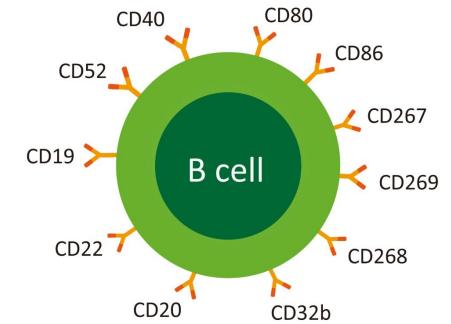
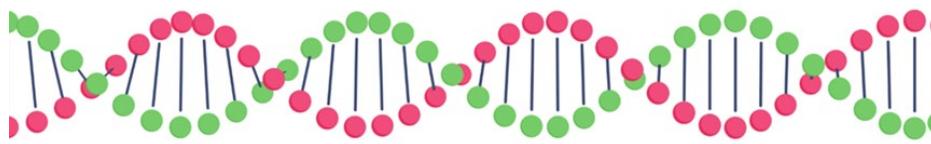
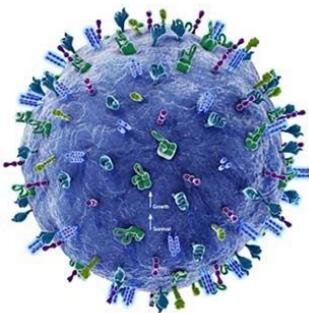




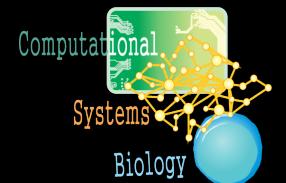
AI – Driven Engineering of the immune system

Aurelien Pelissier



Research summary

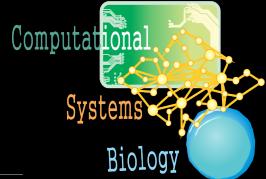
Healthcare &
Life science Dep



Tuesday January 31st, 2023

Our group

Healthcare &
Life science Dep



Maria Rodriguez Martinez
Group leader

Computational systems biology

Developing predictive models for precision medicine

<https://www.zurich.ibm.com/compsysbio/>

*Statistical inference
Mathematical modeling*

Interpretable Machine learning



Aurelien Pelissier
PhD student



Anna Weber
PhD student



An-phi Nguyen
PhD student



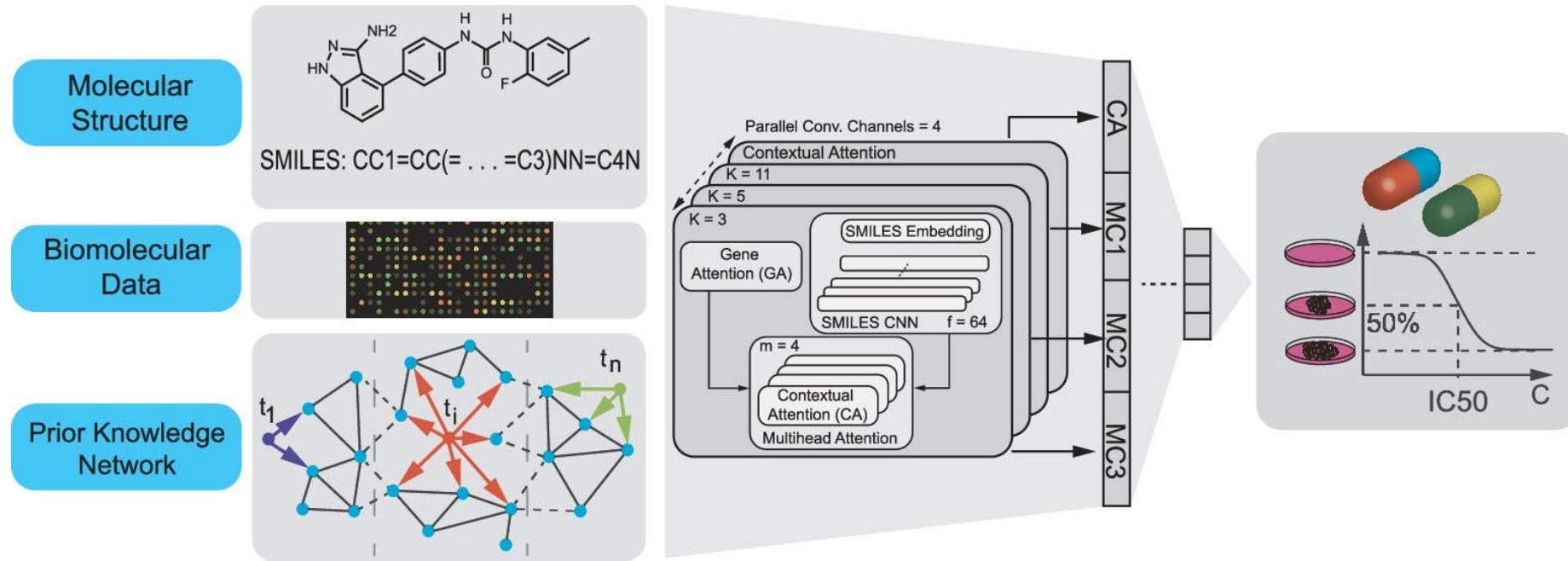
Alice Driessen
PhD student



Nicolas Deutschmann
Postdoc

Drug design

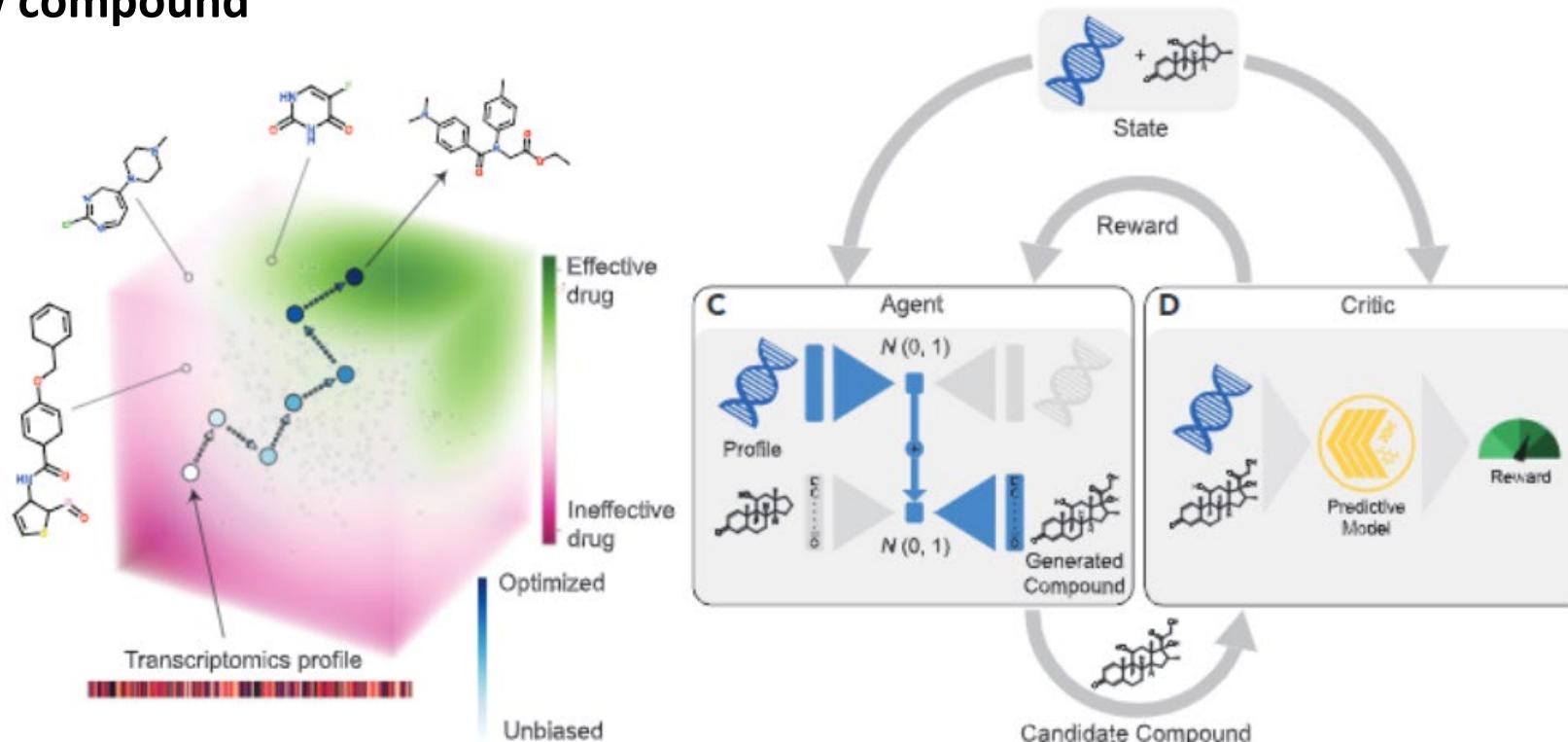
Predict drug sensitivity



Manica, Matteo, et al. "Toward explainable anticancer compound sensitivity prediction via multimodal attention-based convolutional encoders." *Molecular Pharmaceutics* 16.12 (2019)

Drug design

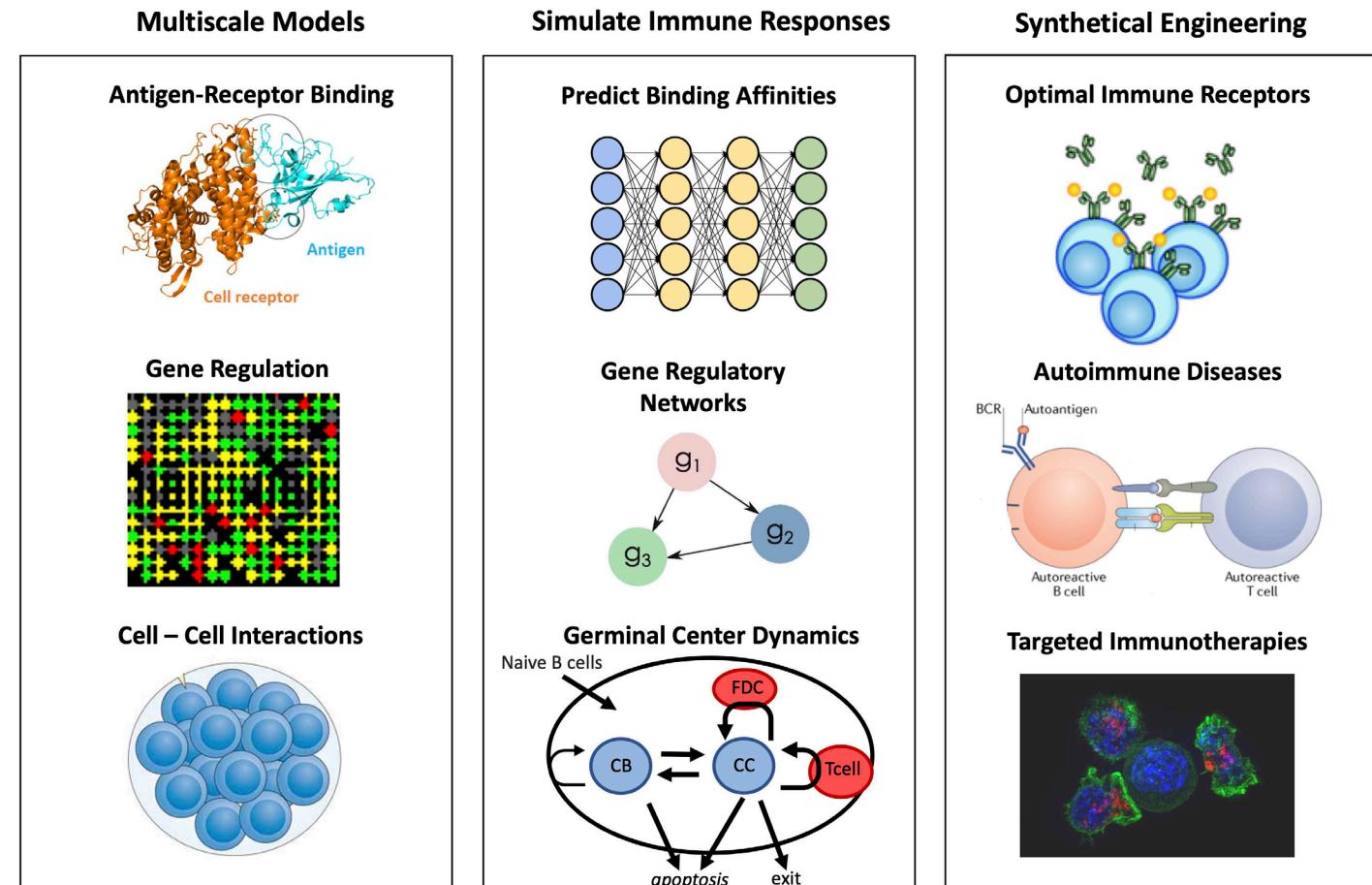
Designing new compound



Born, Jannis, et al. "De novo generation of hit-like anticancer molecules from transcriptomic data via reinforcement learning." *Iscience* 24.4 (2021): 102269.

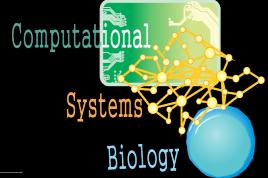
Hybrid models of the immune system:

- Combination of deterministic, stochastic and AI-modelling.
- Prediction of receptor binding to antigen, cellular interactions, etc.
- Predict cell fate following antigen exposure.

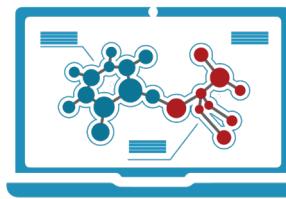


AI Engineering of the immune system

Healthcare &
Life science Dep

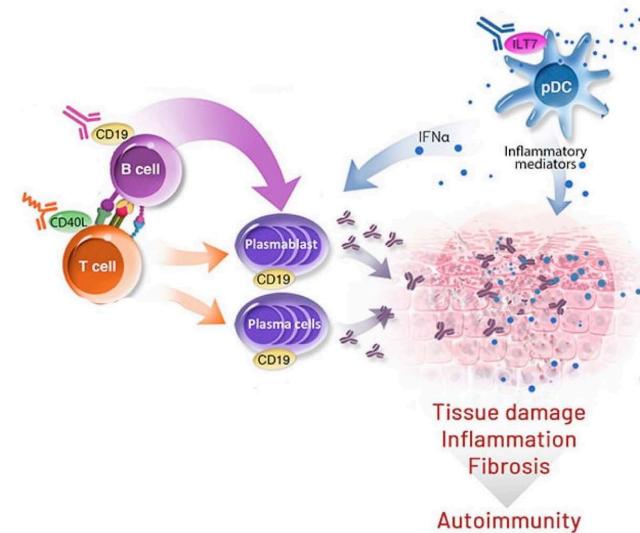


In silico
simulations of
the immune
responses

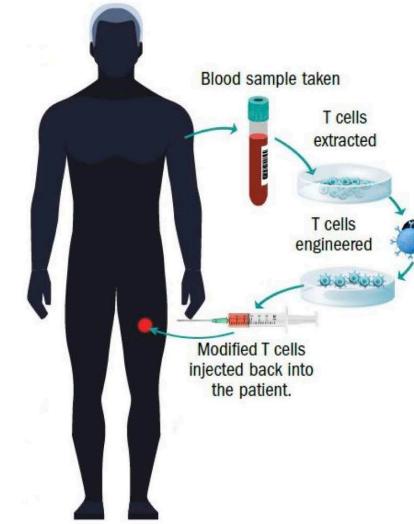


- ✓ Fast
- ✓ Cheap
- ✓ Reproducible

Understanding Autoimmune Diseases



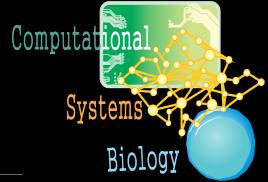
Optimization of Cancer Immunotherapies



Other: vaccine development, optimization of serological tests, better understanding of the immune system, etc.

Background

Healthcare &
Life science Dep



Current position:

PhD researcher at IBM Research, The logo for COSMIC (Computational Systems Biology) features the word "cosmic" in a stylized, colorful font where each letter has a small human-like figure above it, all set against a green and blue background.

Degree:

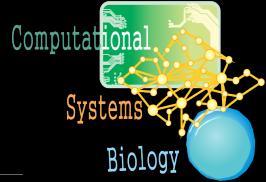
Master in fundamental physics from the
École Normale Supérieure Paris-Saclay (France)

Research experience:

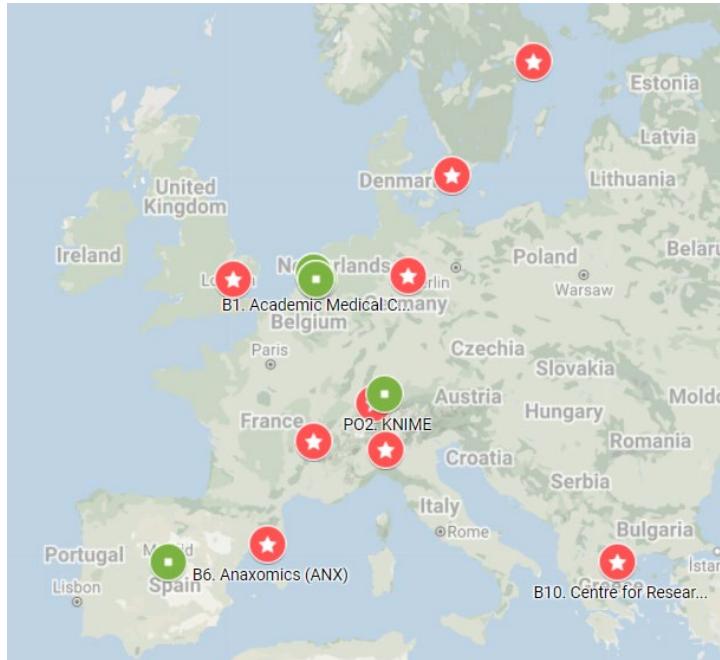
EPFL (Switzerland) – 4 months
University of British Columbia (Canada) – 8months
University of Hokkaido (Japan) – 12 months

COSMIC h2020 Consortium

Healthcare &
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**Combatting Disorders of Adaptive
Immunity with Systems Medicine**



10 Labs in 9 countries

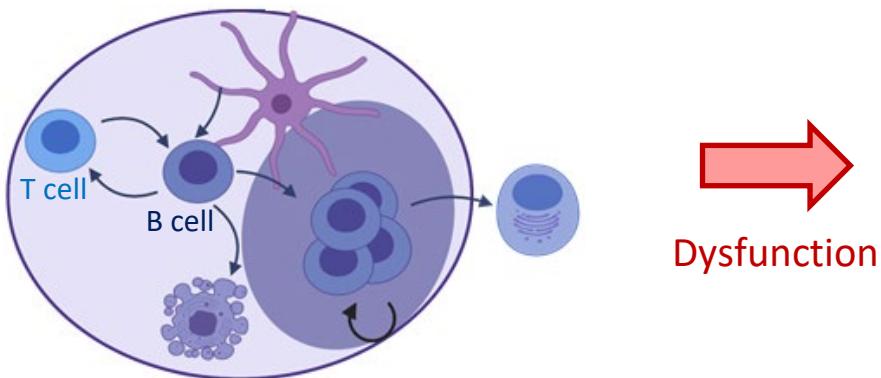


14 PhD student (7 computational, 7 experimental)



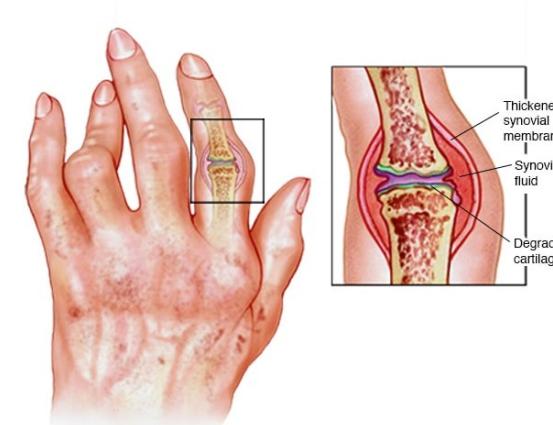
Combatting Disorders of Adaptive Immunity with Systems Medicine

Germinal center



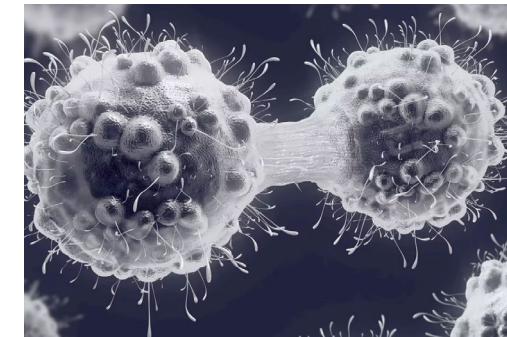
Adaptive immunity

Autoimmune disease



Rheumatoid arthritis (RA)

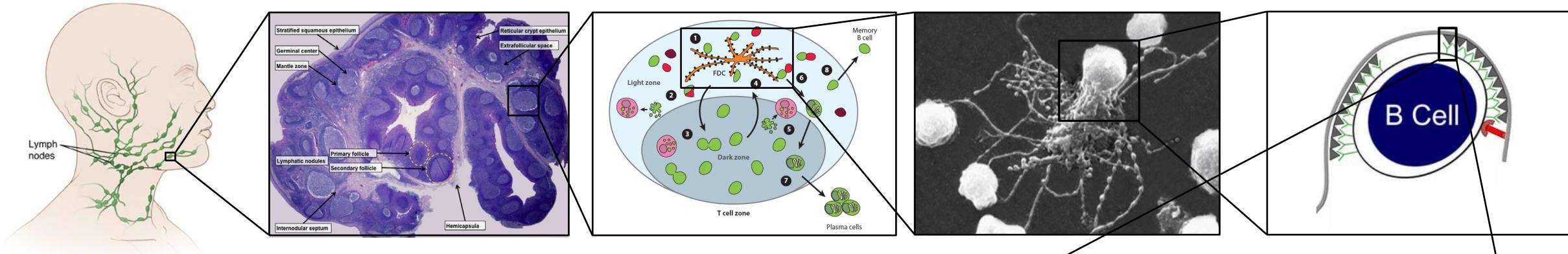
Cancer



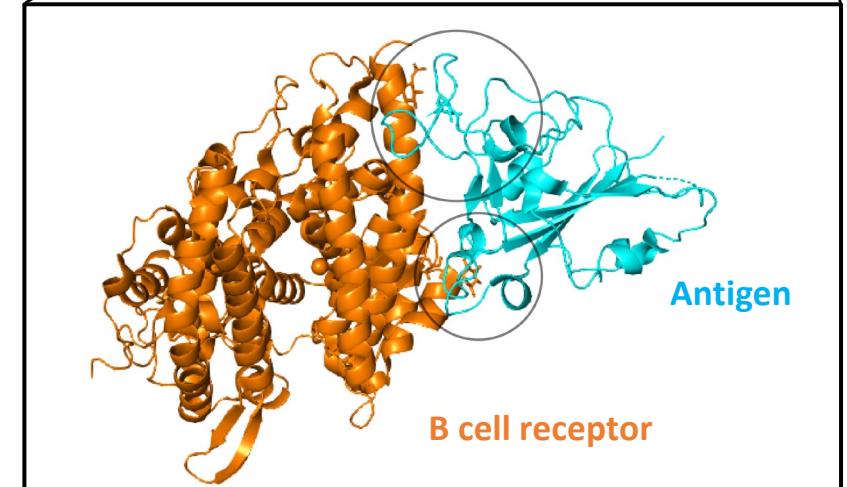
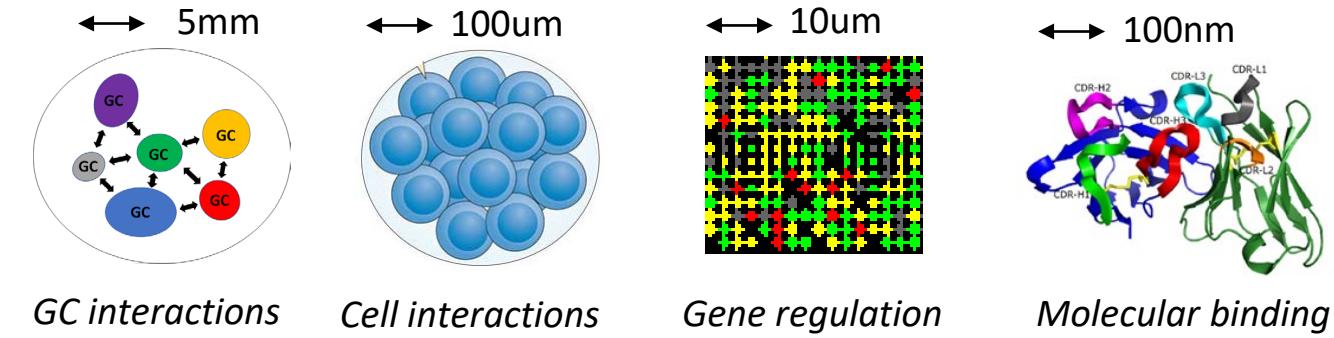
B-cell lymphoma (BCL)

OR

Adaptive Immune system

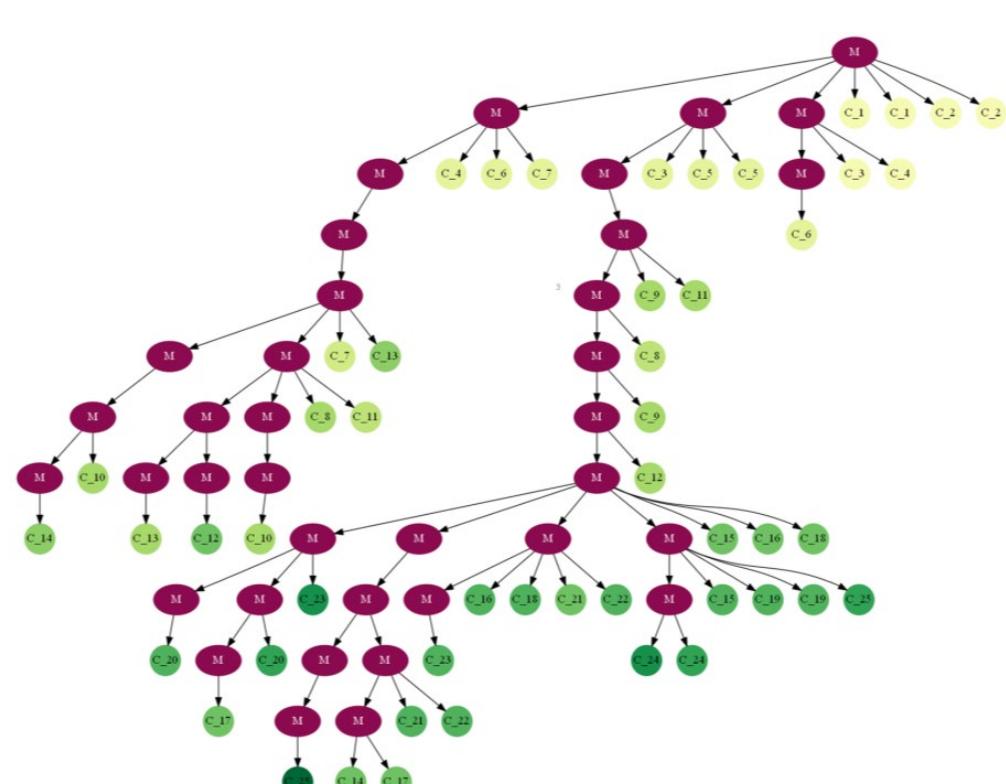


A multiscale problem:



Adaptive Immune system

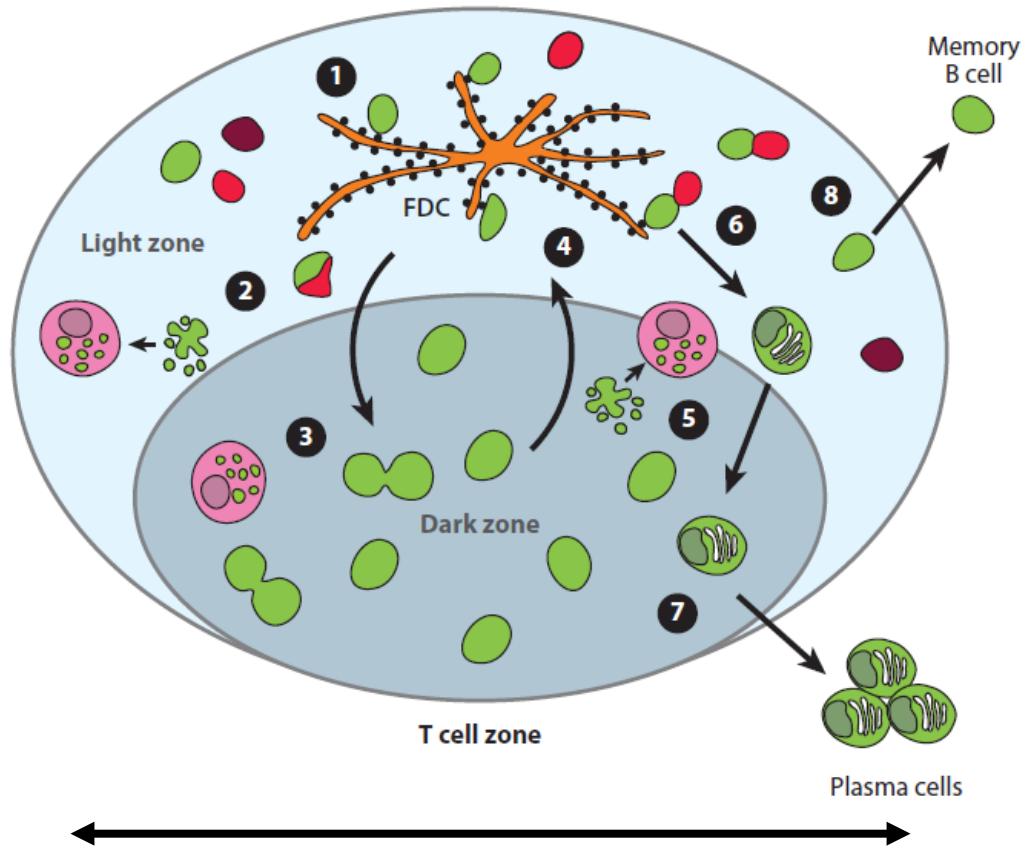
Germinal center



B cell affinity maturation (Phylogenetic tree)

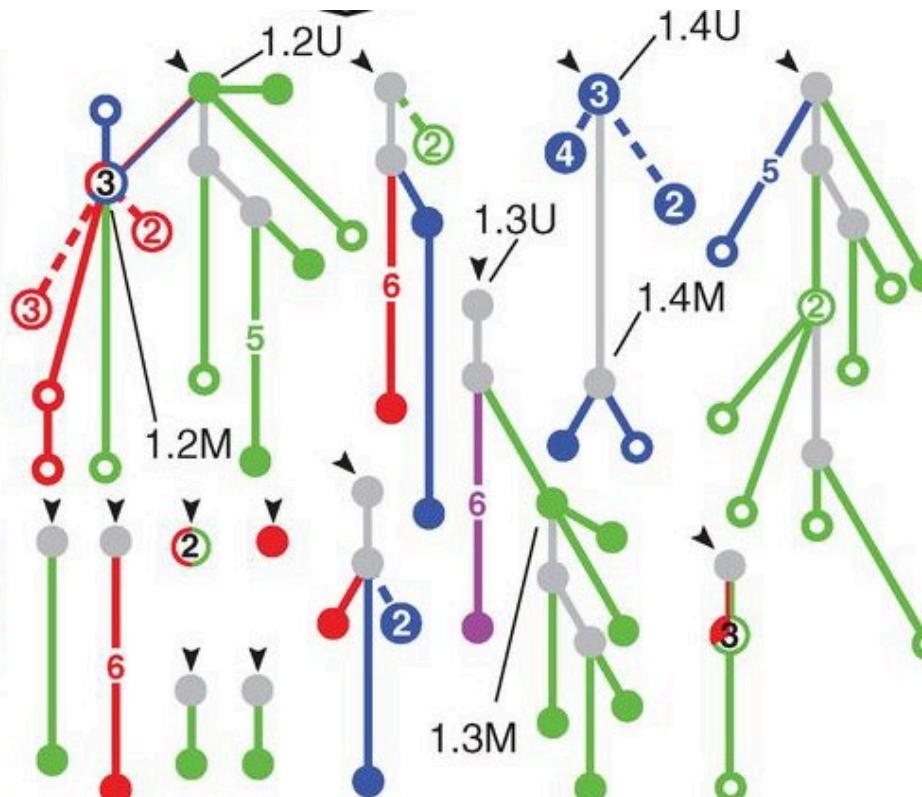
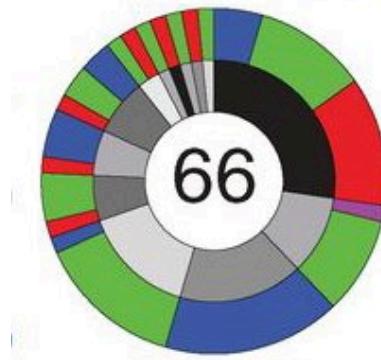
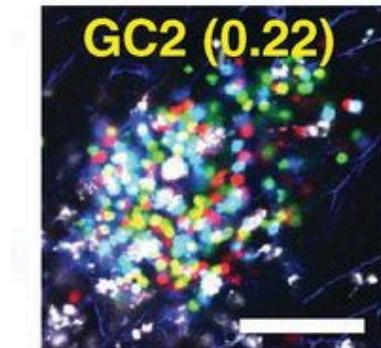
- Antigen
- GC B cell
- Apoptotic B cell
- Plasma cell
- Tfh cell
- Tfr cell
- Tingible body macrophage

Germinal centers dynamics



Adaptive Immune system

Germinal center

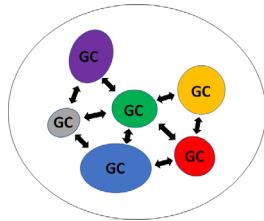


Germinal center seeded by approximately 1000 B cells

These B cells proliferate and compete with other B cell families.

Research Questions

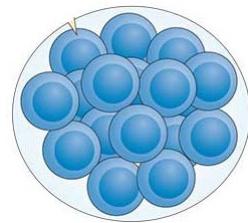
5mm
↔



GC convergent evolution:

How and how often do GCs communicate with each other in the Lymph node ?

100um
↔



GC cells dynamic:

How do cells interact with each other in the Germinal center?

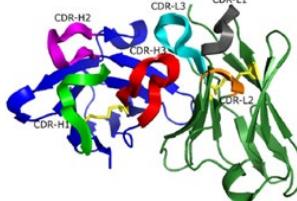
10um
↔



Lymphocytes transcriptomic regulation:

How are B cells and T cells transcriptomic factors regulated?

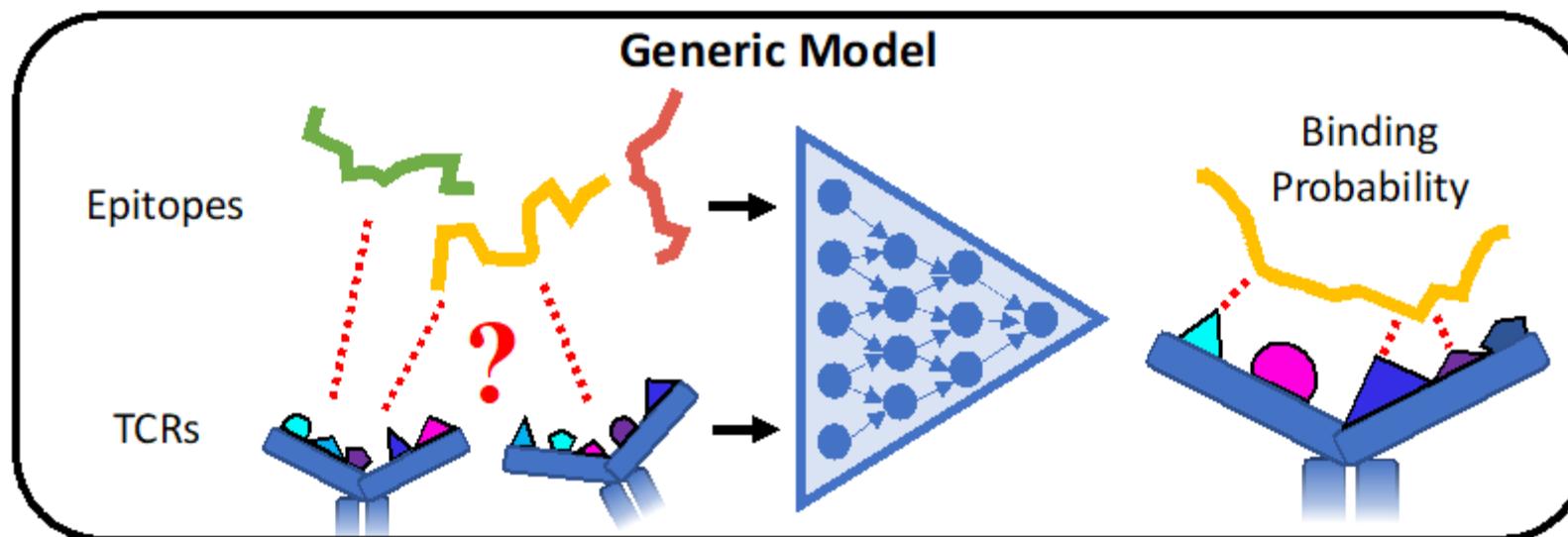
100nm
↔



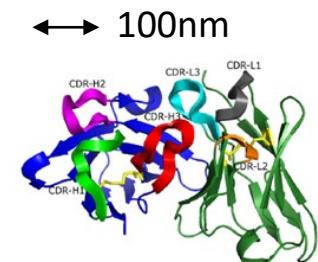
Antigen - Antibody binding:

How do Antibody bind to Antigen, can we predict the affinity ?

T cell receptor binding



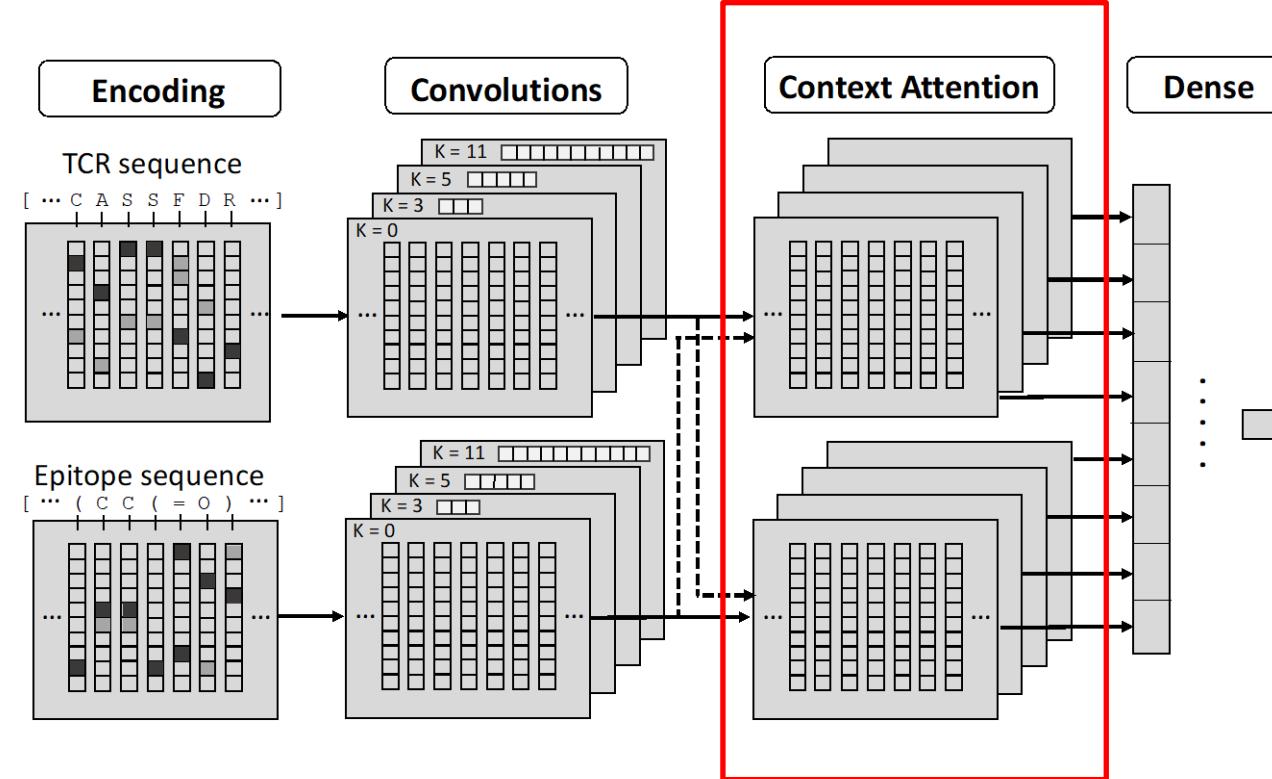
Anna Weber, Jannis Born, María Rodriguez Martínez, **TITAN: T-cell receptor specificity prediction with bimodal attention networks**, *Bioinformatics*, Volume 37



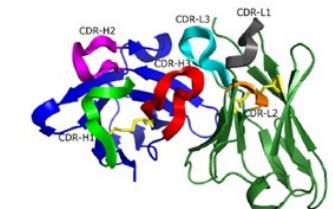
Molecular binding

T cell receptor binding

TITAN Architecture



↔ 100nm



Anna Weber, Jannis Born, María Rodriguez Martínez, **TITAN: T-cell receptor specificity prediction with bimodal attention networks**, *Bioinformatics*, Volume 37



Molecular binding

T cell receptor binding

TITAN performances

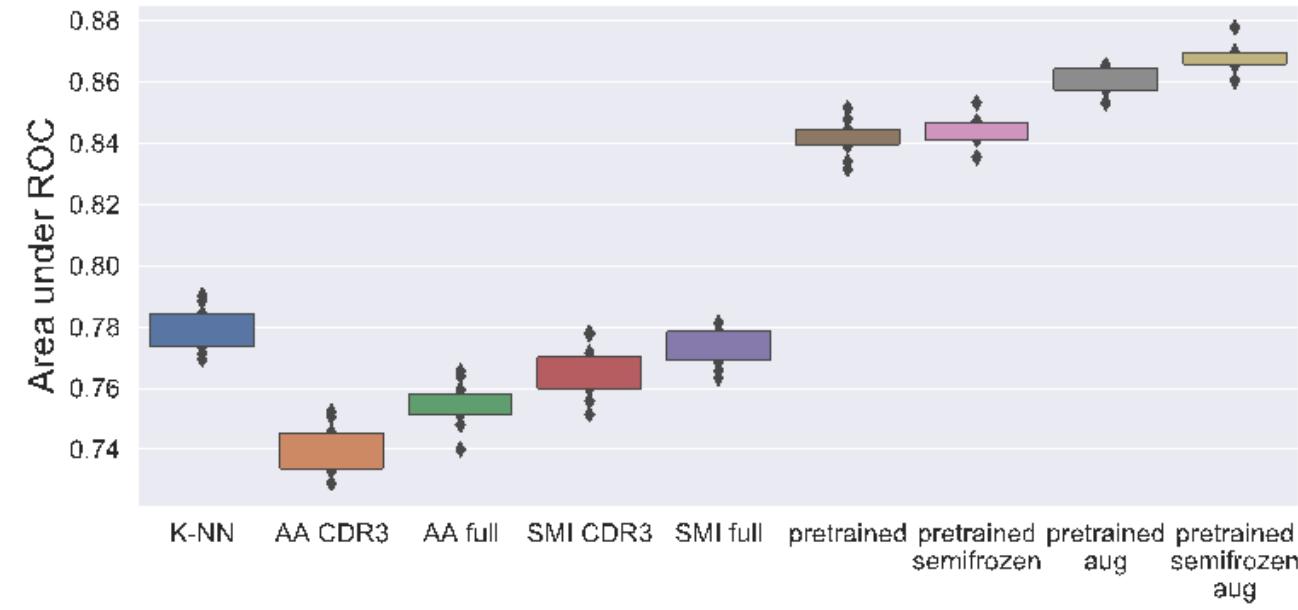
Data:

VDJ database

with 40,438 TCR binding 191 epitopes

Covid Dataset

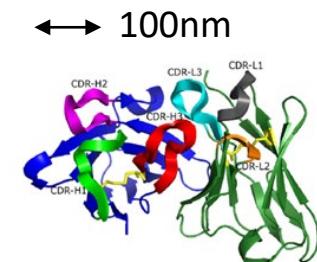
with 154,320 TCR binding 269 epitopes



TITAN models pretrained
on BindingDB



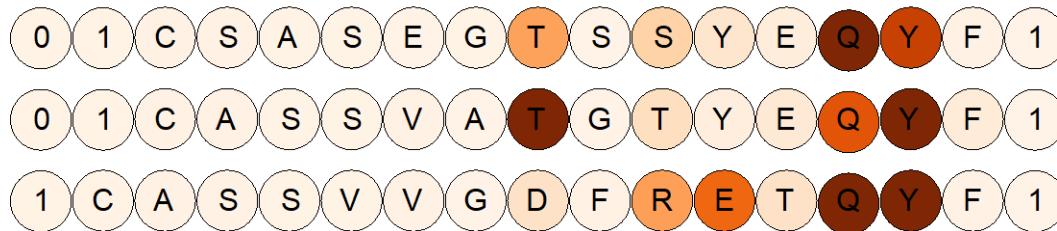
Anna Weber, Jannis Born, María Rodriguez Martínez, **TITAN: T-cell receptor specificity prediction with bimodal attention networks**, *Bioinformatics*, Volume 37



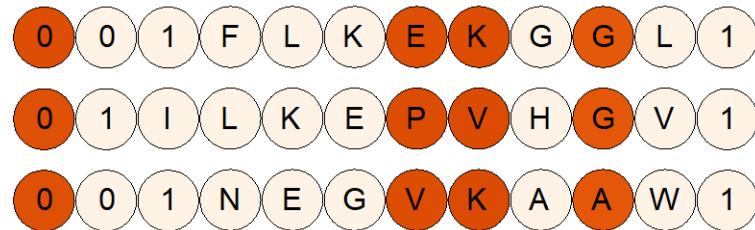
Molecular binding

T cell receptor binding

a CDR3 sequences

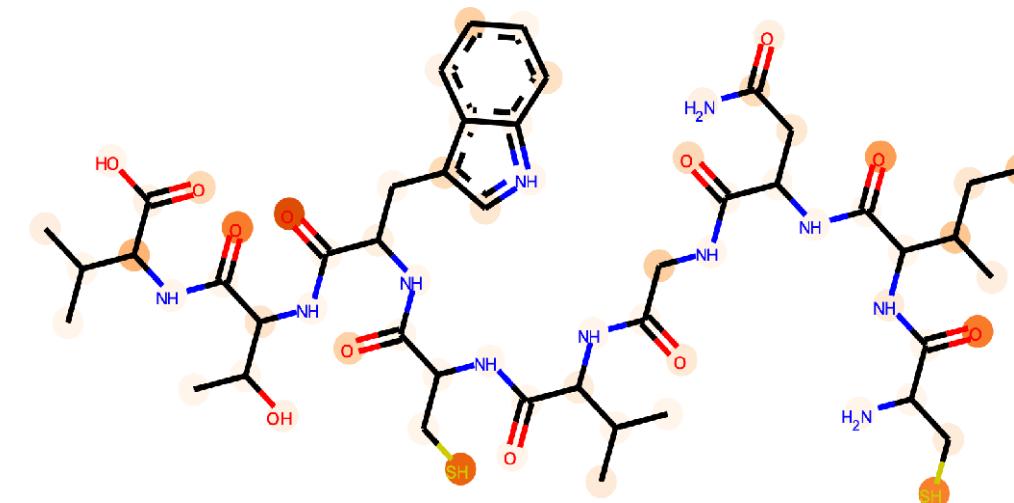


b Epitope sequences

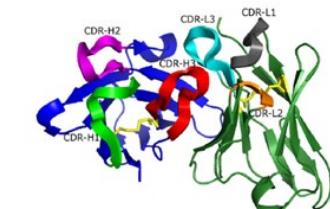


high
AU
low

Epitope CI NGVCWTV



↔ 100nm



Anna Weber, Jannis Born, María Rodriguez Martínez, **TITAN: T-cell receptor specificity prediction with bimodal attention networks**, *Bioinformatics*, Volume 37

Molecular binding

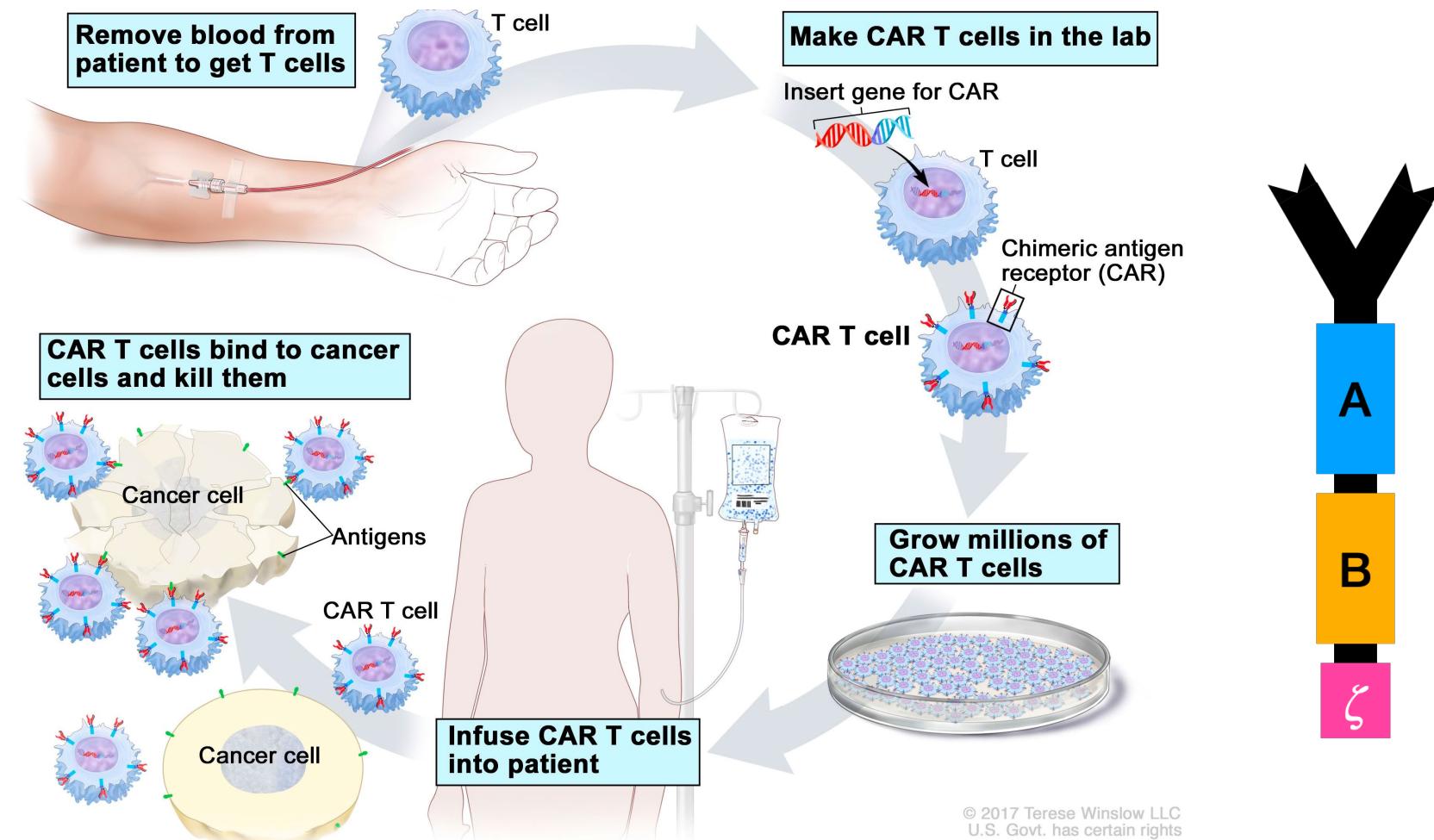
CAR T-cell therapy

Engineering Patients' Immune Cells to Treat Their Cancers

- Different CAR designs (>100 000 options)
- Different T cell functionalities
- Different therapy efficacies
- Predict T cell function from design

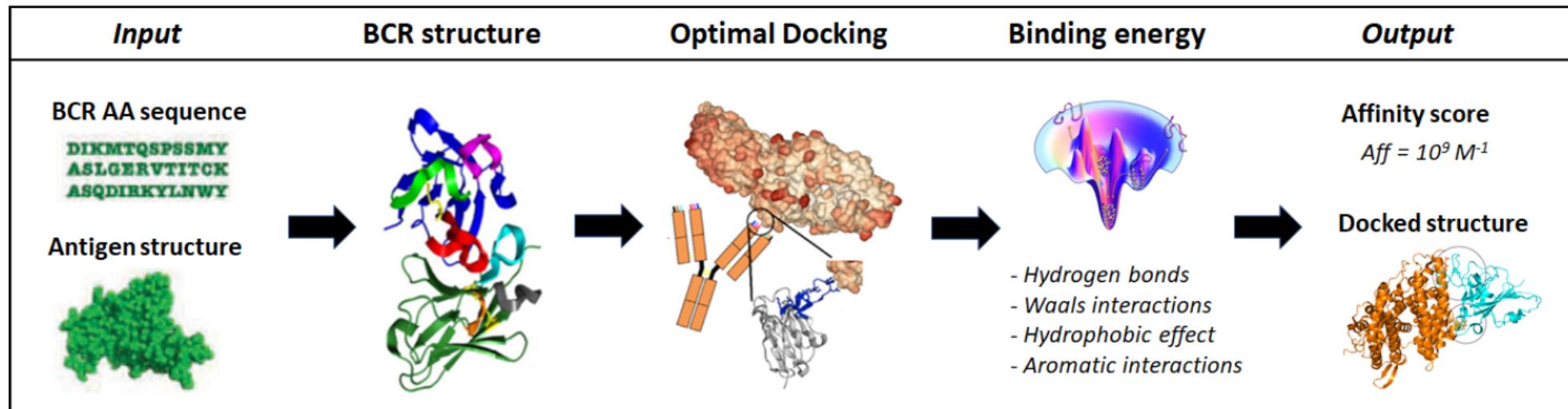


Alice
Driessens



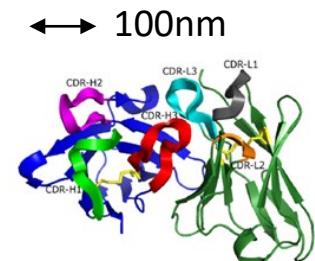
B cell receptor binding

Antibody – Antigen affinity prediction pipeline



Challenges:

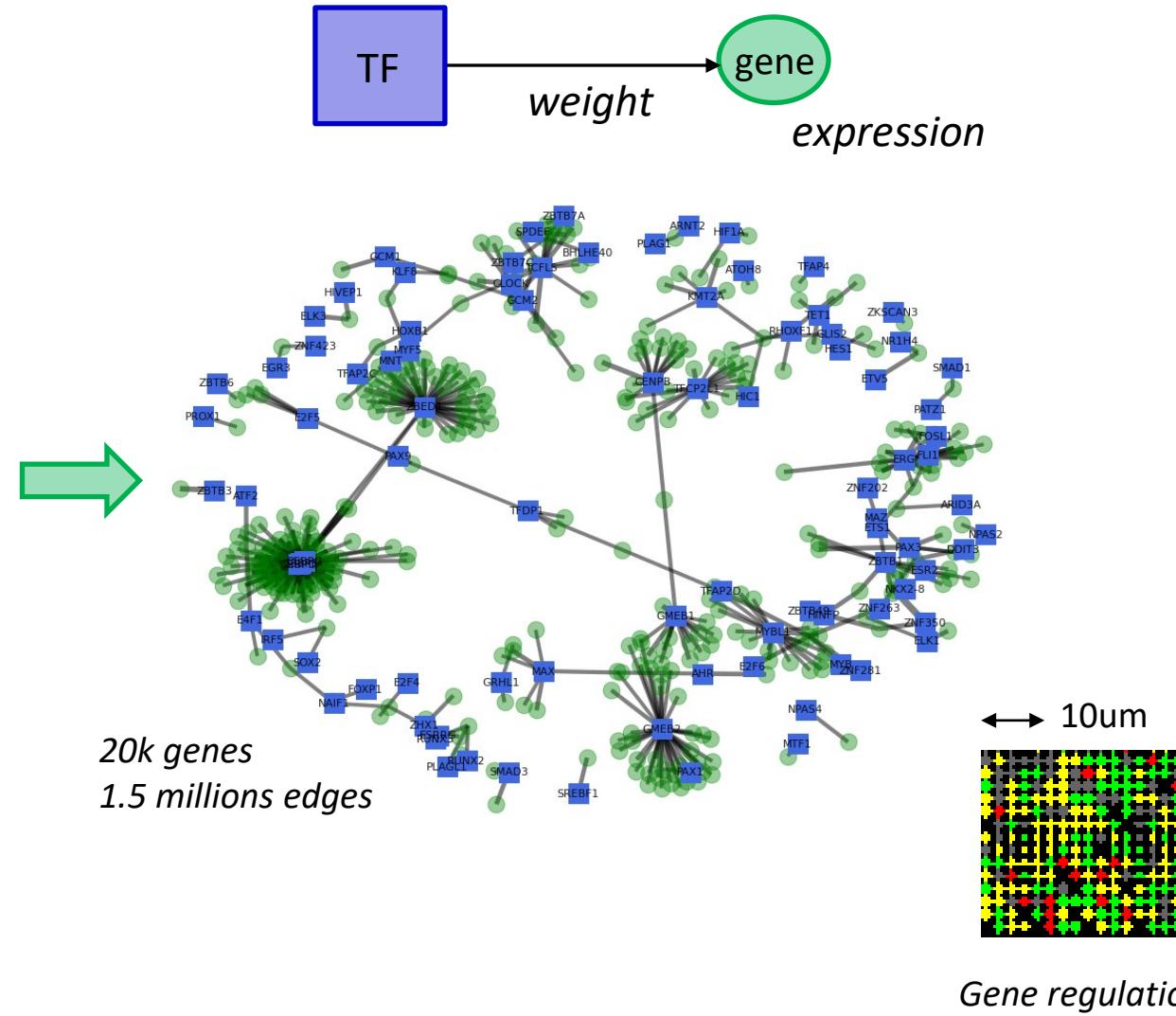
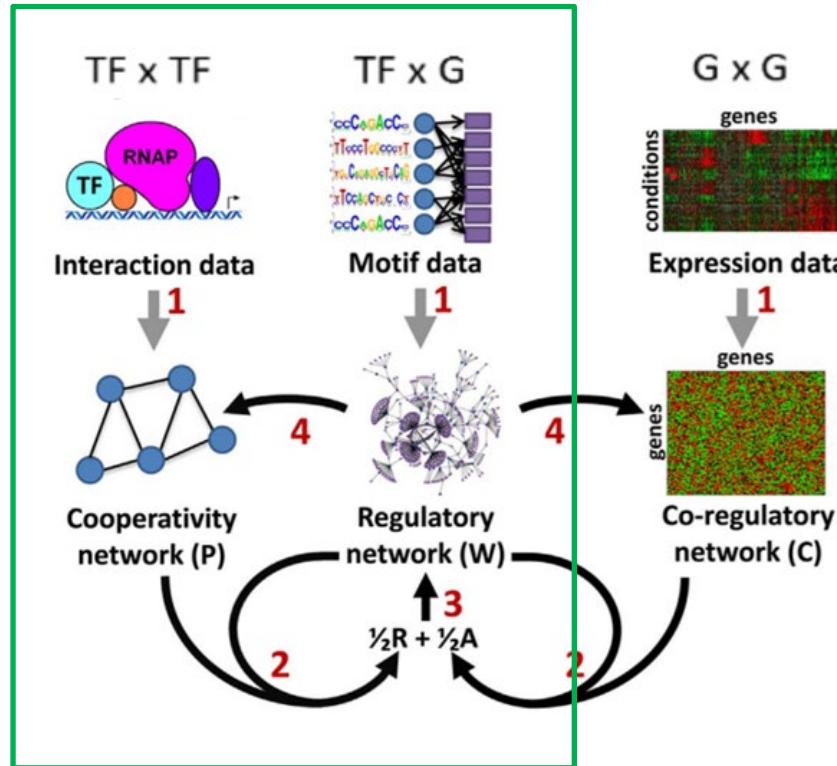
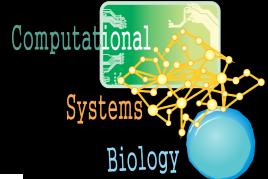
- *B cells are more specific to antigens than TCR*
- *Much less data are available*



Molecular binding

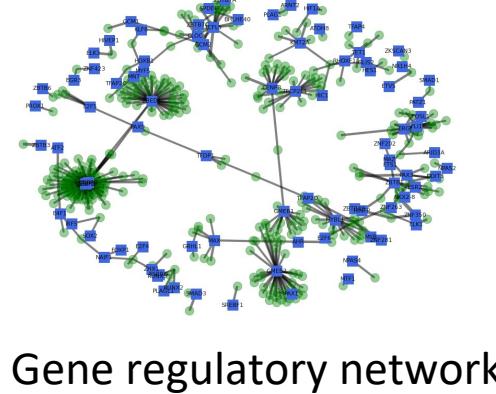
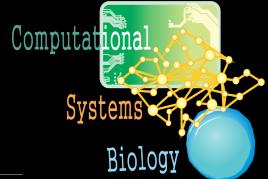
Gene regulatory network

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Gene regulatory network

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Gene regulatory network



STAT1
...
TNF



List of disease associated gene



Key driver analysis
(causality statistical test)

STAT1
...
TNF

List of genes *causative*
of the disease

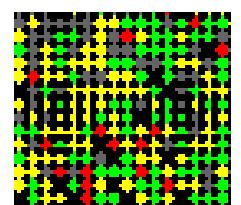


Percio S Gulko,
Medical Doctor

Rheumatologist



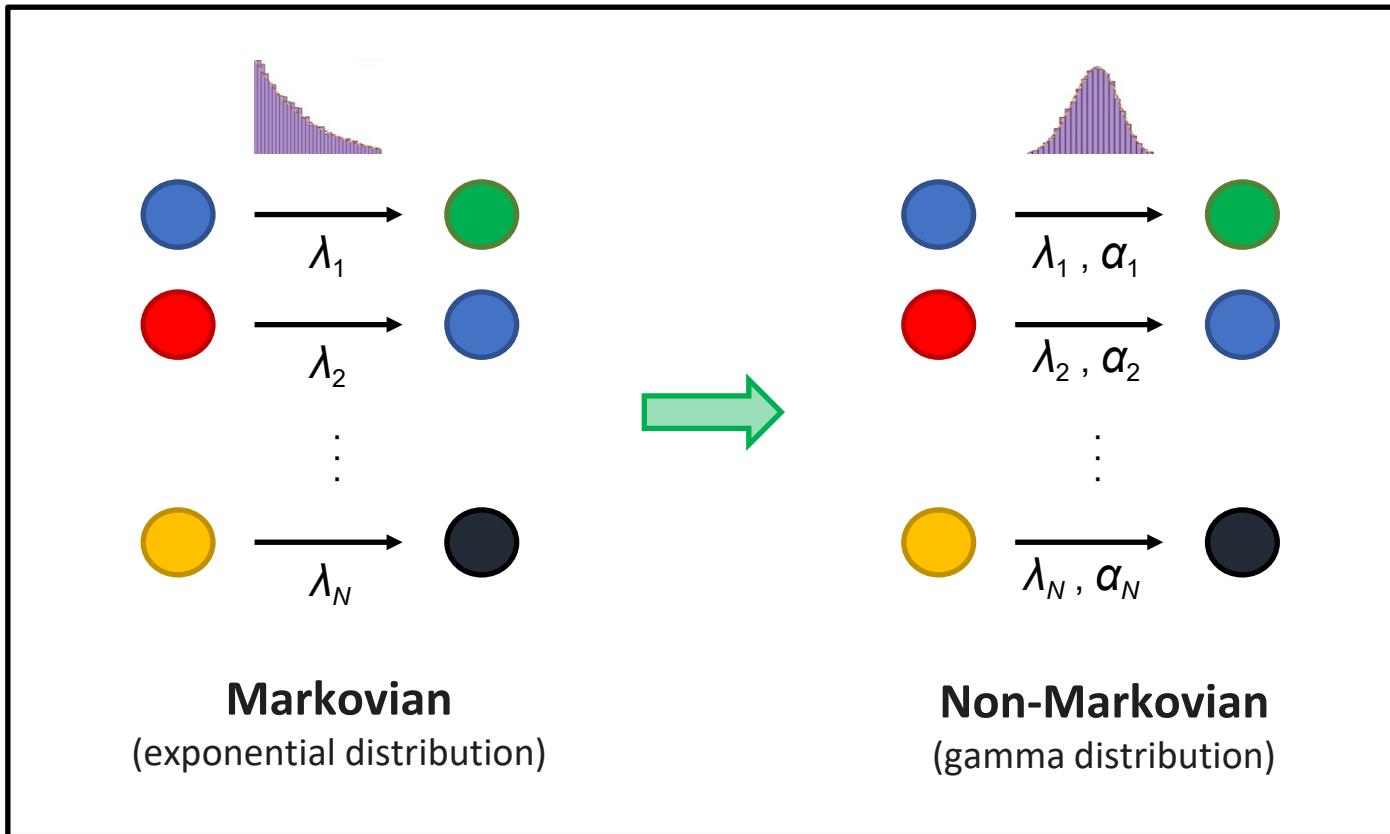
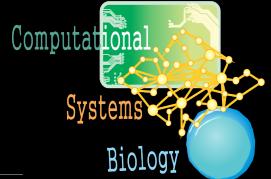
↔ 10um



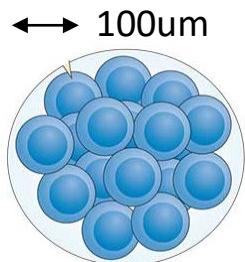
Gene regulation

Simulating Non-Markovian processes

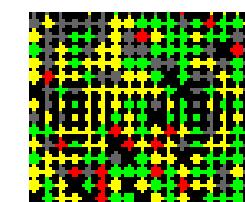
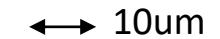
Healthcare &
Life science Dep



Pélissier, Aurélien, et al. “**Simulating Non-Markovian stochastic processes with a Rejection Gillespie algorithm.**” *Proceedings of the National Academy of Sciences* (2022, submitted).



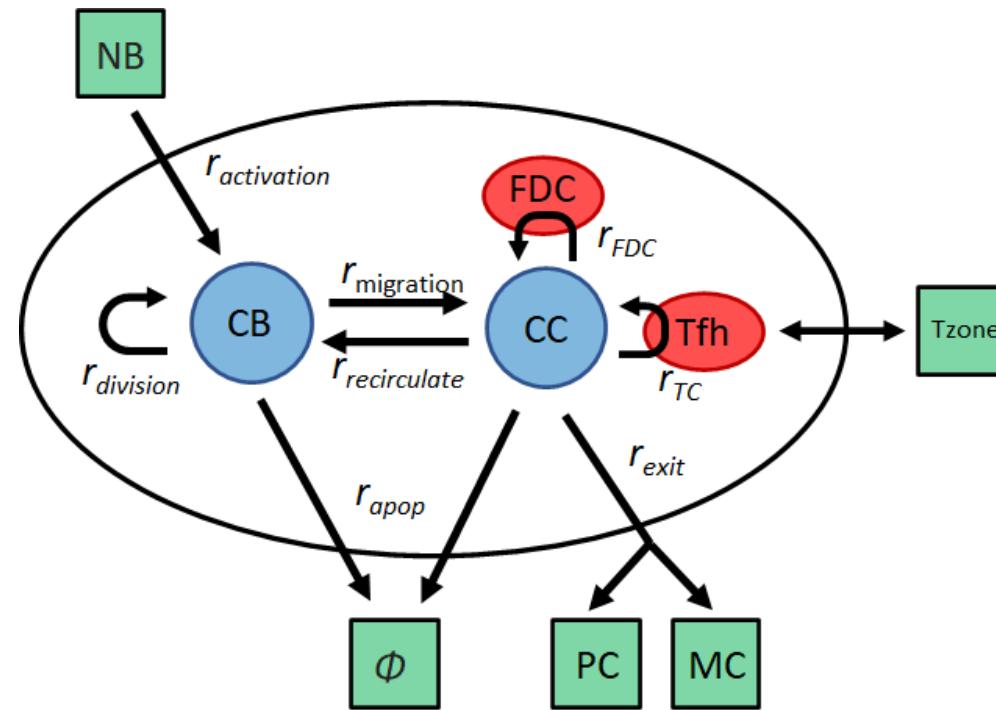
Cell interactions



Simulating Non-Markovian processes

11 stochastic interactions

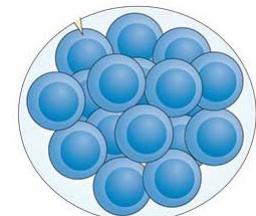
- NB $\xrightarrow[r_{\text{exchange}}]{r_{\text{activation}}} \text{CB}$
- Tfh \longleftrightarrow Tzone
- CB $\xrightarrow[r_{\text{migration}}]{r_{\text{division}}} 2\text{CB}$
- CB $\xrightarrow[r_{\text{migration}}]{r_{\text{apop}}} \emptyset$
- CC or CB $\xrightarrow[r_{\text{apop}}]{r_{\text{TC}}} \emptyset$
- CC + FDC $\xrightarrow{r_{\text{FDC}}} \text{CC} + \text{FDC}$
- CC + Tfh $\xrightarrow{r_{\text{TC}}} [\text{CCTC}]$
- $[\text{CCTC}] \xrightarrow{r_{\text{unbinding}}} \text{CC} + \text{Tfh}$
- $[\text{CC}_1\text{TC}] + \text{CC}_2 \xrightarrow{r_{\text{TC}}} \text{CC}_1 + [\text{CC}_2\text{TC}]$
- CC $\xrightarrow{r_{\text{exit}}} \text{O} (\text{PC or MC})$
- CC $\xrightarrow{r_{\text{recirculate}}} \text{CB}$



↔ 100um



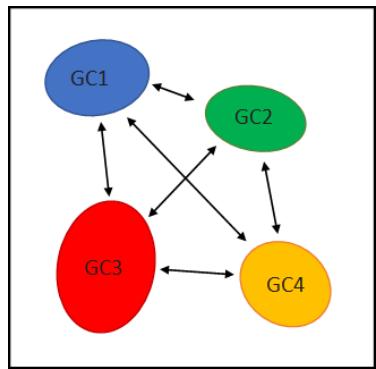
Pélissier, Aurélien, et al. "Computational model reveals a stochastic mechanism behind germinal center clonal bursts." *Cells* 9.6 (2020): 1448.



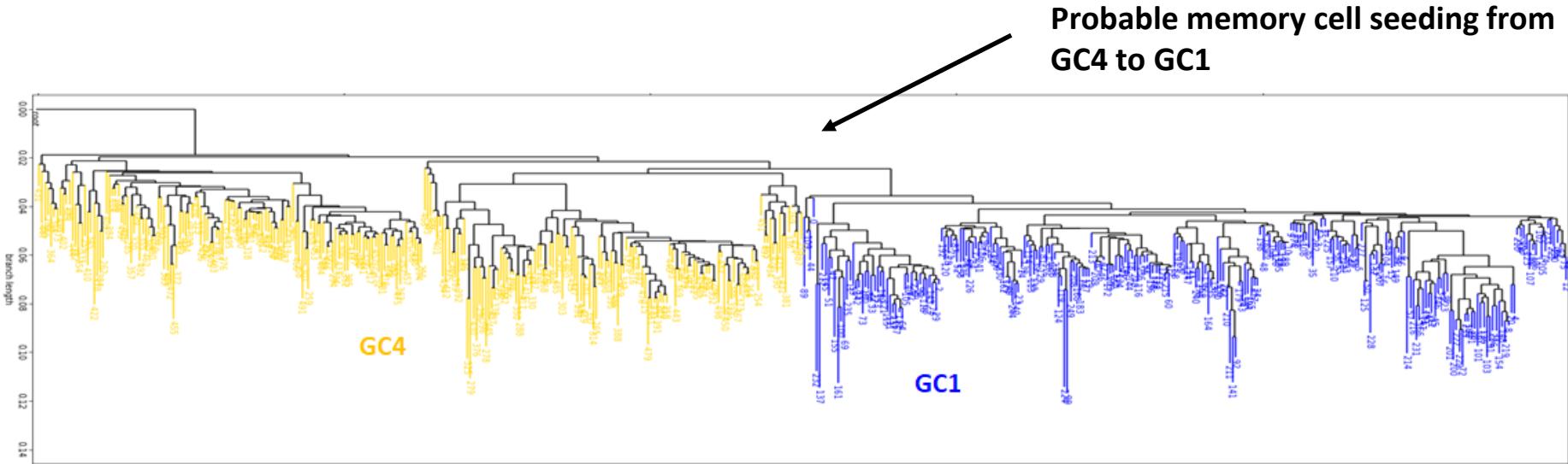
Cell interactions

Germinal center interactions

Lymph node

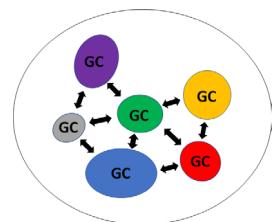


B cell bulk sequencing, in
collaboration with COSMIC partner



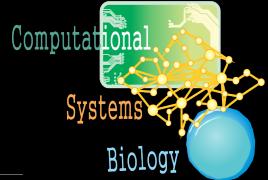
Pélissier, Aurélien, et al. “**Germinal Centers Convergent Evolution and Memory B-cell Reentry in Human Lymph Nodes.**” Molecular Biology and Evolution (2022, submitted).

5mm
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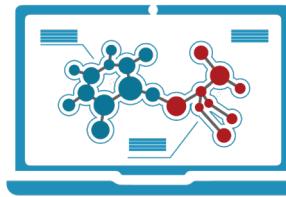


AI Engineering of the immune system

Healthcare &
Life science Dep

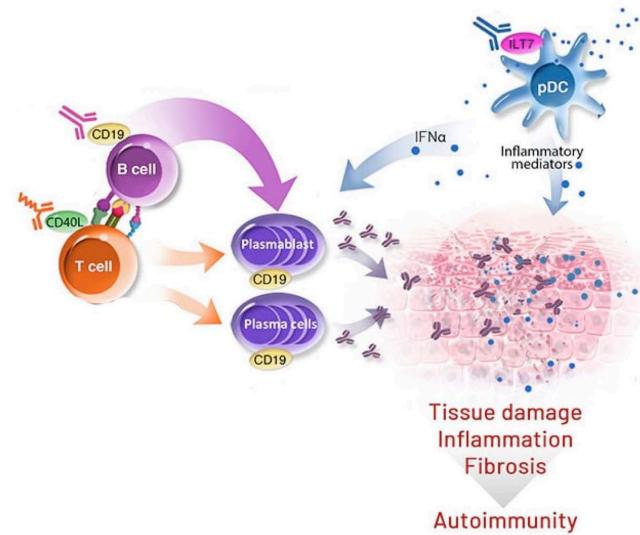


In silico
simulations of
the immune
responses

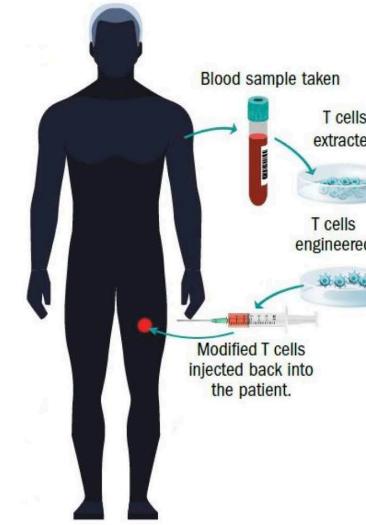


- ✓ Fast
- ✓ Cheap
- ✓ Reproducible

Understanding Autoimmune Diseases



Optimization of Cancer Immunotherapies



Other: vaccine development, optimization of serological tests, better understanding of the immune system, etc.



Thank you for
your attention

Q & A

 <https://www.aurelienpelissier.com/>
 <https://github.com/Aurelien-Pelissier>