ILD 연구회 심포지움

단일세포전사체 기반 염증성 폐질환 연구

2022. 6. 20.

Jeong Seok Lee
Assistant Professor / KAIST GSMSE
Co-founder & CEO / GENOME INSIGHT Inc.

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SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

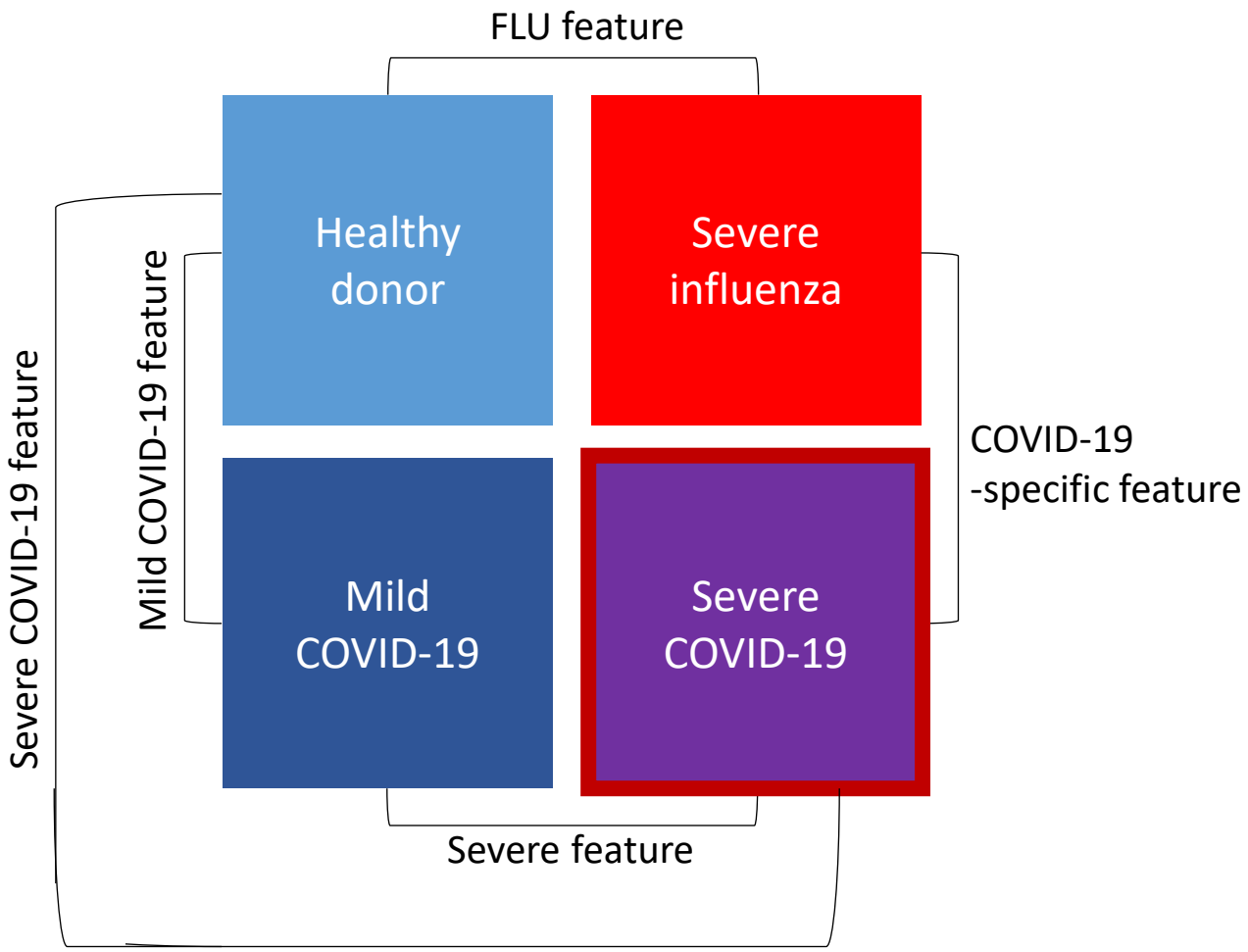
CORONAVIRUS

Immunophenotyping of COVID-19 and influenza highlights the role of type I interferons in development of severe COVID-19

Jeong Seok Lee[1]*, Seongwan Park[2]*, Hye Won Jeong[3]*, Jin Young Ahn[4]*, Seong Jin Choi[1], Hoyoung Lee[1], Baekgyu Choi[2], Su Kyung Nam[2], Moa Sa[1,5], Ji-Soo Kwon[1,6], Su Jin Jeong[4], Heung Kyu Lee[1,5], Sung Ho Park[7], Su-Hyung Park[1,5], Jun Yong Choi[4†], Sung-Han Kim[6†], Inkyung Jung[2†], Eui-Cheol Shin[1,5†]

Lee JS et al., *Sci Immunol*. 2020

Cross-sectional, comparative design

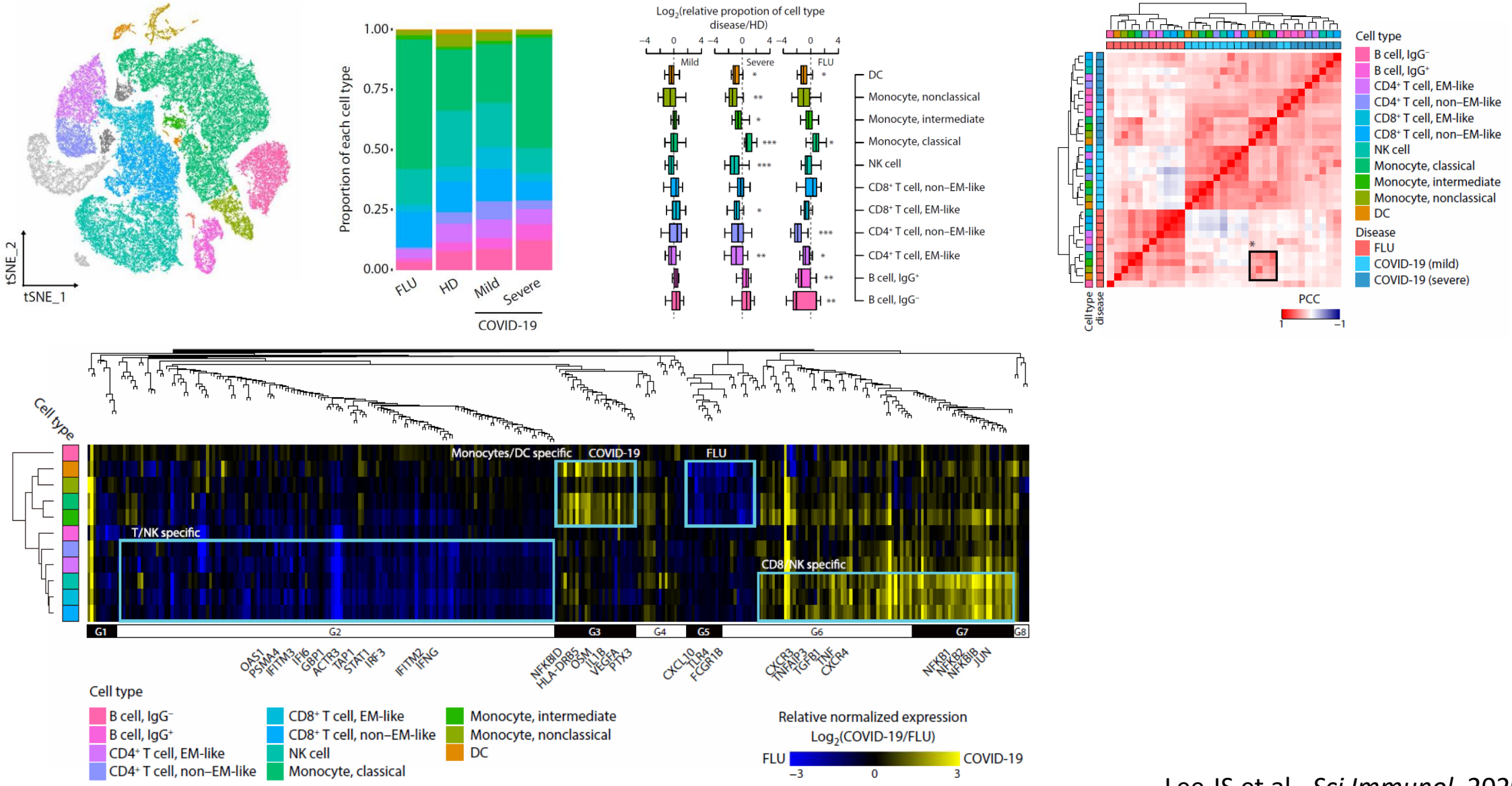


To improve understanding of immune response in severe COVID-19.

To reveal therapeutic targets to suppress severe progression of COVID-19

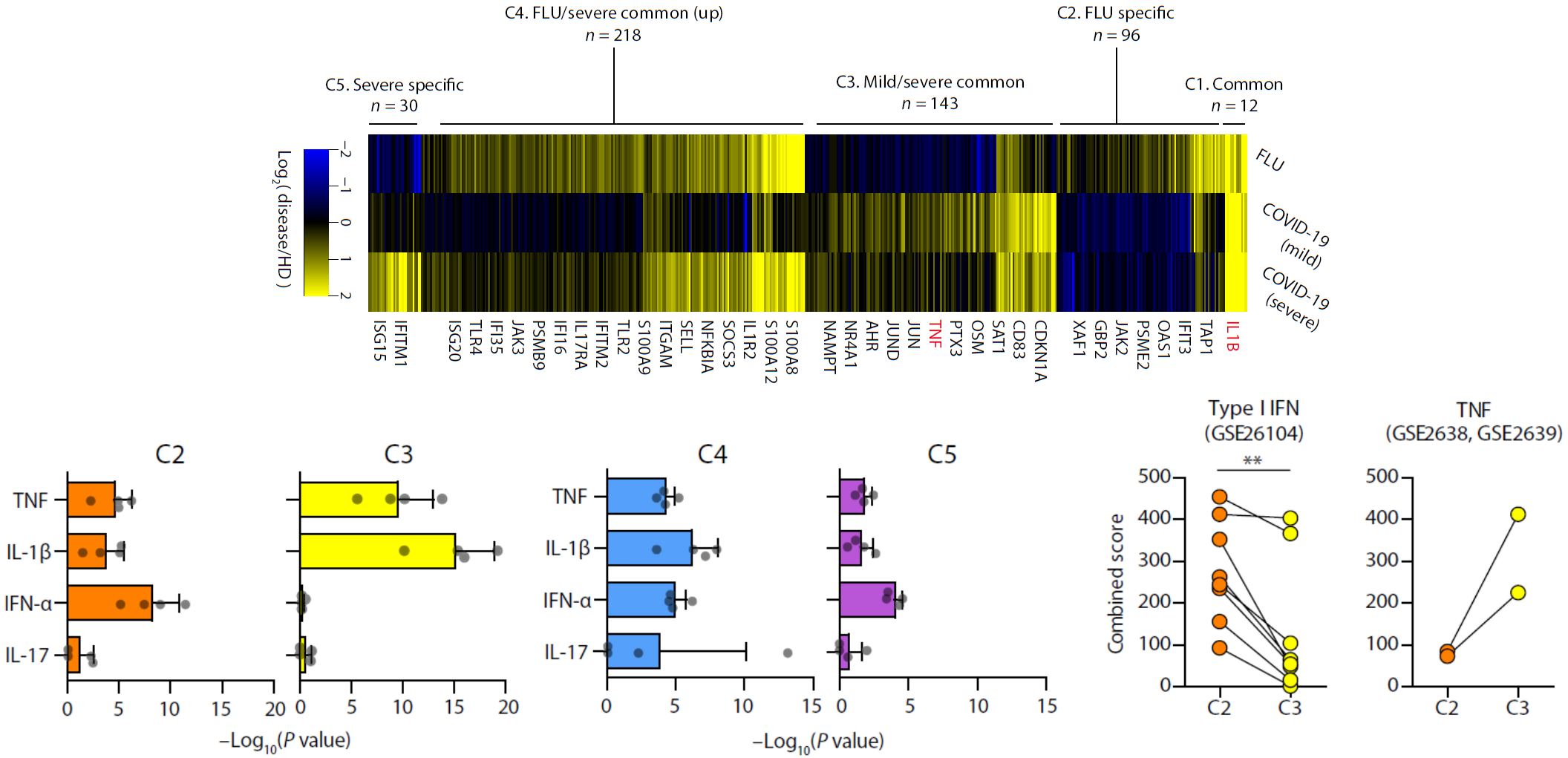
Lee JS et al., *Sci Immunol*. 2020

Comparative landscape of immune response in PBMCs of COVID-19 patients



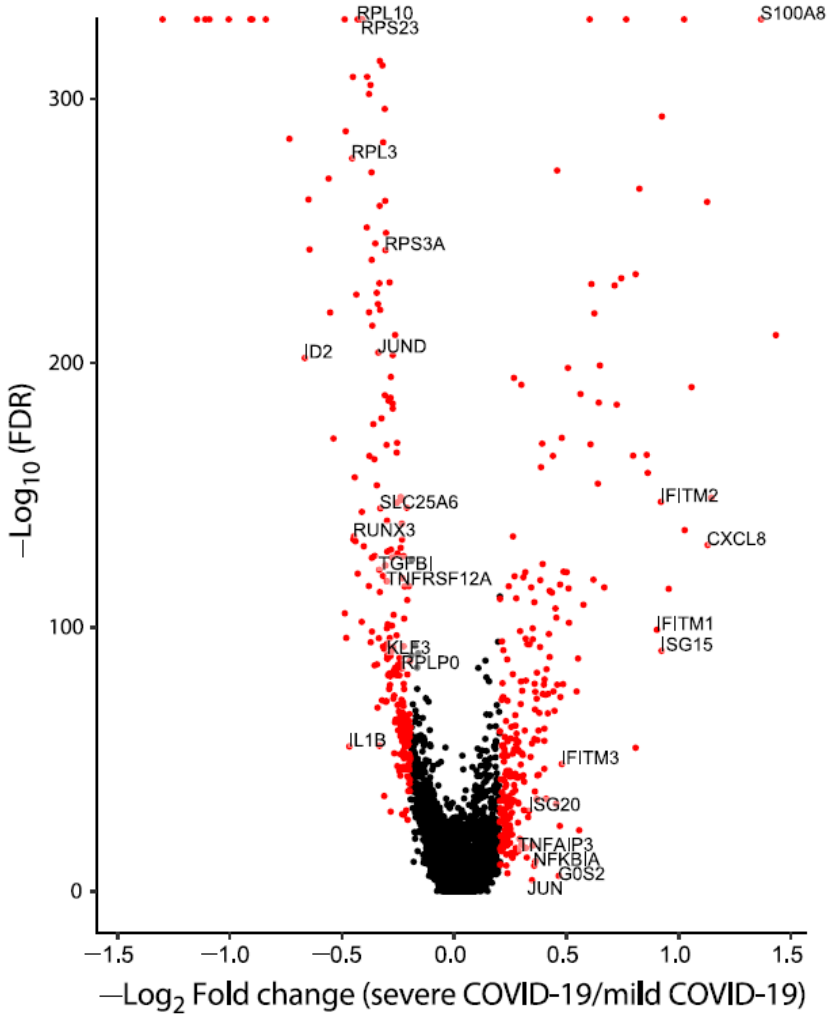
Lee JS et al., *Sci Immunol*. 2020

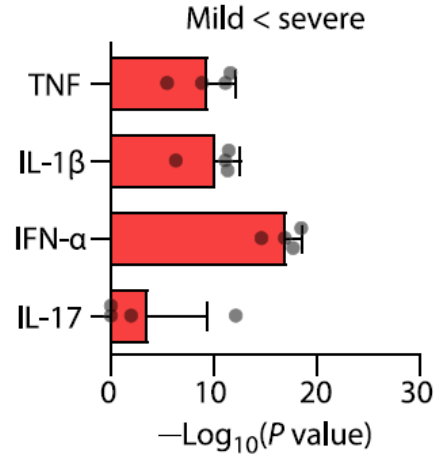
Comparative landscape of immune response in monocytes of COVID-19 patients



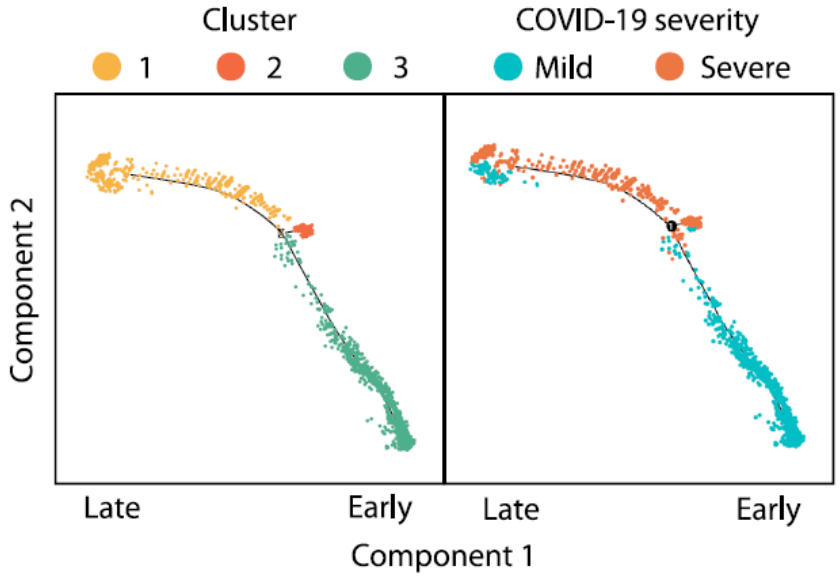
Lee JS et al., *Sci Immunol*. 2020

Defining specific features of monocyte changes in severe COVID-19



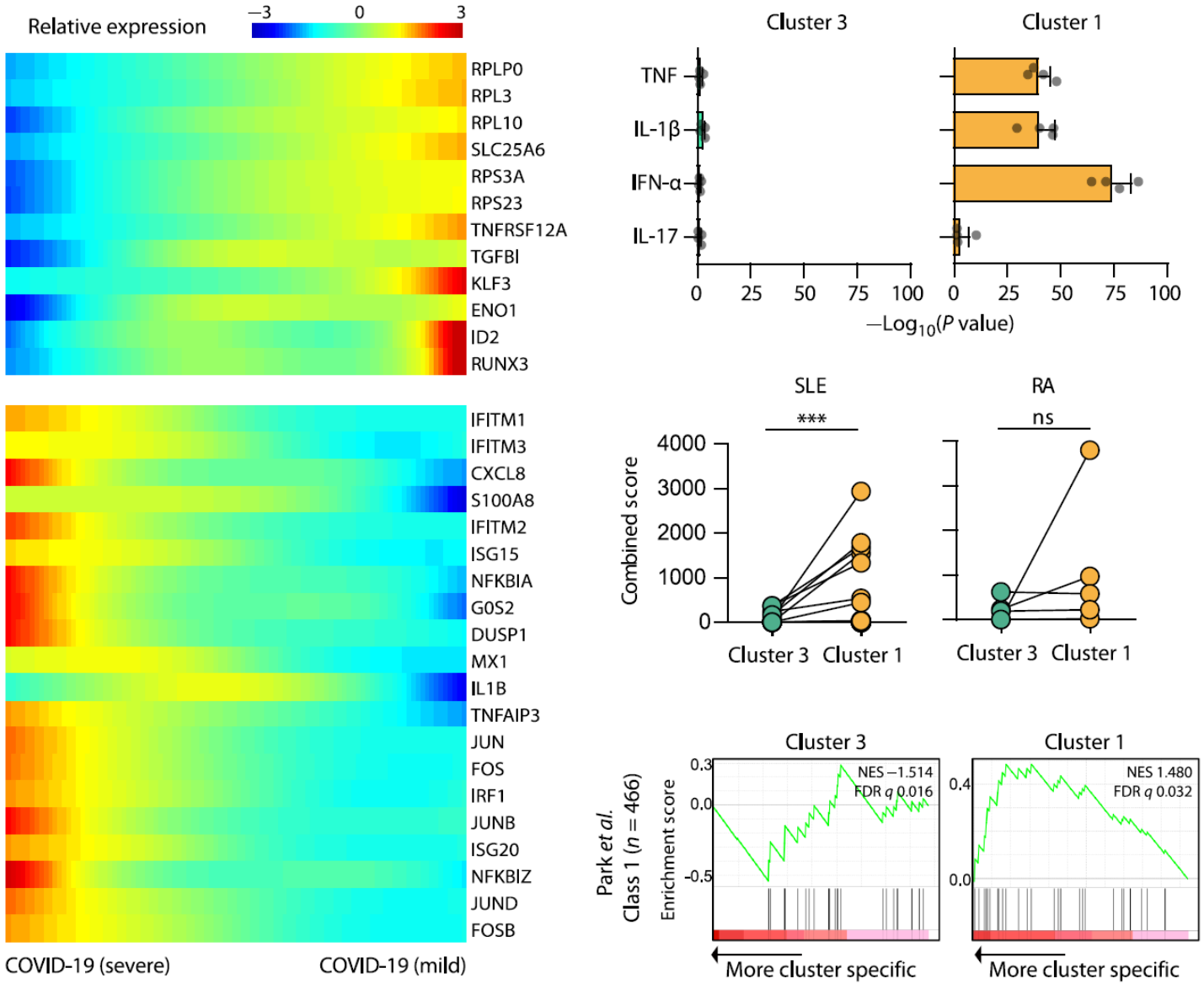


Case with
Mild →→ Severe



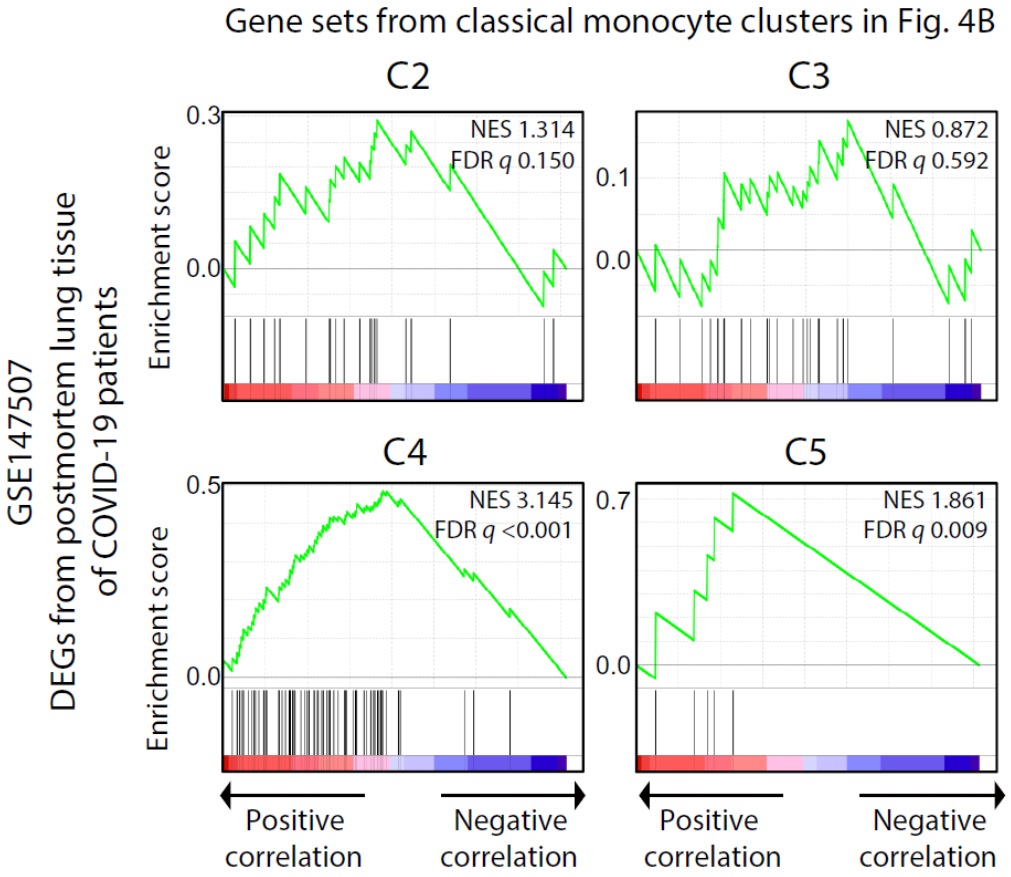
Lee JS et al., *Sci Immunol*. 2020

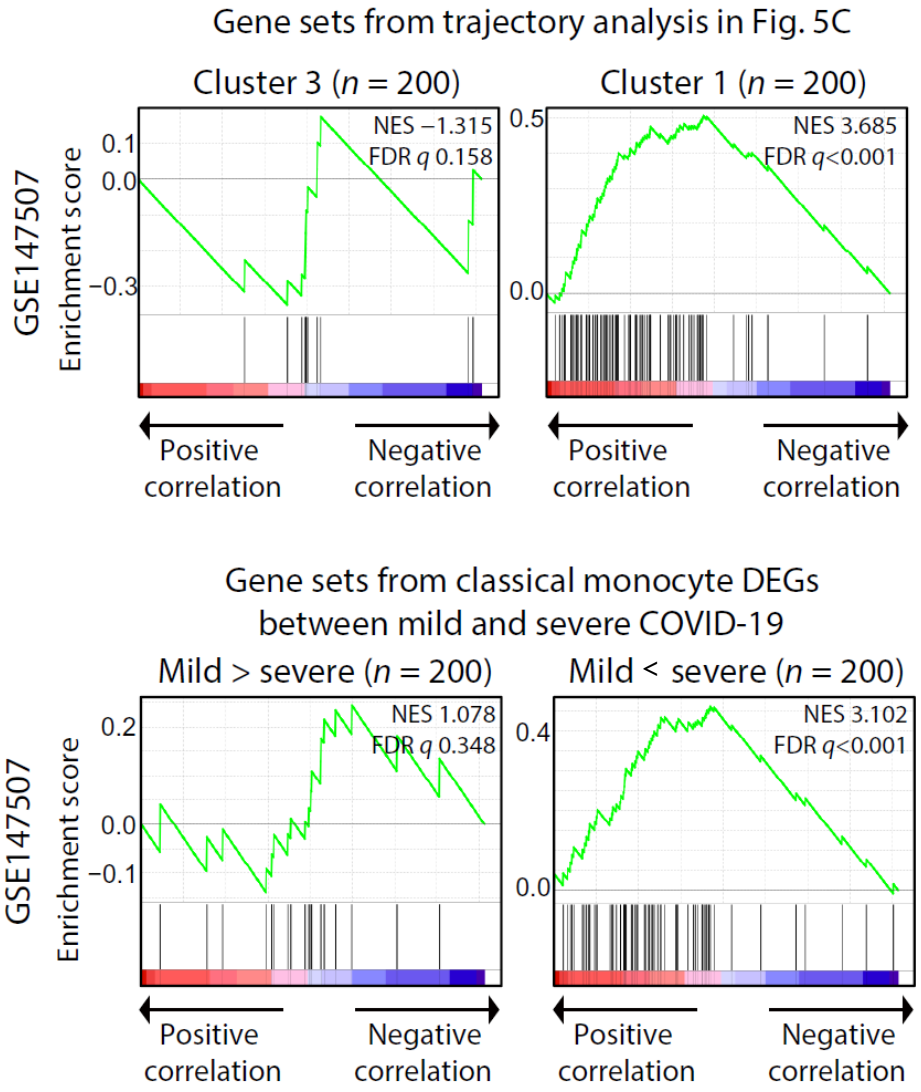
Trajectory analysis: Mild → Severe



Lee JS et al., *Sci Immunol*. 2020

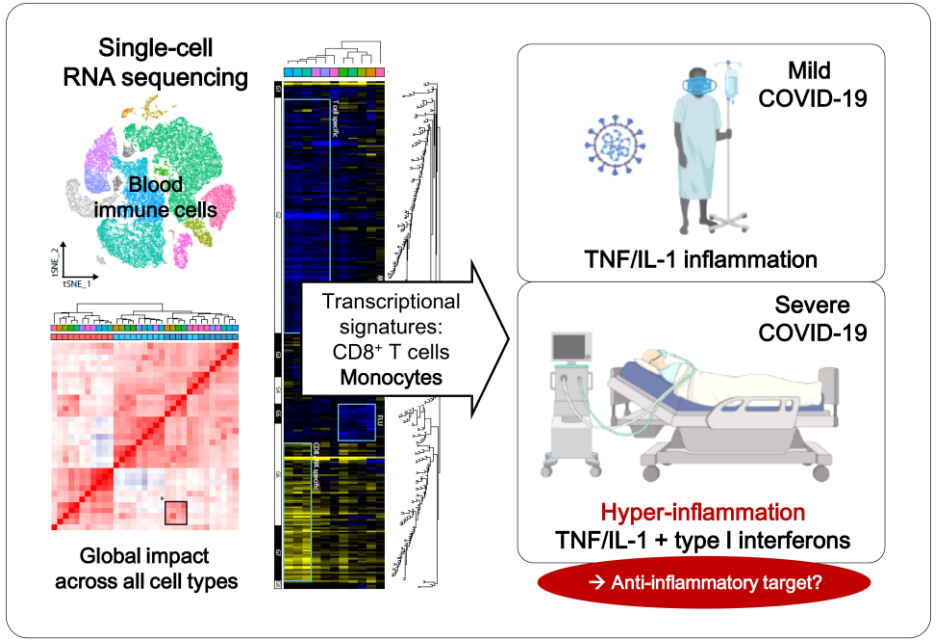
Validation using DEGs from postmortem lung tissue of COVID-19 patients





Lee JS et al., *Sci Immunol*. 2020

Summary (1)



COVID-19 → TNF, IL-1

Severe COVID-19 → +Type 1 IFN

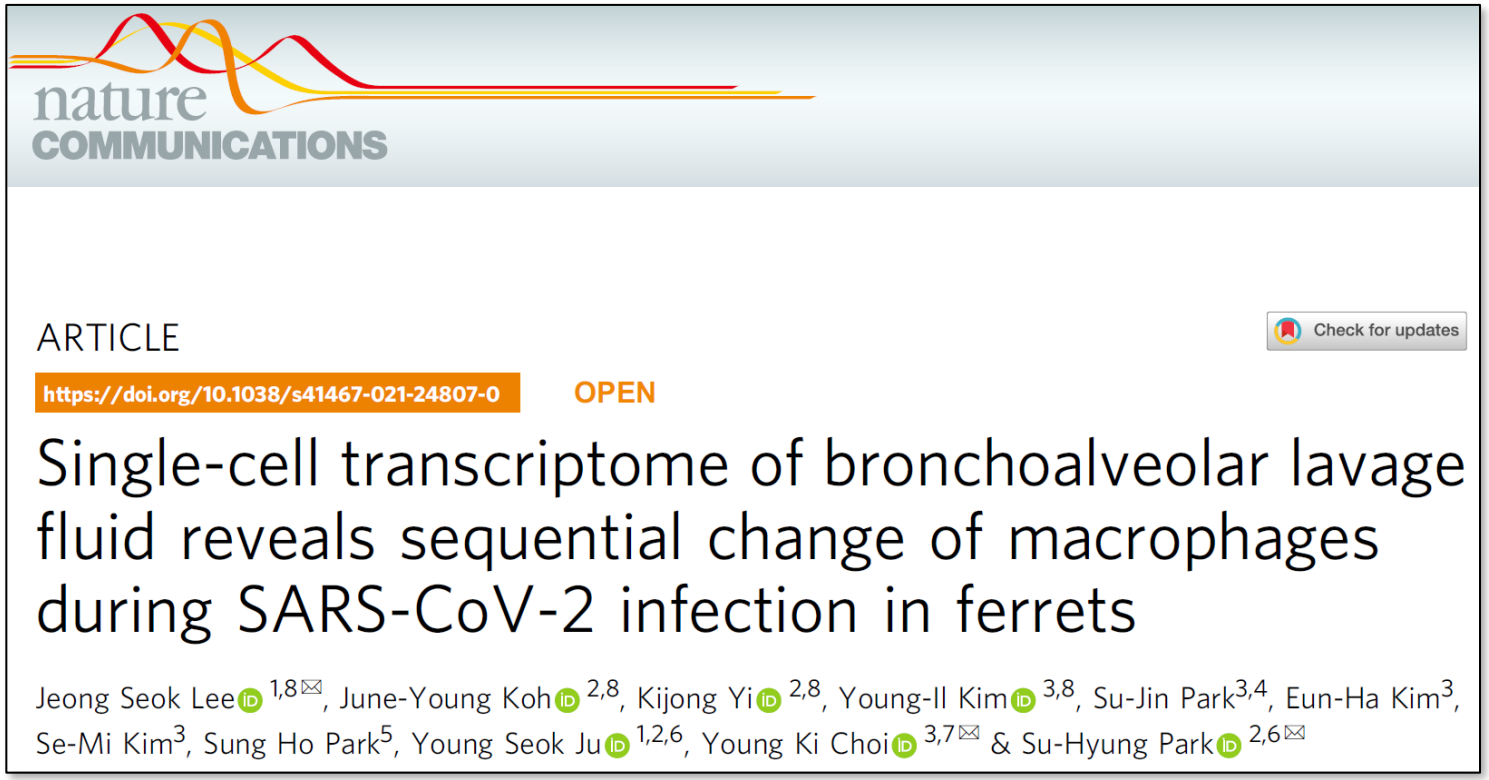
Strength: Landscaping study, Cited more than 200 times.

- Started earlier, and completed faster.
- Providing initial impression of the immune response pattern in COVID-19
- Severe COVID-19 is a real medical issue: contrast severe COVID-19 using 3 control groups

Weakness

- Small size to characterize human subjects (n=20)
- Descriptive, **cross-sectional study**

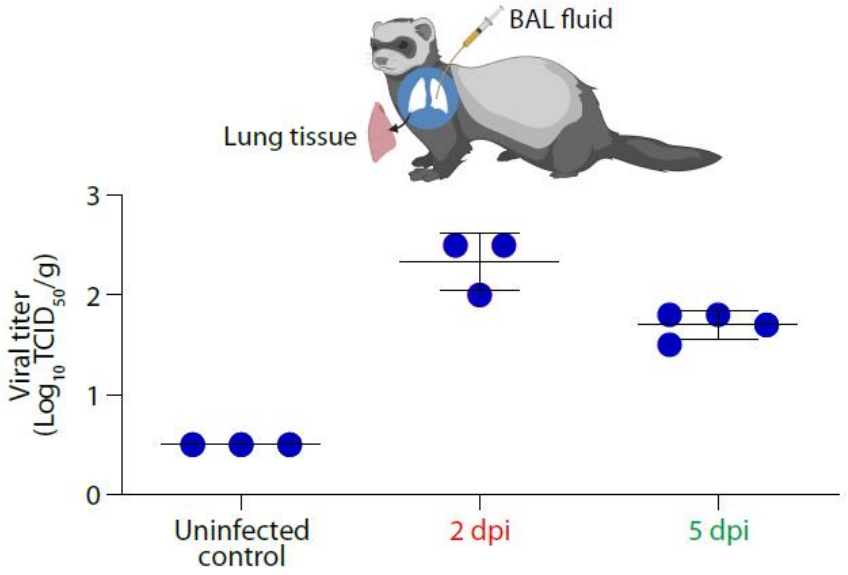
Lee JS et al., *Sci Immunol*. 2020



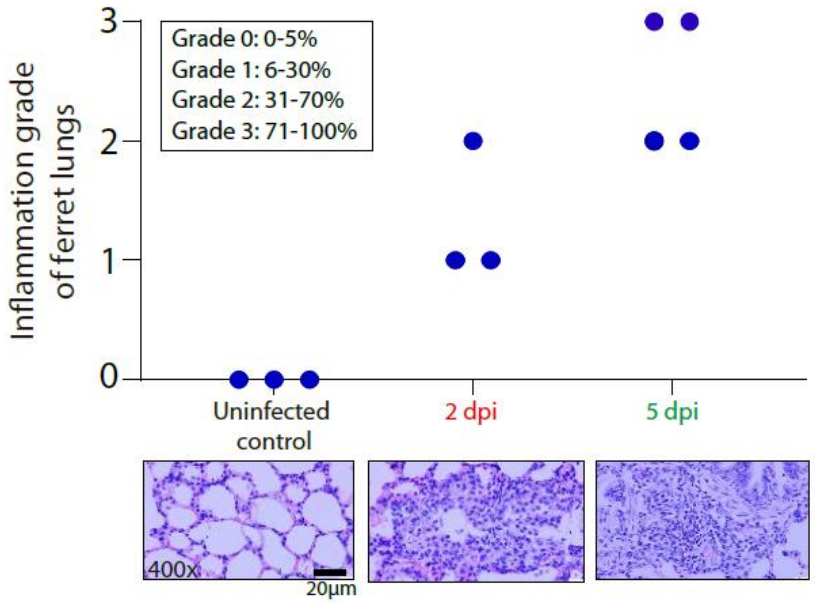
Lee JS et al., *Nat Commun*. 2021

Objectives of this study

Longitudinal Design



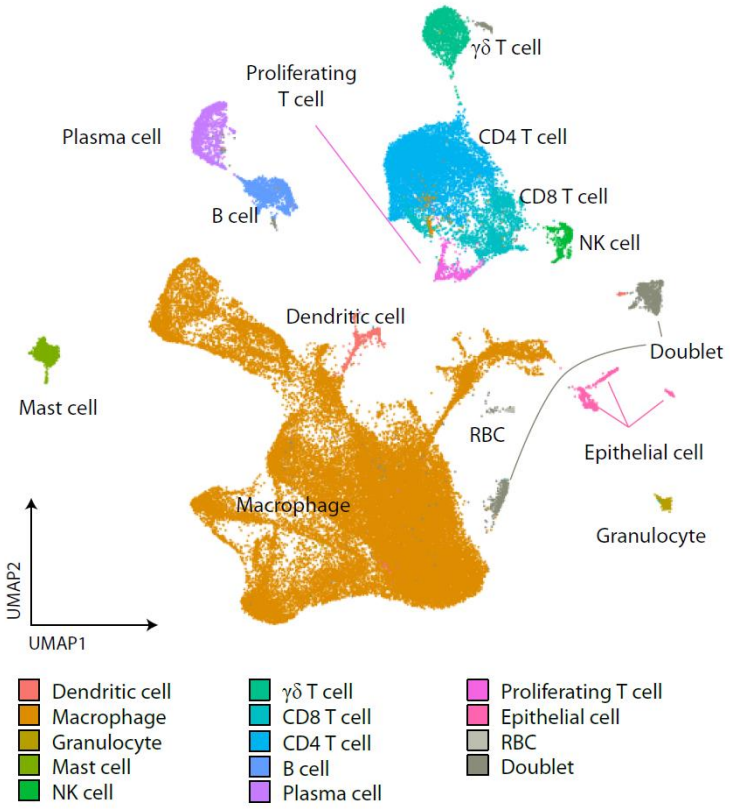
Target organ (Lung)

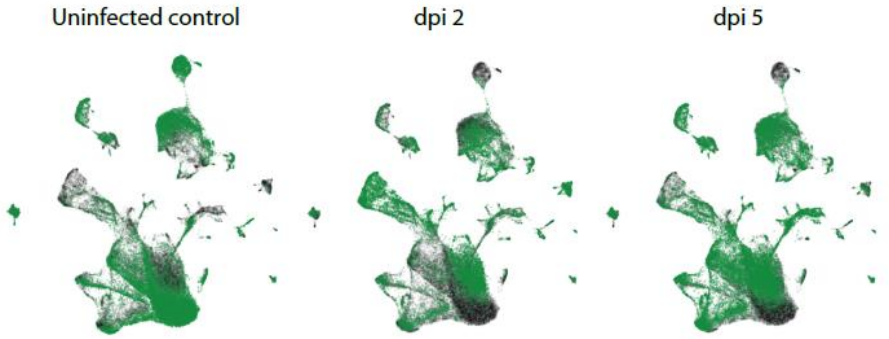


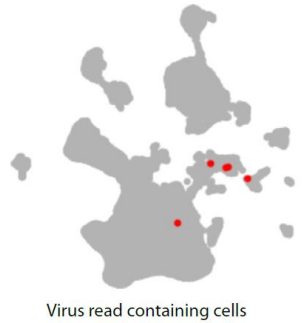
2 dpi: early stage of SARS-CoV-2 infection with peak viral titer
5 dpi: resolution phase with decreasing viral titer and evident histopathological changes

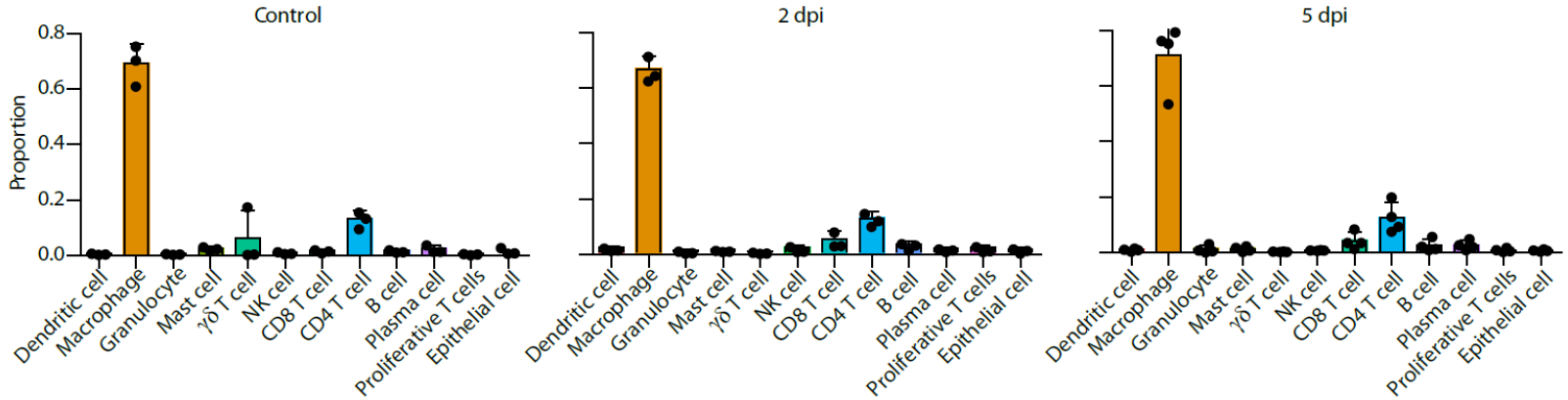
Lee JS et al., *Nat Commun*. 2021

Longitudinal immune landscape of BAL fluid cells



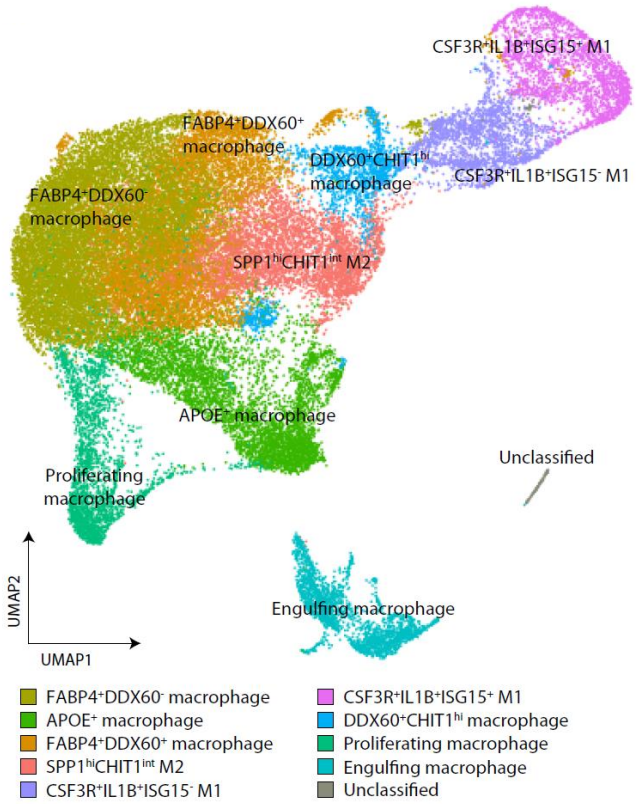


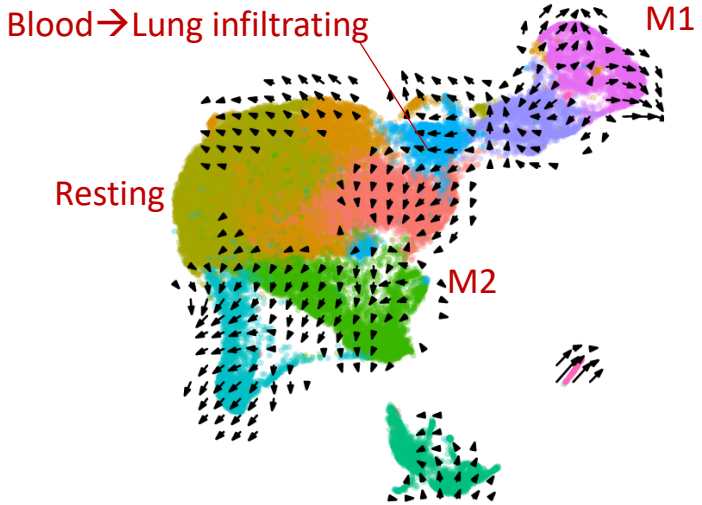


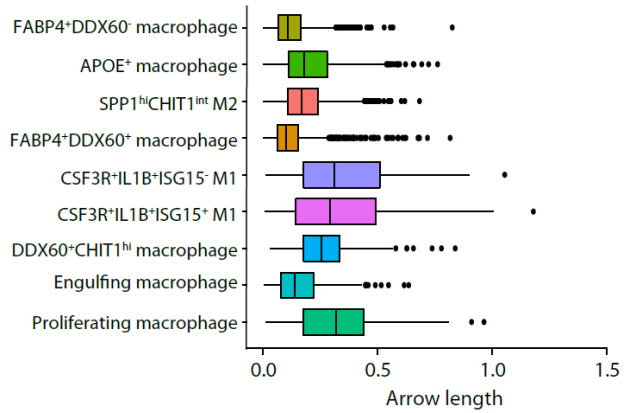


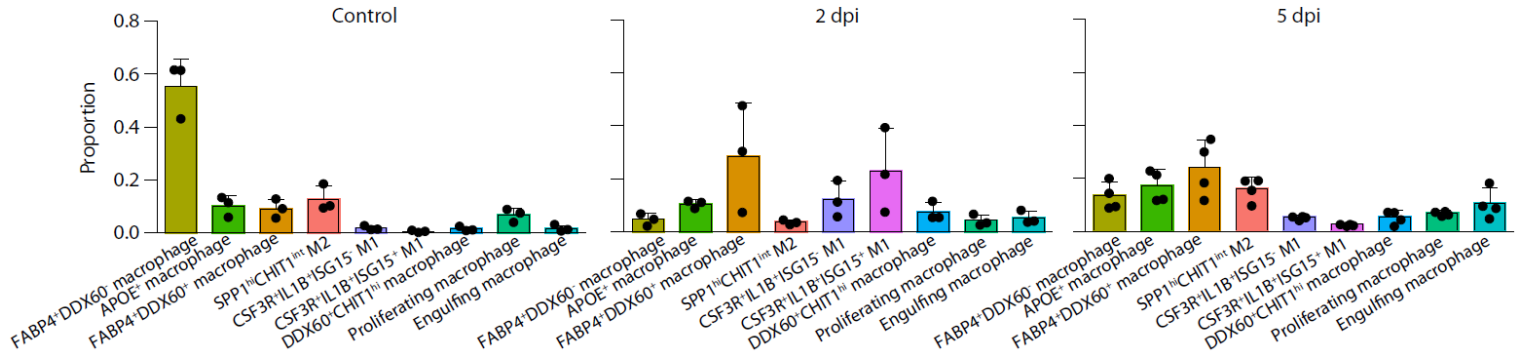
Lee JS et al., *Nat Commun*. 2021

Longitudinal immune landscape of macrophages of BAL fluid cells



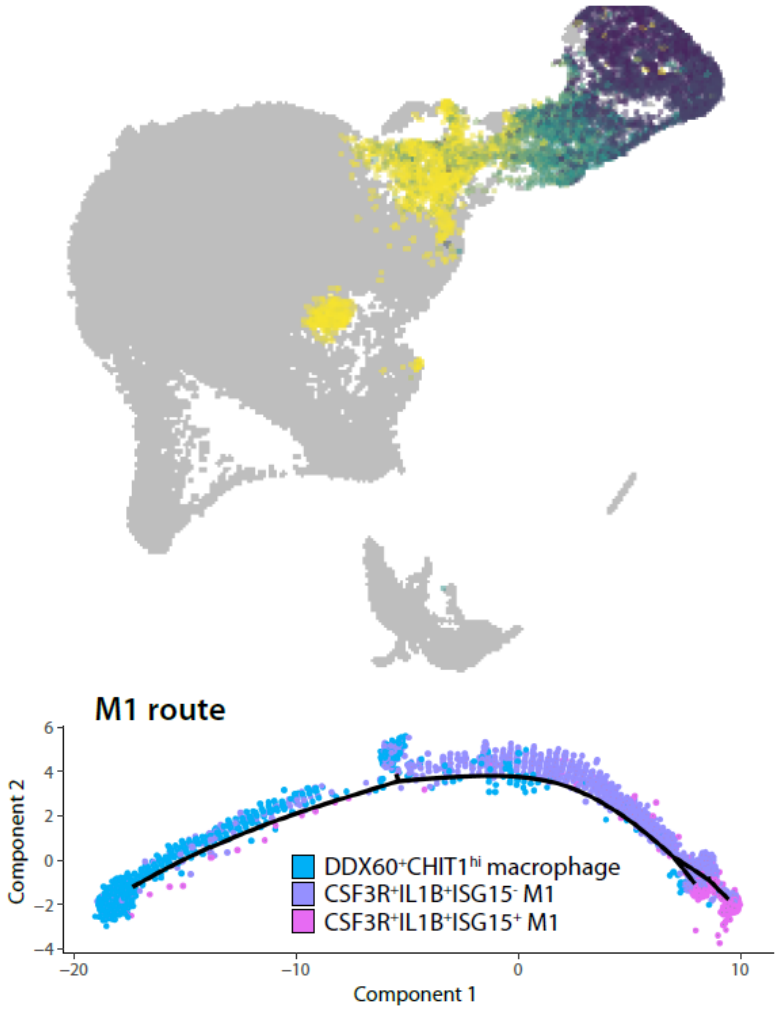


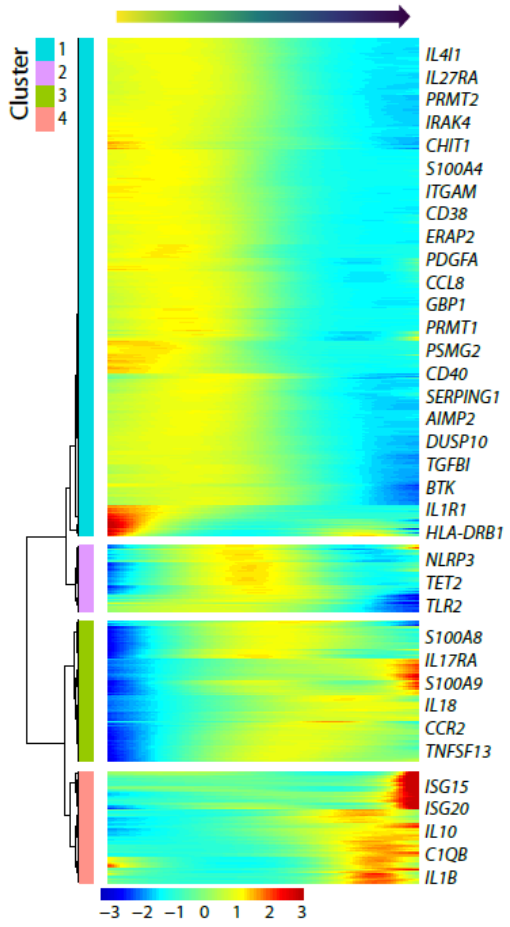


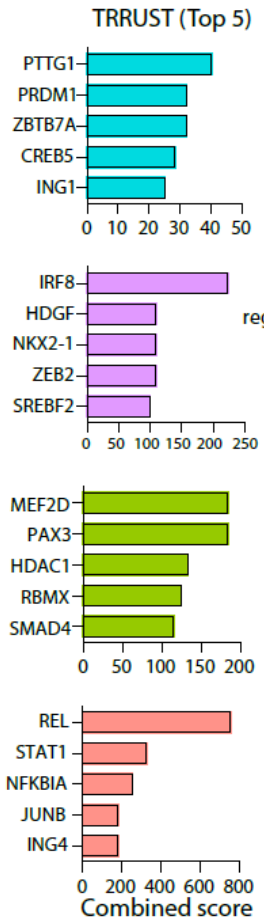


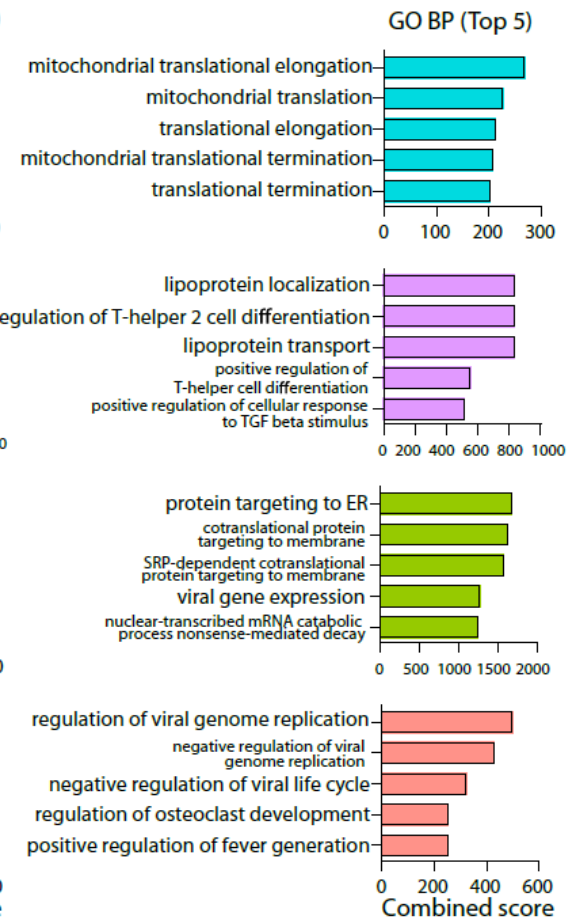
Lee JS et al., *Nat Commun*. 2021

Trajectory from infiltrating monocyte → M1 macrophage



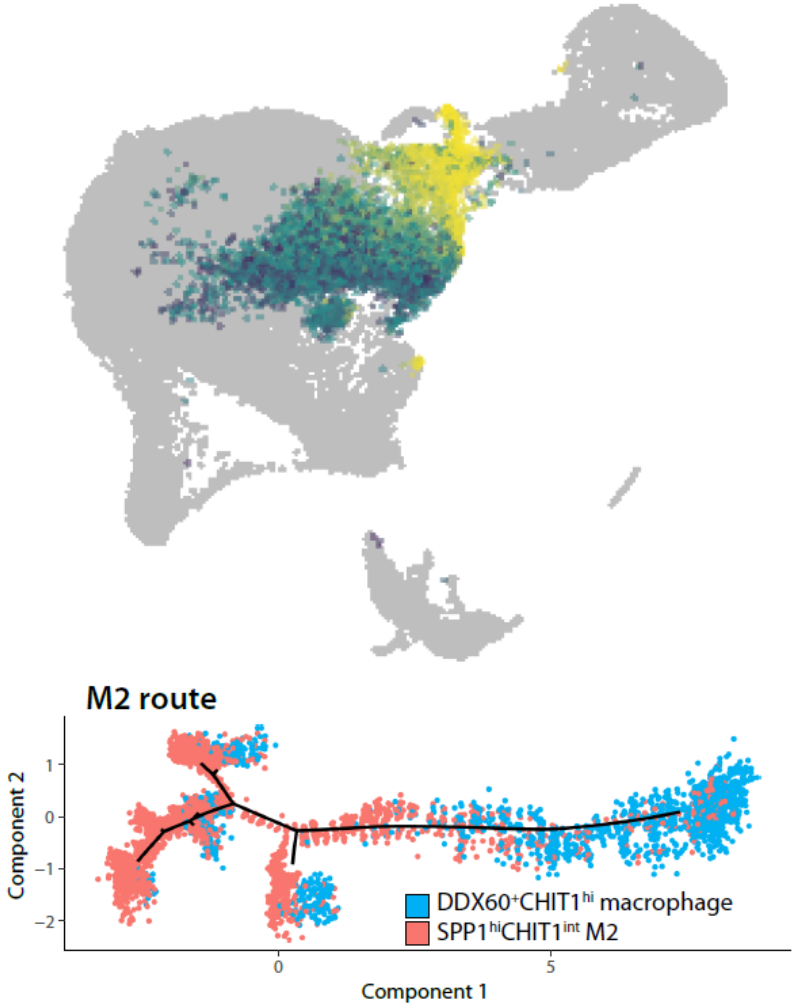


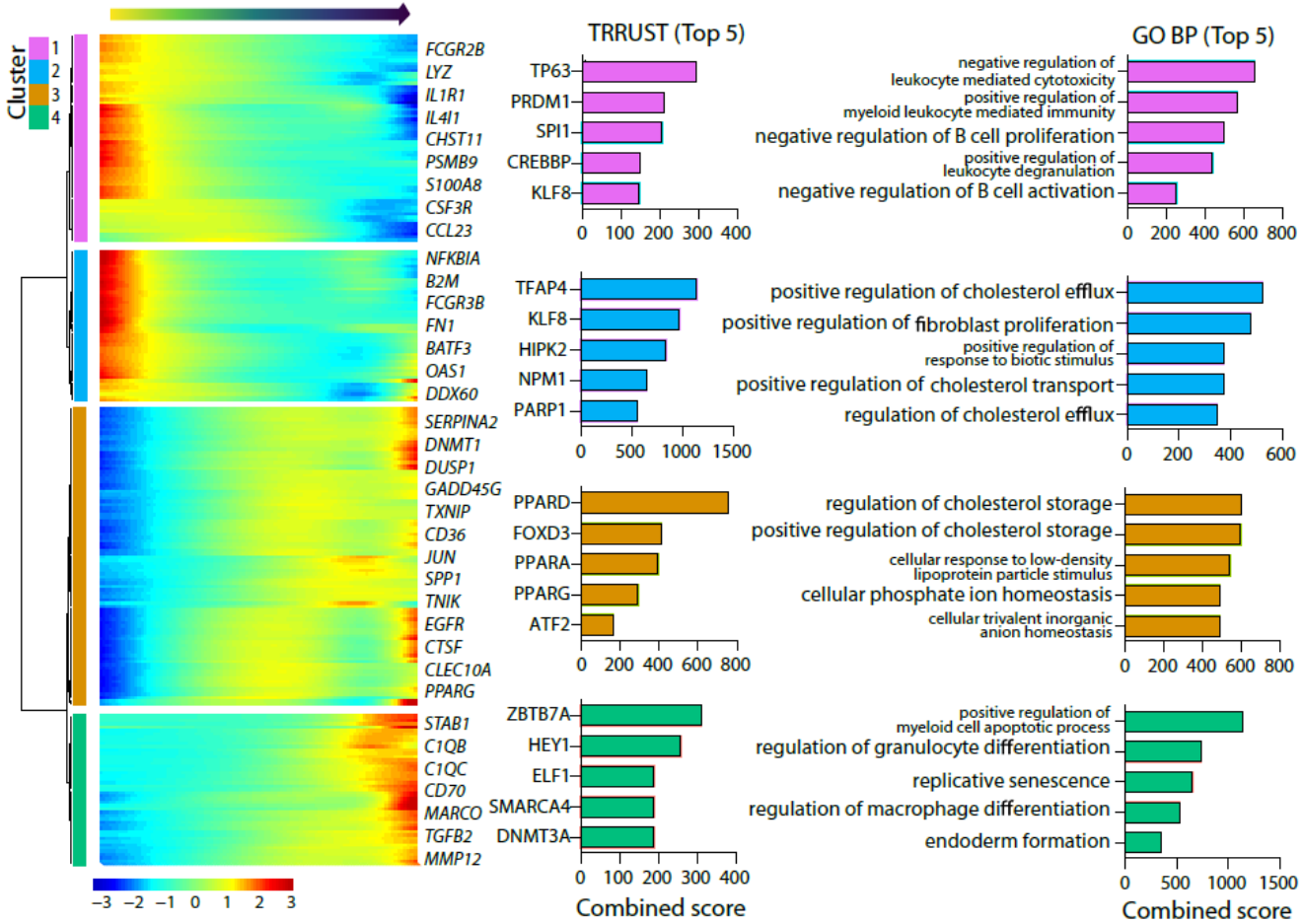




Lee JS et al., *Nat Commun*. 2021

Trajectory from infiltrating monocyte → M2 macrophage





Lee JS et al., *Nat Commun*. 2021

Summary (2)

We have used a longitudinal approach along with the natural disease course of SARS-CoV-2 infection.

Among macrophages—the major population of BAL fluid cells, we identified 10 different subpopulations that exhibited relative proportion changes from 0 to 5 dpi.

The predominant dynamic changes of the transcriptome involved monocyte-derived infiltrating macrophages and differentiated M1/M2 macrophages, especially at 2 dpi.

We also observed distinctive and stepwise differentiation from monocyte-derived infiltrating macrophages toward M1 or M2 macrophages.

Lee JS et al., *Nat Commun*. 2021

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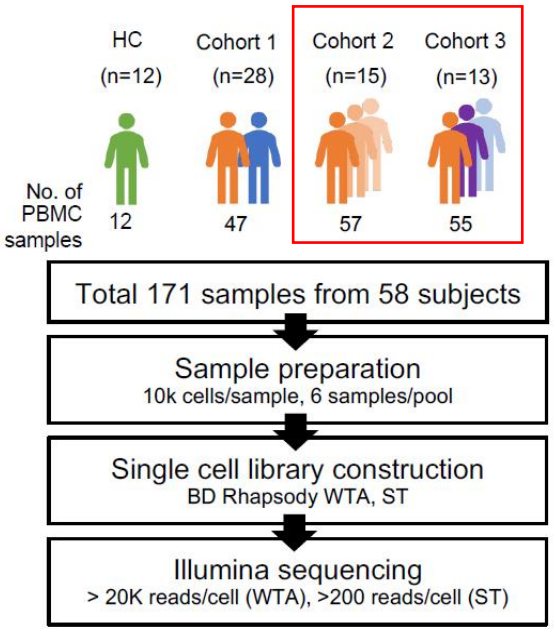
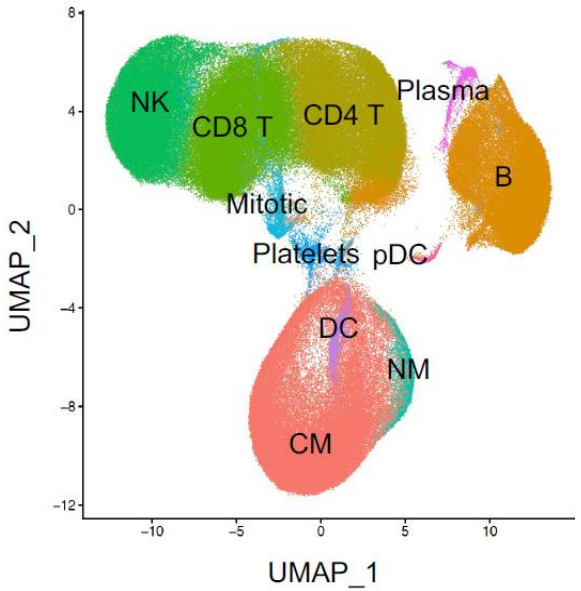
Corticosteroid @ critical COVID-19

Longitudinal cohort



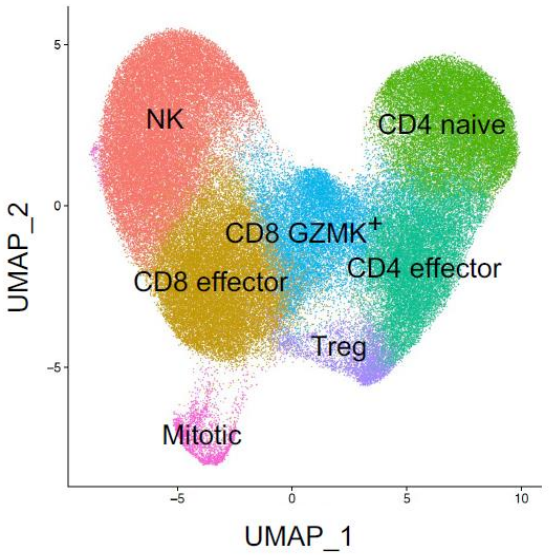
PBMC

171 samples / 244,722 cells



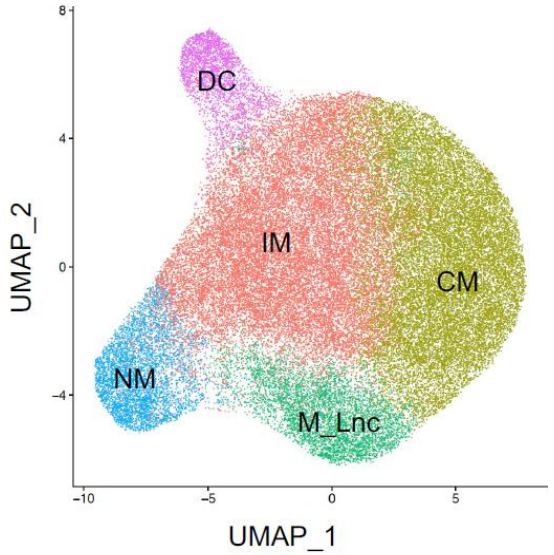
T/NK

124,331 cells



Monocyte/DC

57,928 cells



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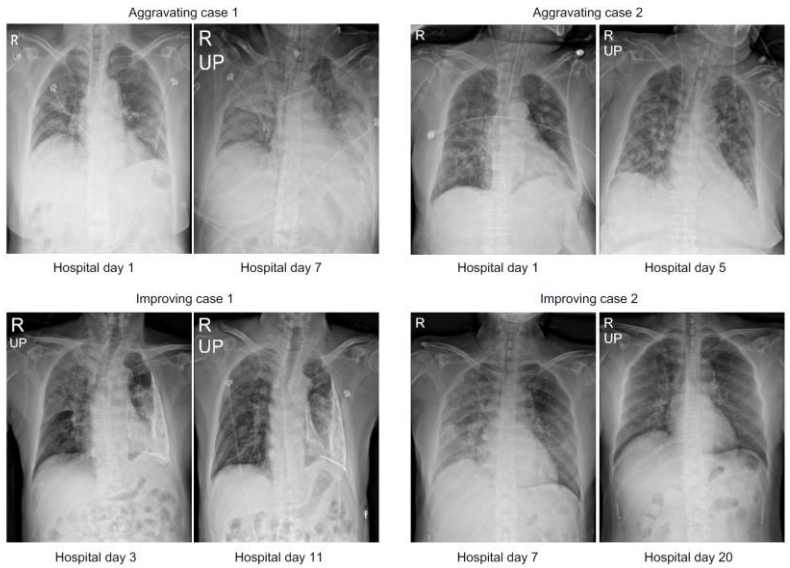
Corticosteroid @ critical COVID-19

Cohort 2: Aggravating vs. Improving

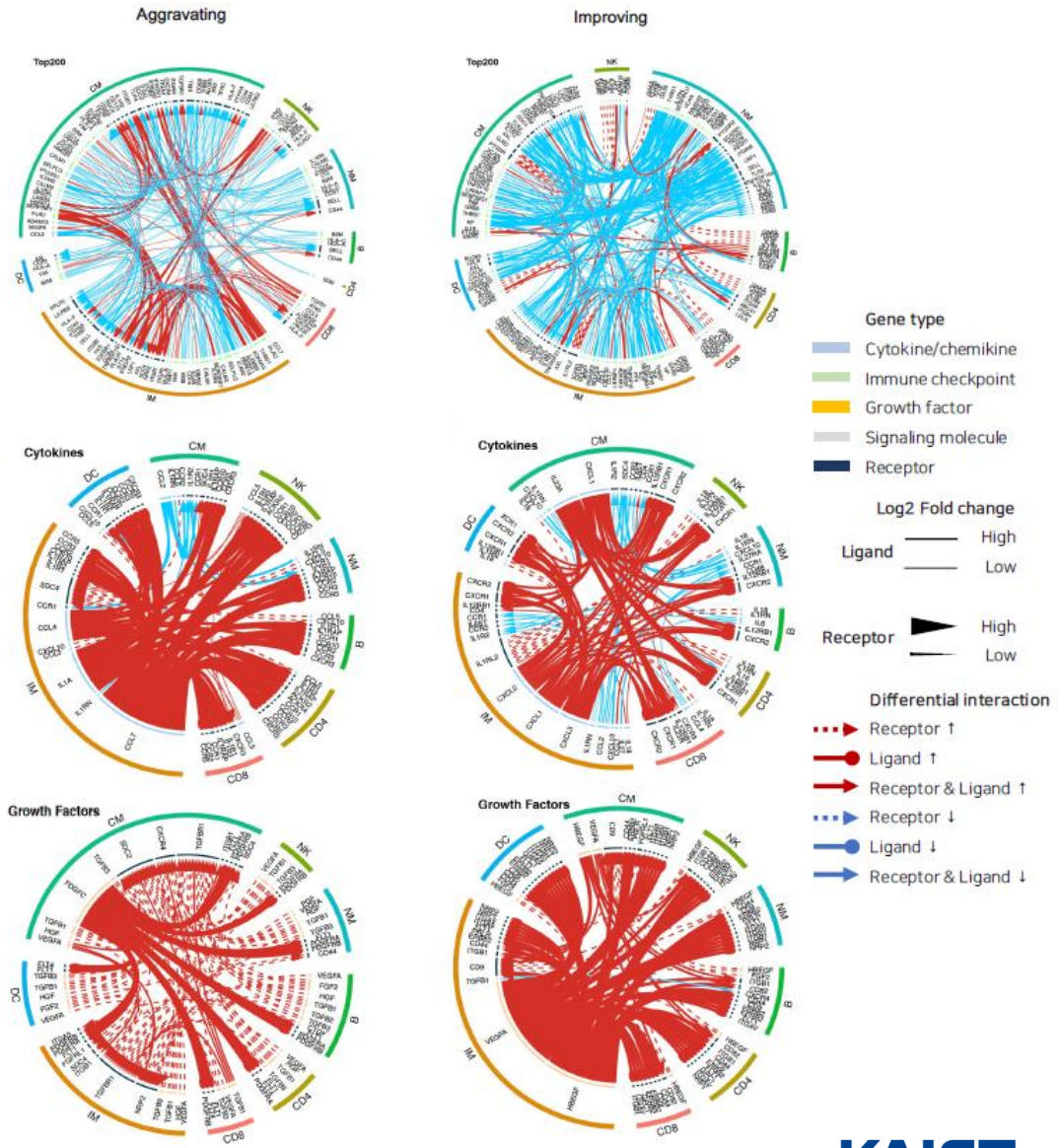
Ligand-receptor interaction



CM → IM

IL-1 → CXCR1-CXCL1
CXCR2-CXCL2
CXCR3-CXCL3

PDGFC → VEGFA
TGFB



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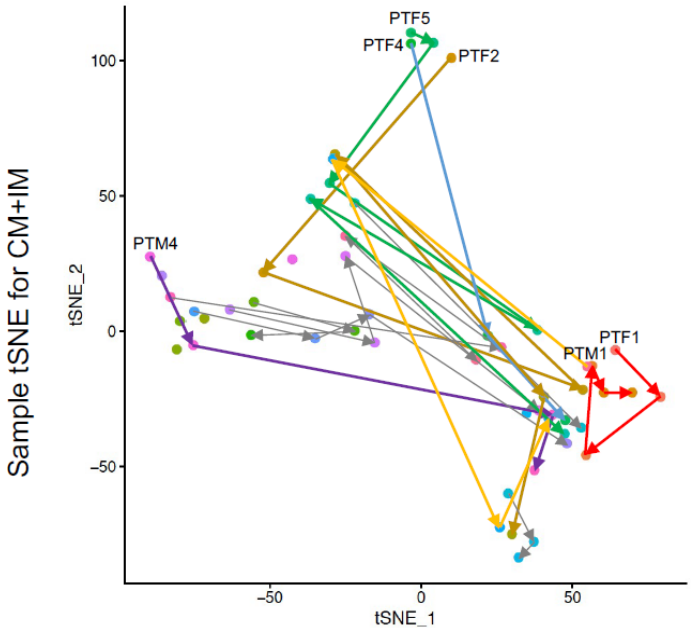
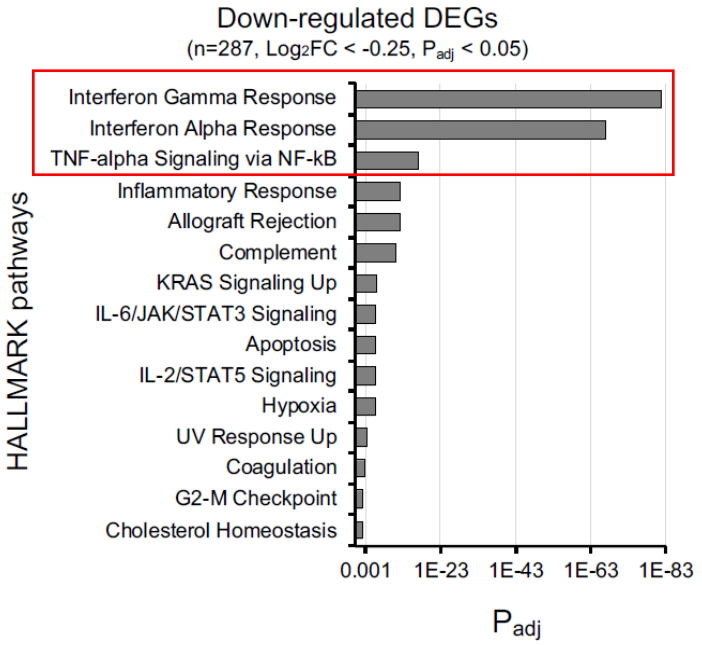
Corticosteroid @ critical COVID-19

Cohort 3: Corticosteroid @ critical COVID-19 – Before and Day 1, 4,..





SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

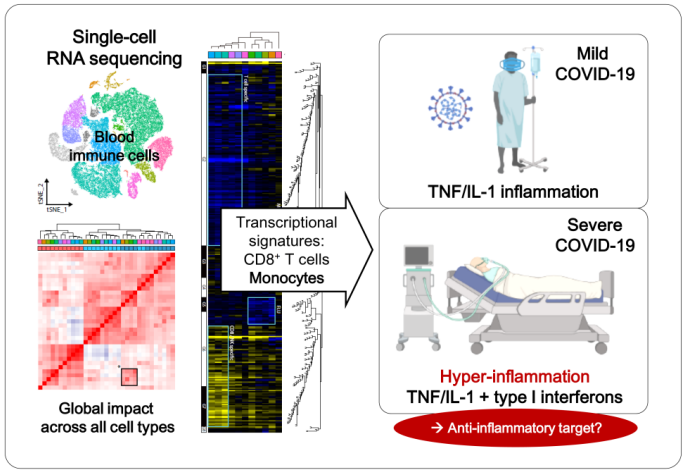
CORONAVIRUS

Immunophenotyping of COVID-19 and influenza highlights the role of type I interferons in development of severe COVID-19

Jeong Seok Lee[1]*, Seongwan Park[2]*, Hye Won Jeong[3]*, Jin Young Ahn[4]*, Seong Jin Choi[1], Hoyoung Lee[1], Baekgyu Choi[2], Su Kyung Nam[2], Moa Sa[1,5], Ji-Soo Kwon[1,6], Su Jin Jeong[4], Heung Kyu Lee[1,5], Sung Ho Park[7], Su-Hyung Park[1,5], Jun Yong Choi[4†], Sung-Han Kim[6†], Inkyung Jung[2†], Eui-Cheol Shin[1,5†]

COVID-19: TNF, IL-1

Severe COVID-19: TNF, IL-1 +Type 1 IFN



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GENOME INSIGHT

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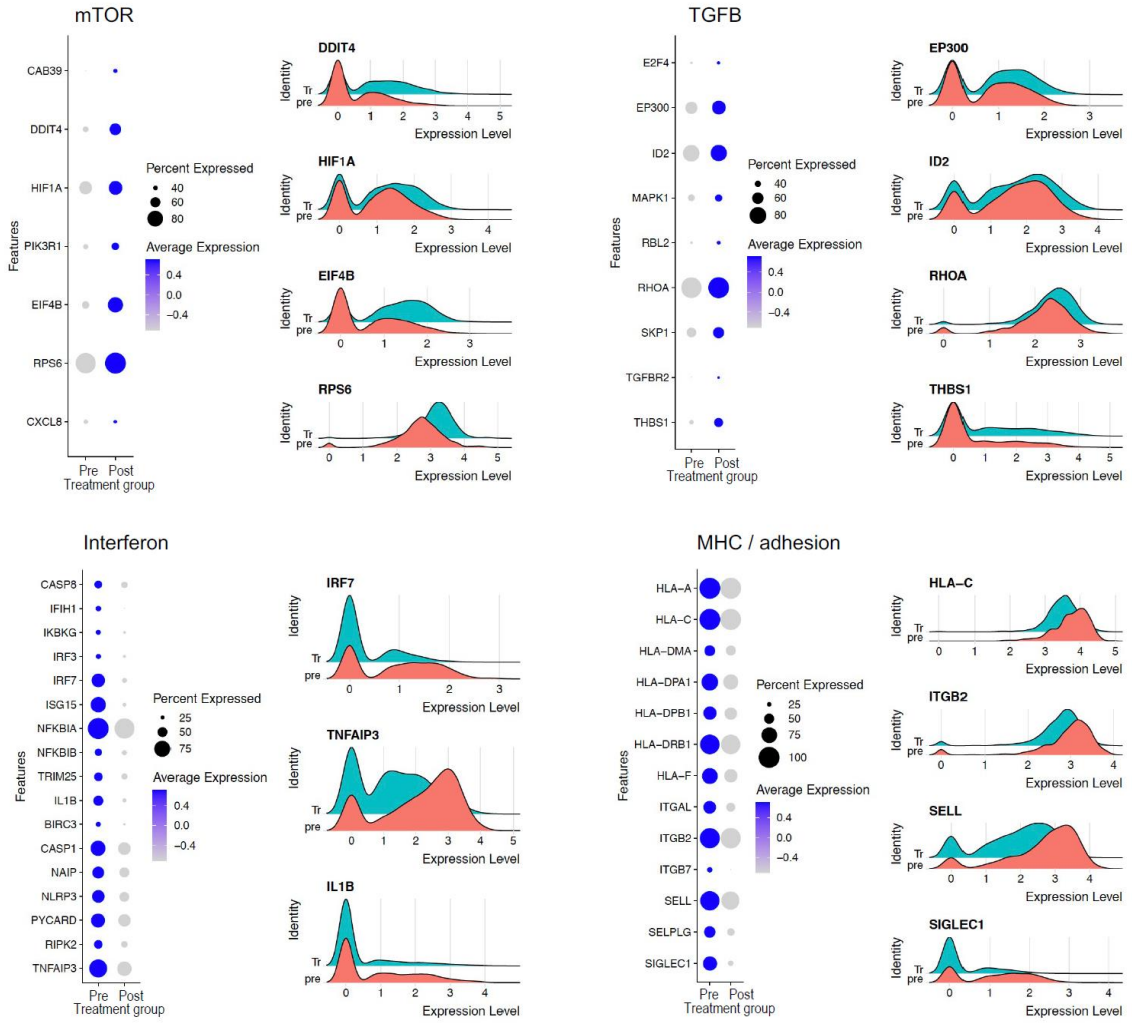
Corticosteroid @ critical COVID-19

Cohort 3: Steroid user – Before and Day 1, 4,..



Downregulated by corticosteroid

Upregulated by corticosteroid

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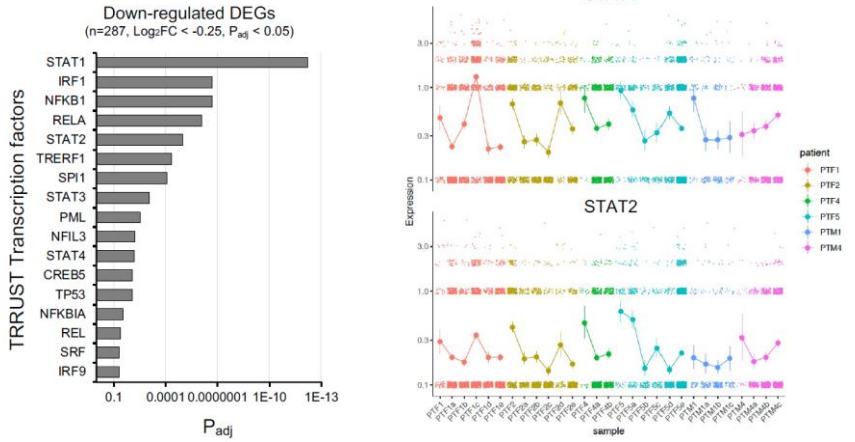

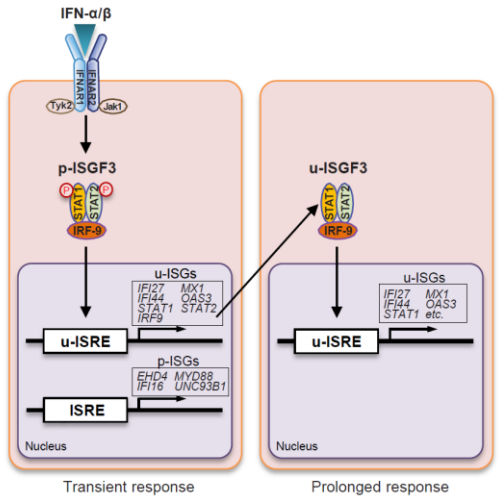

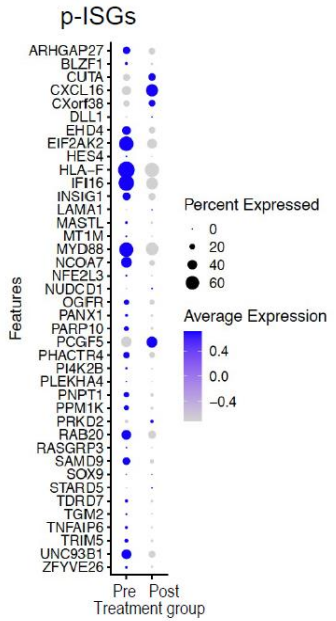

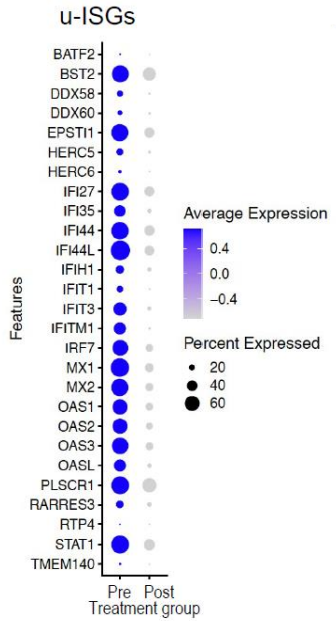

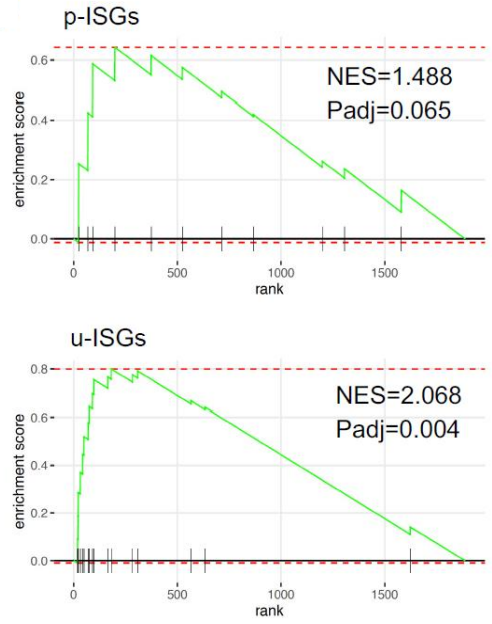

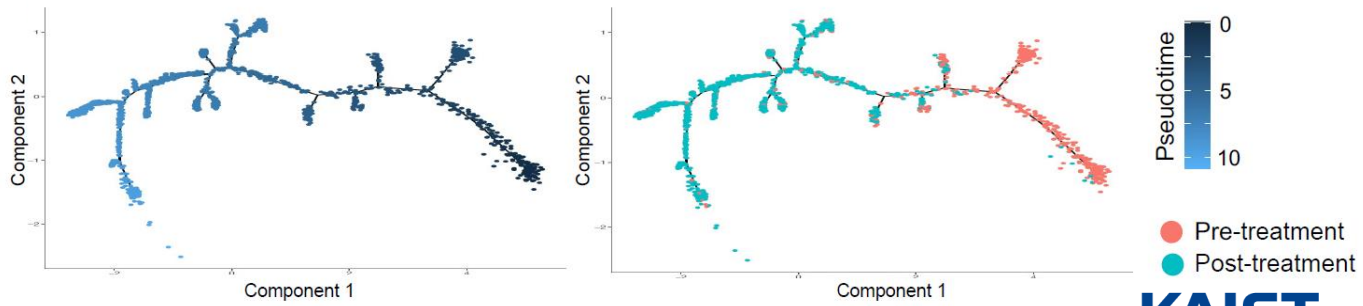

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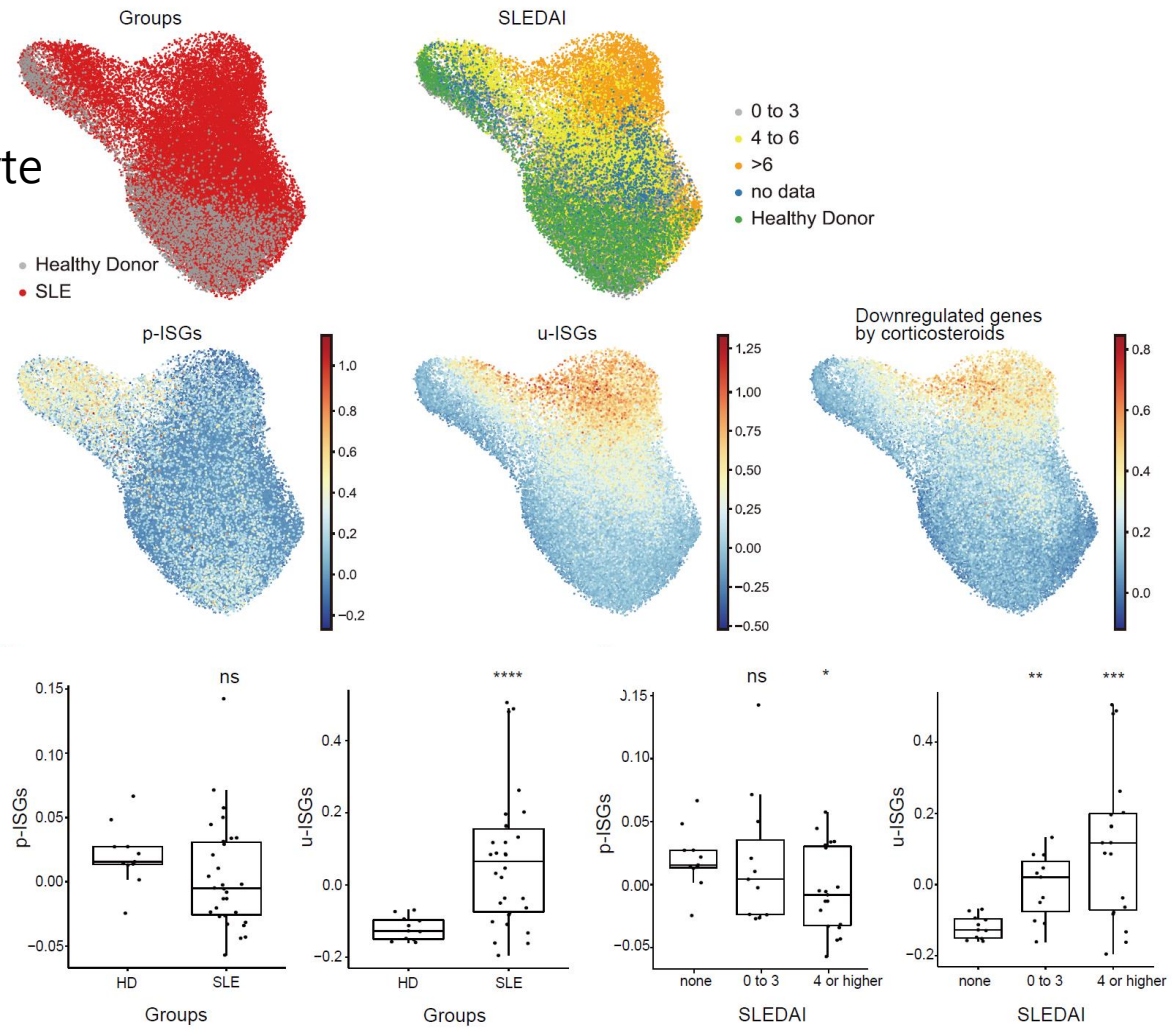
Corticosteroid @ critical COVID-19

Cohort 3: Steroid user – Before and Day 1, 4,..

Lupus monocyte



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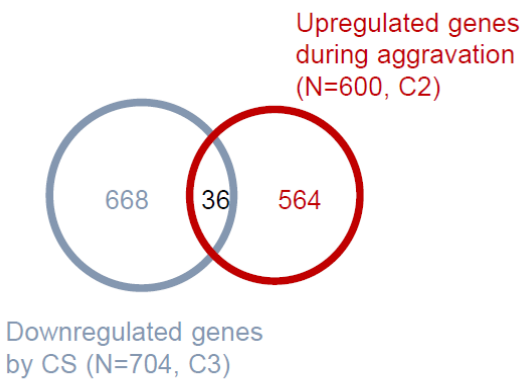

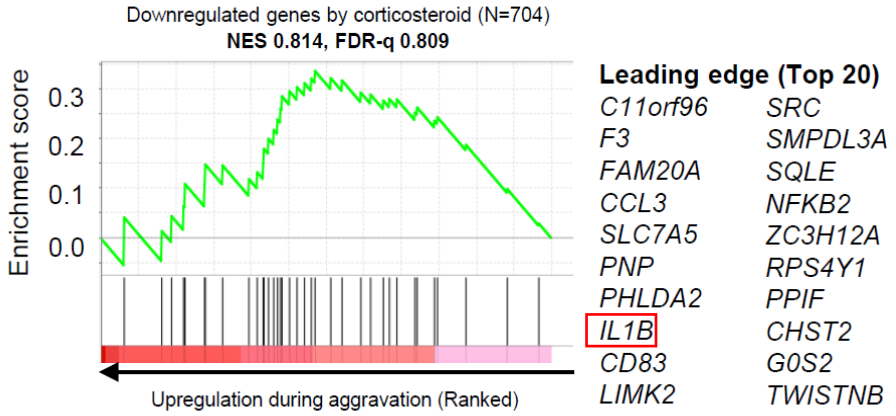

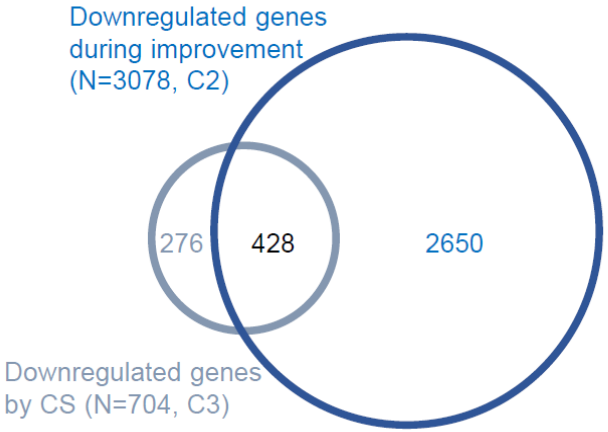

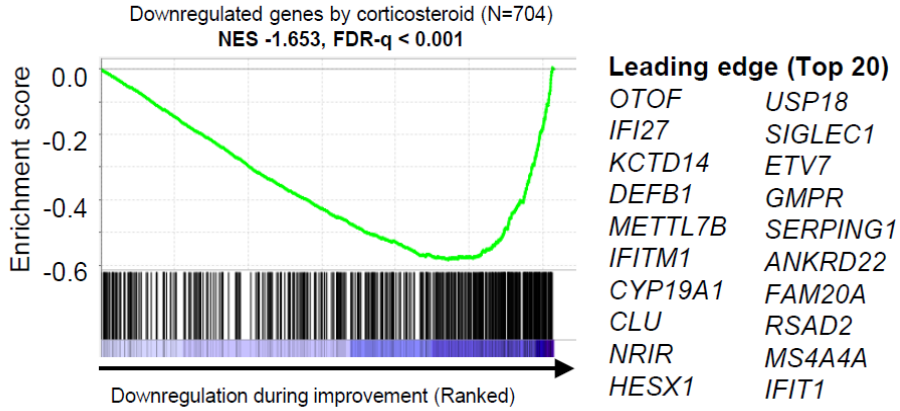

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Corticosteroid @ critical COVID-19: Summary

Corticosteroid treatment suppresses lupus-like dysregulated interferon responses in monocytes by down-regulating STAT1 in patients with critical COVID-19.

Our current study provides insights into the mechanisms underlying aggravation and improvement of COVID-19 and the effects of corticosteroid treatment.

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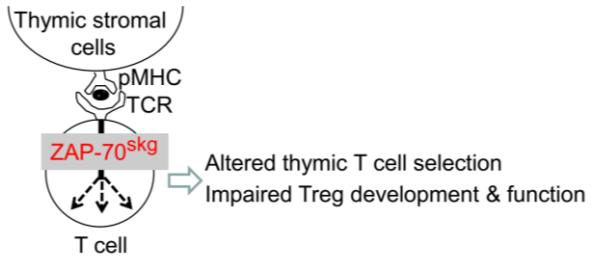
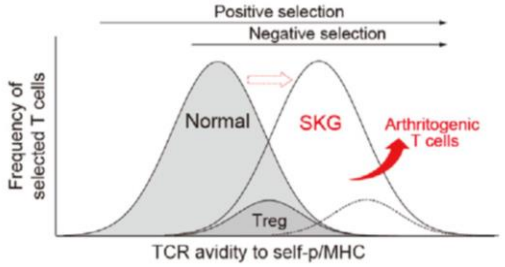
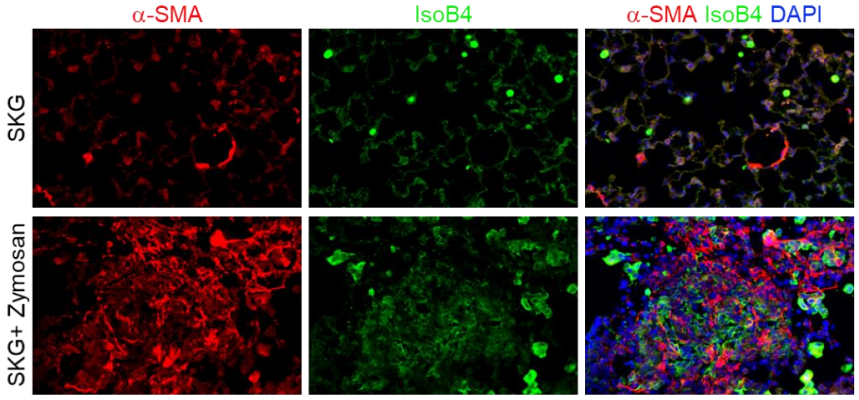
Immunosuppression @ SKG ILD model

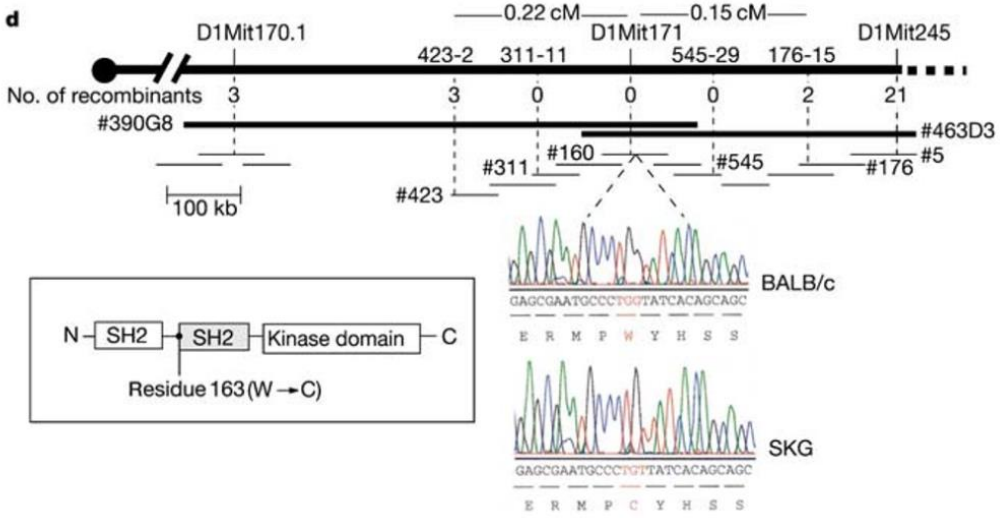
SKG model

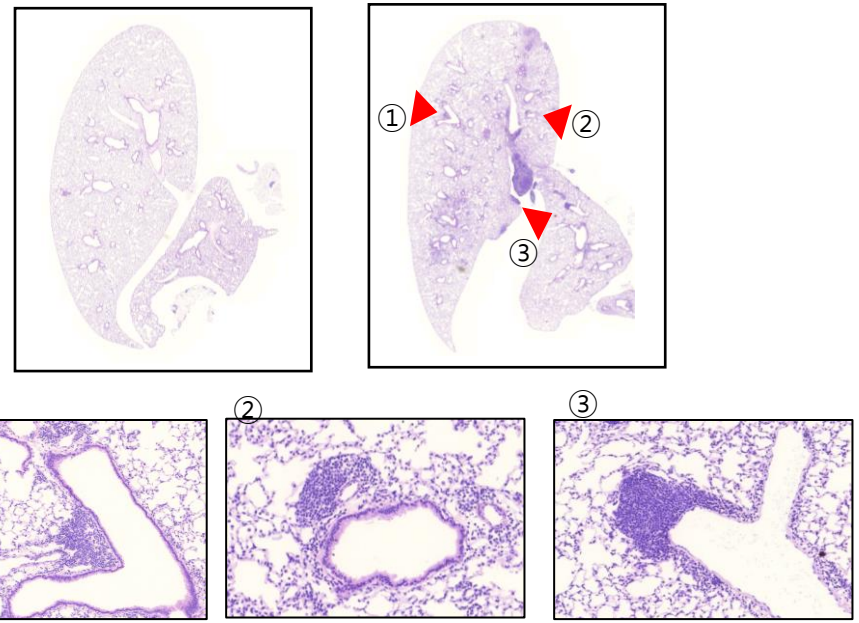






α-SMA, smooth muscle cells and myofibroblasts
Isolectin B4, immune cells and endothelial cells





N Sakaguchi et al. Nature 2003;426:454
S.Sakaguchi, et al. FEBS Letters 2011;585:3633

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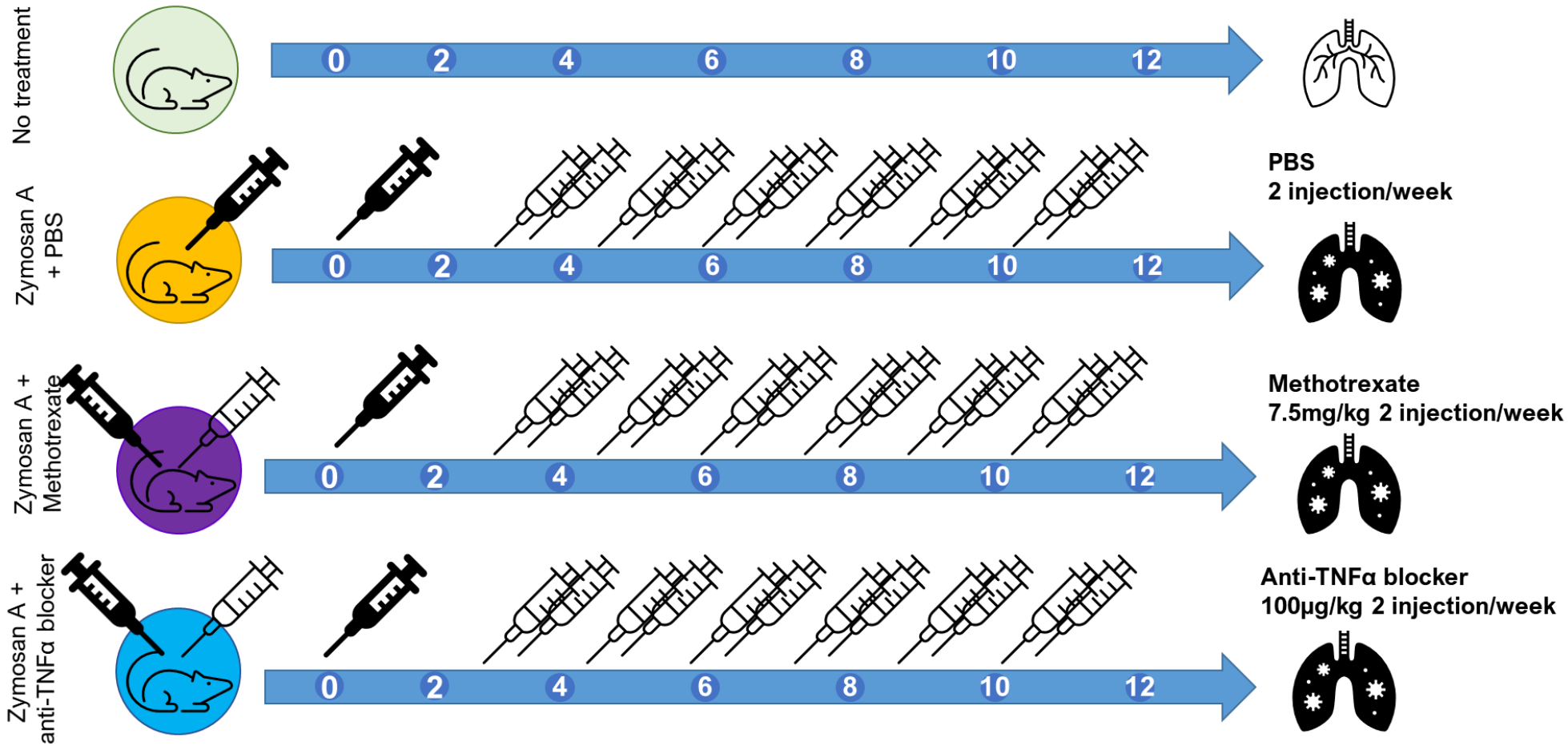
Immunosuppression @ SKG ILD model



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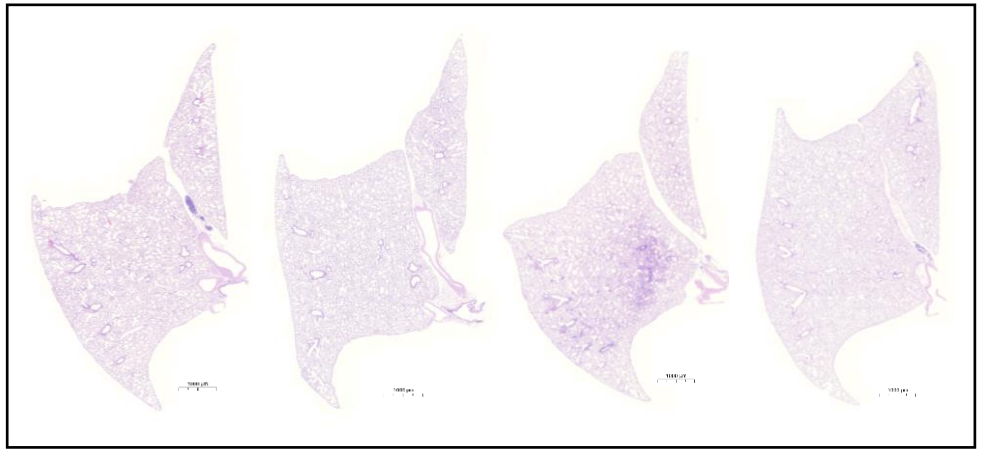
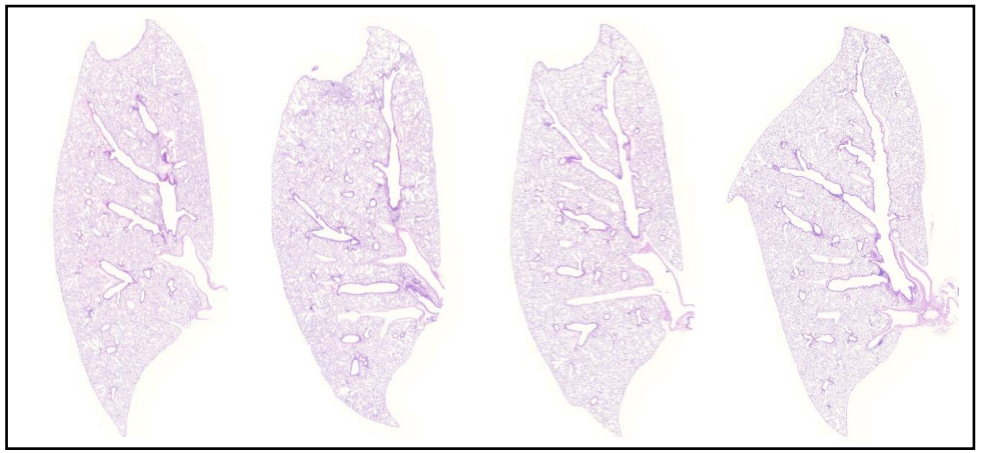
Immunosuppression @ SKG ILD model

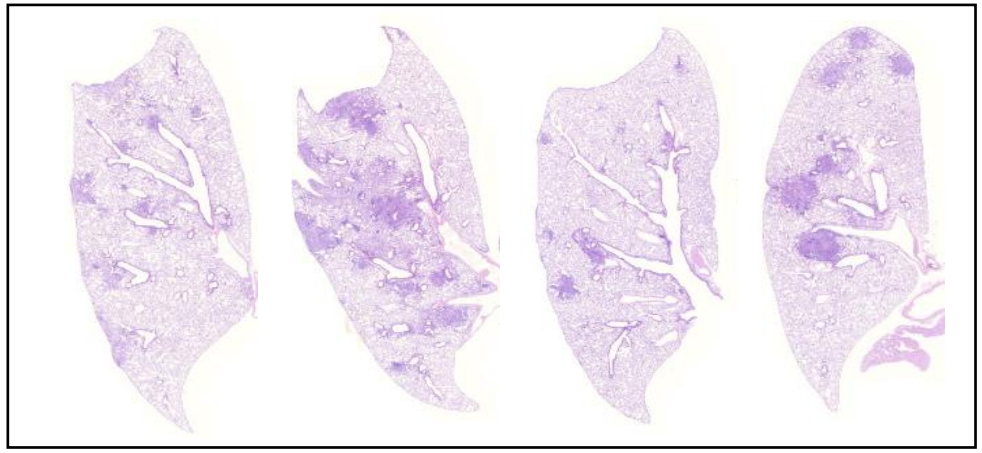
No zymosan A



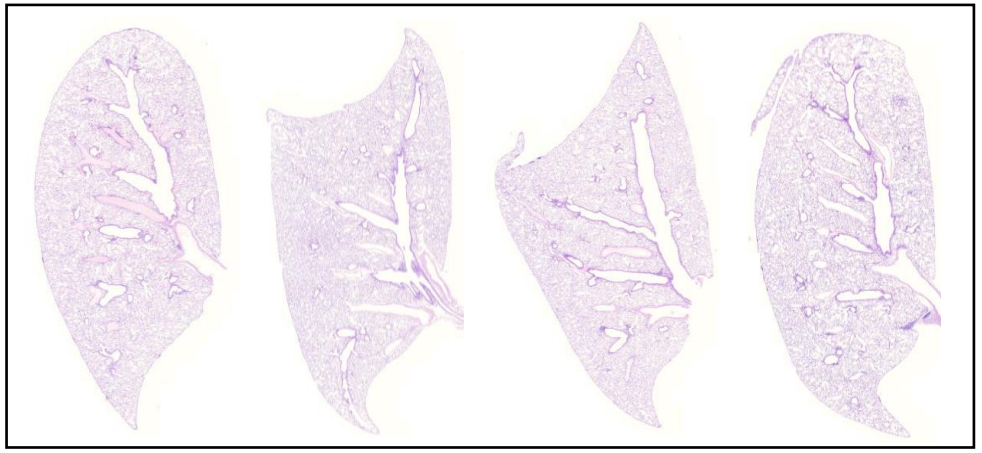
Zymosan A + PBS



Zymosan A + Methotrexate

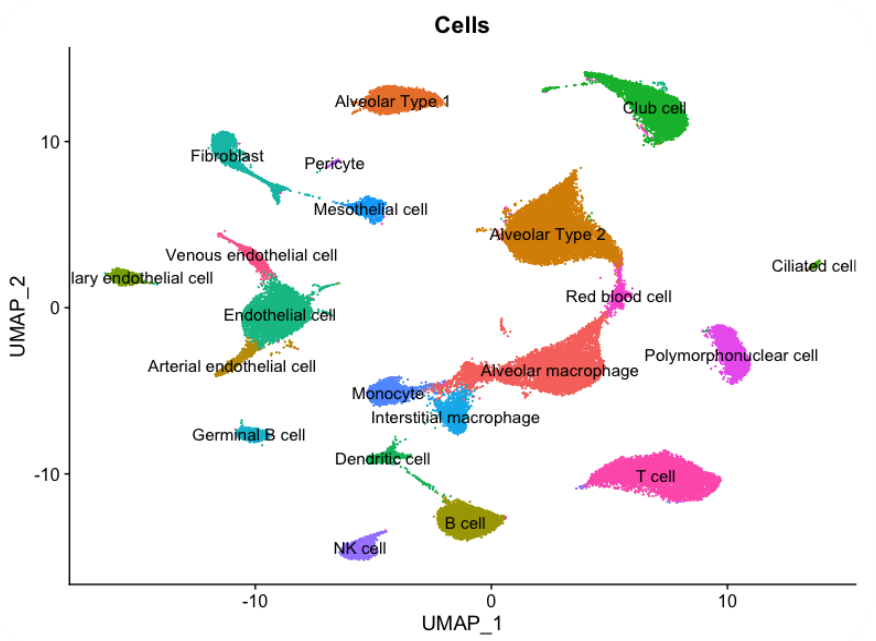


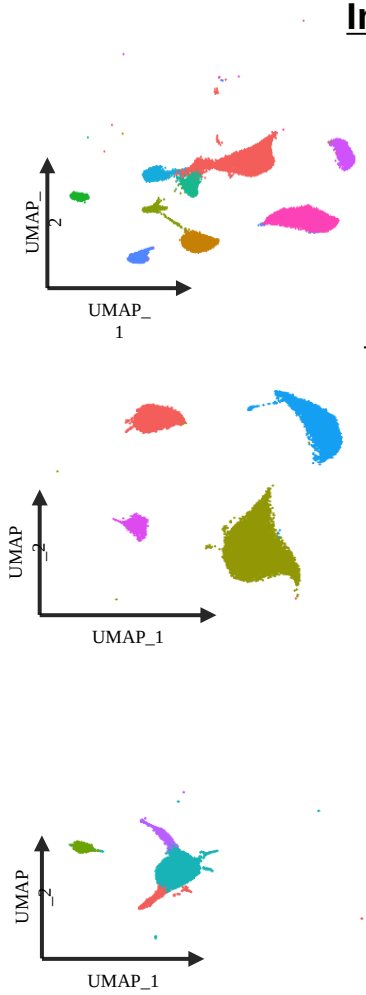
Zymosan A + anti-TNFα blocker



Immunosuppression @ SKG ILD model

Single-nuc seq





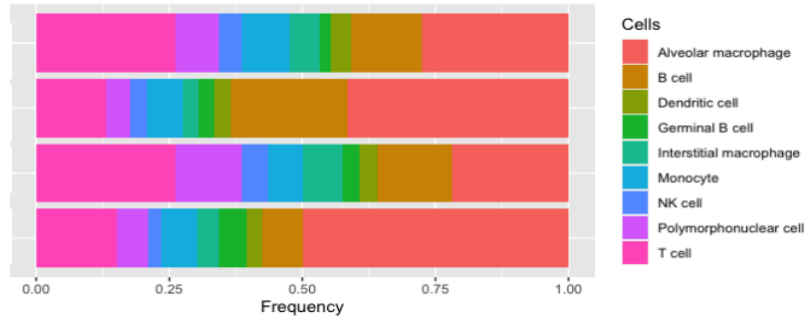
Immune cells

ZyA + MTX

ZyA + anti-TNFα

ZyA + PBS

No ZyA



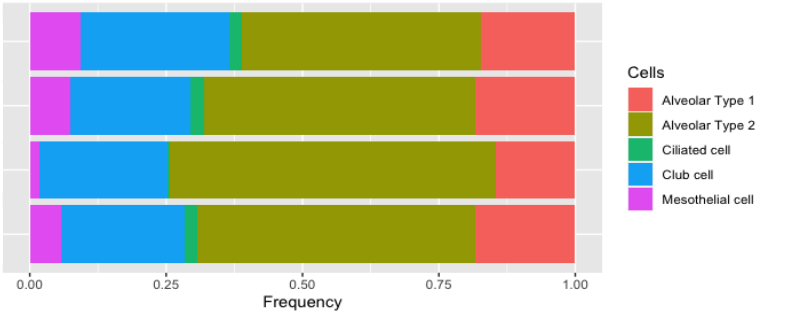
Epithelial cells

ZyA + MTX

ZyA + anti-TNFα

ZyA + PBS

No ZyA



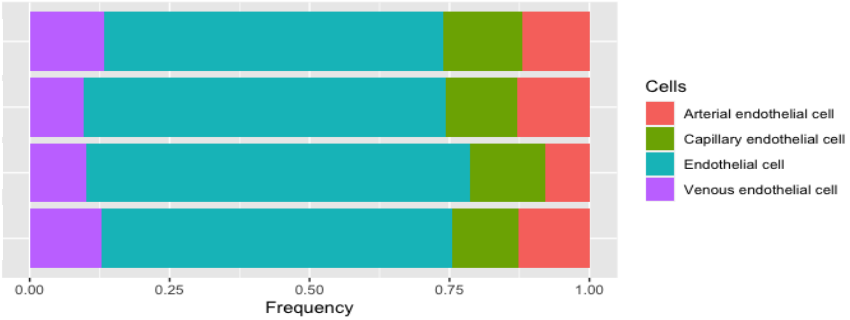
Endothelial cells

ZyA + MTX

ZyA + anti-TNFα

ZyA + PBS

No ZyA



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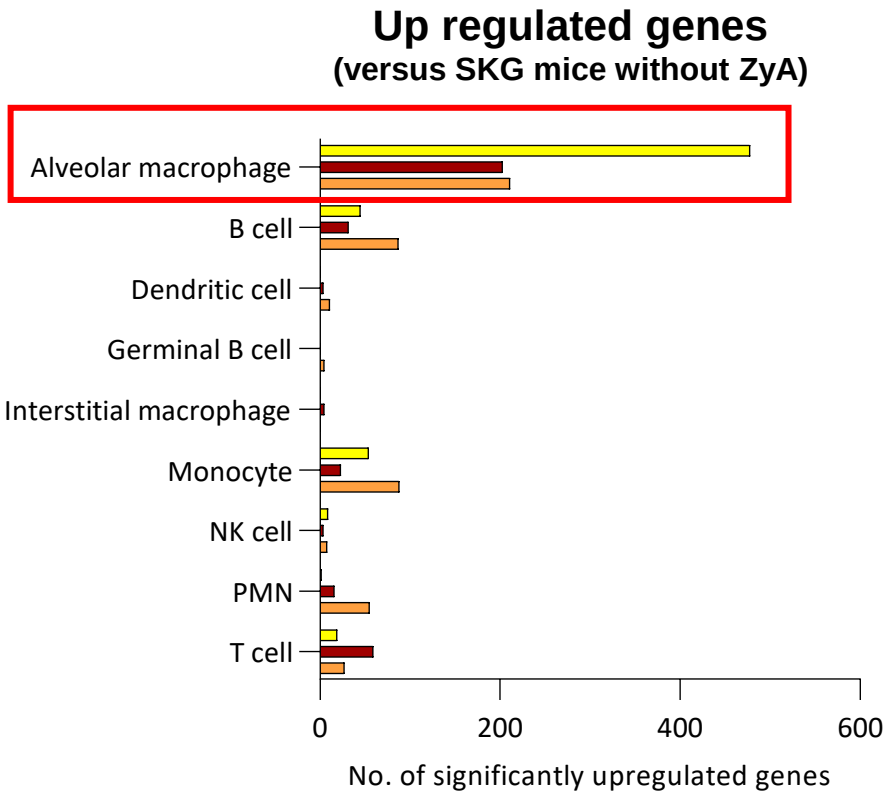
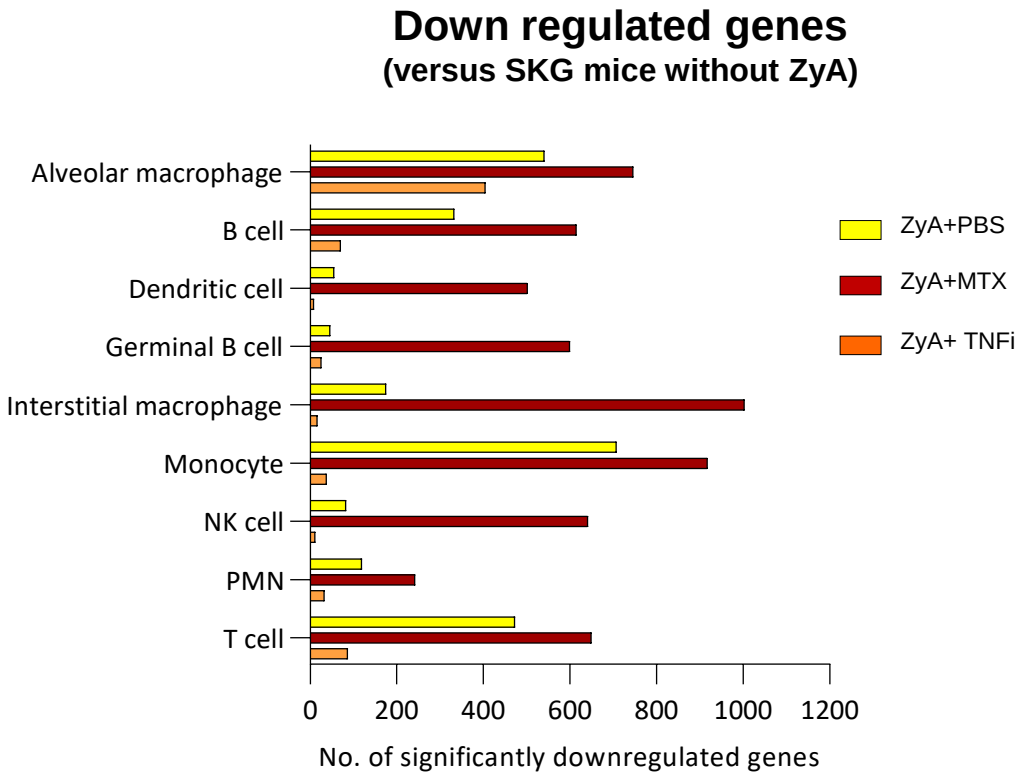
Immunosuppression @ SKG ILD model

Immune cells





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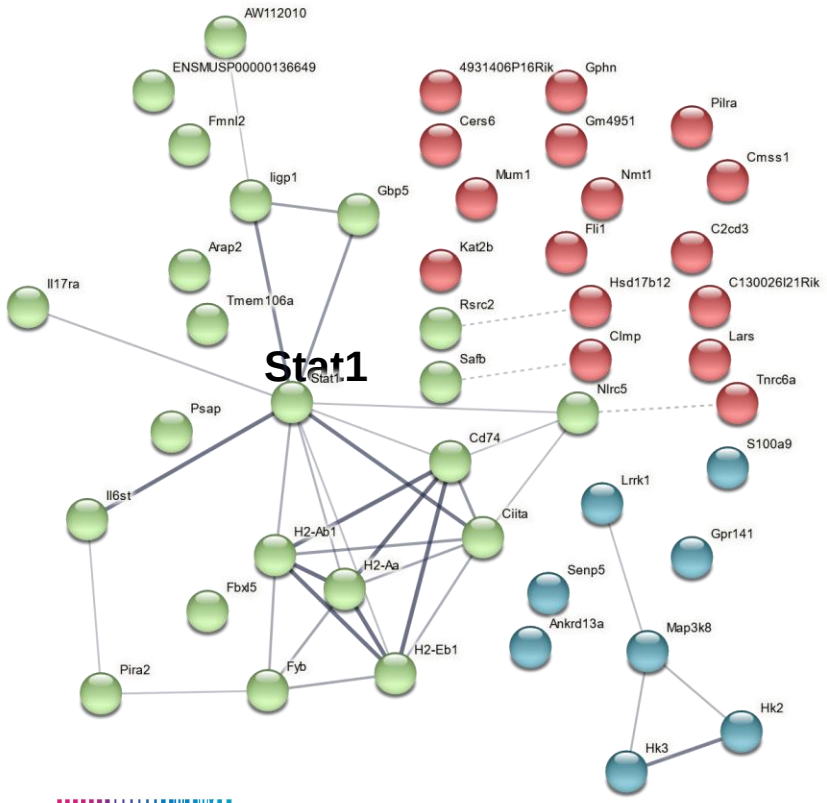
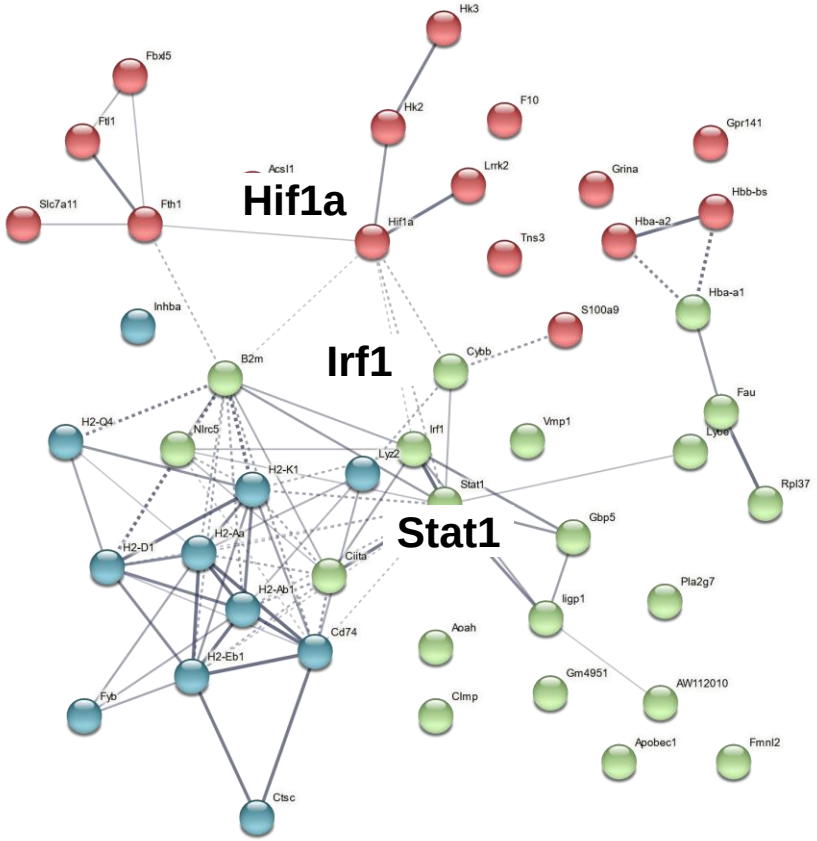
Immunosuppression @ SKG ILD model

STRING analysis of up-regulated genes of alveolar macrophage compared with SKG mice without ZyA injection

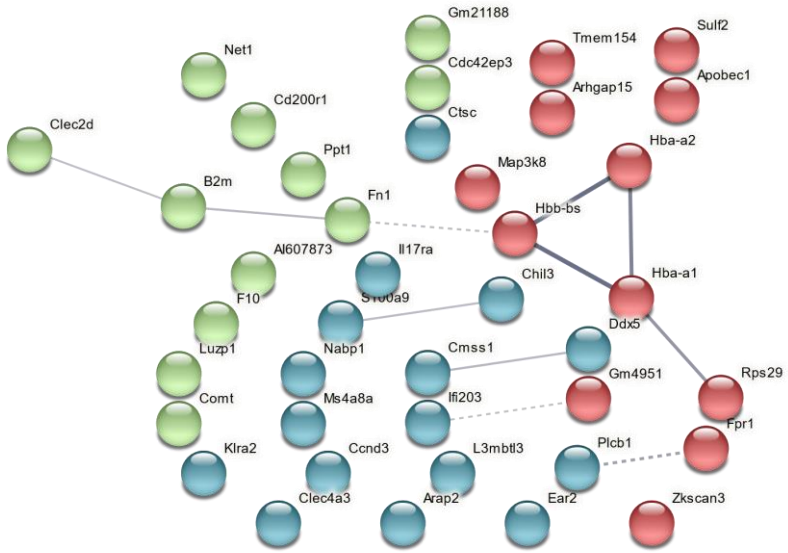
No ZyA vs ZyA + PBS



No ZyA vs ZyA + Methotrexate



No ZyA vs ZyA + TNFi



STRING analysis (Protein-Protein Interaction)
Alveolar macrophage (versus negative control)
Top 50 genes of each group, adj_p<0.05
K-means clustering (n=3)

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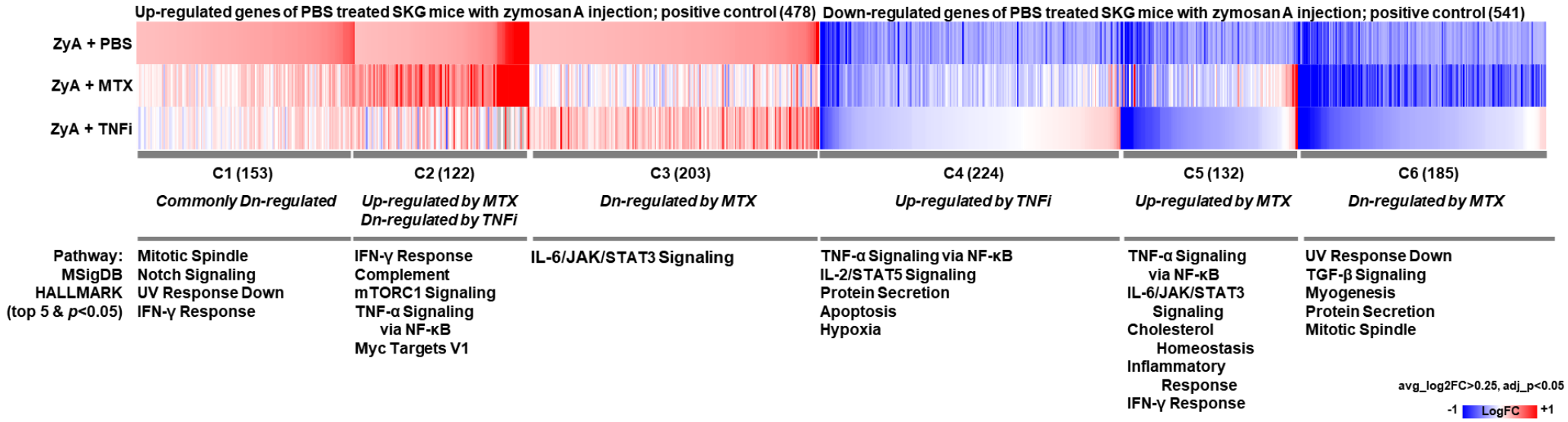

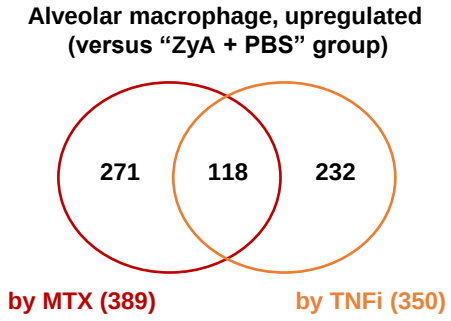

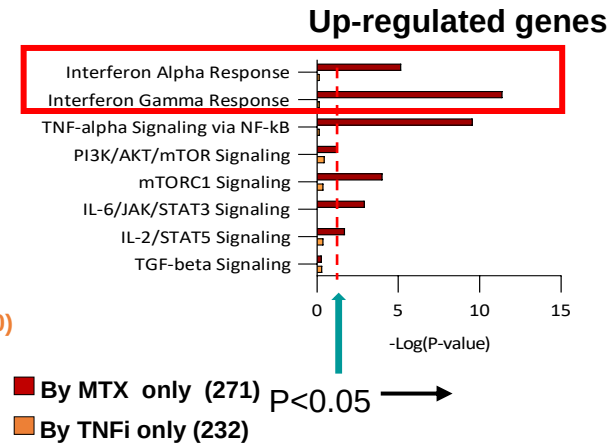

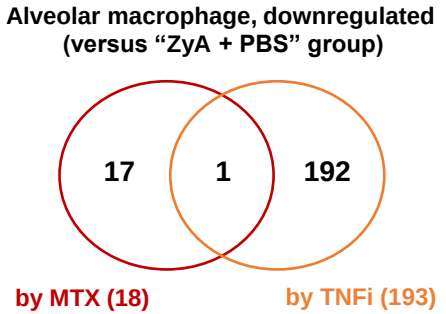

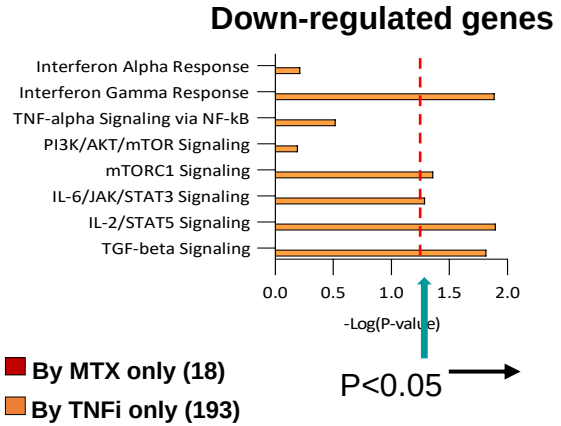

Pathway enrichment analysis using MSigDB hallmark gene collection

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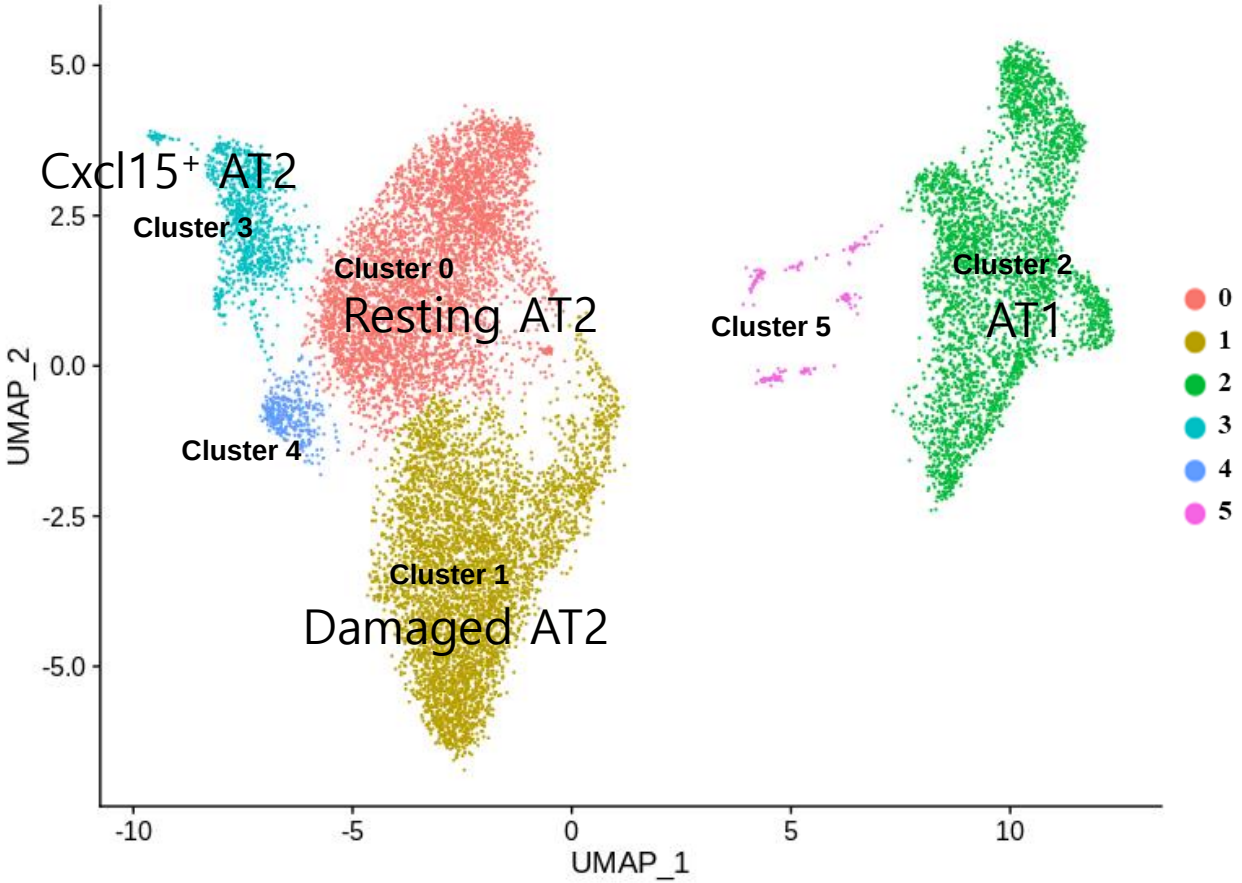
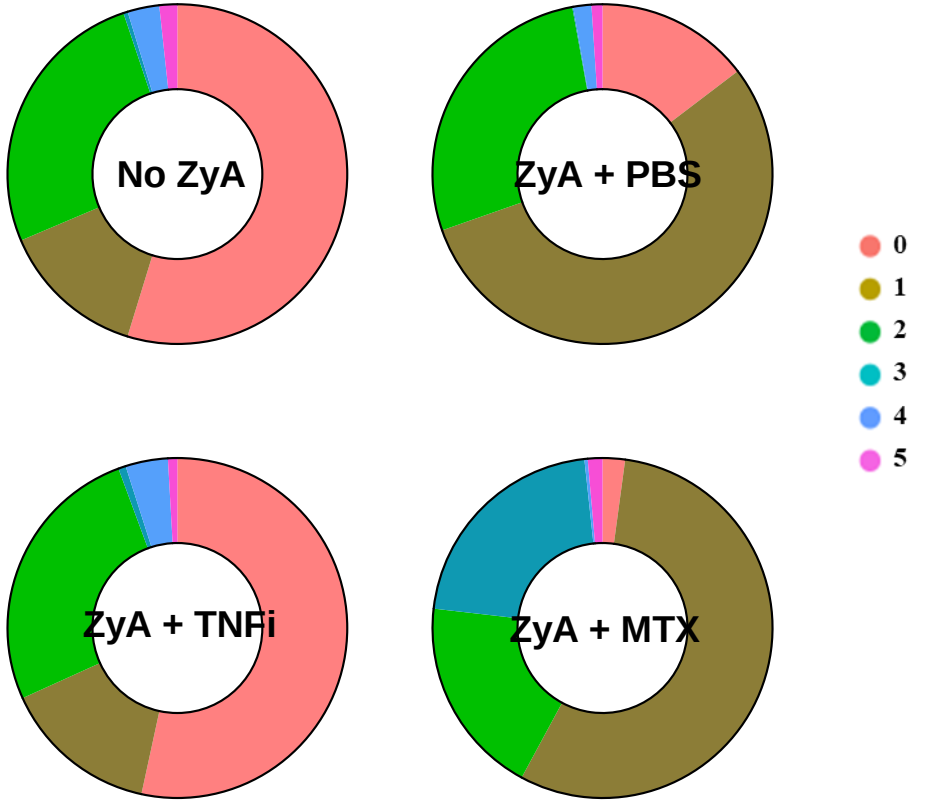
Immunosuppression @ SKG ILD model

Alveolar epithelial cell





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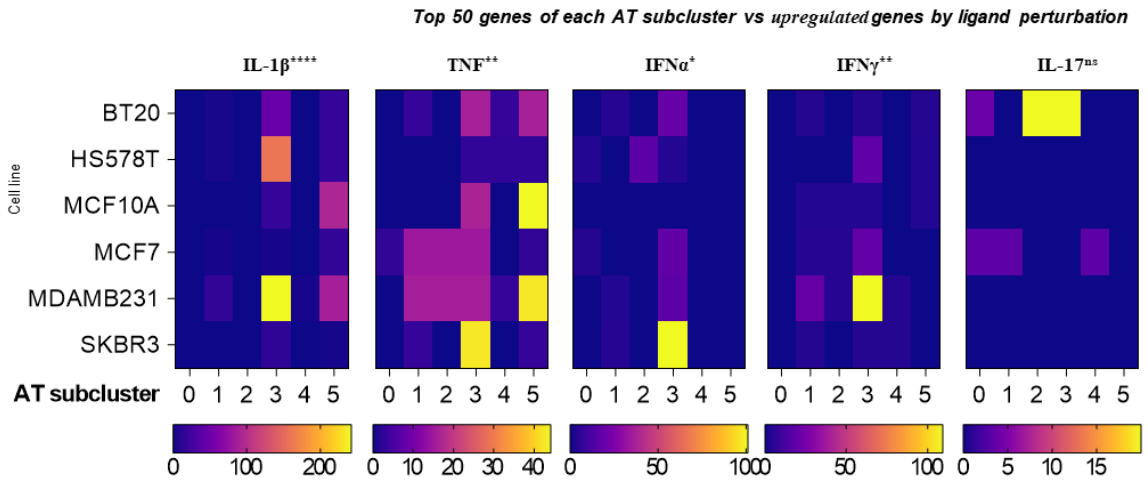
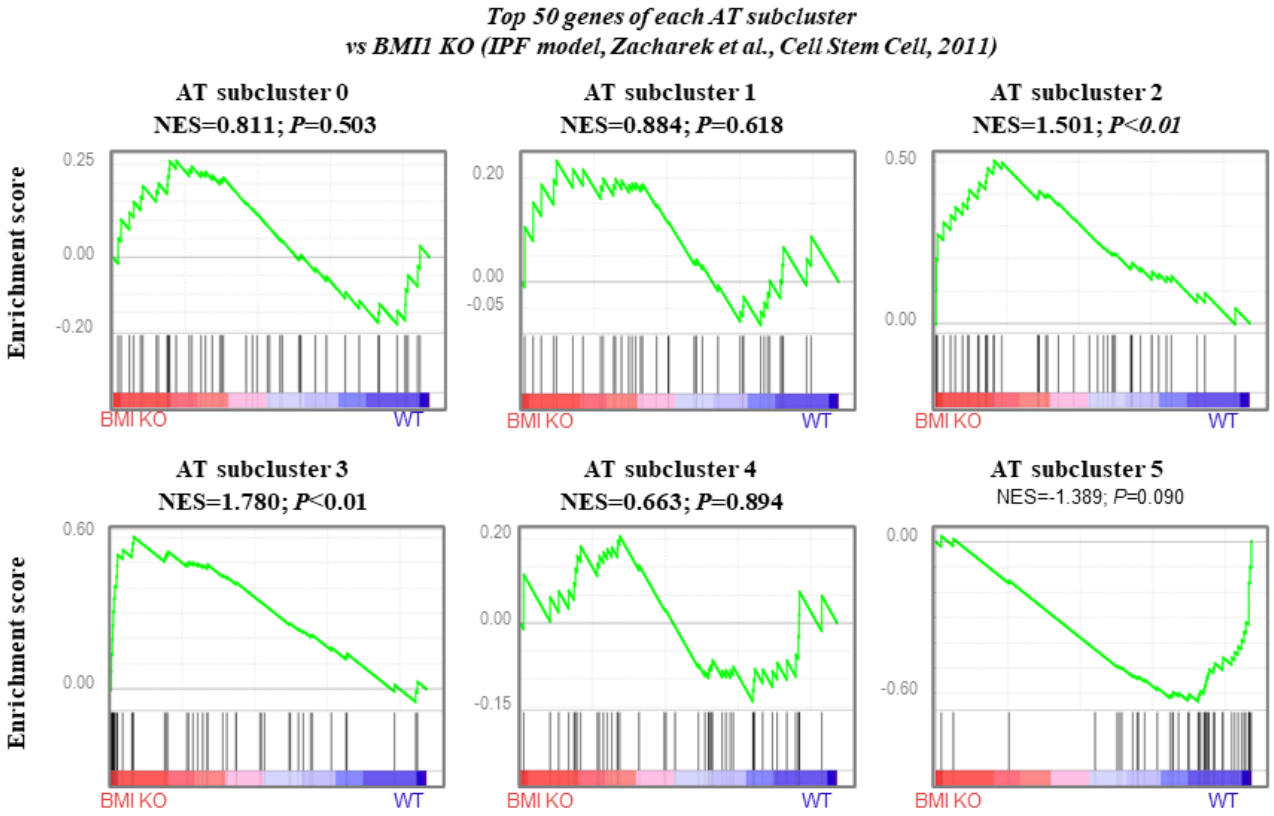
Immunosuppression @ SKG ILD model

Alveolar epithelial cell



LINCS(Integrated Network-based Cellular Signatures)1000 perturbation analysis



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Immunosuppression @ SKG ILD model

In an animal model of rheumatoid arthritis-associated interstitial lung disease using SKG mice, methotrexate administration worsened pneumonitis associated with decreased regenerative capacity of type 2 alveolar cells.

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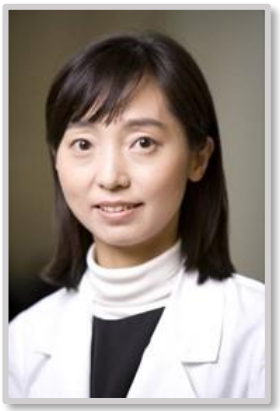
Collaborators

Immunology

- 신의철, 박수형 (KAIST)



Clinicians

- Rheumatology: 이은영 (서울대), 김태환 (한양대), 김태종 (전남대), 장성혜 (순천향대)
- Infection: 고재훈 (성균관대), 김홍빈, 최승진 (분당서울대)
- Oncology: 김형돈, 류민희 (서울아산)
- Cardiology: 이상언 (서울아산)
- Rare disease: 이범희 (서울아산), Radiology: 이정민 (서울성모), Grace Kim (UCLA), Jonathan Goldin (UCLA)

Genomics

- 정인경, 박종은 (KAIST)
- 주영석, 박성열, 이소영, 이기종, 임준오, 김률, 고준영 (GENOME INSIGHT)
- 박웅양 (성균관대/지니너스)
- 박성호 (UNIST)

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