

# Role of $\alpha$ -MSH and related tripeptides as potential anti-inflammatory agents for inflammatory bowel disease



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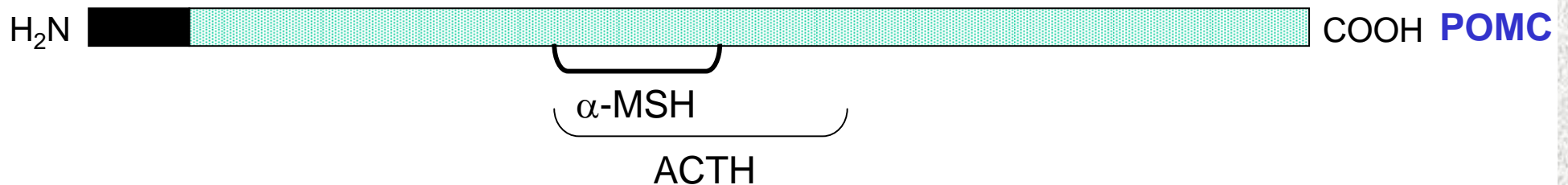
**BMRP**

**Broad Medical  
Research Program**

Inflammatory Bowel Disease Grants  
The Eli and Edythe L. Broad Foundation

# $\alpha$ -Melanocyte-stimulating hormone (MSH)

- $\alpha$ -MSH is a neuroimmunomodulating peptide, that is a postranslational product of pro-opiomelanocortin (POMC).



- It is constitutively expressed in the central nervous system (CNS) as well as by lymphocytes, monocytes, melanocytes and Langerhans cells.
- Alpha-MSH is involved in melanogenesis and exerts antipyretic, antimicrobial, antiinflammatory and immunomodulating activities.
- $\alpha$ -MSH (ACTH (1-13))

Ac- Ser<sup>1</sup>-Tyr<sup>2</sup>-Ser<sup>3</sup>-Met<sup>4</sup>-Glu<sup>5</sup>-His<sup>6</sup>-Phe<sup>7</sup>-Arg<sup>8</sup>-Trp<sup>9</sup>-Gly<sup>10</sup>-Lys<sup>11</sup>-Pro<sup>12</sup>-Val<sup>13</sup>-NH<sub>2</sub>

**KPV (11-13)**

# Melanocortin-Receptors

The effect of  $\alpha$ -MSH is basically mediated through binding to melanocortin receptors

There are five G protein-coupled melanocortin receptors (MCPs) that have been identified and cloned so far.

- MC1-R** → highest affinity to  $\alpha$ -MSH, mediates antiinflammatory effect
- MC2-R** → steroidogenesis
- MC3-R** → energy homeostasis, sexual behaviour
- MC4-R** → energy homeostasis
- MC5-R** → subcutaneous gland secretion

# Immunomodulatory Properties of $\alpha$ -MSH *in vitro* and *in vivo*

- In vitro***
- Inhibition of proinflammatory cytokines (e.g. IL-1, IL-6, TNF $\alpha$ , IL-2, IFN- $\gamma$ , IL4, IL-13). Mediated in part by inhibition of NF $\kappa$ B
  - Antimicrobial activity (*Staphylococcus aureus*, *Candida albicans*).

- In vivo***
- Modulates contact hypersensitivity in C57Bl6 mice and in humans

$\alpha$ -MSH control



Nickelsulfate

- 5%

- 1%

- 0.1%

- 0.01%

- 0%



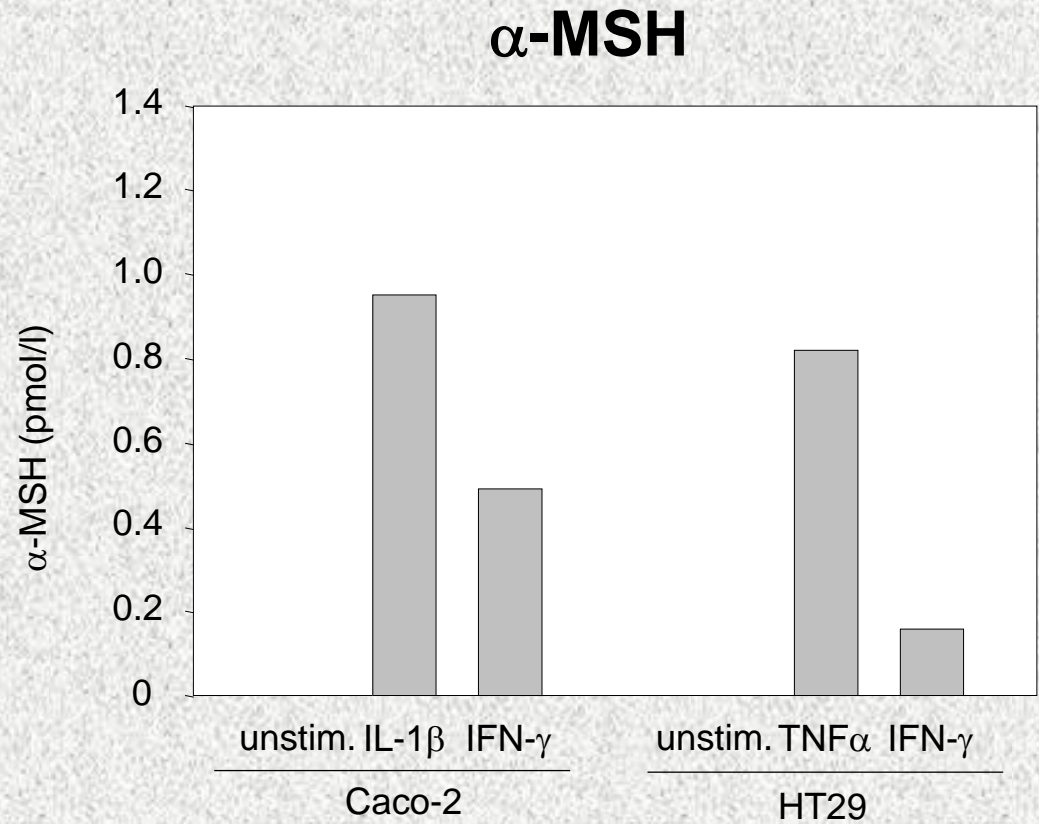
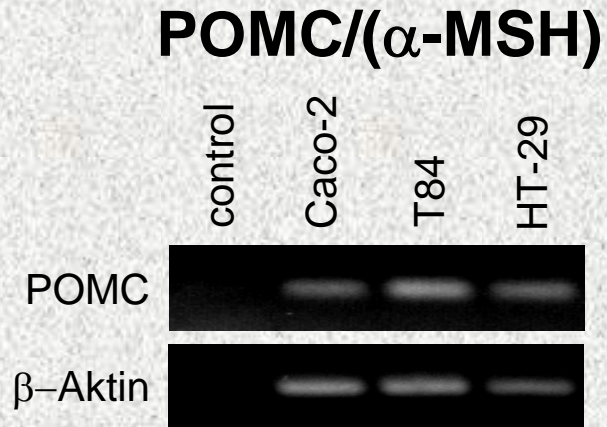
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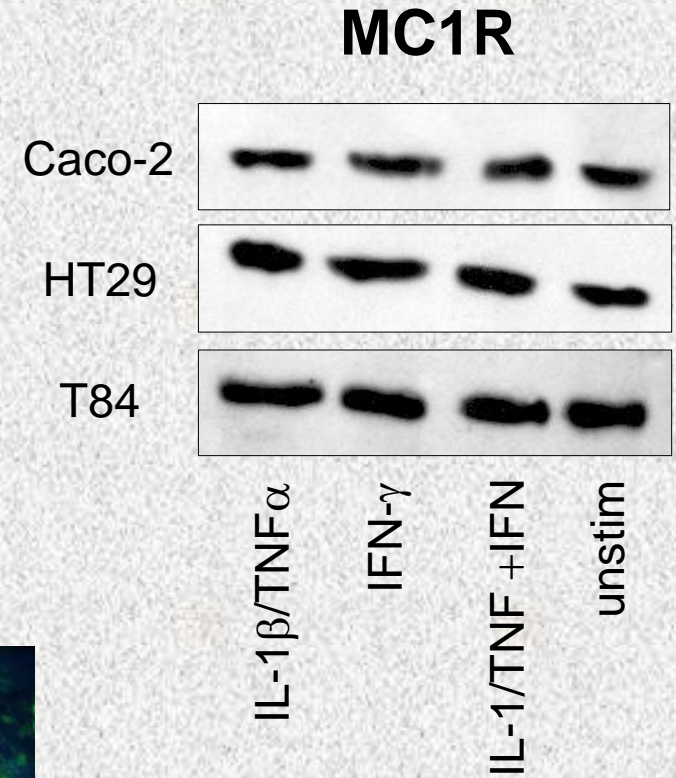
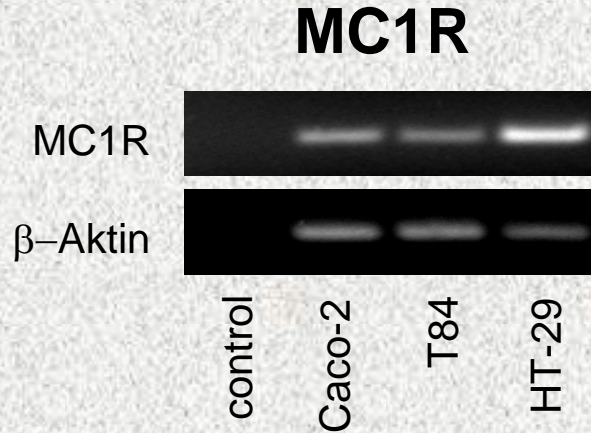


# Intestinal Epithelial Cell Lines - Inducible Expression of $\alpha$ -MSH *in vitro*

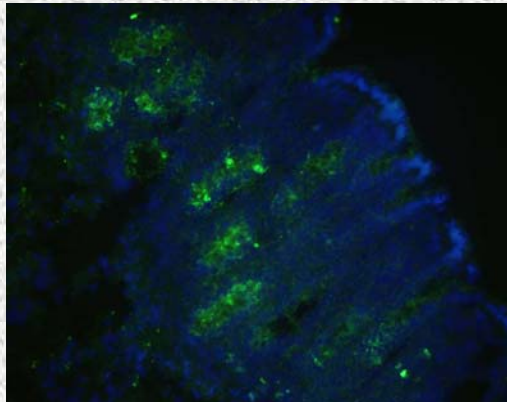


# Intestinal Epithelial Cell Lines

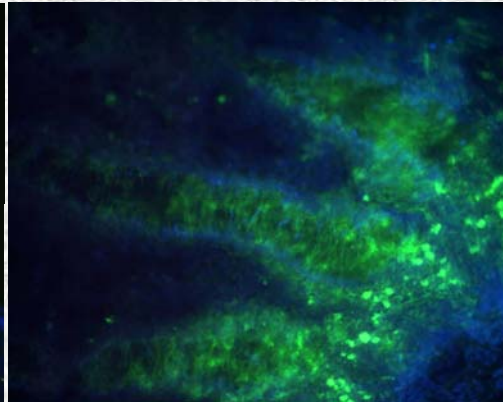
## Expression of MC1R *in vitro* and *in vivo*



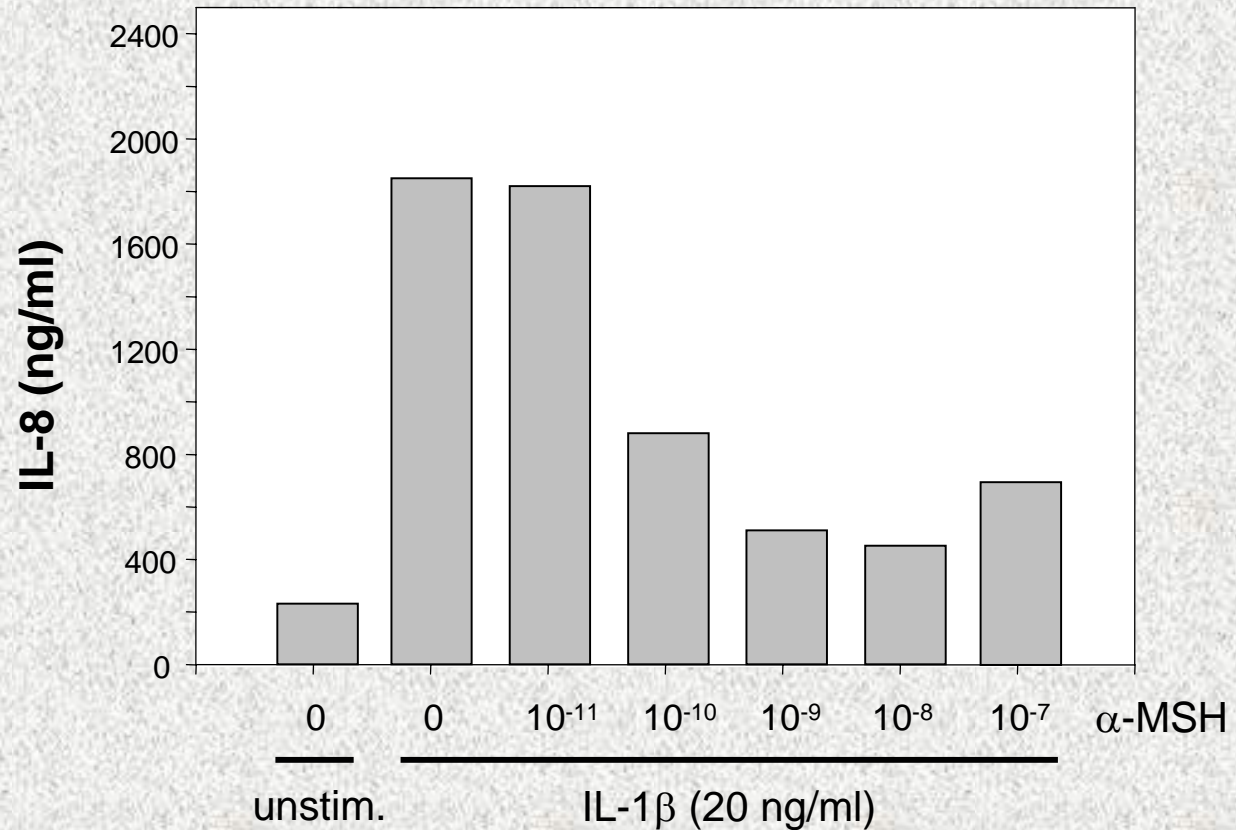
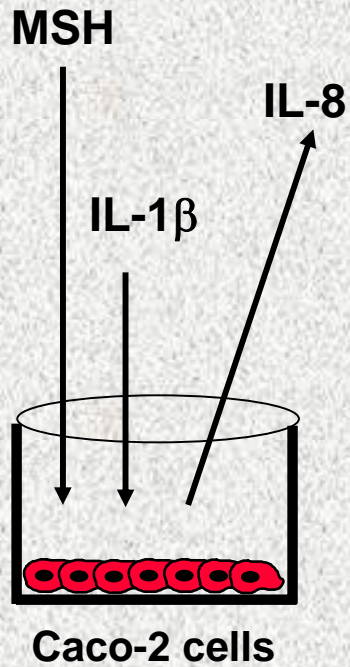
colon  
non-inflamed



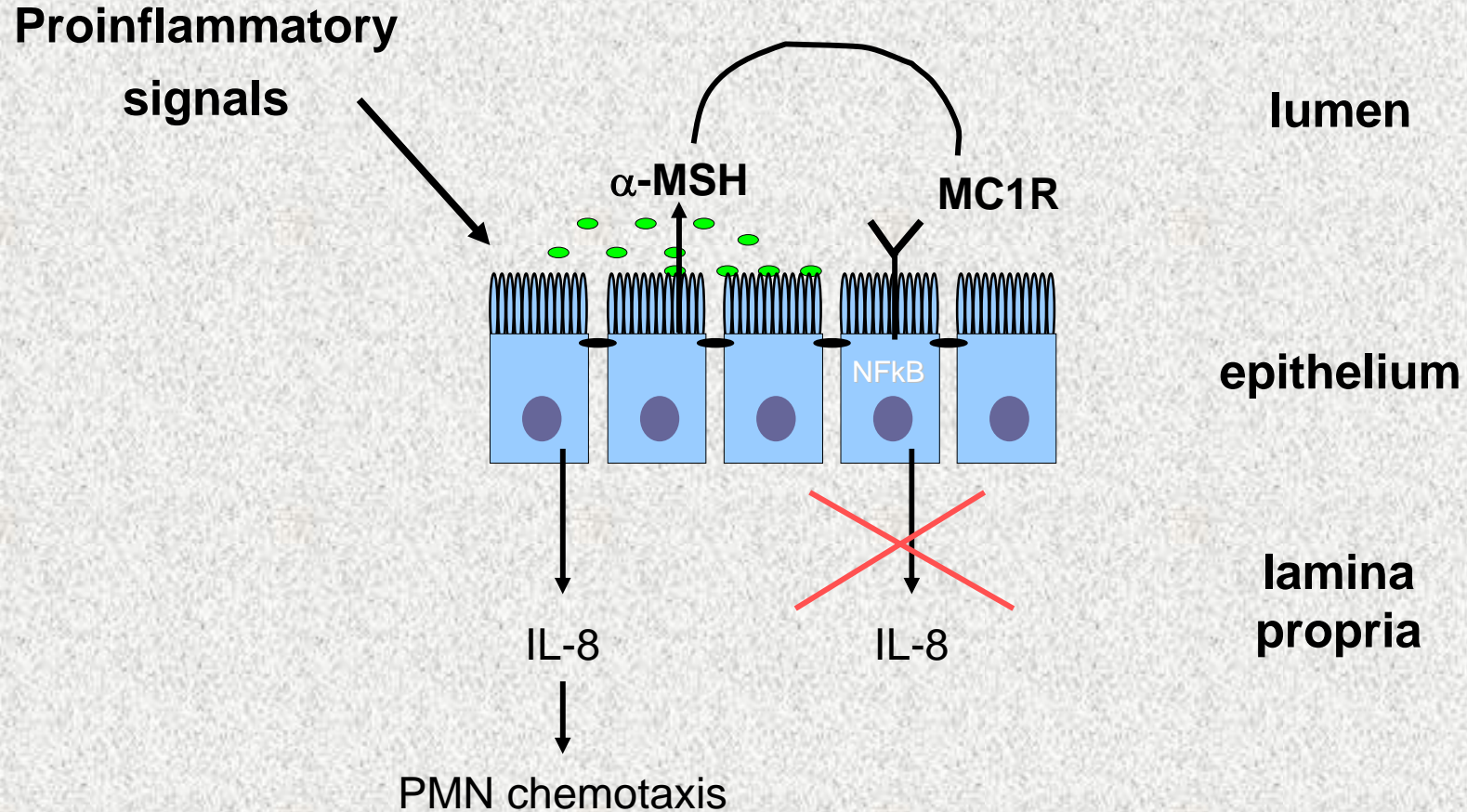
colon  
IBD



# Effect of $\alpha$ -MSH on Cytokine Induced Epithelial Interleukin-8 Secretion

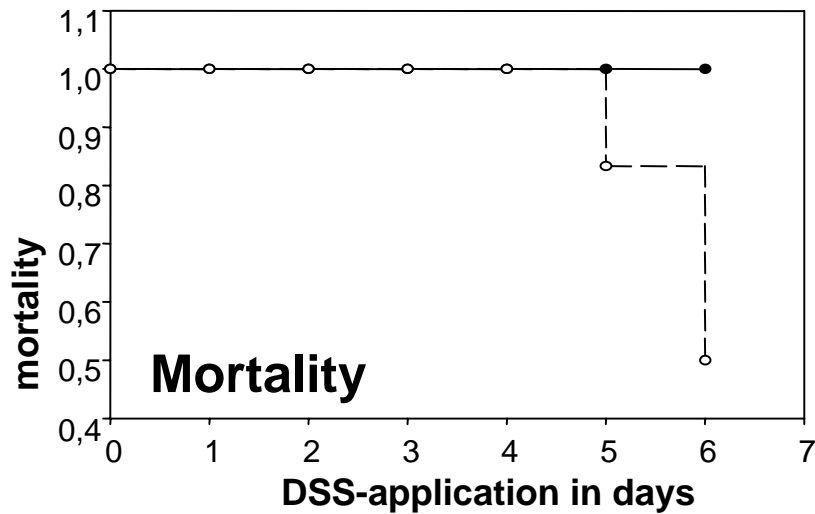
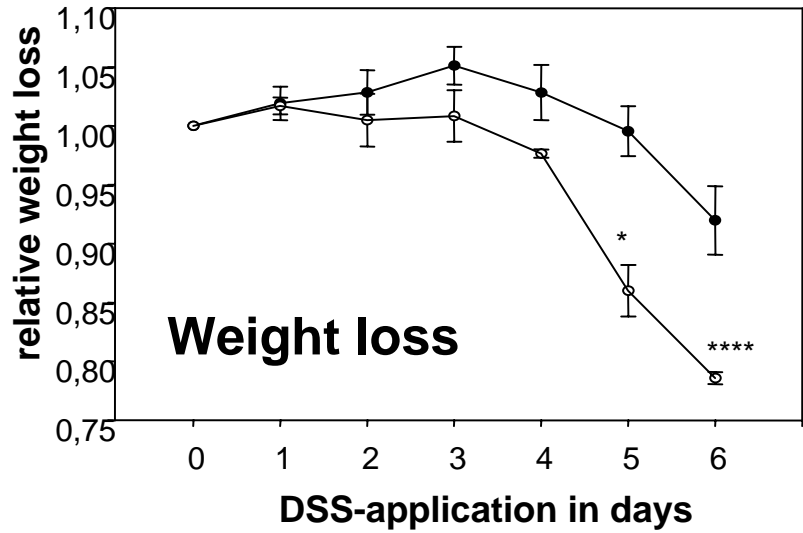


# Potential Autoregulatory Role of $\alpha$ -MSH in the Intestinal Immune System

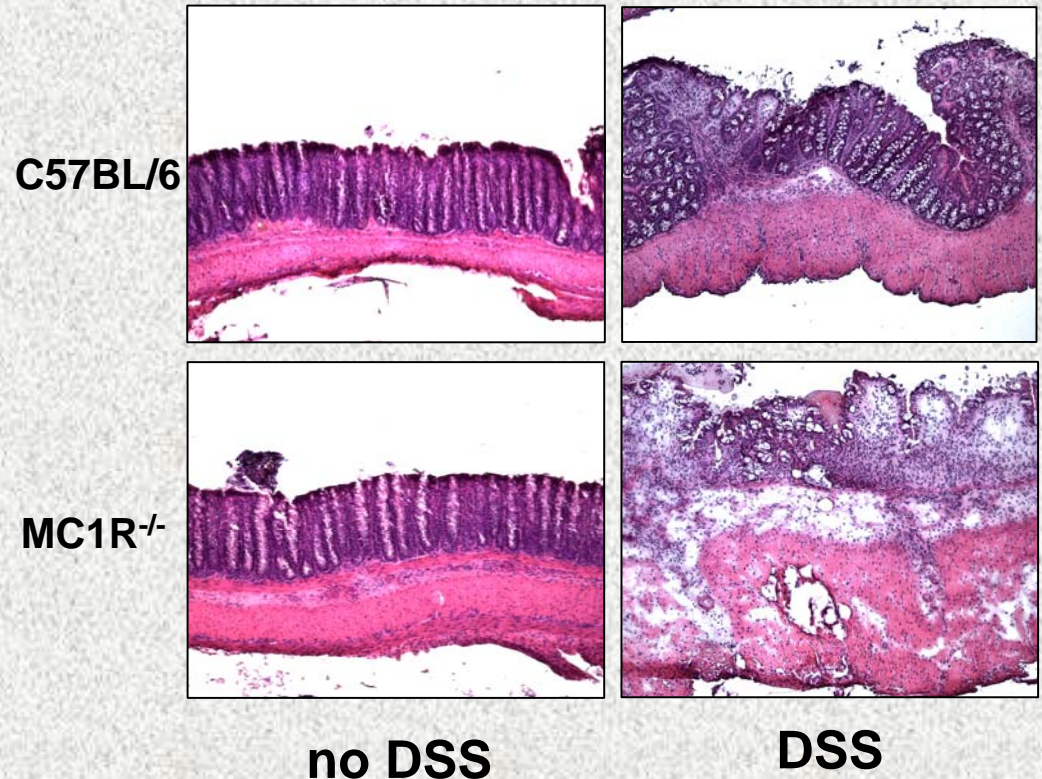


# Role of MC1R during intestinal inflammation

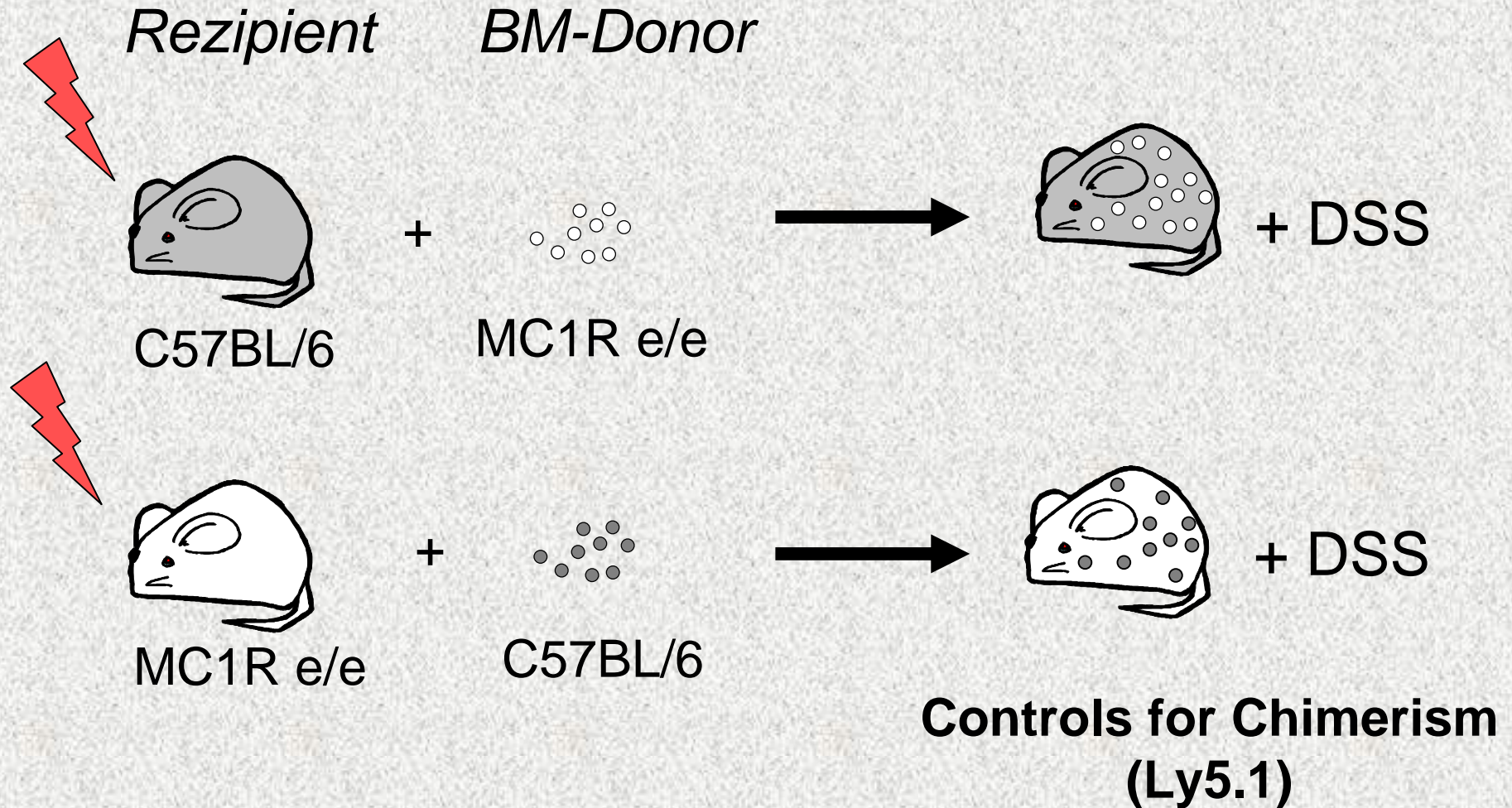
MC1R e/e mice develop severe DSS colitis



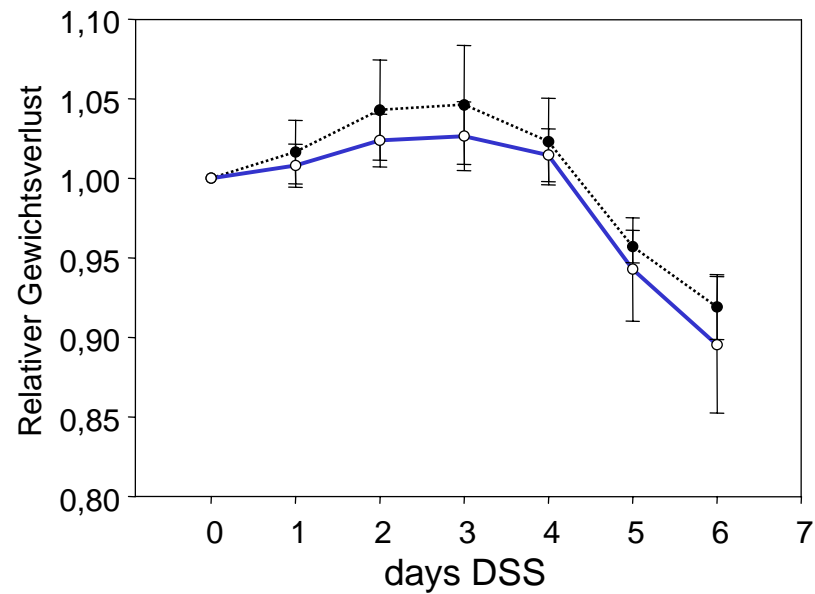
- C57BL/6 WT
- C57BL/6 MC1R e/e



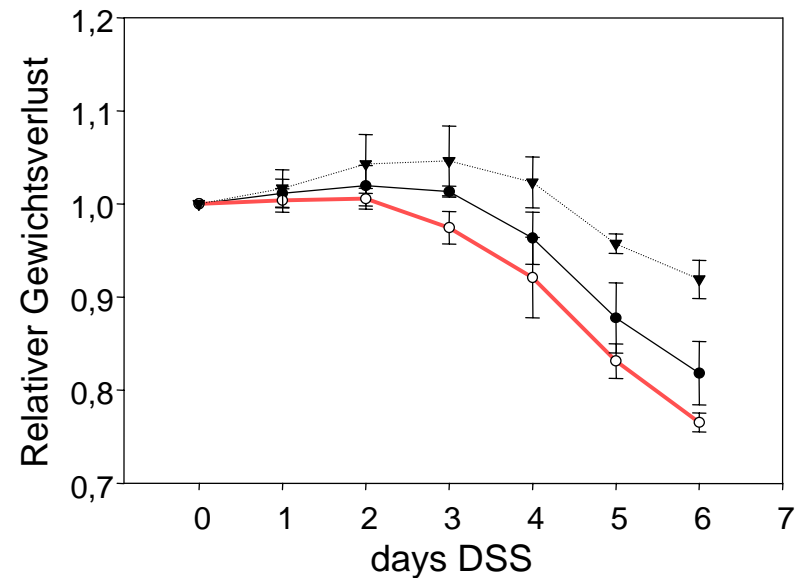
# DSS Colitis in MC1R<sup>e/e</sup> / C57BL/6 - Chimera



# MC1 Receptor on Non-Hematopoietic Cells Mediates Protection during DSS Colitis



- C57Bl/6 WT no radiation
- C57Bl/6 WT + C57Bl/6 MC1R -/- BM

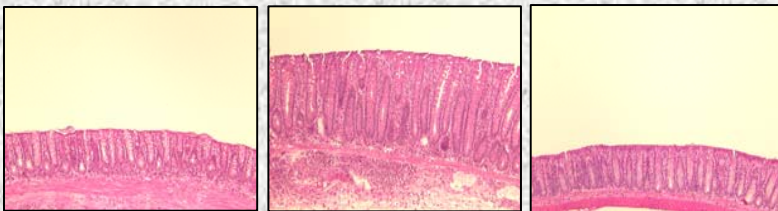


- C57Bl/6 MC1R -/- no radiation
- C57Bl/6 MC1R -/- + C57Bl/6 WT BM
- ▼ C57Bl/6 WT no radiation

# Clearance of *Citrobacter rodentium* in MC1R e/e Mice is prolonged compared to wild-type Mice

## *Citrobacter rodentium*

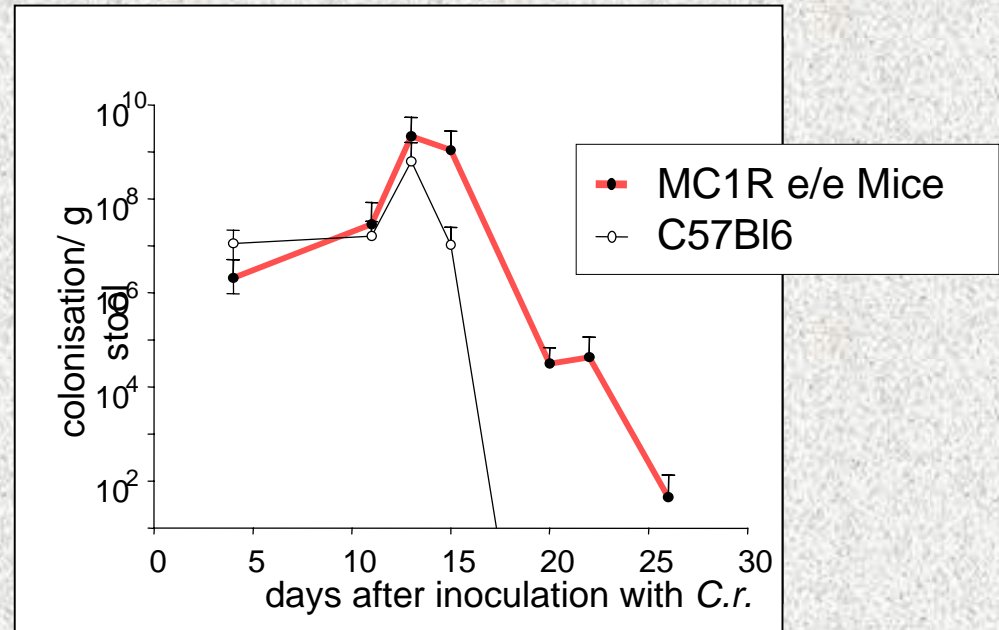
- Induces Murine Transient Intestinal Hyperplasia
- Murine model for human EHEC infection
- Mononuclear cell infiltrate in the lamina propria
- Th1 mediated immune response
- Clearance of *Citrobacter rodentium* after 2 weeks



Week 0 p.i.

Week 2 p.i.

Week 6 p.i.



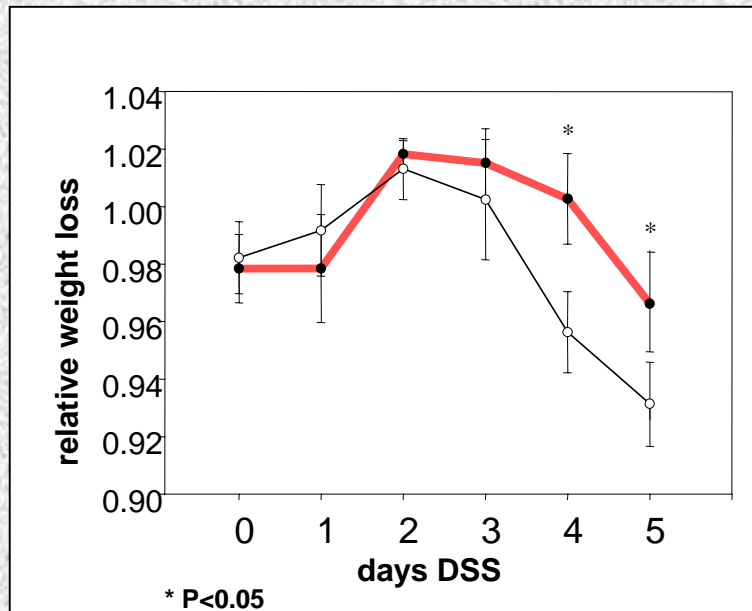
→Aggravation of intestinal inflammation in MC1e/e mice in two different colitis models

→Our data demonstrate for the first time a functional role of MC1 receptor in disease

→Experiments with MC1R e/e chimeras suggest a pivotal role of mesenchymal cell expressed MC1R in the host's response to pathogenic stimuli

# Antiinflammatory properties of $\alpha$ -MSH and its tripeptide KPV in IBD animal models

Protective effect of KPV on the course of DSS-colitis in C57Bl6-mice



● C57Bl6, 10µg KPV i.p.  
○ C57Bl6, PBS i.p.

## fecal blood test

DSS (days)	1	2	3	4	5
PBS	0/5	n.d.	5/5	5/5	5/5
KPV	0/4	n.d.	0/4	1/4	4/4

# Future Projects

## Signaltransduction pathways of $\alpha$ -MSH in intestinal epithelial cells

- c-AMP accumulation after treatment with  $\alpha$ -MSH
- Effect on MAPK and NF $\kappa$ B-pathways
- Effect of  $\alpha$ -MSH agonists and antagonists

## Relevance of melanocortin receptors during inflammatory bowel disease

- Tissue expression of MC receptors in IBD
- Role of MC1R during experimental colitis (effect on barrier function)

## Antiinflammatory capacity of $\alpha$ -MSH and KPV during experimental colitis and in humans

- Citrobacter rodentium* colitis and Oxazolone colitis
- Topic effect of  $\alpha$ -MSH and KPV during colitis



***In vivo* studies in humans**



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**Funded by**

