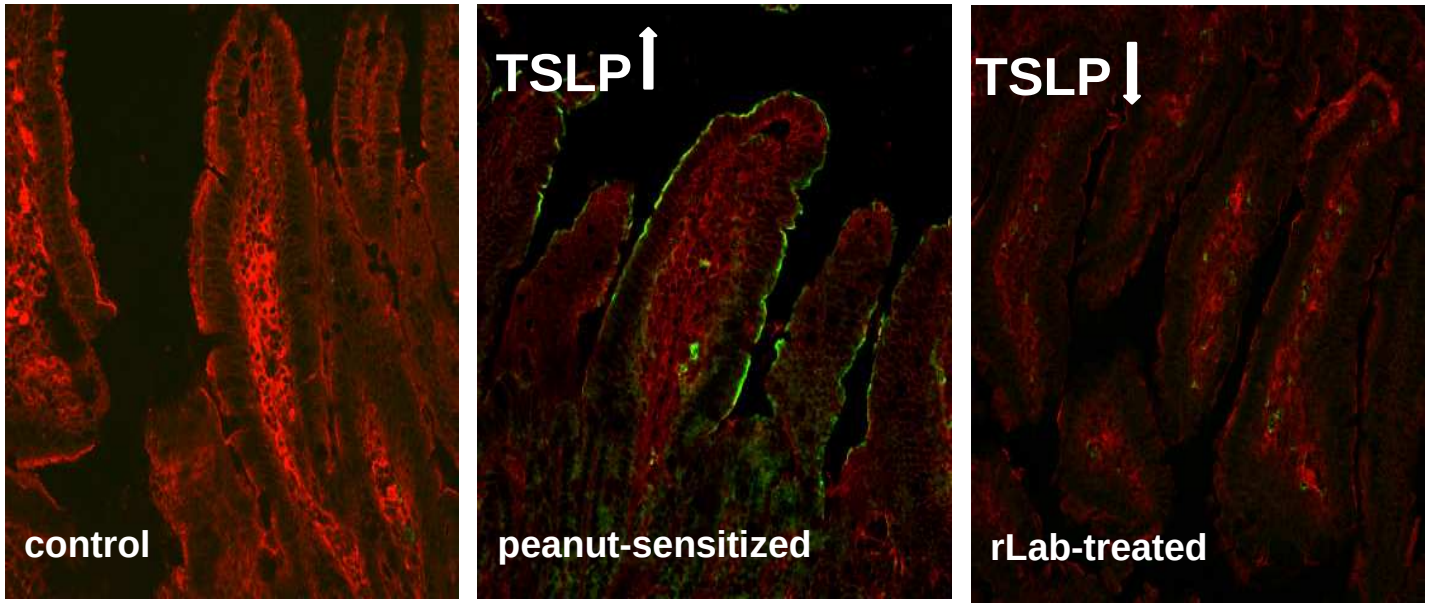


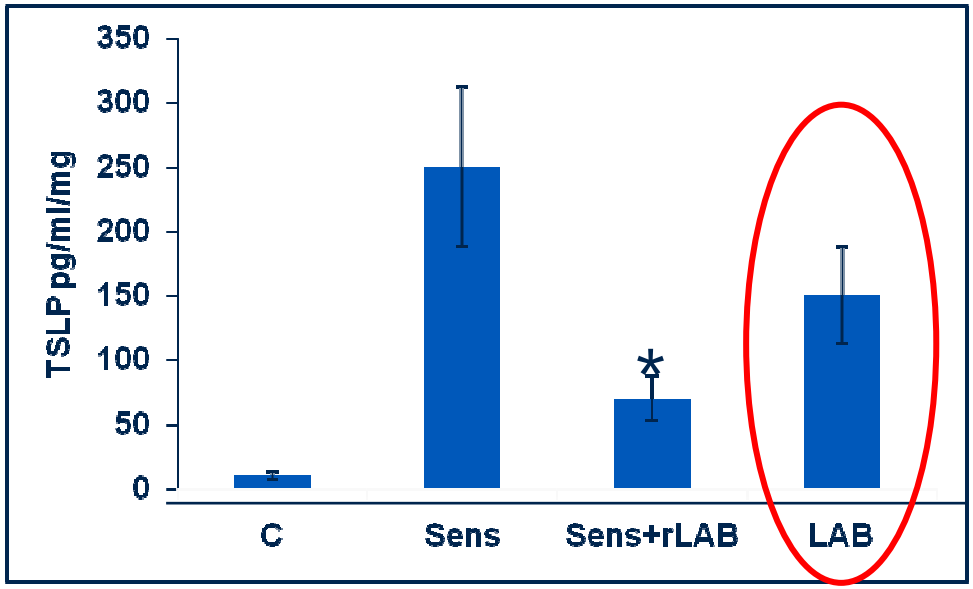
Effects on systemic immunity

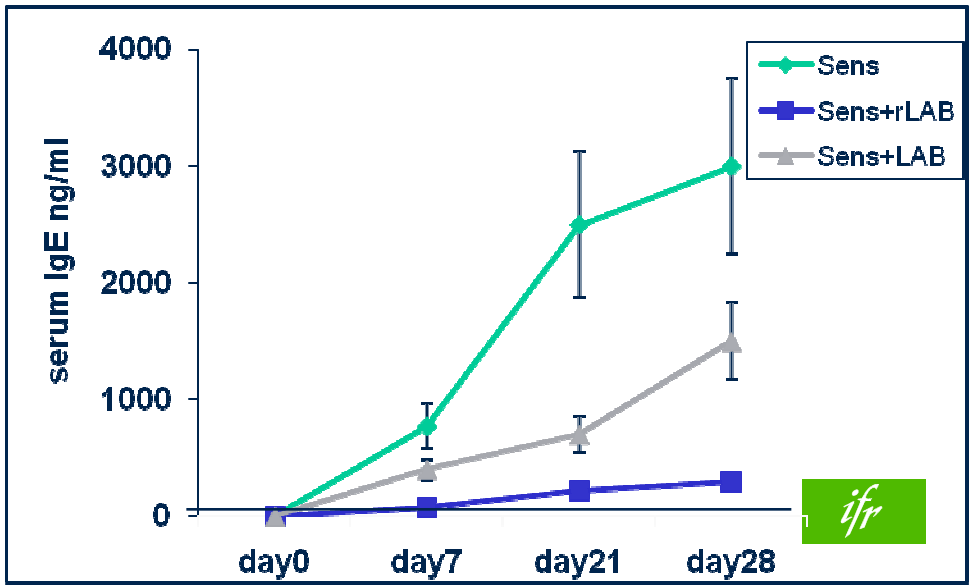
Host-probiotics: lympho-epithelial cross talk



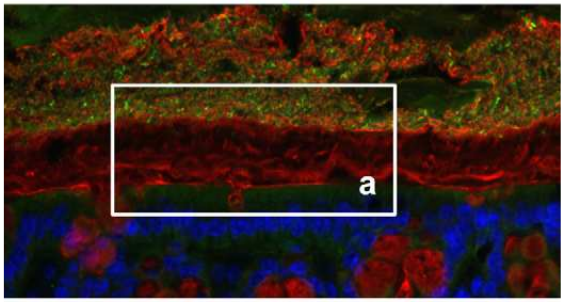
Host-probiotics: lympho-epithelial cross talk in the *small intestine*







In between microbes and gut epithelium



Mucous –outer layer (GFP-bacteria)

Mucous- inner layer (bacteria-free)

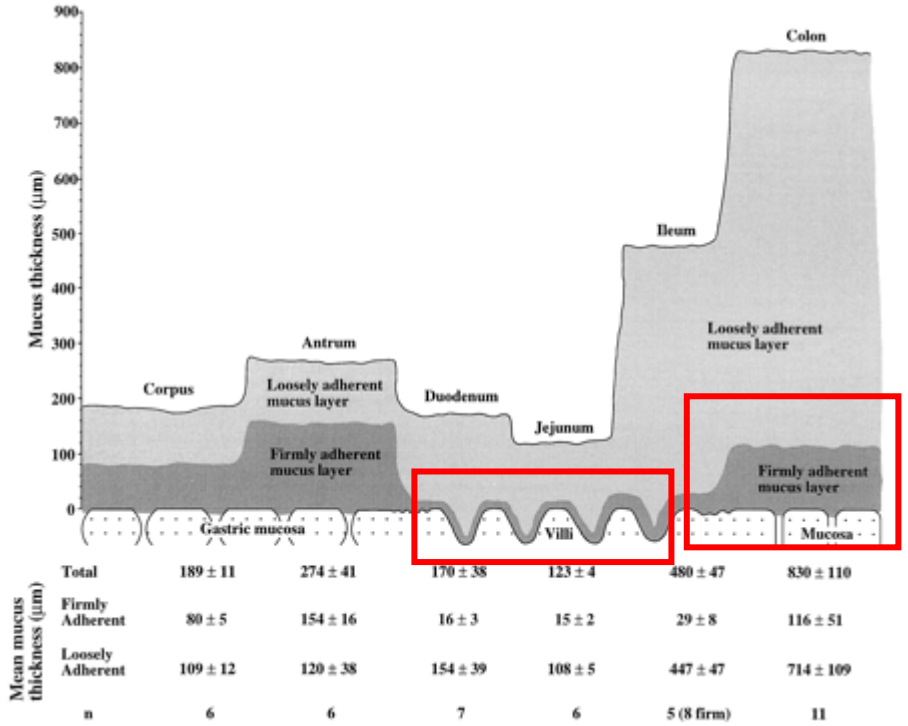
Gut epithelium

colon cancer

colitis

Muc2$^{-/-}$

N. Juge



acknowledgments

- K. Ivory
- AL. Man
- C. Pin
- N. Juge
- S. Chambers
- E. Prieto
- J. Arques
- A. Narbad
- A. Dumont
- M. Westwood
- A. Wilson