



# NOMIS CENTER SYMPOSIUM IN CONCEPTUAL IMMUNOLOGY

ABSTRACT BOOK

MONDAY, MARCH 30, 2026

## SCHEDULE OF EVENTS

- 12:00 p.m.      Registration
- 12:30 p.m.      Opening Remarks: Susan Kaech
- 12:40 p.m.      Jamie Blum  
*Molecular determinants of airway and food allergies*
- 1:05 p.m.      Irene Gutierrez  
*Peripheral infections impair spatial memory and remodel the brain-resident CD8<sup>+</sup> T cells compartment in APP/PS1 mice*
- 1:30 p.m.      Lara Labarta-Bajo  
*The type I Interferon pathway drives astrocyte aging and motor decline*
- 1:55 p.m.      Break
- 2:05 p.m.      Abigail Longtine  
*Disease tolerance mechanisms in aging*
- 2:30 p.m.      Eduardo Veira DeSouza  
*Decoding bacterial communication with a microprotein language model*
- 2:55 p.m.      Danish Umar  
*Role of maternal factors in determining offspring immunity and intestinal disease*
- 3:20 p.m.      Mel Cohn Lecture Introduction: Tony Hunter
- 3:30 p.m.      Mel Cohn Lecture in Conceptual Immunology:  
Douglas Green, St. Jude Children's Research Hospital
- 4:30 p.m.      Closing Remarks: Tony Hunter and Susan Kaech
- 4:40 p.m.      Reception

## SPEAKER ABSTRACTS

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*Salk Institute for Biological Studies*  
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- 2 Irene L Gutierrez, Valisha Shah, Michael Laporte, Victoria Tripple,  
Nick Andrews, Angela Wang, Brian Ware, Jessica Roginsky, Lara Labarta-  
Bajo, Diana Hargreaves, Nicola J Allen, and Susan M Kaech  
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- 3 Lara Labarta-Bajo, Ayesha R Thanawalla, Irene L Gutierrez, Su May Lei Soe,  
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- 4 Abigail G. Longtine and Janelle S. Ayres  
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**Disease tolerance mechanisms in aging**
  
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- 6 Danish Umar, Ivy Tam, Roman Young, Andrea Erkel, Diya Vasanadu,  
Eleni Phung, and Deepshika Ramanan  
*Salk Institute for Biological Studies*  
**Role of maternal factors in determining offspring immunity and  
intestinal disease**

## **Molecular determinants of airway and food allergies**

Tracy Chou, Henry Le, Blair Chang, and Jamie Blum  
Salk Institute for Biological Studies, La Jolla, CA (USA)

Are food allergies *caused* by proteins? This deceptively simple question remarkably remains unanswered. While protein antigens are clearly sufficient to trigger allergic responses in sensitized individuals, the molecular events that drive initial allergic sensitization, the process through which naïve T and B cells become activated and differentiate into effector populations, remain challenging to study due to limited experimental tools. Here, we test whether protein antigens alone are sufficient for allergic sensitization or whether co-encountered molecules (e.g., lipids, small molecules) provide essential adjuvant signals that shape the immune response. We focused on the respiratory tract as a major site of sensitization for diverse aeroallergens and a proposed route for food allergy sensitization. First, we profiled the adaptive immune response following exposure to a panel of diverse allergens: ragweed pollen, birch pollen, house dust mite, *Alternaria Alternata*, and peanut. Distinct responses emerged toward each allergen. For example, *Alternaria* inducing a strong Th17 response, while peanut was distinct for induction of an antibody response. RNA-sequencing revealed that *Alternaria* exposure induced an innate immune program characterized by markers such as serum amyloid A (SAA), consistent with pathways involved in Th17 cell differentiation. We are now determining which *Alternaria* molecules induce SAA production and whether SAA is casually involved in Th17 cell polarization. To define antigen-specific drivers of peanut allergy, we performed epitope mapping of the major allergen Ara h 1 using hybridoma-derived antibodies and identified two immunoreactive epitopes. We are now testing whether respiratory exposure to Ara h 1 is sufficient to drive sensitization or whether additional peanut-derived components are required. In the future, we will test whether respiratory exposure to Ara h 1 is sufficient for allergy induction or identify adjuvant-like molecules from peanut that are critical for sensitization. Overall, this work seeks to distinguish antigen sufficiency from adjuvant dependence in allergic sensitization and to define how the biochemical context of allergen exposure shapes immune outcomes.

## Peripheral infections impair spatial memory and remodel the brain-resident CD8<sup>+</sup> T cells compartment in APP/PS1 mice

Irene L Gutierrez, Valisha Shah, Michael Laporte, Victoria Tripple, Nick Andrews, Angela Wang, Brian Ware, Jessica Roginsky, Lara Labarta-Bajo, Diana Hargreaves, Nicola J Allen, and Susan M Kaech  
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**Alzheimer's disease (AD)** is a complex neurodegenerative disorder influenced by genetic and environmental factors, with inflammation playing a central role. Infections are linked to AD and cognitive decline; however, the impact of prior pathogen exposure on age-related neuroinflammation and disease progression remains unclear. Each infection reshapes the immune system by generating pathogen-specific T cells and other immune cells that infiltrate tissues and trigger inflammation. The brain—traditionally considered immune-privileged—is no exception. Infections produce long-lived memory T cells that either circulate between blood and tissues (TCIRC) or persist as tissue-resident memory T (TRM) cells, including in the brain. While brain TRM cells can provide protection, they may also contribute to inflammation and affect glial function, potentially worsening age-related neuroinflammation and neuronal health.

Recent studies indicate that CD8 T cells accumulate in the cerebrospinal fluid (CSF) and near amyloid plaques in AD patients and in mouse models. However, little is known about how these T cells enter the brain parenchyma, how they influence the local environment, and whether they protect against or exacerbate AD. We hypothesize that the accumulation of TRM cells in the brain, due to repeated infections over a lifetime, contributes to increased age-related neuroinflammation and may worsen AD. Most AD research to date relies on animal models raised in specific-pathogen-free (SPF) conditions, which lack exposure to real-world infections and contain very few memory CD8 T cells, particularly brain TRM cells. To address this gap, we developed novel AD mouse models that incorporate repeated viral and bacterial infections, better simulating the immune challenges encountered by humans.

Using this approach, we demonstrate that peripheral infections impair spatial learning and seed the brains of APP/PS1 mice with bona fide CD8<sup>+</sup> TRM cells. Single-cell RNA sequencing and TCR analysis reveal that clonal expansion of Gzmk<sup>High</sup> T cells is a hallmark of amyloidosis, while infections skew the brain TRM compartment toward Gzmk<sup>Low/Int</sup> subsets. Notably, infection-induced CD8<sup>+</sup> TRM cells exhibit increased IFN- $\gamma$  production and form STAT1<sup>+</sup> T cell aggregates in APP/PS1 mice, accompanied by an interferon-stimulated gene program in microglia. Together, these findings demonstrate that infection history is a critical determinant of CD8<sup>+</sup> T cell composition and function in the AD brain, highlighting the importance of incorporating immunological experience into preclinical models of neurodegeneration.

## **The type I Interferon pathway drives astrocyte aging and motor decline**

Lara Labarta-Bajo<sup>1</sup>, Ayesha R Thanawalla<sup>1</sup>, Irene L Gutierrez<sup>3</sup>, Su May Lei Soe<sup>2</sup>, Brent Y Chick<sup>2,4</sup>, Ioanna Andritsogianni<sup>1,4</sup>, Setareh Metanat<sup>5</sup>, Susan M Kaeck<sup>3</sup>, Eiman Azim<sup>1</sup>, Diana C Hargreaves<sup>2,3</sup>, and \*Nicola J Allen<sup>1,3</sup>

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In aging, inflammation and motor decline are coexisting conditions. Astrocytes are neuroregulatory glial cells that change in aging, particularly in the cerebellum, a brain region essential for motor function. The drivers of cerebellar astrocyte alterations in aging and their impact on motor function are unknown. We show that the type I Interferon (IFN-I) pathway, activated by infections or endogenous nucleotide sensing, drives motor deficits and astrocyte aging in the cerebellum. Transcriptomic analysis identifies an antiviral state in cerebellar astrocytes, but not cortical, that is exacerbated in aging, including elevated Stat1. Enforcing astrocyte Stat1 in adult mice synergizes with peripheral inflammation to cause motor deficits, demonstrating that astrocyte aging features compromise motor behavior. This astrocyte antiviral state is driven by persistent local type I IFN signaling, and its exacerbation in aging is due to a permissive chromatin landscape that amplifies transcriptional responses to type I IFNs. Cerebellar astrocytes harbor double stranded (ds)RNA sensing machinery and endogenous dsRNAs arising from intron retention in mature mRNAs. Astrocyte-specific disruption of dsRNA sensing adaptor MAVS reduces local type I IFN production, which identifies astrocyte-intrinsic dsRNA sensing as an upstream trigger of local type I IFN signaling. Together, these findings establish that astrocyte-intrinsic mechanisms drive brain aging and identify actionable strategies to preserve motor function in aging.

## Disease tolerance mechanisms in aging

Abigail G. Longtine<sup>1</sup> and Janelle S. Ayres<sup>1,2</sup>

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Aging is heterogeneous, with some individuals maintaining health while others experience morbidity and mortality. The Hallmarks of Aging framework posits that aging is due to cellular and molecular changes, and that normalizing these should preserve function. However, normalizing hallmarks does not necessarily restore function, and it remains unclear whether these hallmarks distinguish high- and low-functioning aged organisms. I hypothesize that health is not solely determined by normalizing hallmarks, but also by how organisms adapt to maintain health despite these changes. In infection biology, host survival was long attributed solely to pathogen control via *resistance* mechanisms. However, hosts utilize an additional distinct defense strategy—*disease tolerance*, which limits tissue damage and dysfunction during infection by promoting host adaptation to the infected state without reducing pathogen burdens. In my talk, I will propose that this conceptual framework developed by immunologists, can be applied to aging biology, to overcome the limitations of the Hallmarks of Aging model and uncover novel mechanisms of health maintenance with aging. I propose that, in addition to “resistance”, extension of healthspan involves defense mechanisms akin to disease tolerance that promote physiological adaptation to aging hallmarks, protecting from functional decline. I will discuss: 1) how the resistance-tolerance framework, within the context of the hallmarks of aging, provides a structured approach for classifying aging mechanisms based on their effects on damage accumulation versus functional resilience; 2) how this framework can guide the discovery of signatures associated with preserved healthspan using a comparative biology approach; and 3) how these signatures can be used to discover disease tolerance mechanisms for preserving physiological function with aging. The integration of the concept of disease tolerance into aging research shifts the focus from eliminating adverse factors to enhancing function in their presence and may reveal novel strategies to preserve health and function with aging.

## Decoding bacterial communication with a microprotein language model

Eduardo Vieira de Souza

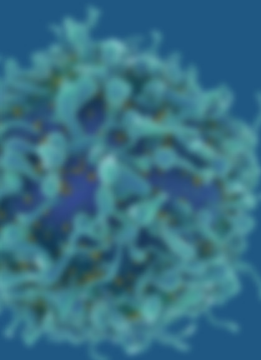
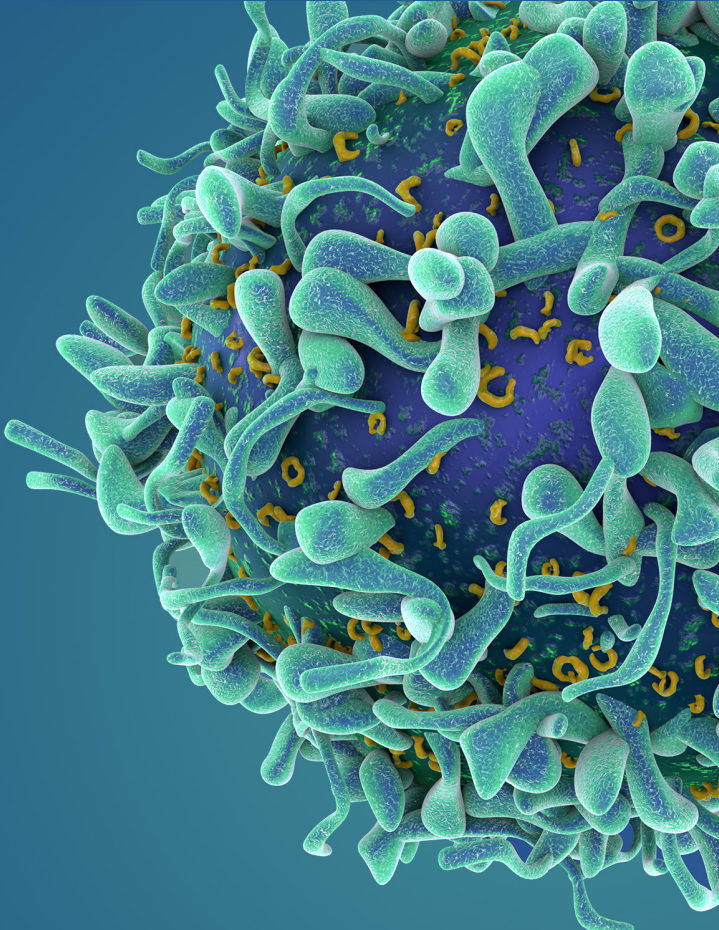
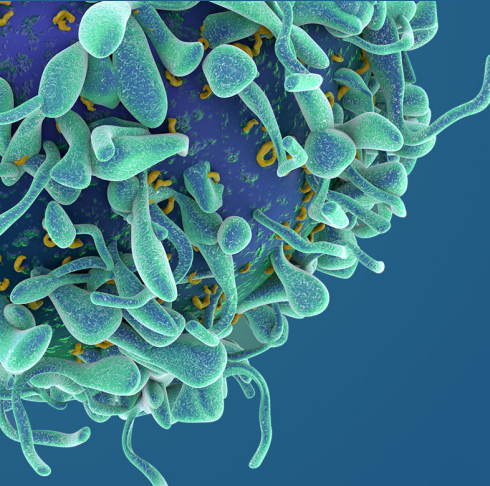
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Bacteria coordinate group behaviors through Quorum Sensing (QS), a chemical communication system mediated by the release of small molecules, including microproteins (<100 amino acids) and peptides. In Gram-positive pathogens such as *Staphylococcus aureus*, the predominant form of QS signaling is driven by Autoinducing peptides (AIPs), which are propeptides encoded by the *Accessory gene regulator (agr)* operon. AIPs are processed by membrane-bound proteins encoded by the same operon, and released into the extracellular medium where they can interact with other nearby bacteria and directly shape host-pathogen interactions and bacterial growth. Despite their clinical relevance, AIPs are difficult to identify due to their short nature and multiple complex sequence motifs required for post-translational processing and signal recognition. To address this gap, we have developed smOracle, a general-purpose protein language model (PLM) trained on millions of microproteins and peptides across the prokaryotic tree of life. Akin to how language models process natural human language, PLMs were repurposed to model protein sequences and accurately “speak the language of proteins” by learning amino acid patterns governing their biology. We show that smOracle successfully generalizes and models short sequences across diverse tasks, including antimicrobial peptide classification, subcellular localization, and functional annotation across dozens of protein families. For this work, we fine-tune smOracle to specialize it on the detection of mature AIPs within their precursor sequences, a key step toward systematic discovery of novel QS circuits in pathogenic and commensal bacteria. By applying smOracle to thousands of bacterial genomes, we annotate hundreds of novel AIPs in biosynthetic operons. We also apply it to metagenomes and delimit previously missed functional AIPs in a mouse gut microbiome. Our predictions are undergoing experimental validation, with the long-term goal of leveraging novel AIPs to modulate microbiome composition. By providing a powerful AI model and a new database of functional AIPs across bacterial families, we expect to improve understanding of bacterial communication within microbiomes and facilitate the development of QS-based therapies, which offer a promising alternative to circumvent antibiotic resistance.

## **Role of maternal factors in determining offspring immunity and intestinal disease**

Danish Umar, Ivy Tam, Roman Young, Andrea Erkel, Diya Vasanadu, Eleni Phung, and Deepshika Ramanan  
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The role of maternal factors in programming offspring intestinal immunity is recognized but remains mechanistically unclear. Using a cross-fostering model in which B6 pups were reared by either B6 or BALB/c dams, we found that high maternal IgA transfer from BALB/c dams reduced microbe-specific regulatory T cells (ROR $\gamma^+$  Tregs) in offsprings. We hypothesize that maternal IgA, together with other bioactive milk factors, shapes early microbiota colonization and the intestinal immune landscape, influencing T cell differentiation and long-term colorectal cancer (CRC) susceptibility. Supporting this, B6 mice nursed by BALB/c dams exhibited reduced susceptibility to colitis-associated colorectal cancer (CAC) compared to controls. These mice showed heightened IFN $\gamma$  responses in CD4 $^+$  T cells and increased induced intraepithelial lymphocytes (iIELs) in tumors and adjacent tissues, respectively. Elevated baseline iIEL levels in healthy BALB/c-nursed B6 mice further underscore profound maternal influence on gut immunity. As these cohorts differed only in postnatal milk exposure, we investigated early-life mechanisms underlying these outcomes. Single-cell RNA sequencing of neonatal intestines revealed striking alterations in epithelial composition and reduced goblet cell populations in BALB/c-nursed B6 pups, preceding the emergence of the ROR $\gamma^+$  Treg and iIEL phenotypes. Ongoing metabolomic, proteomic, and lipidomic analyses of maternal milk aim to identify key factors driving these epithelial and immune changes. Together, these findings demonstrate that maternal cues during breastfeeding exert lasting effects on gut immune development and CAC risk, providing mechanistic insight into early-life immune programming and highlighting maternal factors as potential targets for preventing intestinal inflammation and cancer.



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