

# Systems biology, Systems Medicine, Big Data

How network approaches can improve  
IBD research and clinical outcome

**TAMAS KORCSMAROS**

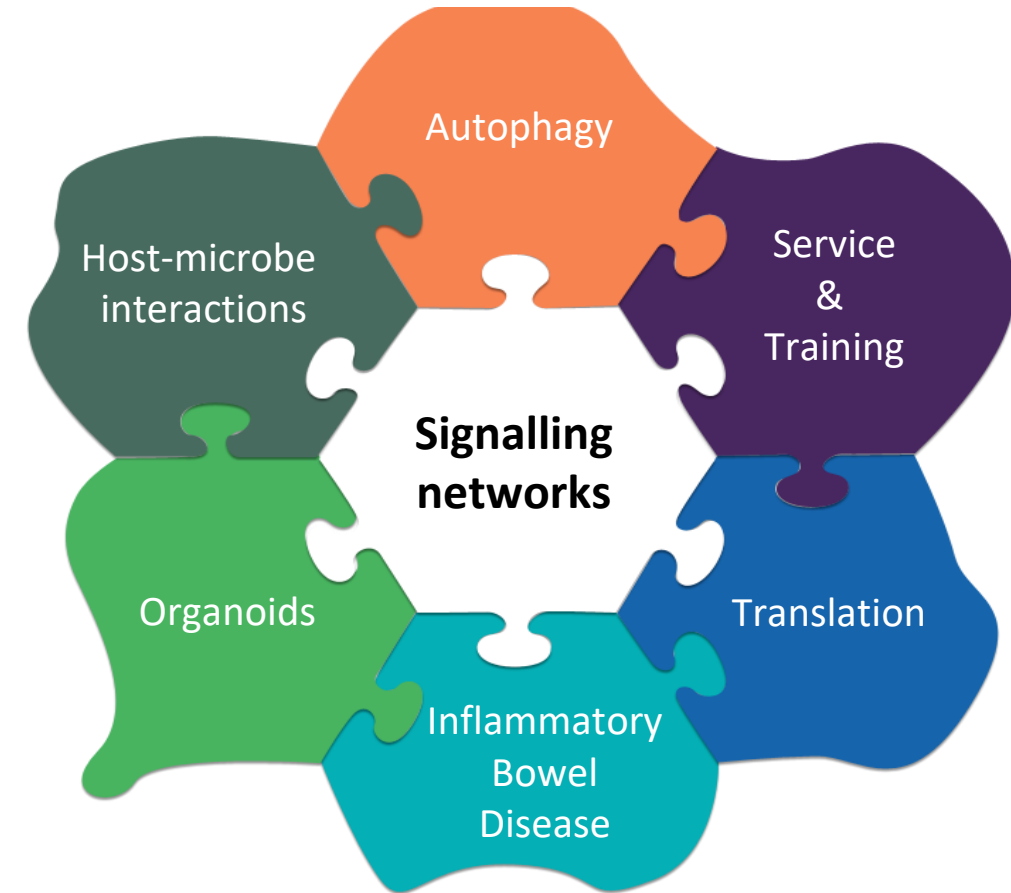
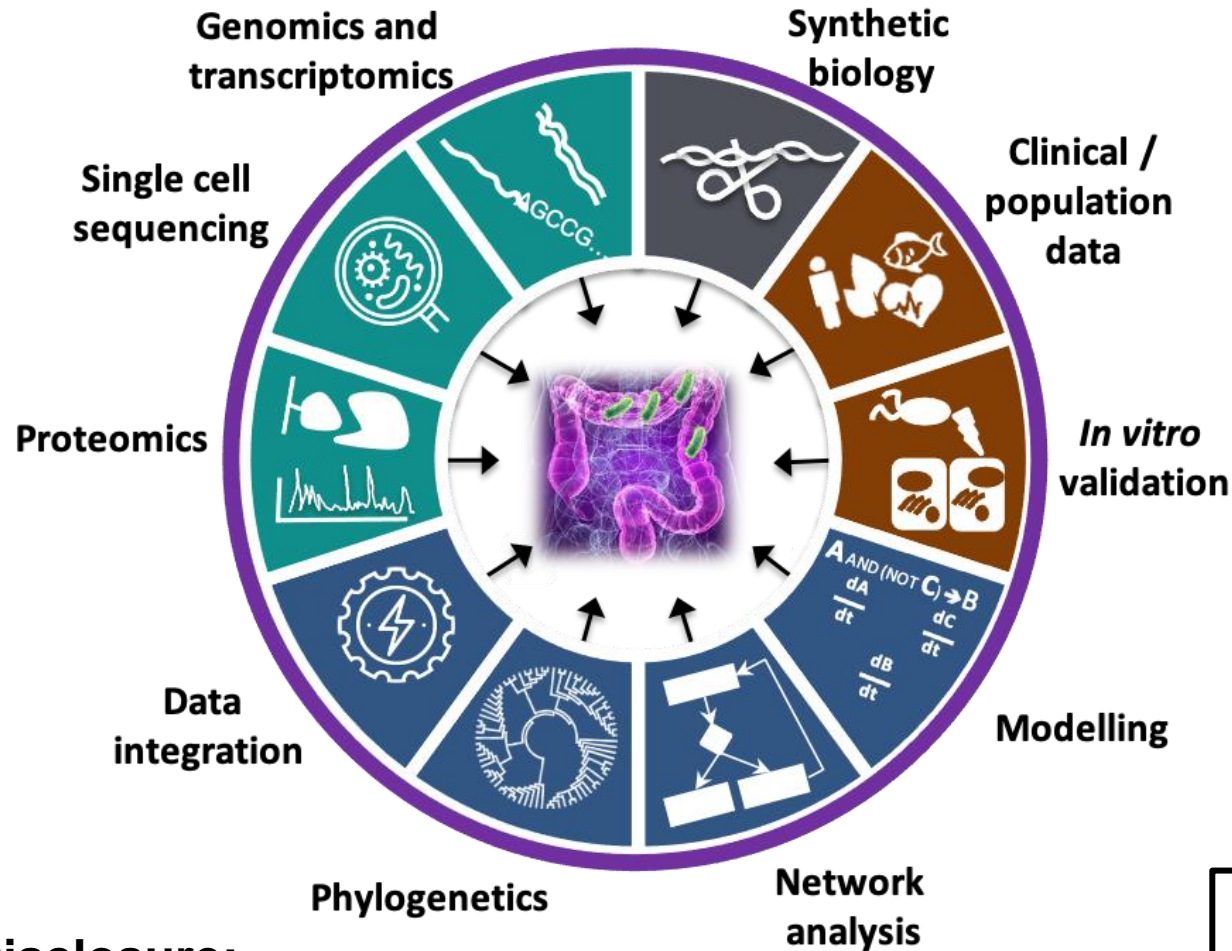
Senior Lecturer

Division of Digestive Diseases



**Imperial College**  
London

**NIHR** | Imperial Biomedical  
Research Centre



Disclosure:

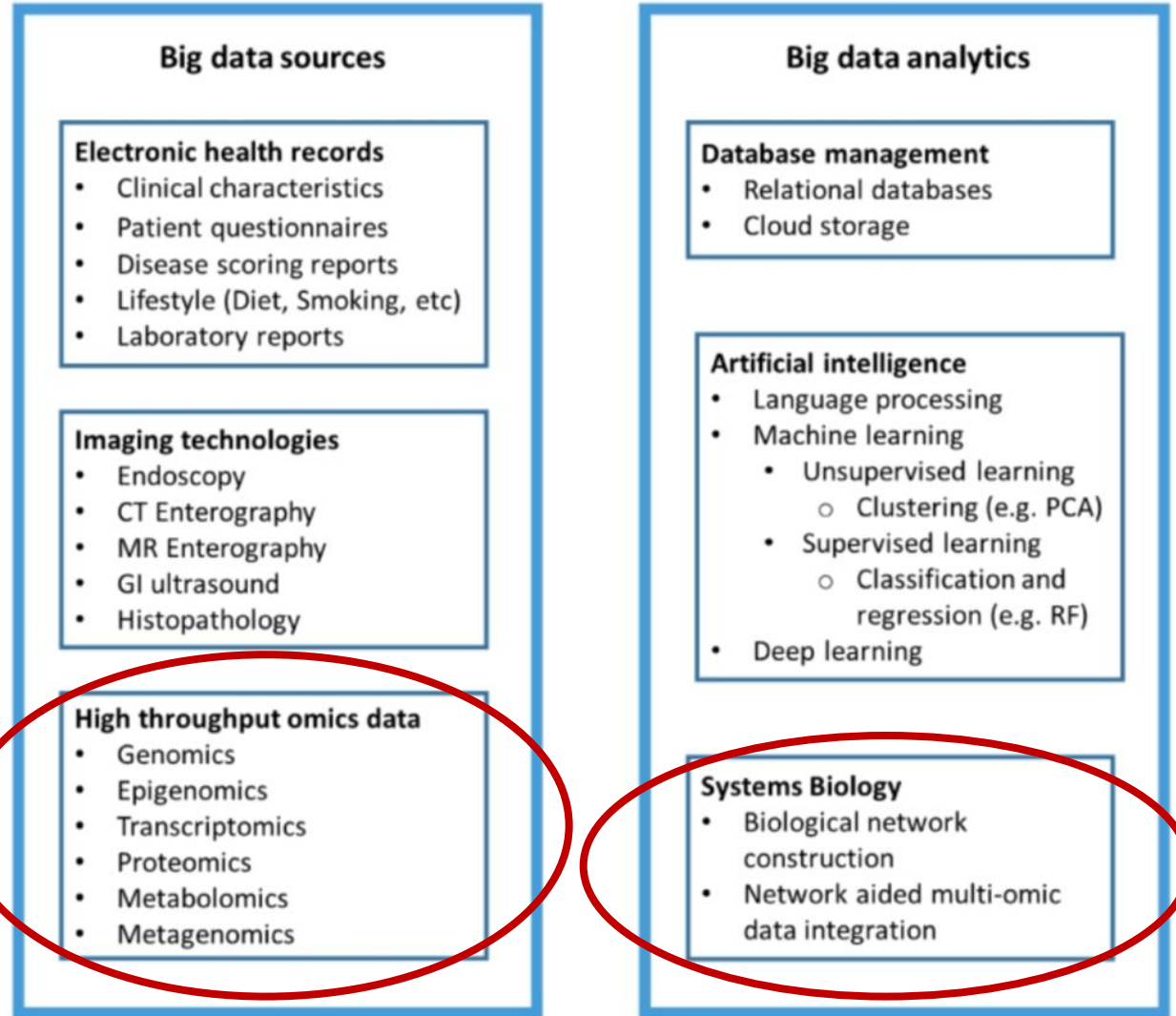
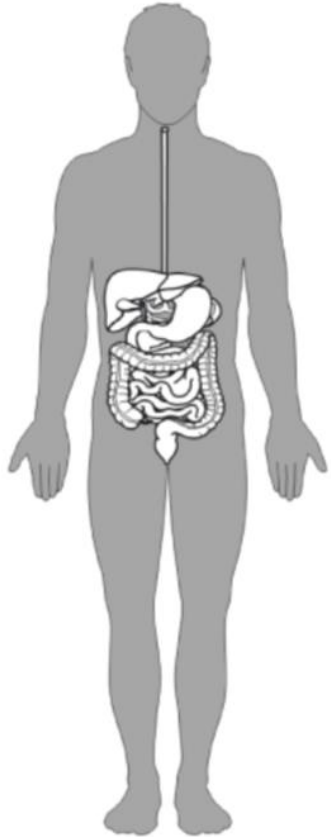
BenevolentAI



Roche

**Goal of the group:** To understand biological systems (cell-cell and cell-microbe interactomes) related to gut homeostasis and to facilitate precision medicine and personalised microbial therapies for inflammatory bowel disease (IBD).

# Big data in IBD

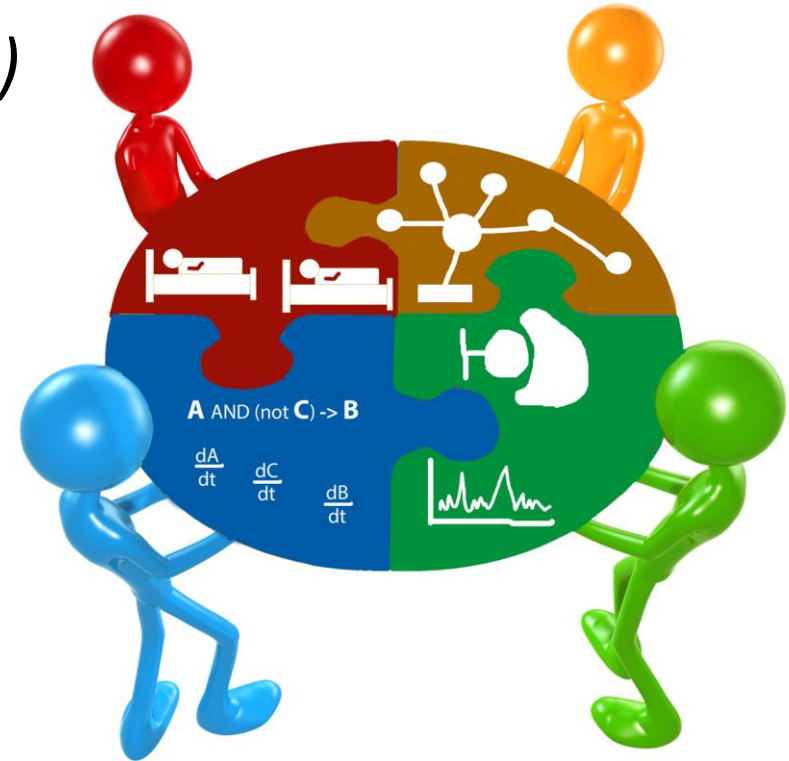


- Patient profiling
- Biomarker investigation
- Patient stratification
- Improved diagnosis
- Drug response prediction
- Improved prognosis

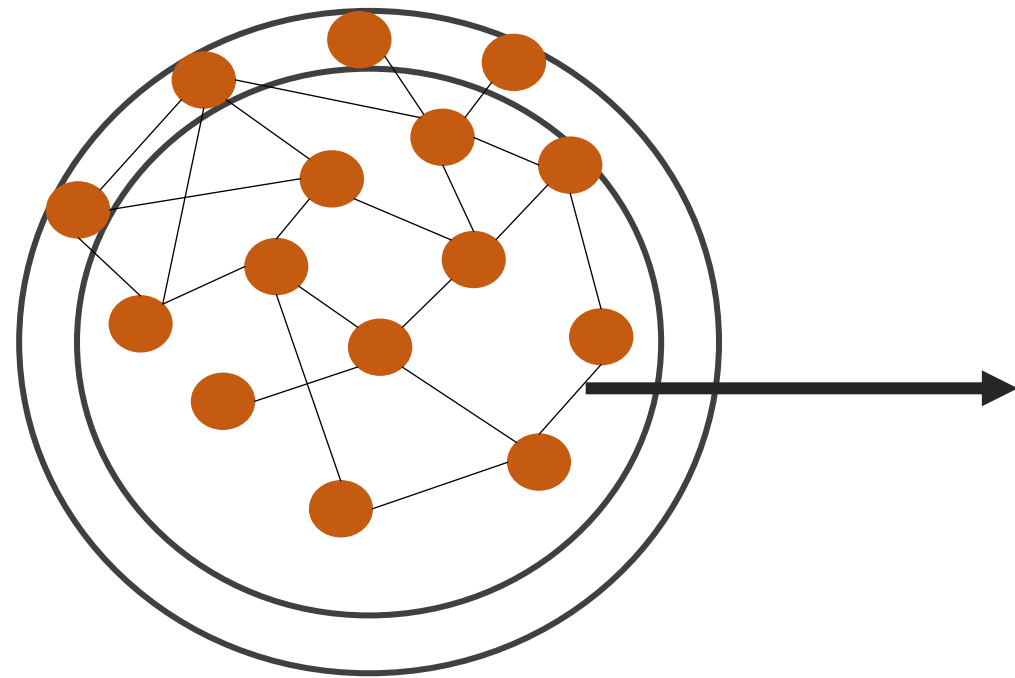


# Network medicine – a promising history

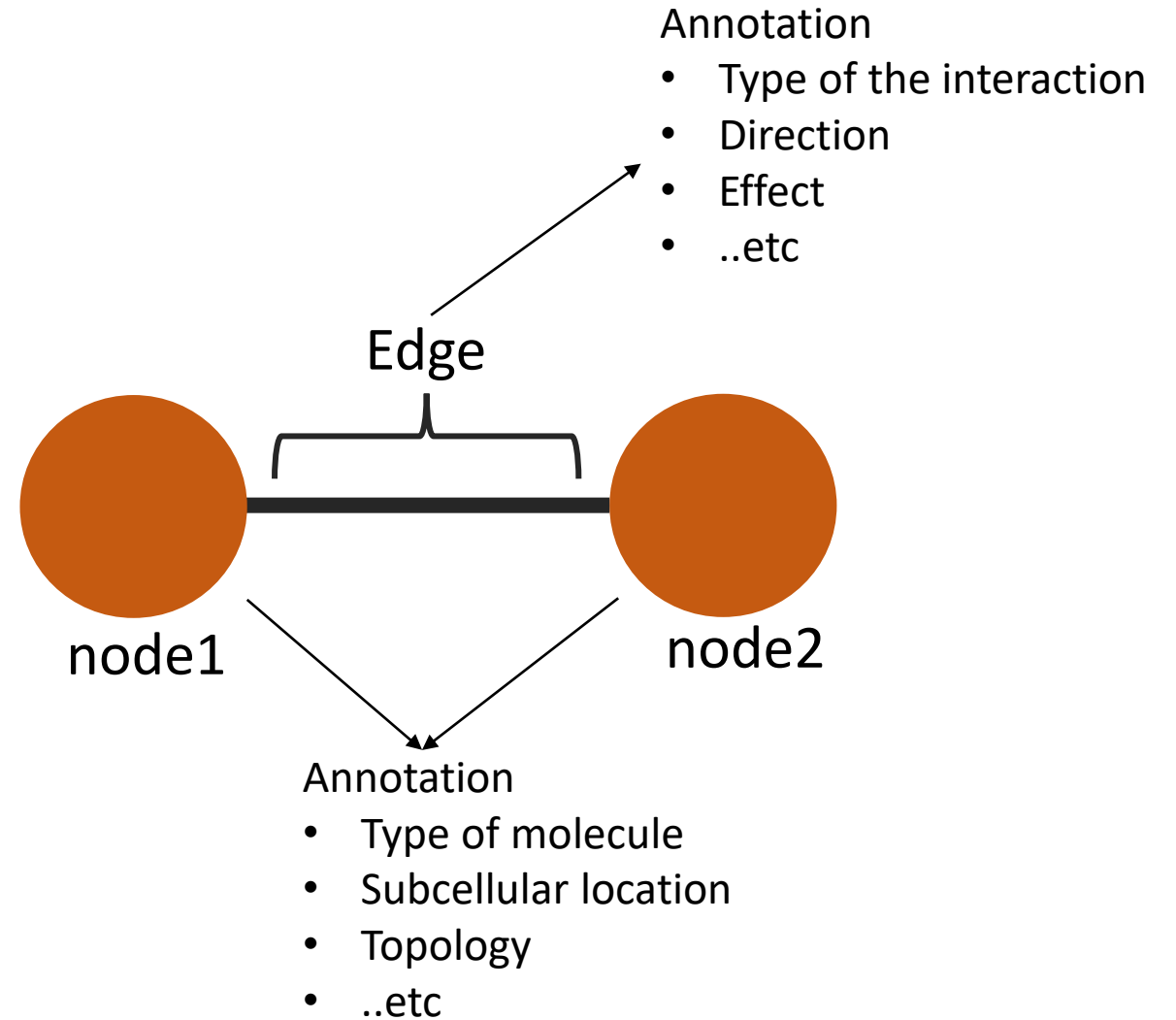
- “Network medicine” (*Barabasi, 2007*)
- “Systems medicine is finally coming of age” (*Lemberger, 2007*)
- Network as the target (*Pawson and Linding, 2008*)
- “Think globally, act locally” (*Barabasi, Loscalzo, 2011*)
- Nowadays considered as a resource for
  - biomarker discovery
  - drug target prediction
  - drug side-effect analysis
  - drug repurposing
  - suggesting new therapies
  - patient-stratification



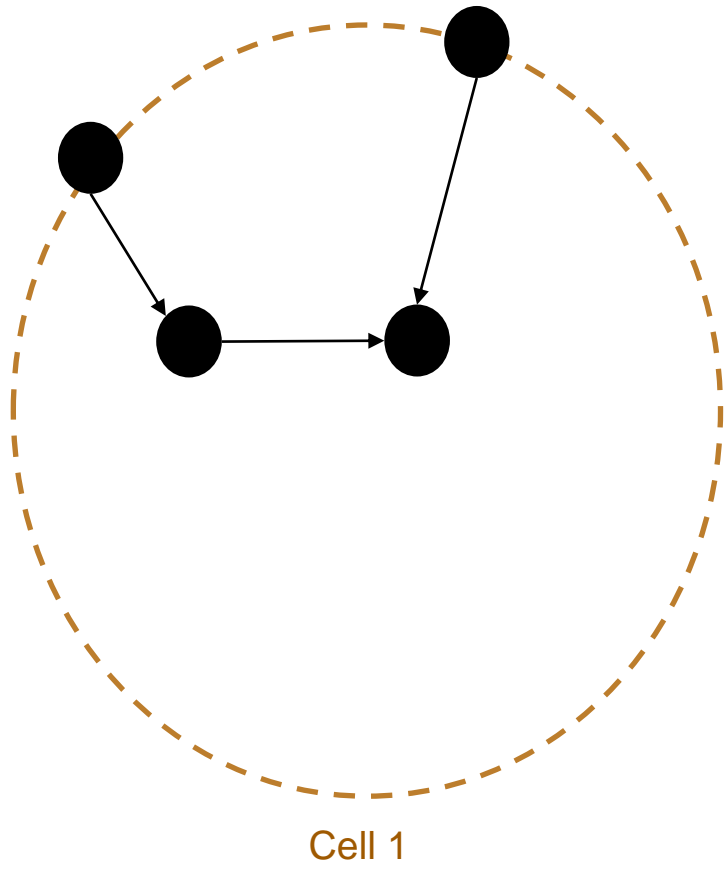
# Molecular interaction networks



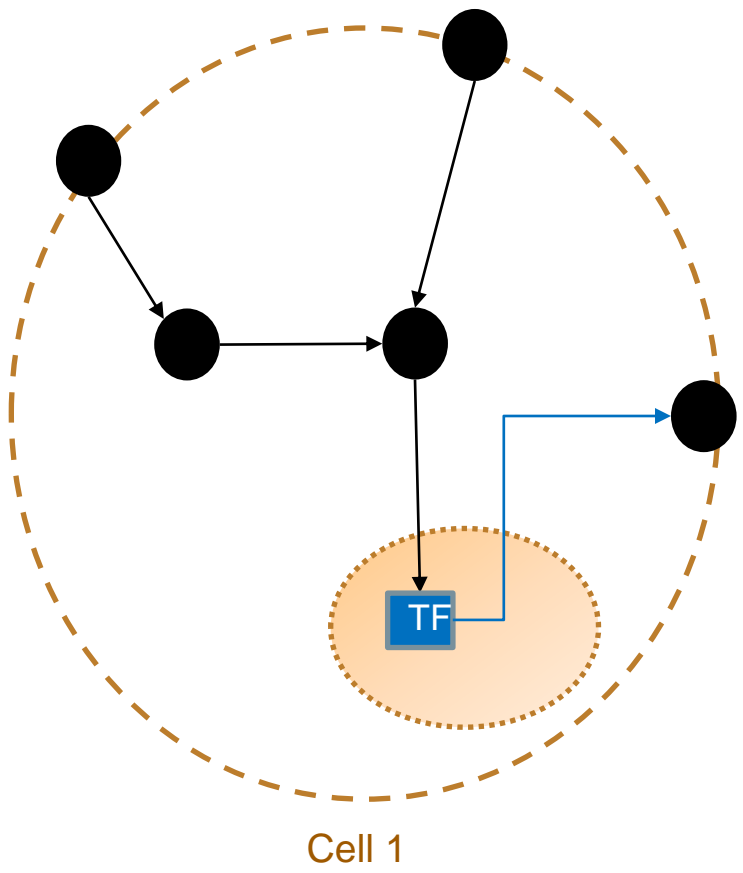
Molecular network of a cell



# Networks in IBD research



# Networks in IBD research

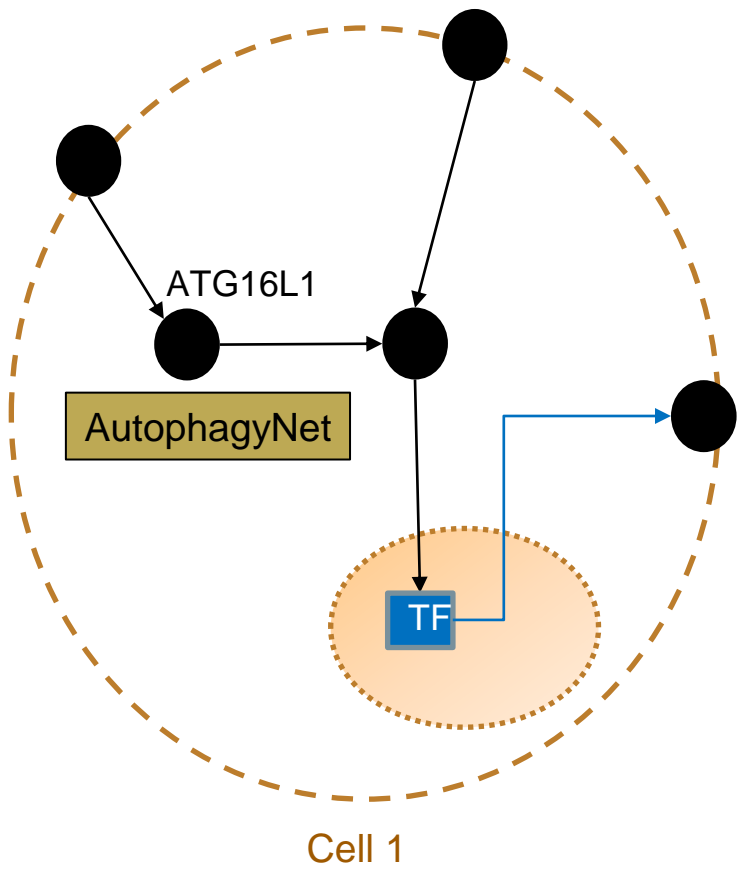


# Networks in IBD research

RESEARCH ARTICLE

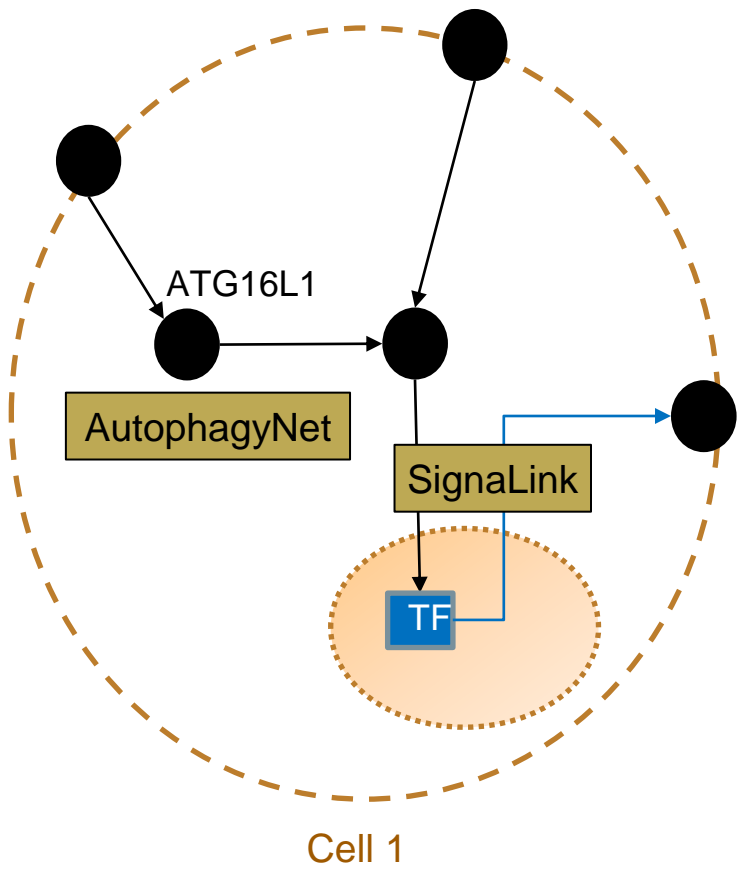
Integrative analysis of Paneth cell proteomic and transcriptomic data from intestinal organoids reveals functional processes dependent on autophagy

Emily J. Jones<sup>1,2,3,\*</sup>, Zoe J. Matthews<sup>3,\*</sup>, Lejla Gul<sup>1,\*</sup>, Padhmanand Sudhakar<sup>1,2</sup>, Agatha Treveil<sup>1,2</sup>, Devina Divekar<sup>2,3</sup>, Jasmine Buck<sup>3</sup>, Tomasz Wrzesinski<sup>1</sup>, Matthew Jefferson<sup>3</sup>, Stuart D. Armstrong<sup>4</sup>, Lindsay J. Hall<sup>2</sup>, Alastair J. M. Watson<sup>2,3</sup>, Simon R. Carding<sup>2,3</sup>, Wilfried Haerty<sup>1</sup>, Federica Di Palma<sup>1</sup>, Ulrike Mayer<sup>5</sup>, Penny P. Powell<sup>3</sup>, Isabelle Hautefort<sup>1</sup>, Tom Wileman<sup>2,3</sup> and Tamas Korcsmaros<sup>1,2,†</sup>





# Networks in IBD research



**Disease Models & Mechanisms**

**RESEARCH ARTICLE**

Integrative analysis of Paneth cell proteomic and transcriptomic data from intestinal organoids reveals functional processes dependent on autophagy

Emily J. Jones<sup>1,2,3,\*</sup>, Zoe J. Matthews<sup>3,\*</sup>, Lejla Gul<sup>1,\*</sup>, Padhmanand Sudhakar<sup>1,2</sup>, Agatha Treveil<sup>1,2</sup>, Devina Divekar<sup>2,3</sup>, Jasmine Buck<sup>3</sup>, Tomasz Wrzesinski<sup>1</sup>, Matthew Jefferson<sup>3</sup>, Stuart D. Armstrong<sup>4</sup>, Lindsay J. Hall<sup>2</sup>, Alastair J. M. Watson<sup>2,3</sup>, Simon R. Carding<sup>2,3</sup>, Wilfried Haerty<sup>1</sup>, Federica Di Palma<sup>1</sup>, Ulrike Mayer<sup>5</sup>, Penny P. Powell<sup>3</sup>, Isabelle Hautefort<sup>1</sup>, Tom Wileman<sup>2,3</sup> and Tamas Korcsmaros<sup>1,2,†</sup>

**ROYAL SOCIETY OF CHEMISTRY**

**Molecular Omics**

**RESEARCH ARTICLE** [View Article Online](#)  
[View Journal](#)

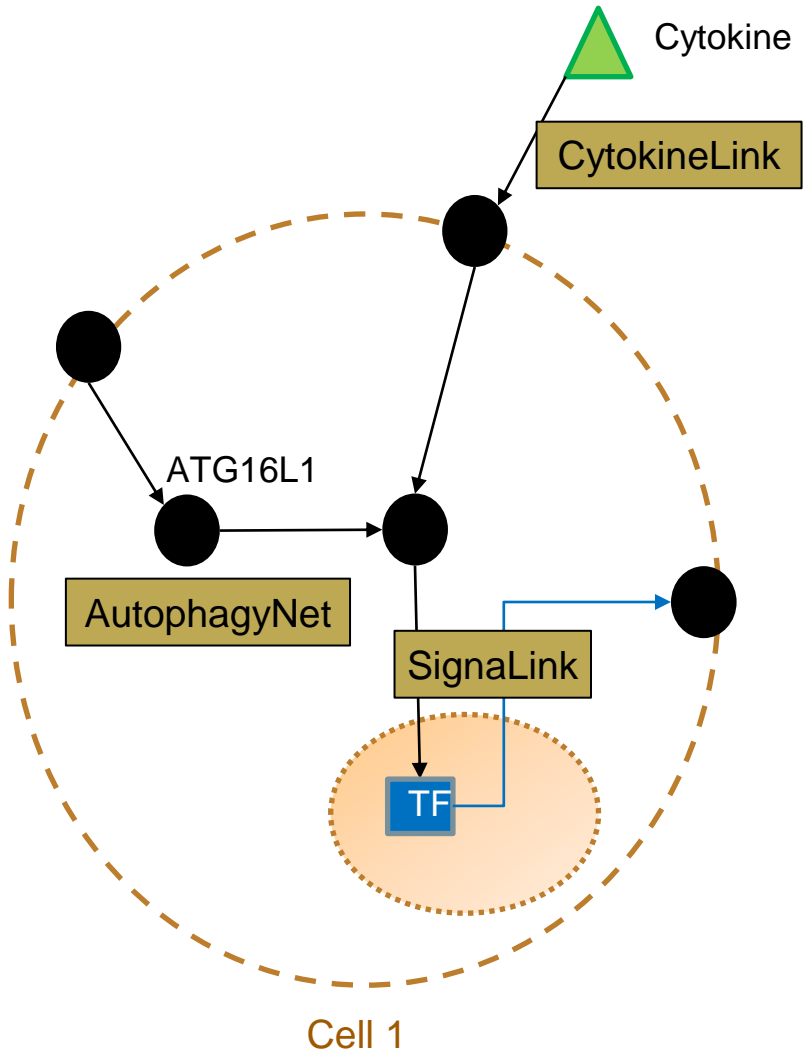
[Check for updates](#)

Cite this: DOI:10.1039/c9mo00130a

**Regulatory network analysis of Paneth cell and goblet cell enriched gut organoids using transcriptomics approaches†**

A. Treveil,<sup>‡</sup> P. Sudhakar,<sup>‡</sup> Z. J. Matthews,<sup>‡</sup> T. Wrzesinski,<sup>‡</sup> E. J. Jones,<sup>ab</sup> J. Brooks,<sup>abde</sup> M. Ölbei,<sup>ab</sup> I. Hautefort,<sup>a</sup> L. J. Hall,<sup>b</sup> S. R. Carding,<sup>bd</sup> U. Mayer,<sup>f</sup> P. P. Powell,<sup>d</sup> T. Wileman,<sup>bd</sup> F. Di Palma,<sup>a</sup> W. Haerty<sup>\*a</sup> and T. Korcsmáros<sup>‡\*ab</sup>

# Networks in IBD research



RESEARCH ARTICLE



Integrative analysis of Paneth cell proteomic and transcriptomic data from intestinal organoids reveals functional processes dependent on autophagy

Emily J. Jones<sup>1,2,3,\*</sup>, Zoe J. Matthews<sup>3,\*</sup>, Lejla Gul<sup>1,\*</sup>, Padhmanand Sudhakar<sup>1,2</sup>, Agatha Treveil<sup>1,2</sup>, Devina Divekar<sup>2,3</sup>, Jasmine Buck<sup>3</sup>, Tomasz Wrzesinski<sup>1</sup>, Matthew Jefferson<sup>3</sup>, Stuart D. Armstrong<sup>4</sup>, Lindsay J. Hall<sup>2</sup>, Alastair J. M. Watson<sup>2,3</sup>, Simon R. Carding<sup>2,3</sup>, Wilfried Haerty<sup>1</sup>, Federica Di Palma<sup>1</sup>, Ulrike Mayer<sup>5</sup>, Penny P. Powell<sup>3</sup>, Isabelle Hautefort<sup>1</sup>, Tom Wileman<sup>2,3</sup> and Tamas Korcsmaros<sup>1,2,†</sup>

Molecular Omics



RESEARCH ARTICLE

View Article Online  
View Journal

Check for updates

Cite this: DOI:10.1039/c9mo00130a

Regulatory network analysis of Paneth cell and goblet cell enriched gut organoids using transcriptomics approaches†

A. Treveil,<sup>‡</sup> P. Sudhakar,<sup>‡</sup> Z. J. Matthews,<sup>‡</sup> T. Wrzesinski,<sup>‡</sup> E. J. Jones,<sup>ab</sup> J. Brooks,<sup>abde</sup> M. Ötbei,<sup>ab</sup> I. Hautefort,<sup>a</sup> L. J. Hall,<sup>b</sup> S. R. Carding,<sup>bd</sup> U. Mayer,<sup>f</sup> P. P. Powell,<sup>d</sup> T. Wileman,<sup>bd</sup> F. Di Palma,<sup>a</sup> W. Haerty<sup>ga</sup> and T. Korcsmáros<sup>gab</sup>

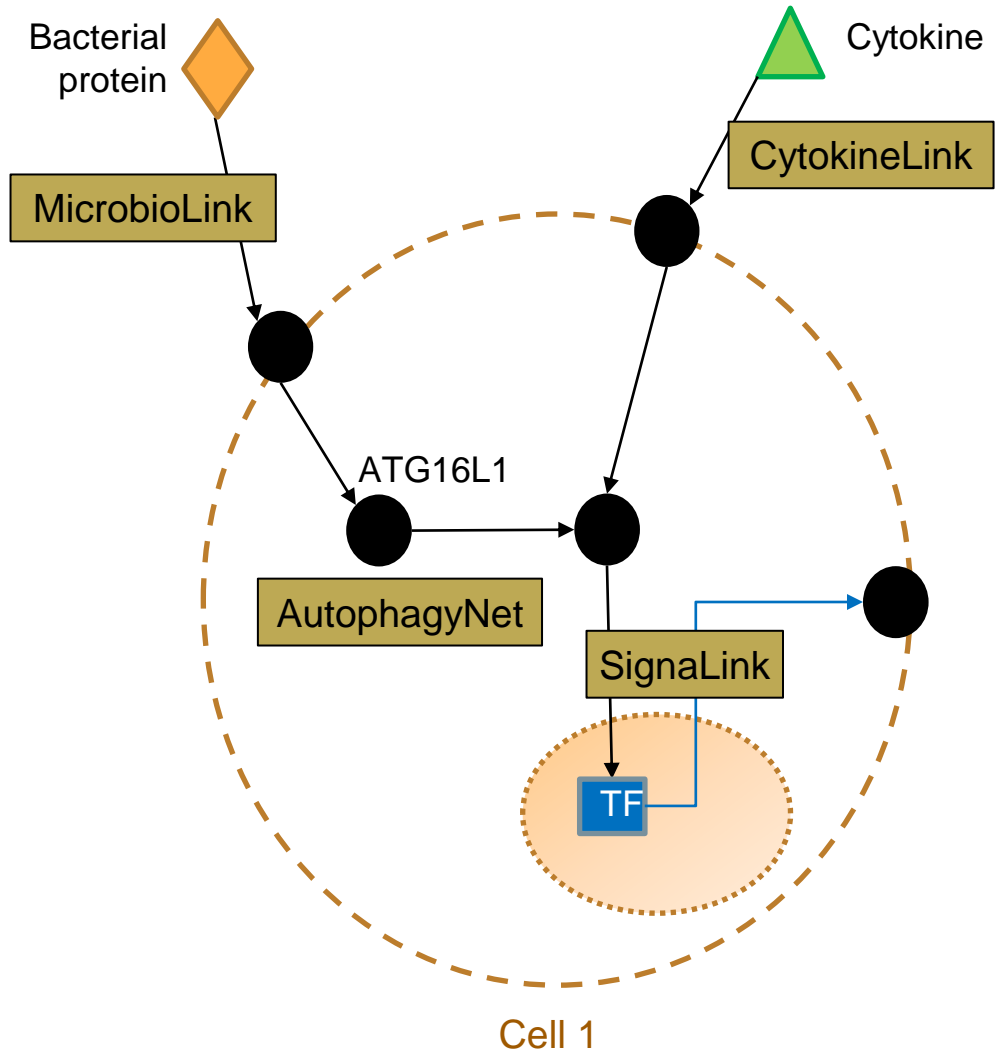
CellPress

Sneak Peek  
A PREVIEW OF PAPERS UNDER REVIEW

Cell Reports

Cytokine Responsive Networks in Human Colonic Epithelial Organoids Unveil a Novel Molecular Stratification of Inflammatory Bowel Disease

# Networks in IBD research



**RESEARCH ARTICLE**  Disease Models & Mechanisms

Integrative analysis of Paneth cell proteomic and transcriptomic data from intestinal organoids reveals functional processes dependent on autophagy

Emily J. Jones<sup>1,2,3,\*</sup>, Zoe J. Matthews<sup>3,\*</sup>, Lejla Gul<sup>1,\*</sup>, Padhmanand Sudhakar<sup>1,2</sup>, Agatha Treveil<sup>1,2</sup>, Devina Divekar<sup>2,3</sup>, Jasmine Buck<sup>3</sup>, Tomasz Wrzesinski<sup>1</sup>, Matthew Jefferson<sup>3</sup>, Stuart D. Armstrong<sup>4</sup>, Lindsay J. Hall<sup>2</sup>, Alastair J. M. Watson<sup>2,3</sup>, Simon R. Carding<sup>2,3</sup>, Wilfried Haerty<sup>1</sup>, Federica Di Palma<sup>1</sup>, Ulrike Mayer<sup>5</sup>, Penny P. Powell<sup>3</sup>, Isabelle Hautefort<sup>1</sup>, Tom Wileman<sup>2,3</sup> and Tamas Korcsmaros<sup>1,2,†</sup>

**Molecular Omics**  ROYAL SOCIETY OF CHEMISTRY

**RESEARCH ARTICLE** [View Article Online](#)  
[View Journal](#)

[Check for updates](#)

Cite this: DOI:10.1039/c9mo00130a

**Regulatory network analysis of Paneth cell and goblet cell enriched gut organoids using transcriptomics approaches†**

A. Treveil,<sup>‡</sup> P. Sudhakar,<sup>‡</sup> Z. J. Matthews,<sup>‡</sup> T. Wrzesinski,<sup>‡</sup> E. J. Jones,<sup>ab</sup> J. Brooks,<sup>abde</sup> M. Ötbei,<sup>ab</sup> I. Hautefort,<sup>a</sup> L. J. Hall,<sup>b</sup> S. R. Carding,<sup>bd</sup> U. Mayer,<sup>f</sup> P. P. Powell,<sup>d</sup> T. Wileman,<sup>bd</sup> F. Di Palma,<sup>a</sup> W. Haerty<sup>ga</sup> and T. Korcsmáros<sup>gab</sup>

**CellPress** **Sneak Peek** **Cell Reports**  
A PREVIEW OF PAPERS UNDER REVIEW

**Cytokine Responsive Networks in Human Colonic Epithelial Organoids Unveil a Novel Molecular Stratification of Inflammatory Bowel Disease**

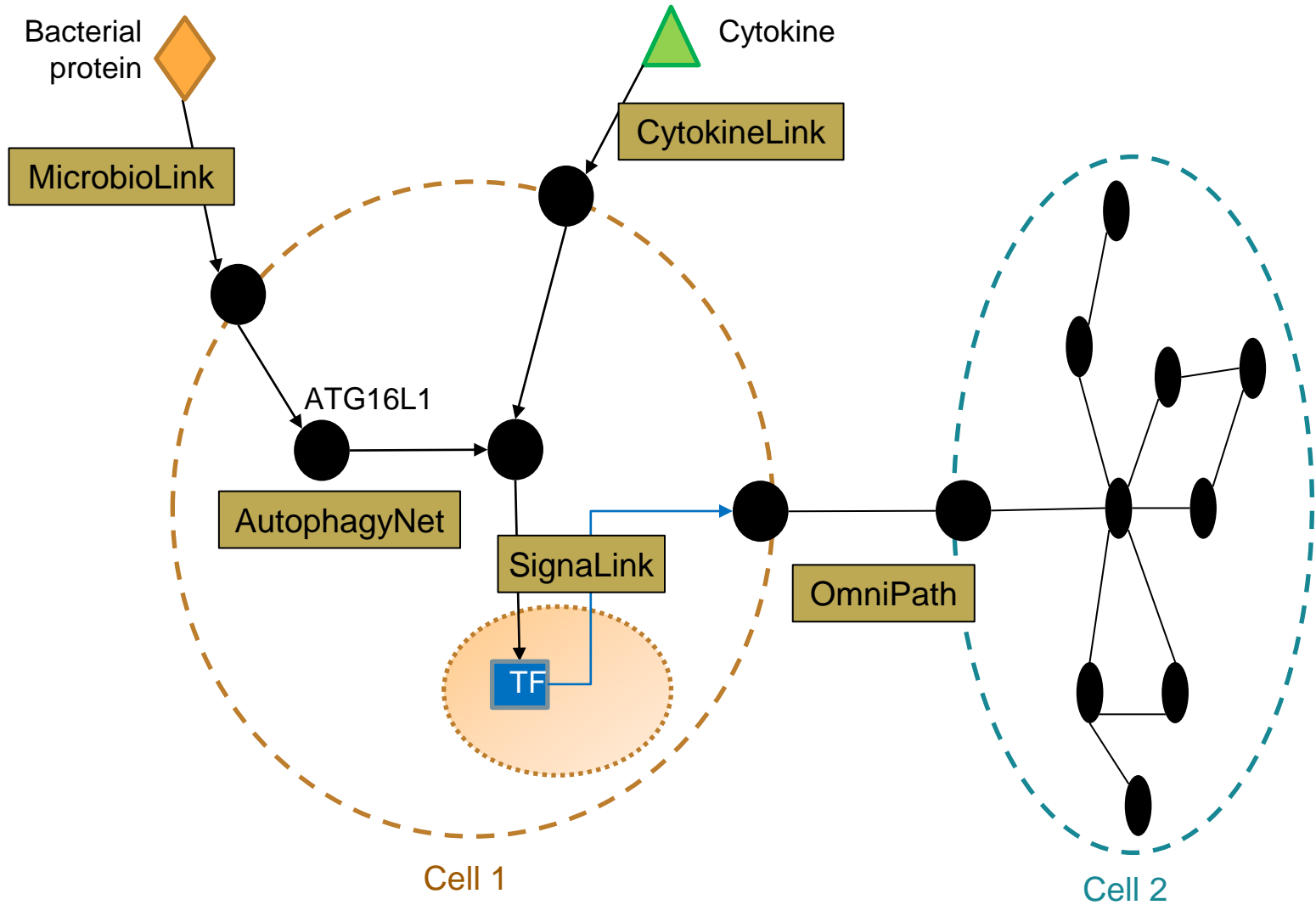
**iScience**  CellPress  
OPEN ACCESS

**Article**

Integrated analysis of microbe-host interactions in Crohn's disease reveals potential mechanisms of microbial proteins on host gene expression

Padhmanand Sudhakar,<sup>1,4,\*</sup> Tahila Andrighetti,<sup>2</sup> Sare Verstockt,<sup>1</sup> Clara Caenepeel,<sup>1,3</sup> Marc Ferrante,<sup>1,3</sup> João Sabino,<sup>1,3</sup> Bram Verstockt,<sup>1,3</sup> and Severine Vermeire<sup>1,3</sup>

# Networks in IBD research



RESEARCH ARTICLE



Integrative analysis of Paneth cell proteomic and transcriptomic data from intestinal organoids reveals functional processes dependent on autophagy

Emily J. Jones<sup>1,2,3,\*</sup>, Zoe J. Matthews<sup>3,\*</sup>, Lejla Gul<sup>1,\*</sup>, Padhmanand Sudhakar<sup>1,2</sup>, Agatha Treveil<sup>1,2</sup>, Devina Divekar<sup>2,3</sup>, Jasmine Buck<sup>3</sup>, Tomasz Wrzesinski<sup>1</sup>, Matthew Jefferson<sup>3</sup>, Stuart D. Armstrong<sup>4</sup>, Lindsay J. Hall<sup>2</sup>, Alastair J. M. Watson<sup>2,3</sup>, Simon R. Carding<sup>2,3</sup>, Wilfried Haerty<sup>1</sup>, Federica Di Palma<sup>1</sup>, Ulrike Mayer<sup>5</sup>, Penny P. Powell<sup>3</sup>, Isabelle Hautefort<sup>1</sup>, Tom Wileman<sup>2,3</sup> and Tamas Korcsmaros<sup>1,2,†</sup>

Molecular Omics



RESEARCH ARTICLE

View Article Online  
View Journal

Check for updates

Cite this: DOI:10.1039/c9mo00130a

Regulatory network analysis of Paneth cell and goblet cell enriched gut organoids using transcriptomics approaches†

A. Treveil,<sup>‡</sup> P. Sudhakar,<sup>‡</sup> Z. J. Matthews,<sup>‡</sup> T. Wrzesinski,<sup>‡</sup> E. J. Jones,<sup>ab</sup> J. Brooks,<sup>abde</sup> M. Ölbei,<sup>ab</sup> I. Hautefort,<sup>a</sup> L. J. Hall,<sup>b</sup> S. R. Carding,<sup>bd</sup> U. Mayer,<sup>f</sup> P. P. Powell,<sup>d</sup> T. Wileman,<sup>bd</sup> F. Di Palma,<sup>a</sup> W. Haerty<sup>ga</sup> and T. Korcsmaros<sup>gab</sup>

CellPress

Sneak Peek  
A PREVIEW OF PAPERS UNDER REVIEW

Cell Reports

Cytokine Responsive Networks in Human Colonic Epithelial Organoids Unveil a Novel Molecular Stratification of Inflammatory Bowel Disease

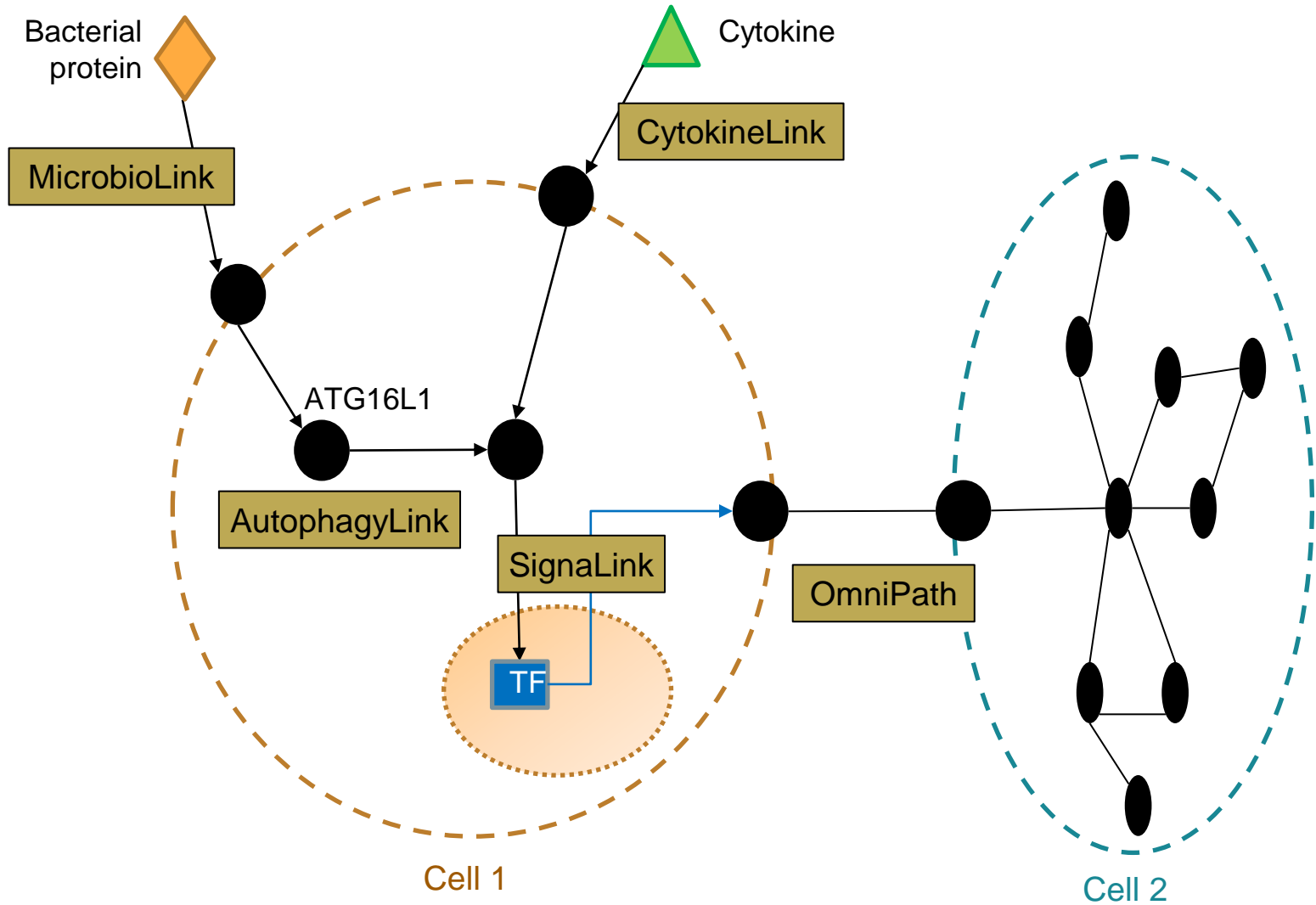
iScience

CellPress  
OPEN ACCESS

Article  
Integrated analysis of microbe-host interactions in Crohn's disease reveals potential mechanisms of microbial proteins on host gene expression

Padhmanand Sudhakar,<sup>1,4,\*</sup> Tahila Andrighetti,<sup>2</sup> Sare Verstockt,<sup>1</sup> Clara Caenepeel,<sup>1,3</sup> Marc Ferrante,<sup>1,3</sup> João Sabino,<sup>1,3</sup> Bram Verstockt,<sup>1,3</sup> and Severine Vermeire<sup>1,3</sup>

# Networks in IBD research



IBD patients have various sets of SNPs affecting different or overlapping sets of proteins, pathways or cells

Can we use network approaches to stratify IBD patients?

frontiers in Genetics

published: 21 October 2021  
doi: 10.3389/fgene.2021.760501

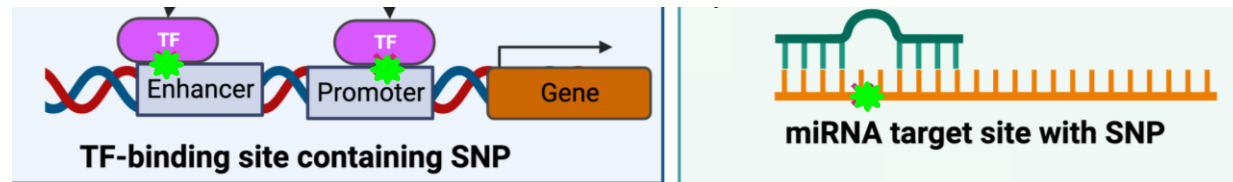
REVIEW  
Check for updates

### Network Biology Approaches to Achieve Precision Medicine in Inflammatory Bowel Disease

John P Thomas<sup>1,2,3</sup>, Dezso Modos<sup>1,2</sup>, Tamas Korcsmaros<sup>1,2\*</sup> and Johanne Brooks-Warburton<sup>4,5</sup>

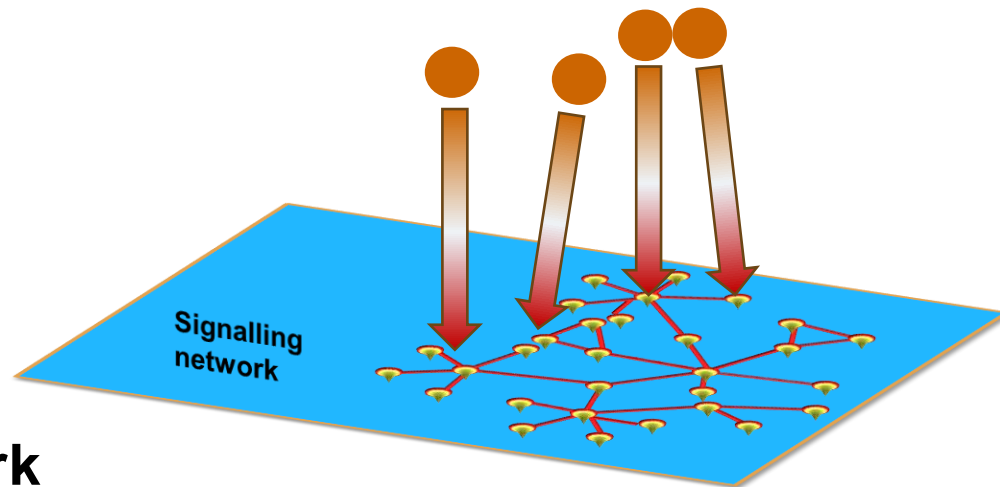


# ★ SNPs from IBD GWAS



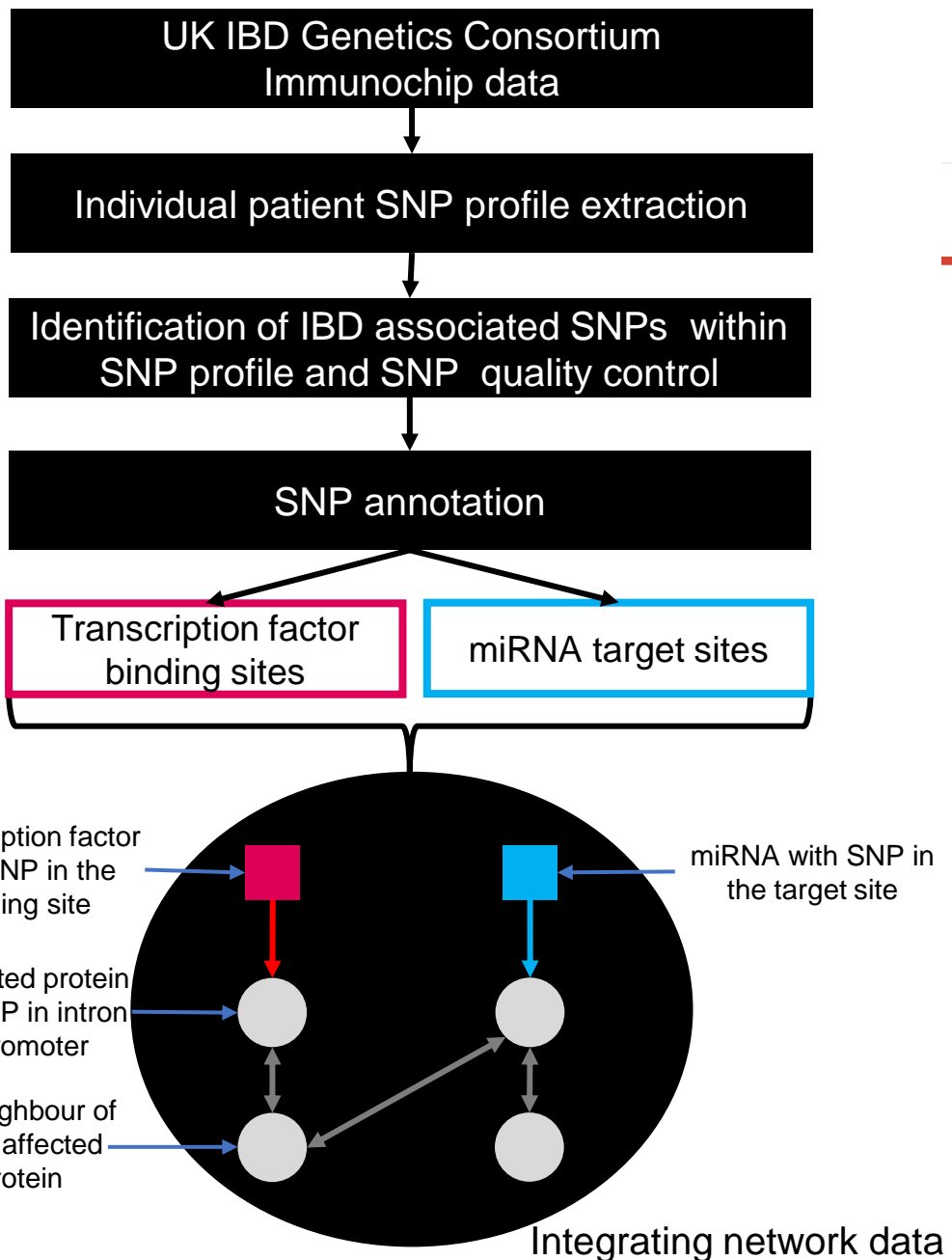
IBD patient cohort

*A priori* network  
interaction information



# Integrated SNP (iSNP) pipeline

Brooks et al, *Nature Communications*, 2022  
Korcsmaros et al, *PCT patent application*, 2019



## nature communications

[Explore content](#) ▾ [About the journal](#) ▾ [Publish with us](#) ▾

[nature](#) > [nature communications](#) > [articles](#) > [article](#)

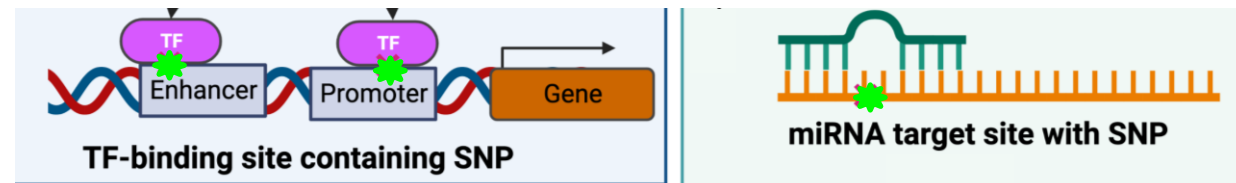
Article | [Open access](#) | [Published: 28 April 2022](#)

### A systems genomics approach to uncover patient-specific pathogenic pathways and proteins in ulcerative colitis

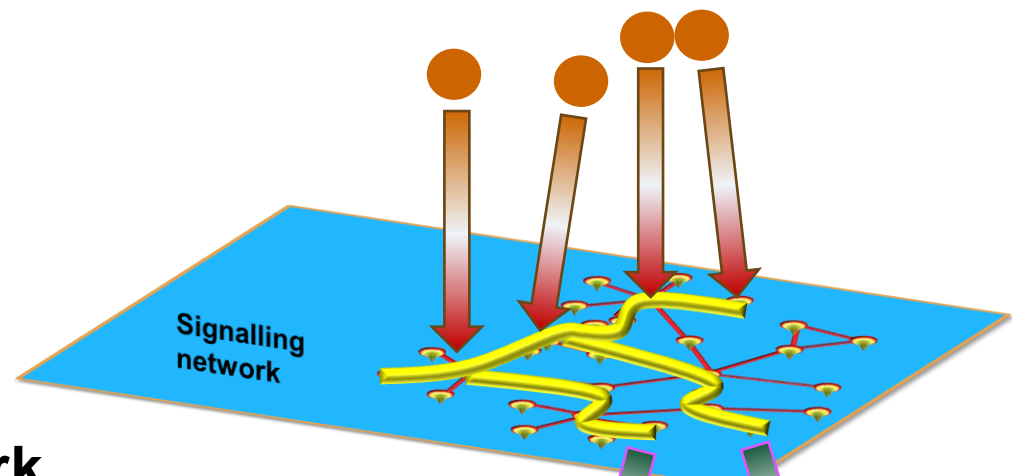
[Johanne Brooks-Warburton](#), [Dezso Modos](#), [Padhmanand Sudhakar](#), [Matthew Madgwick](#), [John P. Thomas](#), [Balazs Bohar](#), [David Fazekas](#), [Azedine Zoufir](#), [Orsolya Kapuy](#), [Mate Szalay-Beko](#), [Bram Verstockt](#), [Lindsay J. Hall](#), [Alastair Watson](#), [Mark Tremelling](#), [Miles Parkes](#), [Severine Vermeire](#), [Andreas Bender](#), [Simon R. Carding](#) ✉ & [Tamas Korcsmaros](#) ✉

[Nature Communications](#) **13**, Article number: 2299 (2022) | [Cite this article](#)

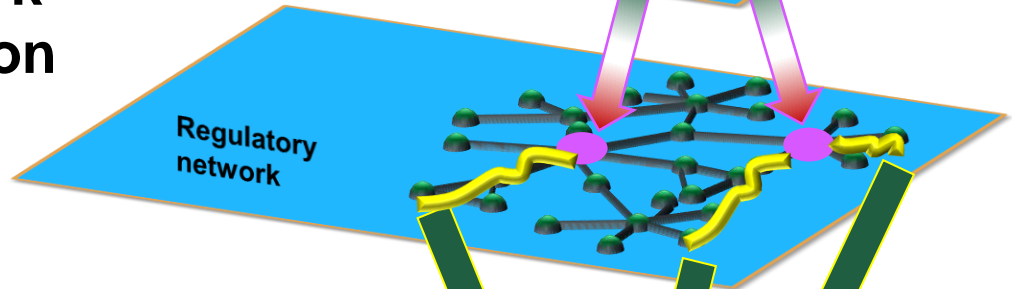
# SNPs from IBD GWAS



SNP affected gene



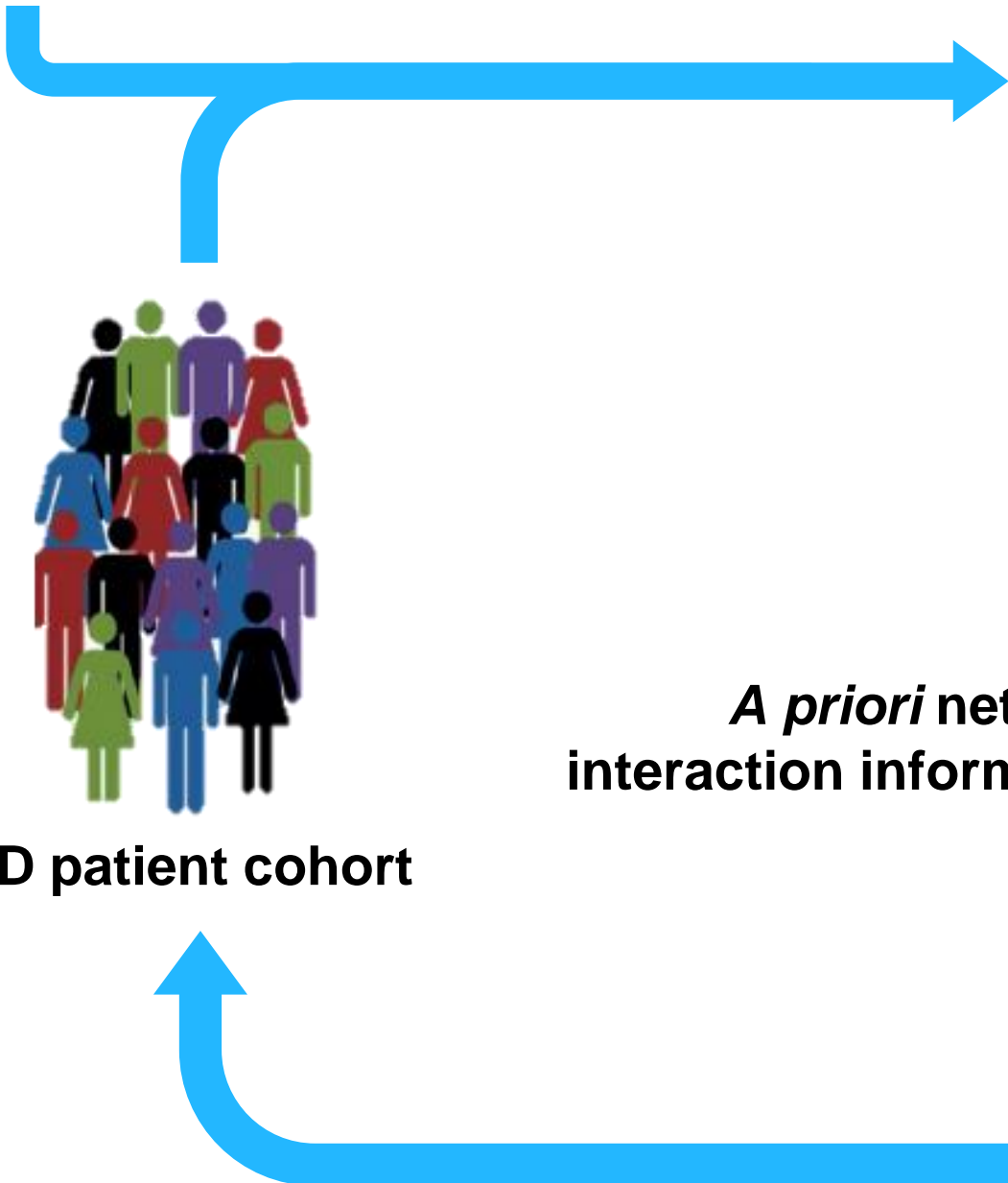
*A priori* network interaction information



Predicted transcriptionally affected genes



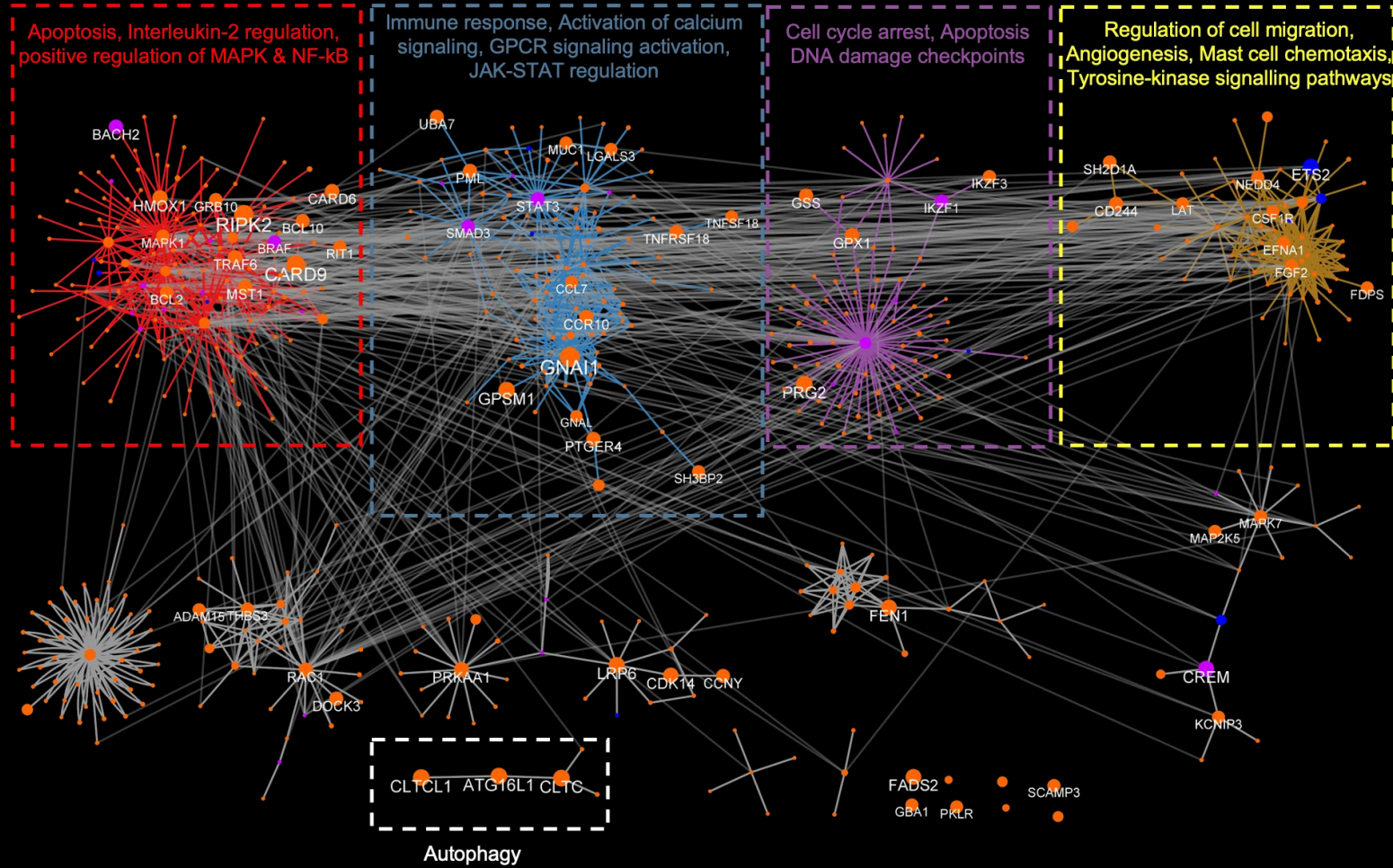
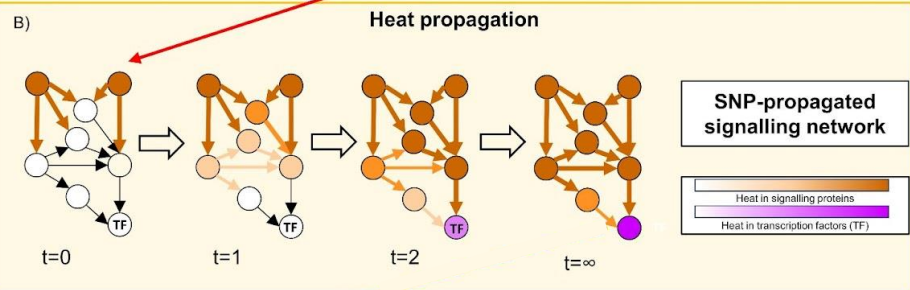
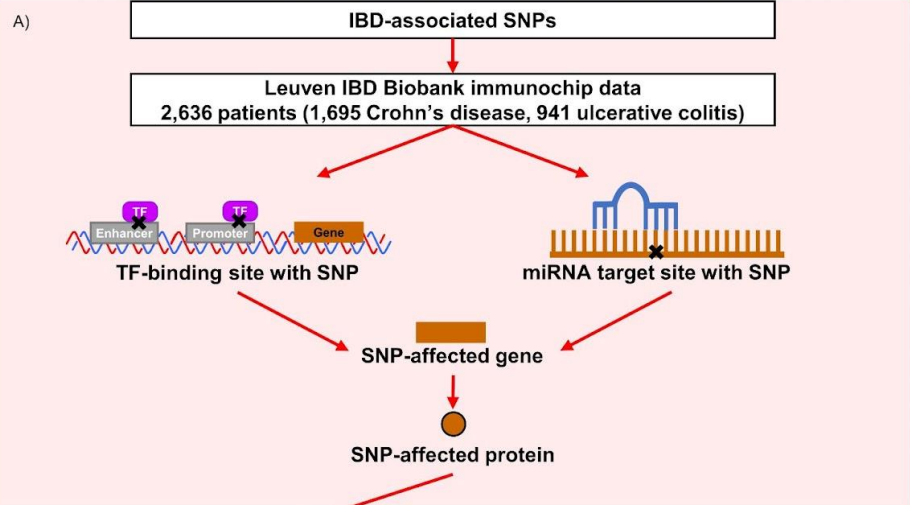
IBD patient cohort



# iSNP2 pipeline

# Impact of CD non-coding SNPs on signalling

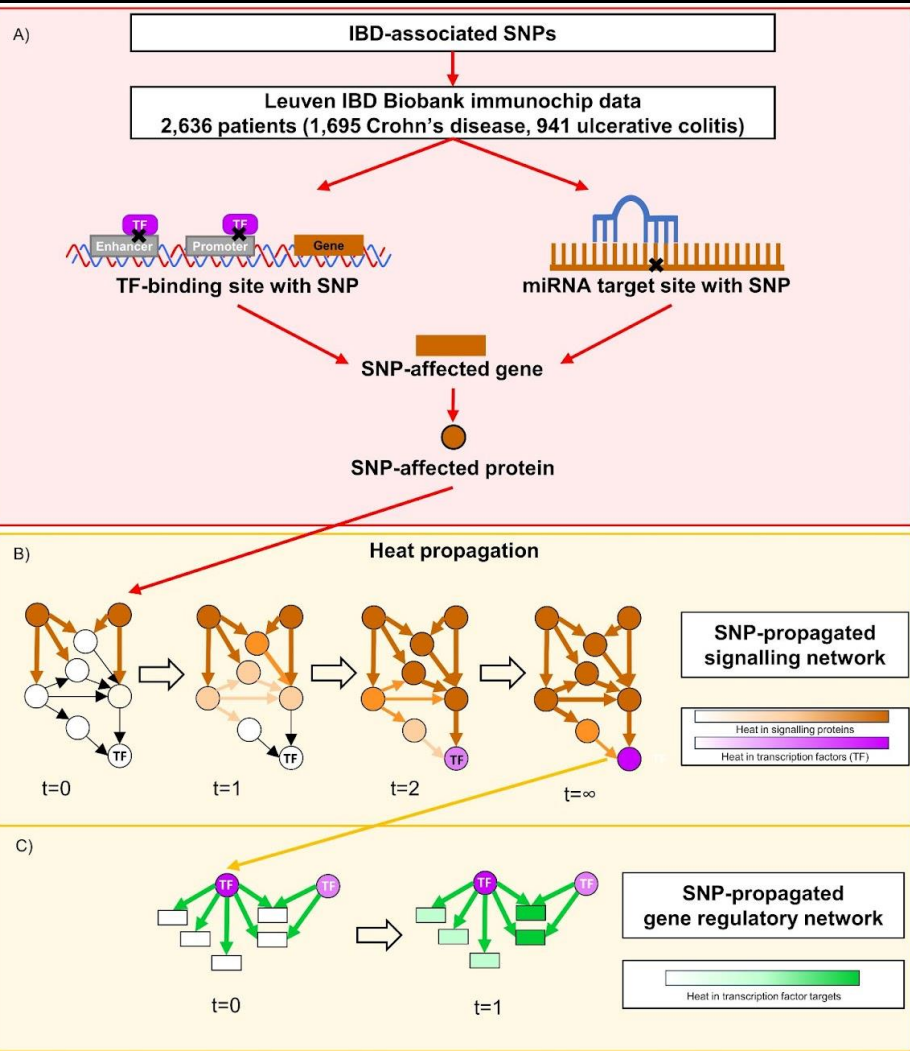
## Convergence on cell cycle and apoptosis



● Signalling protein   ● Transcription factor   ● Transcription factor which is also a target gene   ⊙ % of affected patients

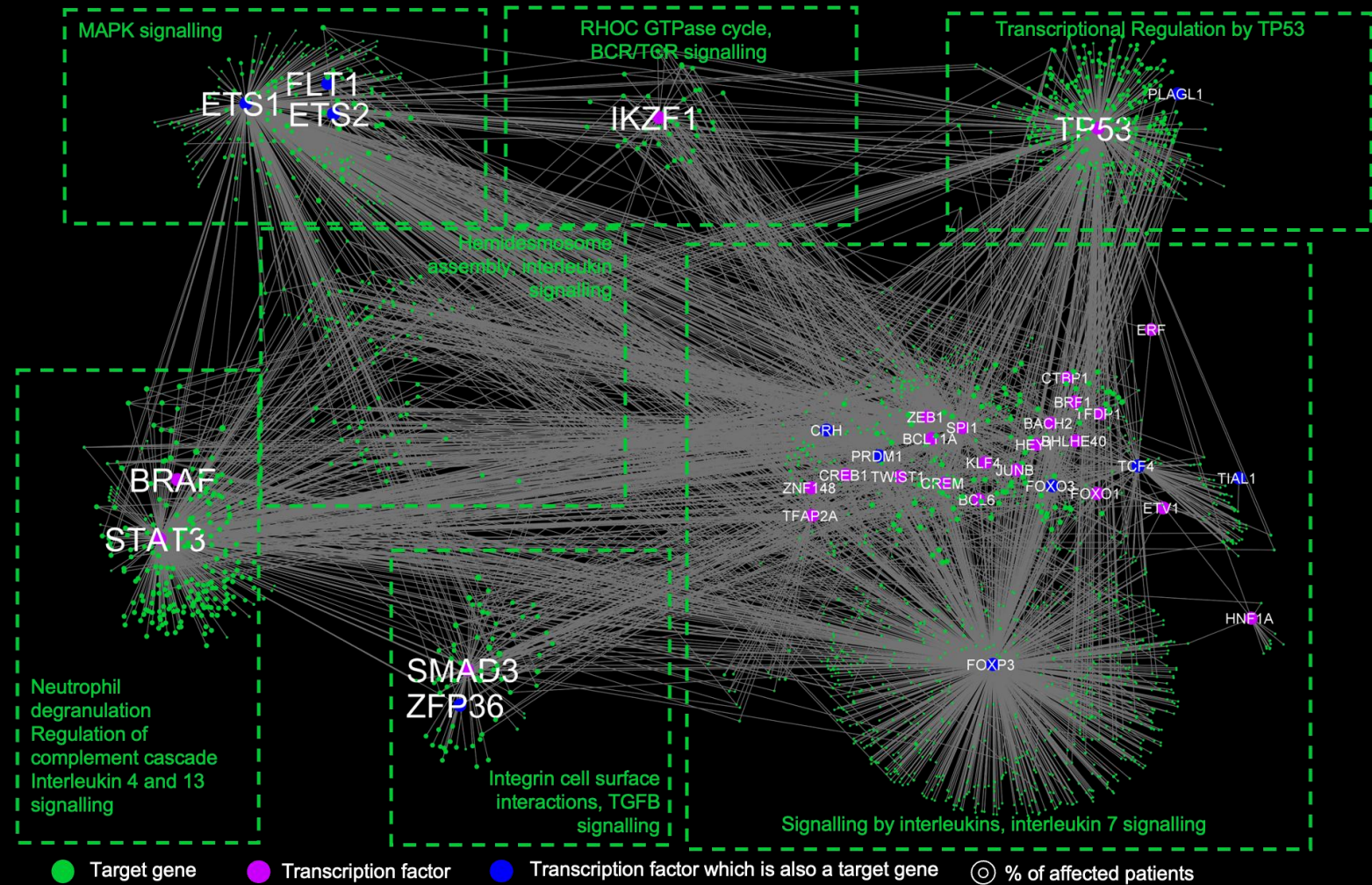


# iSNP2 pipeline



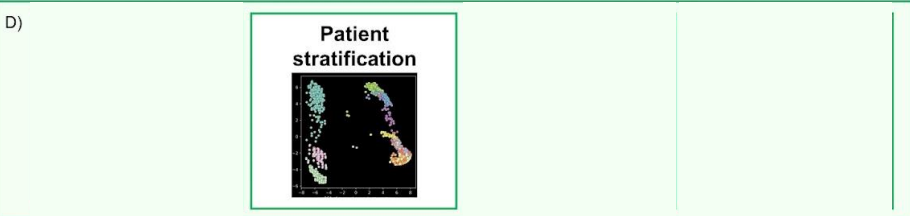
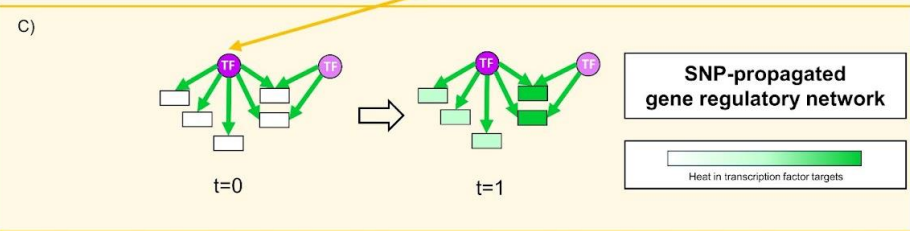
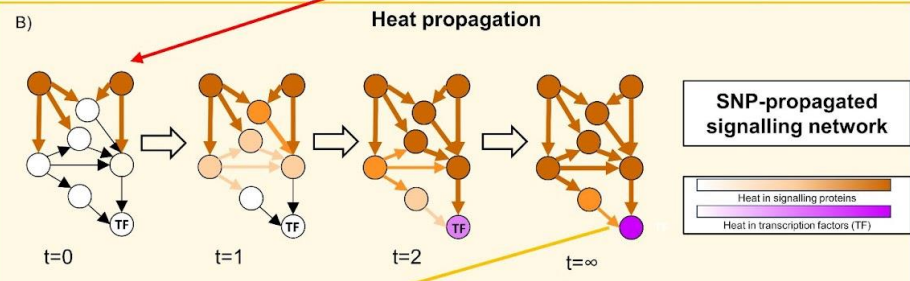
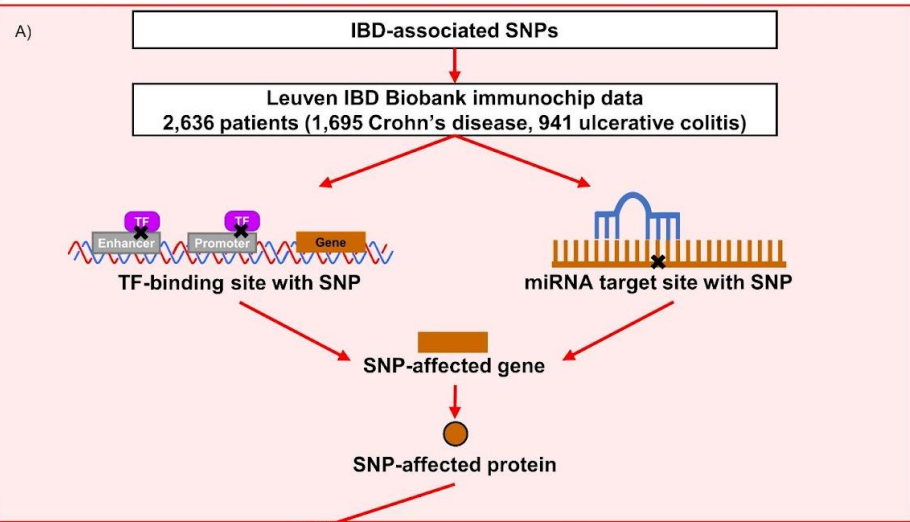
# Impact of CD non-coding SNPs on gene regulation

## Convergence on key transcription factors



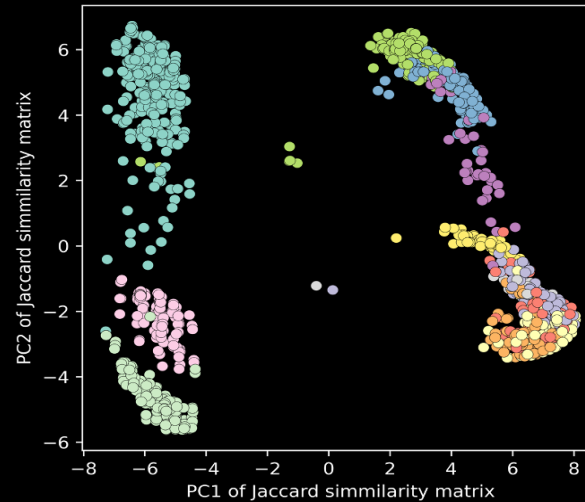


# iSNP2 pipeline



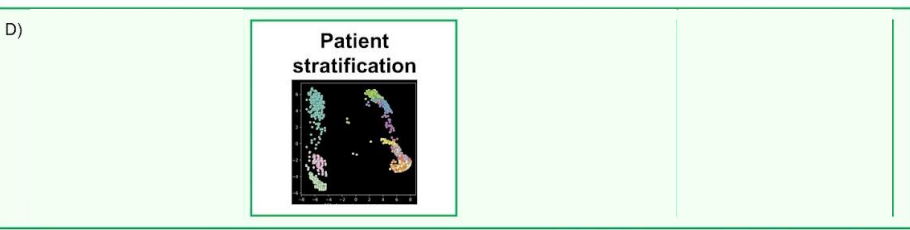
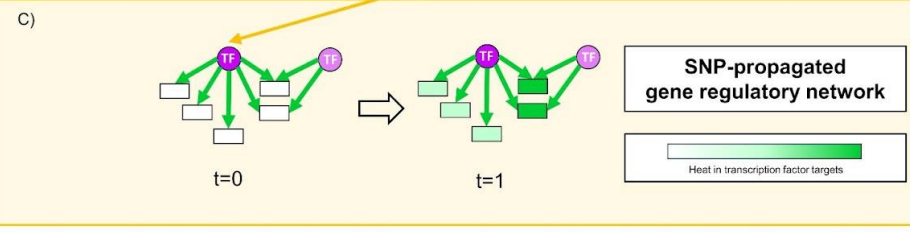
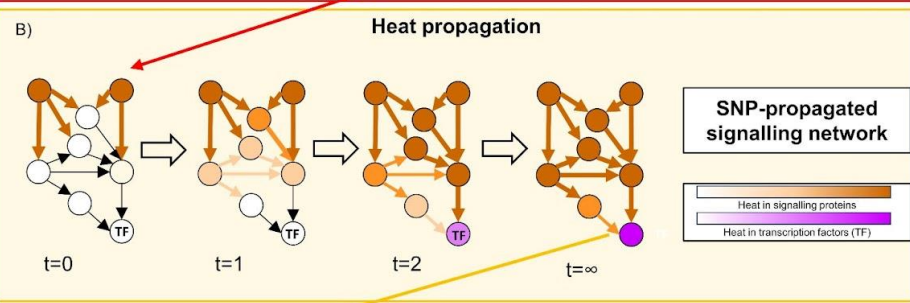
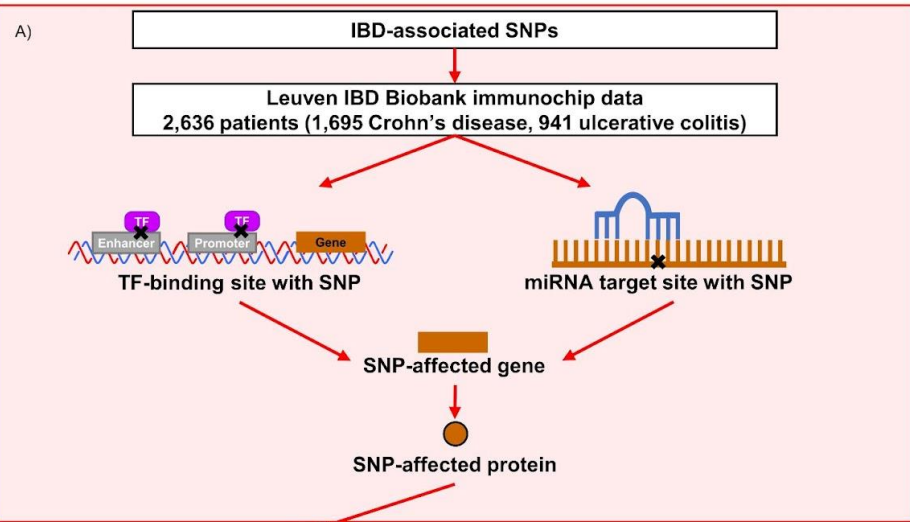
# SNP-propagated gene regulatory networks capture disease heterogeneity in CD

Patient cluster	1	2	3	4	5	6	7	8	9	10	11	12
Number of patients	119	60	376	333	106	43	142	124	37	116	101	138
Main transcription factors	ETS1, ETS2, FTL1	STAT3, ETS1, ETS2, FLT1	Various TFs, low number of targets	TP53	STAT3	STAT3, TP53	Various TFs, high number of targets	STAT3, TP53	STAT3	STAT3, IKZF1	STAT3, SMAD3, ZFP36	STAT3, SMAD3, ZFP36



Patient cluster	1	2	3	4	5	6	7	8	9	10	11	12
Number of patients	119	60	376	333	106	43	142	124	37	116	101	138
ETS1	Green	Green	Black	Black	Black	Black	Green	Black	Black	Black	Black	Black
ETS2	Green	Green	Black	Black	Black	Black	Green	Black	Black	Black	Black	Black
FLT1	Green	Green	Black	Black	Black	Black	Green	Black	Black	Black	Black	Black
STAT3	Black	Green	Black	Black	Green	Green	Green	Green	Green	Green	Green	Green
TP53	Black	Black	Black	Green	Black	Green	Green	Green	Black	Black	Black	Black
IKZF1	Black	Black	Black	Black	Black	Black	Green	Black	Black	Green	Black	Black
SMAD3	Black	Black	Black	Black	Black	Black	Green	Black	Black	Black	Green	Black
ZFP36	Black	Black	Black	Black	Black	Black	Green	Black	Black	Black	Green	Black

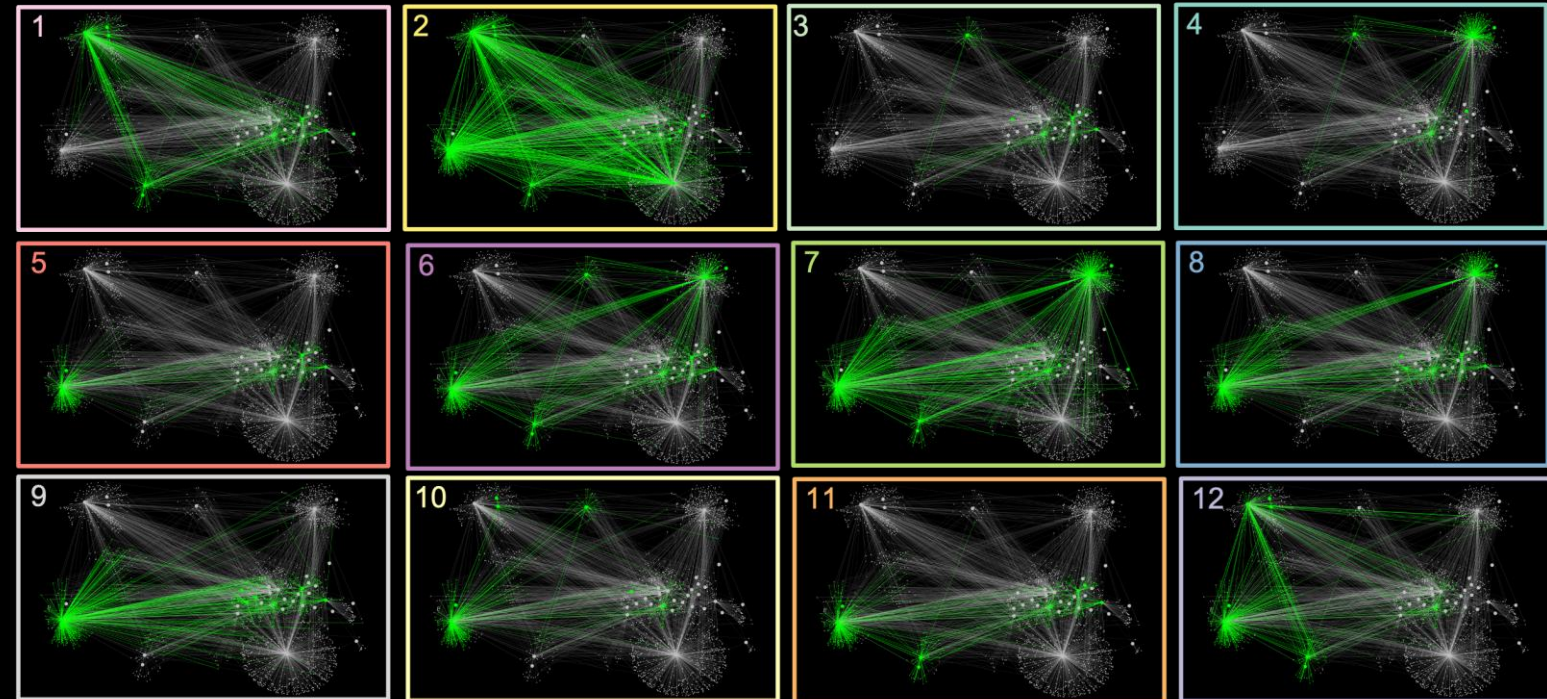
# iSNP2 pipeline



# SNP-propagated GRNs capture disease heterogeneity in CD

Patient cluster	1	2	3	4	5	6	7	8	9	10	11	12
Number of patients	119	60	376	333	106	43	142	124	37	116	101	138
Main transcription factors	ETS1, ETS2, FTL1	STAT3, ETS1, ETS2, FLT1	Various TFs, low number of targets	TP53	STAT3	STAT3, TP53	Various TFs, high number of targets	STAT3, TP53	STAT3	STAT3, IKZF1	STAT3, SMAD3, ZFP36	STAT3, SMAD3, ZFP36

## ETS1/ETS2



## STAT3

## SMAD3



# Summary and next steps

- **Many IBD-associated SNPs have regulatory effects** ➤ **TaMMA**
- **The SNP-set (SNP co-occurrence) is more relevant marker than a single SNP**
- **Including downstream potentially effected processes increases the opportunity to stratify patients** ➤ **sciBD**
- **Aggregated data, randomised trials could miss key signals in complex diseases** ➤ **UK IBD BioResource**
- **To assess the power of iSNP and other network approaches the combination of omics data and clinical metadata is necessary**
- **Patient-type specific changes in host-microbe interactions?** ➤ **RESPONSE**



# Network Medicine in IBD – what is needed from hype to success

- **Higher complexity datasets**

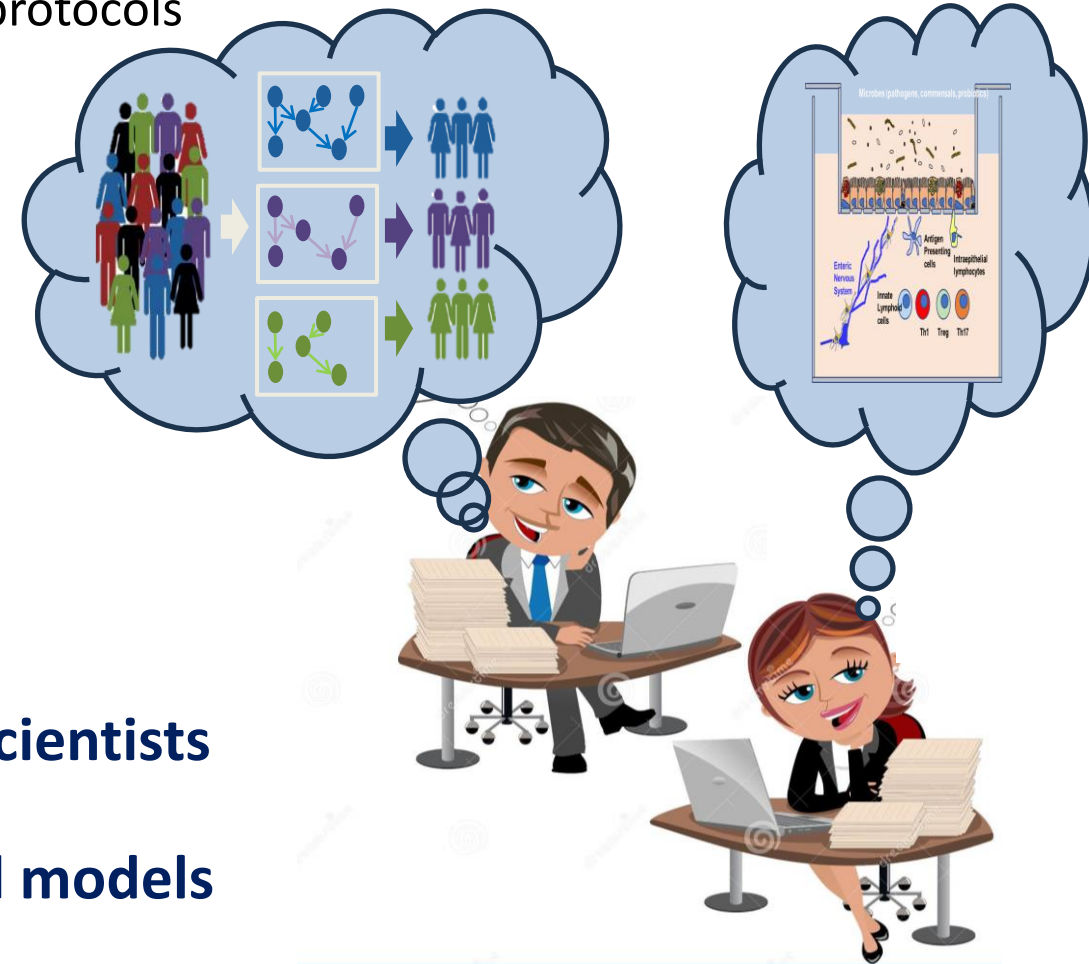
- **Multi-omics** based on IBD definition (genetics, immunology, exposome/microbiome)
- Each collected from the **same patient**, with standardised protocols
- With associated clinical **metadata**

- **Higher resolution datasets**

- **Single-cell** data (more patients, larger sequencing depth)
- Strain level **metagenomics**
- **Spatial** and **time-course** data
- Functional omics (**proteomics, metabolomics**)

- **Training and community between tool developers / data analysts, academic and clinical scientists**

- **Human organoid based, complex IBD experimental models for hypothesis generation and validation**





# Acknowledgements

## Korcsmaros group

- Isabelle Hautefort
- Marton Olbei
- Leila Gul
- Balazs Bohar
- John P. Thomas
- Yufan Liu
- Luca Csabai
- Deema Alassaf
- Polina Kornilova
- Tanvi Tambaku
- Yiran Zhang
- Cynthia Qiu
- Yik Jin Voon
- Jiyeon Choi
- Mira Mazsa

## Alumni (2014-2023)

- Dezso Modos
- Matthew Madgwick
- Martina Poletti
- Jo Brooks
- Amanda Demeter
- Agatha Treveil
- Padhmanand Sudhakar
- Emily Jones
- Denes Turei
- Tamas Kadlecsik
- David Fazekas
- Mate Szalay-Beko
- Wen-Xin Kang
- Georgina Alabone
- Tahila Andrighetti
- Zoltan Dul

Imperial College  
London



NIHR | Imperial Biomedical  
Research Centre



# Acknowledgements

**NIHR** | Imperial Biomedical  
Research Centre

Diana Papp  
Sandra Koigi  
Tamir Rashid



Aimee Parker, Regis Stentz, Federica Di Palma,  
Simon Carding, Neil Hall, Jozsef Baranyi, Rob Kingsley,  
Tom Wileman, Lindsay Hall, Stephen Robinson, Simon  
Rushbrook, Rob Davey, Iain Macaulay, Wilfried Haerty,  
Falk Hildebrand, Cynthia Whitchurch

**Imperial College  
London**

Nick Powell  
and the Powell lab  
Gary Frost  
David Ma



Séverine Vermeire  
Marc Ferrante  
Bram Verstockt  
Kaline Arnout

**UK IBD GENETICS CONSORTIUM**  
Understanding the genetics of Crohn's & Colitis

Miles Parkes  
Carl Anderson



Irene Miguel-Aliaga  
Vivian Li



Dana Philpott  
Mark Silverberg  
Sun-Ho Lee



Gavin Bewick  
Chronis Pavlidis  
Joana Neves

**BenevolentAI**

Mark Davies  
Sam Abujudeh



UNIVERSITÉ DU  
LUXEMBOURG  
Paul Wilmes



**UNIVERSITY OF  
CAMBRIDGE**  
Andreas Bender



**UNIVERSITÄT  
HEIDELBERG**  
ZUKUNFT  
SEIT 1386

Julio Saez-Rodriguez  
Denes Turei

**WARWICK**  
THE UNIVERSITY OF WARWICK  
Ioannis Nezis

  
Unilever  
Janette Jones

  
**Institut Pasteur**  
Jost Enninga

# Thank you!

---

<https://github.com/KorcsmarosGroup/>

<http://KorcsmarosLab.org>

T.Korcsmaros@imperial.ac.uk