

Immunity to the microbiota and tissue physiology



Yasmine Belkaid



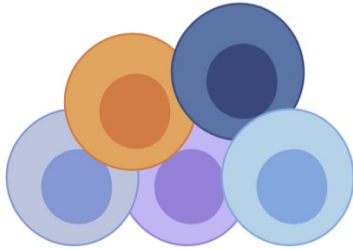
Institut Pasteur

Microbiot

a



Tissue threshold of activation



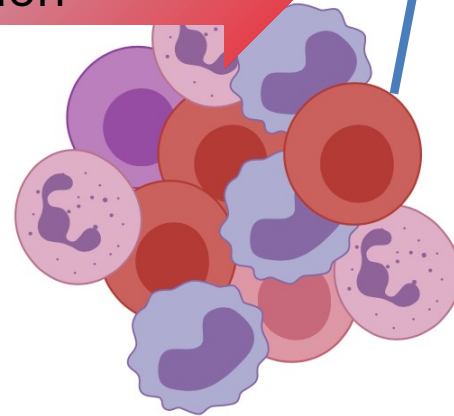
Pathogenic microbes

Toxins

Tissue damage



Pathogen control
Immunopathology



Microbiot

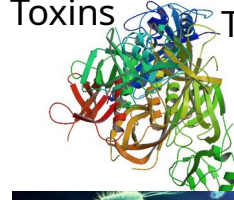
a



Pathogenic microbes

Toxins

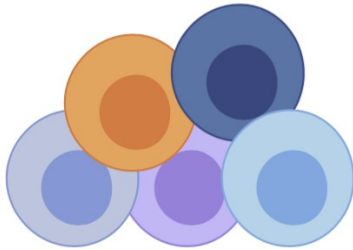
Tissue damage



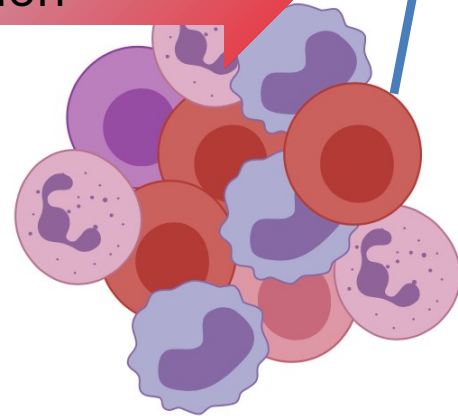
Pathogen control
Immunopathology

Tissue threshold of activation

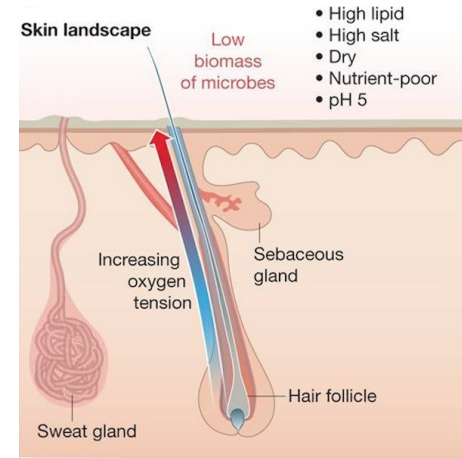
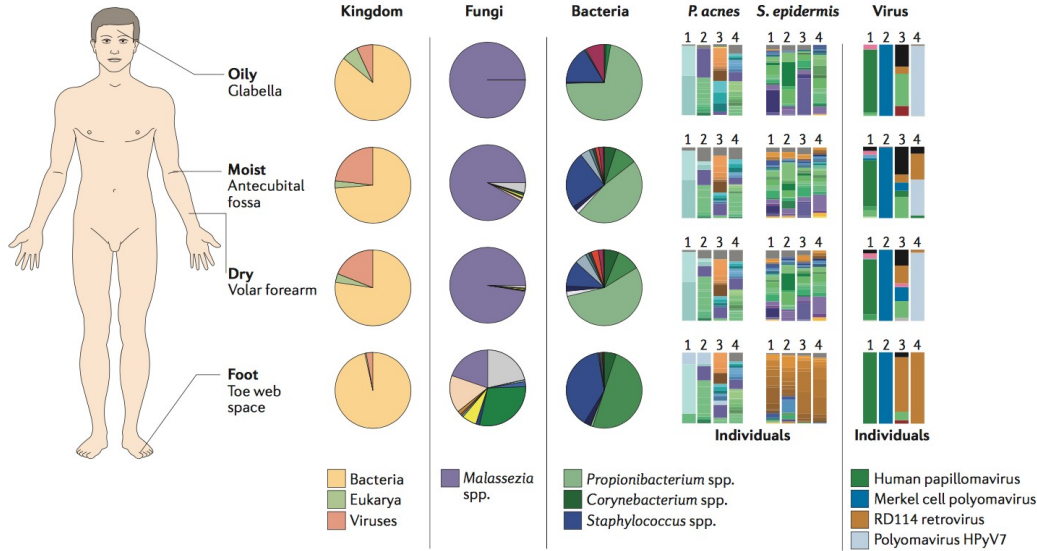
Induction?



Function?



Julie Segre
Heidi Kong



Chen, Nature 2018

Skin microbiota control tissue immunity

Naik, Science 2012
Naik, Nature 2015

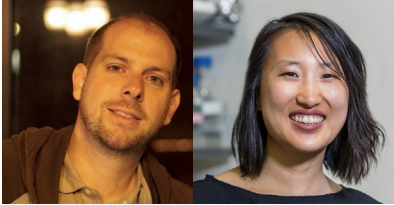


Shruti Naik
Assistant professor
NYU

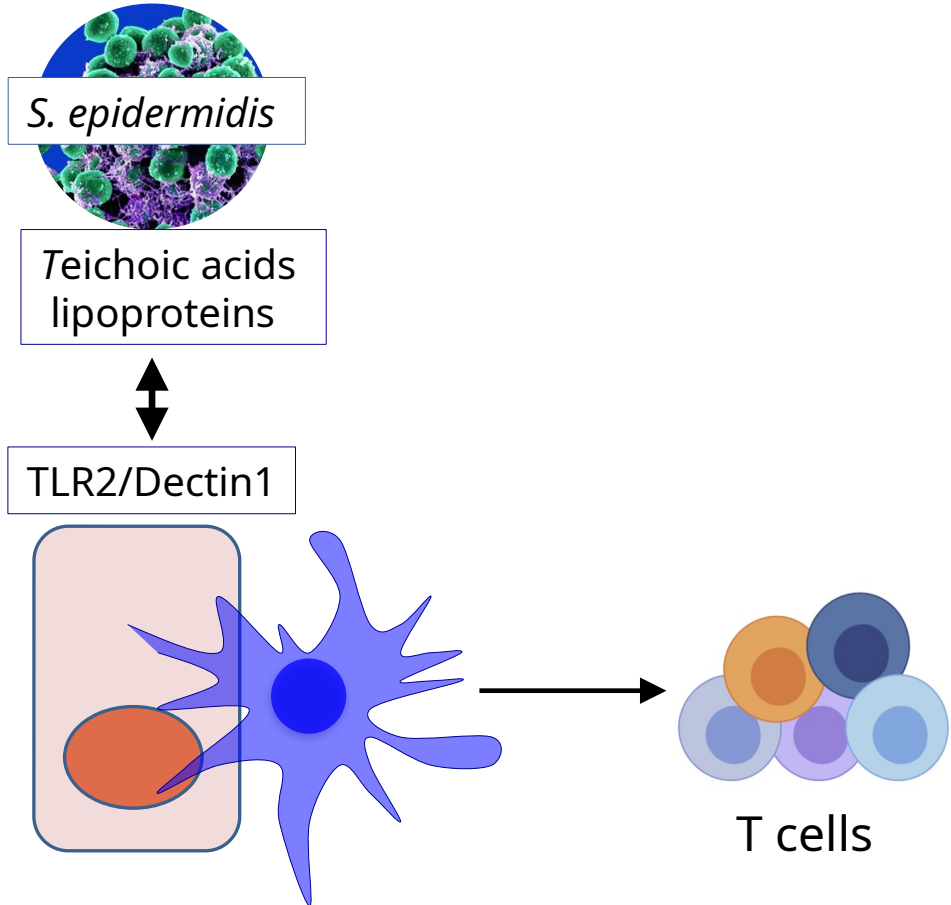
First encounter: critical determinants

Nicolas
Bouladoux

Erin Chen (MIT)
(Michael Fischbach)

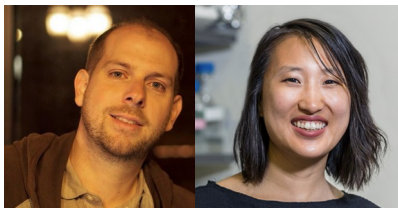


Chen BioRxiv
Chen, *Science* 2023

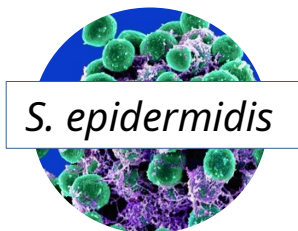


First encounter: critical determinants

Nicolas Bouladoux
Erin Chen (MIT)
(Michael Fischbach)



Chen BioRxiv
Chen, *Science* 2023

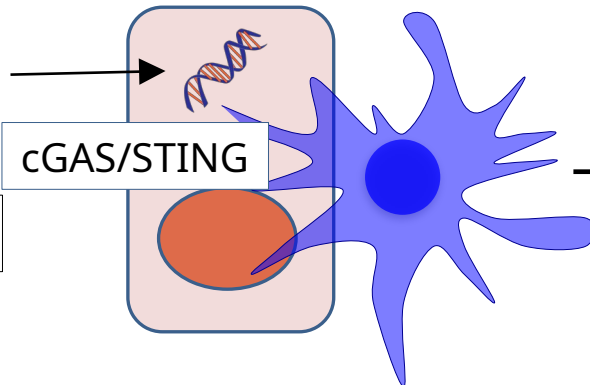
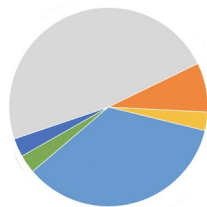


S. epidermidis

Teichoic acids
lipoproteins



TLR2/Dectin1



Djalma Lima
Assistant professor
U Sao Paulo

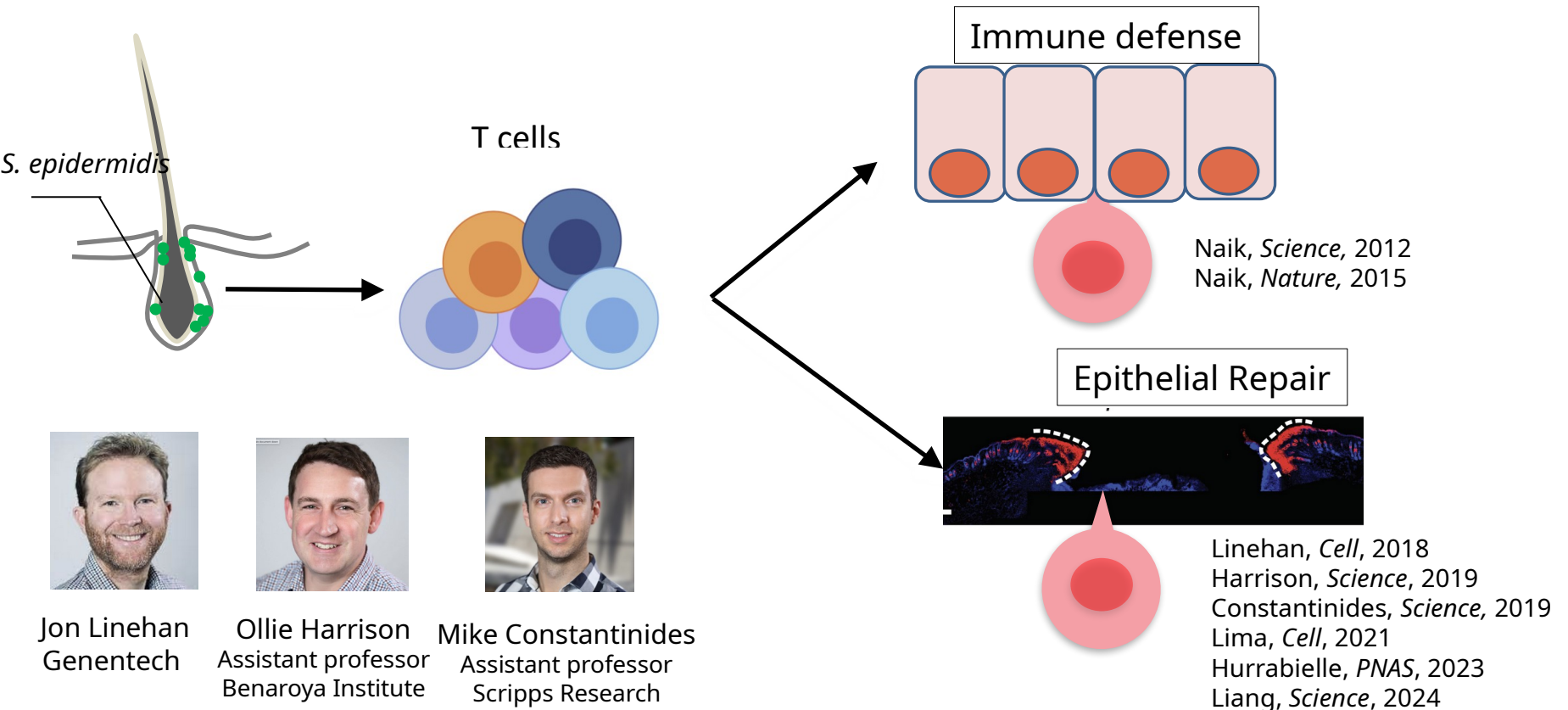


Endogenous retrovirus

Lima, *Cell* 2021

T cells

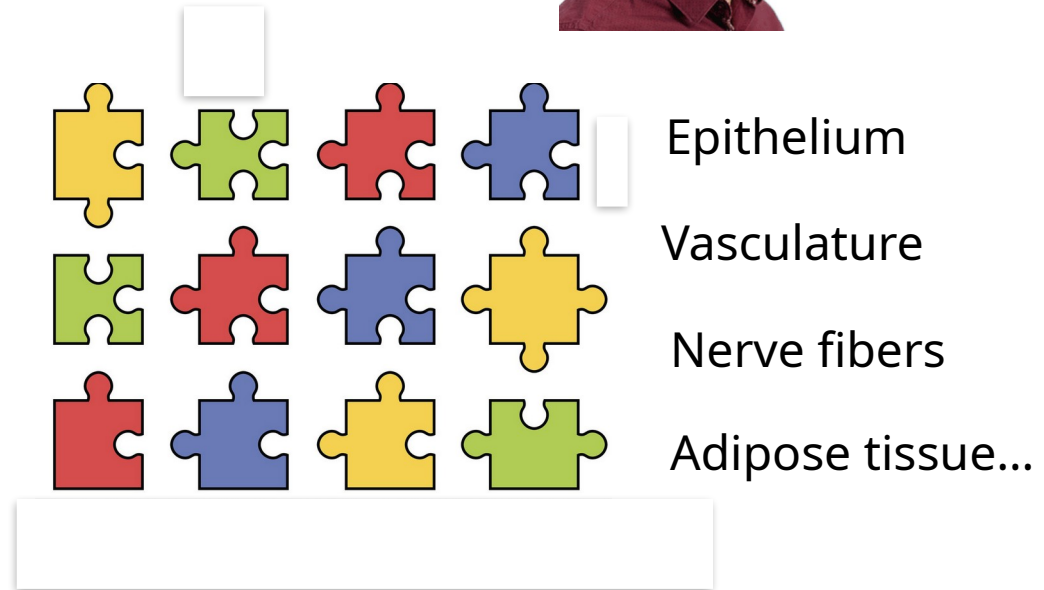
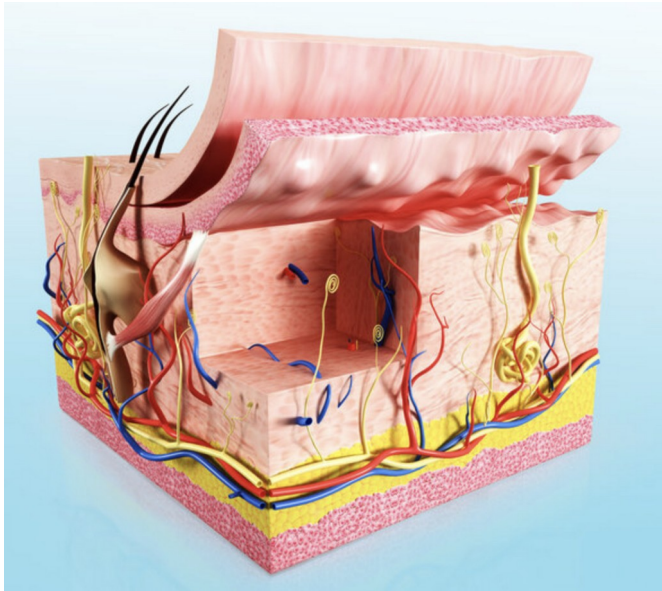
Skin microbiota-specific T cells promote antimicrobial defense and tissue repair



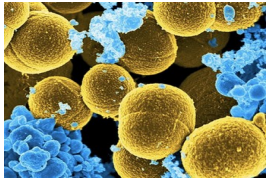
Multisystem repair...



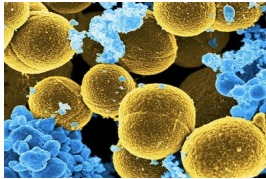
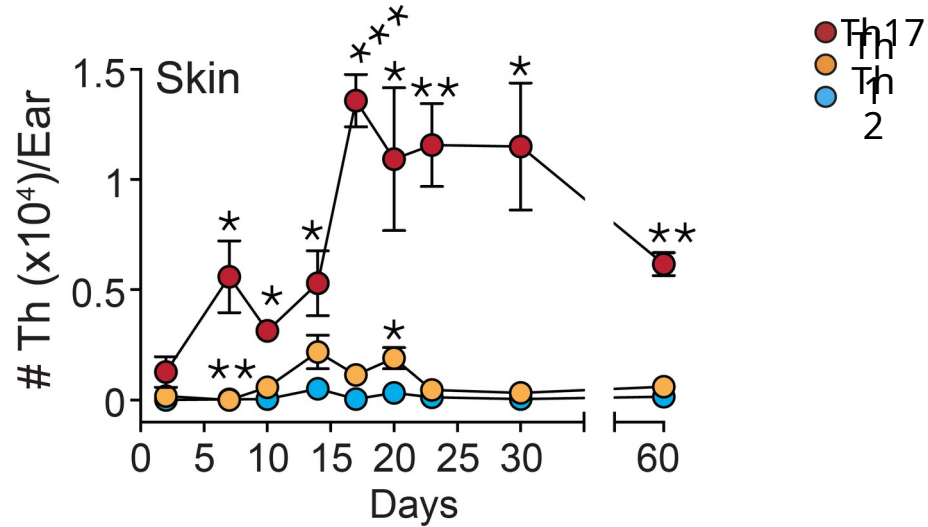
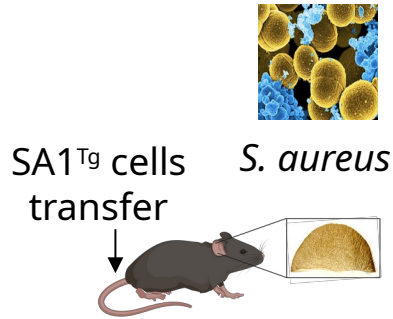
Michel
Enamorados
Assistant professor
Mt Sinai, NY



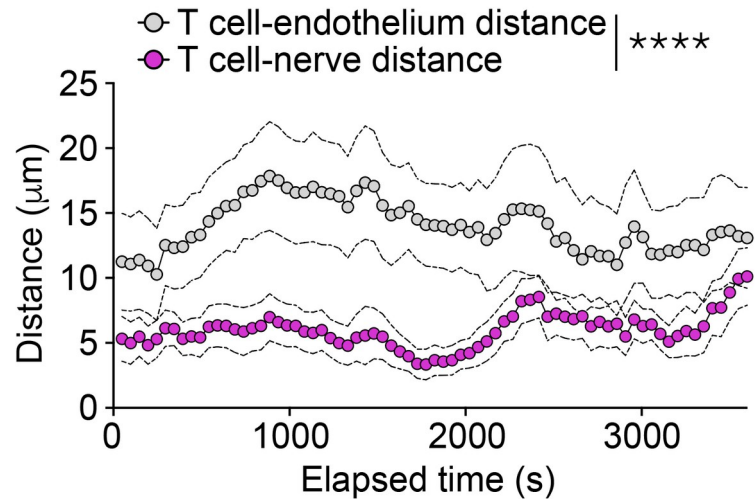
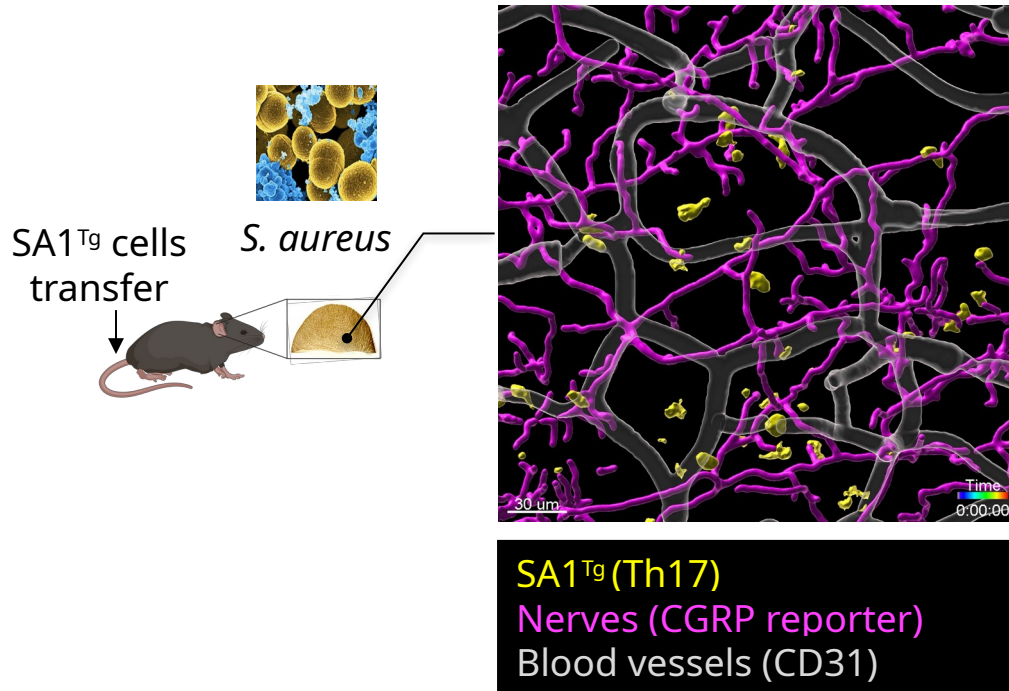
Staphylococcus aureus



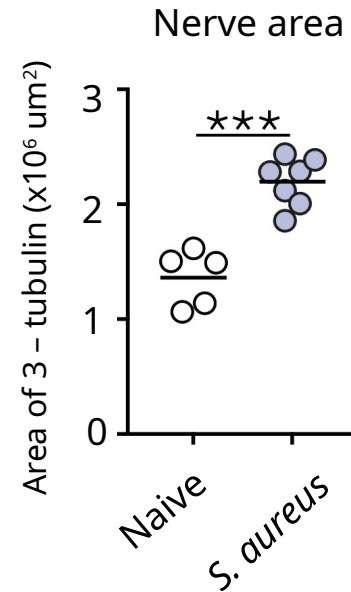
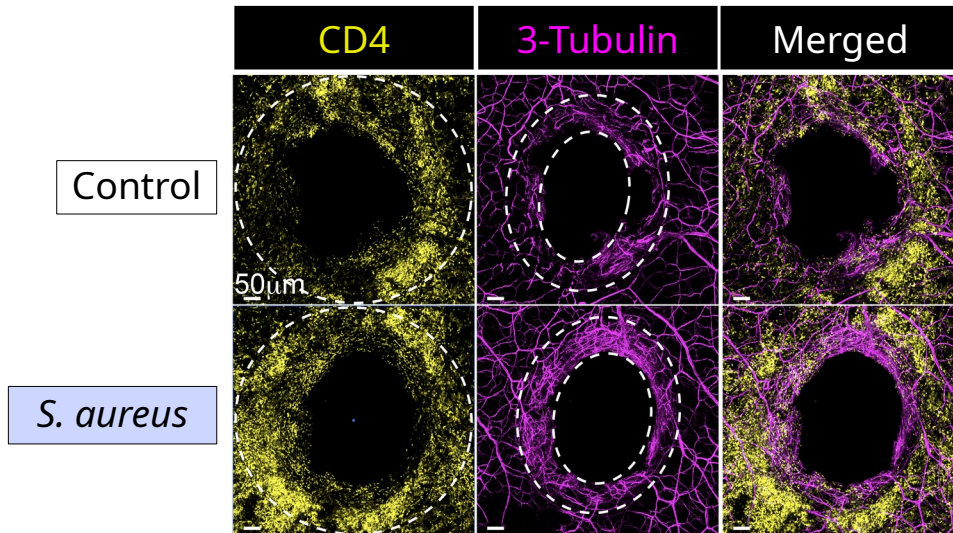
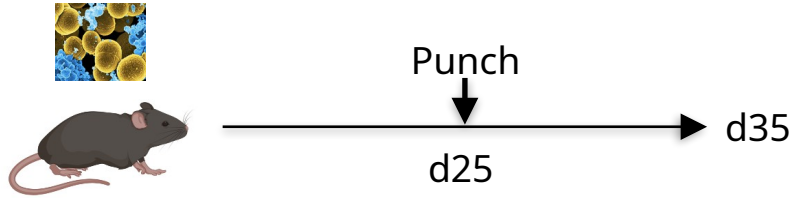
Staphylococcus aureus association promotes Th17 response



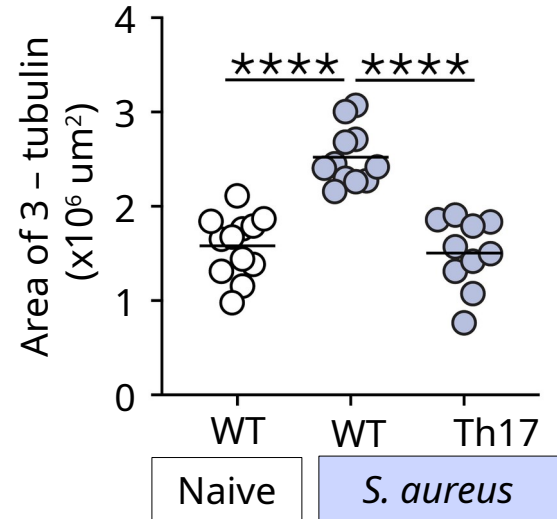
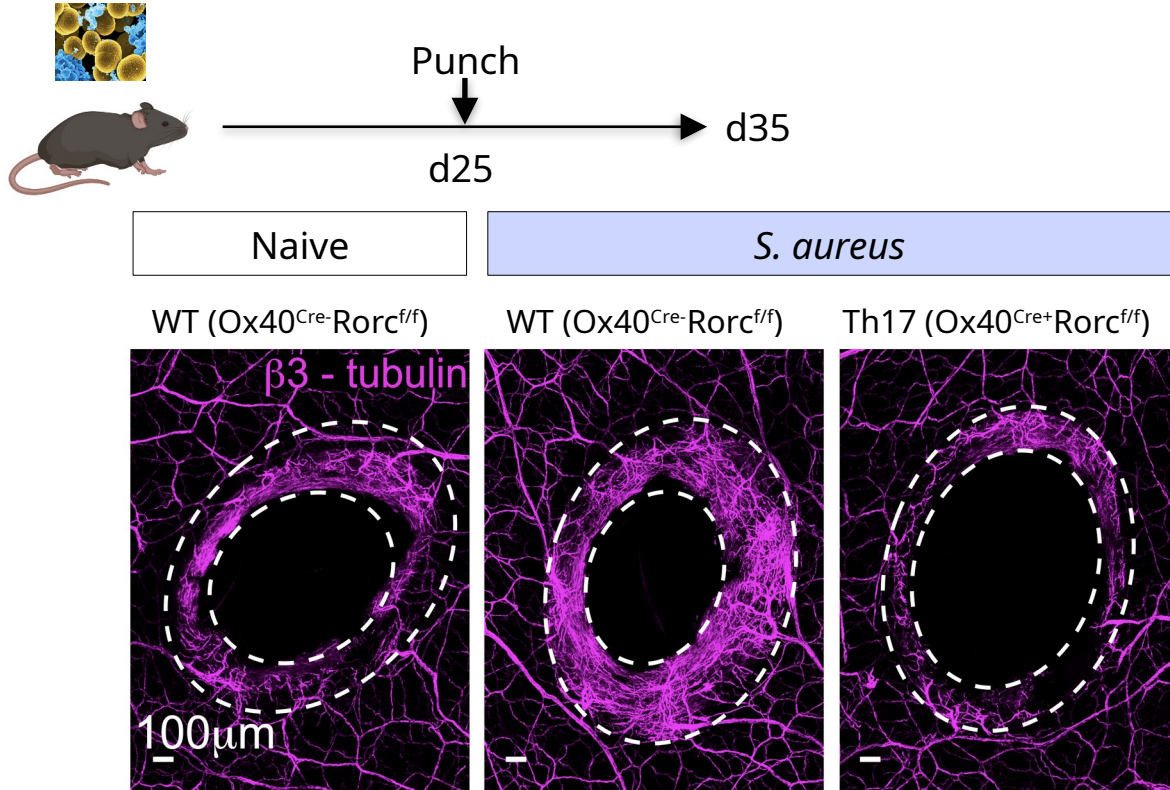
Staphylococcus aureus specific T cells are in close proximity to sensory neurons

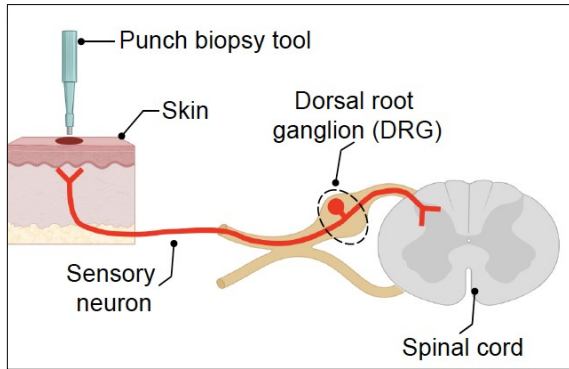


S. aureus association promotes local nerve regeneration



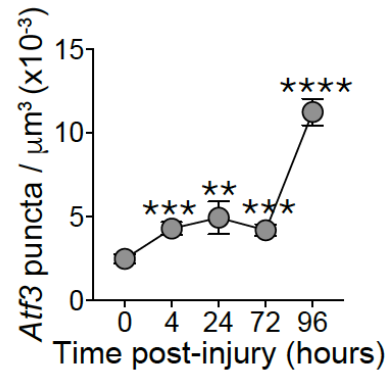
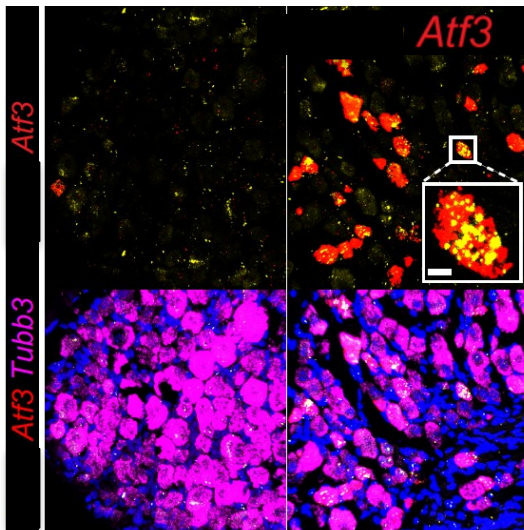
Accelerated nerve regeneration is Th17-dependent



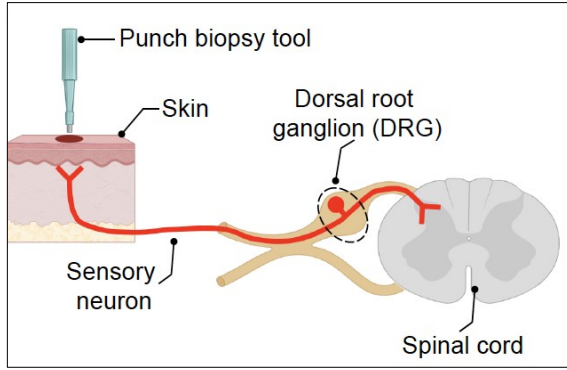


Control

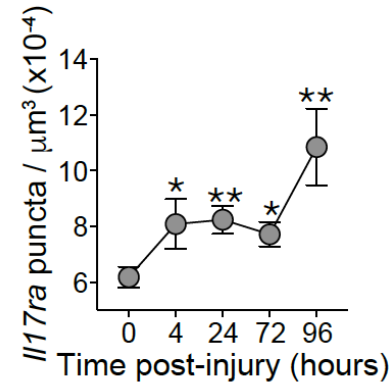
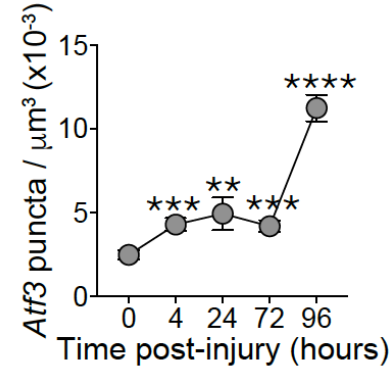
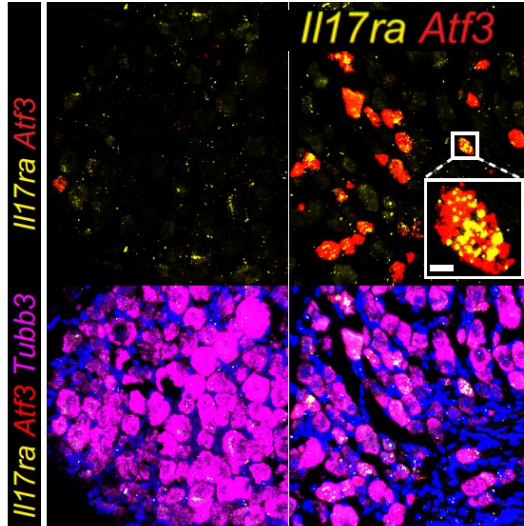
Punch



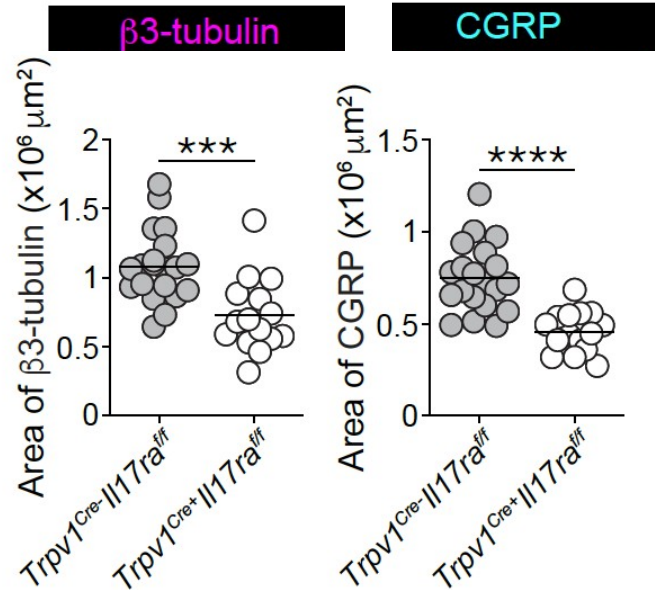
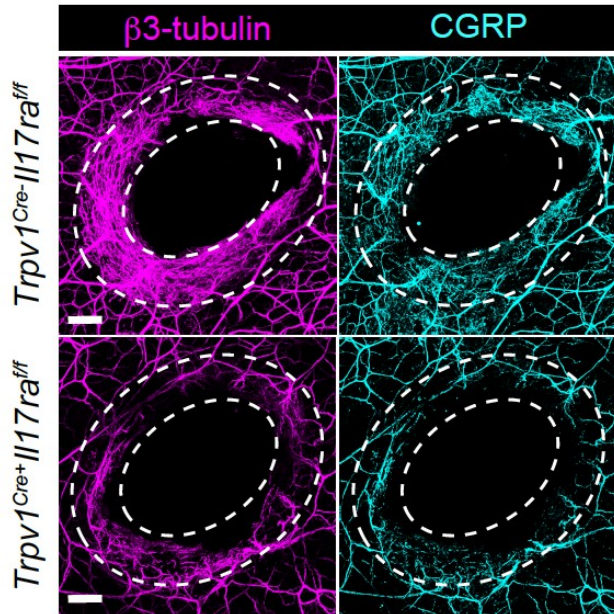
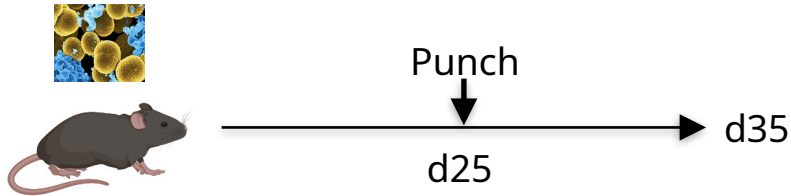
Injured neurons upregulate IL17RA



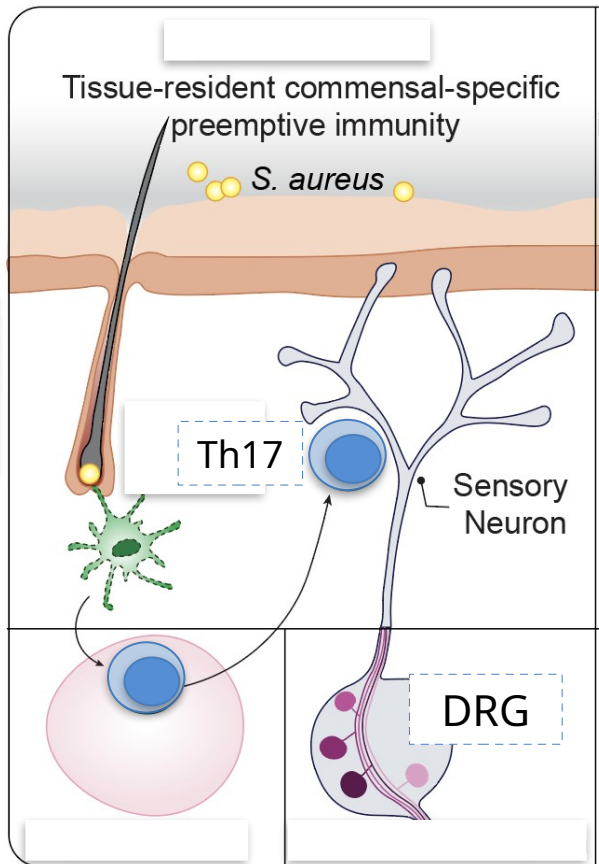
Control Punch



IL-17A directly promotes sensory neuron regeneration



HOMEOSTASIS

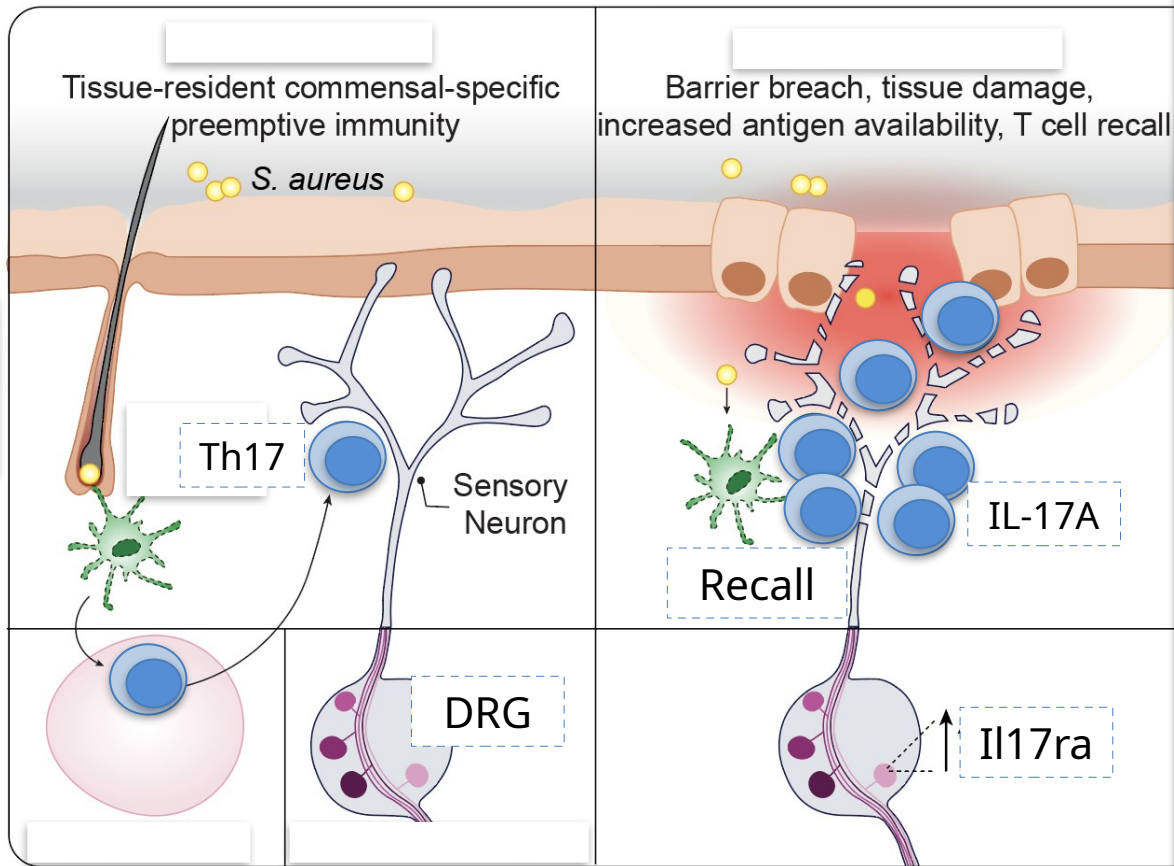


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HOMEOSTASIS

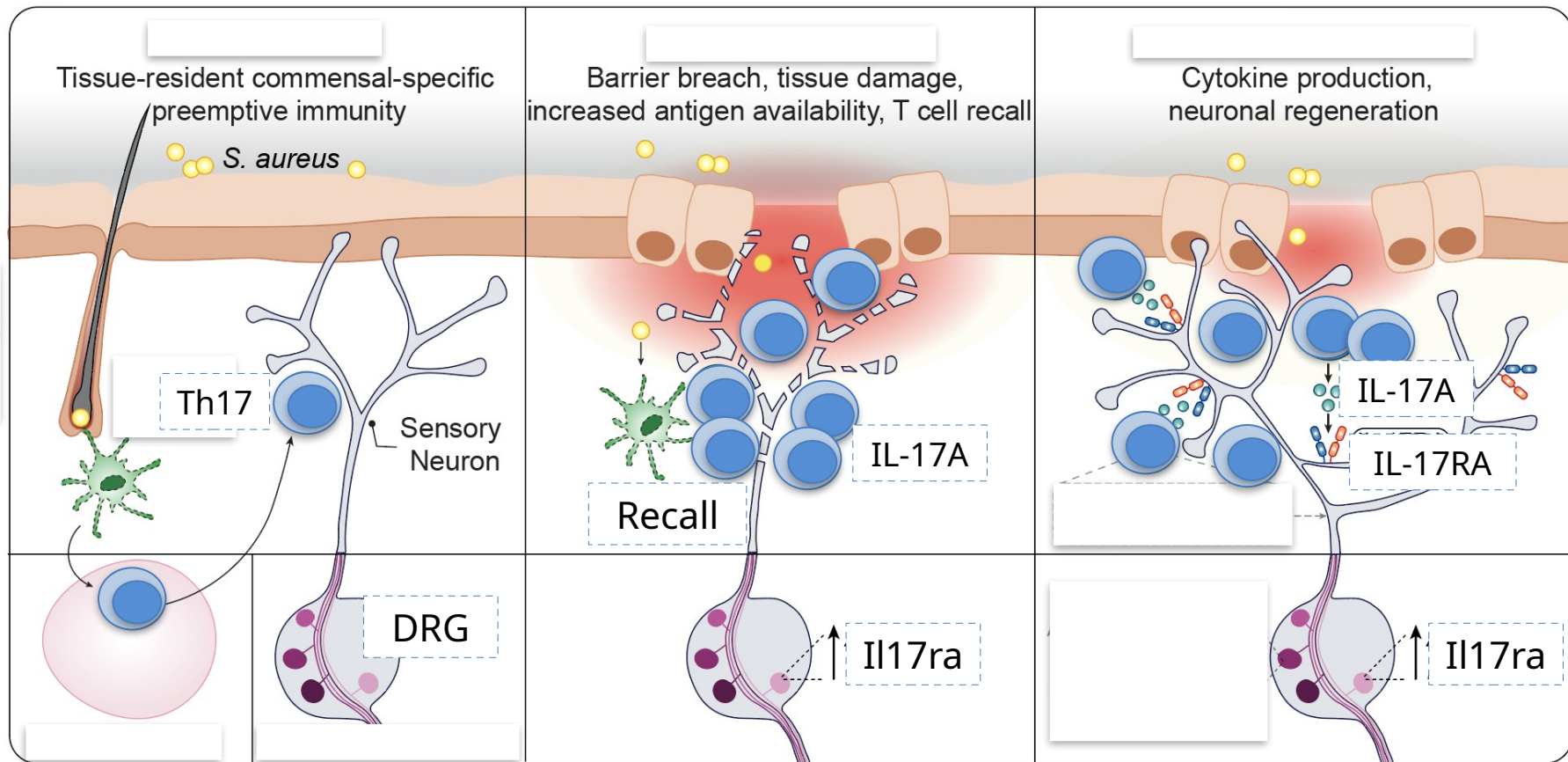
INJURY/INFECTION



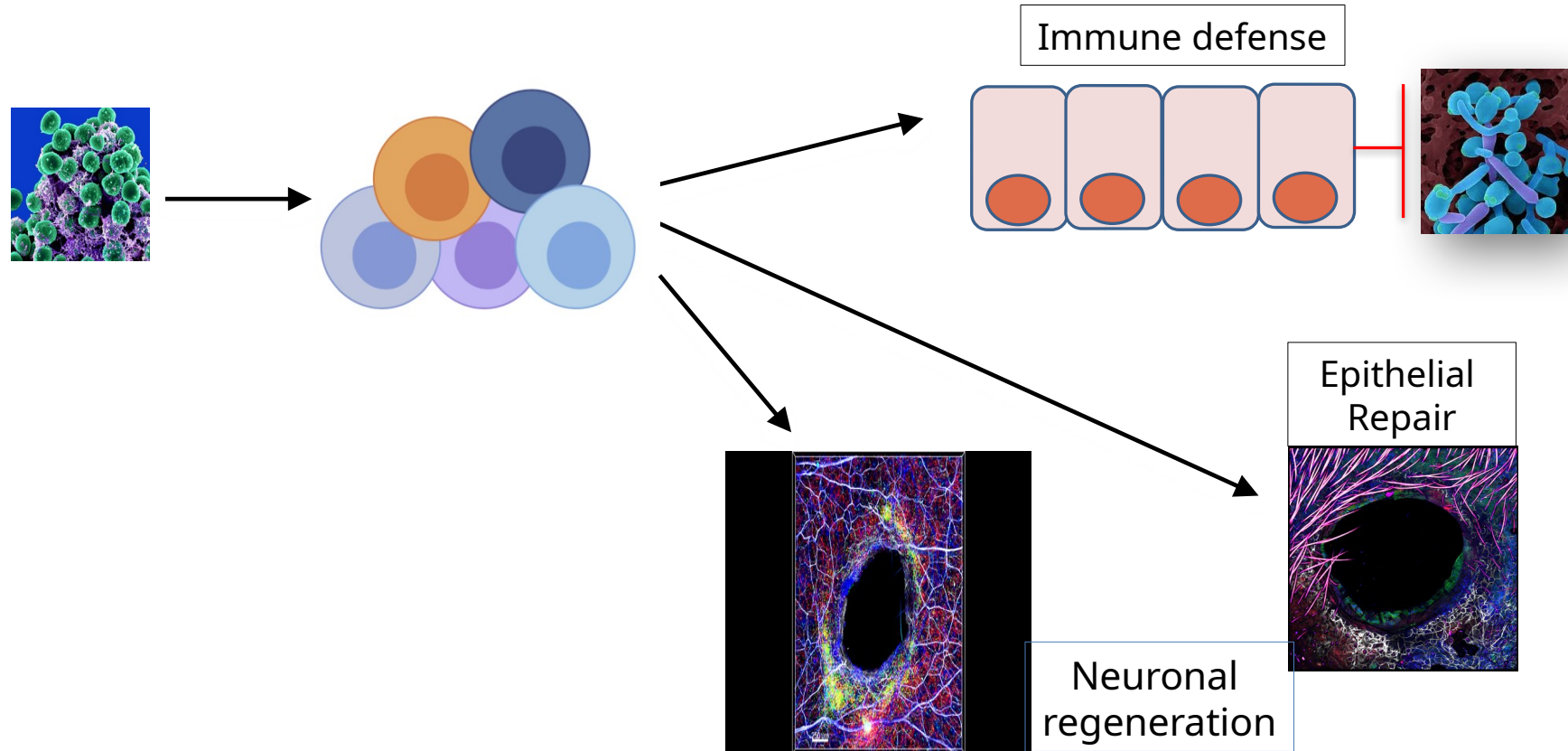
HOMEOSTASIS

INJURY/INFECTION

REPAIR



Microbiota-specific T cells promote tissue physiology



Microbiota-specific T cells promote tissue physiology



RESEARCH

RESEARCH ARTICLE SUMMARY

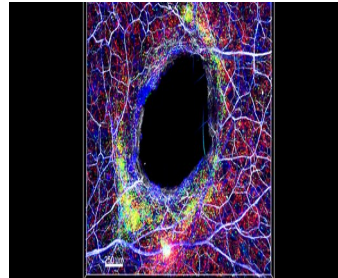
IMMUNOMETABOLISM

Interleukin-17 governs hypoxic adaptation of injured epithelium

Piotr Konieczny†, Yue Xing*†, Ikjot Sidhu, Ipsita Subudhi, Kody P. Mansfield, Brandon Hsieh, Douglas E. Biancur, Samantha B. Larsen, Michael Cammer, Dongqing Li, Ning Xu Landén, Cynthia Loomis, Adriana Heguy, Anastasia N. Tikhonova, Aristotelis Tsirigos, Shruti Naik*

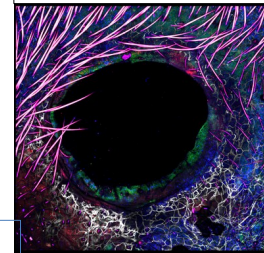
IL17A:

Sensory recovery?
Diabetic Wound ?



Neuronal regeneration

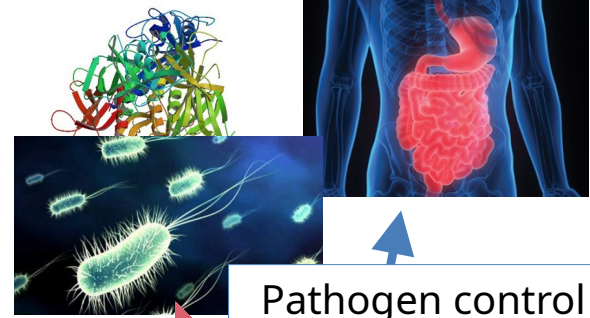
Epithelial Repair



Skin Microbiota

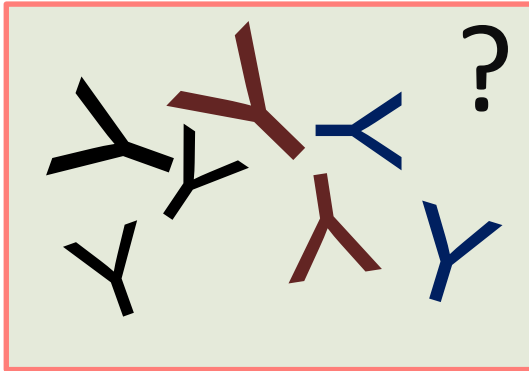


Pathogenic microbes

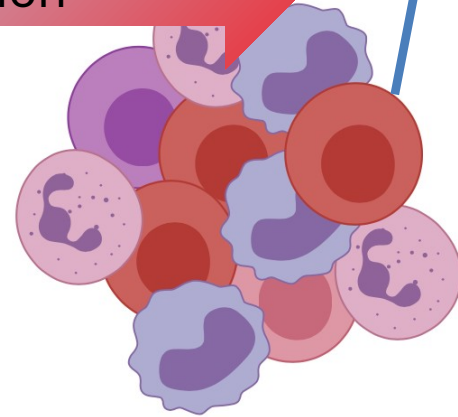


Pathogen control
Immunopathology

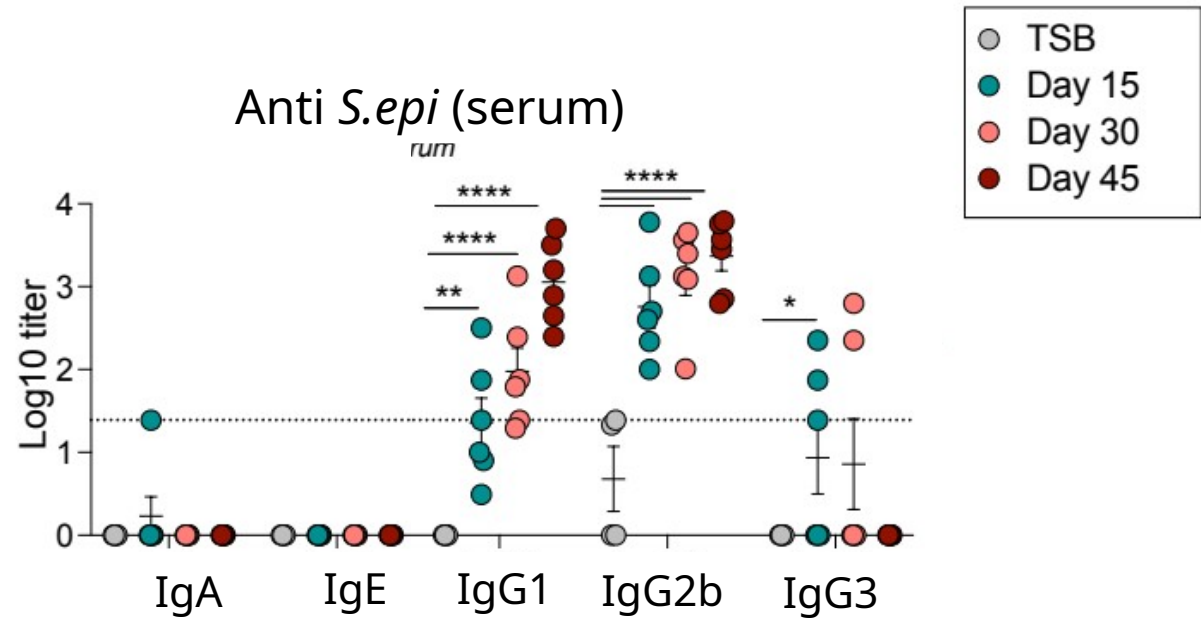
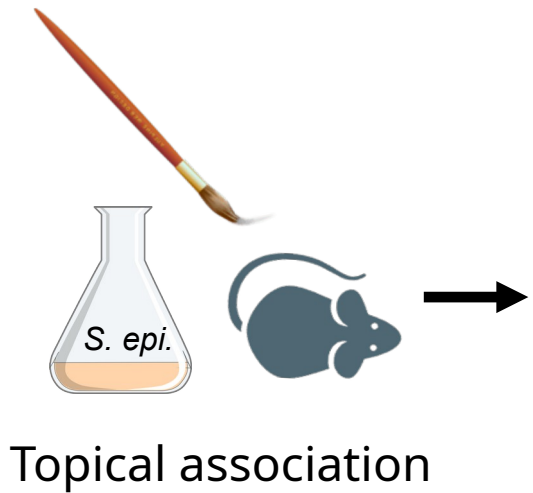
Tissue threshold of activation



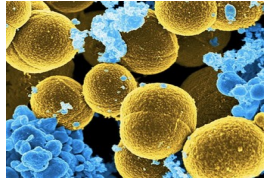
Inta Gribonika



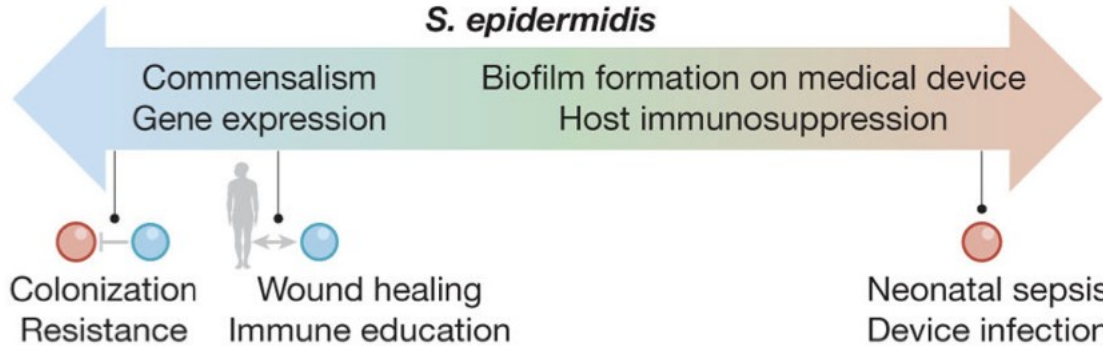
Topical association with a new commensal promotes antibody production



Role of skin commensal antibody responses ?

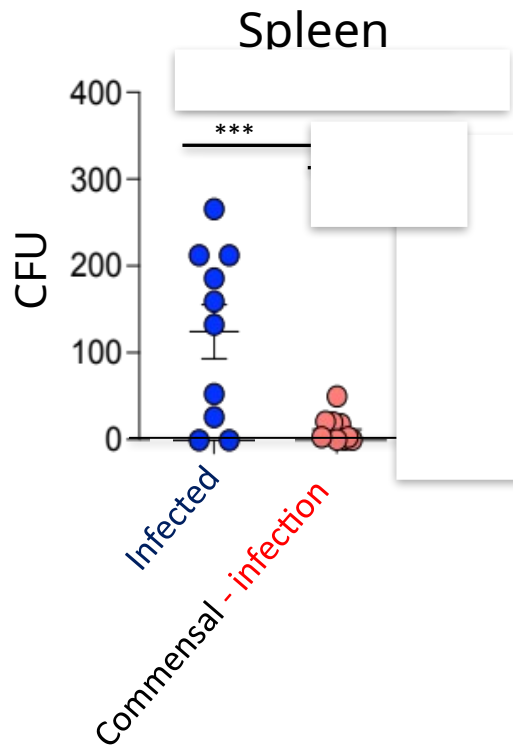
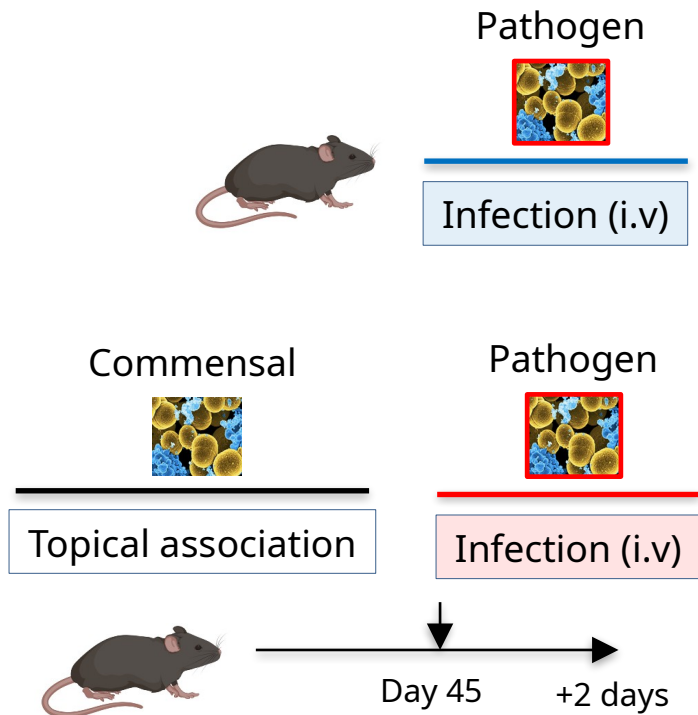


S. epidermidis

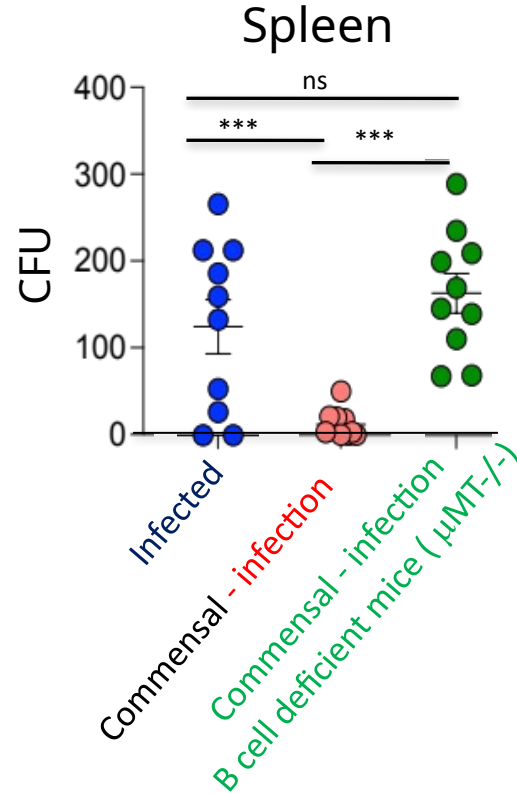
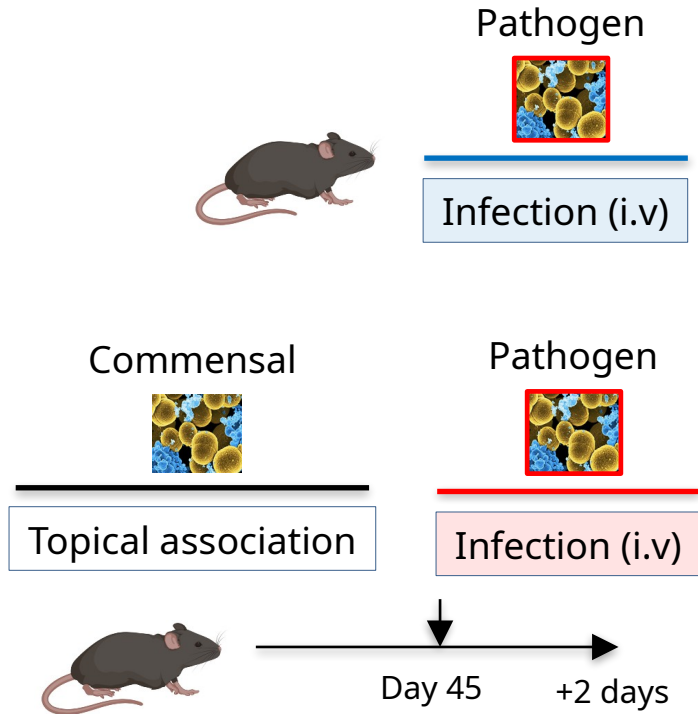


Systemic response:
Control of infection?

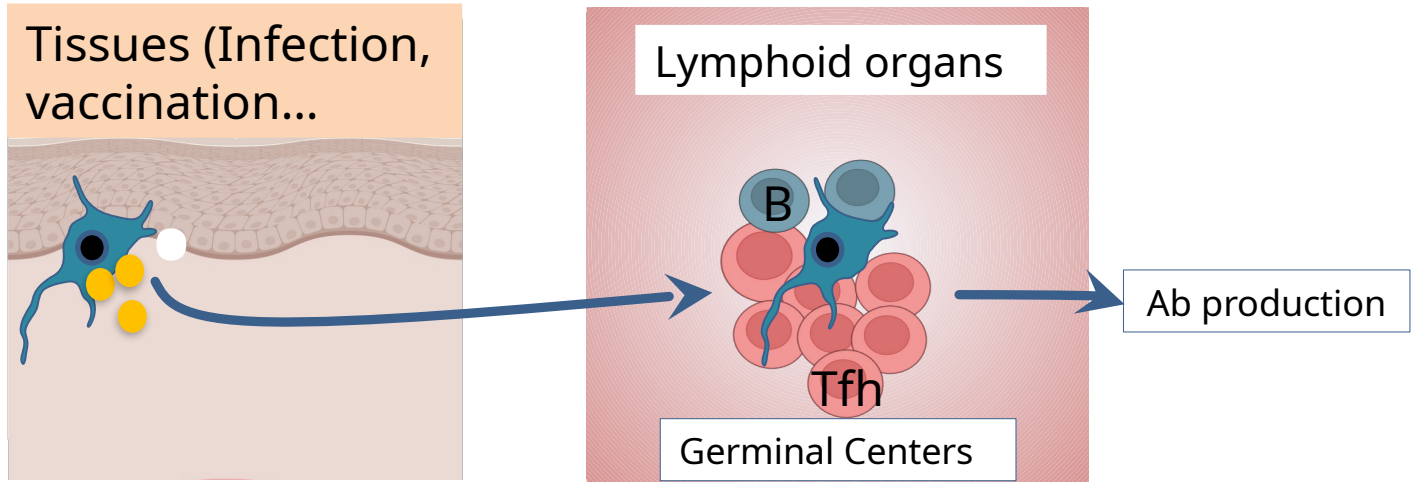
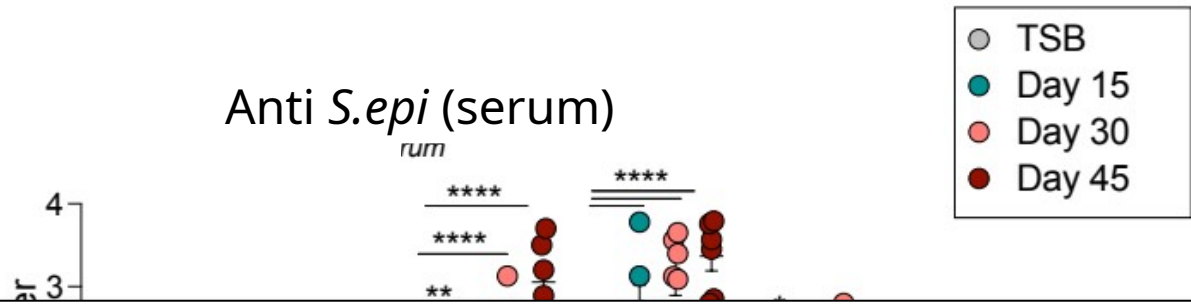
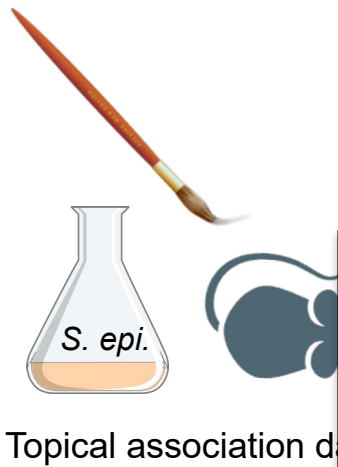
Exposure to a microbe as a commensal protects against subsequent infection



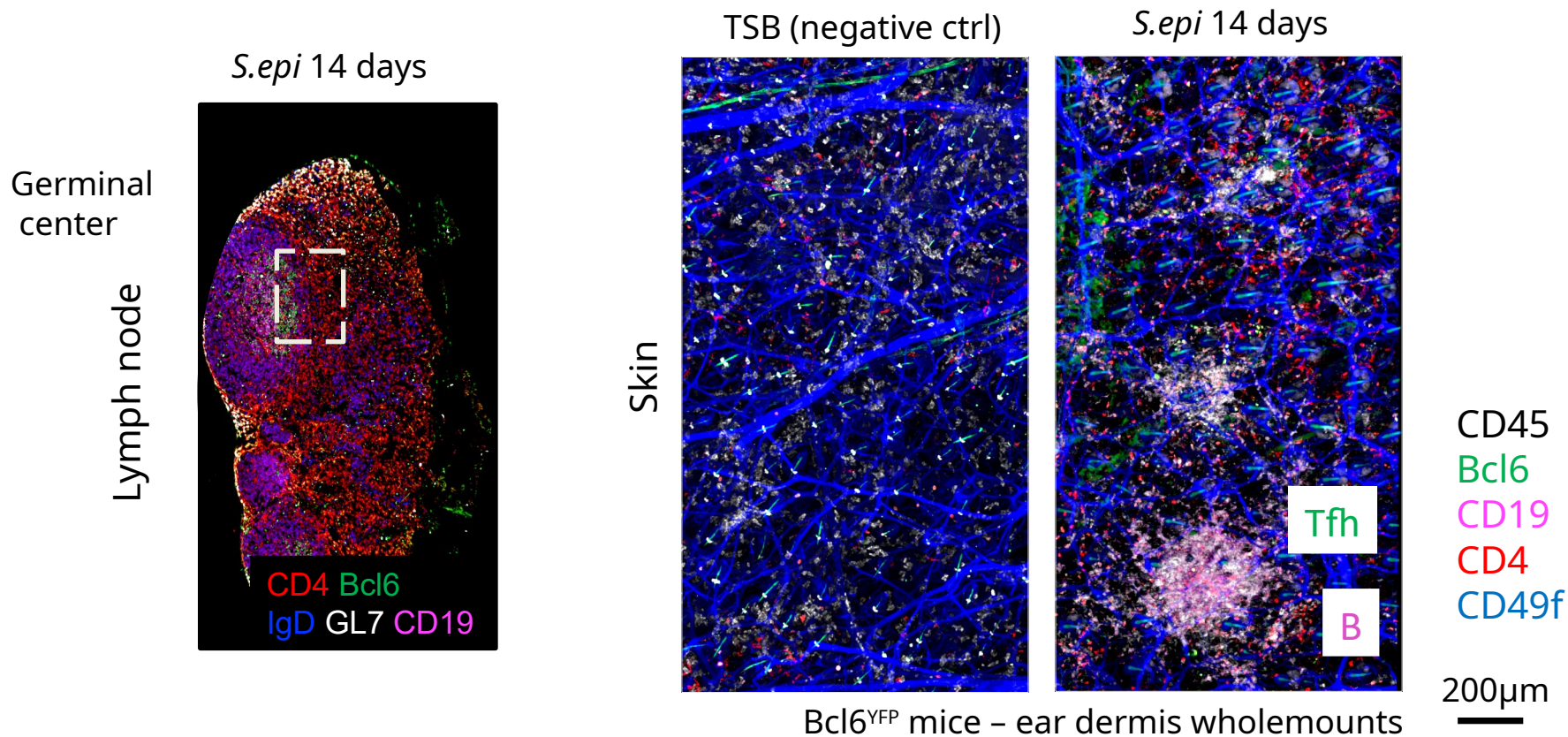
Exposure to a microbe as a commensal protects against subsequent infection in an antibody dependent manner



Topical association with a new commensal promotes antibody production



S.epidermidis association promotes the formation cutaneous tertiary lymphoid organs (TLO)

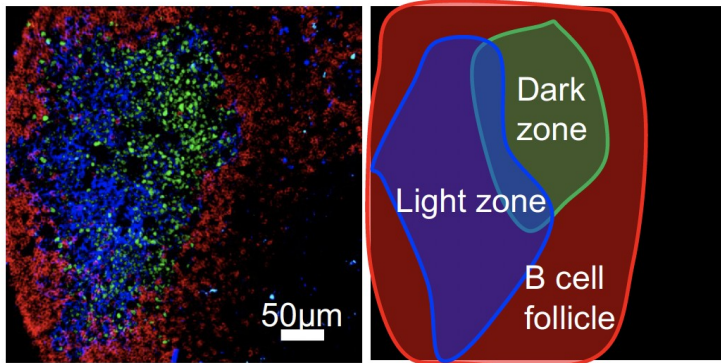


S.epidermidis association promotes the formation cutaneous tertiary lymphoid organs (TLO)

Lymph node

CD19 Bcl6 CD35

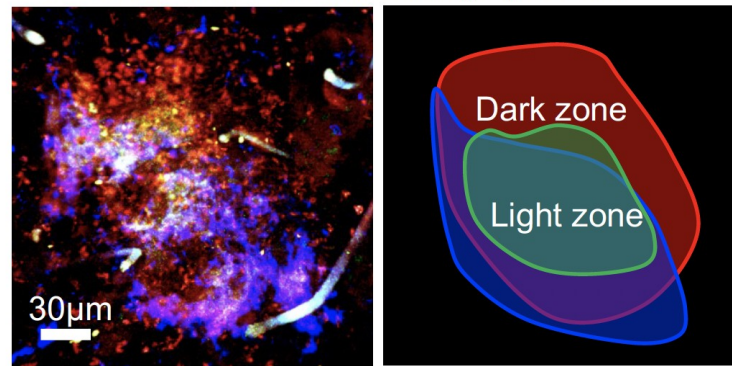
cLN cross-section, 11 μ m thickness; GC



Skin

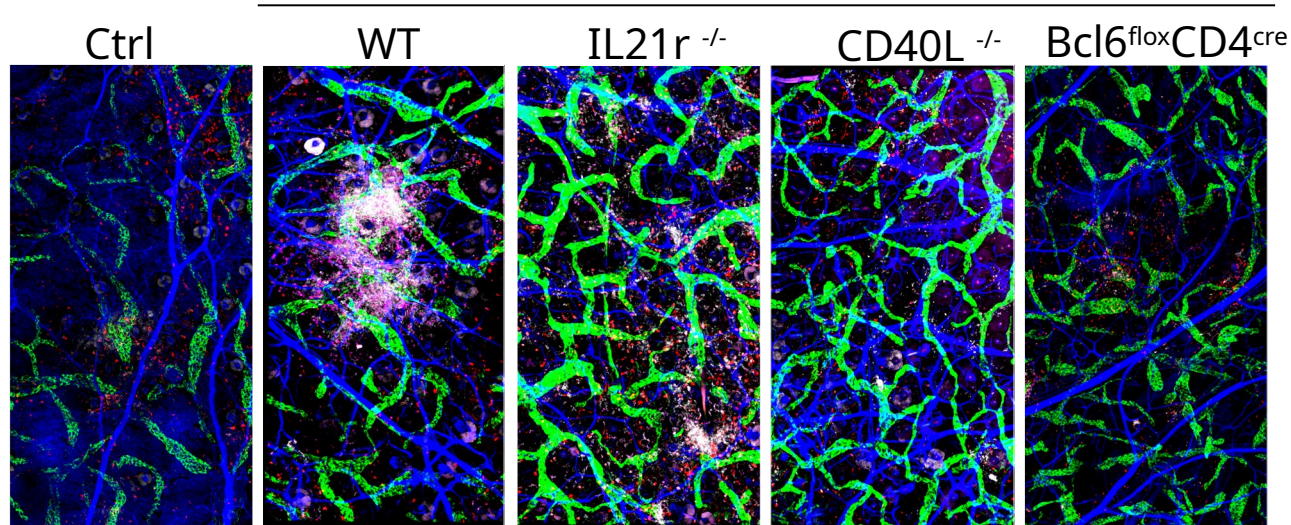
CD19 Bcl6 CD35

Ear dermis wholemount 21 days post-TA

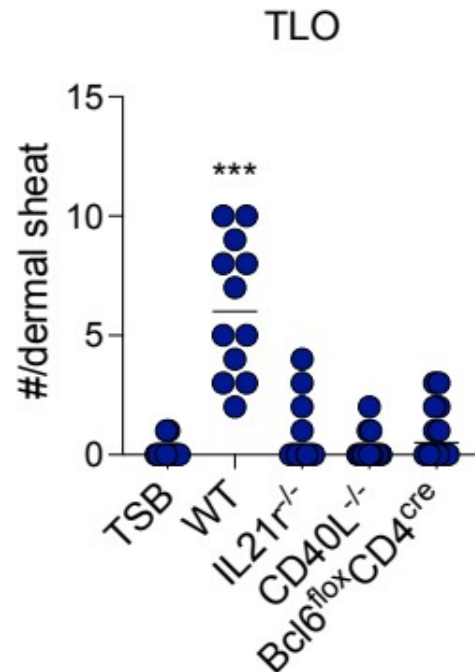


Skin Tertiary Lymphoid Structures (TLO) formation depends on Germinal Center factors

Ear dermis whole-mount 21 days post *S.epidermidis* TA

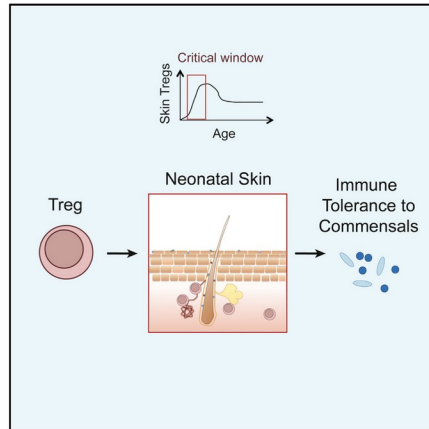


Lyve-1 CD4 CD19 CD45 CD49f



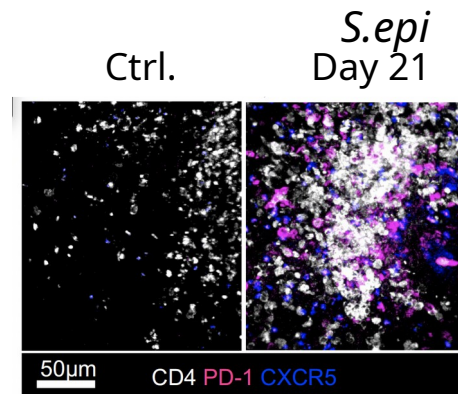
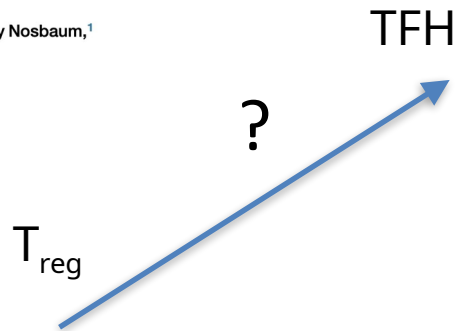
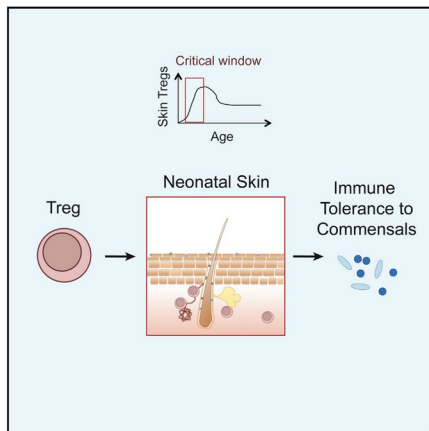
A Wave of Regulatory T Cells into Neonatal Skin Mediates Tolerance to Commensal Microbes

Tiffany C. Scharschmidt,¹ Kimberly S. Vasquez,¹ Hong-An Truong,¹ Sofia V. Gearty,¹ Mariela L. Pauli,¹ Audrey Nosbaum,¹ Iris K. Gratz,² Michael Otto,³ James J. Moon,⁴ Jan Liese,⁵ Abul K. Abbas,⁶ Michael A. Fischbach,⁷ and Michael D. Rosenblum^{1,*}

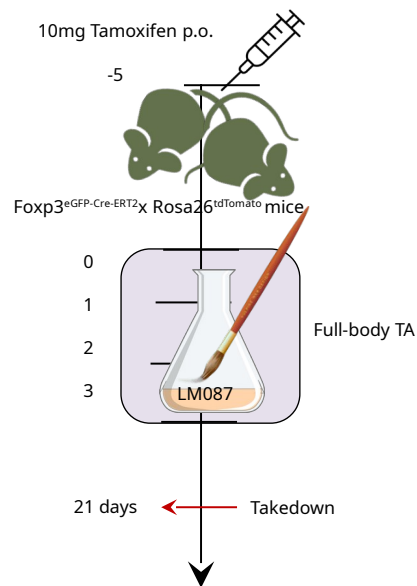


A Wave of Regulatory T Cells into Neonatal Skin Mediates Tolerance to Commensal Microbes

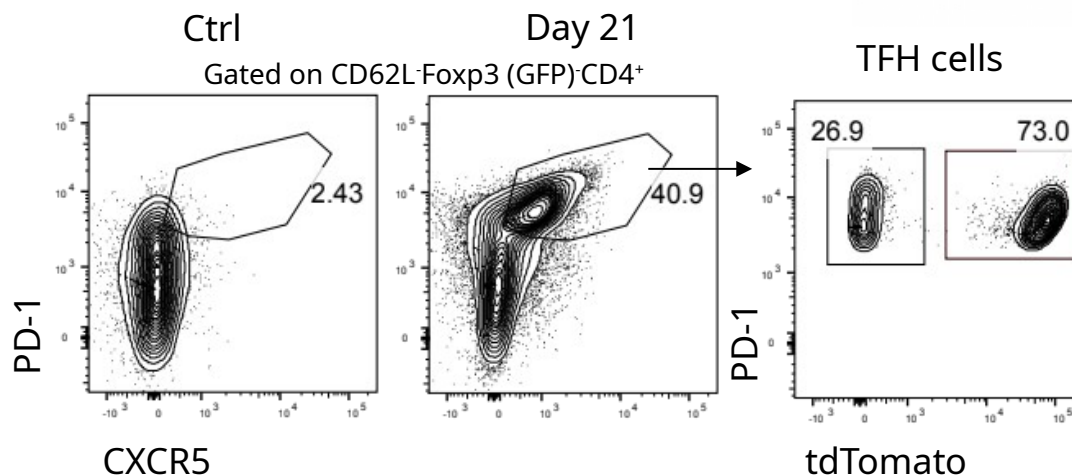
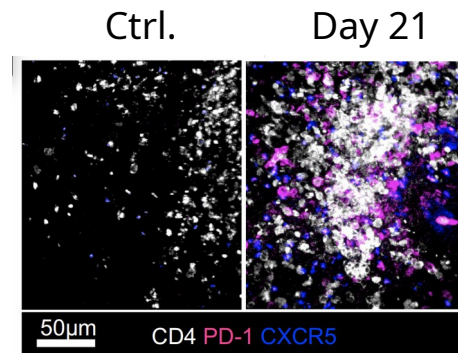
Tiffany C. Scharschmidt,¹ Kimberly S. Vasquez,¹ Hong-An Truong,¹ Sofia V. Gearty,¹ Mariela L. Pauli,¹ Audrey Nosbaum,¹ Iris K. Gratz,² Michael Otto,³ James J. Moon,⁴ Jan Liese,⁵ Abul K. Abbas,⁶ Michael A. Fischbach,⁷ and Michael D. Rosenblum^{1,*}



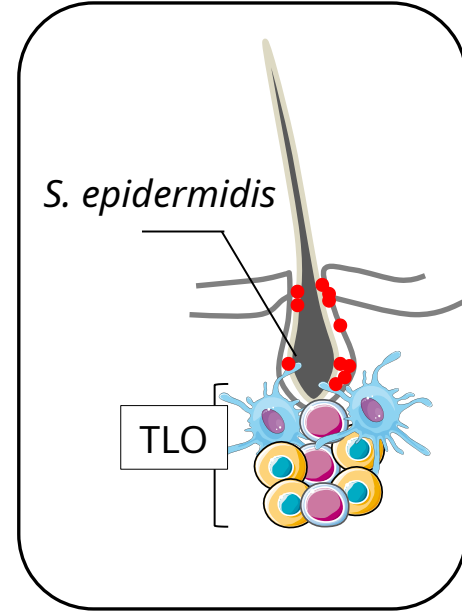
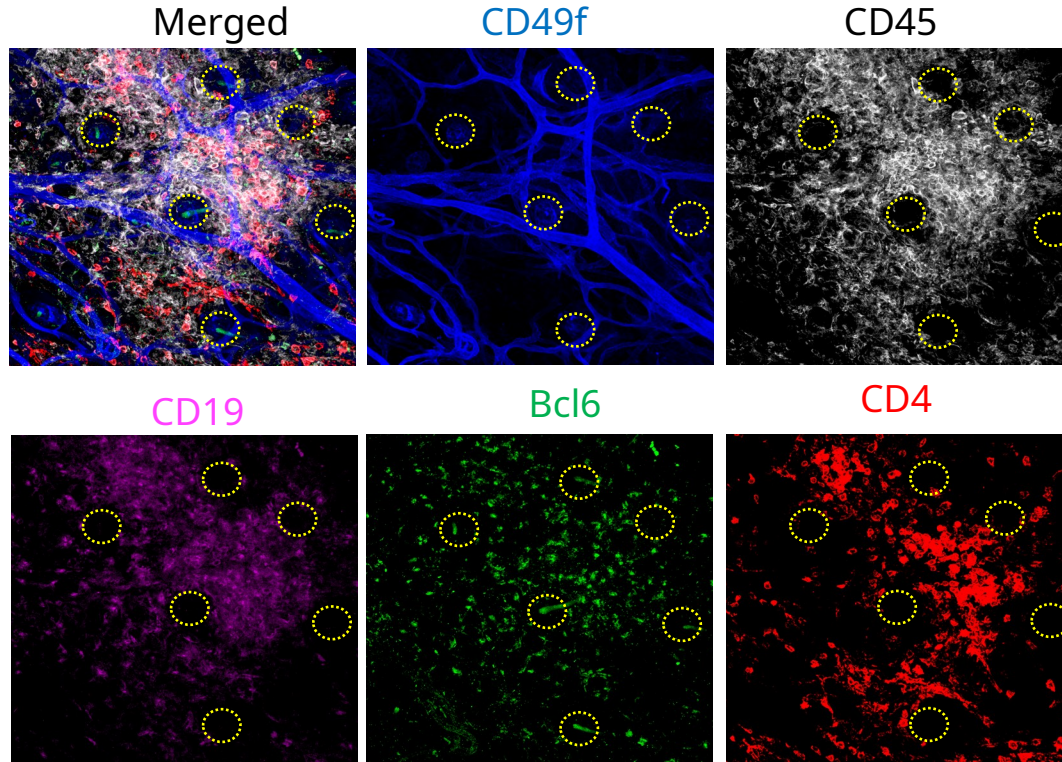
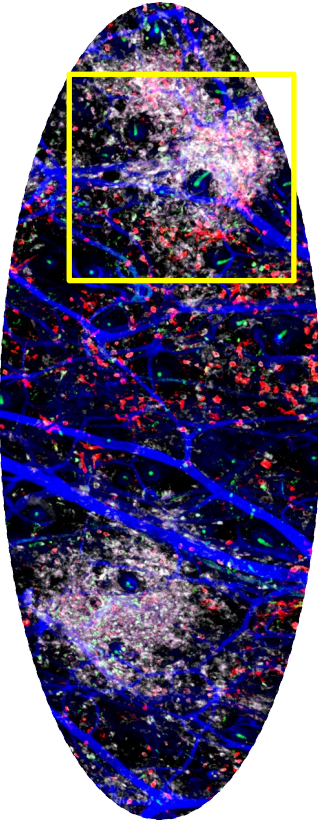
S.epidermidis-induced T follicular helper cells derive from regulatory T cells




Tamoxifen-treated Foxp3^{eGFP-Cre-ERT2}x
Rosa26^{tdTomato} mice



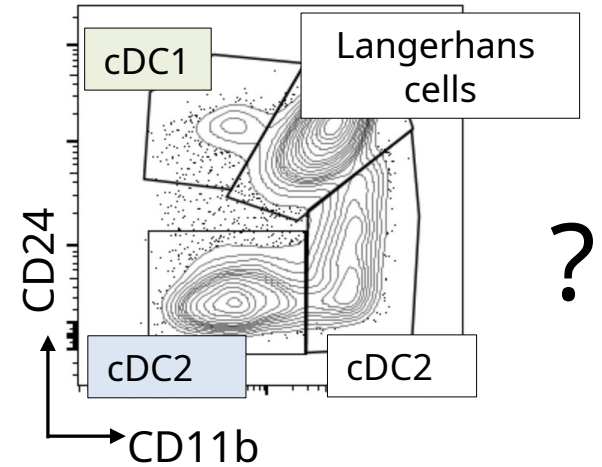
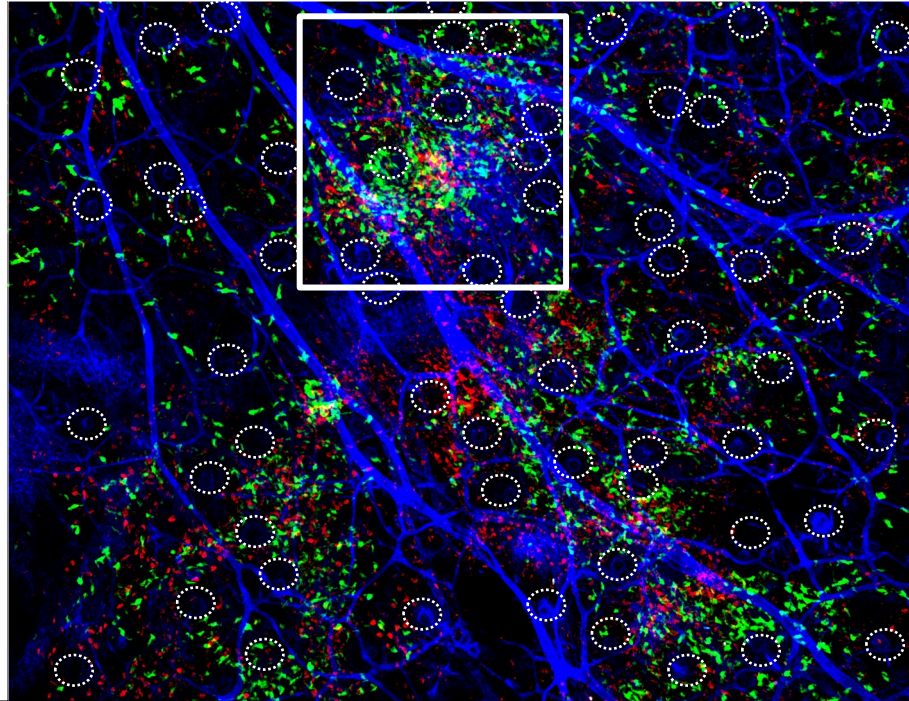
S. epidermidis induced TLO surround hair follicles



 = Hair follicle

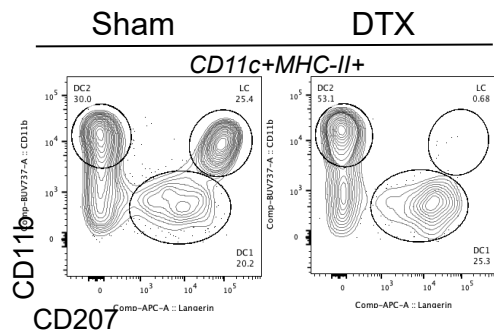
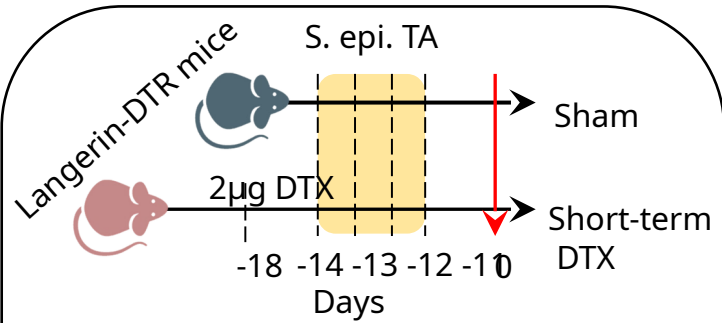
Bcl6^{YFP} mouse- ear dermis
wholemout 21 days post *S. epidermidis*

Antigen-presenting cells survey hair follicles

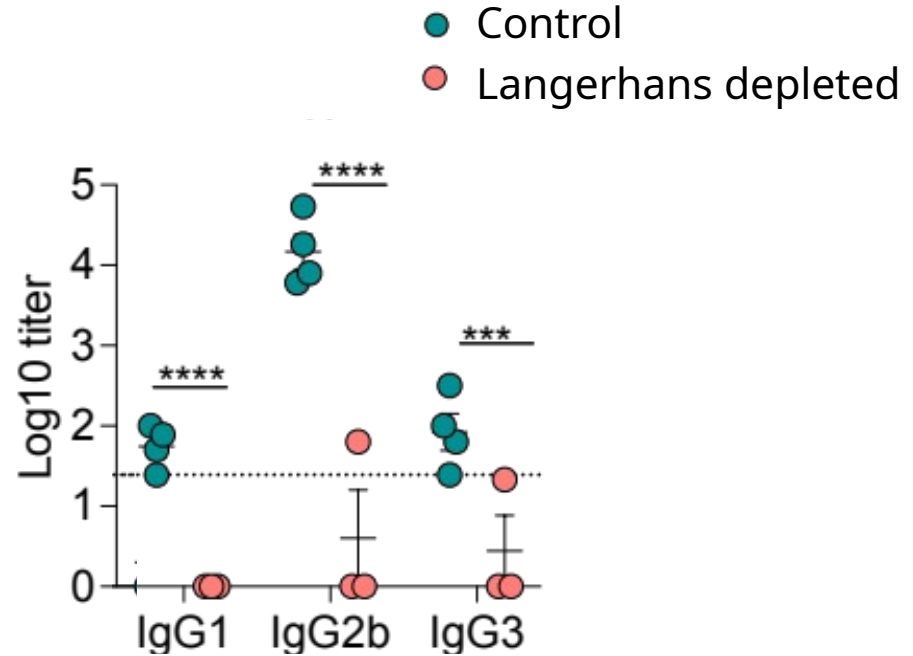
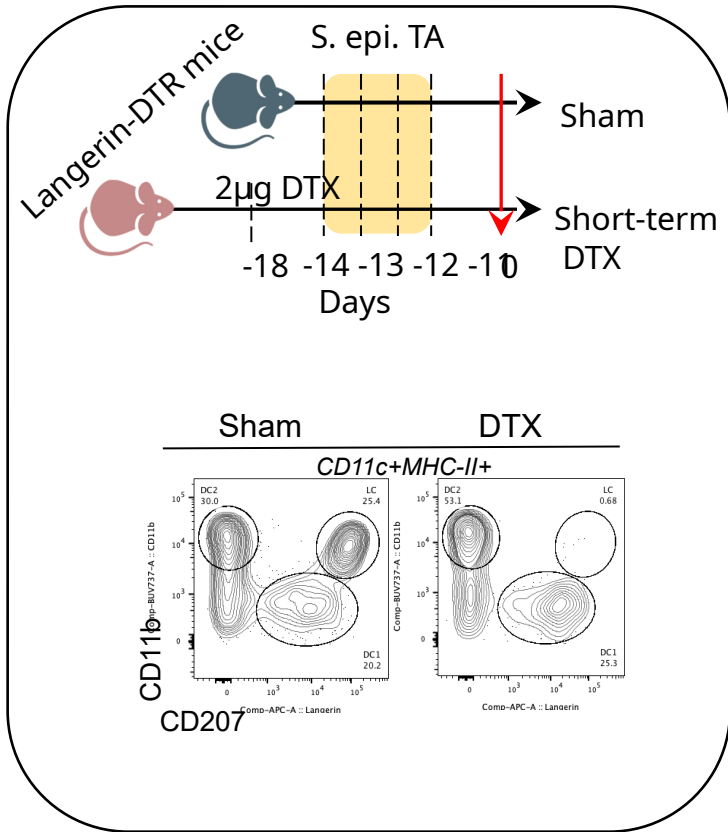


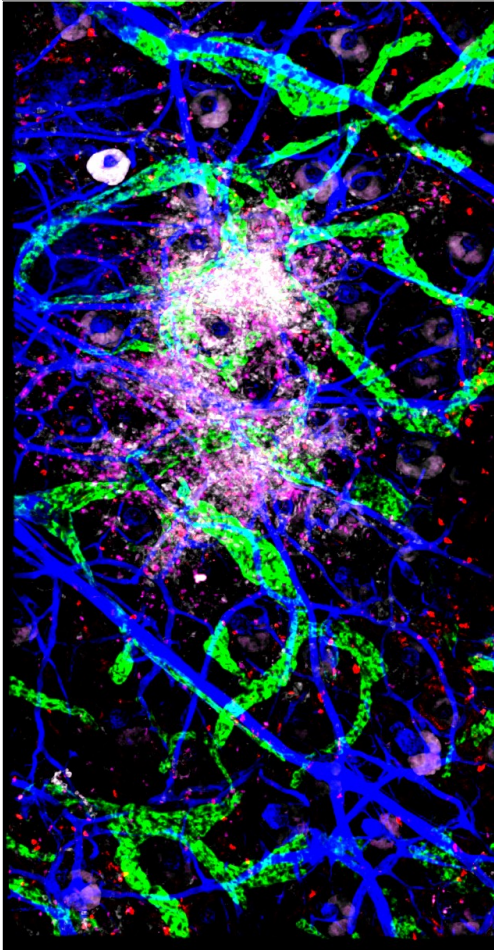
150µm CD11c CD4 CD49f

CD11c^{YFP} mouse— ear dermis wholemount 15 days post *S. epidermidis*

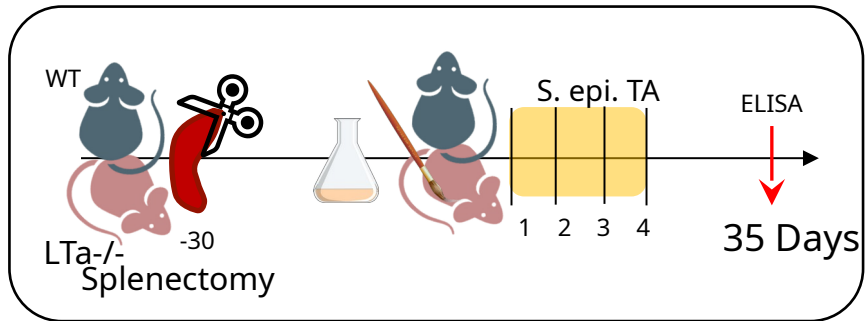


Langerhans cells are required for humoral immunity to skin microbiota

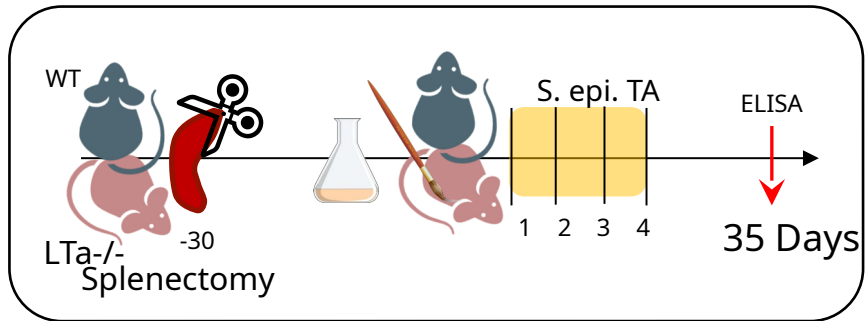




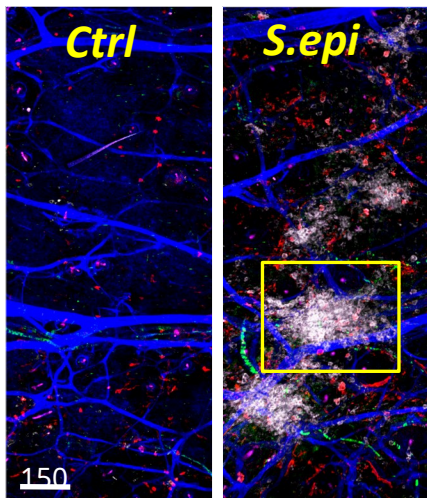
Can the skin microbiota promotes antibody production independently of lymphoid structures ?



S. epidermidis association promotes antibody production independently of lymphoid organs

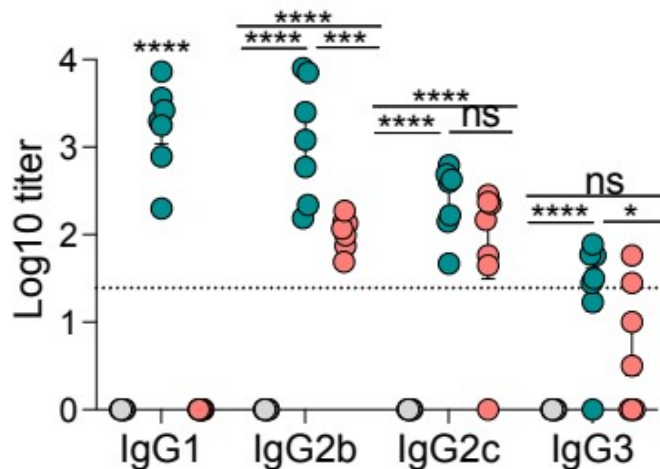


- TSB
 - WT Sham
 - $LT\alpha^{-/-}$ splenectomy
- } TA



$LT\alpha^{-/-}$
splenectomy

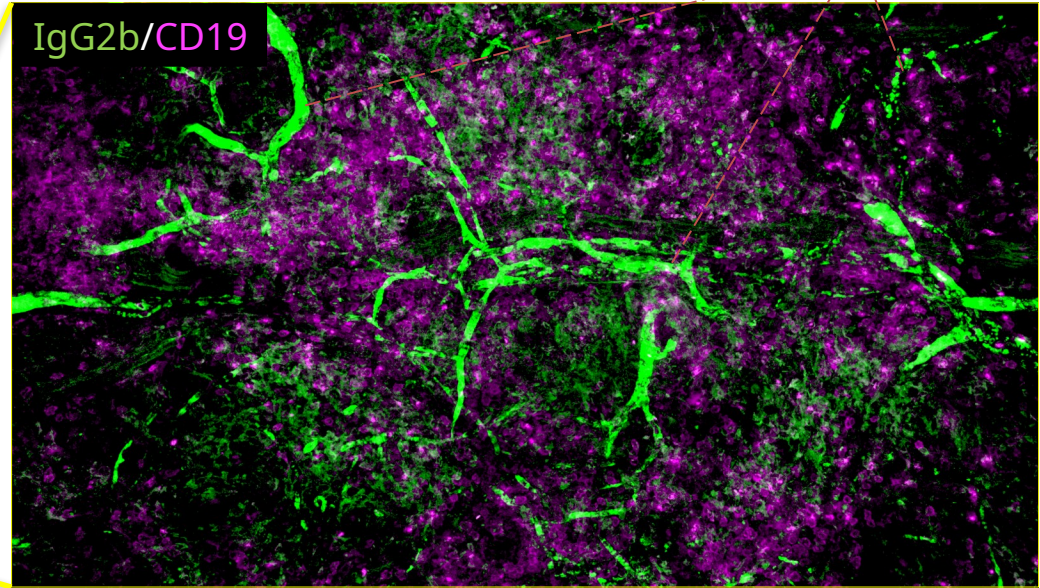
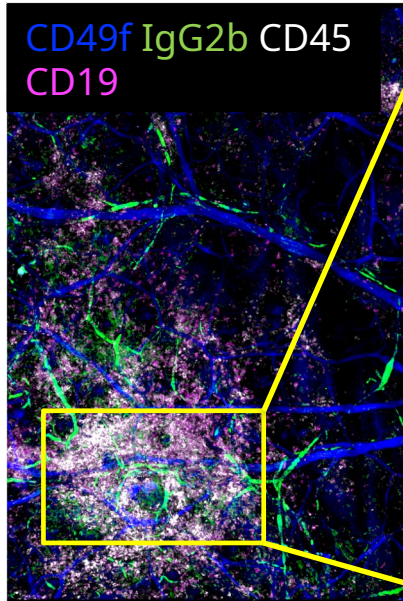
CD45 IgG2b CD4 CD49f CD19



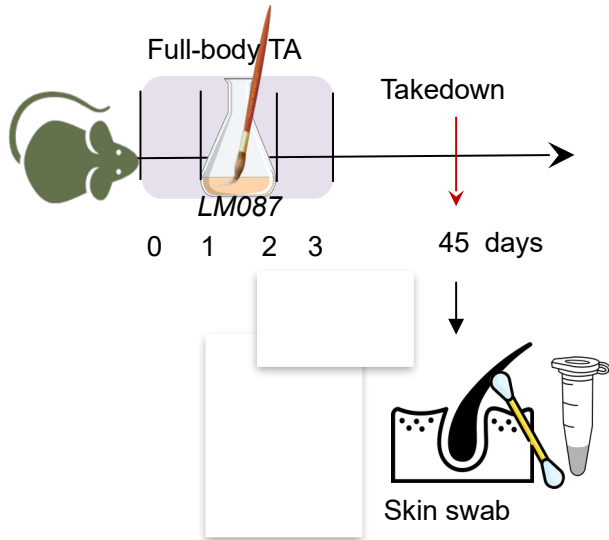
Dermal TLOs secrete IgG2b independently of lymphoid structures

LT $\alpha^{-/-}$
splenectomy

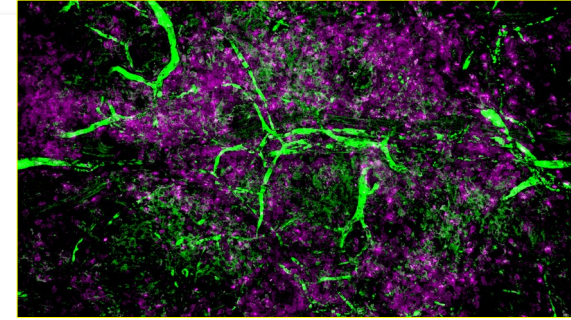
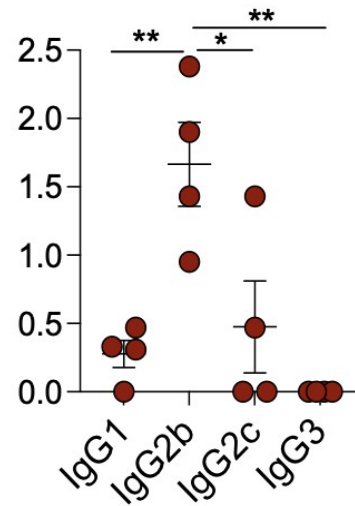
Blood vessels



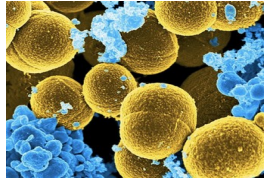
S.epidermidis specific antibodies are released at the surface of the skin



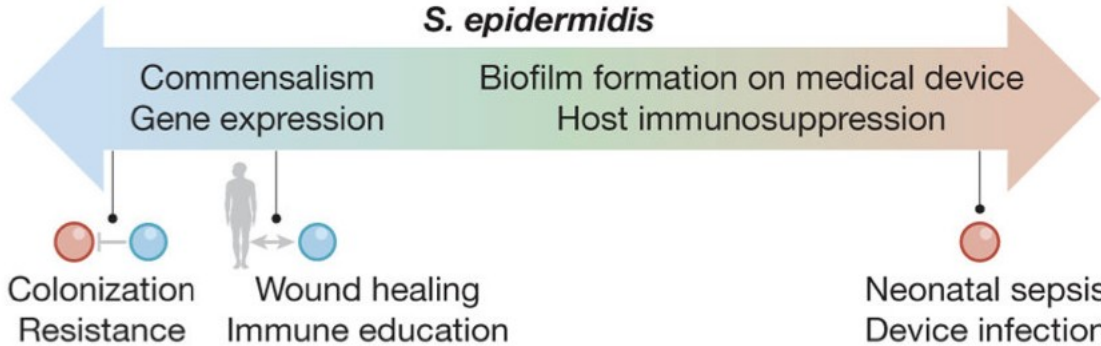
anti-*S.epidermidis*
Skin swab; WT mice



Role of skin commensal local antibody responses ?



S. epidermidis



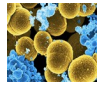
Systemic response:
Control of Infection



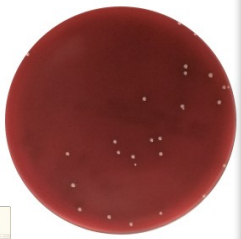
Local antibody response:

Control of symbiotic relationship ?

Topical association



WT

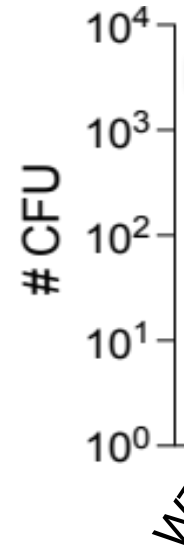


γ

γ

Systemic

Skin Burden



WT

Antibodies are required to limit microbiota burden in the skin

Topical association



WT

$Bcl6^{flx}CD4^{cre}$



Y

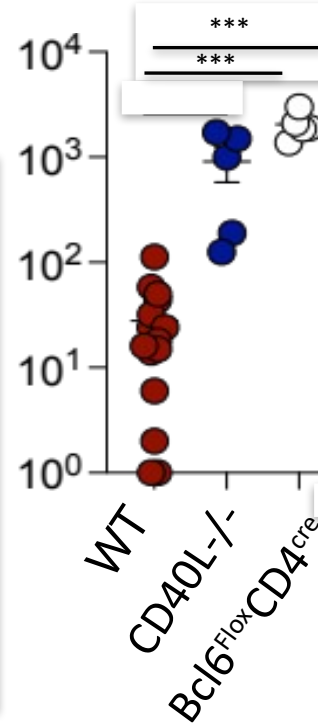
X

Y

X

Systemic

Skin Burden



Skin autonomous production of antibodies is sufficient to control microbiota burden

Topical association



WT

Bcl6^{flox}CD4^{cre}

LT α ^{-/-}



Skin

Y

X

Y

Y

X

X

Systemic

Skin Burden

CFU

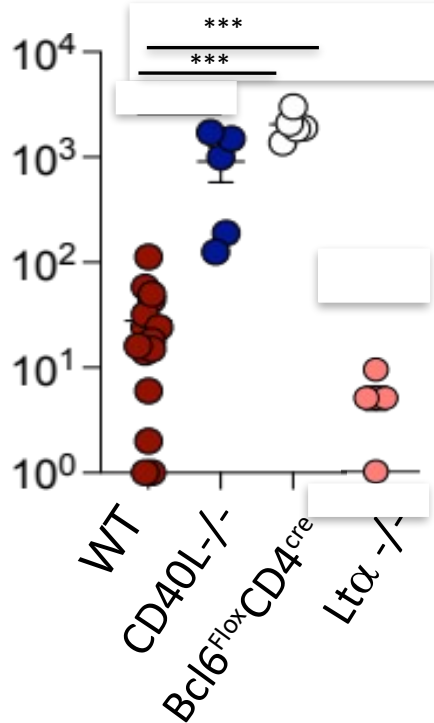
10⁴
10³
10²
10¹
10⁰

WT

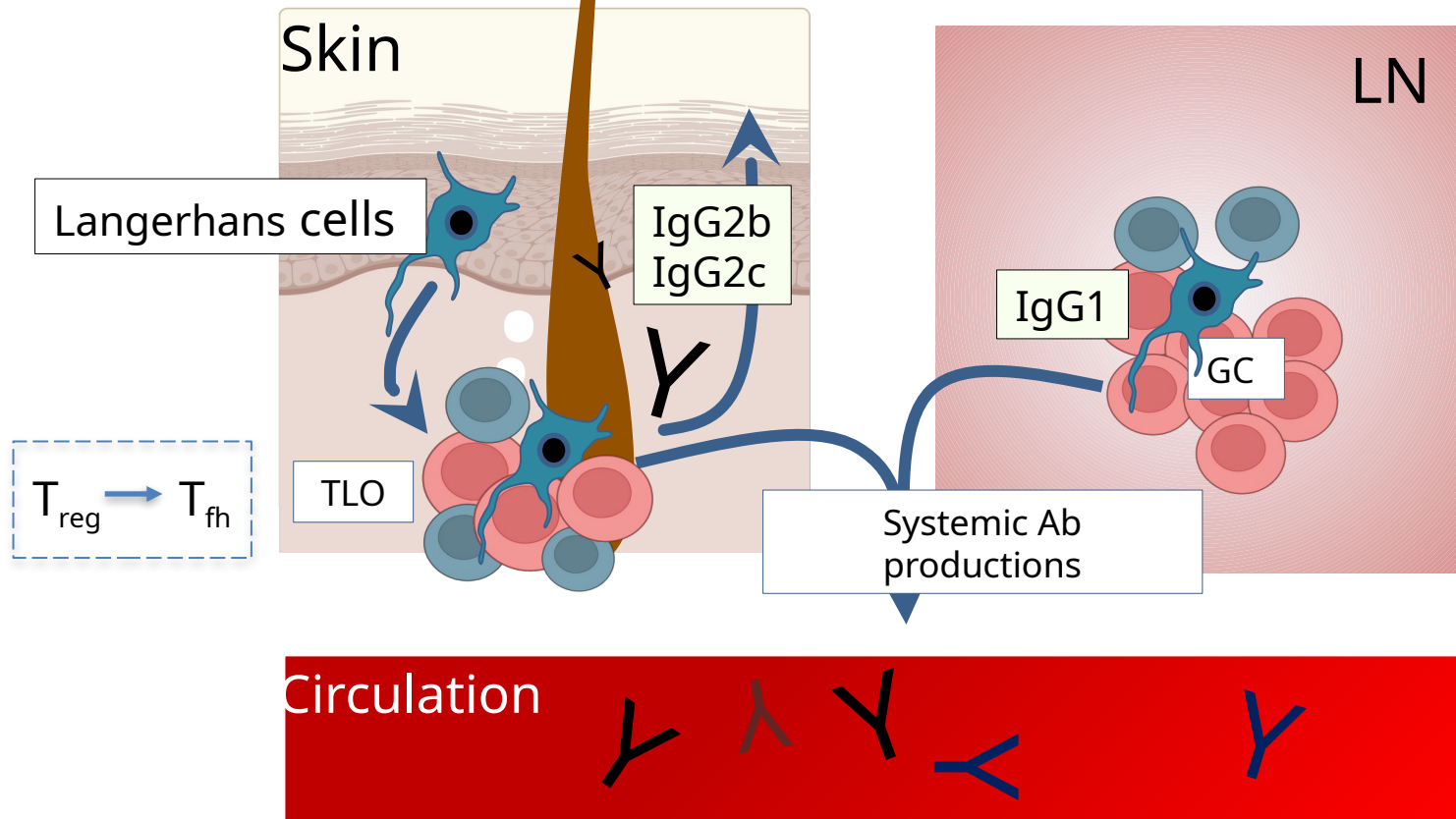
CD40L^{-/-}

Bcl6^{Flox}CD4^{cre}

Lt α ^{-/-}



Compartmentalized immunity to the microbiota



Compartmentalized immunity to the microbiota

Control of microbial burden/ Maintenance of symbiotic relationship

Skin

LN

Langerhans cells

IgG2b
IgG2c

IgG1

GC

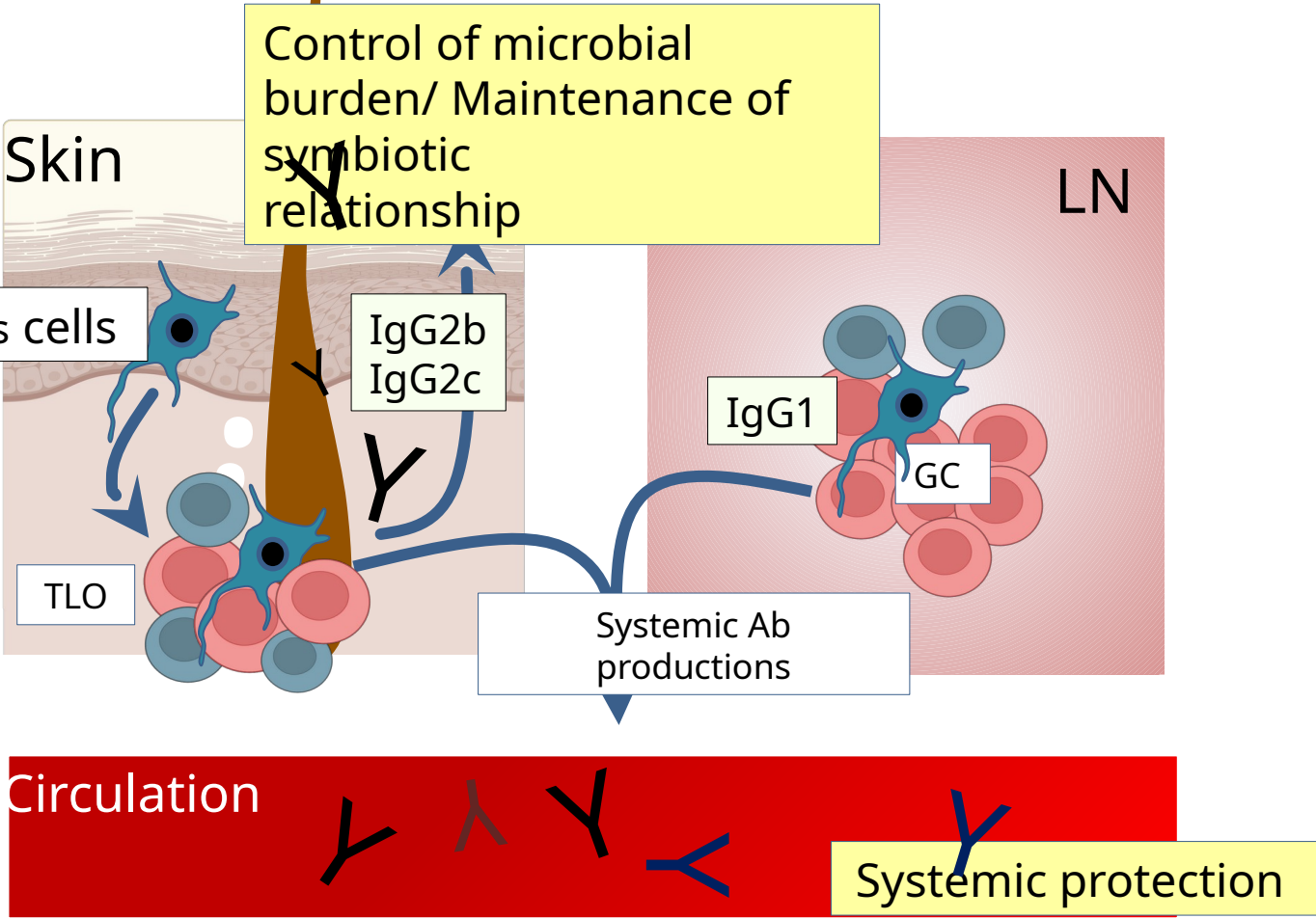
$T_{reg} \rightarrow T_{fh}$

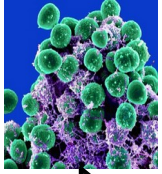
TLO

Systemic Ab productions

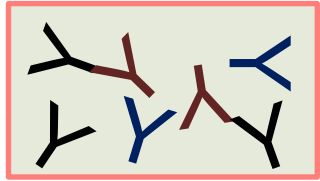
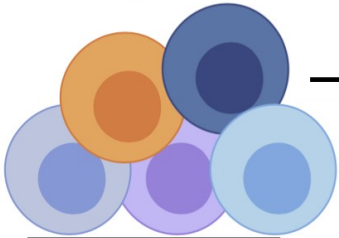
Circulation

Systemic protection





Homeostatic immunity



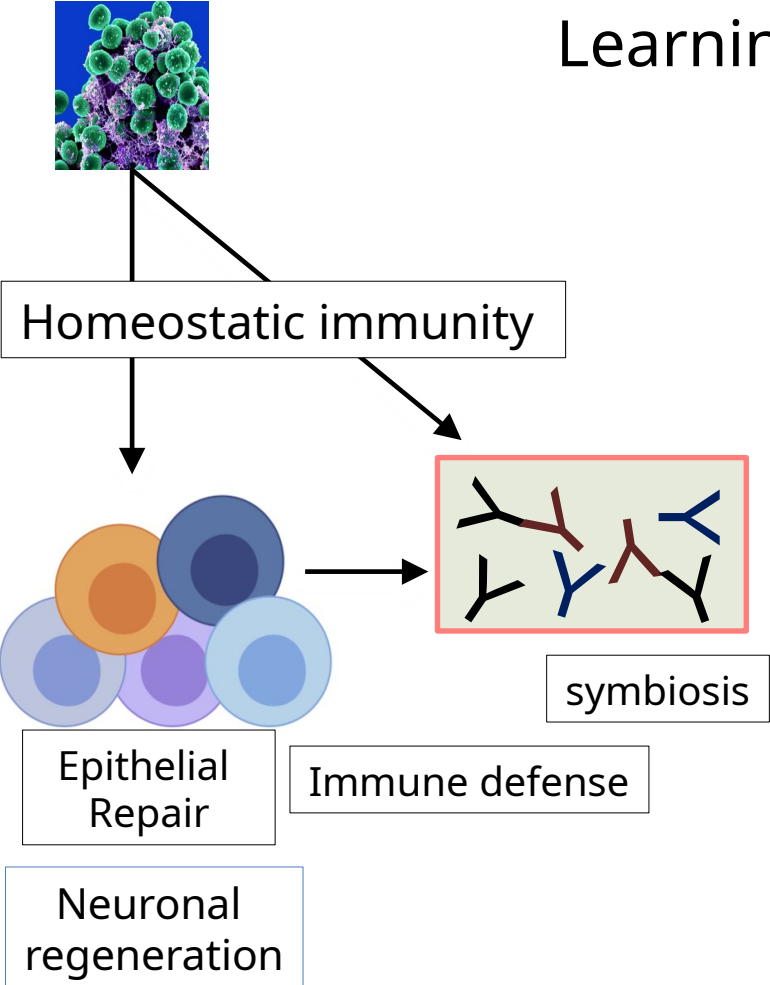
symbiosis

Epithelial
Repair

Immune defense

Neuronal
regeneration

Learning from our evolutionary partners...



Credit: Darryl Leja, NHGRI

MIS section

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Michel Enamorado

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Djalma Lima

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Pete Kulalert

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Harvard

Isaac Chiu

Liwen Deng

NCCIH

Alex Chesler



Skin microbiota-specific T cells promote antimicrobial defense and tissue repair

