

Gut microbes and the cancer macroenvironment

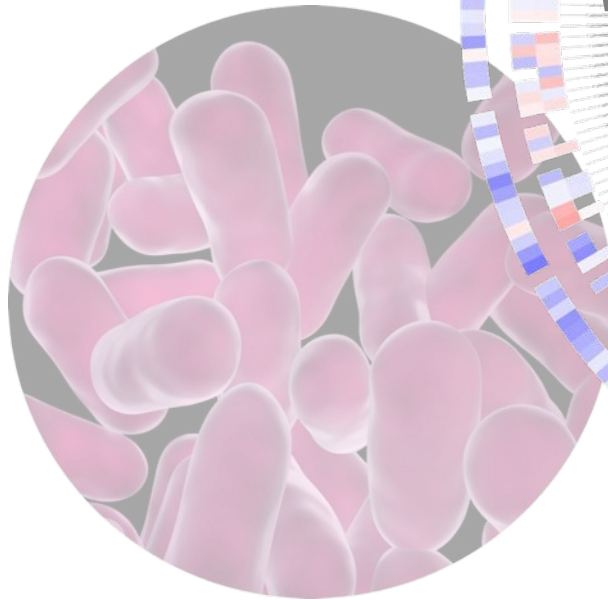


Origins of Cancer
Van Andel Research Institute

July 11, 2014



Susan E. Erdman
Division of Comparative Medicine
Massachusetts Institute of Technology



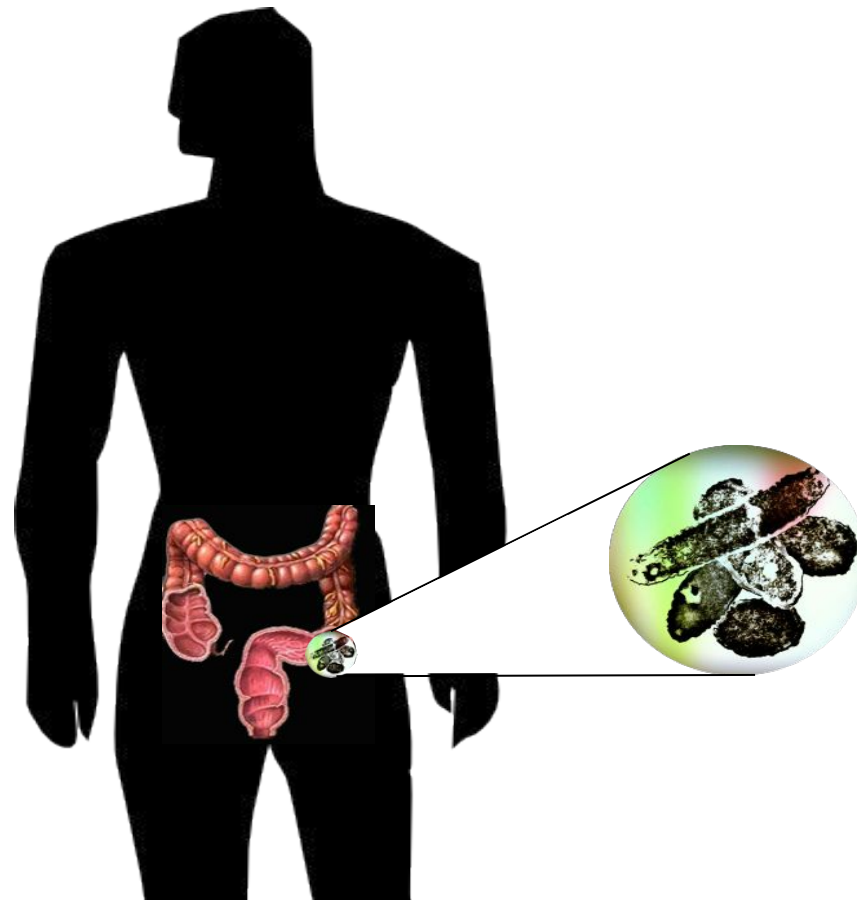
Healthful longevity

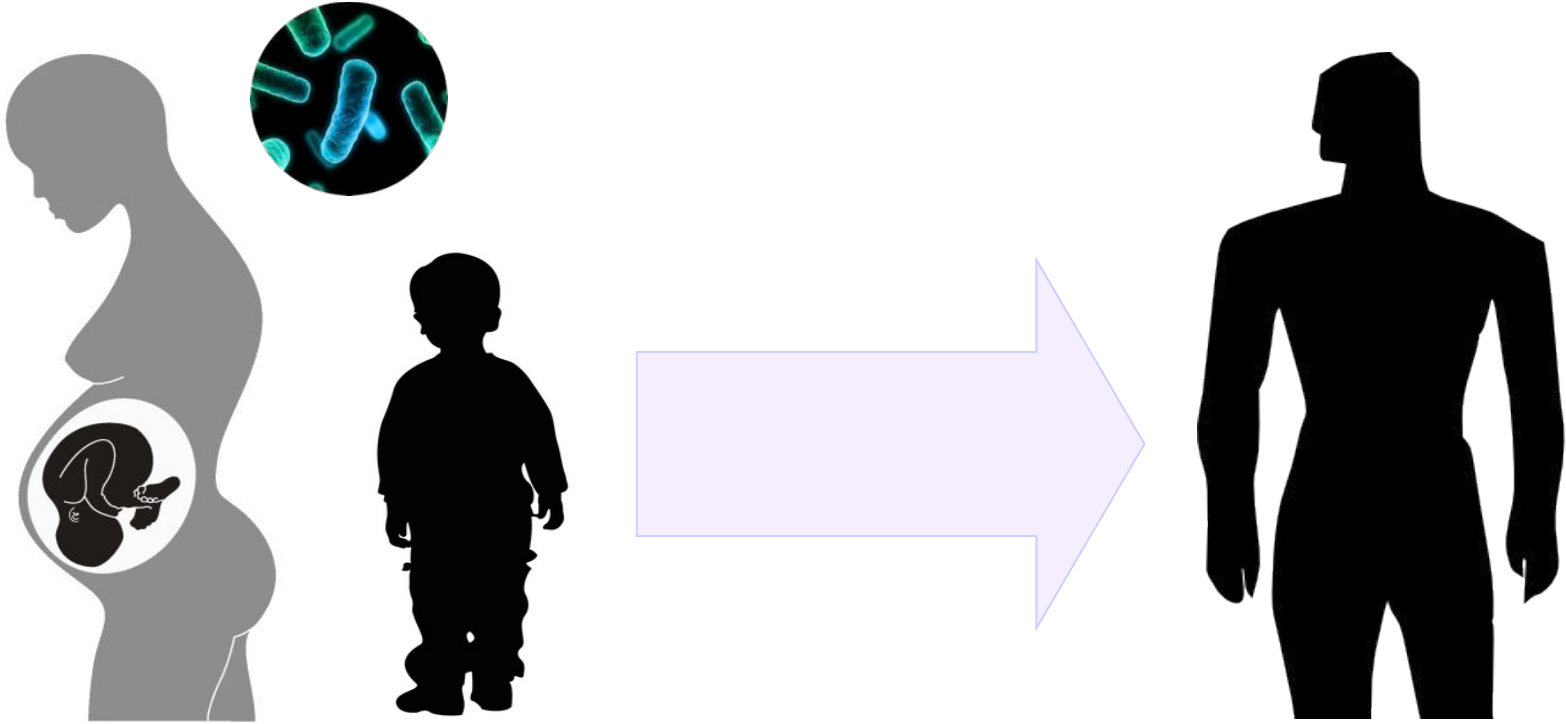
Th-1

Th-2

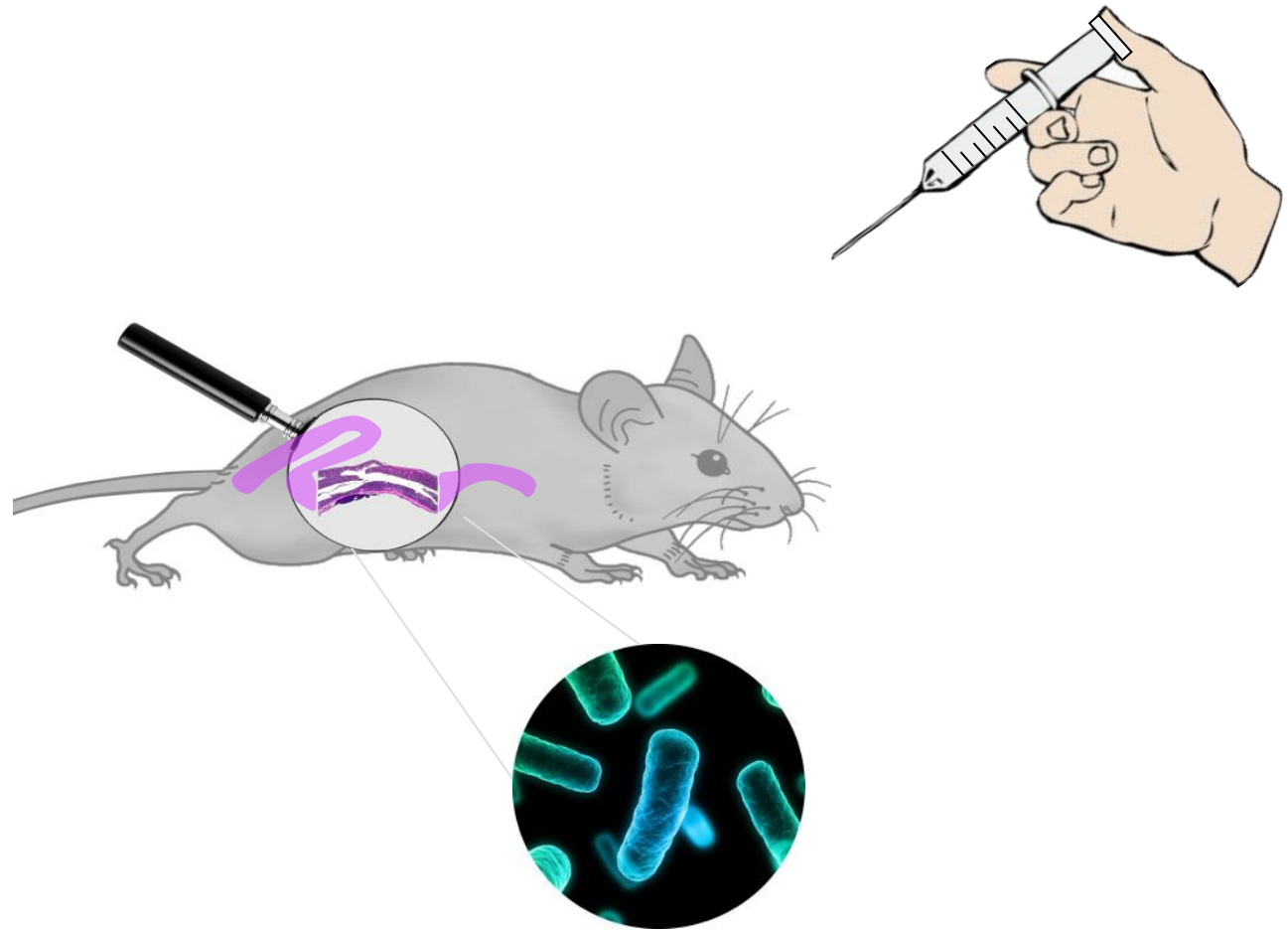
Th-17

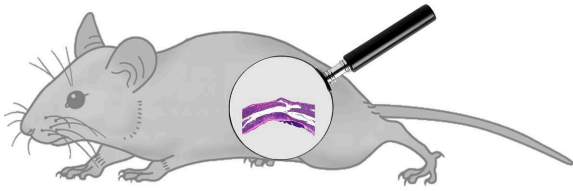
T_{REG}



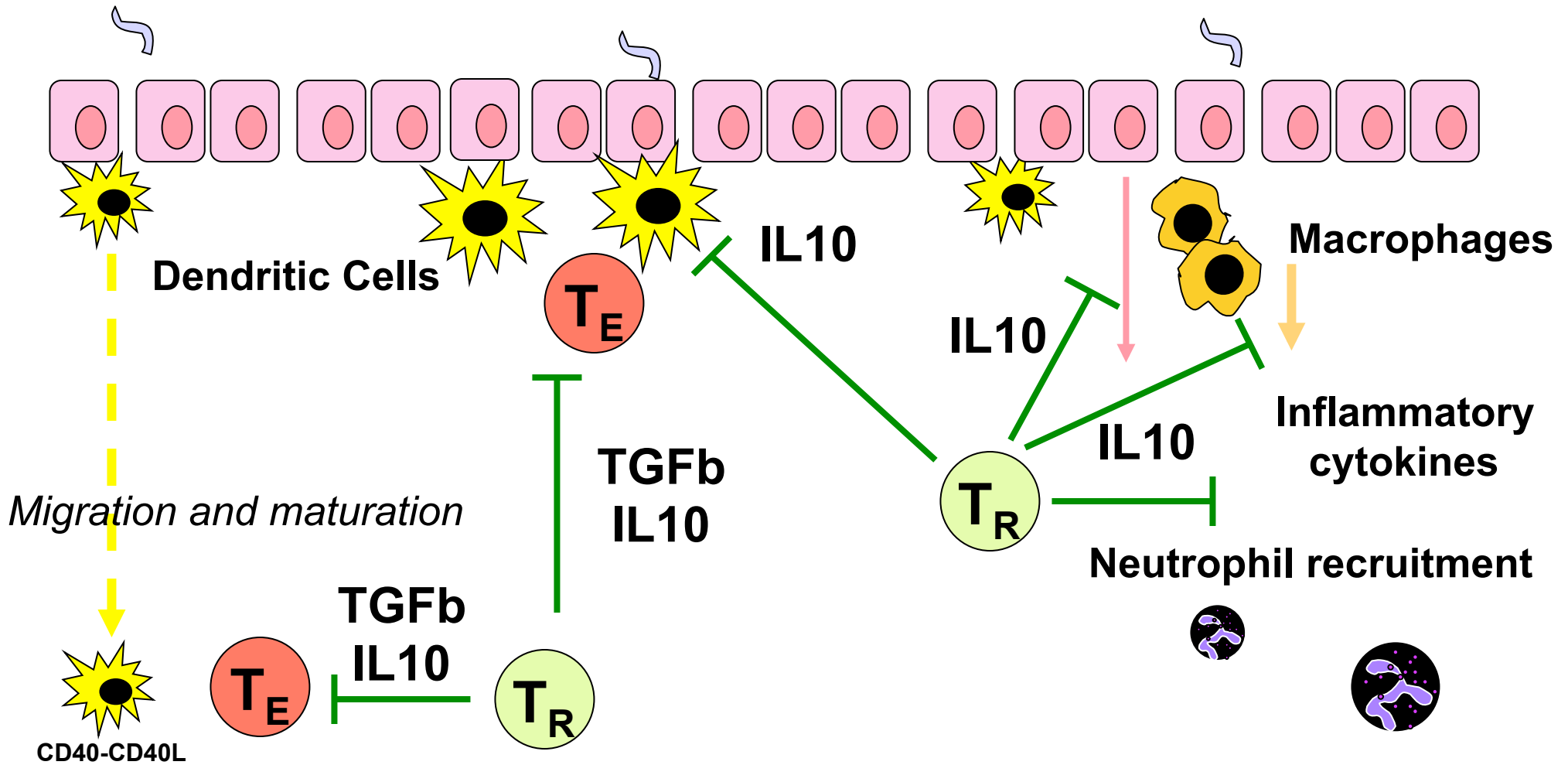


Why use animal models?





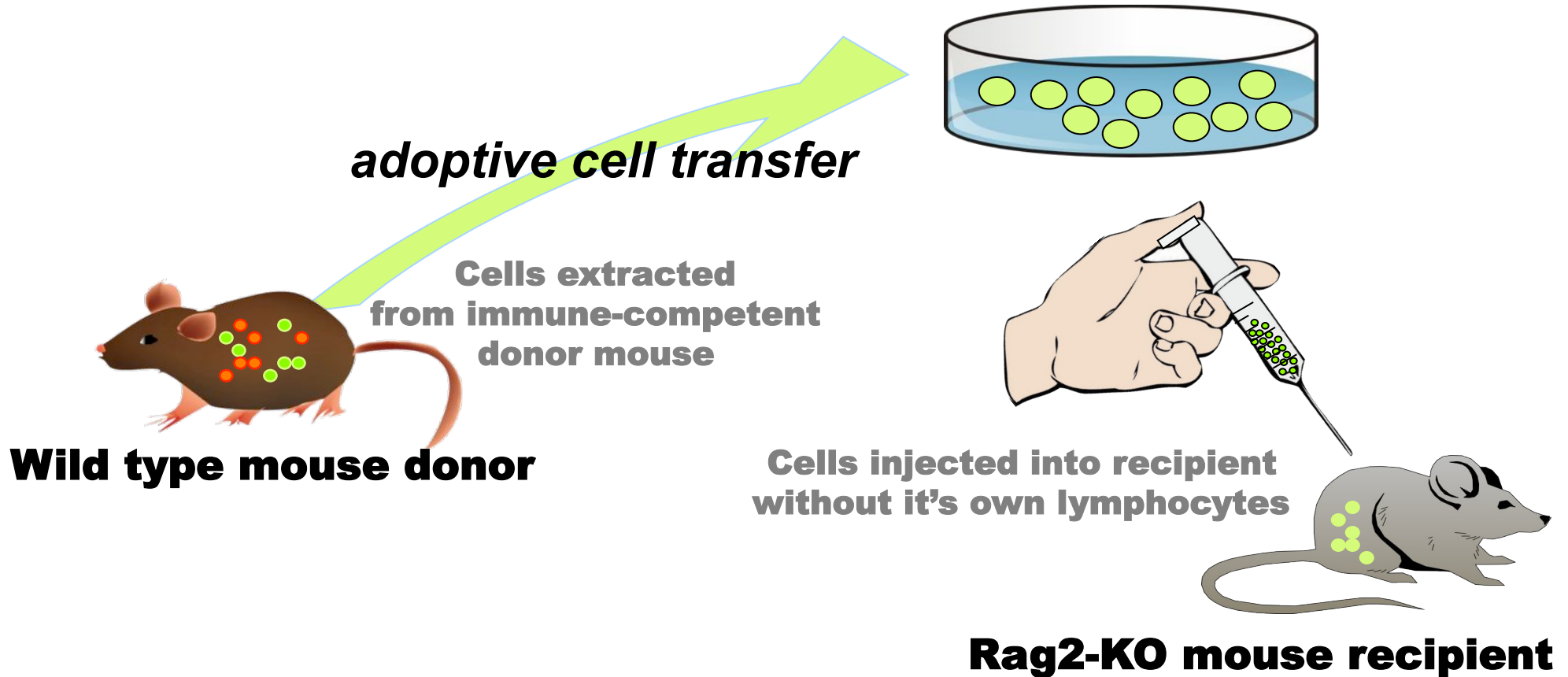
Gut microbe-triggered systemic events

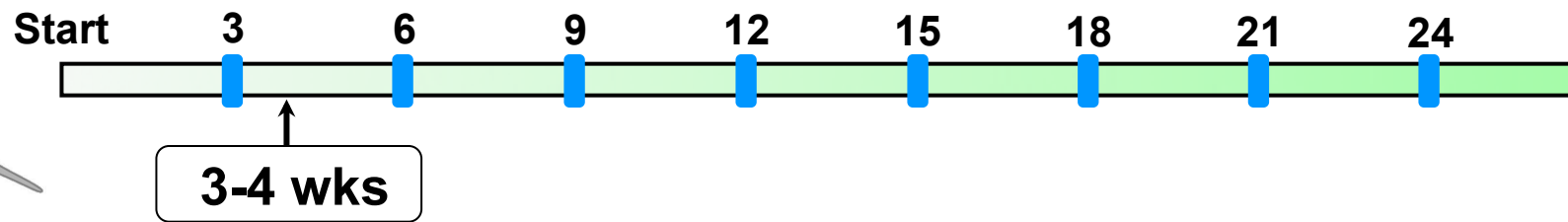
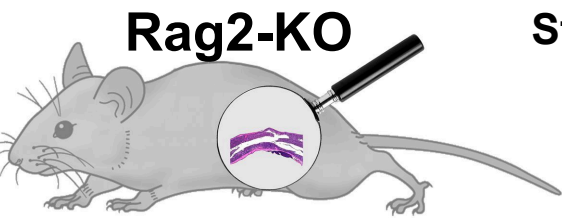


(modified from Coombs, et al 2005; Fiona Powrie lab)

Adoptive Cell Transfer Paradigm

**Transplantable anti-inflammatory
CD4⁺CD45RB^{lo}CD25⁺ lymphocytes**



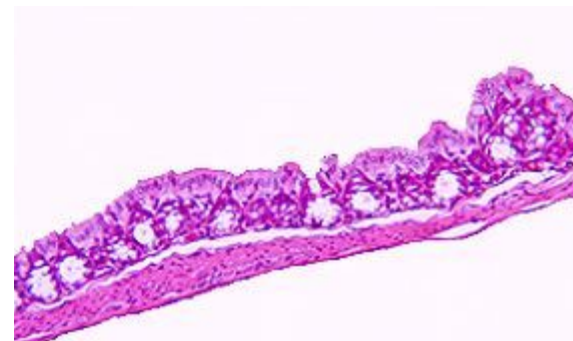


Uninfected

***H. hepaticus*-infected**

***H. hepaticus*-infected**

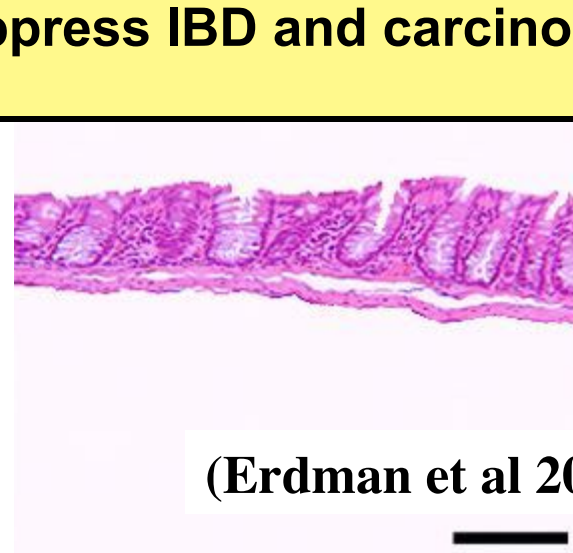
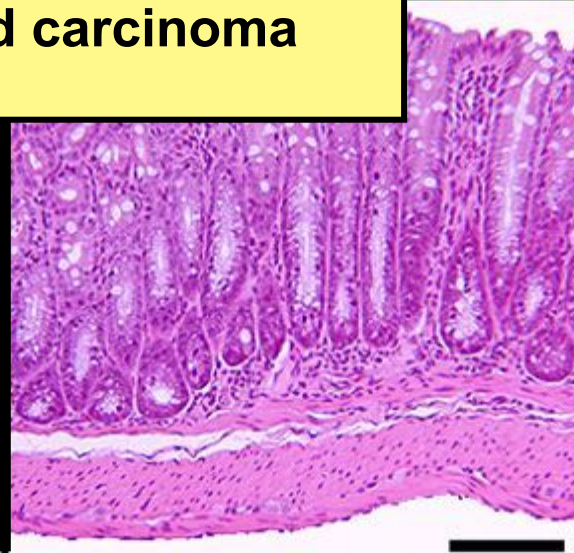
cecum



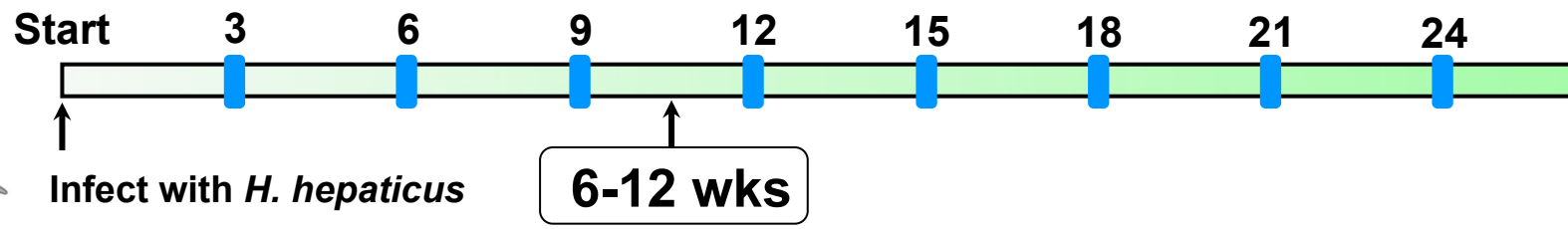
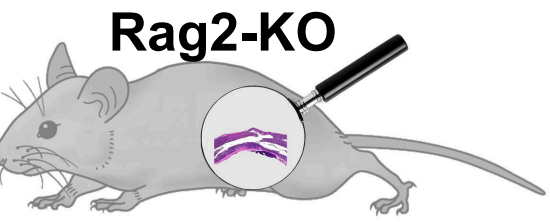
Innate immunity is sufficient for IBD and carcinoma

Cells of adaptive immunity suppress IBD and carcinoma

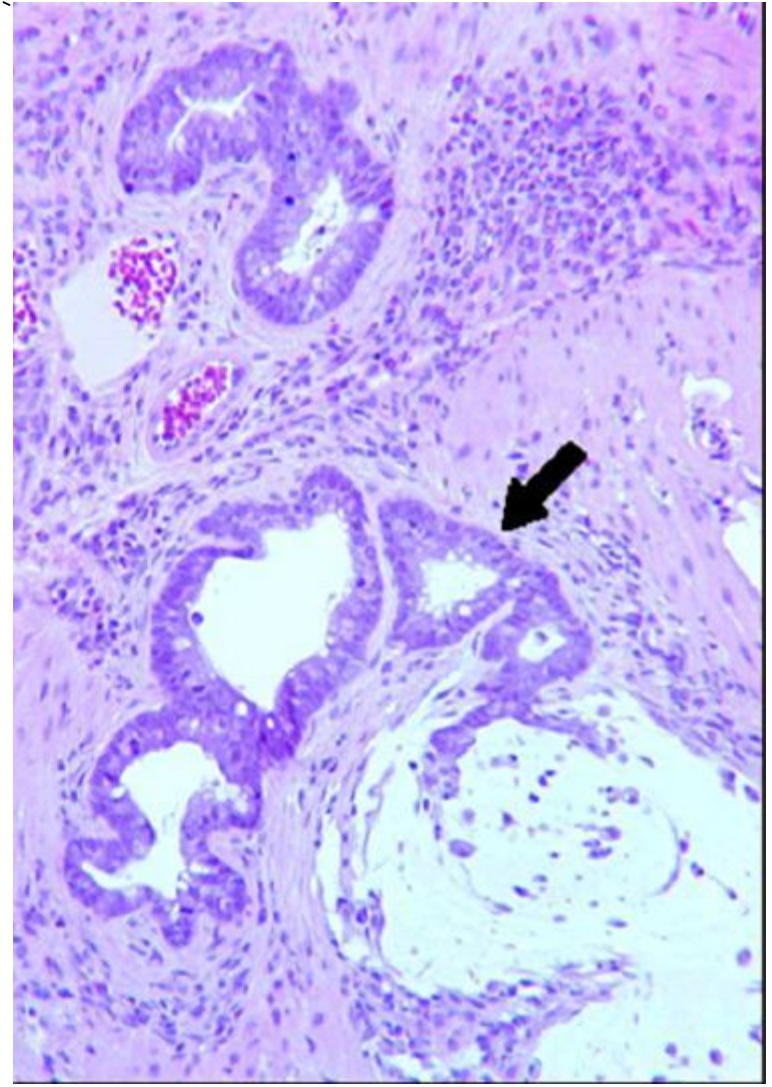
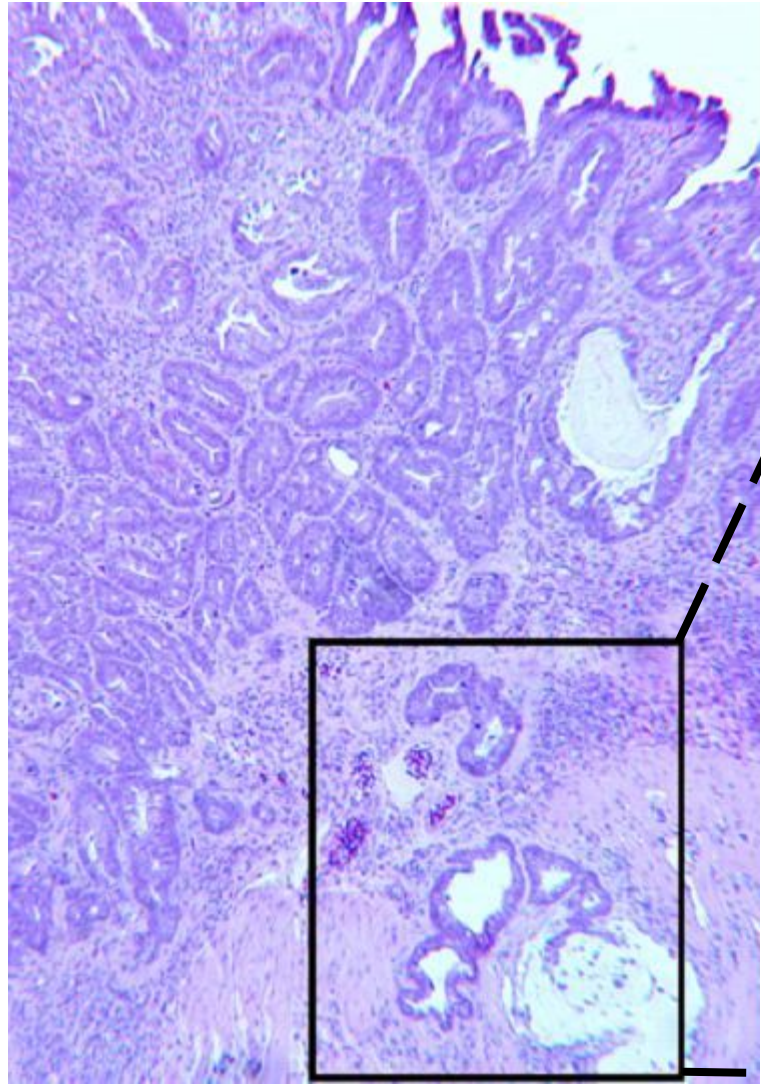
colon



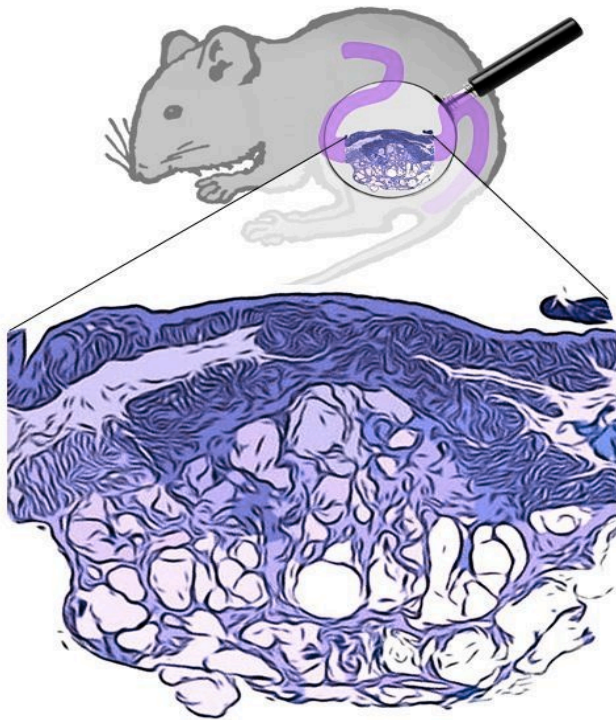
(Erdman et al 2003)



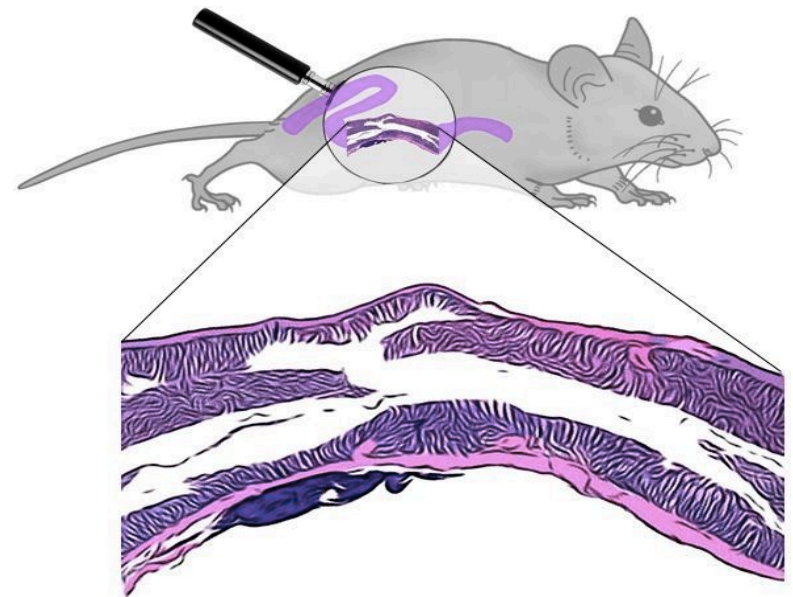
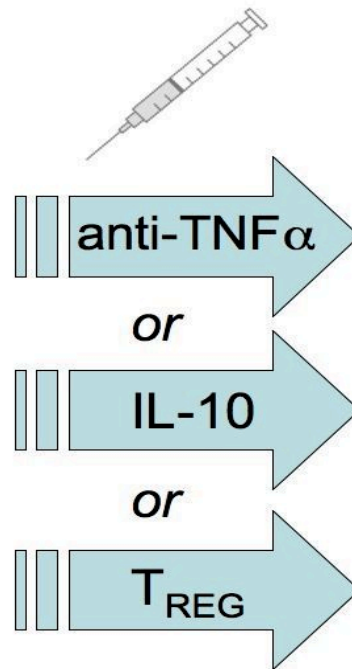
Invasive colonic carcinoma in *H. hepaticus*-infected Rag2^{-/-} mice



Blocking inflammation leads to total remission of established invasive colonic carcinoma

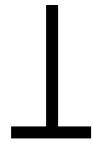
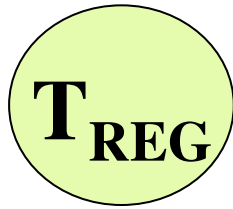


mucinous CRC with peritoneal neoplastic invasion



restoration of normal colonic epithelia after anti-inflammatory treatment

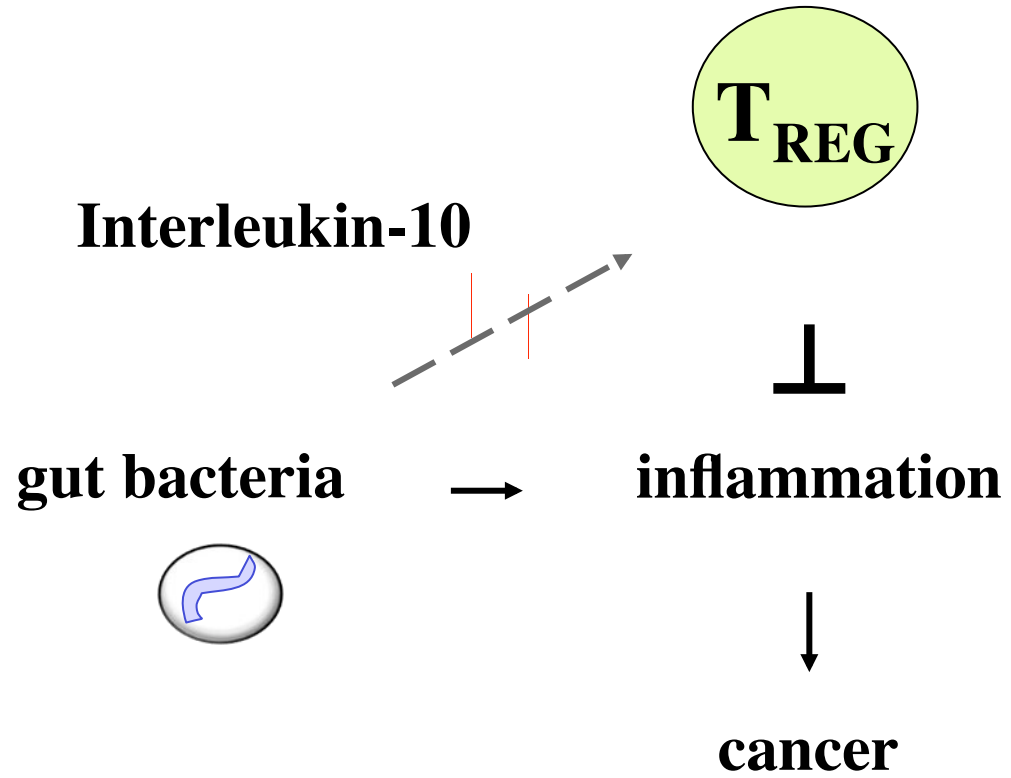
Interleukin-10



**Pro-inflammatory
cells & cytokines**



Tumor growth

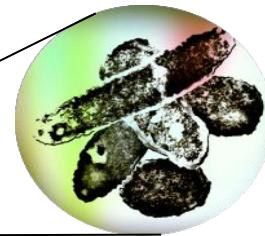
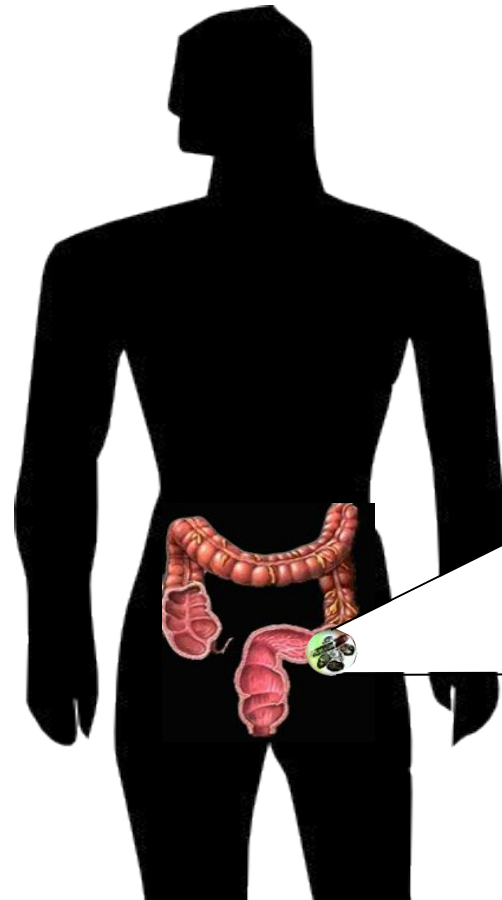


Th-1

Th-2

Th-17

T_{REG}

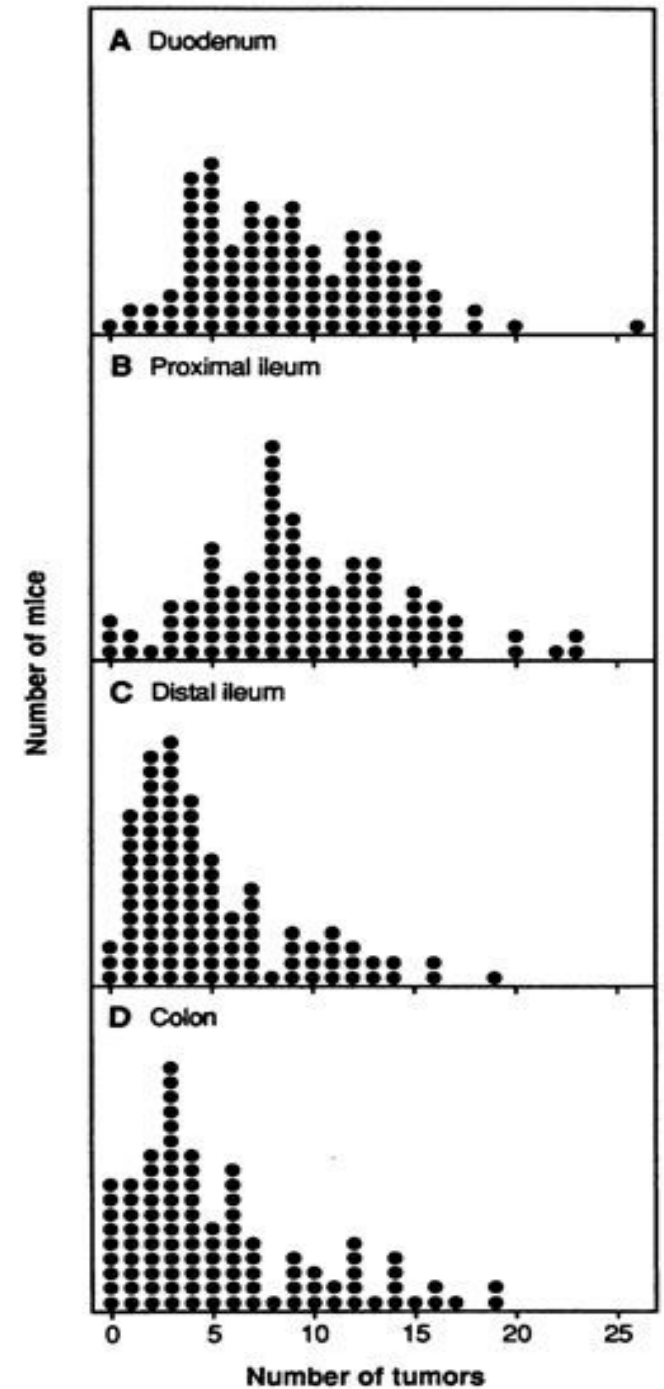
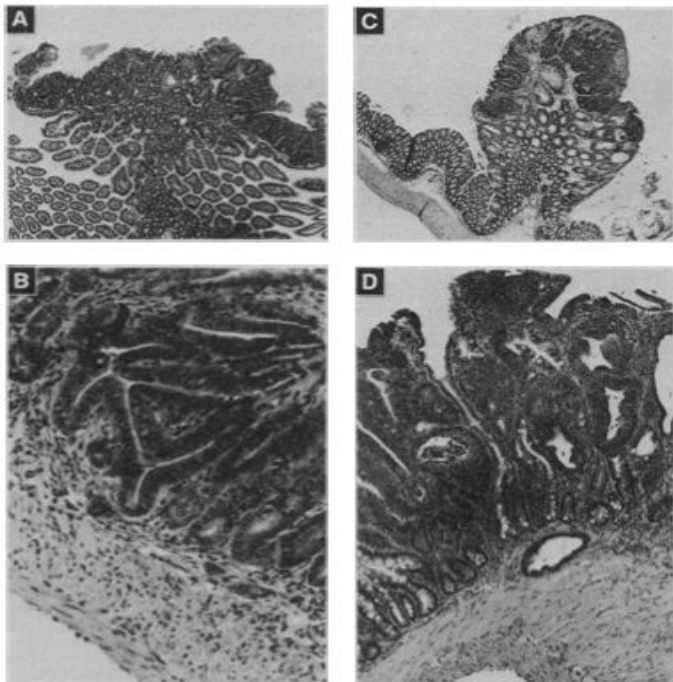


A Dominant Mutation That Predisposes to Multiple Intestinal Neoplasia in the Mouse

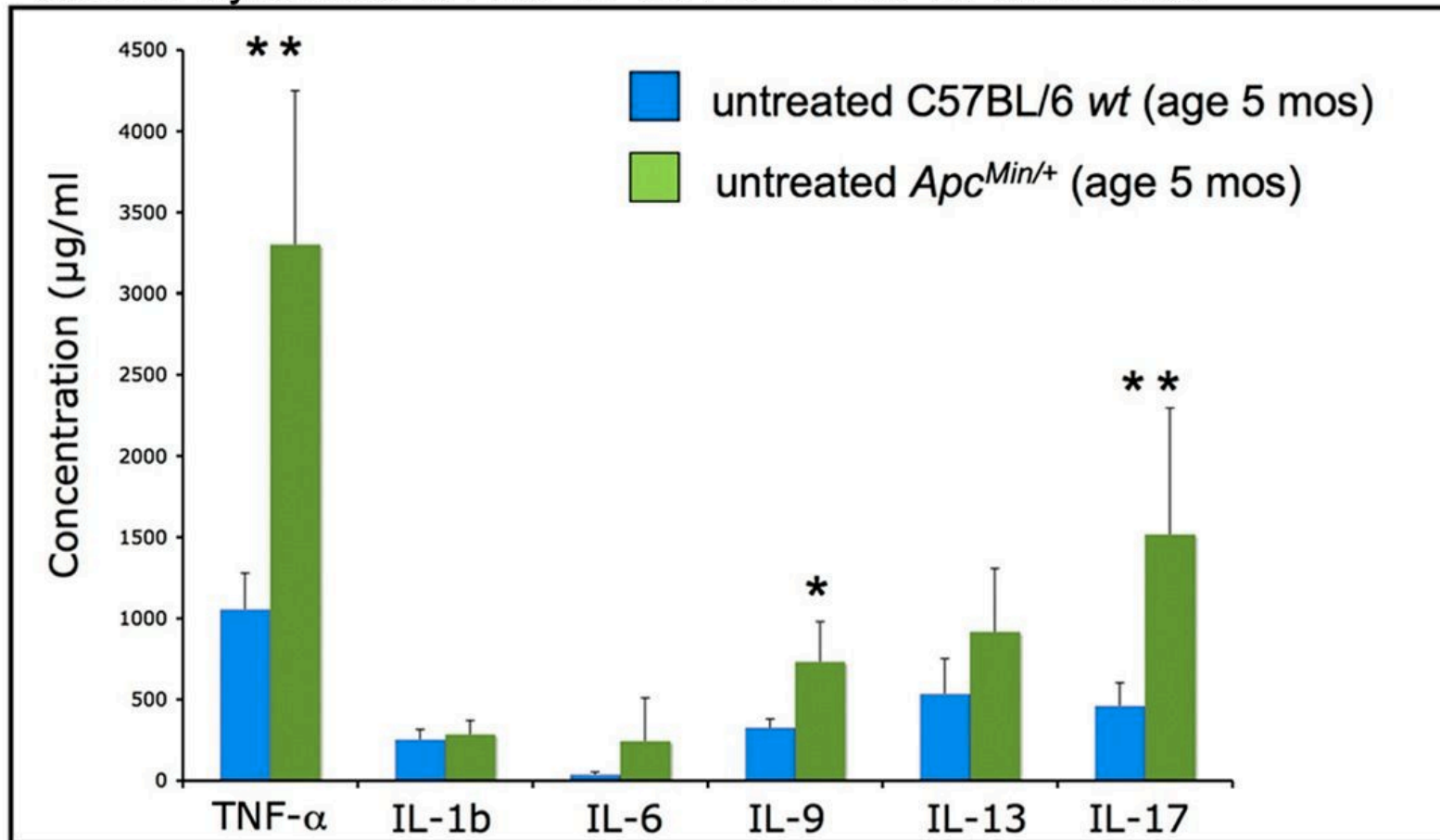
AMY RAPAICH MOSER,* HENRY C. PITOT, WILLIAM F. DOVE

In a pedigree derived from a mouse treated with the mutagen ethylnitrosourea, a mutation has been identified that predisposes to spontaneous intestinal cancer. The mutant gene was found to be dominantly expressed and fully penetrant. Affected mice developed multiple adenomas throughout the entire intestinal tract at an early age.

19 JANUARY 1990 SCIENCE, VOL. 247



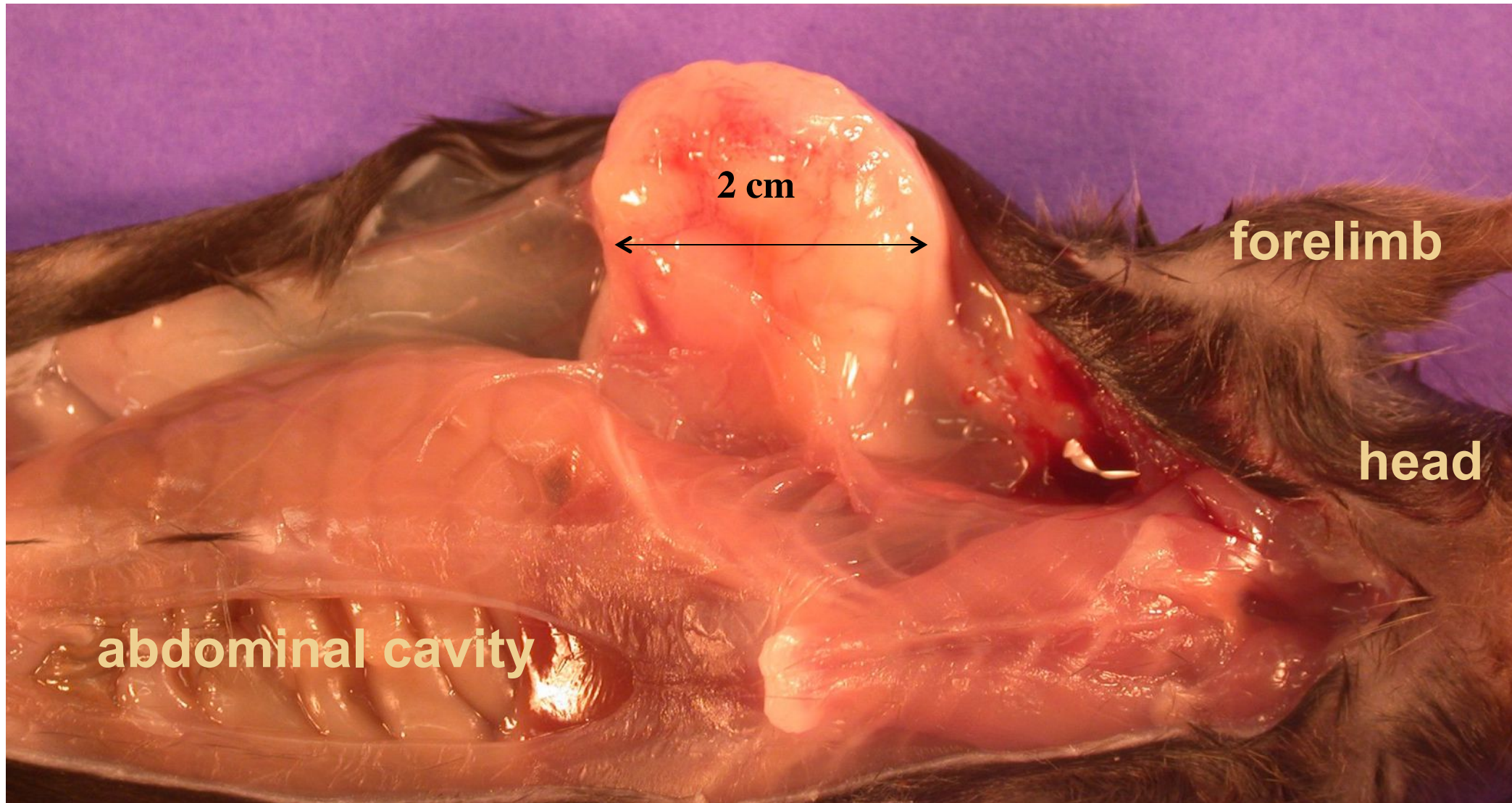
Serum cytokine levels in C57BL/6 wt vs Min mice

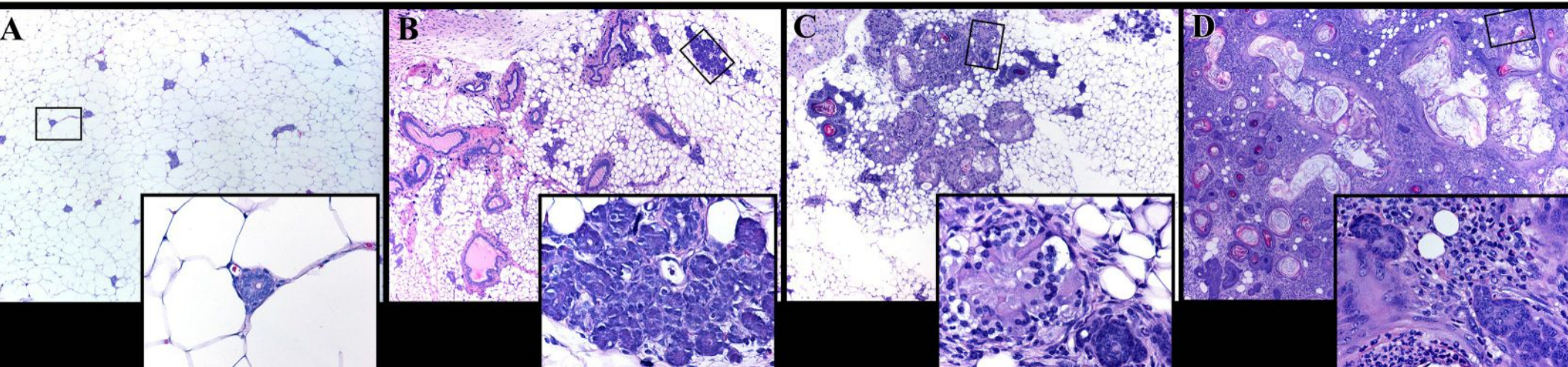
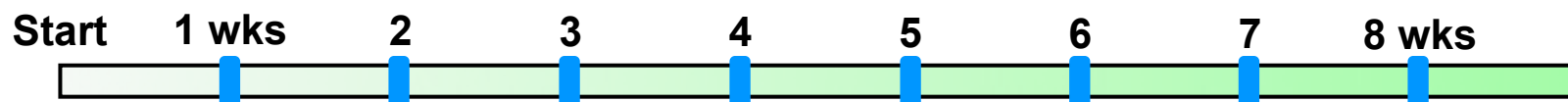


Luminex (serum protein) assay reveals that serum levels of cytokine TNF α and IL17 were significantly increased in aged Min mice at high risk of intestinal polyposis. Serum cytokine levels in pg/ml. Statistics using 2-tailed Student's t-test; ns, not significant *= $p > 0.05$. **= $P > 0.01$.

we thank Werner Olipitz

H. hepaticus-infected *Apc*^{Min/+} mice rapidly develop mammary tumors





Priority Report

Innate Immune Inflammatory Response against Enteric Bacteria *Helicobacter hepaticus* Induces Mammary Adenocarcinoma in Mice

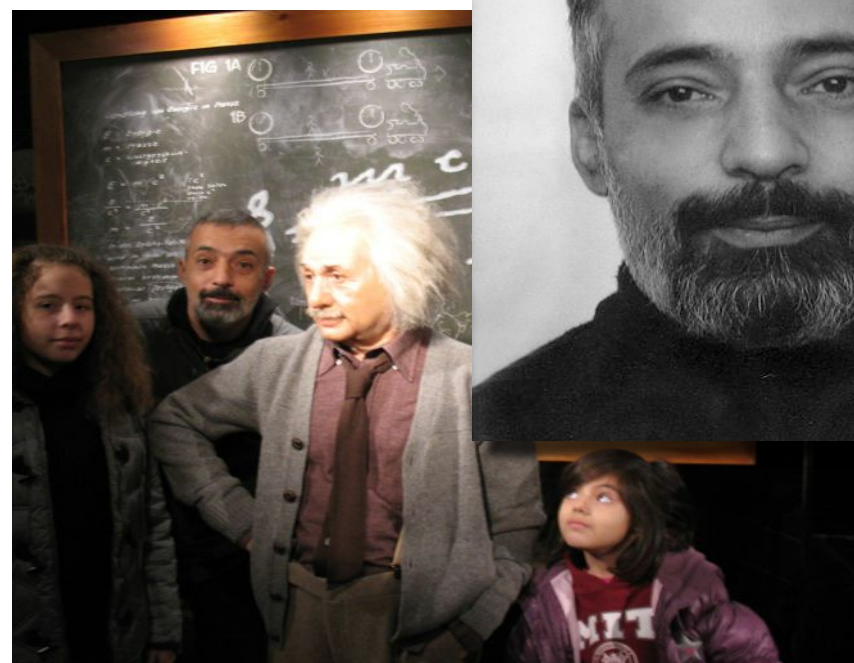
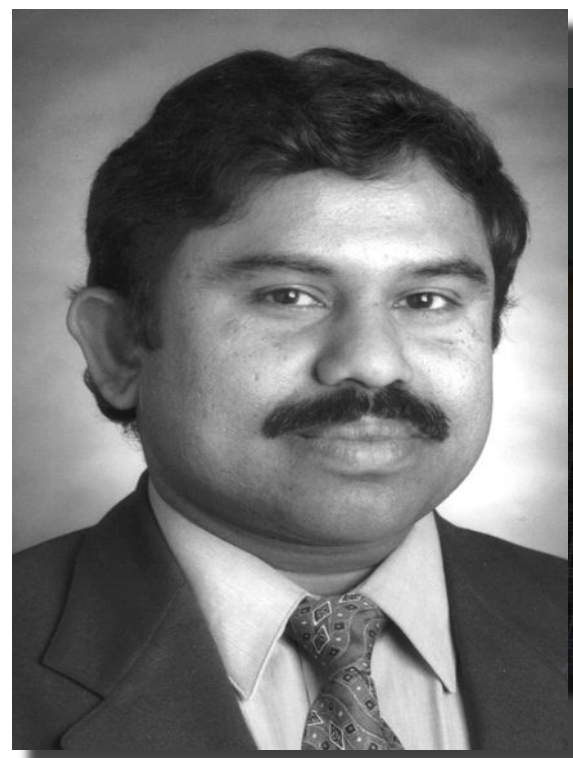
Varada P. Rao,¹ Theofilos Poutahidis,^{1,3} Zhongming Ge,¹ Prashant R. Nambiar,¹
 Chakib Boussahmain,¹ Yan Yan Wang,² Bruce H. Horwitz,²
 James G. Fox,¹ and Susan E. Erdman¹

Cancer Res 2006; 66: (15). August 1, 2006

Breast Cancer: Should Gastrointestinal Bacteria Be on Our Radar Screen?

Varada P. Rao,¹ Theofilos Poutahidis,^{1,2} James G. Fox,¹ and Susan E. Erdman¹

¹Division of Comparative Medicine, Massachusetts Institute of Technology, Cambridge, Massachusetts and ²Laboratory of Pathology, Faculty of Veterinary Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece



Cancer Res 2007; 67: (3). February 1, 2007

Do intestinal bacteria modulate breast cancer?

INTESTINE

BREAST

In pathogenic gut infection

In health

Bowel epithelia

Systemic elevation in cytokines or activated cells?

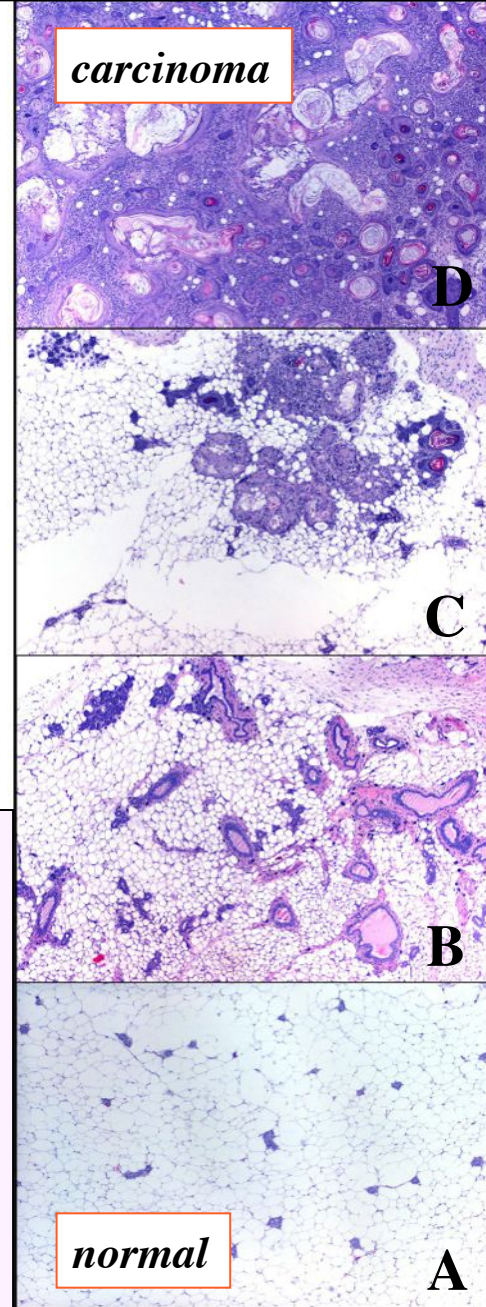
Translocation of bacteria or antigens?

Systemic inflammatory response

IL-10

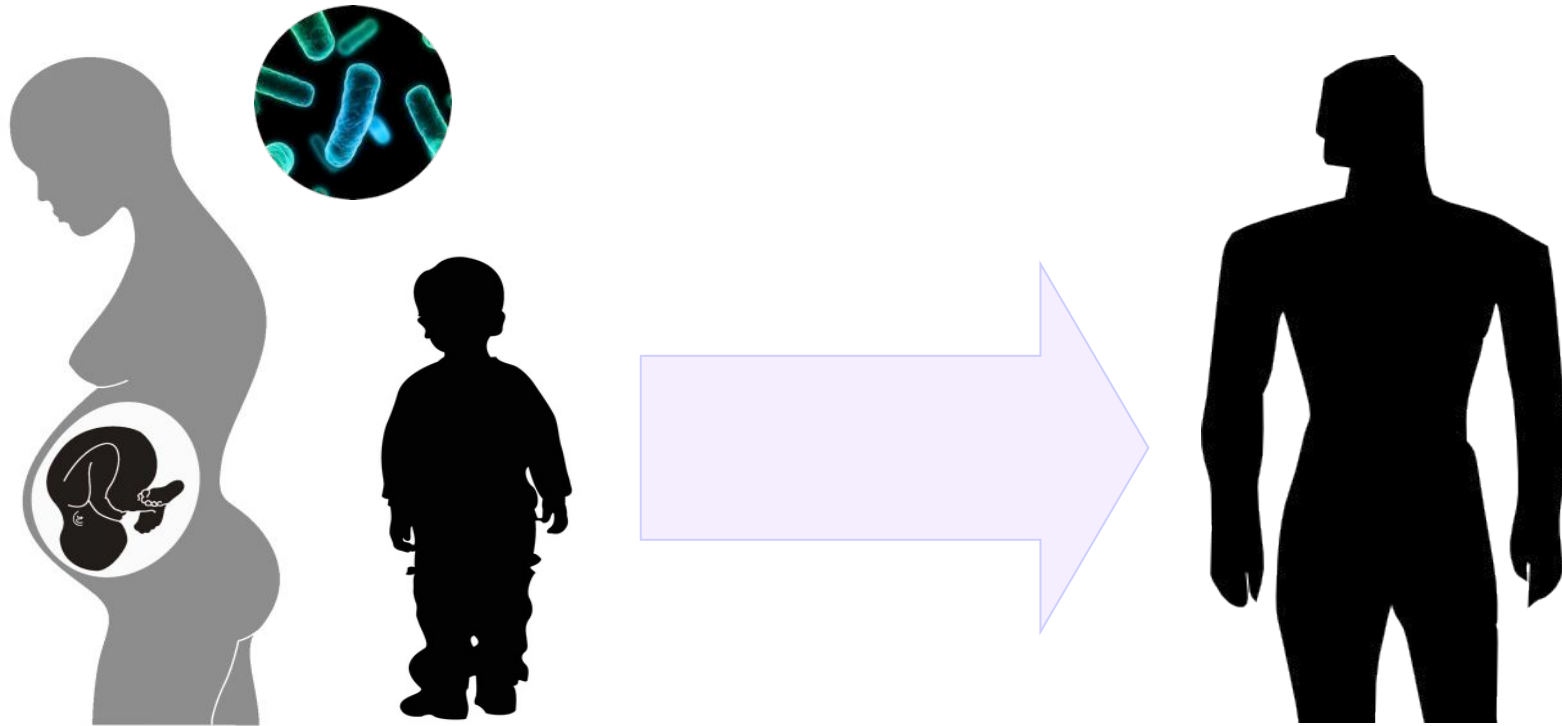


Breast epithelial injury & dysregulation

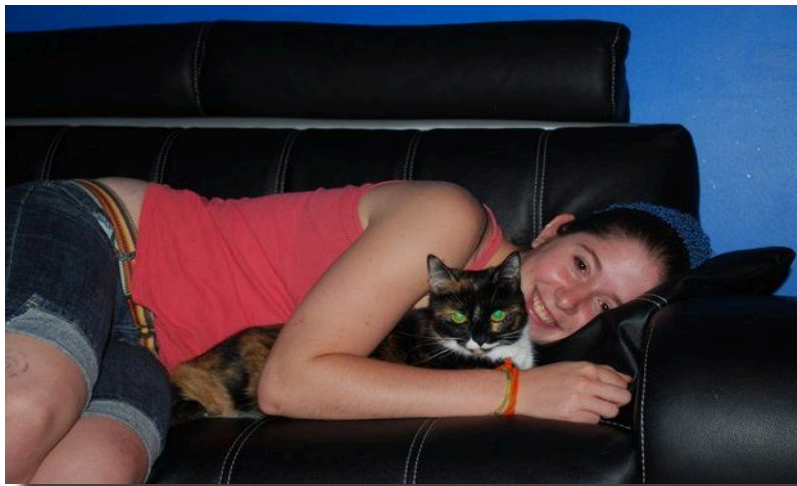


Modern Hygiene Practices

From the above discussion, it is clear that pathogenic gut bacteria may pose a trigger for breast cancer. However, this seems to be only half the story. It does not explain why breast cancer risk is increasing in developed countries with more rigorous hygiene practices, or answer how chronic use of prescribed antibiotics enhances the risk for breast cancer in women (4). The “hygiene hypothesis” is based on the observation that early childhood infections reduce the incidence of allergies (24). A later counter-regulatory model of the hygiene hypothesis, forwarded by Wills-Karp et al. (24), postulates that microbial infections have a beneficial role in the developing immune system and that the anti-inflammatory cytokine interleukin 10 (IL-10), produced by cells of both innate and adaptive immune



Can a beneficial 'probiotic' microbes of the perinatal window induce host immune stability later in life?



Kelsey Cappelle



Jessica Lakritz



Yassin Ibrahim



Bernard Varian

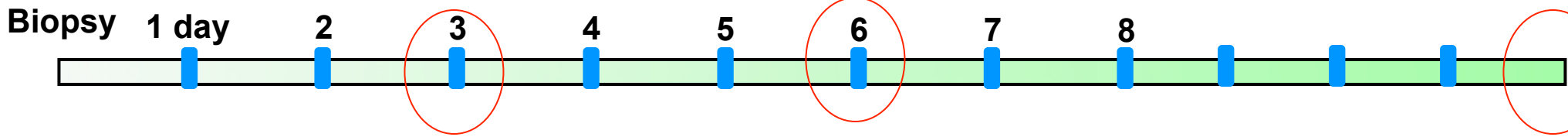


Tatiana Levkovich





Skin wounds heal twice-as-fast when mice eat beneficial microbes



Wound Closure

Wound Histopathology

day 3

day 6

day 12

day 3

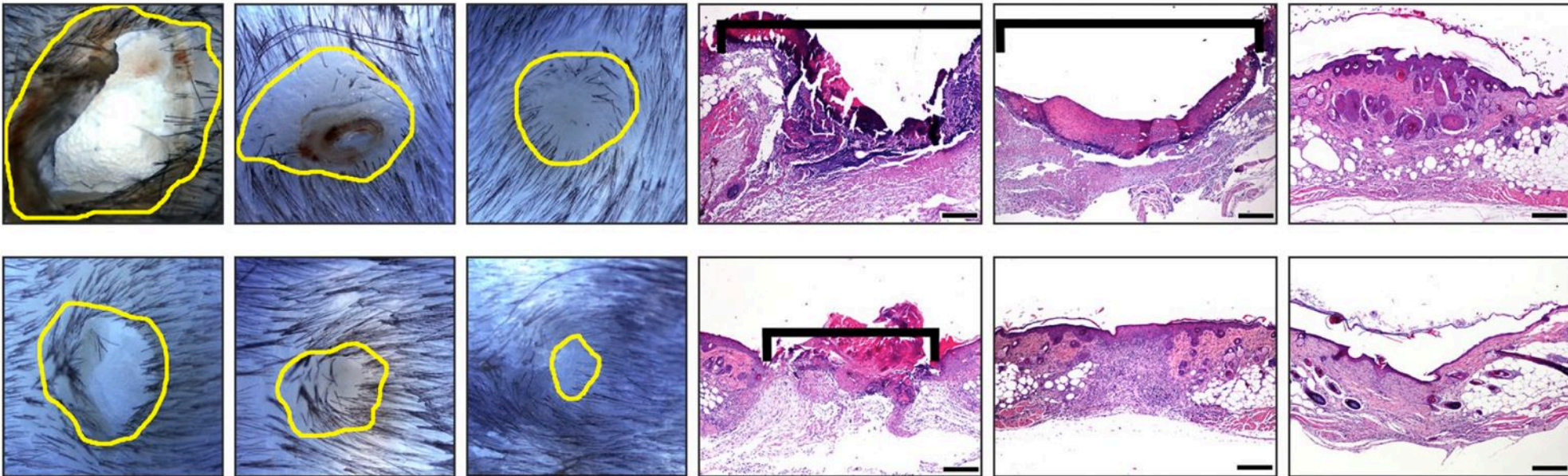
day 6

day 12

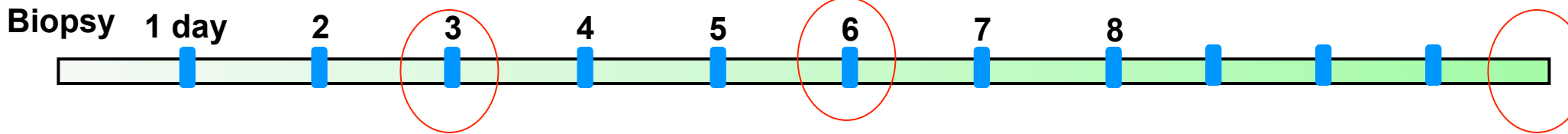
a.

Control

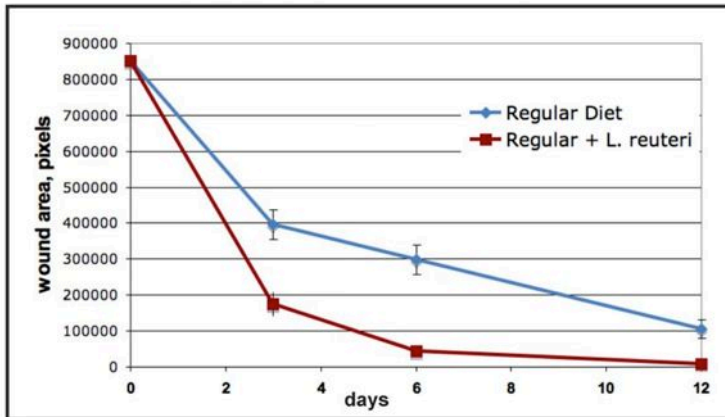
L. reuteri



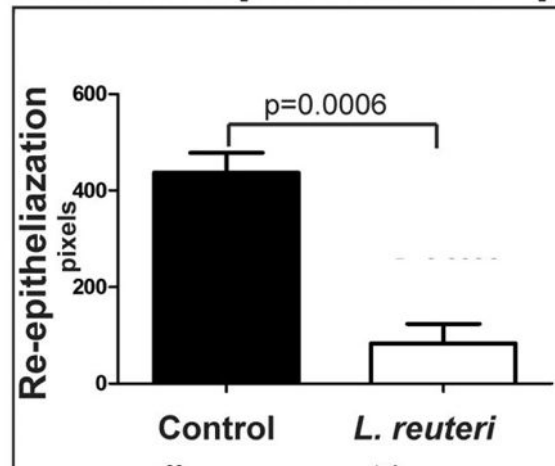
Skin wounds heal twice-as-fast



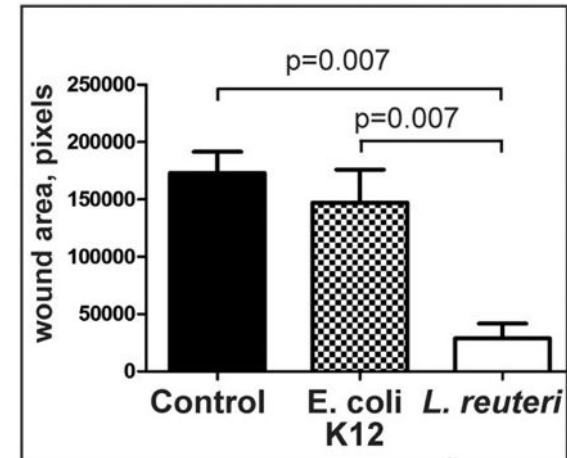
Wound Closure Rate



Wound Epidermal Gap

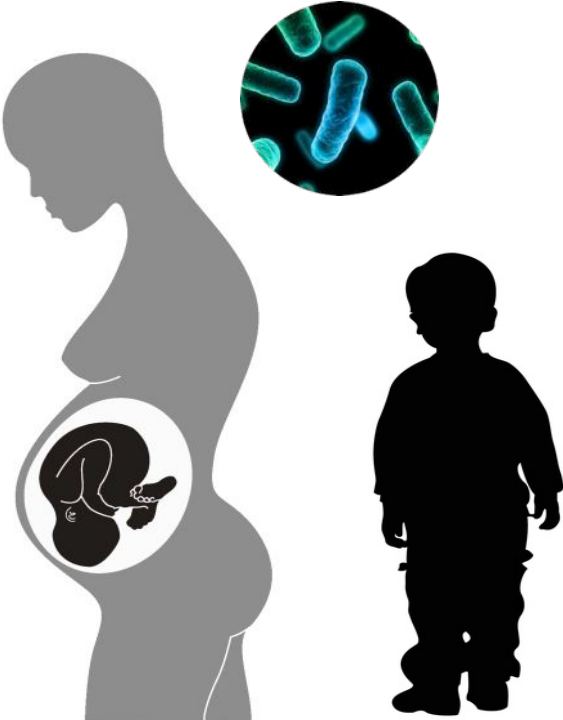


E. coli K12 sham



Poutahidis et al 2013

MICROBES

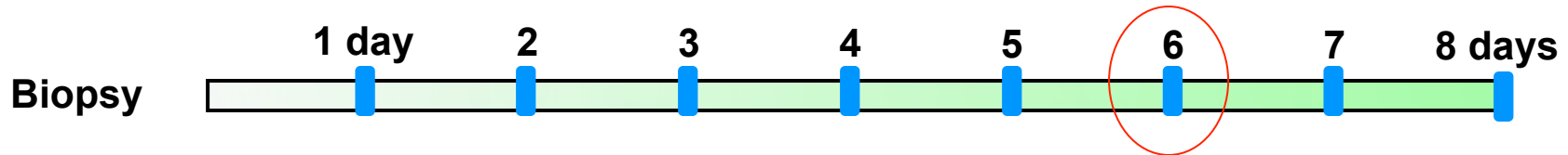


OXYTOCIN



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Microbe-induced benefit in wound repair requires oxytocin



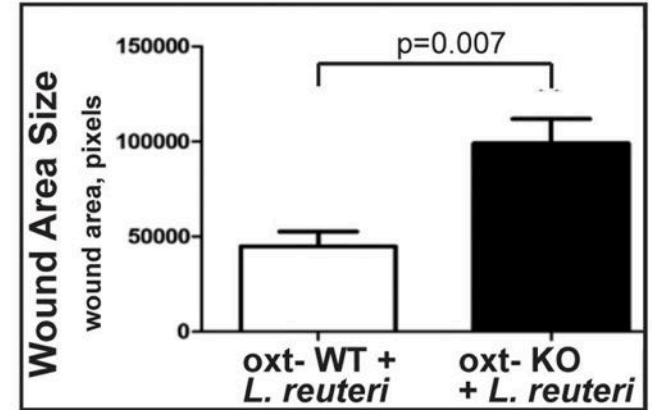
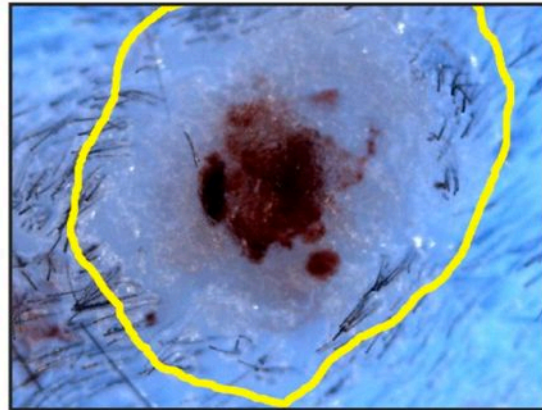
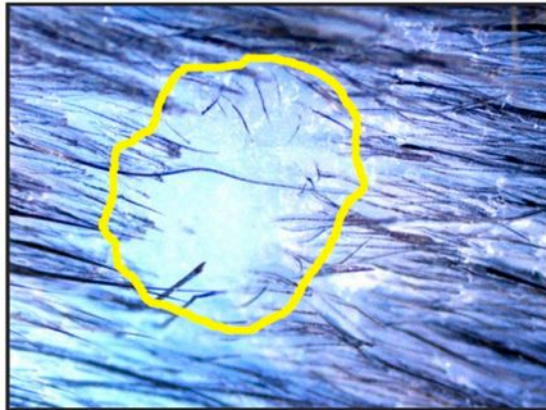
a.

oxt- WT + *L. reuteri* (D6)

oxt- KO + *L. reuteri* (D6)

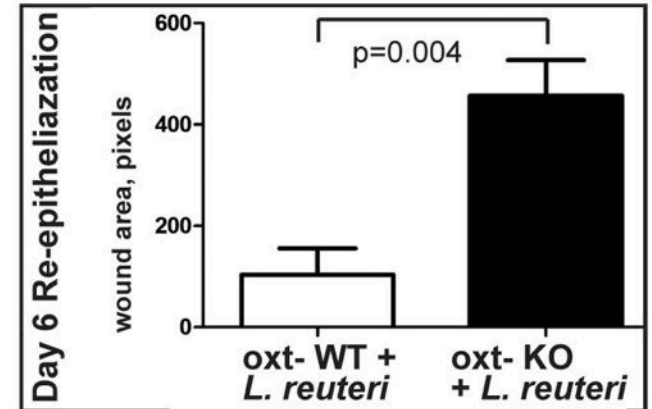
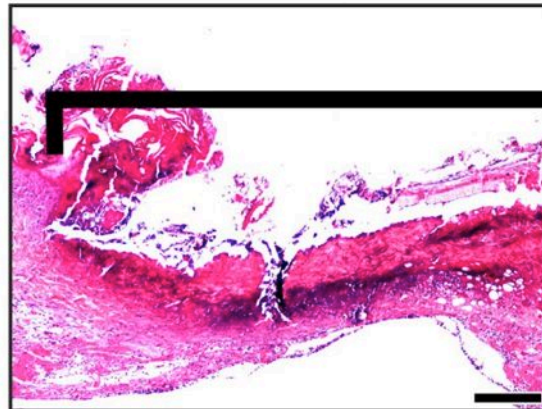
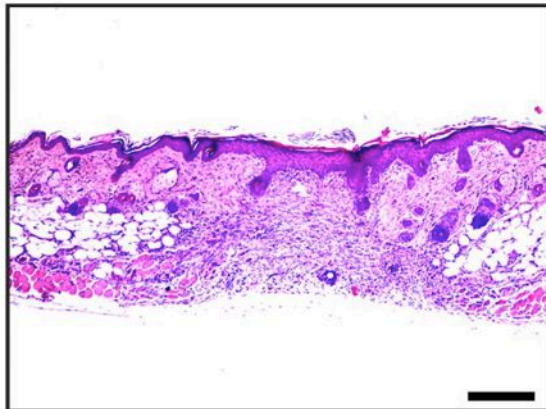
Morphometric Analysis

Wound Closure



b.

Histopathology



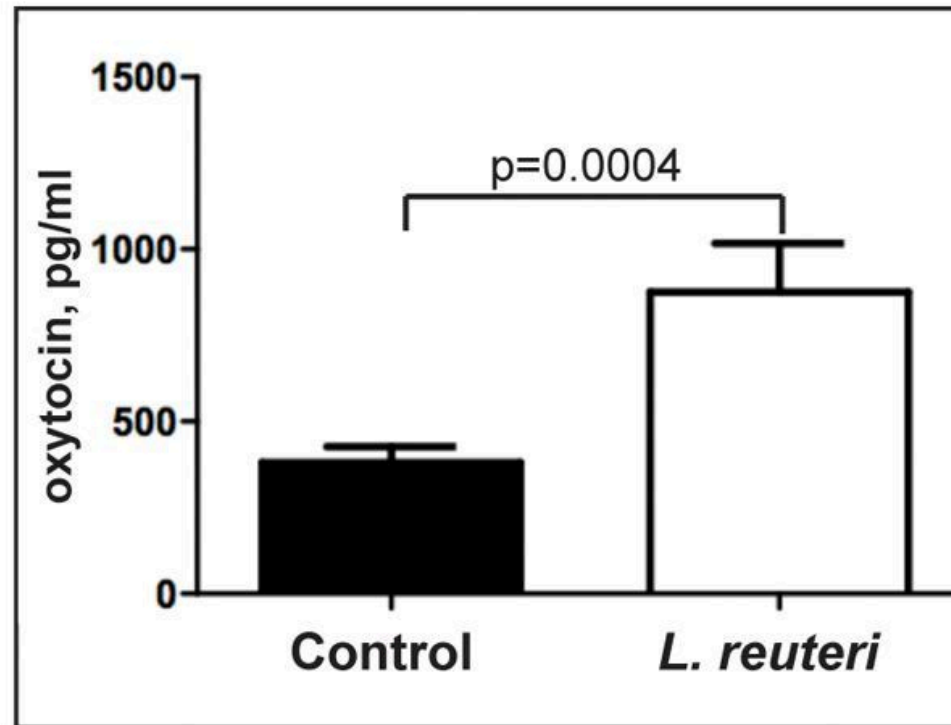
Hypothalamic pathways?



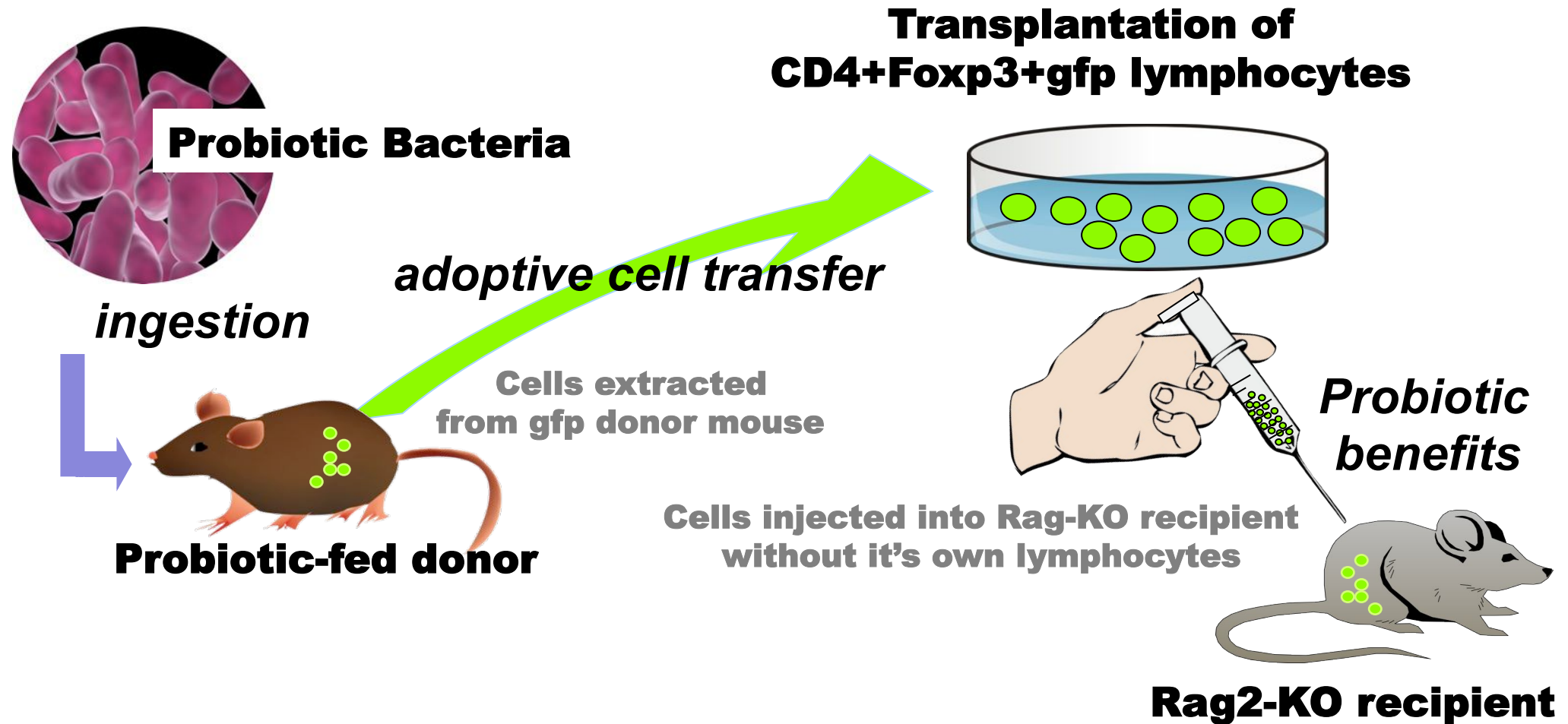
Physical, mental & social fitness

“my bacteria made me do it”

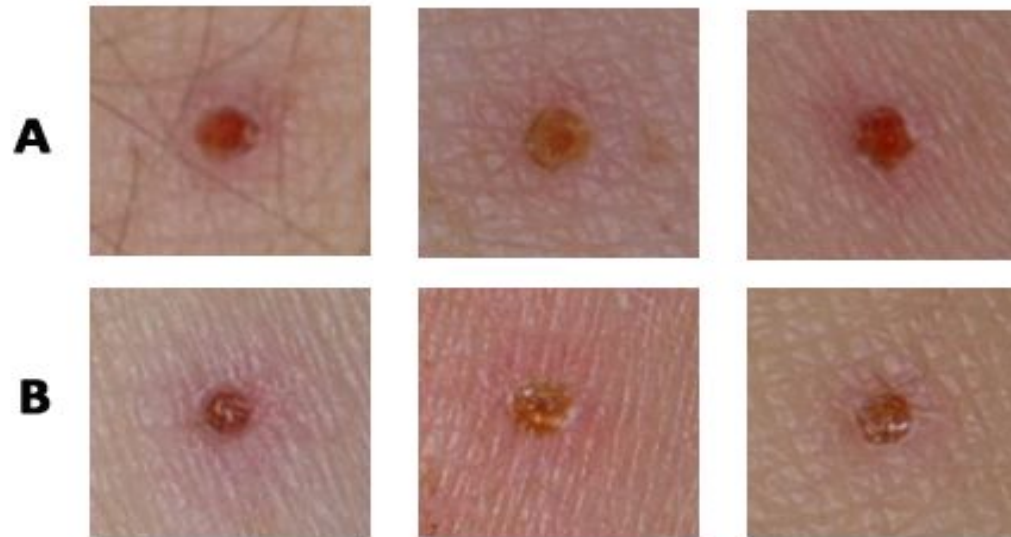
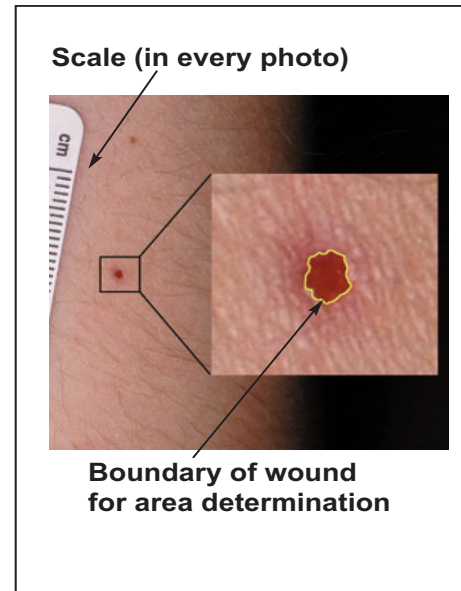
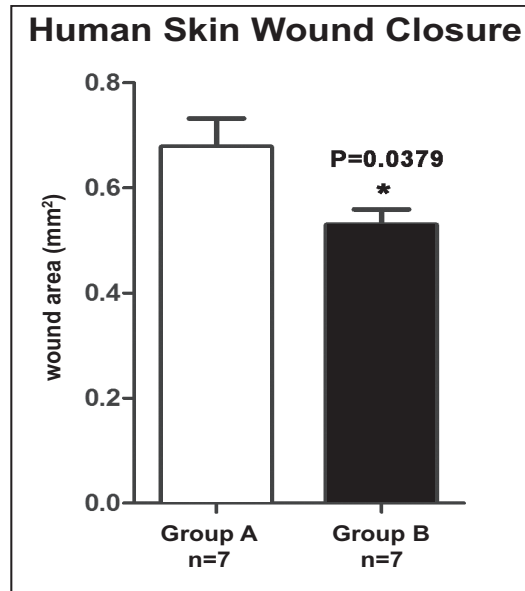
Plasma Oxytocin



Gut microbe-induced phenotypes are transplantable

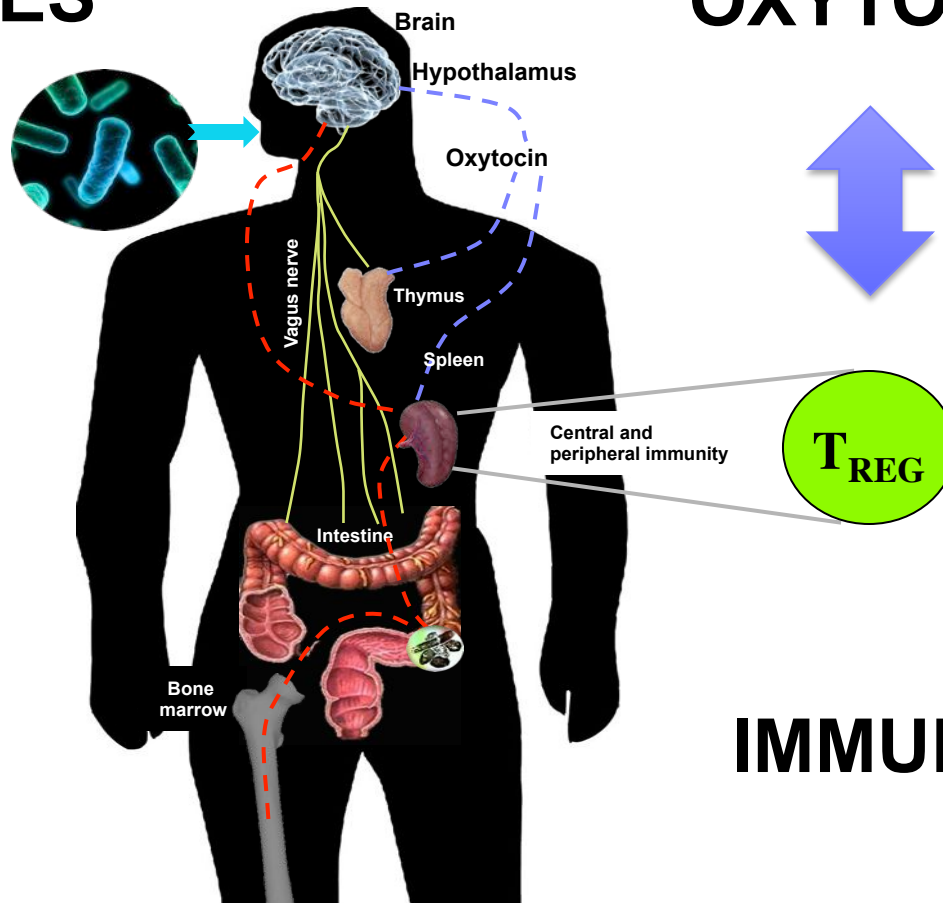


Pilot Study in Human Subjects



Wound healing capacity

MICROBES

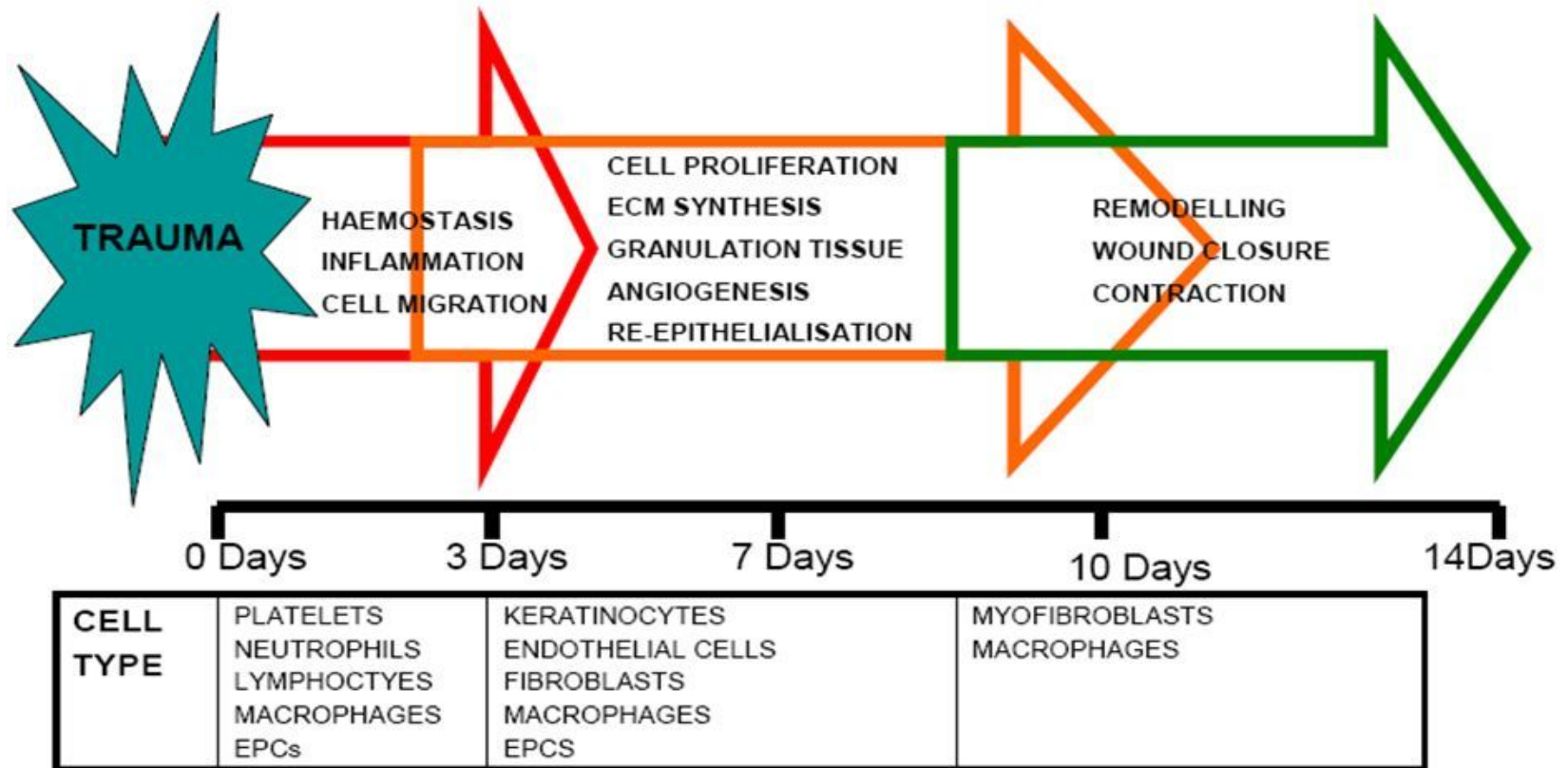


OXYTOCIN

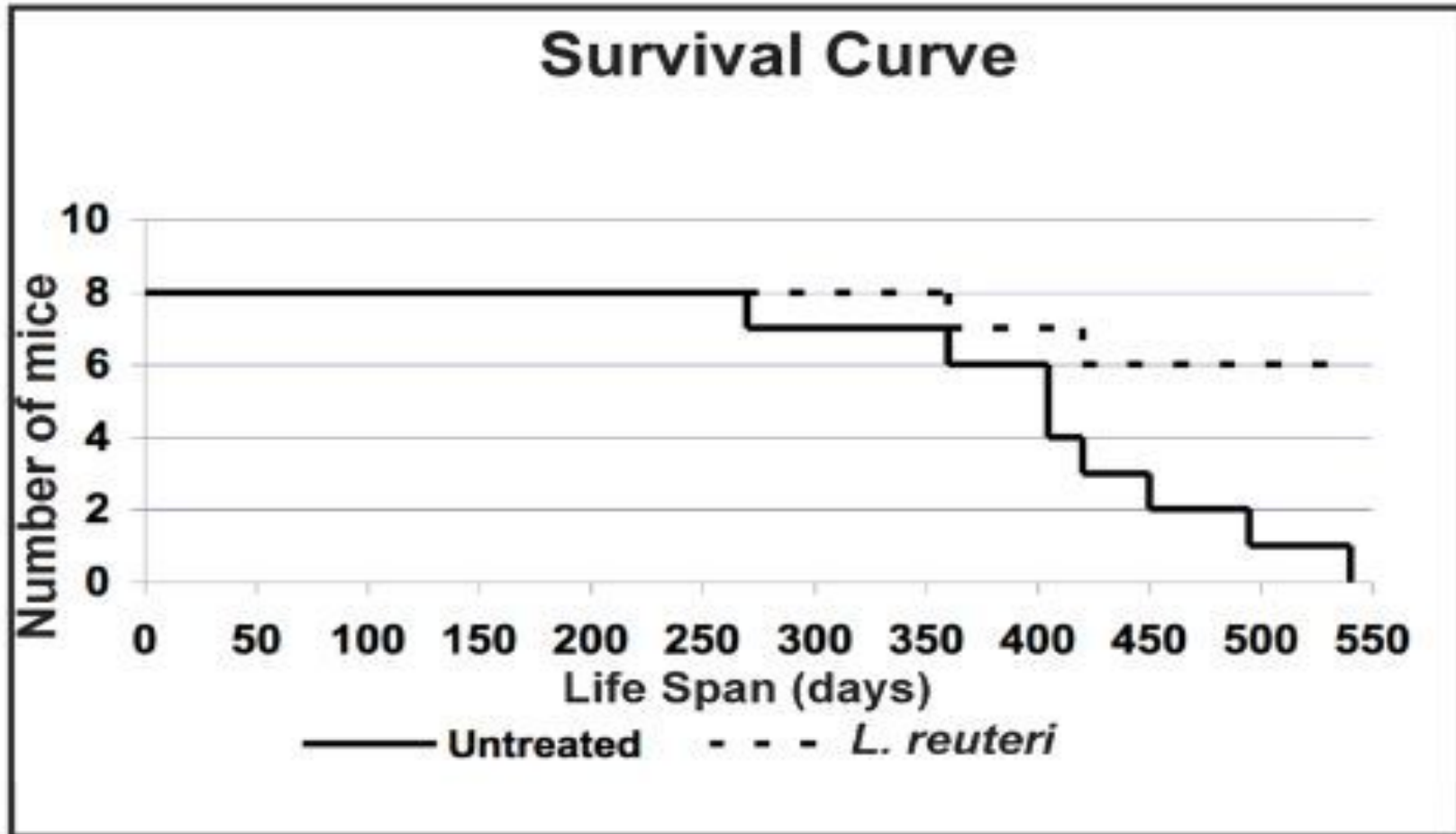
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Importance of wound healing capacity

Stages of Normal Cutaneous Wound Healing



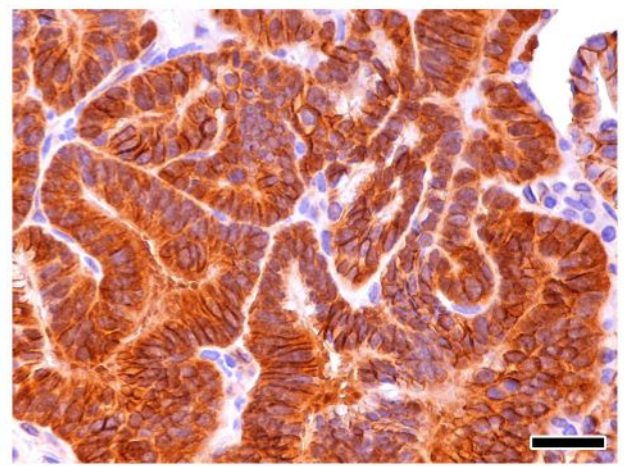
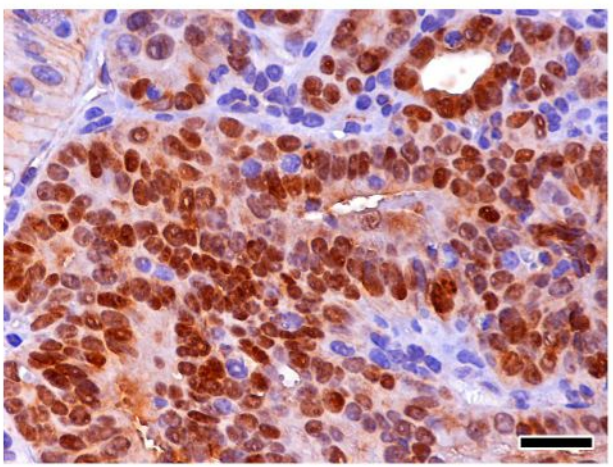
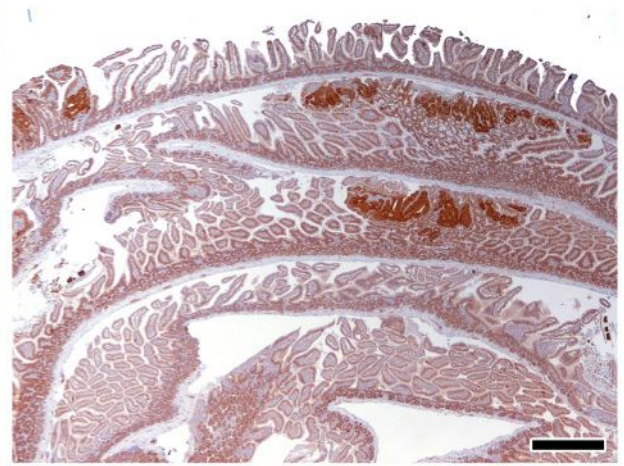
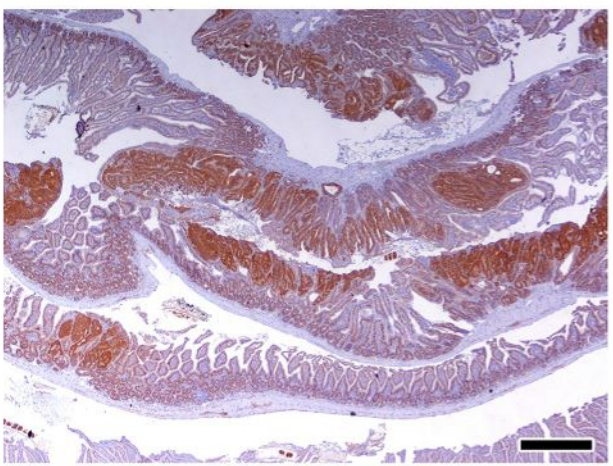
Improved wound healing → longevity



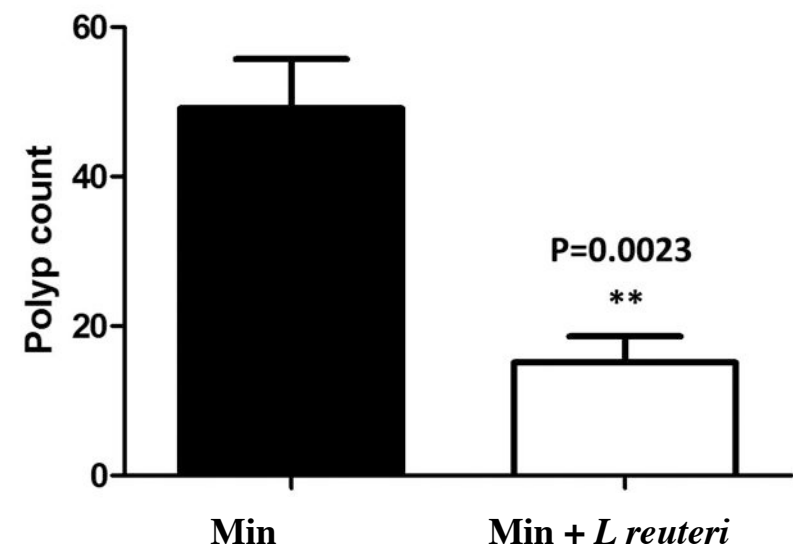
Feeding of probiotic microbes inhibits intestinal polyposis in Min mice

Min+Control

Min+LR :

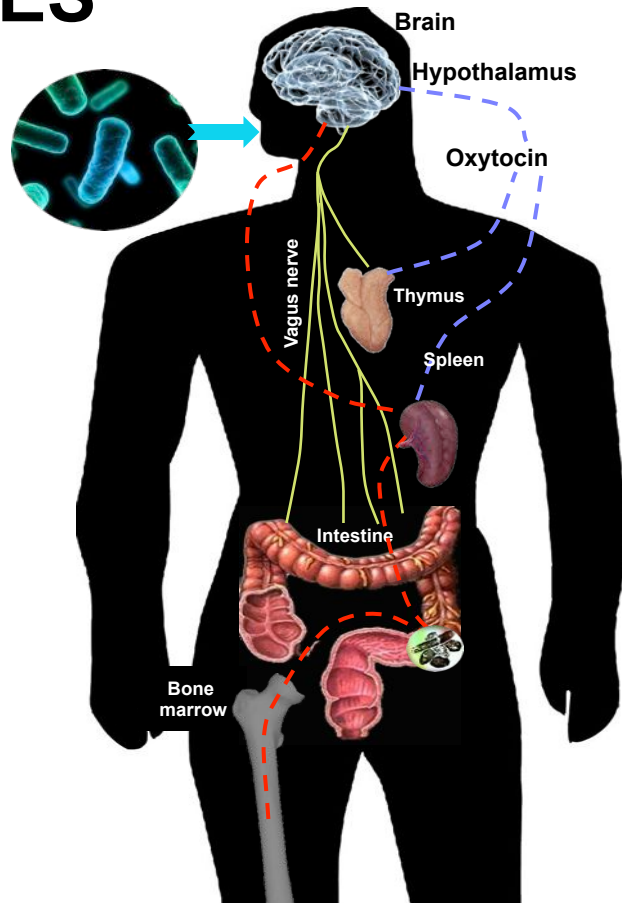


β-catenin



Healthful Longevity

MICROBES

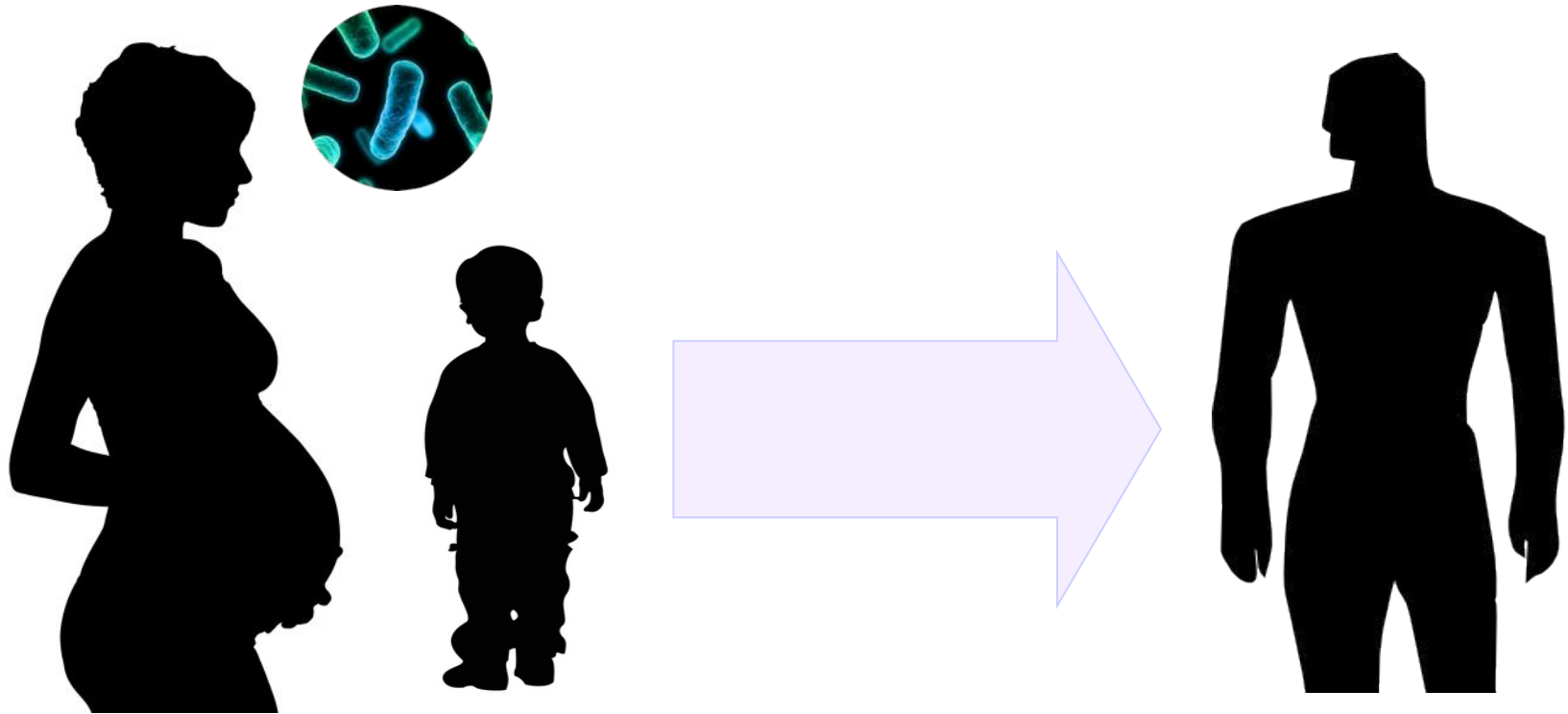


BRAIN



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Harnessing microbes for public health



A photograph of three white mice on a white background. One mouse is in the foreground, looking towards the right. Two other mice are behind it, one slightly to the left and one to the right, both looking towards the right. The mice have pinkish-red noses and ears.

Thank you!

- **Eric Alm**
- **Karen Sue Anderson**
- **Christina Clarke-Dur**
- **Bevin Engelward**
- **John Essigmann**
- **James G Fox**
- **David A Hafler**
- **Bruce H Horwitz**
- **Theofilos Poutahidis**
- **Leona D Samson**
- **David B Schauer**
- **James Versalovic**
- **Jerrold Ward**
- **Timothy C Wang**