STp – protease resistant peptide from *Lactobacillus plantarum* with therapeutic potential in gut inflammation

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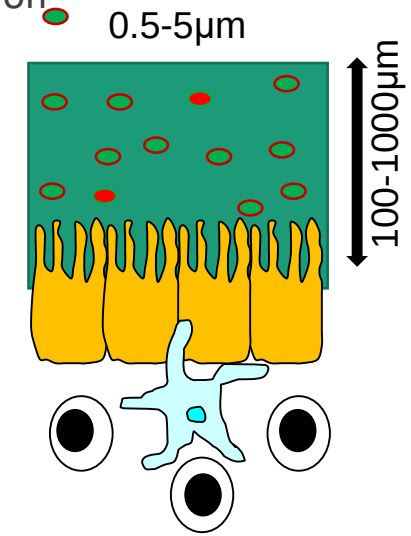
Highlights

- Novel probiotic-derived immunotherapy for IBD, suitable for oral administration
- Promising *in vivo* data showing reduced inflammation and reversal of symptoms in a model of Ulcerative Colitis
- Proposed to act as an immuno-modulator as an immuno-modulator of Dendritic Cells, restoring gut immune homesotasis
- Potential for development of a companion diagnostic
- Research group based at St. Mark's Hospital, an international referral centre for intestinal and colorectal disorders
- Composition of matter and method of use patent published as WO2013/034795
- Seeking co-development and/or licensing partners

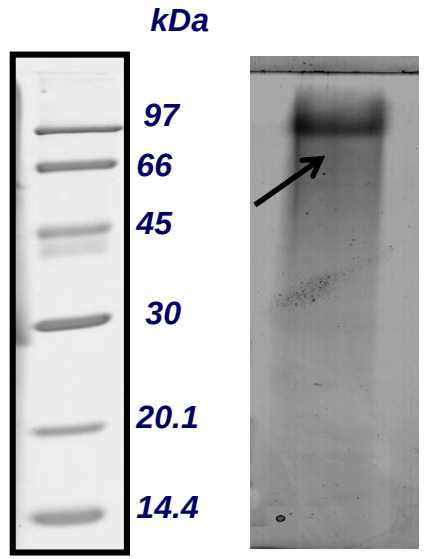
Commensal microbiota regulate the balance: *Lactobacillus plantarum* as a model

- Intestinal DCs are regulatory
  [*Hart et al Gut 2004; Hart et al Gastroenterology 2005*]
- DCs cross-talk with the commensal microbiota (species specific)
  [*Feng & Elson CO Muc Immunol 2011, Sansonetti Muc Immunol 2011, Chung et al, Cell 2012*]
- DC/microbiota cross-talk is altered in IBD
  [*Hart et al Gastroenterology 2005, Quinn et al, Nature 2010*]
  - immune response in IBD mainly directed against luminal microbiota
  - exposing DCs to commensal bacteria can affect DC phenotype and function
- *Lactobacilli plantarum* is the lactic-acid-producing bacterium with the largest genome – some extracellular proteins have been characterised
  - Imperial group used *L plantarum* as a model to explore the role of soluble factors
  - Characterised a secreted protein with a 66aa, protease-resistance domain
  - High in serine and threonine residue content (STp)



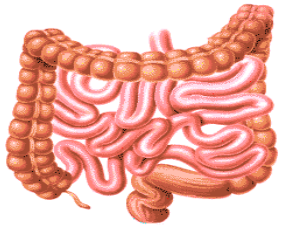
Peptide (STp) from *L. plantarum*

- **72 residue, protease resistant domain**
- **predicted molecular mass 6,8 kDa**
- **22% serine, 31.8% threonine**
- **cloned from *L plantarum* DNA**
- **expression in lactococcus lactis**
- **recombinant STp purified**
- **antibody produced - Western blots**

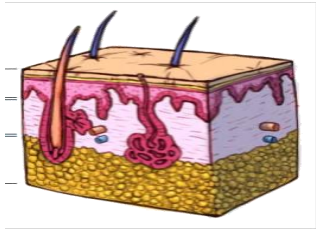


D. Bernardo et al. 2012 Plos ONE

STp in human colonic microenvironment



Gut biopsies

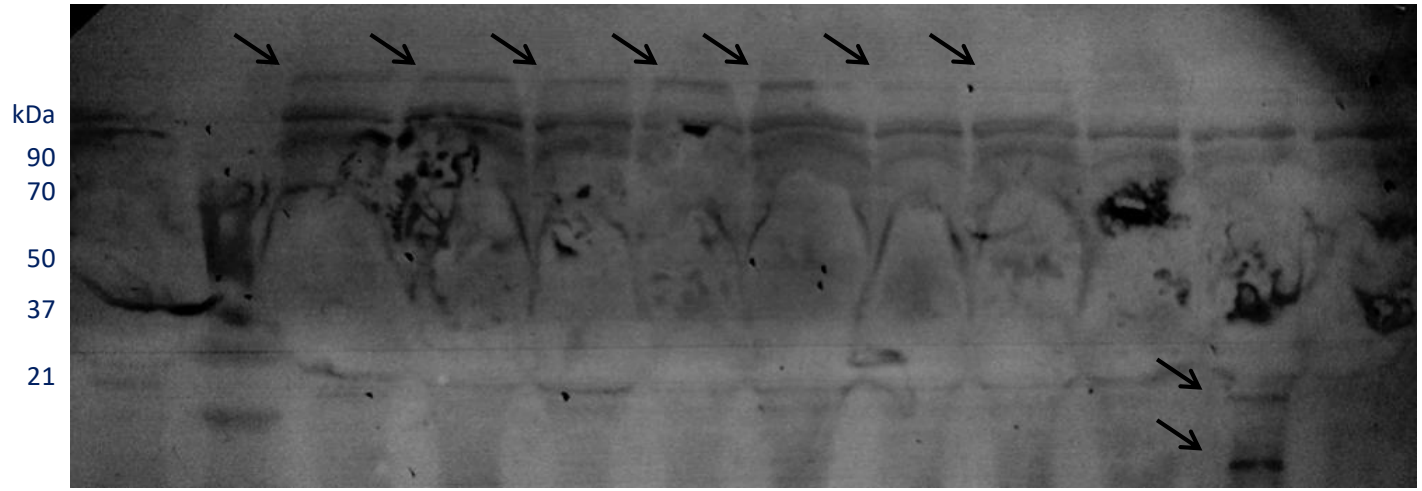


Skin biopsies

24h culture

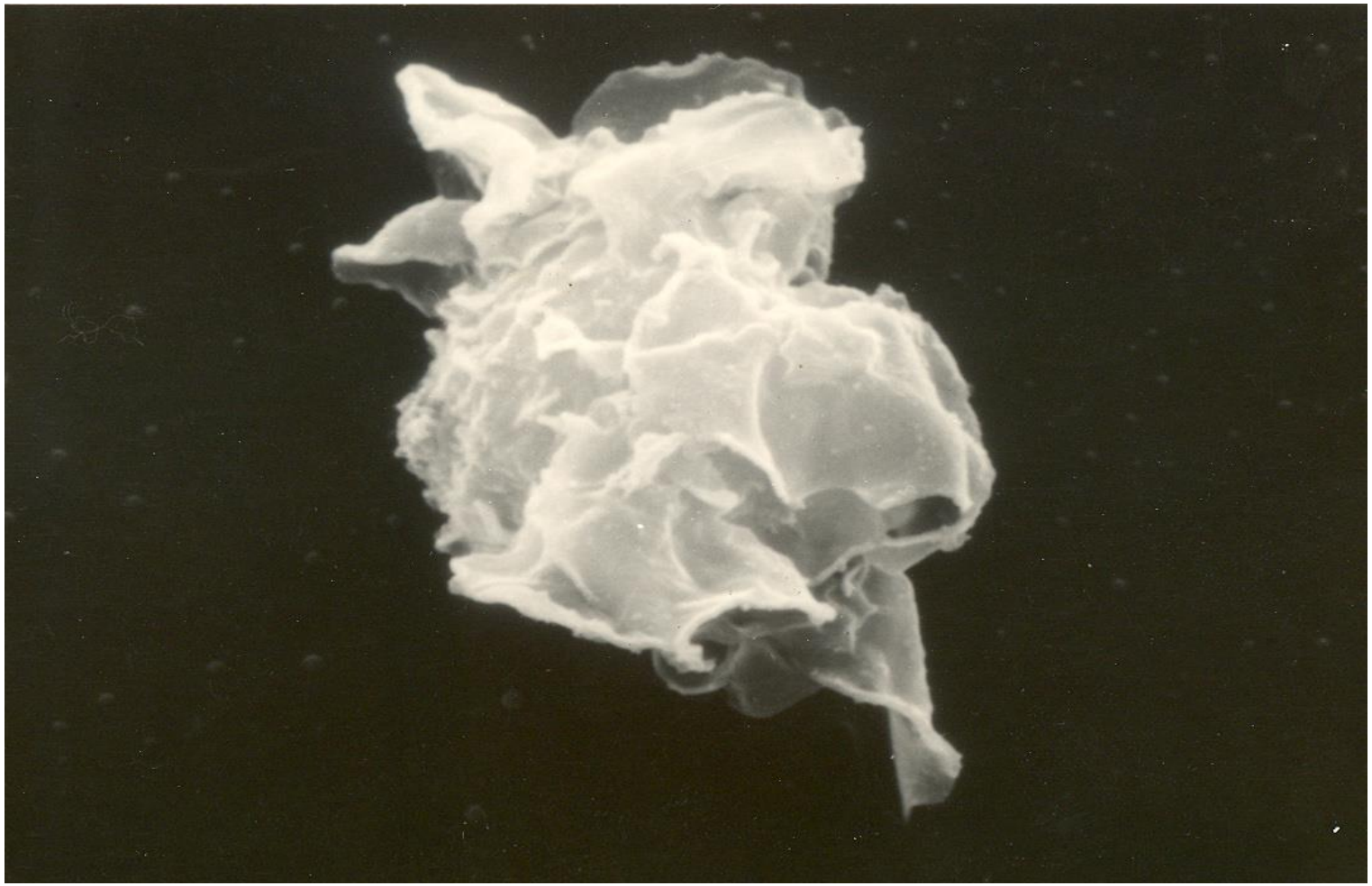
Western blots of cell-free culture supernatants

CM - HC1----------->HC10



- STp in 80% normal colons
- STp absent in normal skin
- STp found in only 21% UC colons

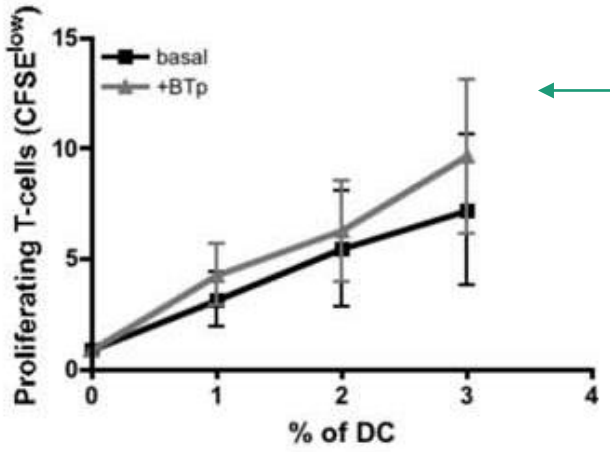
Dendritic antigen-presenting cells (DC)



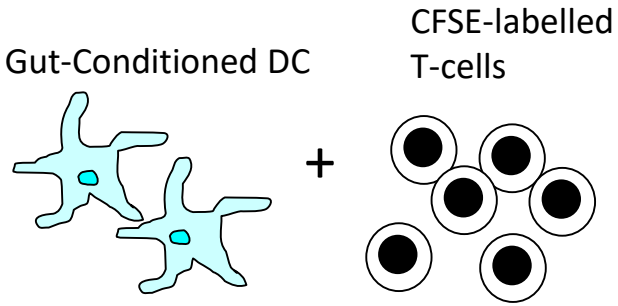
DC determine:-

Immune response +/-
Type of response
-CMI,Ab
Tissue location
-Tissue specific integrins

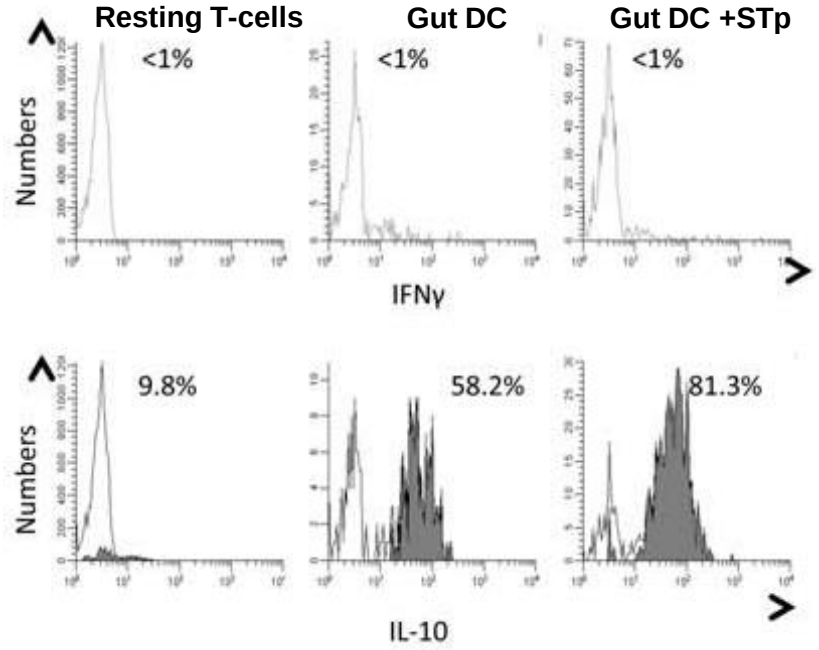
STp-treated DCs do not promote pro-inflammatory T cells

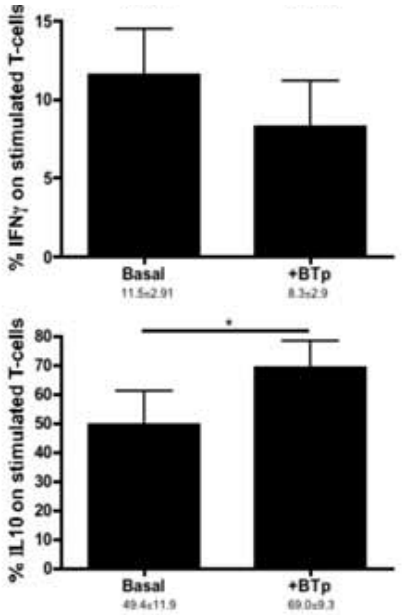


- STp conditioning of intestinal DCs does not alter their T cell stimulatory capacity.

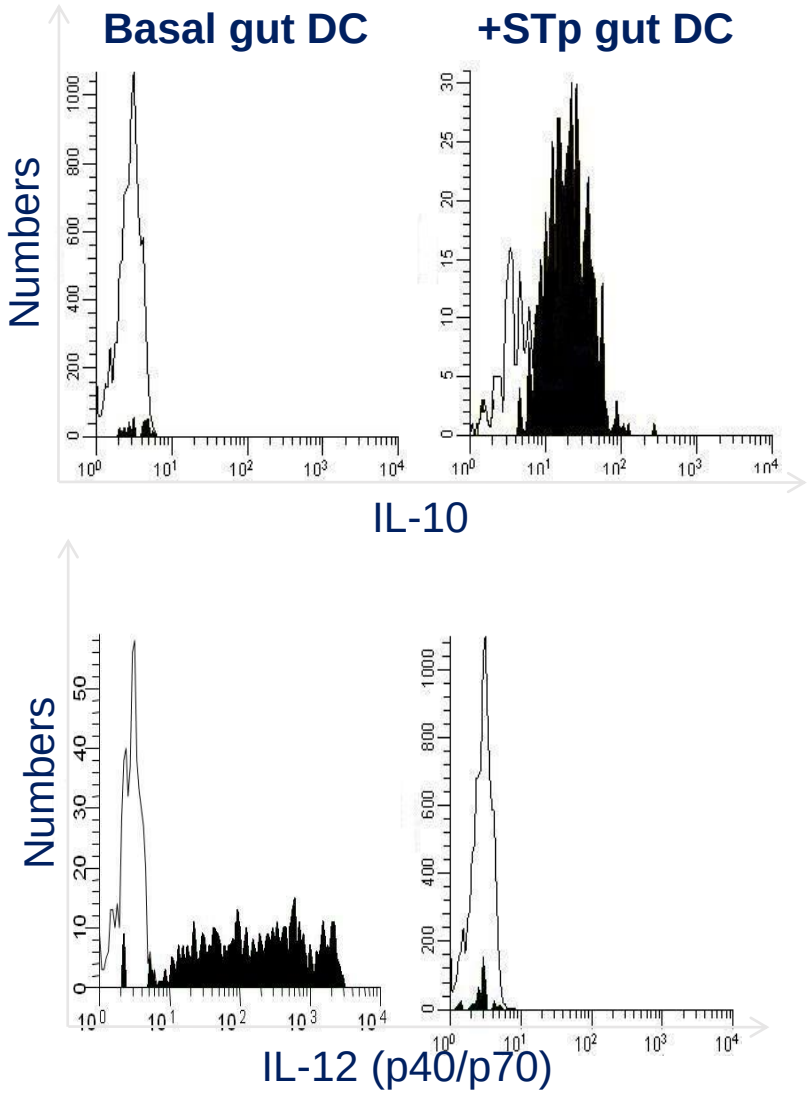


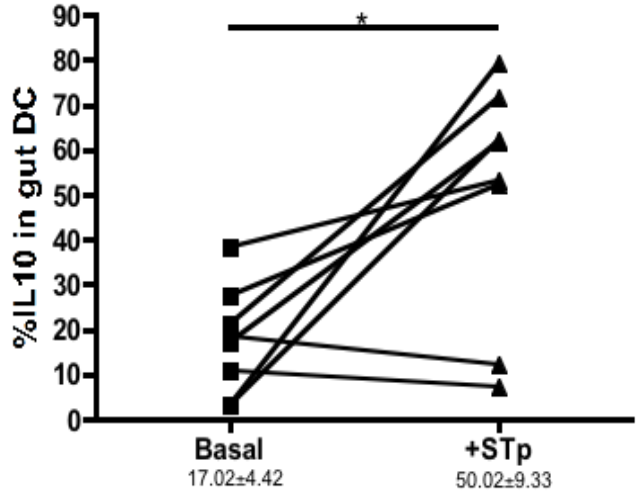
- IL10 production by stimulated T cells was increased whilst IFNγ production is unchanged, suggesting STp treated DCs do not promote pro-inflammatory T cells

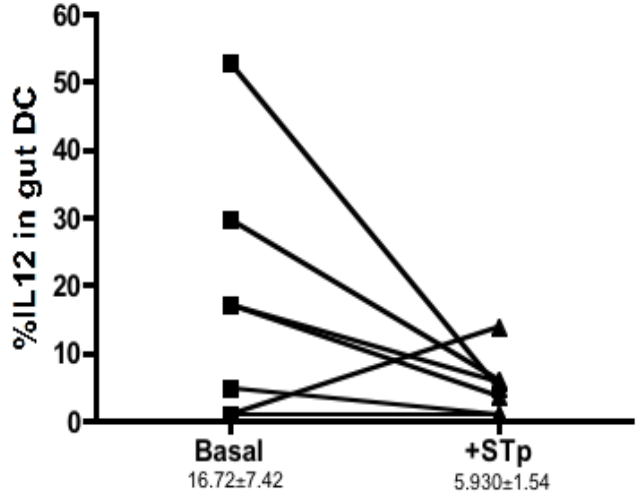




STp promotes “homeostatic” intestinal DC in UC

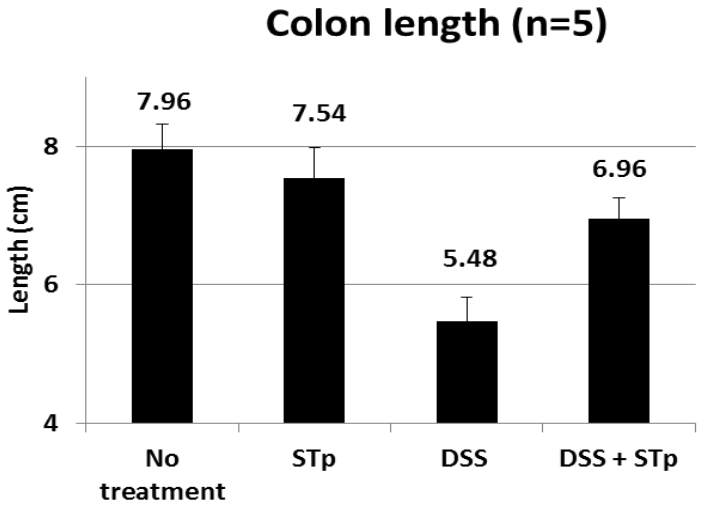


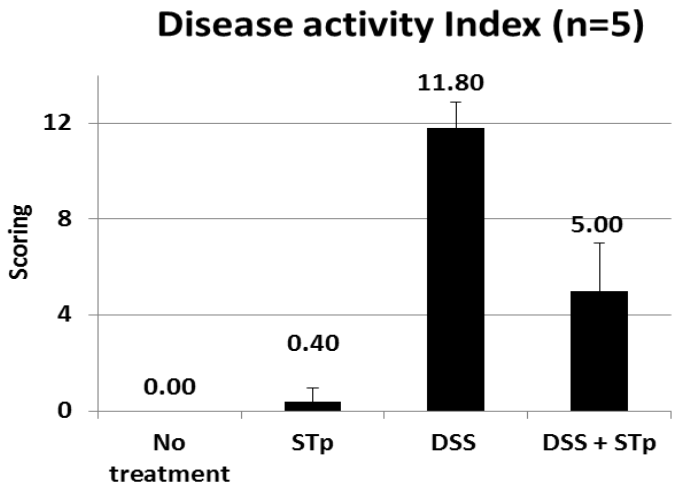


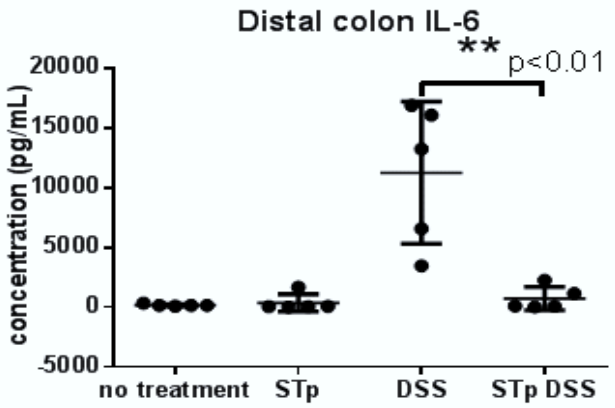


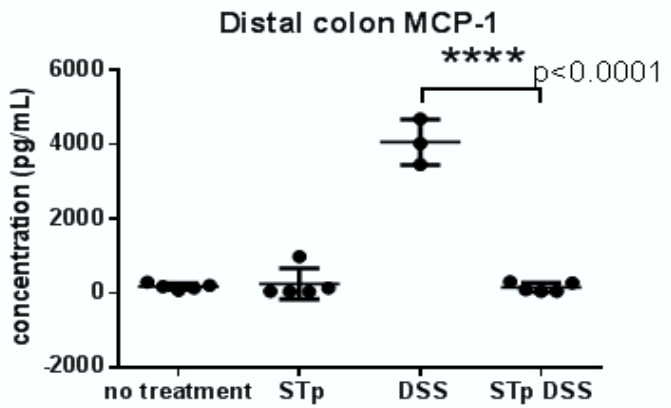
Al- Hassi et al. Mol Nutr. Food Res 2014

Therapeutic effects of STp in DSS mouse colitis
STp given on days 1,3 and 5 post colitis induction









Peptides from bacteria- the new “postbiotics”?

- STp peptide secreted from *Lactobacillus plantarum*
- Resistant to degradation by gut proteases
- Present in healthy gut – lost in UC
- Promotes regulatory cytokine profile in DC &T cells
- Reduces gut homing, promotes skin homing DC&T cells
- Reduces TLR expression
- Restores normal DC phenotype/function in UC *ex vivo*
- May help repair of gut epithelium