

# **Heterogeneity of macrophages in Staphylococcal Enterotoxin B induced Acute Respiratory Distress Syndrome**

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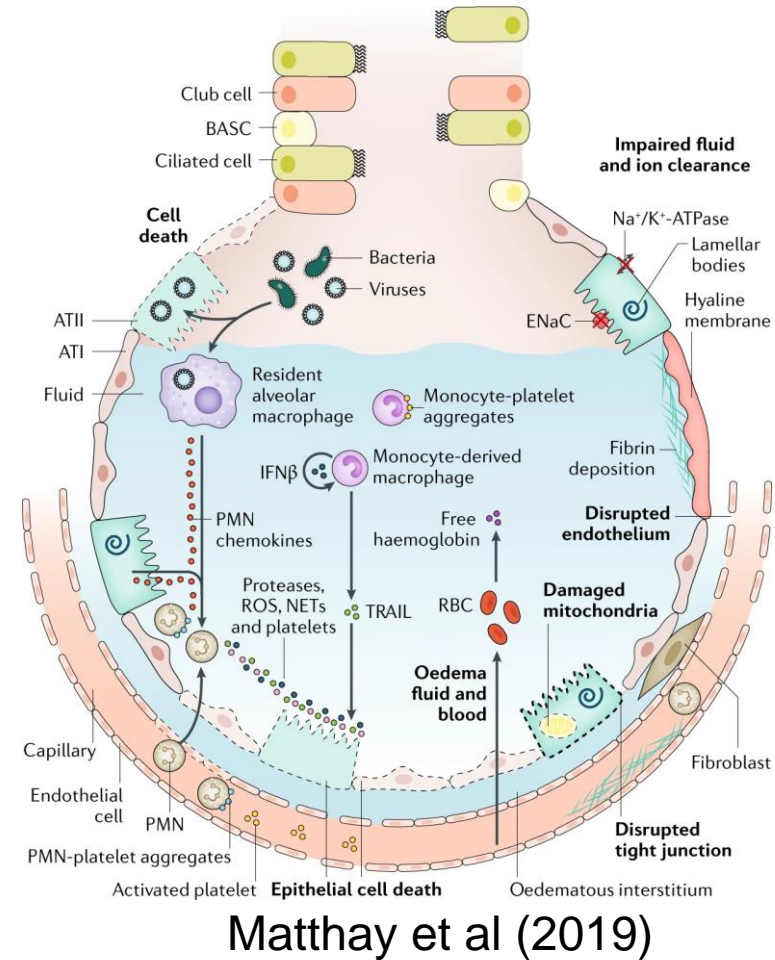


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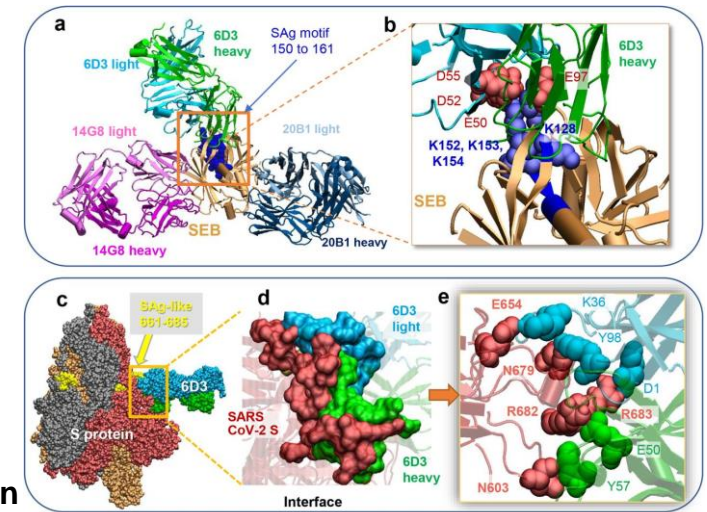
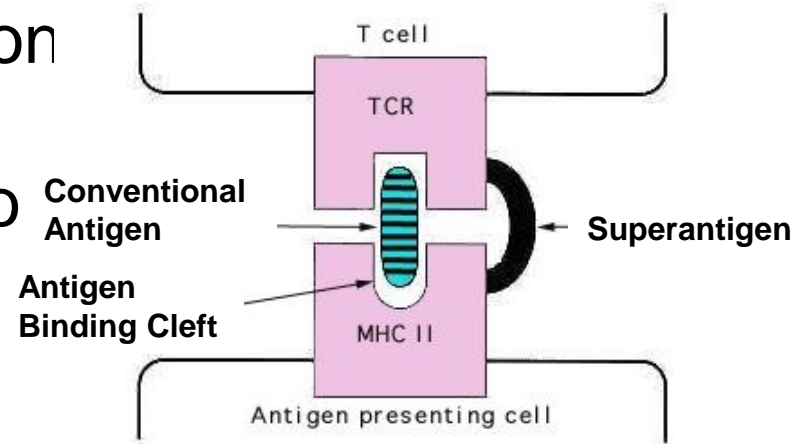
# Acute Respiratory Distress Syndrome (ARDS)

- Acute Respiratory Distress Syndrome (ARDS)
  - Cytokine storm
  - Fluid build
- Epidemiology
  - 30-40% mortality based on severity of disease.
  - No Cure
    - Treatment includes: Ventilation, Oxygen Support, and Fluid Management.



# Staphylococcus Enterotoxin B (SEB)

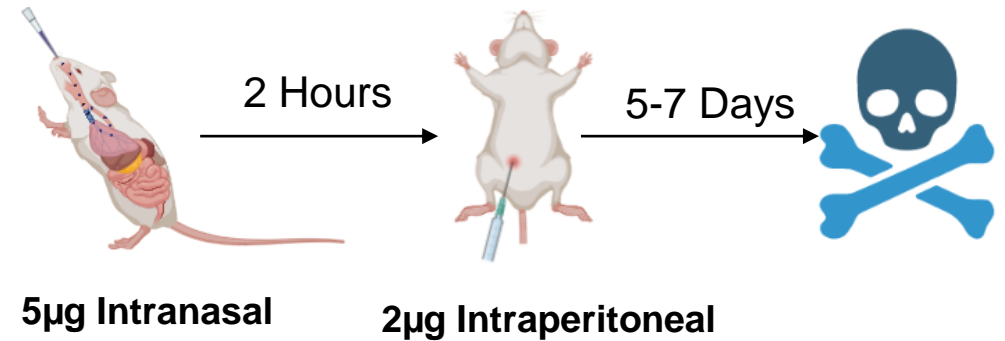
- Staphylococcal Enterotoxin B (SEB)
  - Superantigenic region of SEB similar to SARS-CoV-2 spike protein motif (Function Differs)
  - Superantigen sAG binds to MHC and activates T-cells
  - Toxic Shock Syndrome, Food Poisoning, ARDS, Sepsis
  - Biowarfare



Cheng et al (2021)

# PROJECT OVERVIEW

- SEB-induced ARDS is fatal in C3H/HeJ mice when given as a dual dose within 7 days
- Tissues collected 72 hours post-toxin introduction
- Single Cell RNA-seq and Single Cell ATAC-seq performed on whole lung single cell suspension



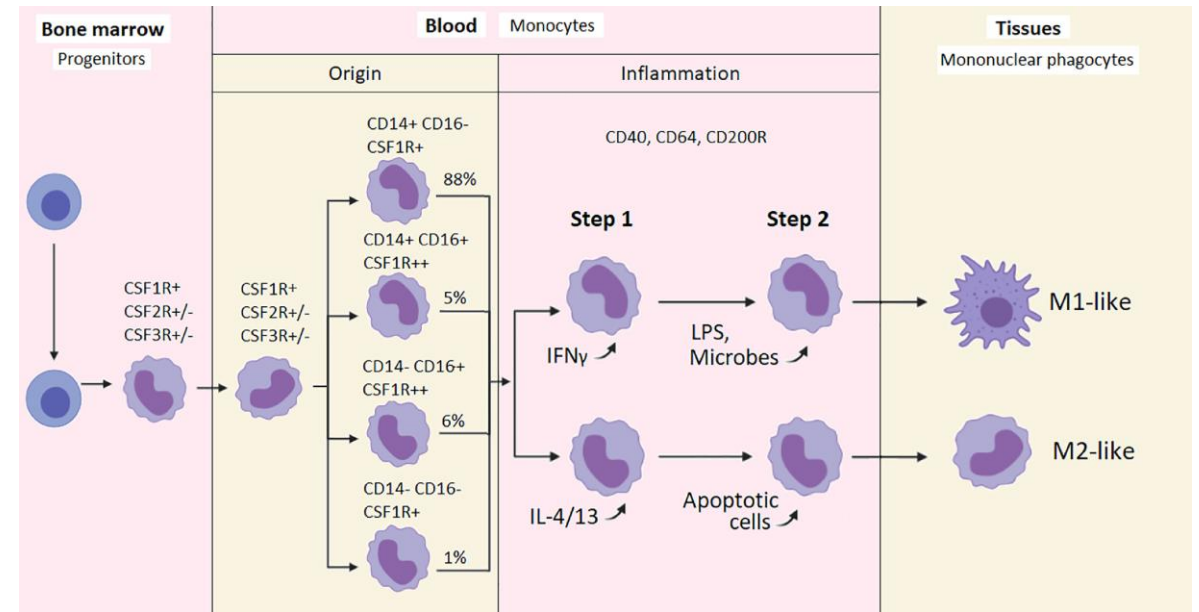
# Macrophage Differentiation

- Monocyte/Macrophage Differentiation

- Bone Marrow Derived
- CD14<sup>++</sup>, CD14<sup>+</sup>/CD16<sup>+</sup>, CD16<sup>+</sup>
- APC

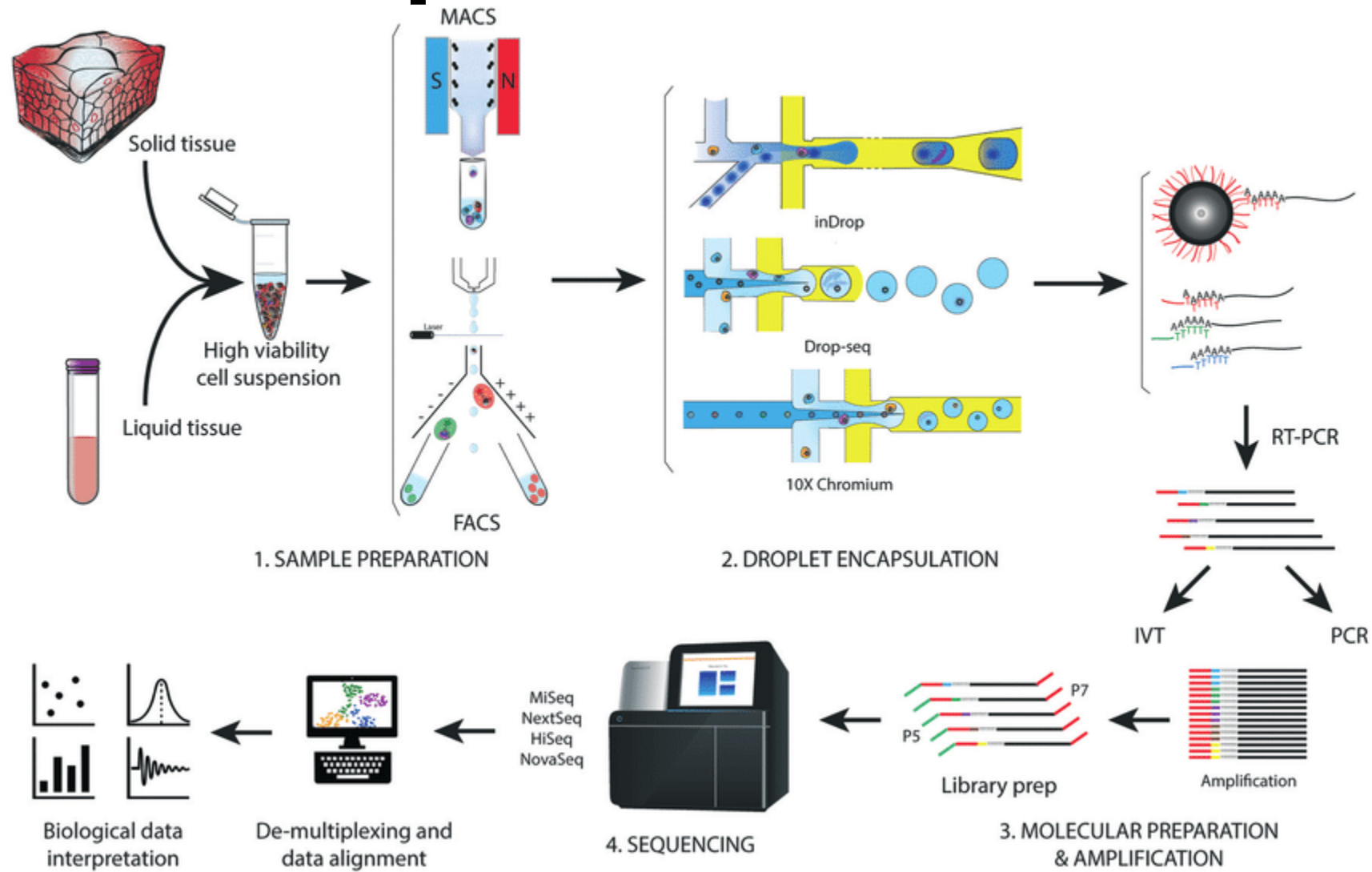
- Alveolar and Interstitial Macrophages

- SiglecF<sup>+</sup>, CD11c<sup>+</sup>, CD11b<sup>-</sup>
- Cx3cr1<sup>+</sup>, CD11b<sup>+</sup>, CD64

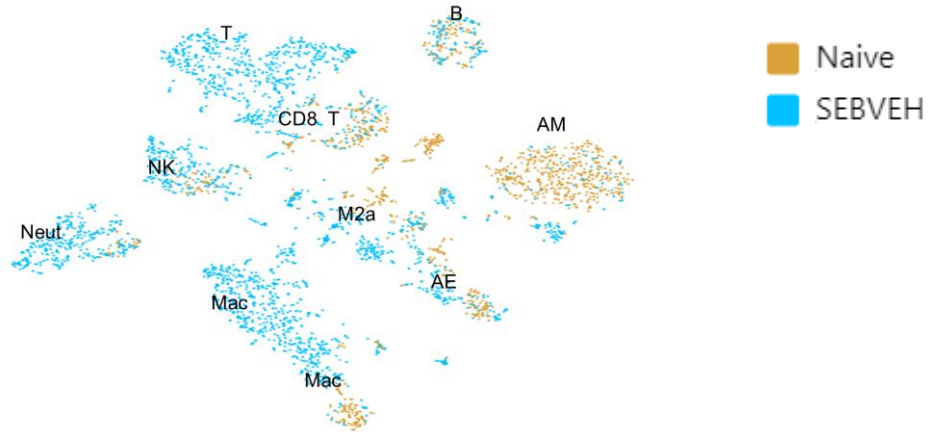


Martinez et. Al (2020)

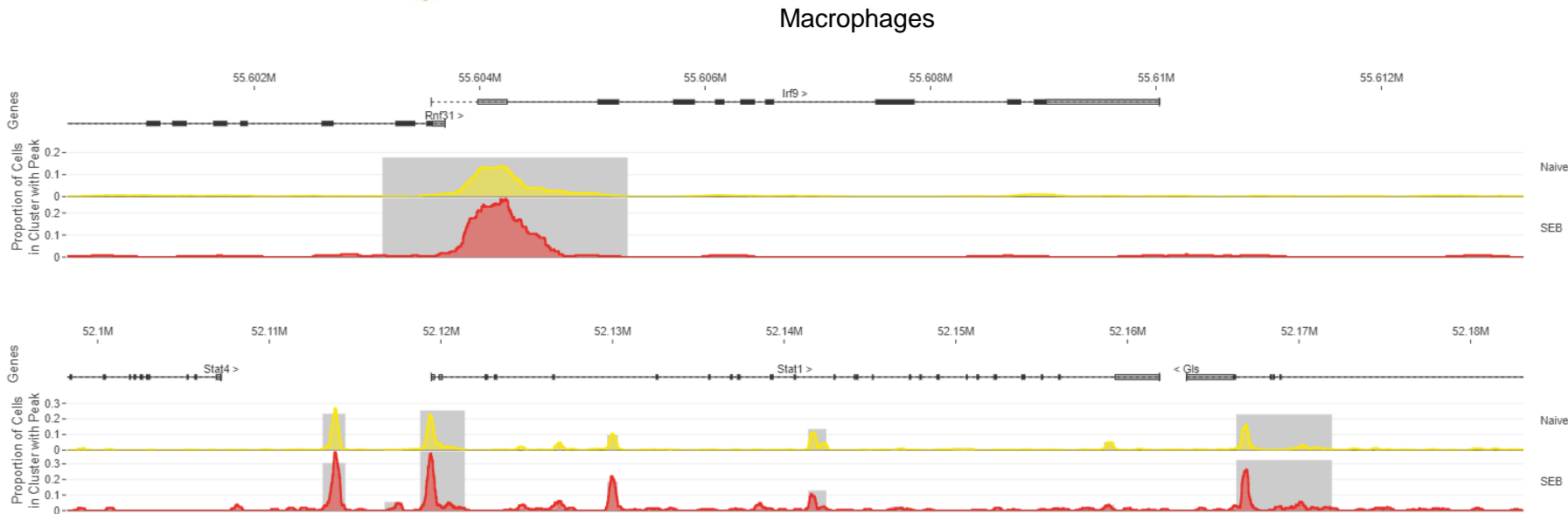
# Single Cell RNA Seq



# SEB causes Increased chromatin accessibility of IFSG in myeloid cells



*Increased chromatin accessibility Stat1 and Irf9 critical regulators of severe COVID-19 associated ARDS*

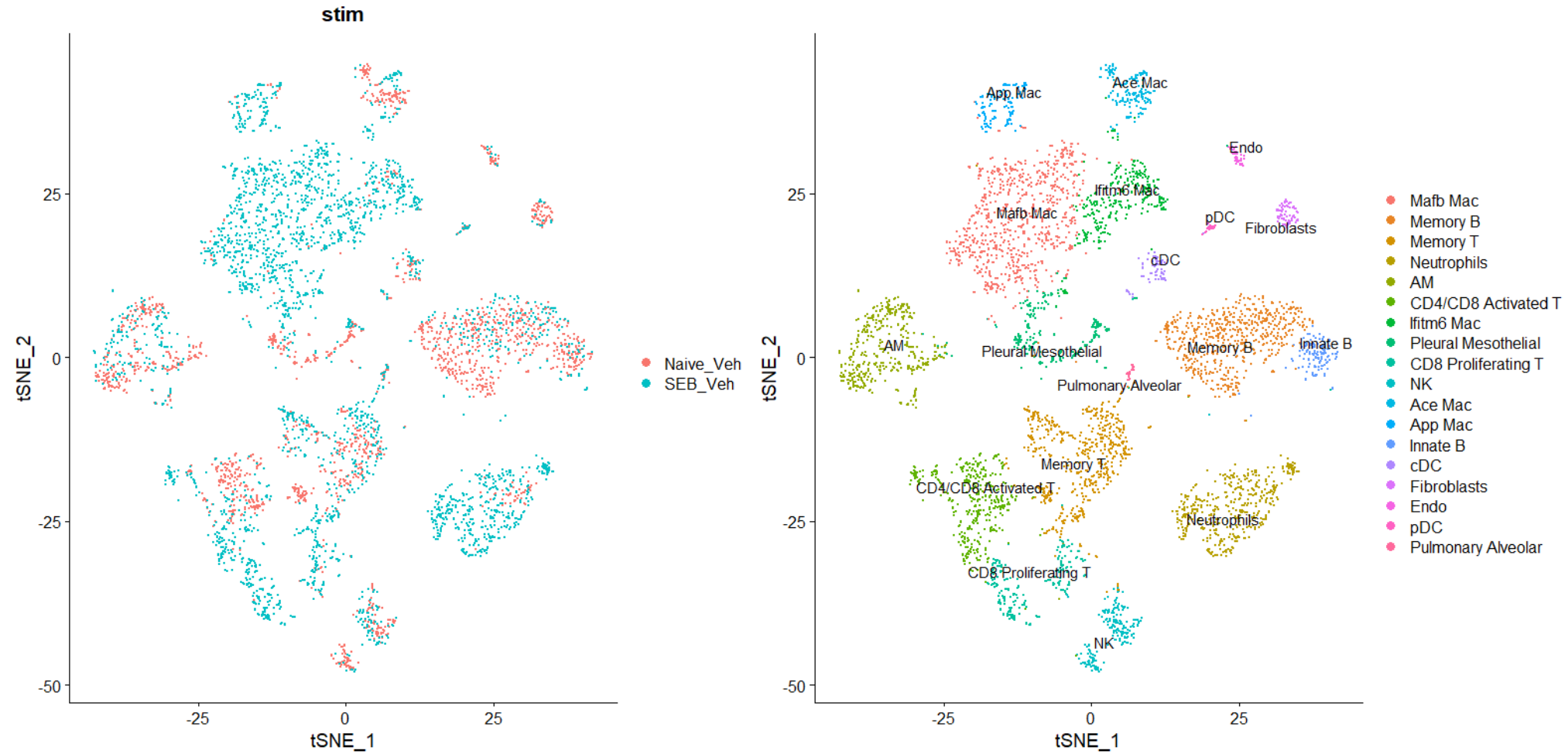


Irf9

Stat1



# scRNA-seq shows SEB increases myeloid cells

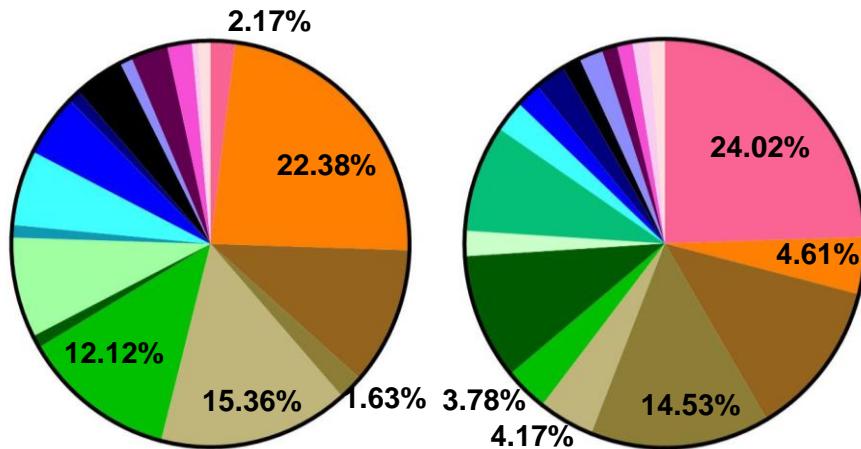




# scRNA-seq shows SEB increases myeloid cells

Naive + VEH

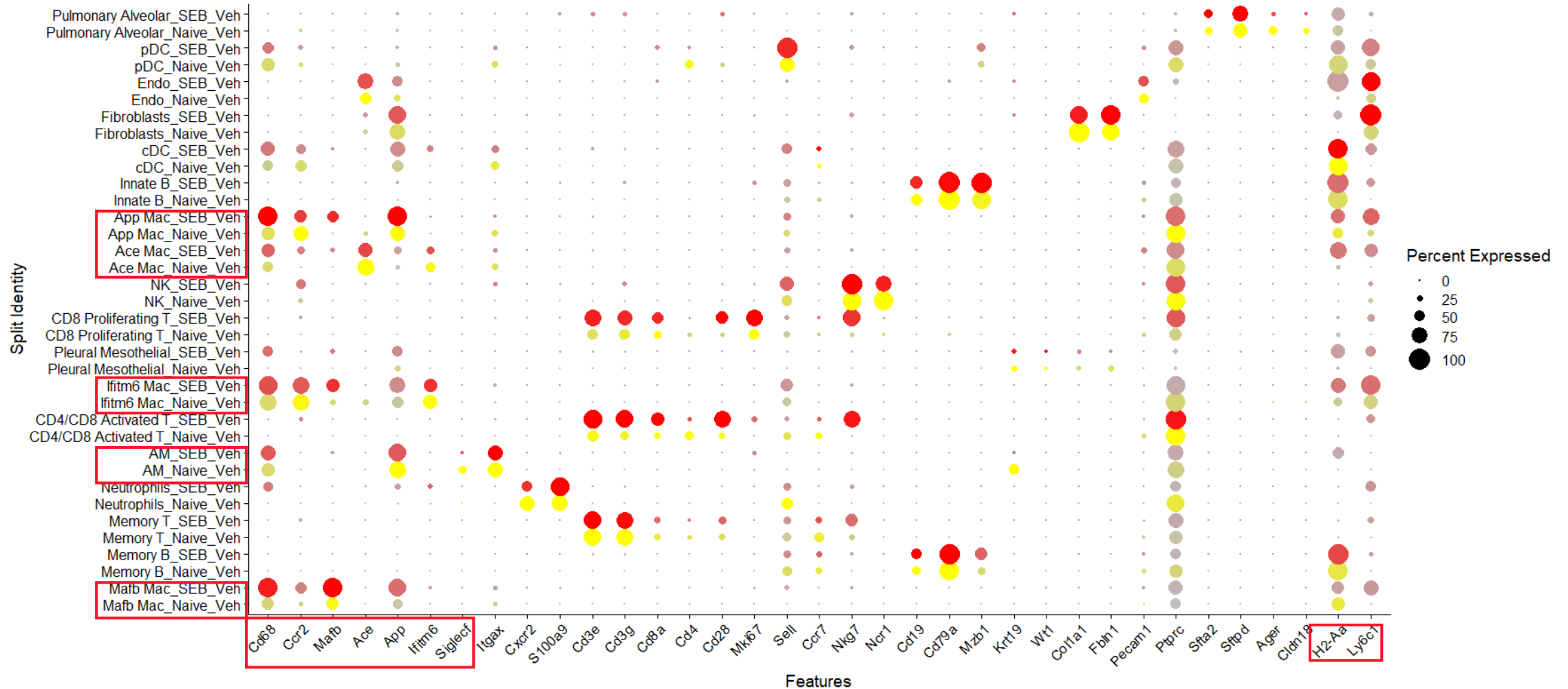
SEB + VEH



- Mafb Mac
- Memory B
- Memory T
- Neutrophils
- Alveolar Macrophage
- Activated T
- Ifitm6 Mac
- Pleural Mesothelial
- CD8 Proliferating T
- NK
- Ace Mac
- App Mac
- Activated B
- cDC
- Alveolar Epithelial
- Endothelial
- pDC
- Pulmonary Alveolar

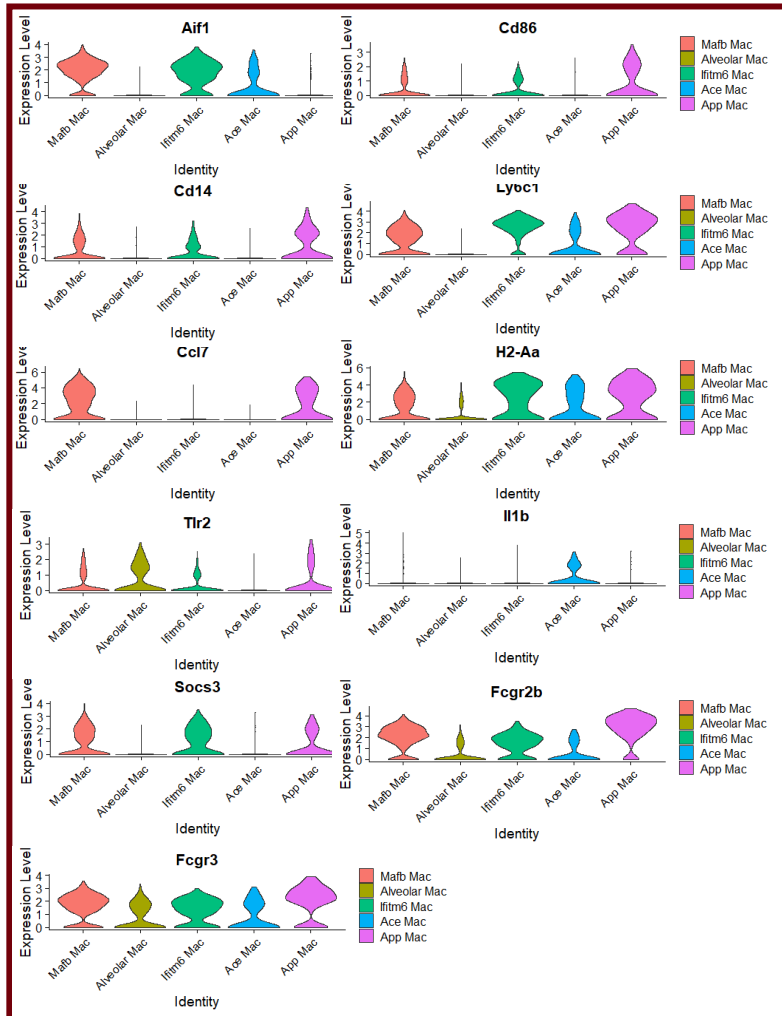
Cell Distribution %		
	Naïve	SEB
Mafb Mac	2.17	24.02
Memory B	22.38	4.61
Memory T	11.31	12.14
Neutrophils	1.63	14.53
Alveolar Macrophage	15.36	4.17
Activated T	12.12	3.78
Ifitm6 Mac	1.22	10.68
PM	7.91	1.96
CD8 Proliferating T	0.89	8.94
NK	6.06	2.05
Ace Mac	4.57	1.97
App Mac	1.64	2.52
Activated B	4.21	1.32
cDC	0.95	1.94
Alveolar Epithelial	3.74	1.47
Endothelial	2.15	1.29
pDC	0.43	1.36
Pulmonary Alveolar	1.26	1.25

# scRNA-seq shows SEB increases Ccr2 positive myeloid cells

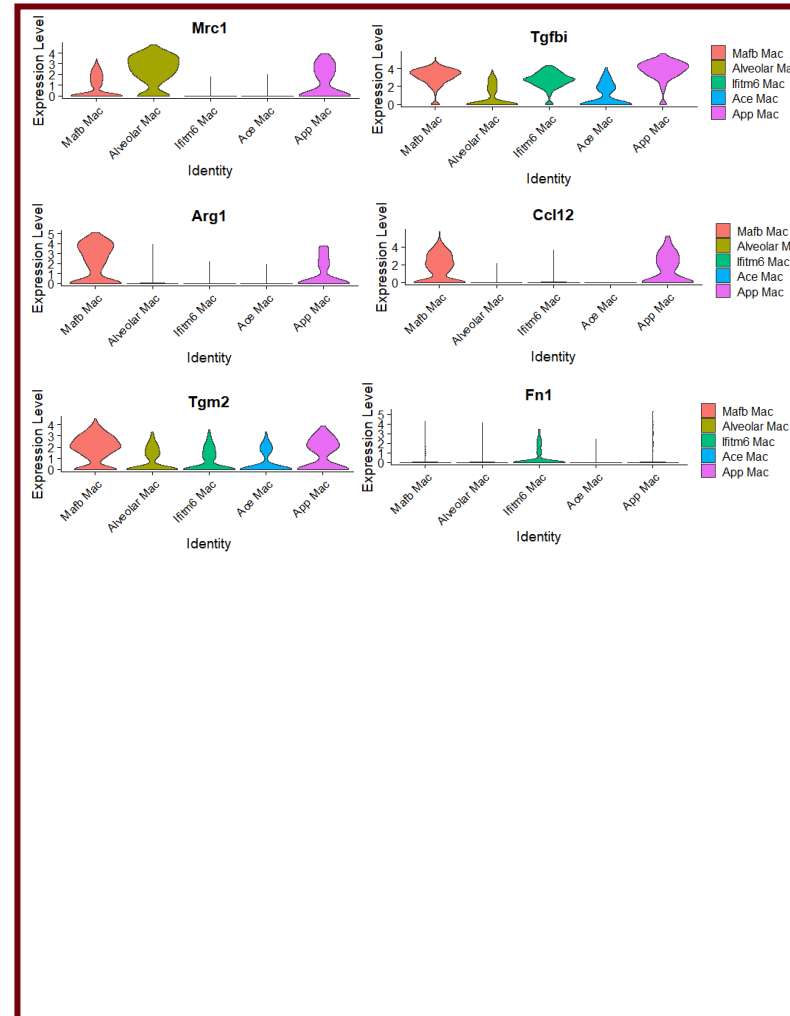


# SEB induces diverse macrophage populations associated with M1 and M2 phenotype

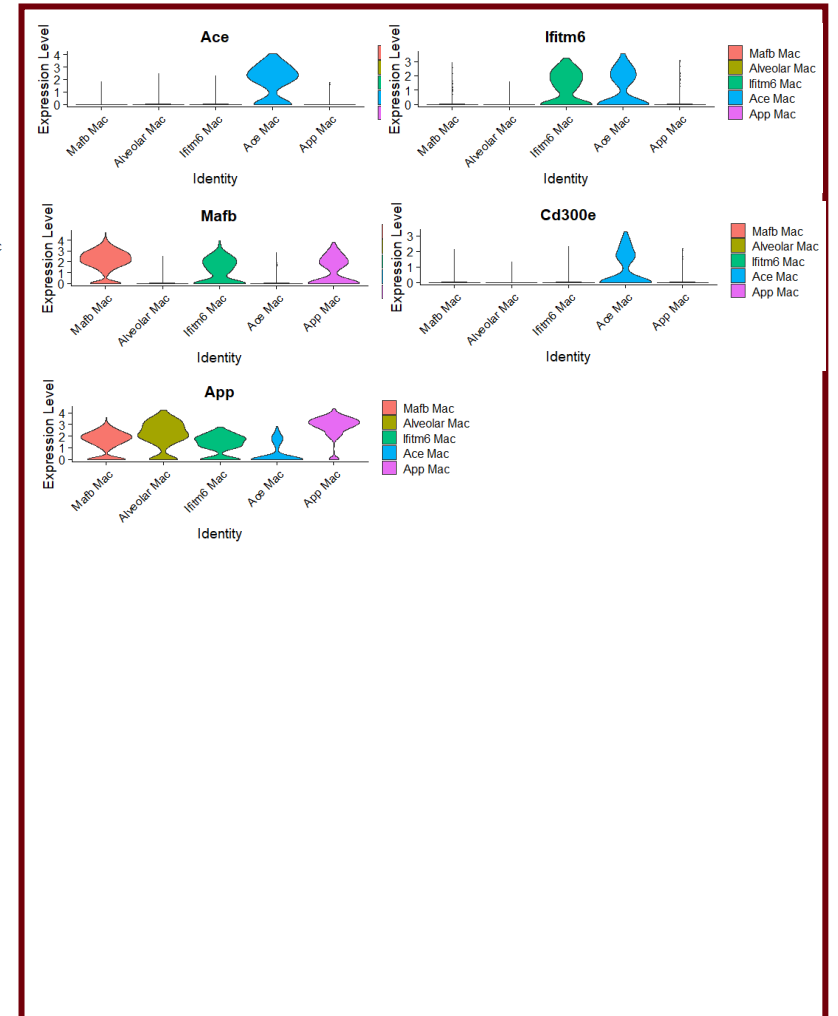
## M1



## M2

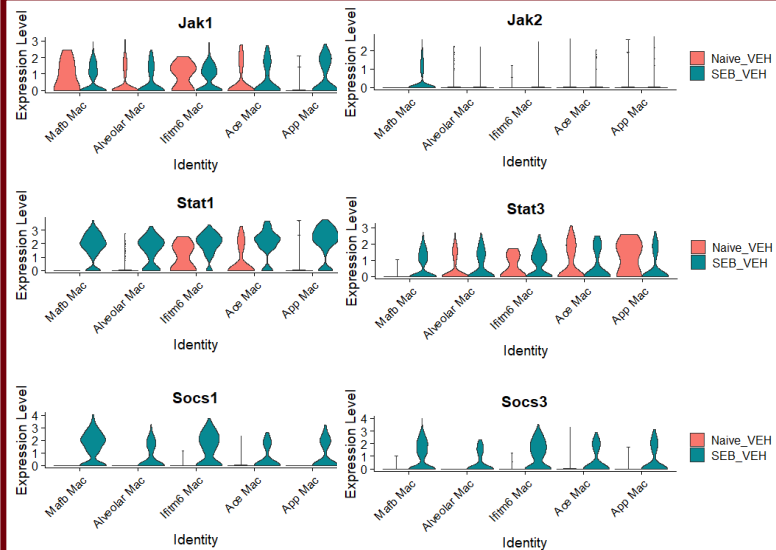


## Group Specific

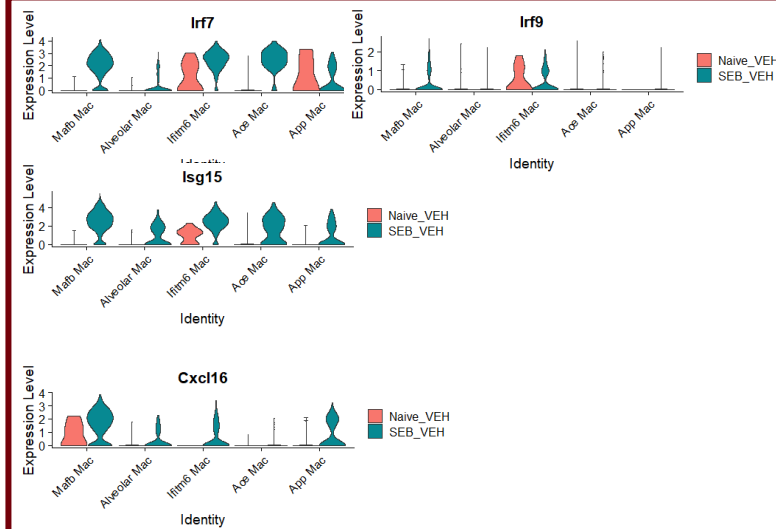


# SEB induces diverse macrophage populations that express factors associated with Interferon and JAK/STAT signaling

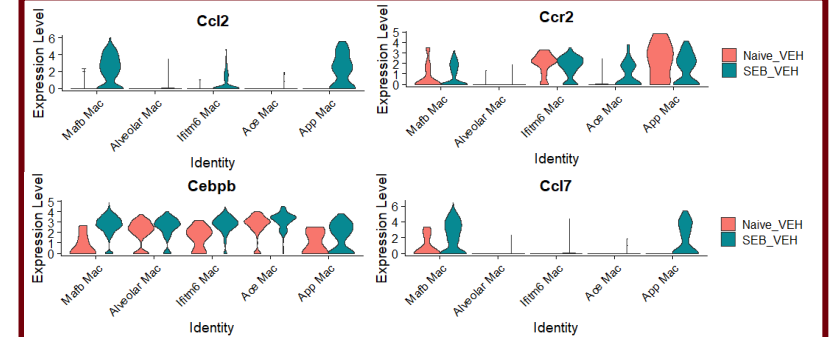
## Jak/Stat



## ISG



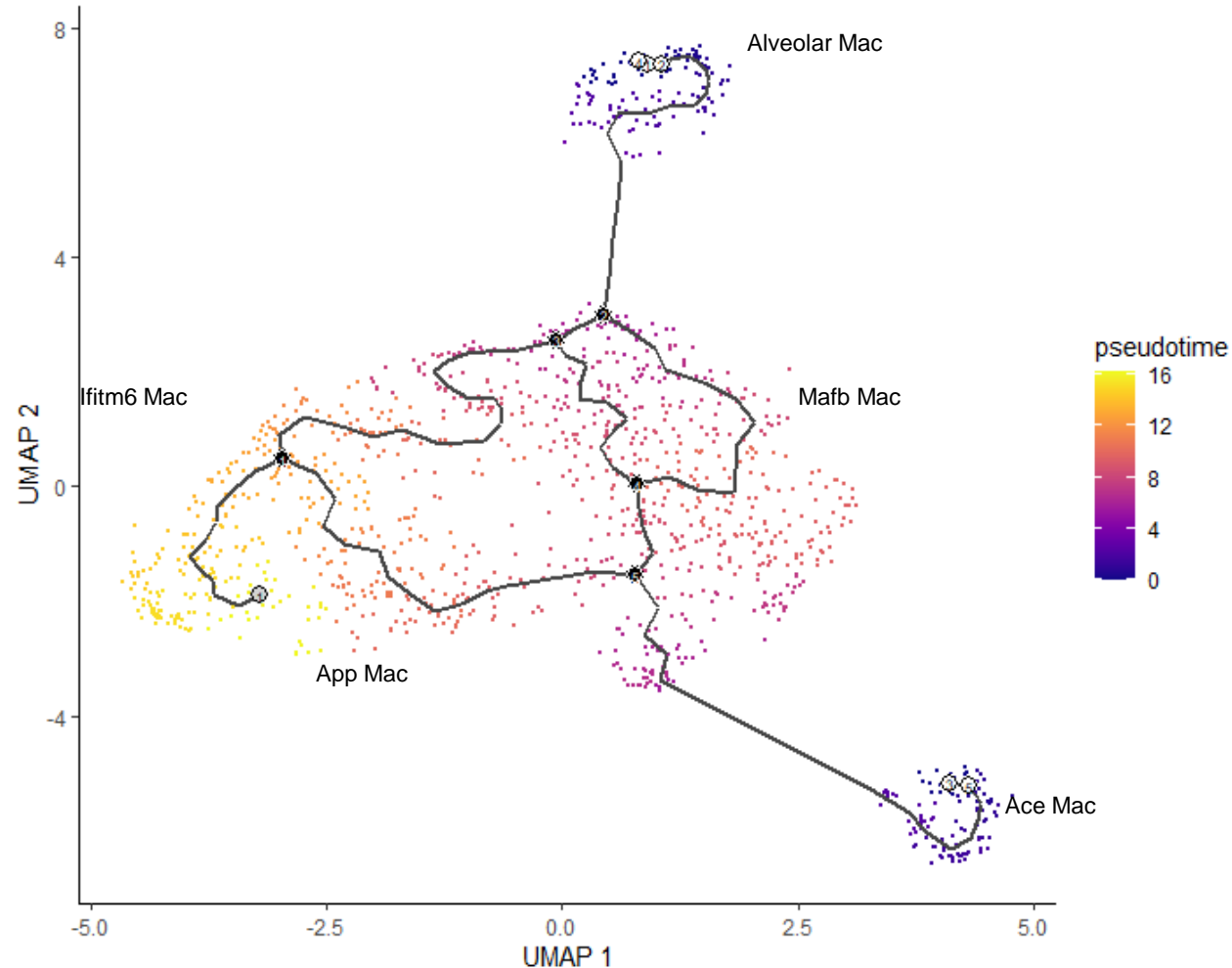
## Activation/Chemotaxis



# Cell Trajectory of Macrophages

*Pseudotime analysis is used to order individual cells along a continuous trajectory representing a biological process.*

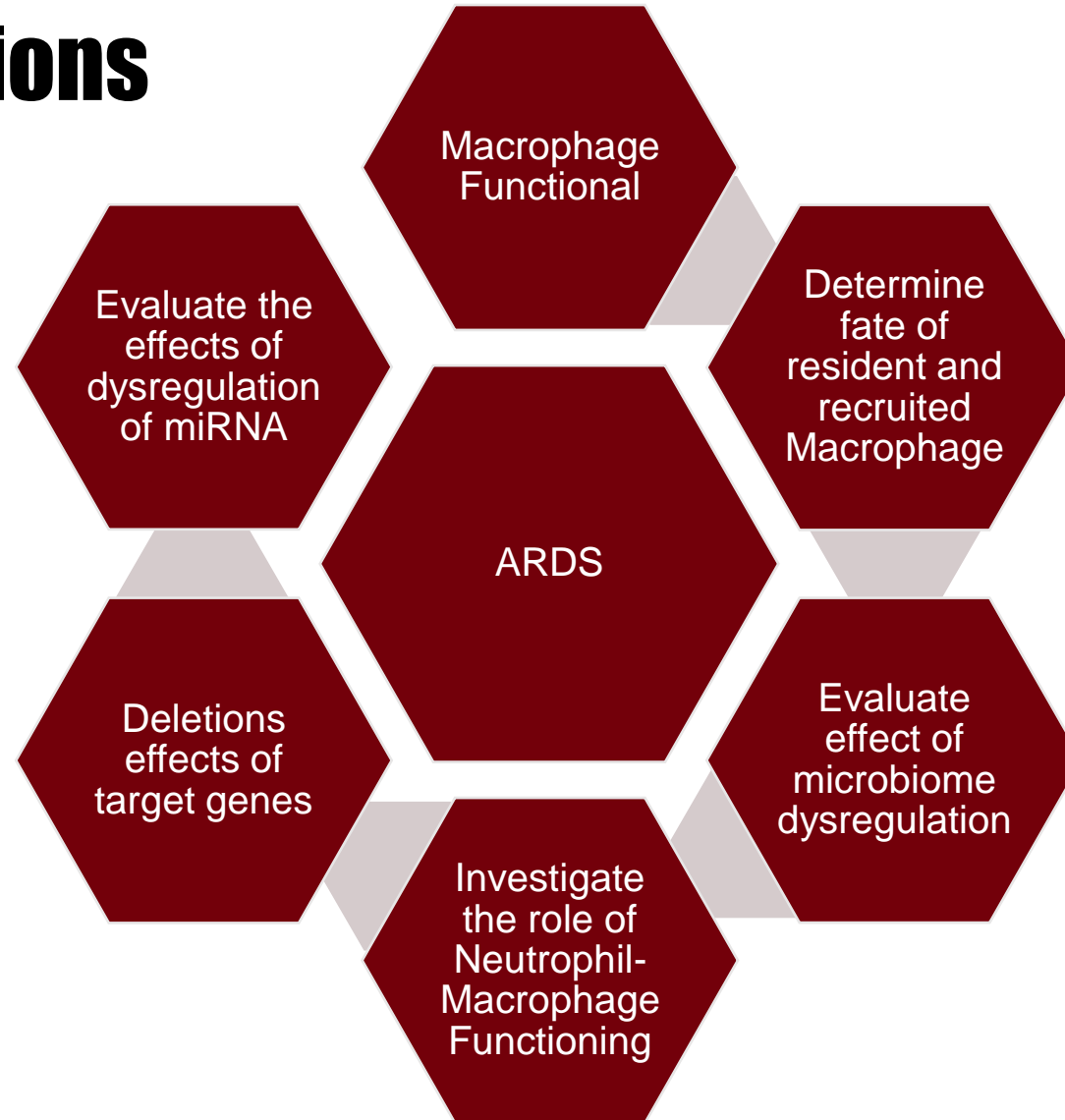
*This ordering is inferred based on similarities in gene expression profiles*



# Conclusions

- Infiltrating macrophages were the most abundant cell type post-SEB treatment.
- Increased chromatin accessibility was observed for interferon and STAT genes found in the macrophage.
- Interferon-regulated macrophage activation may play a significant role in ARDS progression.
- Resident macrophage may be polarizing to a more M1 phenotype as well as a M2 phenotype.

# Future Directions





# IMPLICATIONS FOR PUBLIC HEALTH?

- Precision Medicine
- Disease Understanding and Diagnosis
- Infectious Disease Management
- Public Health Surveillance
- Therapeutic Monitoring and Prognosis
- Health Disparities and Equity

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