

Single-cell based integrative analysis of transcriptomics and genetics reveals robust associations and complexities for inflammatory diseases

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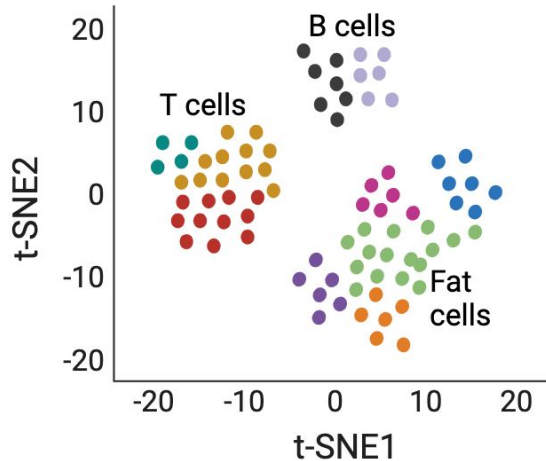
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Most successful treatments have *both* physiological & genetic support

single-cell RNA-seq
-> cell states & activities



Genome-wide
association studies
-> disease associated SNPs

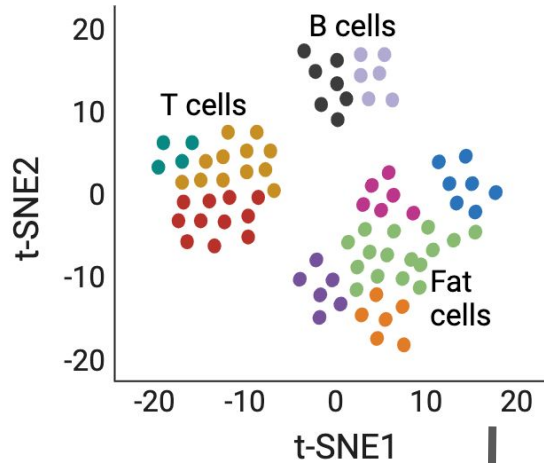


GWAS
Catalog

100k+
phenotypes

variant	association
SNP 1	0.45
SNP 2	0.89
...	
SNP 1000	0.36

Unbenchmarked recent work to integrate single-cell RNA-seq & GWAS



100k+ phenotypes

variant	association
SNP 1	0.45
SNP 2	0.89
...	
SNP 1000	0.36

disease relevant cell-states & gene networks
with **genetic** support

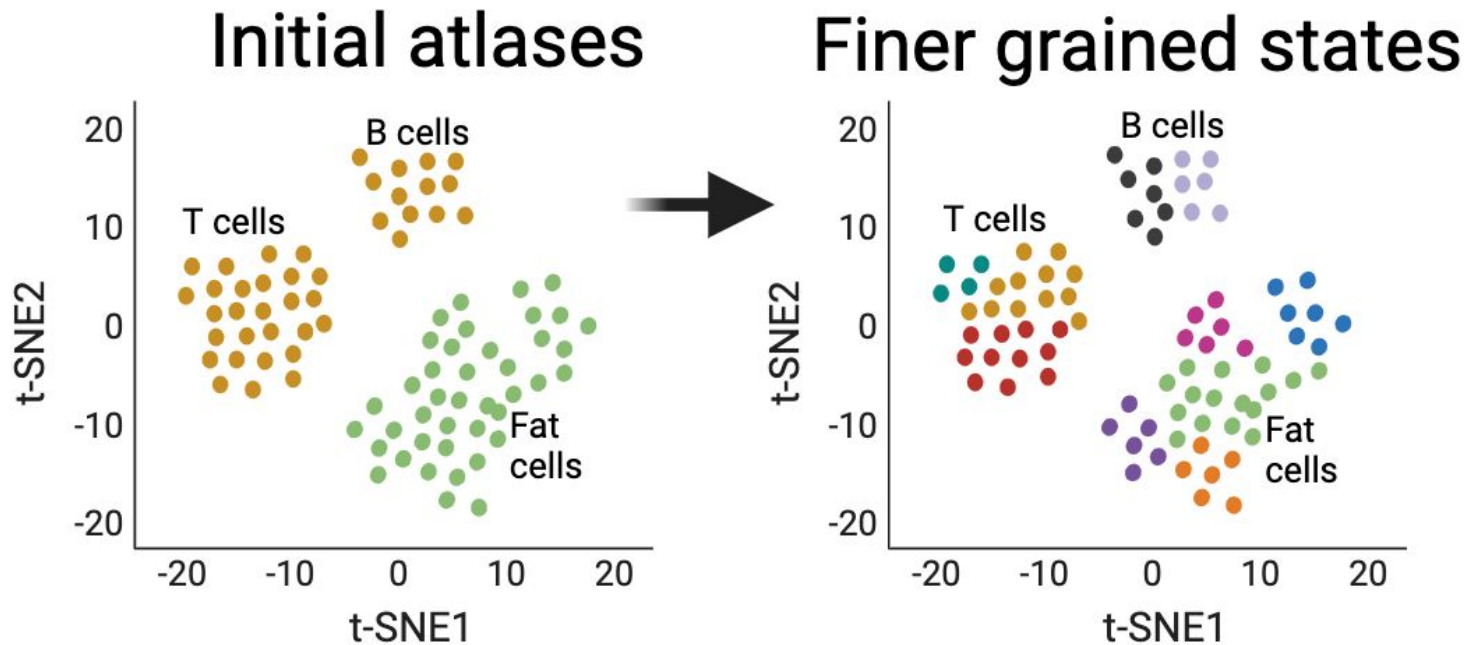
3-prong study design addressing scRNA-seq + GWAS integration

Benchmarking

Disease Separation

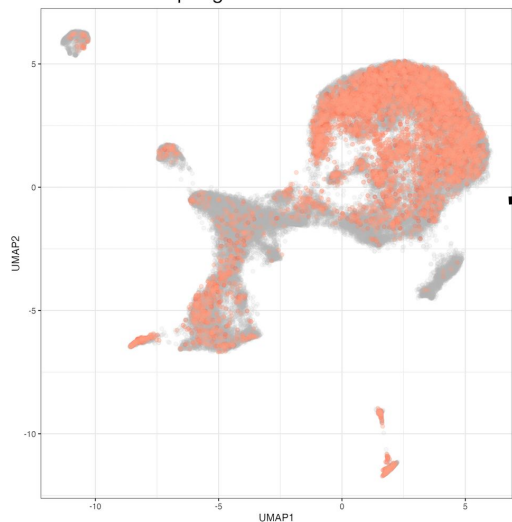
SNP-Gene Linking

A) Benchmarking of available tools with fine-grained atlases

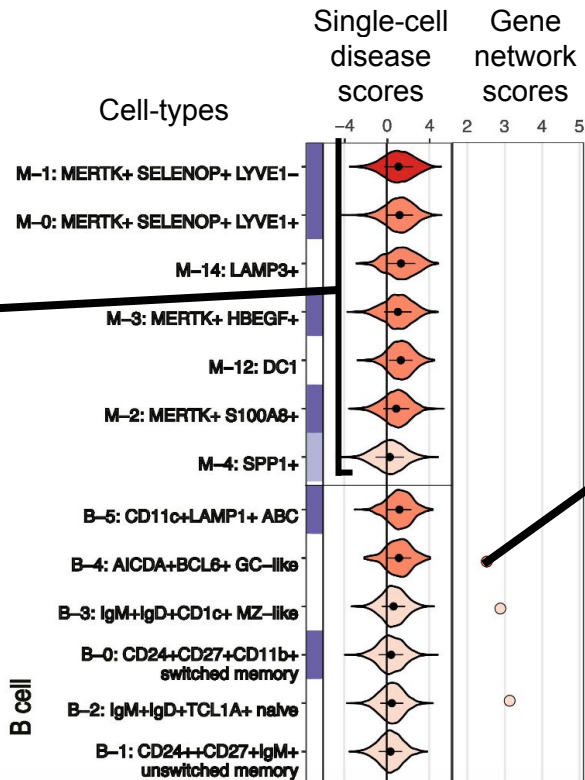


Single-cell disease scores increased sensitivity at the cost of interpretability

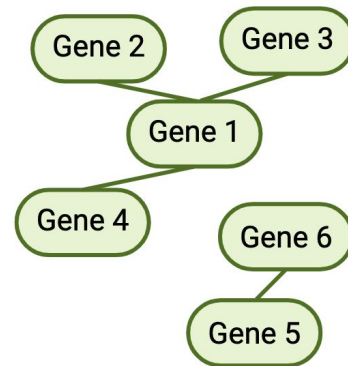
Single cell disease Scores



Rheumatoid Arthritis myeloid cell atlas: (Zhang, et al, Nature, 2023)

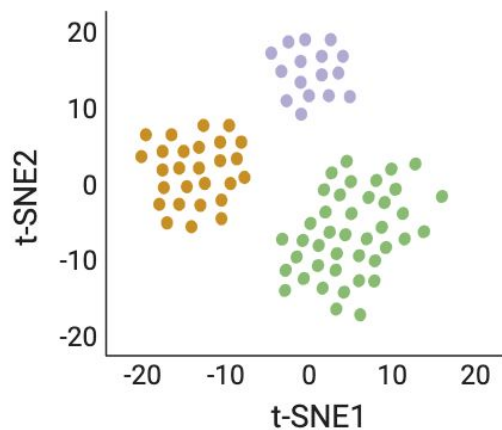


Gene networks

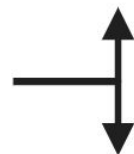


B) Distinguishing between diseases with different causes but similar phenotypes

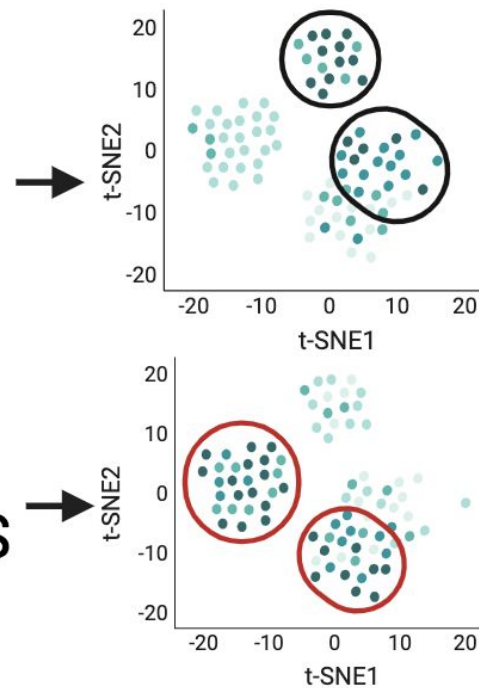
Disease 1 based
scRNA-seq



Disease 1
based GWAS



Disease 2
based GWAS

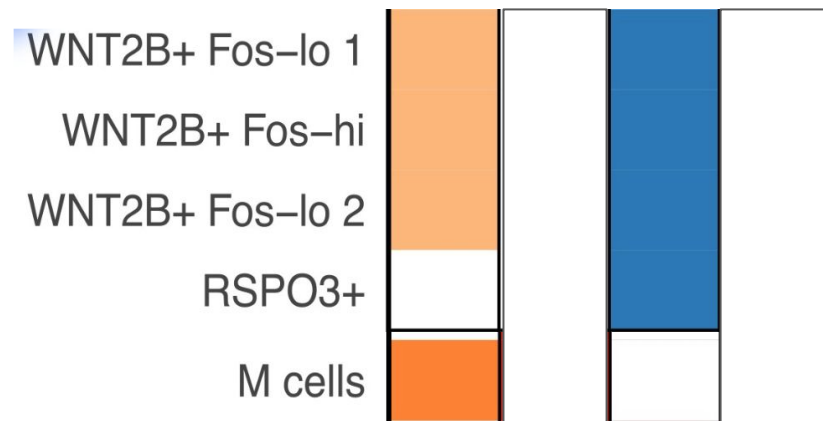
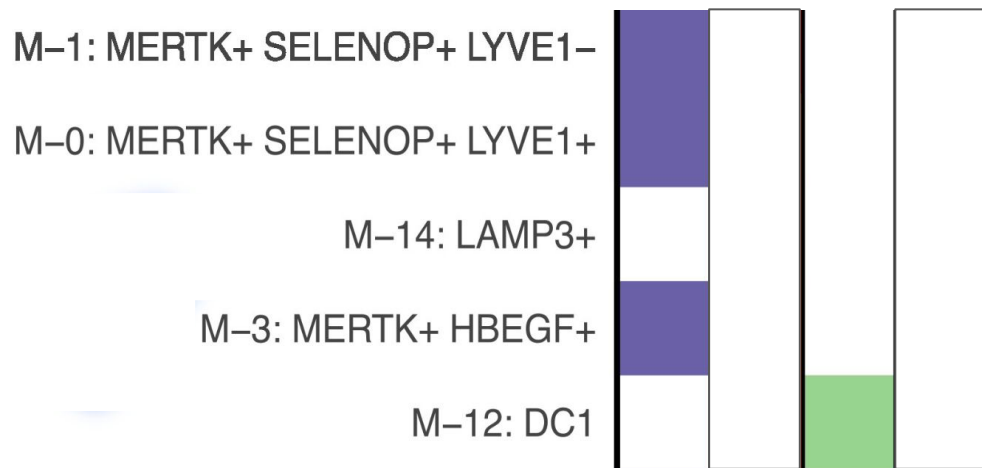


B) Distinguishing between diseases with different causes but similar phenotypes



Rheumatoid Arthritis
Ankylosing Spondylitis

Ulcerative Colitis
Crohn's Disease



Identified nuanced differences: known & previously hypothesized



Expected
Call



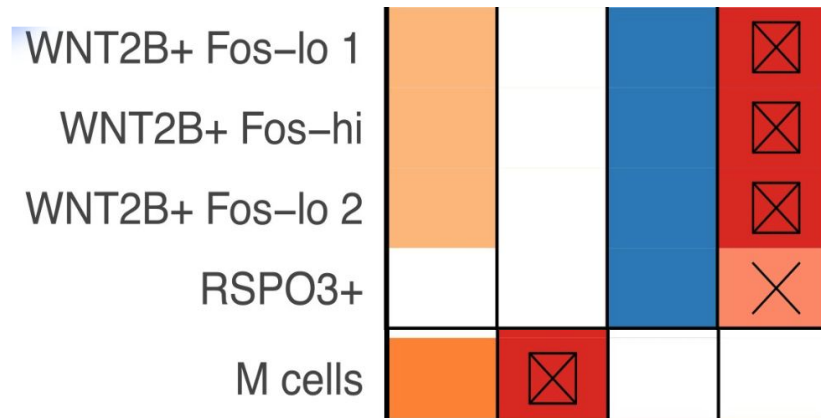
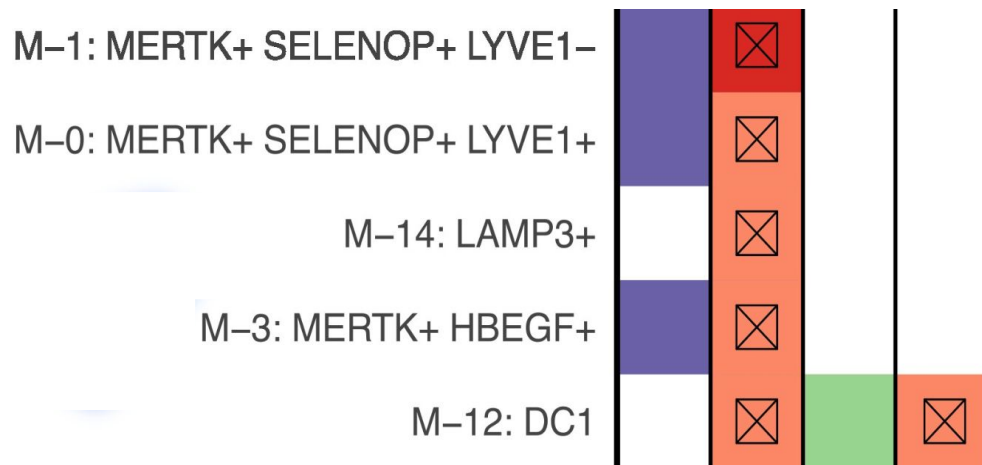
Significant
Call

Rheumatoid
Arthritis

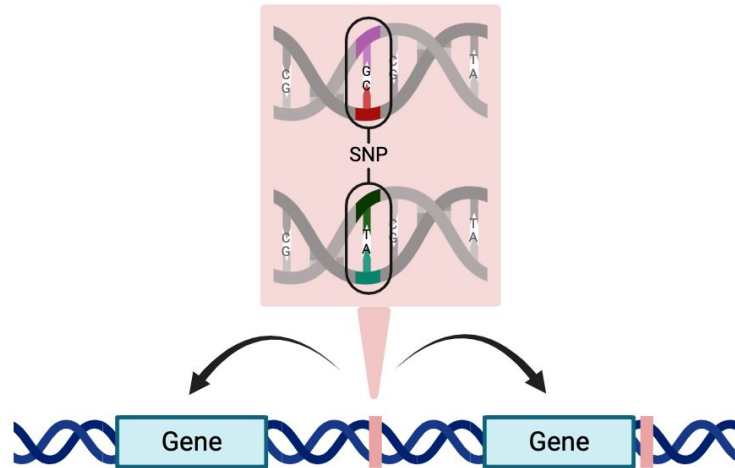
Ankylosing
Spondylitis

Ulcerative
Colitis

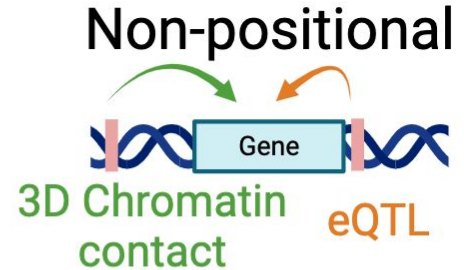
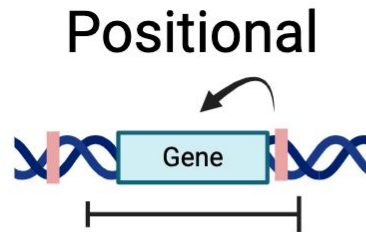
Crohn's
Disease



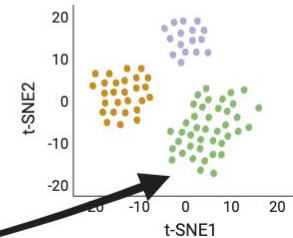
C) Assessing impact of SNP-Gene Linking across three methods



Gene	Score
Gene 1	9.8
Gene 2	8.7
...	
Gene 1000	1.6

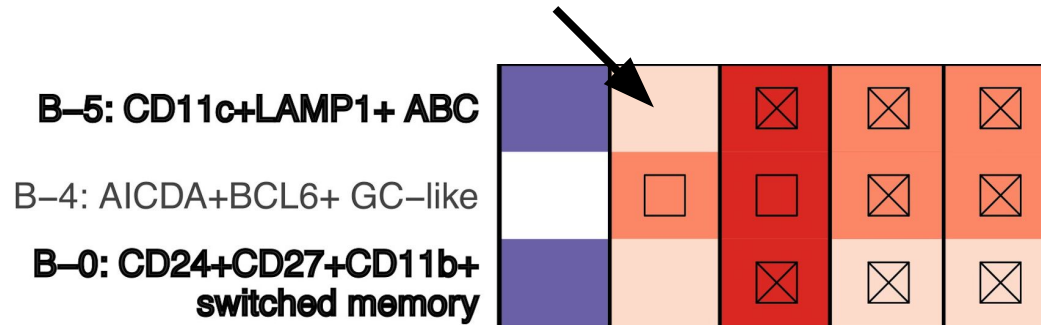


Cis-regulatory element
single cell transcriptomics
(5' scRNA-seq)



Statistical power & appropriate atlases currently overshadow SNP-Gene linking precision

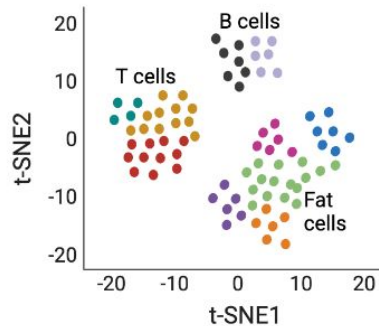
- 3D Chromatin & eQTL data → >50% missed calls



- <5% calls change >1 from 0kb-100kb windows
- Non-disease relevant tissue → inaccurate calls

Conclusions

- Novel insights into immune-mediated inflammatory diseases
- Best practices/guidelines for GWAS & scRNA-seq integration



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Thank you for listening and all of my support!

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