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AUDACIS - Antwerp Unit for Data Analysis and Computation in Immunology and Sequencing
University of Antwerp

Revealing vaccine-induced T-cell responses using Artificial Intelligence

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17 October 2024

Gent, Belgium

The T-cell receptor

PDB: 3PL6

T-cell epitope recognition

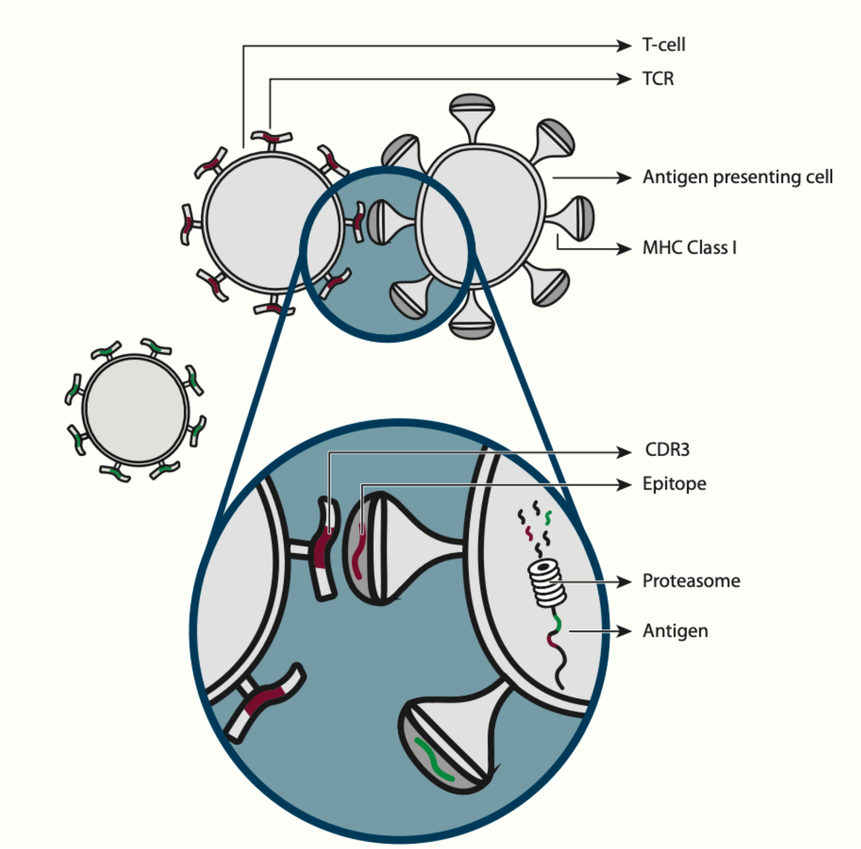


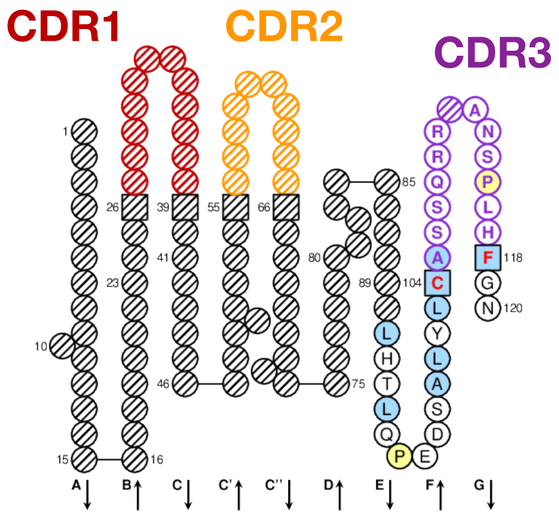
Image credit: Seppe Wouters

T-cell receptor (TCR) complex binds immunogenic epitopes

- First step in triggering an adaptive immune response
- Each T-cell clone has a unique TCR complex that binds a unique set of epitopes
- Each TCR complex consists of an alpha/beta or gamma/delta pair

Fixed structure with variable regions

Beta chain example:



IMGT/Collier de Perles
Protein representation

TRBV4-2*01 — *V gene*

CASSQRRANSPLHF — *CDR3 junction*

TRBJ1-6*02 — *J gene*

We need AI to study TCRs

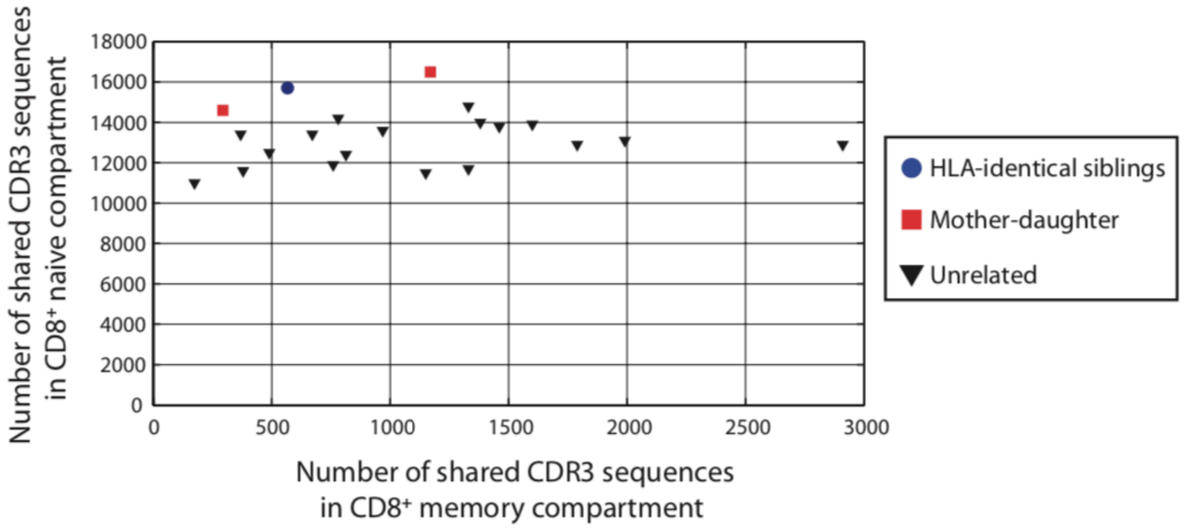
TCR repertoires are big

- Typical sample generates thousands of unique TCRs

aminoAcid	frequencyCount (%)	vGeneName	jGeneName
CASSYGVDRQETQYF	0.002746821535080840	TCRBV06-05	TCRBJ02-05
CASSPGGSGSSYEQYF	0.0010045518756867100	TCRBV04-02	TCRBJ02-07
CASSLAGGSVNTEAFF	0.0015539161827028700	TCRBV05-01	TCRBJ01-01
CSVPRVDYGYTF	7.06325537592215E-04	TCRBV29-01	TCRBJ01-02
CASSYRRELNTEAFF	0.001161513106262750		TCRBJ01-01
CSVRGMVNTEAFF	5.96452676188981E-04	TCRBV29-01	TCRBJ01-01
CAWSLSAFNSPLHF	5.80756553131377E-04	TCRBV30-01	TCRBJ01-06
CASSSQTDRANYGYTF	7.06325537592215E-04	TCRBV06-05	TCRBJ01-02
CSVAALRGTEAFF	4.55187568670538E-04	TCRBV29-01	TCRBJ01-01
CSATPNRGRSEQYF	8.47590645110658E-04		TCRBJ02-07
CASSQGVWSSRETQYF	0.001098728614032330	TCRBV14-01	TCRBJ02-05
CASSQSTLNTEAFF	6.43541045361796E-04	TCRBV04-02	TCRBJ01-01
CASSDQGWKGYTF	8.47590645110658E-04	TCRBV27-01	TCRBJ01-02
CSATSNTGELFF	7.53413906765029E-04		TCRBJ02-02
CAWSGGLGLAGVLETQYF	1.41265107518443E-04	TCRBV30-01	TCRBJ02-05
CASSDRNTEAFF	5.17972060900958E-04	TCRBV04-02	TCRBJ01-01
CASSPGTVASPLHF	4.23795322555329E-04		TCRBJ01-06
CASSTGQGQAFF	4.08099199497724E-04	TCRBV06-05	TCRBJ01-01
CARS*PGGLNTEAFF	7.84806152880239E-04	TCRBV05-03	TCRBJ01-01
CASSYSRTGGGYGYTF	5.33668183958562E-04	TCRBV06-05	TCRBJ01-02
CASWGISLLNYGYTF	4.86579814785748E-04	TCRBV28-01	TCRBJ01-02

TCRs are unique

- Few shared TCRs between individuals
- How can we start comparing them?



Robins et al. "Overlap and effective size of the human CD8+ T cell receptor repertoire." *Science translational medicine* 2.47 (2010): 47ra64-47ra64.

TCRs aren’t readily interpretable

TRBV4-2*01	CASSQRRANSPLHF	TRBJ1-6*02
V gene	*CDR3 region*	*J gene*

How to interpret these sequences?

- No reference genome for TCR sequences
- No pathways, ontologies, etc for TCR sequences
- No functional information

Epitope specificity

Determine the epitope target of TCR sequences

- Train a machine learning model to identify those TCR sequences that target a specific epitope

TRBV4-2*01 *V region*

CASSQRRANSPLHF *CDR3 region*

TRBJ1-6*02 *J region*

+

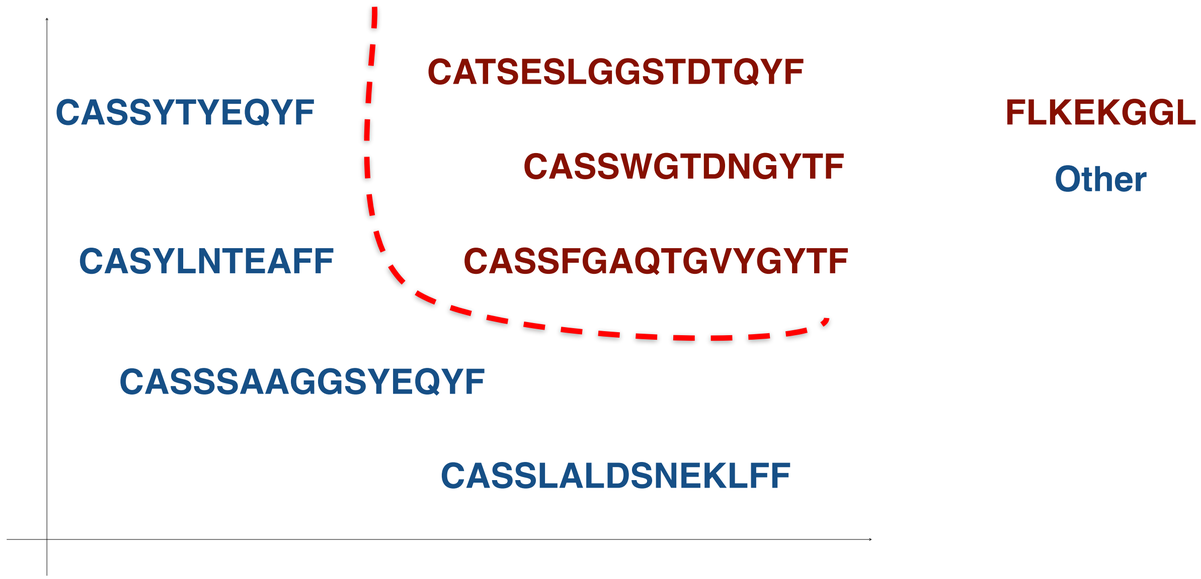
IIFLFILLLCLIFLL

Hepatitis B surface antigen epitope

Binding?

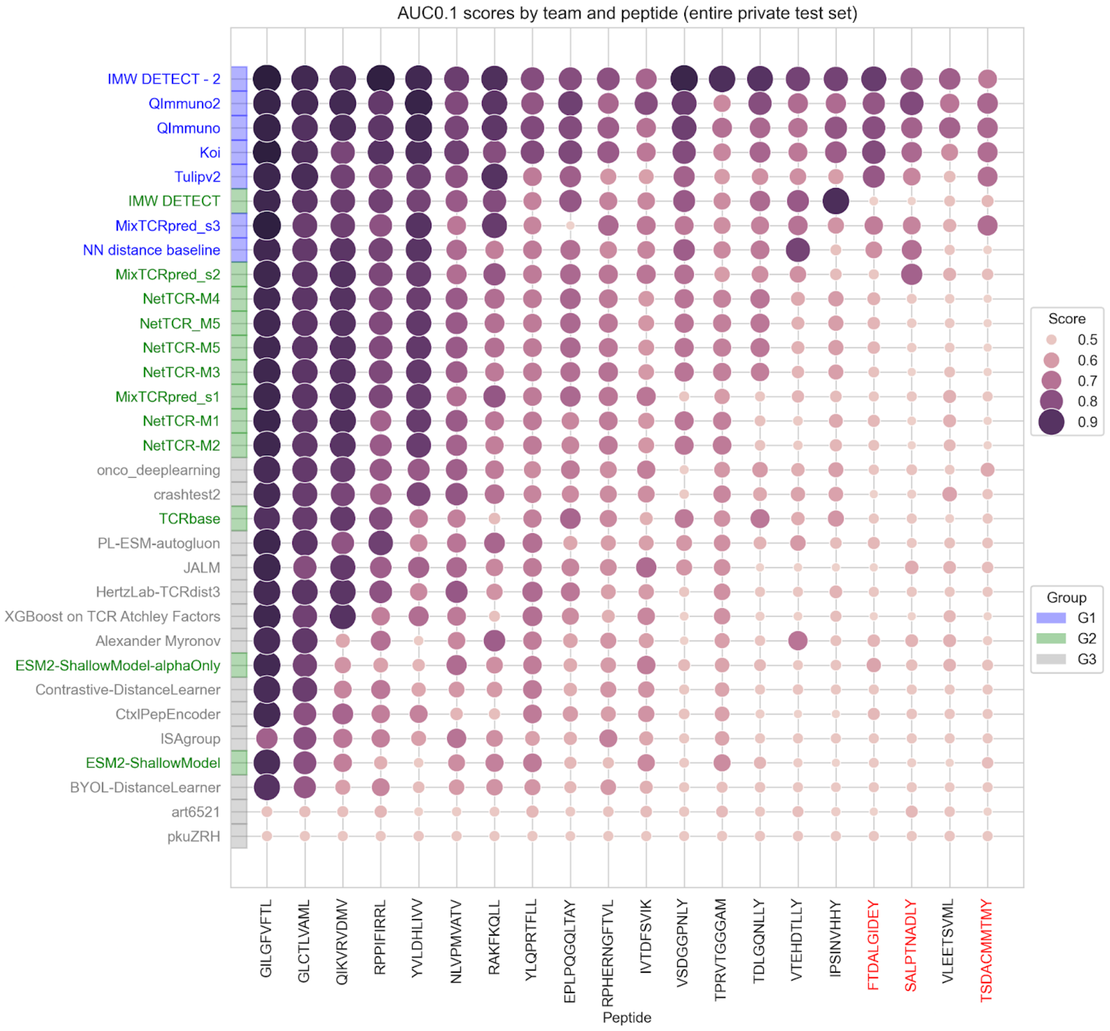
Seen epitope prediction

Predict for a set of T-cell receptor if they bind a specific epitope by projecting the TCR sequences into numerical feature space.



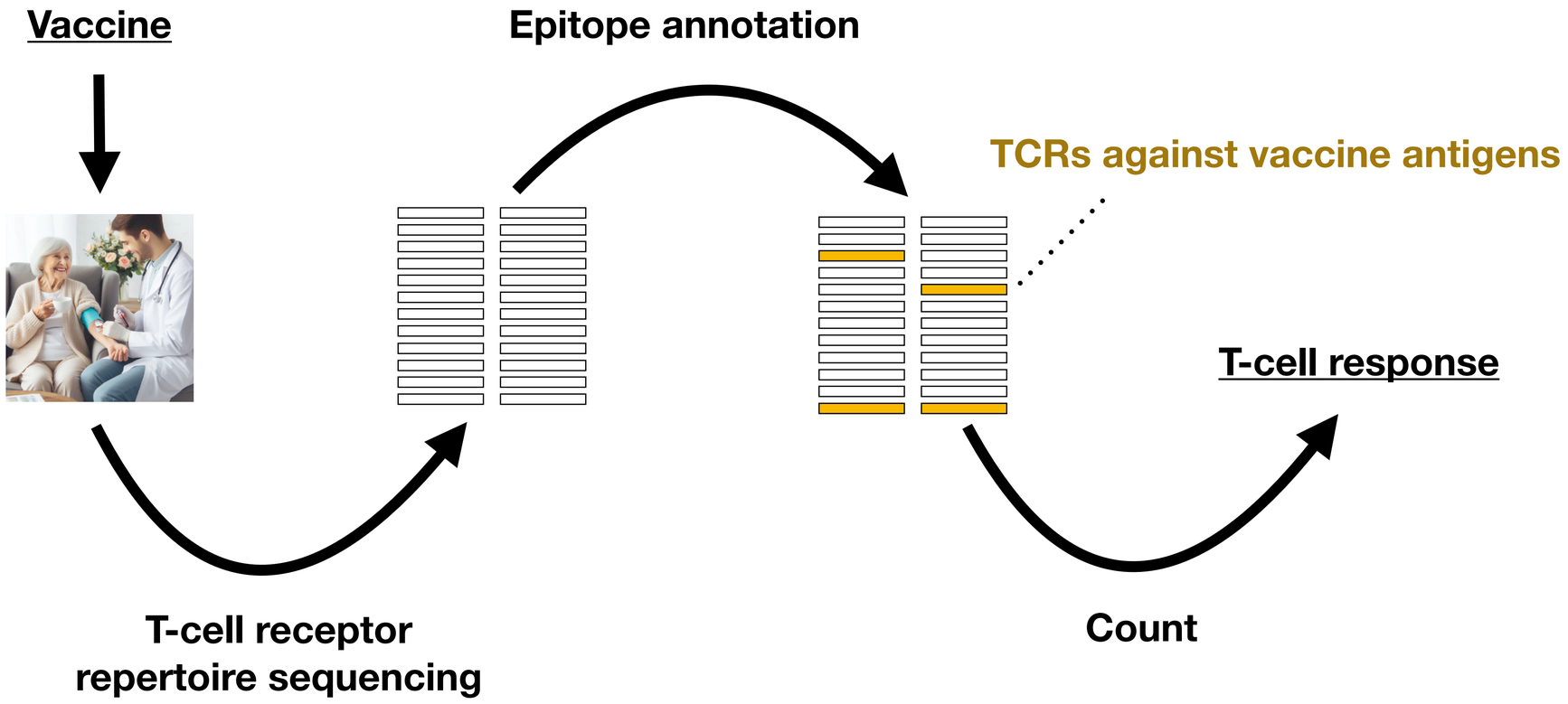
Gielis, S. et al. (Nov 2019). Detection of enriched T cell epitope specificity in full T cell receptor sequence repertoires. Frontiers in immunology

IMMREP23 benchmark



Nielsen, M., Eugster, A., Jensen, M.F., Goel, M., Tiffeau-Mayer, A., Pelissier, A., Valkiers, S., Martínez, M.R., Meynard-Piganeeau, B., Greiff, V. and Mora, T., Lessons learned from the IMMREP23 TCR-epitope prediction challenge. ImmunoInformatics.

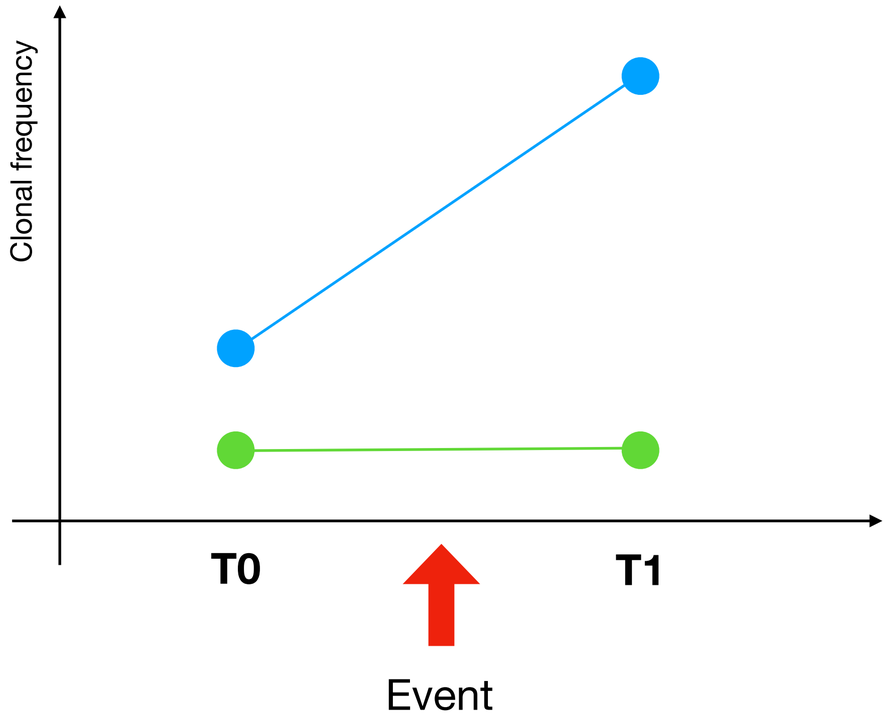
Why predict epitope-TCRs?



Tracking clonotypes by TCRs

- Each clonotype can be typed by a unique (alpha/beta/gamma/delta) TCR

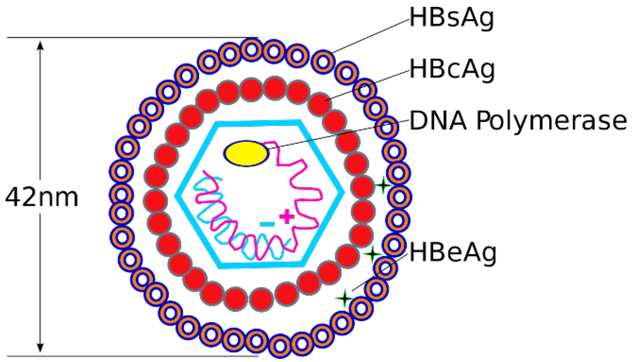
- T-cells can then be tracked in time and space.



Hepatitis B vaccine

Hepatitis B vaccine

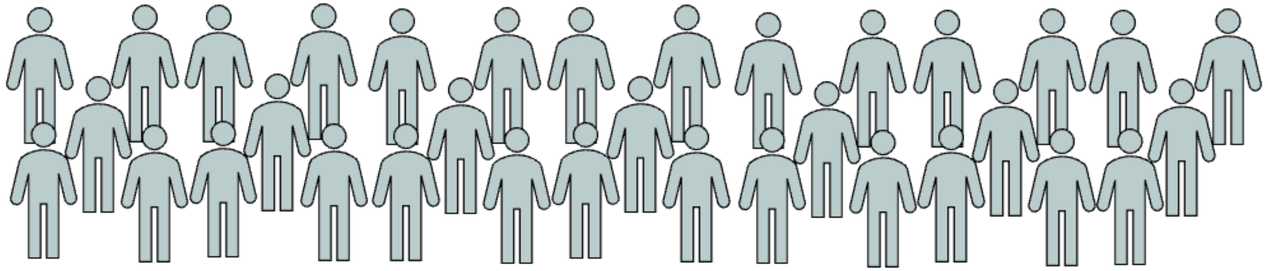
- 3- to 4-dose vaccination scheme
- 5%-10% non-responders
- Known risk factors:
  - Age
  - Male gender
  - HLA genotypes
  - Chronic disease
  - Immunomodulatory medication



Source: Wikimedia commons

Hepatitis B vaccine

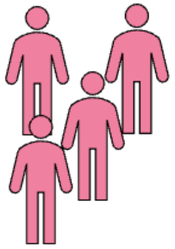
Recruited 34 individuals with no prior Hepatitis B vaccination or disease history



Elias et al. Preexisting memory CD4 T cells in naïve individuals confer robust immunity upon hepatitis B vaccination. Elife. 2022

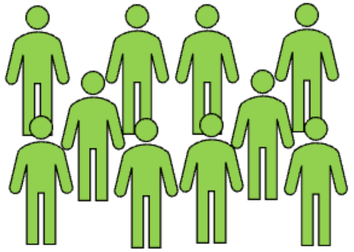
Vaccine response

4 Non-responders



Ab titer < 10 mIU/ml

9 Late responders



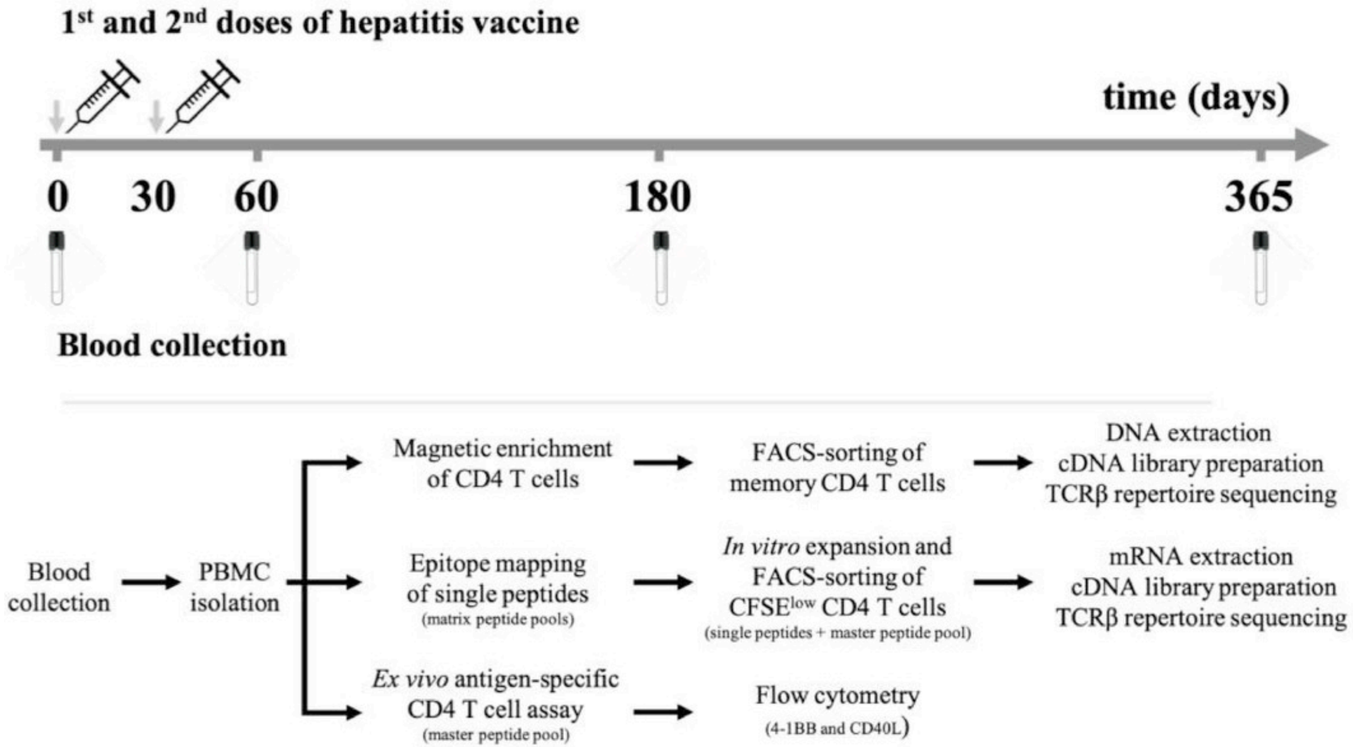
Ab titer > 10 mIU/ml
only at day 180

21 Early responders

Ab titer > 10 mIU/ml
after first dose

Elias et al. Preexisting memory CD4 T cells in naïve individuals confer robust immunity upon hepatitis B vaccination. Elife. 2022

Vaccine response



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Vaccine response

CD4+ memory TCR repertoire beta chains

aminoAcid	frequencyCount (%)	vGeneName	jGeneName
CASSYGVDRQETQYF	0.002746821535080840	TCRBV06-05	TCRBJ02-05
CASSPGGSGSSYEQYF	0.0010045518756867100	TCRBV04-02	TCRBJ02-07
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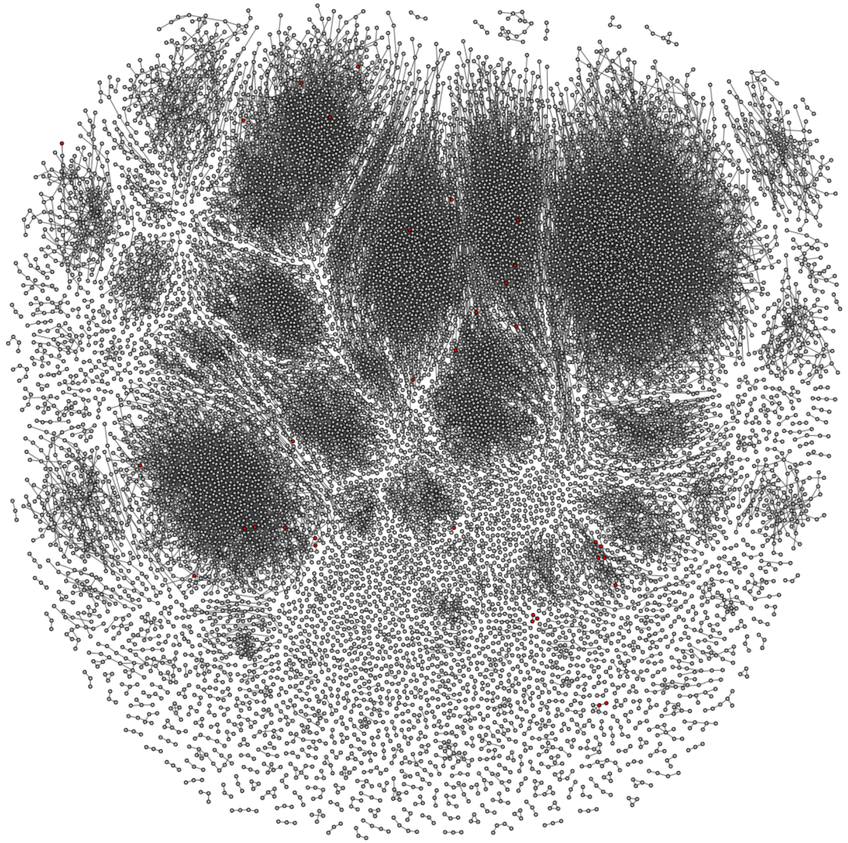
CASWGISLLNYGYTF	4.86579814785748E-04	TCRBV28-01	TCRBJ01-02

Memory repertoire

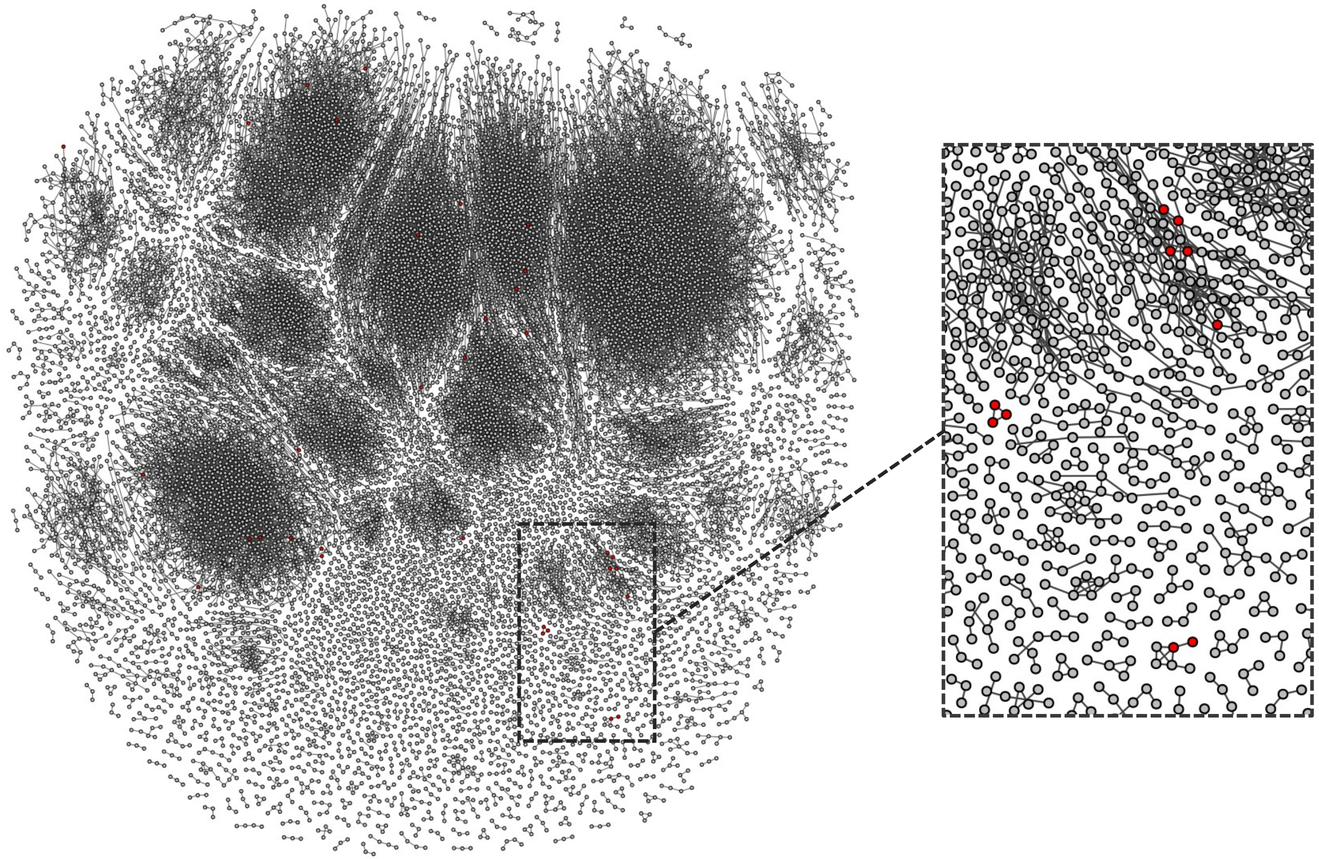
CD4+ memory TCR repertoire of volunteer H35



- **Each node is a single T-cell clone typed by its unique T-cell receptor sequence**

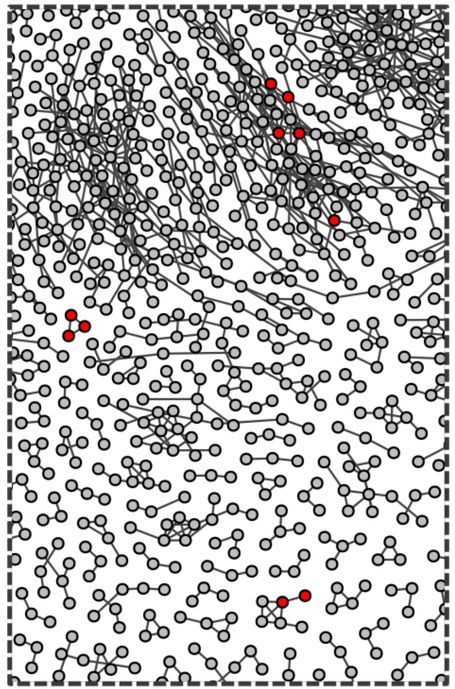
Vaccine response

CD4+ memory TCR repertoire with HepB predicted TCR marked in red



Vaccine response

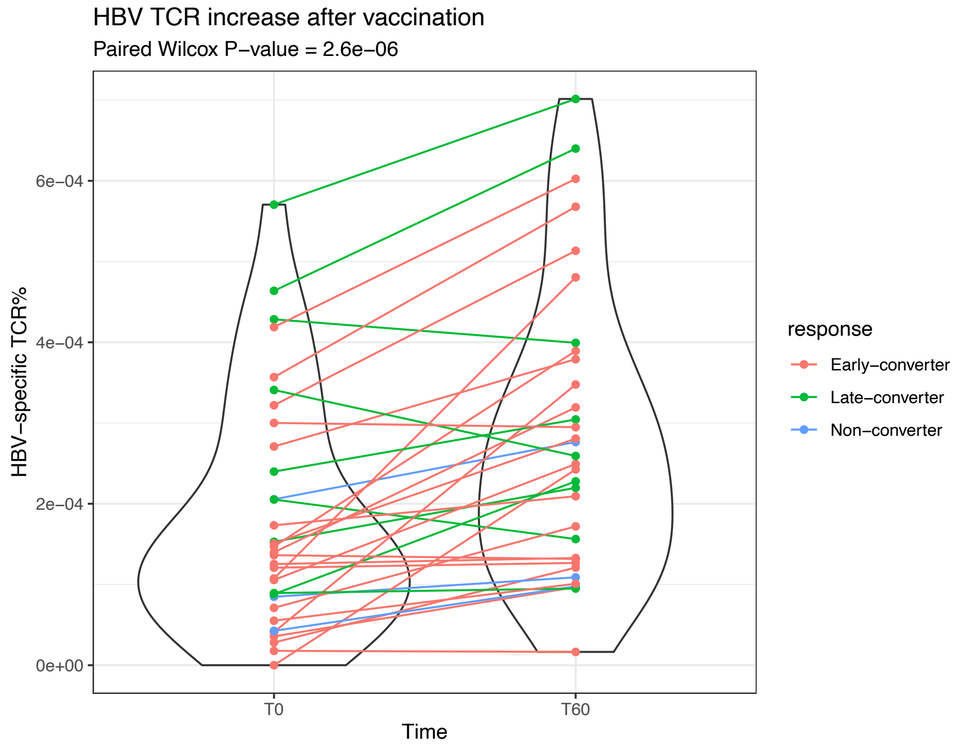
CD4+ memory TCR repertoire with HepB predicted TCR marked in red



- **Vaccine-responsive T-cells are rare**
- **Vaccine-responsive T-cells can be grouped by the similarity of their receptor**

Vaccine response

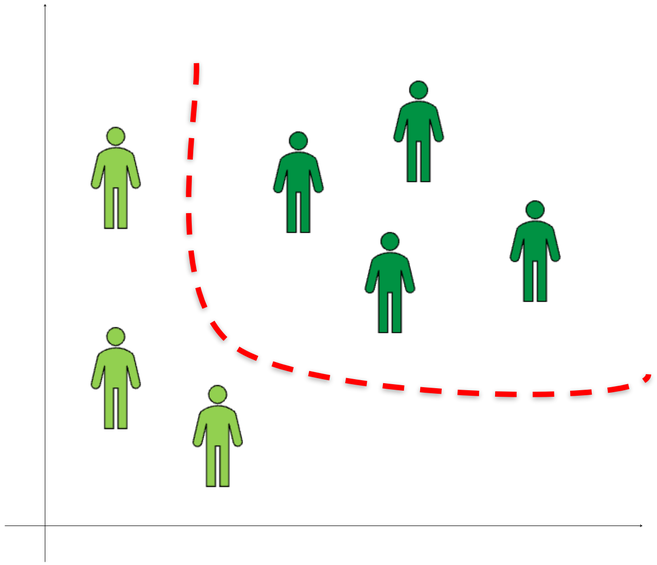
Predicted HepB-reactive TCR breadth increases after vaccination



Elias et al. Preexisting memory CD4 T cells in naïve individuals confer robust immunity upon hepatitis B vaccination. Elife. 2022

Vaccine response

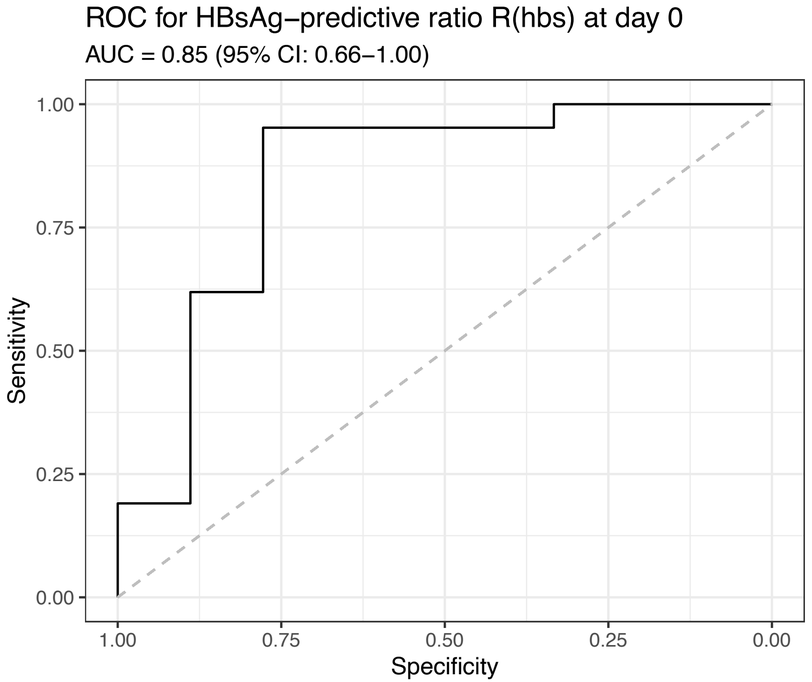
Pre-vaccination HepB-reactive TCR breadth is predictor of vaccine response



Fast responders

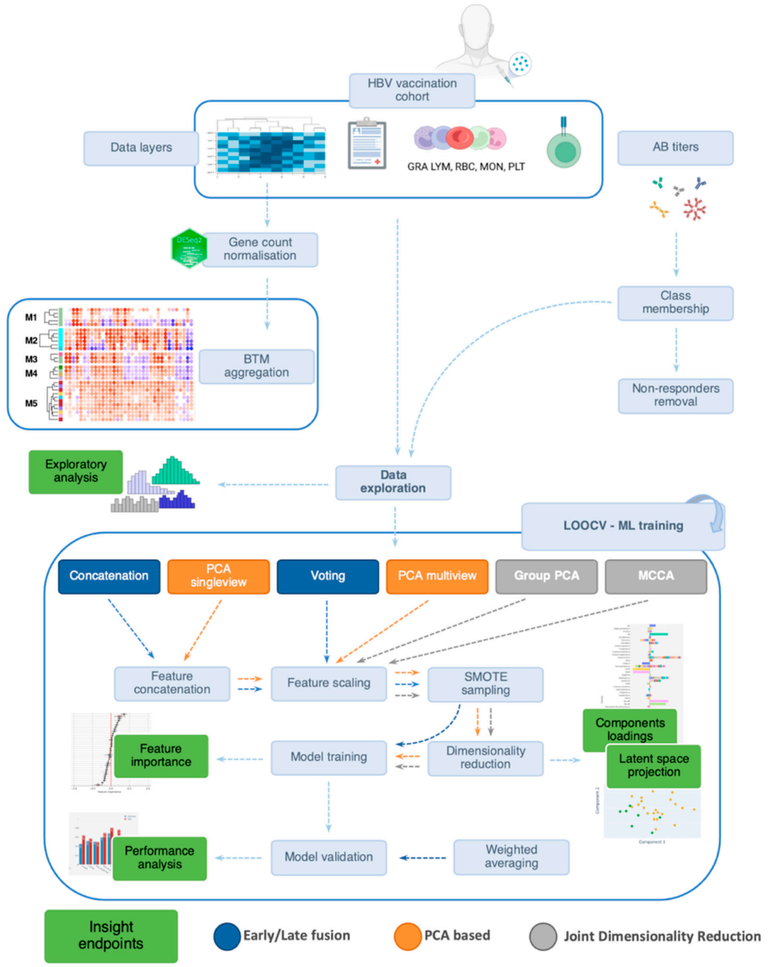
<>

Slow responders



Elias et al. Preexisting memory CD4 T cells in naïve individuals confer robust immunity upon hepatitis B vaccination. Elife. 2022

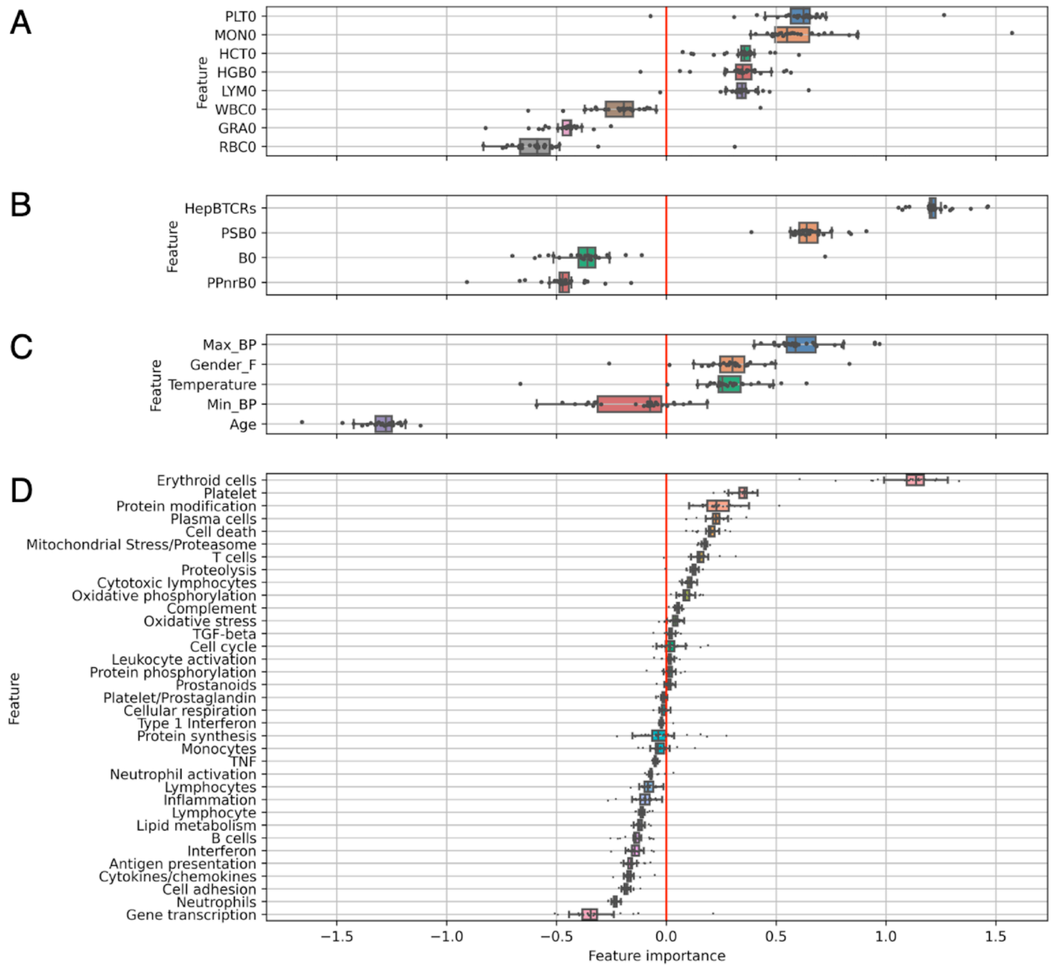
Other data levels



- Blood cell counts
- T-cell receptor data
- Clinical parameters
- Transcriptomics data

Affaticati et al. Multi-view learning to unravel the different levels underlying hepatitis B vaccine response. Vaccines. 2024

Relation to response



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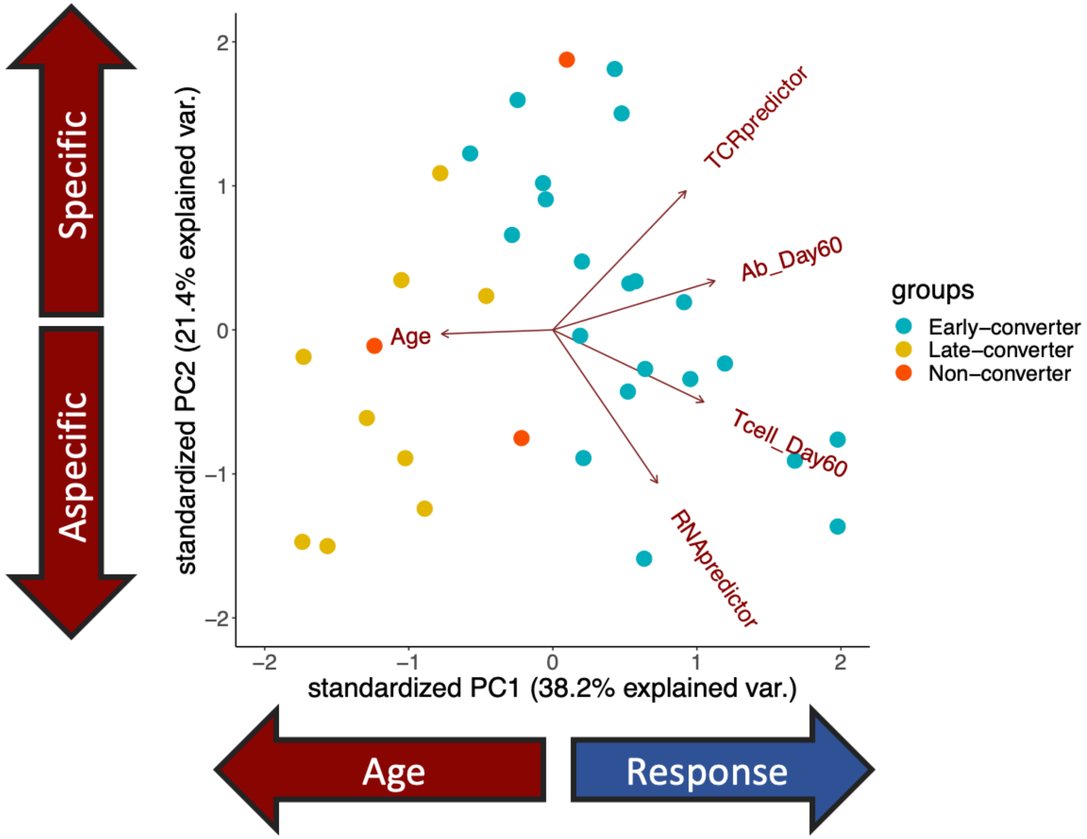
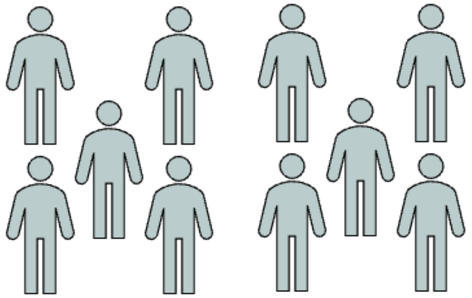
Relation to response



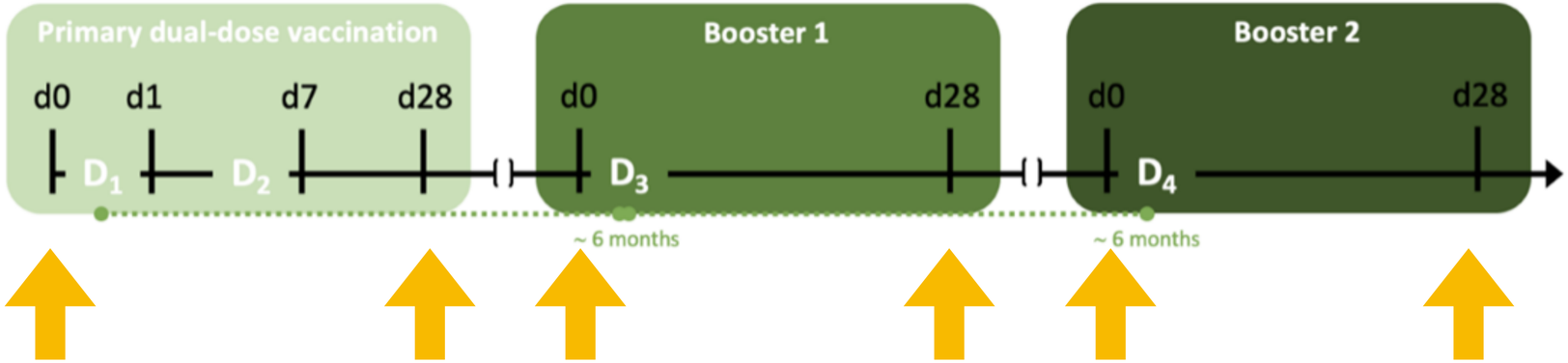
Affaticati et al. Multi-view learning to unravel the different levels underlying hepatitis B vaccine response. Vaccines. 2024

COVID19 vaccine

Cohort of 10 cancer patients without prior COVID history (B-VOICE cohort)



Vaccination with BNT162b2 COVID-19 vaccination

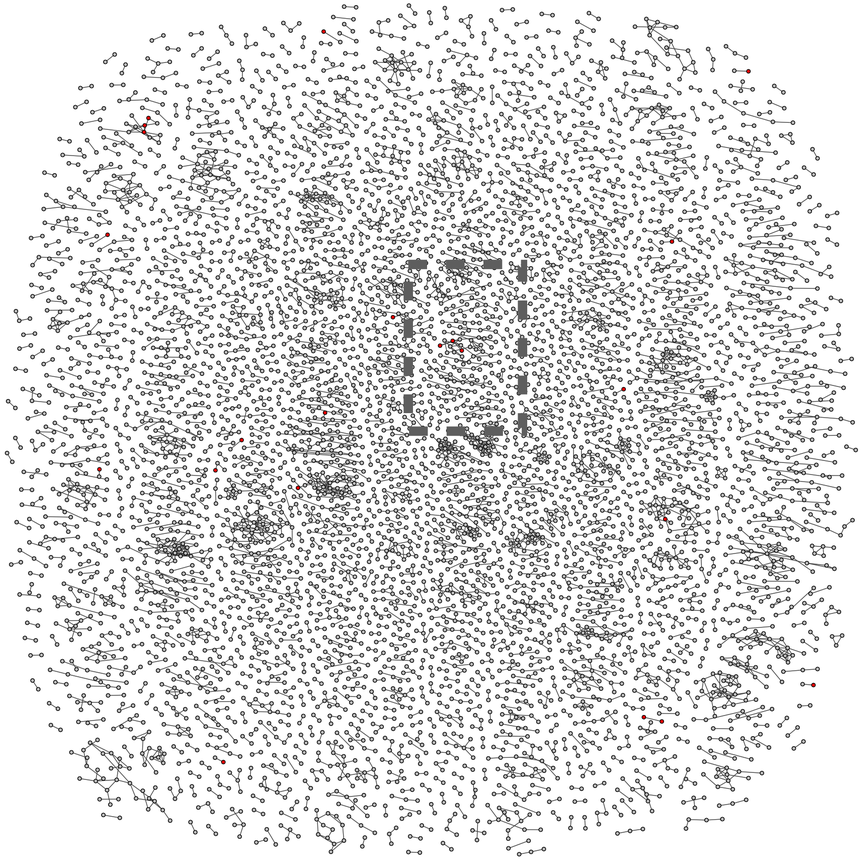


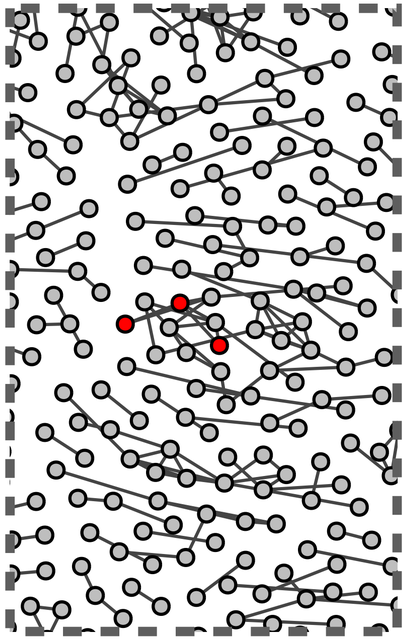
TCR sequencing at six time points

Debie et al.Modelling longitudinal T-cell receptor data after SARS-CoV-2 vaccination and breakthrough infection reveals distinct CD4 and CD8 T-cell dynamics. *In preparation*

COVID19 vaccine

Full TCR repertoire of volunteer BV051

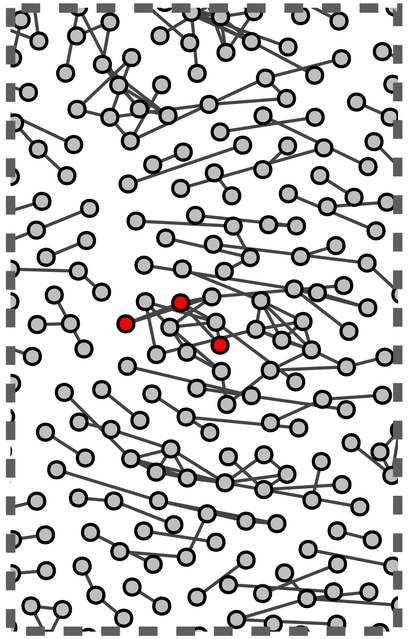




SARS-CoV-2 reactive TCRs

Debie et al.Modelling longitudinal T-cell receptor data after SARS-CoV-2 vaccination and breakthrough infection reveals distinct CD4 and CD8 T-cell dynamics. *In preparation*

COVID19 vaccine

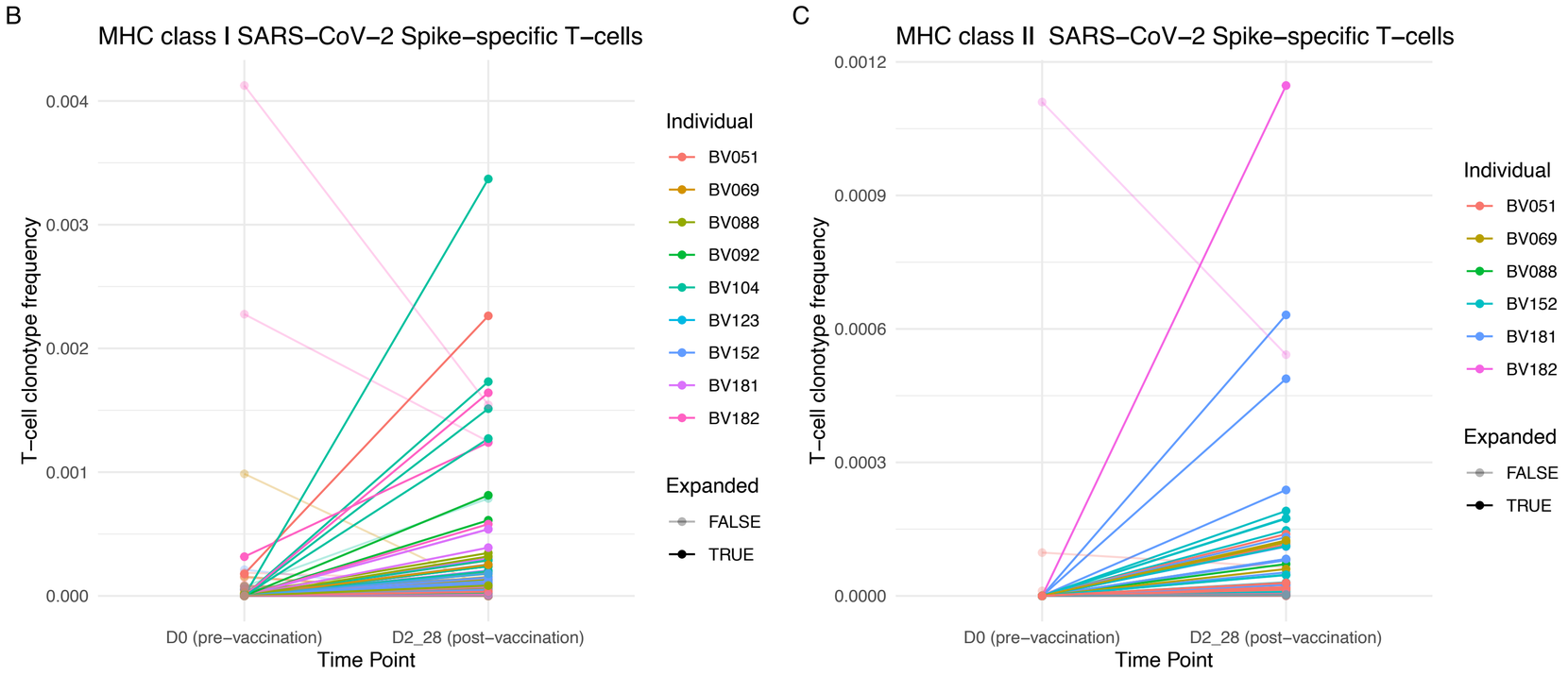


SARS-CoV-2 reactive TCRs

- **What does a vaccine-specific T-cell do after vaccination?**

Debie et al.Modelling longitudinal T-cell receptor data after SARS-CoV-2 vaccination and breakthrough infection reveals distinct CD4 and CD8 T-cell dynamics. *In preparation*

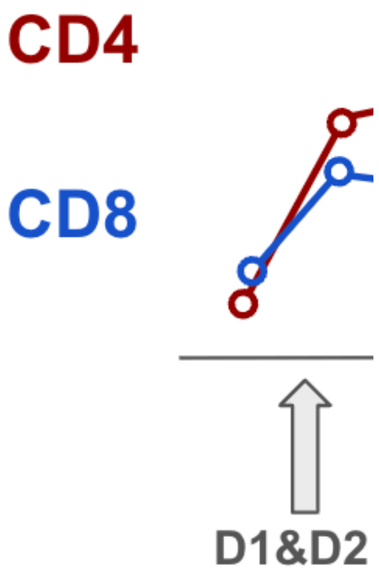
COVID19 vaccine



28 days after second dose, vaccine-specific T-cells have expanded

Debie et al.Modelling longitudinal T-cell receptor data after SARS-CoV-2 vaccination and breakthrough infection reveals distinct CD4 and CD8 T-cell dynamics. *In preparation*

COVID19 vaccine

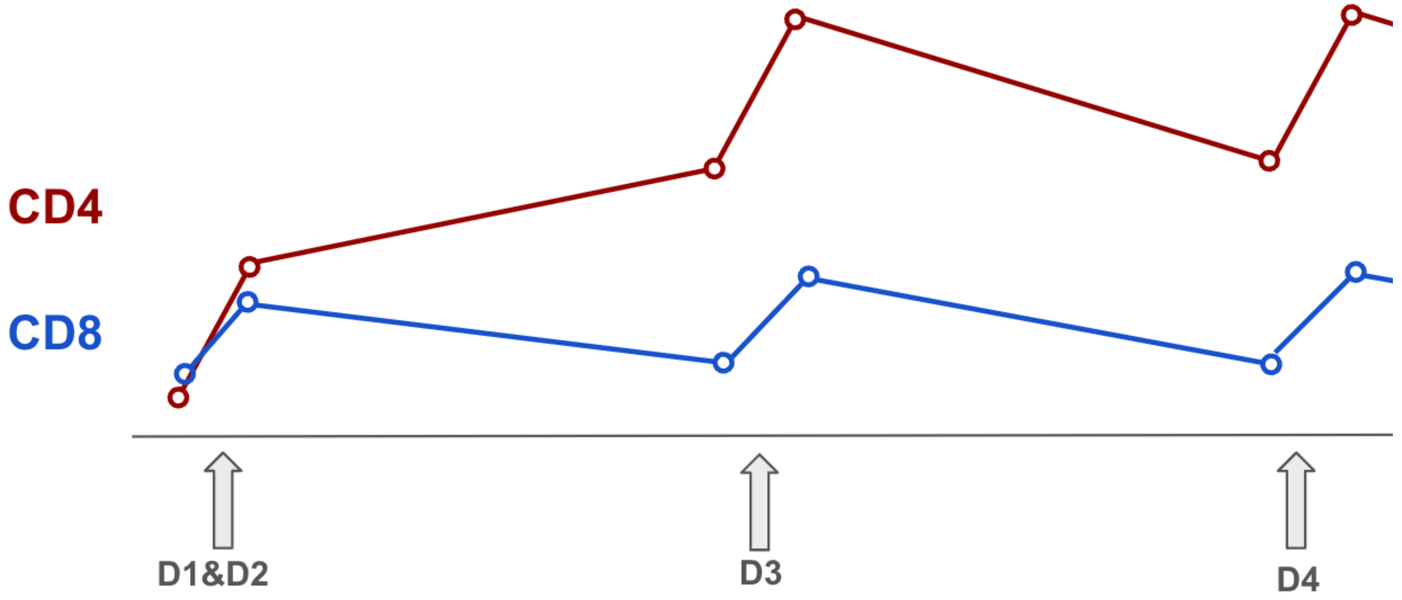


But what happens later?

Debie et al.Modelling longitudinal T-cell receptor data after SARS-CoV-2 vaccination and breakthrough infection reveals distinct CD4 and CD8 T-cell dynamics. *In preparation*

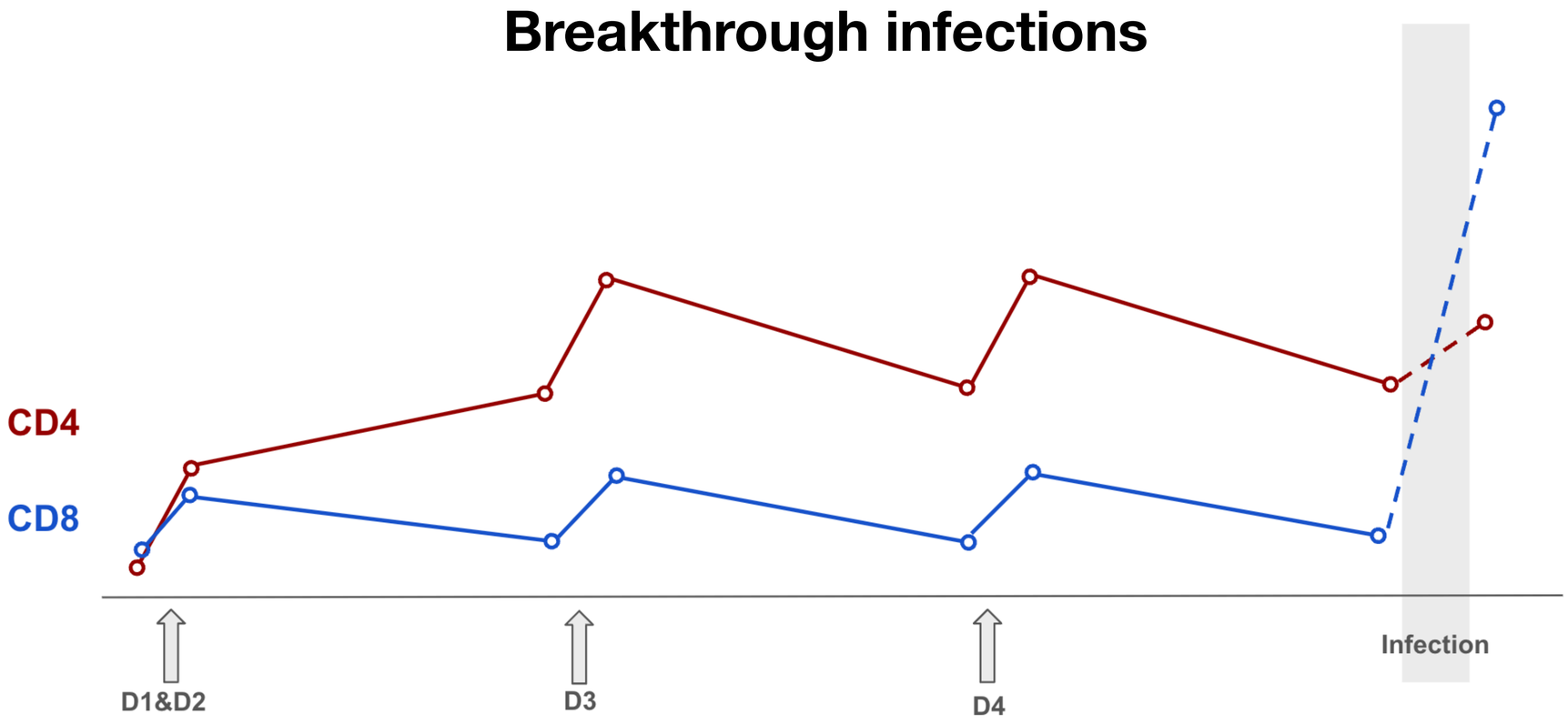
COVID19 vaccine

Vaccine-induced expansion and contraction to baseline



Debie et al.Modelling longitudinal T-cell receptor data after SARS-CoV-2 vaccination and breakthrough infection reveals distinct CD4 and CD8 T-cell dynamics. *In preparation*

COVID19 vaccine



Debie et al.Modelling longitudinal T-cell receptor data after SARS-CoV-2 vaccination and breakthrough infection reveals distinct CD4 and CD8 T-cell dynamics. *In preparation*

Summary

TCR sequencing offers new insights into the T-cell response during vaccination

- Uniqueness of TCRs allows tracking of expansion
- AI allows annotation of TCRs with their putative targets

Acknowledgements

Spokespersons

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- Karin Peeters

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- Wout Bittremieux (ADReM, UAntwerp)
- Peter Delputte (LMPH, UAntwerp)
- Niel Hens (CHERMID, UAntwerp)
- Eva Lion (LEH, UAntwerp)
- Peter Ponsaerts (LEH, UAntwerp)
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- Sébastien Anguille (MOCA, UZA)
- Timon Vandamme (CORE, UAntwerp)
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