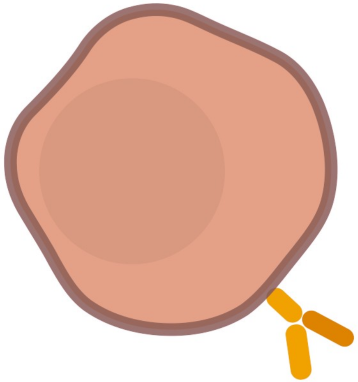
Dynamics of the B-cell repertoire: shared receptors, shared fate ?

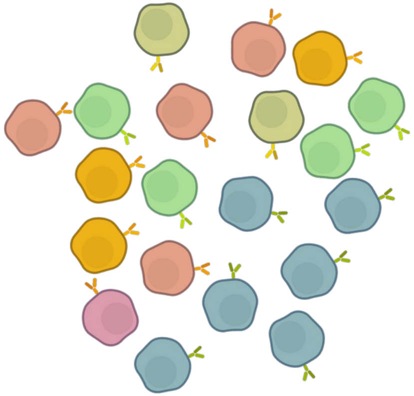
Thomas Dupic

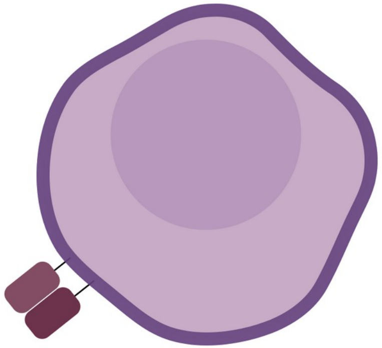
September 17th, 2025 – CIML Master PhD Week

The immune repertoire



Immune repertoire: Set of all **B-cell** / T-cell receptors



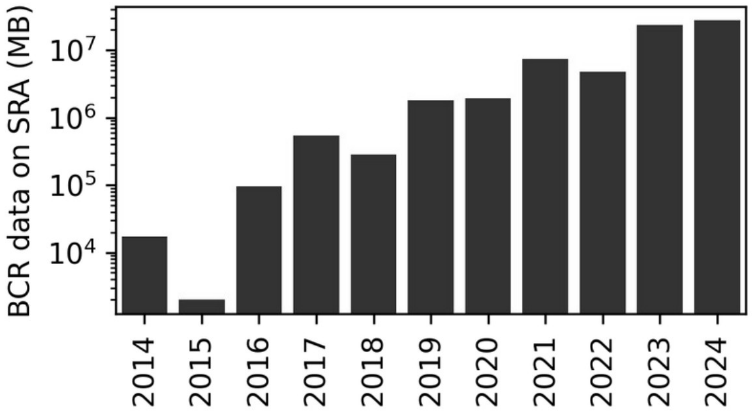


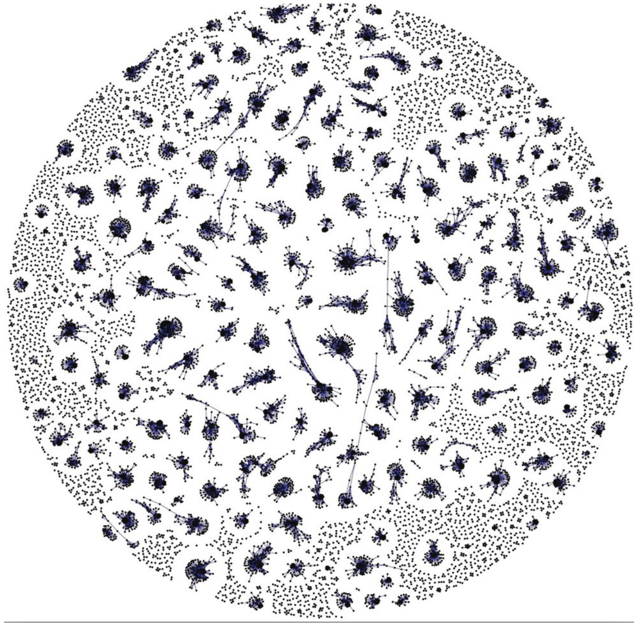
Extremely high diversity, at least 10^9 receptors in one individual.

...
CASTSTGGGAGGYTF
CASSQSYRGGTEAFF
CASSQGGTATYEQYF
CASSQSTGVGYGYTF
CASSPRAAGANVLTF
CASLAPGPGAYEQYF
...

The immune repertoire

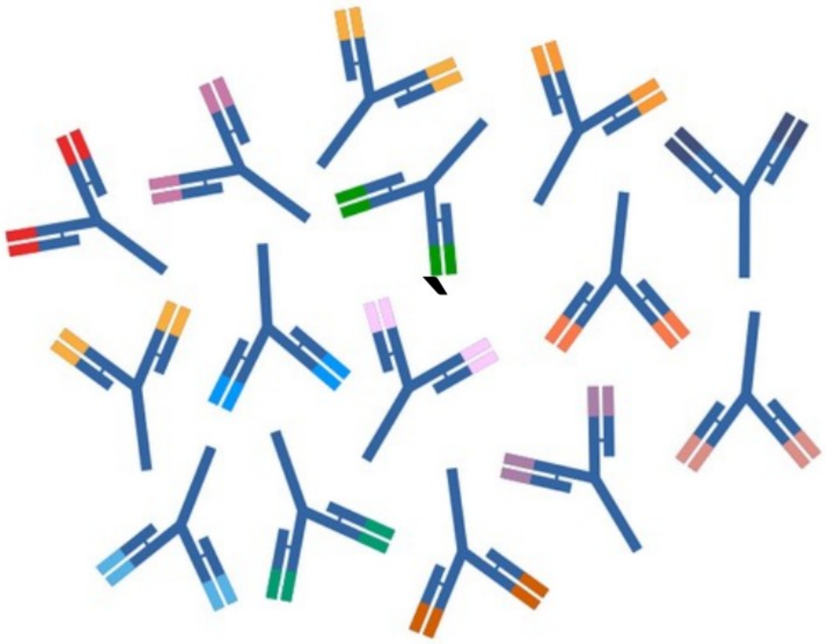
The genes coding the receptors can be sequenced relatively easily.





But what can we do with it ?

Why do we care ?

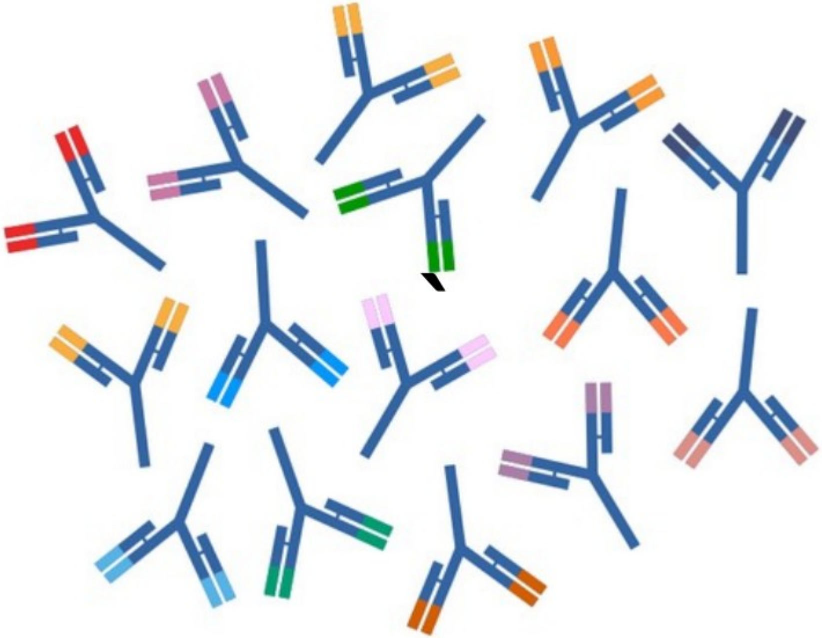


⇒ Prognosis ?

⇒ Medical history ?

⇒ Identify specific antibodies ?

Why do we care ?



⇒ Prognosis ?

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How is a B cell repertoire made ?

V(D)J recombination

Bone marrow, early stage of B-cell development

⇓

Selection

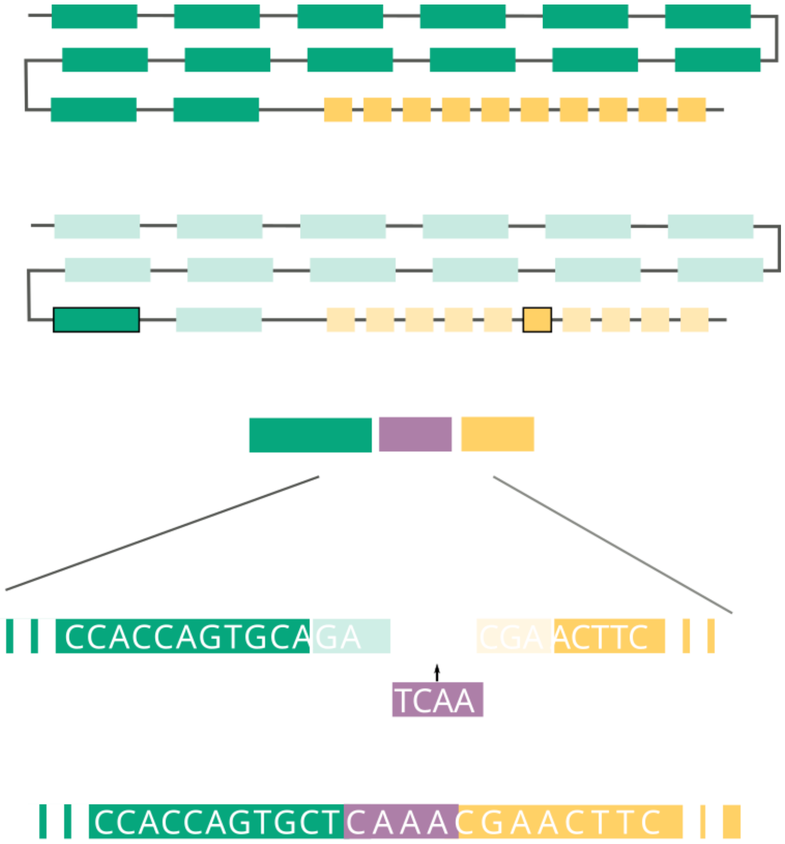
Bone marrow and later life

⇓

Amplification / Mutation / Evolution

Post antigen encounter

V(D)J recombination



- Generate random genes

- 10-100 millions early B-cells created each day, > 70% die here.

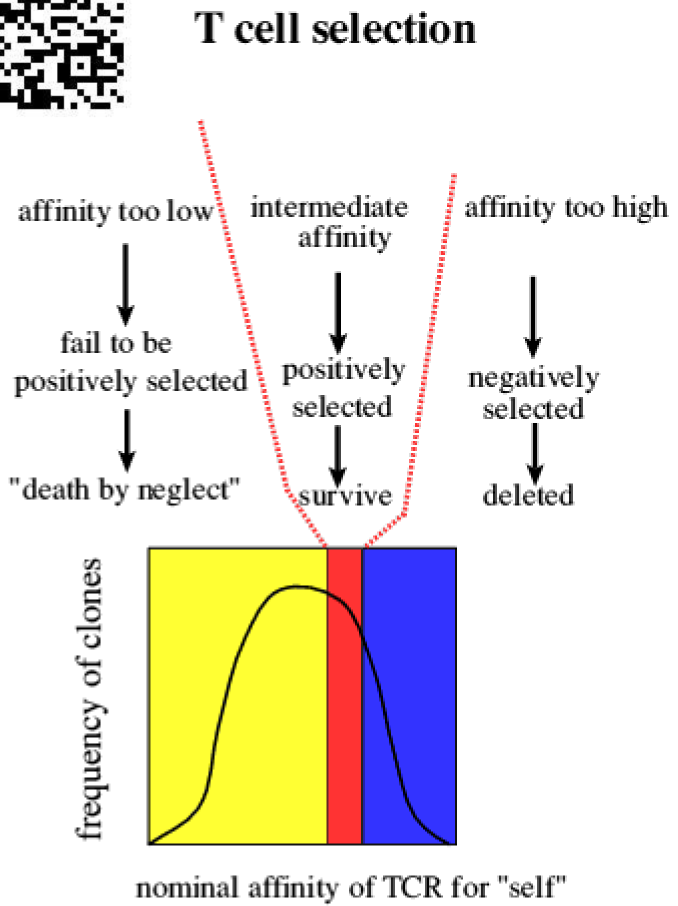
- Biochemical process

Positive & Negative Selection

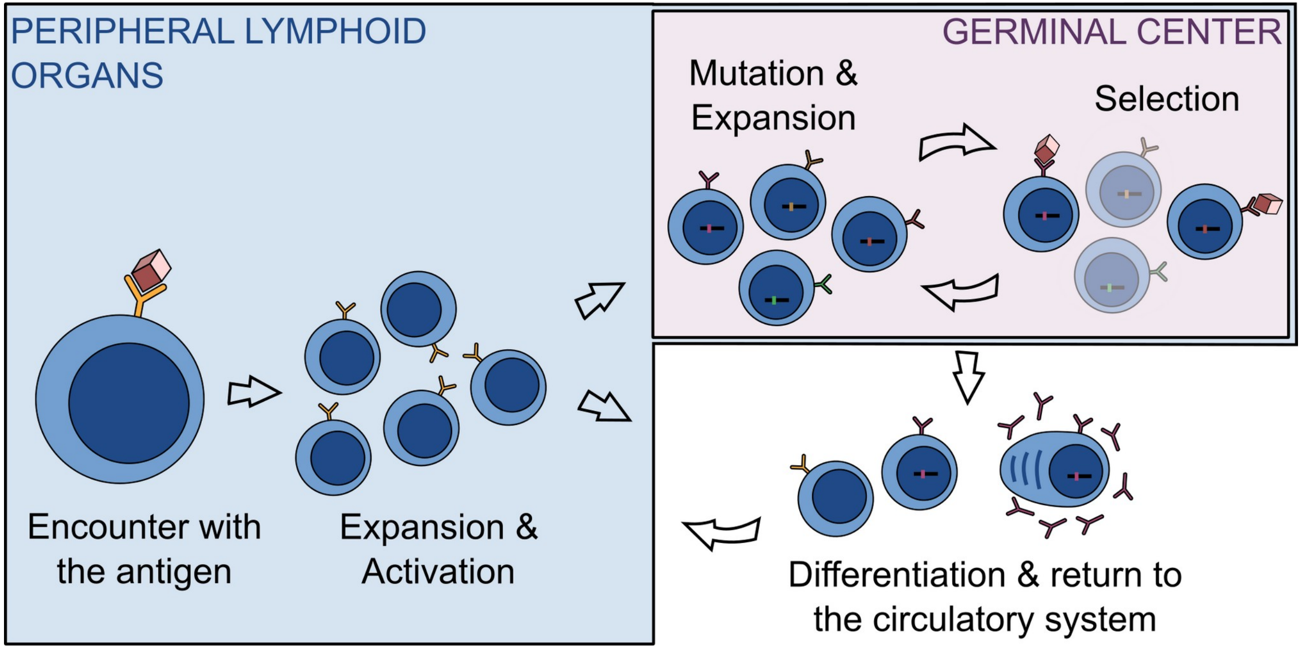
- Both T & B cells undergo positive and negative selection, different survival rates

- T cell specificity/affinity will also influence differentiation (T -regs / CD4-8 / MAIT)

- Less true for B cells



Encounter with an antigen



PERIPHERAL LYMPHOID ORGANS

Encounter with the antigen

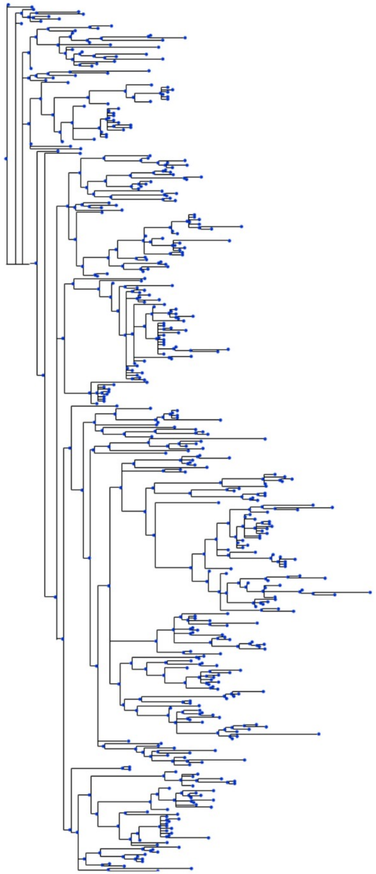
Expansion & Activation

GERMINAL CENTER

Mutation & Expansion

Selection

Differentiation & return to the circulatory system



What makes the repertoire ?

V(D)J recombination

⇓

Selection

⇓

Amplification / Mutation / Evolution

What influences the repertoire the most ?

What makes the repertoire ?

V(D)J recombination

⇓

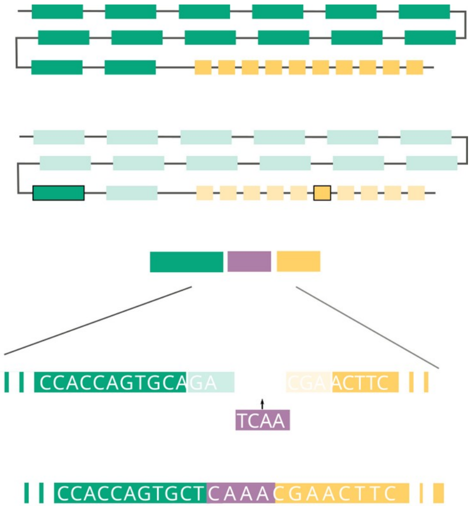
Selection

⇓

Amplification / Mutation / Evolution

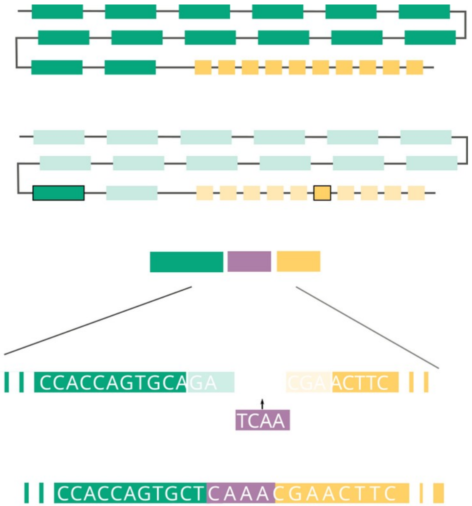
What influences the repertoire the most ?

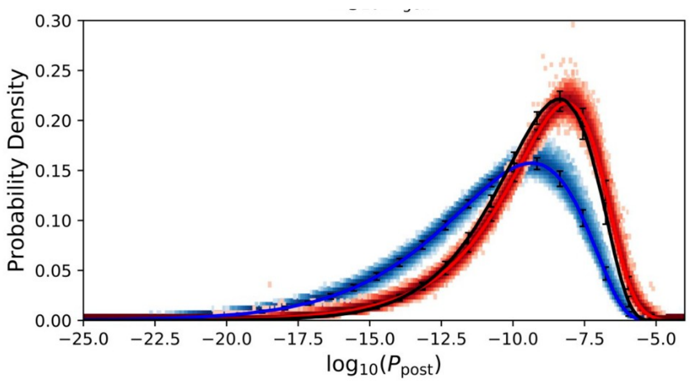
Generation probability



We can compute the probability that each sequence has of being generated.

Generation probability



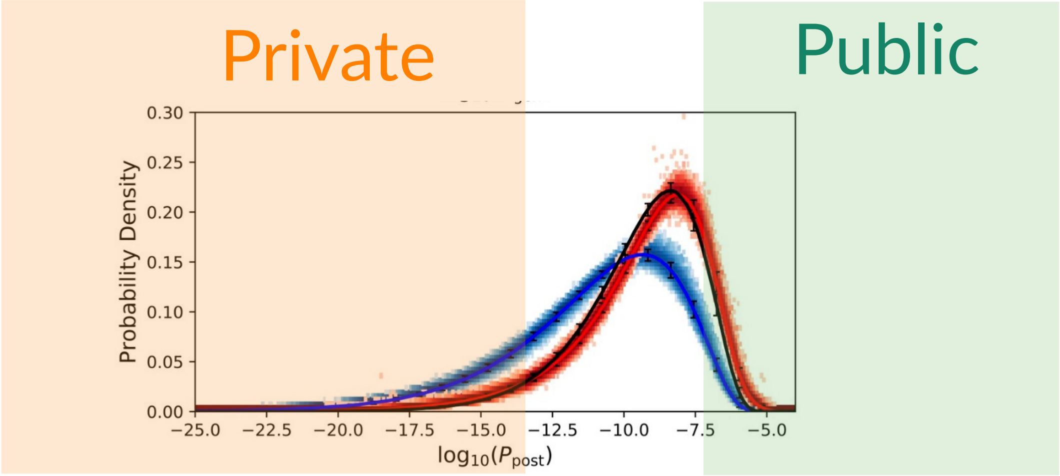


We can compute the probability that each sequence has of being generated.

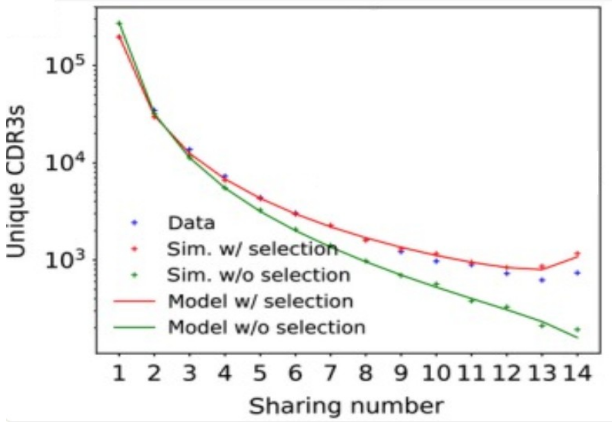
$$P(V,J)P\left(\text{del}V|V\right)P\left(\text{del}J|J\right)$$
$$\times P\left(\text{insVJ}\right)\prod_{i}^{\text{insVJ}}P_{\text{VJ}}\left(n_i|n_{i-1}\right)$$

Public vs Private repertoire

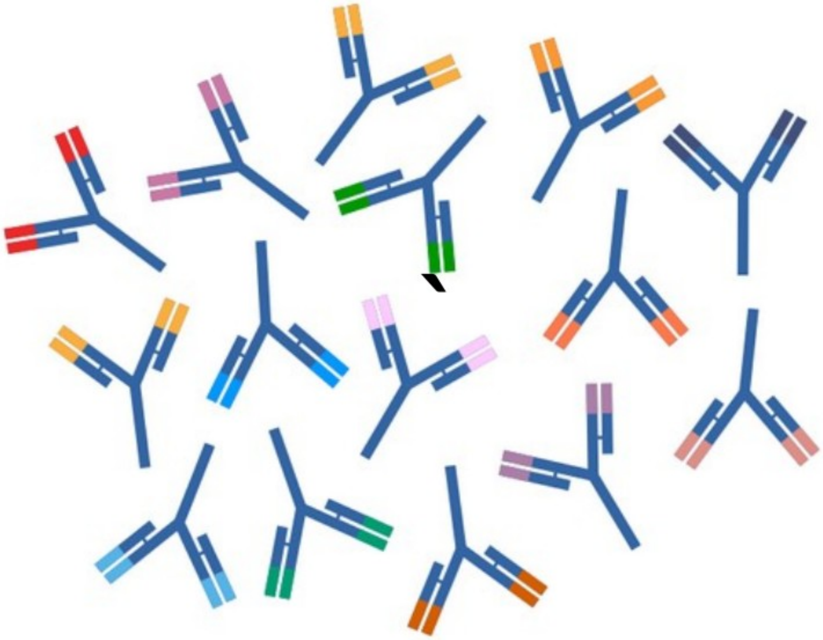
Can we extract information from the public repertoire ?



We can predict precisely the number of shared sequences between individuals



So what can we do with the repertoire ?



- As a barcode

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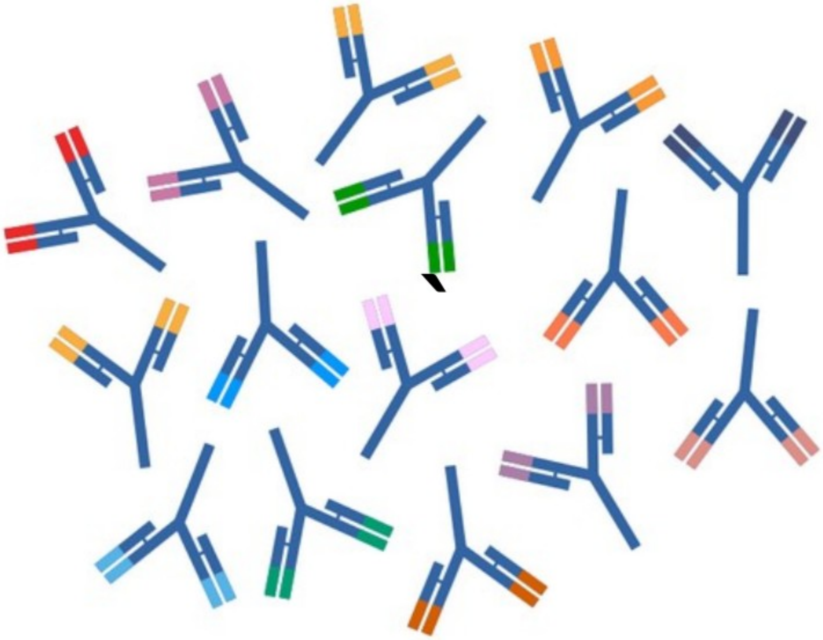

- As a barcode
- As a way to study recombination & selection

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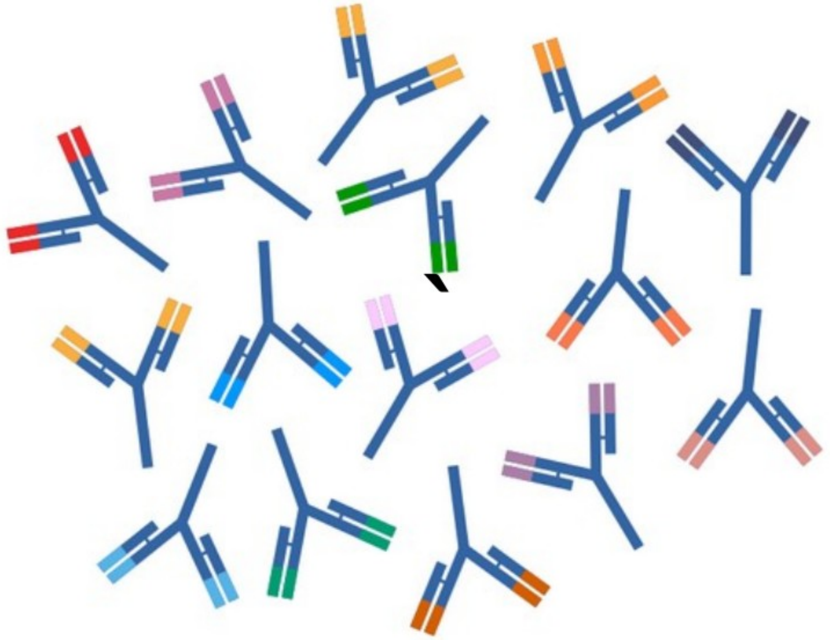
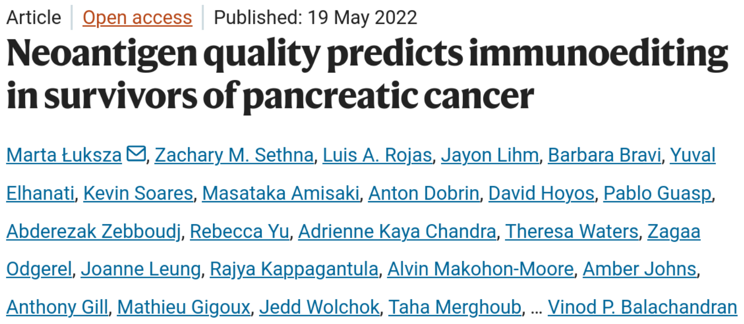


- As a barcode
- As a way to study recombination & selection
- Progress in prediction / diagnostic

Disease diagnostics using machine learning of B cell and T cell receptor sequences

MAXIM E. ZASLAVSKY, ERIN CRAIG, JACKSON K. MICHUDA, NIDHI SEHGAL, NIKHIL RAM-MOHAN, JI-YEUN LEE, KHOA D. NGUYEN, RAMONA A. HOH, THO D. PHAM, [...], AND SCOTT D. BOYD +27 authors Authors Info & Affiliations

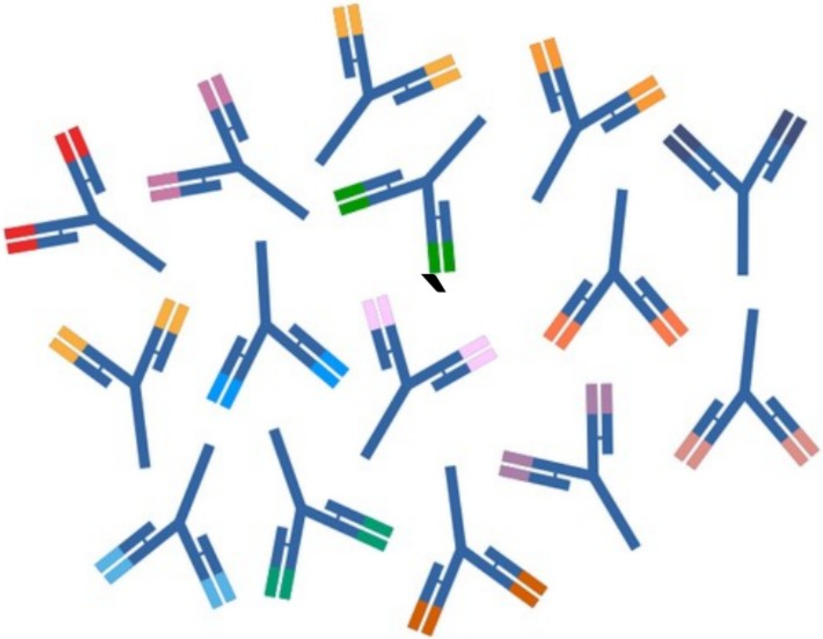


Article | Open access | Published: 19 May 2022

Neoantigen quality predicts immunoediting in survivors of pancreatic cancer

Marta Łuksza, Zachary M. Sethna, Luis A. Rojas, Jayon Lihm, Barbara Bravi, Yuval Elhanati, Kevin Soares, Masataka Amisaki, Anton Dobrin, David Hoyos, Pablo Guasp, Abderezak Zebboudj, Rebecca Yu, Adrienne Kaya Chandra, Theresa Waters, Zagaa Odgerel, Joanne Leung, Rajya Kappagantula, Alvin Makohon-Moore, Amber Johns, Anthony Gill, Mathieu Gigoux, Jedd Wolchok, Taha Merghoub, … Vinod P. Balachandran

So what can we do with the repertoire ?

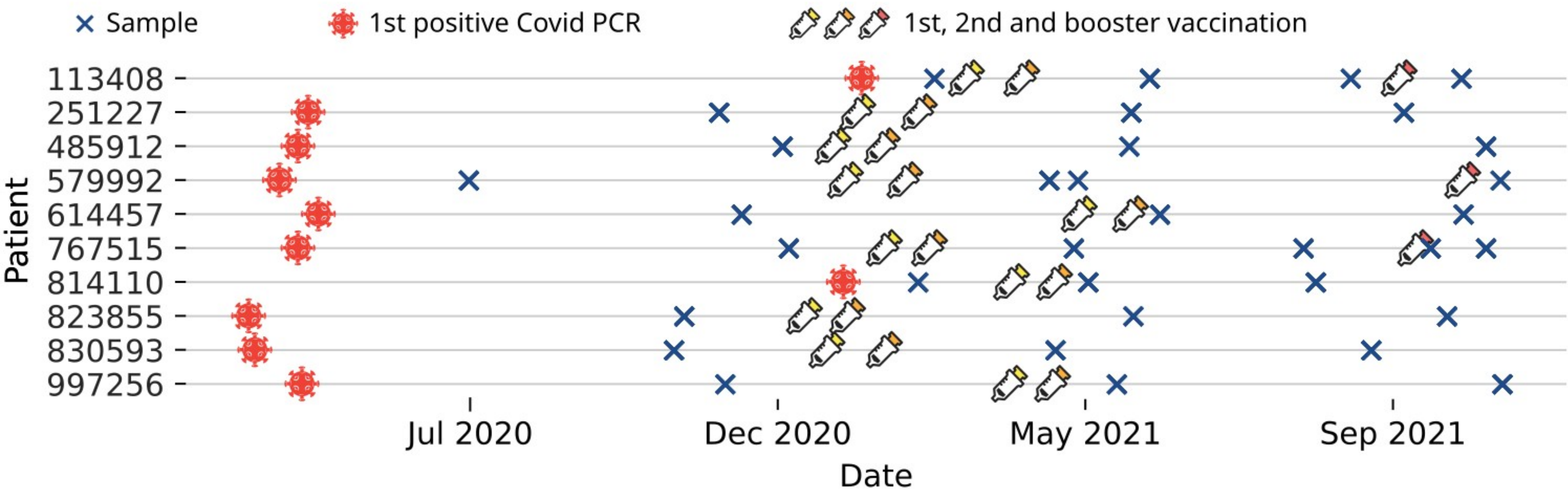


⇒ Prognosis ?

⇒ Medical history ?

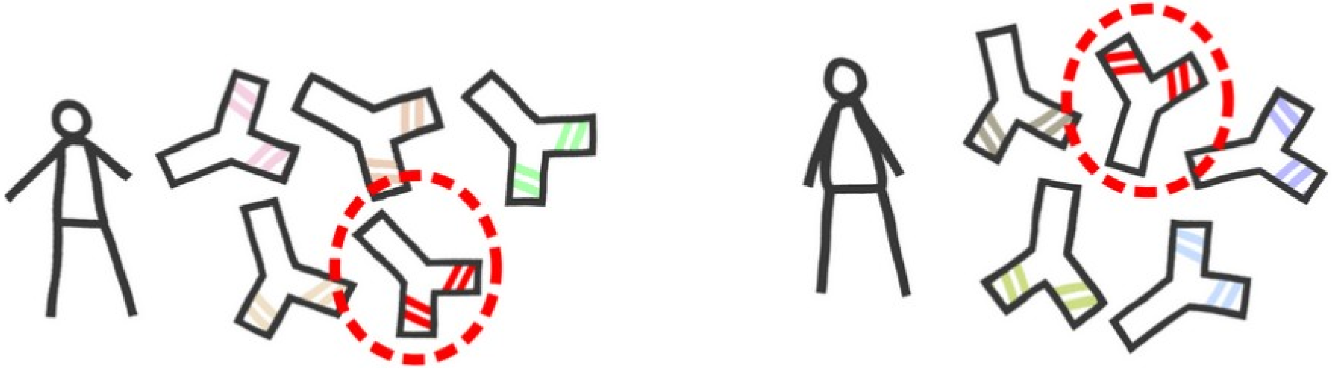
⇒ Identify specific antibodies ?

SARS-CoV-2 repertoire



Longitudinal sampling on 10 individuals. Collaboration with the Yu lab at the Ragon institute, 10^9 B cellls.

Panning the shared repertoire



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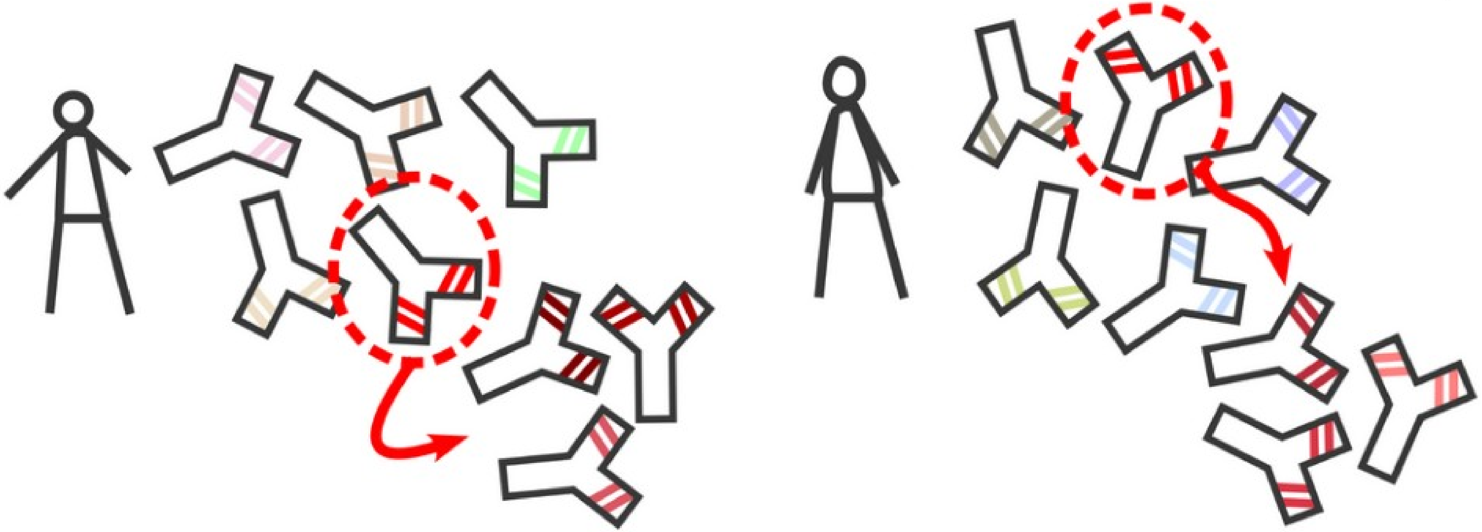
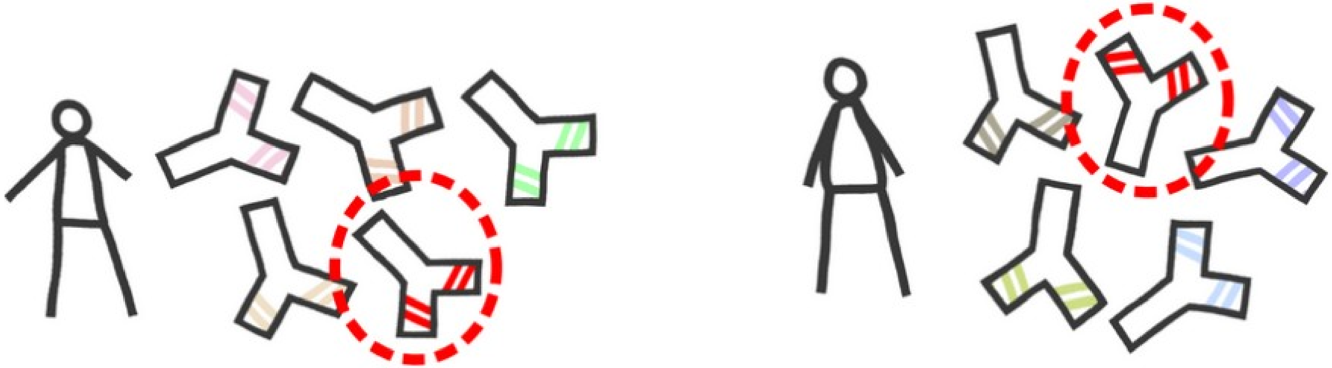
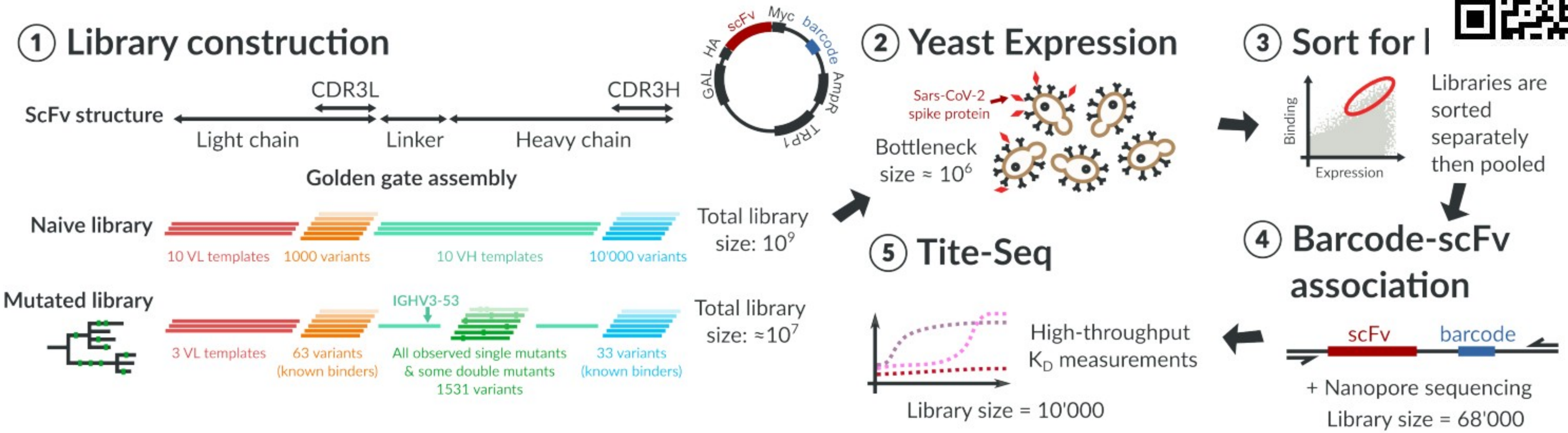


Panning the shared repertoire

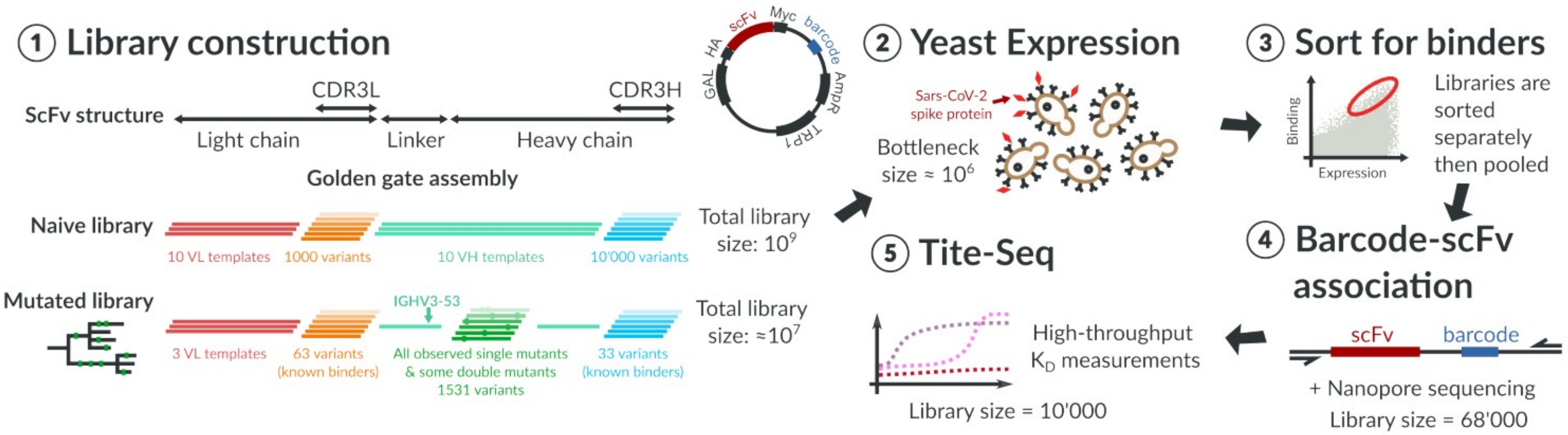


Phenotype measurement



Big in-house experiment that can measure a lot of antibodies affinities at once

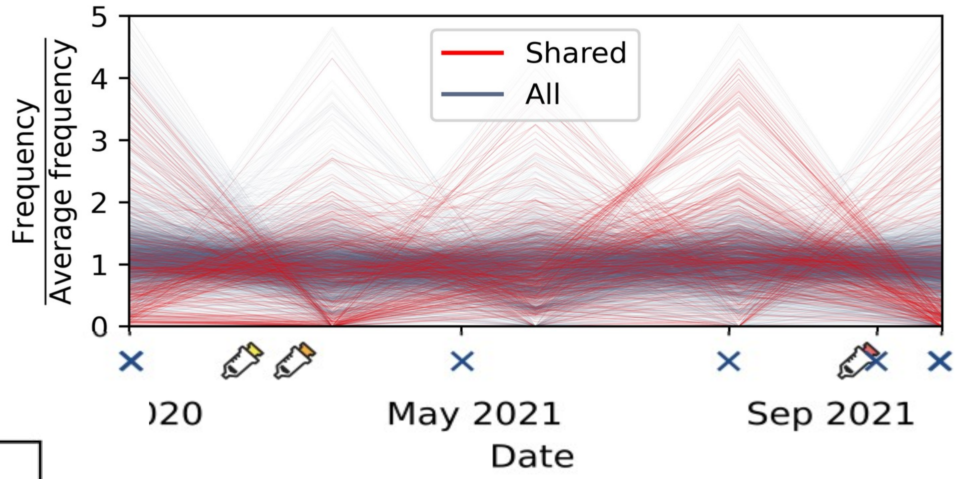
Phenotype measurement

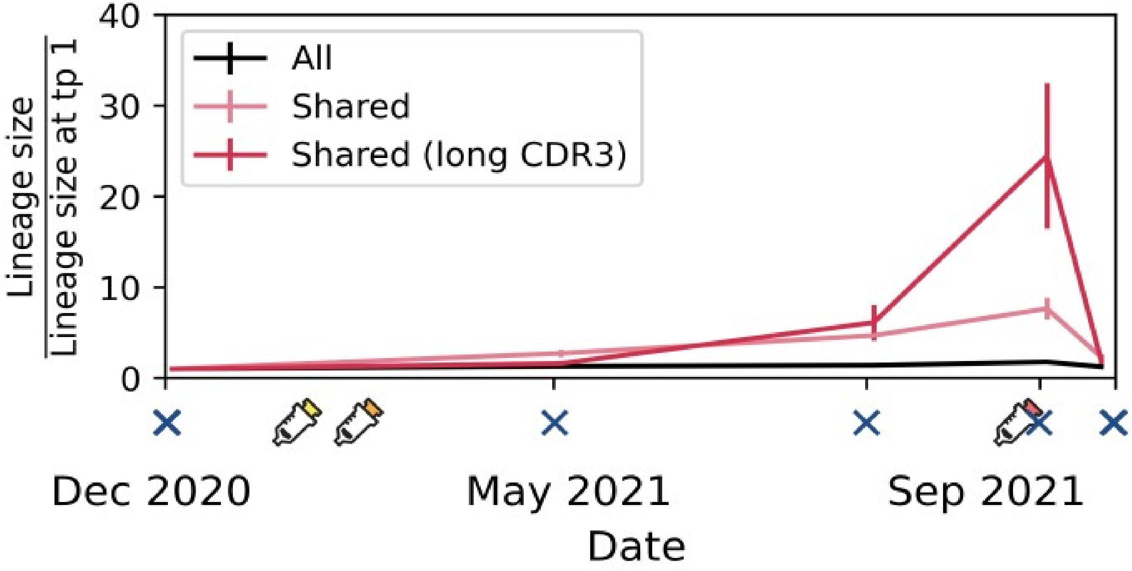


In the original repertoire, < 0.1% of BCRs bind, we get **1 in 6** from the sequences we selected.

Homeostasis of the PBMC repertoire

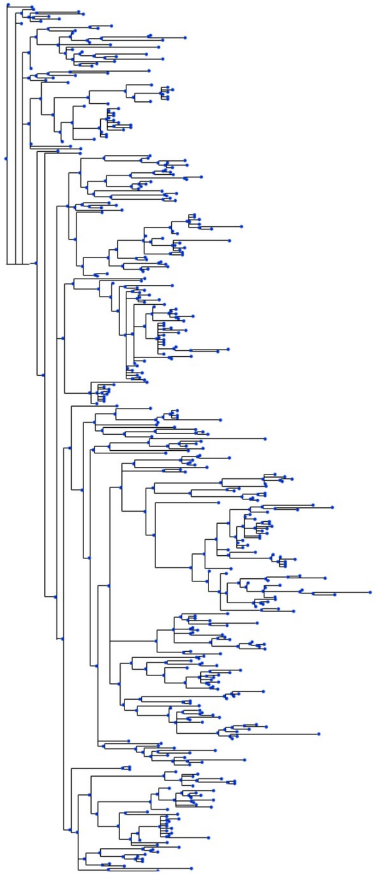
On long timescales the PBMC repertoire is stable. Shared lineages are more active.





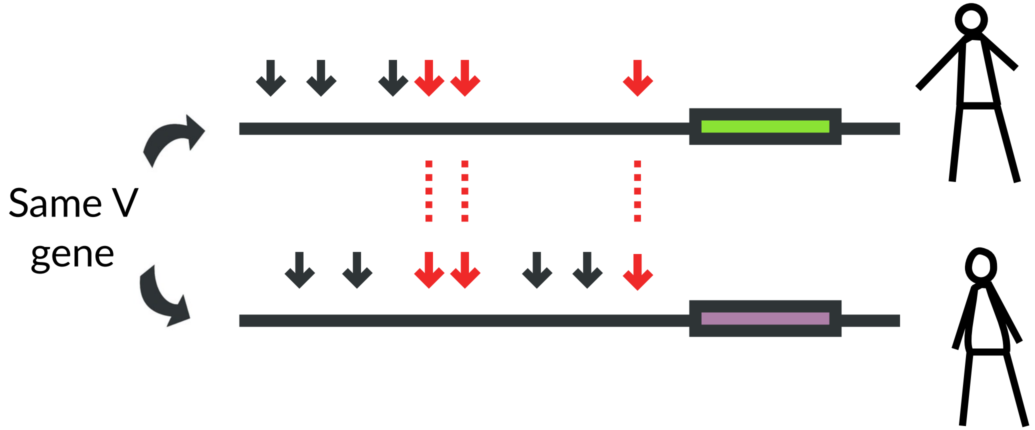
On average, shared lineages increase in size.

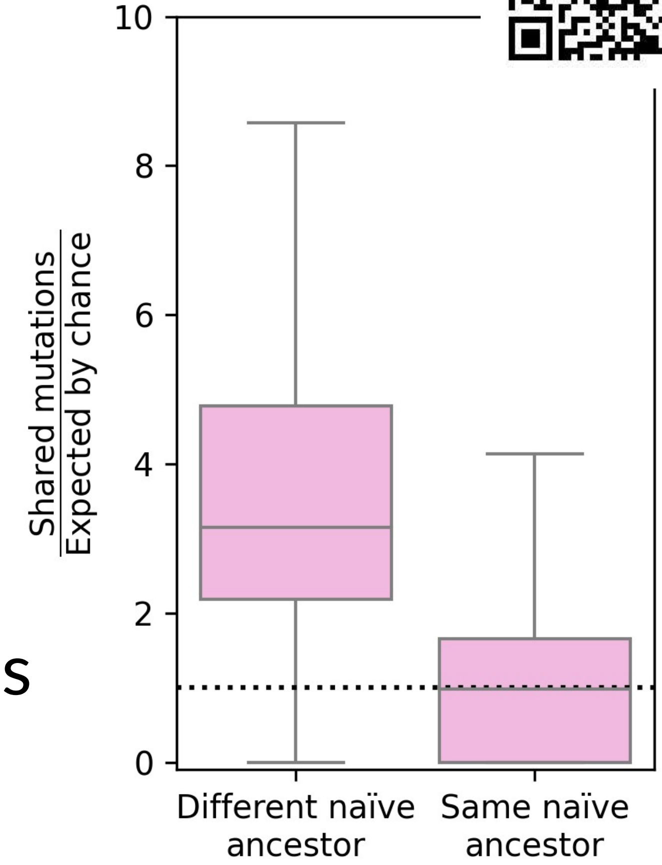
Homeostasis of the PBMC repertoire



Are B-cells evolving the same way across individuals ?

Mutational Convergence

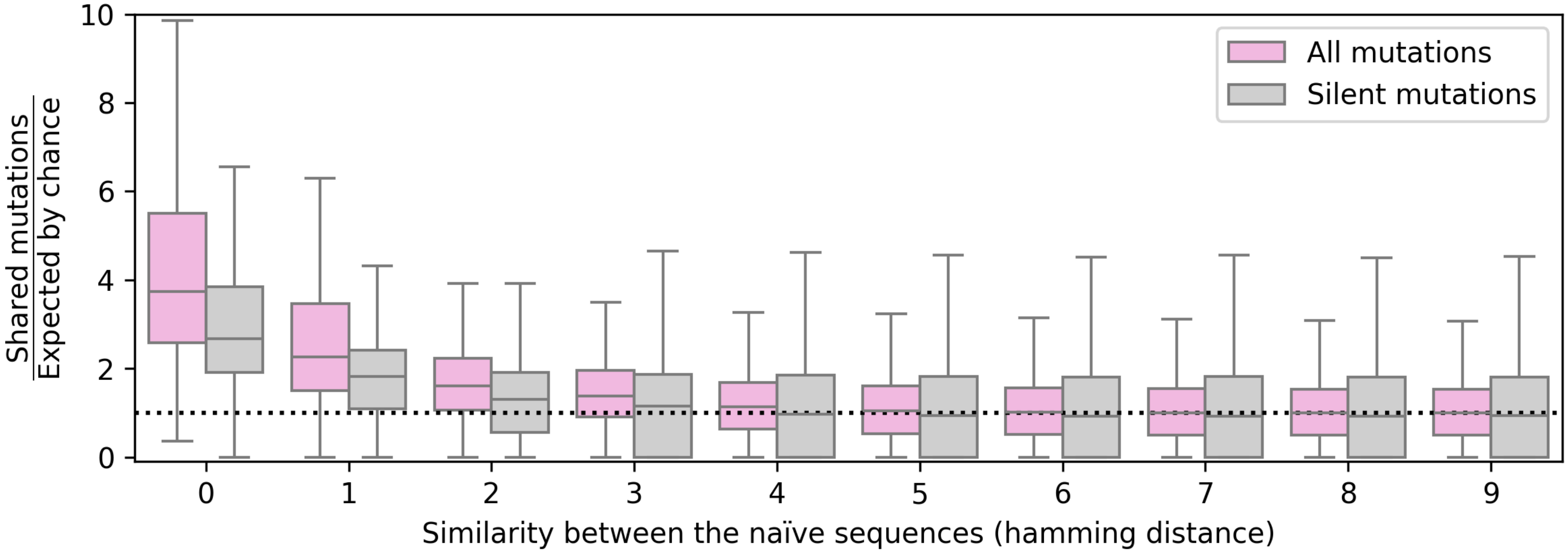




Identical ancestors share more mutations than expected in different individuals

Mutational convergence

What about sequences that are not exactly shared, but close enough ?



THANKS !

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Joao Ascensao
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Aleksandra Walczak

dupic@ciml.univ-mrs.fr