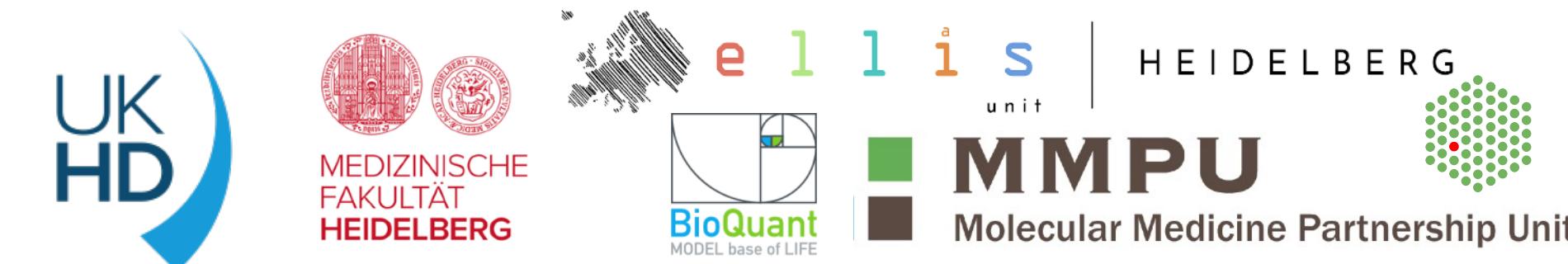


Knowledge-based machine learning from multi-omics data for personalized medicine

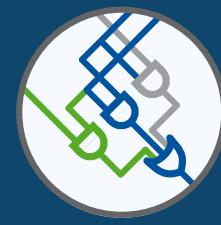
Julio Saez-Rodriguez

Institute for Computational Biomedicine, Heidelberg University, Univ. Hospital Heidelberg
EMBL - University Hospital Heidelberg Molecular Medicine Partnership Unit
ELLIS - Heidelberg
Bioquant

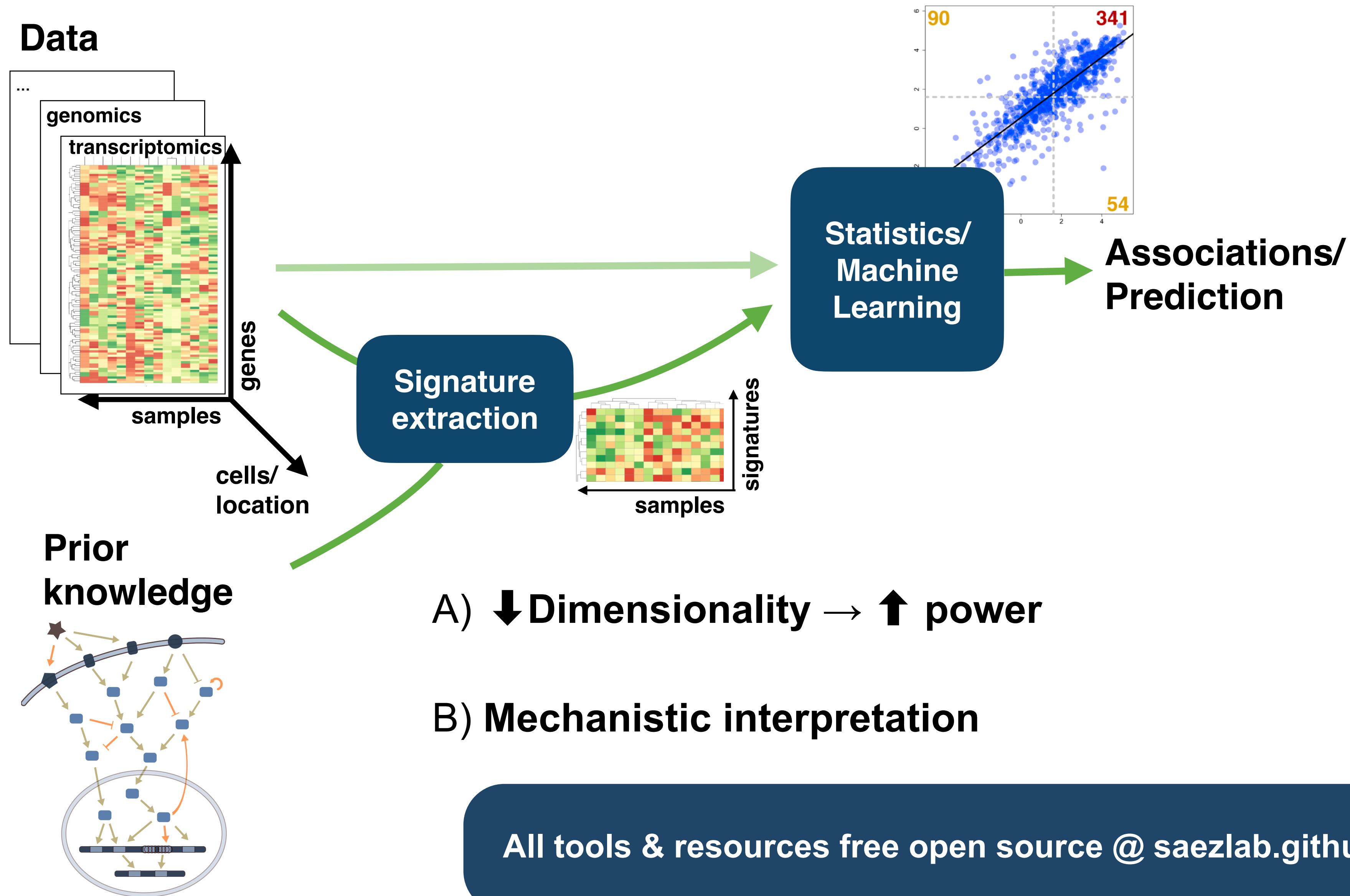


Conflict of Interest: JSR reports funding from GSK and Sanofi and fees from Travere Therapeutics and Astex Therapeutics

Image by
Alex Cagan



Supporting Stats&ML with biological knowledge



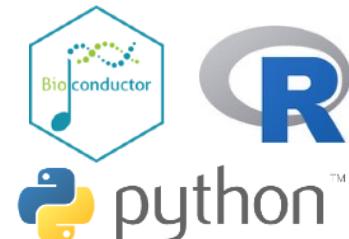
Omnipath: Integration of over 100 knowledge resources

>2Mi annotations
>20k proteins
>16k complexes



www.omnipathdb.org

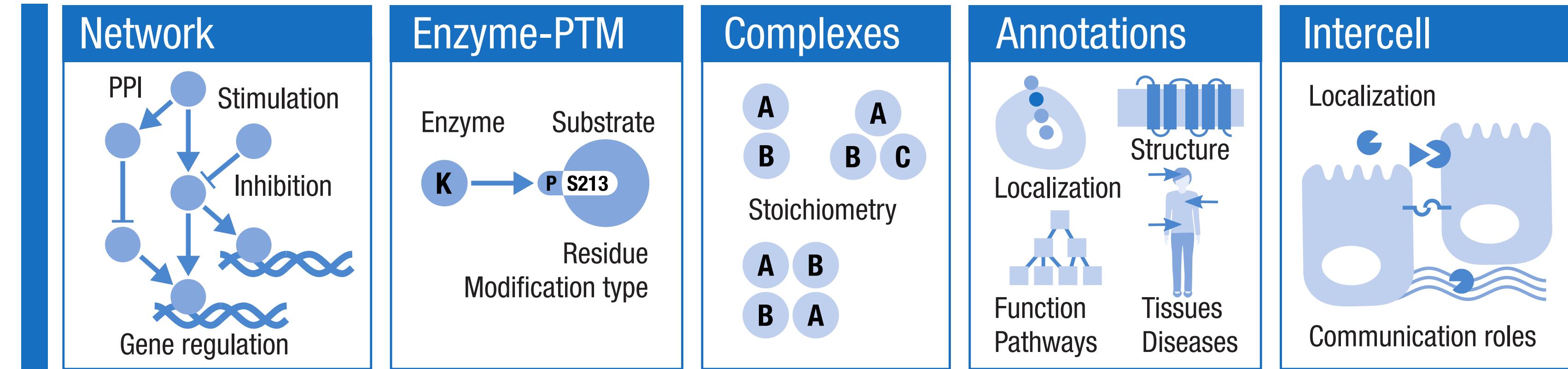
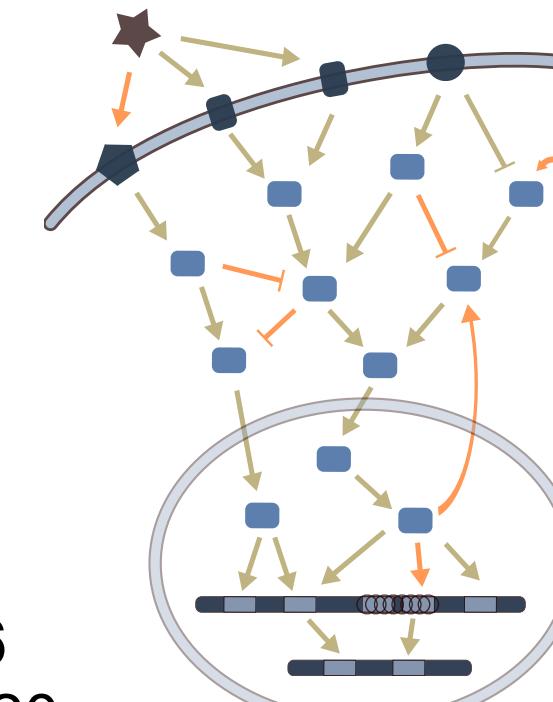
omnipathdb



python™



**Prior
knowledge**



Turei *Nature Methods* 2016
Cecarelli *Bioinformatics* 2020
Turei *Mol Sys Bio* 2021

Ongoing: Unified language for
biomedical Graph databases



Omnipath: Integration of over 100 knowledge resources

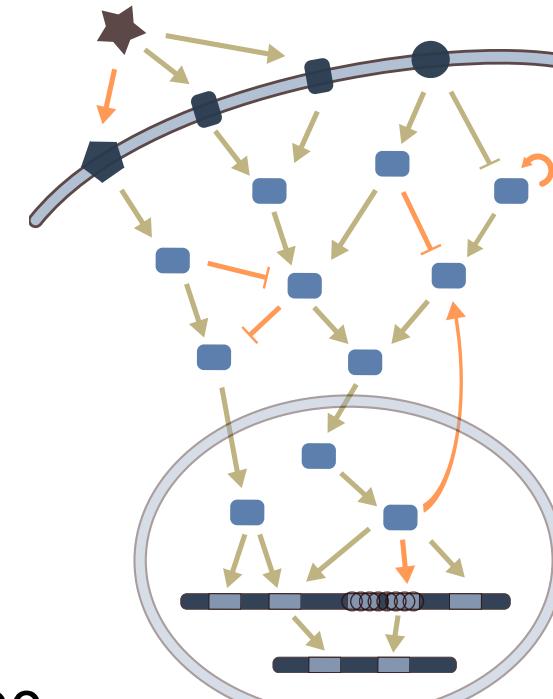
>2Mi annotations
>20k proteins
>16k complexes



www.omnipathdb.org



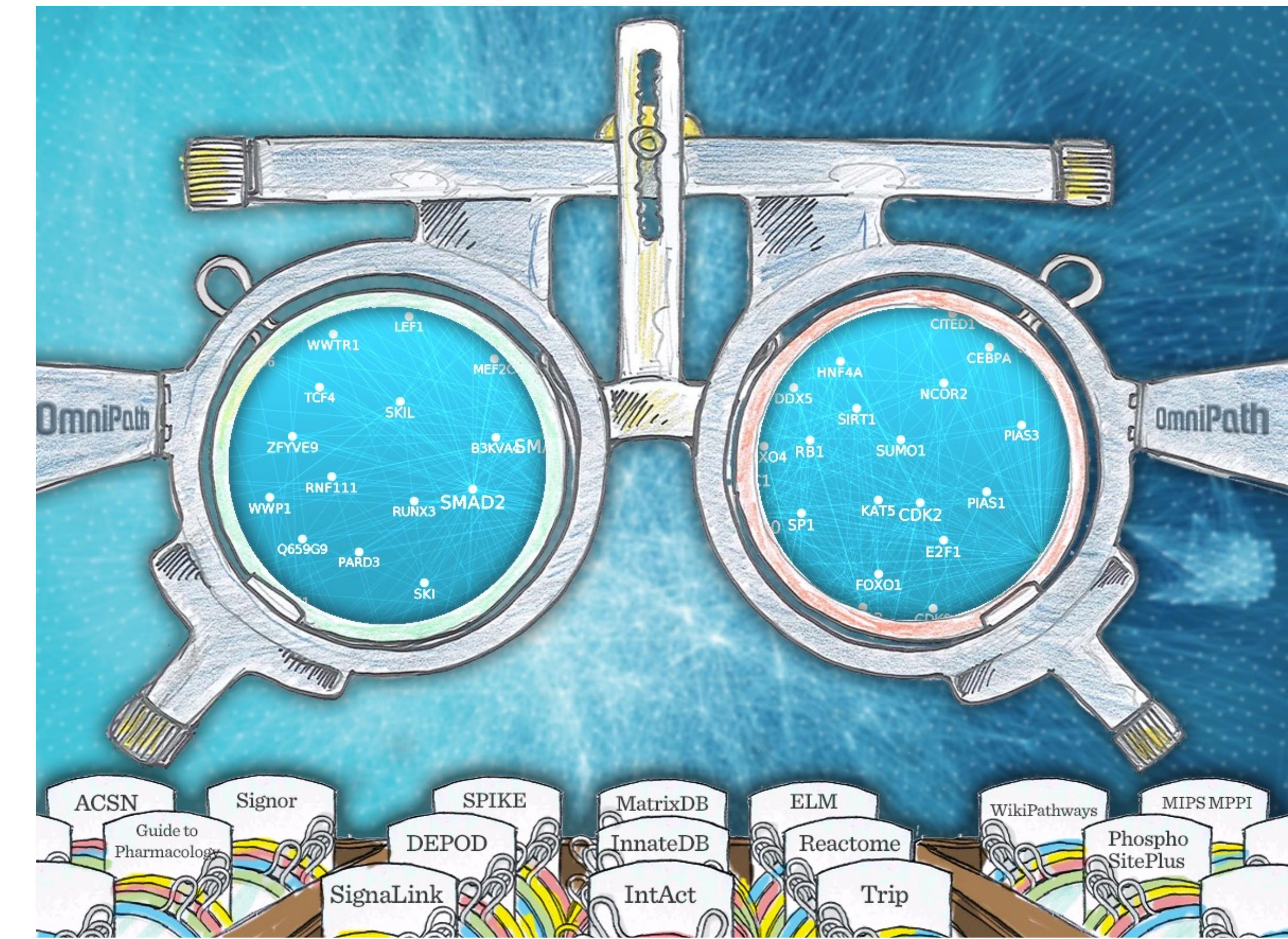
Prior knowledge



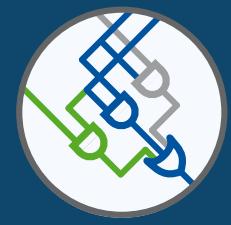
Turei *Nature Methods* 2016

Cecarelli *Bioinformatics* 2020

Turei *Mol Sys Bio* 2021



Artwork by S Philips; appeared in Dec 2016 cover of *Nature Methods*



Footprint signatures from omics data

Transcriptomics

→ Pathways activity

Schubert *Nature Comm* 2018

→ TFs activity

Garcia-Alonso *Genome Res* 2019

(Phospho)proteomics

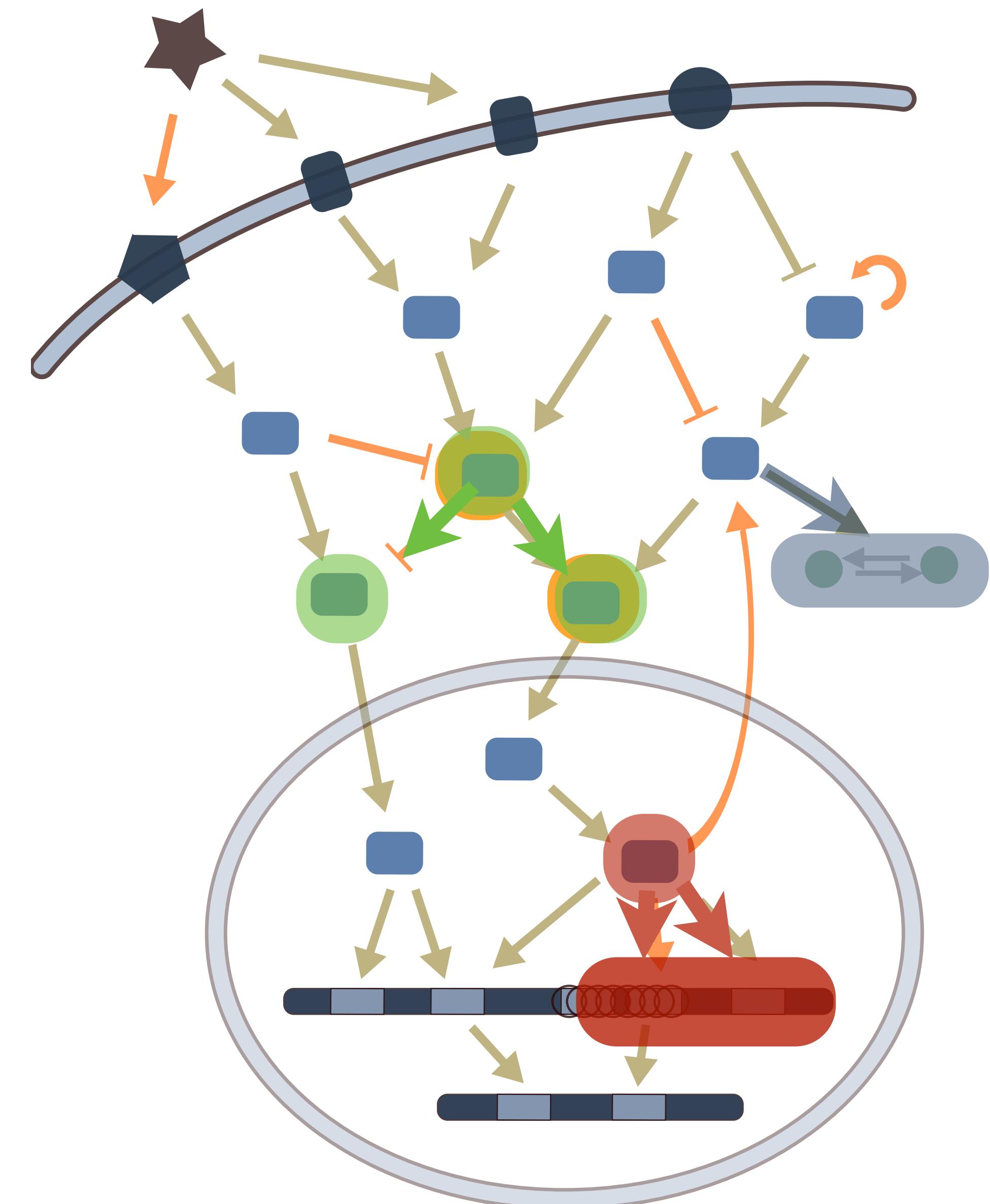
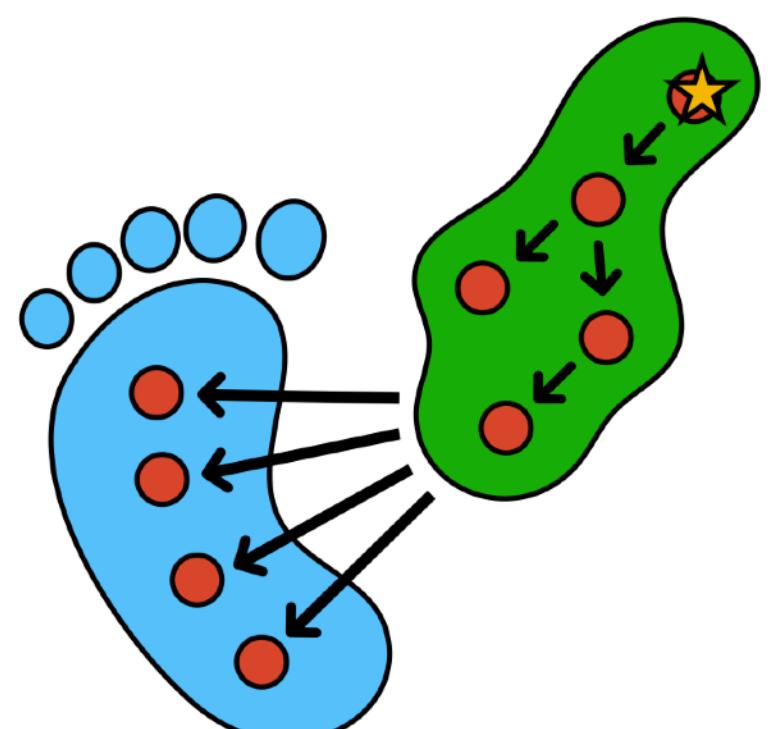
→ Kinase activity

Wirbel *Meth. Mol. Biol.* 2018

Metabolomics

→ Metab enzyme activity

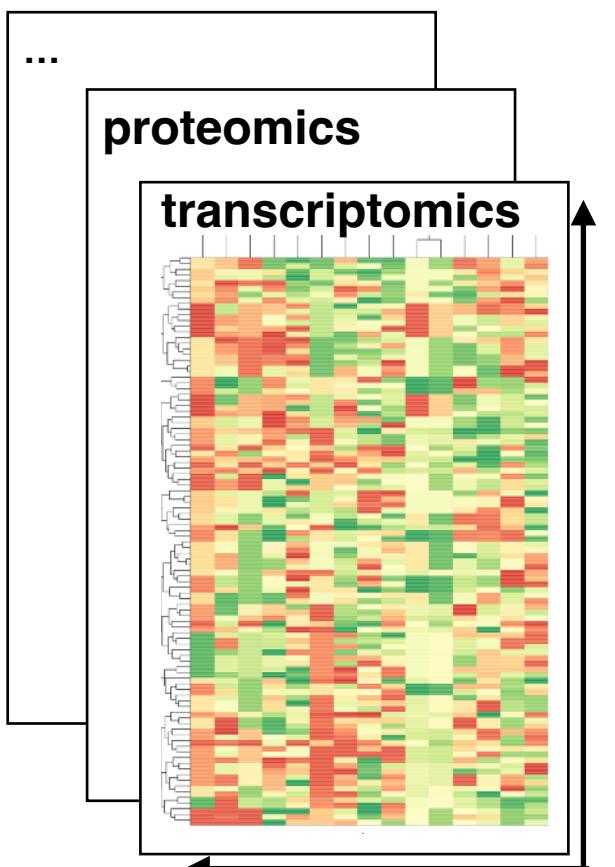
Scaciovelli, Dugourd, *biorxiv*



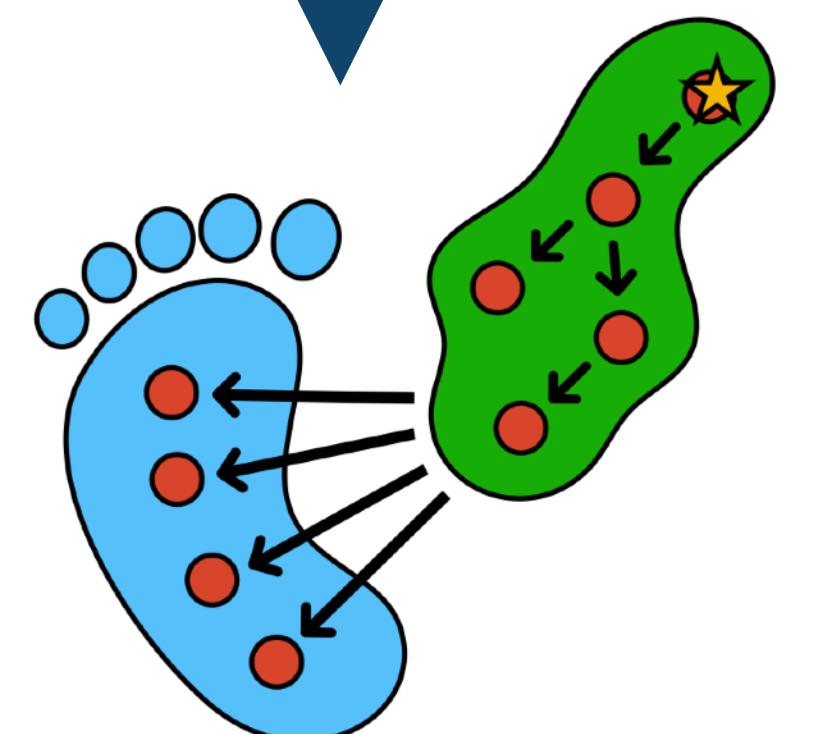
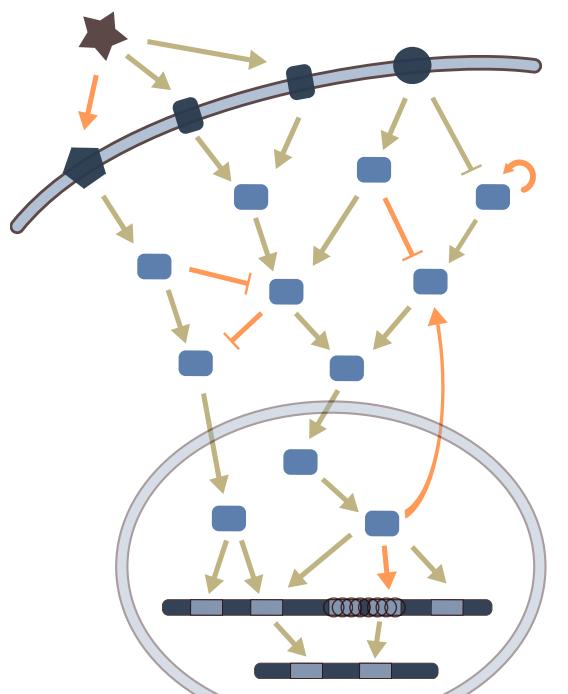


Footprint + causal network inference for multi-omics data analysis

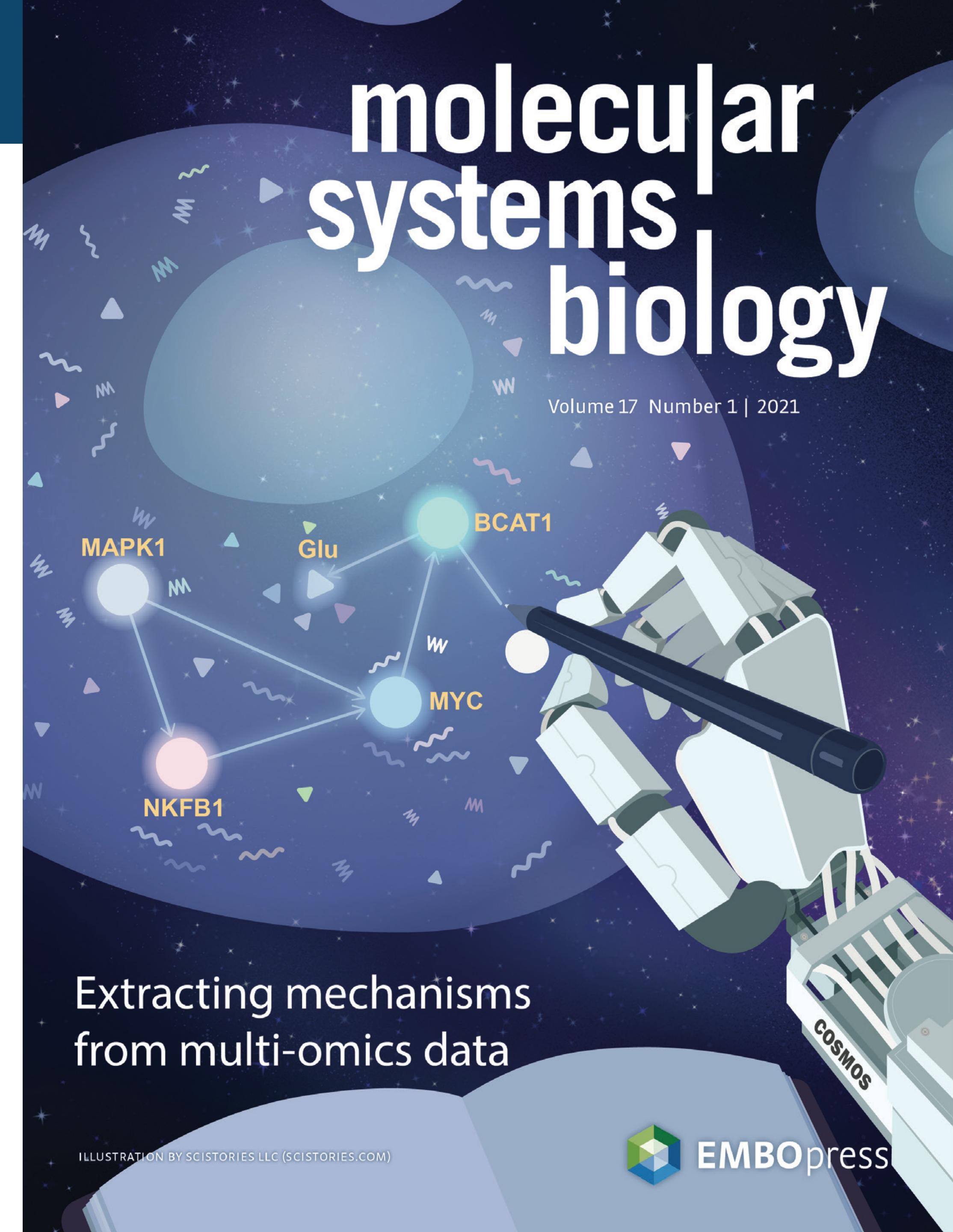
Data



Prior
knowledge



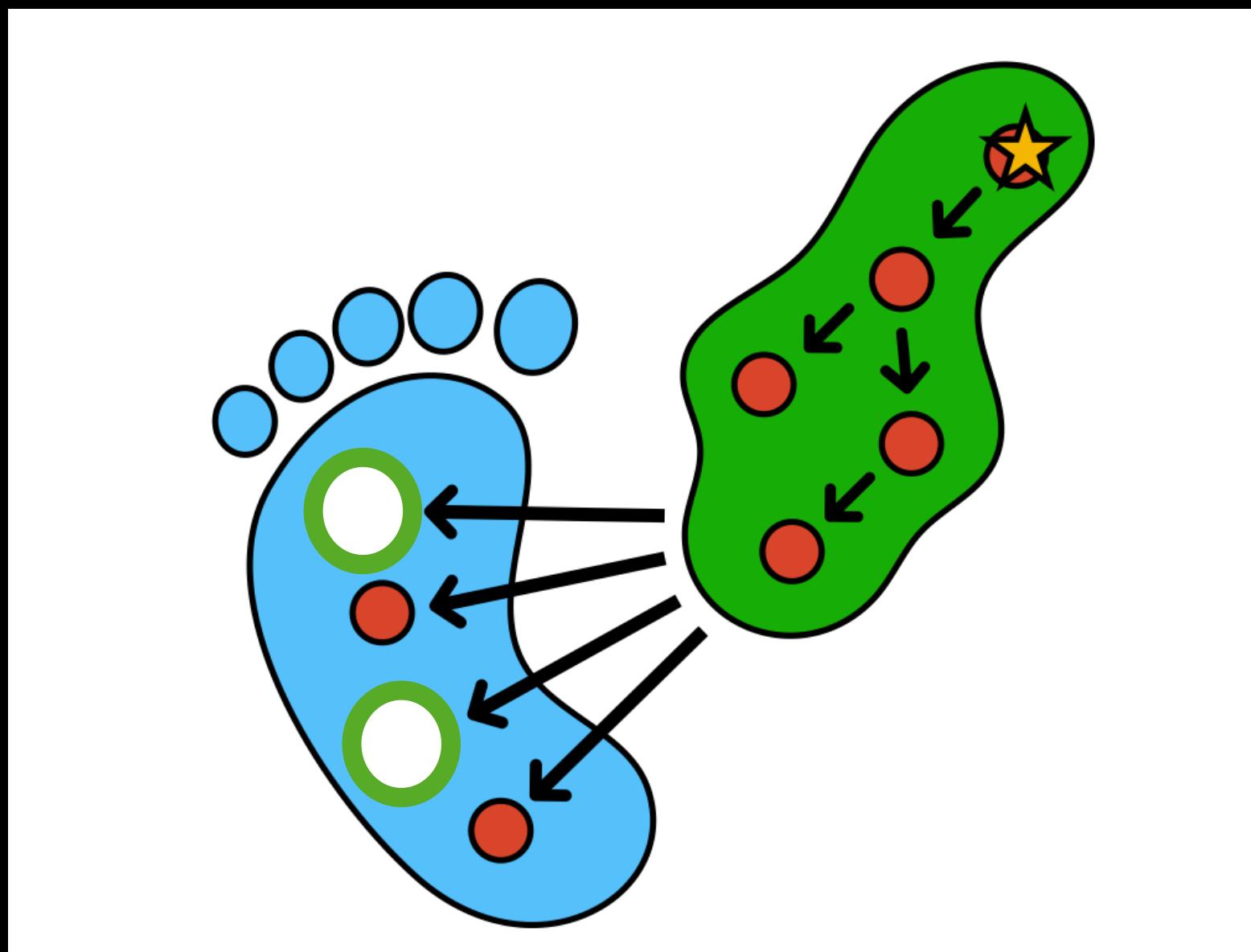
COSMOS



Footprint methods work on bulk RNA... Do they work on single-cell RNA?

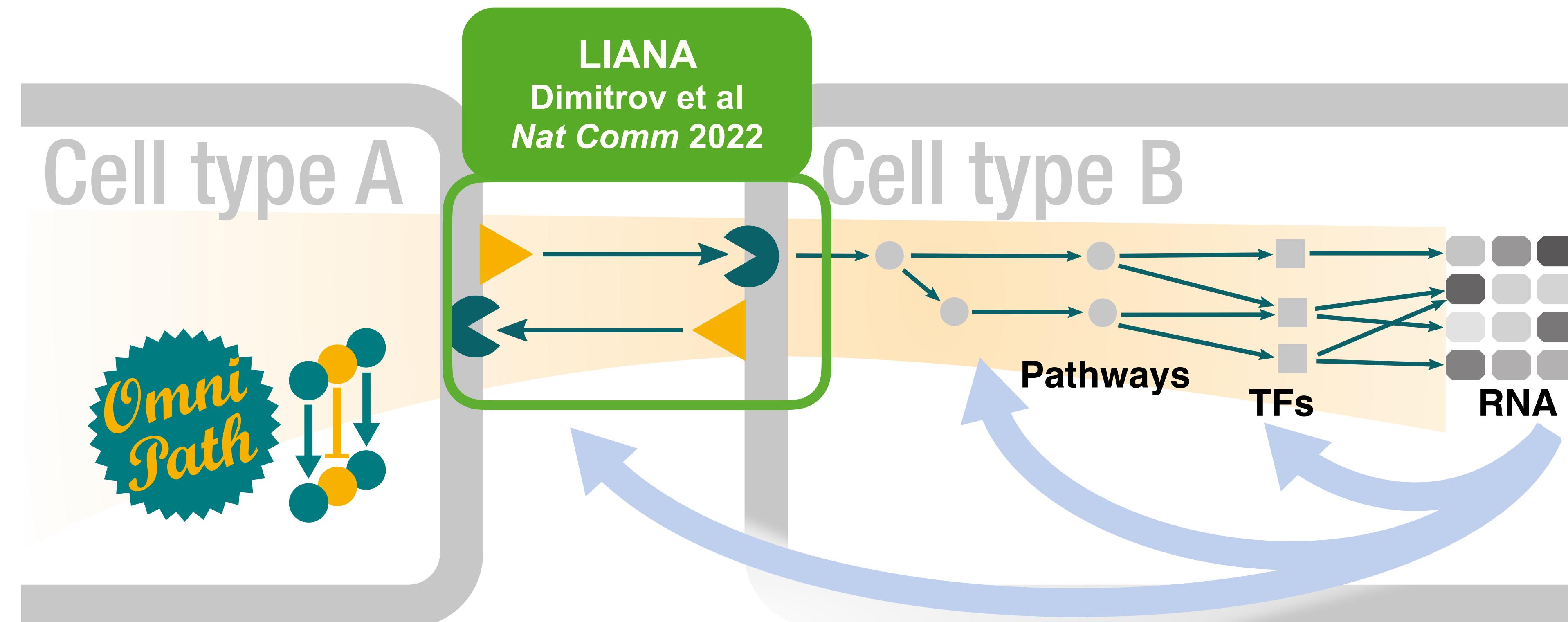
Yes

(at least in to our benchmarks; Holland *Genome Bio* 2020)



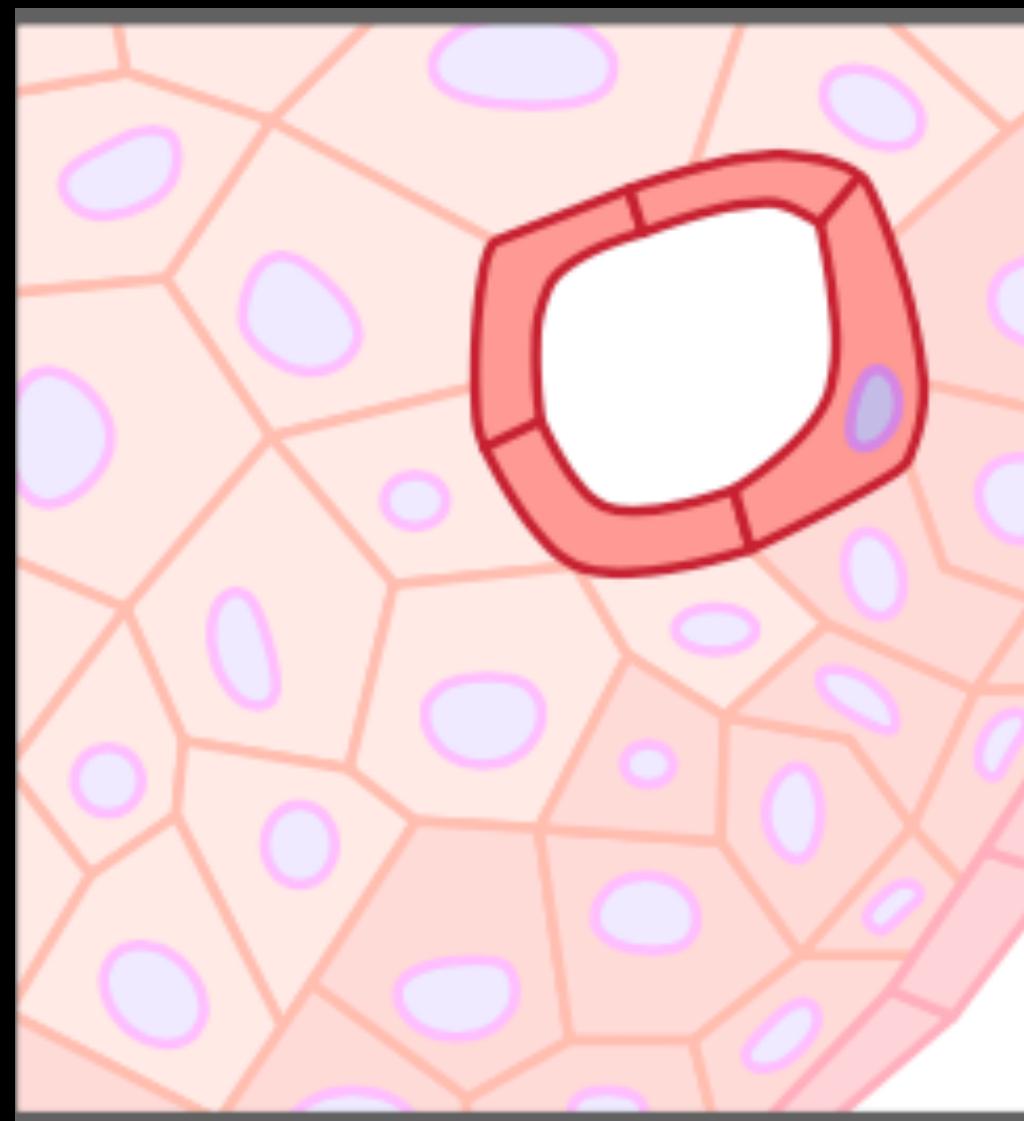
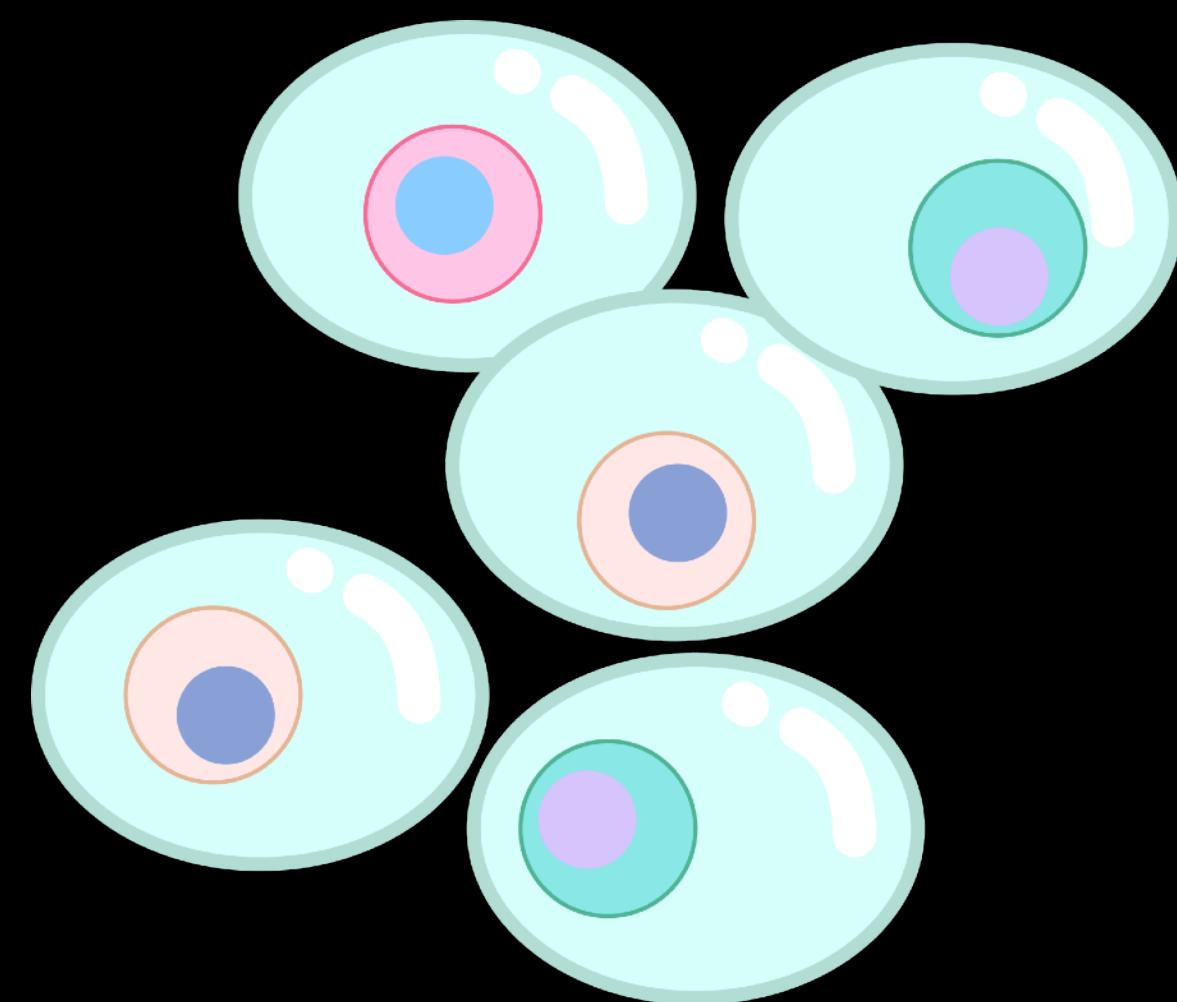


Analysis of Intra- and intercellular communication using scRNA



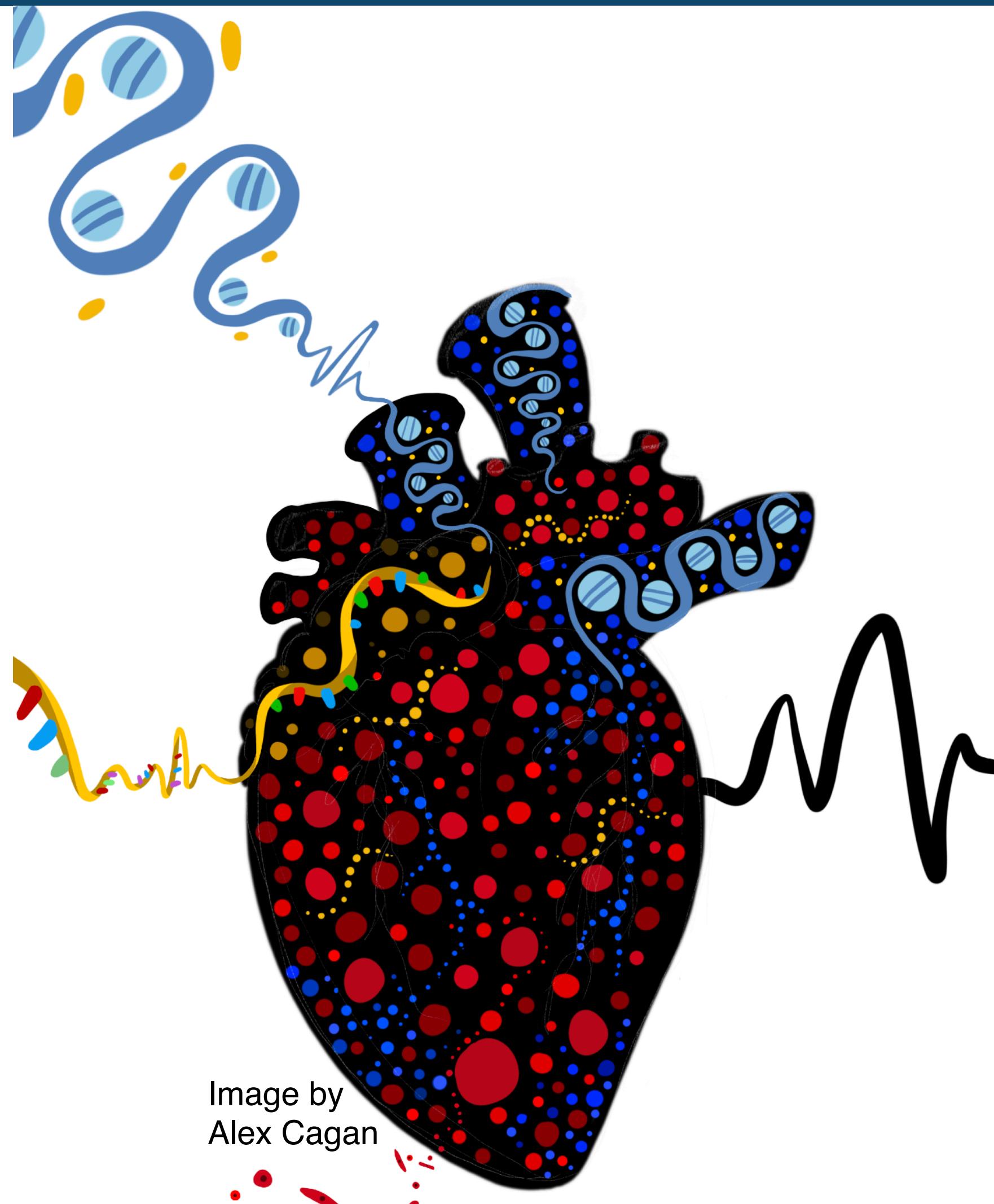
Automated workflows for diverse tools extracting required knowledge from *Omnipath*

How to add the spatial context?

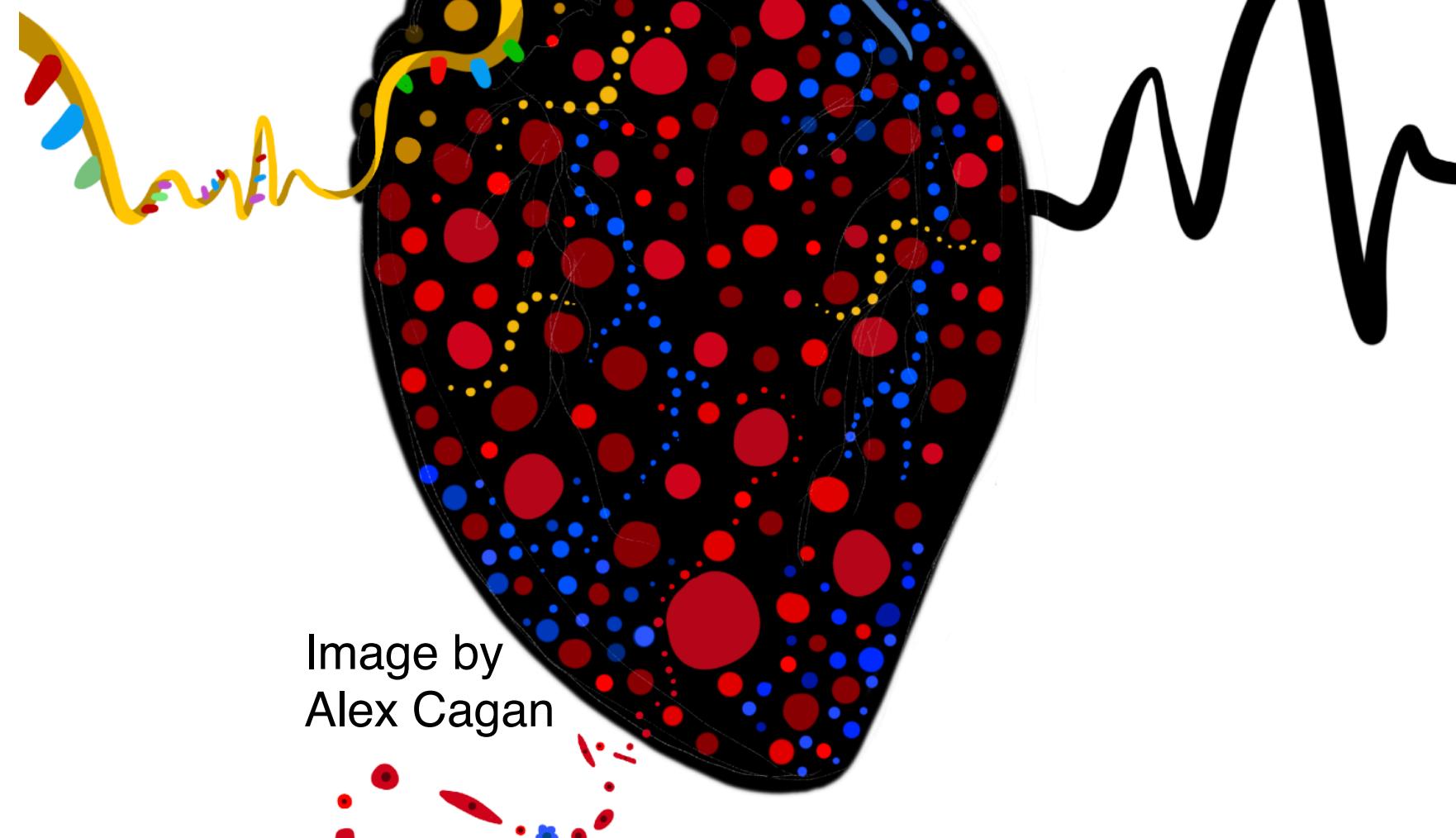


Spatial multi-omic map of human myocardial infarction

snATAC-Seq

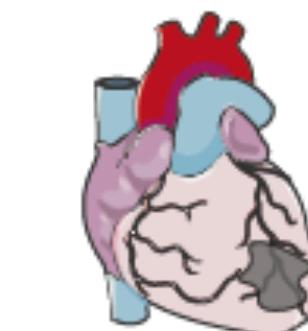
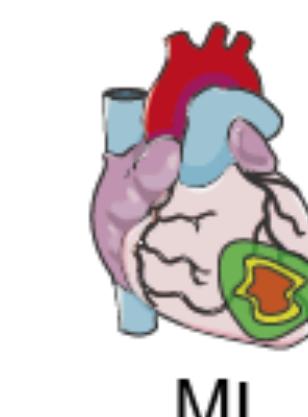
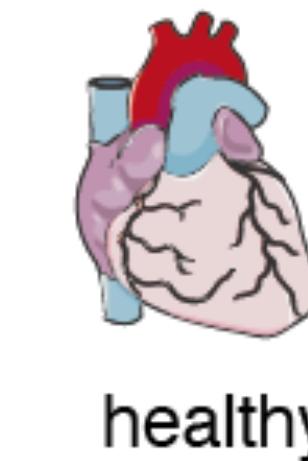


snRNA-Seq

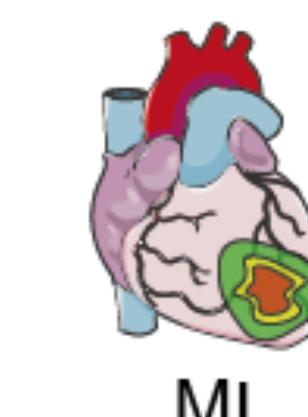
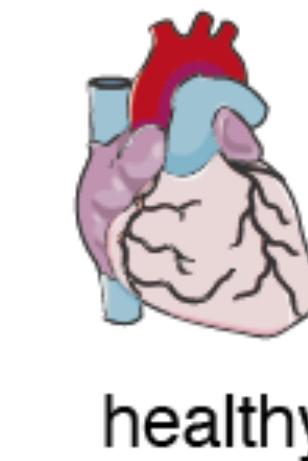


Spatial
RNA-seq

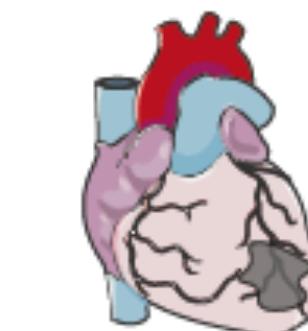
Kuppe, Ramirez Flores, Li, et al.
Nature 2022



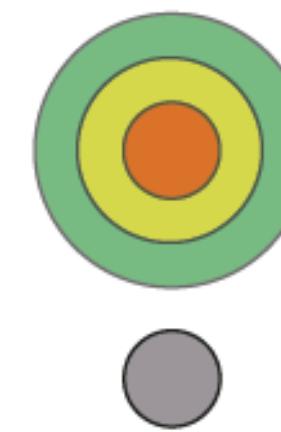
chronic



MI

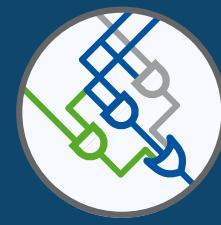


chronic



IZ (ischemic zone)
BZ (border zone)
RZ (remote zone)
FZ (fibrotic zone)

patients	RZ	BZ	IZ	FZ
1 healthy	●			
2 acute MI		○	●	
3 acute MI	●	○	●	
4 chronic (MI)				●
5 chronic (non-MI)				●

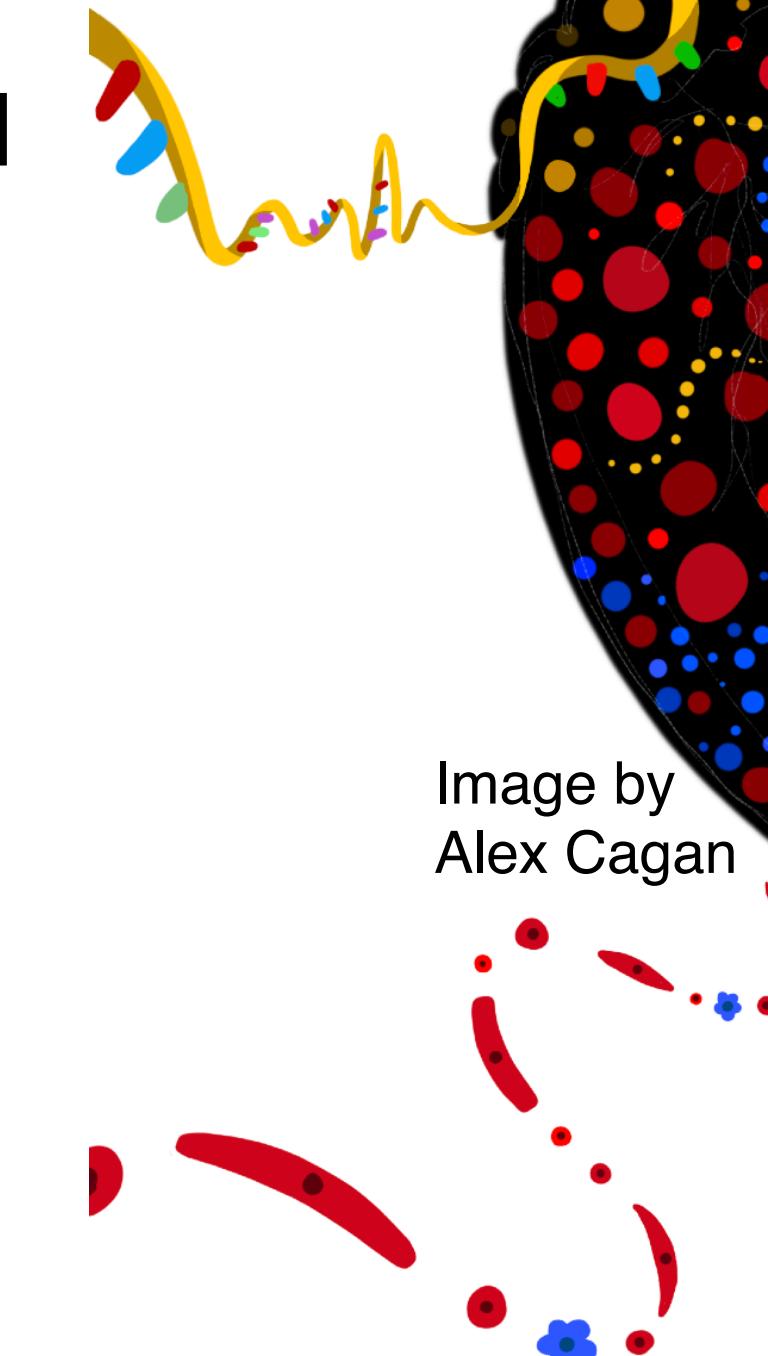


Integrative analysis to find deregulated intra- and intercellular processes

snATAC-Seq

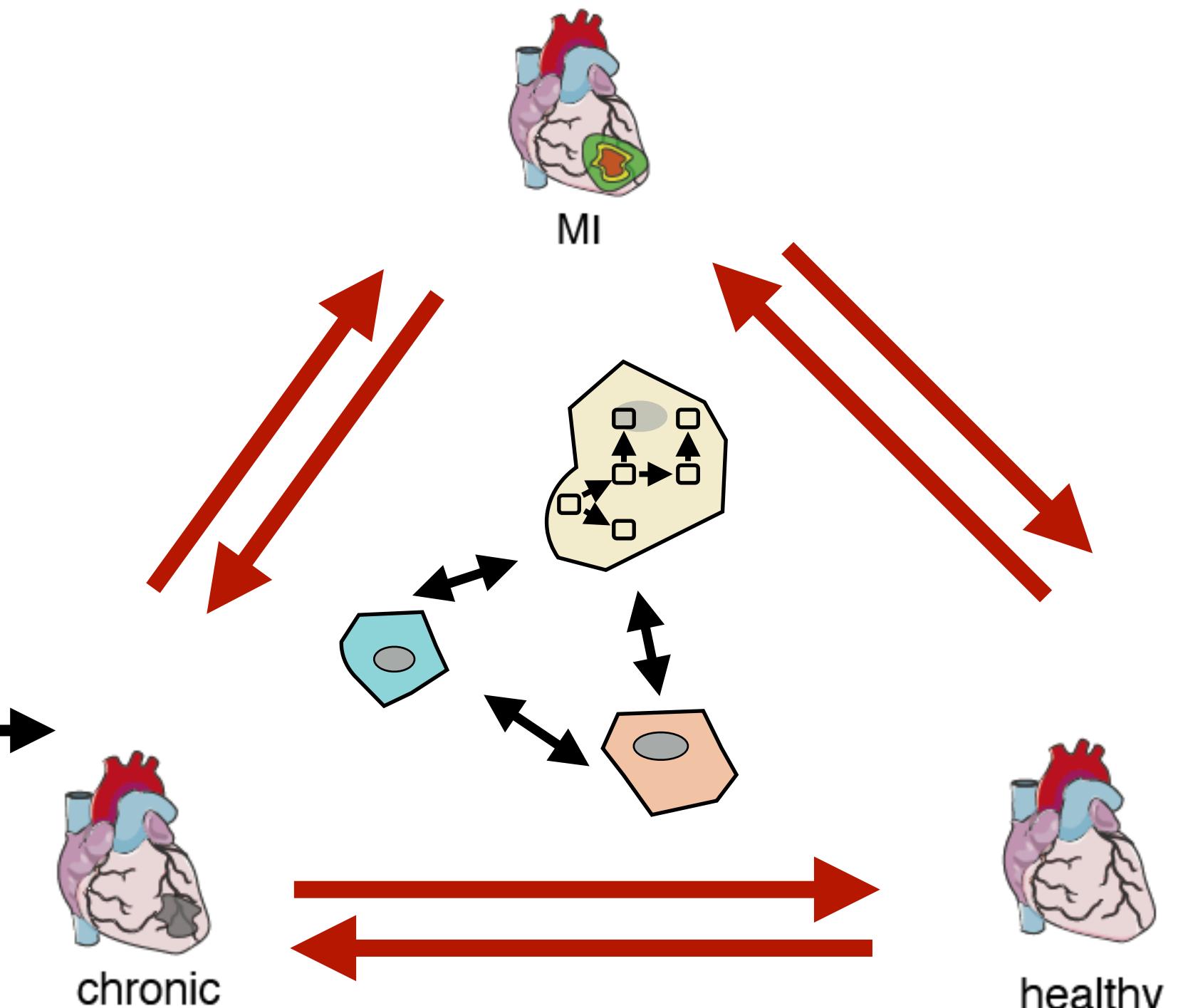
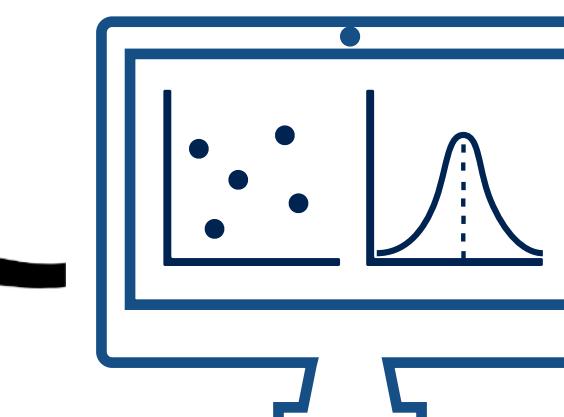


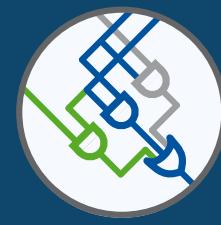
snRNA-Seq



Spatial
RNA-seq

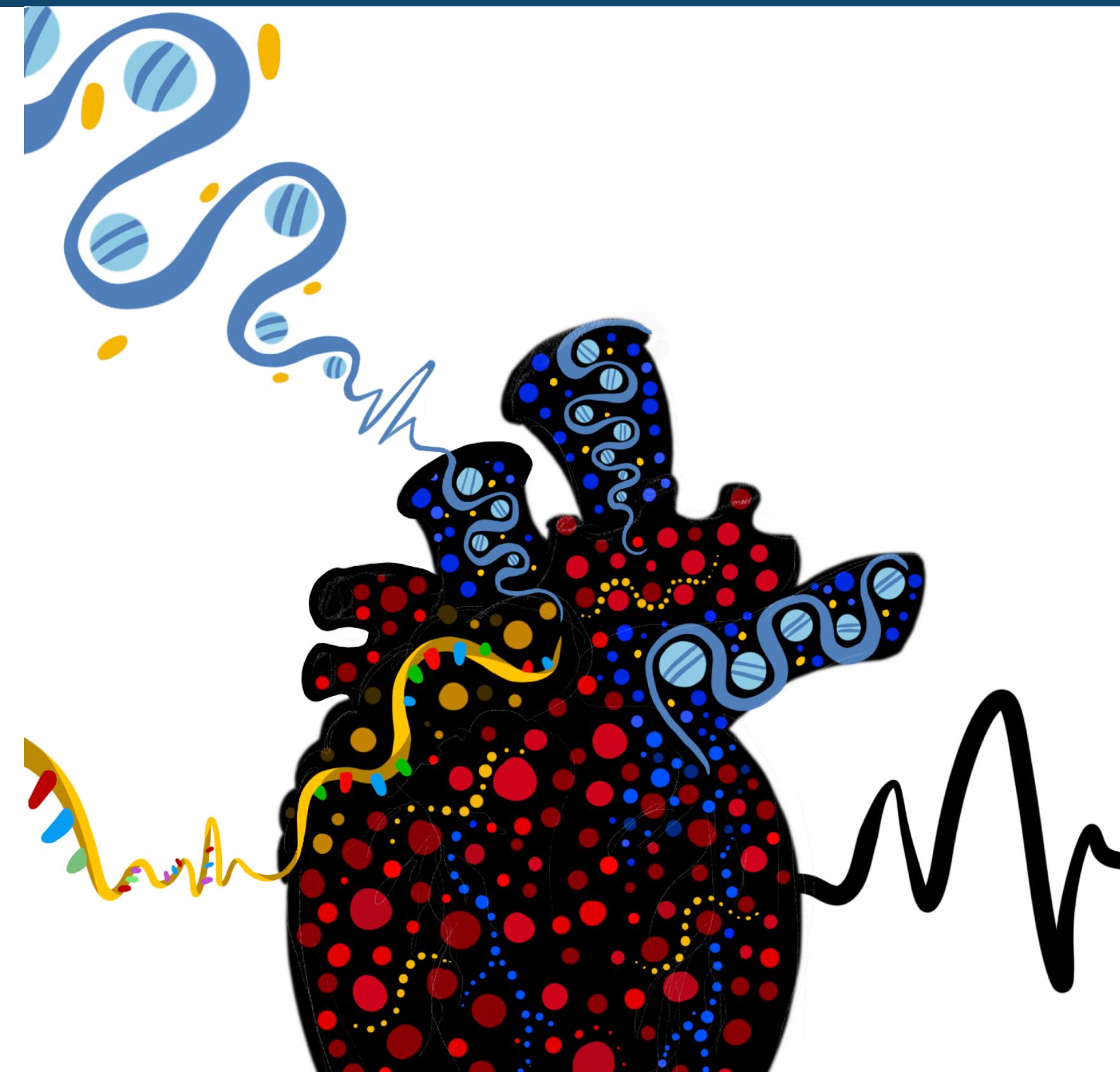
Kuppe, Ramirez Flores, Li, et al.
Nature 2022



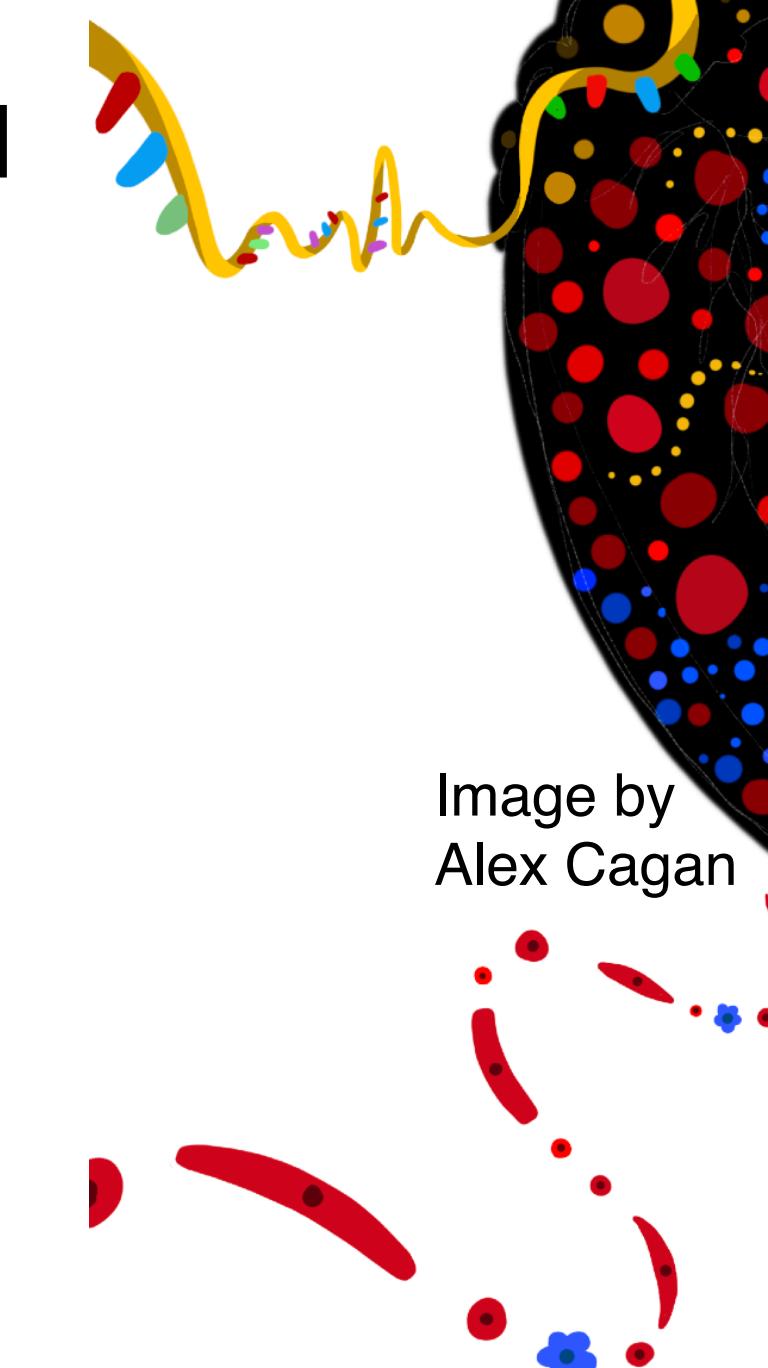


Mechanistic insights on fibrotic tissue on human heart

snATAC-Seq

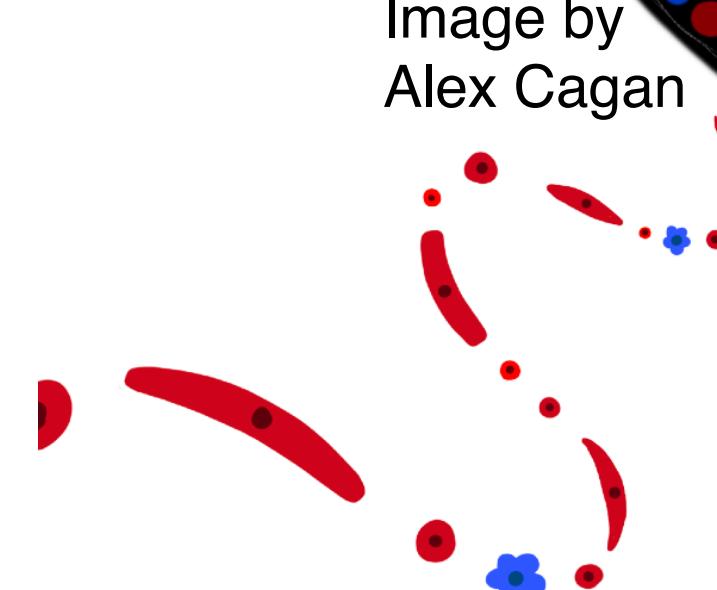


snRNA-Seq

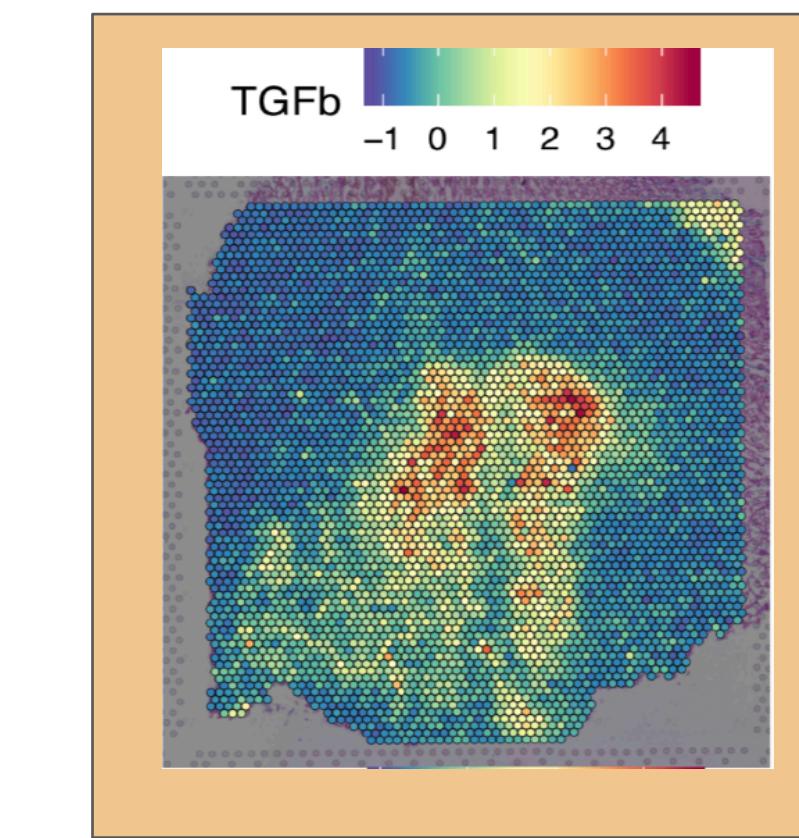


Spatial
RNA-seq

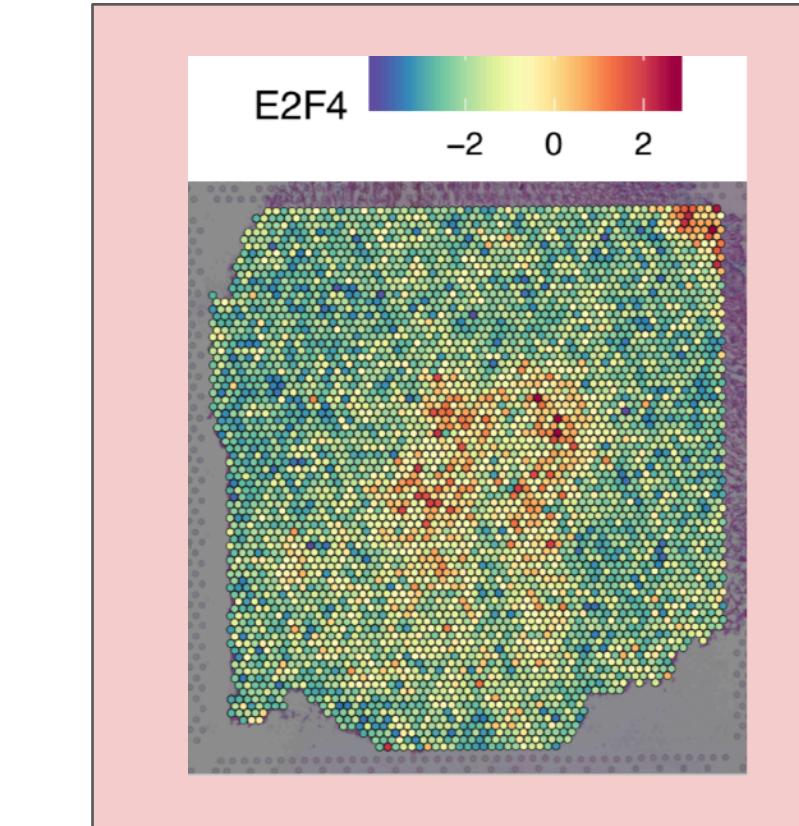
Image by
Alex Cagan



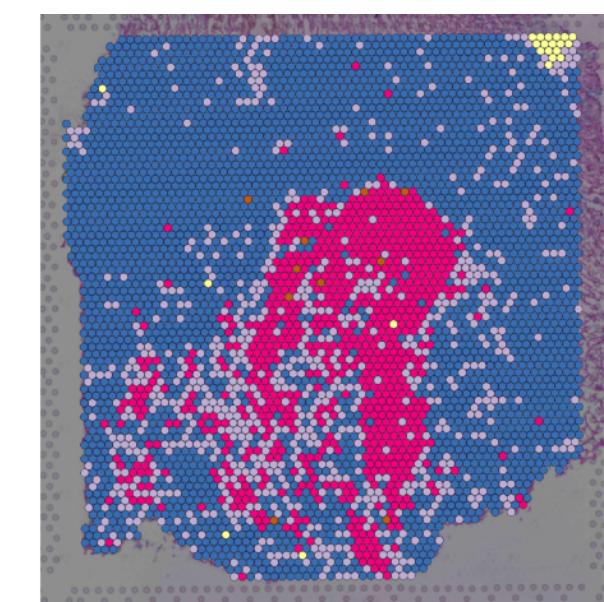
Pathway Activity



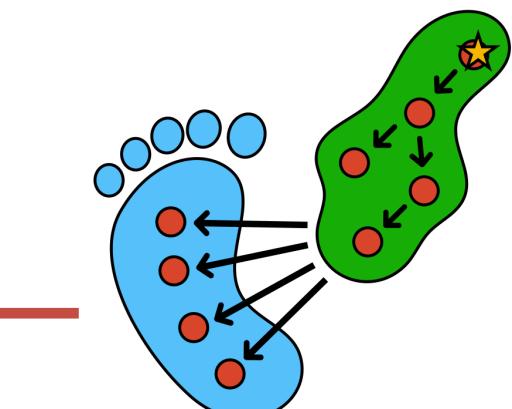
Transcription Factor



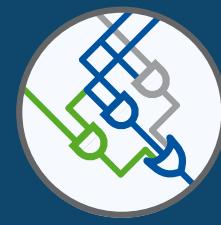
Fibrotic zone
in chronic MI



Fib1 Fib2

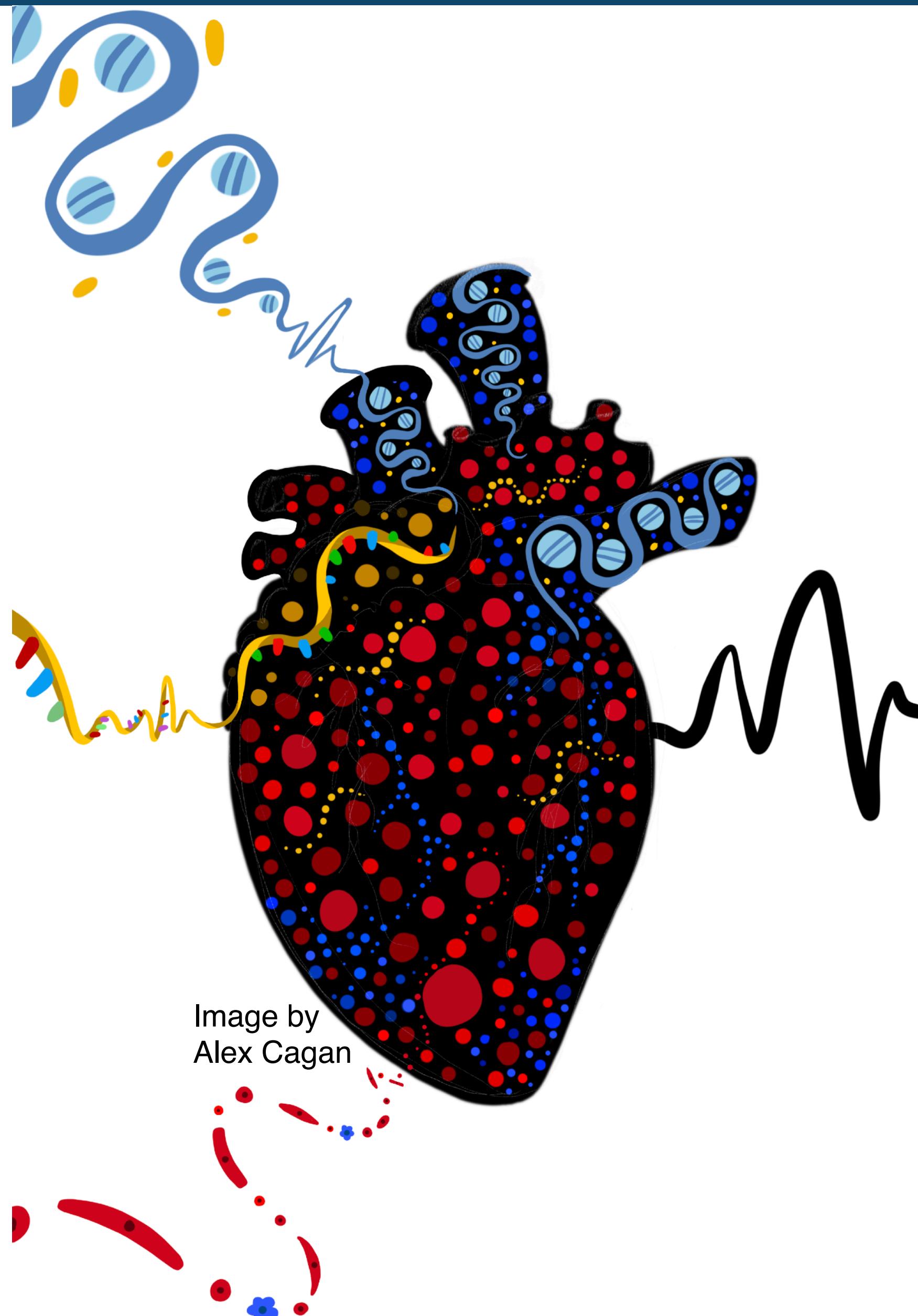


Mechanistic
Knowledge

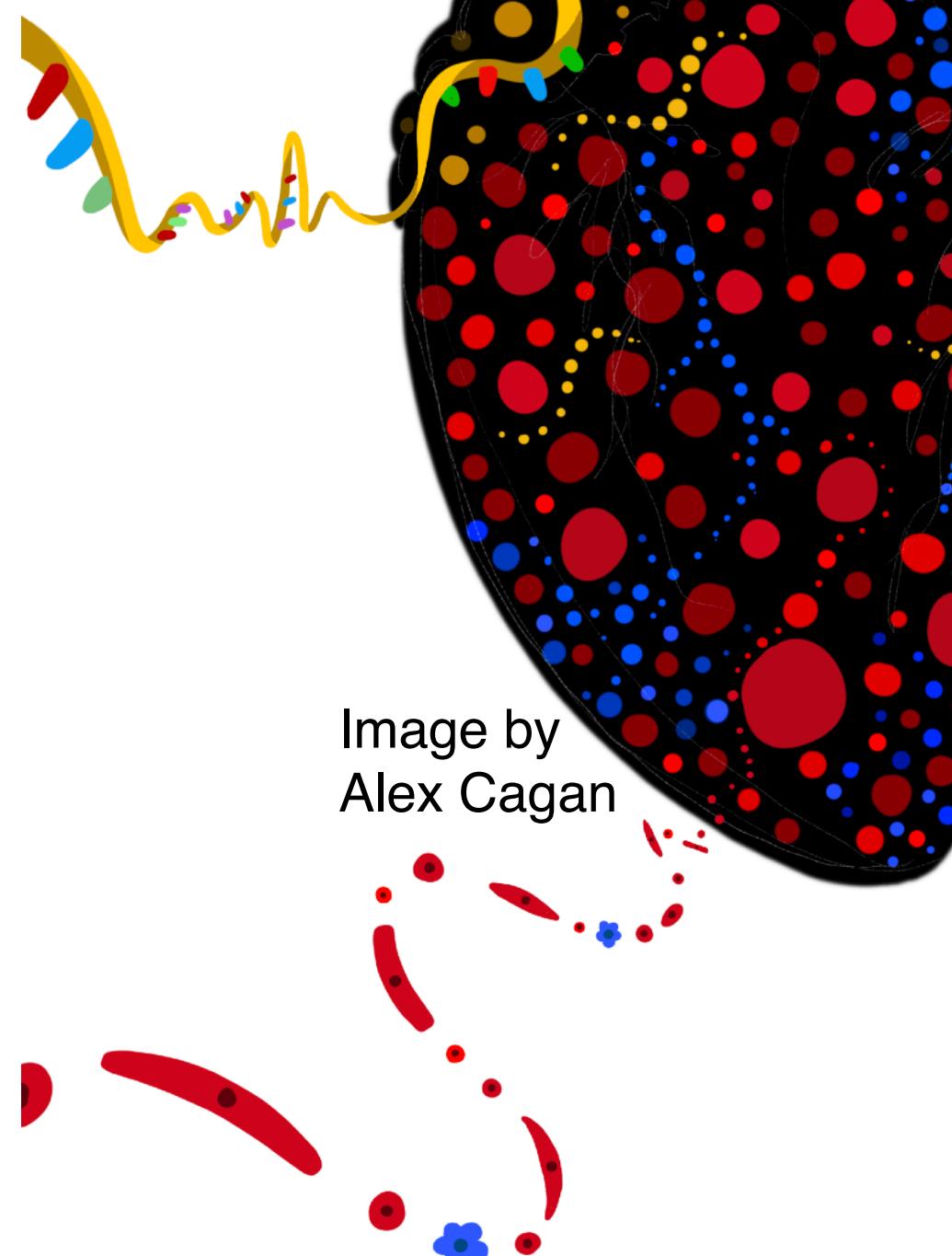


Leveraging spatial information to study interactions

snATAC-Seq

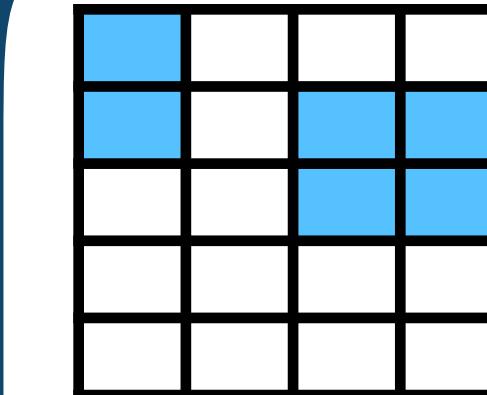


snRNA-Seq

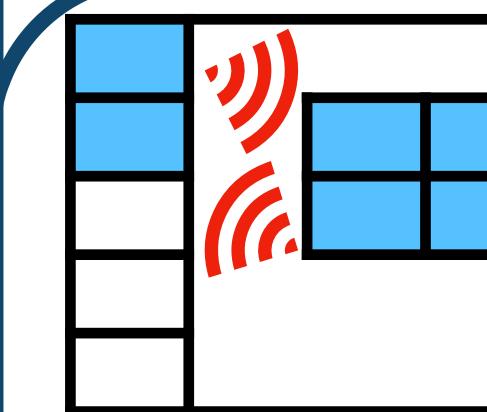
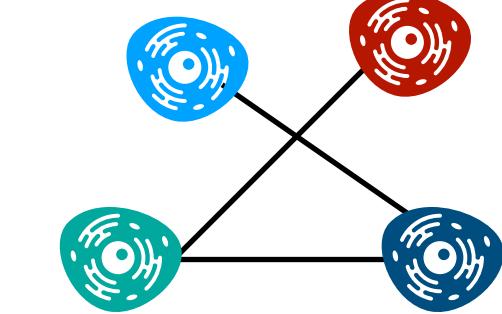


Spatial
RNA-seq

Tissue Architecture

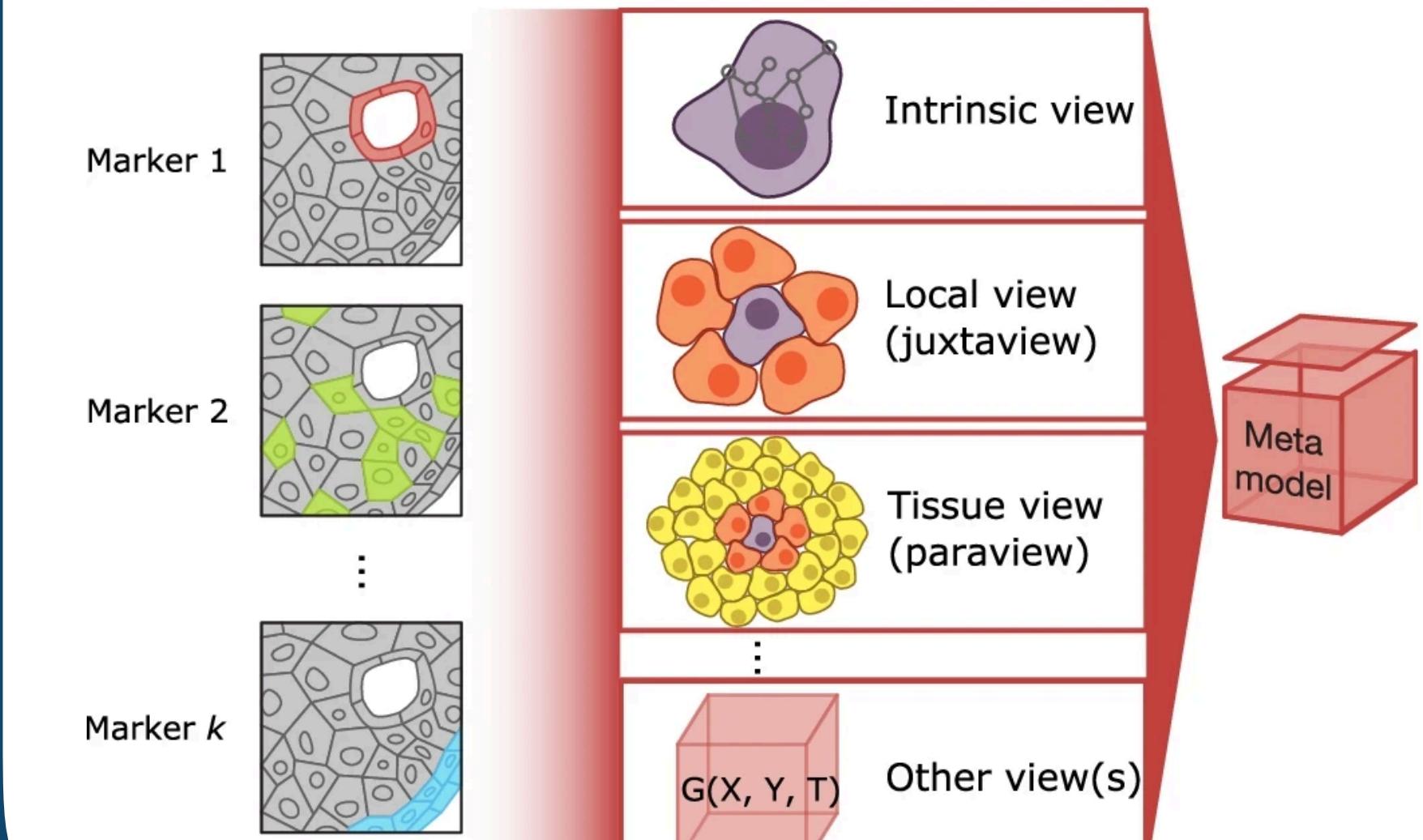


Spatial
patterns

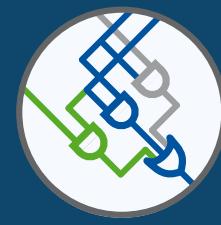


Interactions

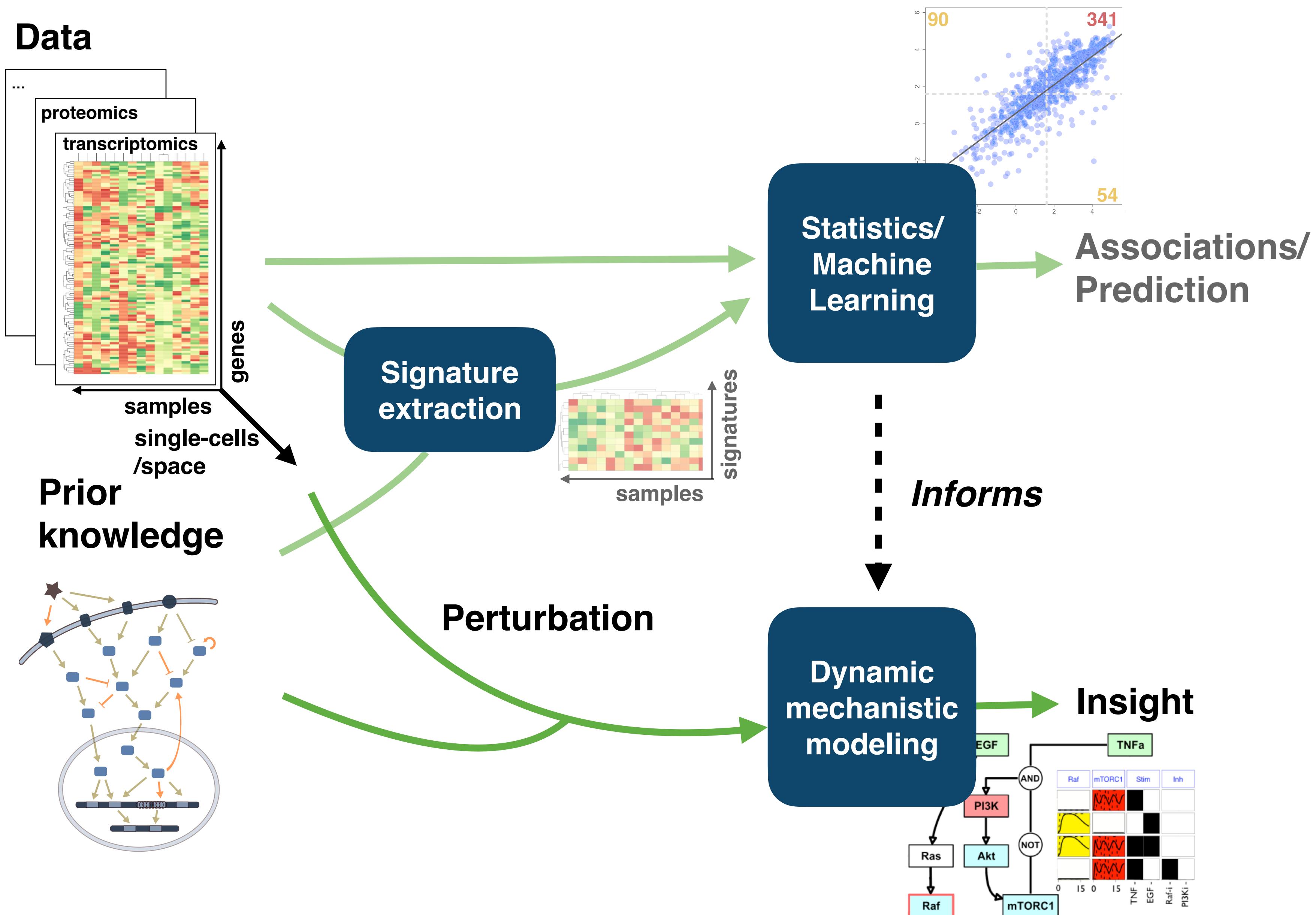
MISTy
Dissecting spatial
relationships w
multi-view models

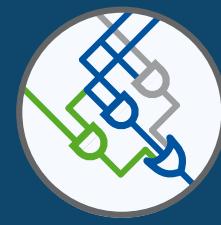


Tanevski et al., Gen Bio 2022

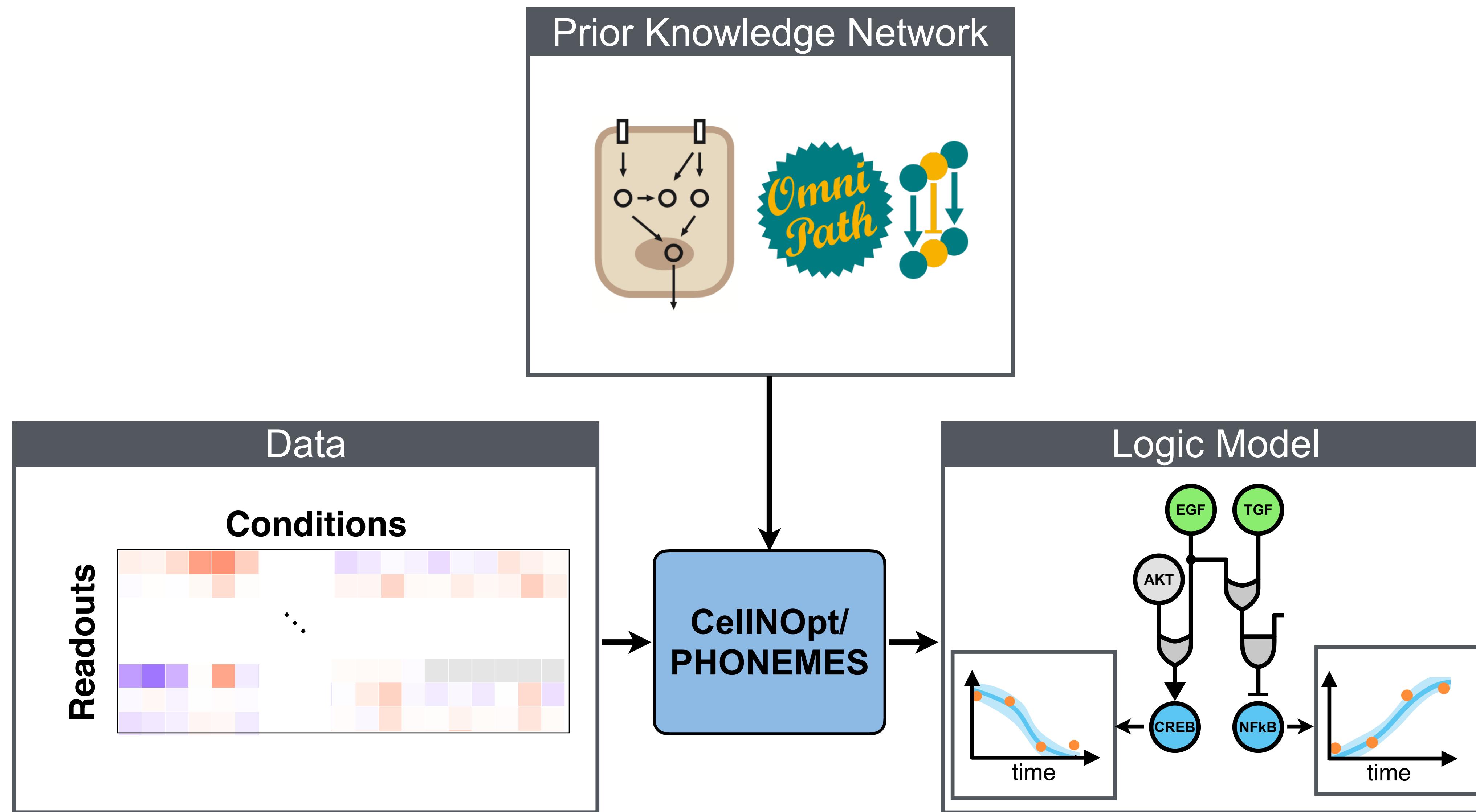


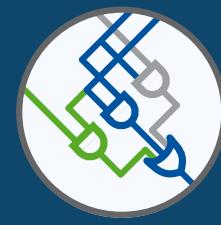
Dynamic models complement basal-based machine learning



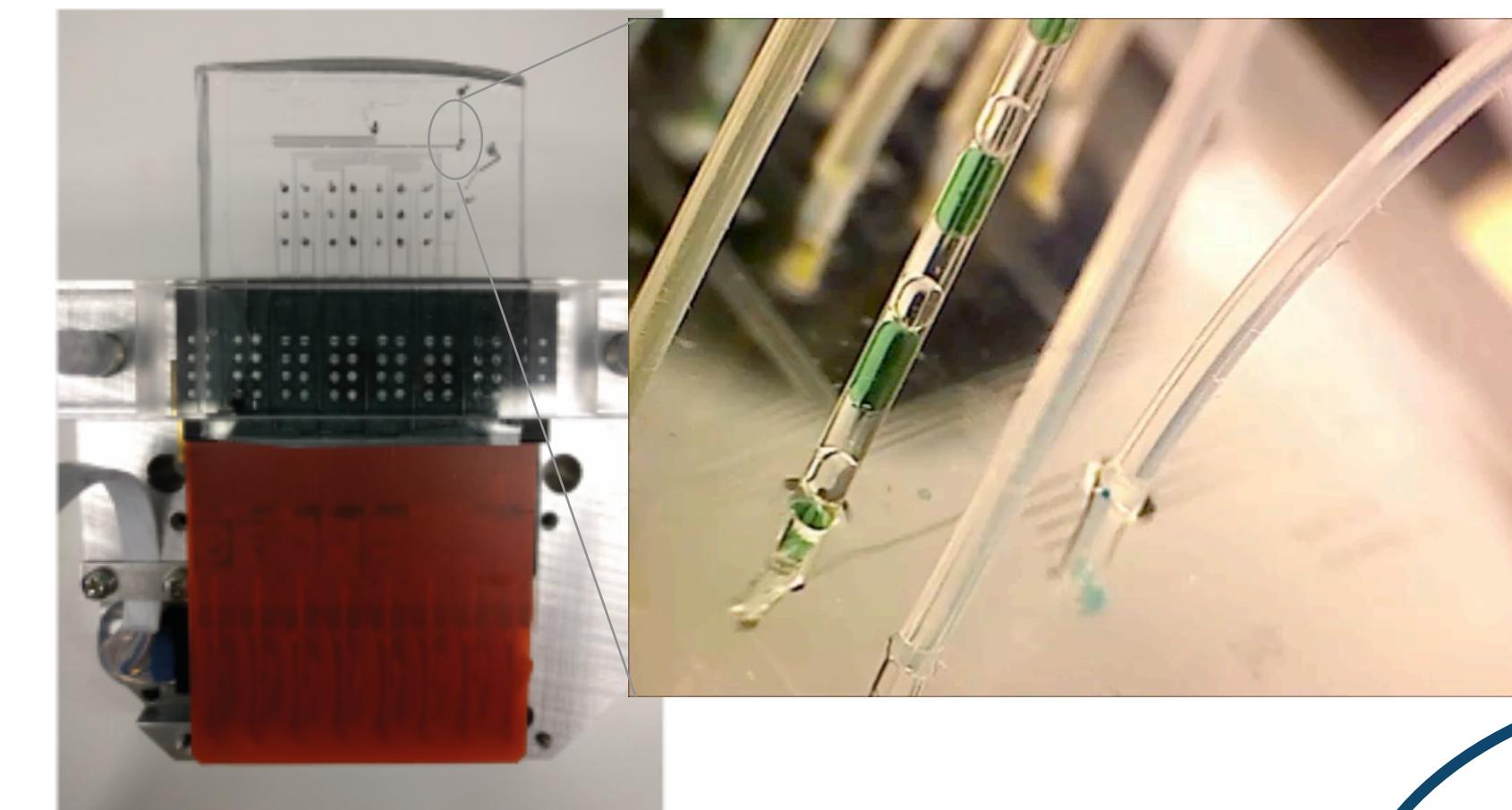
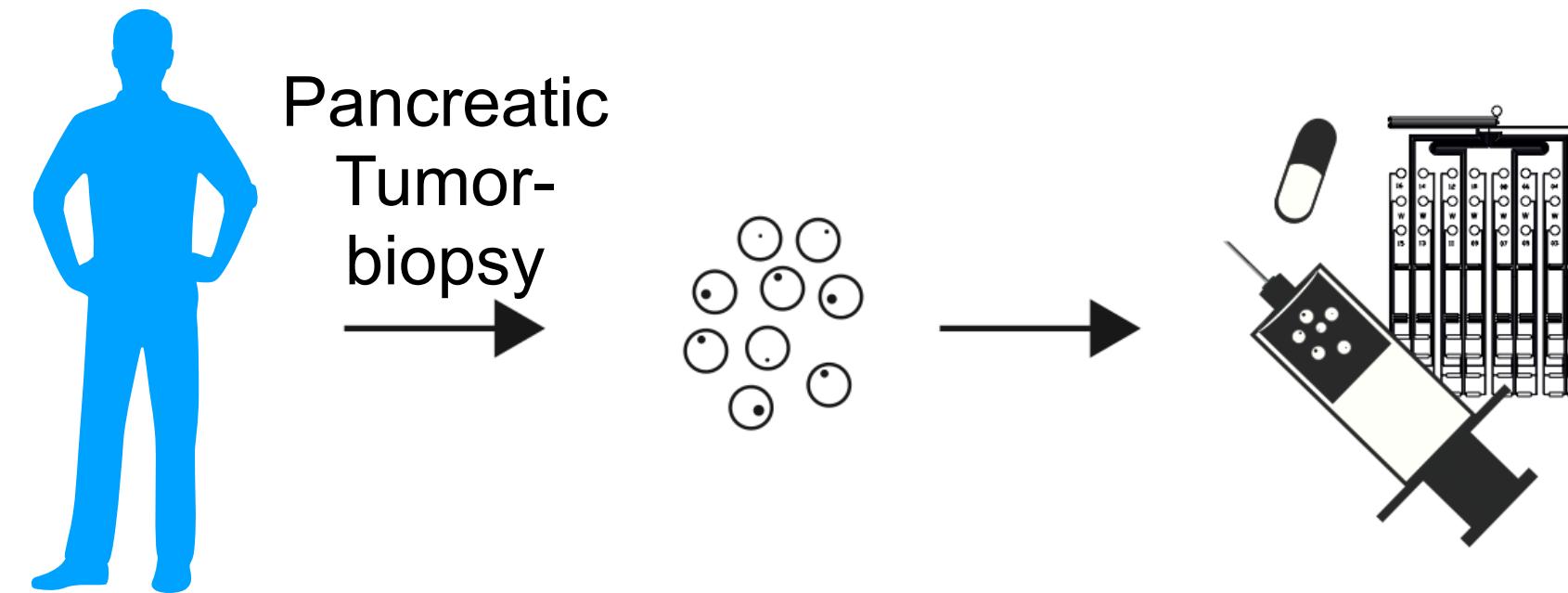


Dynamic logic models from prior knowledge and perturbation data





Microfluidics to screen drugs combinations ex vivo

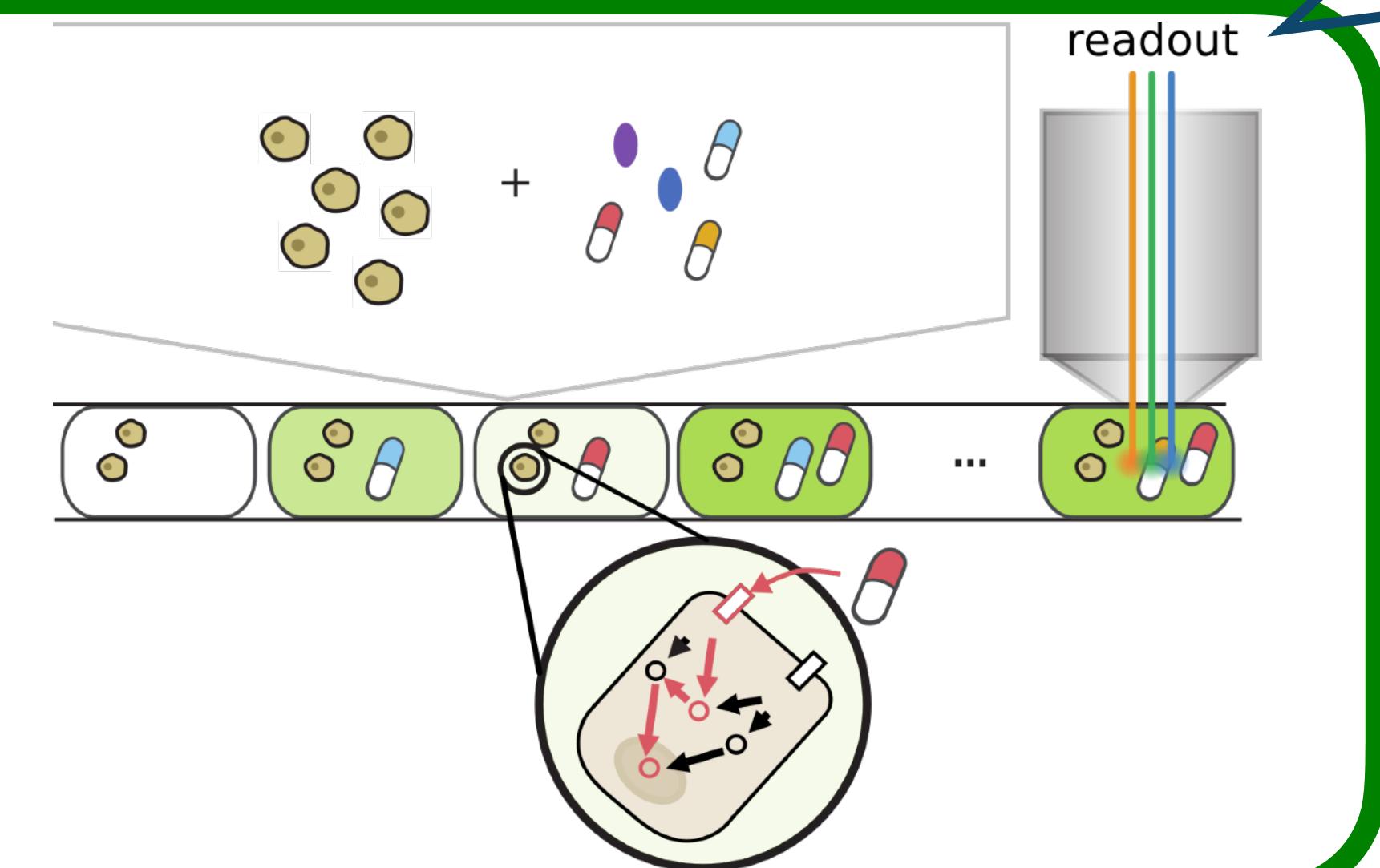


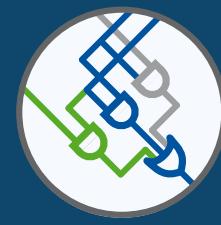
Caspase reporter
+ RNA-seq
Noegel Szalai et al
Nat Comm, 2022

Microfluidic-based screenings of drugs

w. C. Merten (EMBL-HD)
& T. Cramer/U. Neumann (UKAACHEN)

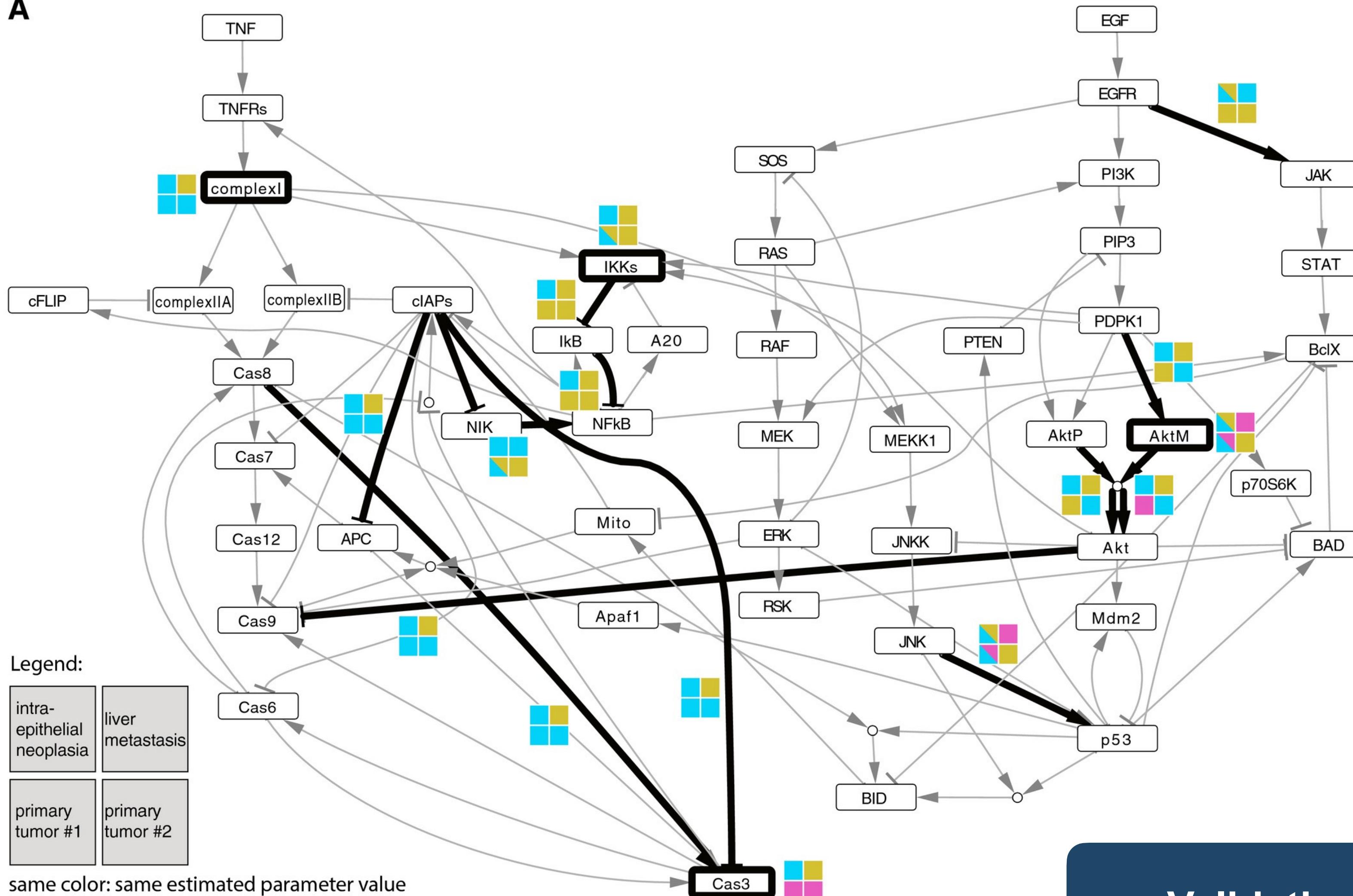
Eduati Utharala et al *Nature Comm* 2018
Utharala et al *Nature Protocols* in press





Model provides patient-specific combinations therapies

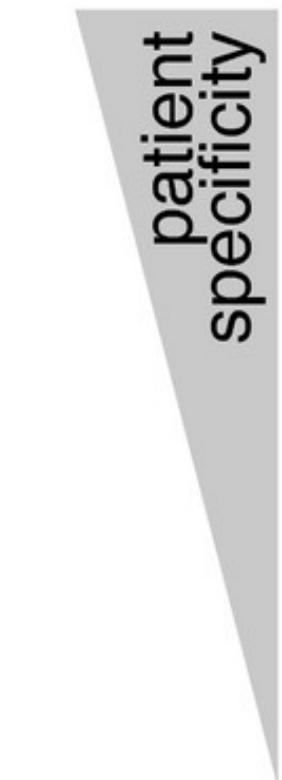
A



biopsy:
primary tumor #1

JAK + Mdm2
IKKs + Mdm2
Mdm2
ktP + PDPK1 + RAS
JAK + JNK
BclX
BclX + Mdm2
JAK + BclX
EGFR + Mdm2
JAK + RAS

psy: primary tumor #2
biopsy: liver metastasis
traepithelial neoplasia

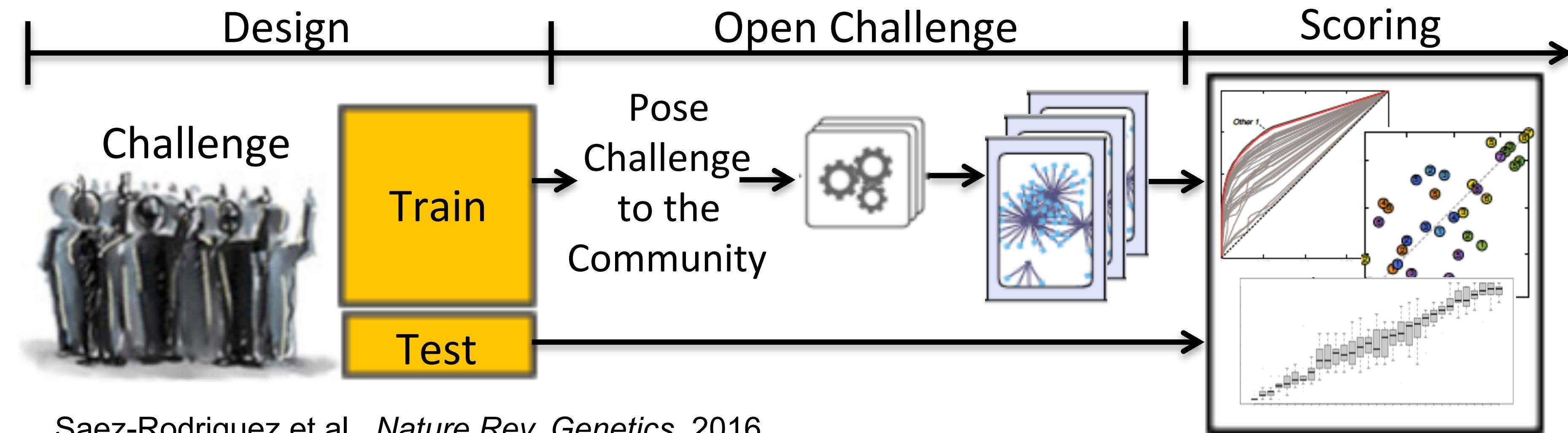


- higher efficacy
- lower efficacy
- equal efficacy

**Validation of predicted drug combinations
in vitro (cell lines) and *in vivo* (xenographs)**



DREAM Challenges: Crowdsourcing computational biomedicine



- **Unbiased** assessment & enhances **reproducibility**
- Can be run on confidential data via virtualisation of algorithms
(Guinney & Saez-Rodriguez, *Nature Biot*, 2018)
- Enables gathering **Wisdom of the Crowds**
- Applied to different contexts from digital mammography analysis to prediction of heart failure from genetics and microbiome



Acknowledgements

SaezLab members
& alumni, sp.

Denes Turei

Aurelien Dugourd

Ricardo Ramírez

Jovan Tanevski

Federica Eduati



Collaborators

Founders

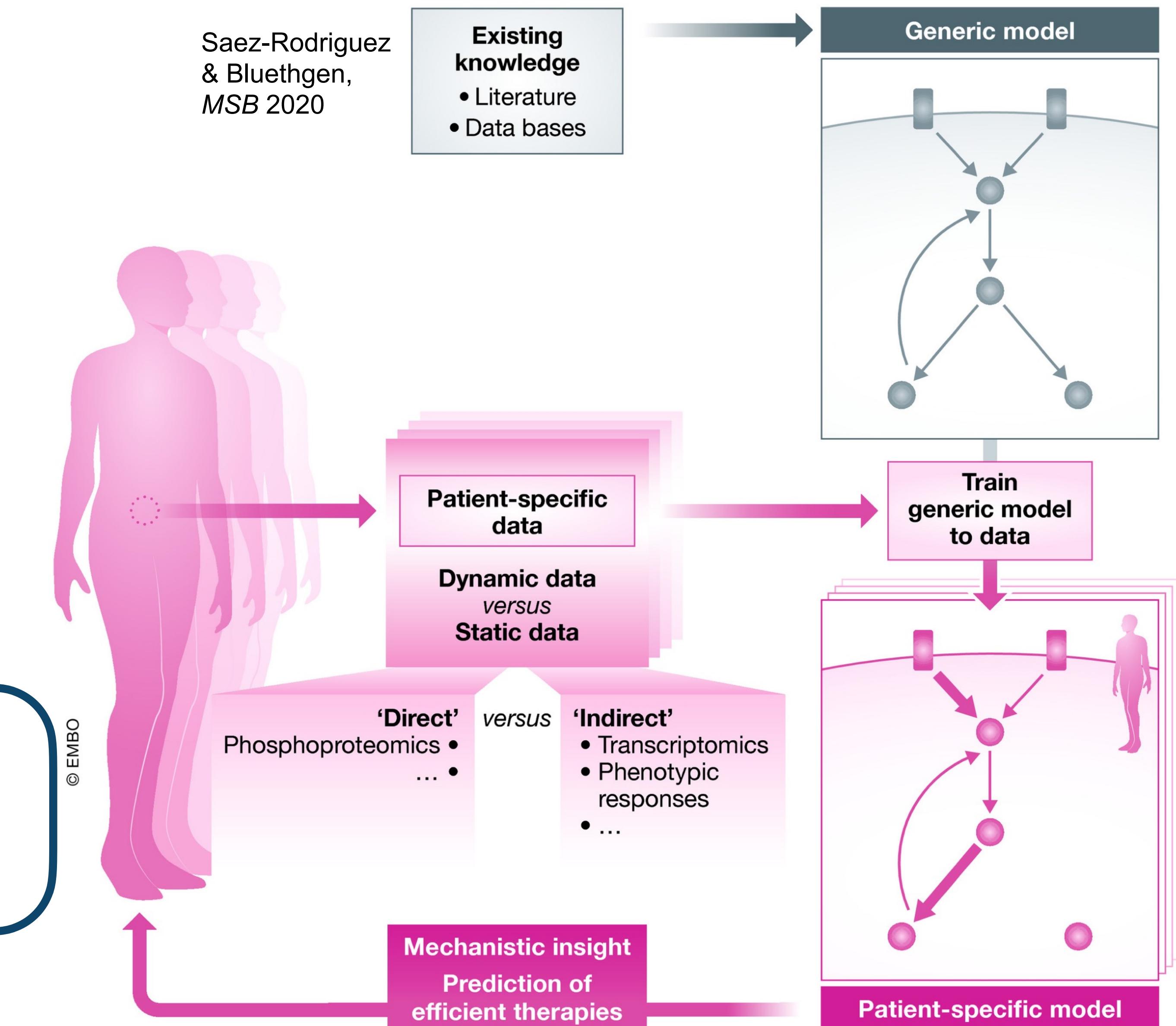


Conflict of Interest: JSR reports funding from GSK and Sanofi & fees from Travere Therapeutics and Astex Therapeutics



Summary: ML + knowledge & dynamic modeling for precision medicine

- Machine learning from omics for personalized medicine: long way to go
 - Biological knowledge: ↑ performance + interpretability
- Footprints: robust features
- Single-cell & spatial omics: new opportunities + challenges
- Dynamic modeling complements ML



saezlab

www.saezlab.org

All tools & resources free open-source
@ saezlab.github.io