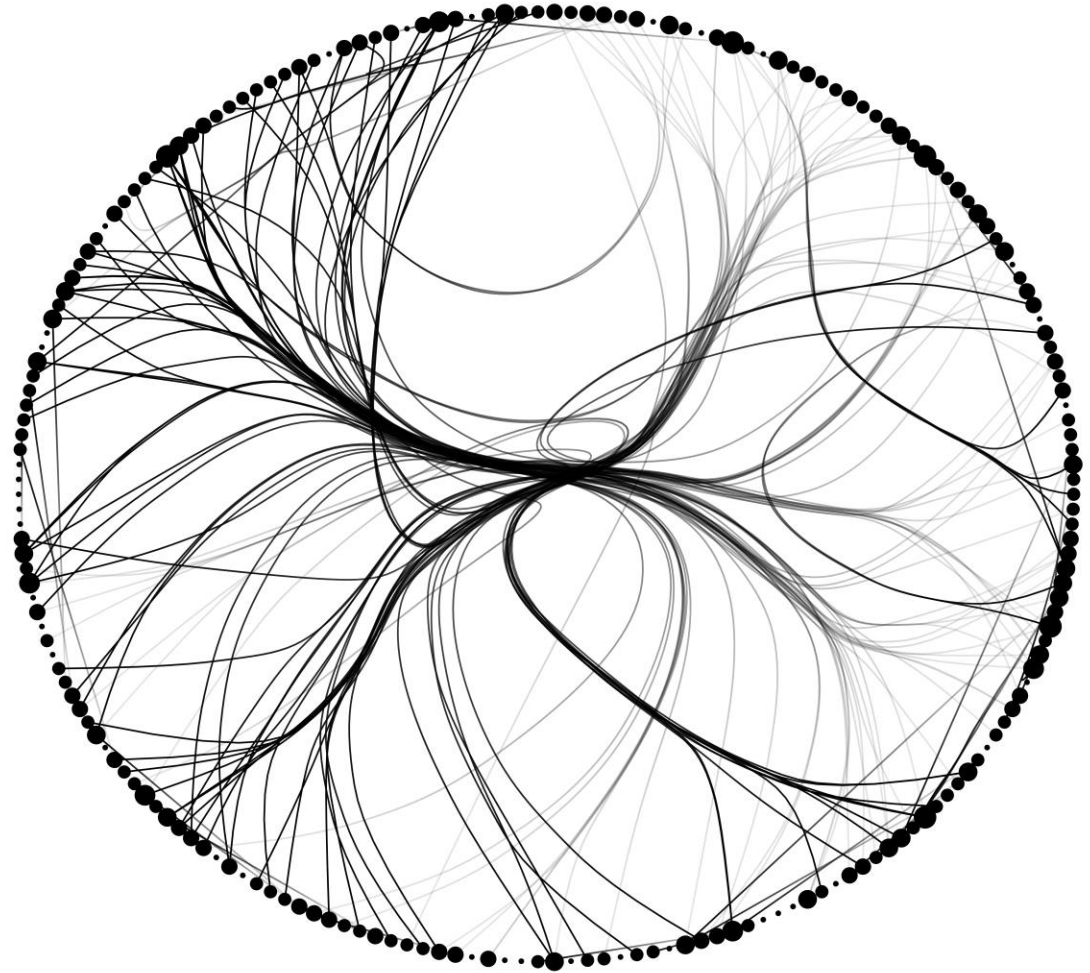


Cytokine networks: a systems perspective on immune regulation

Dr. Marton Olbei
Department of Metabolism,
Digestion and Reproduction
Faculty of Medicine



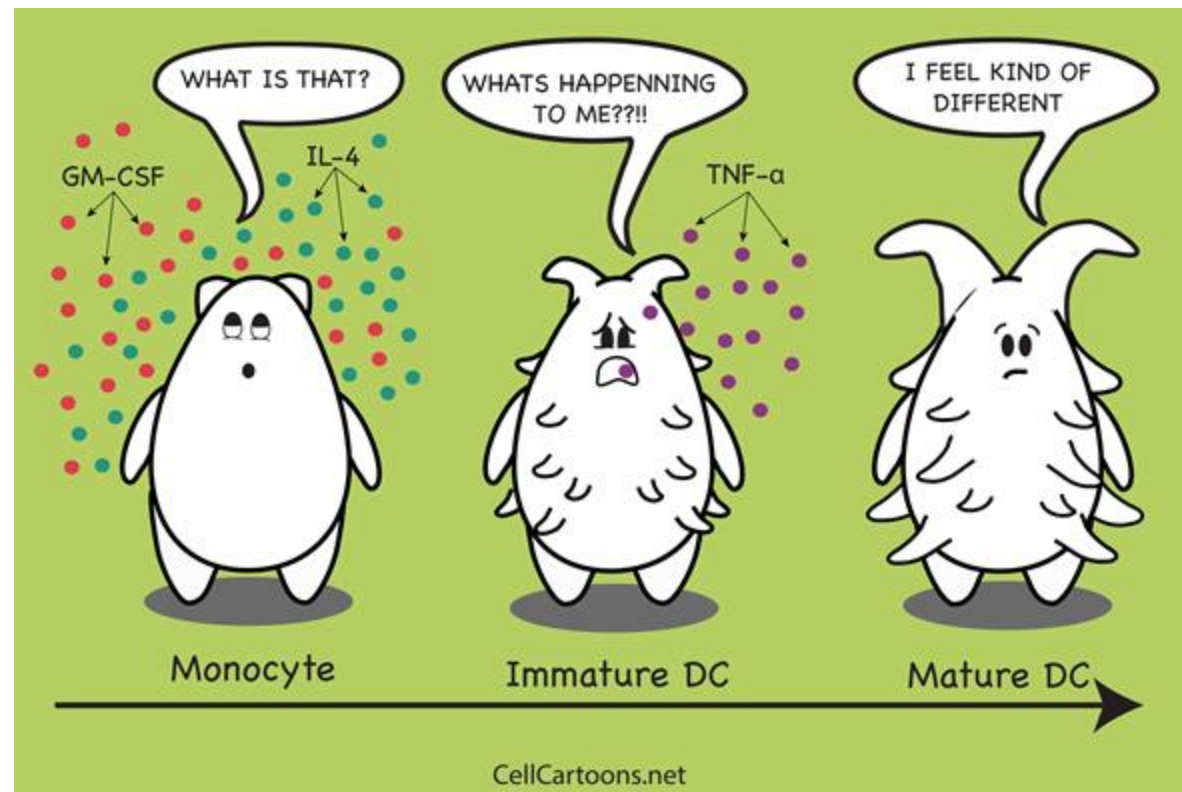
*What are
cytokines?*



Cytokines

Cytokines are essential **signalling proteins** that enable **communication between immune and non-immune cells**

They help **orchestrate immune responses, differentiation, proliferation** between cells

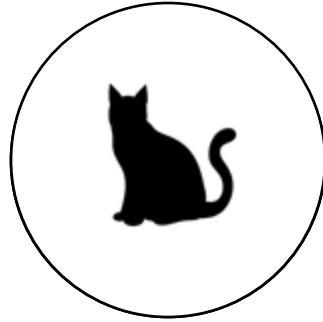


What is a network?



Networks

This is a *node*



In network biology nodes can represent various components:

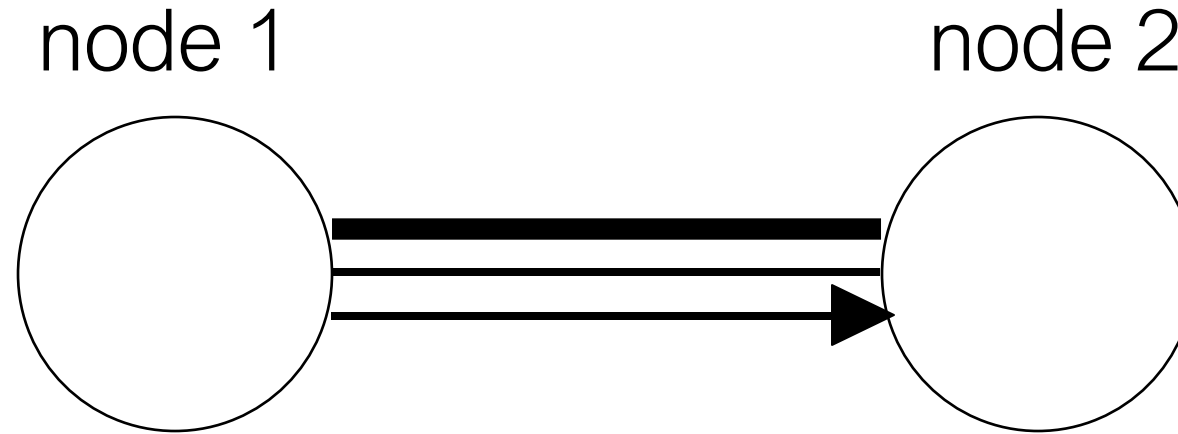
Genes

Proteins

RNAs

and other biological entities

This is an *edge*



Edges represent the interactions occurring between our nodes

They can be:

Directed or undirected

Weighted or unweighted

Stimulatory or inhibitory

Networks are collections of nodes and edges



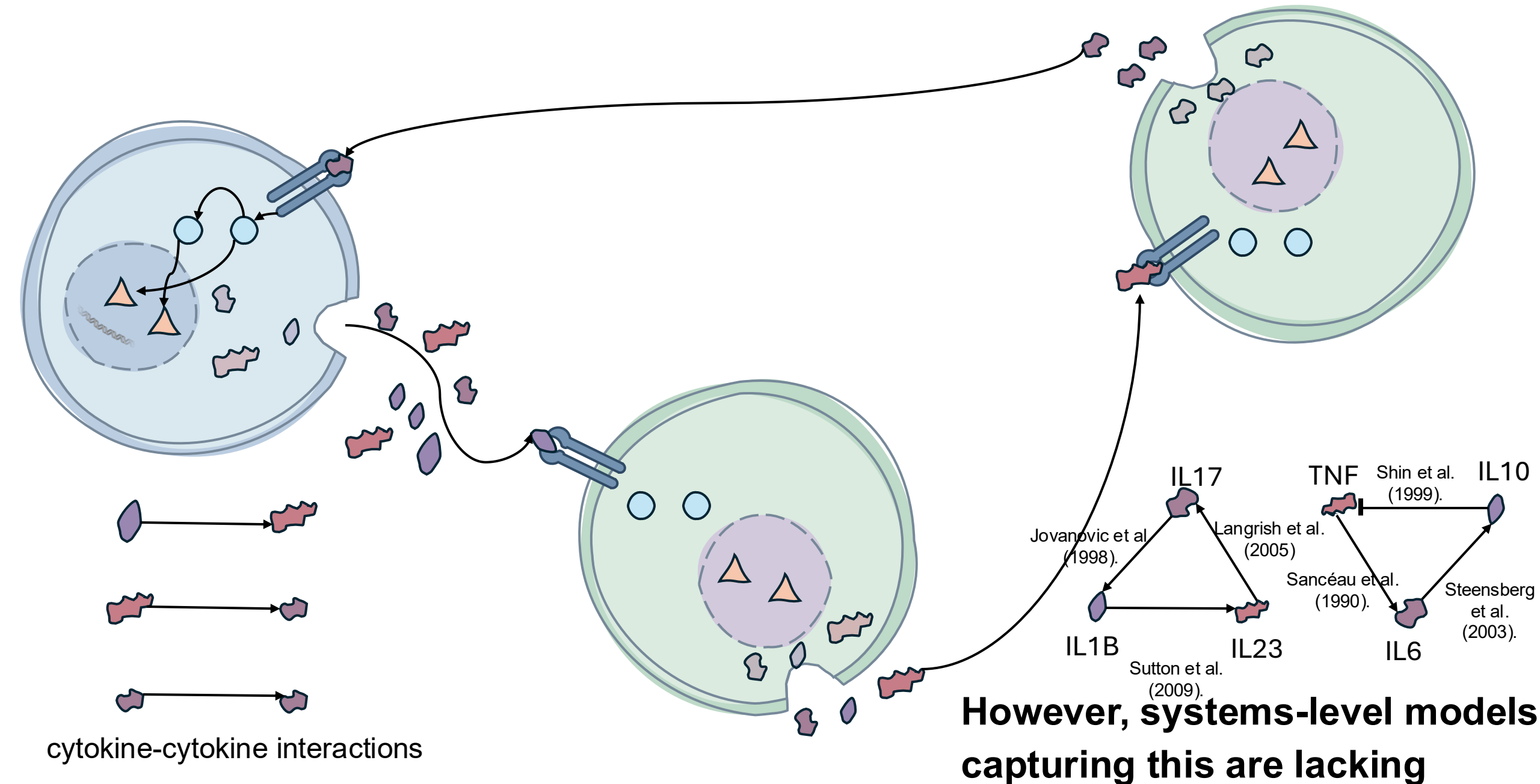
In network biology we use them to:

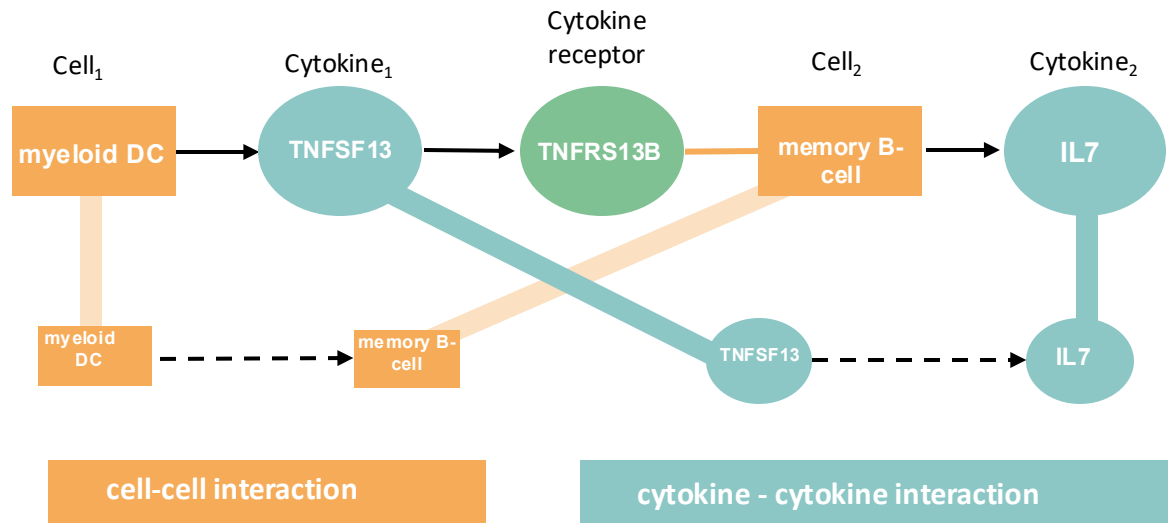
- Visualize our biological entities

- See overrepresented functions and their interactions

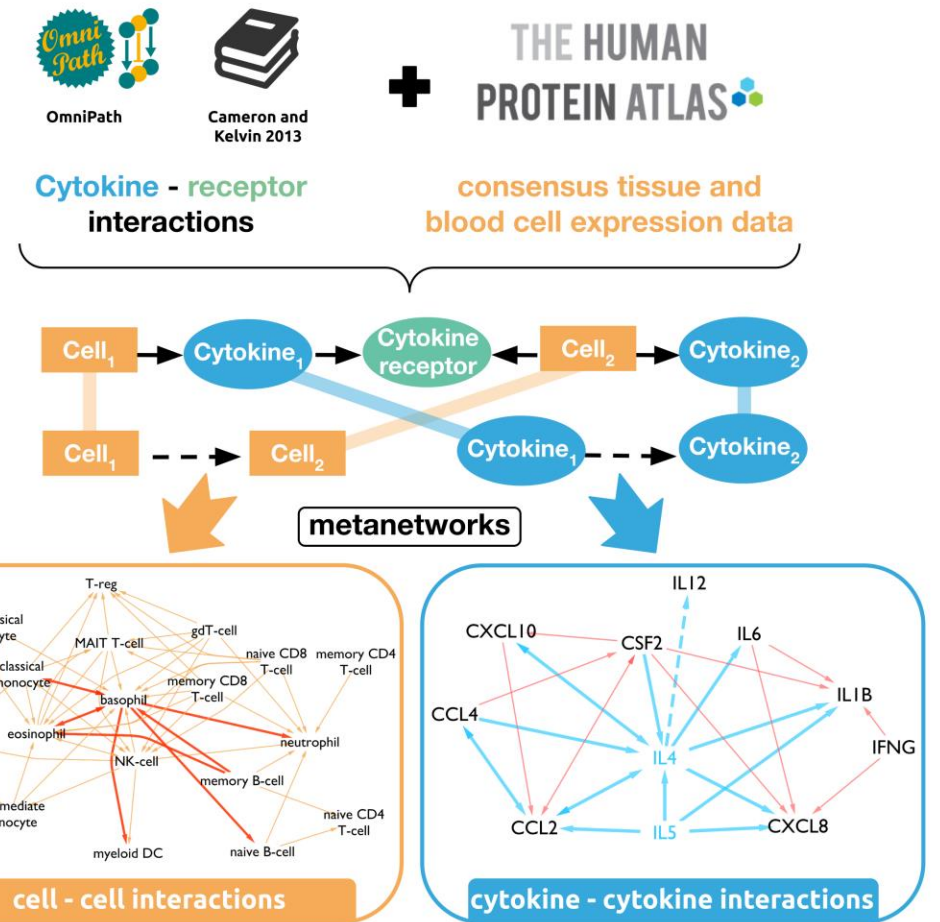
- Make predictions about potential interactions

From cytokine-cytokine interactions to cytokine networks



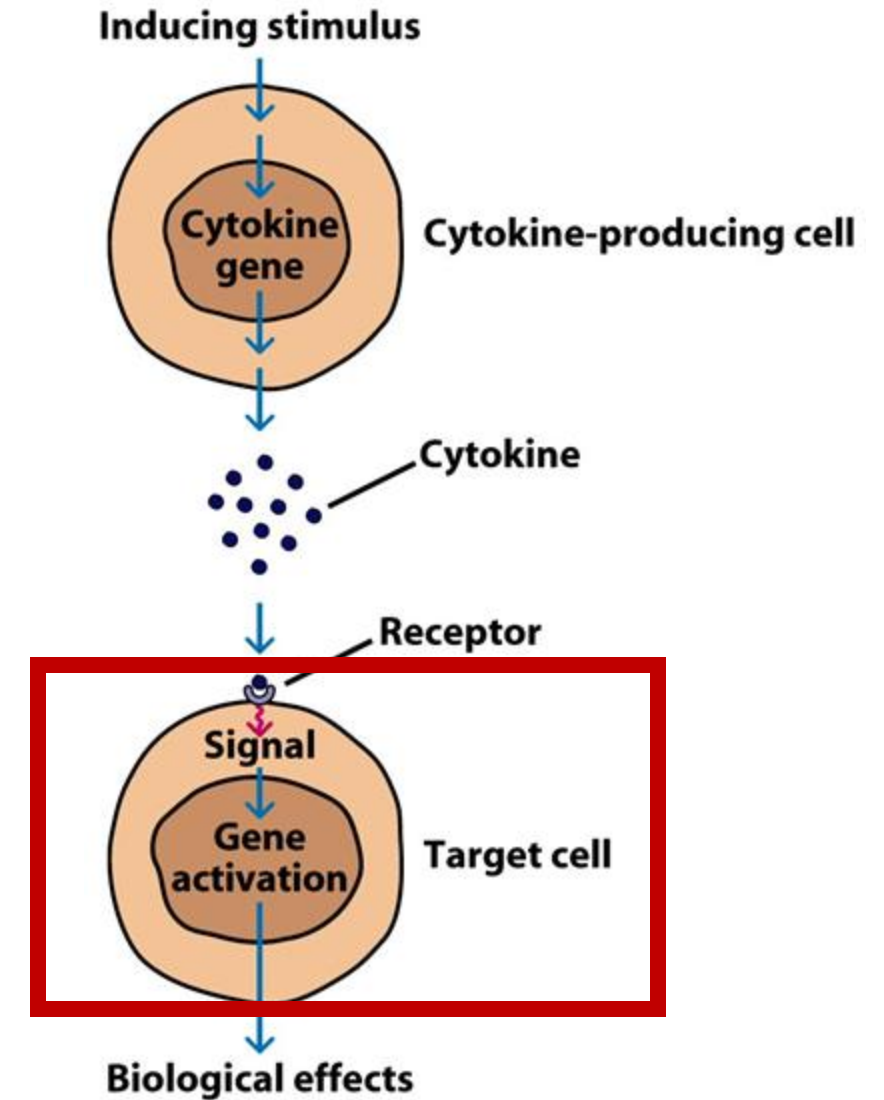
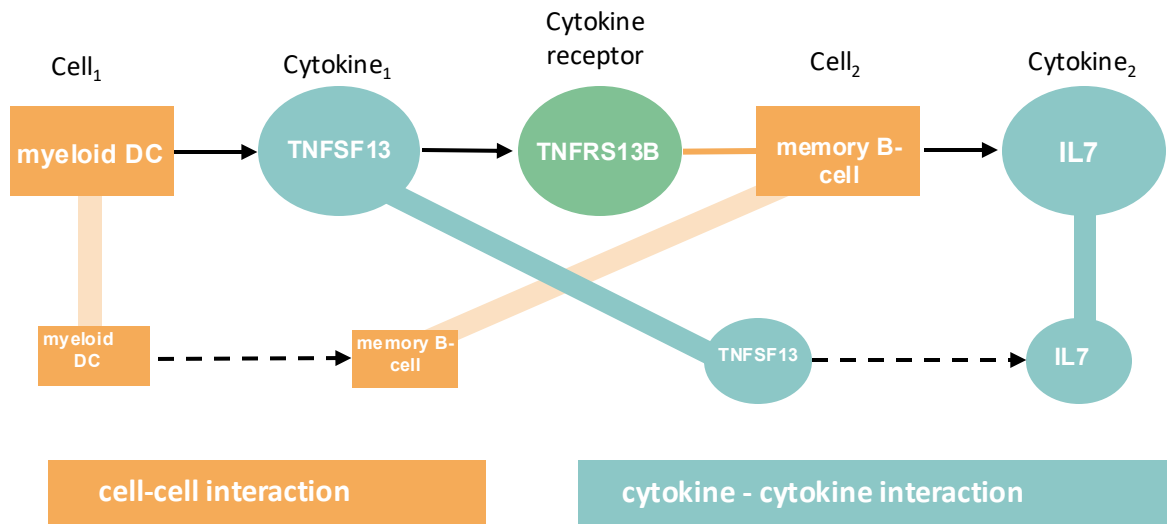


Olbei et al., 2021



- Establishing the concept of cytokine-cytokine interactions
- Creating a resource from publicly available data

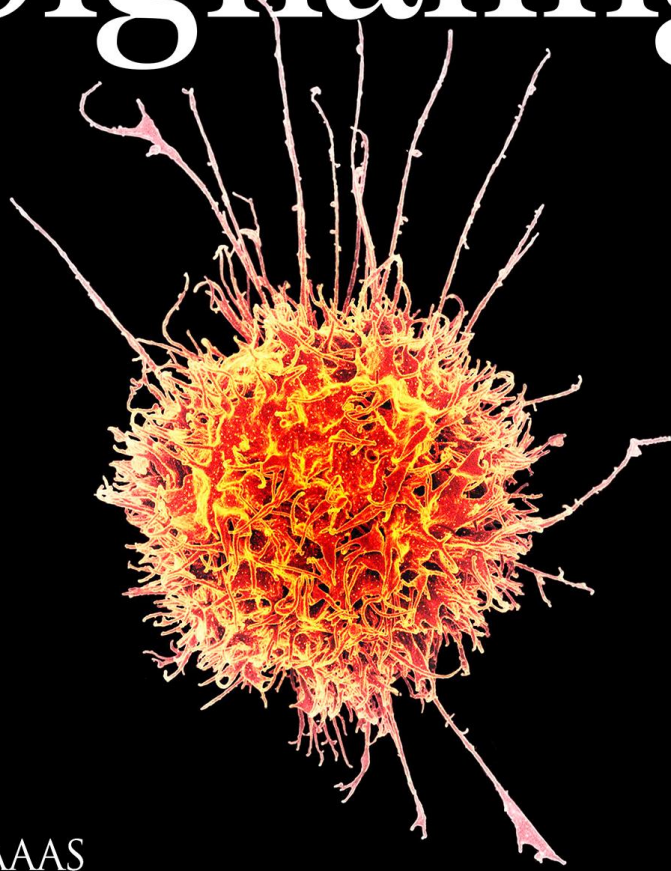
From association to mechanism



Goal: moving from **association** closer to **mechanism**

Science Signaling

3 FEBRUARY 2026



AAAS

SCIENCE SIGNALING | RESEARCH ARTICLE

INFLAMMATION

Decoding cytokine networks in ulcerative colitis to identify pathogenic mechanisms and therapeutic targets

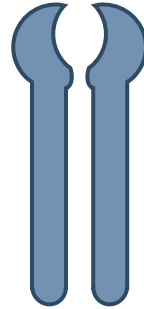
Marton Olbei¹, Isabelle Hautefort^{1,2,3,4}, John P. Thomas^{1,5}, Luca Csabai⁶, Balazs Bohar¹, Sandra S. Koigi⁴, Hajir Ibraheim¹, Aamir Saifuddin¹, Diana Coman⁷, Emma Højmosse Kromann⁷, Joana F. Neves⁷, Diana Papp^{1,4}, Nick Powell¹, Dezso Modos^{1,3}, Tamas Korcsmaros^{1,2,3,4*}

The pipeline constructs the chain of events from upstream to downstream cytokines

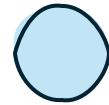
Cytokine₁



Receptor



Signalling protein



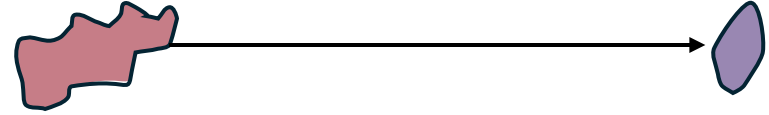
Transcription factor



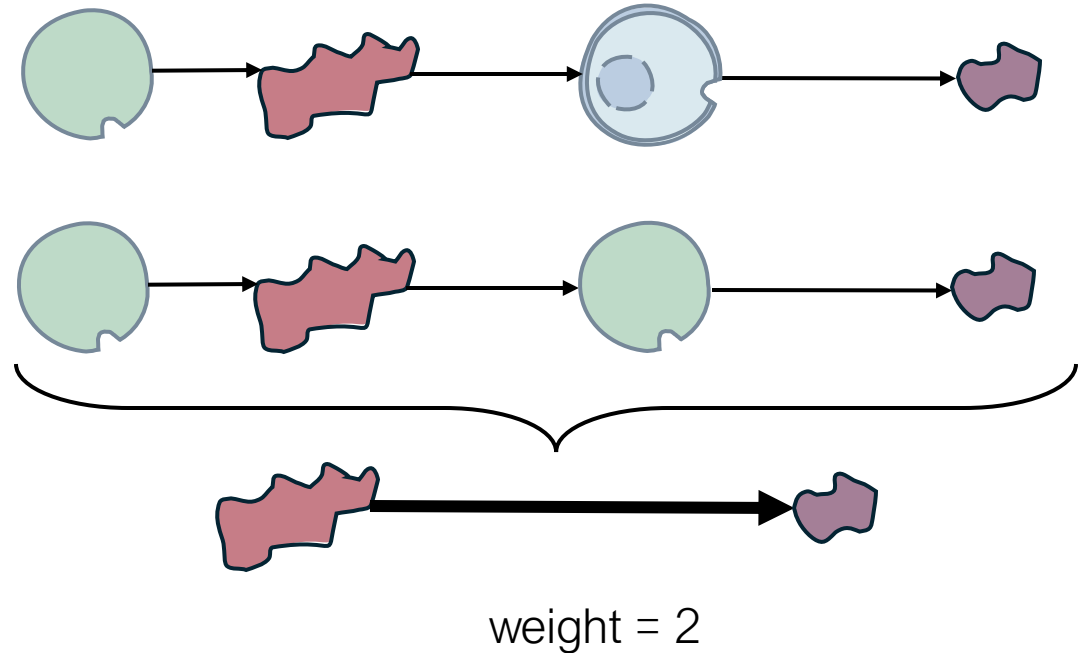
Cytokine₂

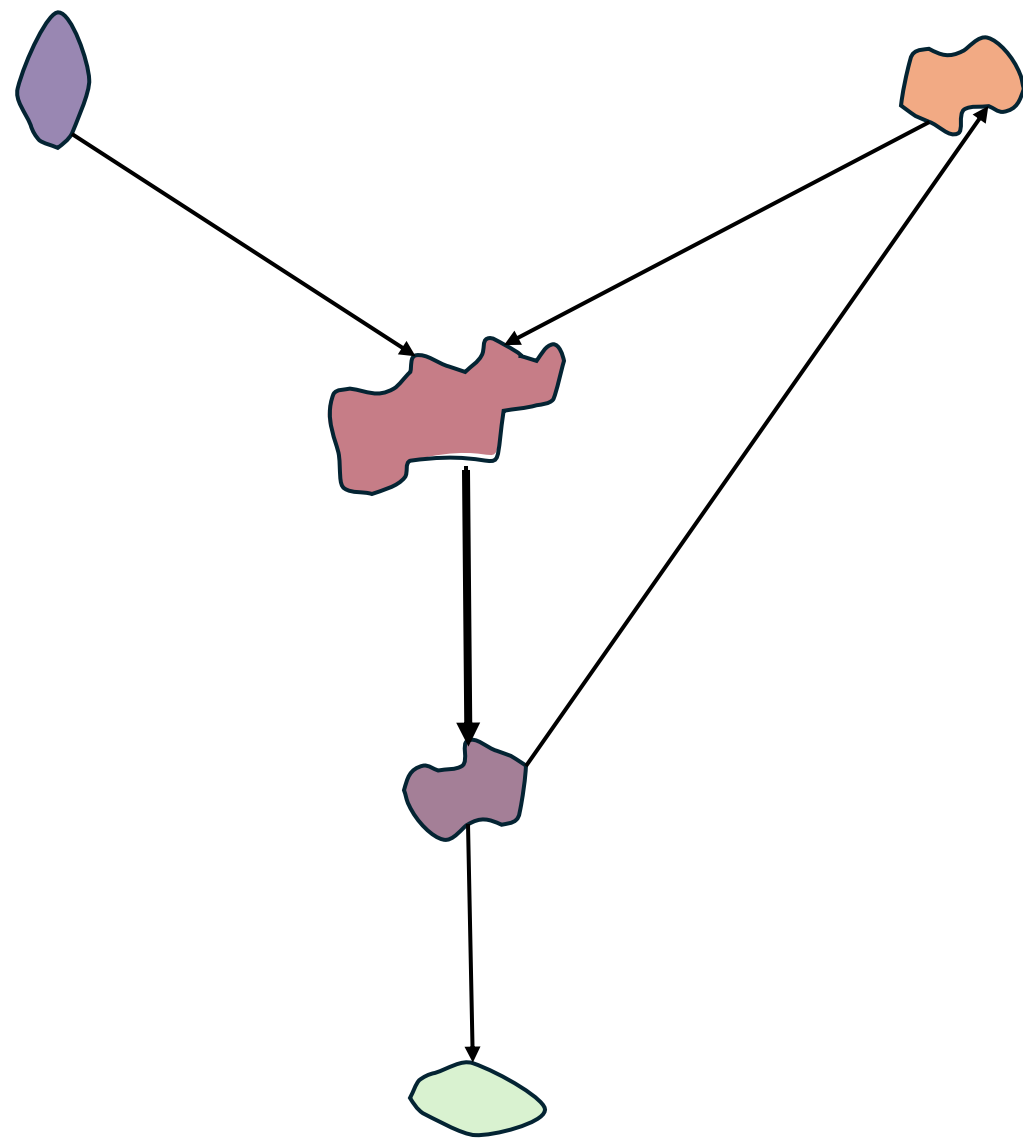
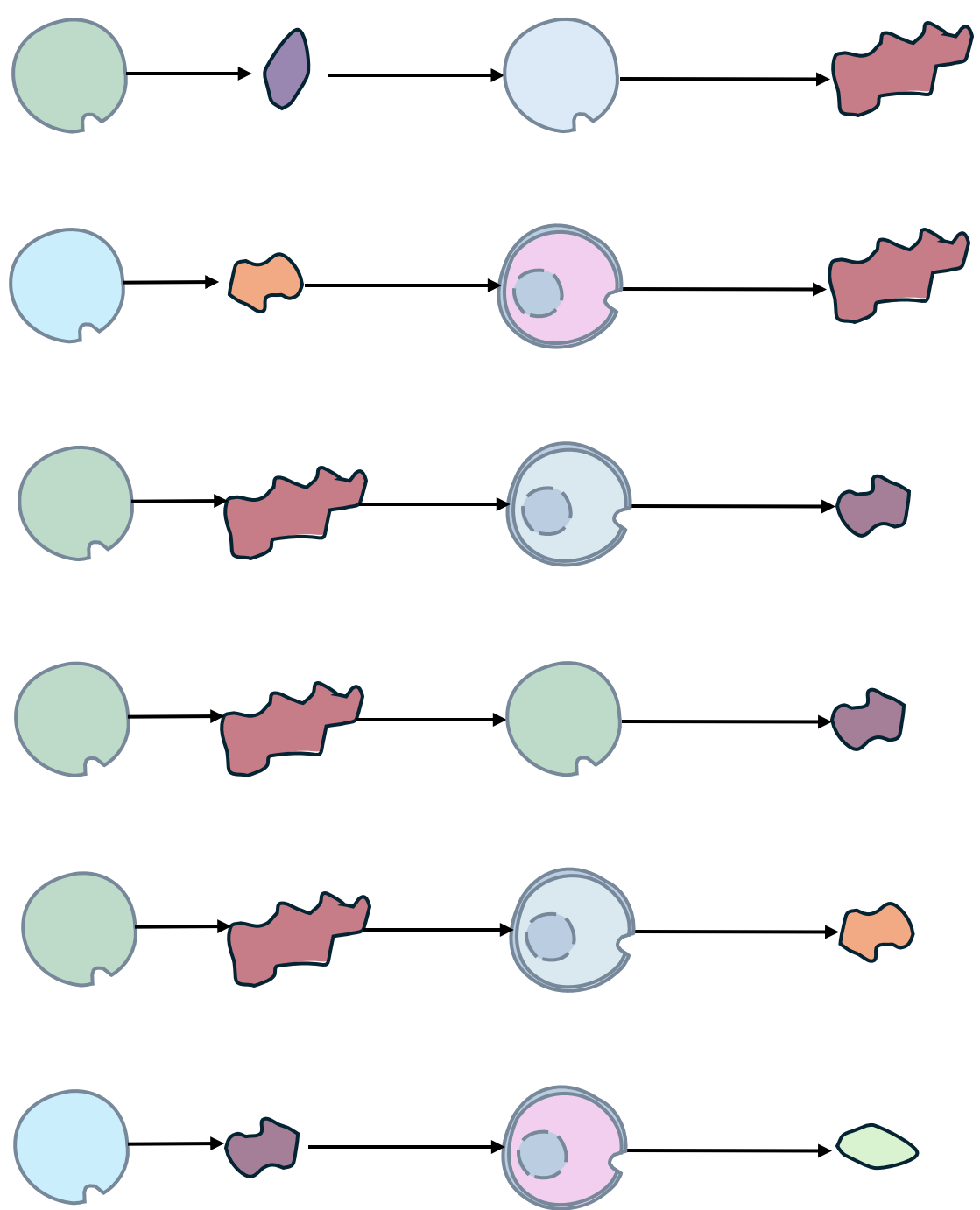


Resulting in cytokine – cytokine interactions



Since multiple cell types can participate in the same cytokine – cytokine interaction, the links are weighted by the number of participating cell type pairs





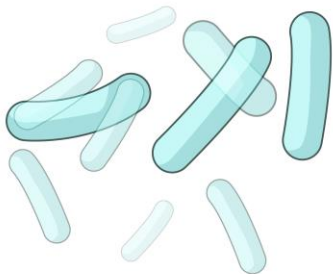
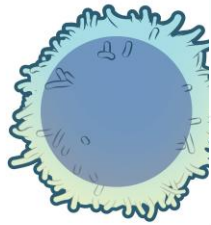
Result: a pipeline that maps cytokine-cytokine interactions from scRNA-Seq data

Why is this relevant?

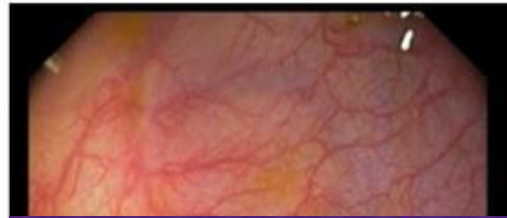
Cytokine networks in treatment naïve ulcerative colitis

Inflammatory Bowel Disease

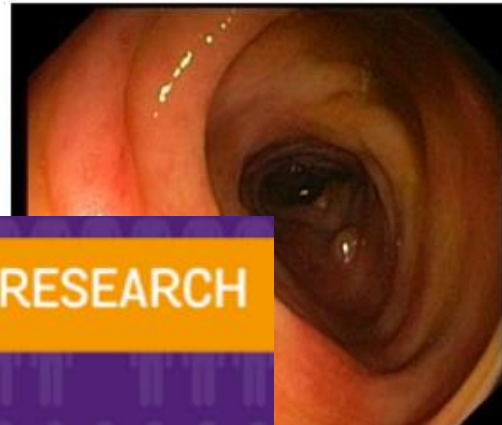
Ulcerative colitis
and
Crohn's disease



Normal mucosa



Mild inflammation



CROHN'S &
COLITIS UK

NEW RESEARCH

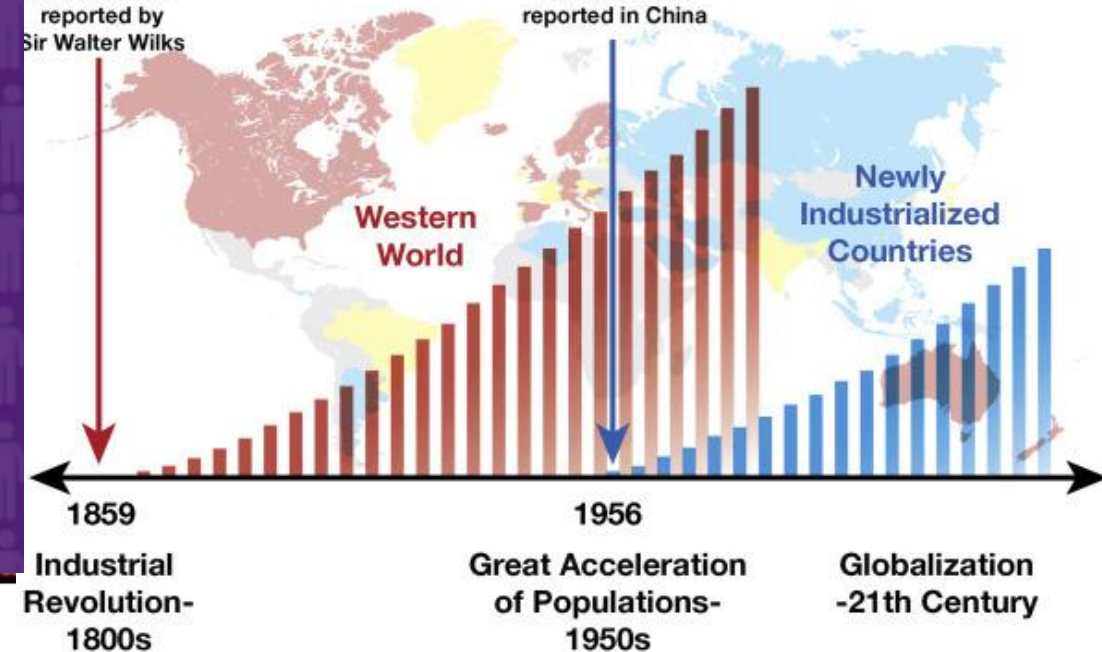
1 in 123
people have
Crohn's or
Colitis.



These are painful, debilitating conditions.
And there is no known cure.

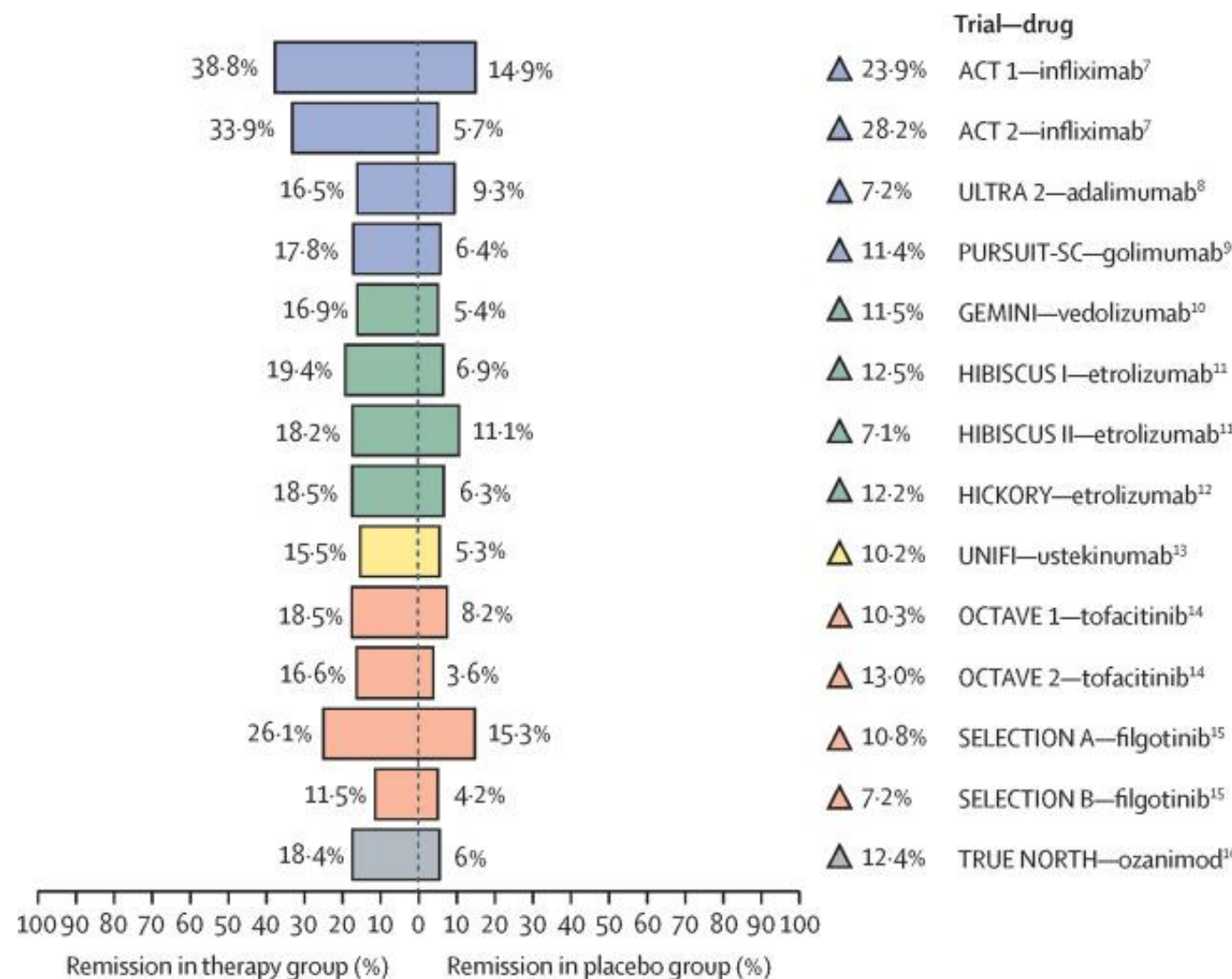
1st case of UC
reported by
Sir Walter Wilks

1st case of UC
reported in China

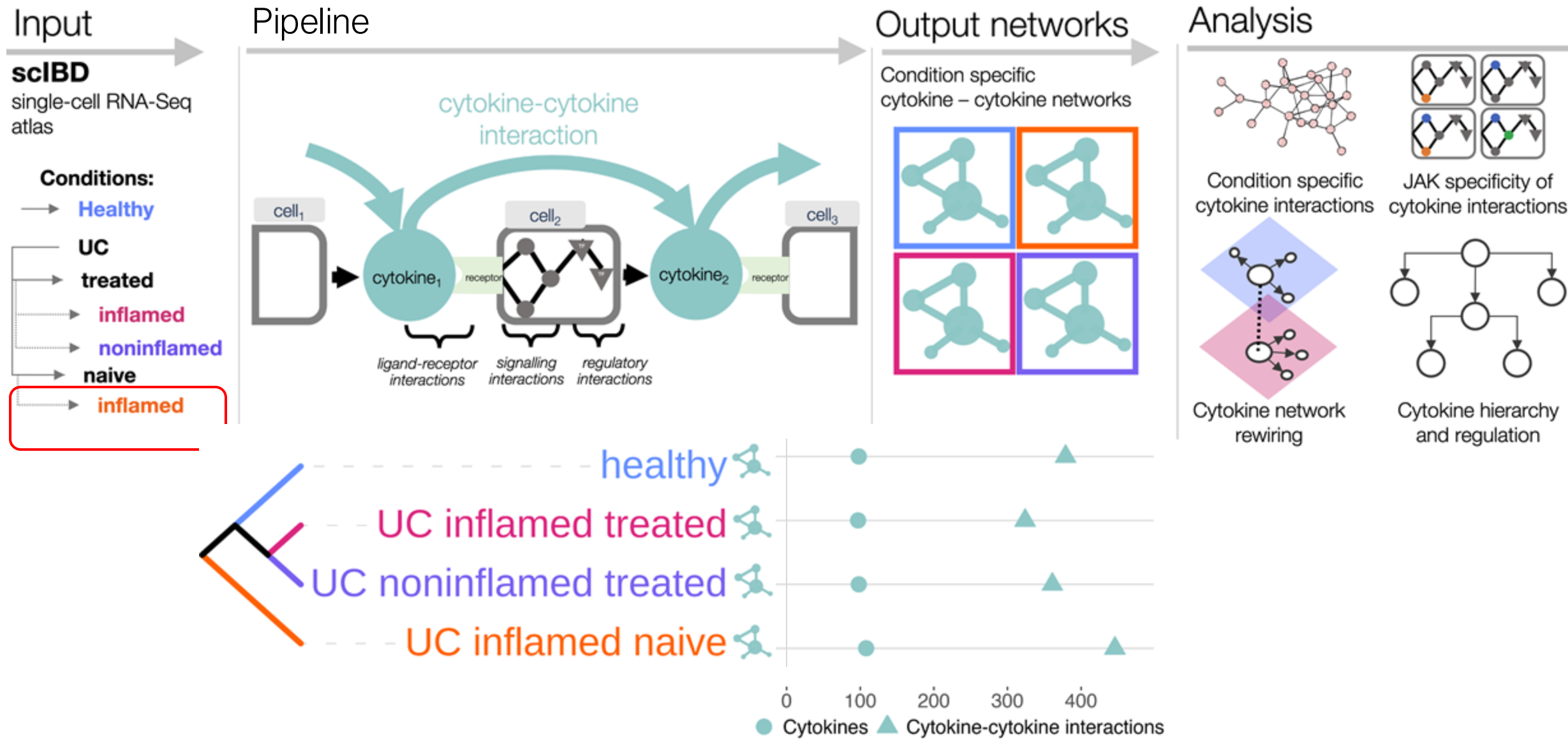


Cytokine networks in IBD - motivation

- Problem: a large percentage of patients do not respond / become resistant to anti-cytokine drugs
- Mapping cytokine networks can offer alternative targets, and help us understand why drugs may not work



Generation of cytokine networks for ulcerative colitis

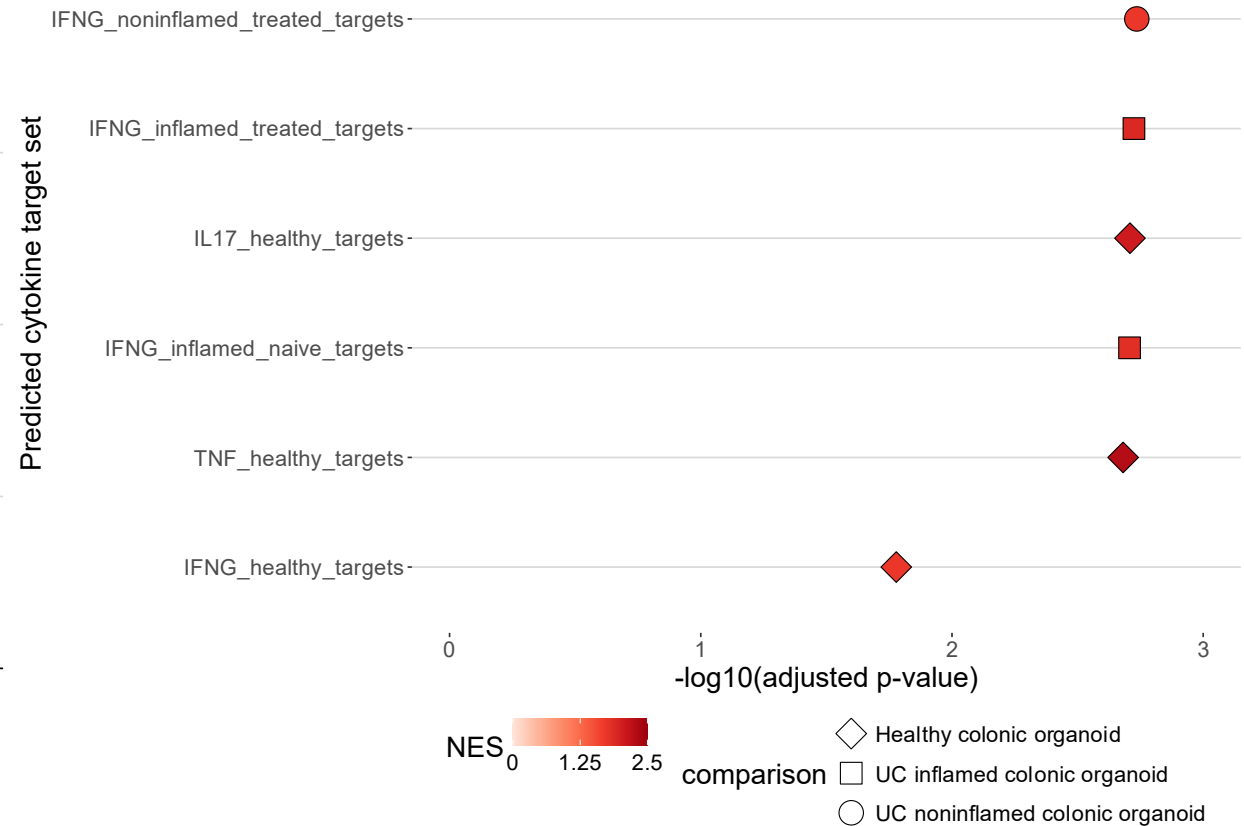
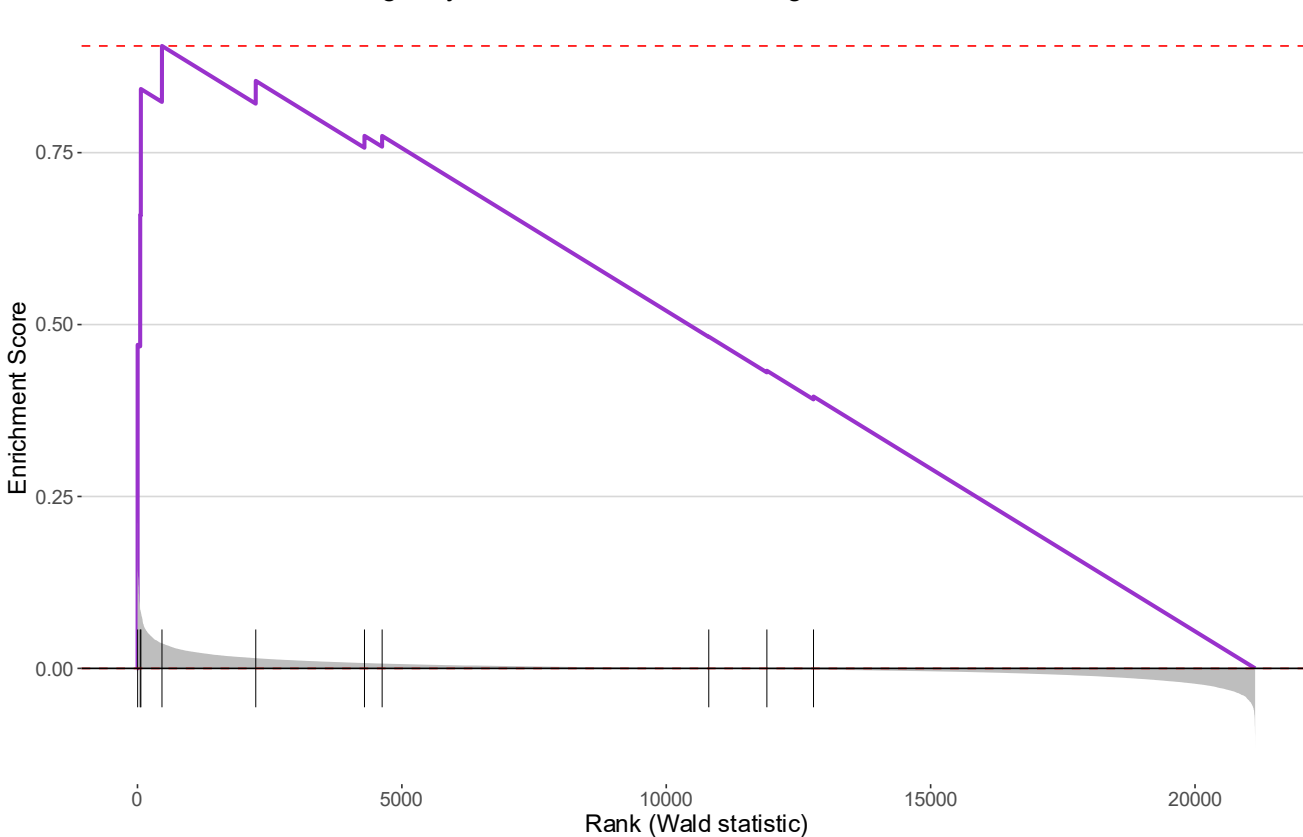


Using the sample metadata from the individual paper’s supplementary materials we found treatment naïve patients

Validation I: epithelial cell data from UC patient derived colonic organoids



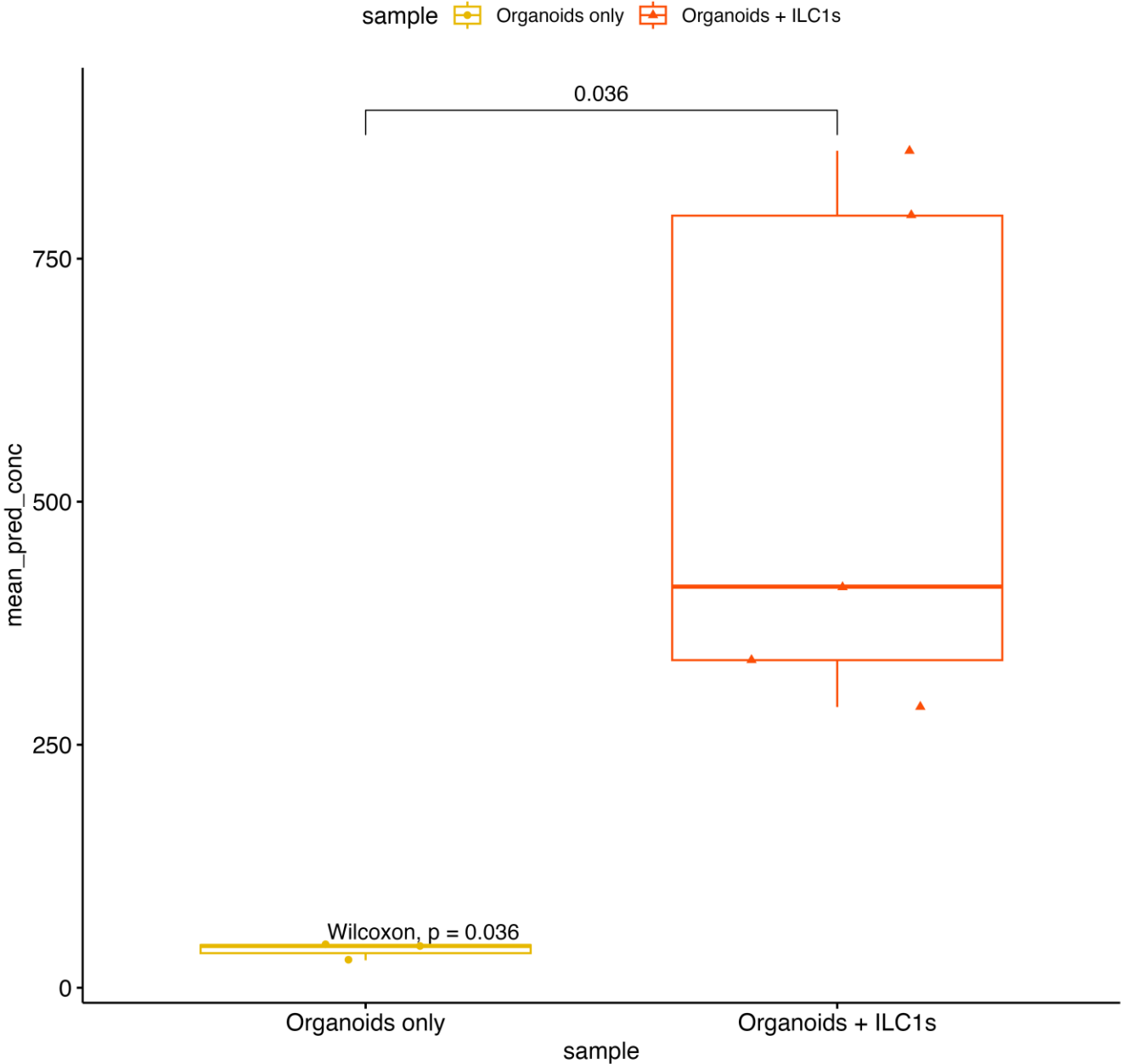
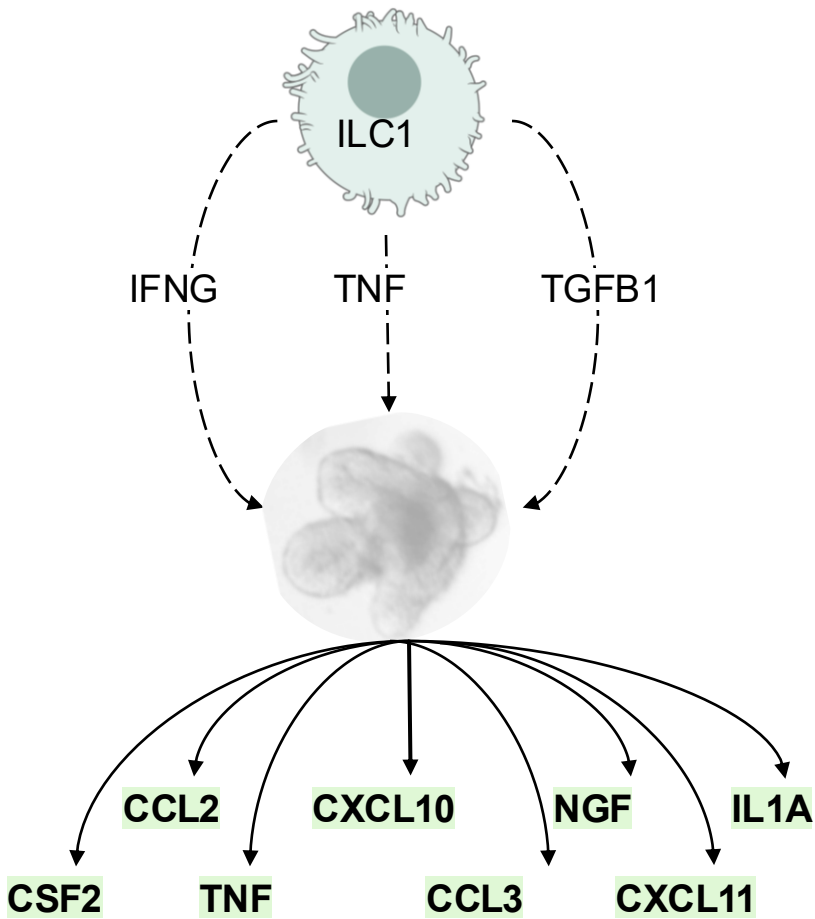
Enrichment of IFNG target cytokines in UC inflamed organoid treated with IFNG

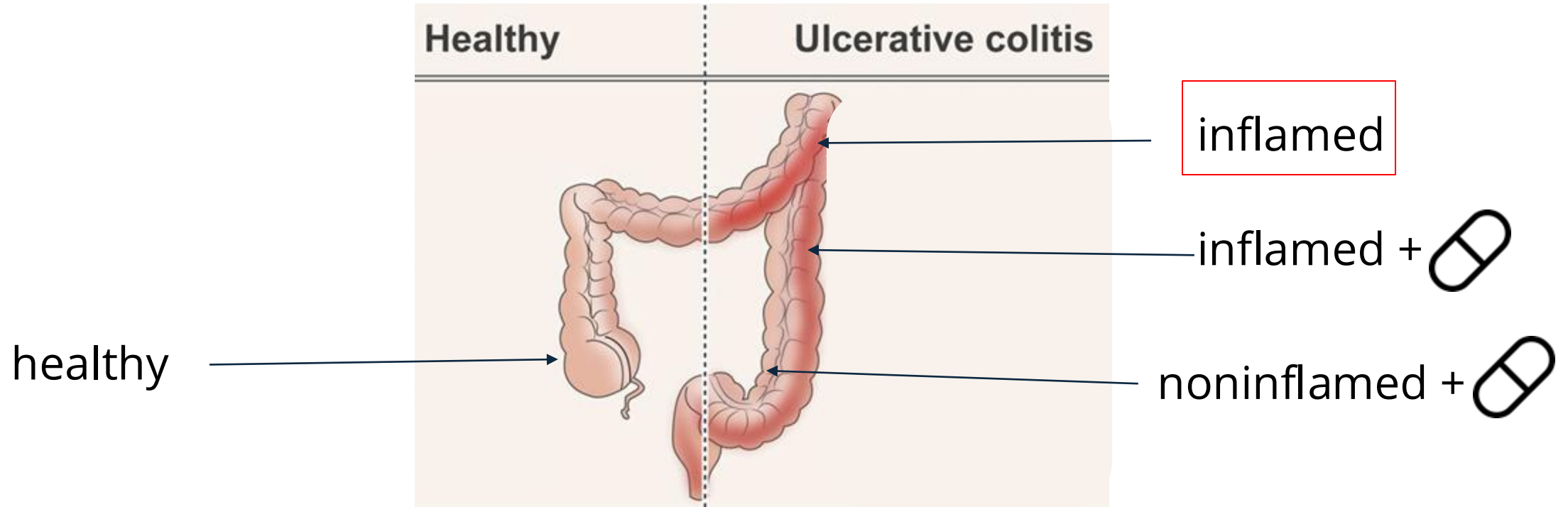


Validation II: cytokine concentration data from immune-cell co-cultured organoids



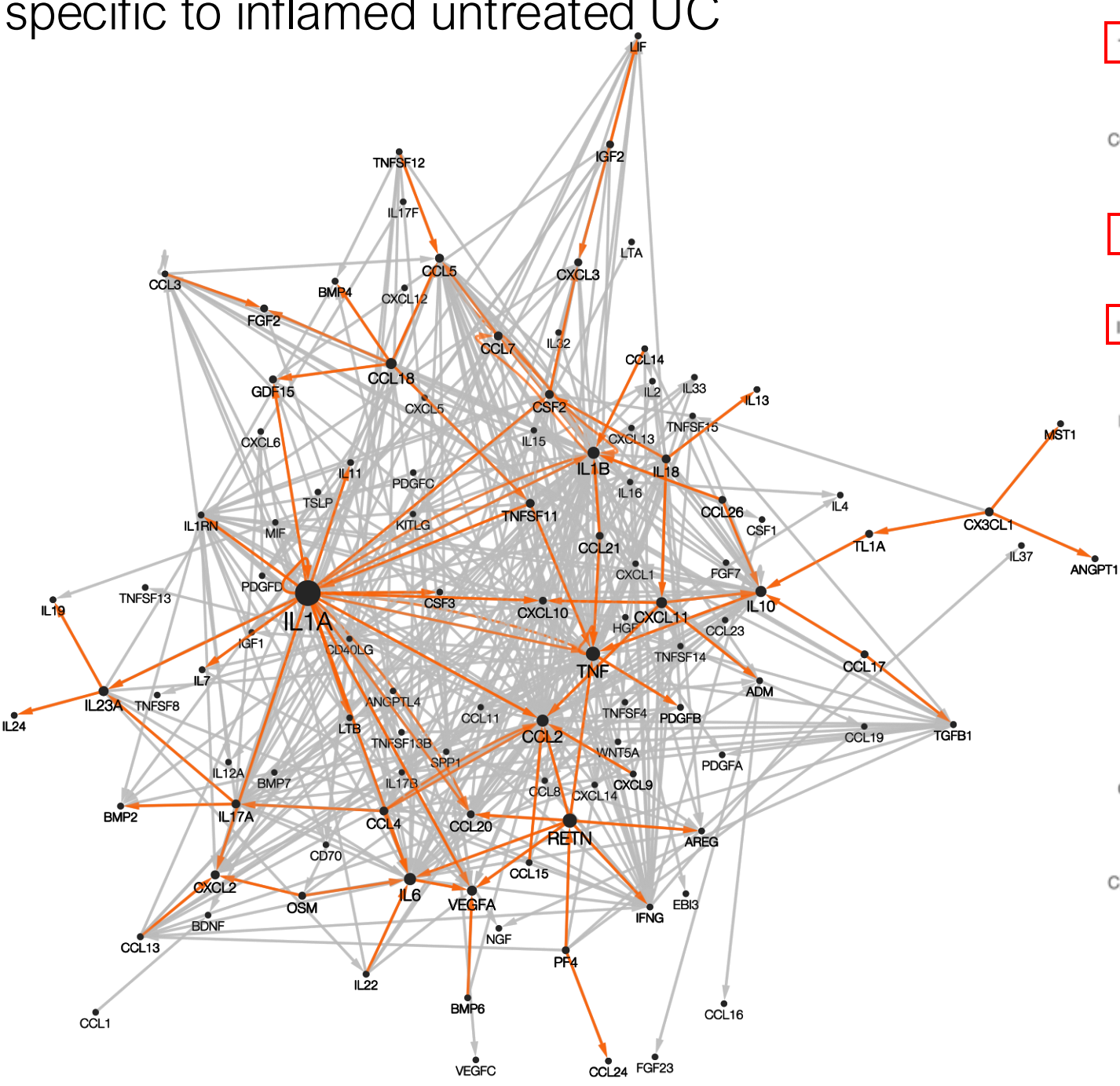
CXCL11





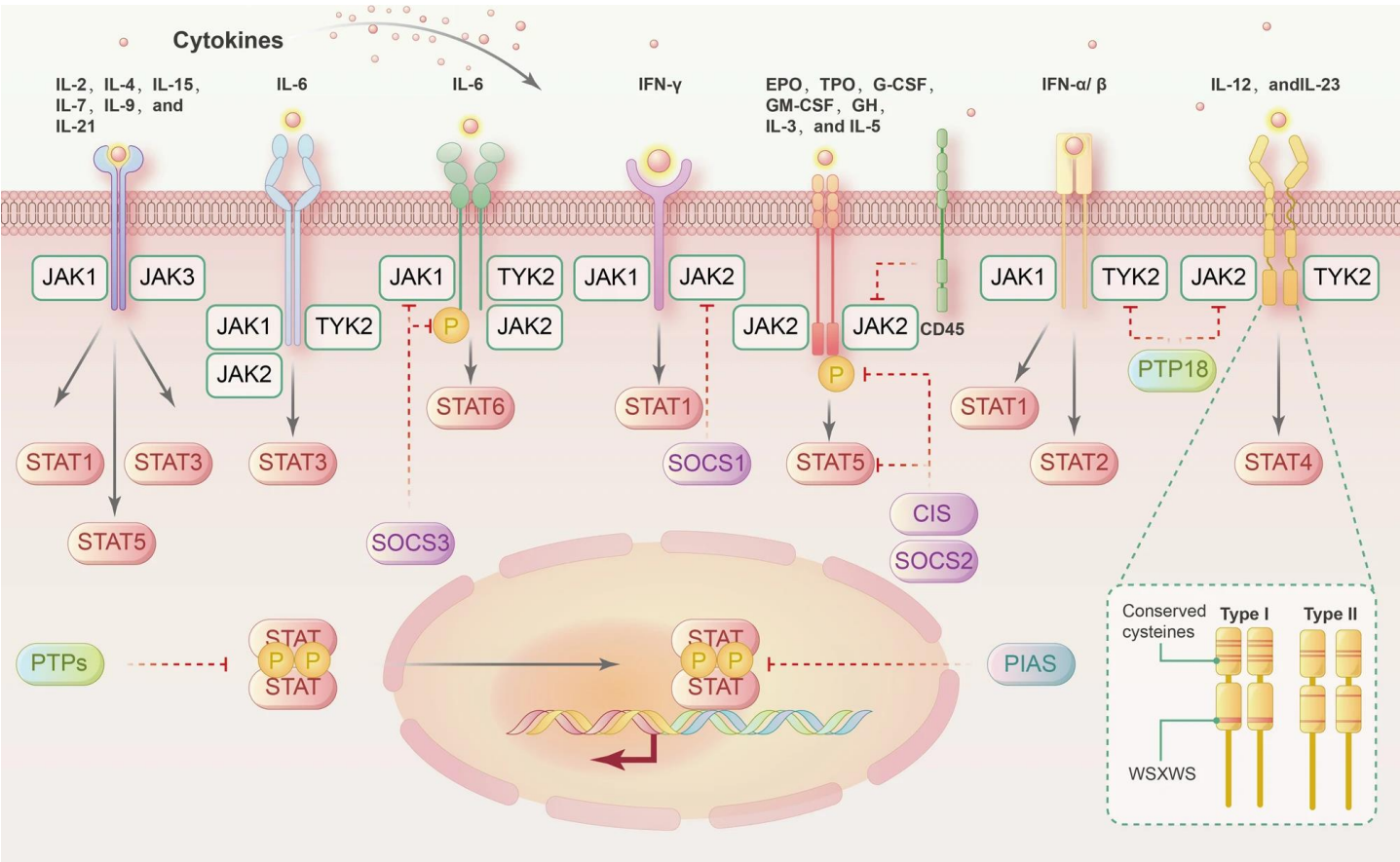
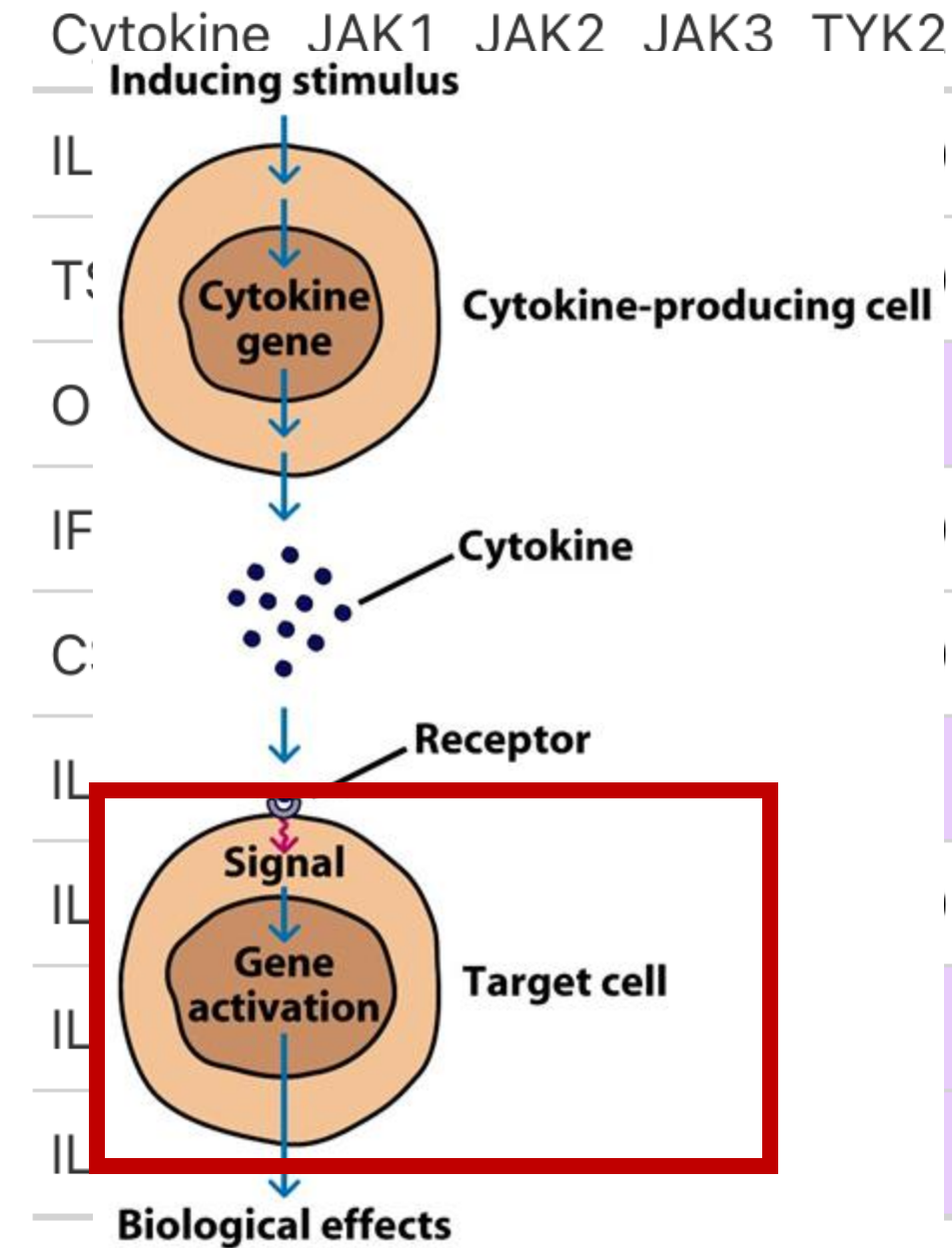
Question: What is unique to treatment naive ulcerative colitis?

A cytokine subnetwork specific to inflamed untreated UC

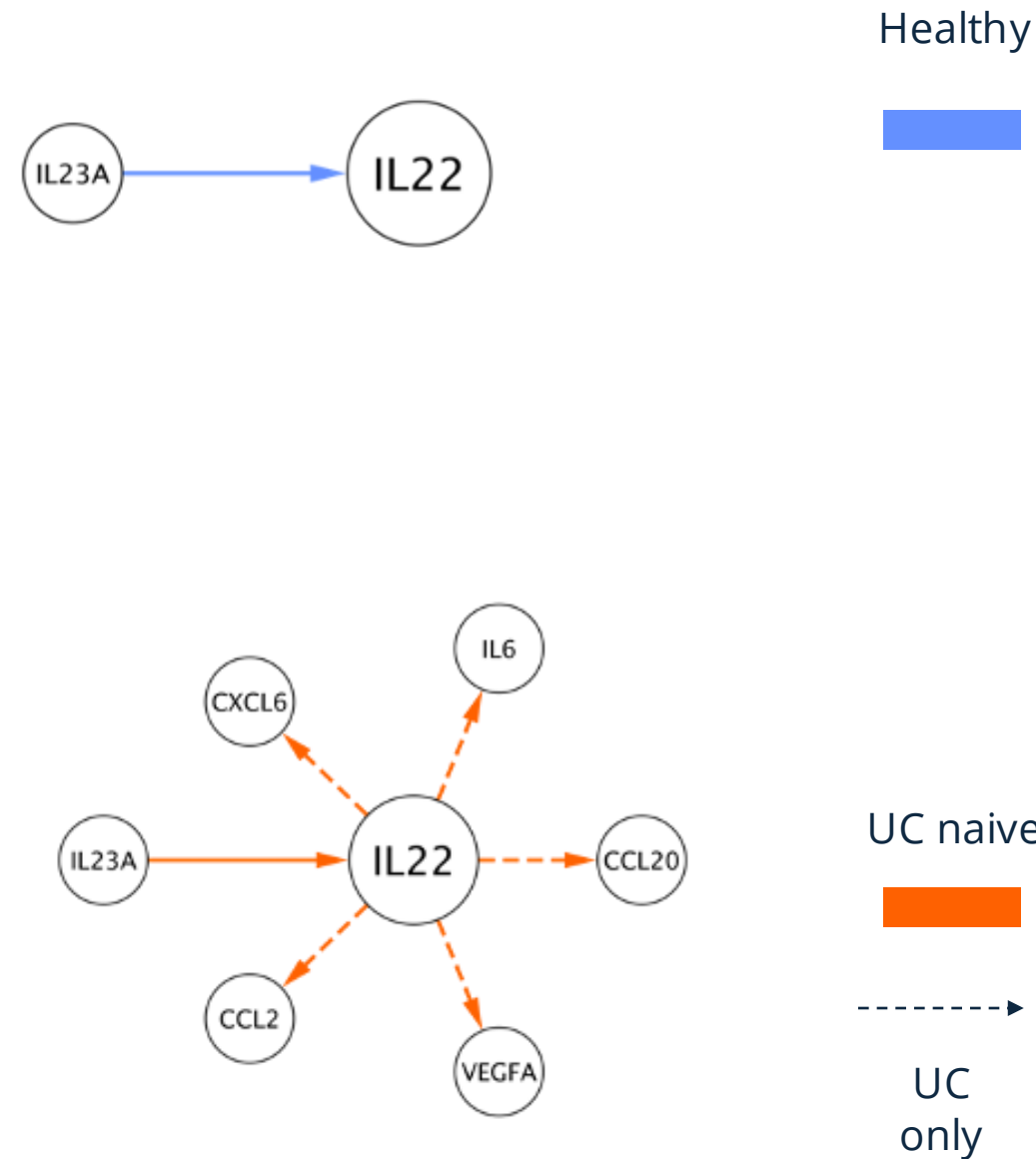
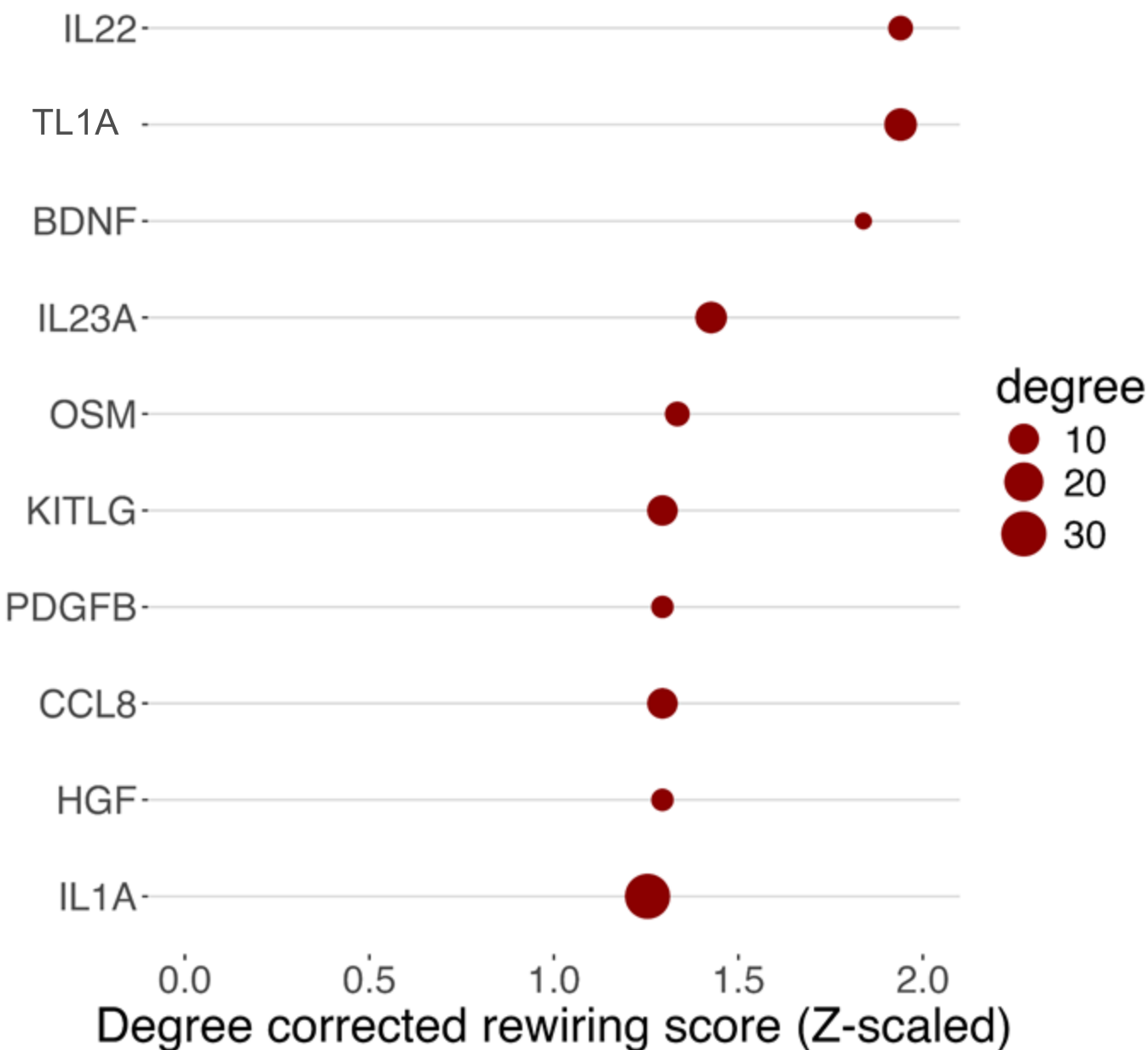


Interactions unique to treatment naive UC (77 links, 19% of total interactions in network)

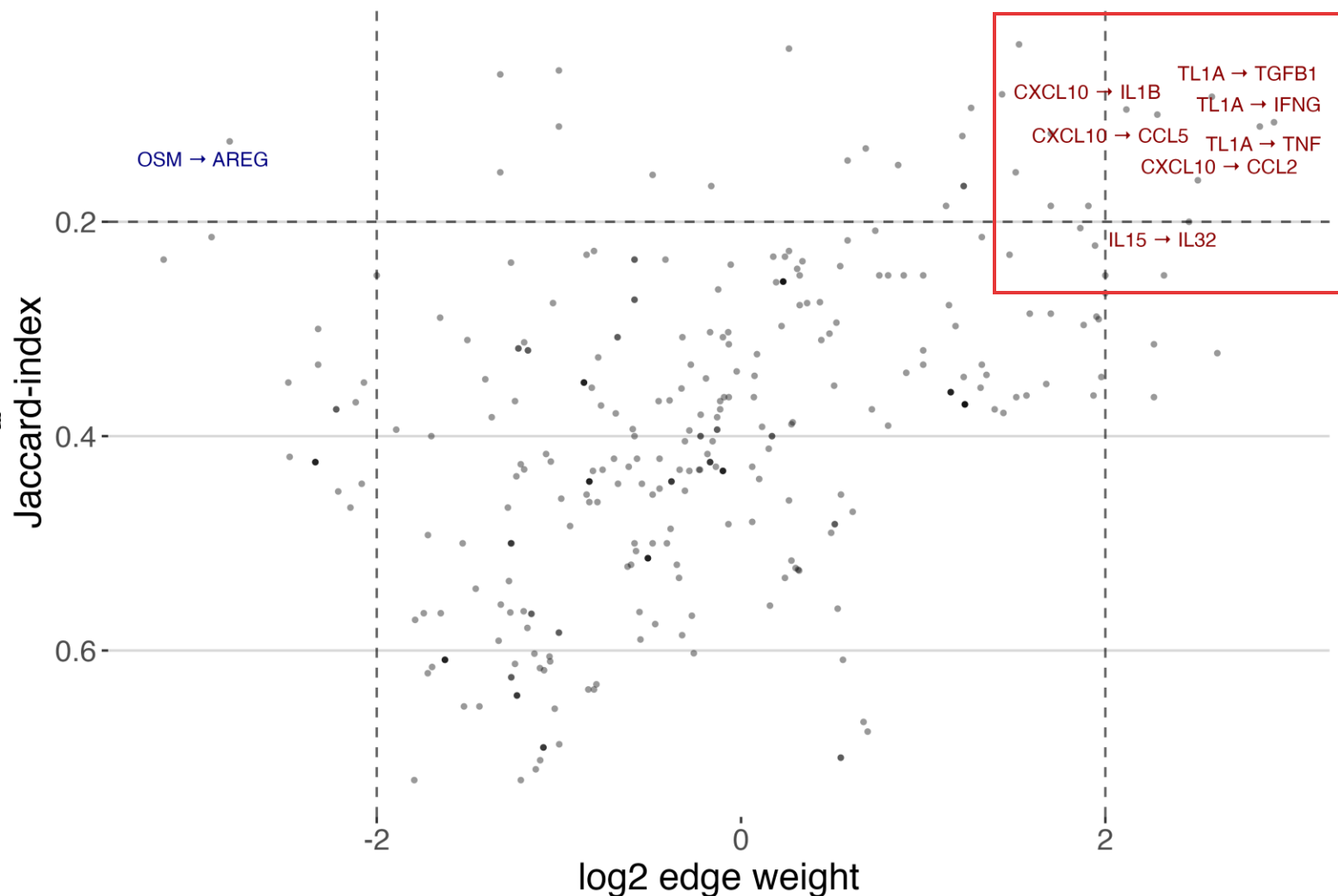
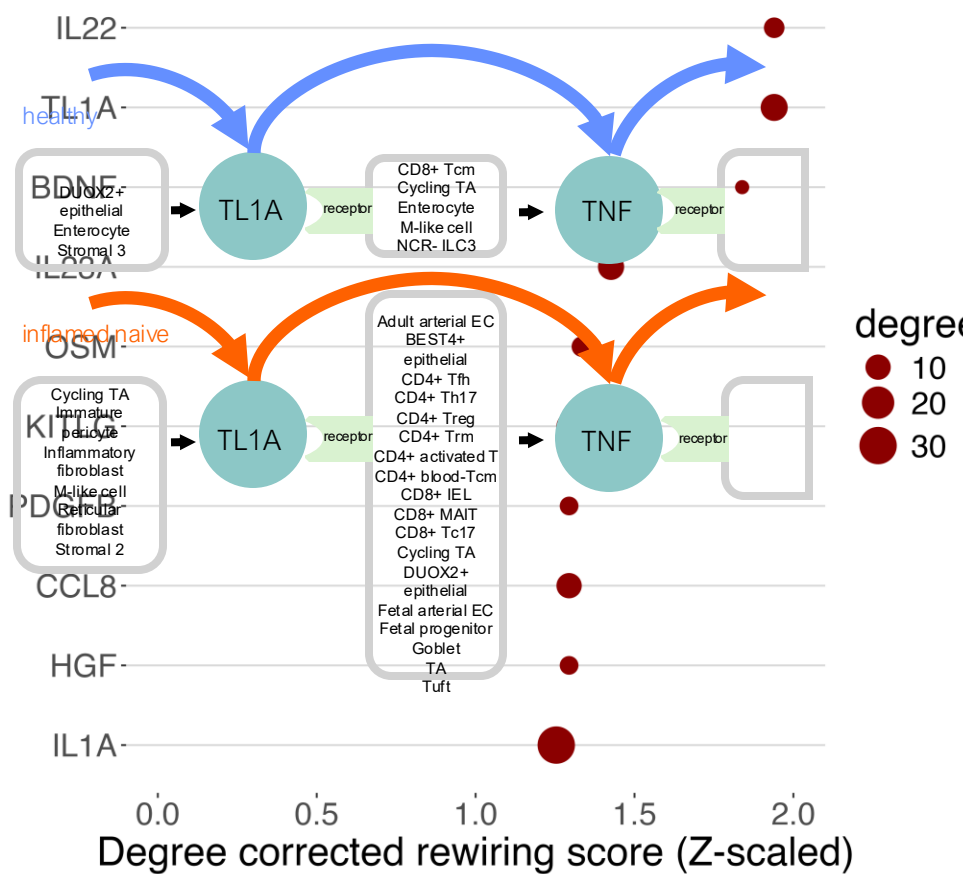
JAK inhibition of cytokine networks



Network rewiring identifies altered cytokine signalling in UC

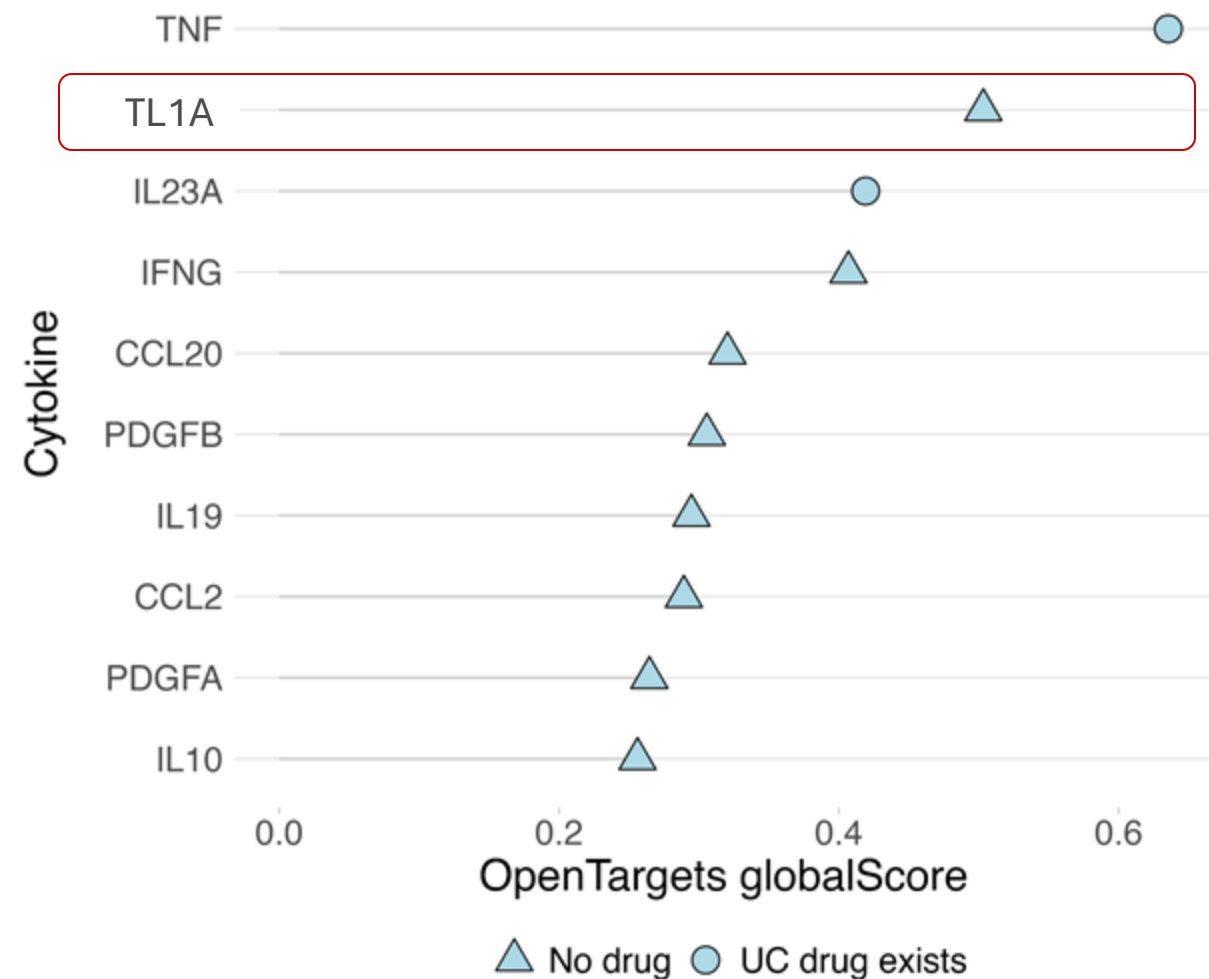
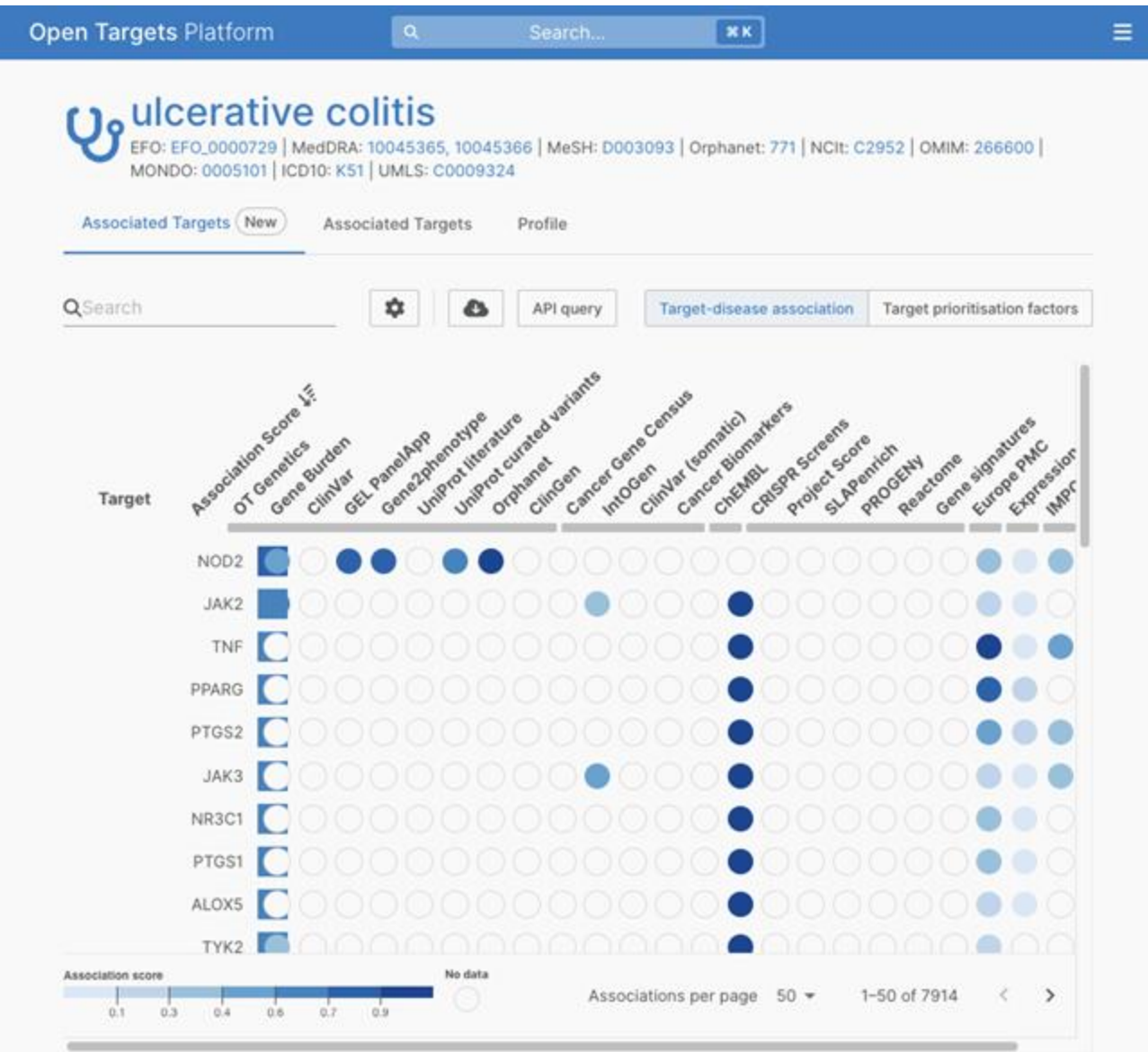


TL1A is the most rewired cytokine, and sends many of the strongest interactions compared to health



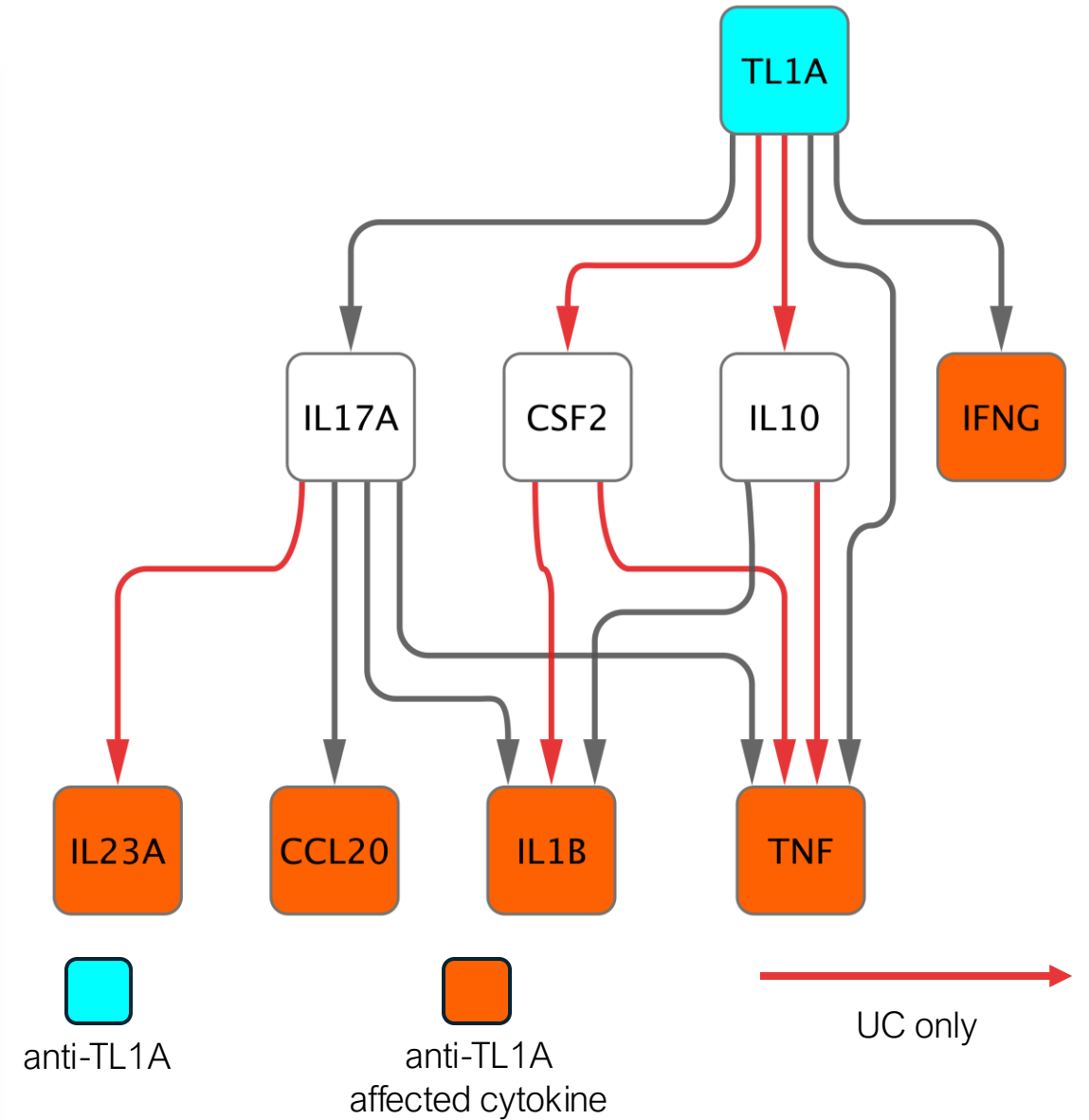
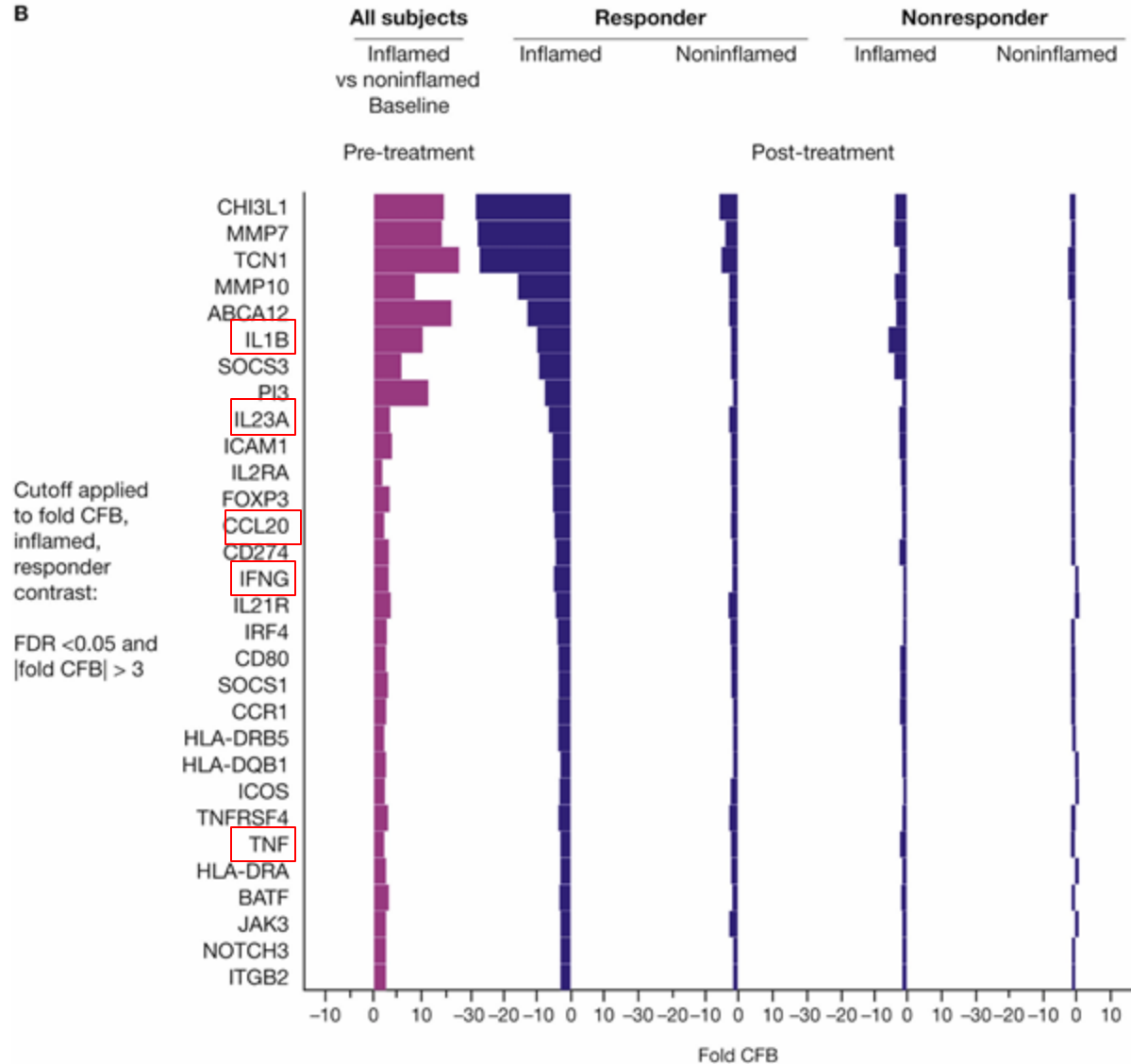
interaction_type a expanding a shrinking

TL1A is the highest scoring cytokine without an approved drug in OpenTargets



TL1A as a potential regulator of TNF and IL23A in UC

B



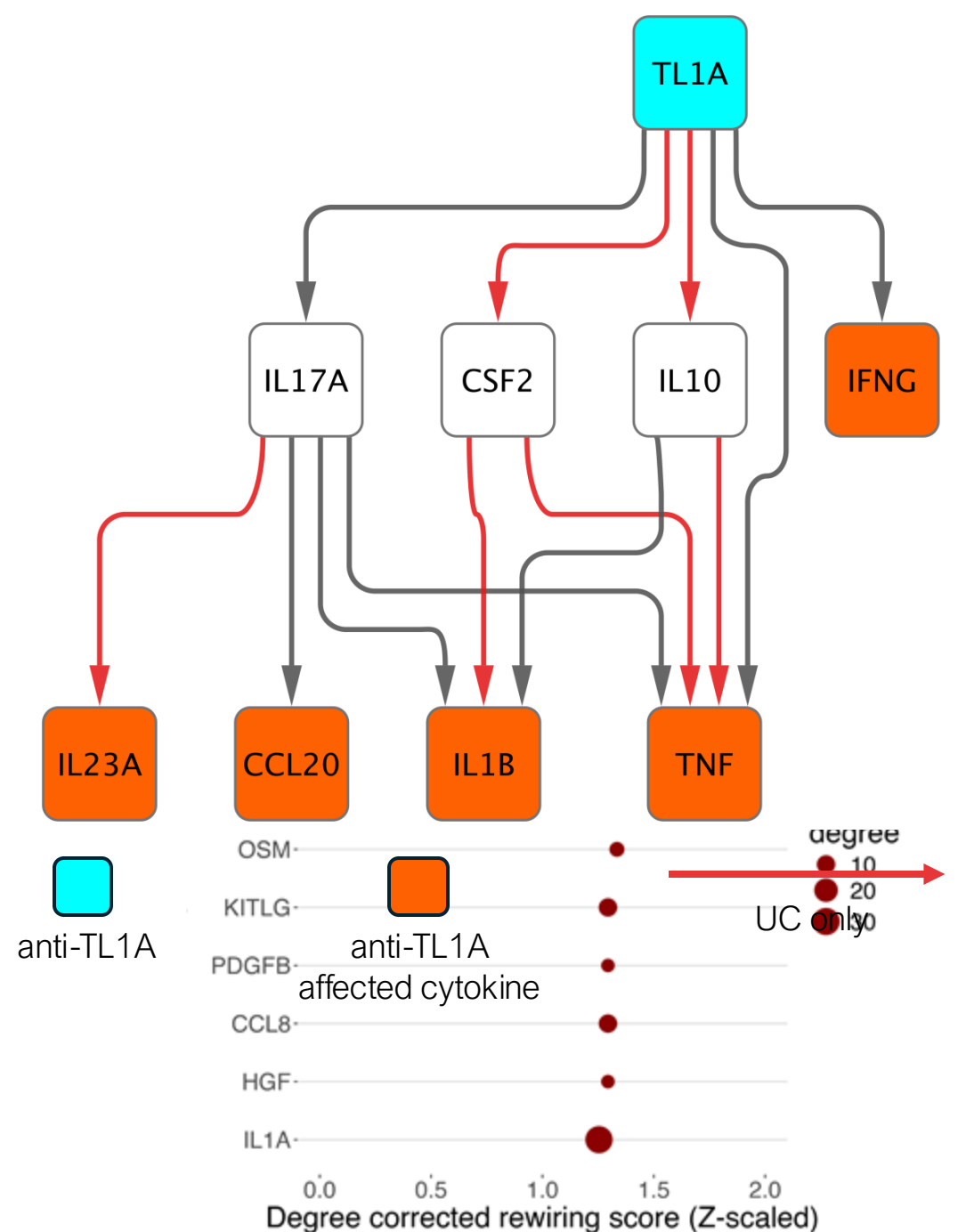
Summary #1

We generated **cytokine interaction networks** for **ulcerative colitis**, a subtype of IBD

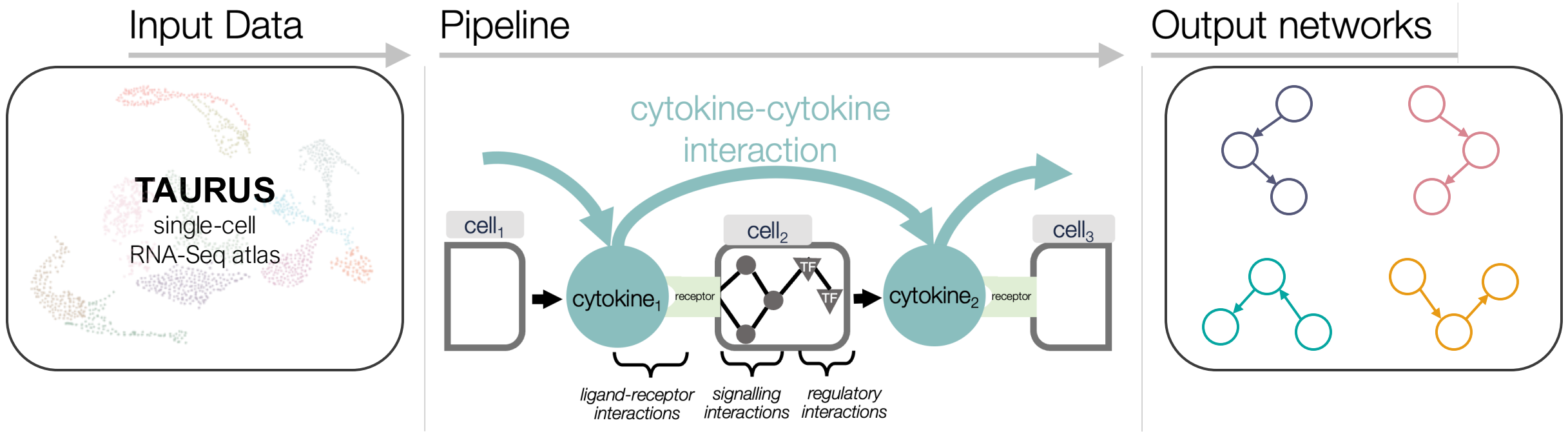
We **validated the interactions** on **RNA and protein level** using **patient derived organoids**,

In treatment naive ulcerative colitis patients:

- **20% of interactions are unique to them, targeting the major proinflammatory cytokines TNF, IL1B and IL6**
- Cytokine interactions are highly rewired, with **TL1A being the top rewired cytokine across the networks**
- **TL1A sends some of the strongest signals to its target cytokines in untreated UC**
- **TL1A may be a regulator of TNF and IL23A, the two cytokines already pharmaceutically targeted in UC**



Cytokine networks in Crohn's disease anti-TNF non-response

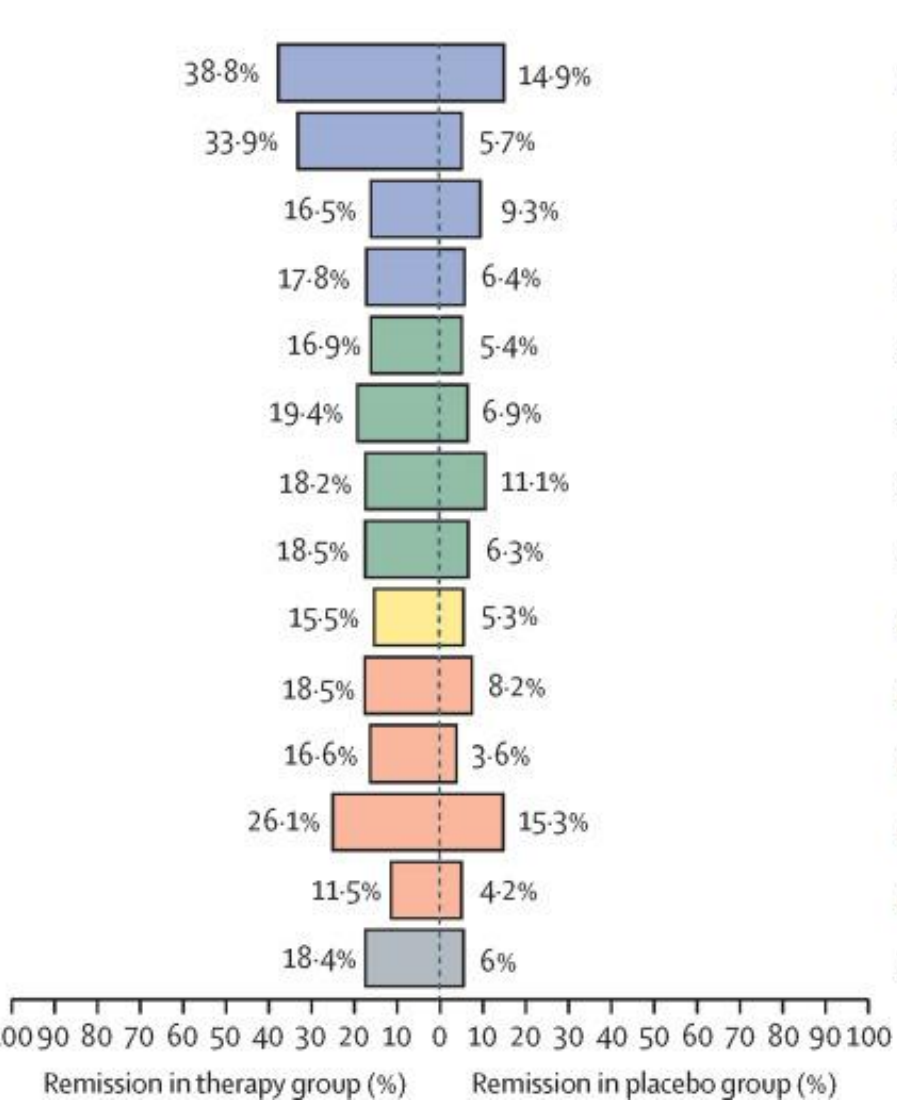


Single-cell RNA-Seq
resource of 16 CD
patients, sampled before
and after anti-TNF
treatment

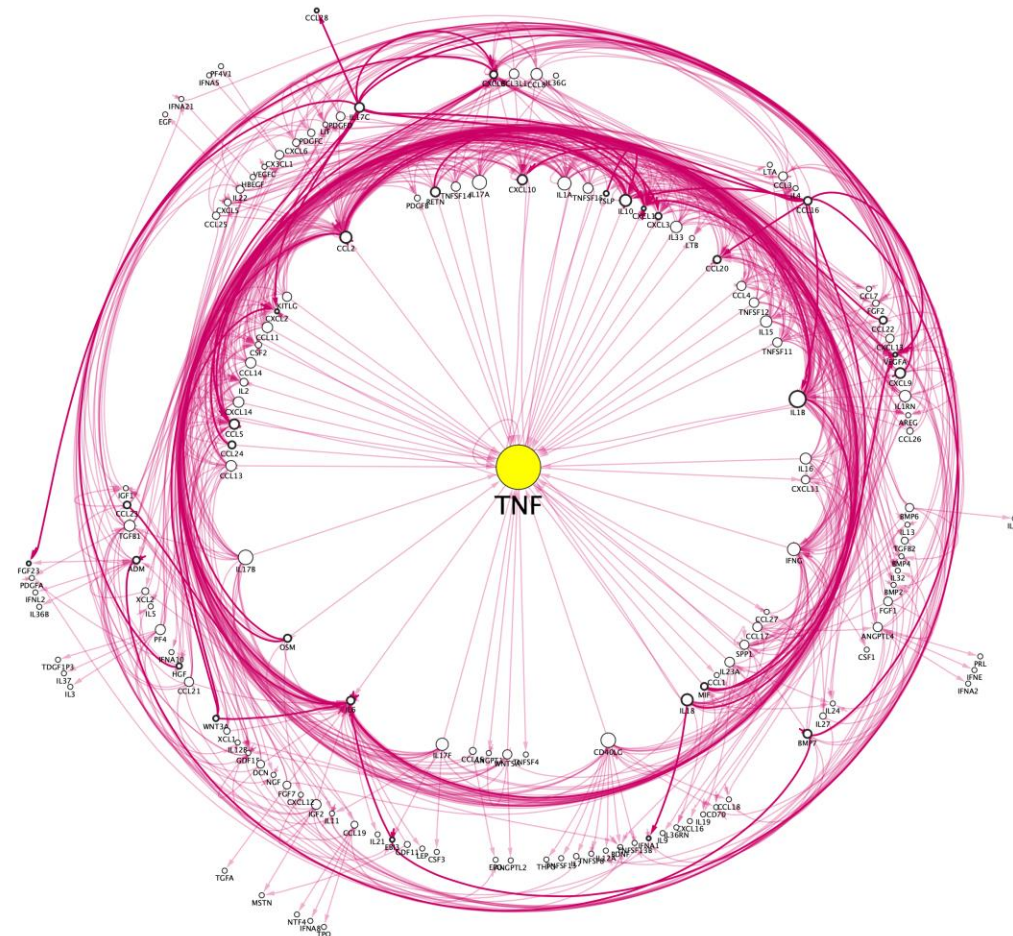
CytokineLink pipeline

Treatment, response,
and inflammation state
specific cytokine
networks

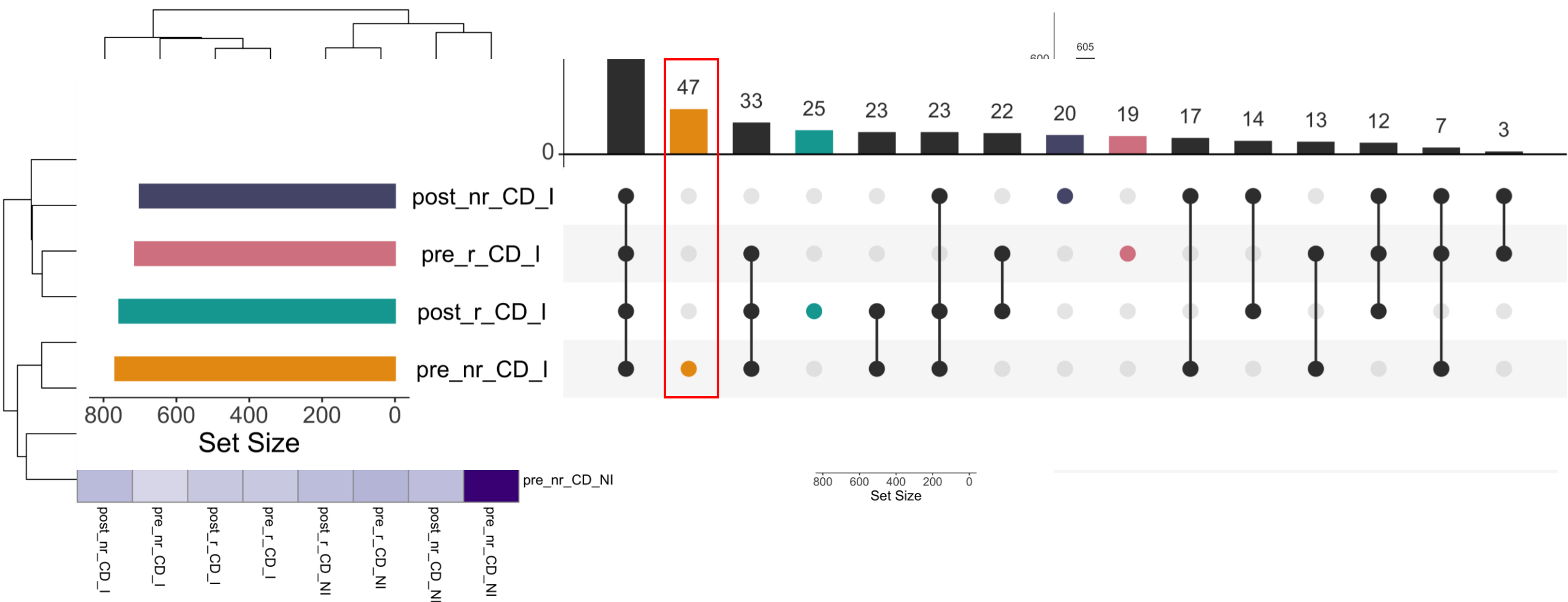
Anti-TNF efficacy



	Trial—drug
▲ 23.9%	ACT 1—infliximab ⁷
▲ 28.2%	ACT 2—infliximab ⁷
▲ 7.2%	ULTRA 2—adalimumab ⁸
▲ 11.4%	PURSUIT-SC—golimumab ⁹
▲ 11.5%	GEMINI—vedolizumab ¹⁰
▲ 12.5%	HIBISCUS I—etrolizumab ¹¹
▲ 7.1%	HIBISCUS II—etrolizumab ¹¹
▲ 12.2%	HICKORY—etrolizumab ¹²
▲ 10.2%	UNIFI—ustekinumab ¹³
▲ 10.3%	OCTAVE 1—tofacitinib ¹⁴
▲ 13.0%	OCTAVE 2—tofacitinib ¹⁴
▲ 10.8%	SELECTION A—filgotinib ¹⁵
▲ 7.2%	SELECTION B—filgotinib ¹⁵
▲ 12.4%	TRUE NORTH—ozanimod ¹

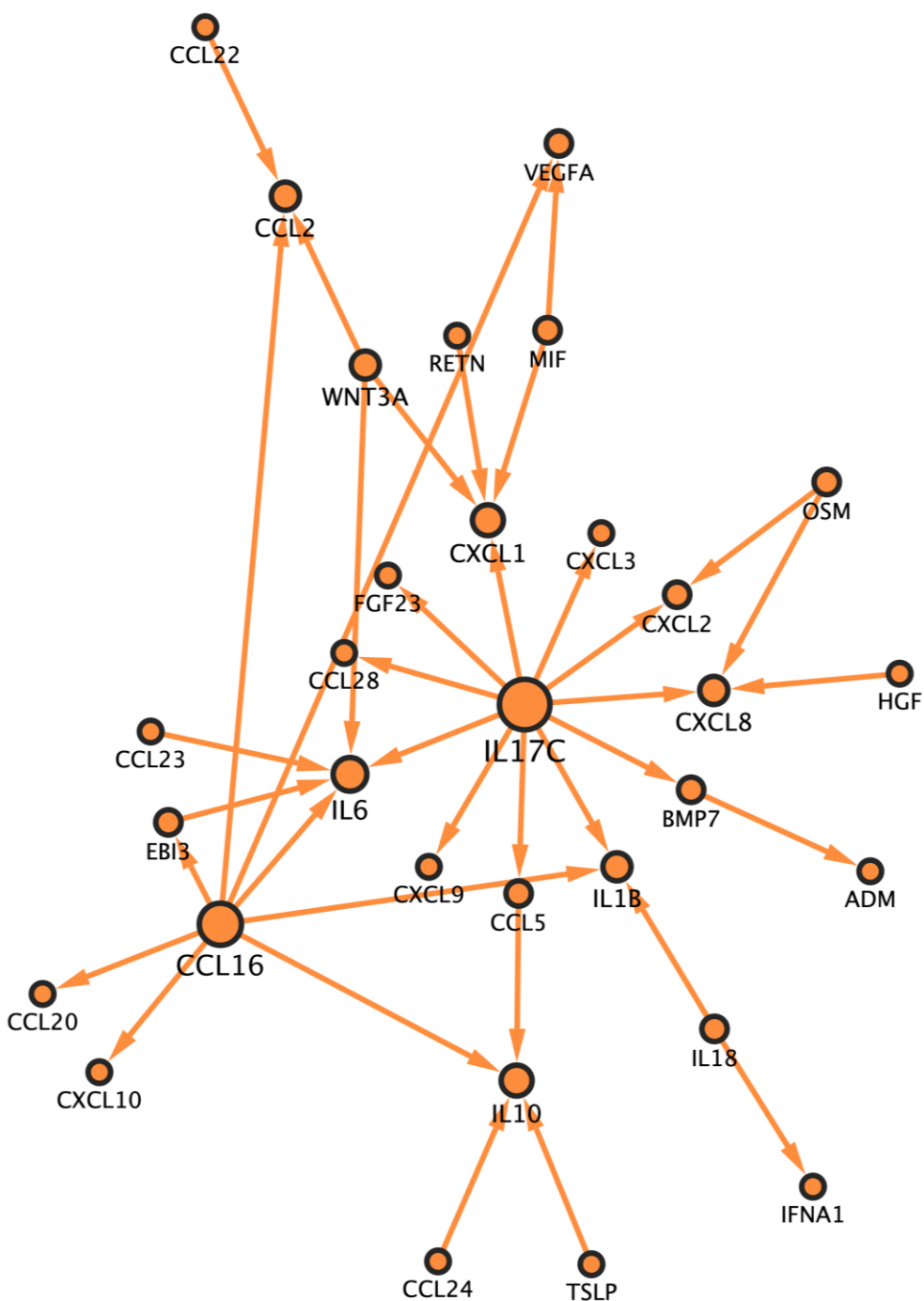


Treatment and response specific cytokine networks in Crohn's disease



The resulting networks cluster according to inflammation, response and treatment status

While many of their interactions overlap, there are distinct state-specific cytokine interactions



This pre-treatment non-responder specific module is primarily driven by **IL17C**

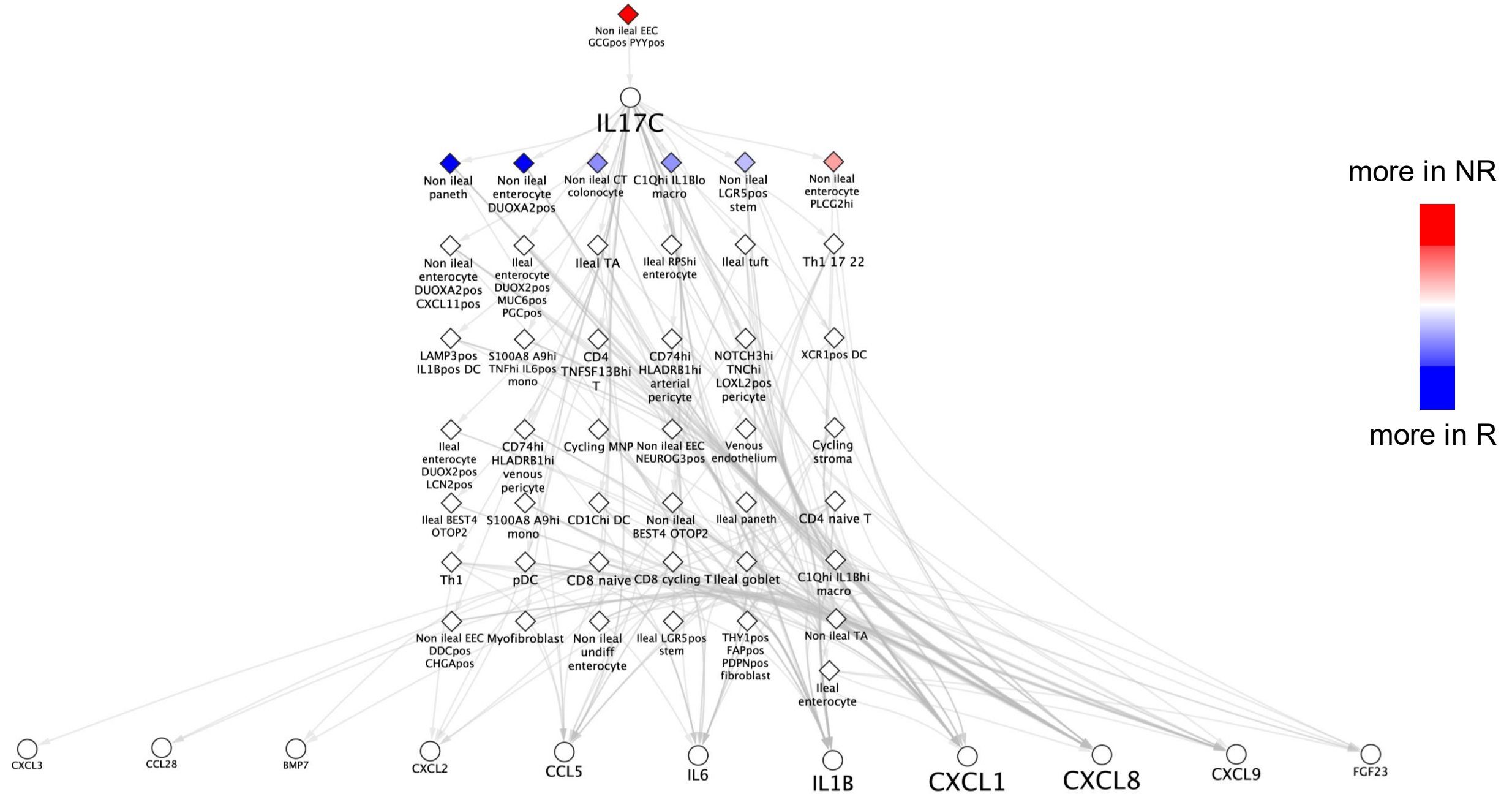
- **IL17C** is a member of the IL17 family of cytokines
- **IL17C** is normally only produced by **epithelial cells**
- **IL17C** has been found to be elevated in active CD
- **IL17C** is targeting IL1B, IL6, and multiple neutrophil attracting chemokines (CXCL1/2/3/8) in the module
- **IL17C** is known to be induced by bacterial stimuli at mucosal surfaces, particularly in enteroendocrine and goblet cells



Who's producing IL17C, why isn't it showing up in responders?



IL17C is produced by the most differentially abundant cell type between pre-treatment response groups

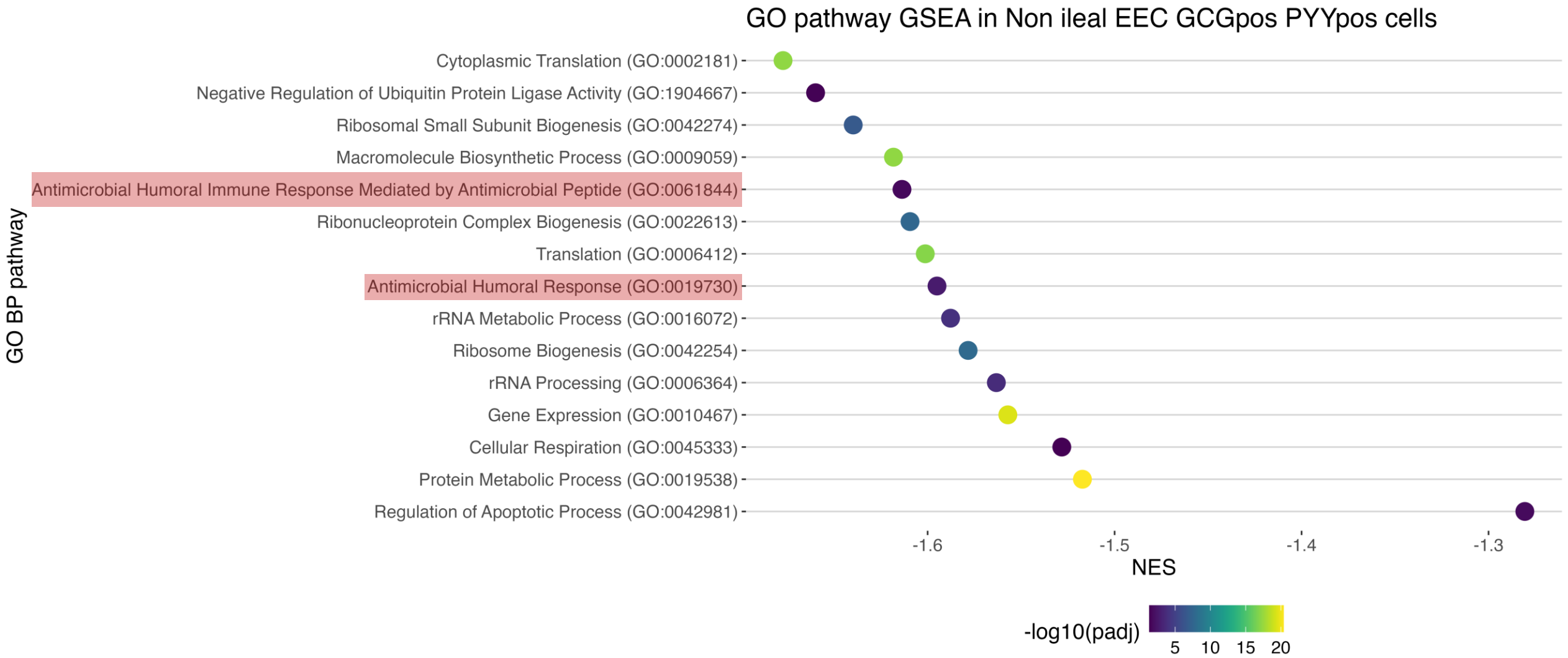


*IL17C is known to be **induced by bacterial stimuli at mucosal, epithelial surfaces**, particularly in enteroendocrine and goblet cells*



Is it possible that NR have inadequate antimicrobial defenses, leading to more encounters with the microbiome?

GSEA analysis of epithelial cell populations between pre-treatment NR and R

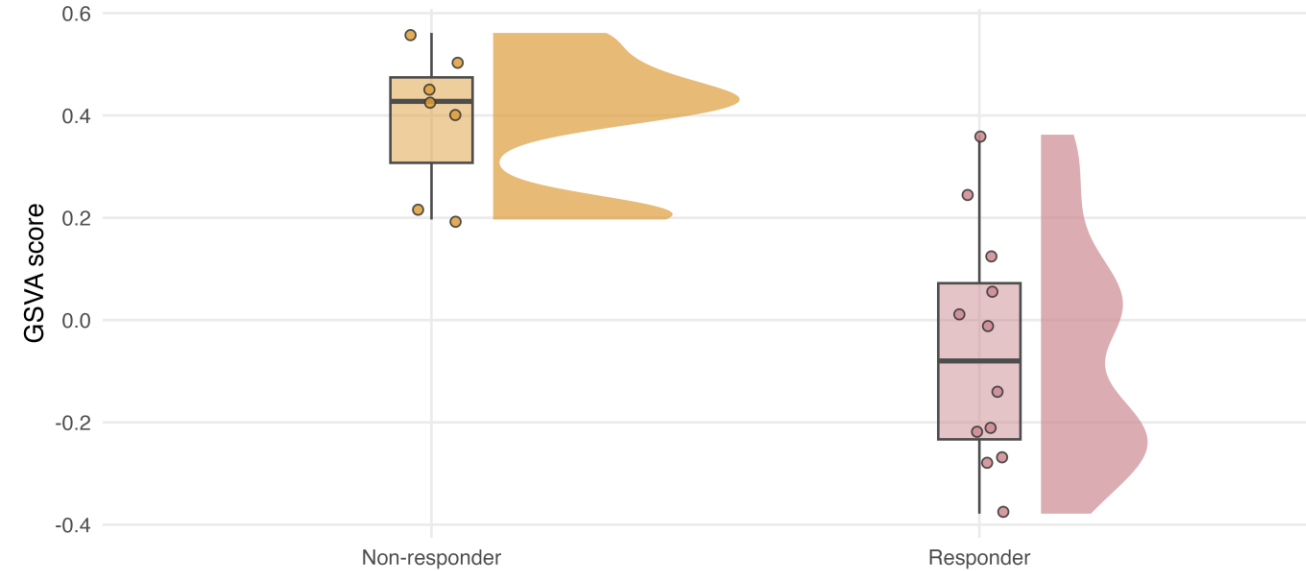


The IL17C producing cell type is negatively enriched in bacterial defense pathways in non-responders

The non-responder module separates colonic non-responders in an independent dataset

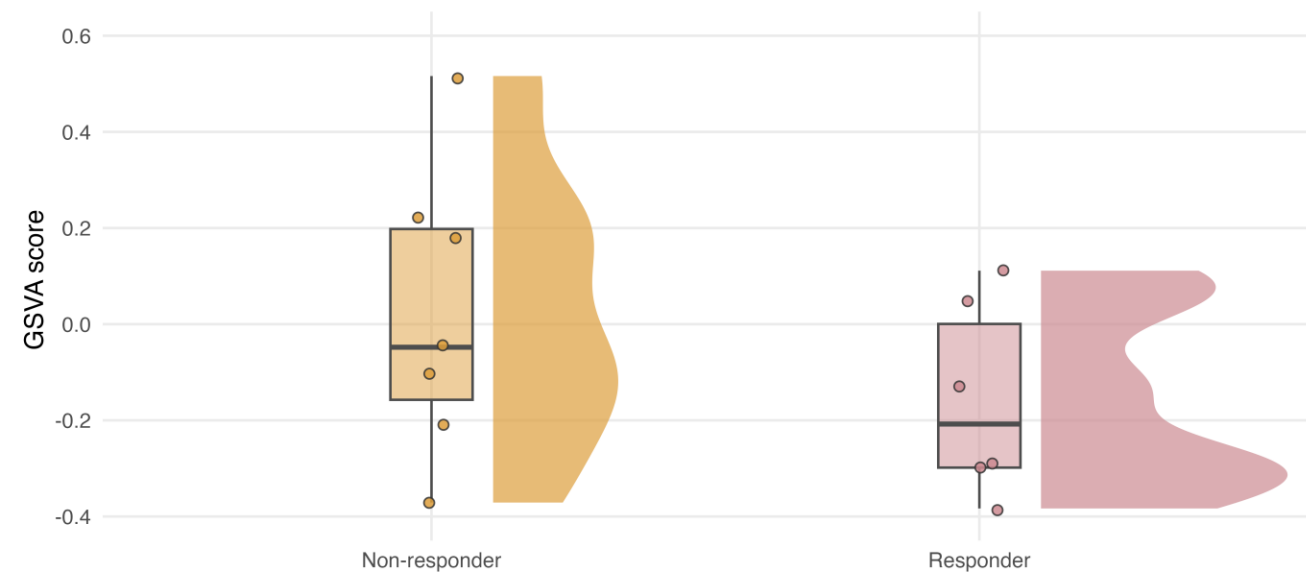
Colonic CD NR module (Arijs et al., 2009)

p = 0.0005 | AUC = 0.9524 | NR n=7, R n=12



Ileal CD NR module (Arijs et al., 2009)

p = 0.1728 | AUC = 0.7000 | NR n=10, R n=8



The module is significantly enriched in non-responders in an independent dataset, specifically in colonic Crohn's, consistent with the colonic origin of the differentially abundant IL17C producer cells

Model

Non-ileal EEC GCGpos PYYpos cells are the most differentially expanded cell type in pre-treatment non-responders vs responders

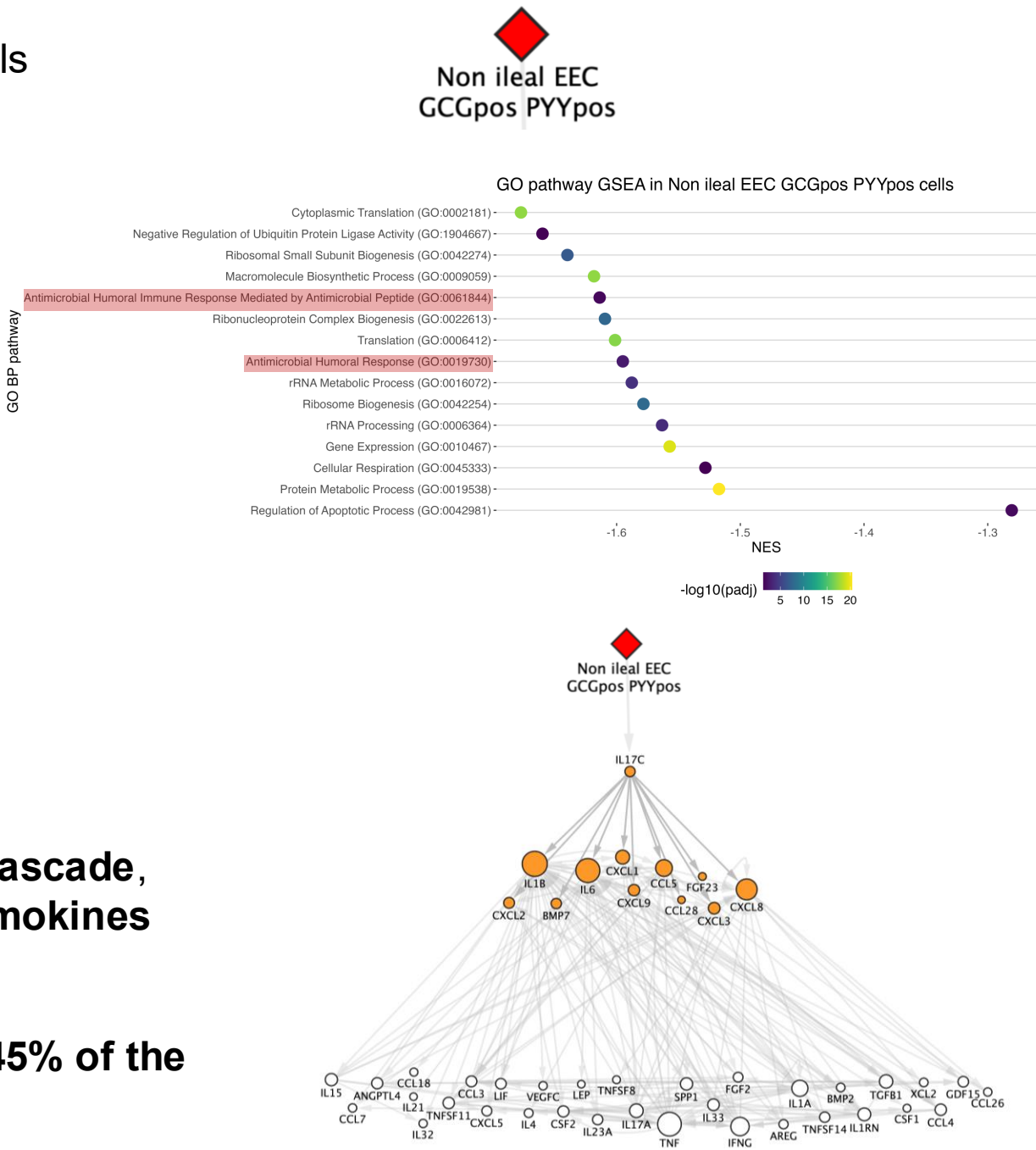
These cells have **downregulated antimicrobial defense pathways** compared to responders

This antimicrobial deficiency may **increase their susceptibility to microbiome interactions**

Microbiome engagement **triggers IL17C secretion** from these cells

IL17C induces a broad inflammatory cascade, targeting IL6, IL1B, and neutrophil chemokines (CXCL1/2/3/8)

Through first-neighbours, **this impacts 45% of the entire cytokine network**



Dysregulated celltype

Dysregulated cytokine signalling

you

Use it if you:

- have single-cell RNA-Seq data of your condition of interest
- cytokine communication is relevant to your biological question
- **It can**
 - Highlight the cytokines potentially behind the observed phenotype (*TL 1A*)
 - Show what are the differences in cytokine regulation between health and disease (*rewiring; state-specific clusters*)
 - Point out misbehaving cell types driving cytokine secretion (*IL 17C*)
- The resulting cytokine network is the immune equivalent of a regulatory network:
 - if regulatory rewiring, immune dysregulation plays a role in your research, this method might elucidate some aspects of it

It cannot:

- Show you all differences in cell-cell communication (that's a different, much broader analysis)
- Tell you what non-cytokine genes are regulated – that needs to be followed up separately
- be used on bulk data (unfortunately, but we are working on a solution)

https://github.com/korcsmarosgroup/CytokineLink_pipeline



Acknowledgements

Korcsmaros group

Tamas Korcsmaros
Isabelle Hautefort
John P. Thomas
Luca Csabai
Balazs Bohar
Yufan Liu
Leila Gul



Imperial BRC Organoid

Facility

Diana Papp
Sandra S. Koigi

Modos group

Dezso Modos

https://github.com/korcsmarosgroup/CytokineLink_pipeline

<https://github.com/olbeimarton/dynetR>

Powell group

Nick Powell
Hajir Ibraheim
Aamir Saifuddin
Sadek Malas

Joana F. Neves group

Joana F. Neves
Diana Coman
Emma Højmosen Kromann



✉ m.olbei@imperial.ac.uk

🐦 [@martonolbei](https://twitter.com/martonolbei)

🦋 [@martonolbei.bsky.social](https://bsky.social/martonolbei)



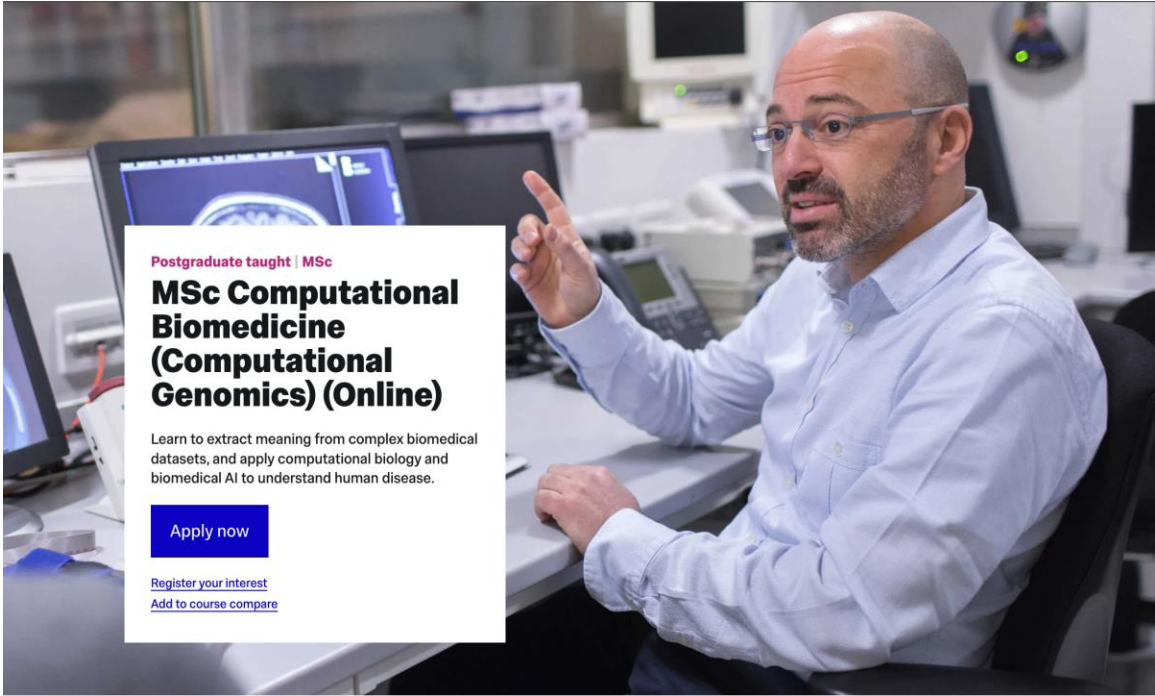
Biotechnology and
Biological Sciences
Research Council

Imperial College
London

NIHR | National Institute
for Health Research

Imperial BRC
Organoid Facility

Thank you for your attention!



Postgraduate taught | MSc

MSc Computational Biomedicine (Computational Genomics) (Online)

Learn to extract meaning from complex biomedical datasets, and apply computational biology and biomedical AI to understand human disease.

[Apply now](#)

[Register your interest](#)
[Add to course compare](#)

Overview	Structure	Teaching and assessment	Entry requirements	How to apply	Fees and funding	Request info
----------	-----------	-------------------------	--------------------	--------------	------------------	--------------

Acquire a solid foundation in computational biology, data science and biomedical AI

Gain skills in integrating, mining, modelling, visualising, and analysing biomedical data

Develop expertise in single cell omics and network biology