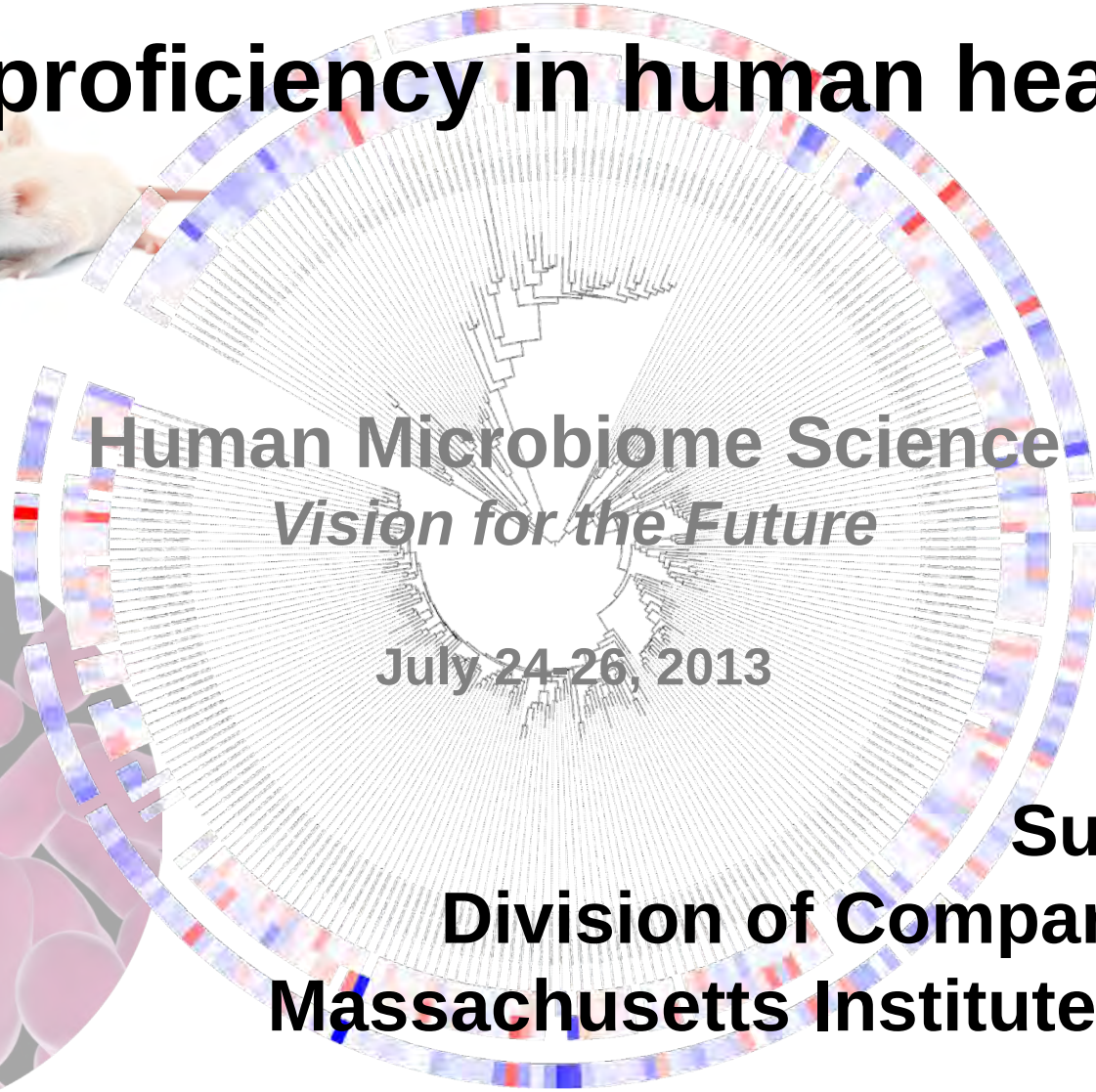
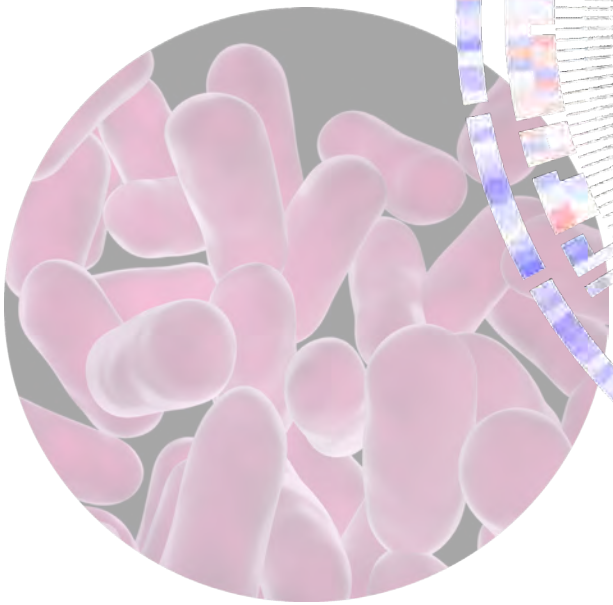
Wound healing to longevity: Microbe-induced immune proficiency in human health



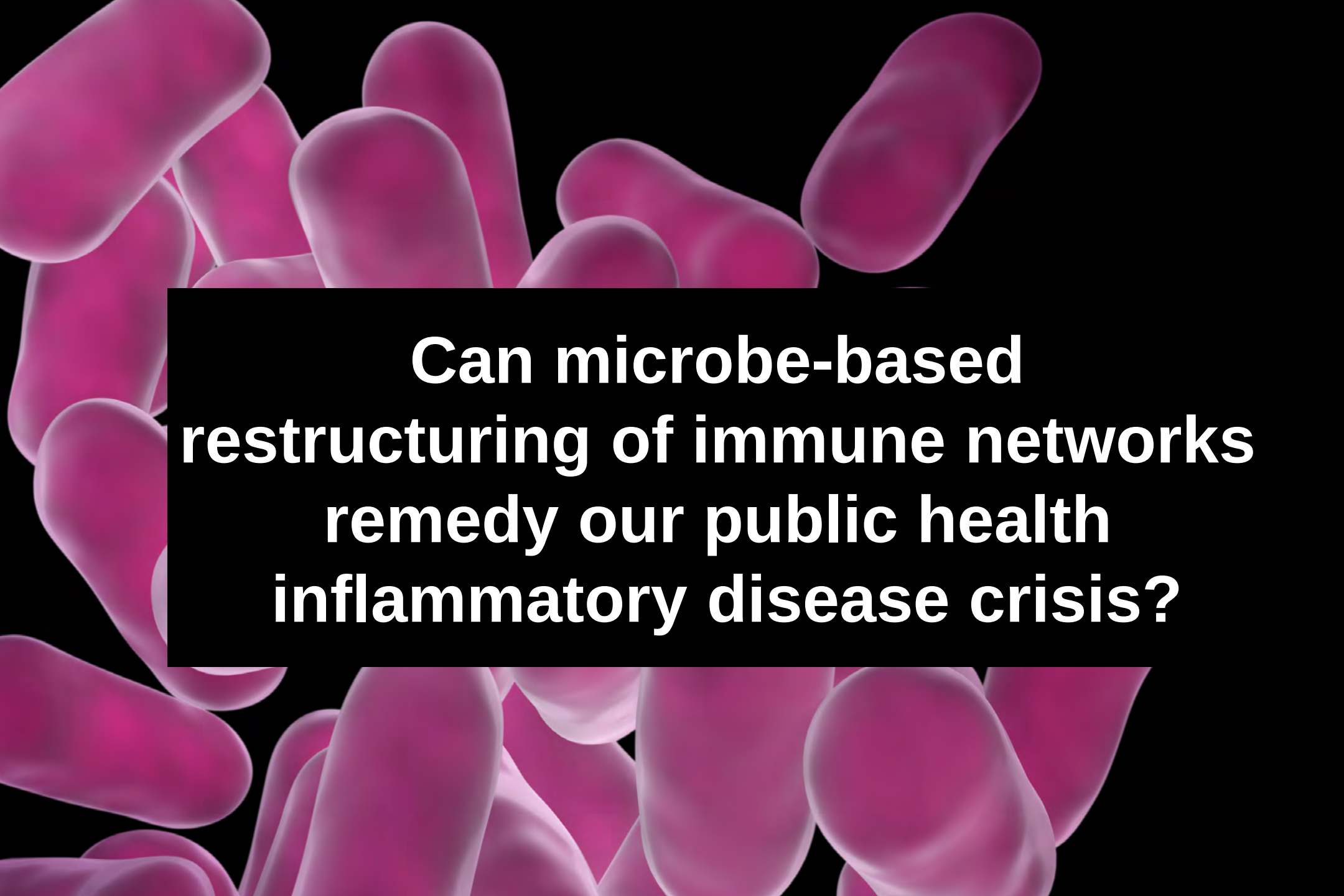


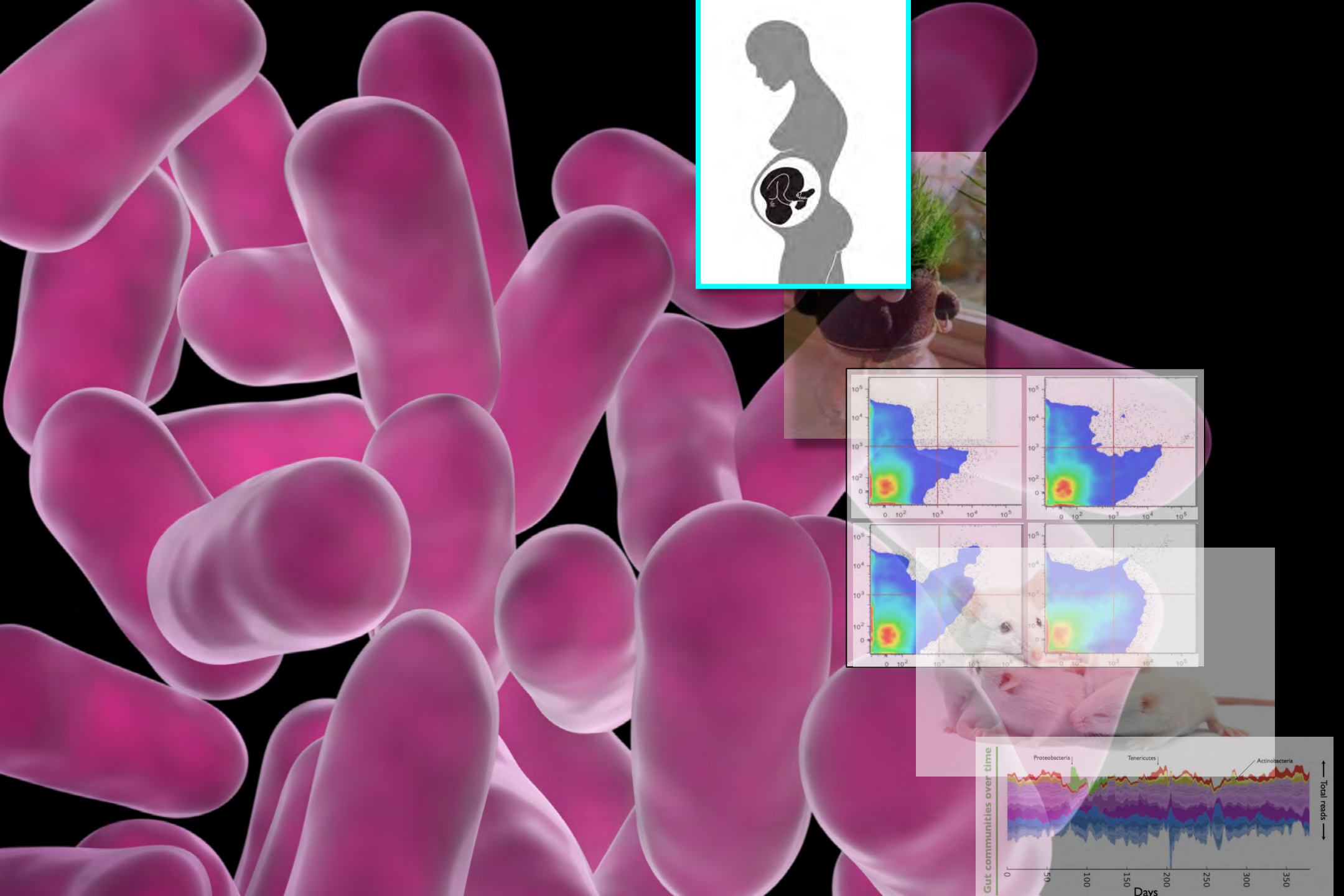
Human Microbiome Science

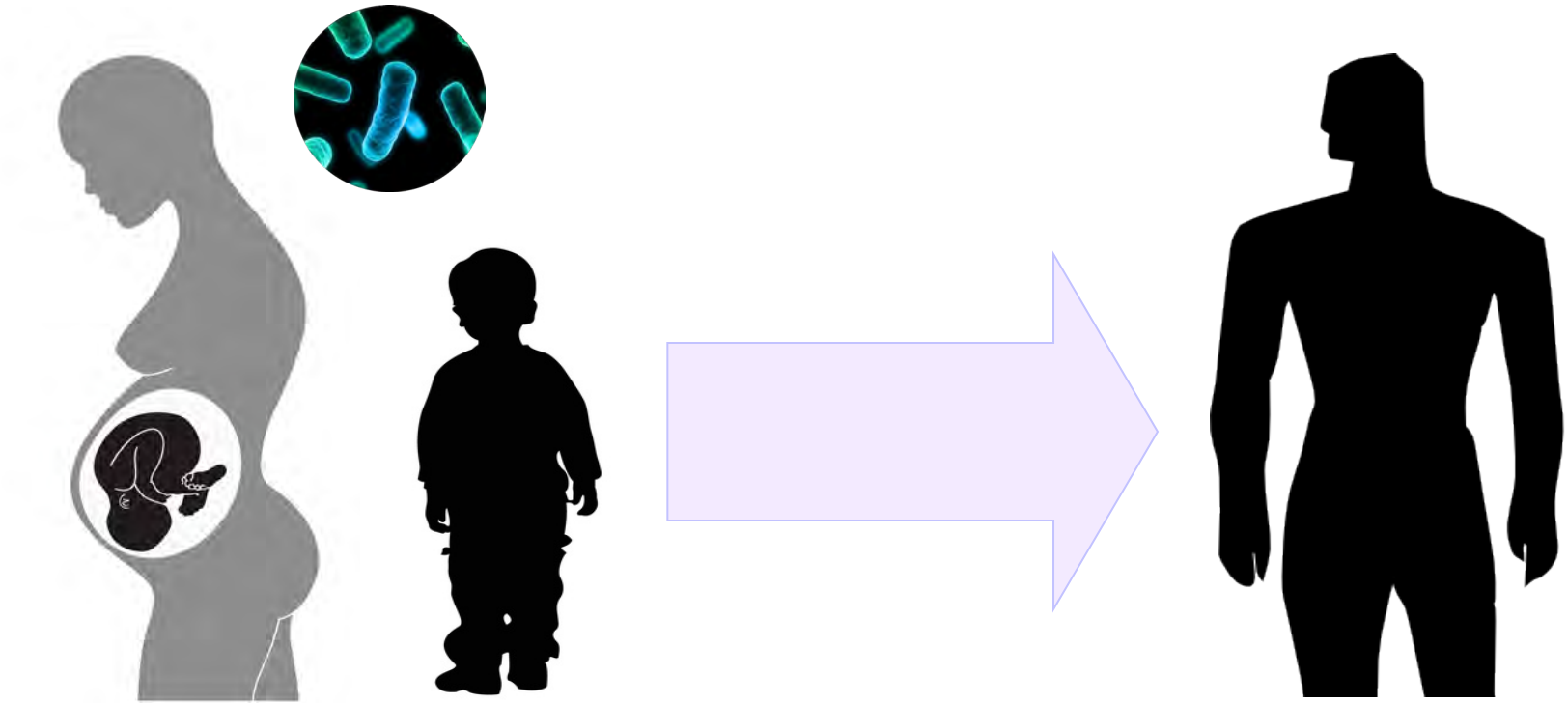
Vision for the Future

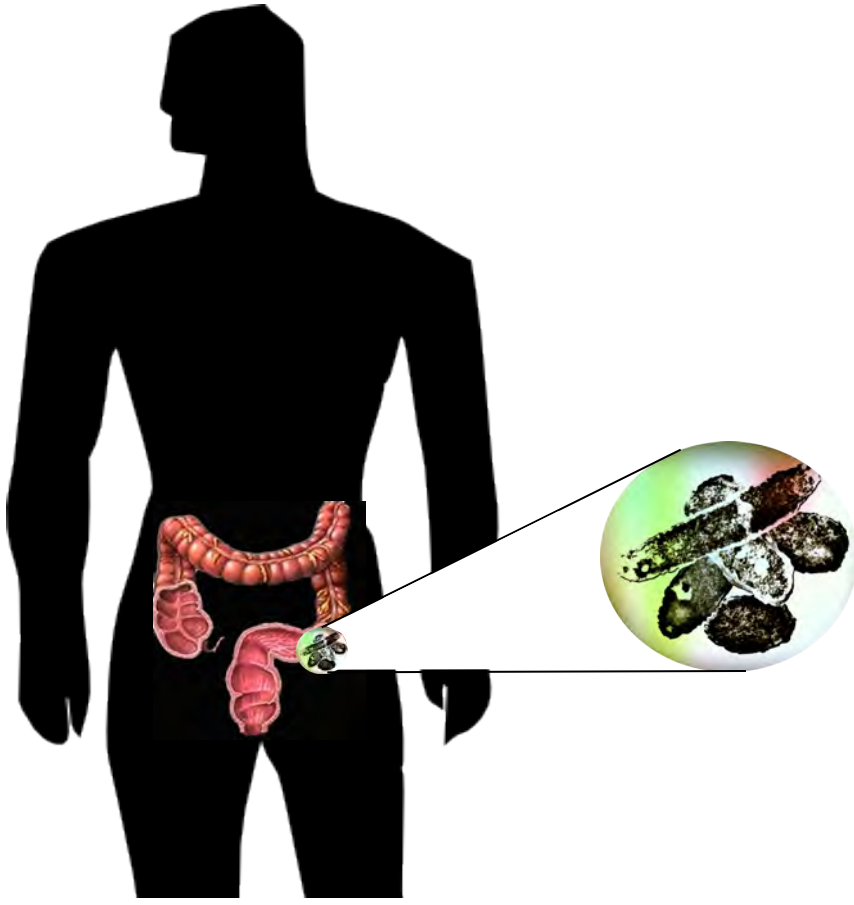
July 24-26, 2013

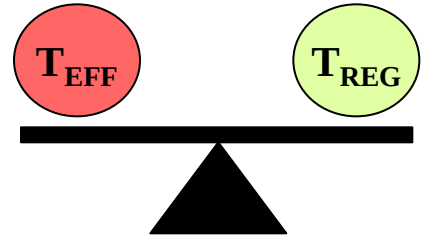
Susan E. Erdman
Division of Comparative Medicine
Massachusetts Institute of Technology


Can microbe-based restructuring of immune networks remedy our public health inflammatory disease crisis?

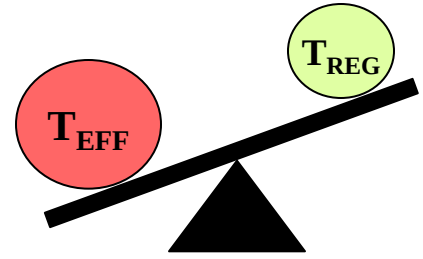

Gut communities over time
Proteobacteria
Tenericutes
Actinobacteria
Total reads
0
50
100
150
200
250
300
350
Days





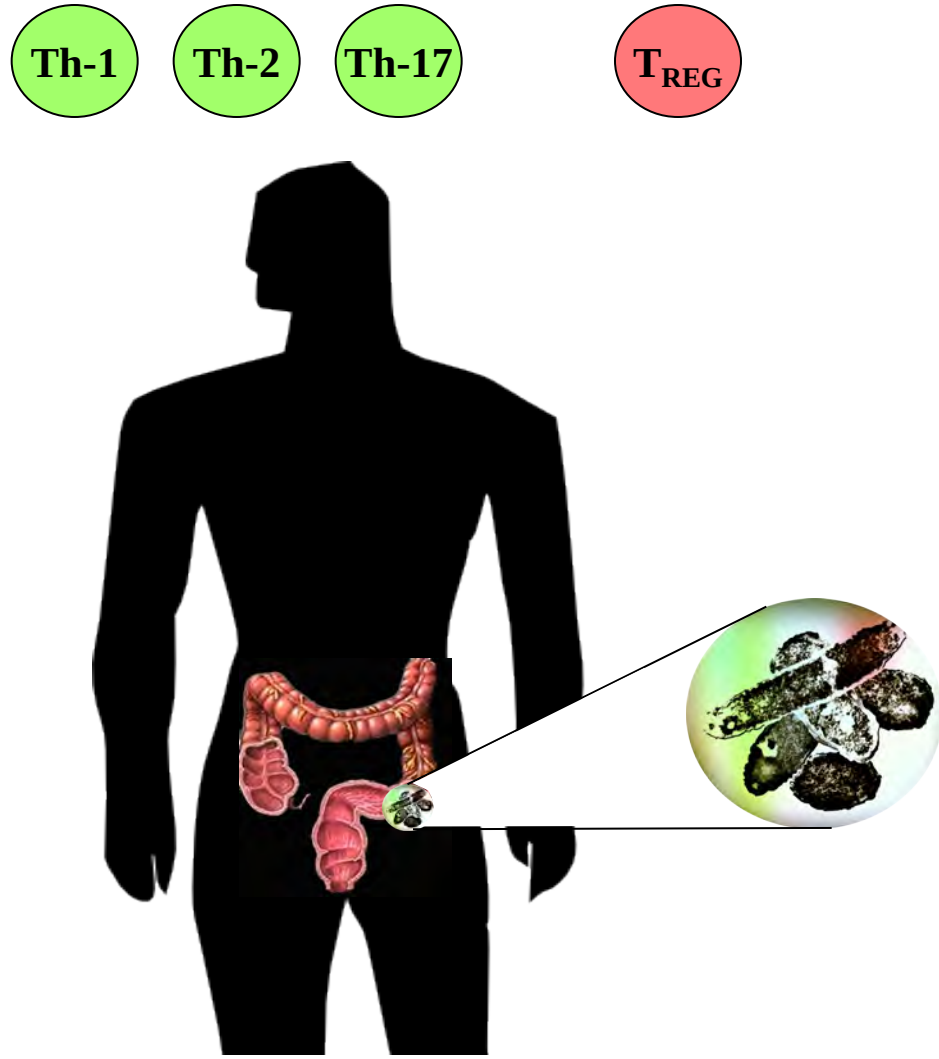

T_{EFF}
T_{REG}


healthy


T_{REG}
T_{EFF}


sick

Healthful longevity



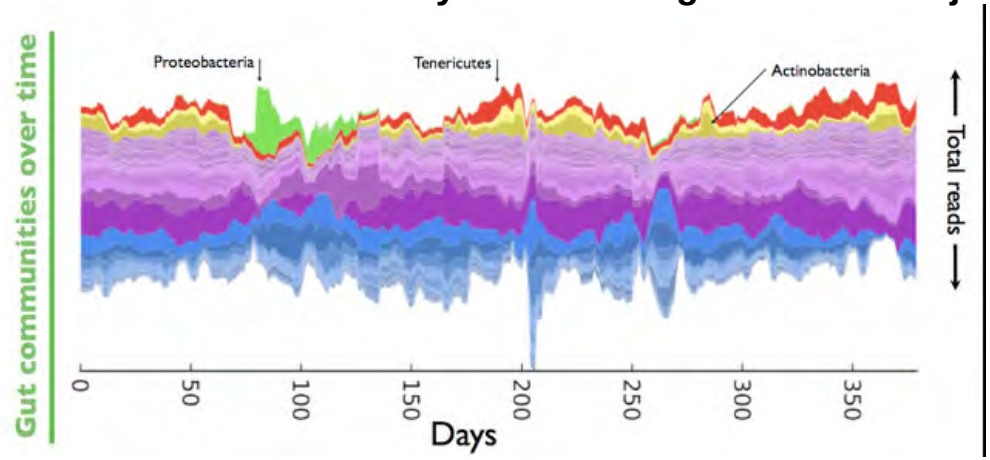
California Teacher Study
60,000+ women

Christina Clarke-Dur
CPIC &
Stanford University

Eric J Alm
Massachusetts Institute of Technology
& Broad Institute

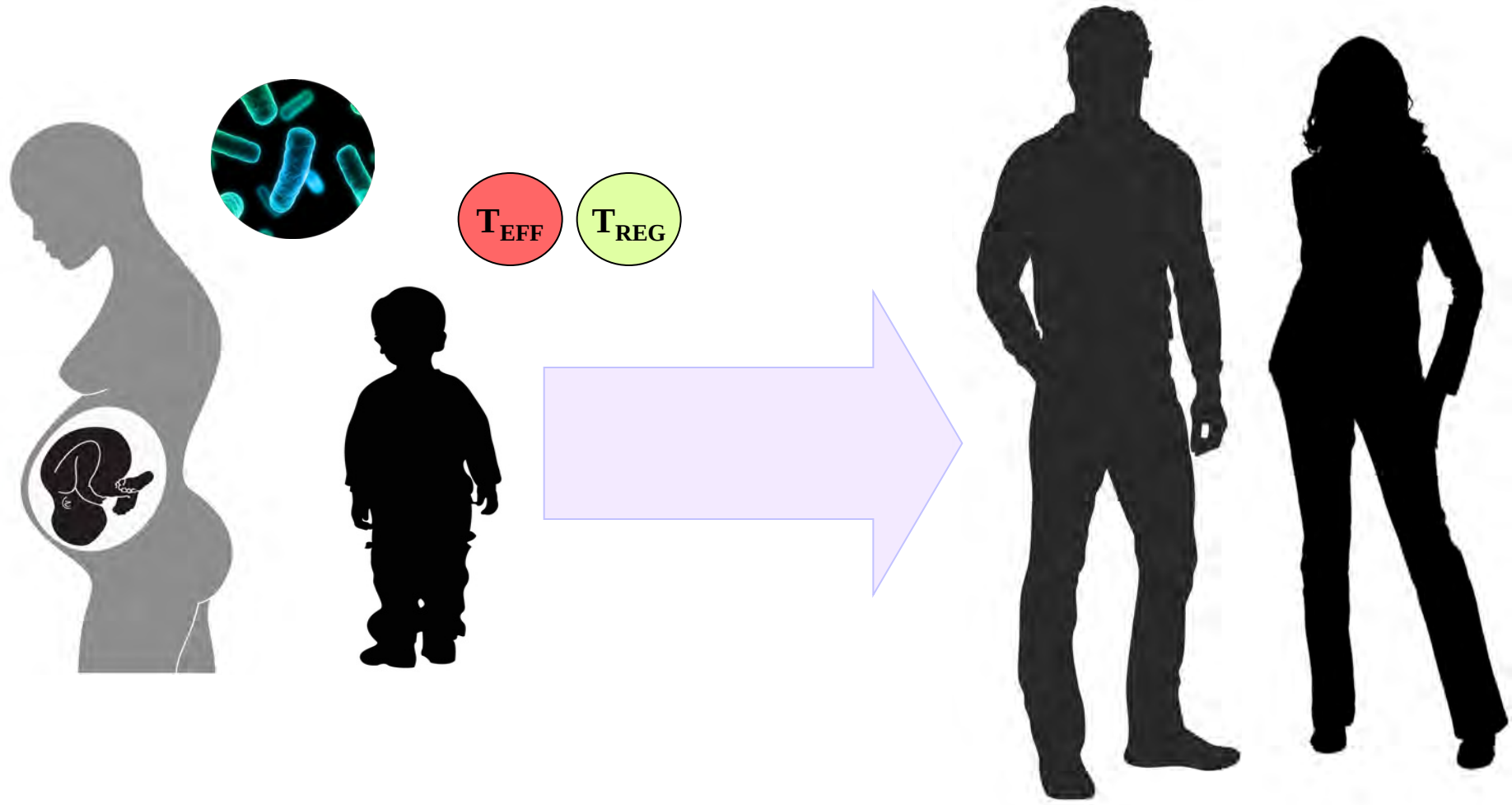
David A Hafler
Yale University & Broad Institute

Gut microbiota community restructuring in human subjects

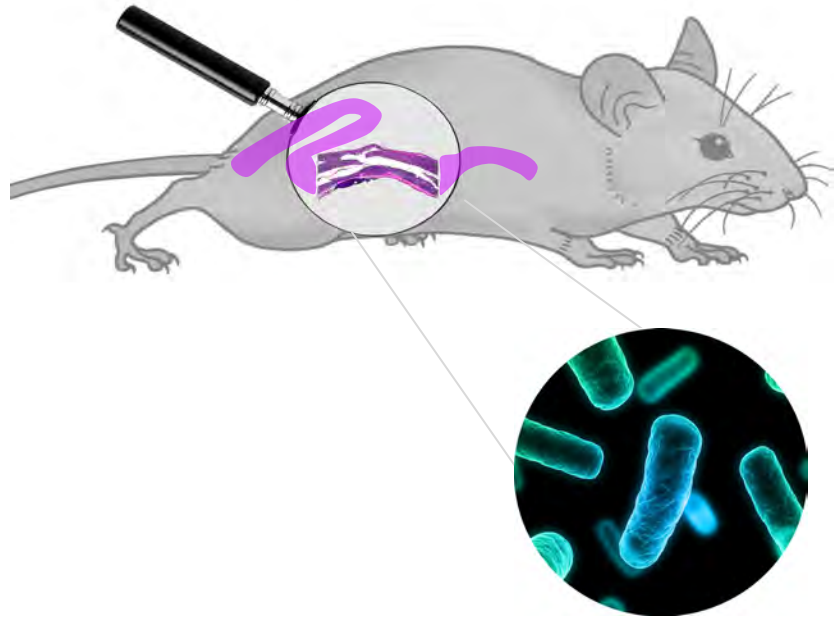


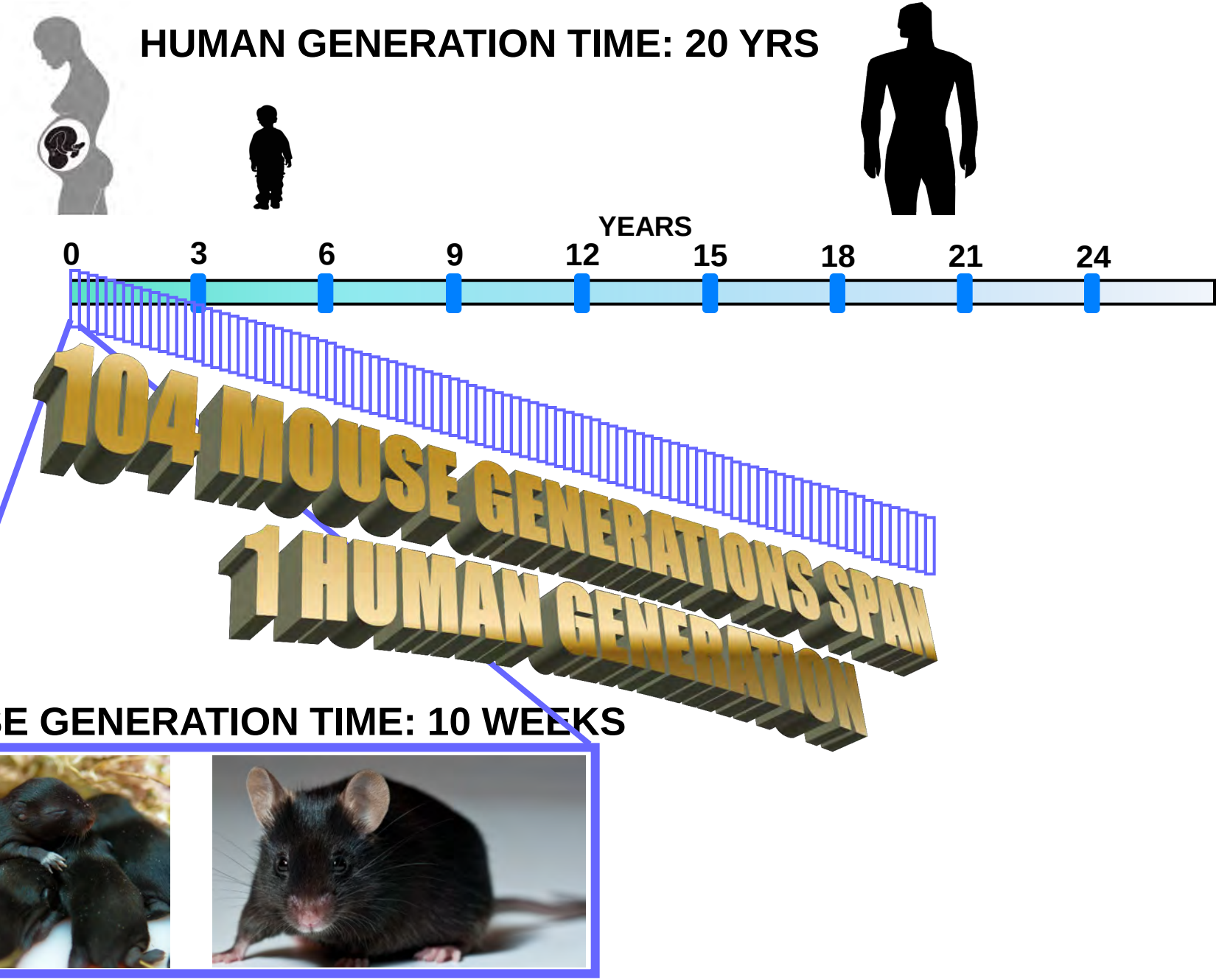
NIH U01 CA164337. ***GI Tract Dysbiosis and Breast Cancer*****. [PIs: Erdman, Alm & Wang] 2012 – 2017**

Does maternal and infant microbial ecology offer opportunity to impart good health to future generations?



Why use animal models?




HUMAN GENERATION TIME: 20 YRS
YEARS
0
3
6
9
12
15
18
21
24
104 MOUSE GENERATIONS SPAN
1 HUMAN GENERATION
MOUSE GENERATION TIME: 10 WEEKS

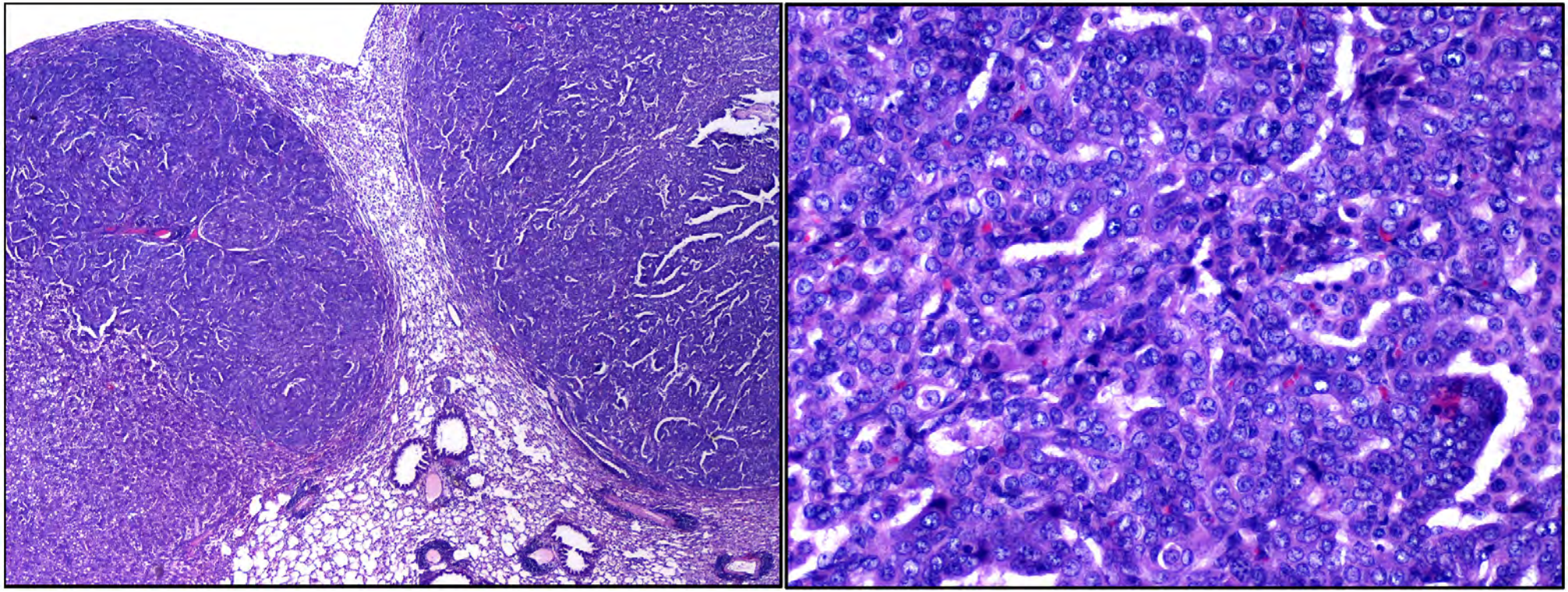
NIEHS P30 ES002109. [P30 PIs: Leona Samson → John Essigmann]
***Perinatal microbe exposures*. Pilot project co-PIs: SE Erdman & EJ Alm**
2011 – 2013

Grandma's microbial ecology may put grandchild at risk for cancer?

Preliminary cancer outcomes in 'grandchildren' mice:

- **1/3 liver cancer (hepatocellular carcinoma)**
- **2/3 lymphoma (high grade)**
- **3/3 lung cancer (bronchoalveolar adenocarcinoma)**

Bronchoalveolar adenocarcinoma in 3/3 'grandchild' outbred Swiss mice (age = 5 months)



Gut microbe-triggered systemic events

Dendritic Cells

T_E

IL10

IL10

Macrophages

Inflammatory cytokines

IL10

TGFb
IL10

Migration and maturation

T_R

Neutrophil recruitment

TGFb
IL10

T_E

T_R

CD40-CD40L

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

Gut microbe-triggered systemic events

Dendritic Cells

Macrophages

Inflammatory cytokines

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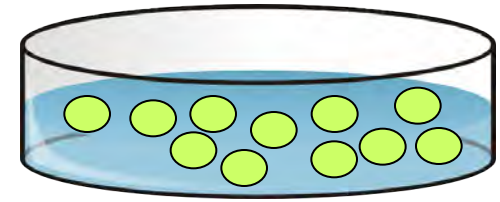
Neutrophil recruitment

CD40-CD40L

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

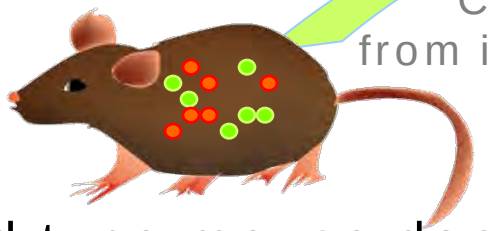
Adoptive Cell Transfer Paradigm

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



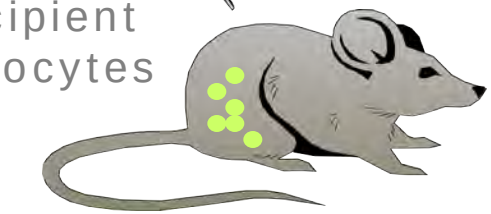
adoptive cell transfer

Cells extracted
from immune-competent
donor mouse

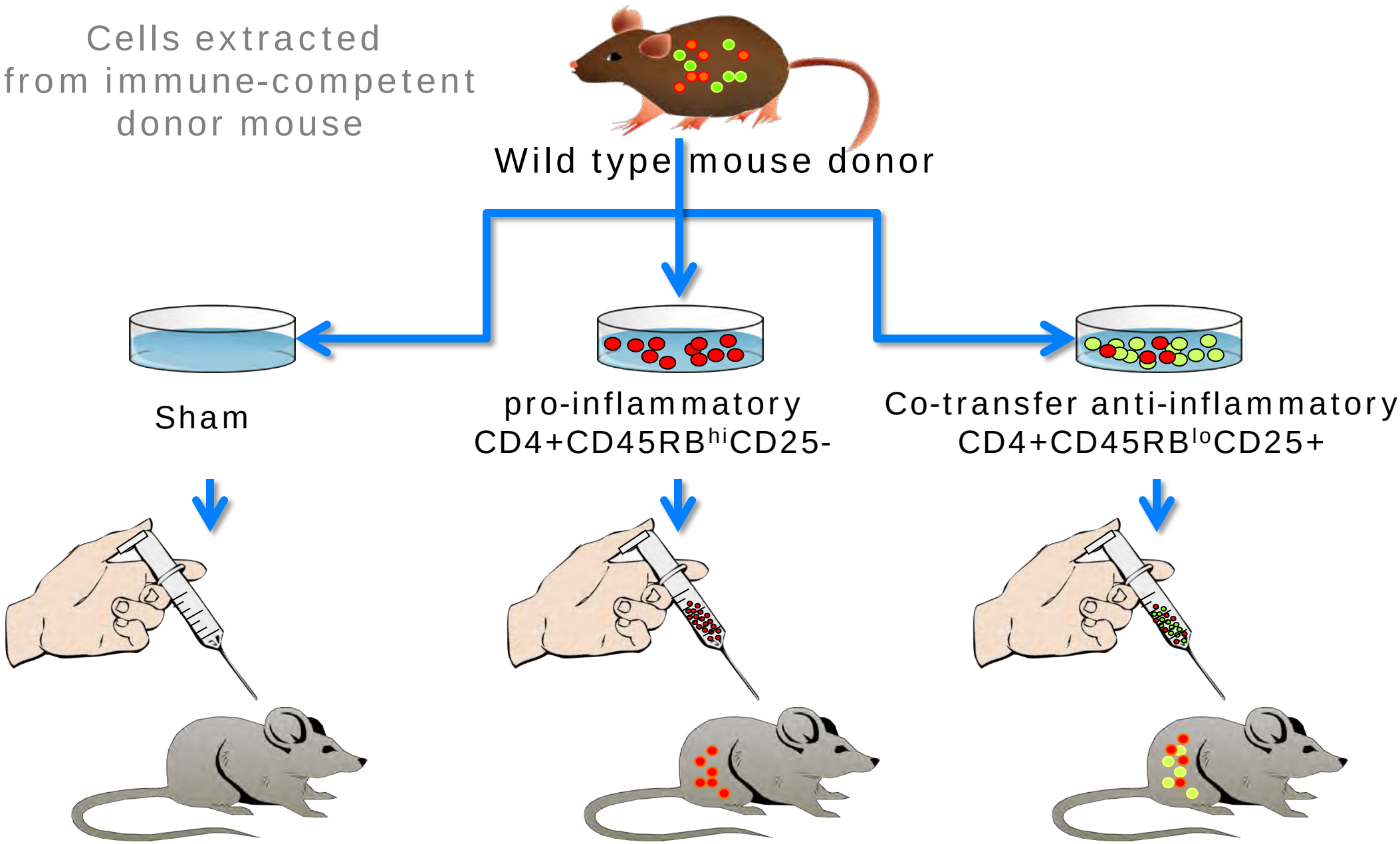


Wild type mouse donor

Cells injected into recipient
without it's own lymphocytes

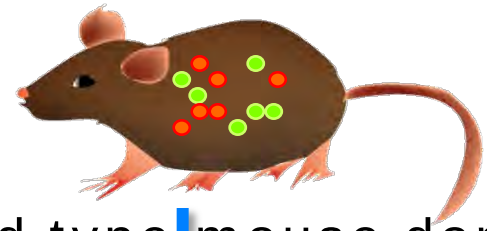


Rag2-KO mouse recipient


Cells extracted
from immune-competent
donor mouse
Wild type mouse donor
Sham
pro-inflammatory
CD4+CD45RB^hiCD25-
Co-transfer anti-inflammatory
CD4+CD45RB^loCD25+
Cells injected into Rag2-KO recipient without it's own lymphocytes

We thank Bruce H Horwitz & James G Fox

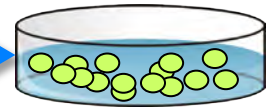
Cells extracted from immune-competent donor mouse



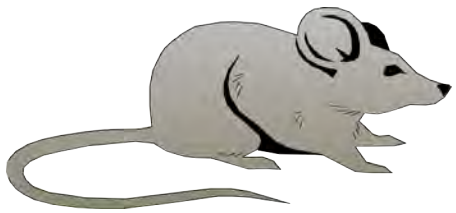
Wild type mouse donor

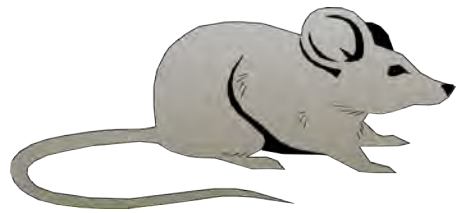
Sham

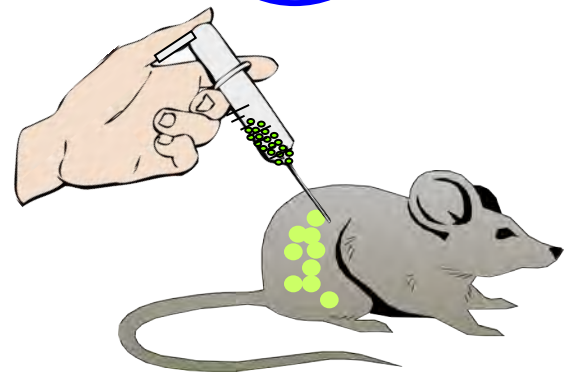
Transfer anti-inflammatory CD4+CD45RB^{lo}CD25+



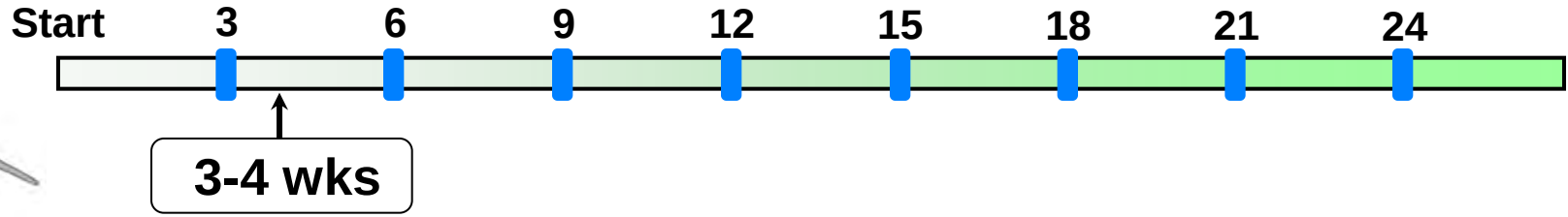
Helicobacter hepaticus







Microbe infection into Rag2-KO recipient without it's own lymphocytes



Uninfected

H. hepaticus-infected

H. hepaticus-infected

cecum

colon

Innate immunity is sufficient for IBD and carcinoma

Cells of adaptive immunity suppress IBD and carcinoma

(Erdman et al 2003)

Gut microbe-triggered systemic events

Dendritic Cells

Macrophages

Inflammatory cytokines

Migration and maturation

Neutrophil recruitment

CD40-CD40L

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

Gut microbe-triggered systemic events

Dendritic Cells

IL10

IL10

Macrophages

Inflammatory cytokines

IL10

TGFb
IL10

T_R

Neutrophil recruitment

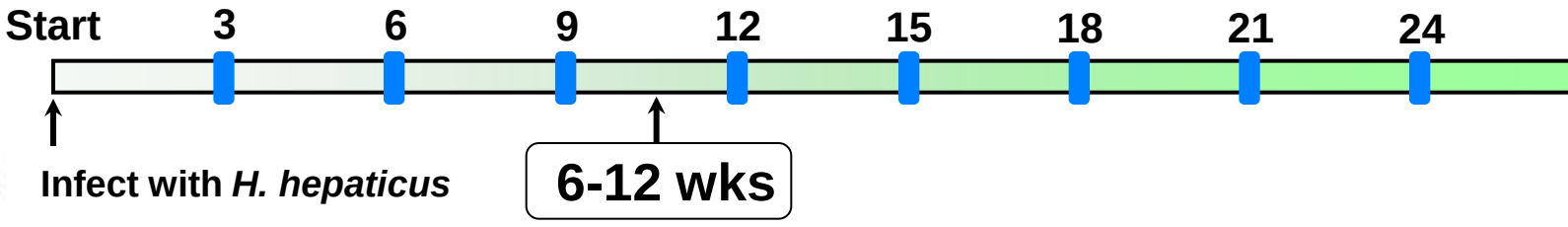
Migration and maturation

TGFb
IL10

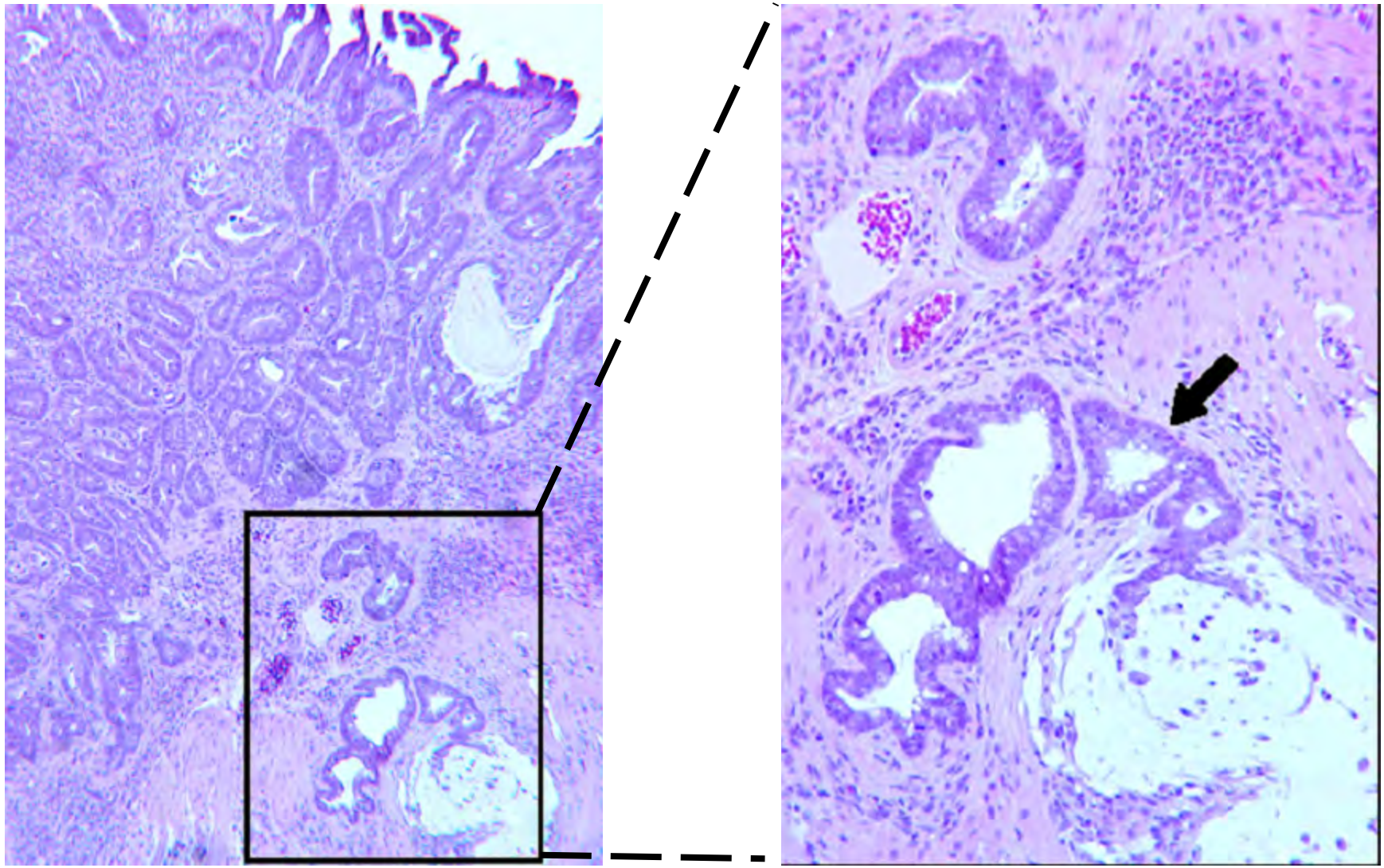
T_R

CD40-CD40L

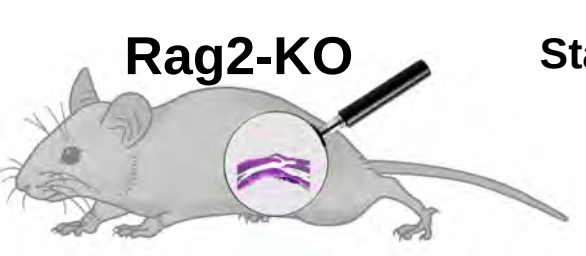
(modified from Coombs, et al 2005; Fiona Powrie lab)

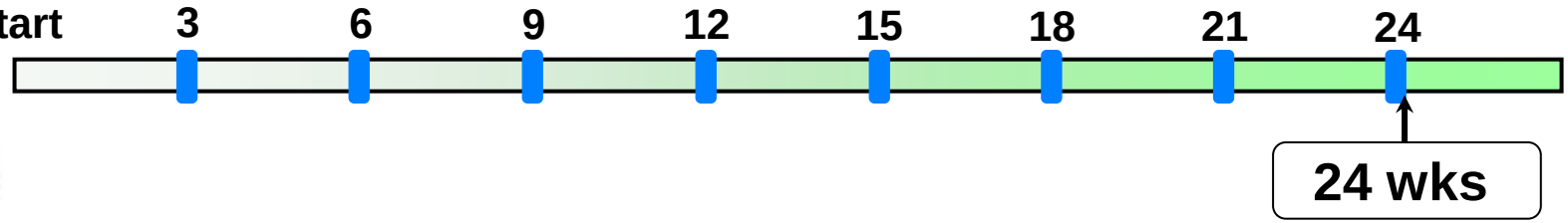


Invasive colonic carcinoma in *H. hepaticus*-infected Rag2-/- mice



Erdman, et al, Am J Path, 2003



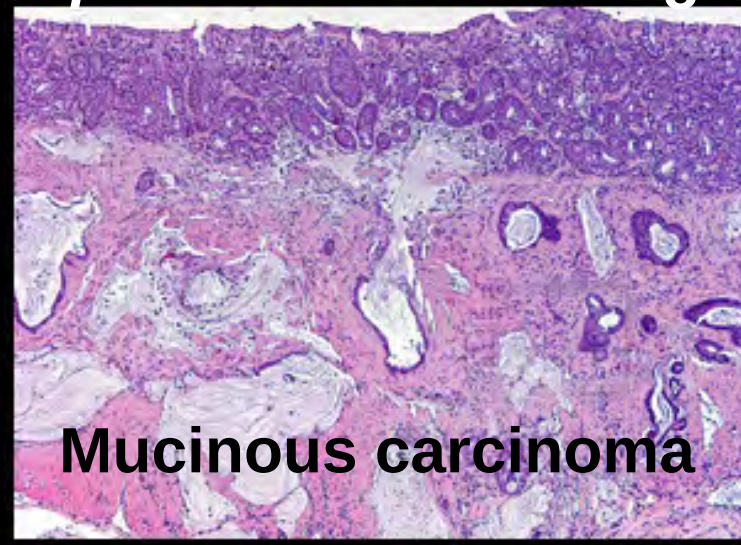


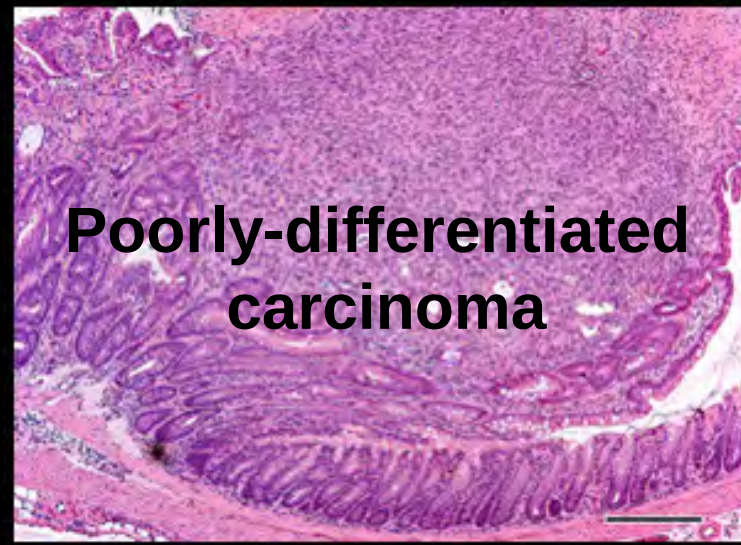
Colonic carcinoma in
H. hepaticus-infected Rag2-/- mice

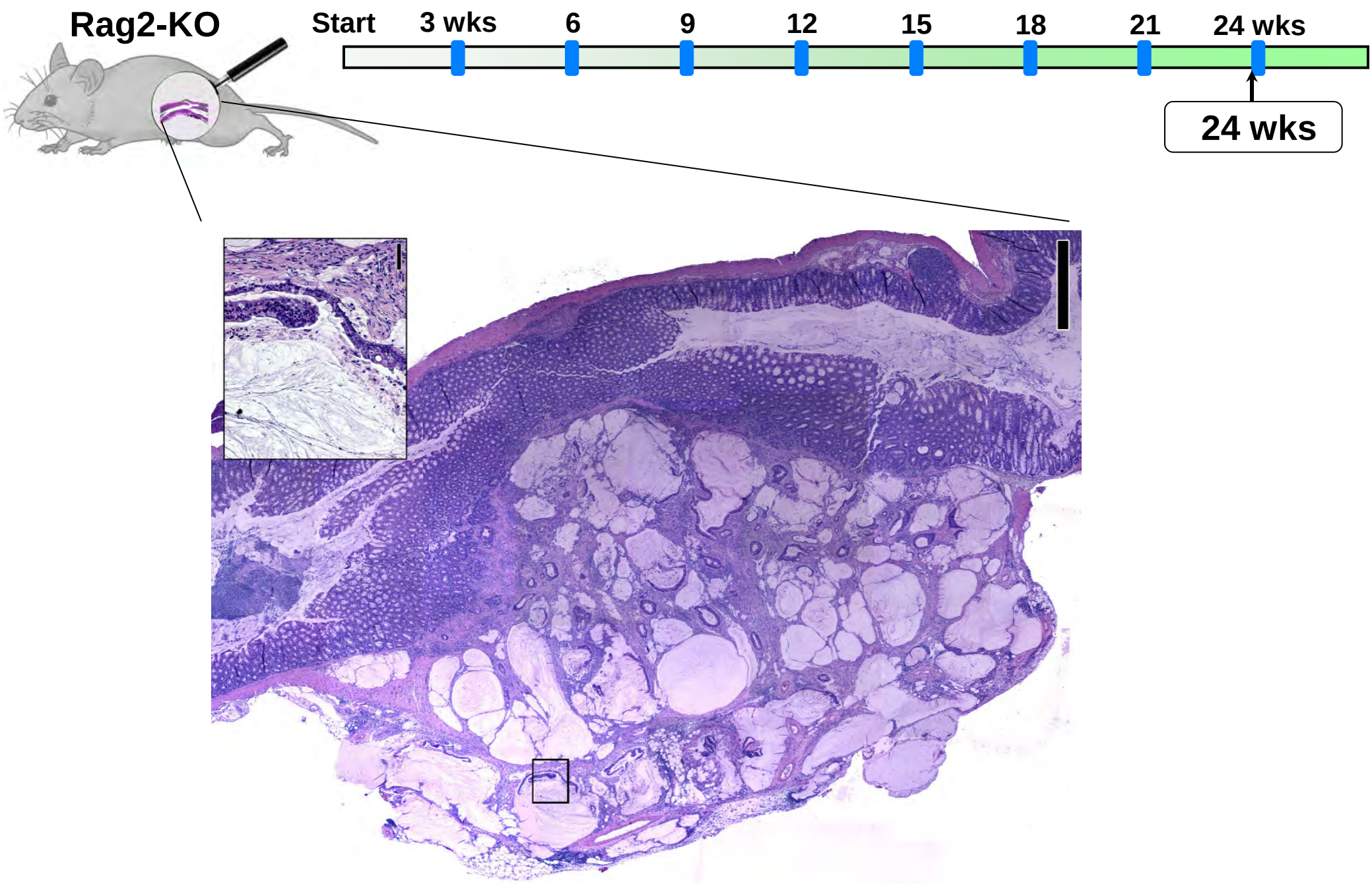
H hepaticus-infected Rag2-/-

uninfected Rag2-/-

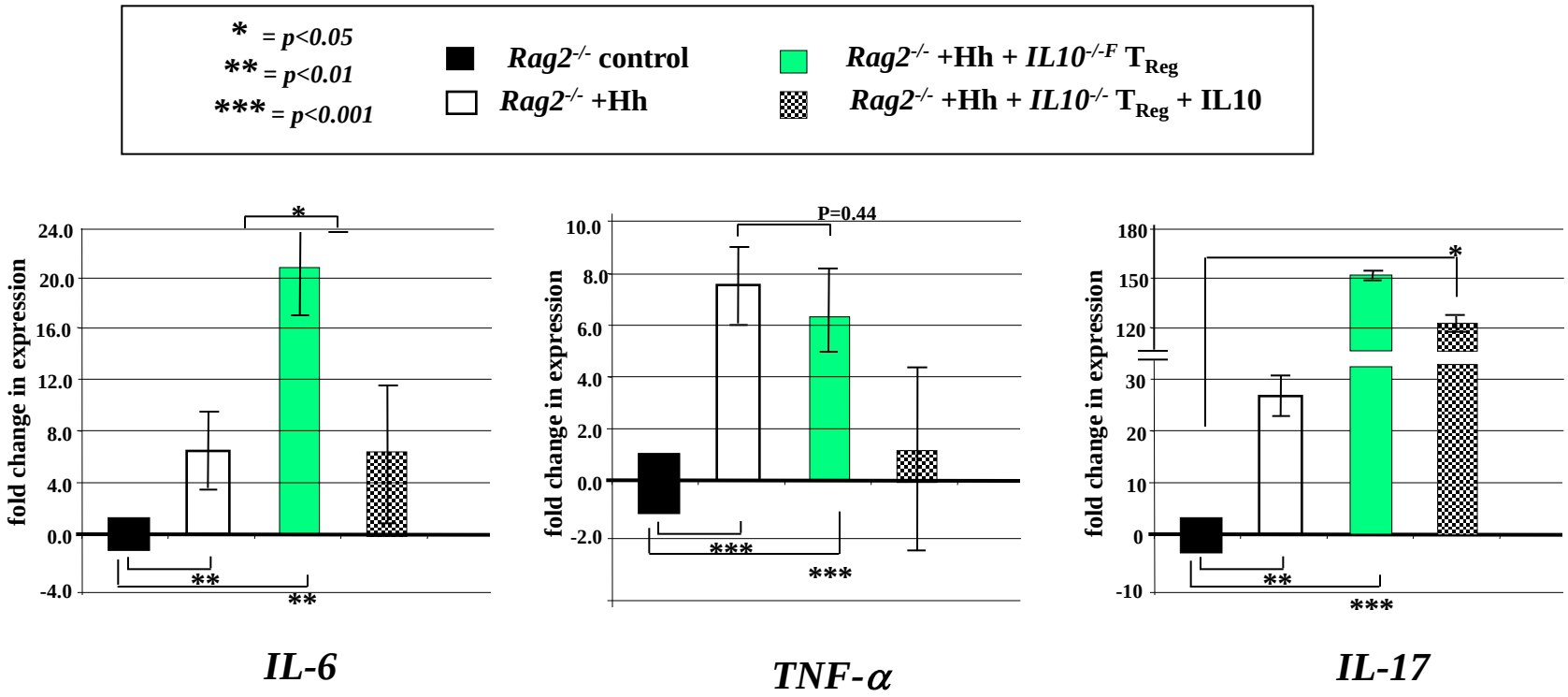
Erdman, et al, 2003



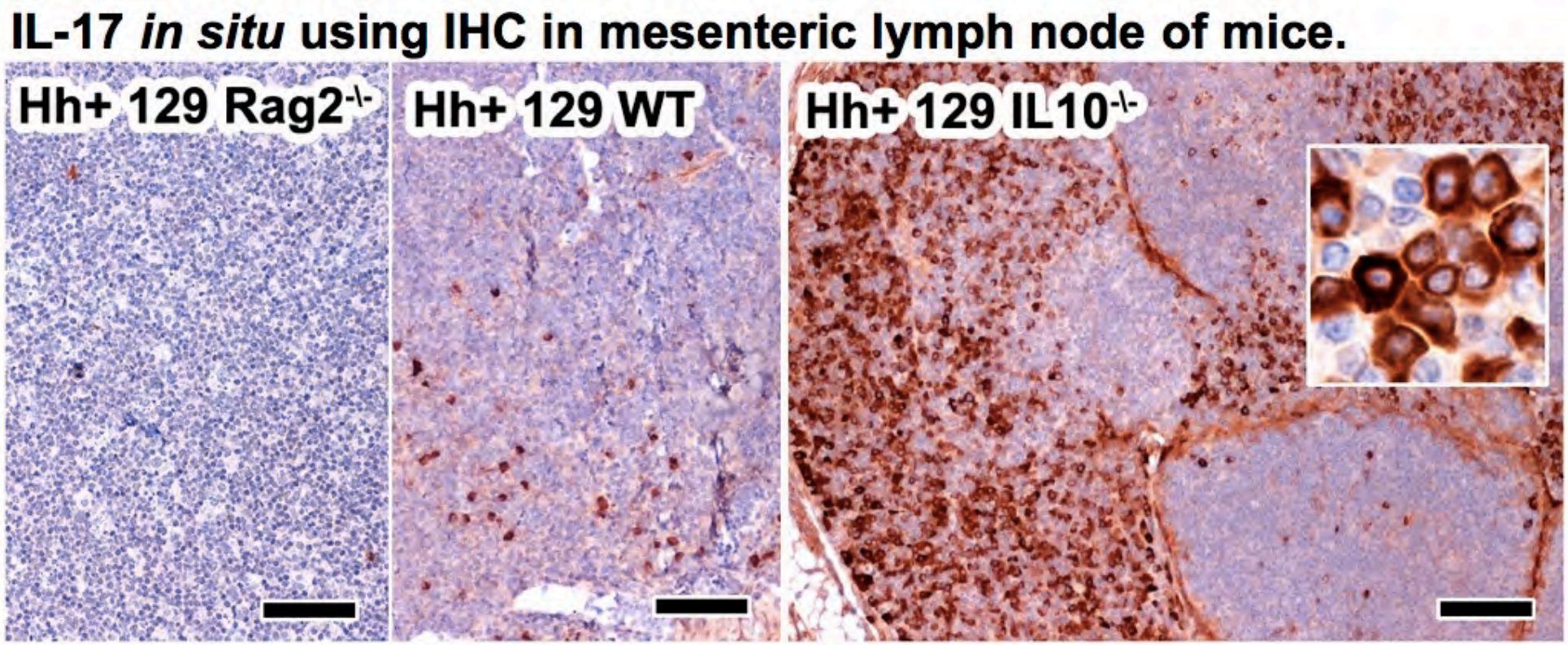



Rag2-KO
Start
3 wks
6
9
12
15
18
21
24 wks
24 wks

H. hepaticus infection up-regulates pro-inflammatory cytokines

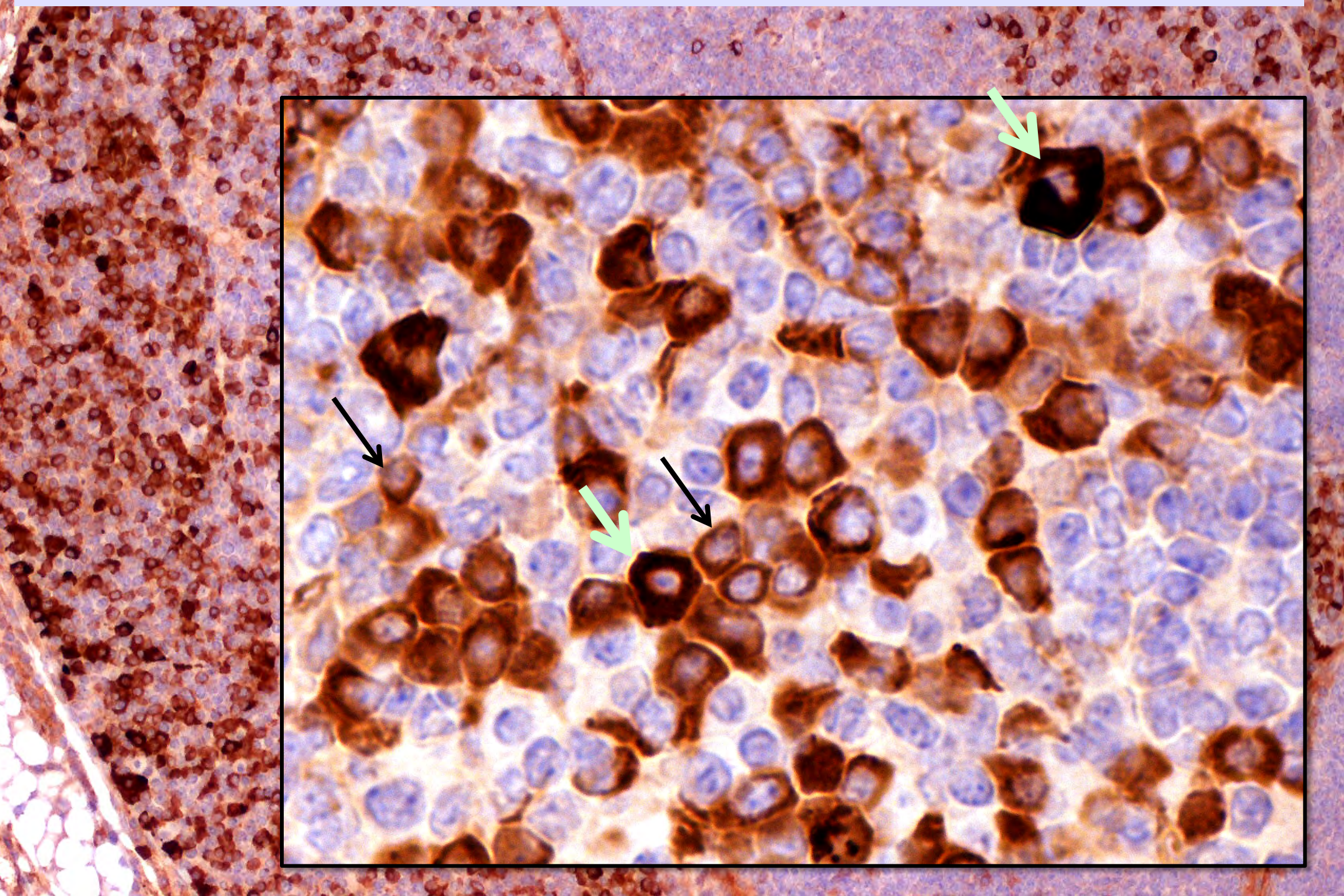


Reciprocal relationships exist between Interleukin (IL)-10 and IL-17

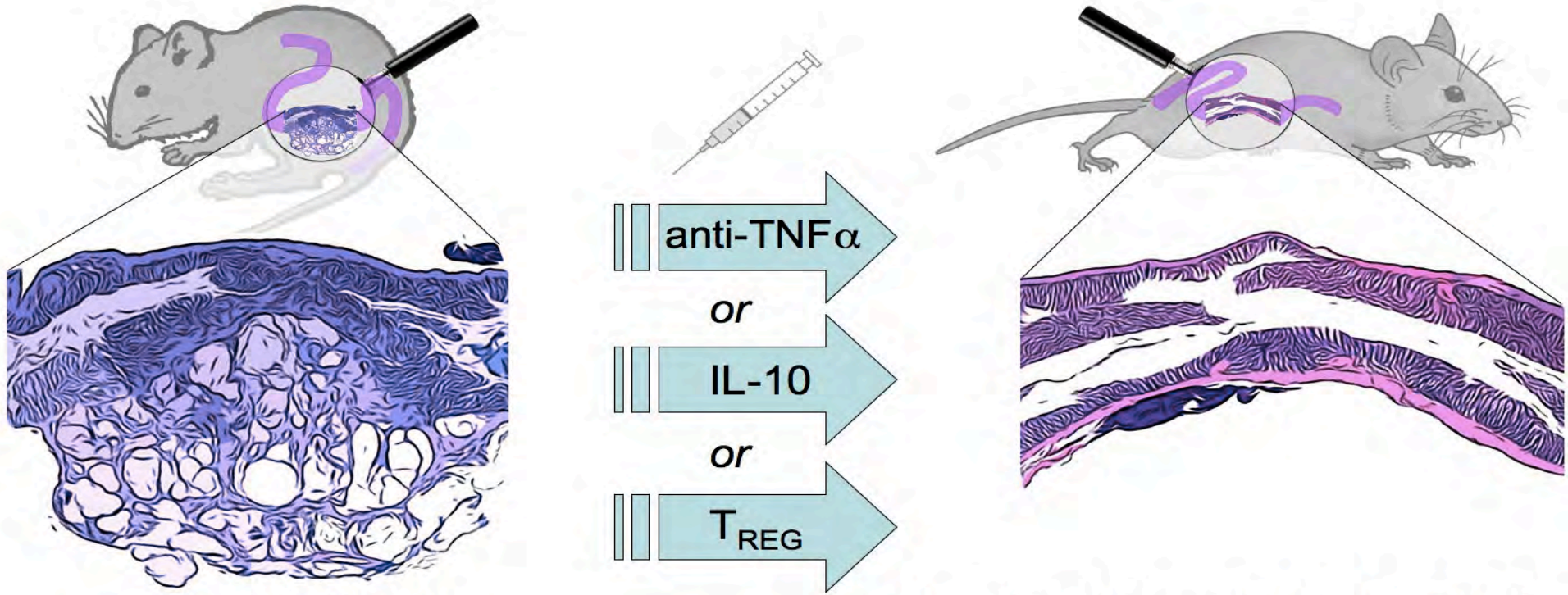


We thank Theofilos Poutahidis

Erdman et al 2010

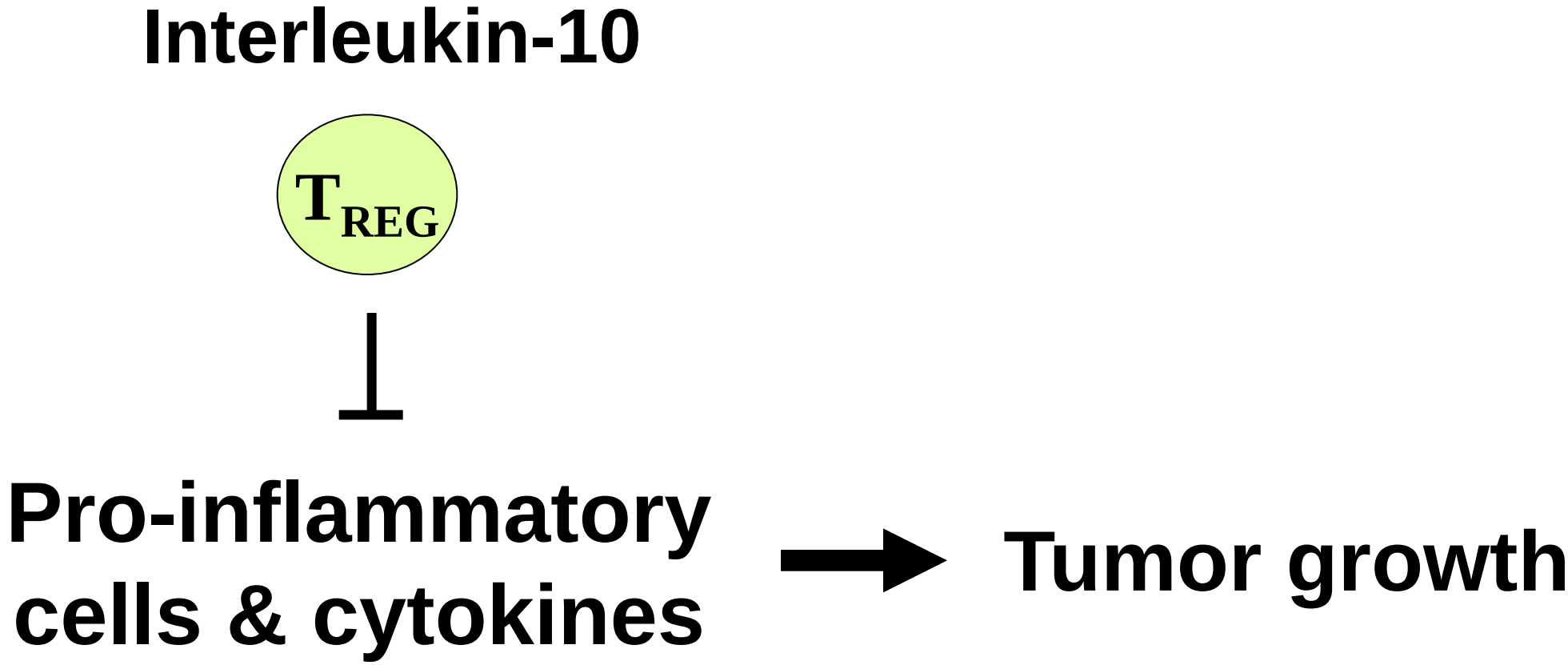


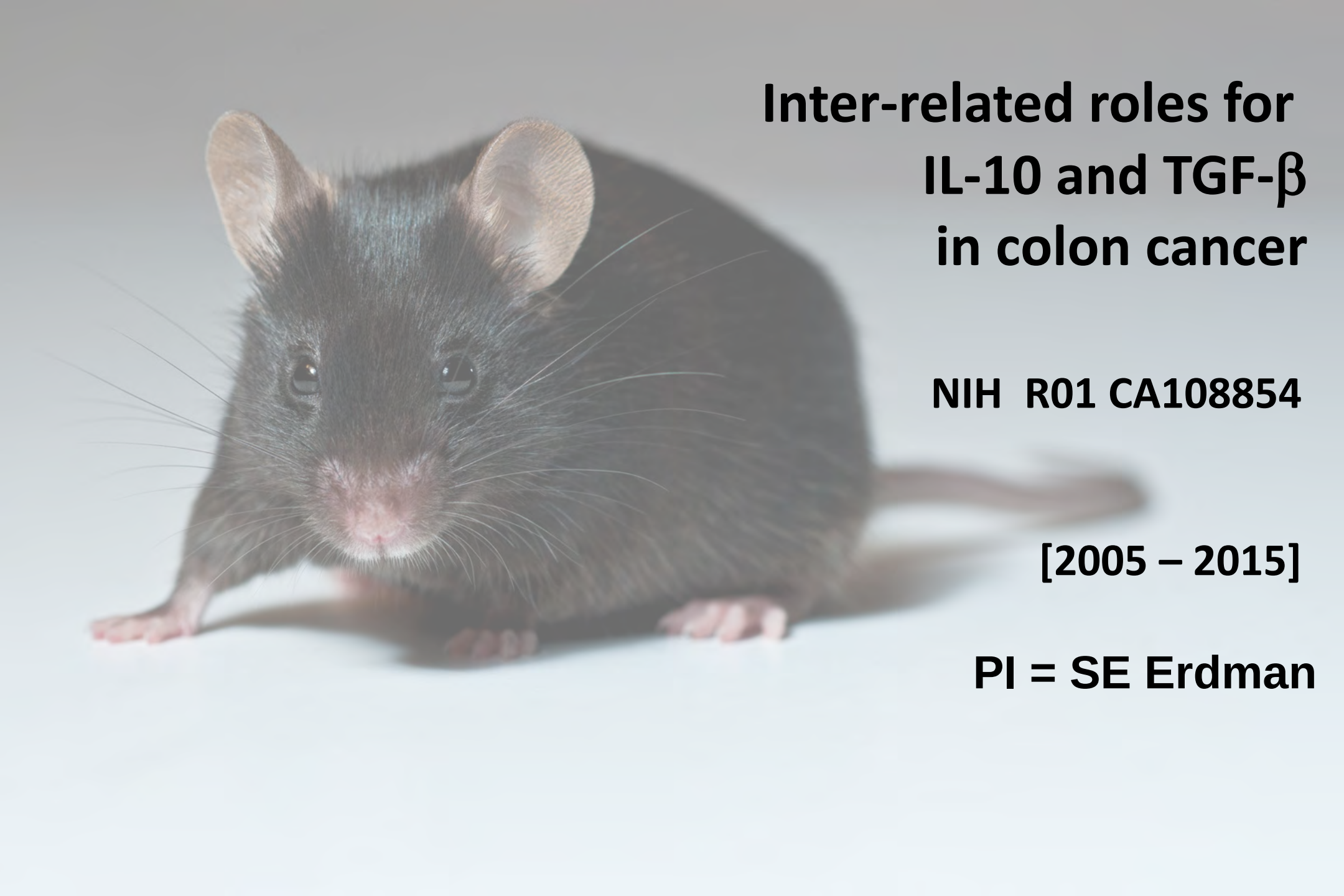
Blocking inflammation leads to total remission of established invasive colonic carcinoma



mucinous CRC with peritoneal neoplastic invasion

restoration of normal colonic epithelia after anti-inflammatory treatment


Interleukin-10
T_{REG}
Pro-inflammatory cells & cytokines
Tumor growth



Inter-related roles for IL-10 and TGF-β in colon cancer

NIH R01 CA108854

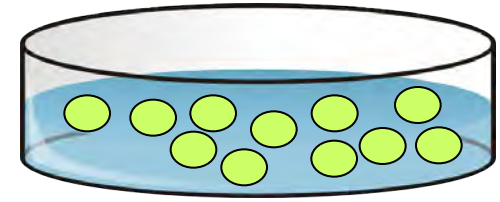
[2005 – 2015]

PI = SE Erdman

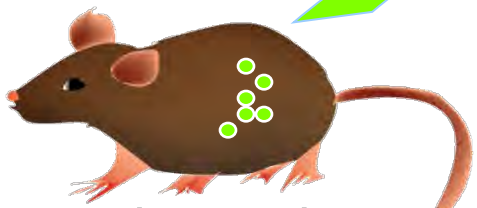
Prior microbe exposures convey health benefits transplantable via purified immune cells

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

H. hepaticus dosed orally by gastric gavage

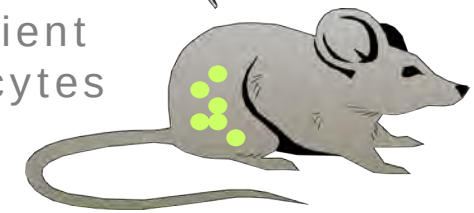


adoptive cell transfer



H. hepaticus-fed donor

Cells injected into recipient without it's own lymphocytes



Rag2-KO mouse recipient

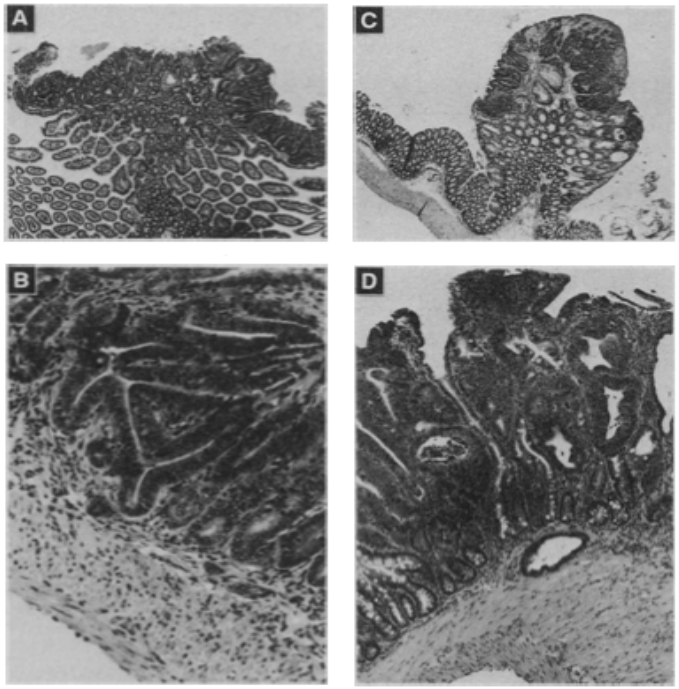
Science

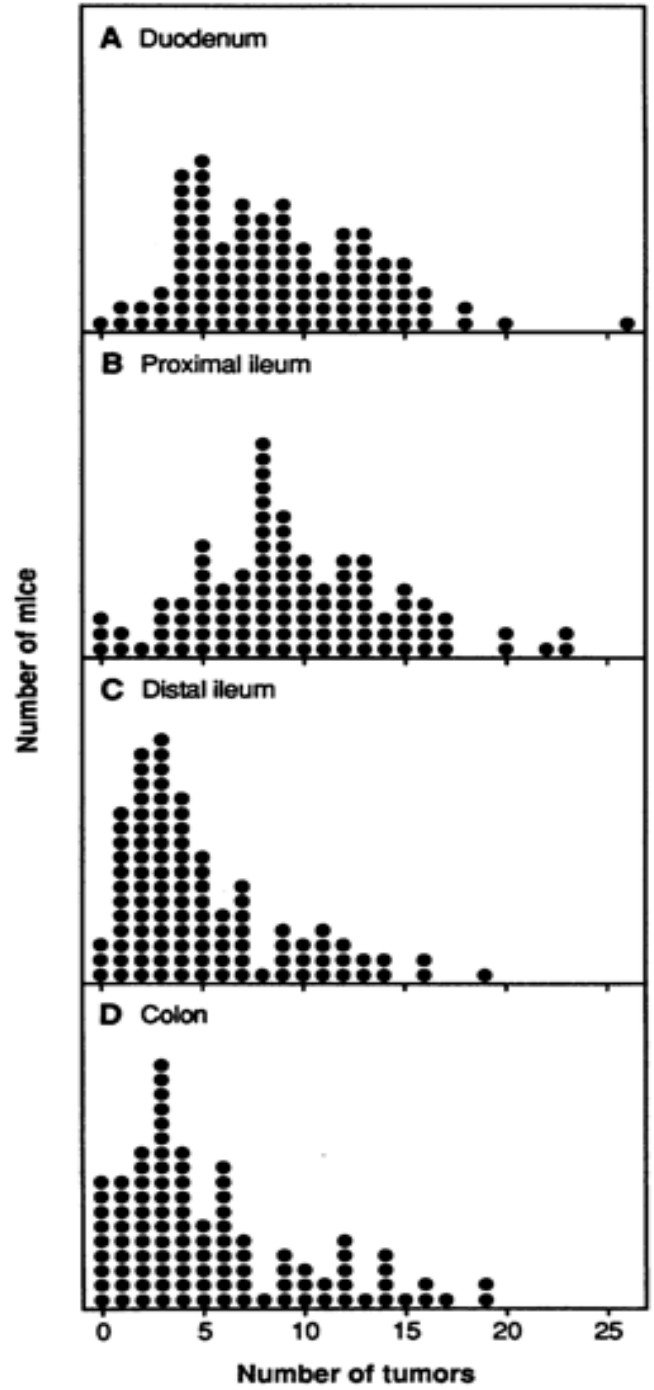
A Dominant Mutation That Predisposes to Multiple Intestinal Neoplasia in the Mouse

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

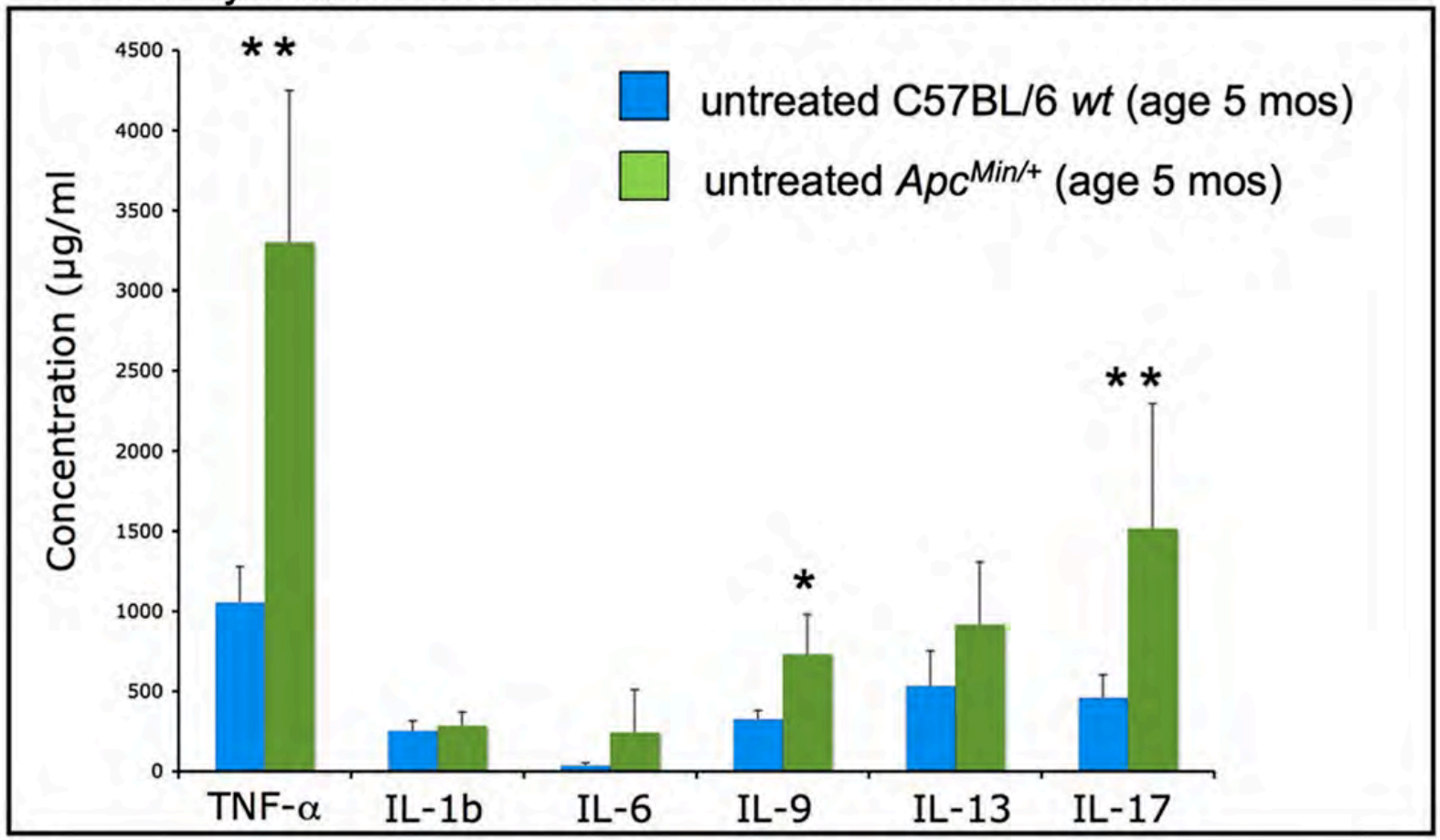
In a pedigree derived from a mouse treated with the mutagen ethylnitrosourea, a mutation has been identified that predisposes to spontaneous intestinal cancer. The mutant gene was found to be dominantly expressed and fully penetrant. Affected mice developed multiple adenomas throughout the entire intestinal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

19 JANUARY 1990 SCIENCE, VOL. 247





Serum cytokine levels in C57BL/6 wt vs Min mice

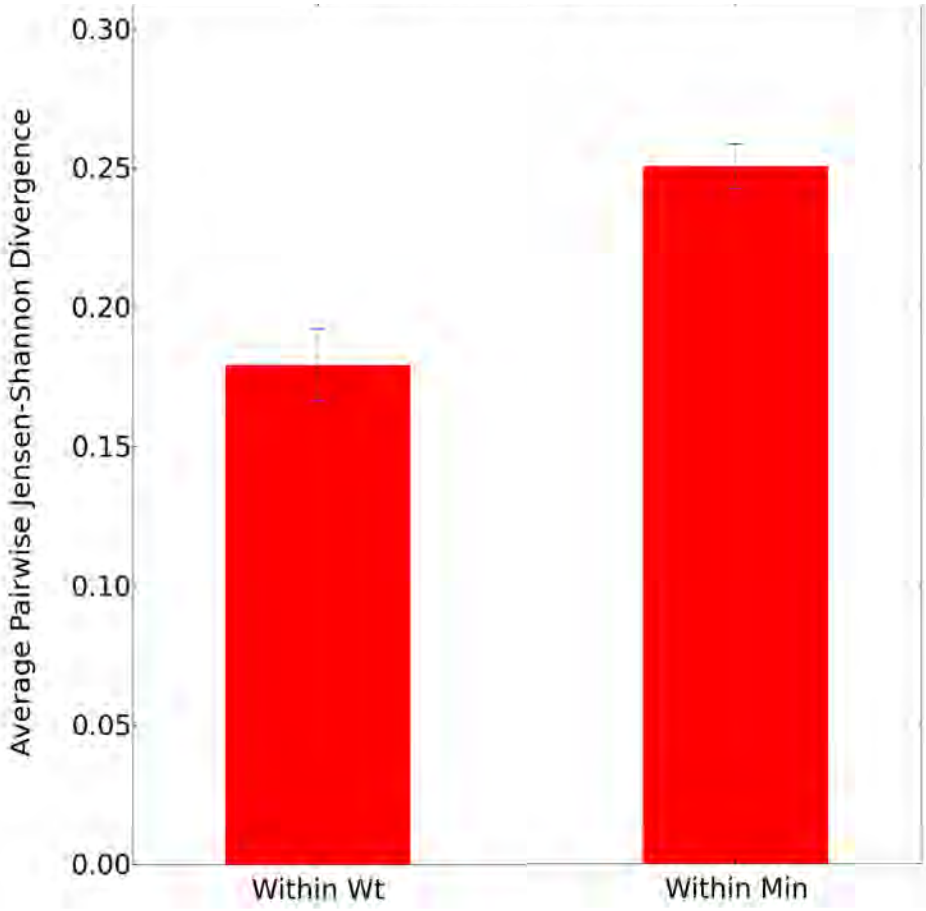


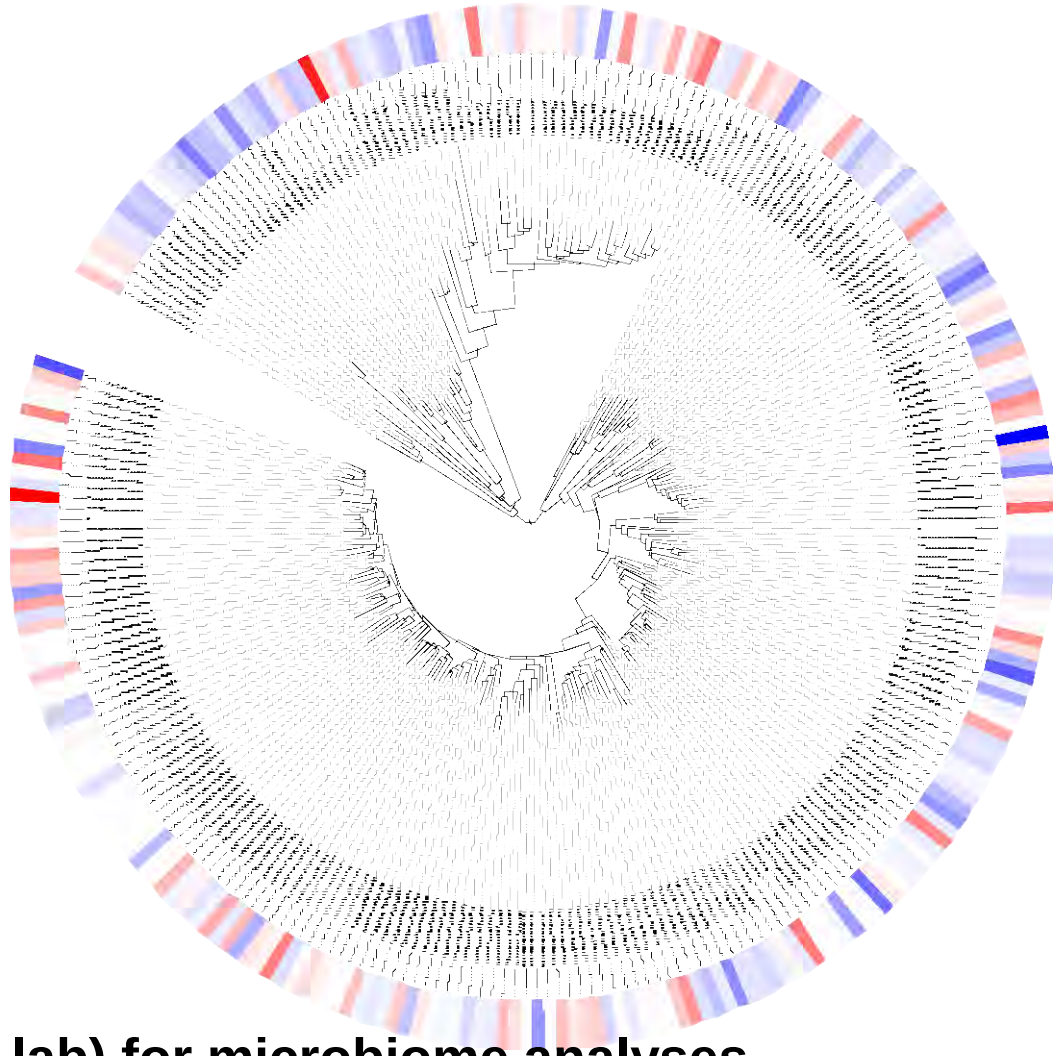
Luminex (serum protein) assay reveals that serum levels of cytokine TNFα and IL17 were significantly increased in aged Min mice at high risk of intestinal polyposis. Serum cytokine levels in pg/ml. Statistics using 2-tailed Student's t-test; ns, not significant *=p>0.05. **=P>0.01.

we thank Werner Olipitz

Significant differences exist between microbiota in Min mice and their co-housed wild type littermates

Min mouse microbiomes deviate from co-housed Wild type littermate mice

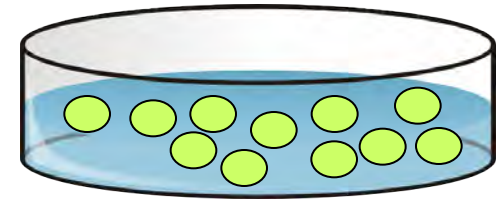




We thank Mark Burnham-Smith (EJ Alm lab) for microbiome analyses

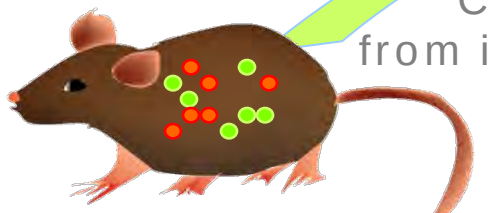
Adoptive Cell Transfer Paradigm

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



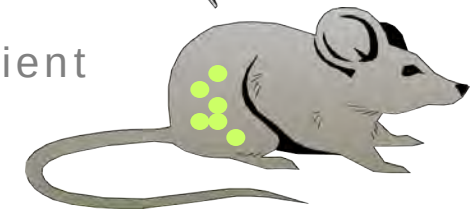
adoptive cell transfer

Cells extracted
from immune-competent
donor mouse



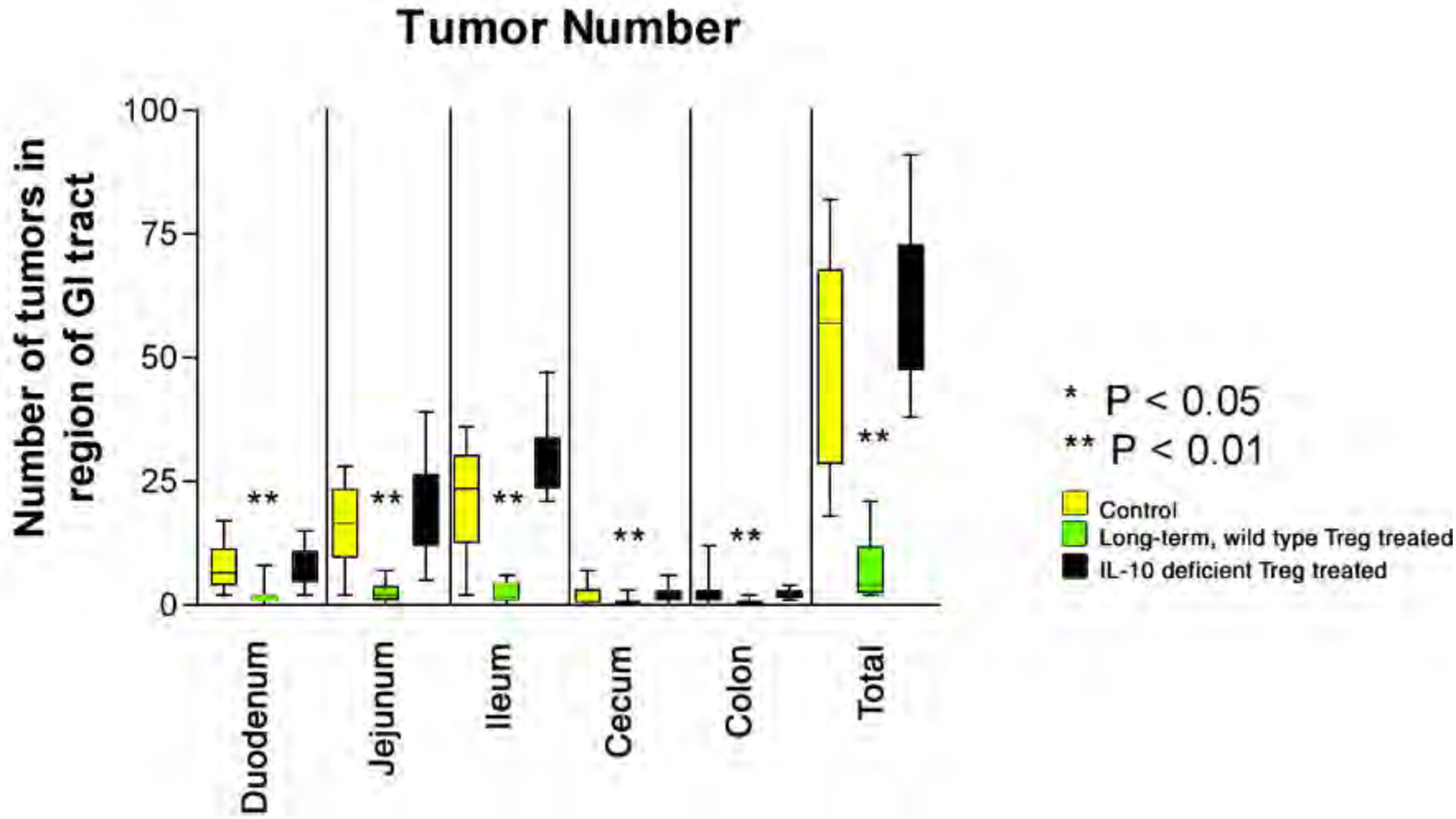
Wild type litter mate
mouse donor

Cells injected into recipient



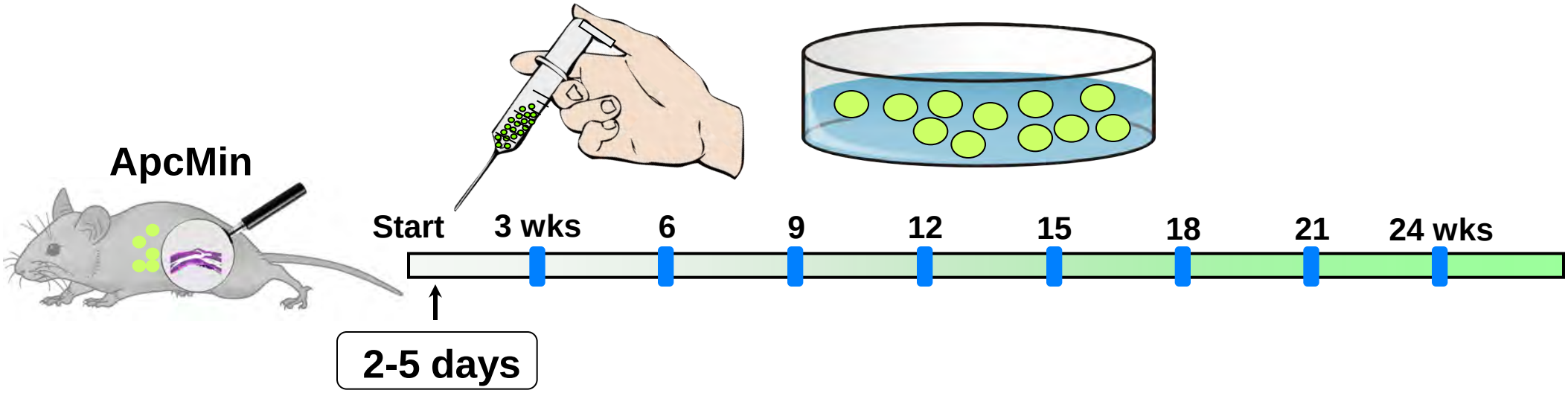
Apc $^{Min/+}$ mouse recipient

T_{REG} cells require IL-10 to prevent intestinal adenomas in *Apc*$^{Min/+}$ mice

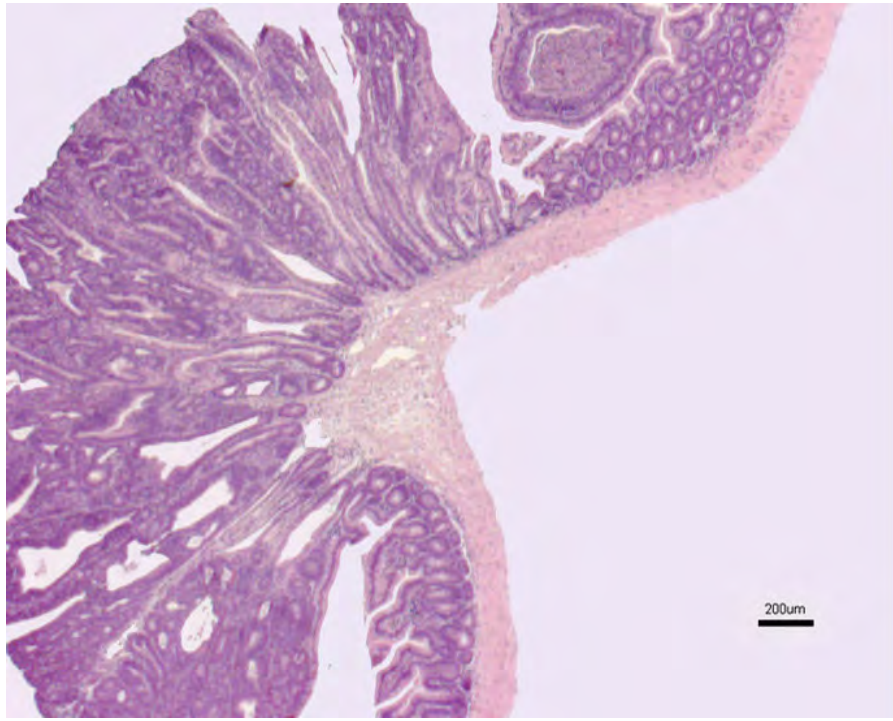


Erdman, et al, 2005

We thank David B Schauer



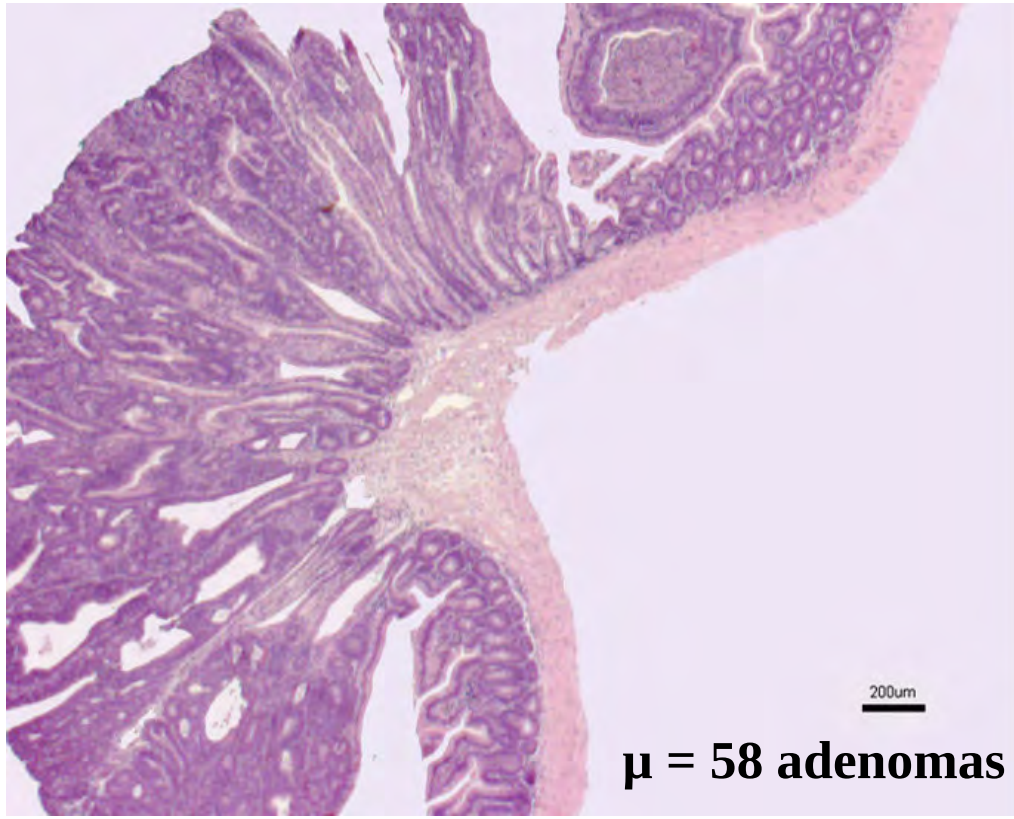
Sham-treated ApcMin



ApcMin + 3ooK wt Treg cells

T_{REG} cells induce regression of intestinal adenomas in $Apc^{Min/+}$ mice

untreated Apc $^{Min/+}$



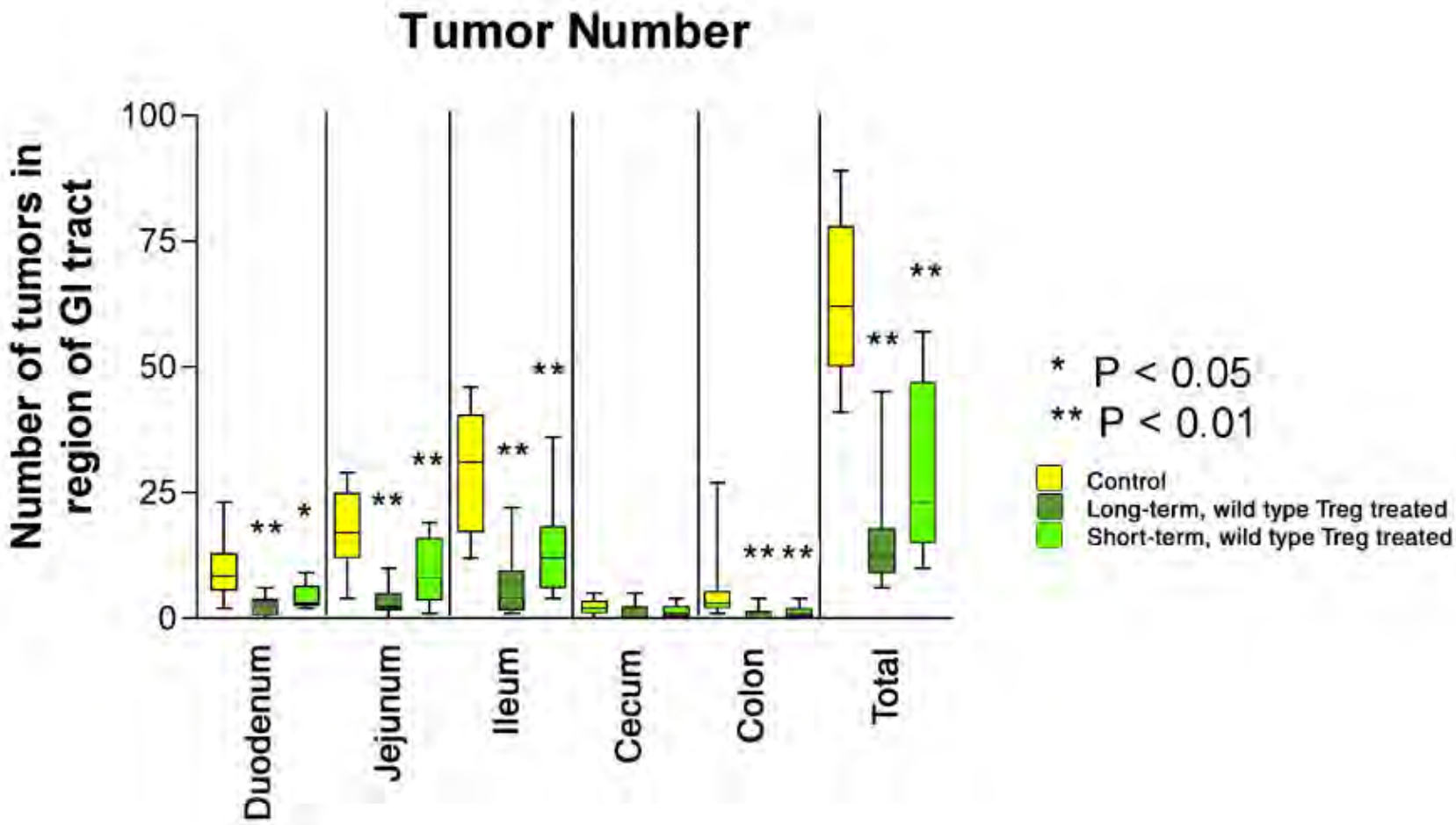
Apc $^{Min/+}$ plus T_{REG} cells

N = 14; total intestinal adenomas μ = 58 (37-91)

N = 14; total intestinal adenomas μ =12(6-43) (p<0.01)

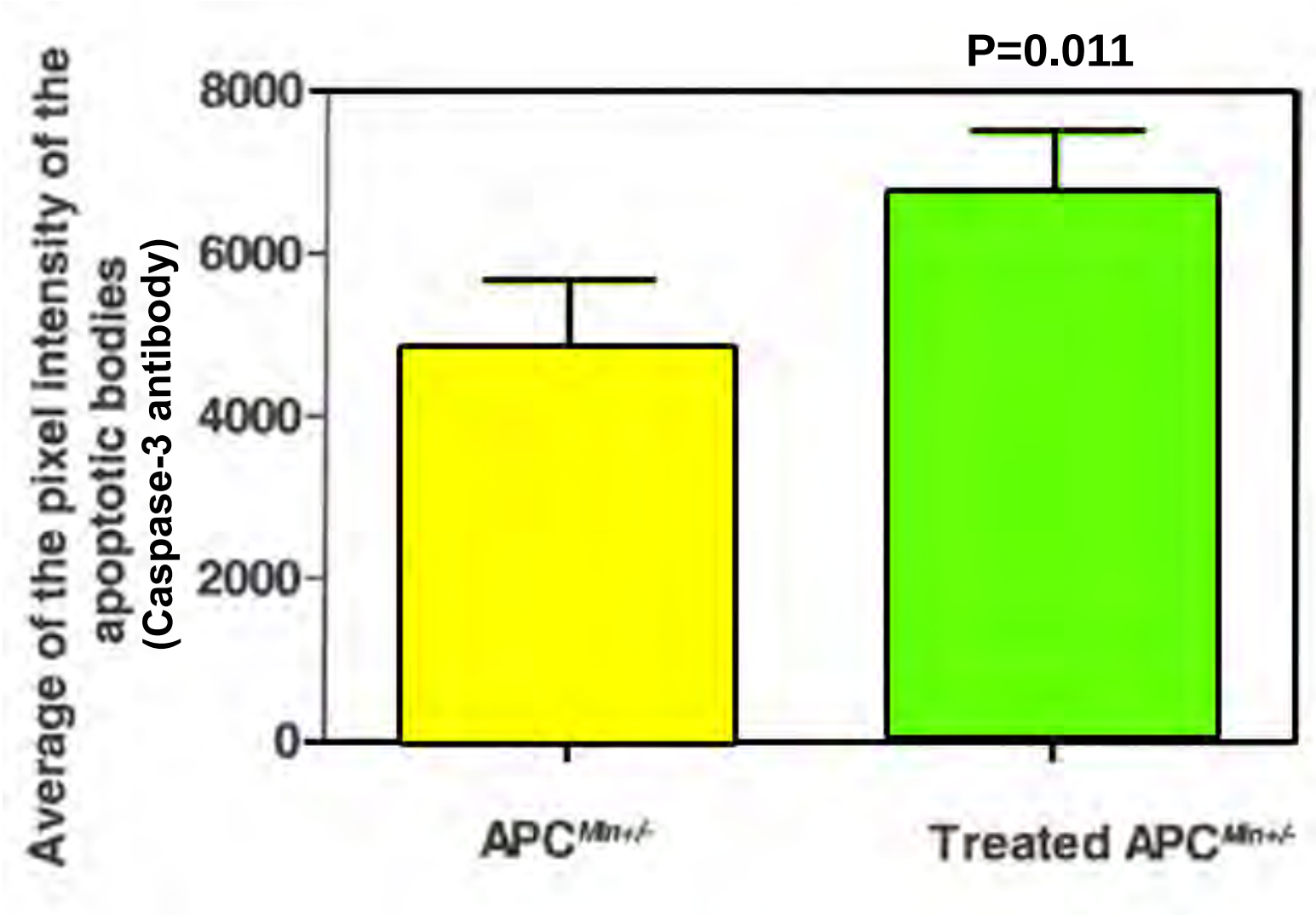
Age at treatment 4.5 - 6 months (μ age = 5.6 mos)

T_{REG} cells induce regression of intestinal adenomas in Apc $^{Min/+}$ mice

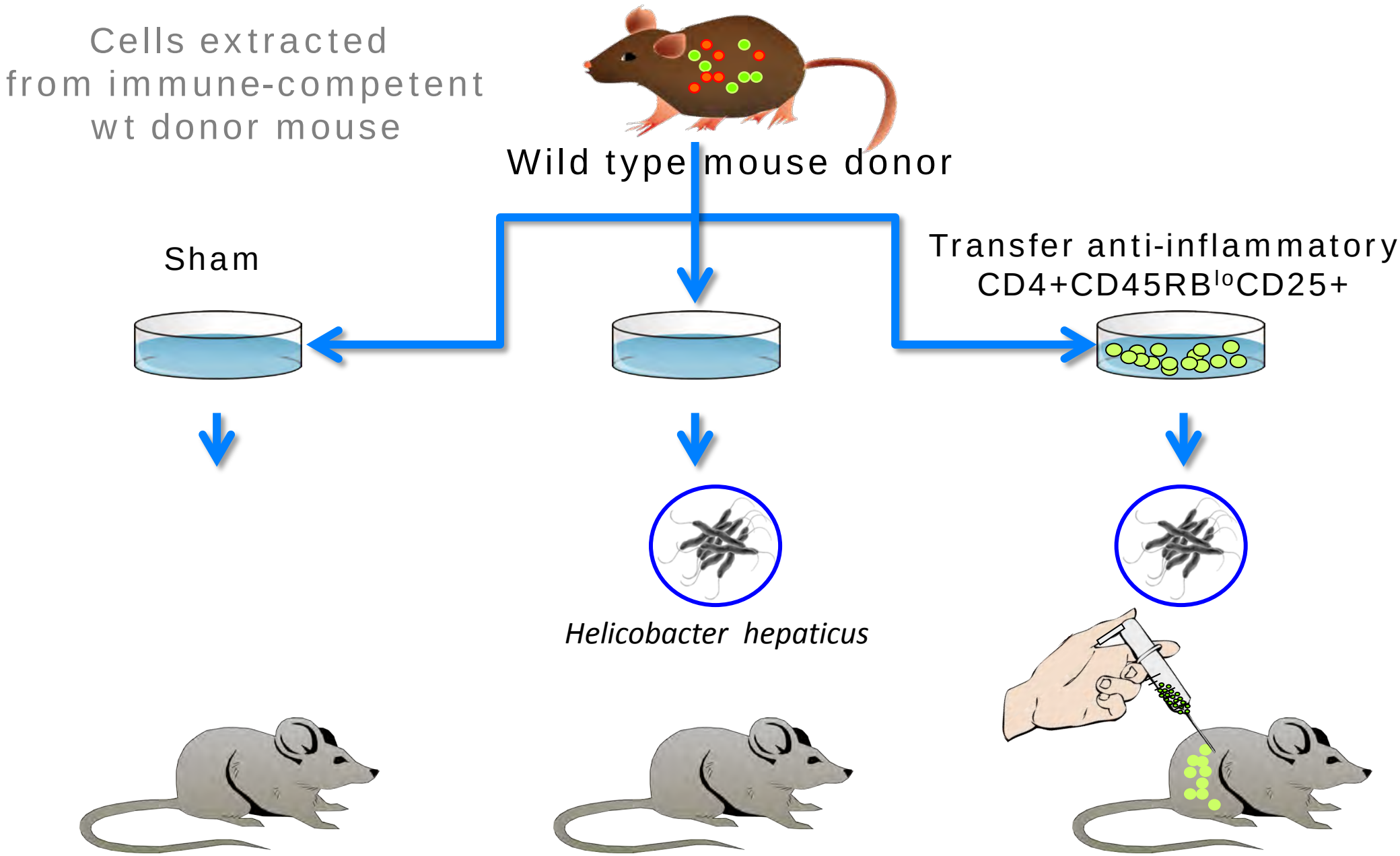


Erdman, et al, 2005

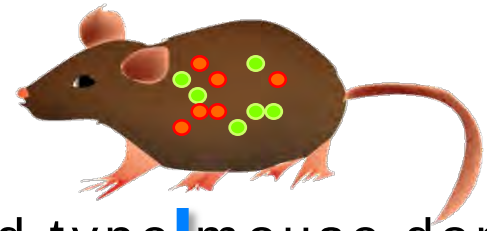
T_{REG} cells induce apoptosis within intestinal adenomas



Erdman, et al, 2005


Cells extracted
from immune-competent
wt donor mouse
Wild type mouse donor
Sham
Transfer anti-inflammatory
CD4+CD45RB^{lo}CD25+
Helicobacter hepaticus
Microbe infection in Min or Min/Rag2-KO recipients

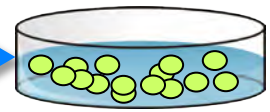
Cells extracted
from immune-competent
wt donor mouse



Wild type mouse donor

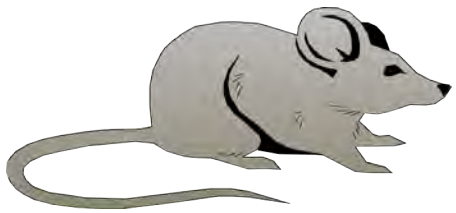
Sham

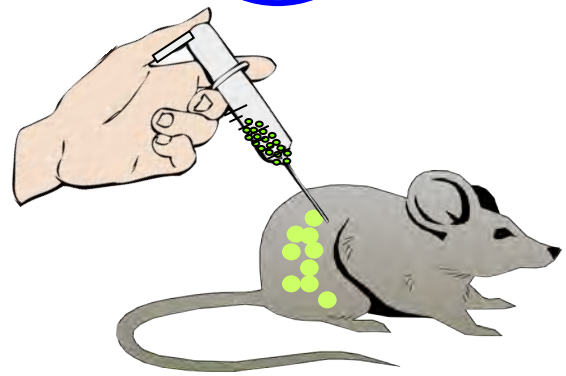
Transfer anti-inflammatory
CD4+CD45RB^{lo}CD25+



Cells of adaptive immunity suppress IBD and carcinoma

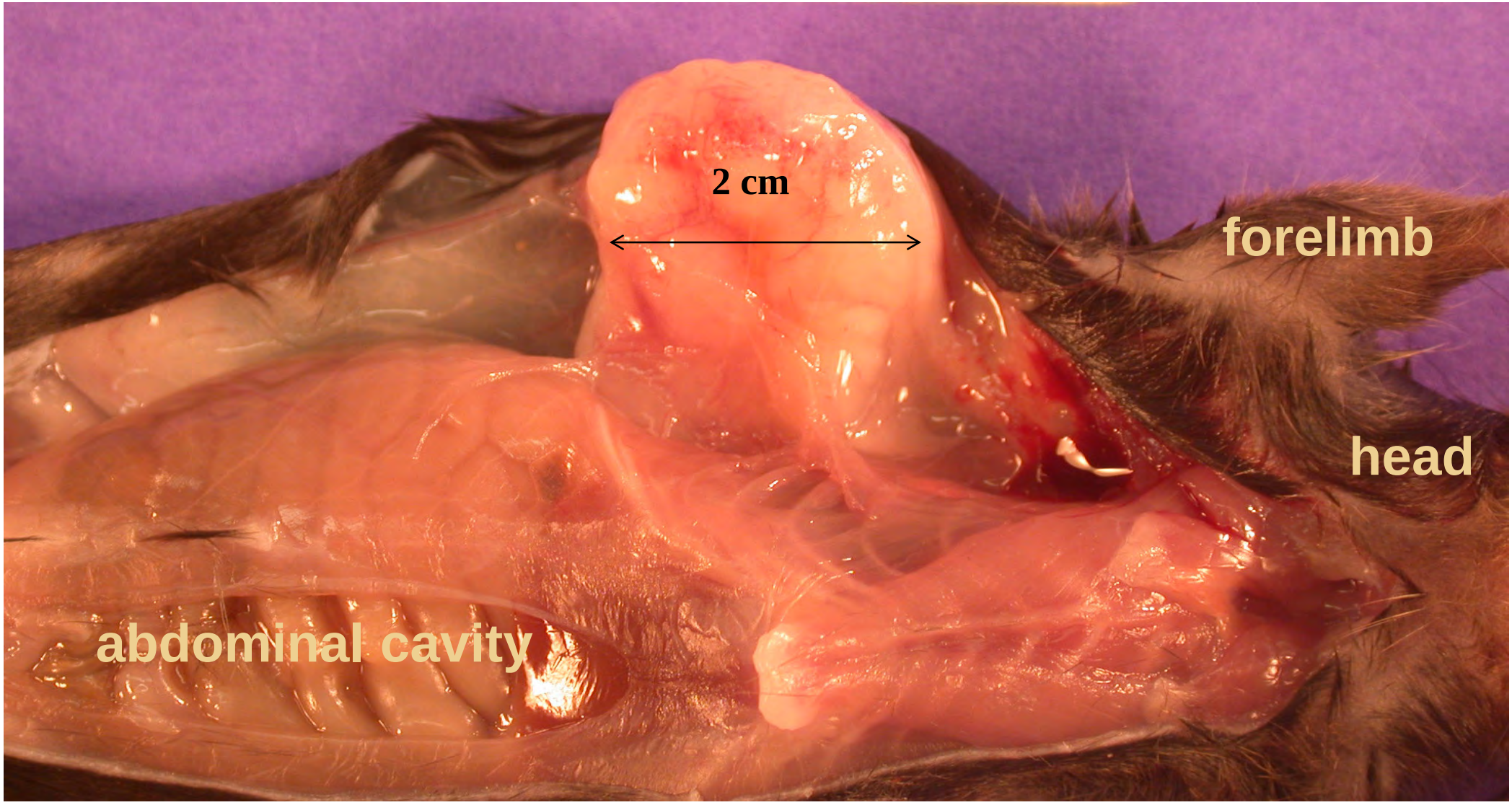
Innate immunity is sufficient for IBD and carcinoma

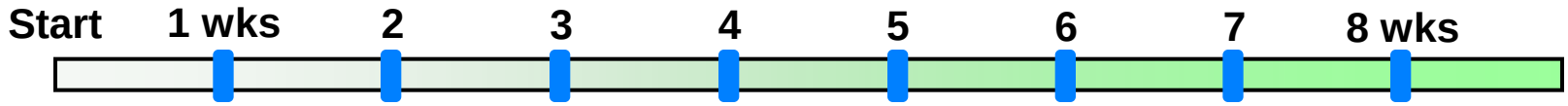


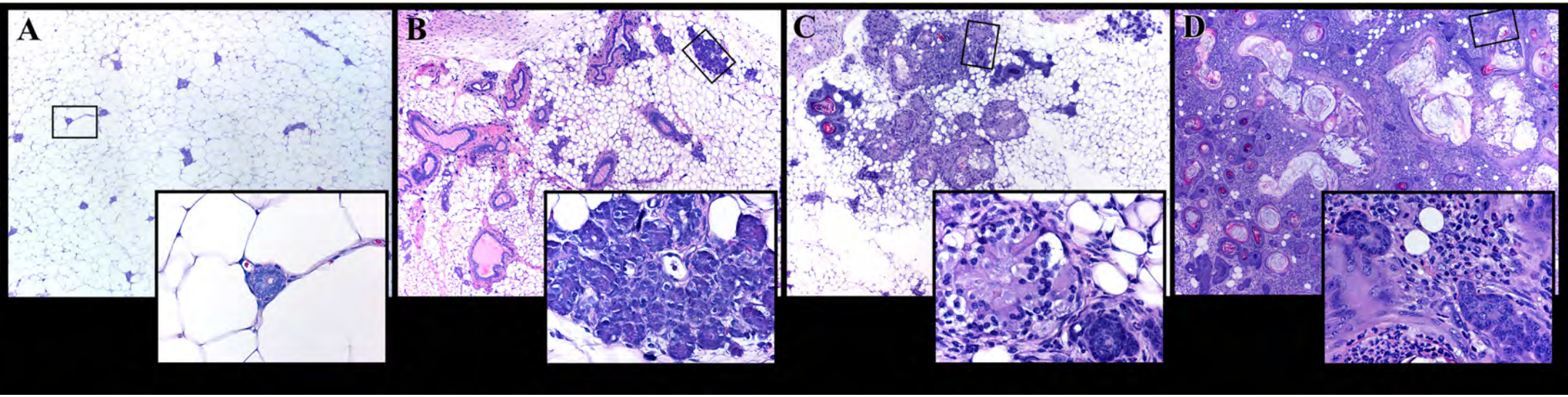


Microbe infection in Min or Min/Rag2-KO recipients

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





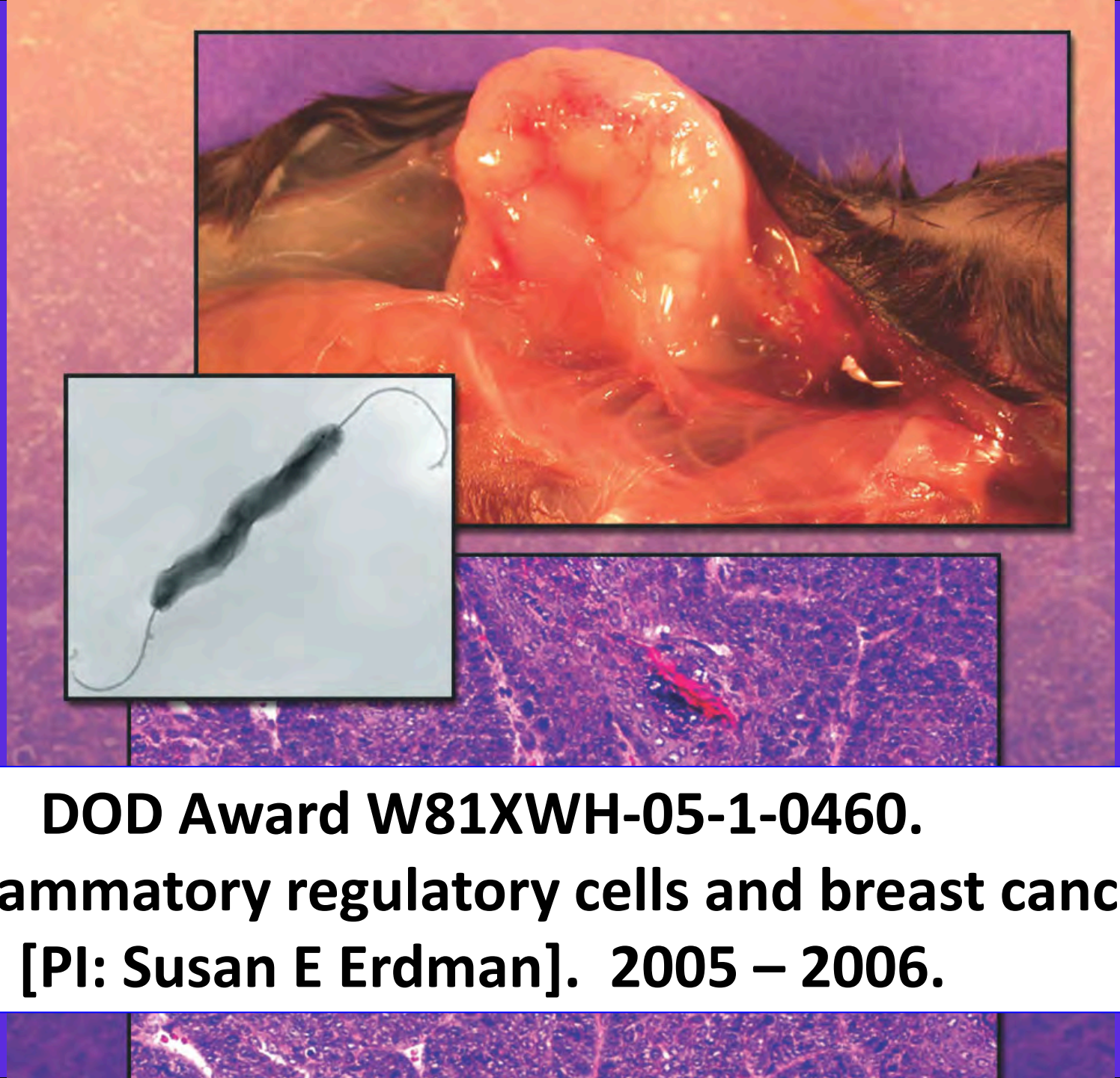


Priority Report

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. Erdman[1]

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

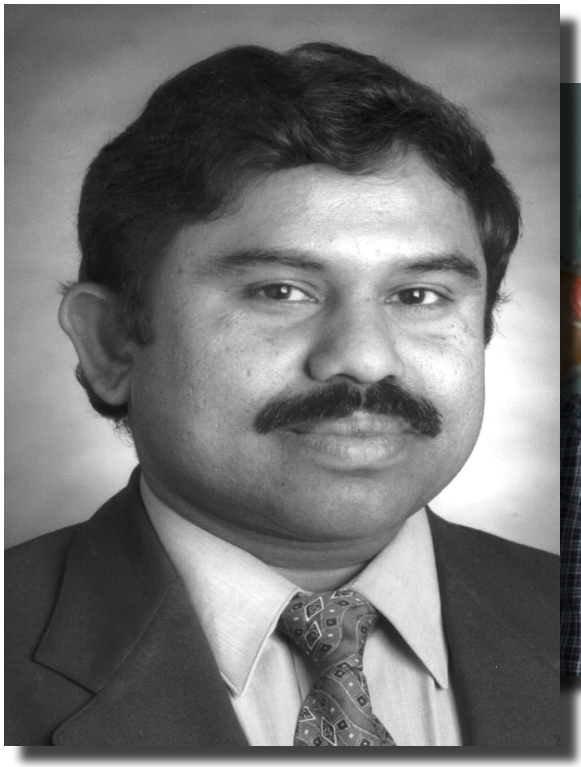


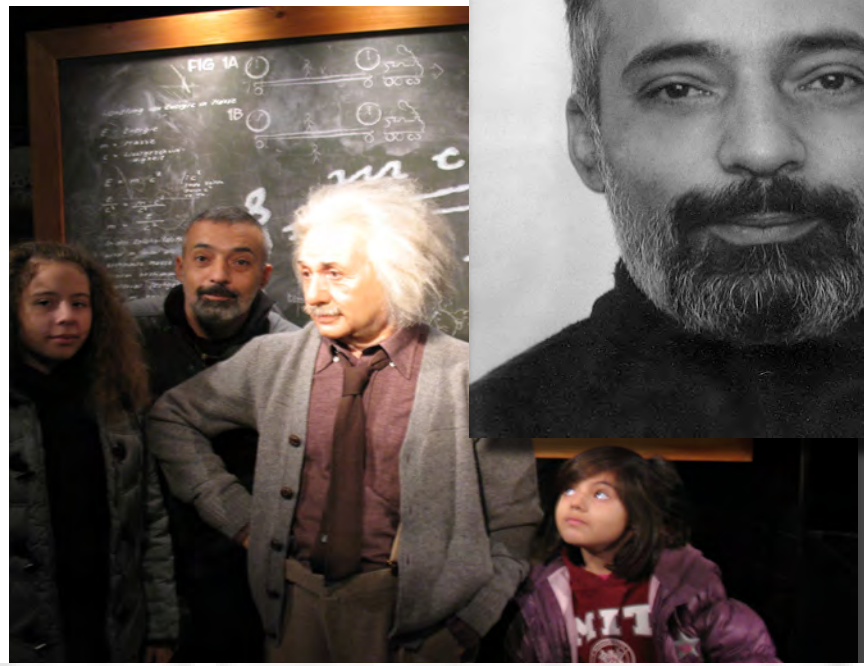
DOD Award W81XWH-05-1-0460.
Anti-inflammatory regulatory cells and breast cancer.
[PI: Susan E Erdman]. 2005 – 2006.

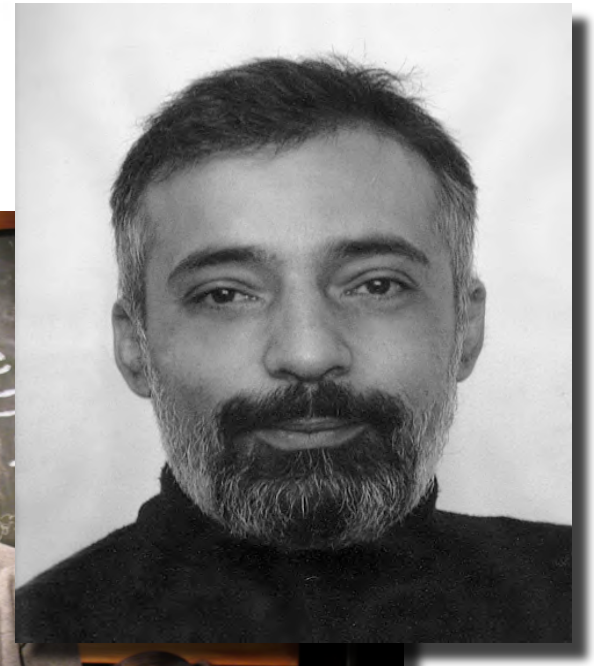
Breast Cancer: Should Gastrointestinal Bacteria Be on Our Radar Screen?

Varada P. Rao,[1] Theofilos Poutahidis,[1,2] James G. Fox,[1] and Susan E. Erdman[1]

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



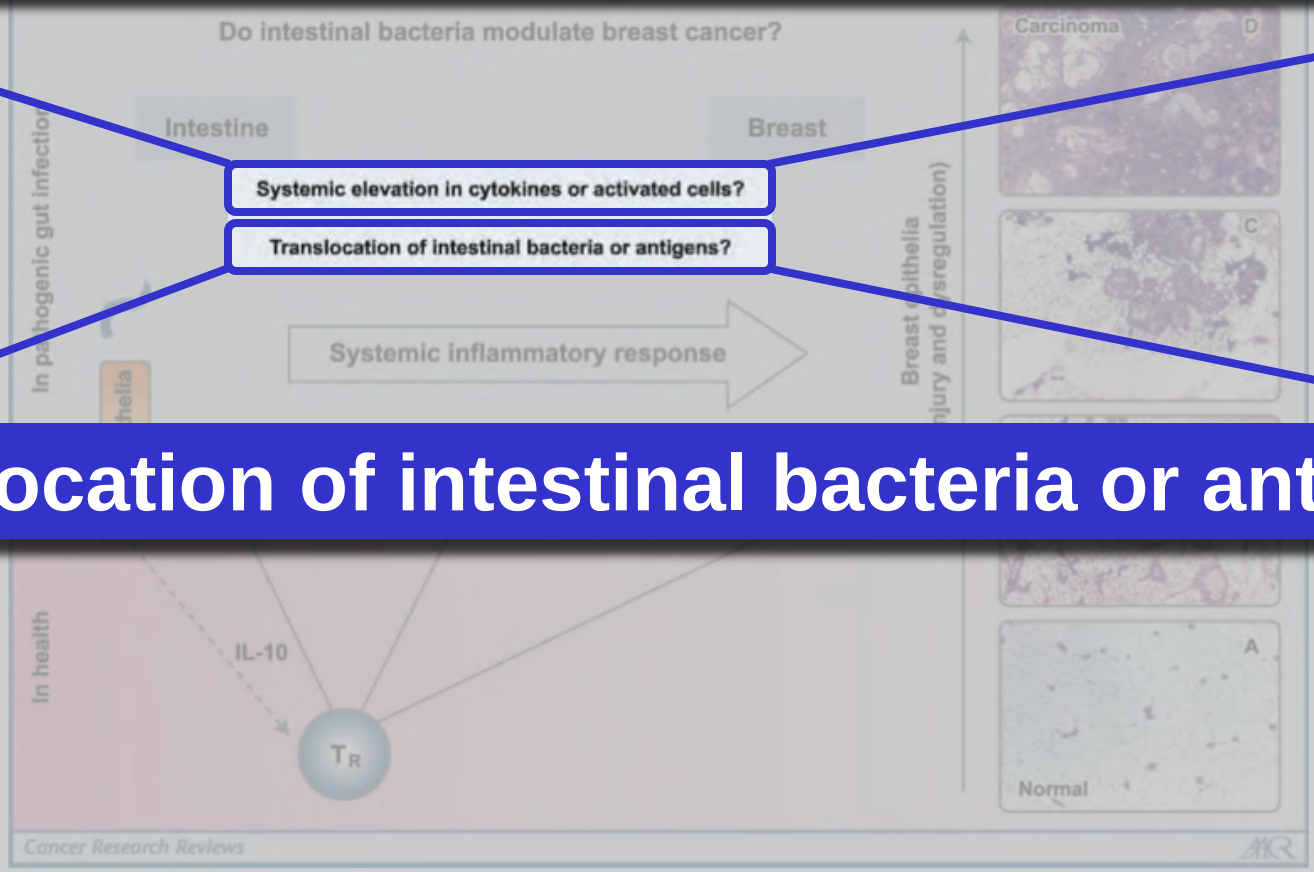




Cancer Res 2007; 67: (3). February 1, 2007

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

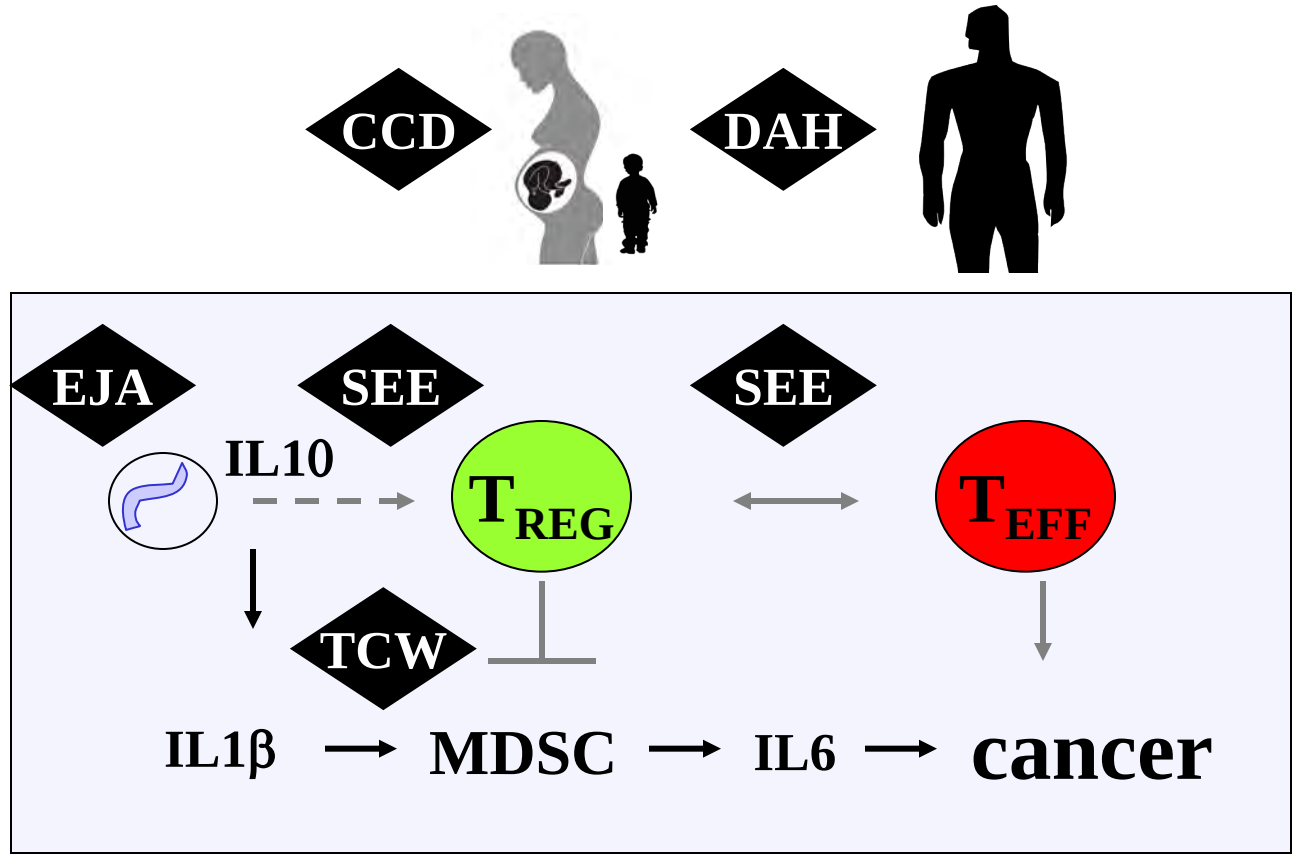
Systemic elevation in cytokines or activated cells?



Translocation of intestinal bacteria or antigens?

TMEN U01 U01 CA164337

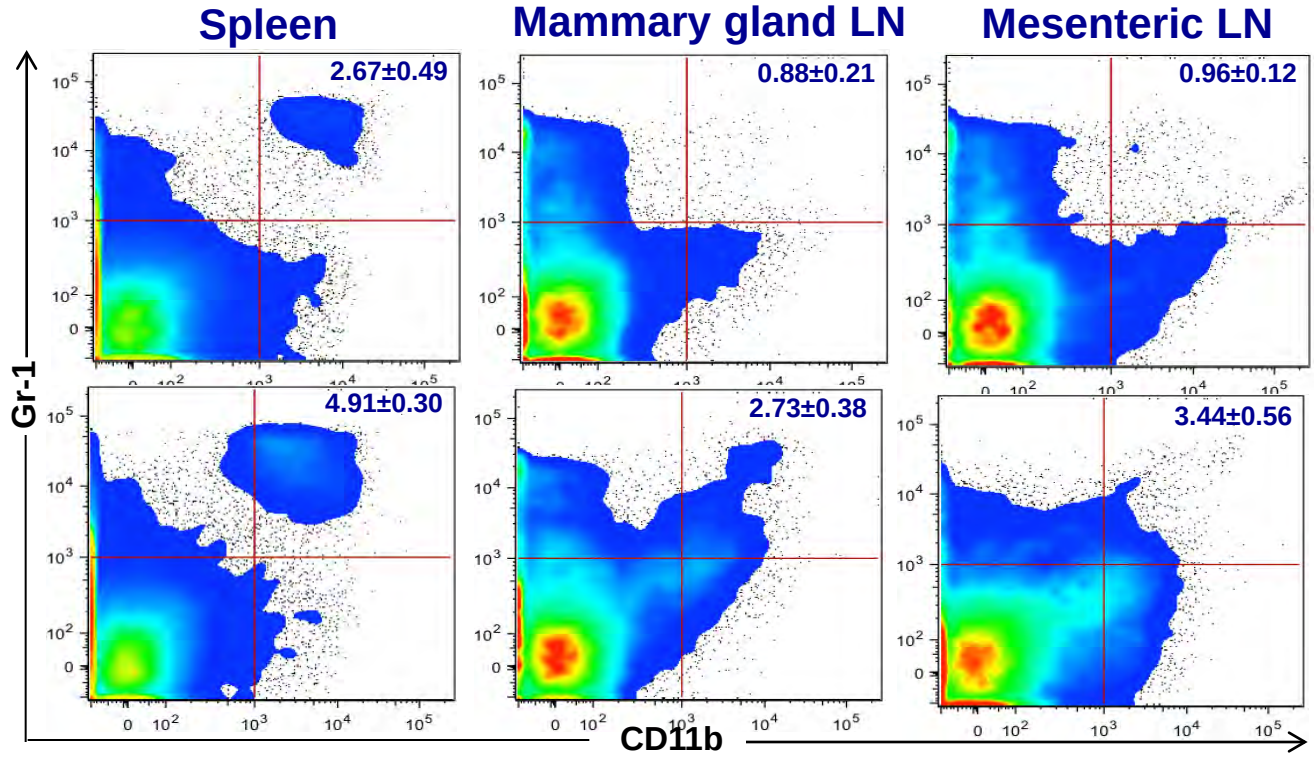
SE Erdman (MIT) and EJ Alm (MIT) and TC Wang (Columbia U)



TC Wang (Columbia) **C Clarke-Dur (CPIC)**

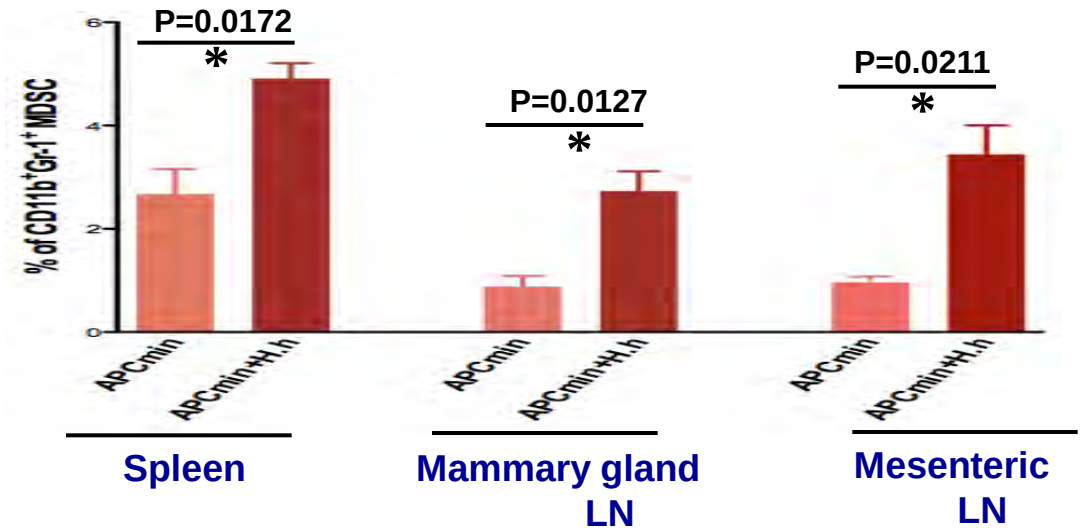
SE Erdman and EJ Alm (MIT) **DA Hafler (Yale)**

H. hepaticus triggers accumulation of MDSCs



$Apc^{Min/+}$

$Apc^{Min/+}$
H. hepaticus

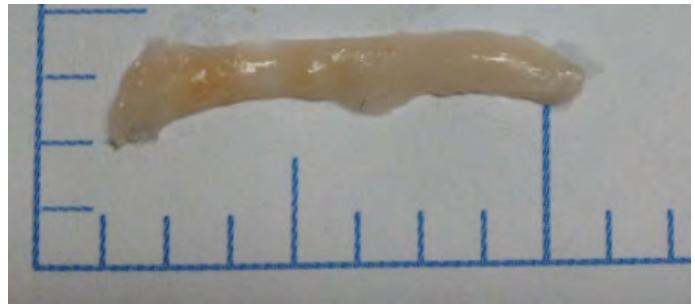


(we thank TC Wang)

H. hepaticus infection promotes mammary tumorigenesis

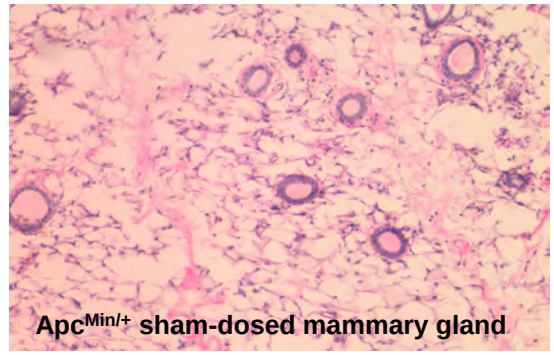
in C57BL/6 $Apc^{Min/+}$ mice

$Apc^{Min/+}$ sham mammary gland

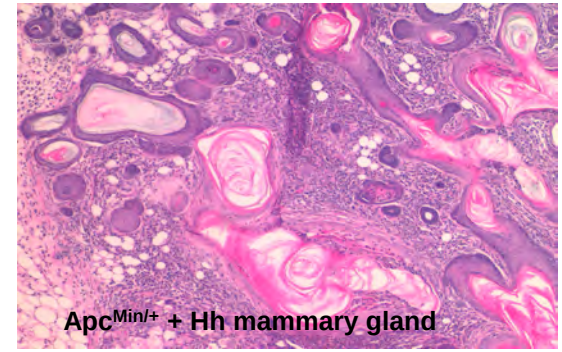


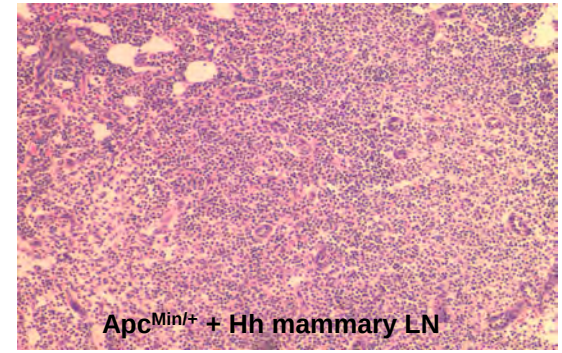
$Apc^{Min/+}$ + Hh mammary gland (tumor)

$Apc^{Min/+}$



$Apc^{Min/+}$ + Hh

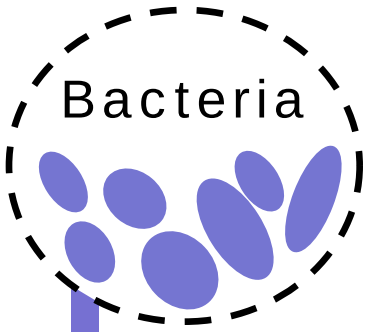




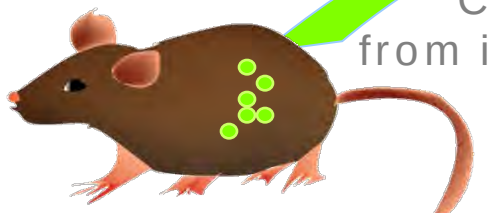
(we thank TC Wang)

Adoptive Cell Transfer Paradigm

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



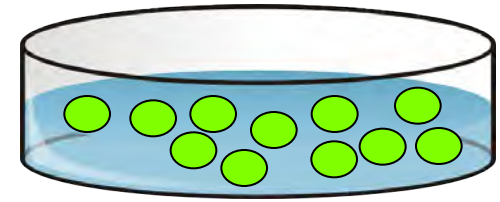
ingestion



Microbe-fed wt donor

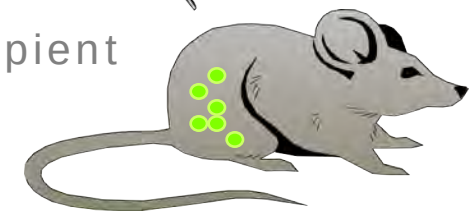
adoptive cell transfer

Cells extracted
from immune-competent
donor mouse

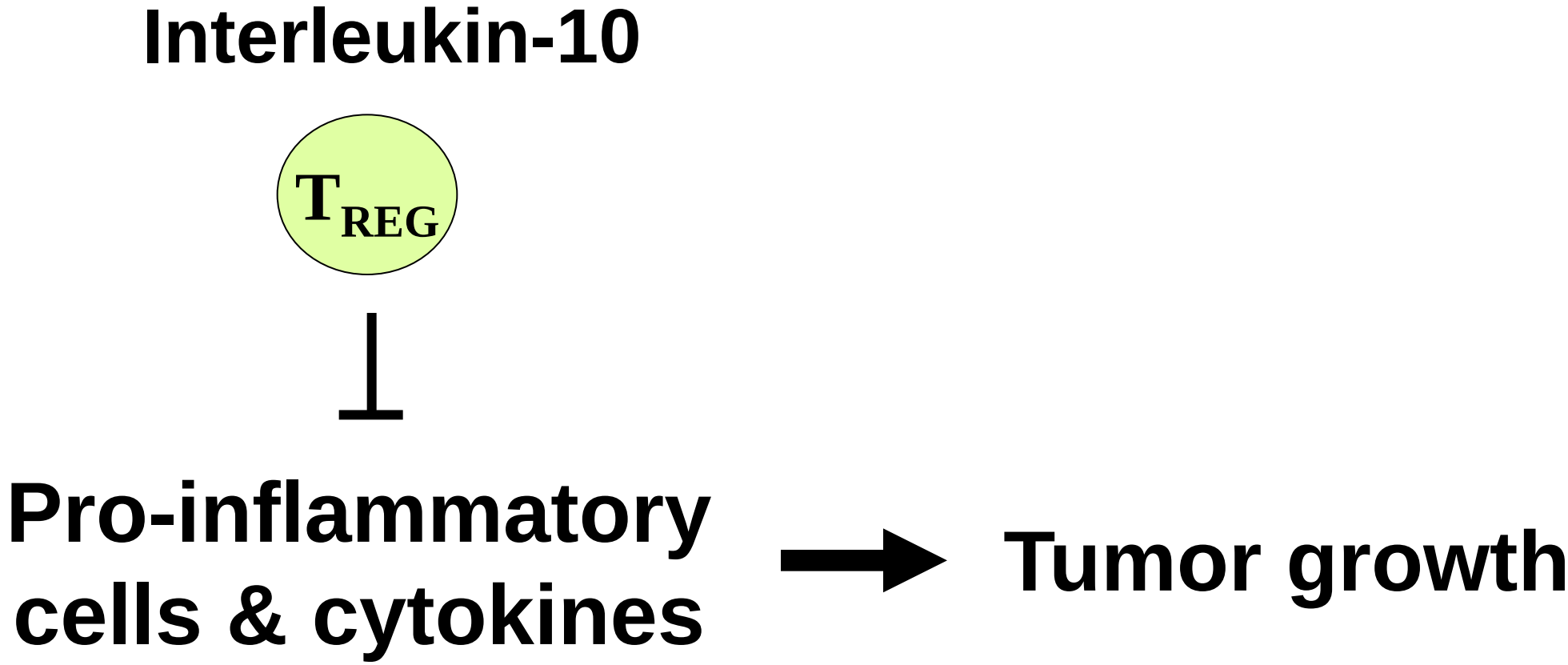


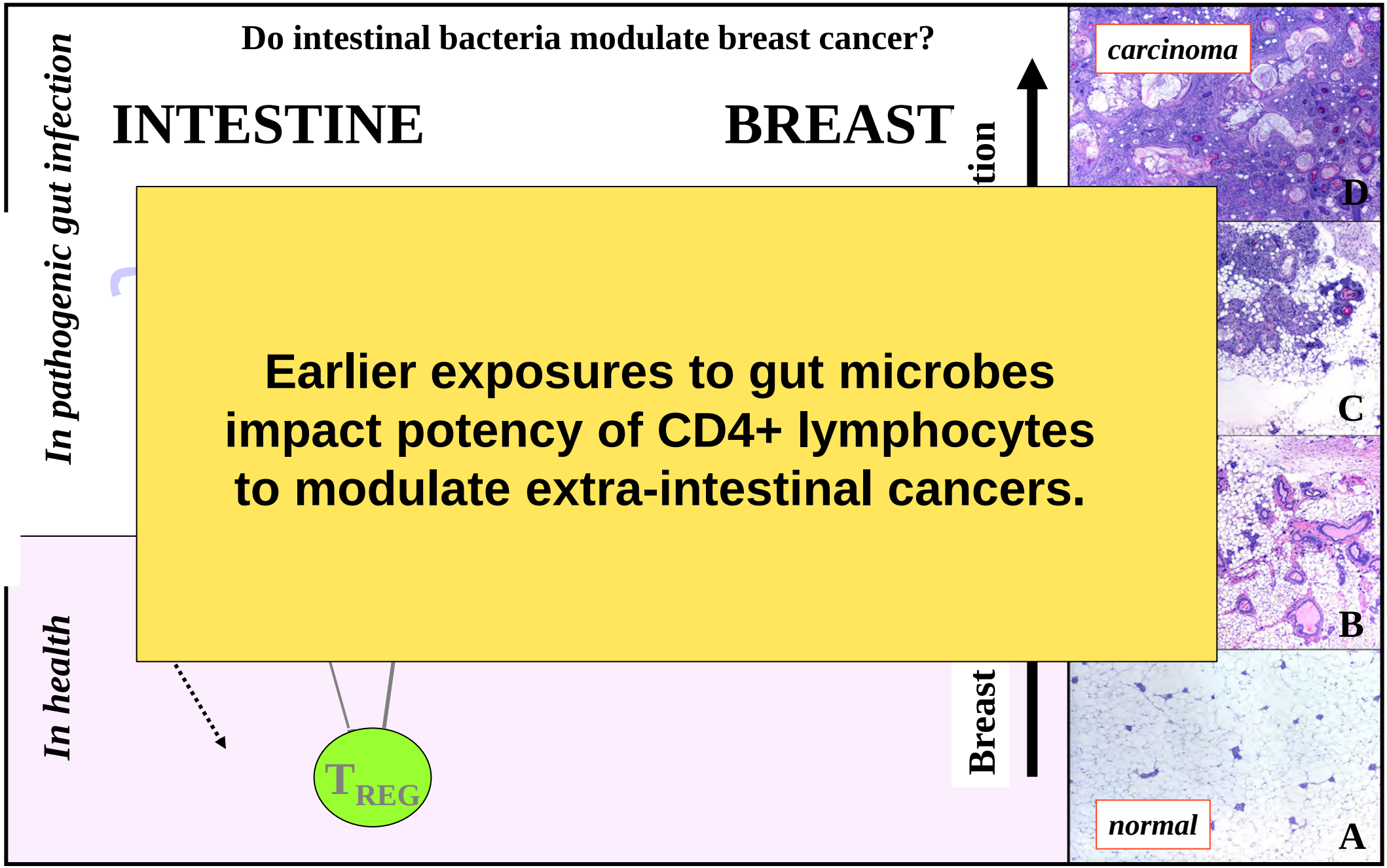
Microbial benefits

Cells injected into recipient



RagMin or Min
recipient


Interleukin-10
T_{REG}
Pro-inflammatory cells & cytokines
Tumor growth

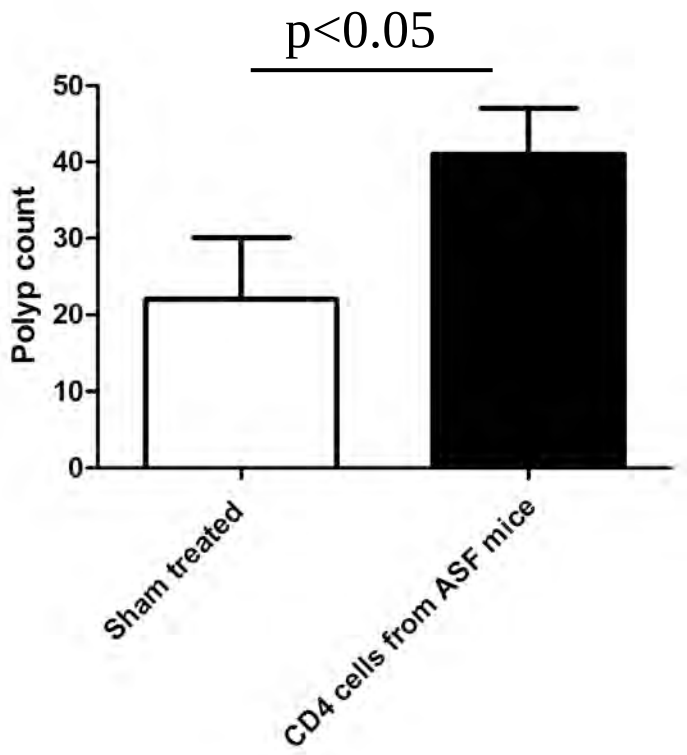

Do intestinal bacteria modulate breast cancer?
INTESTINE
BREAST
In pathogenic gut infection
In health
Earlier exposures to gut microbes impact potency of CD4+ lymphocytes to modulate extra-intestinal cancers.
T REG
Breast
carcinoma
normal
A
B
C
D

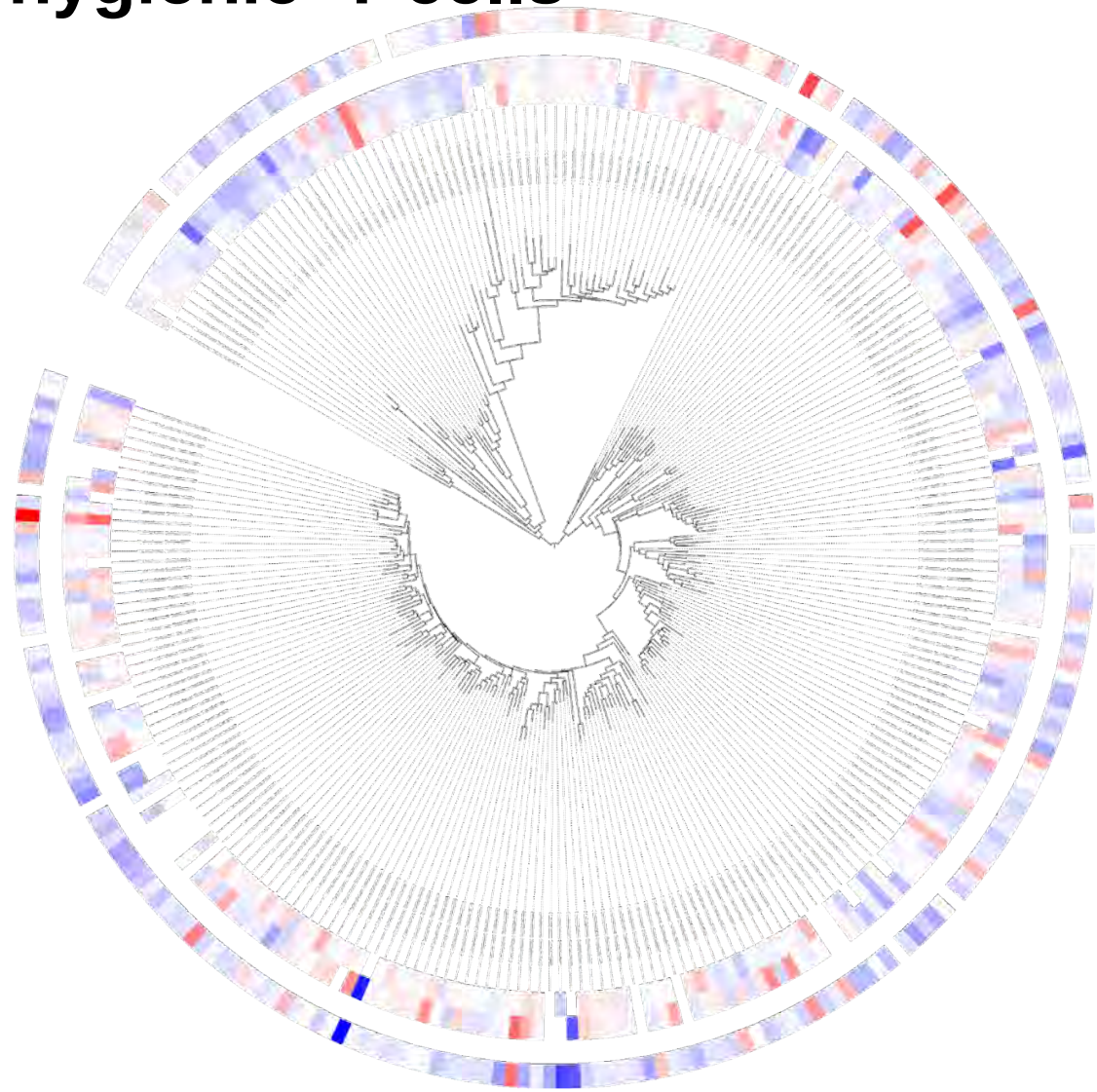
Modern Hygiene Practices

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

Significant changes occur in Min mice after adoptive transfer of ‘hygienic’ T cells

Increased polyposis in Min mice after adoptive transfer of ‘hygienic’ T cells

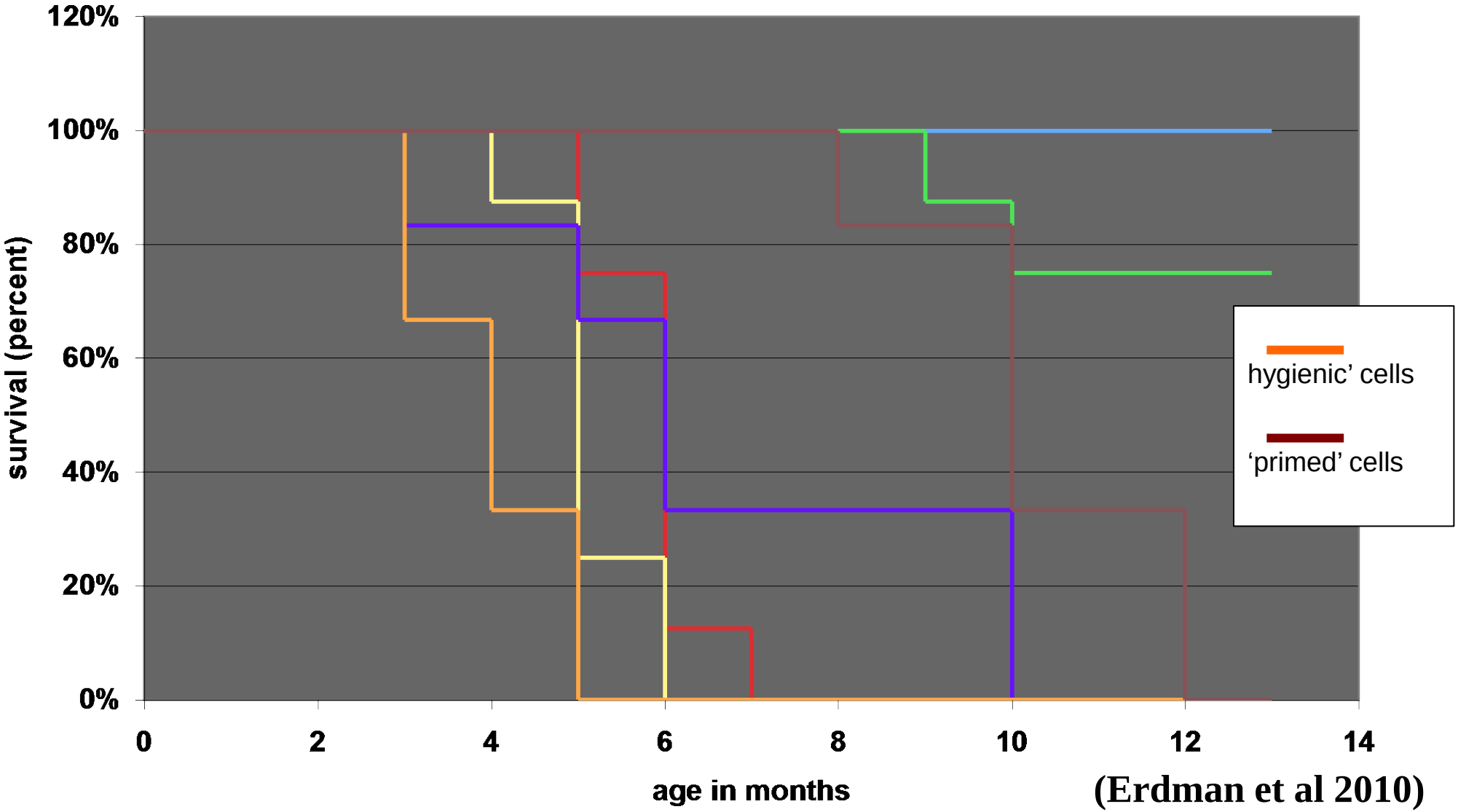




We thank Mark Burnham-Smith (EJ Alm lab) for microbiome analyses

Microbe-educated lymphocytes impart longevity

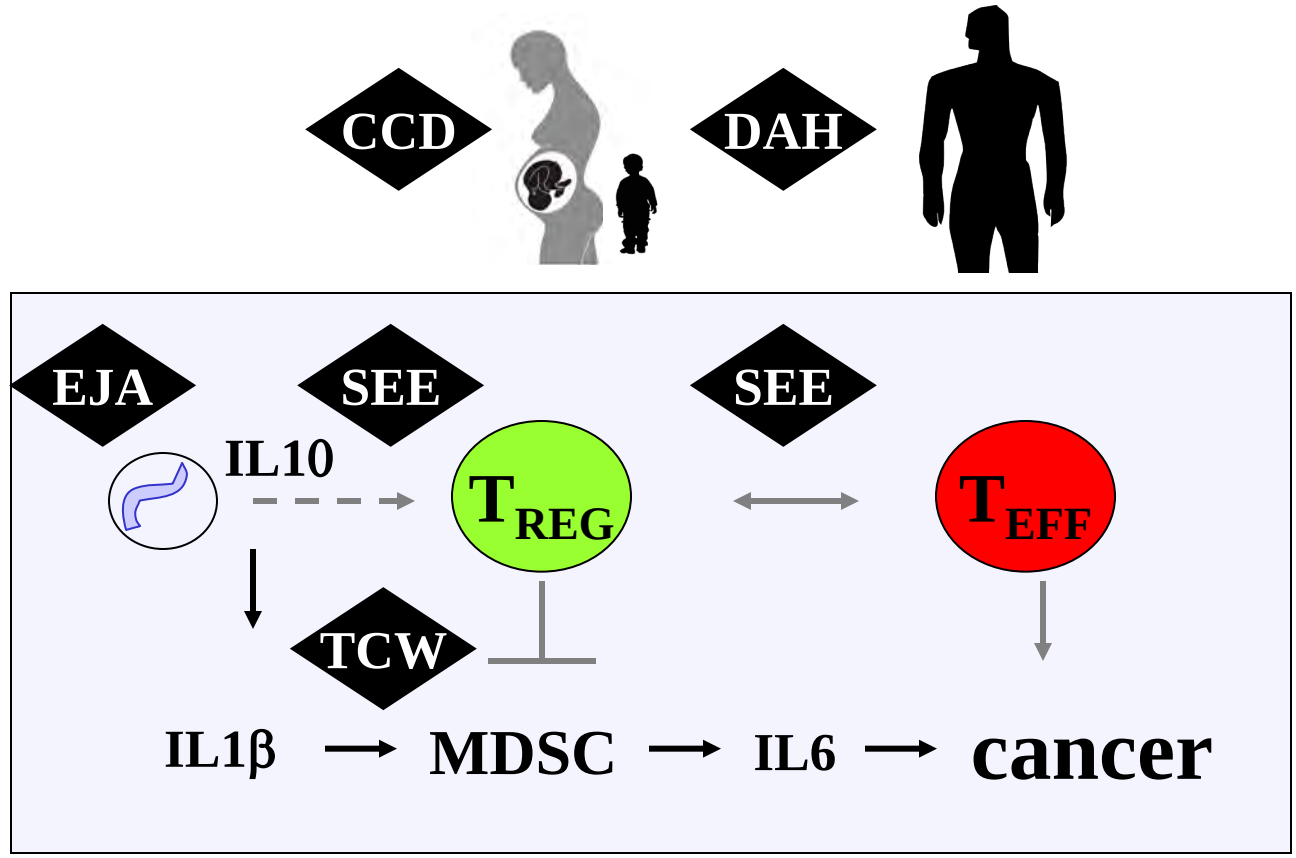
Survival Curve by Treatment in Female Min Mice



(Erdman et al 2010)

TMEN U01 U01 CA164337

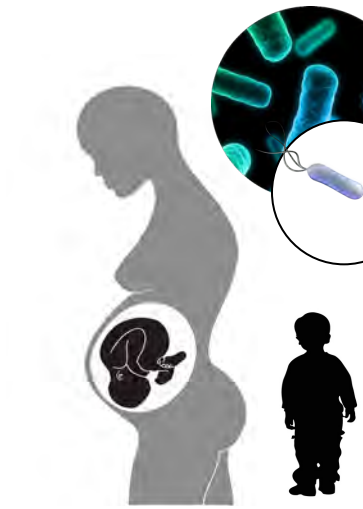
SE Erdman (MIT) and EJ Alm (MIT) and TC Wang (Columbia U)

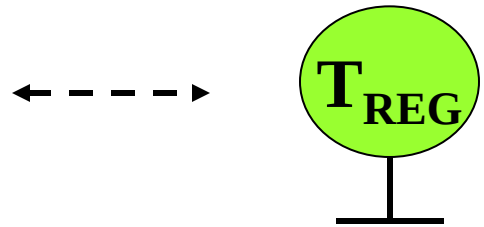


TC Wang (Columbia) **C Clarke-Dur (CPIC)**

SE Erdman and EJ Alm (MIT) **DA Hafler (Yale)**

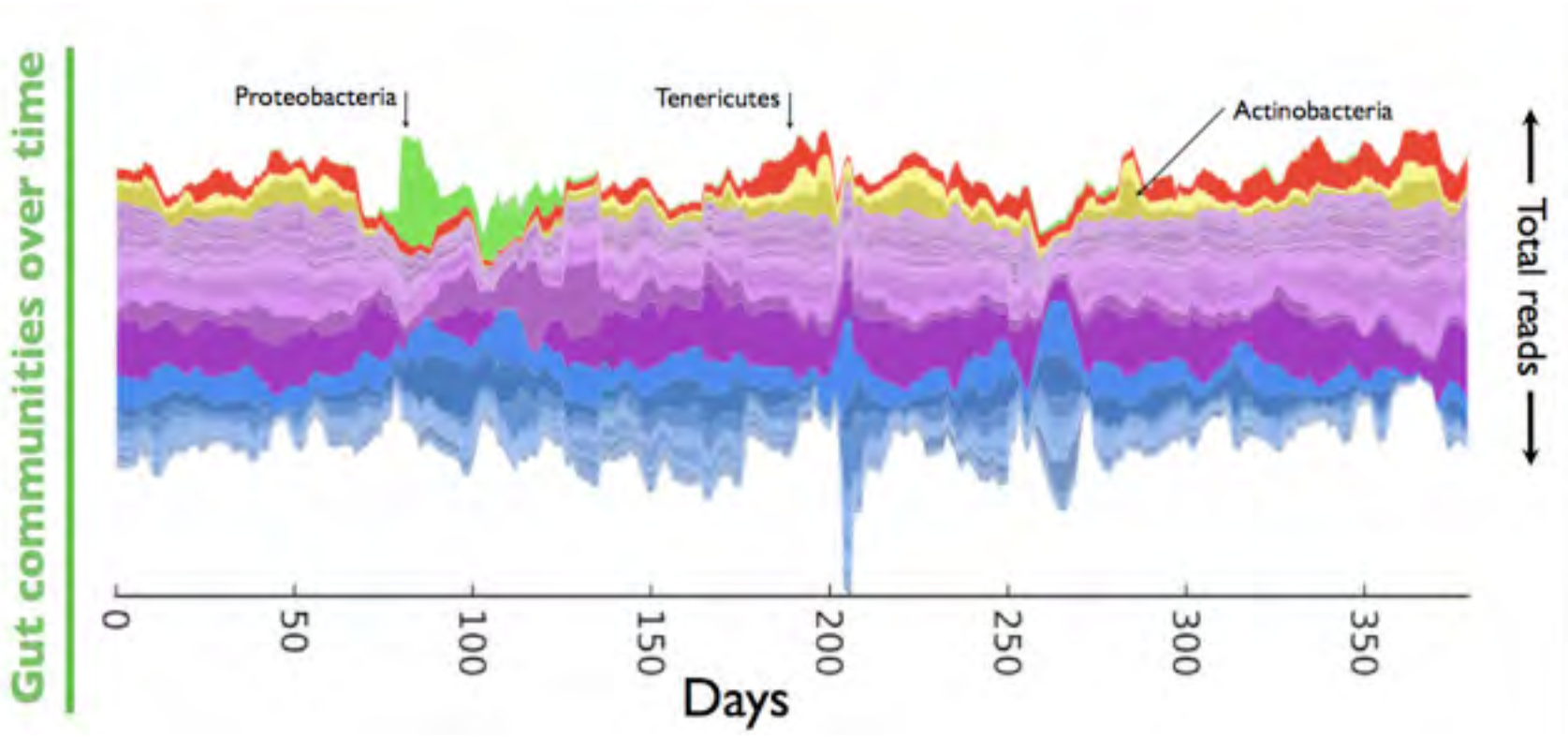
Hygienic rearing & GI tract dysbiosis (Christina Clarke-Dur)





inflammation ⟷ **breast cancer**
ovarian cancer
endometrial cancer
thyroid cancer
melanoma

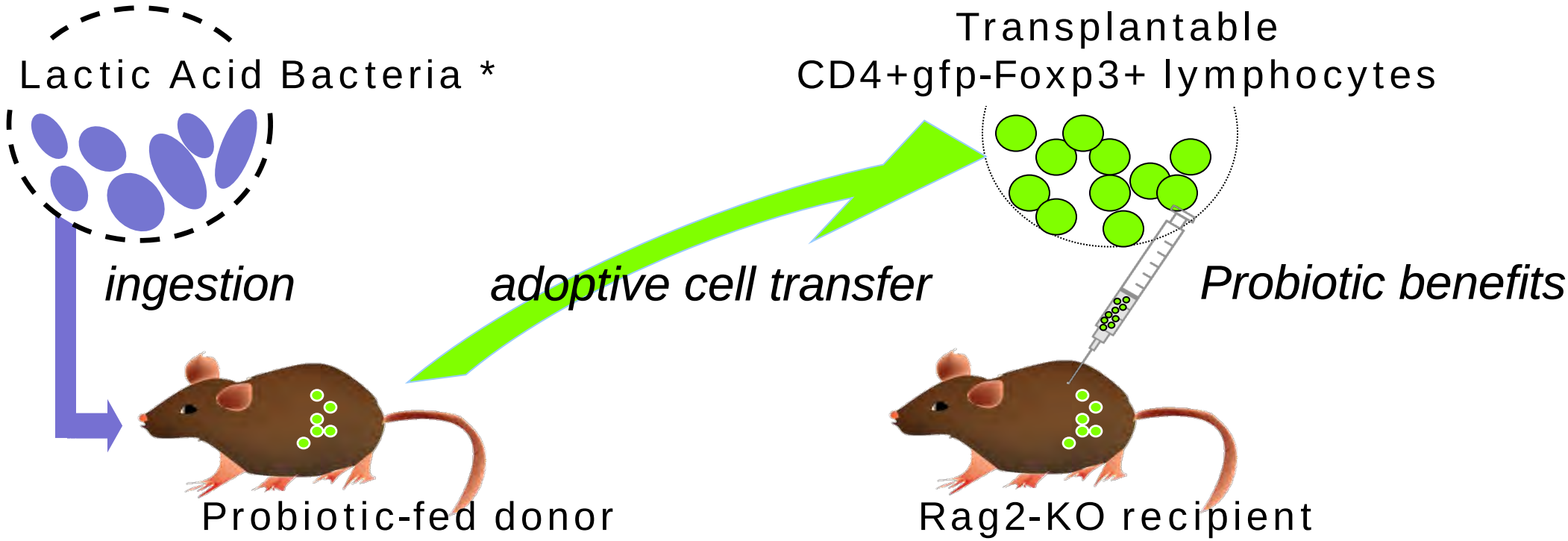
Gut microbiota community restructuring in human subjects after novel exposures



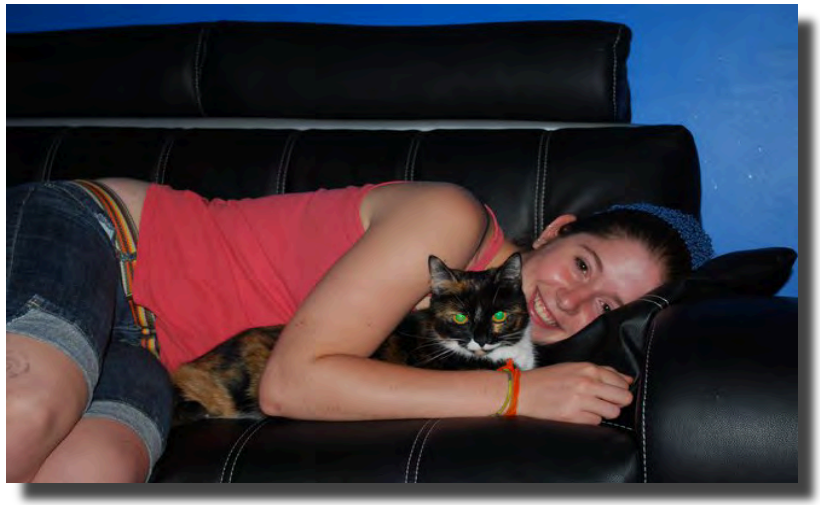
disorders in later life. Whether the increased protection against cancer involves only regulatory T cells of thymic origin (19) or also peripherally recruited IL-10–dependent regulatory subsets is not well understood. We speculate that immune competency may be suboptimal in individuals with more stringent hygiene practices, and when combined with other known risk factors of Western lifestyle this contributes to the paradoxical increase in inflammation-associated cancers seen in developed countries. Likewise, antibiotics may deplete intestinal bacteria directly or indirectly essential for enteric homeostasis, thereby leading to increased risk of breast cancer in women undergoing chronic antimicrobial therapy (4). Interestingly, it seems that the long-term health benefits imparted by intestinal bacterial infections early in life may also be achieved in other ways. Recently, probiotic bacteria were shown to reduce IBD in mice through an IL-10–dependent regulatory lymphocyte–mediated mechanism (26), and clinical


Gut communities over time
Proteobacteria
Tenericutes
Actinobacteria
Total reads
0
50
100
150
200
250
300
350
Days

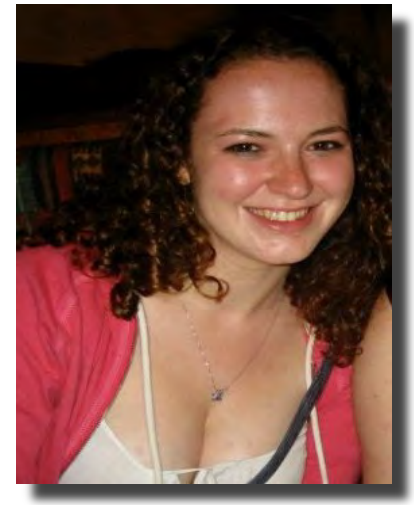
Microbe benefits are transplantable via immune cells



*** We thank James Versalovic for the gift of *Lactobacillus reuteri* ATCC 6475**



Kelsey Cappelle



Jessica Lakritz

Yassin Ibrahim

Bernard Varian

Tatiana Levkovich

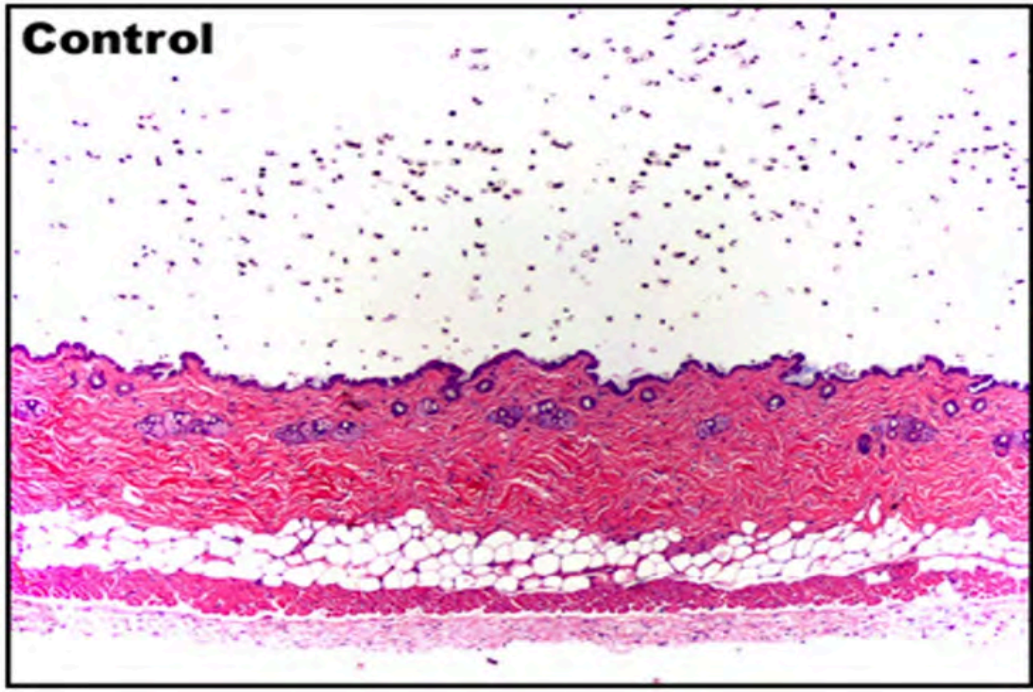
Growing luxuriant hair

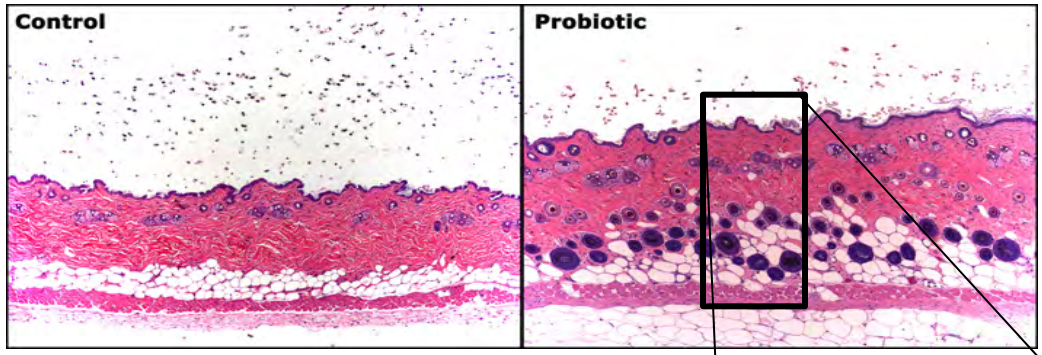
SHAVED

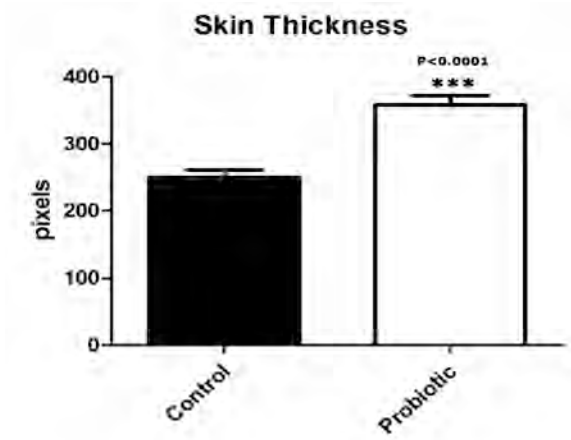
PURIFIED PROBIOTIC, 5 DAYS AFTER SHAVING

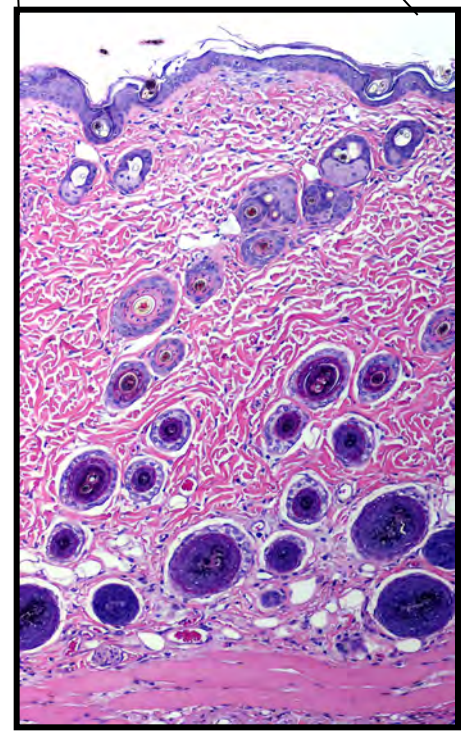
SHAVED

PURIFIED PROBIOTIC, 5 DAYS AFTER SHAVING

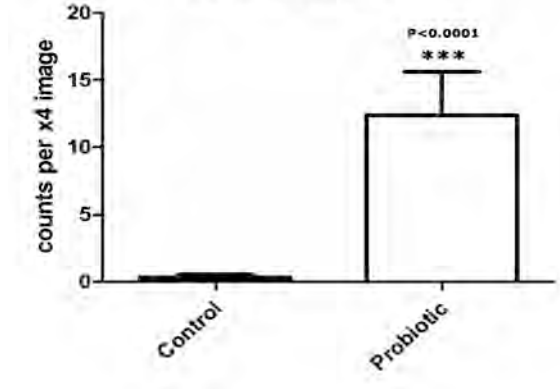


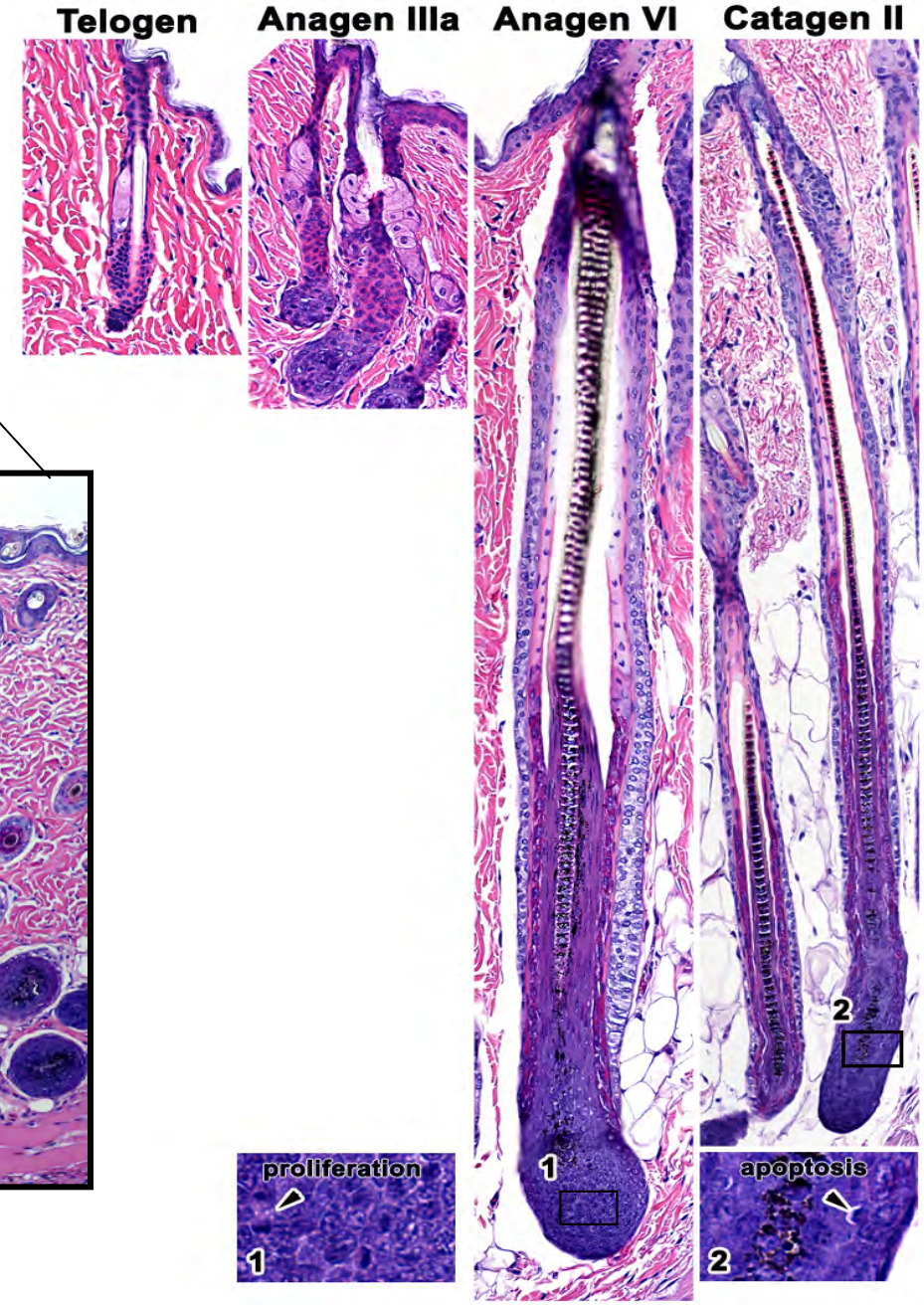




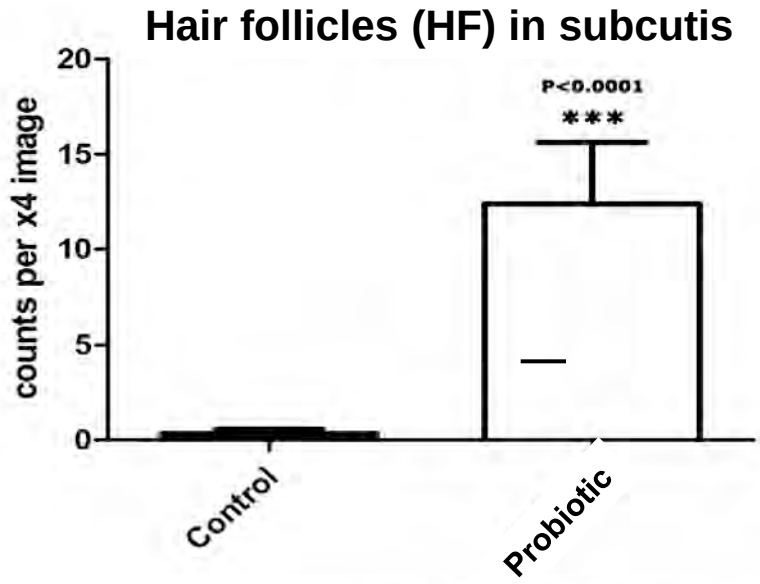


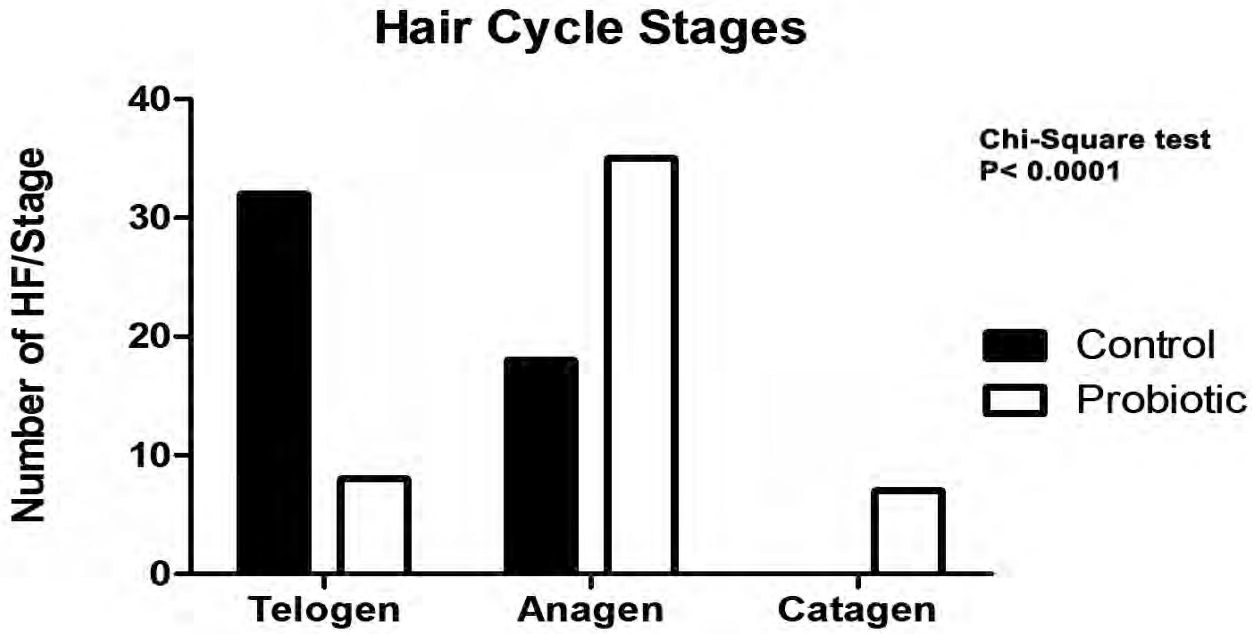
Hair follicles (HF) in subcutis

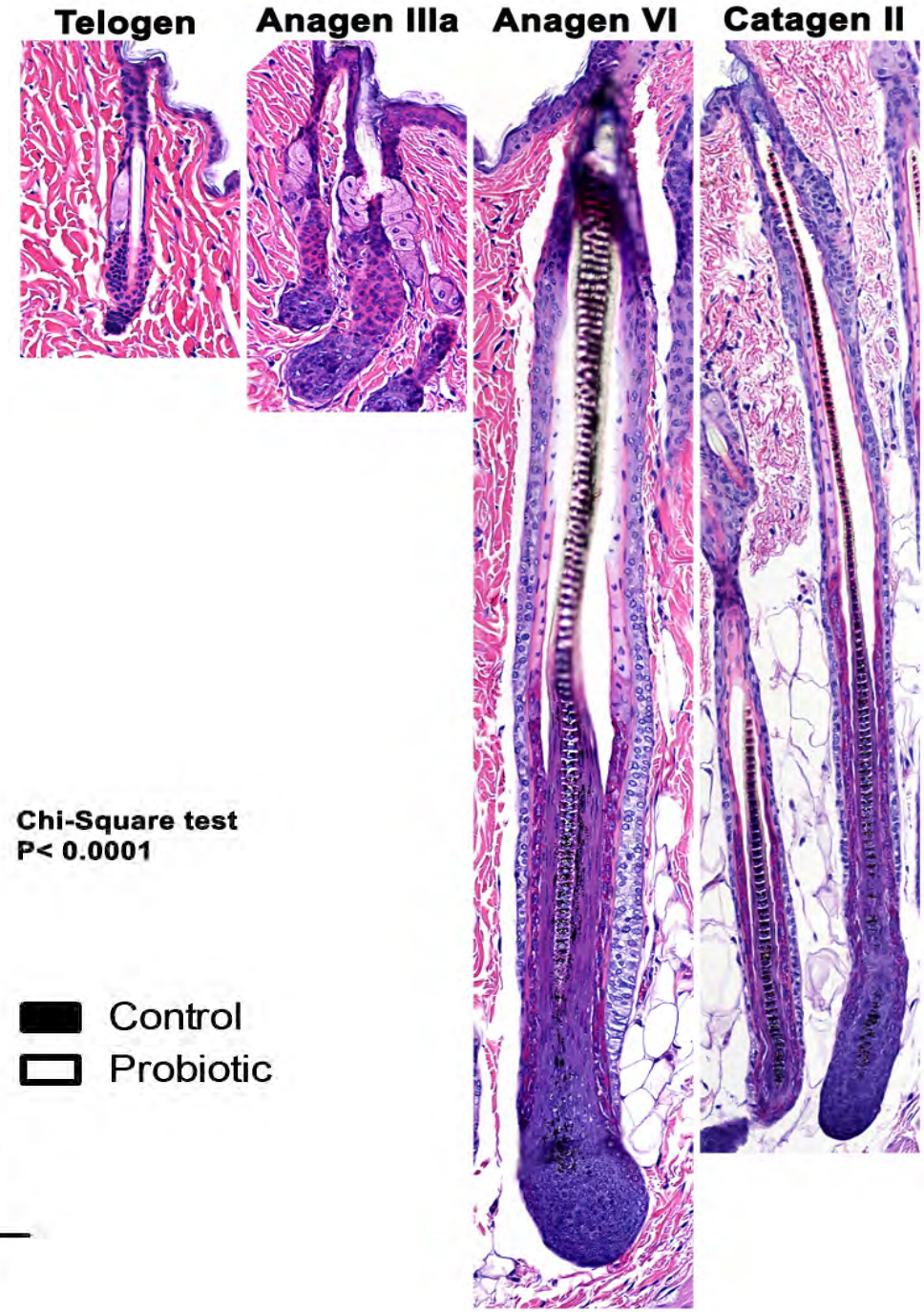




Glow of health

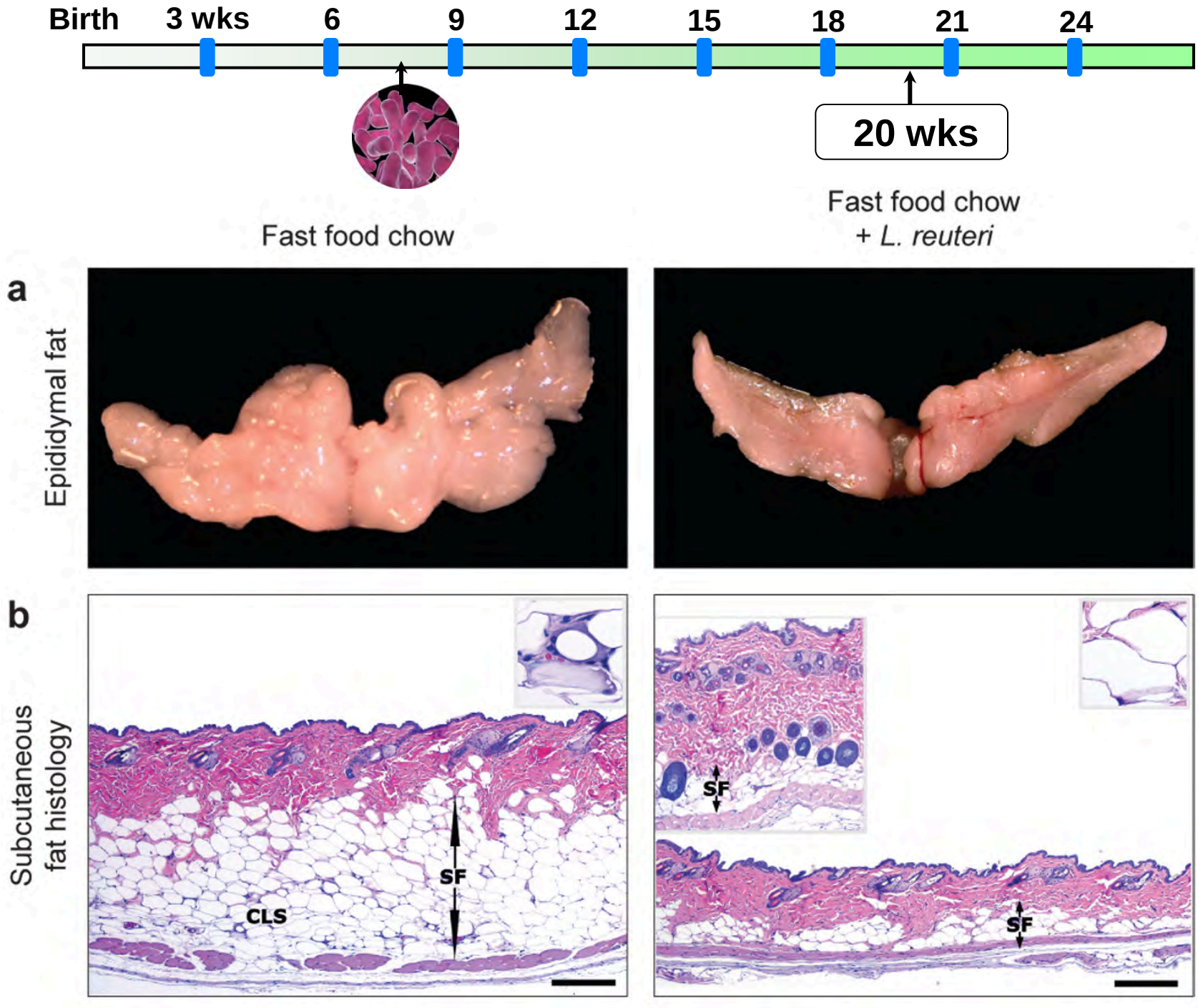


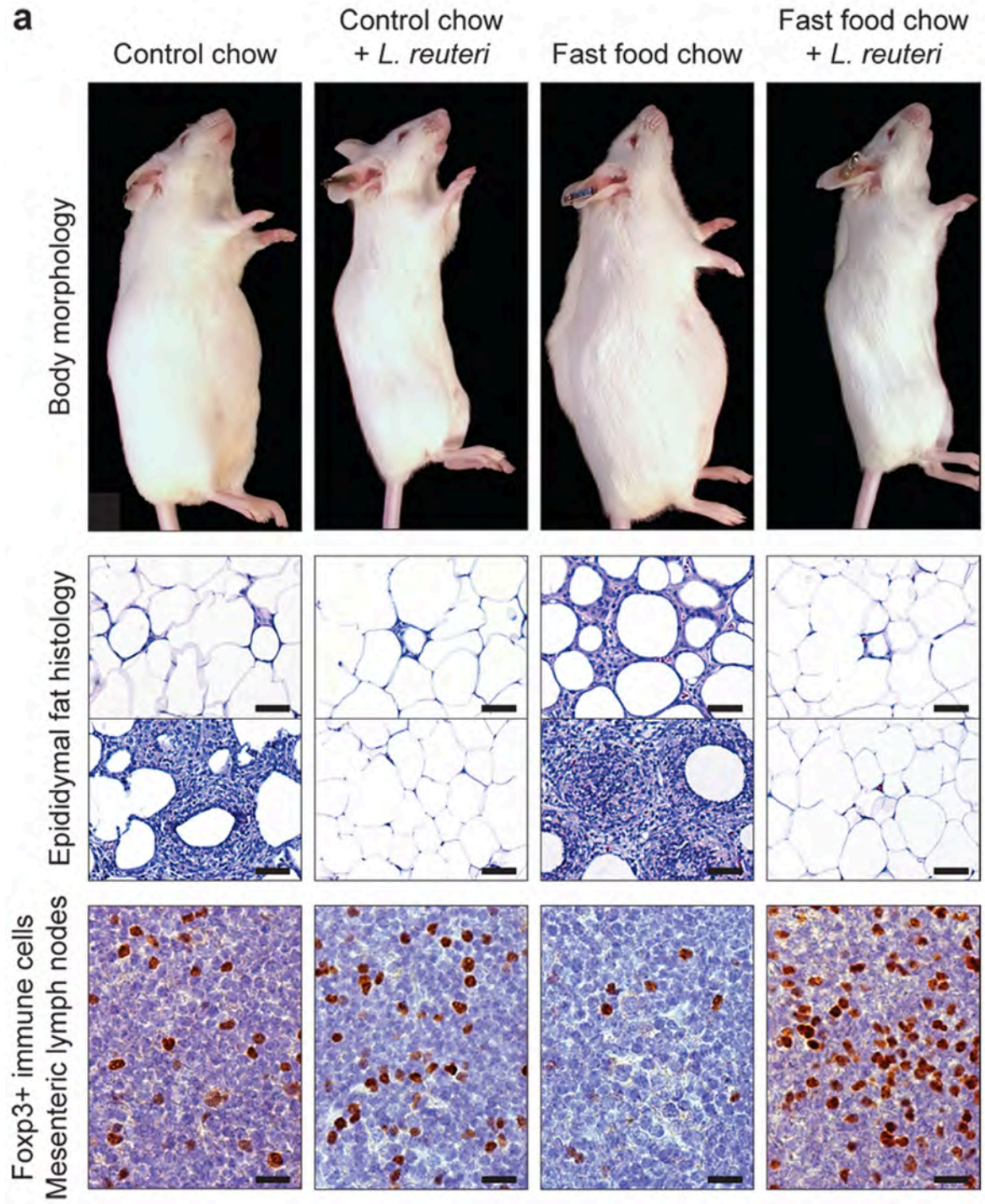




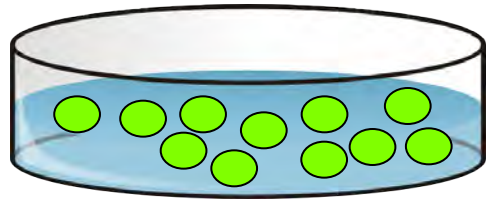
Staying slender

Probiotics help reduce body fat – even while eating a 'fast food' diet.


Birth
3 wks
6
9
12
15
18
21
24
20 wks
Fast food chow
Fast food chow
+ L. reuteri
a
Epididymal fat
b
Subcutaneous
fat histology
SF
CLS
SF
SF

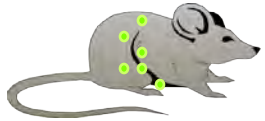

a
Control chow
Control chow
+ L. reuteri
Fast food chow
Fast food chow
+ L. reuteri
Body morphology
Epididymal fat histology
Foxp3+ immune cells
Mesenteric lymph nodes

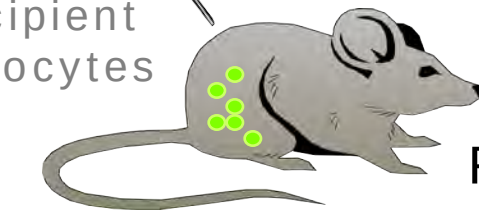
Probiotic benefits transplantable via lymphocytes



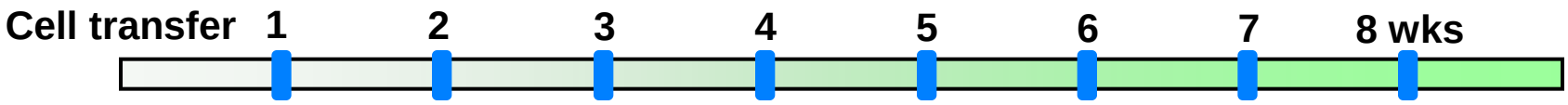
Gfp-Foxp3+ cells

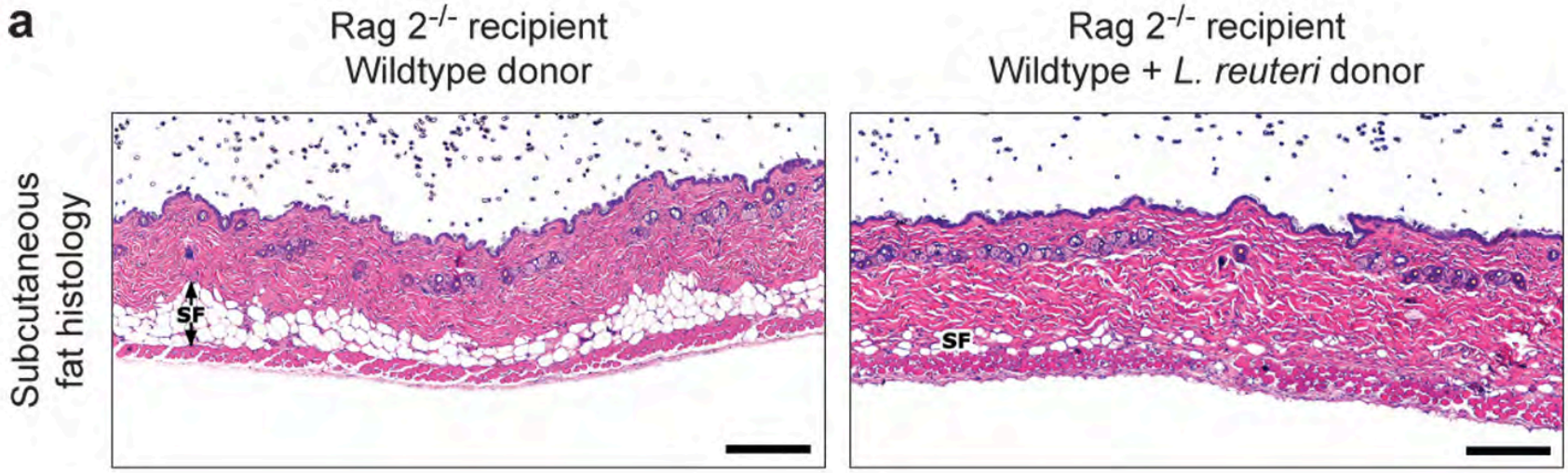
Cells injected into recipient
without it's own lymphocytes

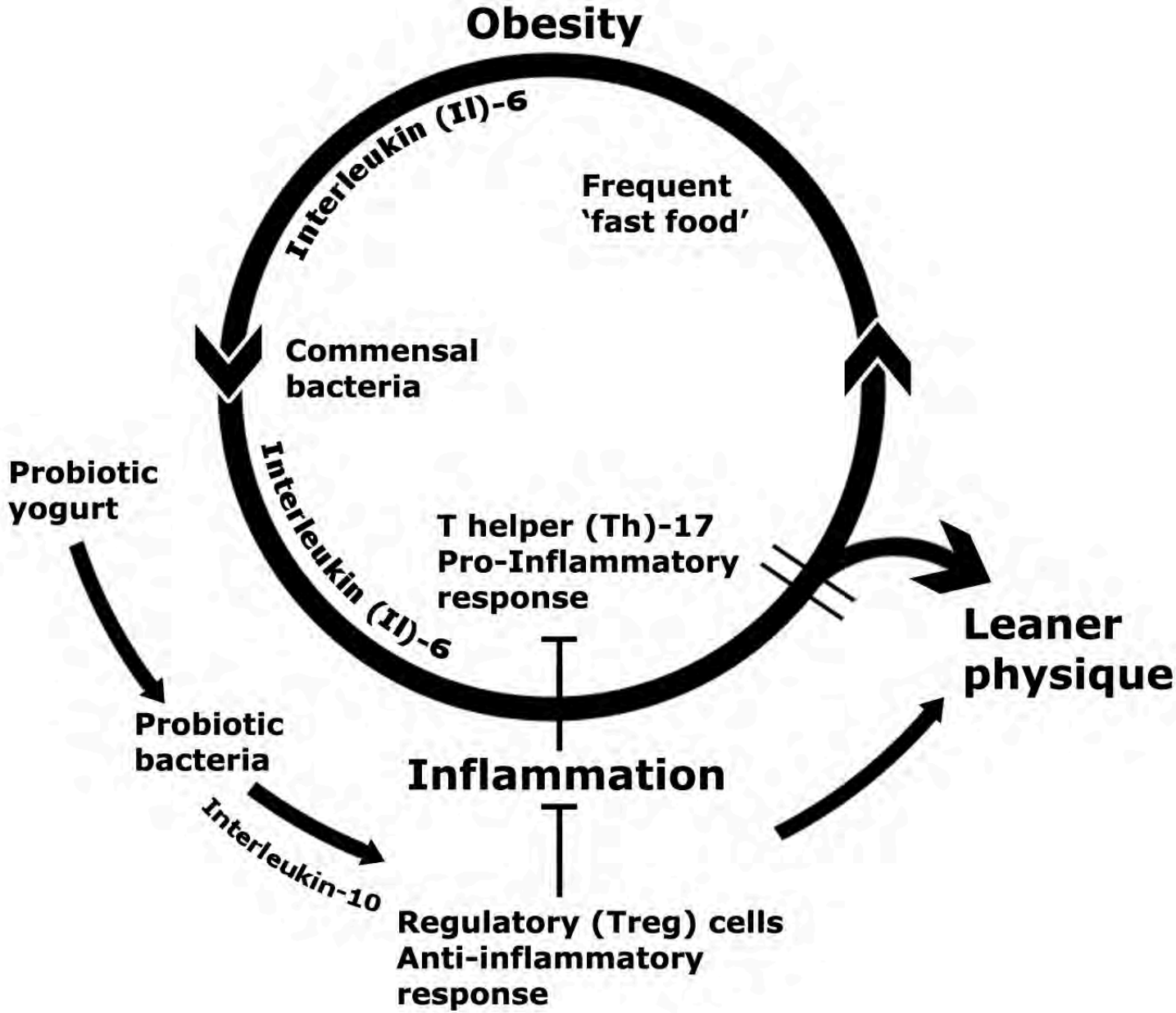


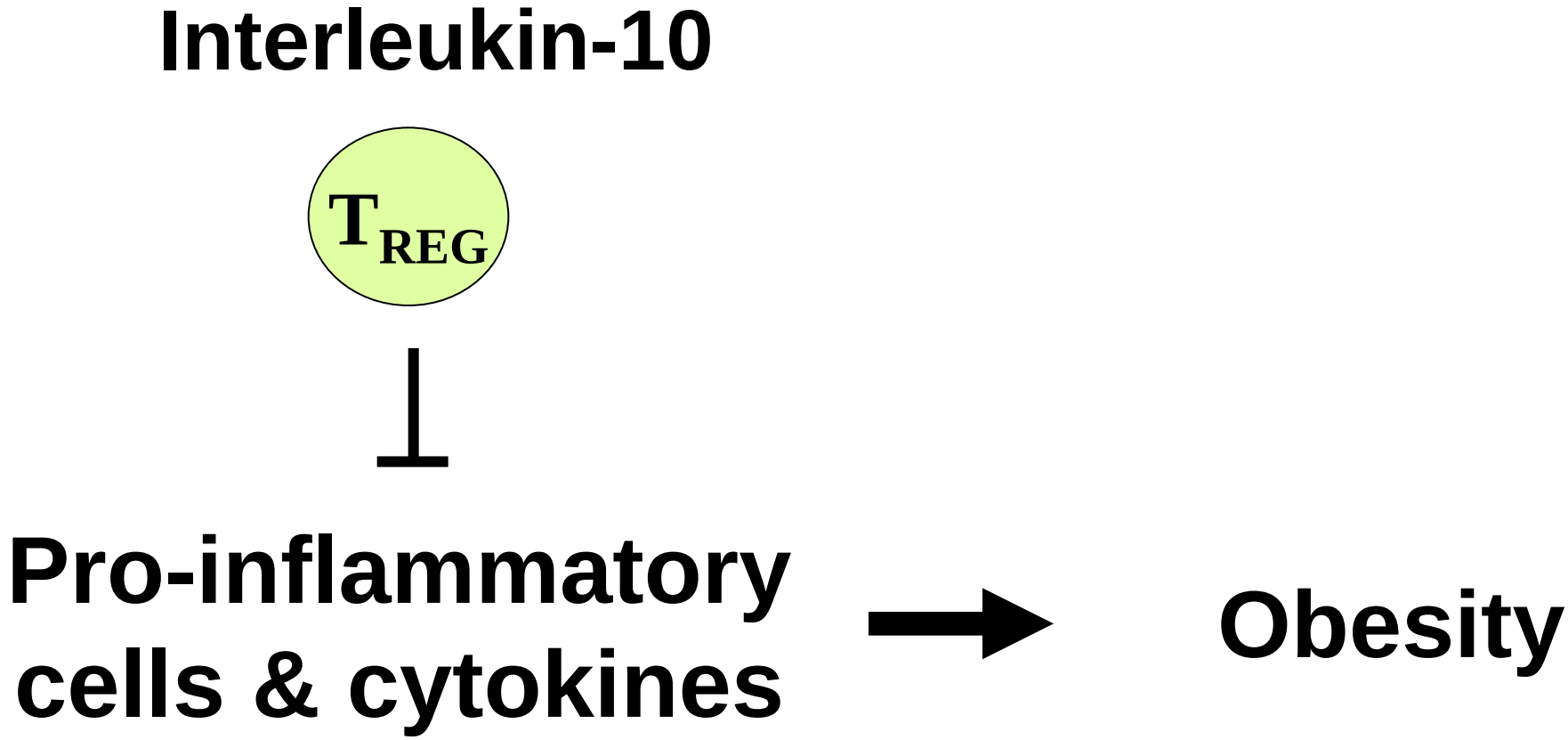


Rag2-KO






Obesity
Interleukin (Il)-6
Frequent
'fast food'
Commensal
bacteria
Interleukin (Il)-6
Probiotic
yogurt
T helper (Th)-17
Pro-Inflammatory
response
Leaner
physique
Probiotic
bacteria
Inflammation
Interleukin-10
Regulatory (Treg) cells
Anti-inflammatory
response

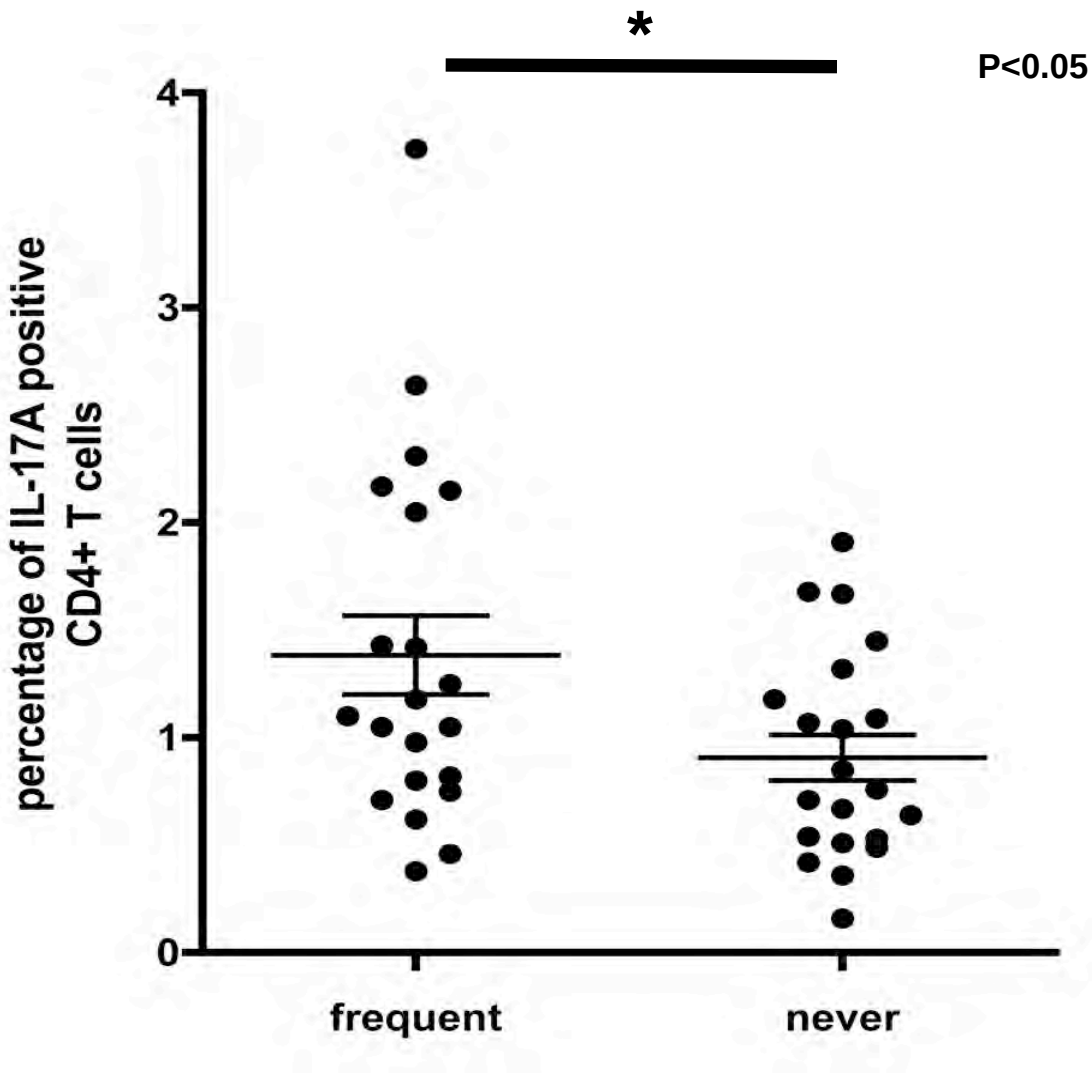

Interleukin-10
T_{REG}
Pro-inflammatory cells & cytokines
Obesity

N Engl J Med. 2011 June 23; 364(25): 2392–2404. doi:10.1056/NEJMoa1014296.

Changes in Diet and Lifestyle and Long-Term Weight Gain in Women and Men

Dariush Mozaffarian, M.D., Dr.P.H., Tao Hao, M.P.H., Eric B. Rimm, Sc.D., Walter C. Willett, M.D., Dr.P.H., and **Frank B. Hu, M.D., Ph.D.**
Division of Cardiovascular Medicine (D.M.) and Channing Laboratory (D.M., E.B.R., W.C.W., F.B.H.), Brigham and Women's Hospital and Harvard Medical School; and the Departments of Epidemiology (D.M., T.H., E.B.R., W.C.W., F.B.H.) and Nutrition (D.M., E.B.R., W.C.W., F.B.H.), Harvard School of Public Health — all in Boston

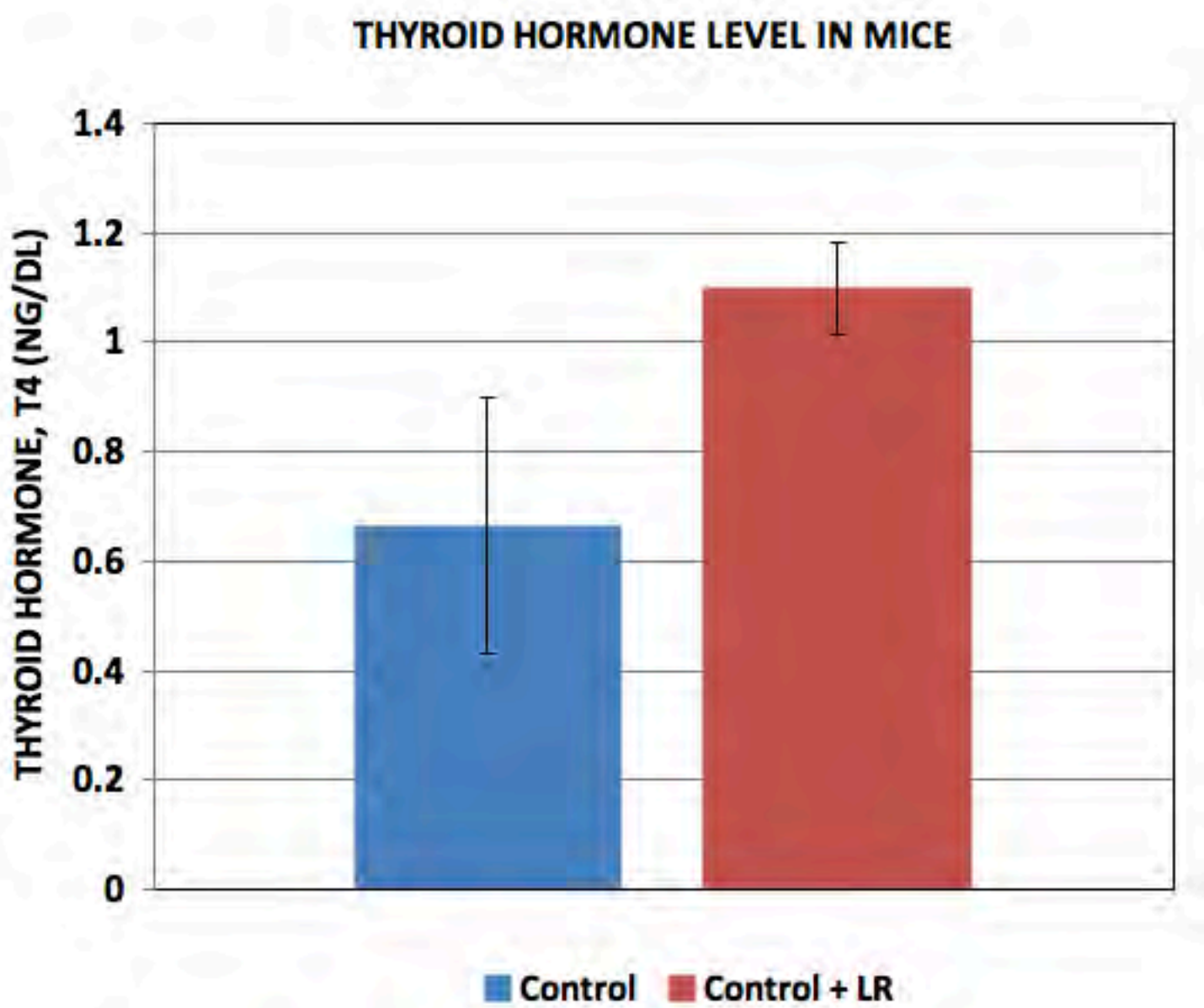
Humans Eating at Fast Food Restaurants



frequent = at least once a week up to daily

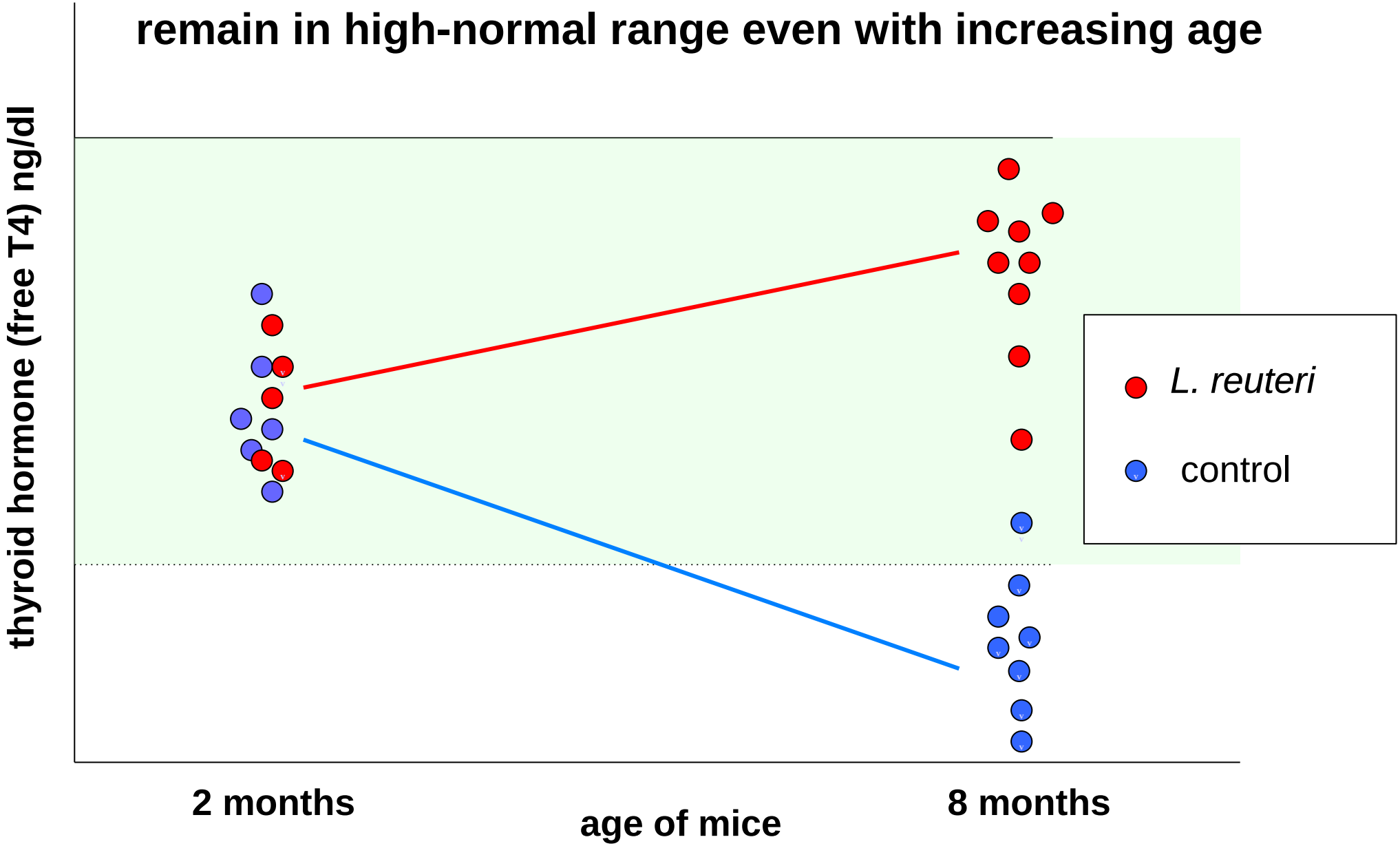
These mice are wild type litter mate brothers …..

The one that eats probiotics daily, left, is slimmer and shinier than his brother


THYROID HORMONE LEVEL IN MICE
THYROID HORMONE, T4 (NG/DL)
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Control
Control + LR

Serum thyroid hormone (free T4) levels

remain in high-normal range even with increasing age

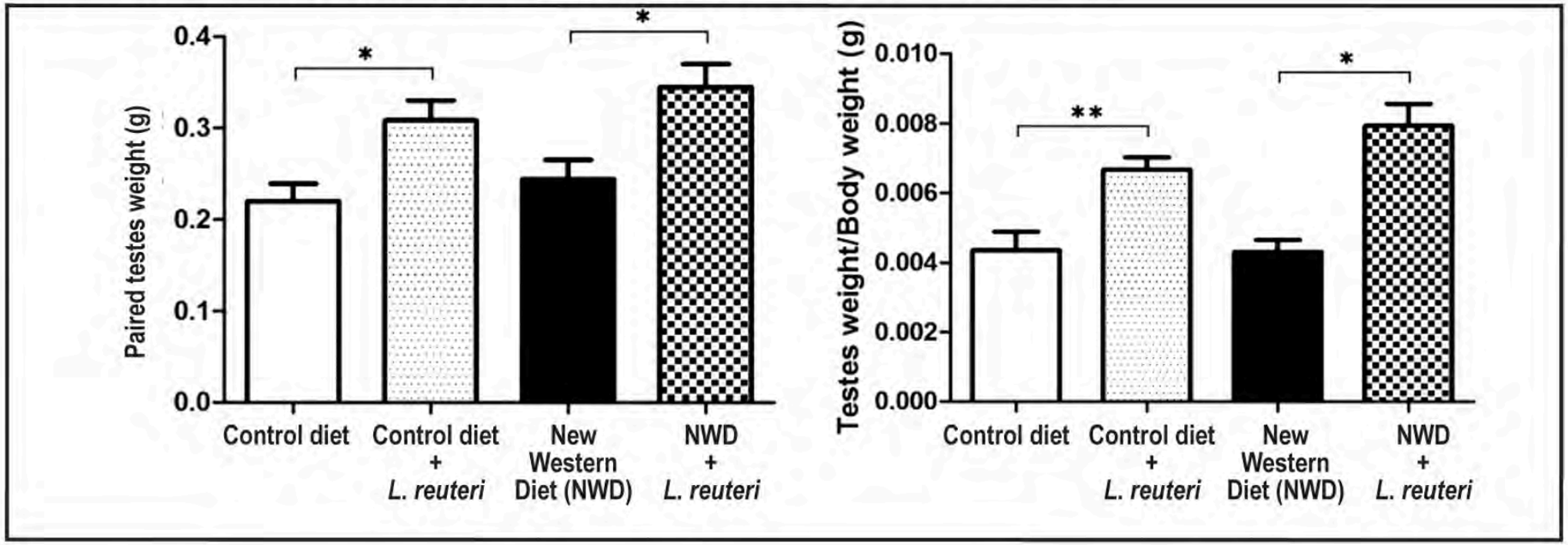


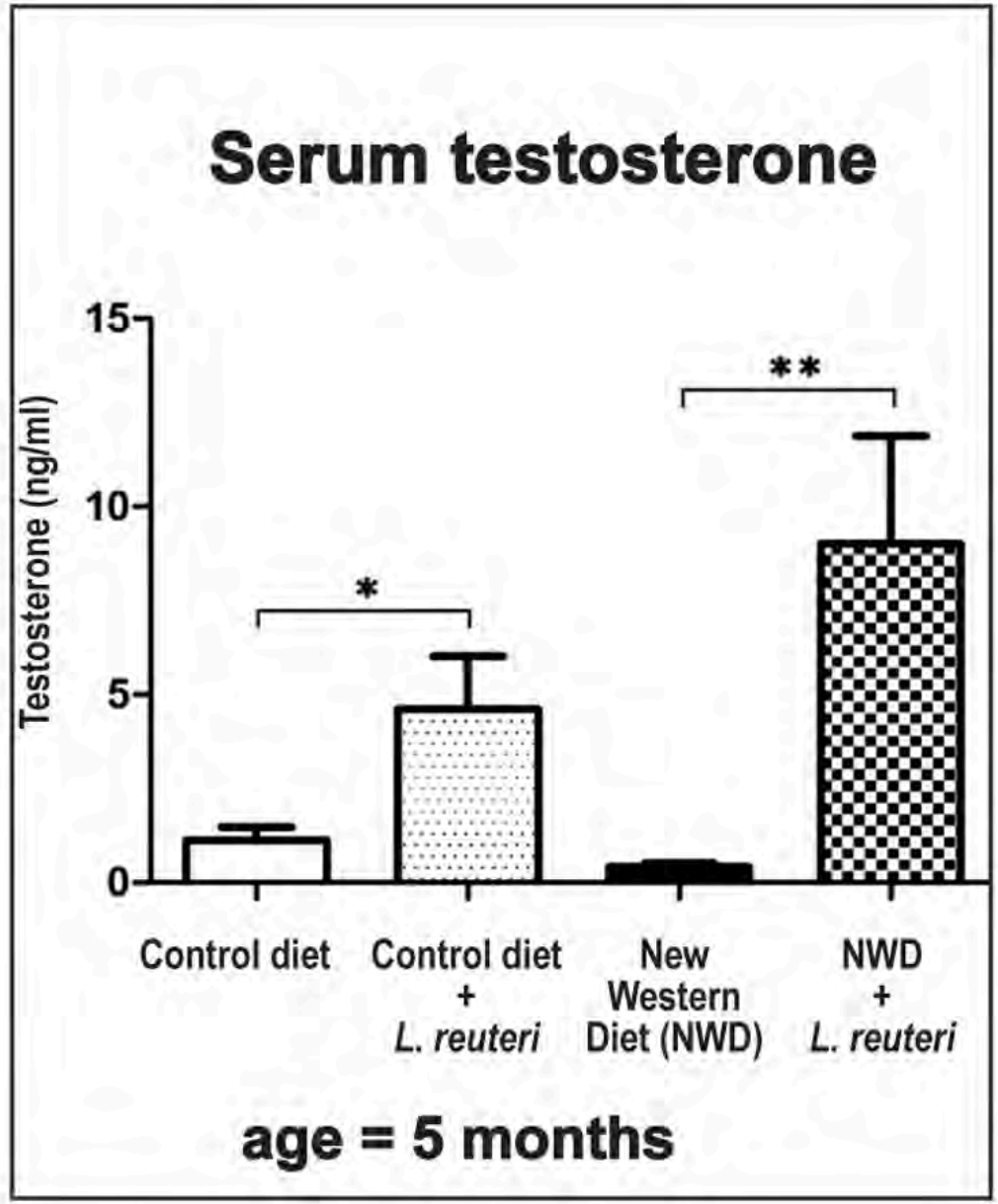
Mice That Eat Yogurt Have Larger Testicles

Probiotics may endow rodents with a "mouse swagger"

By Elie Dolgin

L. reuteri-treated mouse paired-testes weights



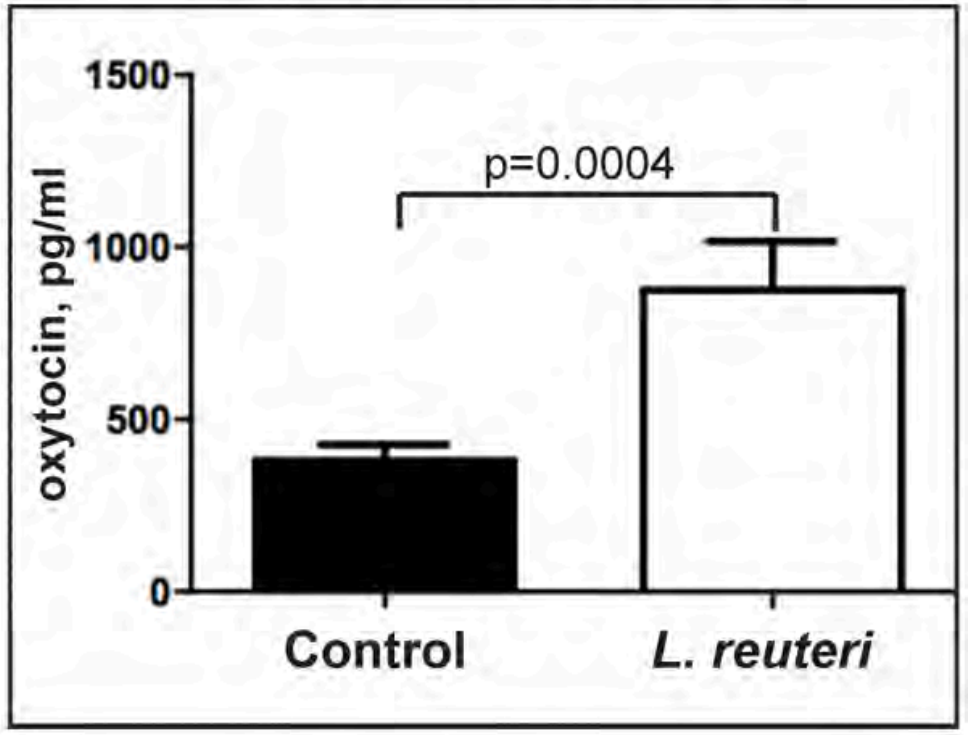

Serum testosterone
Testosterone (ng/ml)
15
10
5
0
*
**
Control diet
Control diet + L. reuteri
New Western Diet (NWD)
NWD + L. reuteri
age = 5 months

Reproductive Fitness

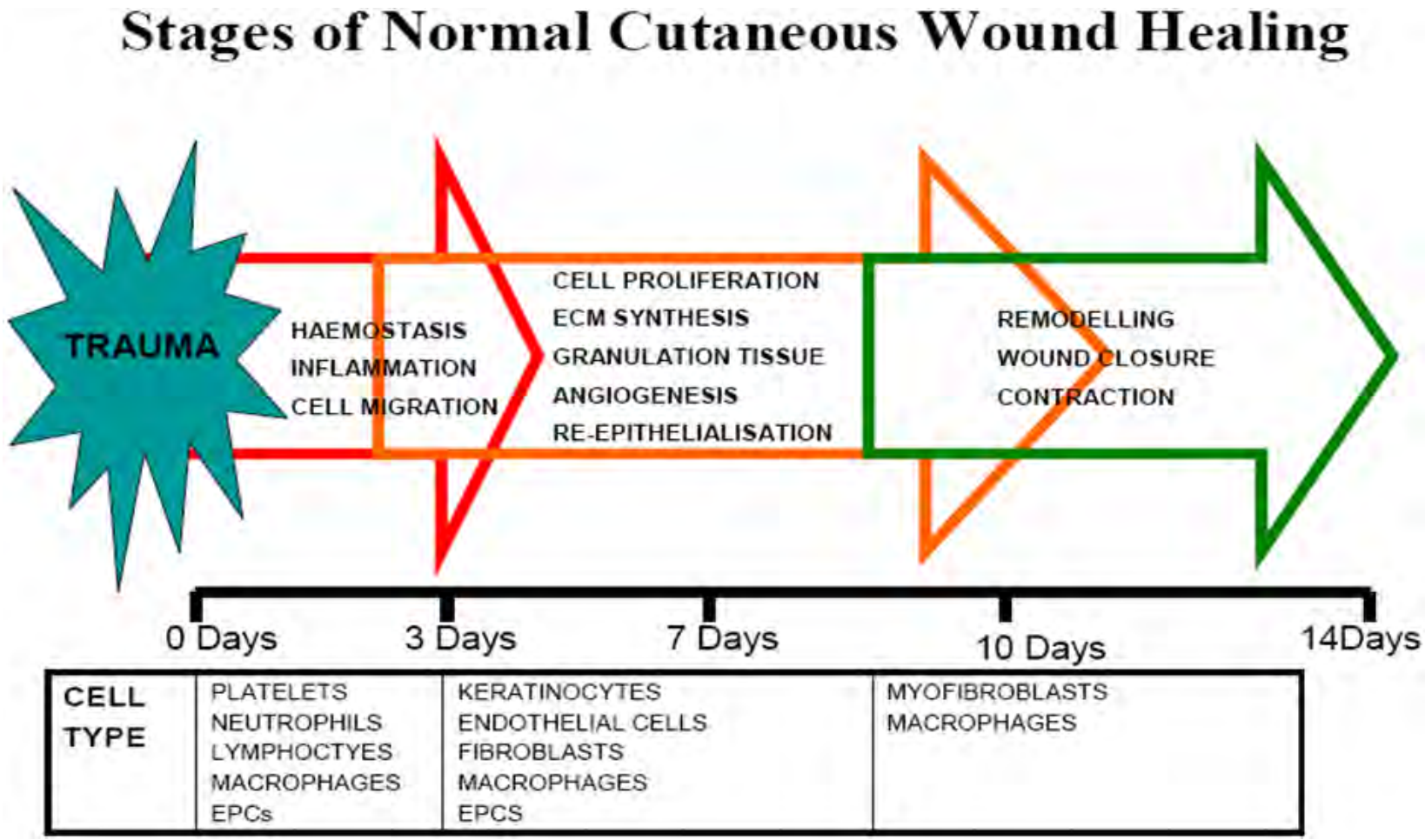
Survival to wean (control) = 67% (351/563)
(*L. reuteri*) = 98% (622/630)

Reproductive Fitness

“my bacteria made me do it”

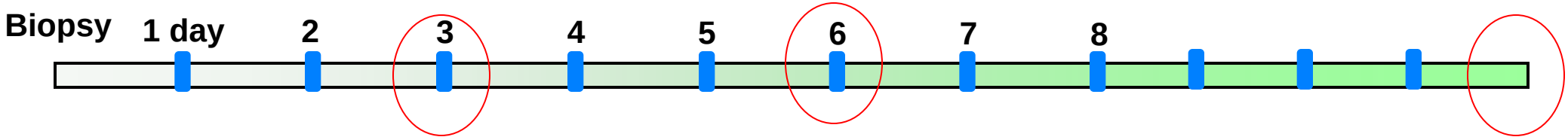


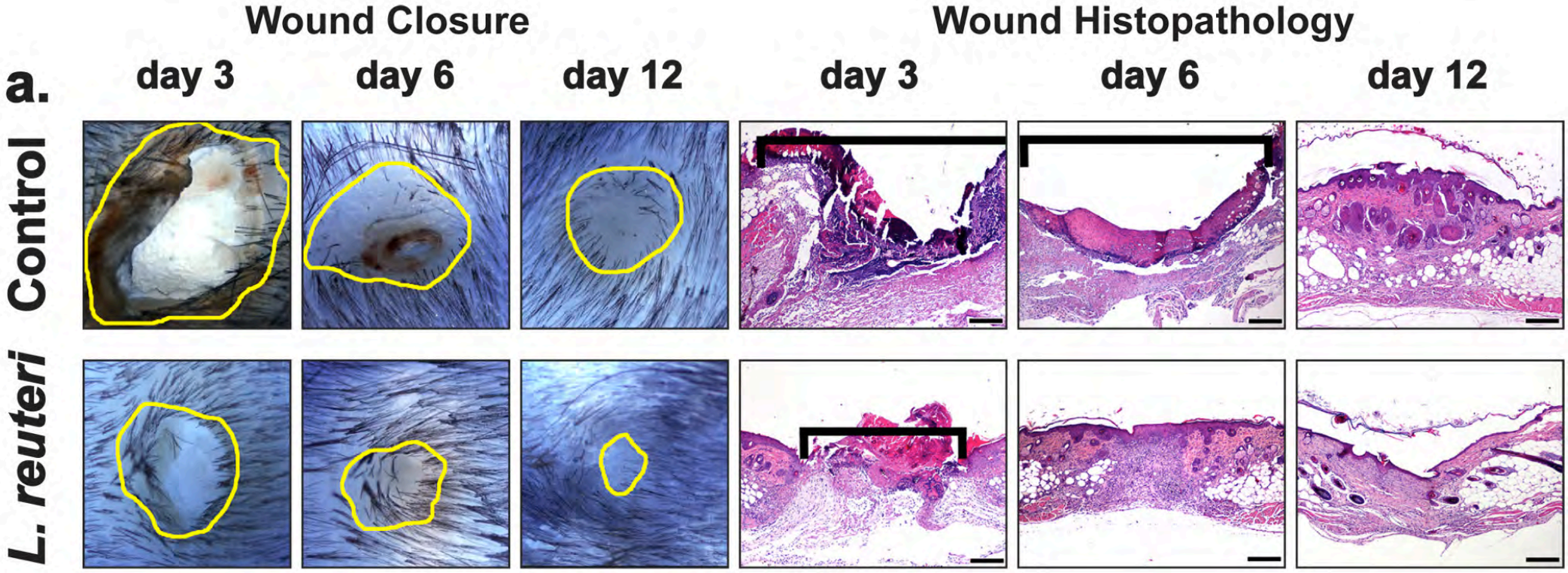
Importance of wound healing capability



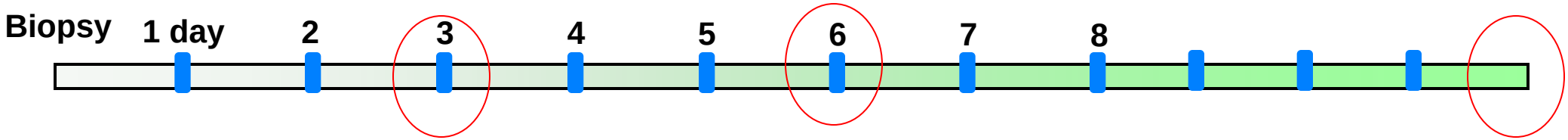
Aonghus O' Loughlin and Timothy O' Brien (2011). Topical Stem and Progenitor Cell Therapy for Diabetic Foot Ulcers, Stem Cells in Clinic and Research, Dr. Ali Gholamrezanezhad (Ed.), ISBN: 978-953-307-797-0, InTech, DOI: 10.5772/19070.

Skin wounds heal twice-as-fast when mice are eating L. reuteri

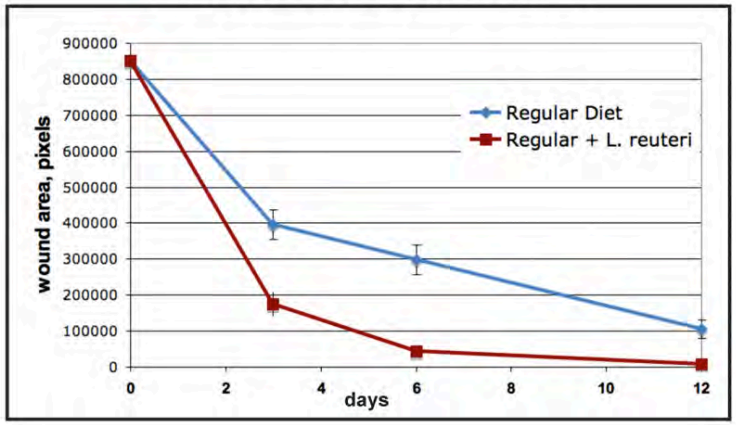




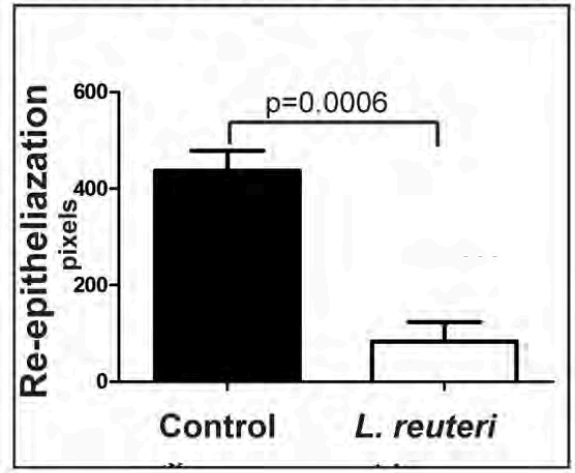
Skin wounds heal twice-as-fast when mice are eating L. reuteri



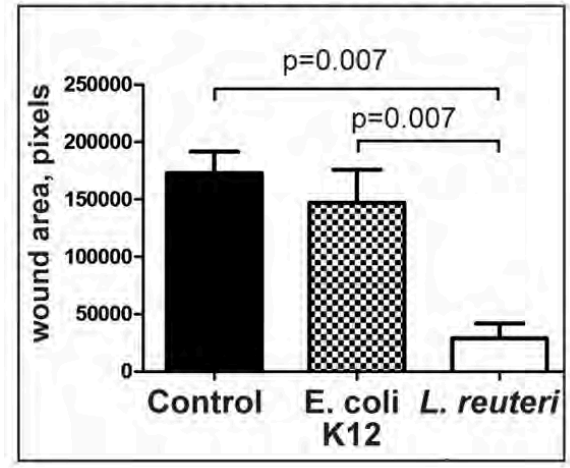
Wound Closure Rate



Wound Epidermal Gap



E. coli K12 sham



Lactobacillus reuteri-induced phenotypes are transplantable

Lactic Acid Bacteria

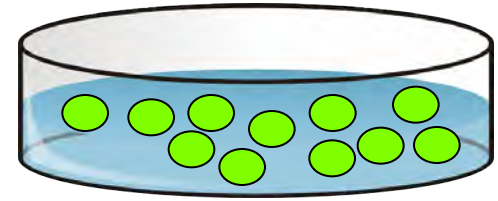
ingestion

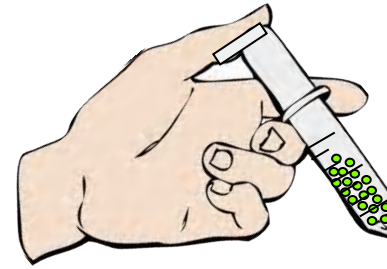
Probiotic-fed donor

adoptive cell transfer

Cells extracted
from gfp donor mouse

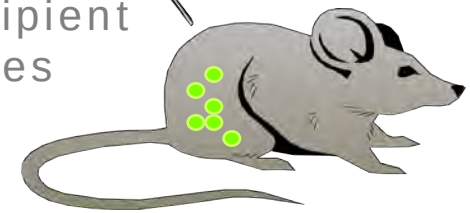
Transplantation of
CD4+Foxp3+gfp lymphocytes





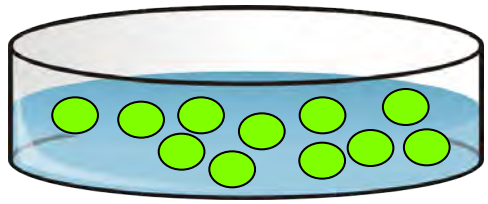
Cells injected into Rag-KO recipient
without it's own lymphocytes

Probiotic benefits



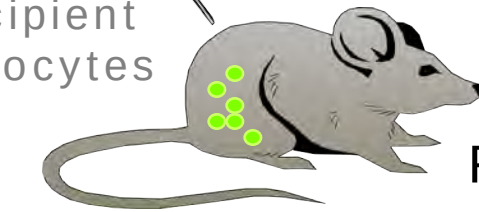
Rag2-KO recipient

Probiotic benefits transplantable via lymphocytes

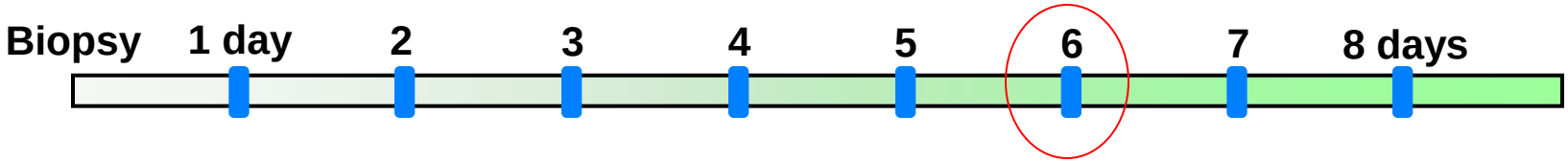


Gfp-Foxp3+ cells

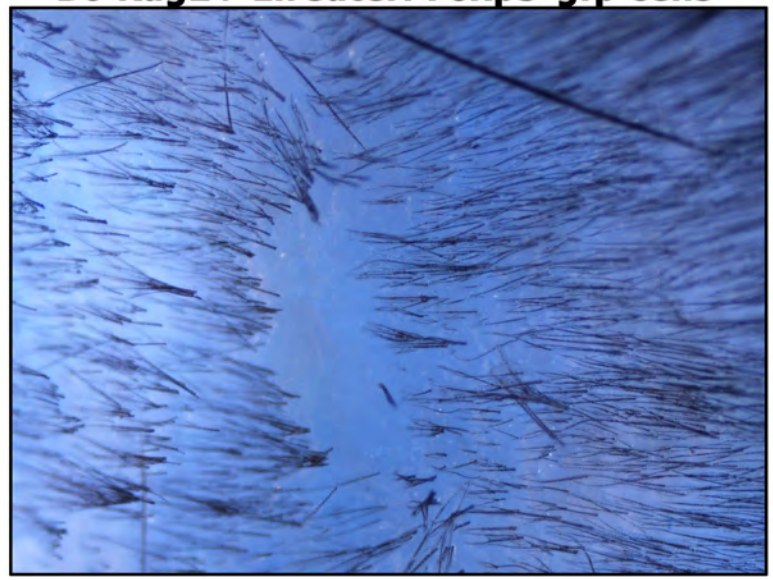
Cells injected into recipient
without it's own lymphocytes



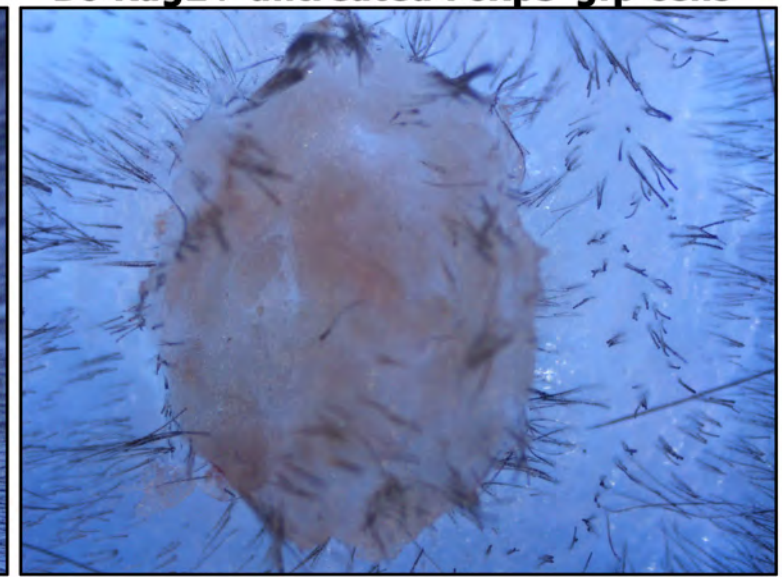
Rag2-KO

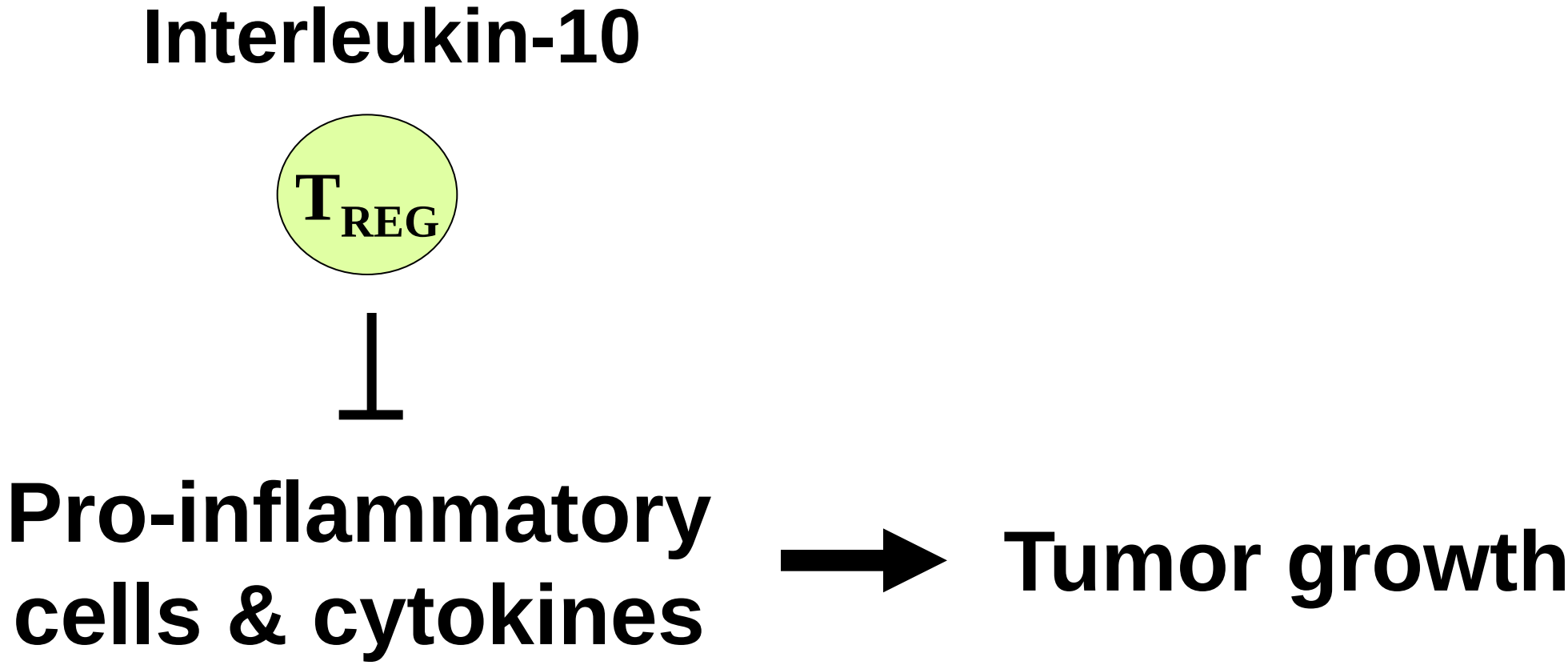


B6 Rag2+ L.reuteri Foxp3-gfp cells

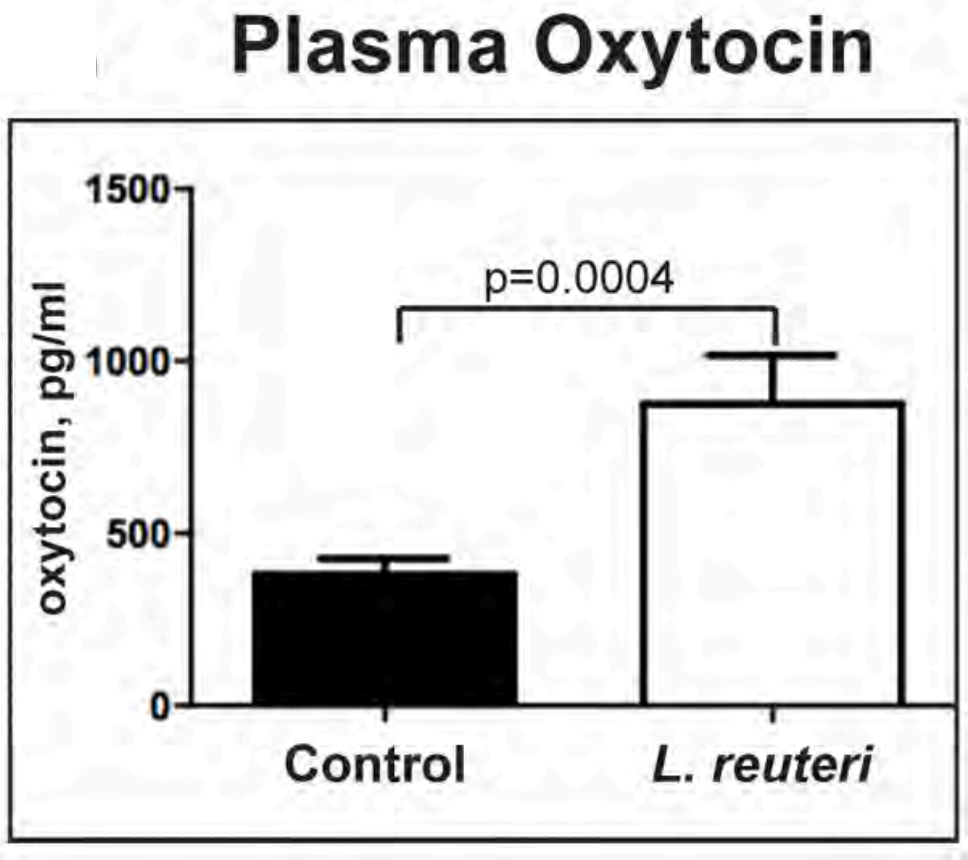


B6 Rag2+ untreated Foxp3-gfp cells

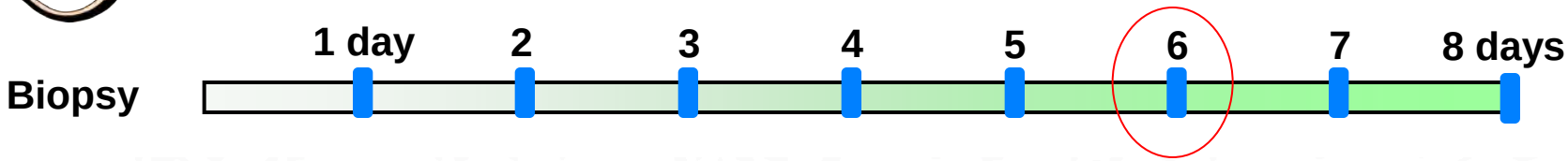



Interleukin-10
T_{REG}
Pro-inflammatory cells & cytokines
Tumor growth

“my bacteria made me do it”



L. reuteri-induced improvement in wound repair requires oxytocin



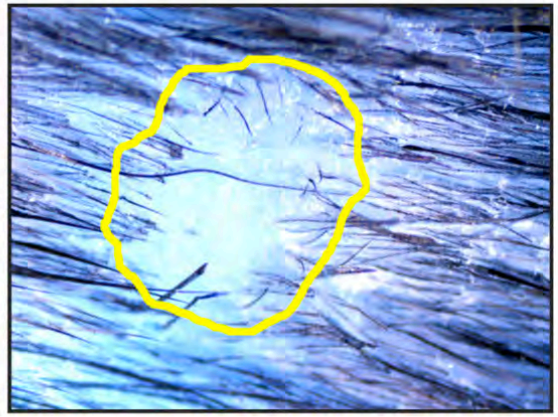
a.

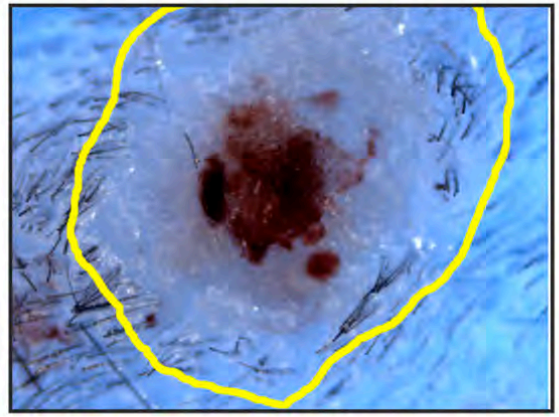
oxt- WT + *L. reuteri* (D6)

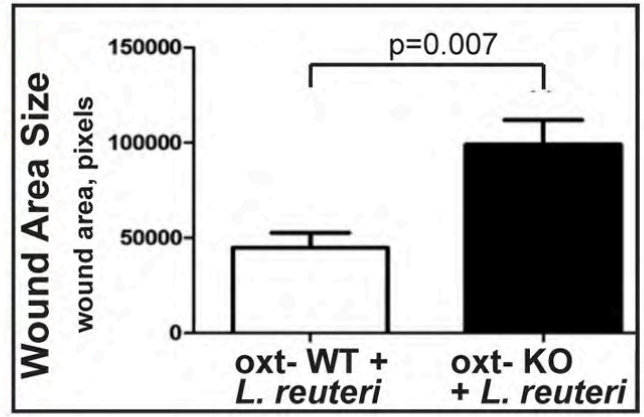
oxt- KO + *L. reuteri* (D6)

Morphometric Analysis

Wound Closure

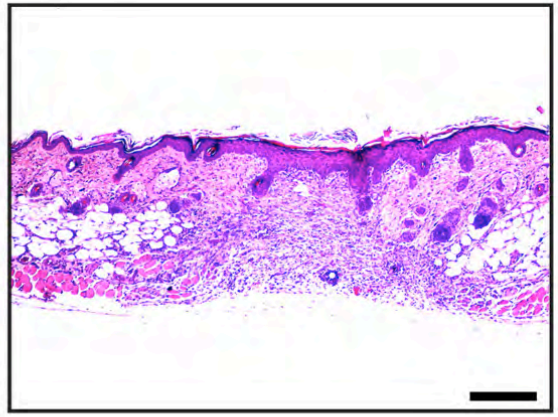


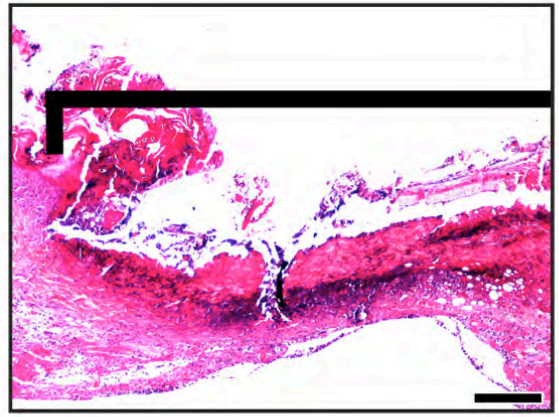


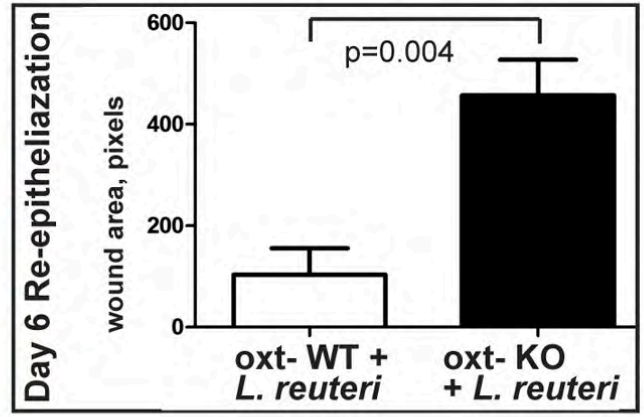


b.

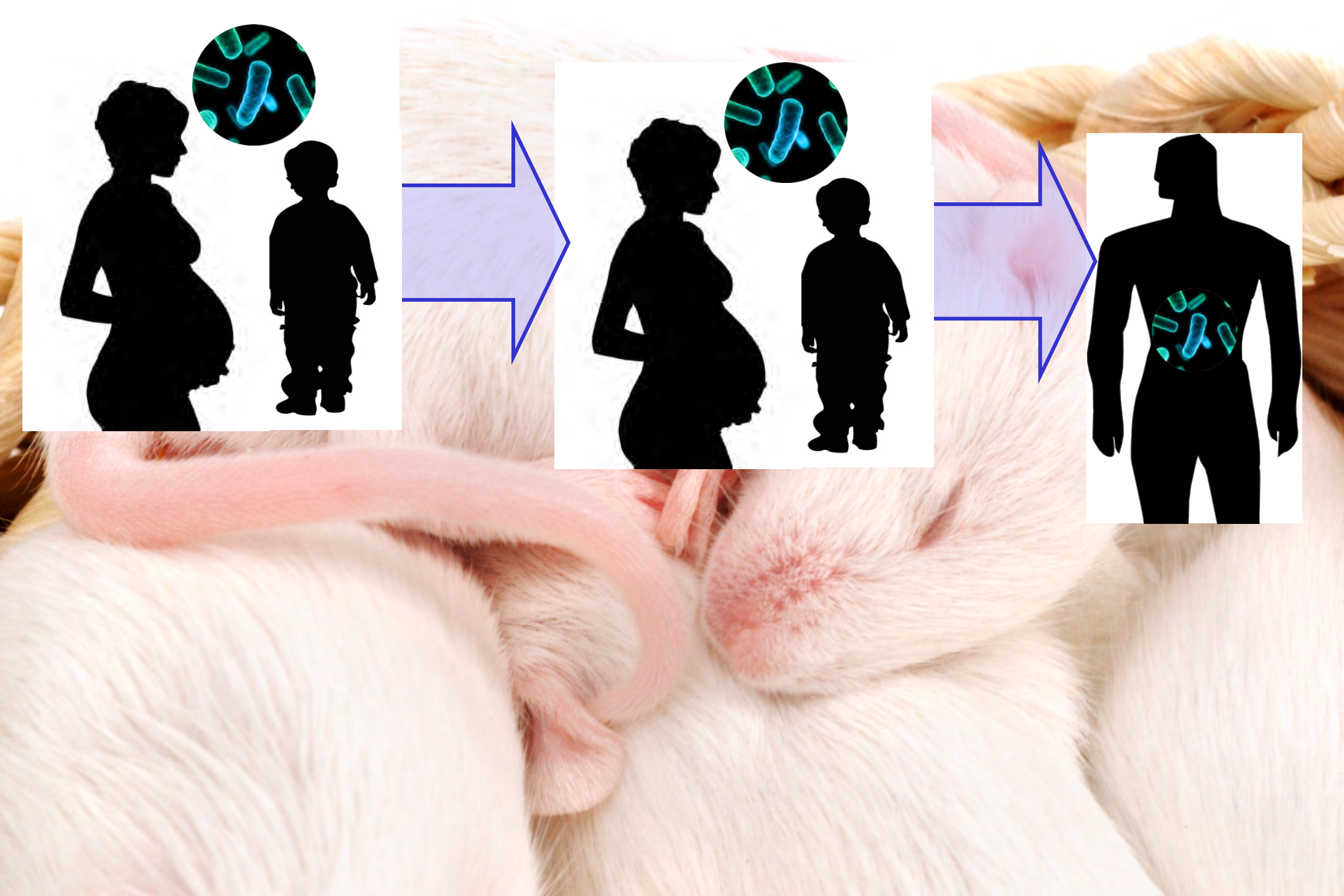
Histopathology



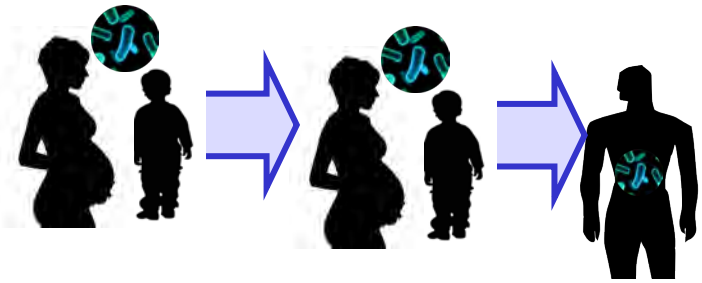




NIEHS P30 ES002109. [P30 PIs: Leona Samson → John Essigmann]
***Perinatal microbe exposures*. Pilot project co-PIs: SE Erdman & EJ Alm**
2011 – 2013



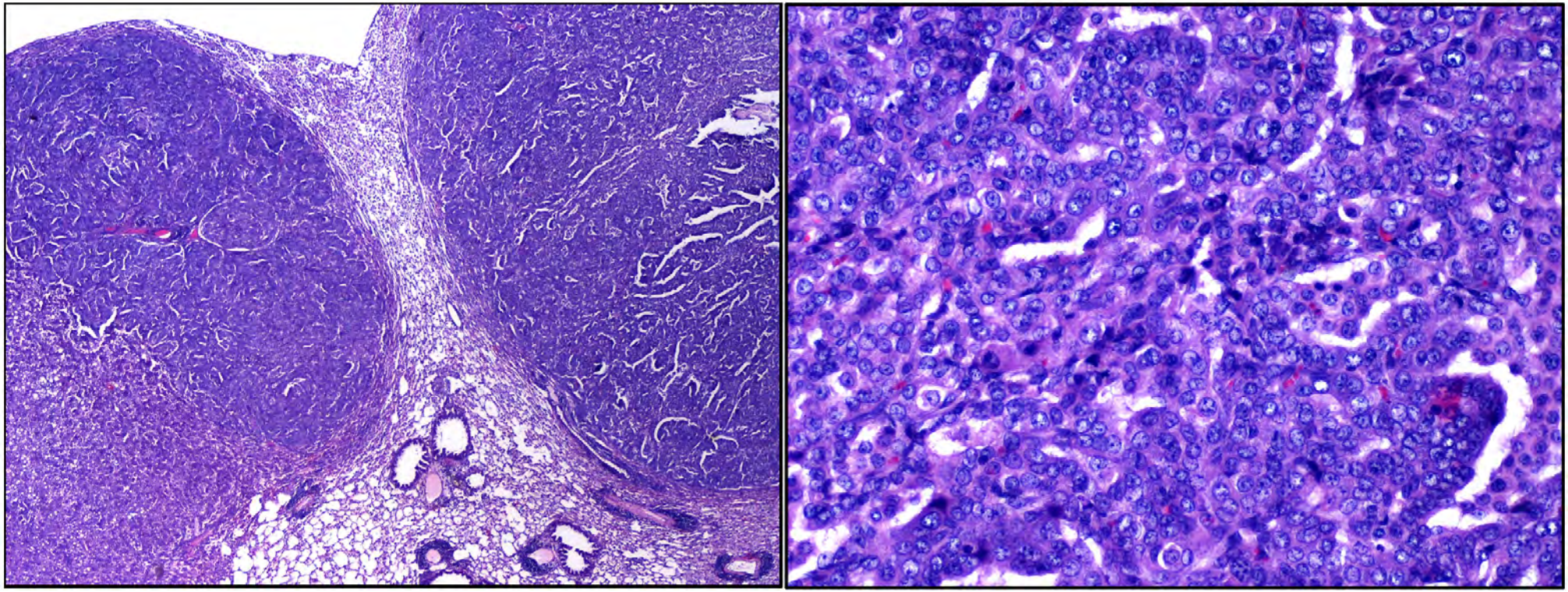
Grandma's microbial ecology may put grandchild at risk for cancer?



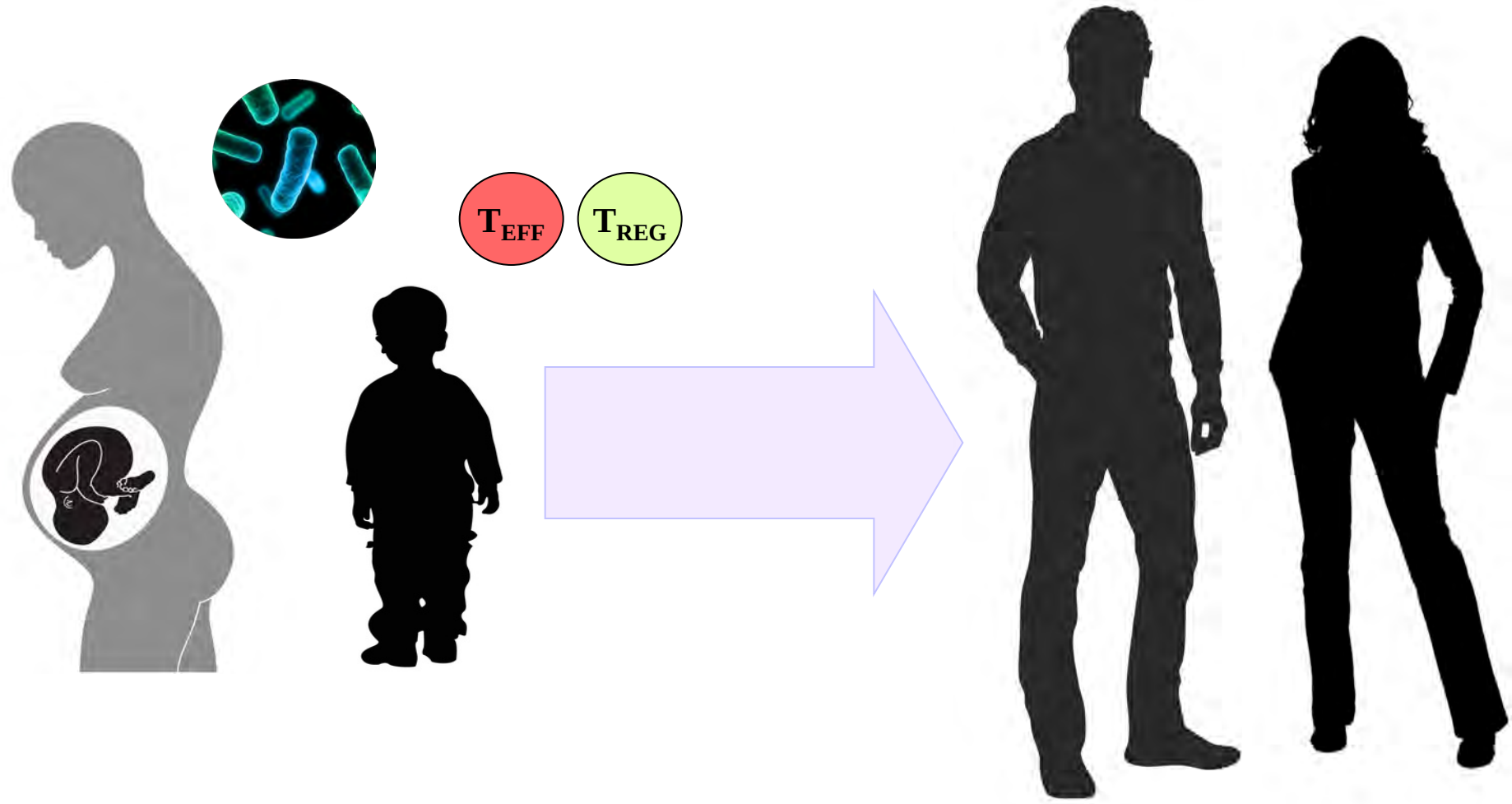
Preliminary cancer outcomes in 'grandchildren' mice:

- 1/3 liver cancer (hepatocellular carcinoma)
- 2/3 lymphoma (high grade)
- 3/3 lung cancer (bronchoalveolar adenocarcinoma)

Bronchoalveolar adenocarcinoma in 3/3 'grandchild' outbred Swiss mice (age = 5 months)



Does human maternal and infant microbial ecology offer opportunity to impart good health to future generations?

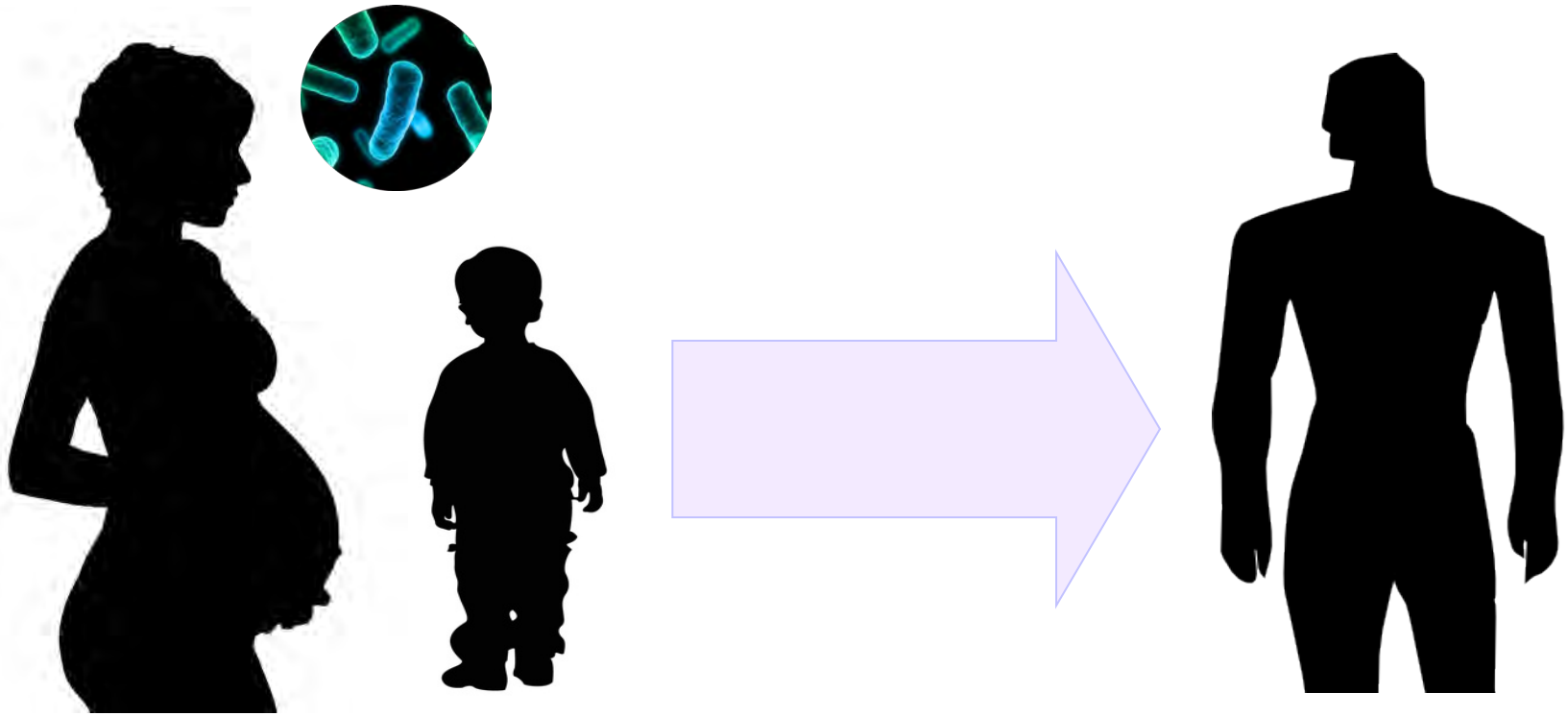



Can microbe-based restructuring of immune networks improve our public health?

Harnessing microbes for public health

Do lactic acid bacteria offer an immediate palatable public health remedy ?

Harnessing microbes for public health



Prospective longitudinal studies to identify hygienic signatures for risk assessment and microbial rescue strategies ?

Harnessing microbes for public health

Probe epigenetic/genetic impact of microbes upon host progeny and their offspring

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