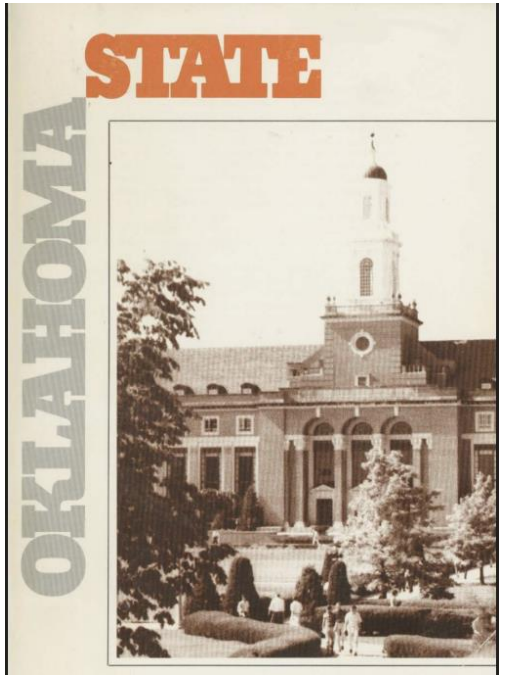
Sensing danger: *How the nervous and immune systems coordinate inflammation*

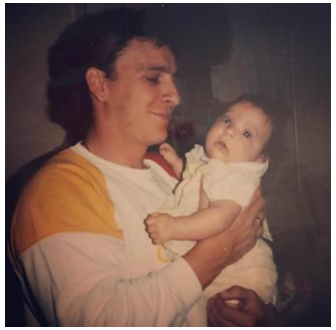
Alejandra Mendoza, PhD
Assistant Professor
Department of Immunology and Microbiology

Front Row Lecture Series
Wednesday, November 5th, 2025

Scripps Research
Immunology & Microbiology

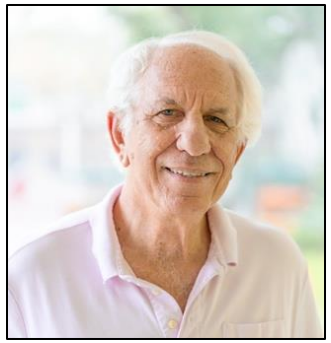
From Stillwater, Oklahoma to Scripps Research
And the many stops in between





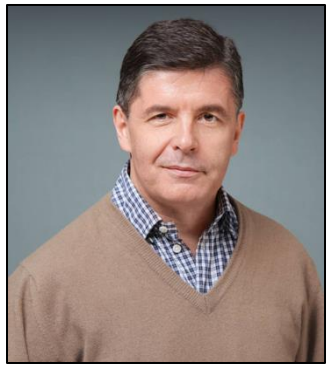
Raul Sojo Montes

From Stillwater, Oklahoma to Scripps Research
And the many stops in between



Michael Gaines
University of Miami
Undergraduate Research and Community Outreach

Gary Kleiner
University of Miami
Miller School of Medicine



Juan Lafaille
New York University
Skirball Institute

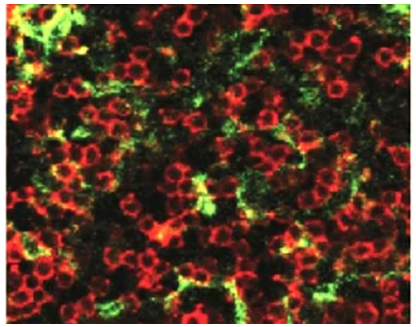
Scripps Research
Immunology & Microbiology

Mendoza Lab

From Stillwater, Oklahoma to Scripps Research
And the many stops in between

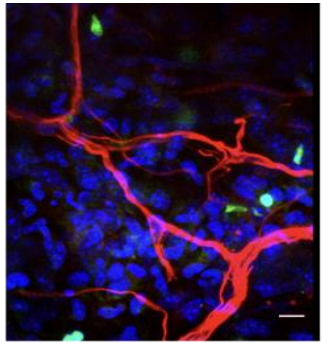
Susan Schwab
New York University
Skirball Institute

Endothelial cell – T cell

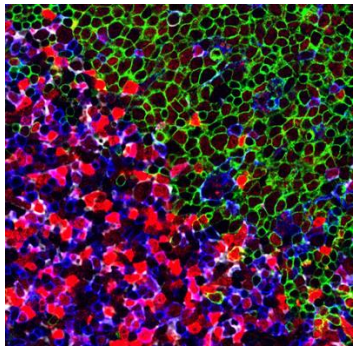


Alexander Rudensky
Memorial Sloan Kettering Cancer Center

Neuro-immune



T and B cell



Scripps Research
Immunology & Microbiology

Mendoza Lab

Scripps Research

Chemists at Scripps Research have won

6 Wolf Prizes

THE NOBEL PRIZE

Scientists here have won

6 Nobel Awards

Scripps Faculty include 4

Howard Hughes Medical Institute Investigators

One has received the **Breakthrough Prize in Life Sciences**

Our faculty hold **29 memberships** in the prestigious National Academies of Sciences, Engineering, and Medicine

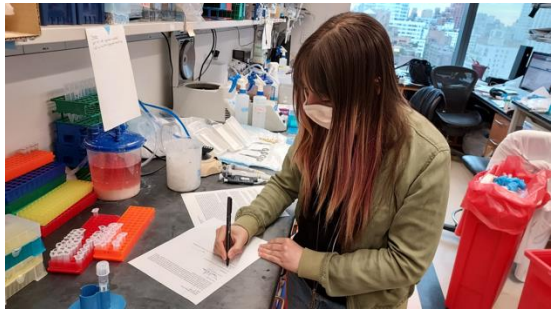
The faculty currently includes 2 MacArthur Fellows

17 FDA-approved drugs and vaccines have arisen from our discoveries

The Skaggs Graduate School of Chemical and Biological Sciences at Scripps Research is consistently ranked among the **10-best graduate programs** of its kind in the nation by *U.S. News & World Report*

Where do I sign?

The beginnings and growth of the Mendoza Lab



November 2022

March 2023

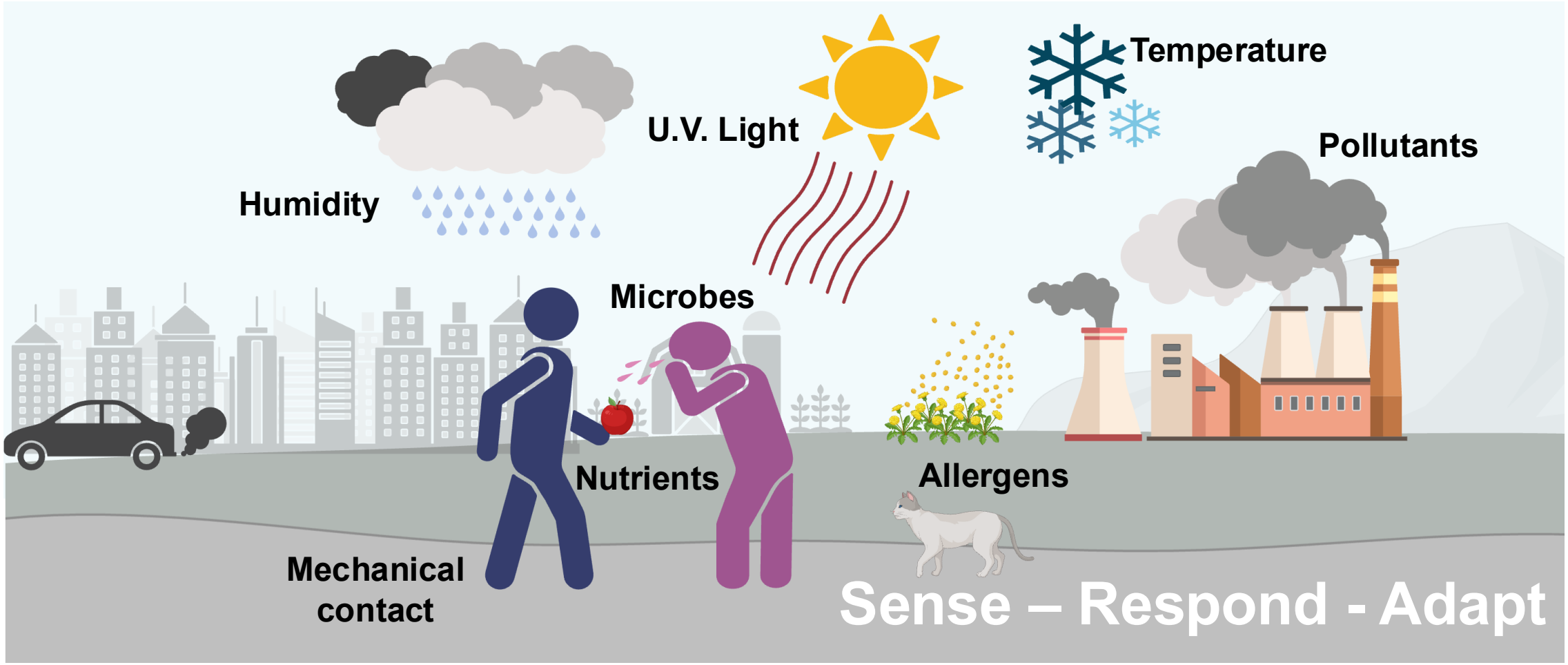
November 2025

Scripps Research
Immunology & Microbiology

Mendoza Lab

Life is not lived in a vacuum

It unfolds at the interface between the organism and its surroundings



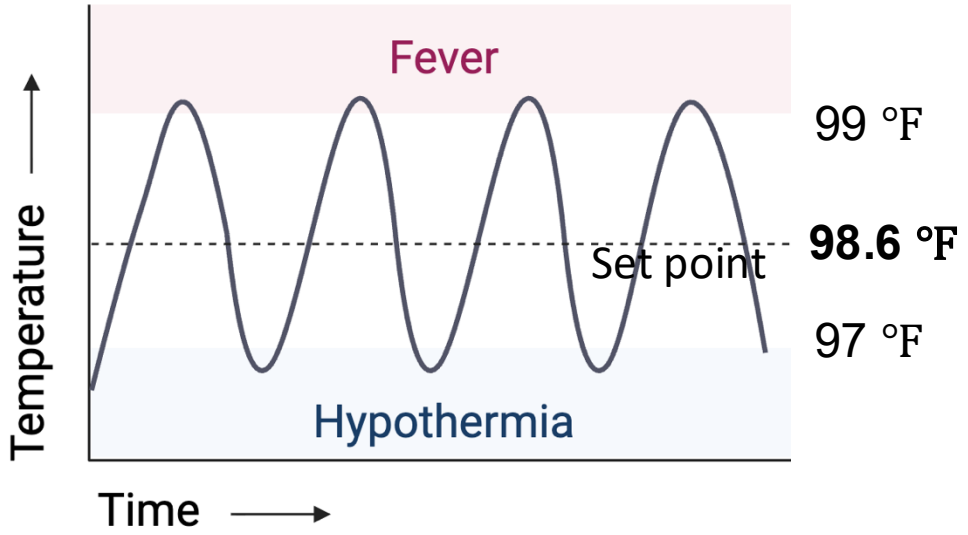
Maintaining internal stability is necessary for organ function

Cell and organs work properly at optimal ranges:
Set Points.

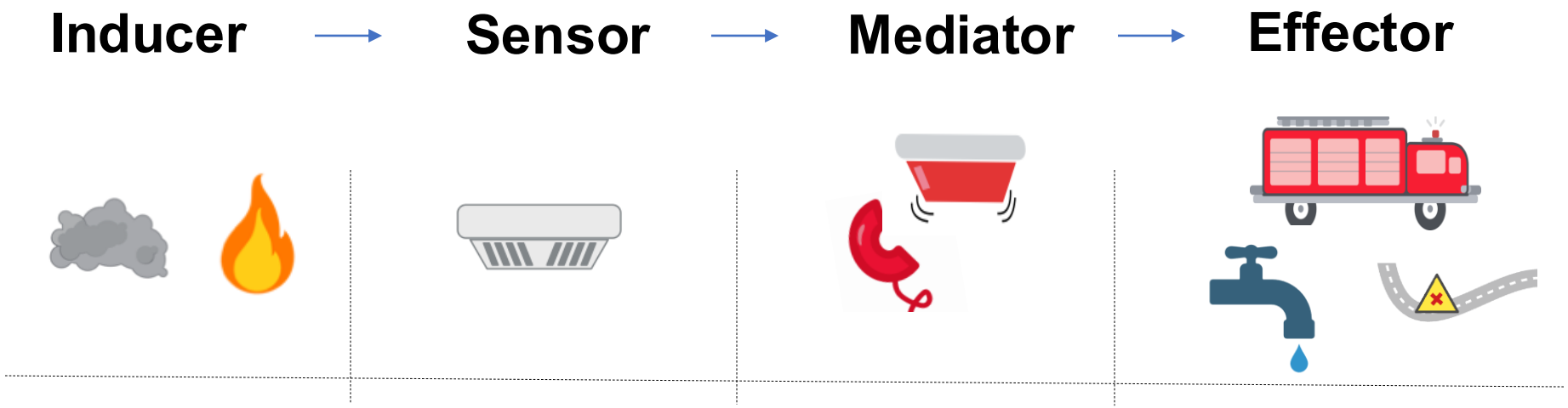
Deviations from set points can impair enzyme activity, cell functions, disrupt cell-cell communication, and **damage tissues**.

Homeostasis is the maintenance of stable internal conditions despite environmental perturbations.

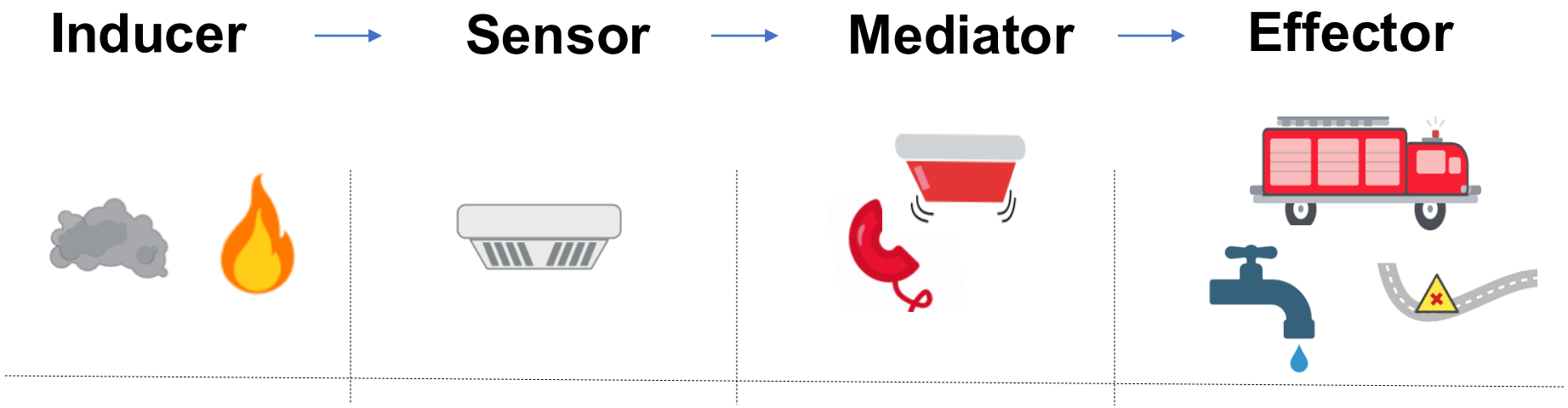
Resilience to **environmental fluctuations.**



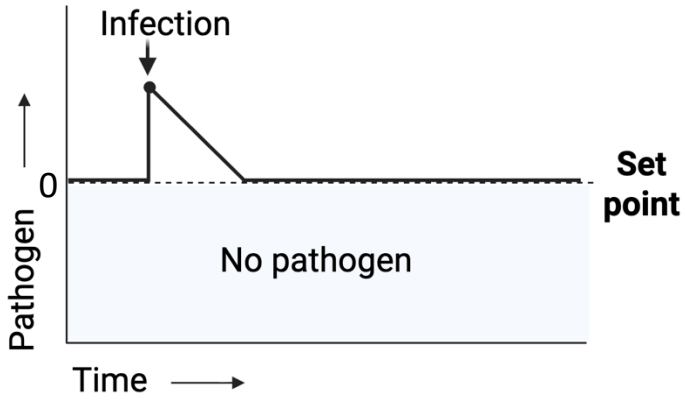
Homeostasis: maintaining stable internal conditions despite environmental perturbations



Homeostasis and **inflammation** are interlinked networks



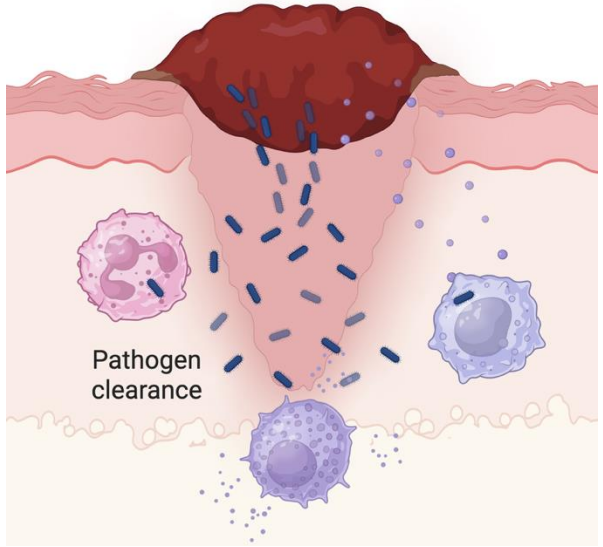
Inflammation: *Inflammare*: “to set on fire” (*in-* = in, *flammare* = to burn)



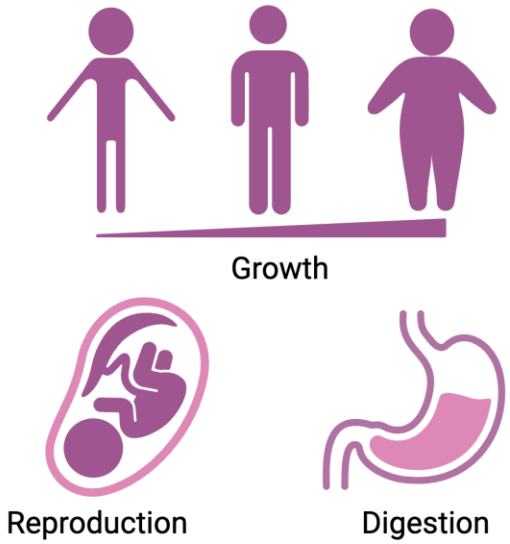
Inflammation seeks to maintain homeostasis

Defense comes at a cost

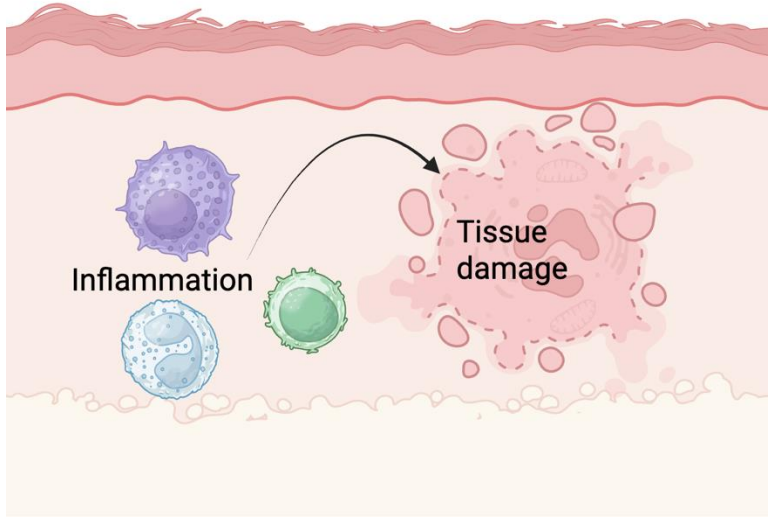
Defense against infection

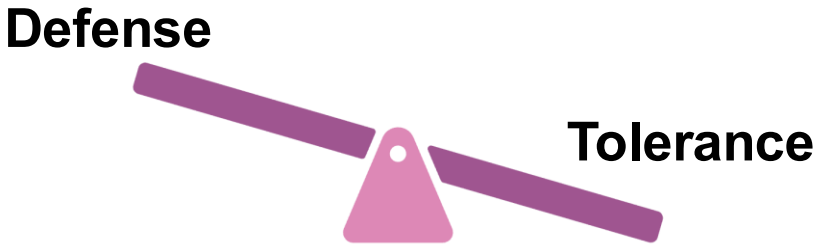


Intentional trade-offs

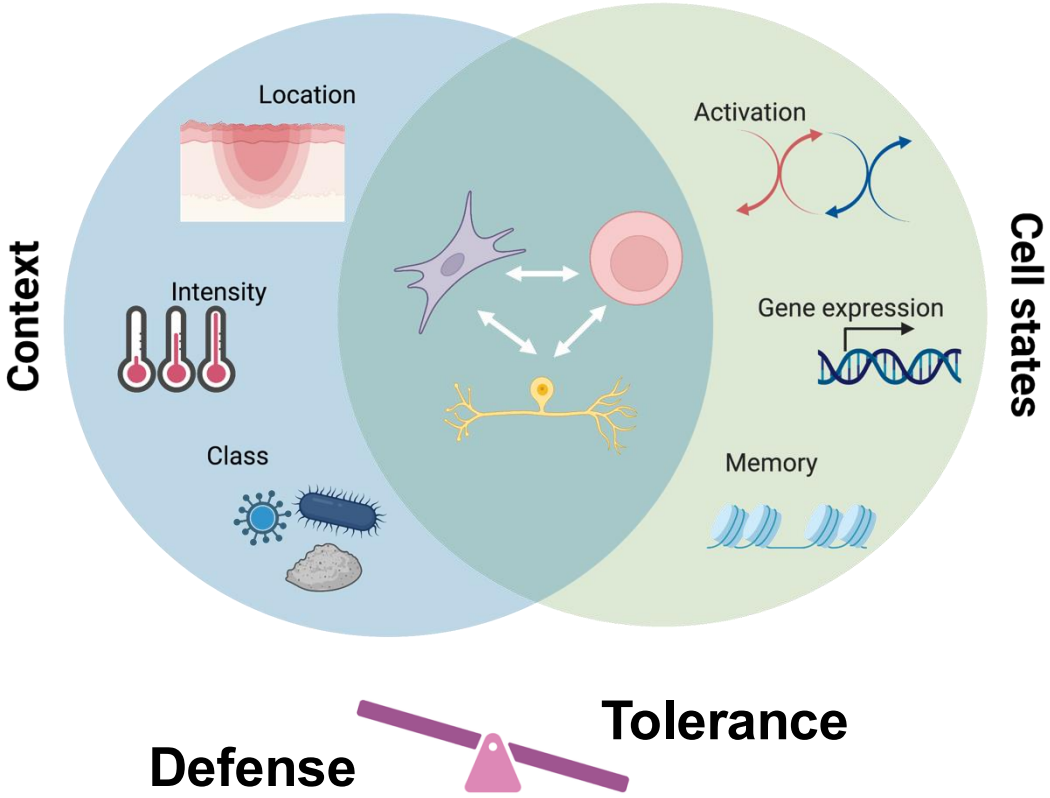


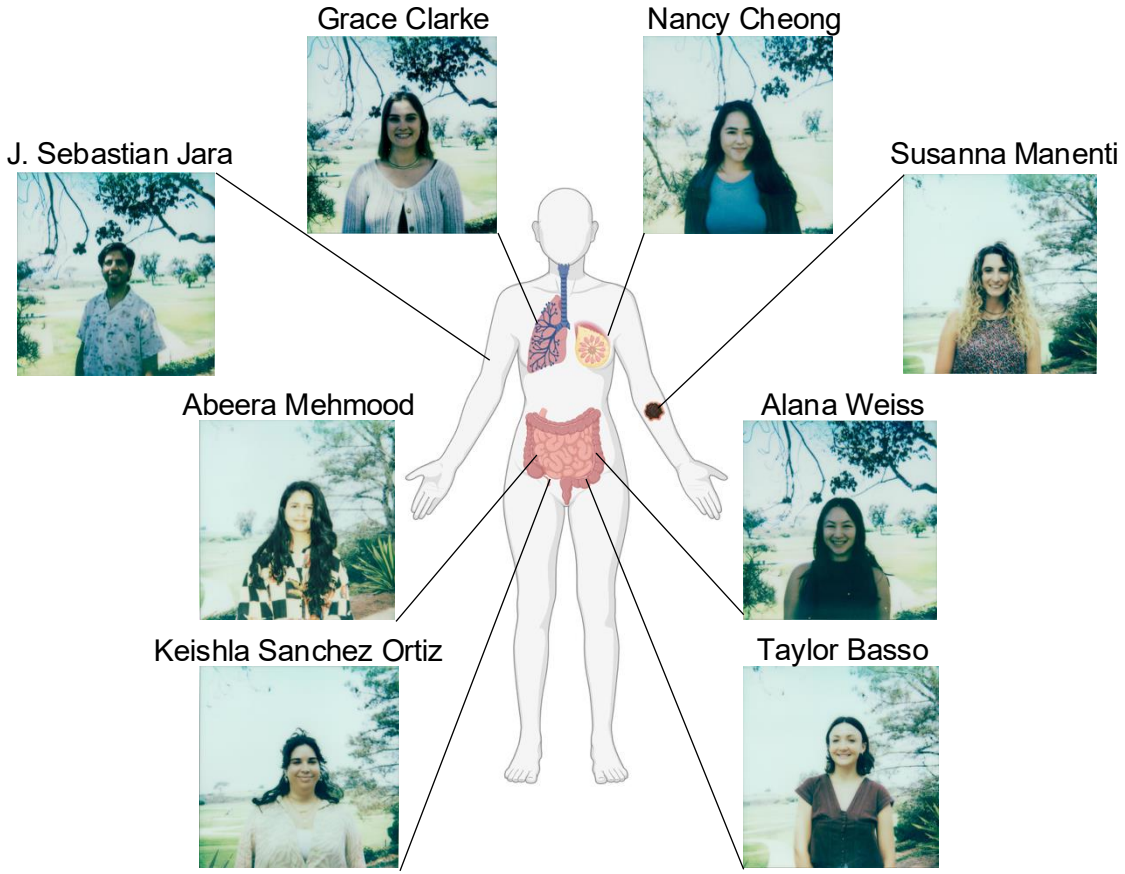
Collateral damage





At environmental interfaces, how do cells work together to maintain homeostasis?





Scripps Research
Immunology & Microbiology

Mendoza Lab

The skin is your body's living shield, **never at rest**

Physical **barrier** to outside world.

Constantly exposed to a variety of stimuli

- Noxious and benign

Major entry site for **pathogens**

- Bacteria
- Viruses
- fungi

Associated with large number of diseases.

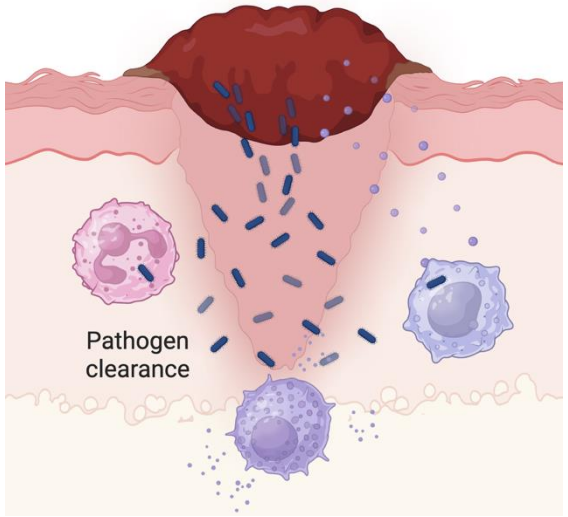
John Hoffman 2024

too little or **too much** inflammation in the skin results disease

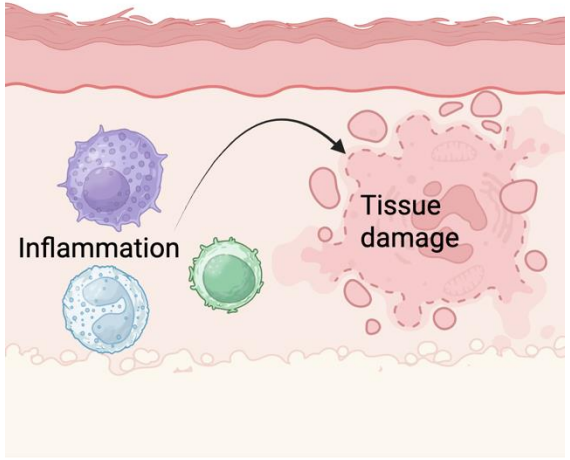
Infectious
Impetigo, cellulitis
Herpes (simplex, zoster)
Warts, Candidiasis, molluscum contagiosum
Athlete's foot, ringworm
Scabies, leishmaniasis

Neoplastic / Cancer
Basal cell carcinoma
Squamous cell carcinoma
Melanoma
Actinic keratosis
Cutaneous lymphomas

Defense

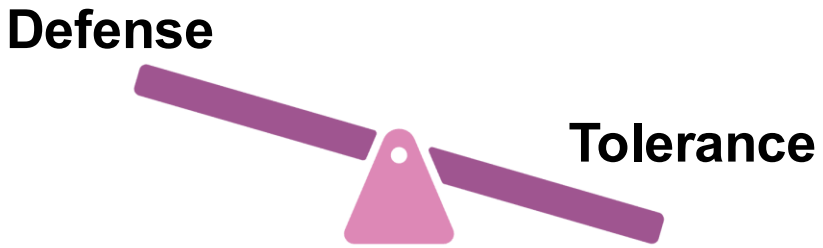


Collateral damage



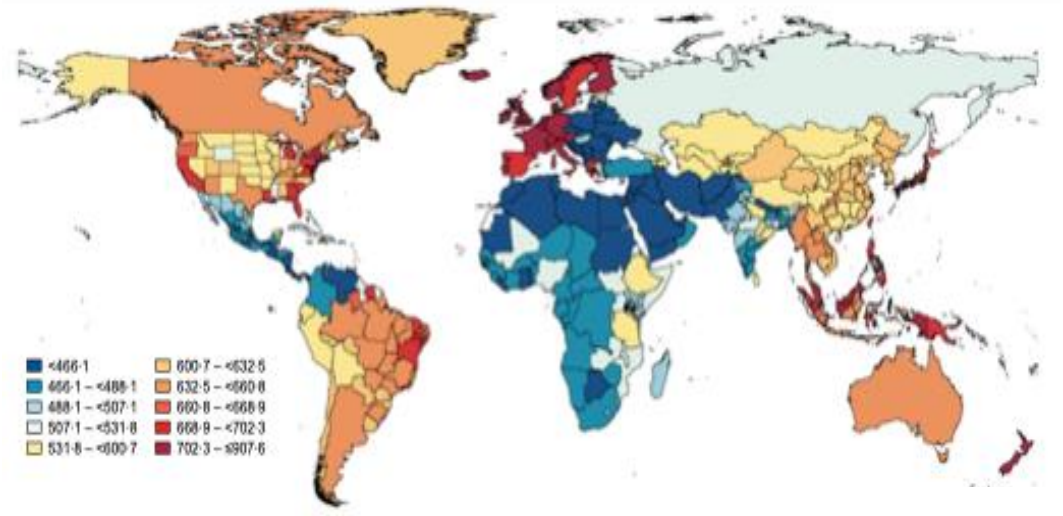
Inflammatory / Autoimmune
Psoriasis
Atopic & contact dermatitis
Vitiligo
Lupus erythematosus
Scleroderma
Bullous pemphigoid, pemphigus vulgaris

Sensory / Neurocutaneous
Neuropathic pain syndromes
Post-herpetic neuralgia
Chronic itch disorders

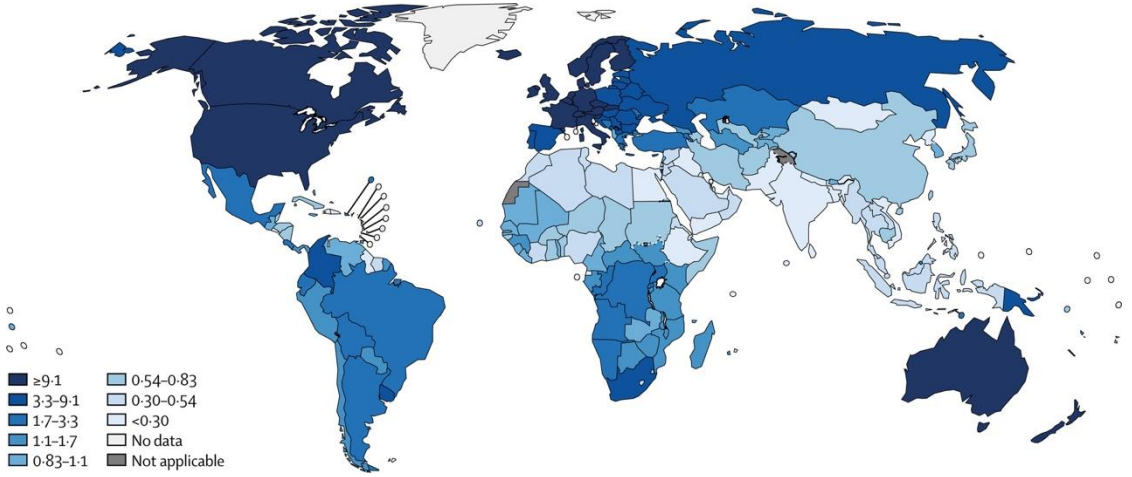


too little or **too much** inflammation in the skin results disease

4.86 billion cases of skin diseases



6.64 million cases of skin cancers



Skin Disorders and cancer are a worldwide burden

Global Health Metrics, *The Lancet* Vol 396, 2020
World Health Organization, *Executive Board 156th session Feb 2025*
C. Flohr & R. Hay *British Journal Dermatology 2021*
L. Zhou Sci Rep 2025

Scripps Research
Immunology & Microbiology

Mendoza Lab

How do neuro-immune interactions regulate skin immune homeostasis?

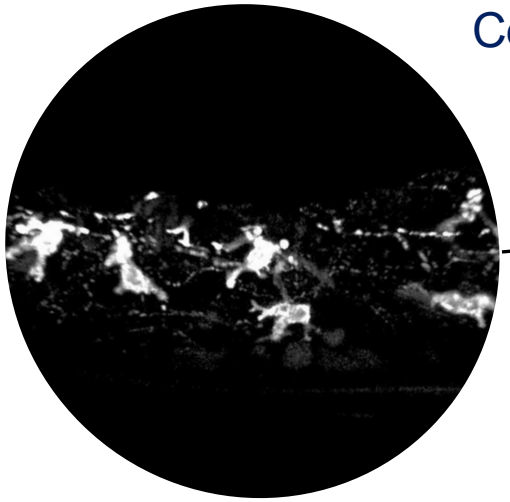
Pathogens

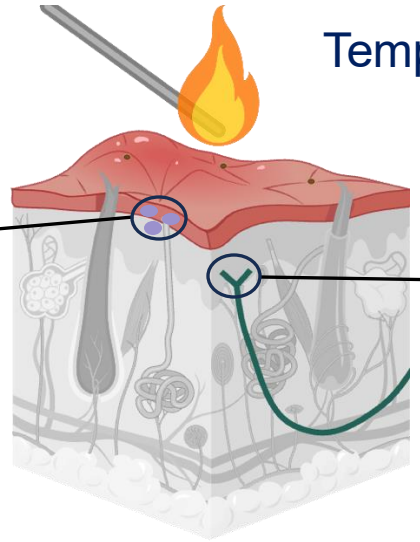
Commensals

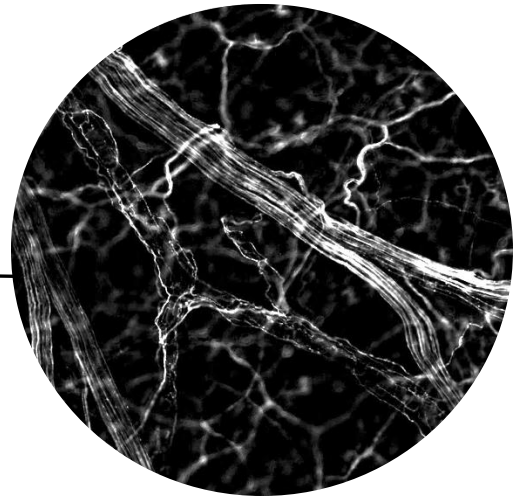
Tissue damage

Mechanical stimulus

Temperature







Protective immunity
Sense and kill pathogens and infected cells

Protective behavior
Pain / Avoidance / Itch

Defense

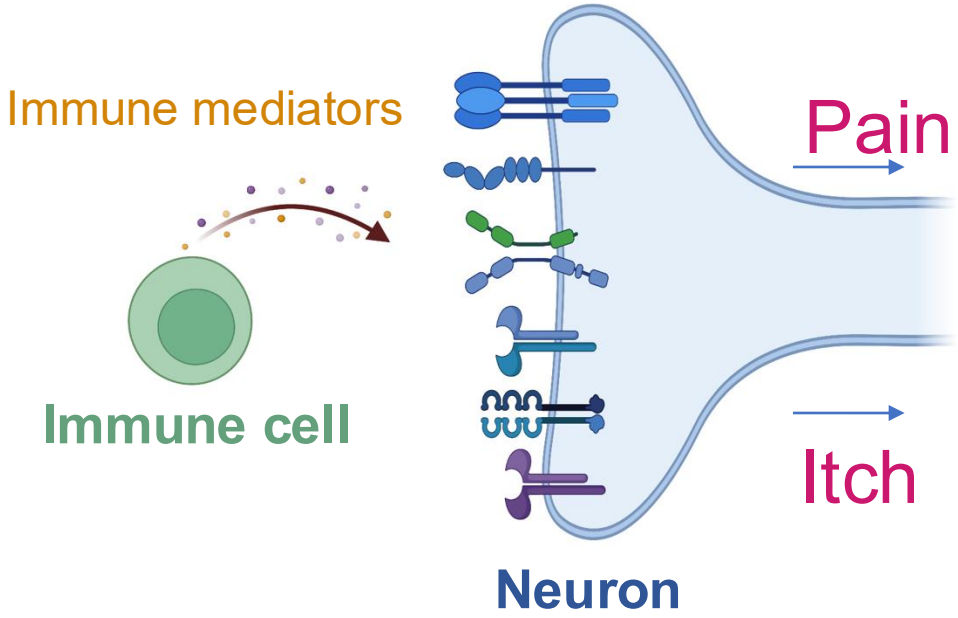
Tolerance

Scripps Research
Immunology & Microbiology

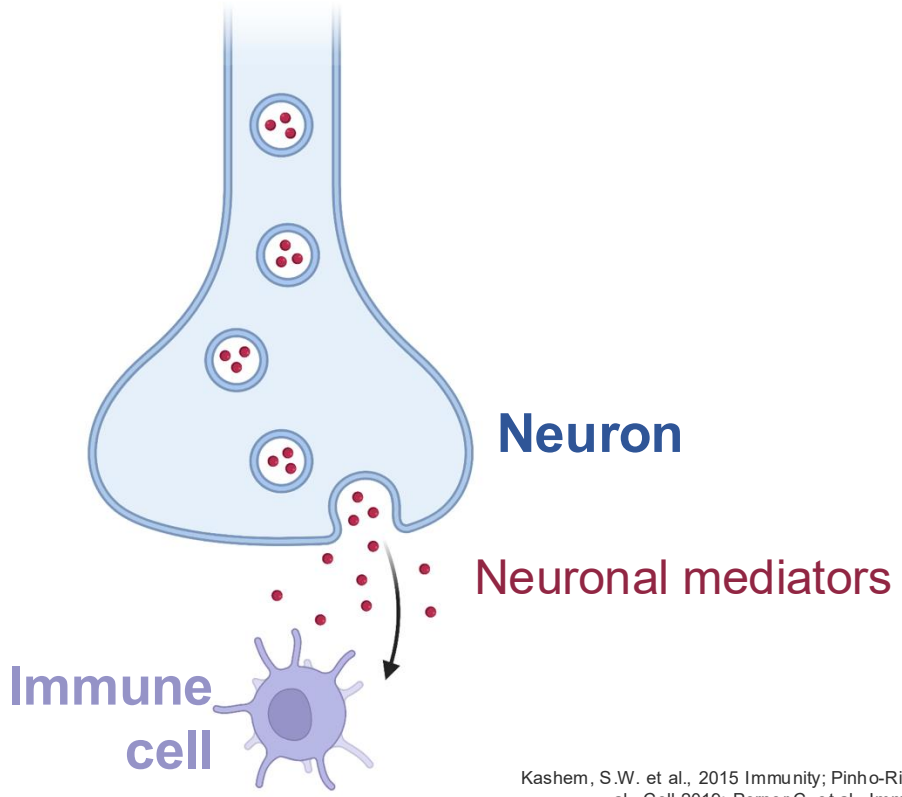
Mendoza Lab

Sensory Integration: Crosstalk between sensory neurons and immune cells regulates inflammation

Sensitization of neurons by immune cells



Neuronal modulation of immune cells



Ferreira S. H. et al., Nature 1988; Schäfers M. et al, J. Neurosci. 2003; Richter F. et al., Arthritis Rheum. 2012; Wilson S. R. et al., 2013 Cell; Fang D. et al, Pain 2015; Liu B. et al., PNAS 2016

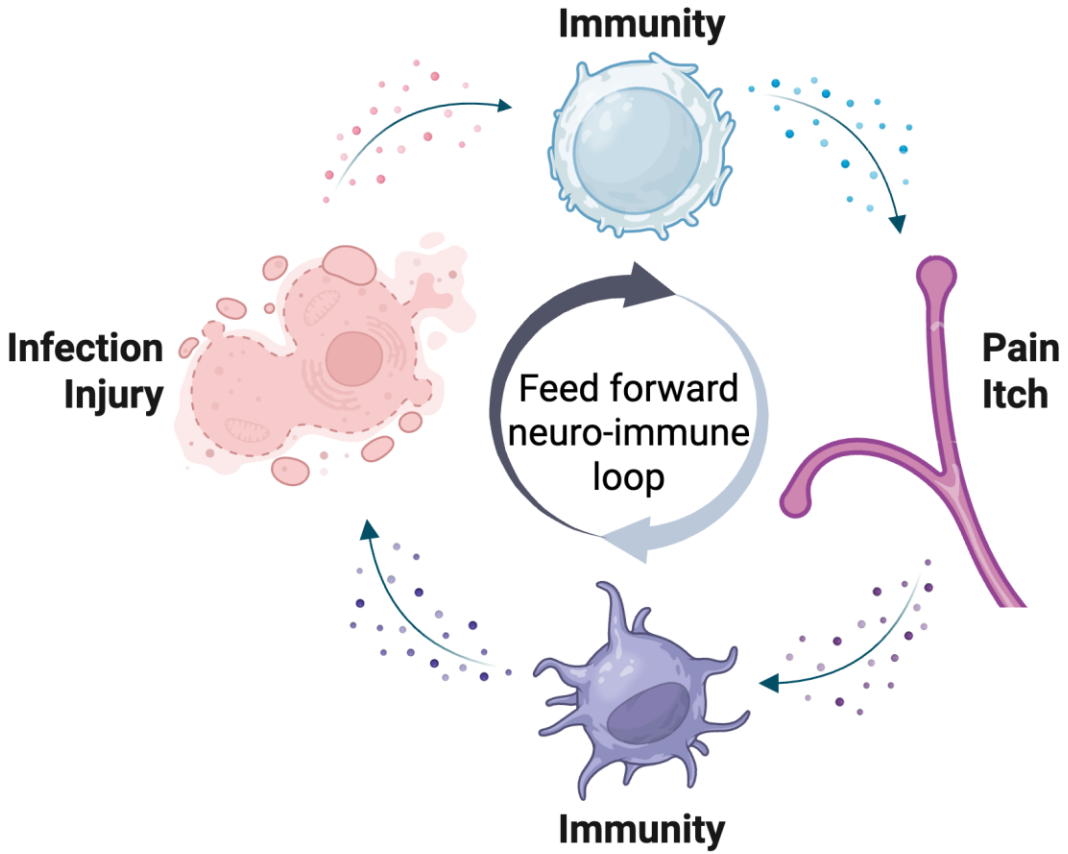
Kashem, S.W. et al., 2015 Immunity; Pinho-Ribeiro F.A. et al., Cell 2018; Cohen J.A. et al., Cell 2019; Perner C. et al., Immunity 2020; Hoeffel g. et al., Nature 2021

Scripps Research
Immunology & Microbiology

Mendoza Lab

Feed Forward Loops can result in maladaptive states

Chronic inflammation, pain and itch



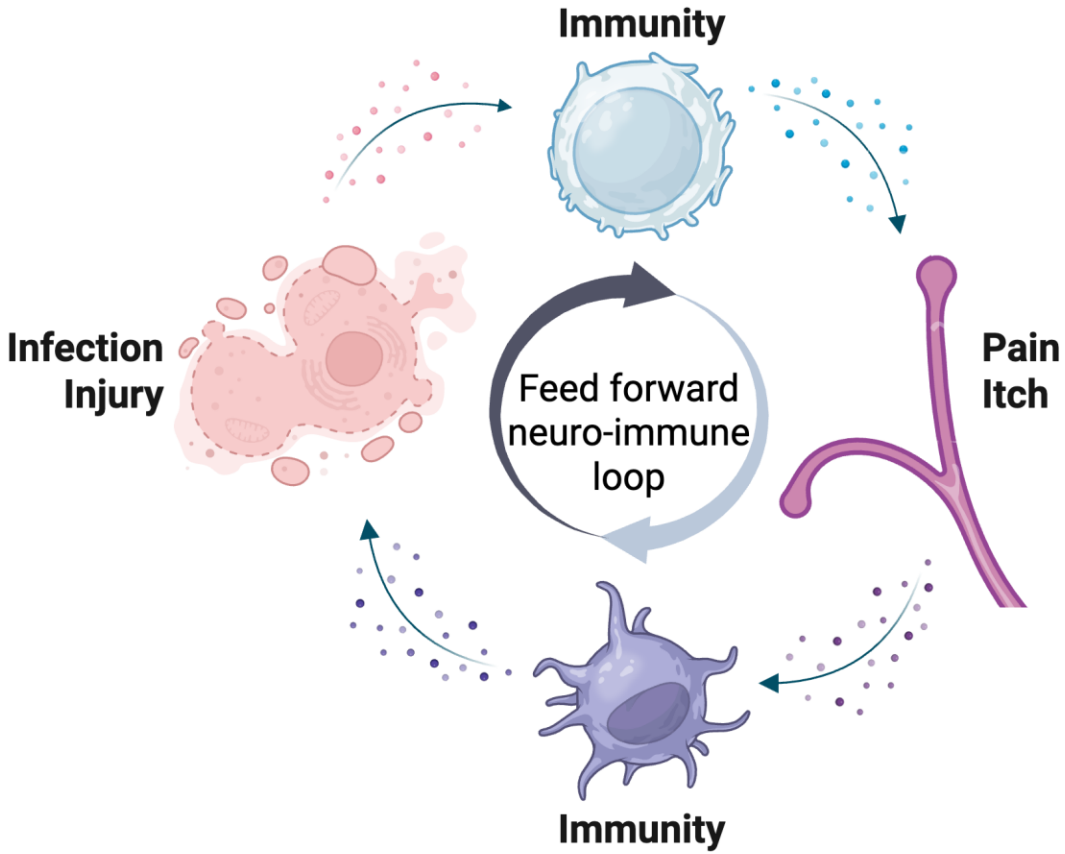
If Immune cells can activate sensory neurons…

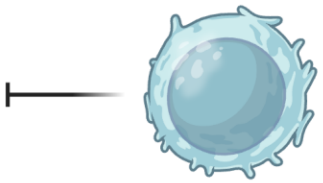
And Sensory neurons can activate immune cells…

Then there must negative regulators preventing feed forward inflammatory loops.

Feed Forward Loops can result in maladaptive states

Chronic inflammation, pain and itch





Regulatory T cells

Do immune cells interact with sensory neurons to act as negative regulators of inflammation?

Regulatory T cells

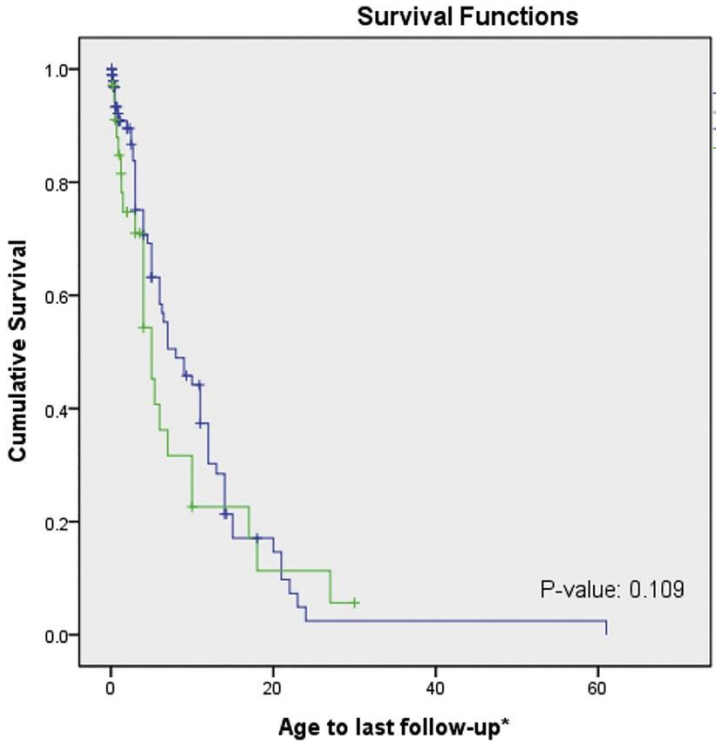
A small immune population with a big job

Immune cell subset that regulates immunity

>0.1% of cells in the body are T_{reg} cells

T_{reg} cells are dependent on **FOXP3** for their identity and function**.**

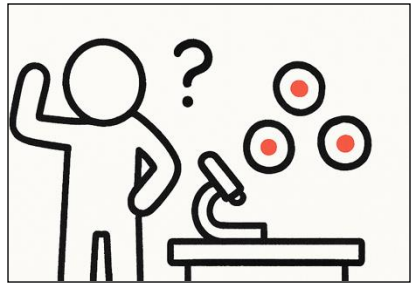
FOXP3 mutations in humans cause **fatal systemic autoimmunity** (IPEX syndrome).



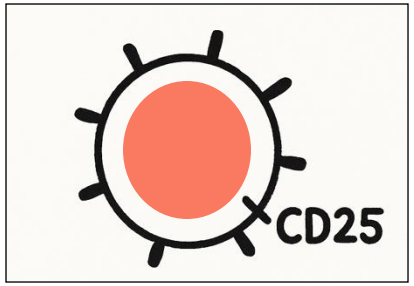
Park J.H. *et al., Autoimmun Rev 2020*

A quick detour for T_{reg} cell history

1970's -1980's



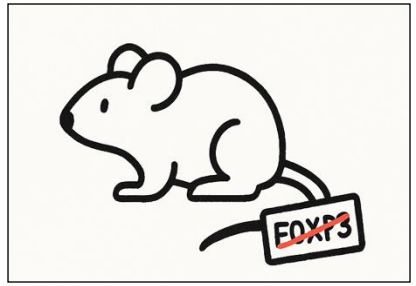
1990's



Morrissey… Watson *JEM 1993*
Powrie… Coffman *Int Immunol 1993*
Powrie… Coffman *JEM 1994*
Sakaguchi *et al. J Immunol 1995*
Malmstrom and Powrie *JEM 2000*
Takahashi… **Sakaguchi** *JEM 2000*

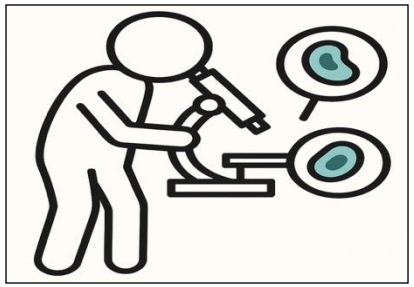
2000's

Chatila… Bowcock *JCI 2000*
Brunkow… **Ramsdell** *Nat Genet 2001*
Bennett… Ochs *Nat Genet 2001*



Fontenot... Rudensky *Nat Immunol 2003*
Khattri… **Ramsdell** *Nat Immunol 2003*
Hori, Nomura, and **Sakaguchi** *Science 2003*
Fontenot… Rudensky *Immunity 2005*
Gavin… Rudensky *Nature 2007*

2000's - present

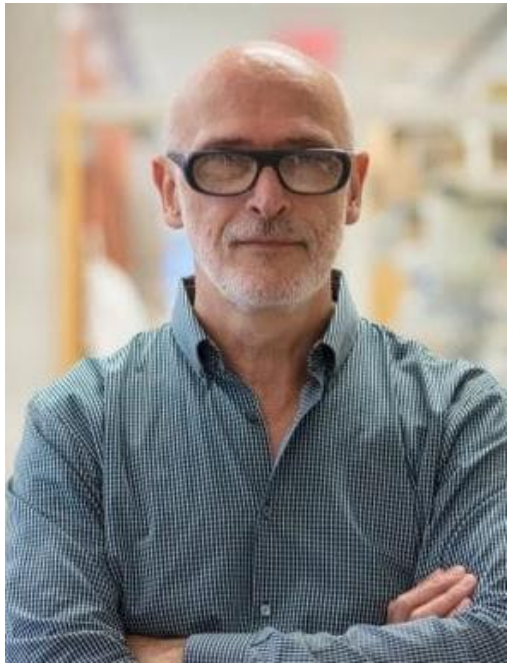


>40,000 publications

>200 clinical trials

2025

Is there a neuro-modulating role for T_{reg} cells to balance responses to environmental stimuli?



Alexander Rudensky

Paolo Giovanelli

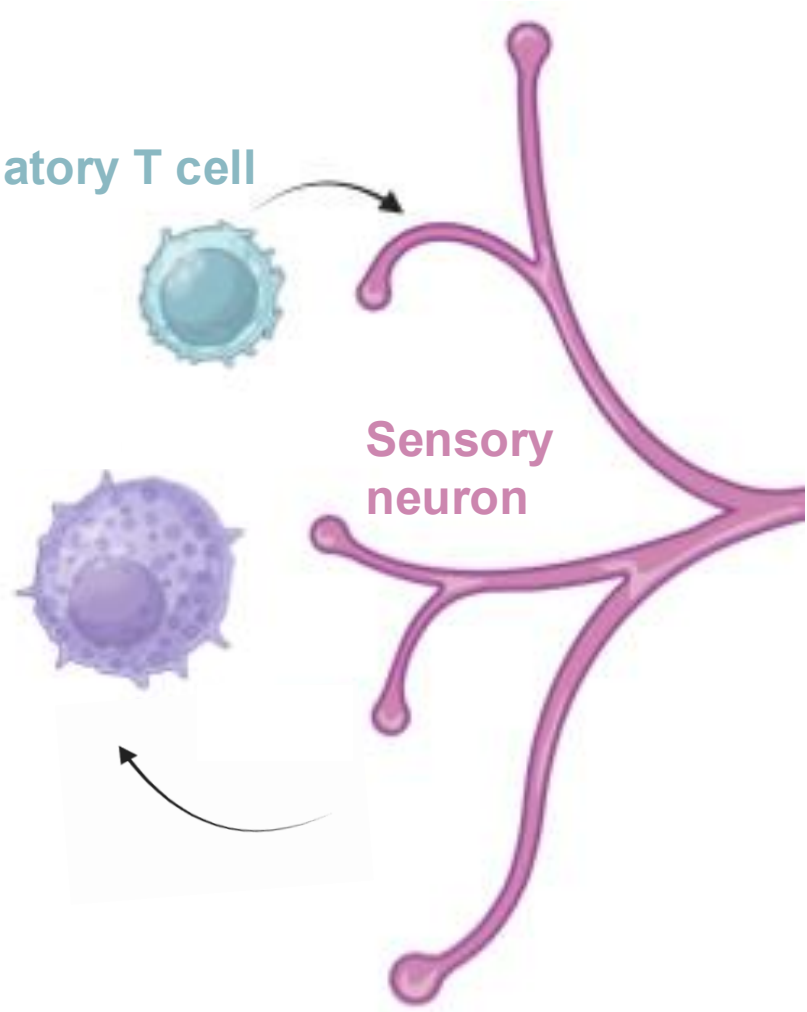
Regina Bou-Puerto

Emma Andretta

Stanislav Dikiy

J. Sebastian Jara

Susanna Manenti

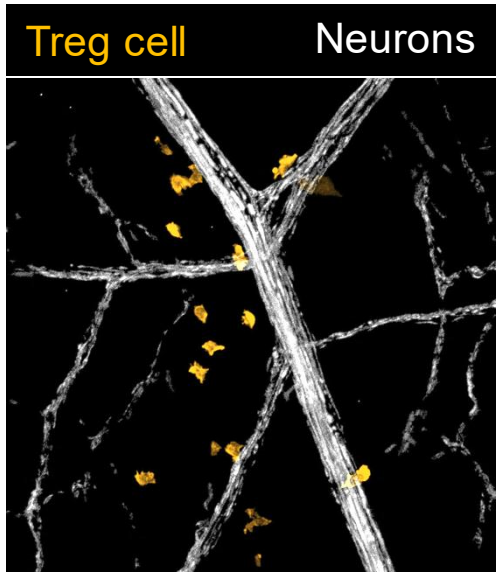


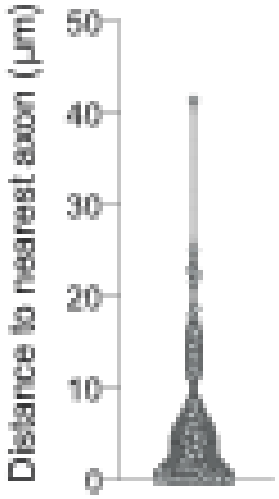
Mendoza A. *et al., Science Immunology 2025*

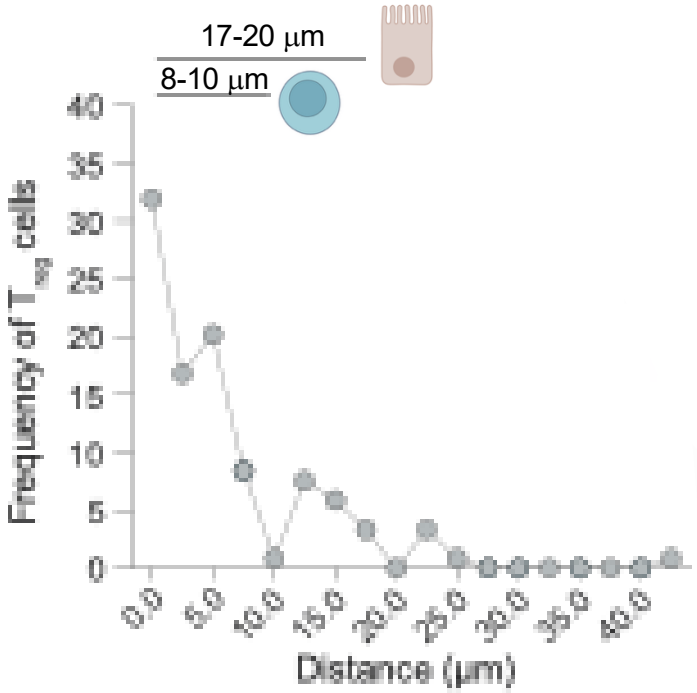
Scripps Research
Immunology & Microbiology

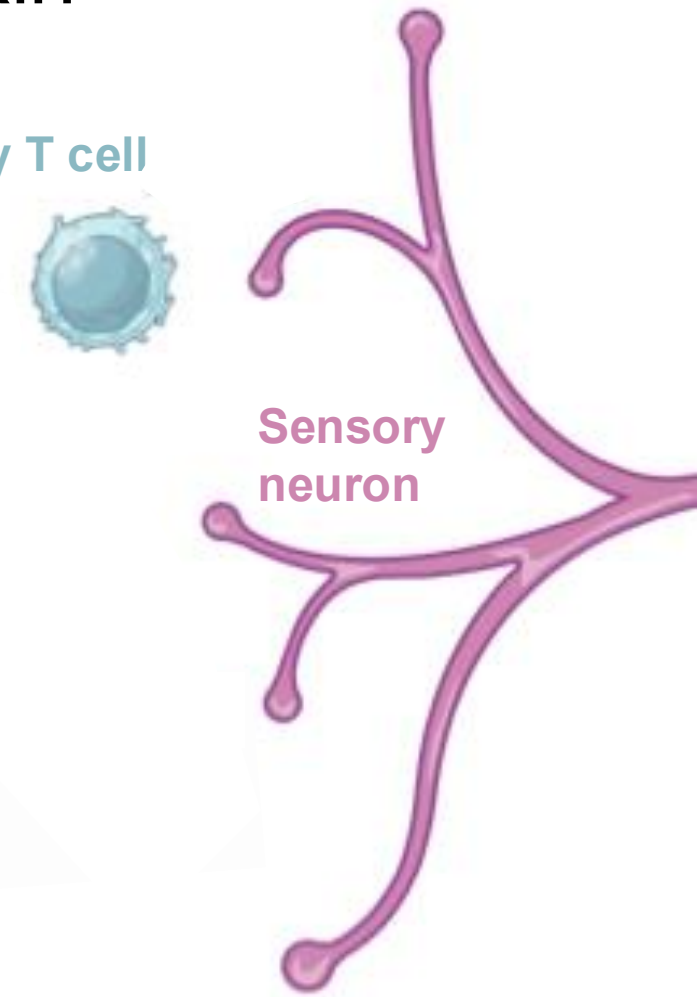
Mendoza Lab

T_{reg} cells localize near axons innervating the skin







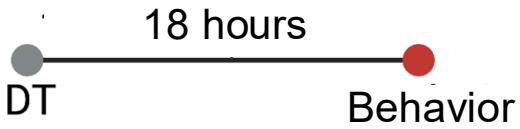


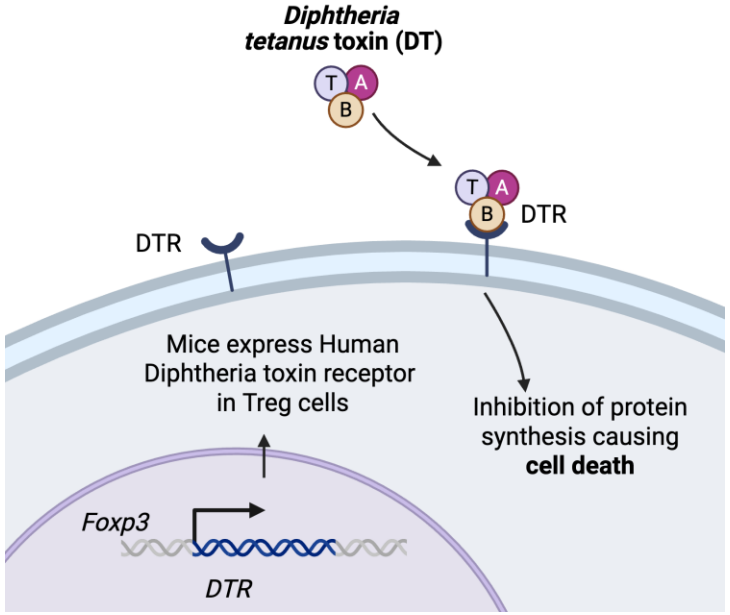
Scripps Research
Immunology & Microbiology

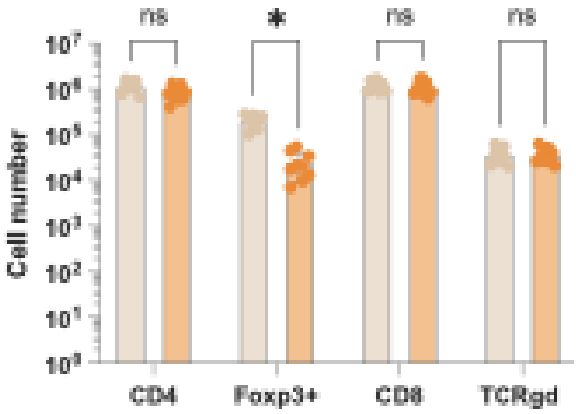
Mendoza Lab

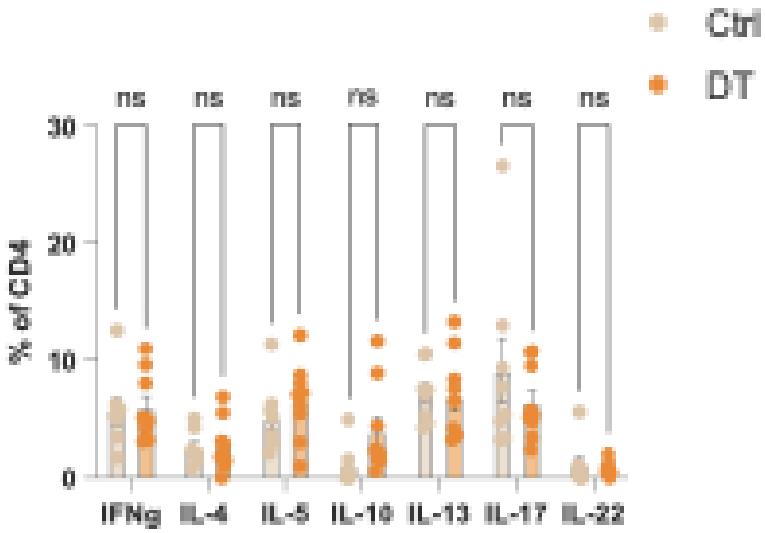
T_{reg} cells decrease responses to sensory stimuli

Foxp3^{DTR}





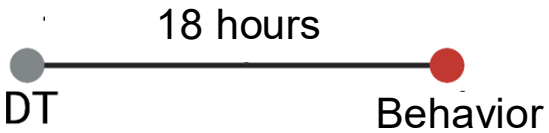




Kim *et al., Nat Immunol 2007*

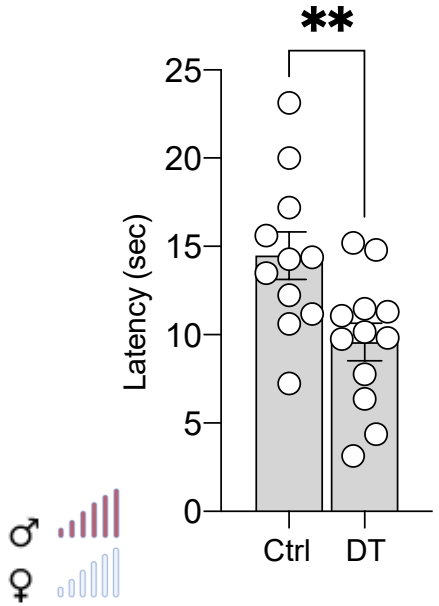
T_{reg} cells decrease responses to sensory stimuli

Foxp3^{DTR}



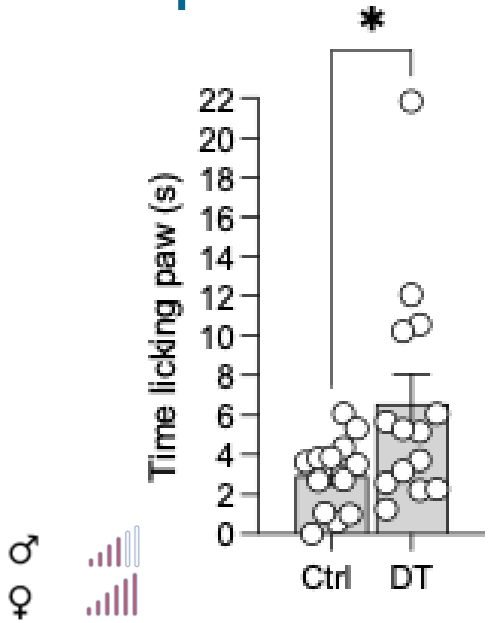
Heat sensitivity

Hot plate



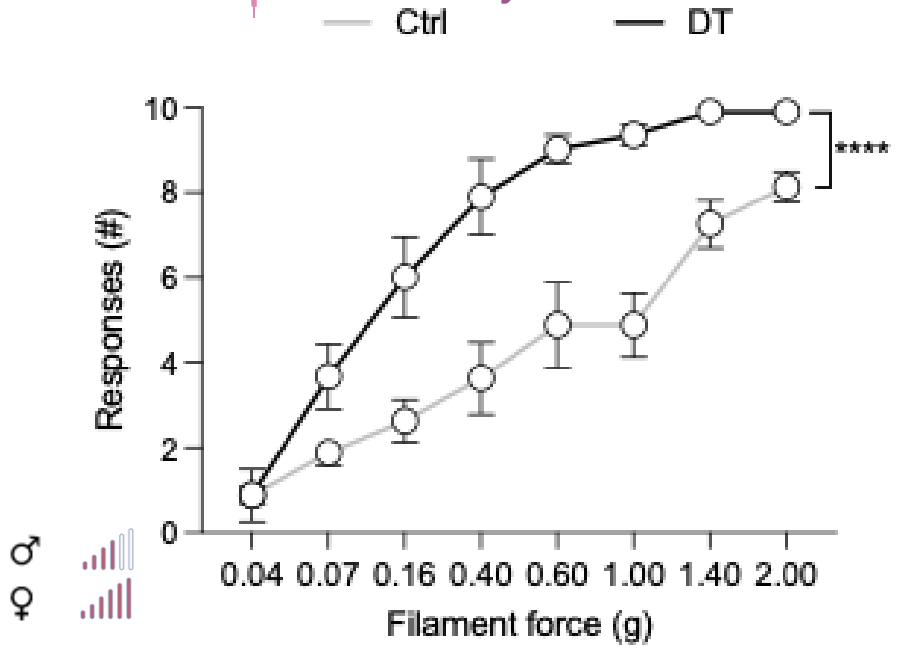
Cold sensitivity

Acetone



Mechanical sensitivity

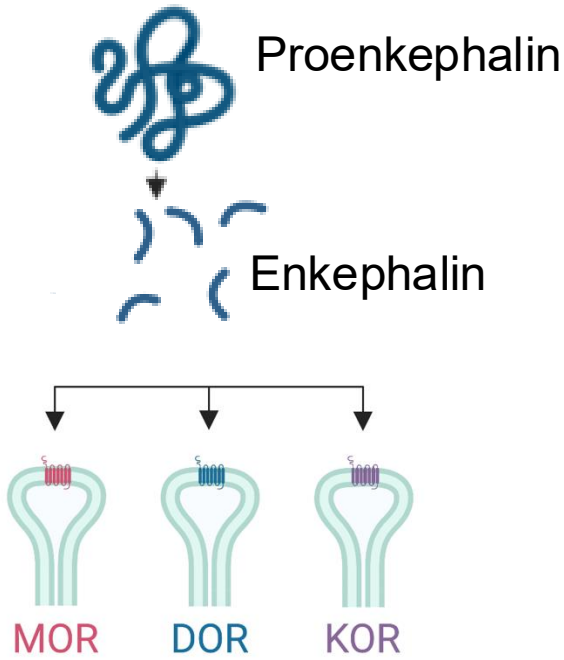
Von Frey



Scripps Research
Immunology & Microbiology

Mendoza Lab

How do T_{reg} cells modulate sensory perception?



Opioid Receptors

Some T_{reg} cells express *Proenkephaklin*, the precursor for **enkephalins**.

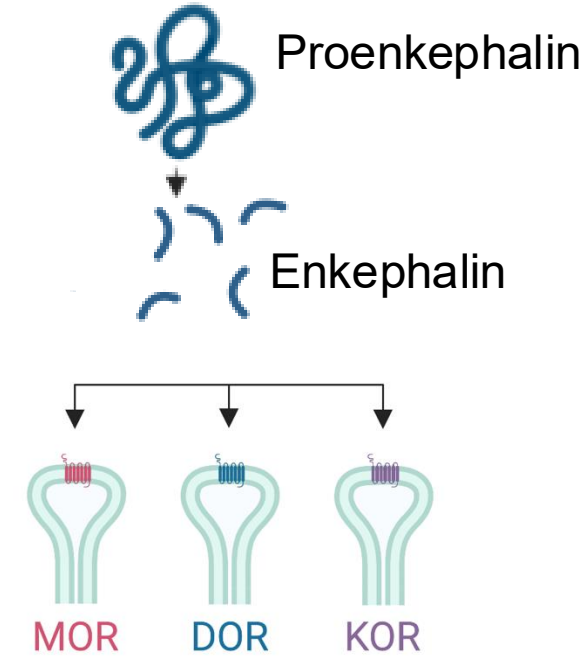
Enkephalins are **endogenous opioids**.

Small **peptides produced by our own cells** to reduce pain and stress.

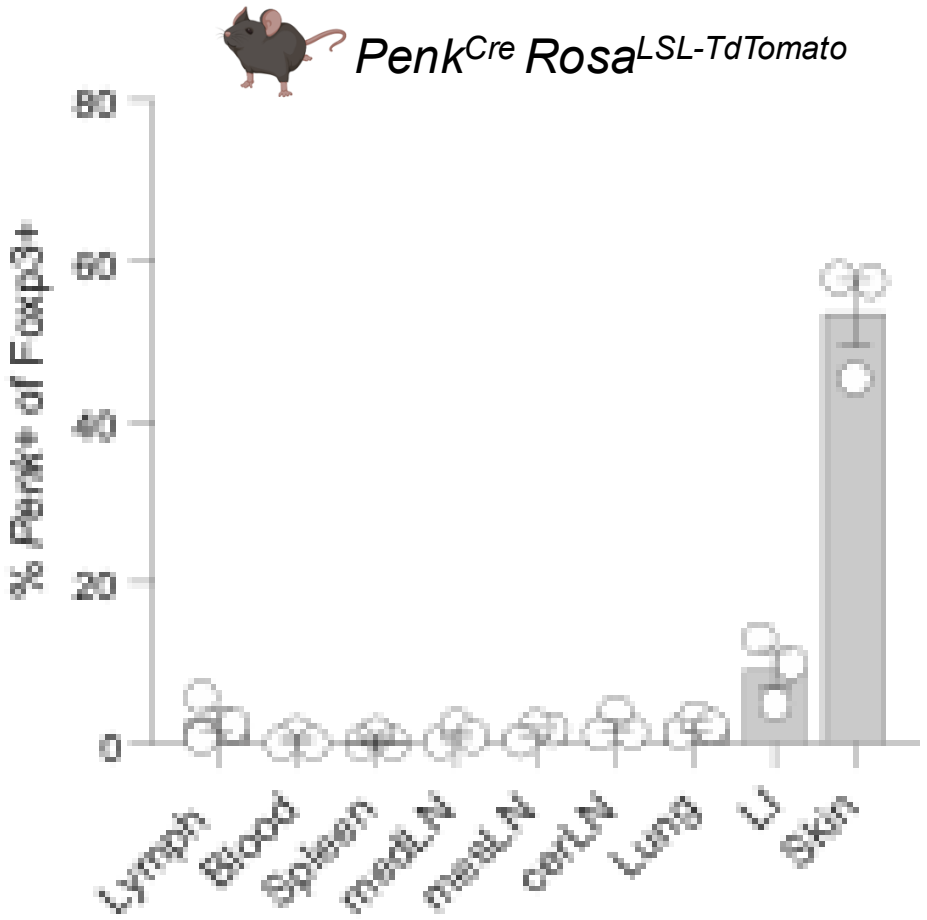
Bind to **opioid receptors**, the same targets as morphine or fentanyl.

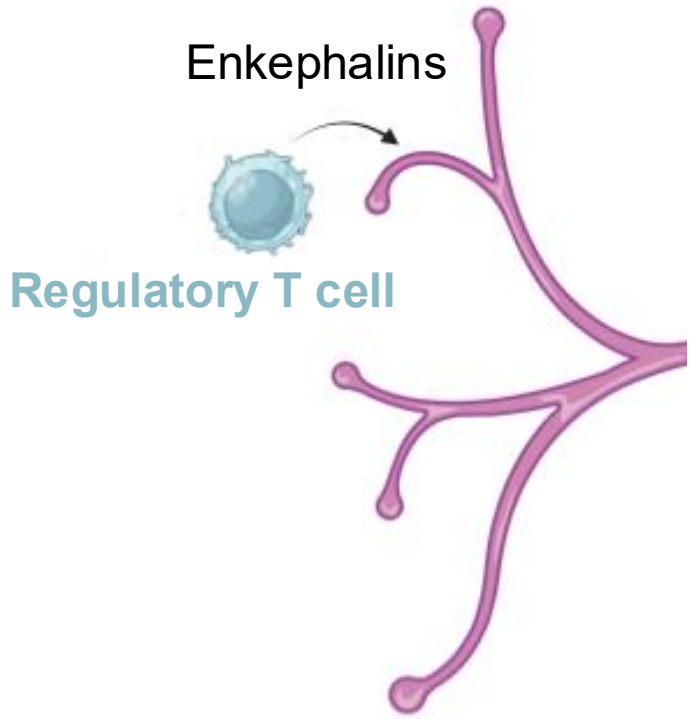
Konig, M., *et al.*, Nature 1996
Frederickson, R.C. and F.H. Norris, Science 1976
Belluzzi, J.D., *et al.*, Nature 1976
Hughes, J., *et al.*, Nature 1975

How do T_{reg} cells modulate sensory perception?



Opioid Receptors





Scripps Research
Immunology & Microbiology

Mendoza Lab

Enkephalins *from* T_{reg} cells modulate sensory perception

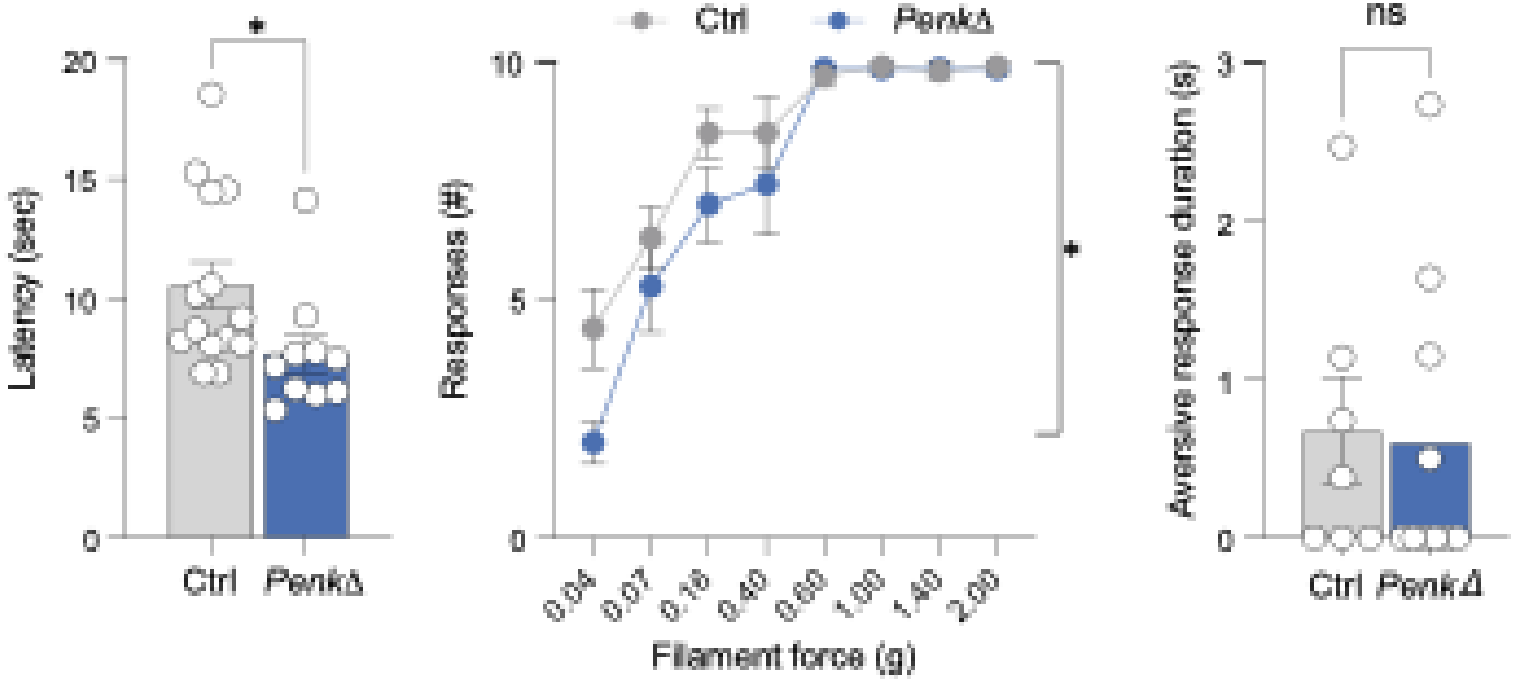
○ *Penk*$^{fl/wt}$ *Foxp3*^{CreERT2} (Ctrl)

● *Penk*$^{fl/fl}$ *Foxp3*^{CreERT2} *(Penk∆)*

Heat sensitivity
Hot plate

Mechanical sensitivity
Von Frey

Cold sensitivity
Acetone



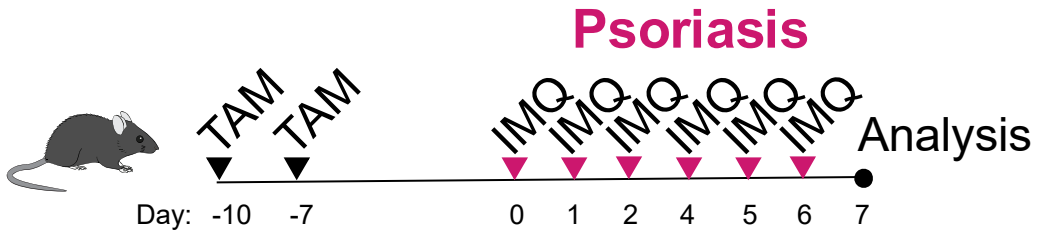
Scripps Research
Immunology & Microbiology

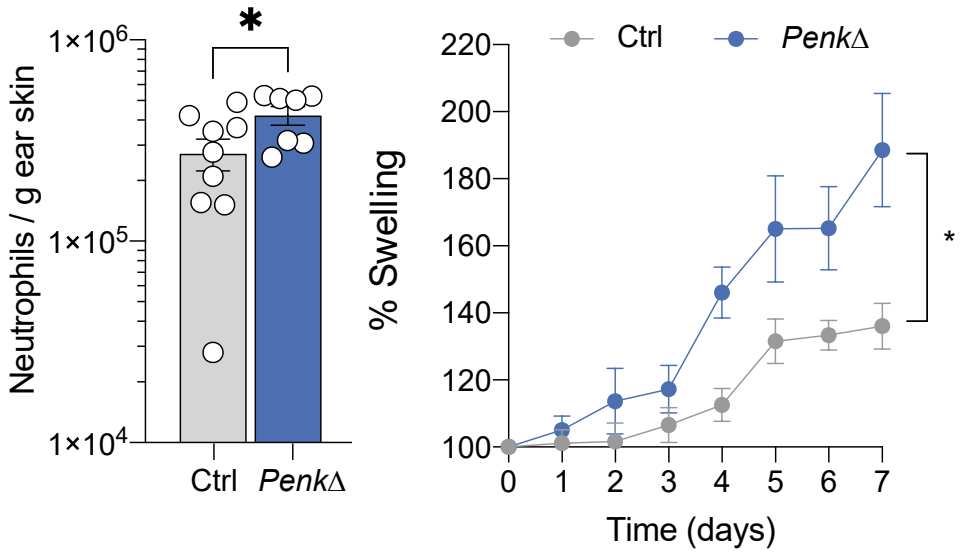
Mendoza Lab

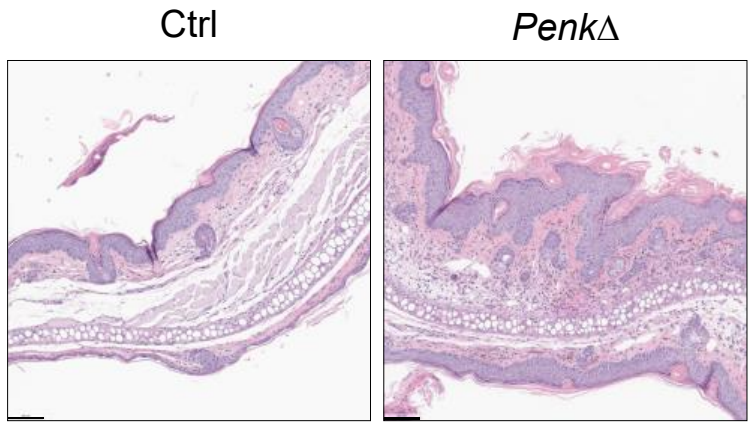
Enkephalins *from* T_{reg} cells modulate skin inflammation

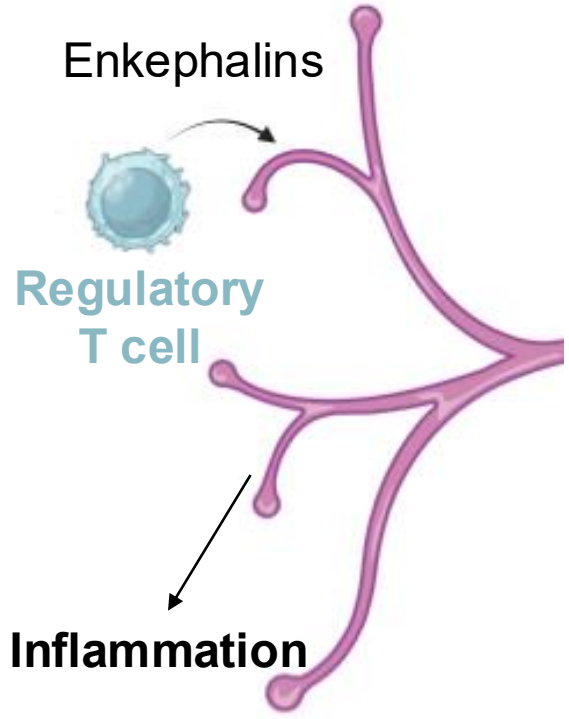
Penk$^{fl/wt}$ *Foxp3*^{CreERT2} (Ctrl)

Penk$^{fl/fl}$ *Foxp3*^{CreERT2} (*Penk*Δ)









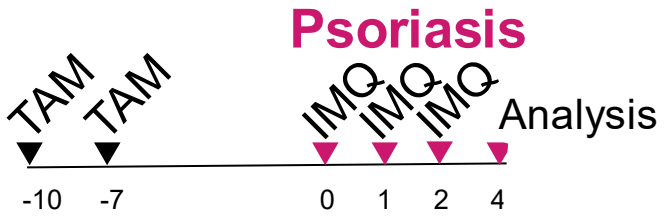
Scripps Research
Immunology & Microbiology

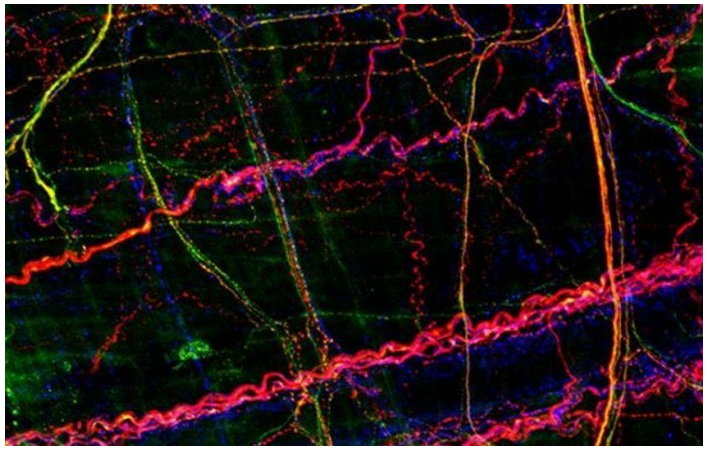
Mendoza Lab

T_{reg} cells restrain a pro-inflammatory program in populations of sensory neurons through Enkephalins

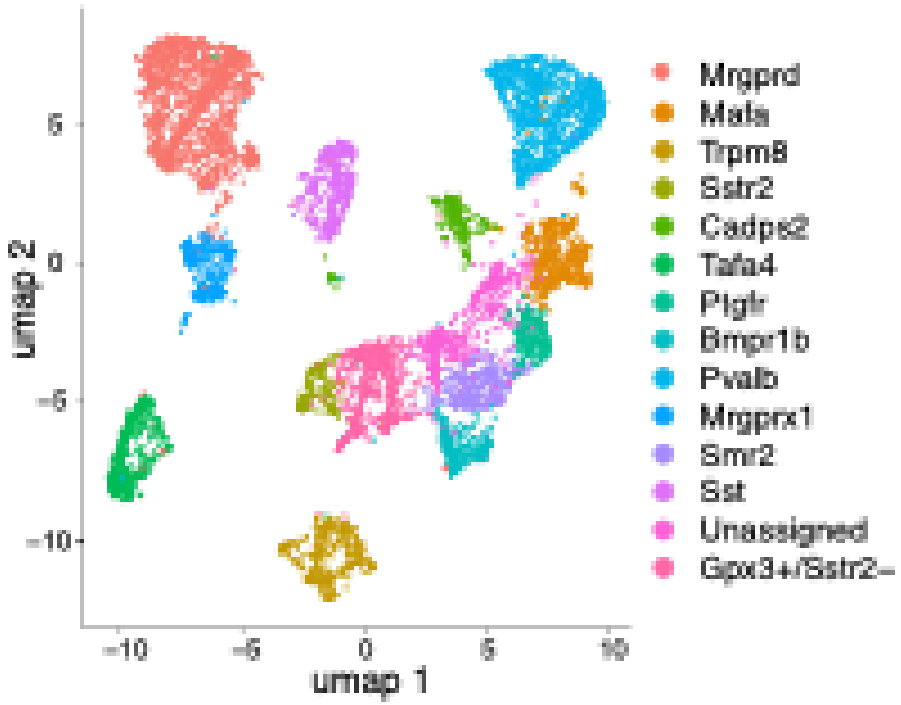
Penk$^{fl/wt}$ *Foxp3*^{CreERT2} (Ctrl)

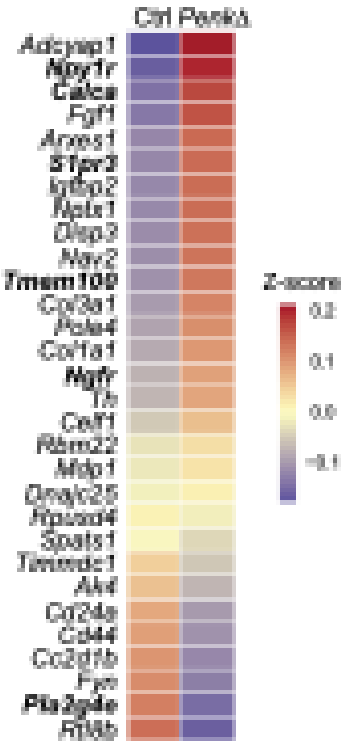
Penk$^{fl/fl}$ *Foxp3*^{CreERT2} *(Penk*Δ*)*





Wolfson *et al.*, *Cell* 2023

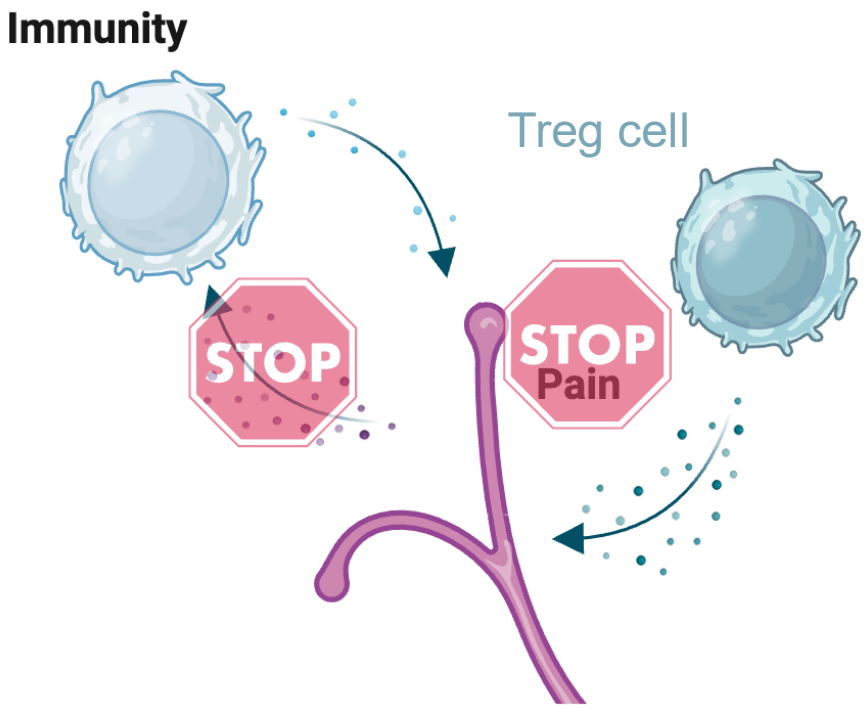




Scripps Research
Immunology & Microbiology

Mendoza Lab

Sensory and immune crosstalk modulates inflammation and sensory perception



Inflammation causes pain.

T_{reg} cells modulate inflammation and therefore were thought to modulate pain indirectly.

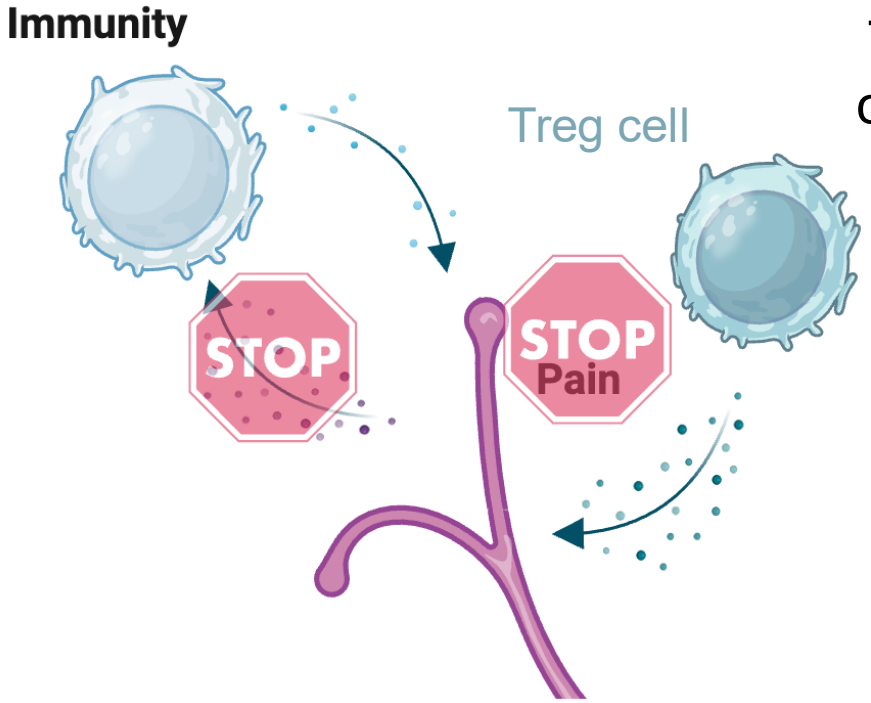
T_{reg} cells modulate neuronal activity by secreting an endogenous opioid aacting as cellular analgesics.

By modulating pain T_{reg} cell suppress inflammation.

Therapeutic intervention for chronic diseases that involve pain and inflammation.

Sensory and immune crosstalk modulates inflammation and sensory perception

Neuro-immune Therapeutic intervention



Targeting neuro-immune crosstalk can break **pain-inflammation** feed forward loops

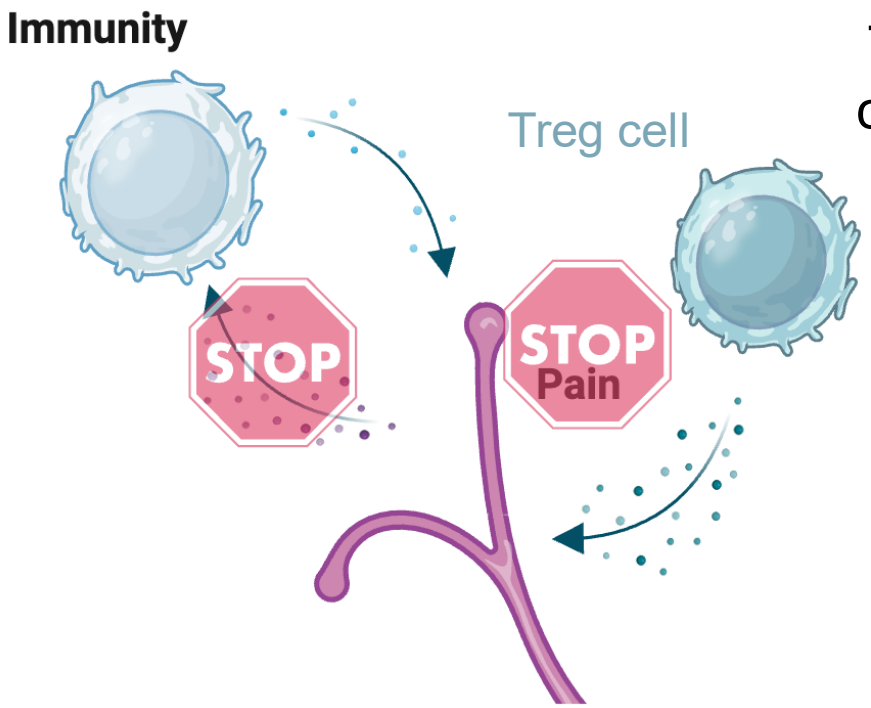
Finding small molecules that target the neuro-immune axis

High Throughput Screens

Luke Lairson
Scripps Research
Chemistry

Sensory and immune crosstalk modulates inflammation and sensory perception

Neuro-immune Therapeutic intervention



Targeting neuro-immune crosstalk can break **pain-inflammation** feed forward loops

Finding more players in the neuro-immune axis

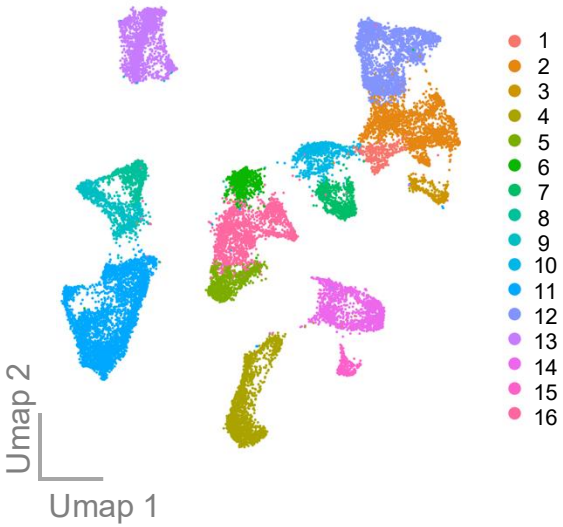
Cellular programs

Pathways

Molecular mechanisms

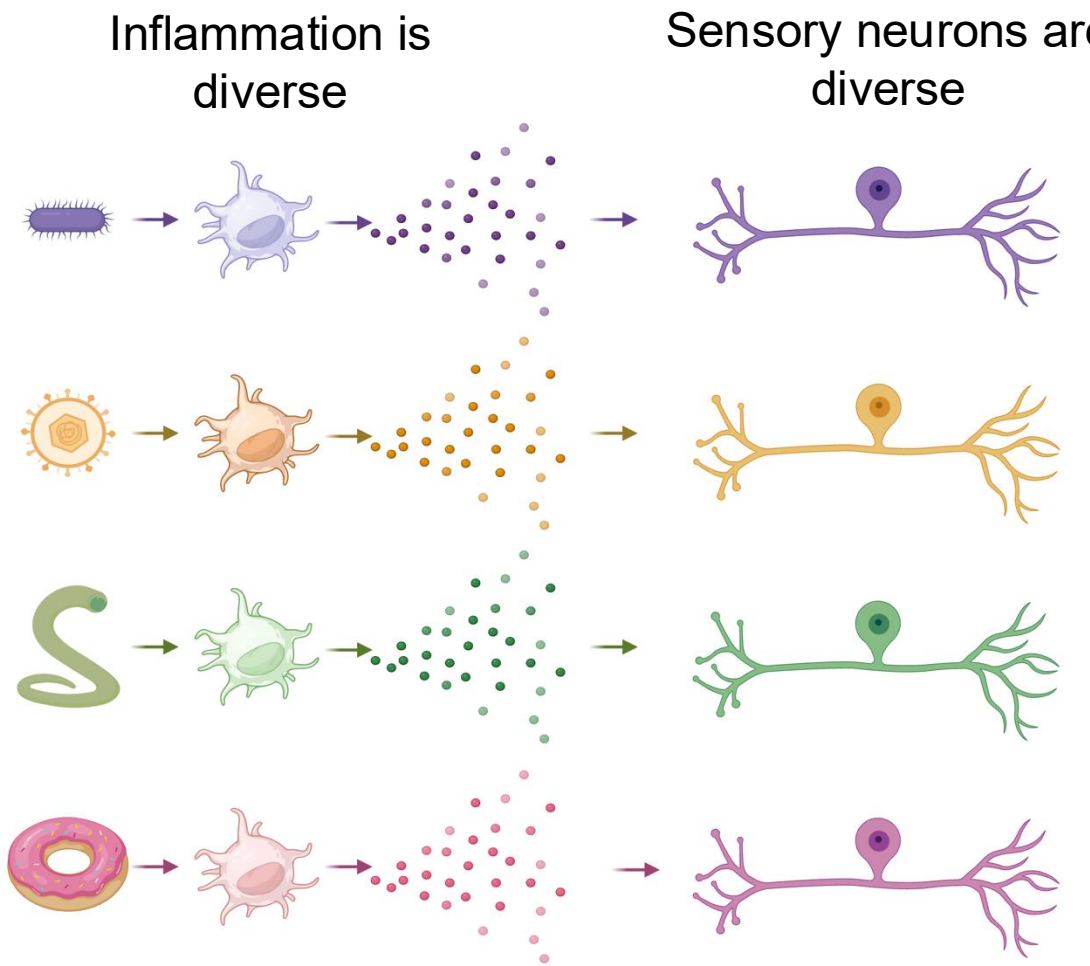
Decoding **Immuno-sensation**

How do sensory neuron responsed to immune challenges?



J. Sebastian Jara

Scripps Research
Immunology & Microbiology

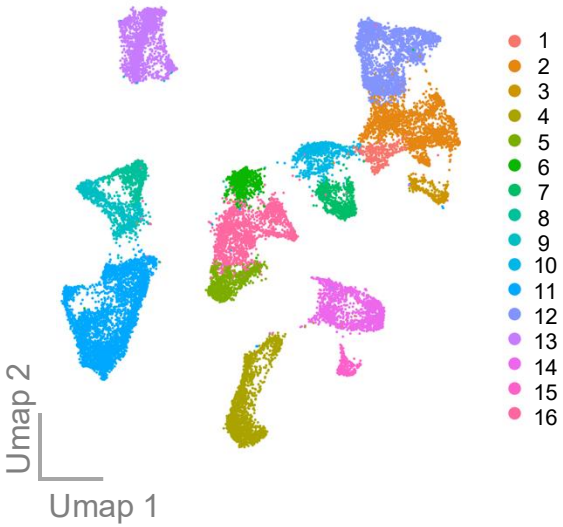


Unpublished

Mendoza Lab

Decoding **Immuno-sensation**

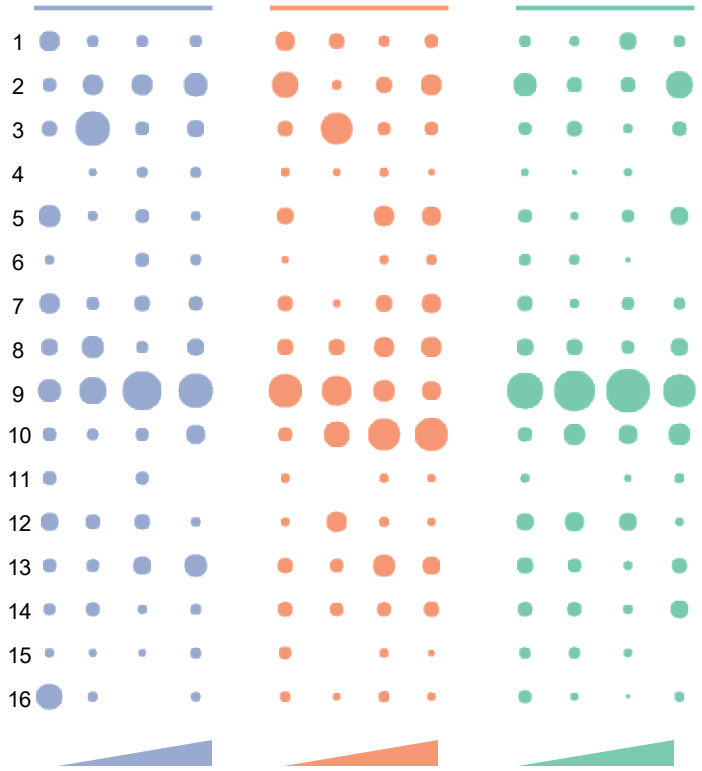
Sensory neurons respond distinctly to different immune stimuli



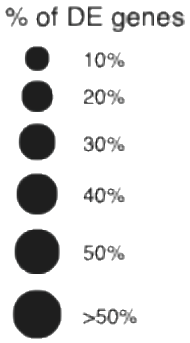
J. Sebastian Jara

Scripps Research
Immunology & Microbiology

Neuronal responses to Immune challenges



Time after challenge

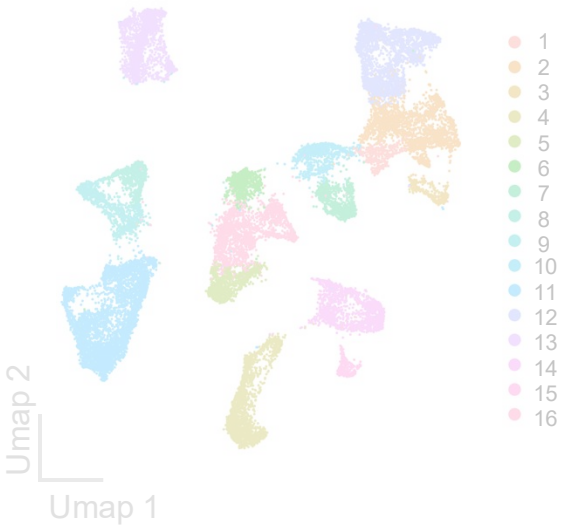


Unpublished

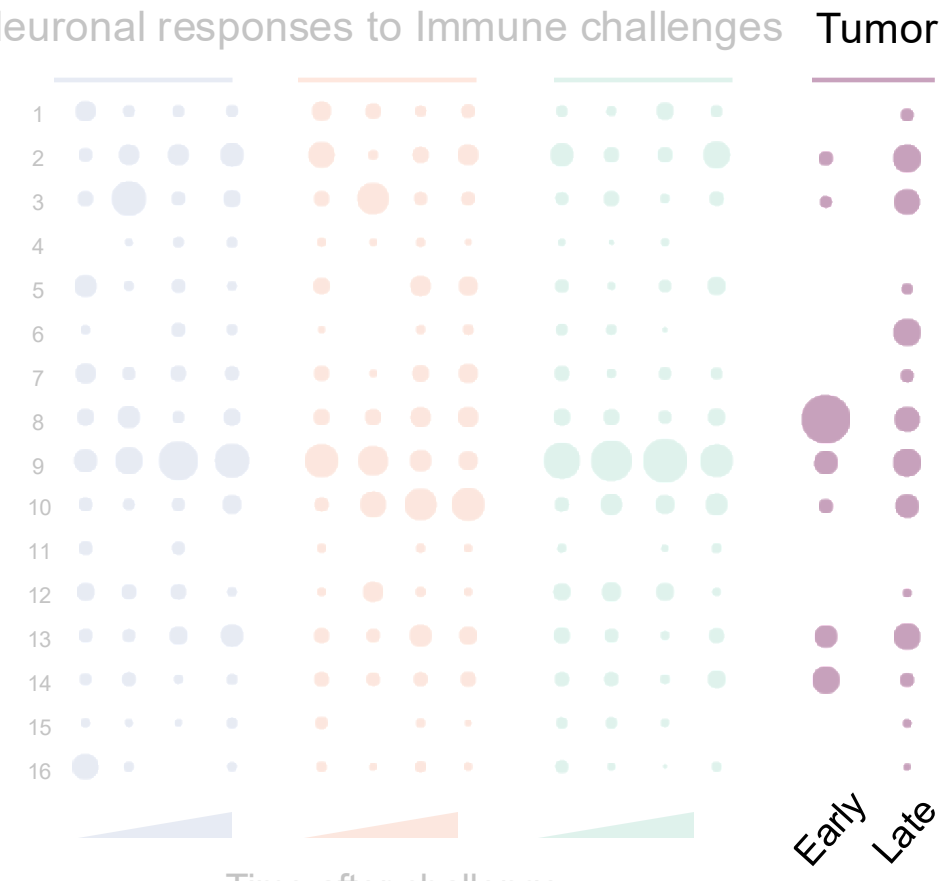
Mendoza Lab

Decoding **Immuno-sensation**

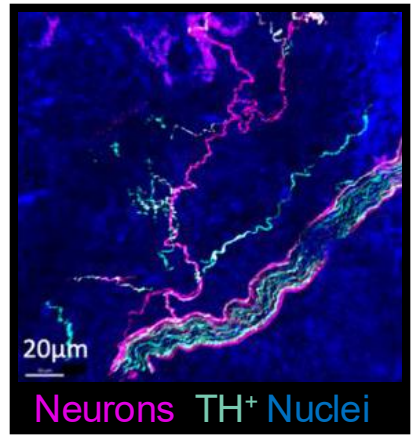
Harnessing *Sensory responses to modulate immunity*



J. Sebastian Jara

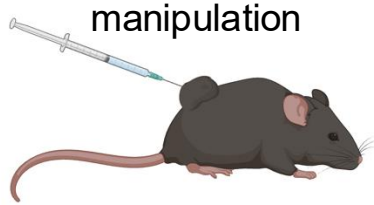


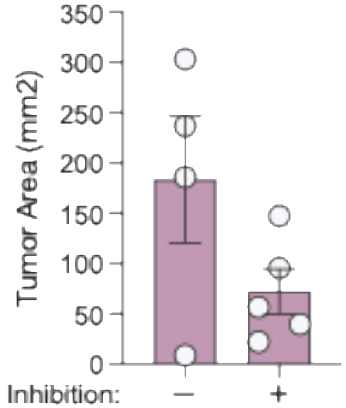
B16 Melanoma



Susanna Manenti

Chemogenetic manipulation



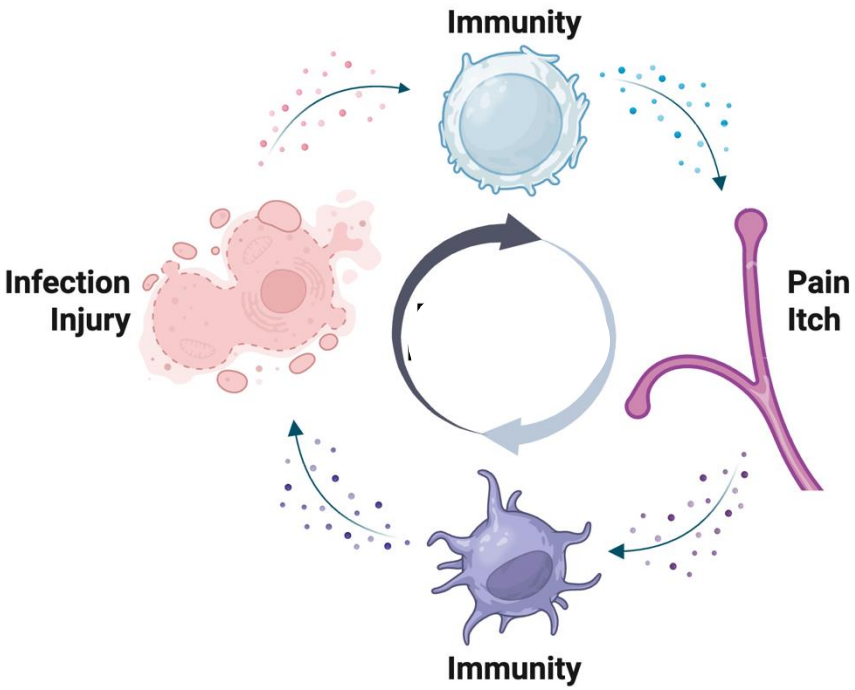


Scripps Research
Immunology & Microbiology

Unpublished

Mendoza Lab

Key take aways



Organisms must continuously sense and respond to surroundings to **maintain homeostasis**.

Barrier tissues balance **defense and tolerance** because inflammation is both **protective** and potentially **destructive**.

The nervous system is **an active participant in immunity**, not a bystander.

Sensory neurons **communicate** with immune cells to shape inflammatory outcomes.

Understanding mechanisms of neuro-immune cross-talk can open new **therapeutic paths**.

Mendoza Lab

J. Sebastian Jara
Susanna Manenti
Nicole Wolman
Abeera Mehmood
Keishla Sanchez Ortiz
Nancy Cheong Ka Neng
Grace Clarke
Alana Weiss
Taylor Basso
Hinda Sittnick

Funding

NIH Helping to End Addiction Long-term Initiative (HEAL)
DP2AR085223
Prebys Foundation

Stanislav Dikiy

Scripps Research

Executive Office
Office of Sponsored Programs
Department of Animal Resources

Skaggs Graduate School of Chemical and Biological Sciences

Keary Engle
Katja Lamia
Lucas Aponte-Collazo
Paul Cognata

Behavior Core
Genomics Core
Microscopy Core
Flow cytometry Core

Memorial Sloan Kettering

Alexander Rudensky
Stanislav Dikiy
Regina Bou Puerto
Paolo Giovanelli
Emma Andretta

Environmental Health and Safety
IT and Facilities
Environmental Services

University of Bonn

Andreas Zimmer

Weill Cornell

Chitra Dahia
Danilo Correa

NIH HEAL INITIATIVE
PREBYS FOUNDATION
hhmi Howard Hughes Medical Institute
CANCER RESEARCH INSTITUTE
Memorial Sloan Kettering Cancer Center
NIH
LUDWIG CANCER RESEARCH

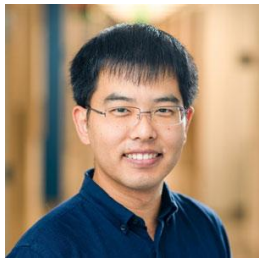
Collaborators at Scripps Research

Howard Hang
Scripps Research
Immunology
& Microbiology

Tiantian Liu
Scripps Research
Immunology
& Microbiology

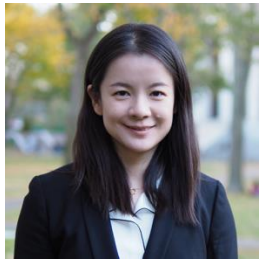
Bryan Briney
Scripps Research
Immunology
& Microbiology

Darrell Irvine
Scripps Research
Immunology
& Microbiology

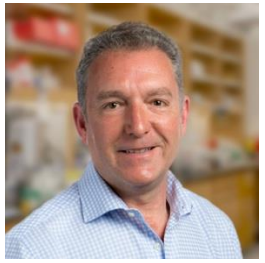


Chen Ran
Scripps Research
Neuroscience

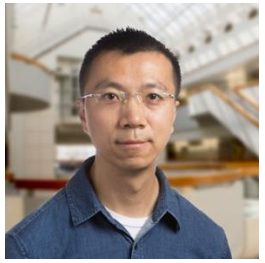
Luke Wiseman
Scripps Research
Molecular and Cellular Biology



Meng Zhang
Scripps Research
Molecular and Cellular Biology



Enrique Saez
Scripps Research
Molecular and Cellular Biology



Peng Wu
Scripps Research
Molecular and Cellular Biology

Supriya Srinivasan
Scripps Research
Neuroscience

Kristian Andersen
Scripps Research
Translational Medicine

Luke Lairson
Scripps Research
Chemistry

Andrew Ward
Scripps Research
Integrative Structural
and Computational Biology

Amy Lightner
Calibr-Skaggs Institute for Innovative Medicines | Scripps Research

Scripps Research
Immunology
& Microbiology

Dennis Burton

Howard Hang

Scripps Research
Neuroscience

Hollis Cline

Anton Maximov

Front Row Lecture Series

Scripps Research

Pete Schultz

Jamie Williamson

Communications

Anna Rauh Krueger
Desi McCoy
Monique Casellas
Jeremy Pyle
Gaby Miles
Brendan Cleak
Rick Crouse

Thank you for caring about science
Your curiosity and support make discovery possible