



Myeloid reprogramming drives enhanced defense against *Streptococcus pneumoniae* after commensal *Prevotella* exposure

Sara Stoner, PhD

Clark Lab

**Biology of Acute Respiratory Infection Gordon
Research Seminar**

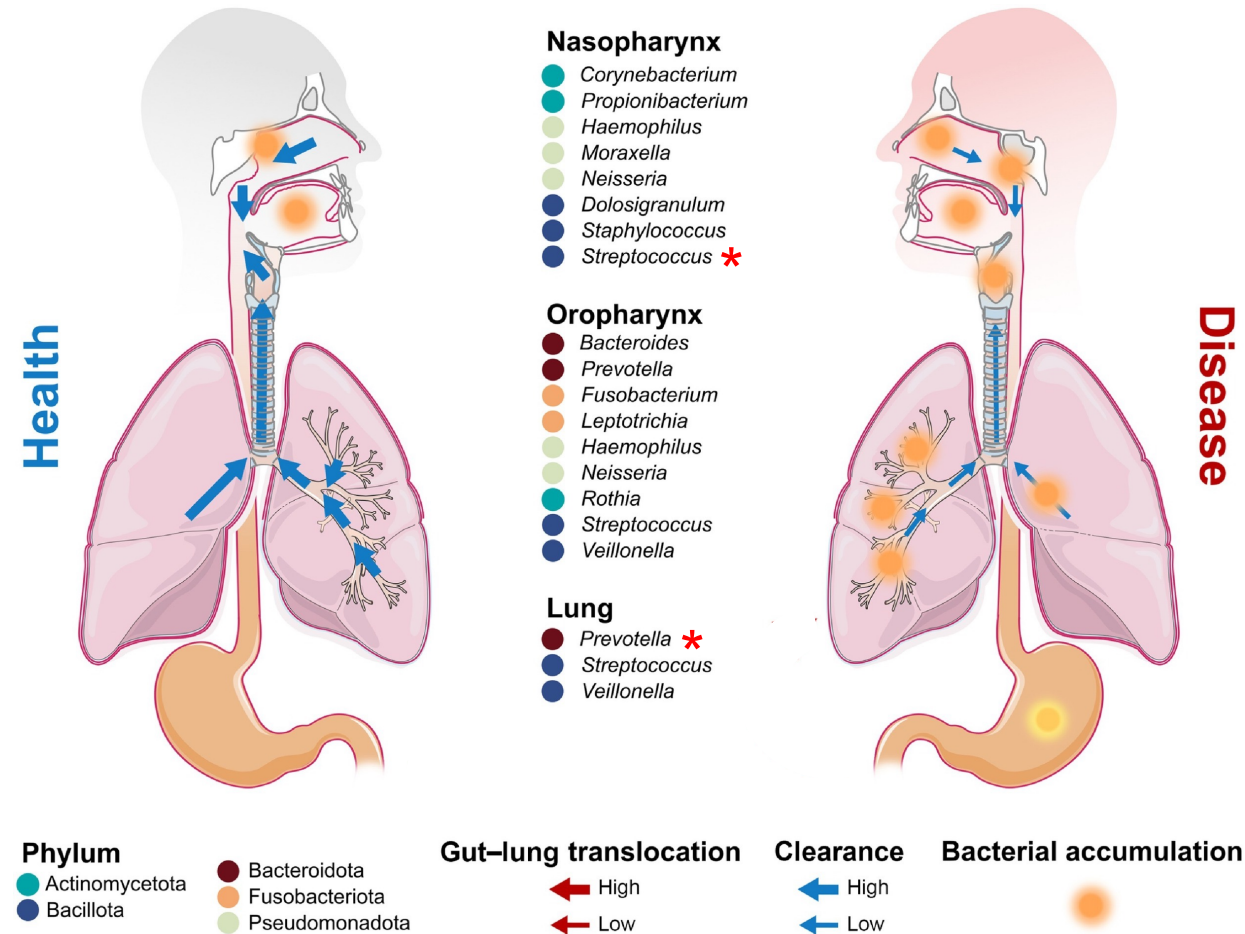
February 21st, 2026



University of Colorado
Anschutz Medical Campus

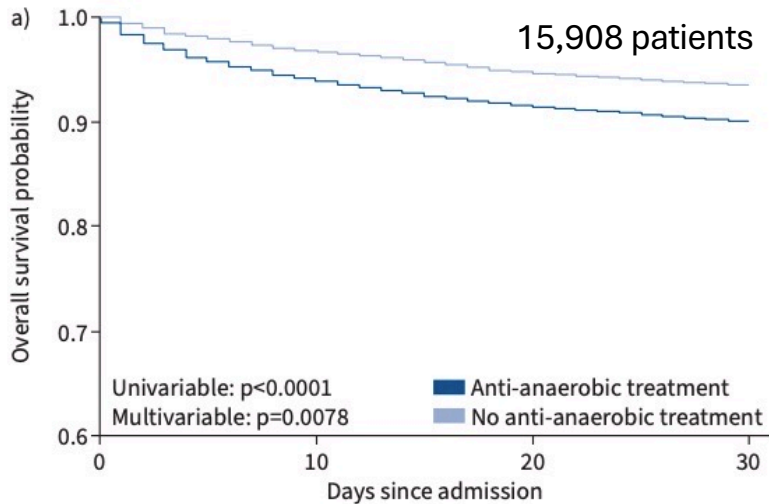
Streptococcus pneumoniae

- Opportunistic pathogen that asymptomatically colonizes ~5-10% of healthy adults and ~20-40% of children
- Pneumococcal vaccines more effective for invasive pneumococcal infections than pneumococcal pneumonia
- Airway microbiome diversity is a predictor for clinical outcomes in pneumonia patients

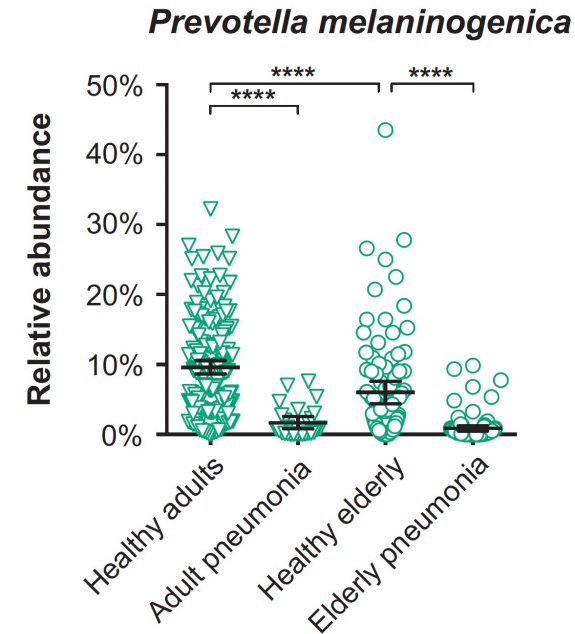


Pérez-Cobas et al., 2023. *Trends in Microbiology*.

Depletion of anaerobes is associated with worse pneumonia outcomes



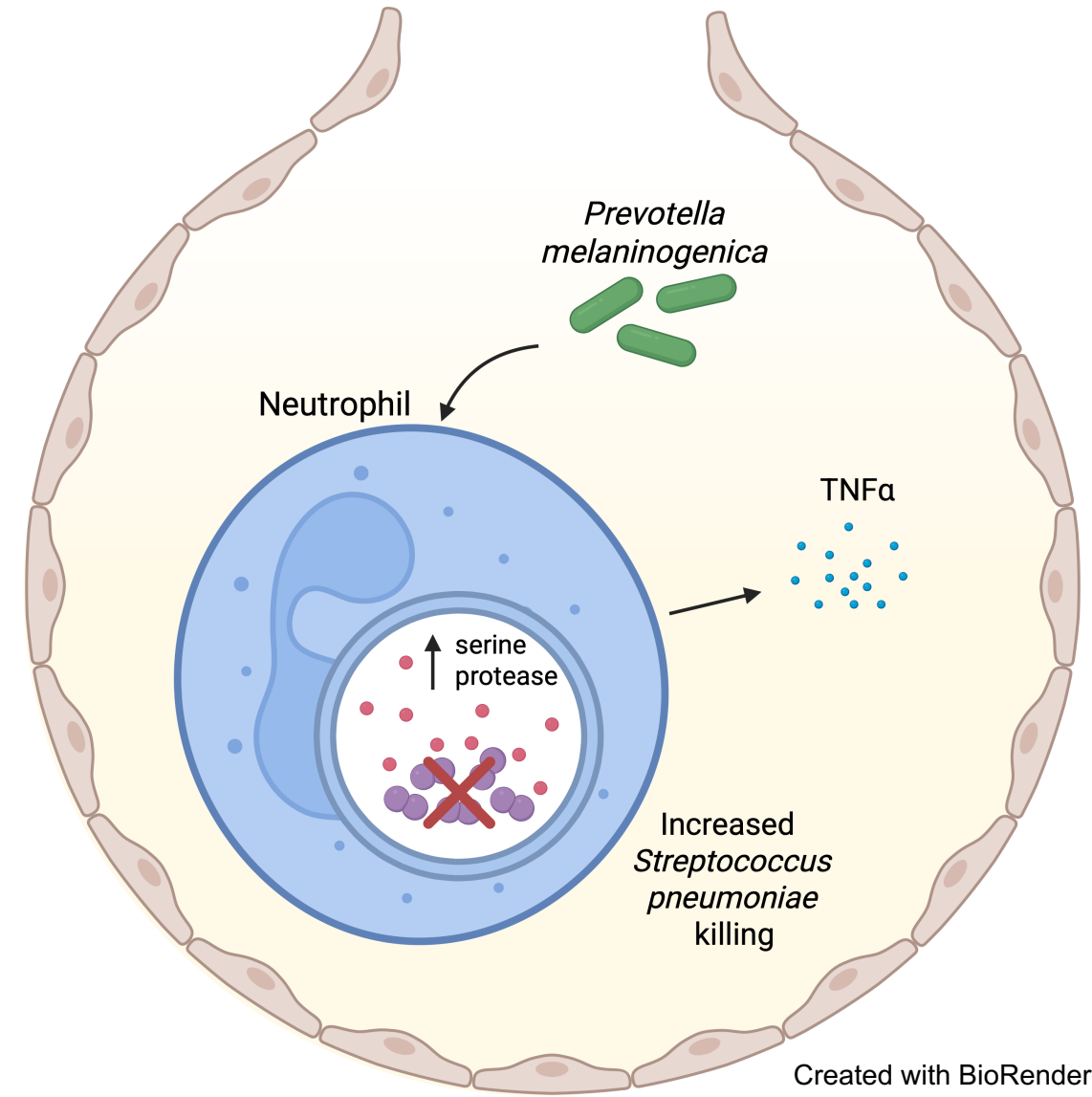
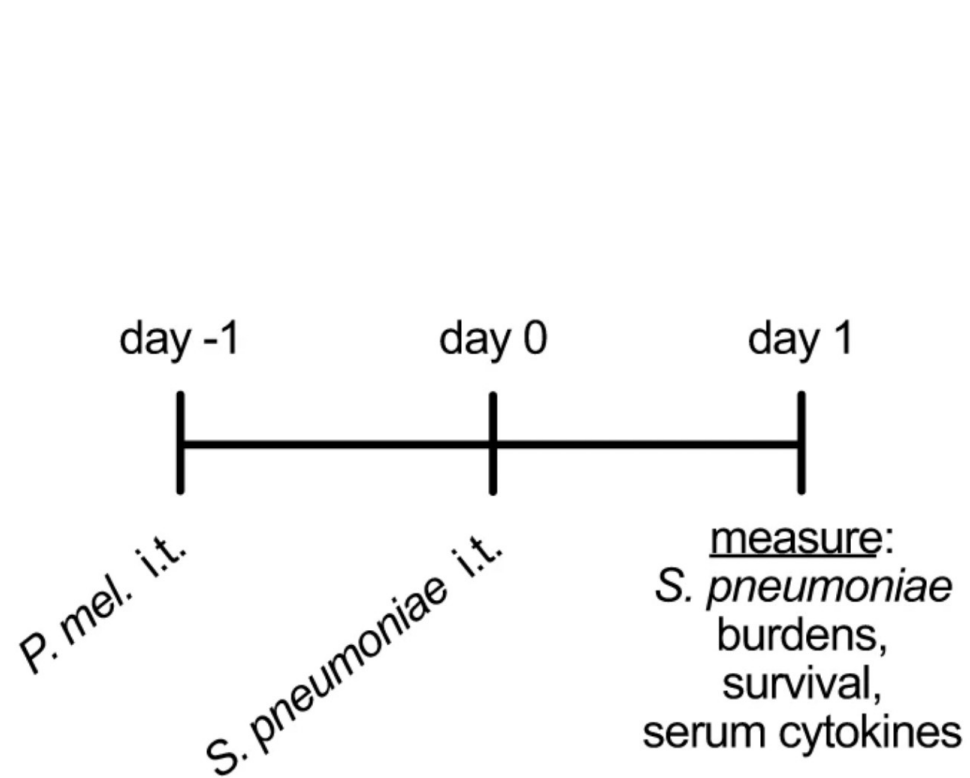
Kullberg et al., 2023. *European Respiratory Journal*
Chanderraj R et al., 2023. *European Respiratory Journal*



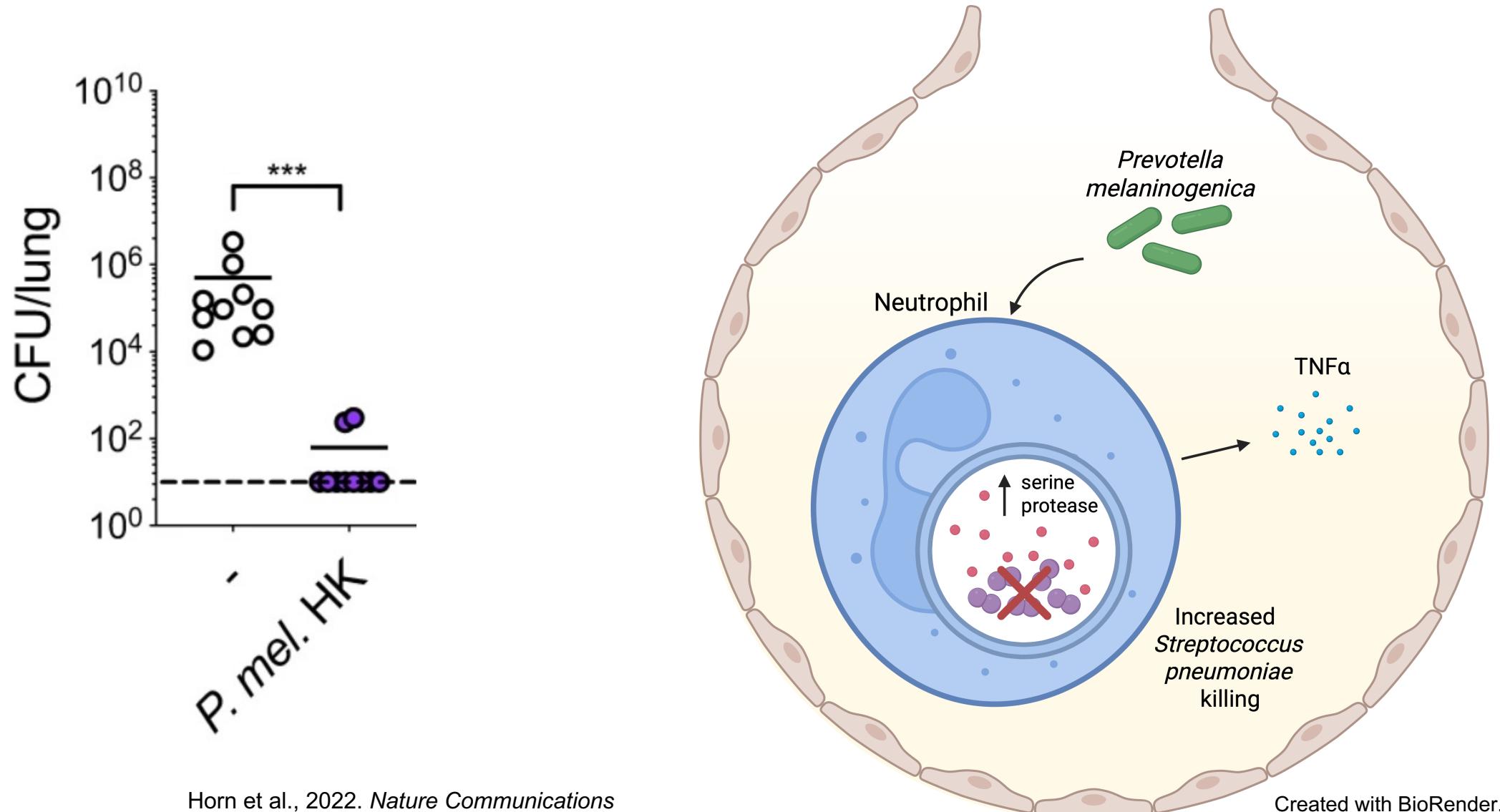
Piters et al., 2016. *The ISME Journal*

- Anti-anaerobic antibiotic treatment was associated with reduced survival in patients with severe pneumonia
- *Prevotella melaninogenica* is associated with health and is significantly lower in pneumonia patients

Intratracheal exposure to *Prevotella melaninogenica* leads to rapid *S. pneumoniae* airway clearance



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How does *Prevotella* regulate lung immune homeostasis and defense against *Streptococcus pneumoniae*?

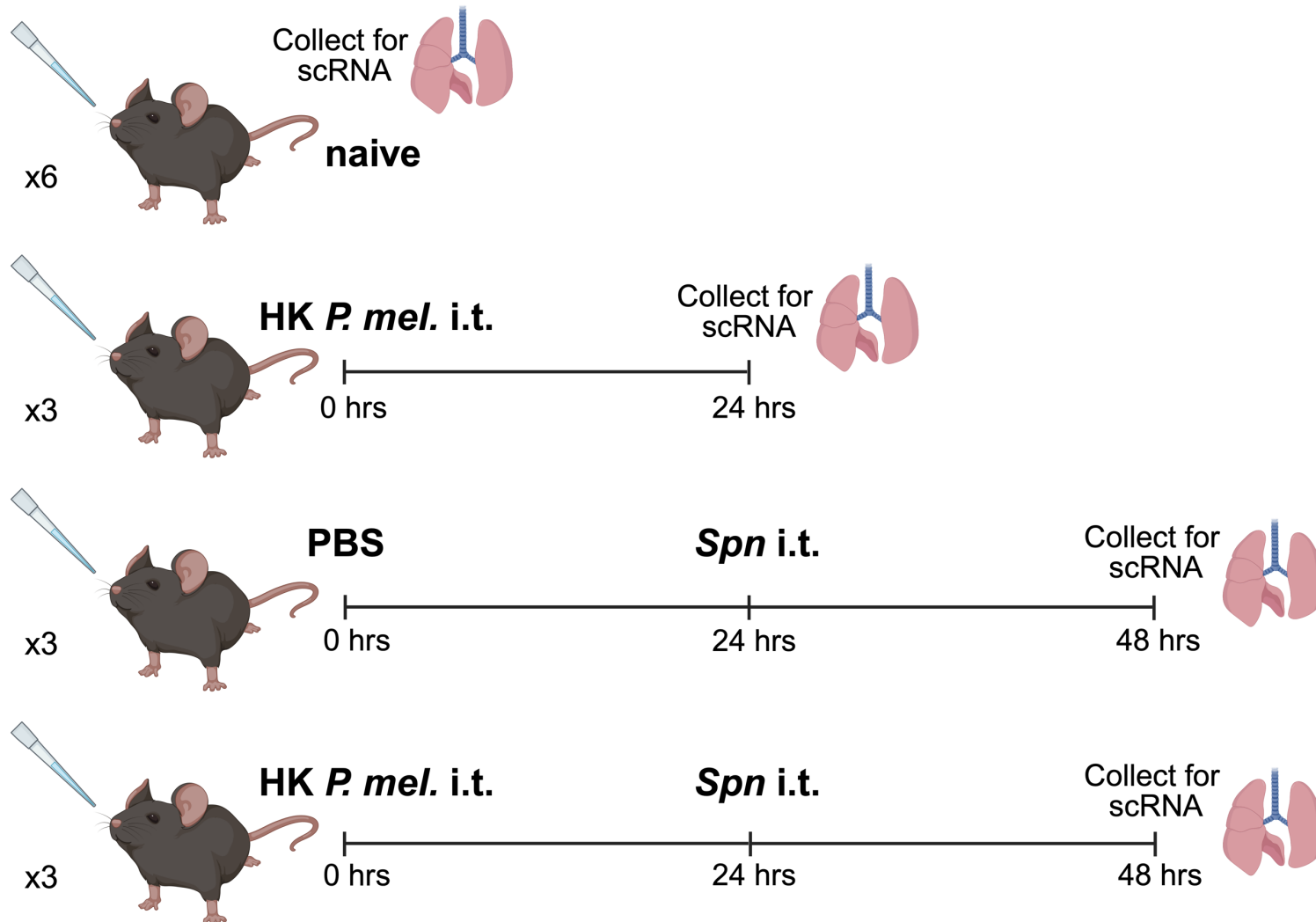
P. mel. HK

Increased
Streptococcus pneumoniae
killing

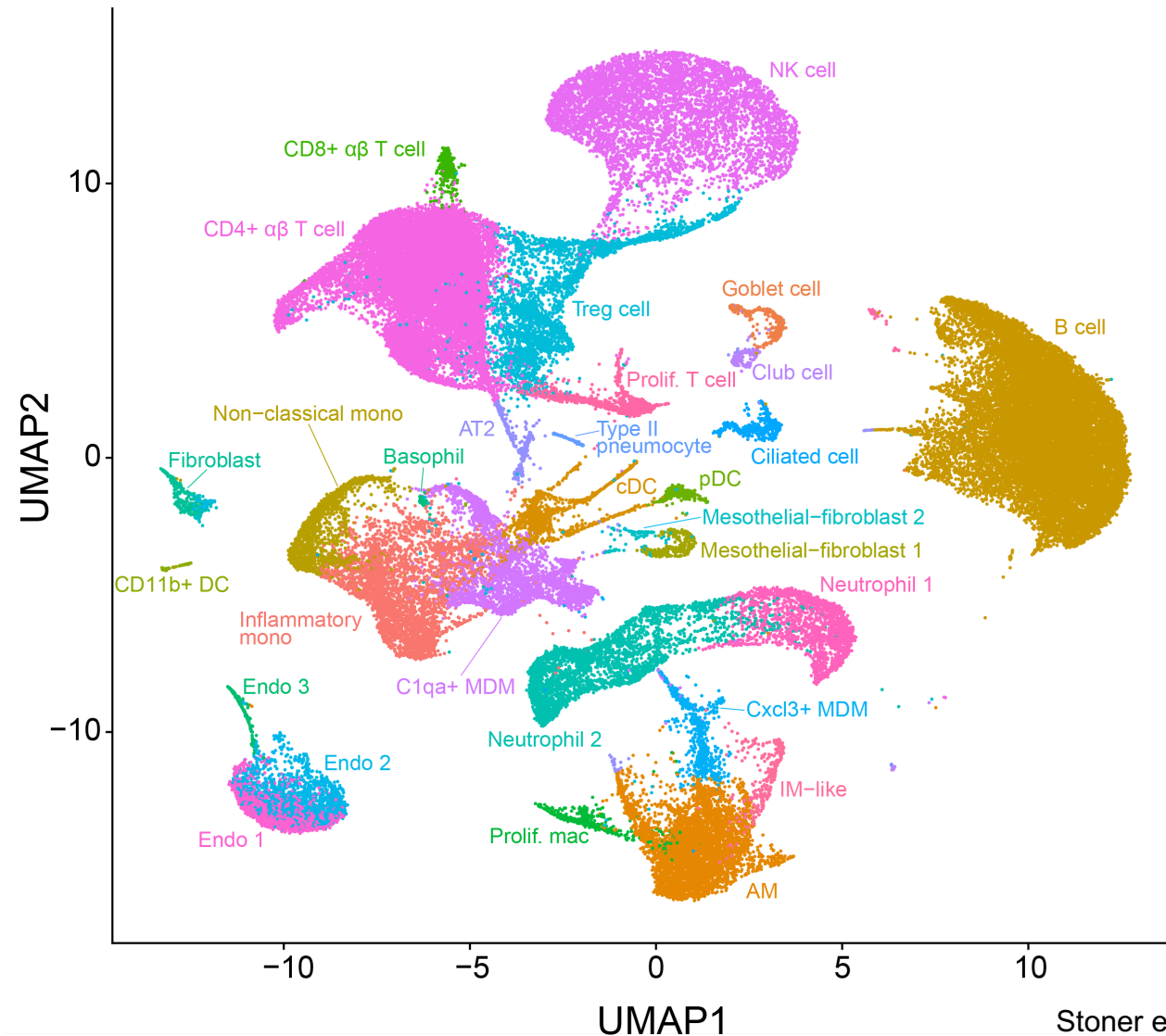
Single cell RNA Sequencing



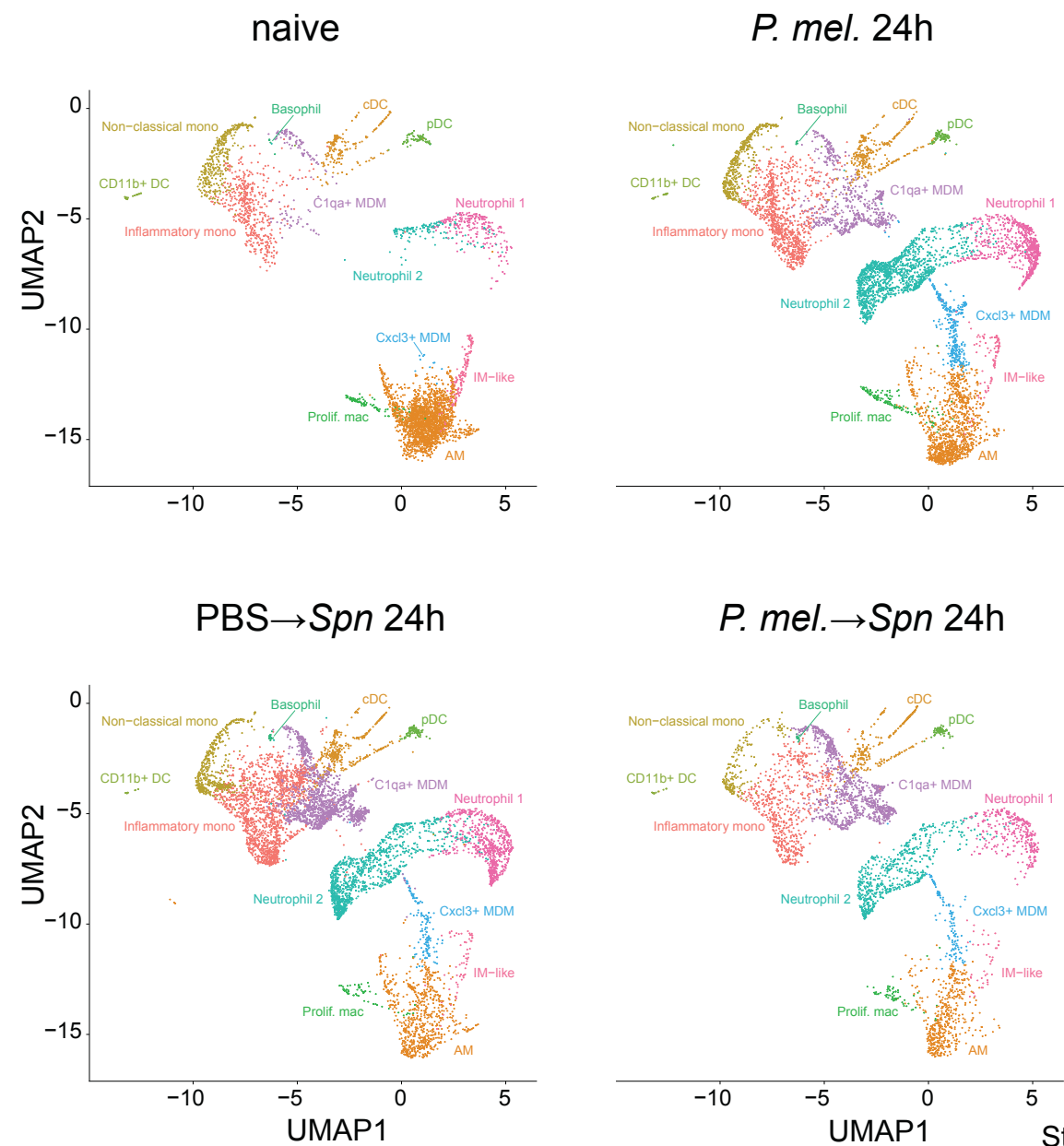
Eric Larson, PhD
UPenn



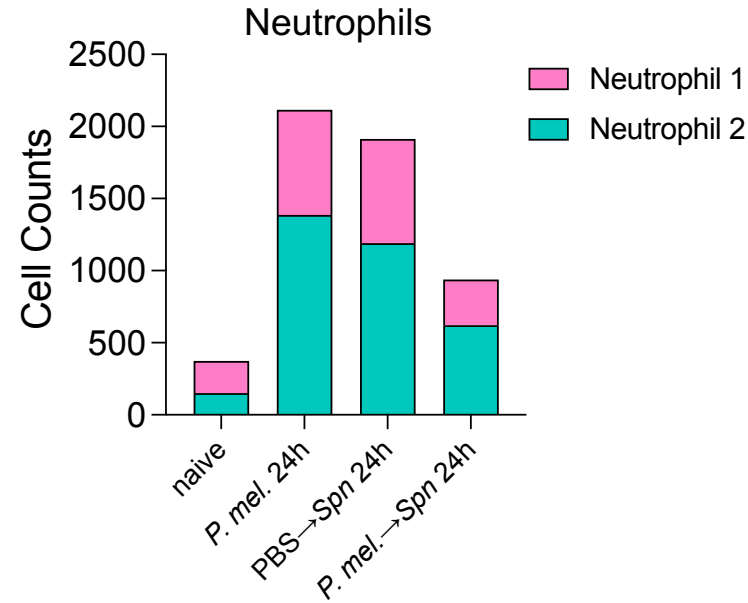
Single cell RNA sequencing identifies a variety of immune cells in the lungs of *Prevotella* and *S. pneumoniae*-exposed mice



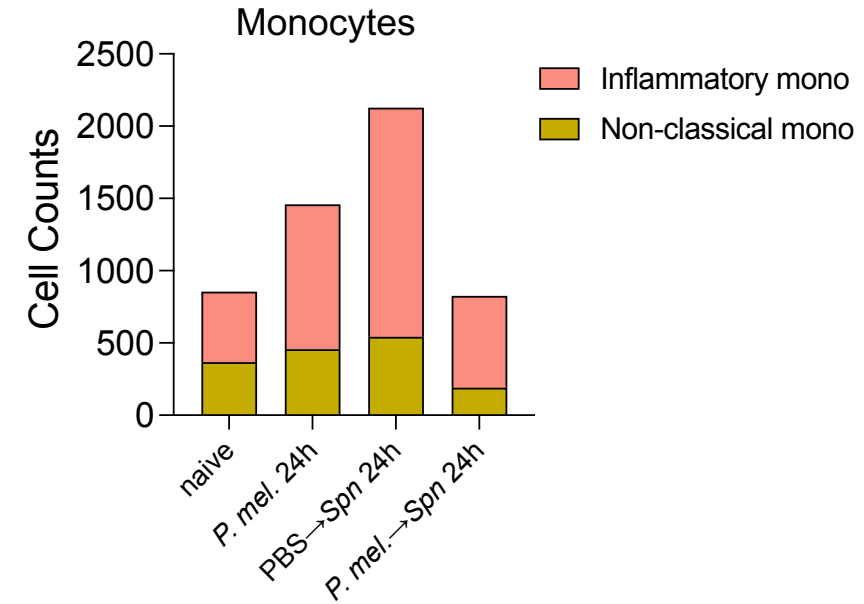
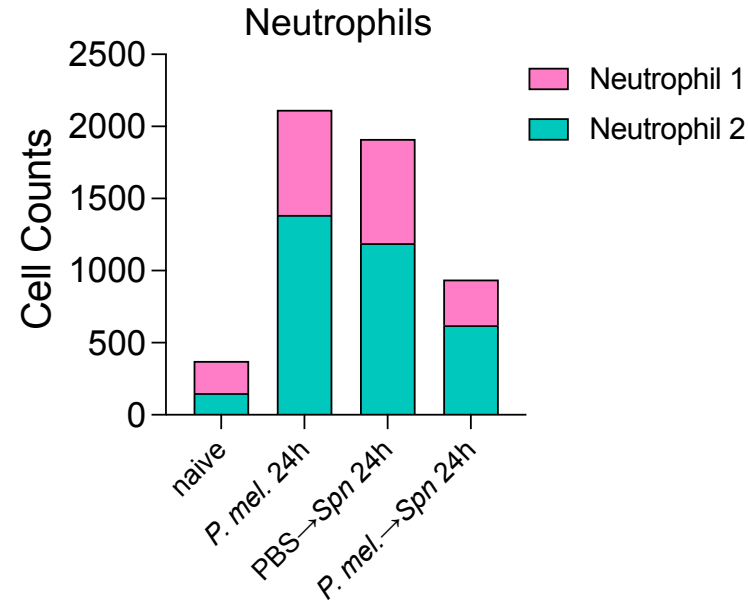
Broad myeloid population shifts are observed across conditions



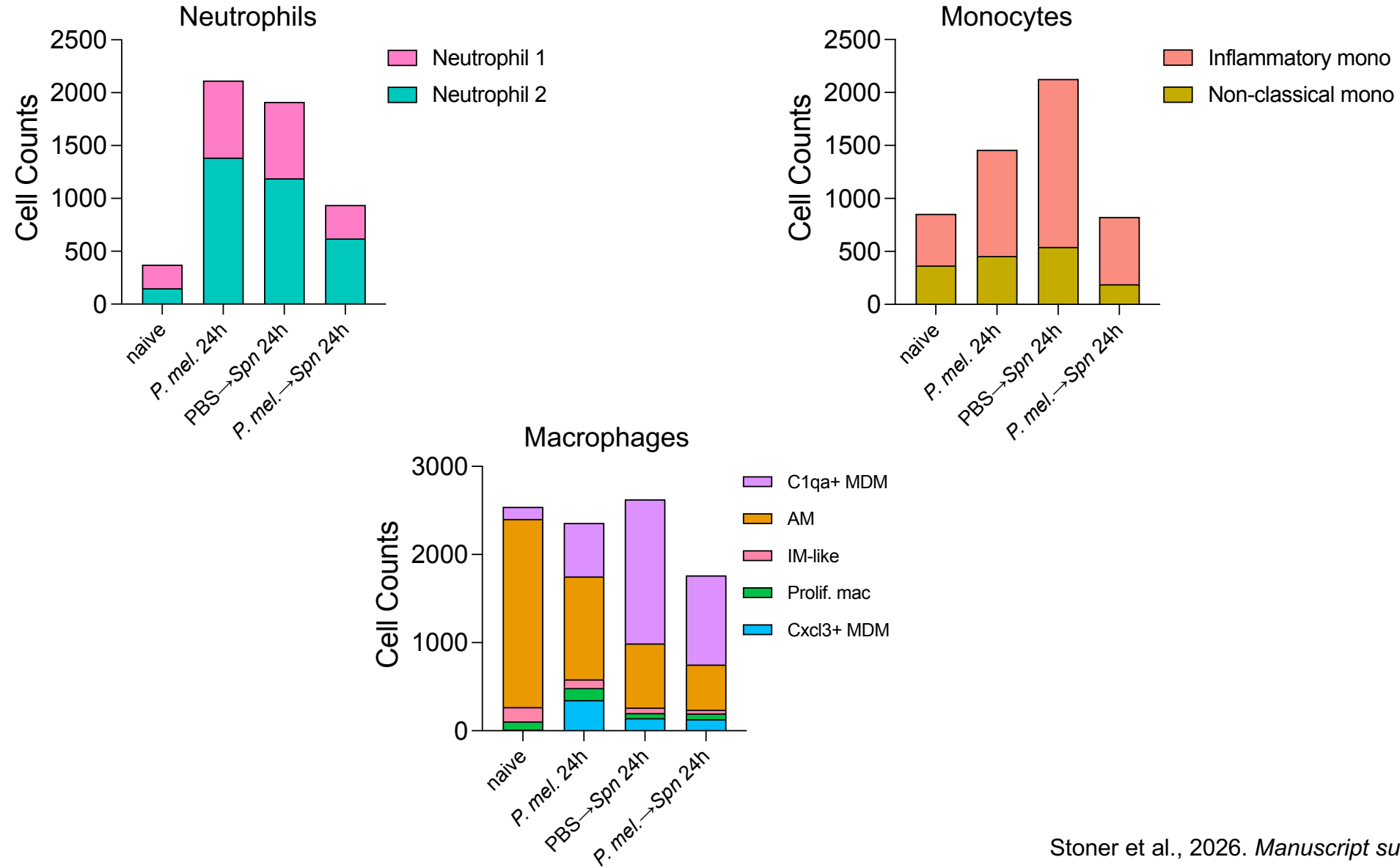
Myeloid cell composition changes upon exposure to *P. melaninogenica* and *S. pneumoniae*



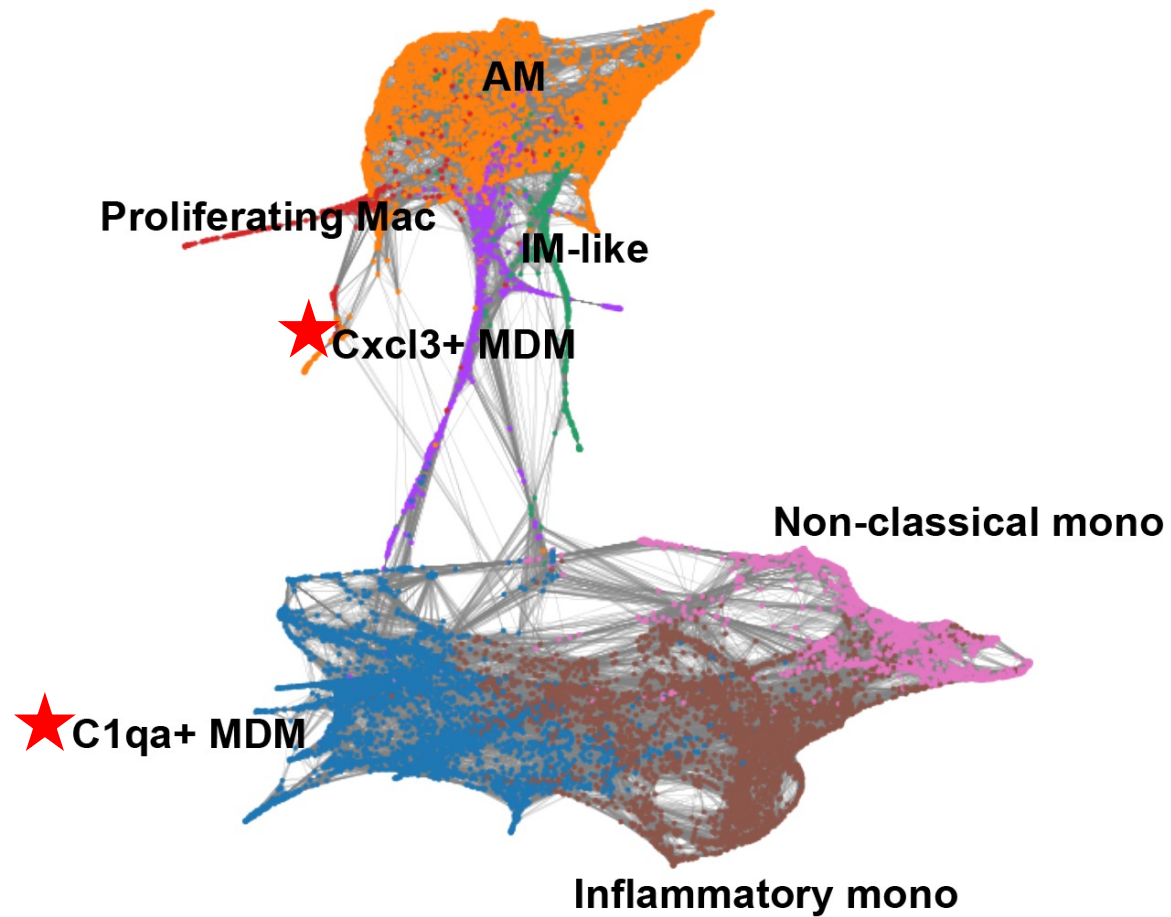
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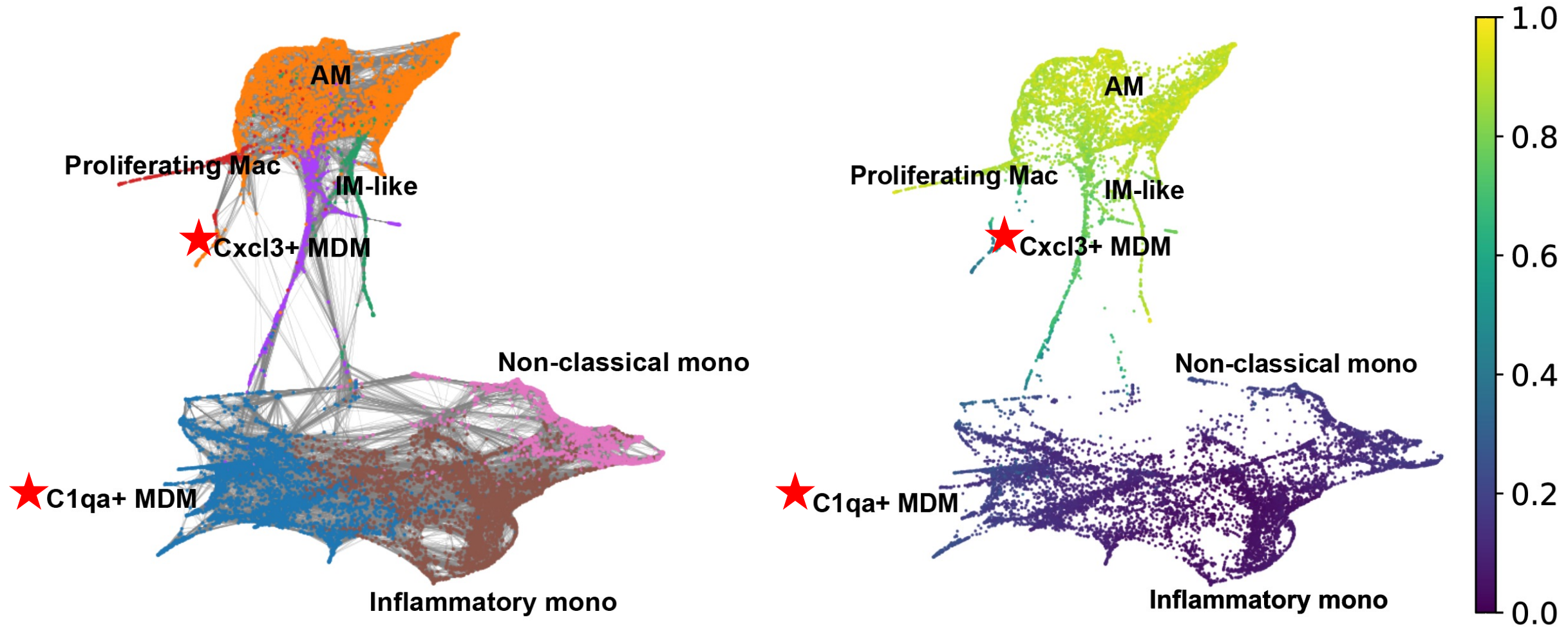
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Prevotella exposure alters monocyte-derived macrophage population profiles

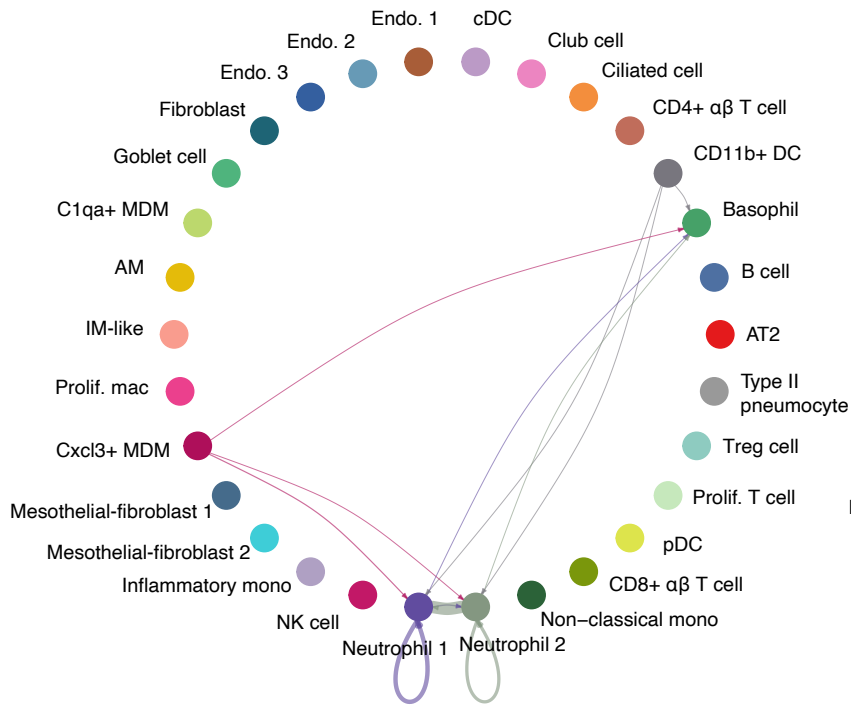


Prevotella exposure alters monocyte-derived macrophage population profiles

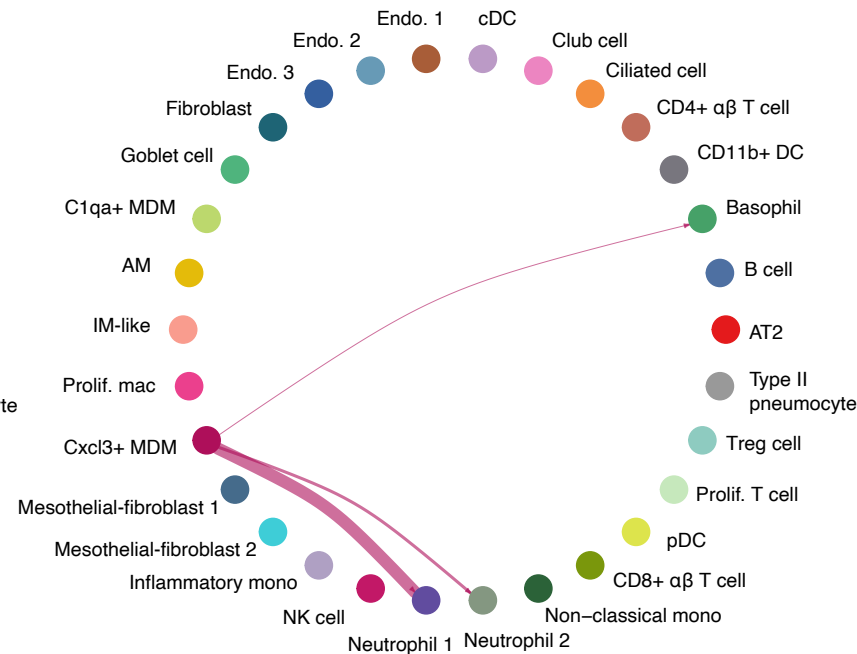


Prevotella-associated macrophages are a major source of chemokine signals for neutrophil recruitment

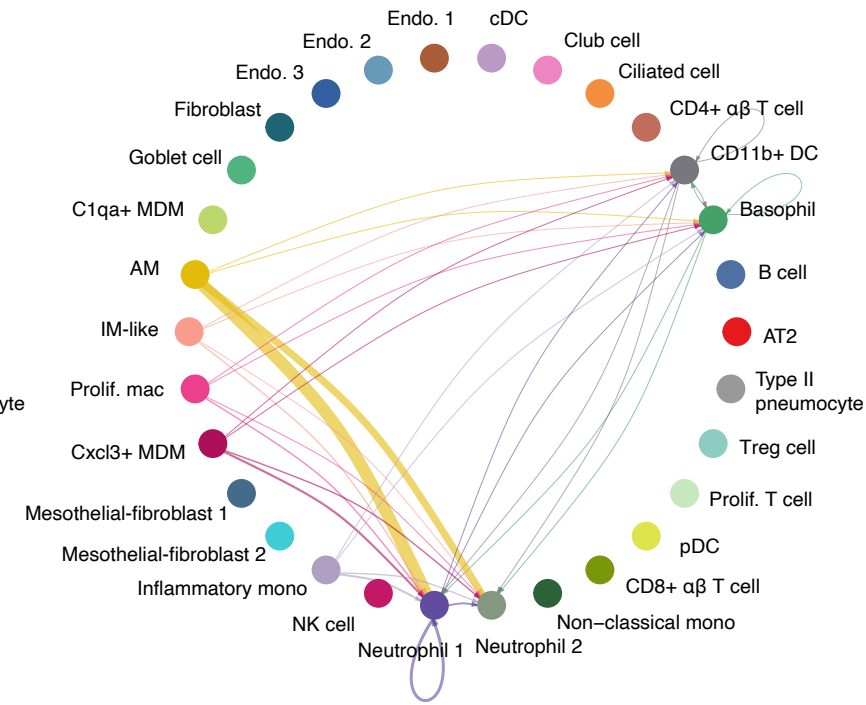
Cxcl2 – Cxcr2



Cxcl3 – Cxcr2

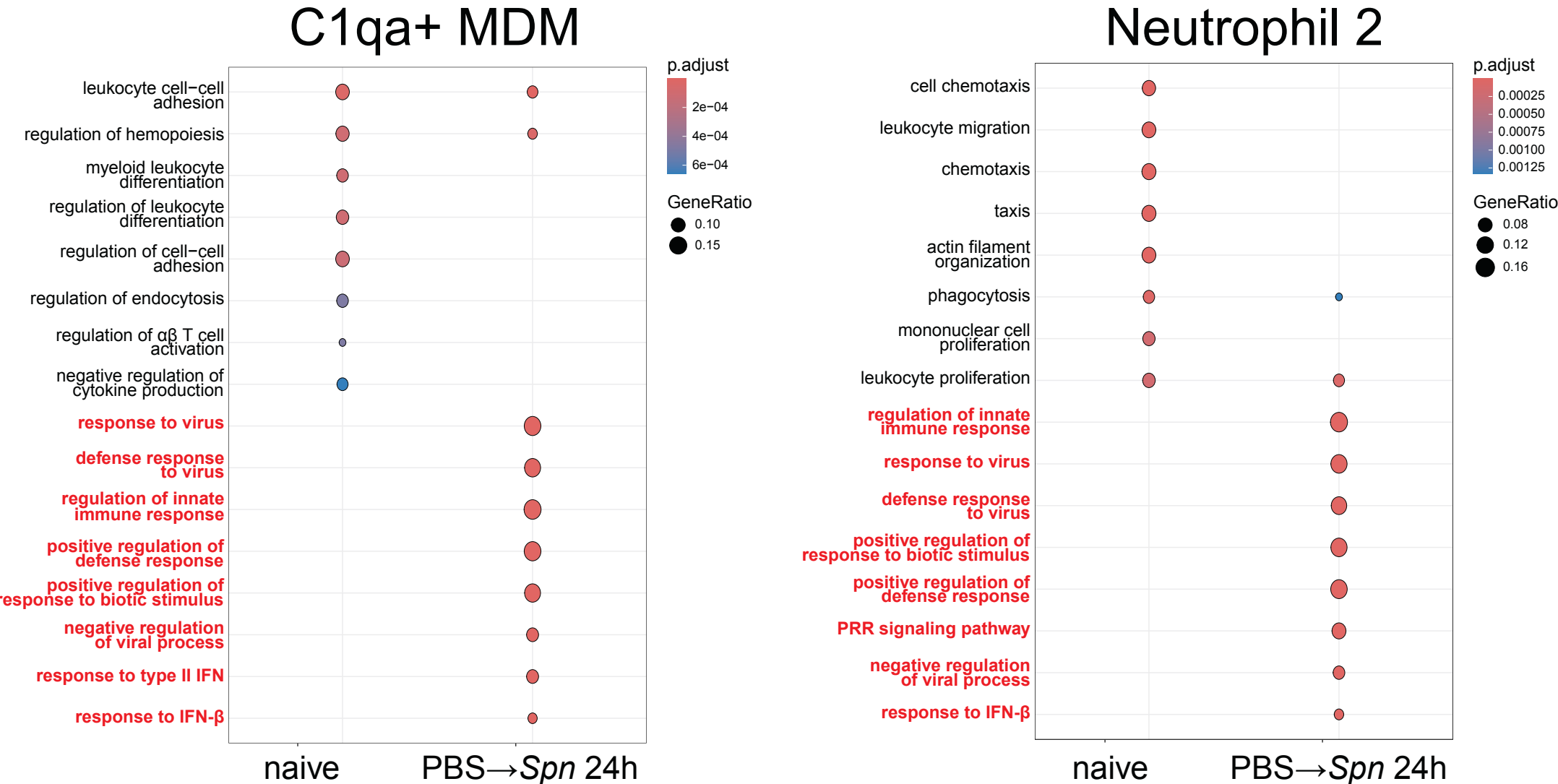


Ccl6 – Ccr1

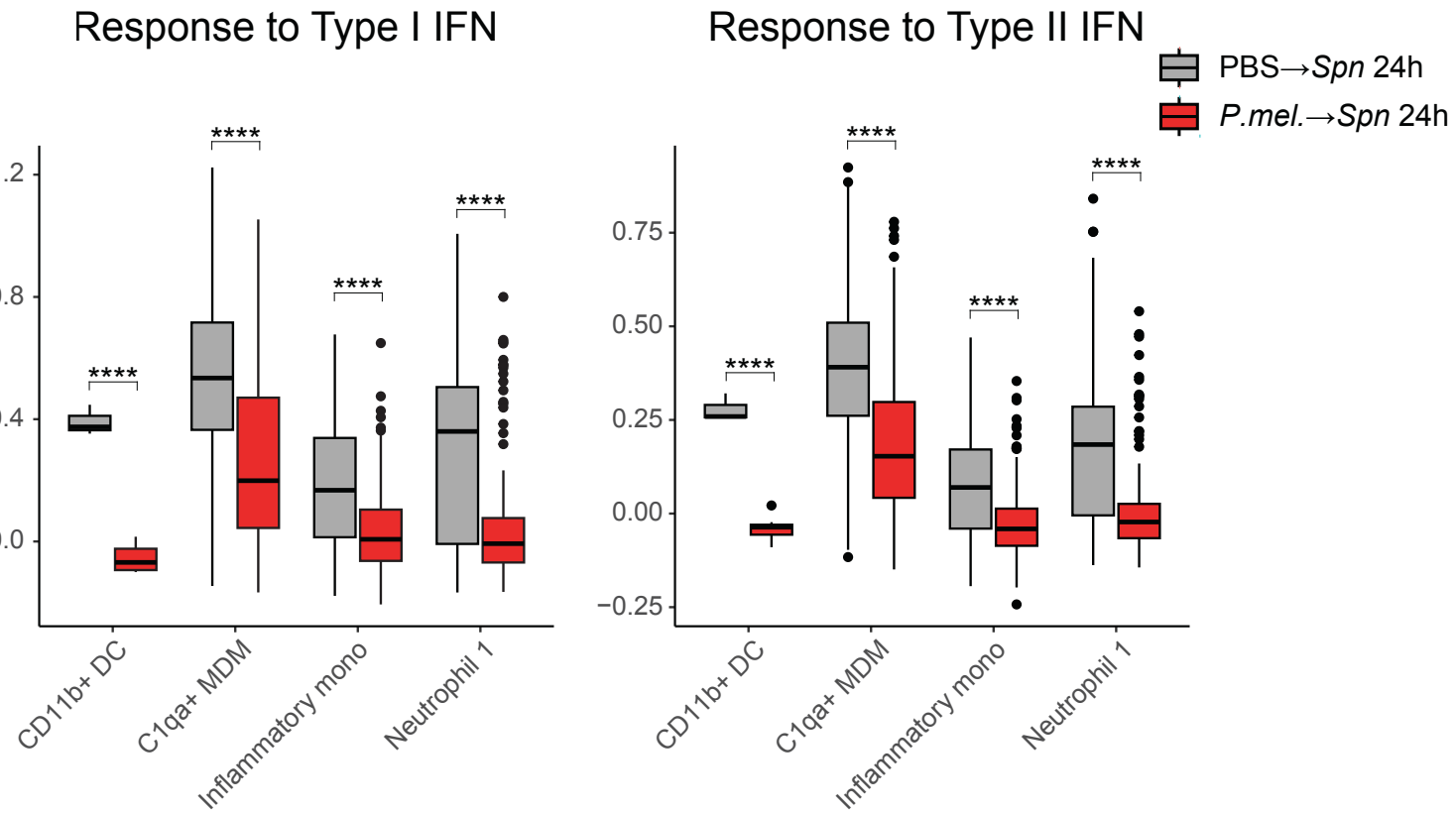


What are the top differentially enriched pathways in *Prevotella* and *S. pneumoniae*-exposed mice?

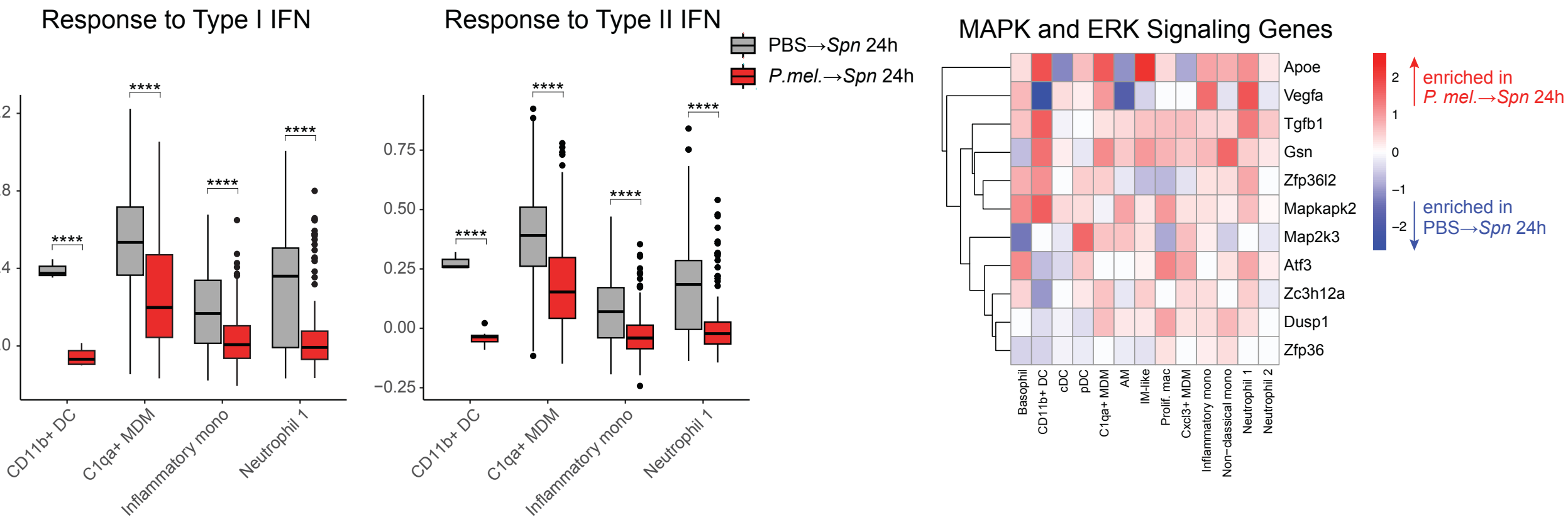
S. pneumoniae infection induces interferon gene expression in lung immune cells



Prevotella priming skews the myeloid response to *S. pneumoniae*
away from interferon dominance

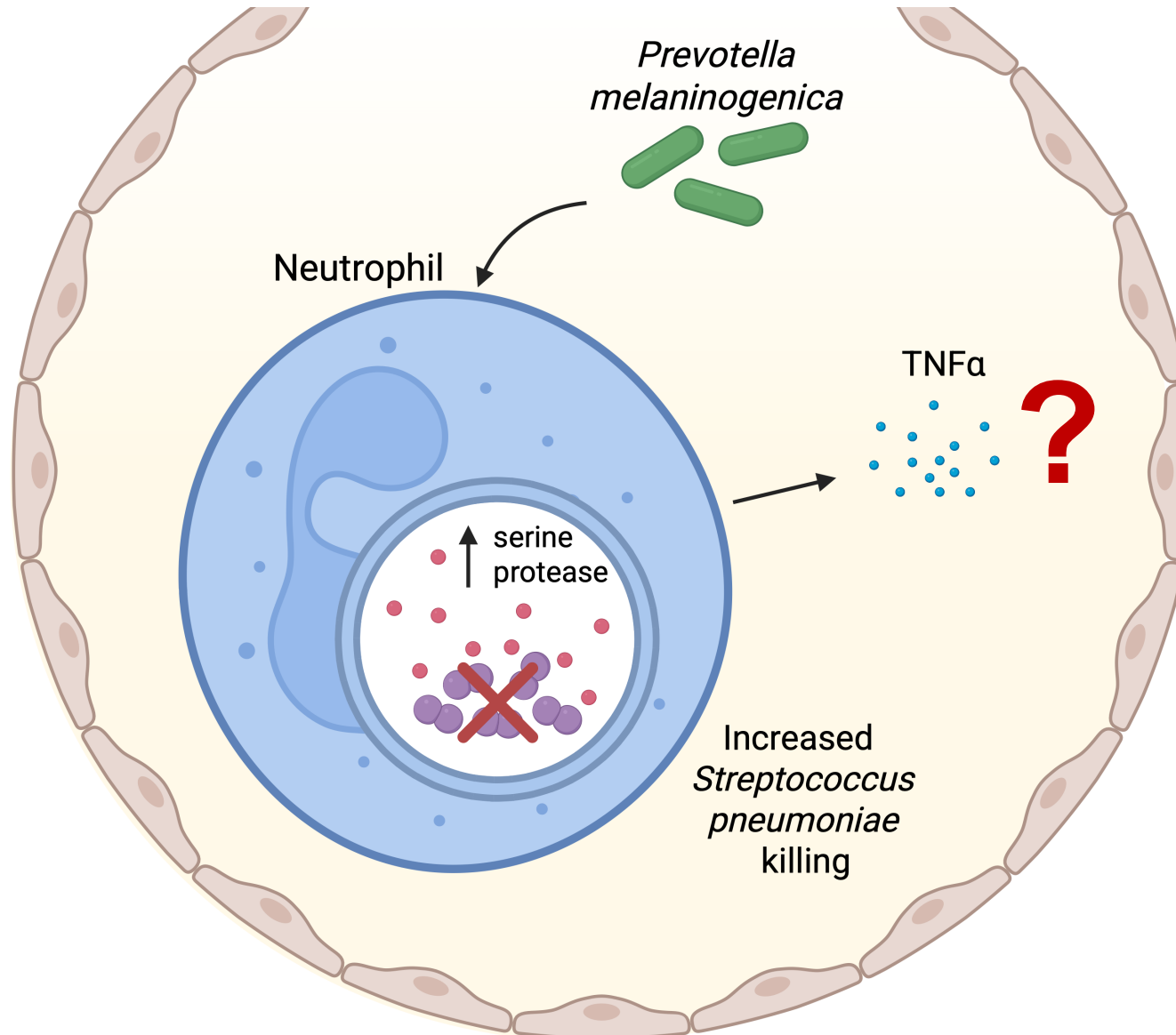


Prevotella priming skews the myeloid response to *S. pneumoniae* away from interferon dominance

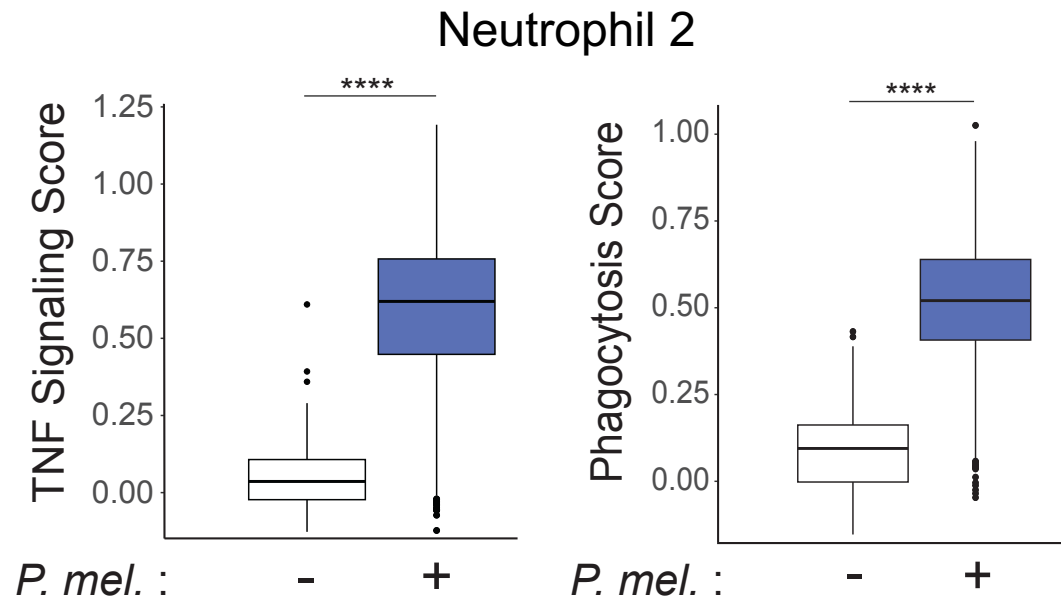


How is *Prevotella*-induced, neutrophil-mediated clearance of *S. pneumoniae* regulated?

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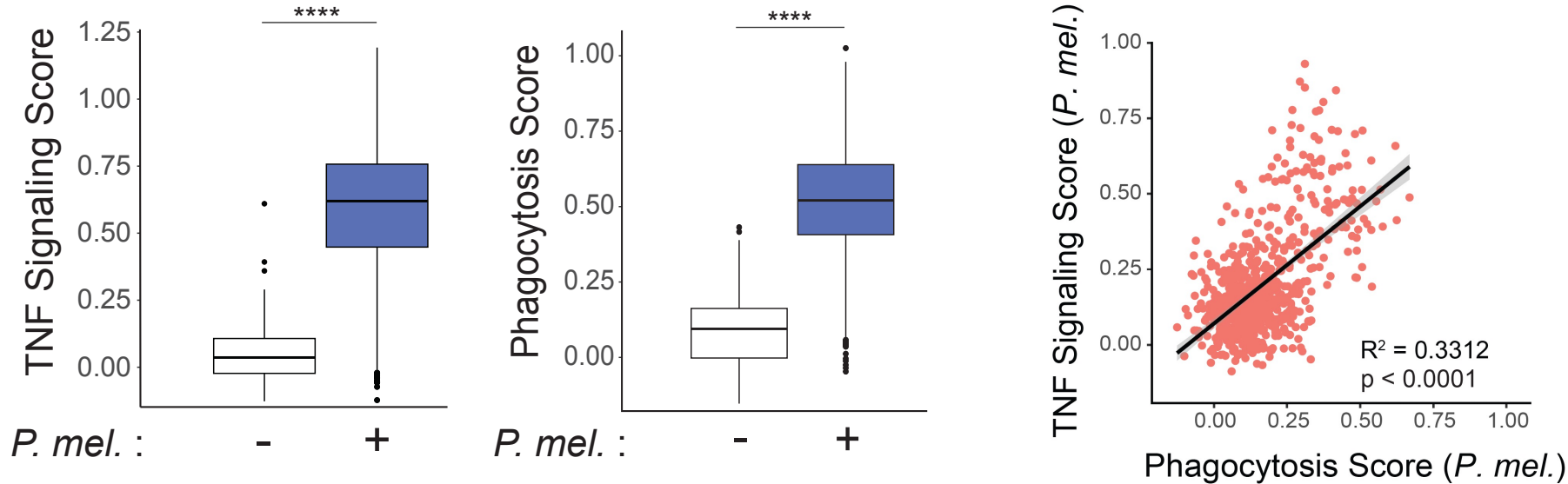


TNF signaling is induced by *Prevotella* exposure and regulates neutrophil bacterial uptake and serine protease activity

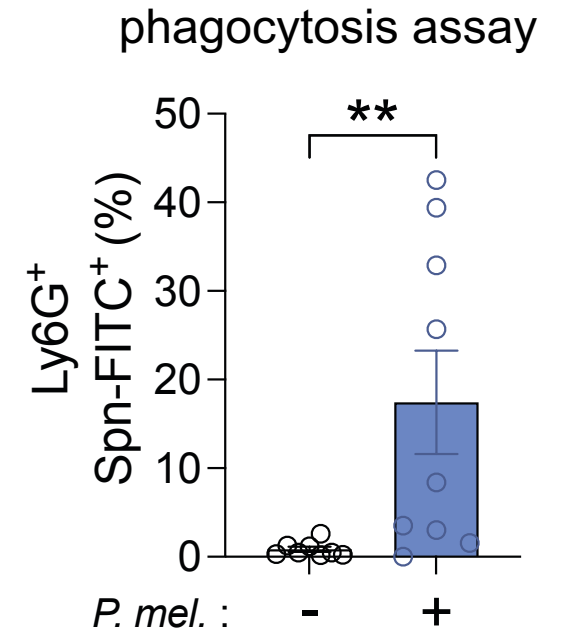
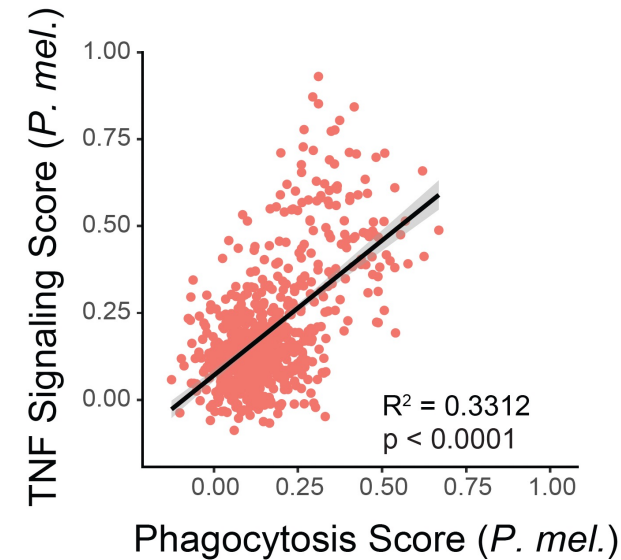
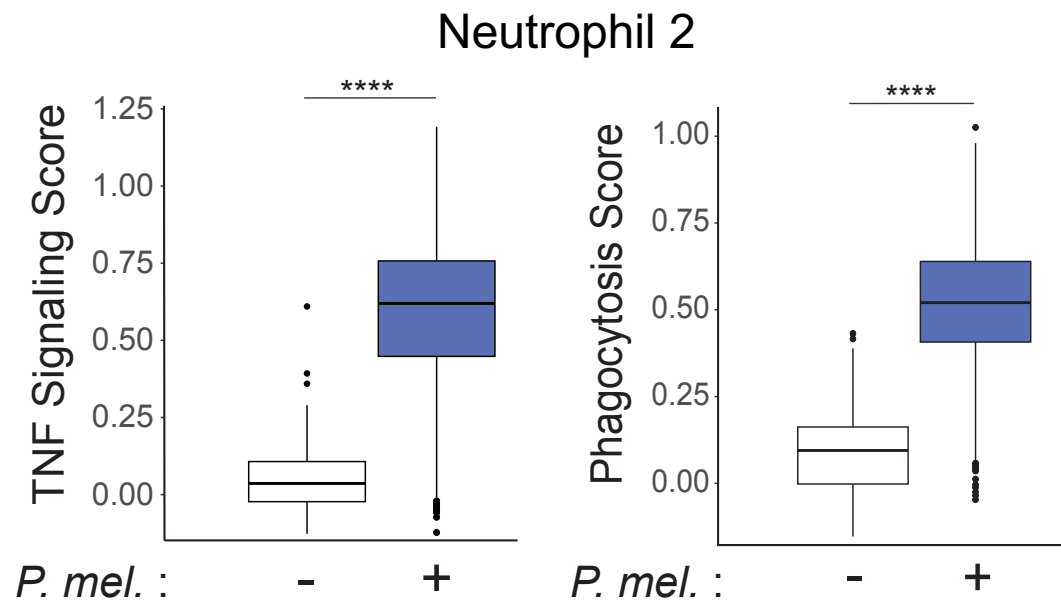


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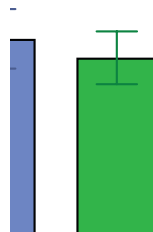
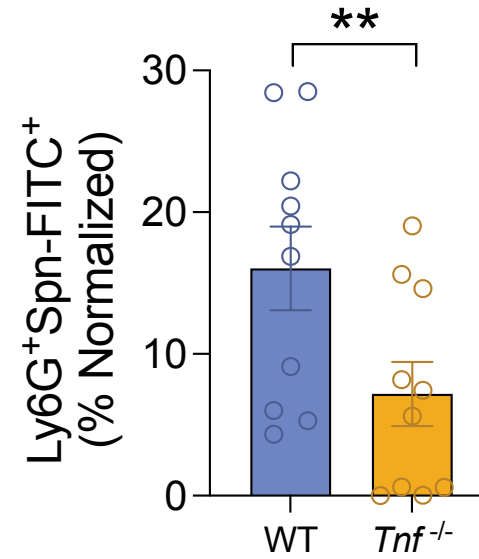
Neutrophil 2



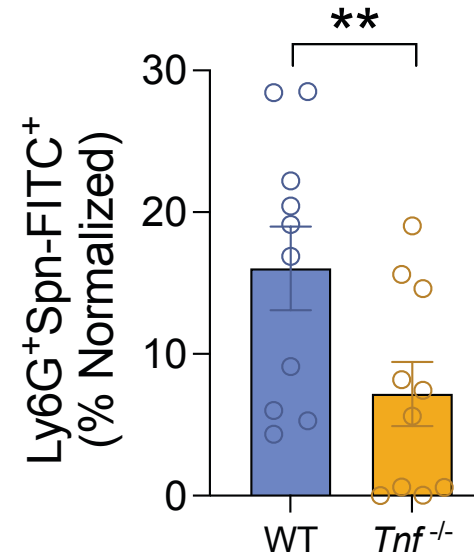
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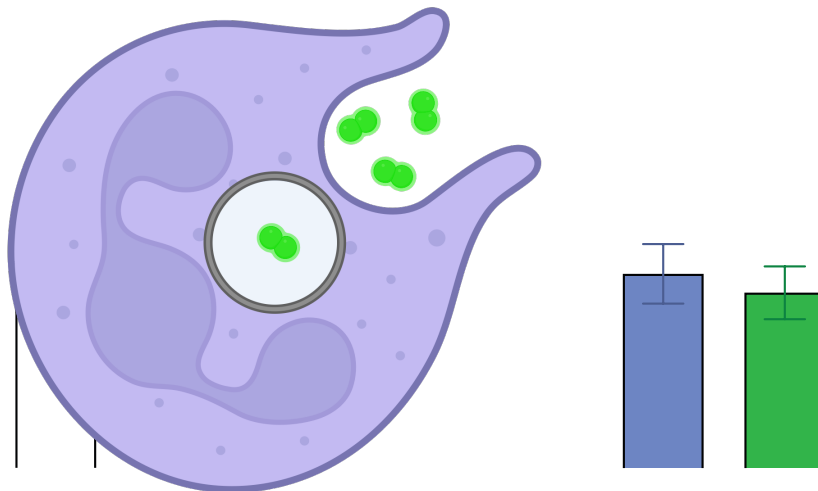
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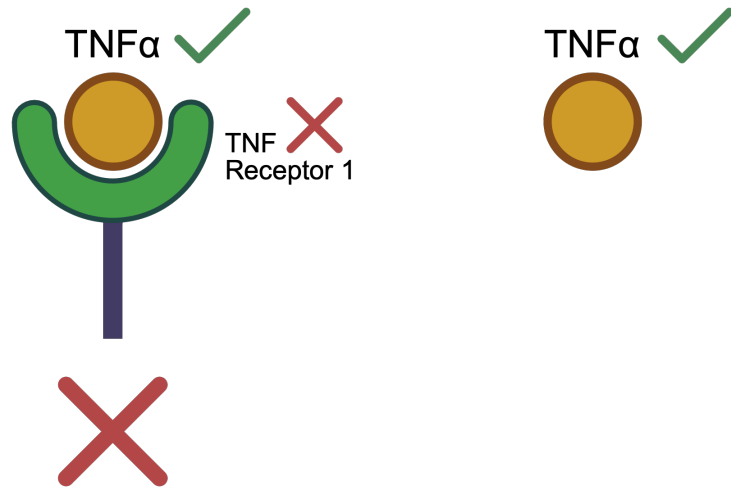
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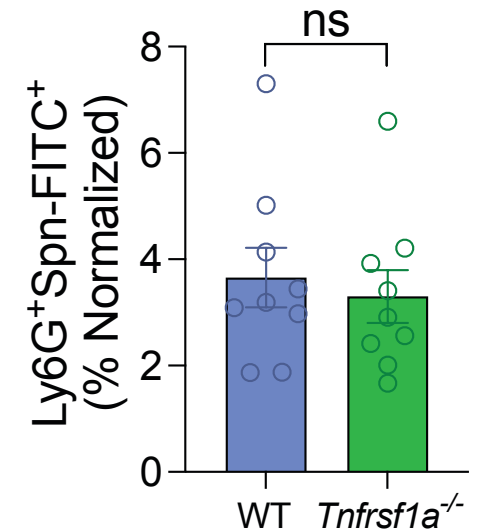
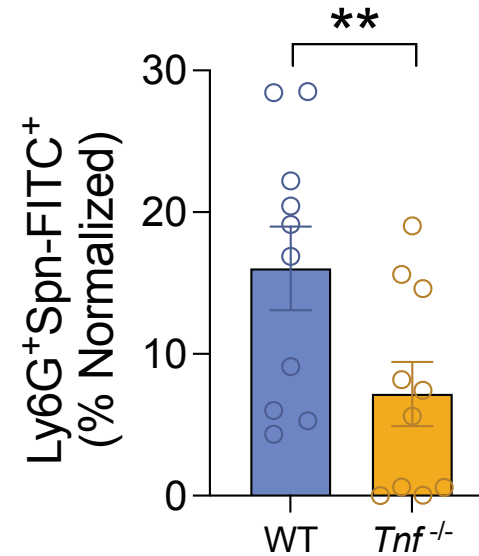
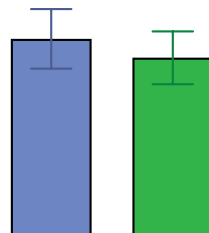
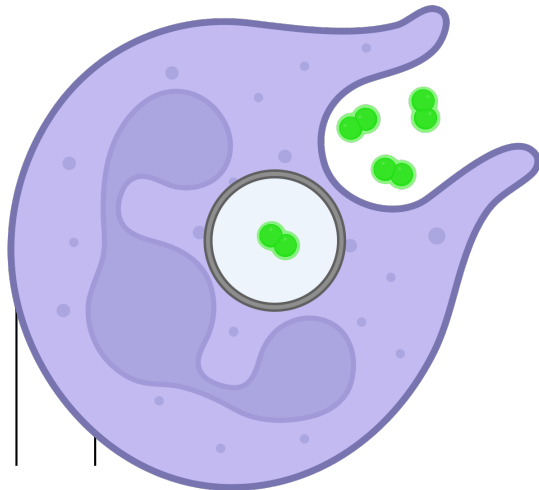
Phagocytosis of *S. pneumoniae*



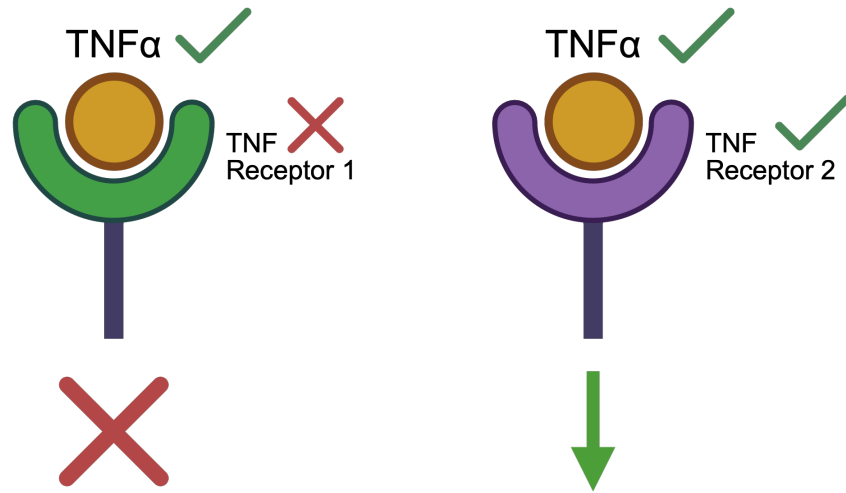
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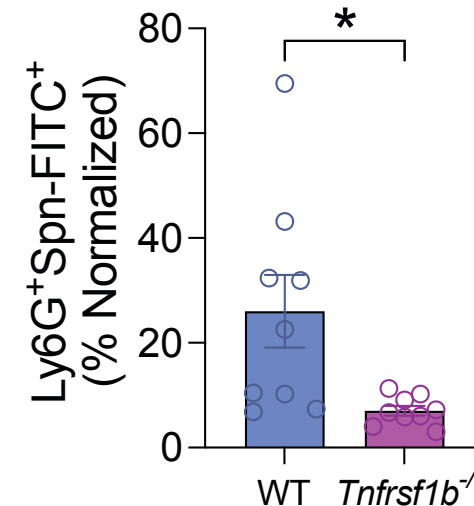
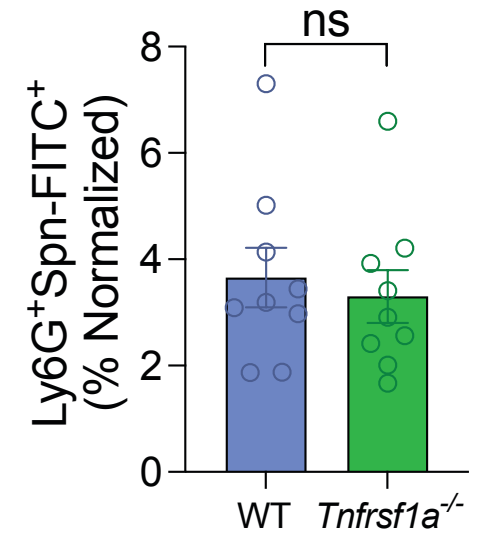
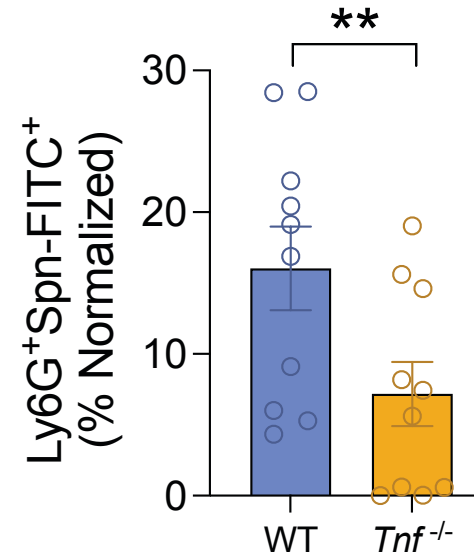
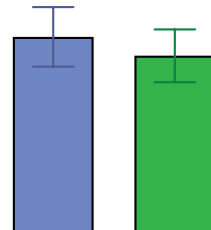
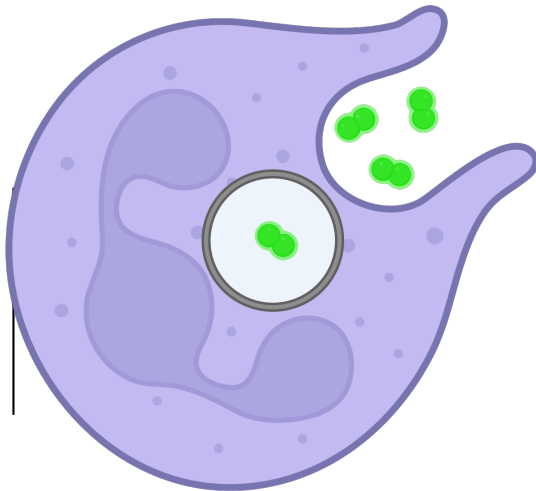
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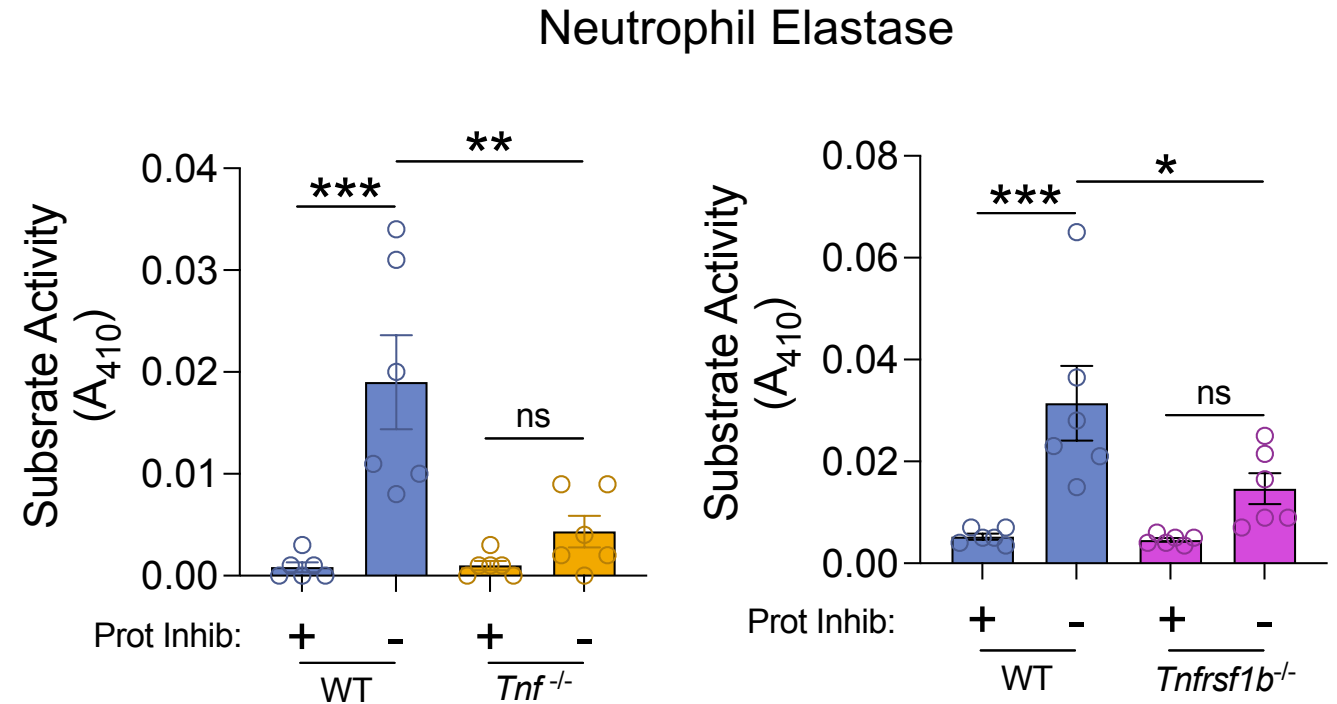
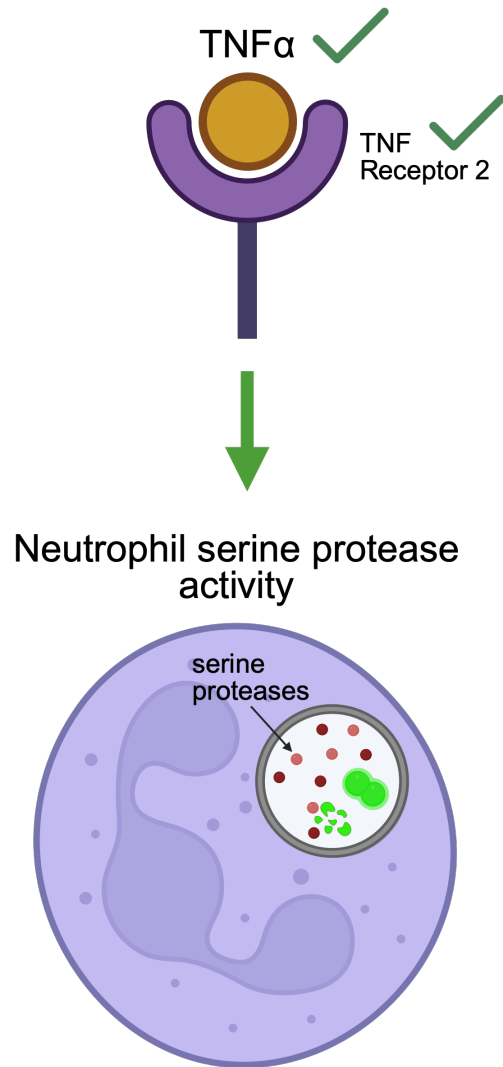
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Phagocytosis of *S. pneumoniae*



TNF signaling is induced by *Prevotella* exposure and regulates neutrophil bacterial uptake and serine protease activity



*similar results for serine protease Cathepsin G

Do recruited monocytes and macrophages
contribute to enhanced clearance of
S. pneumoniae after *Prevotella* exposure?

C1qa+ MDM

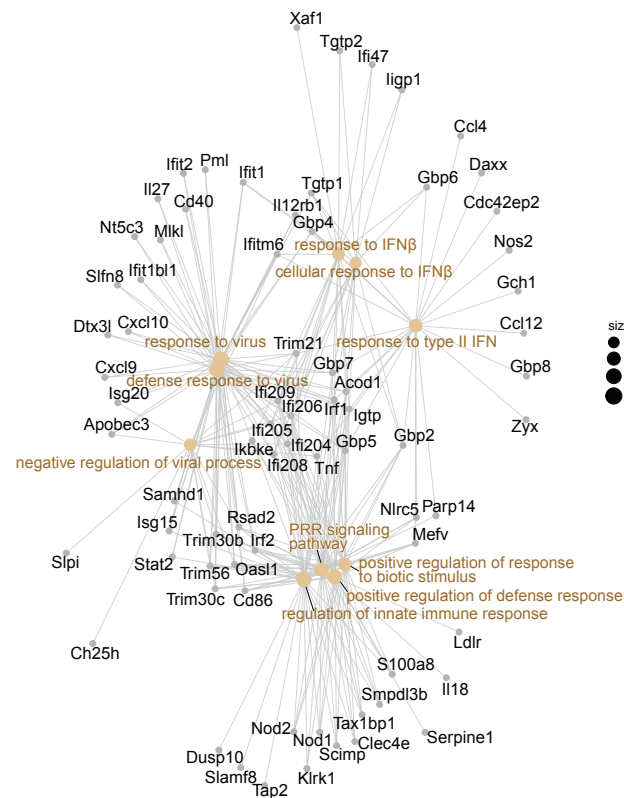
P. mel. → *Spn* 24h



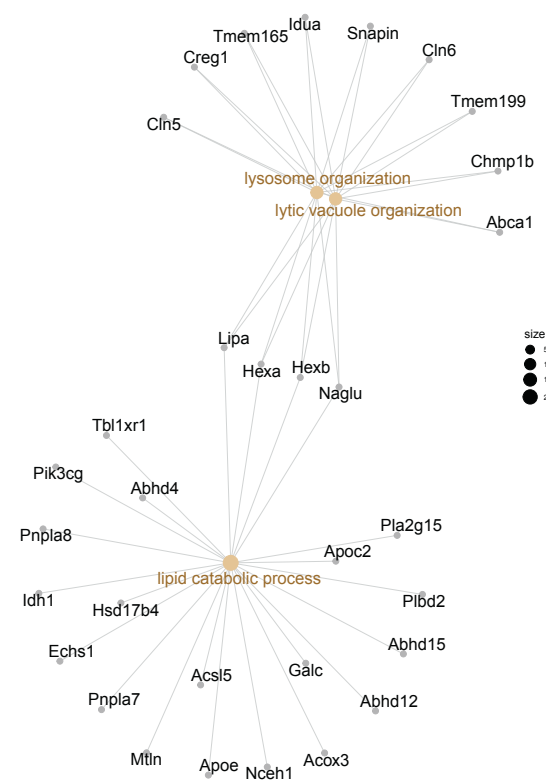
Phagocytosis genes are enriched in macrophages and monocytes of *Prevotella*-exposed mice

C1qa+ MDM

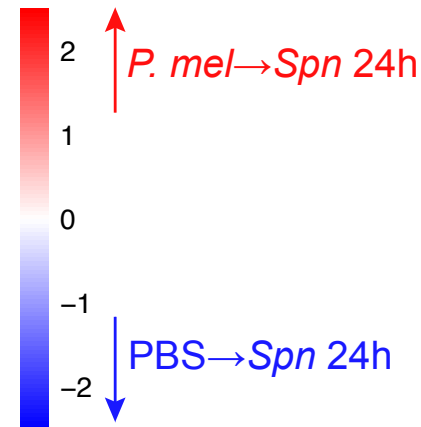
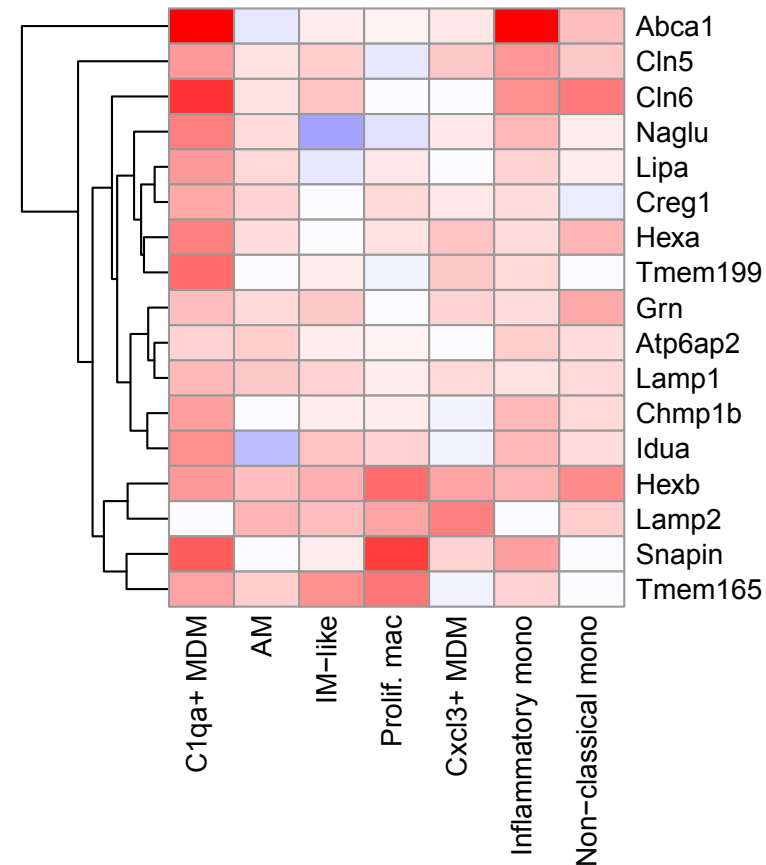
PBS→*Spn* 24h



P. mel.→*Spn* 24h

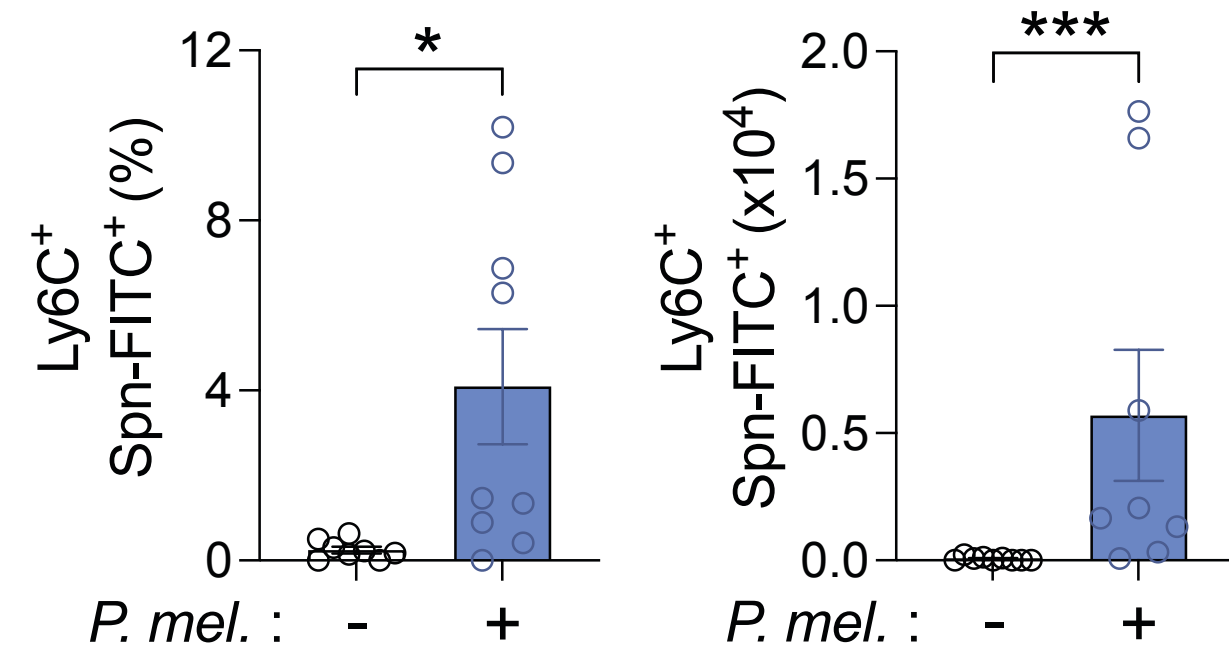


Lysosomal Genes



Prevotella exposure increases monocyte and alveolar macrophage phagocytosis of *S. pneumoniae*

Ly6C⁺ Monocytes

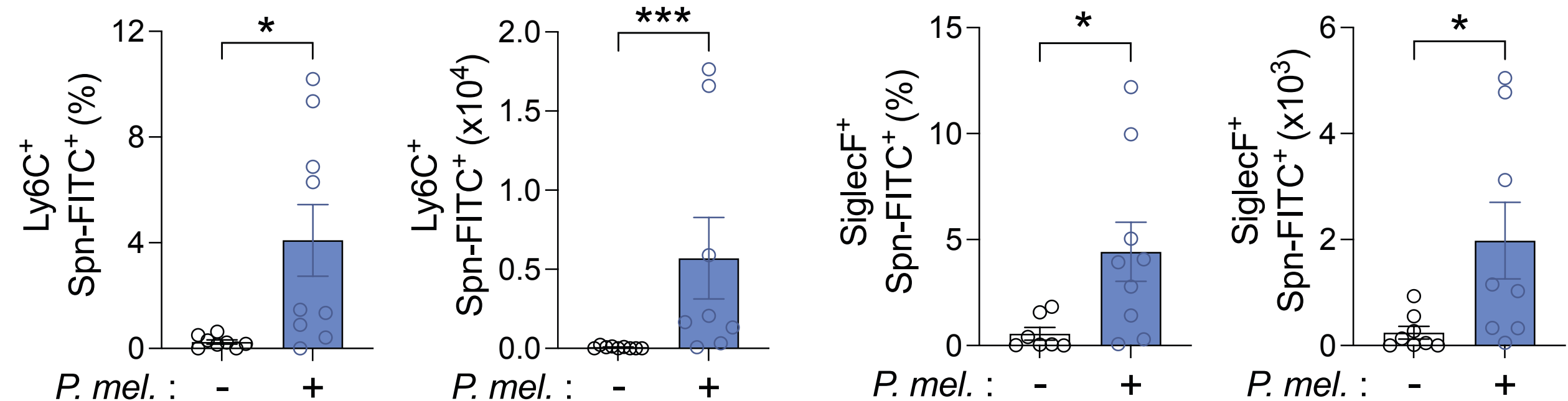


Mann-Whitney
*p<.05
n=3 biological, 3 technical replicates

Prevotella exposure increases monocyte and alveolar macrophage phagocytosis of *S. pneumoniae*

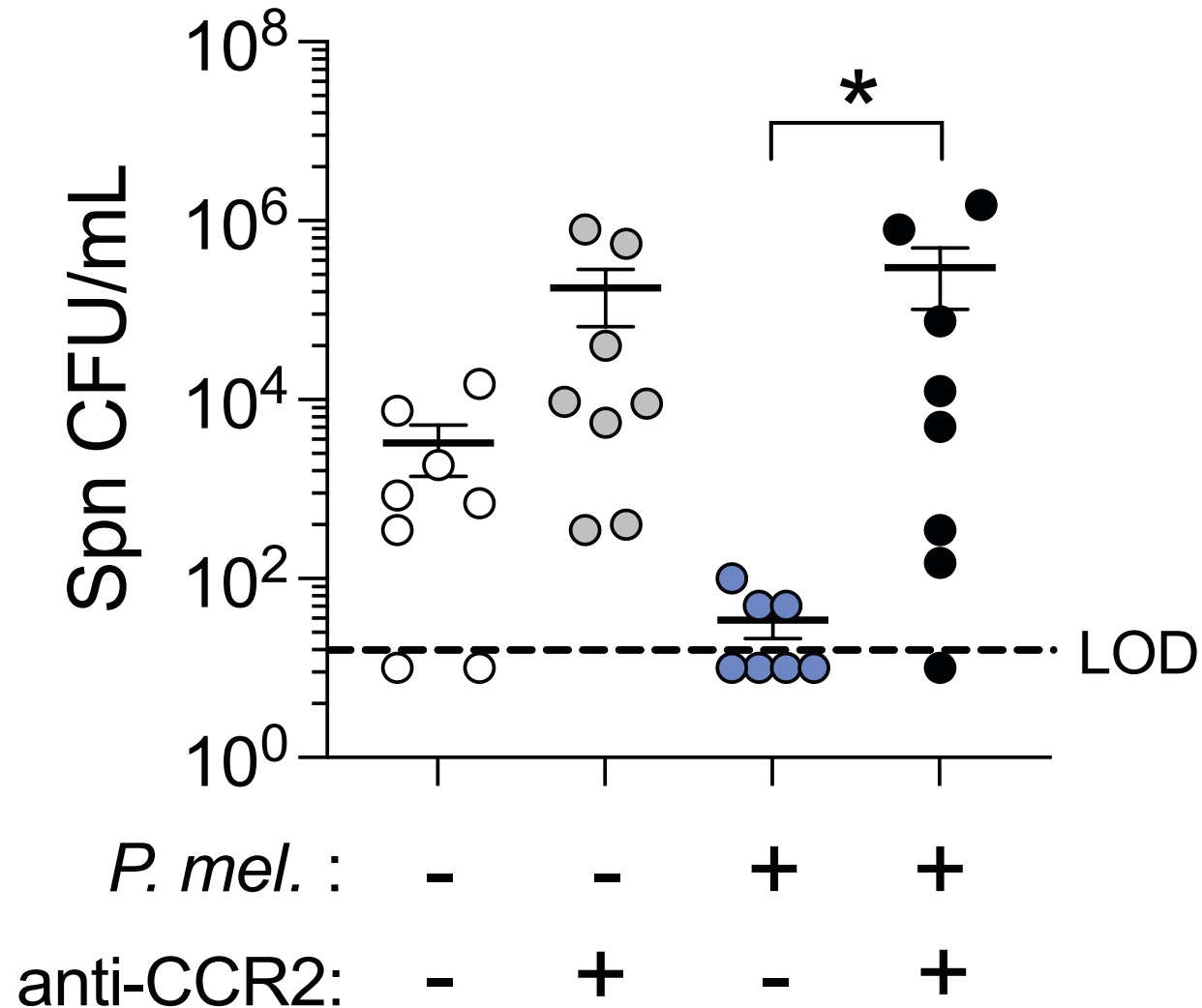
Ly6C⁺ Monocytes

Alveolar Macrophages



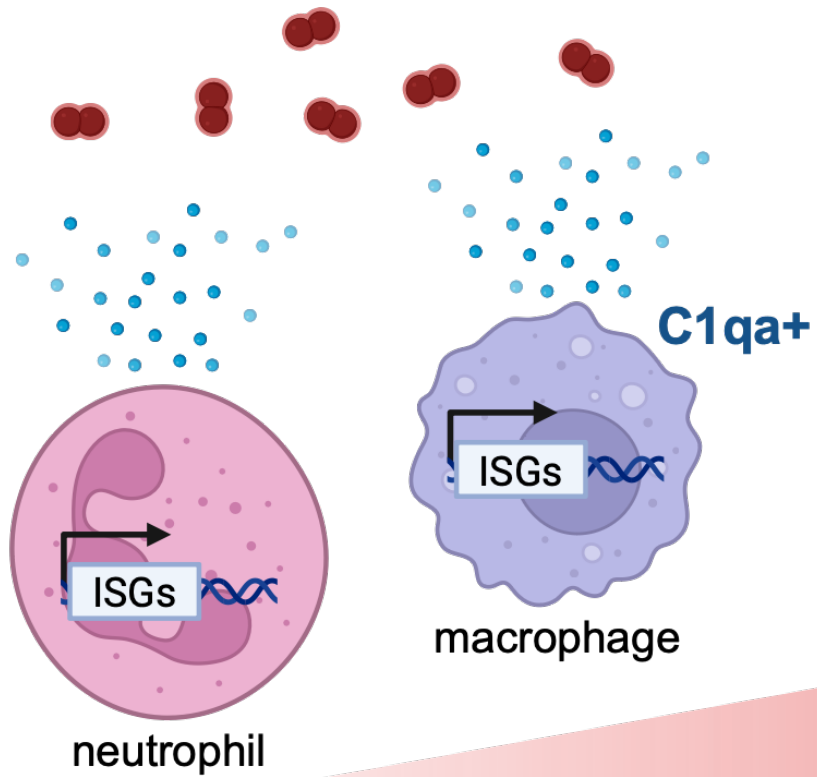
Mann-Whitney
*p<.05
n=3 biological, 3 technical replicates

Depletion of recruited monocytes/macrophages leads to loss of *P. melaninogenica*-induced pathogen clearance

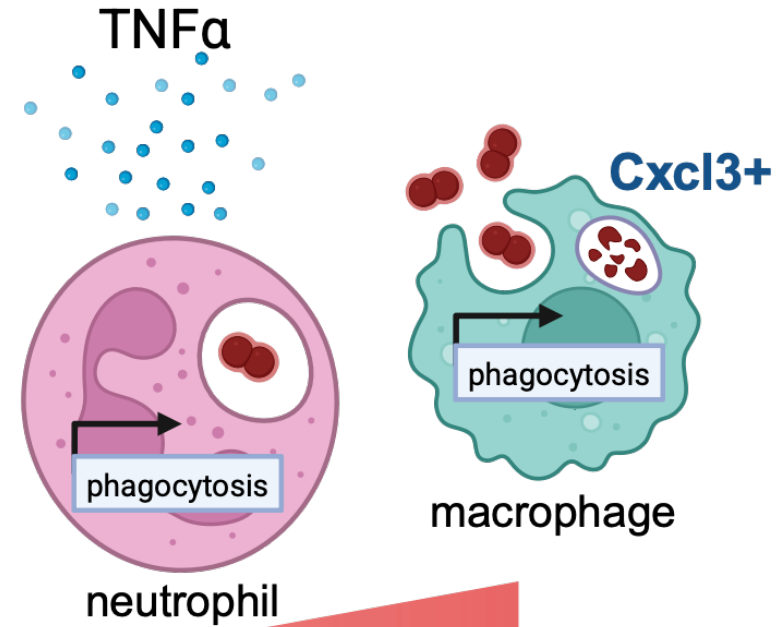


Conclusions

Non-primed



Prevotella-primed



Bacterial Killing



Future Directions

- Determine whether long-term exposures to *P. melaninogenica* lead to enhanced *S. pneumoniae* clearance
- Determine whether *P. melaninogenica* exposure induces long-term metabolic changes in macrophage populations

Acknowledgments

Clark Lab

Sarah Clark, PhD

Steven Shaw, MS

Sam Fulte

Ana Fairbanks-
Mahnke

Ari McCarty

Taylor Jamil, MD

Marika Orlov, MD PhD

Elizabeth Loy, MD
PhD

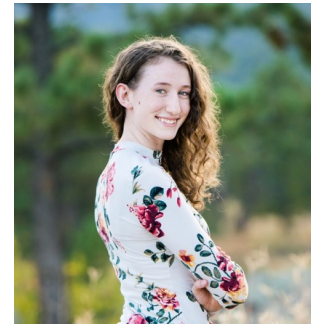
Erin Fish

Collaborators

Eric Larson, PhD (UPenn)

Matthias Mack, PhD (University
Hospital Regensburg)

Ed Janoff, MD (CU Anschutz)



Sunday: Poster #19
Wednesday/Thursday: Poster #40



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