

# Dynamics of immune repertoires in COVID-19 patients

Armita Nourmohammad

Department of Physics, University of Washington

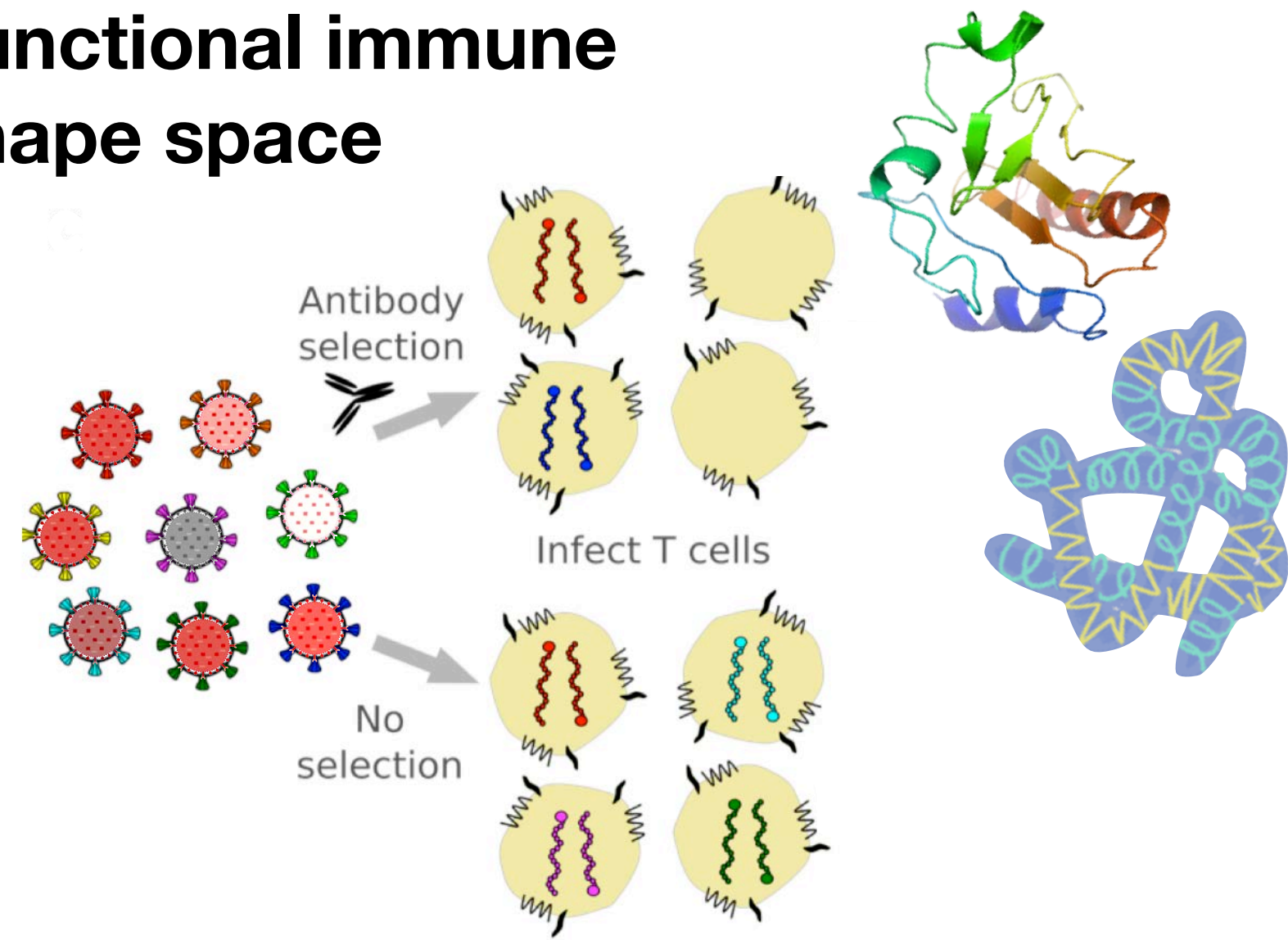
MPI for Dynamics and Self-Organization, Göttingen

Fred Hutch Cancer Research Center, Seattle

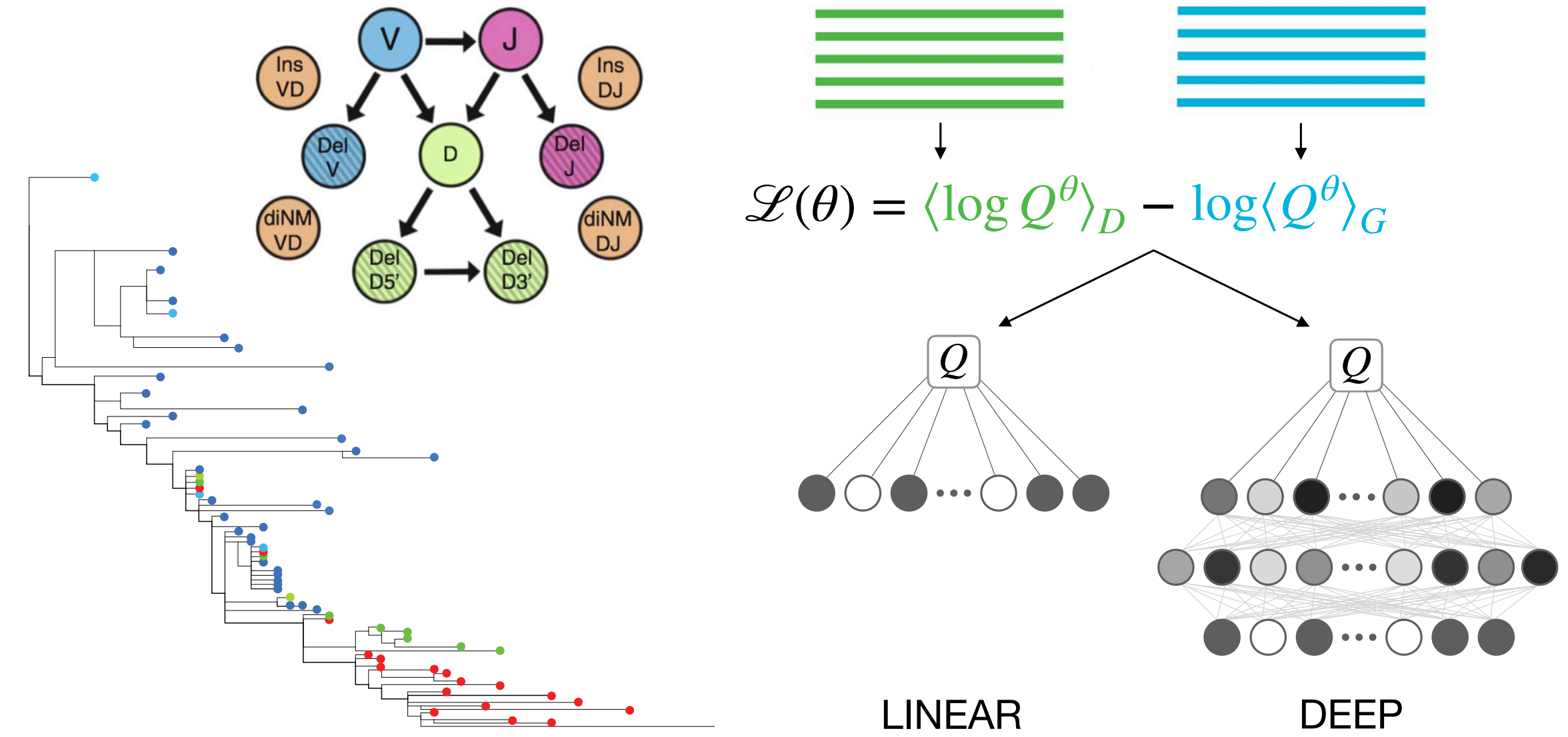




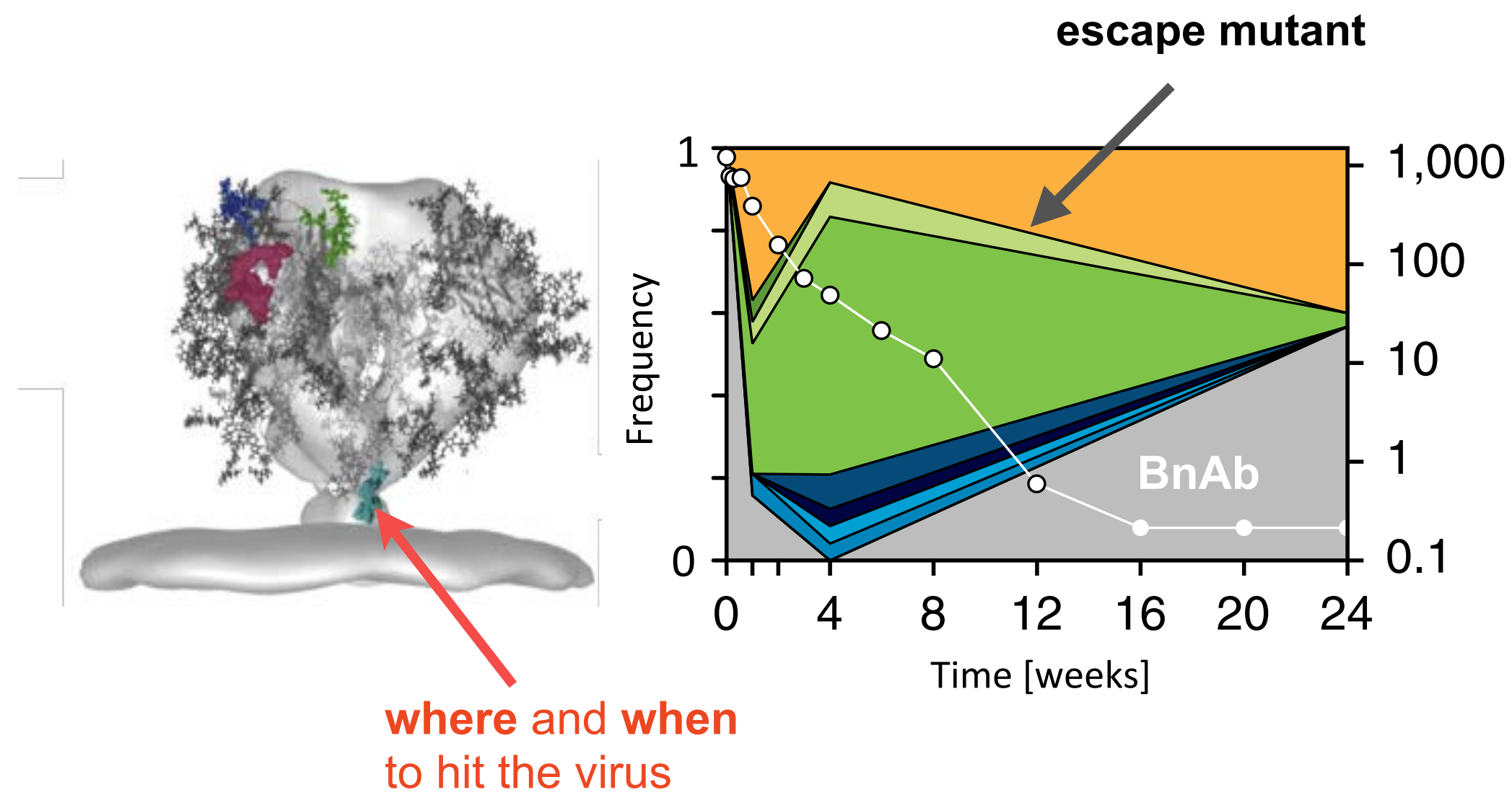
# Functional immune shape space



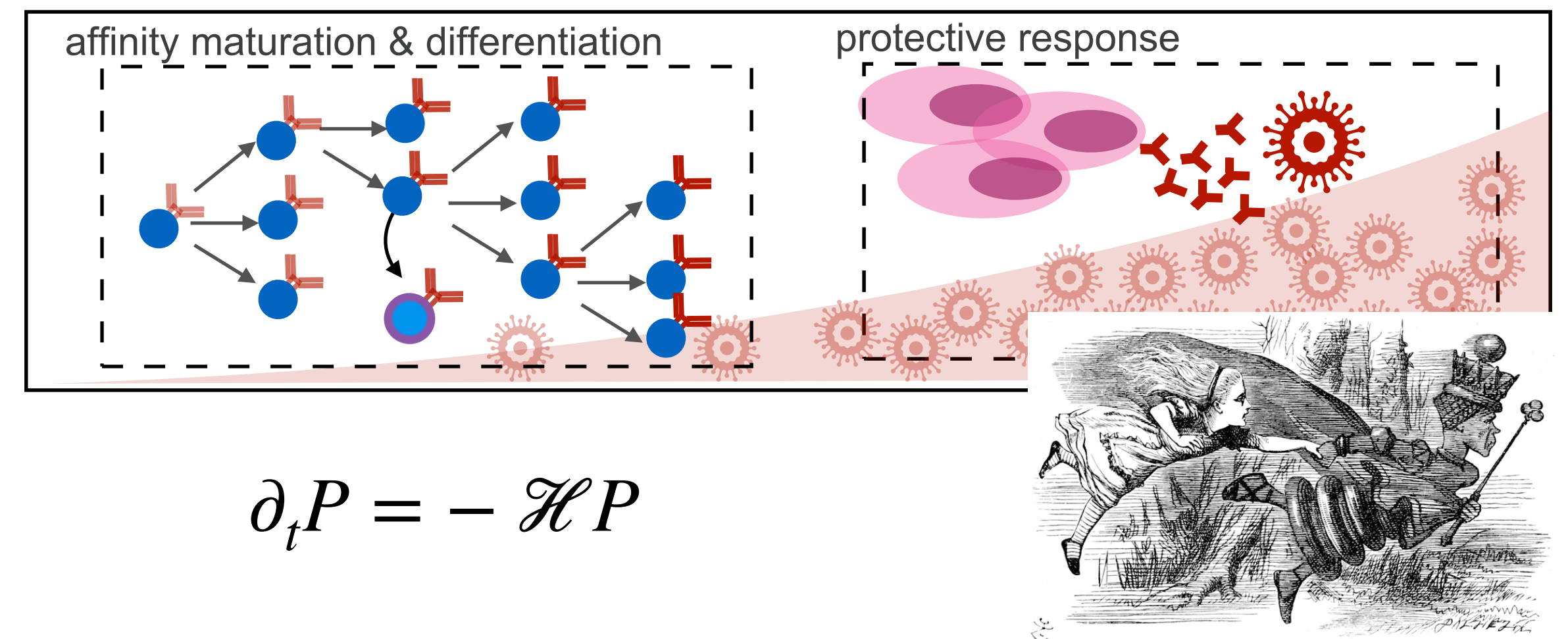
# Statistical inference in B-cell & T-cell repertoires



# Immune-based control strategies

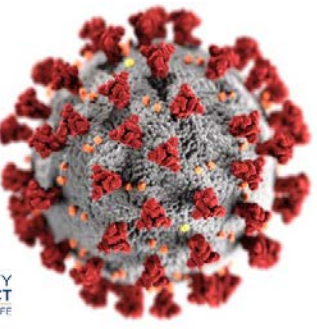


# Coevolutionary modeling



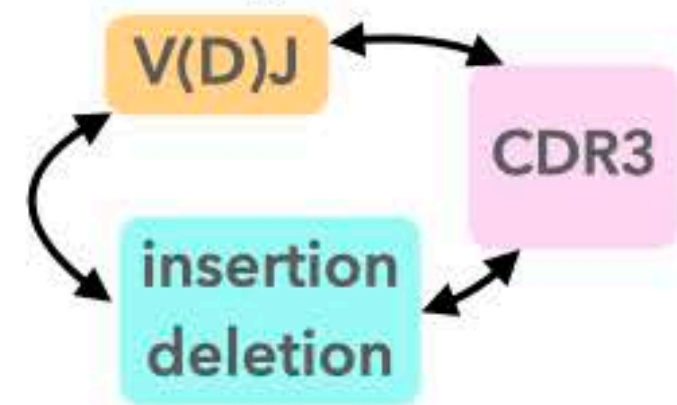


# Dynamics of immune repertoires

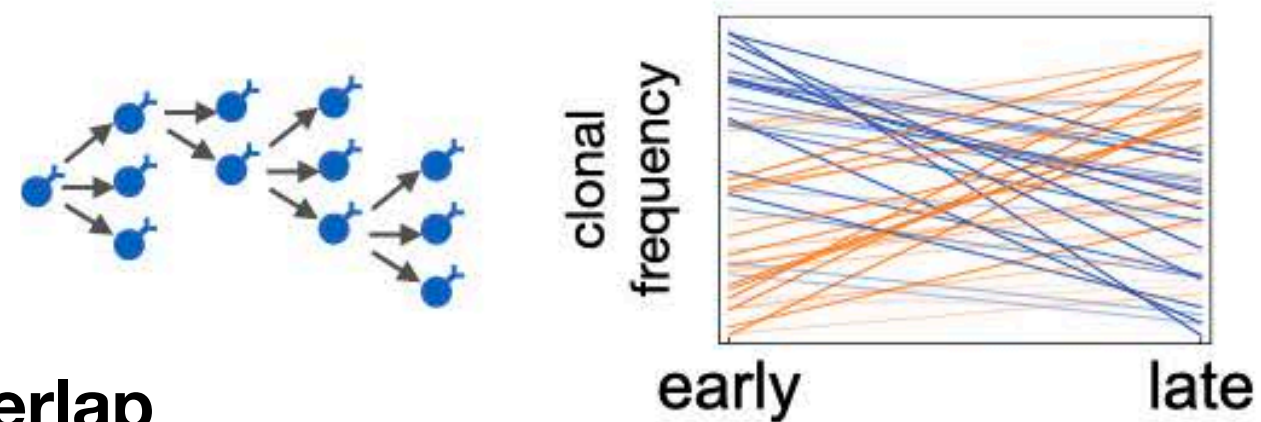


## B-cell response to **acute** SARS-CoV-2 (**weeks**) (**population dynamics**)

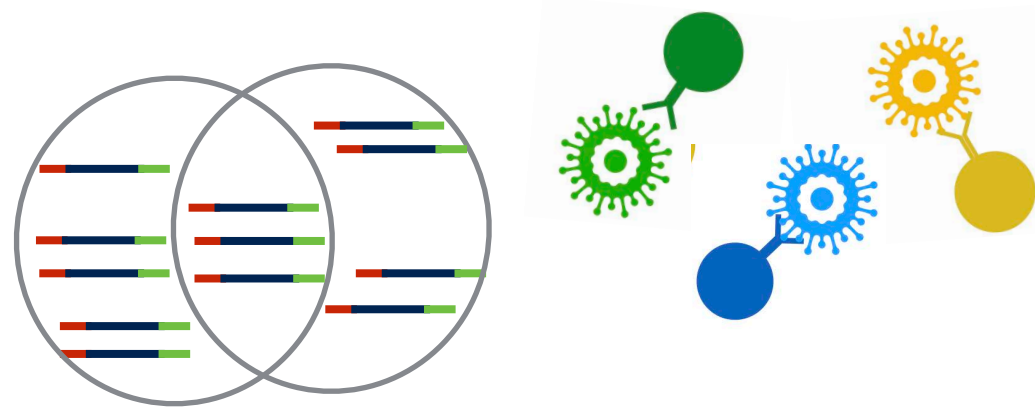
Differential statistical features of BCRs in healthy & COVID-19 patients



Dynamics of clonal lineages in COVID-19 patients

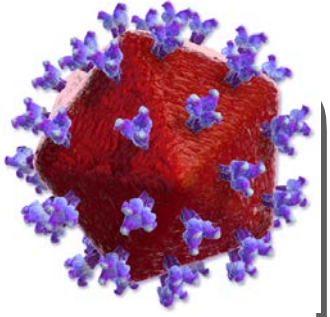


Sharing of BCR clones and overlap with verified nAbs.

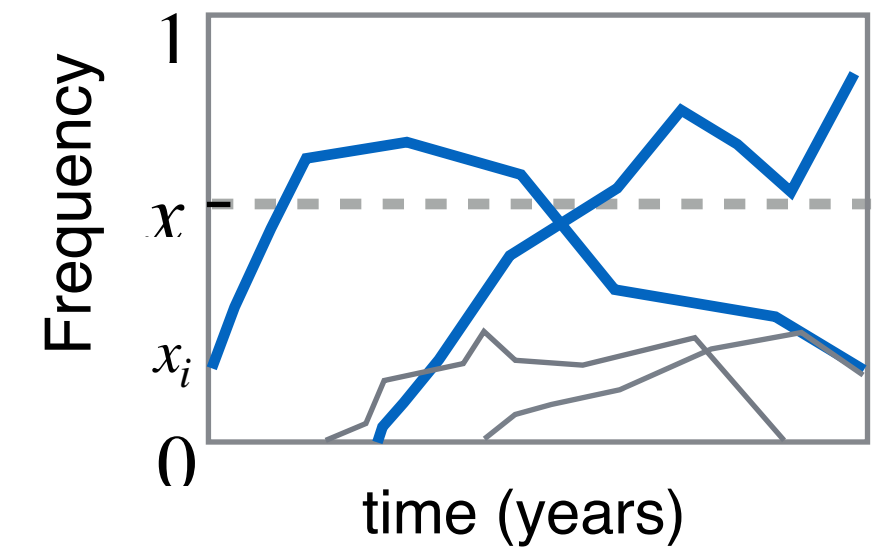
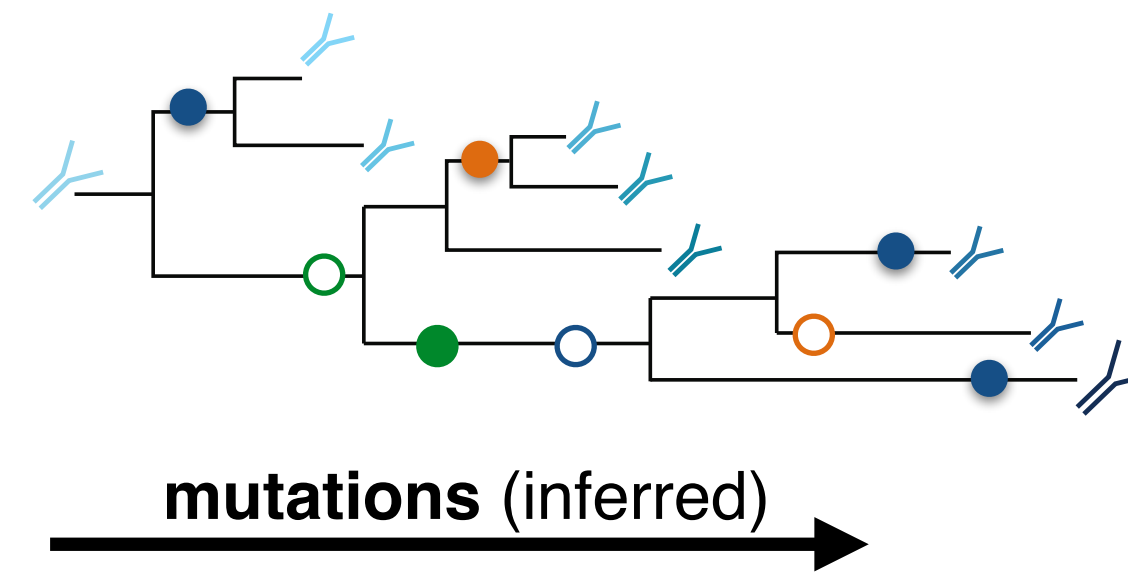


*medRxiv* 2020.07.13.20153114

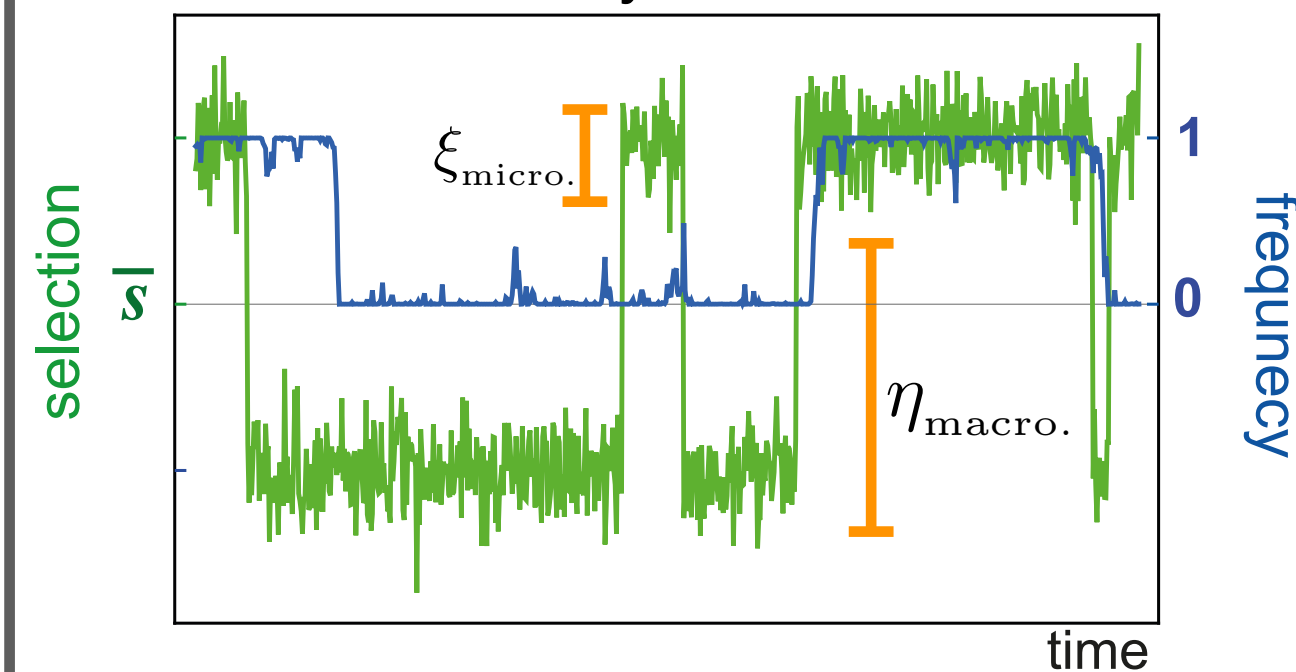
with, **Z. Montague**, H. Lv, N. Wu, C. Mok



## B-cell response to **chronic** HIV-1 (**years**) (**population genetics**)



fitness landscape  
antibody evolution



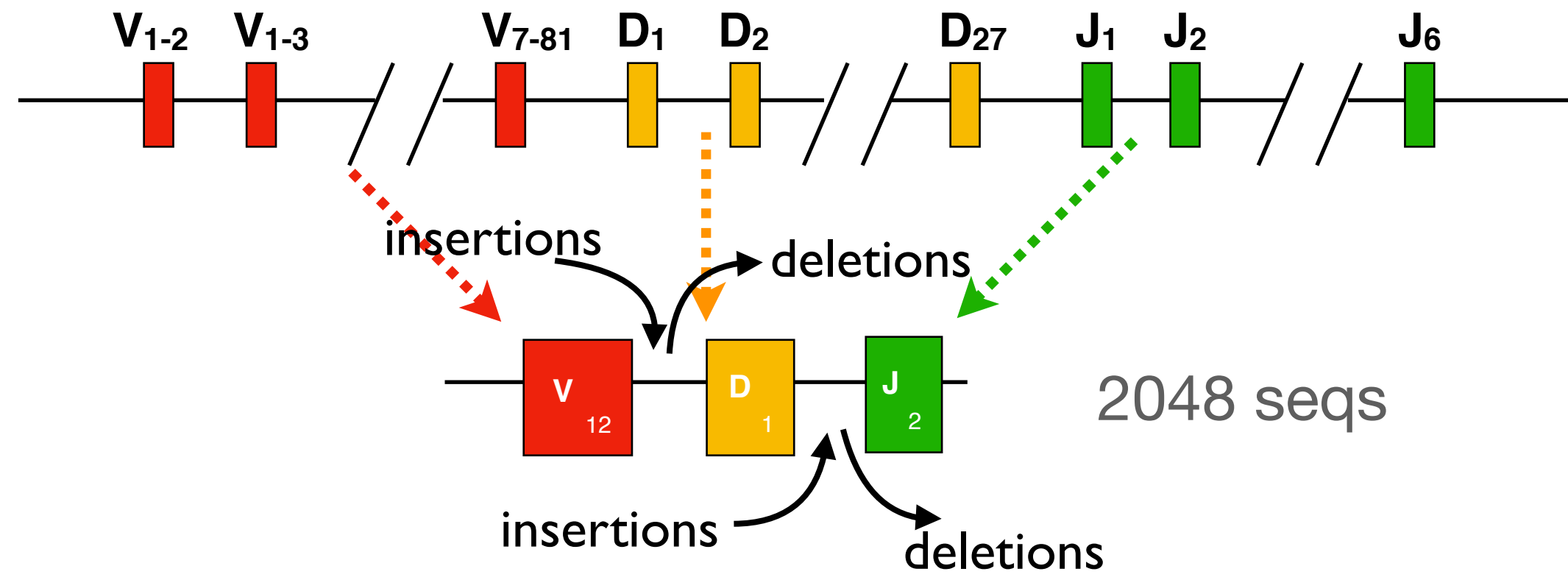
*Mol. Biol. Evol.* 2019

with, J. Otwinowski, M. Luksza, A. Walczak, T. Mora

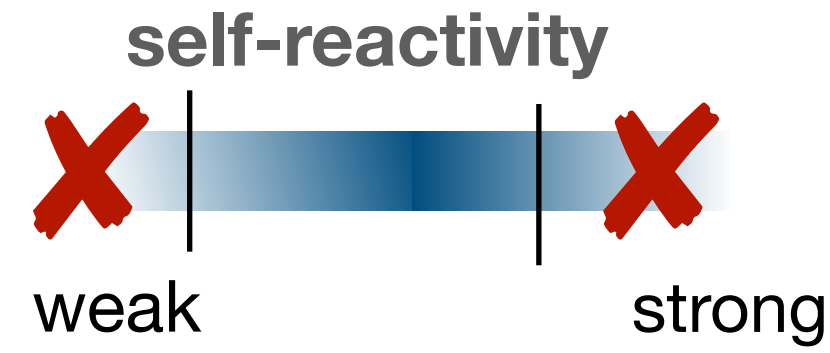
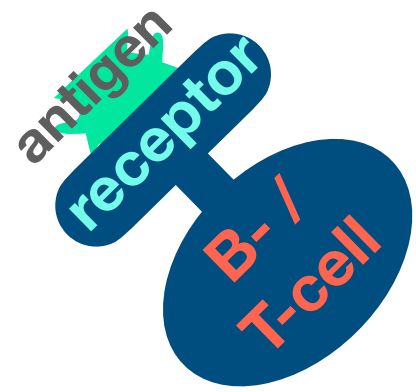
# adaptive immunity



gene rearrangement: B-cell, T-cell  
large receptor diversity



+ selection **against self-reaction**



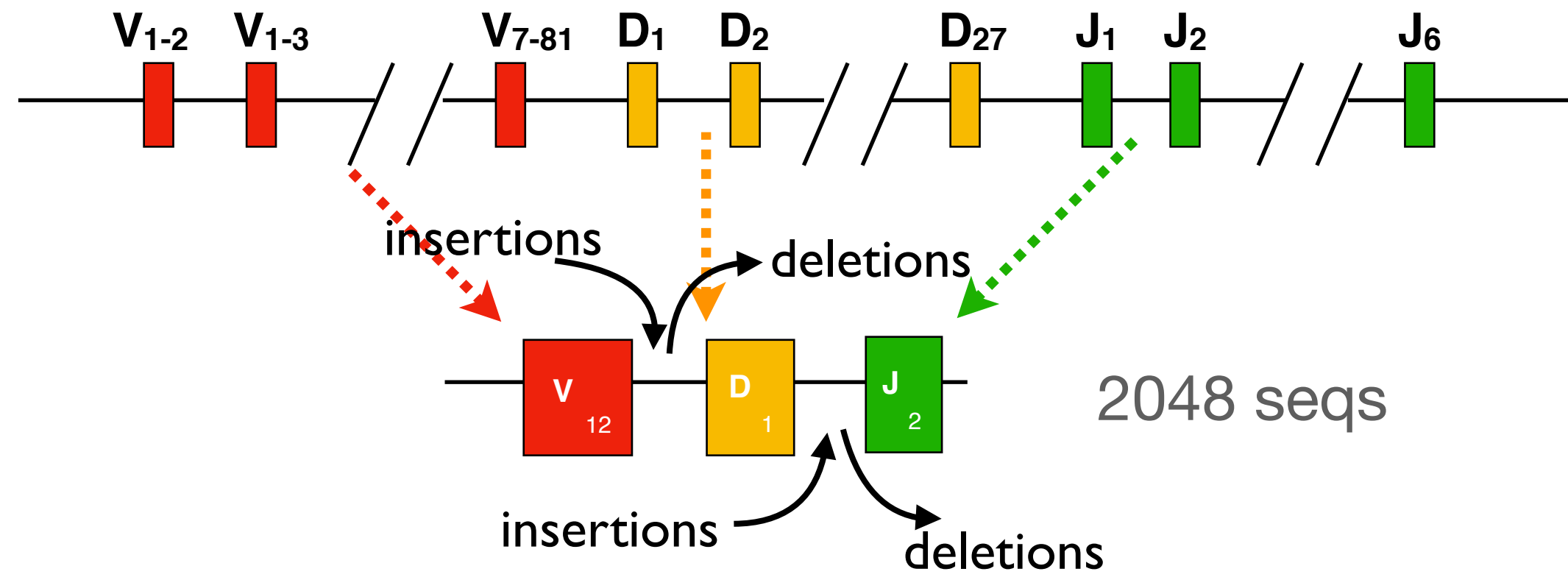
$10^{16} - 10^{18}$  seqs  
 $\gg 10^{12}$



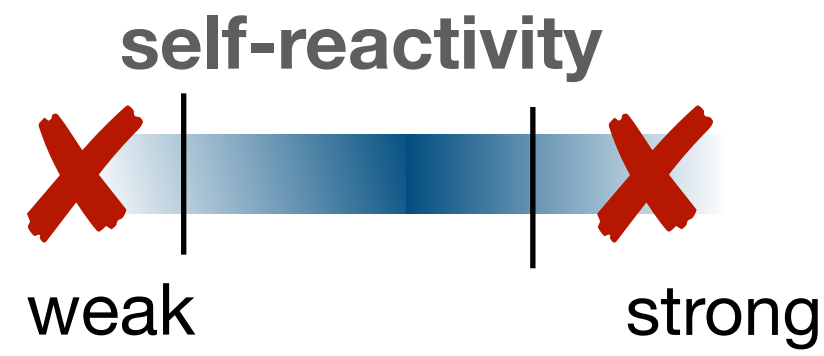
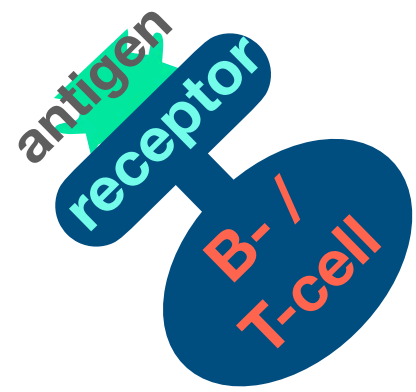
# adaptive immunity



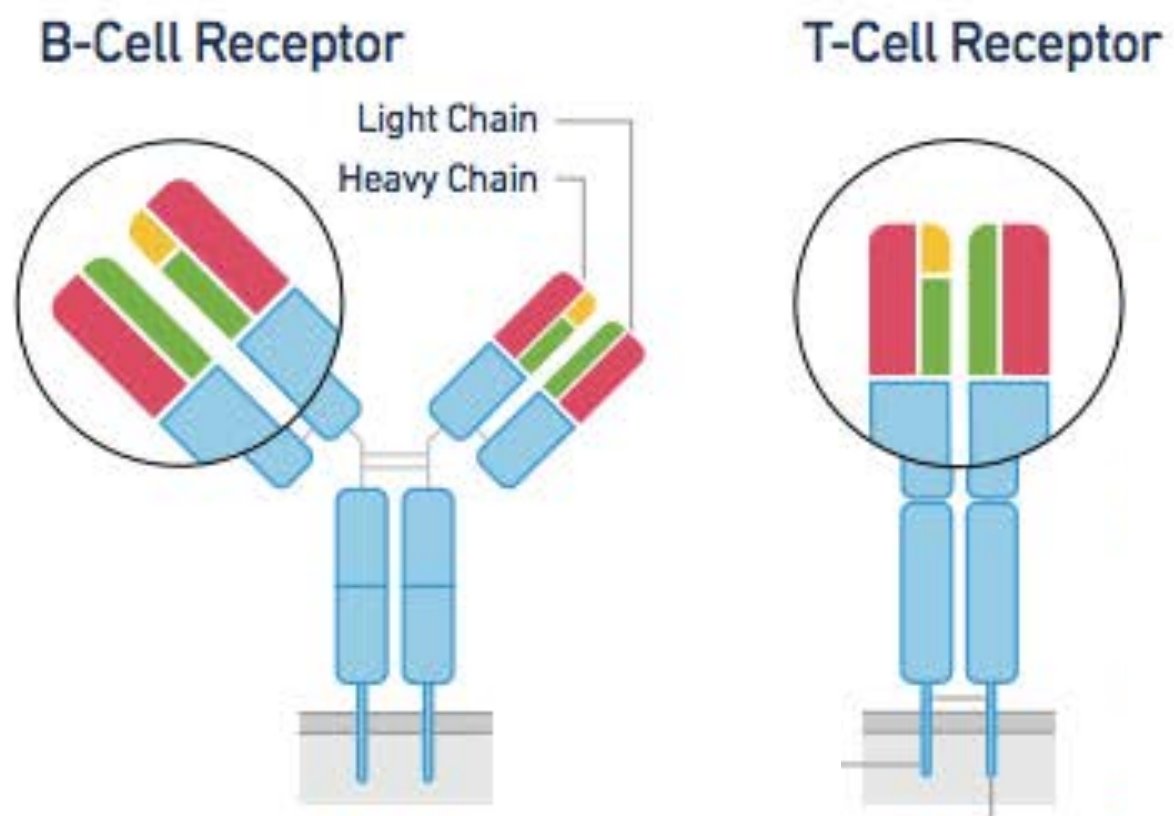
gene rearrangement: B-cell, T-cell  
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$10^{16} - 10^{18}$  seqs  
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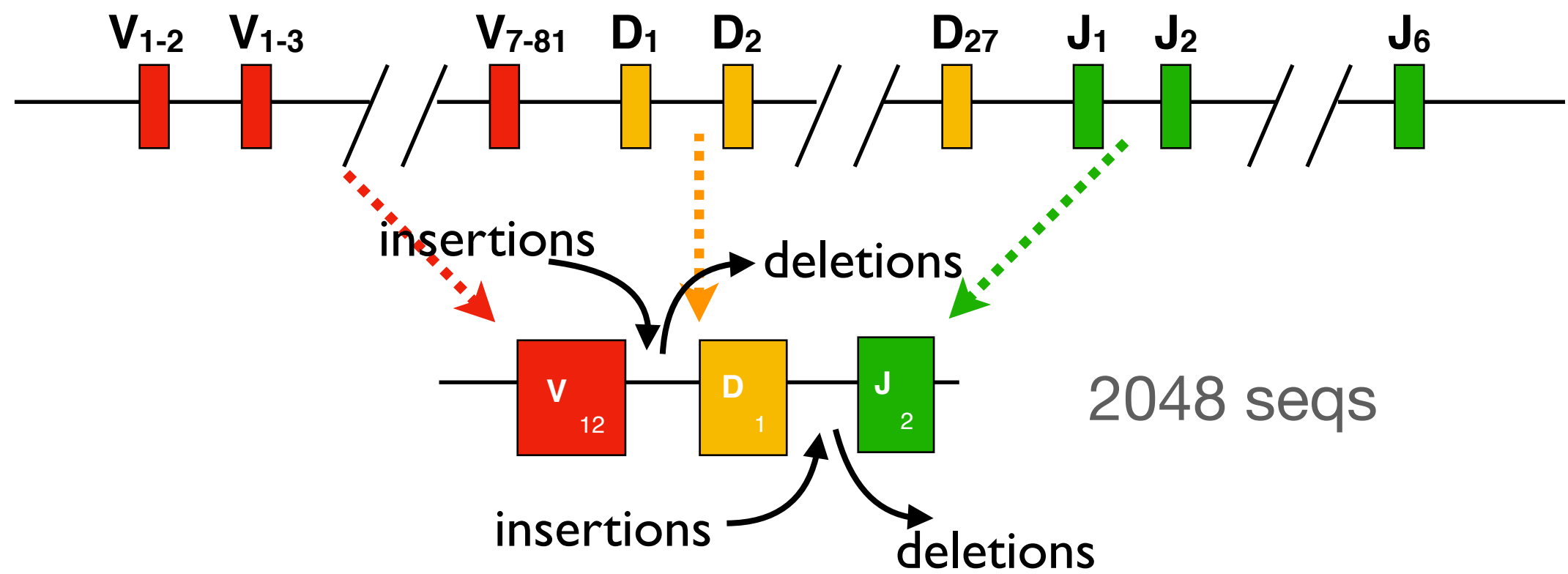




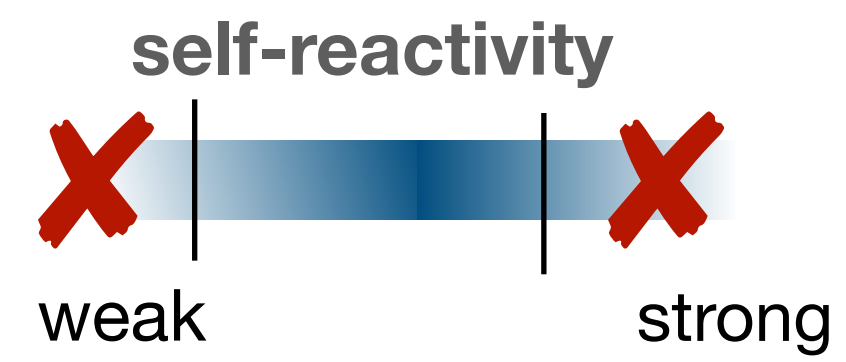
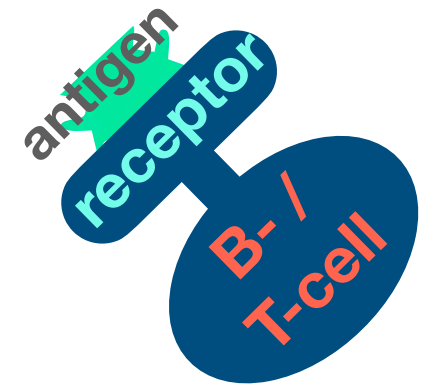
# adaptive immunity: evolution within us



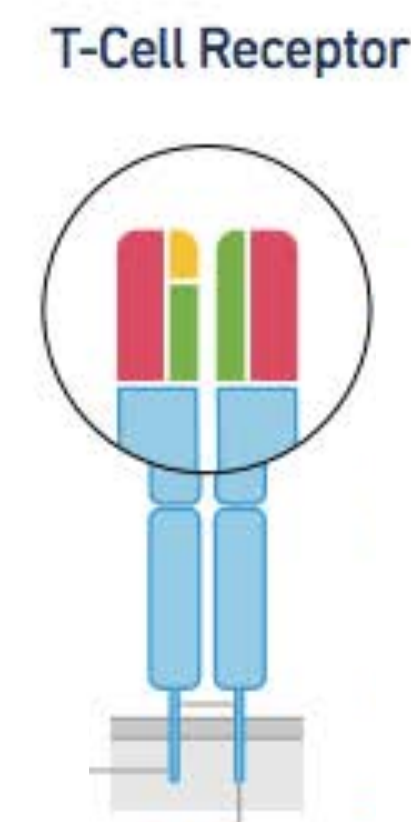
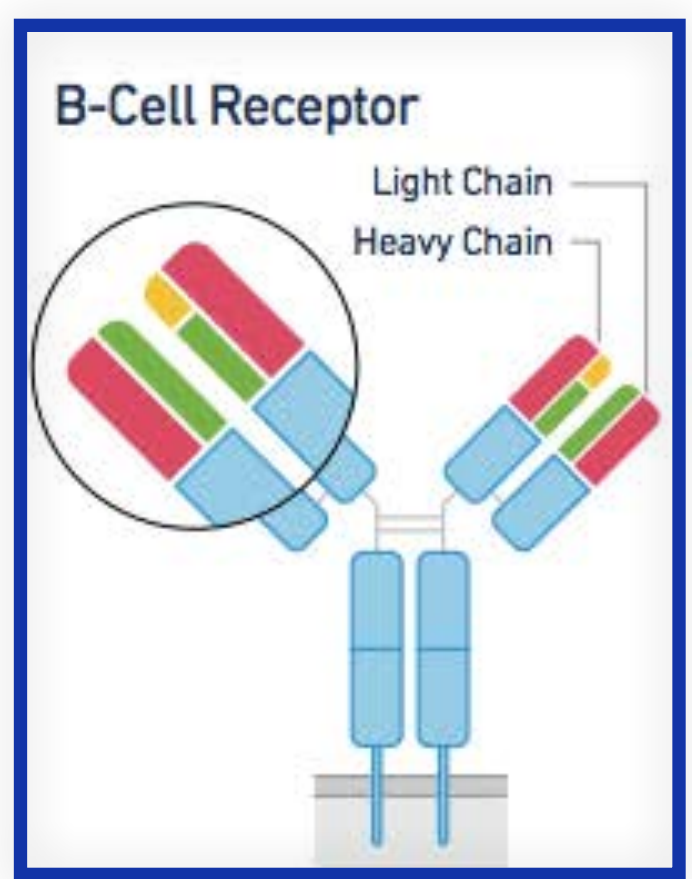
gene rearrangement: B-cell, T-cell  
large receptor diversity



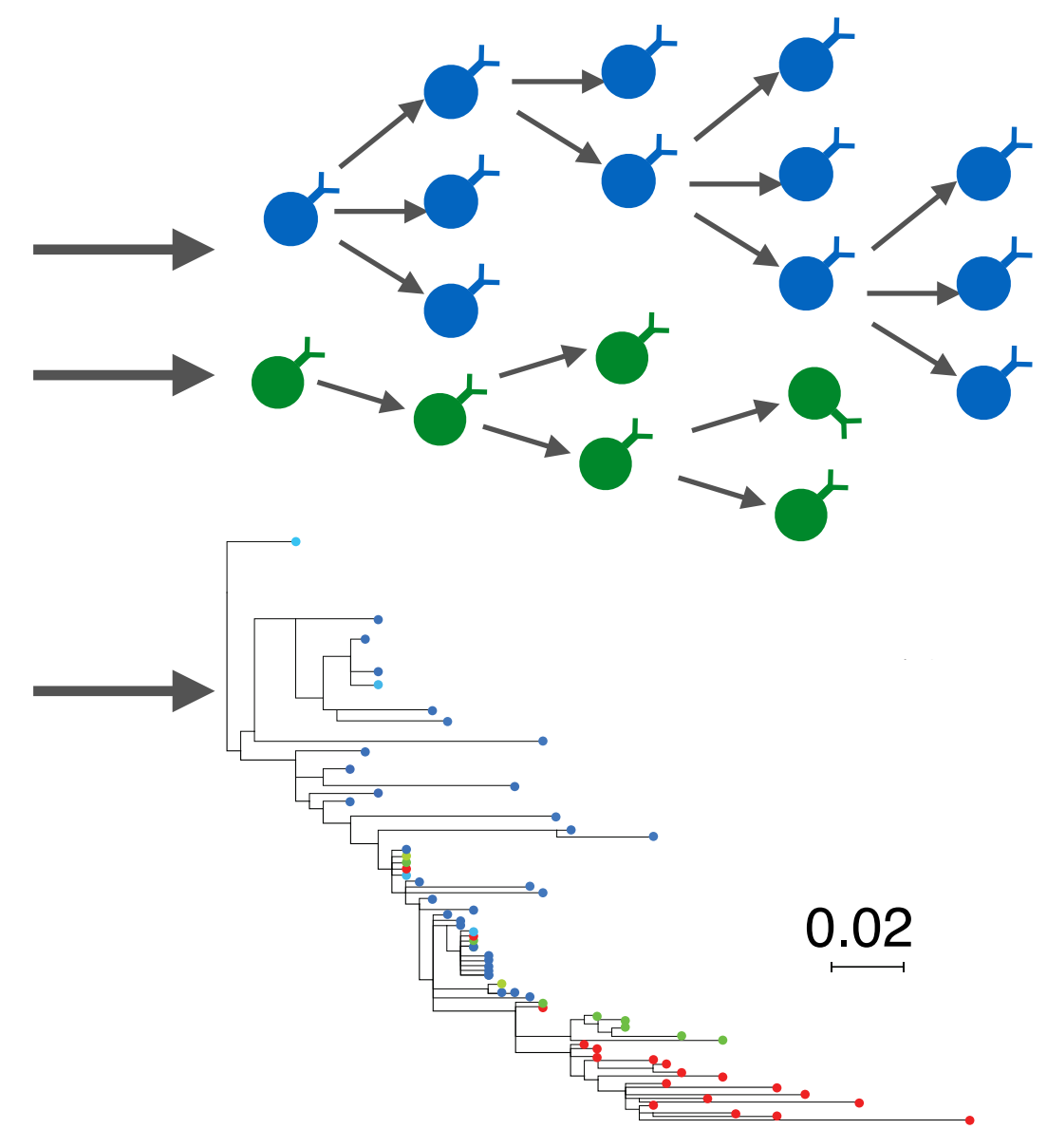
+ selection against self-reaction



$10^{16} - 10^{18}$  seqs  
 $\gg 10^{12}$



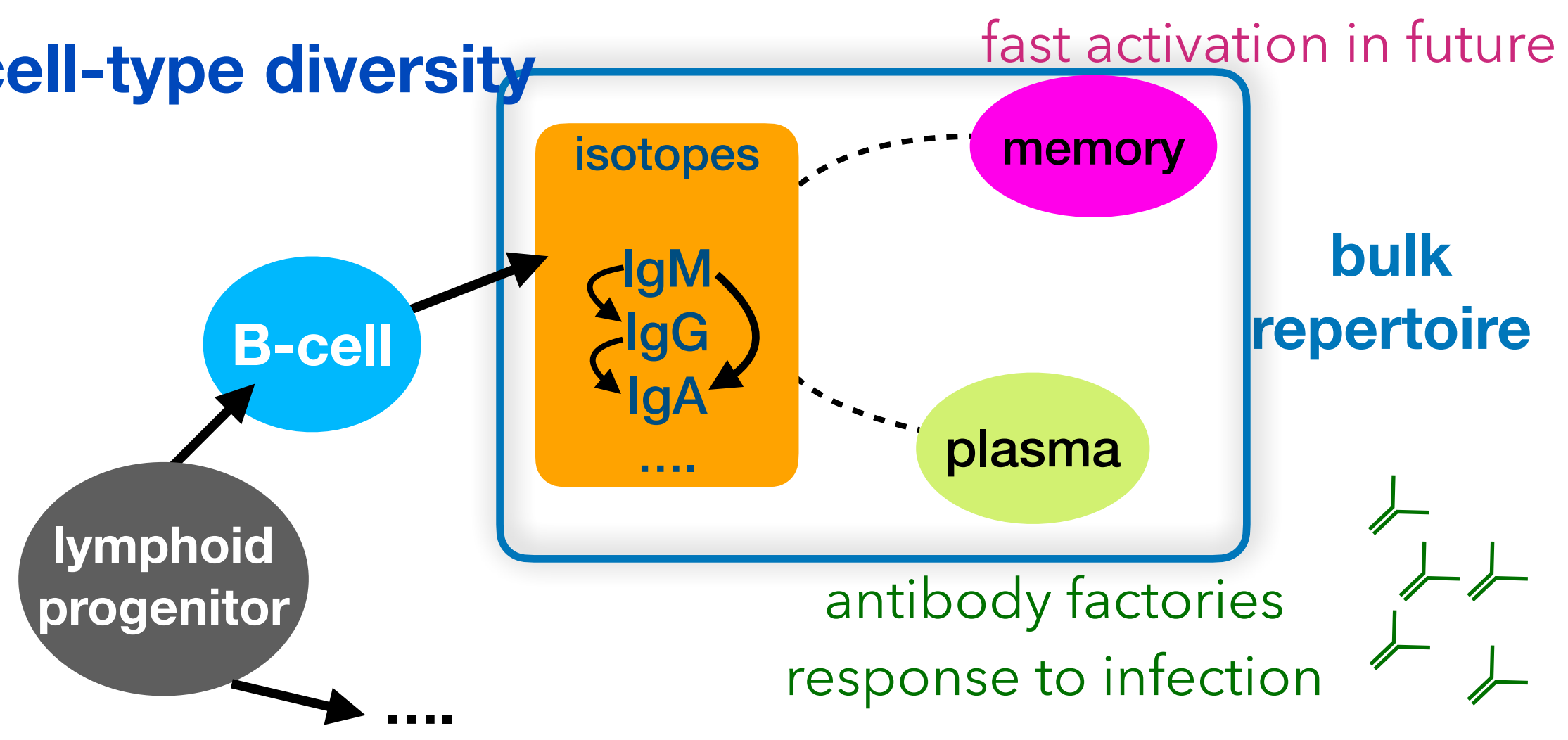
somatic affinity maturation: B-cell  
**Darwinian Evolution**



10-10000 fold  
affinity increase

hypermutation / selection  
many B-cell lineages

cell-type diversity



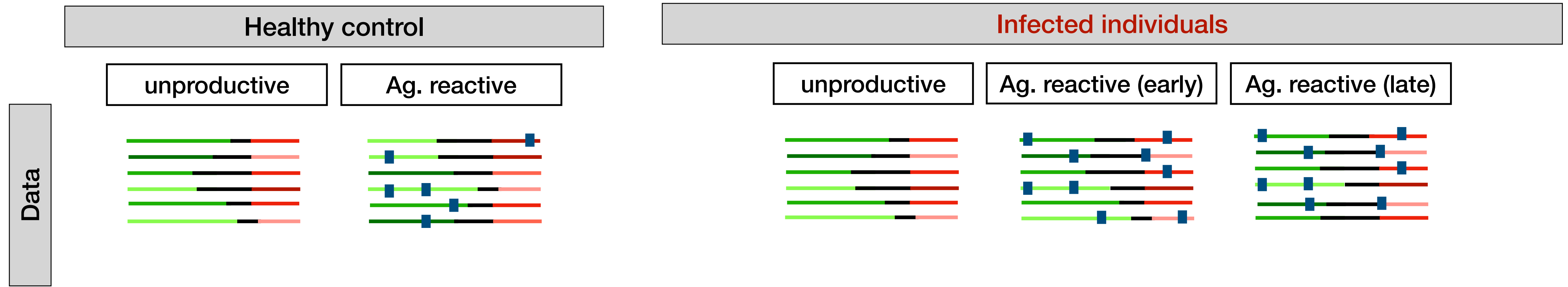
fast activation in future

bulk  
repertoire

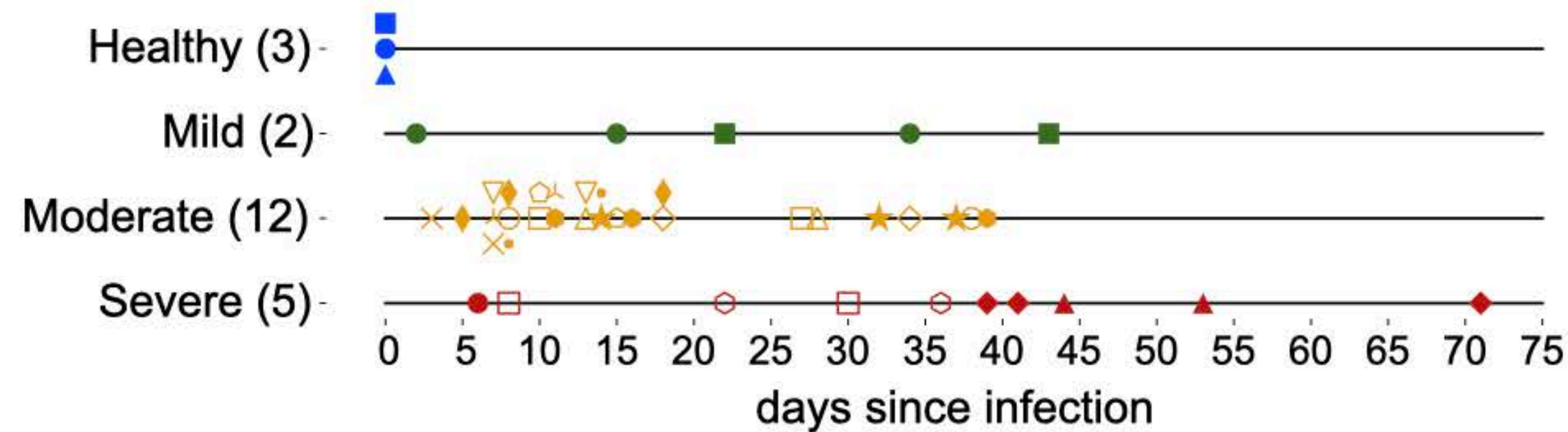
antibody factories  
response to infection



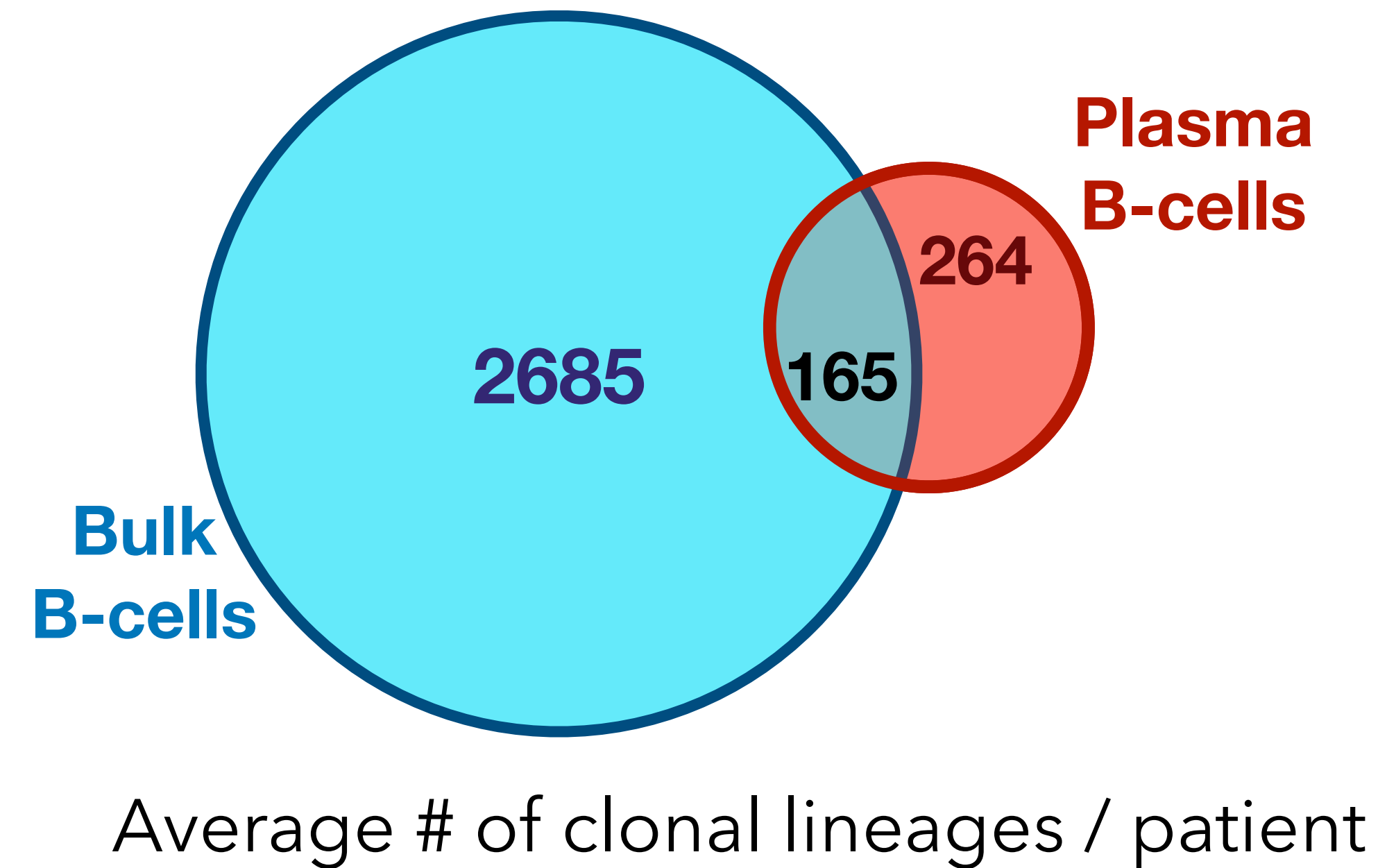
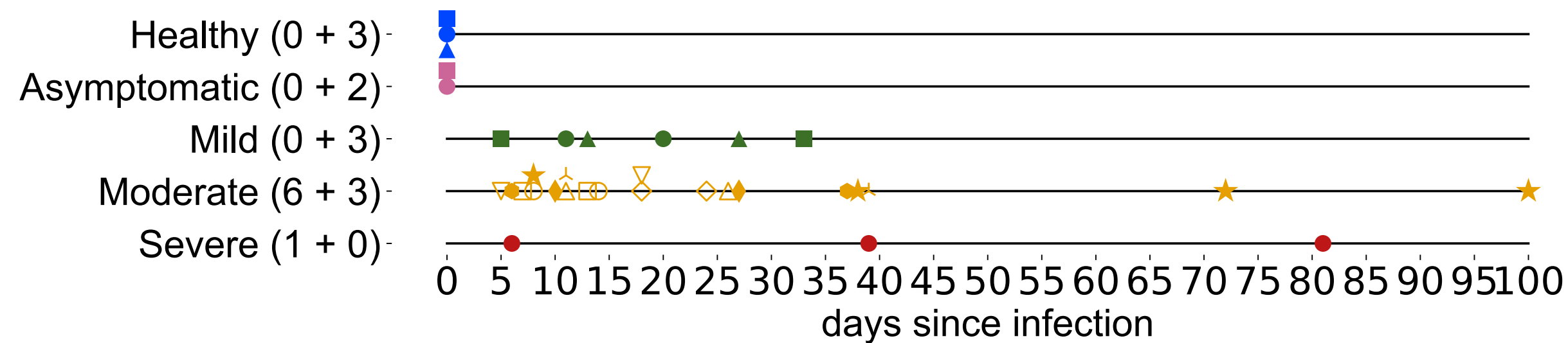
# How to interpret immune repertoire data?



## Bulk repertoire (19 patients)



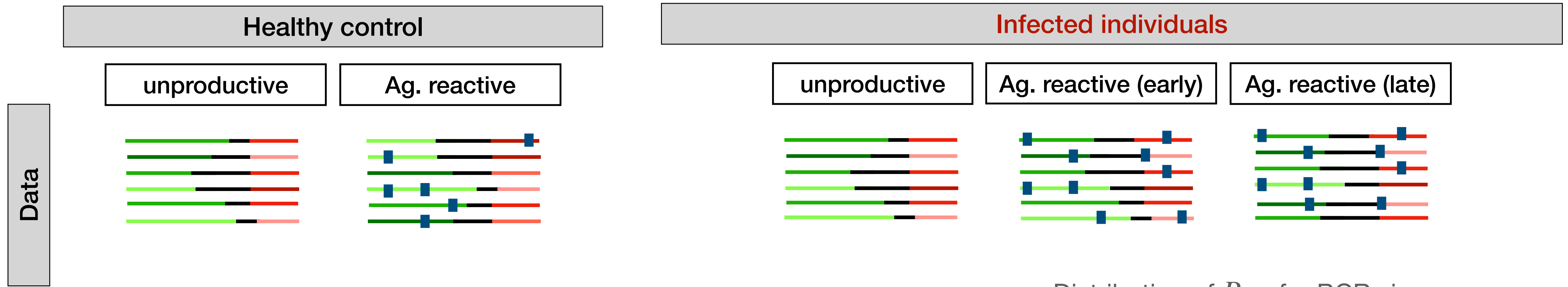
## Plasma repertoire (15 patients)



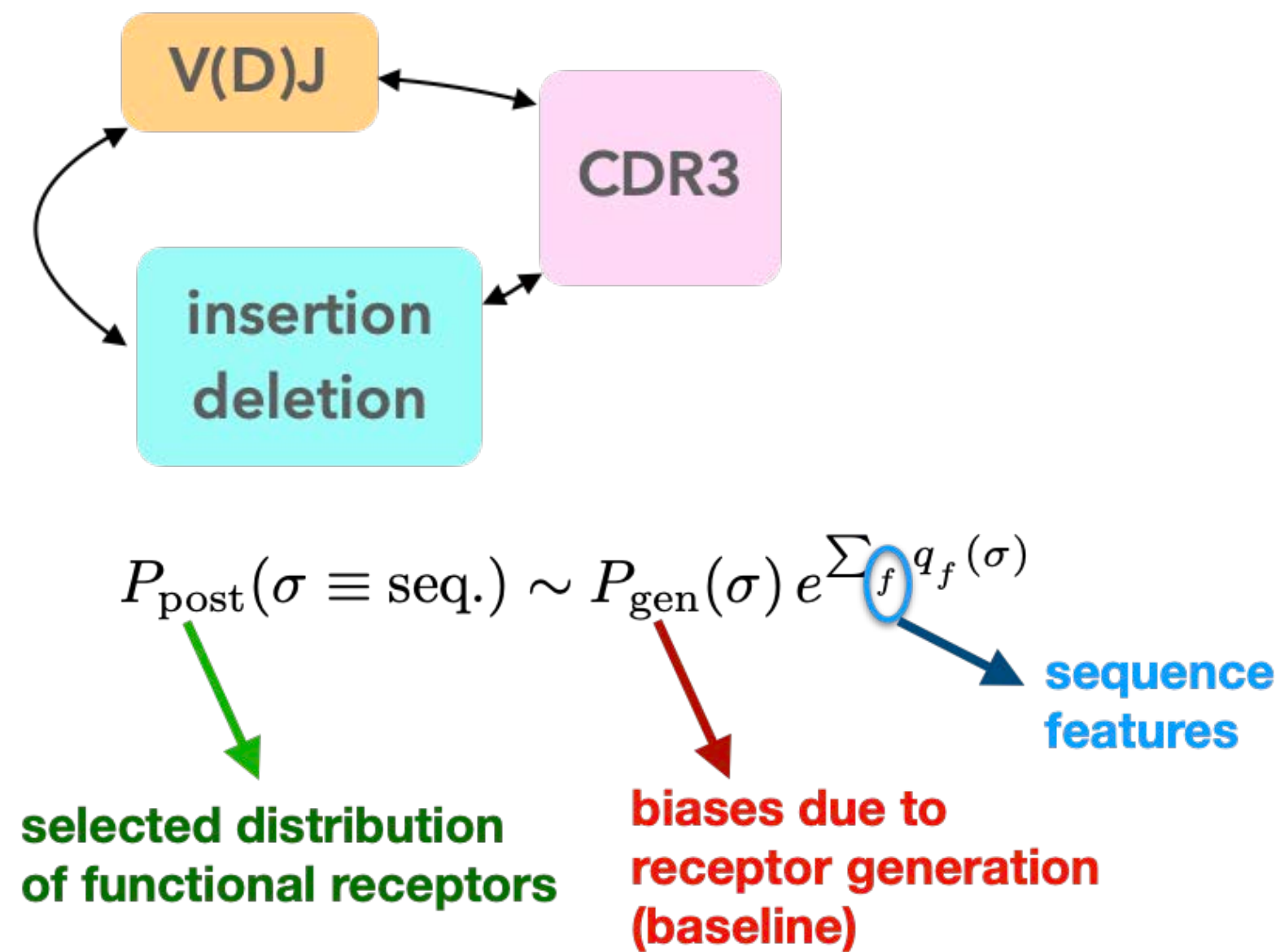
Average # of clonal lineages / patient



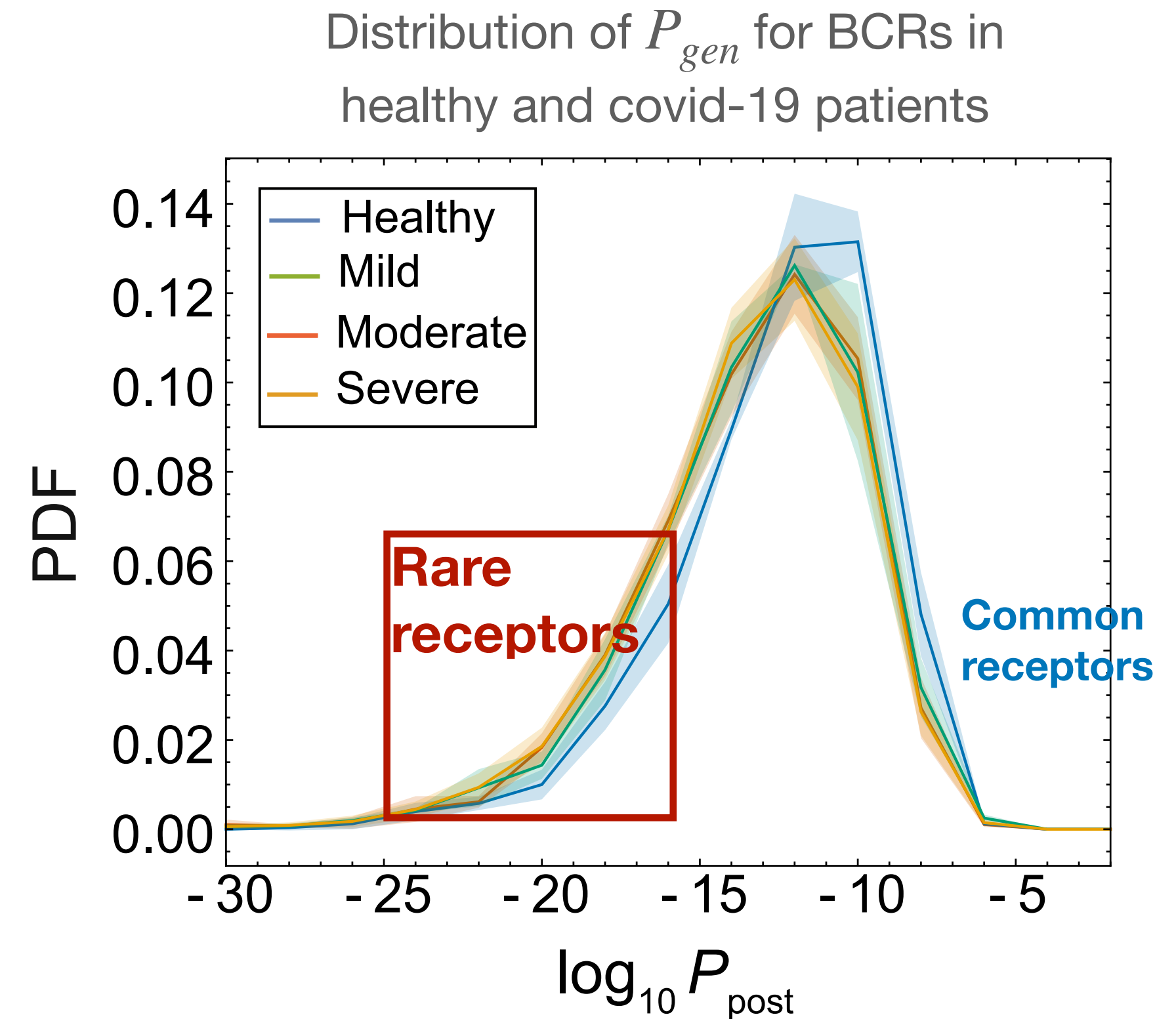
# How to interpret immune repertoire data?



## 1. Differential statistical features of BCRs in healthy vs. infected individuals



See: Marcou, Mora & Walczak (2018), .....



Montague, [...], AN, Mok (MedArxiv 2020)

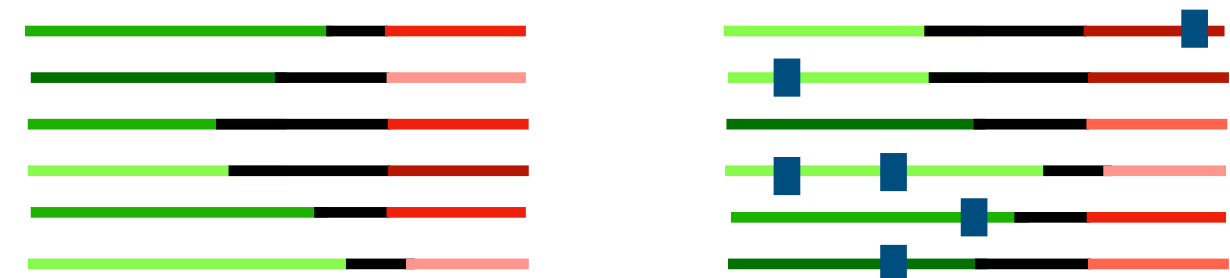


# How to interpret immune repertoire data?

Data

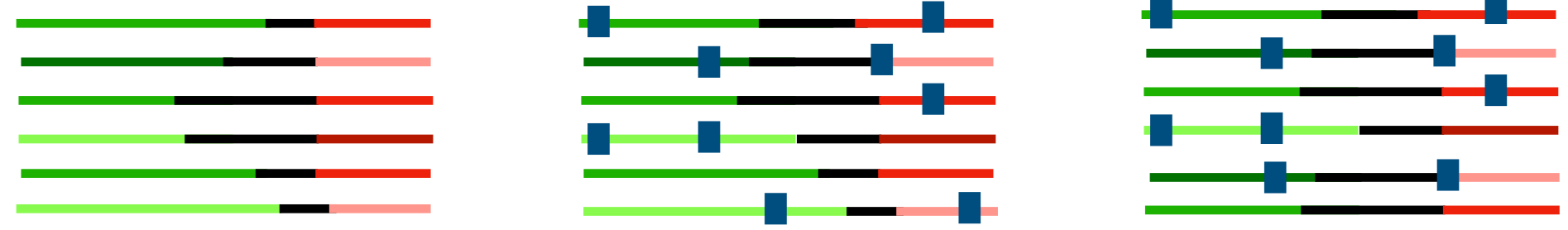
## Healthy control

unproductive      Ag. reactive



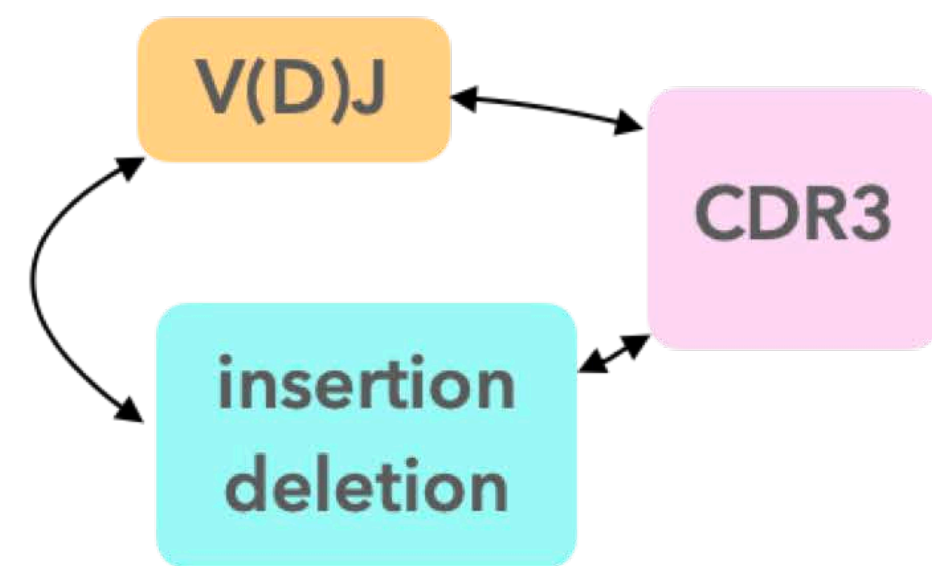
## Infected individuals

unproductive      Ag. reactive (early)      Ag. reactive (late)



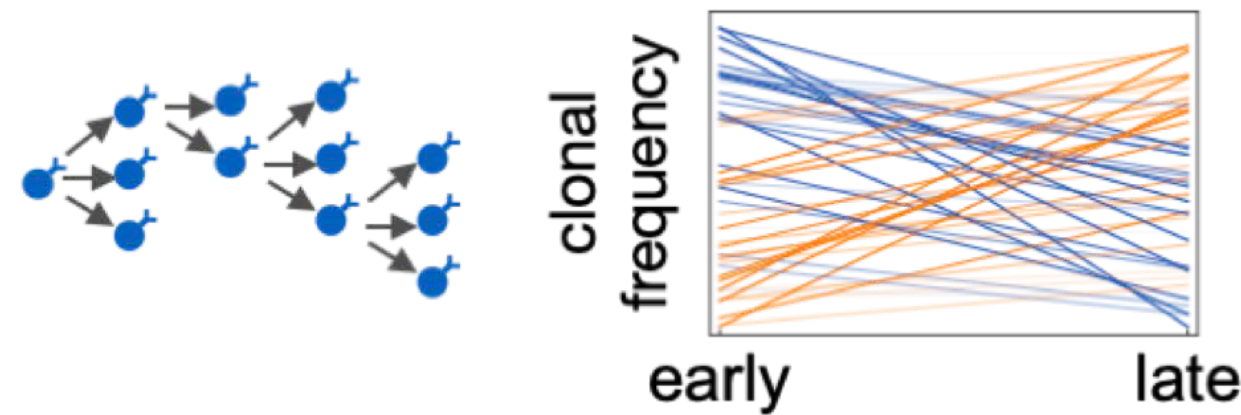
Model & Analysis

### 1. Differential statistical features of BCRs in healthy vs. infected individuals



$$P_{\text{post}}(\sigma \equiv \text{seq.}) \sim P_{\text{gen}}(\sigma) e^{\sum_f q_f(\sigma)}$$

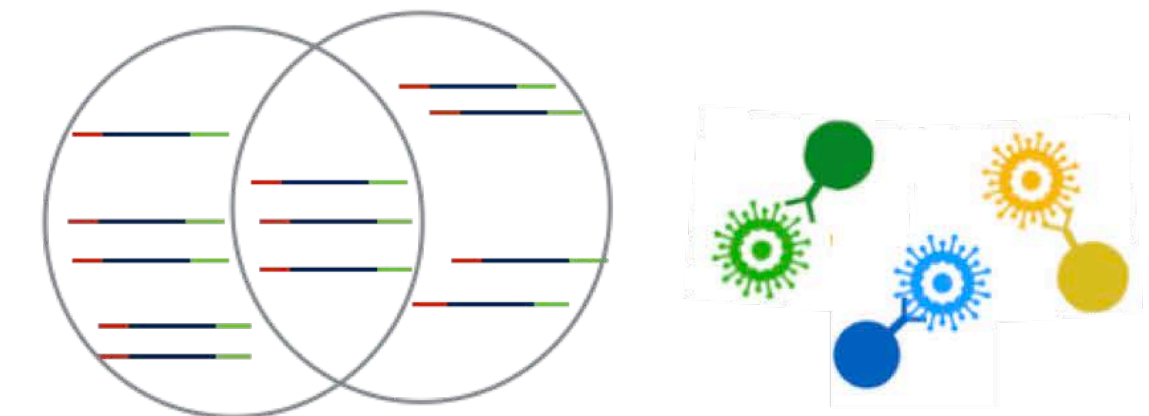
### 2. Dynamics of clonal lineages short- and long-term



- Expansion and contraction of lineages
- Generation of new BCRs by mutations

**Important:** dealing with noise and error  
Dynamical evolutionary models

### 3. Sharing of BCR clones and overlap with verified nAbs.



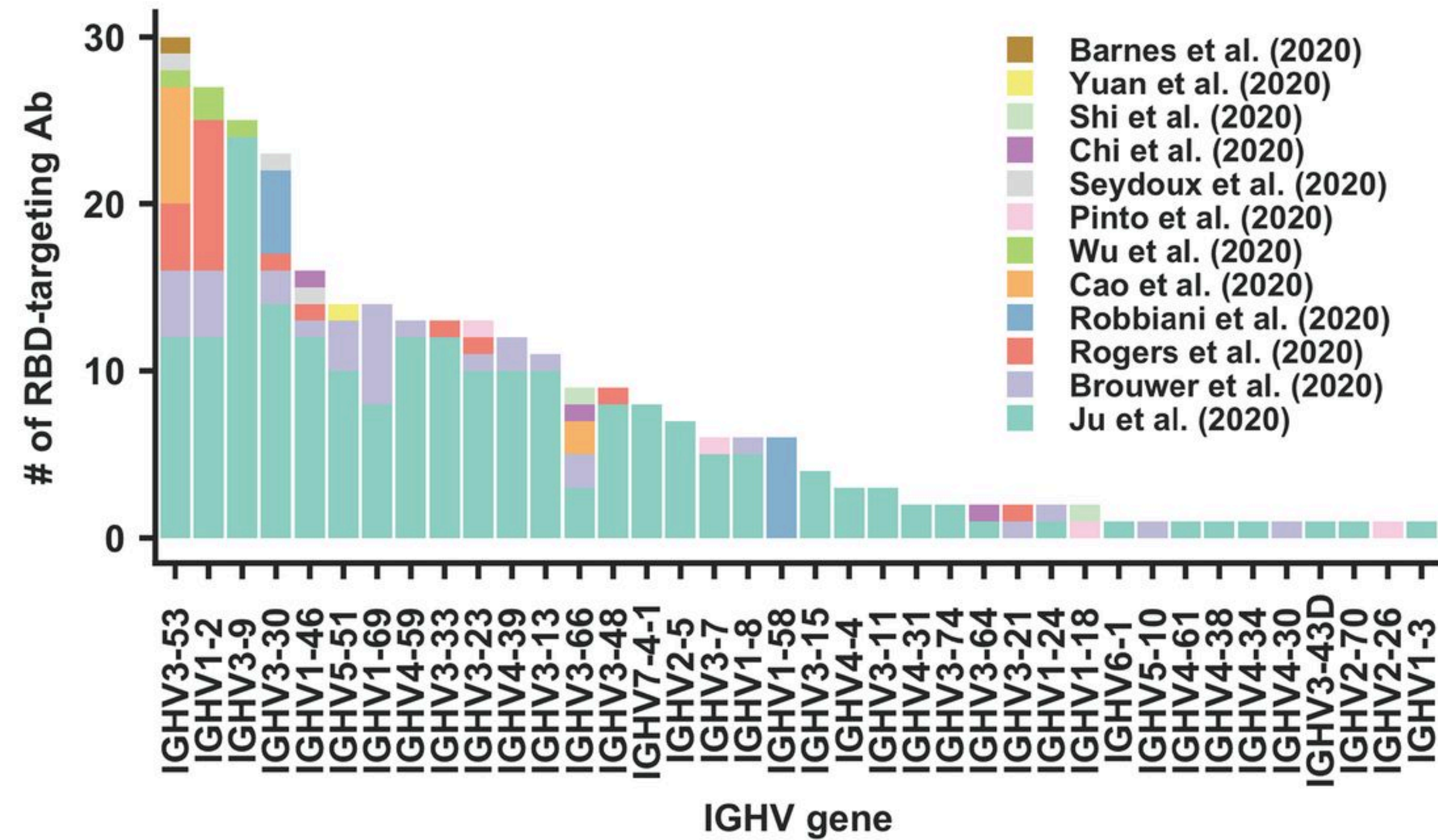
See: Marcou, Mora & Walczak (2018), .....

Montague, [...], AN, Mok (MedArxiv 2020)



# Differential selection on receptor **statistics** across cohorts

- V-gene usage biases in monoclonal antibodies

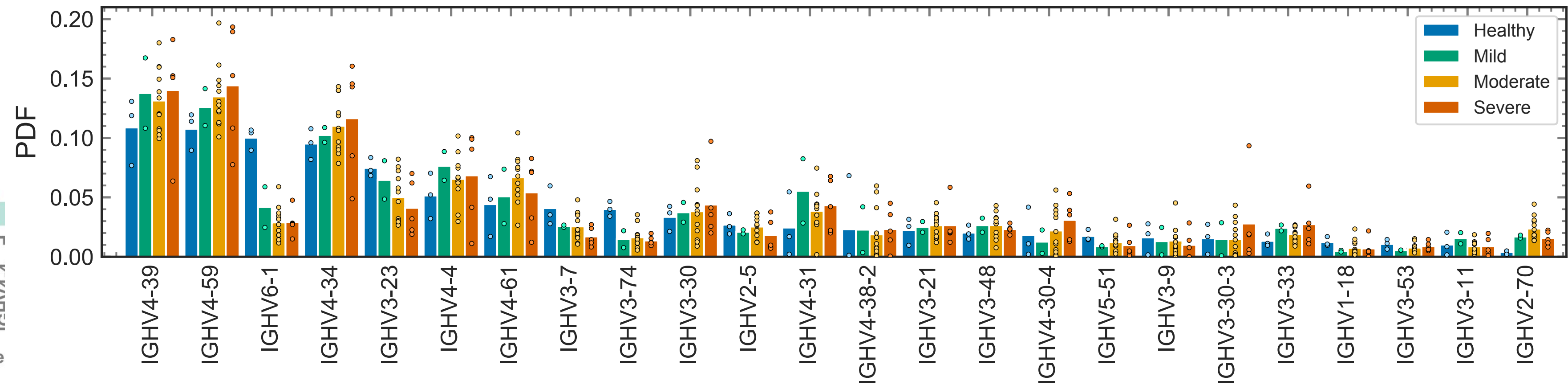
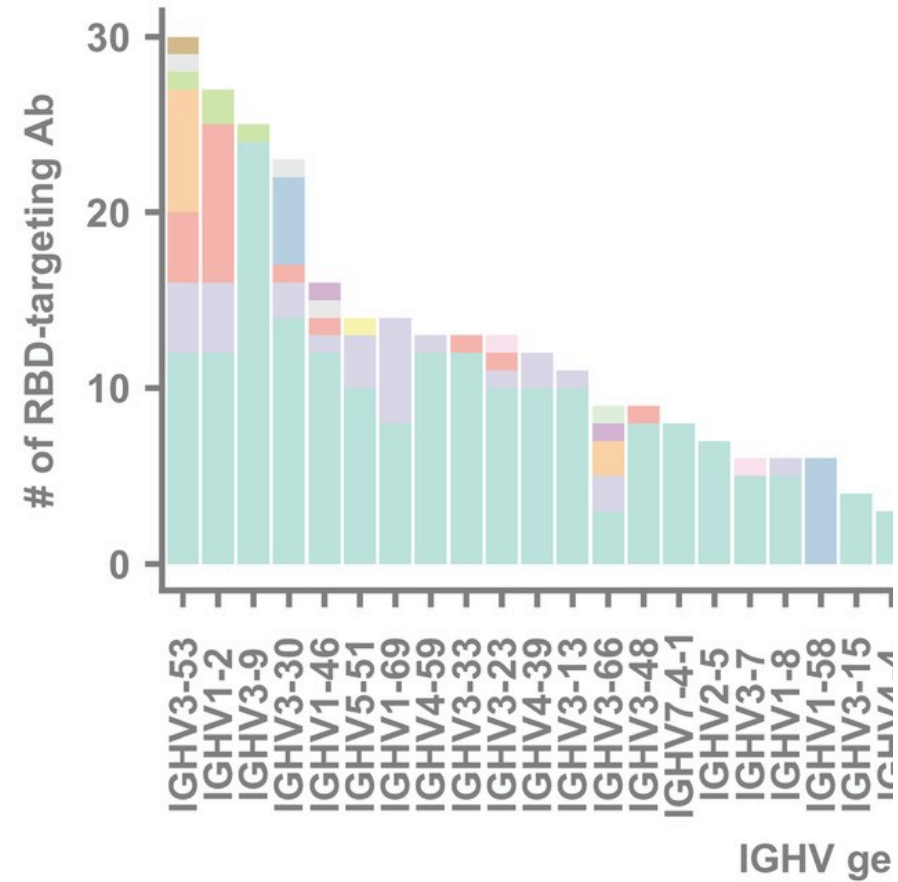


Yuan et al, Science 2020

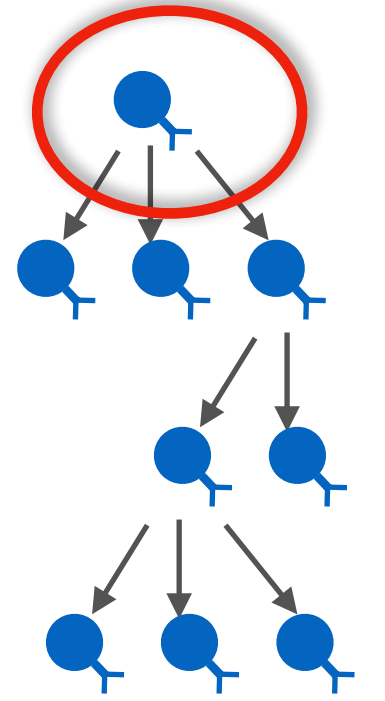


# Differential selection on receptor **statistics** across cohorts

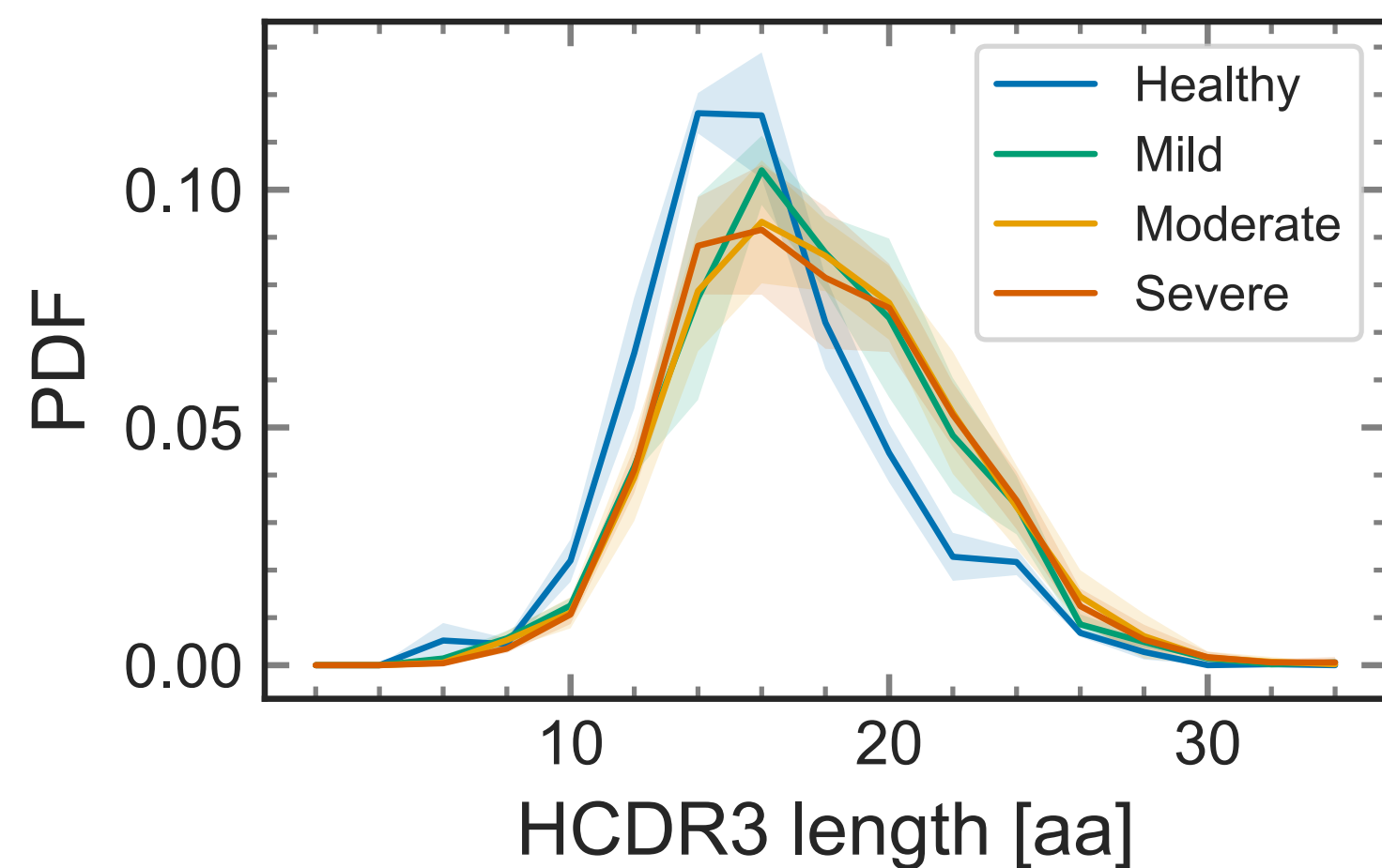
- V-gene usage biases in monoclonal antibodies
- within-cohort variability of **V-gene usage comparable** to cross-cohort (same for plasma)



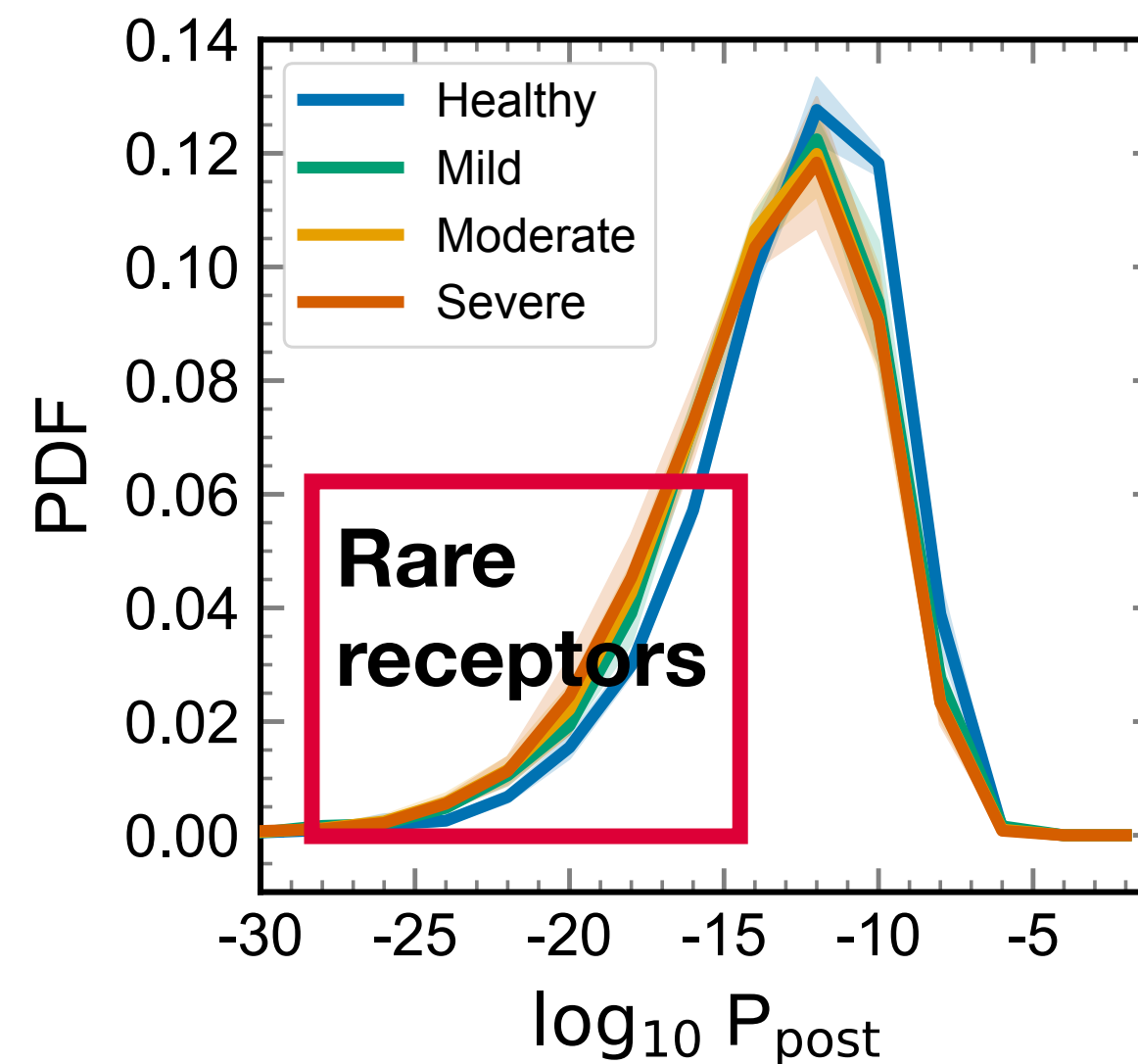
unique progenitor



- **longer CDR3** in COVID-19 patients



- clonal **diversity** increases with **disease severity**

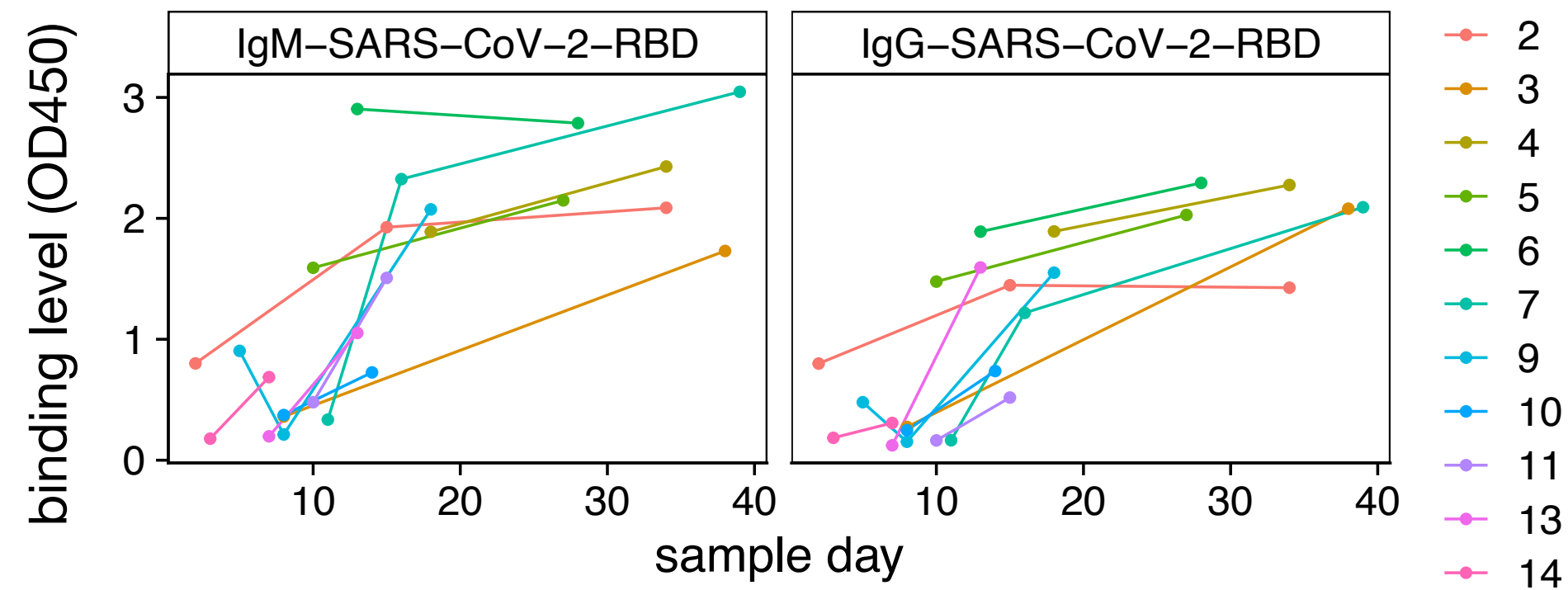


	repertoire entropy (bits)
Healthy	39.8 ± 0.3
Mild	41.9 ± 0.7
Moderate	42.7 ± 0.3
Severe	42.9 ± 0.5

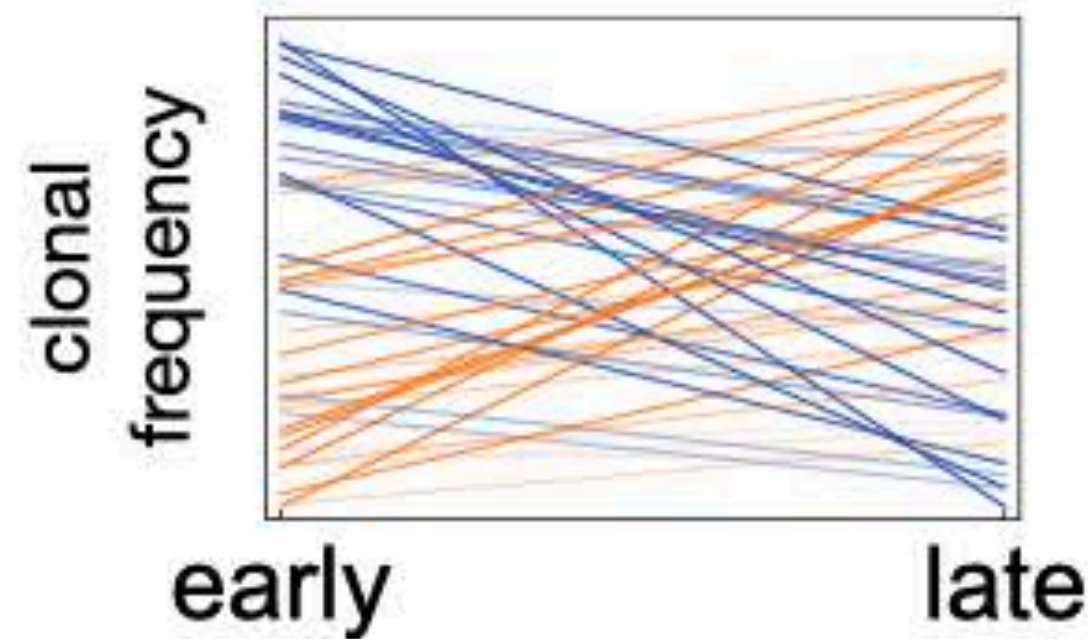


# Clonal dynamics in response to SARS-CoV-2

- IgG and IgM **reactivity** to RBD **increases** over time



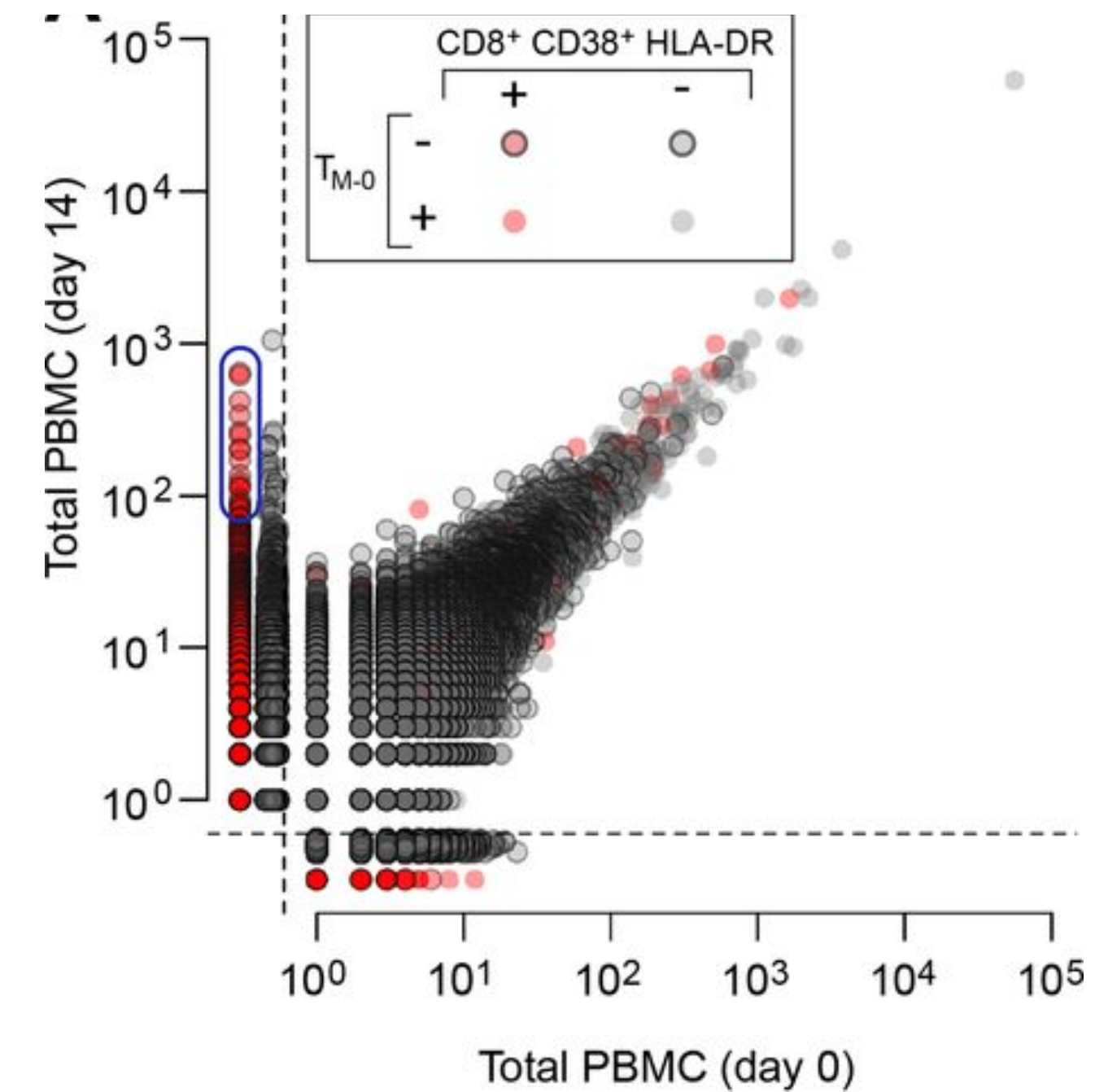
- Clonal expansion in response to immune challenge



## T-cell Interlude:

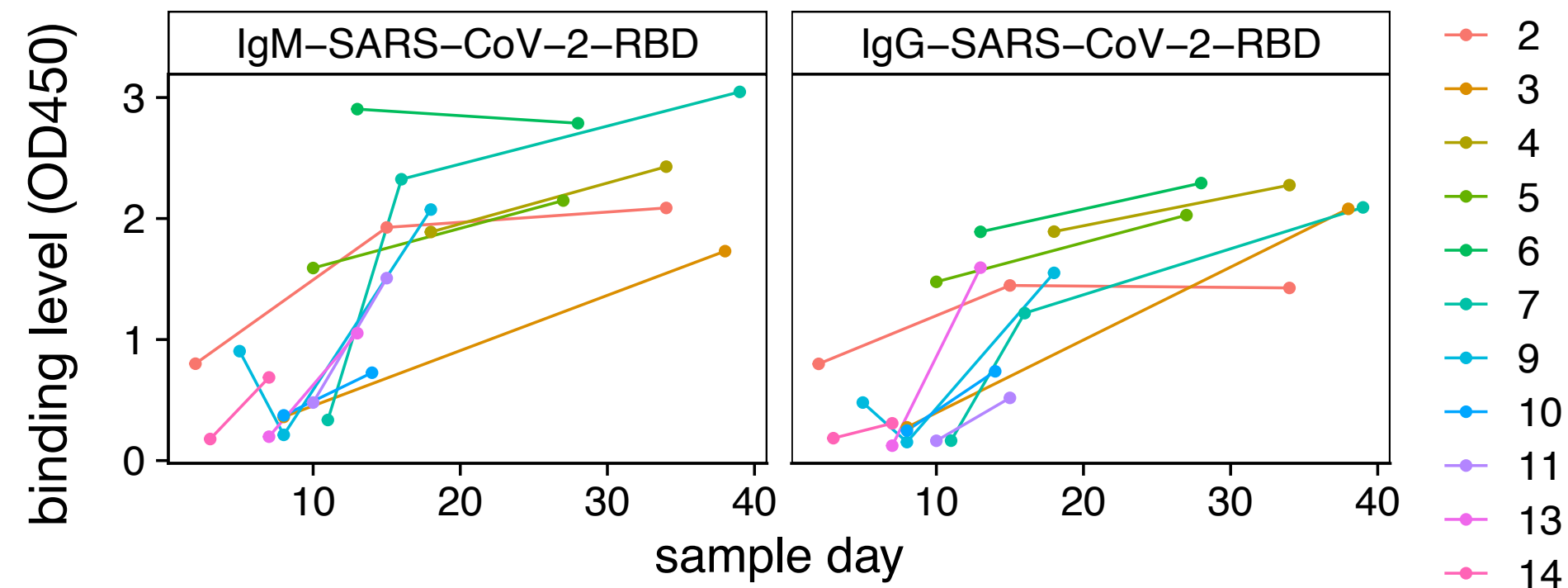
Identifying significantly expanded CD8<sup>+</sup> T-cells in response to yellow fever vaccine

[deWitt et al 2015]

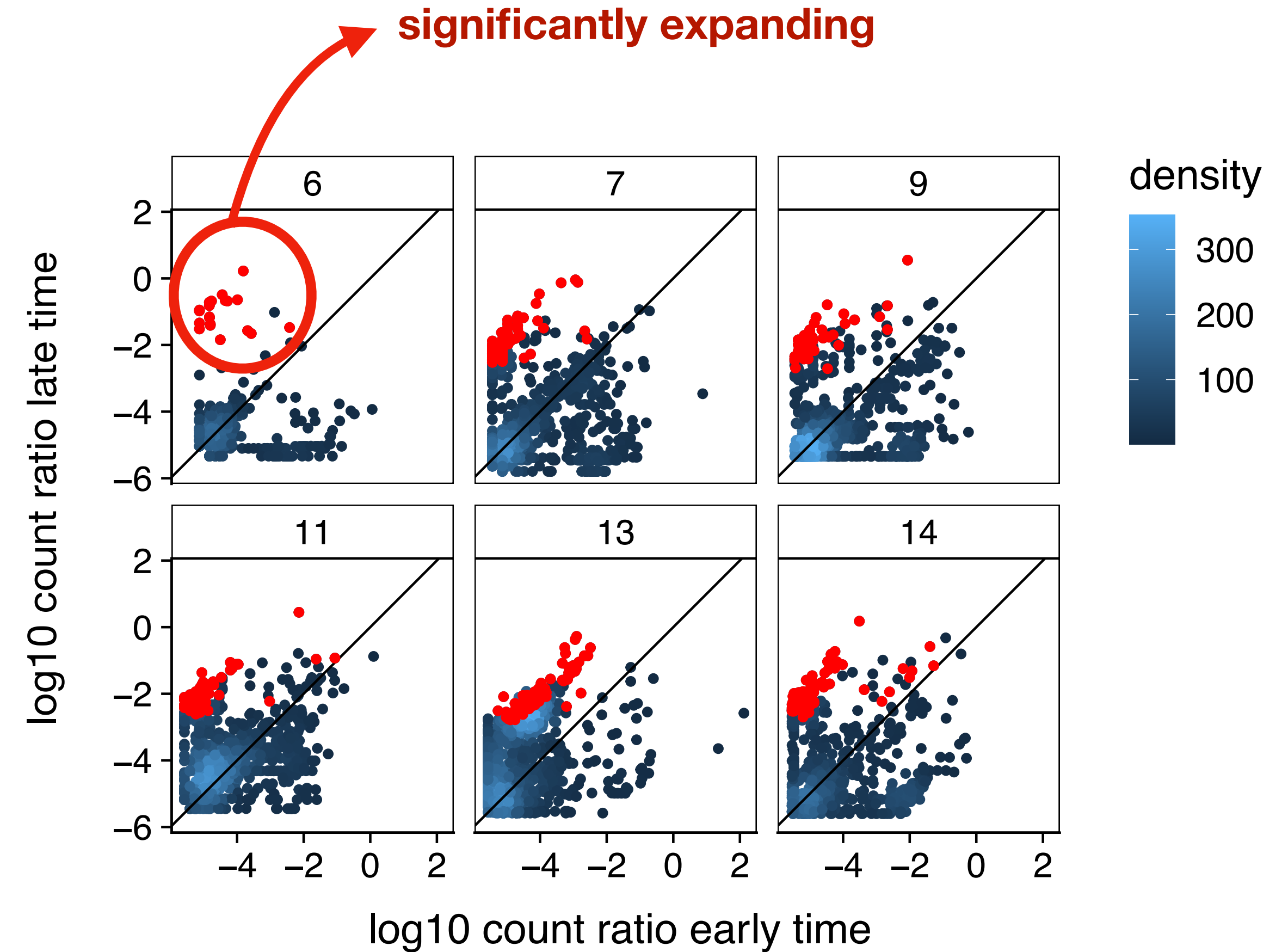
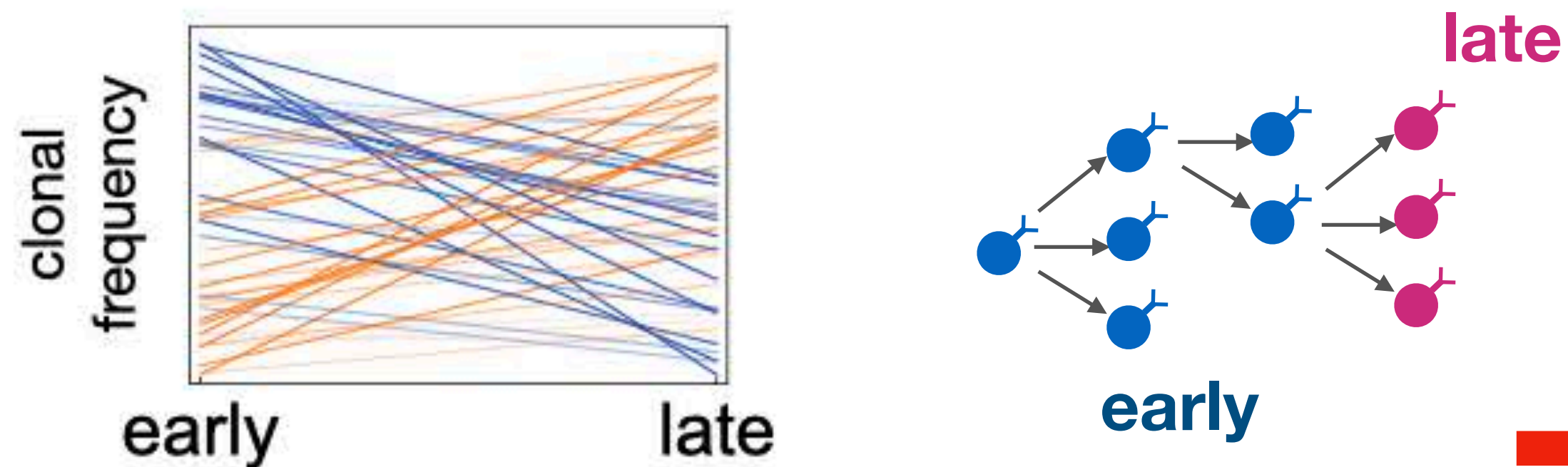


# Clonal dynamics in response to SARS-CoV-2

- IgG and IgM **reactivity** to RBD **increases** over time



- Clonal expansion in response to immune challenge



➔ **B-cell expansion analysis messier than T-cells**

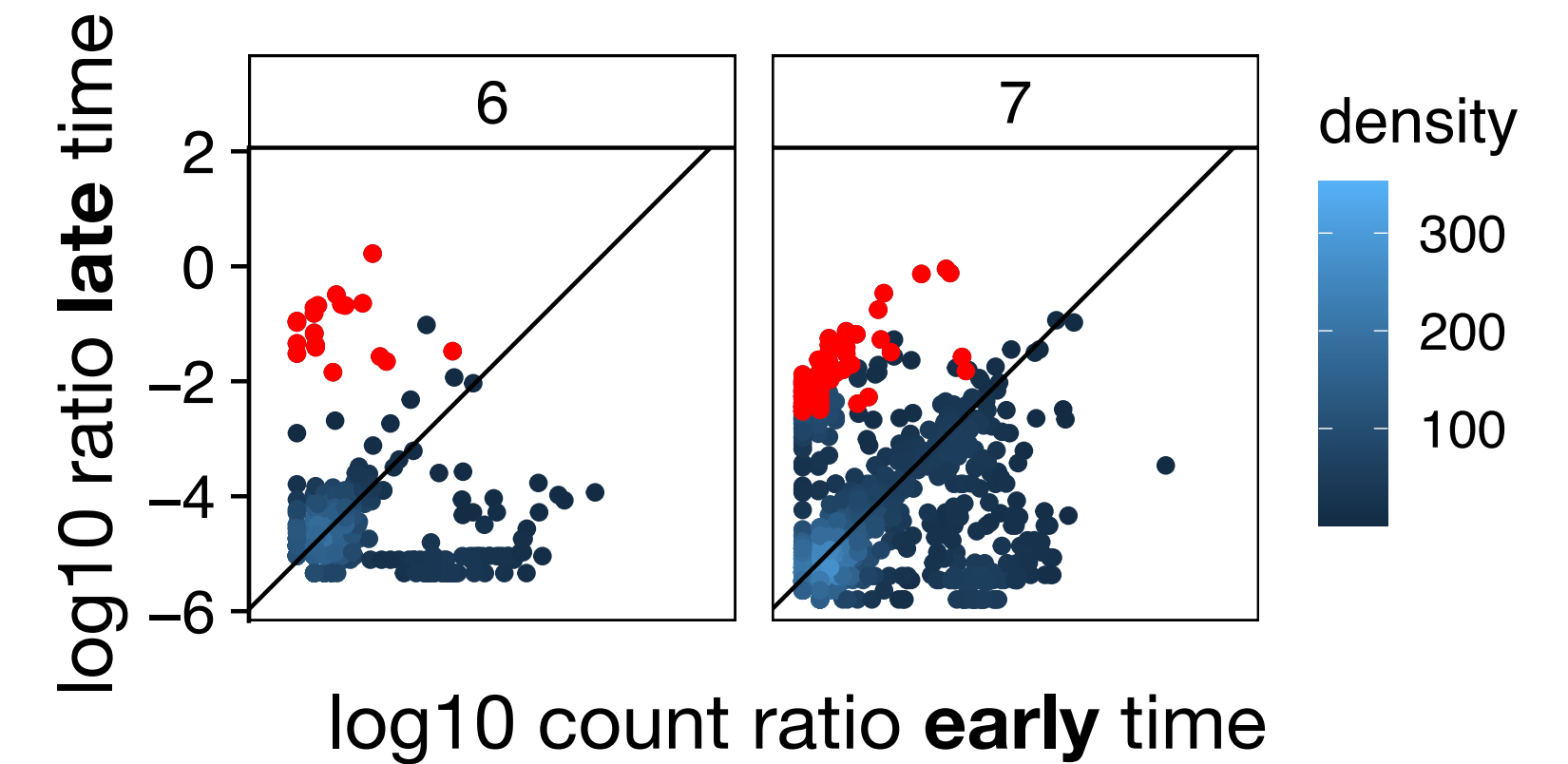
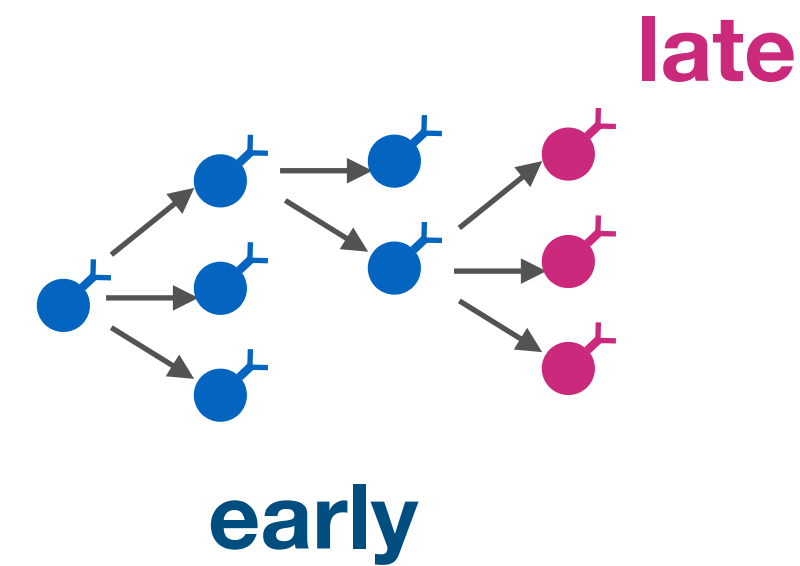
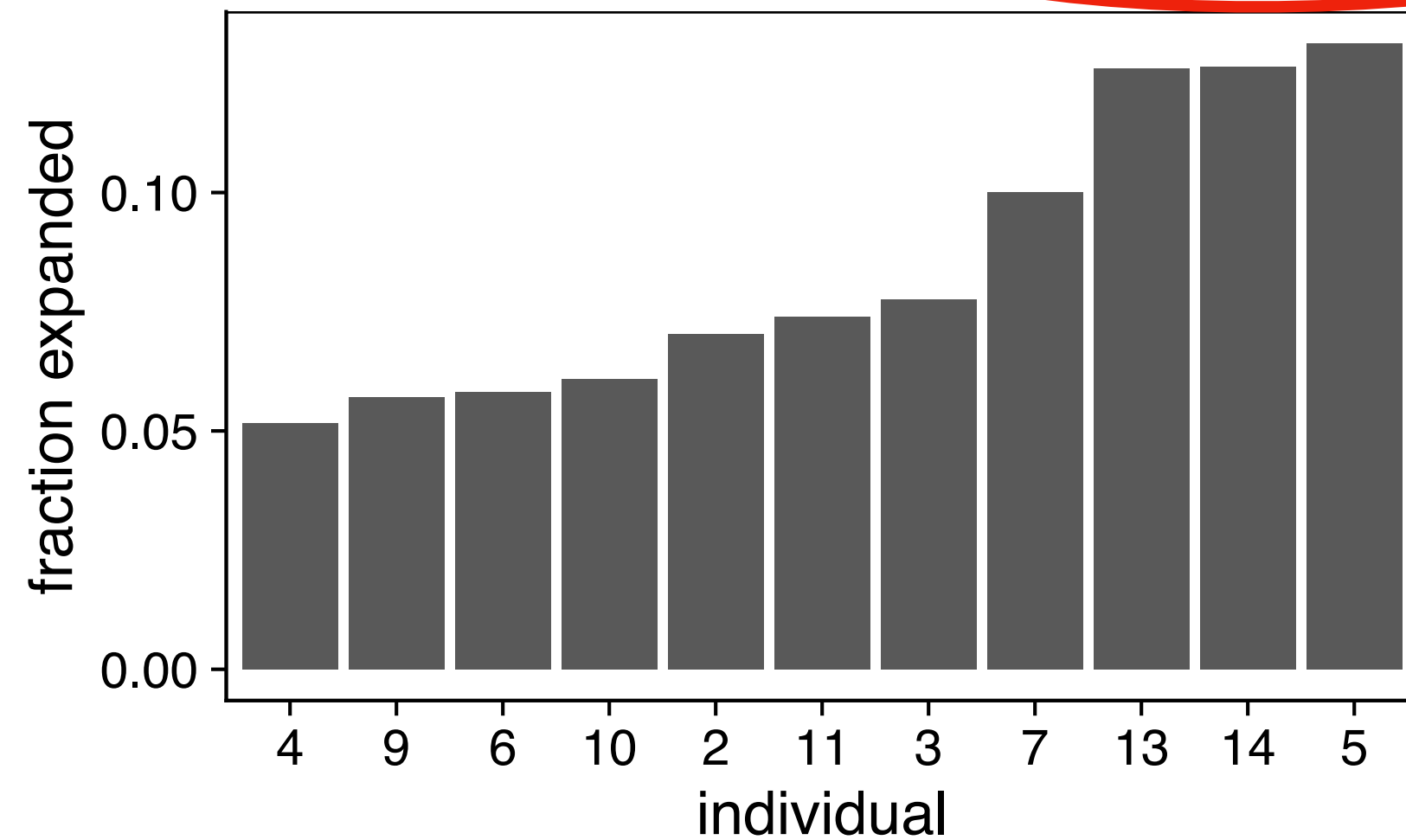
1. **Use replicate data** to calibrate significance (under-sampling)
2. **Normalize** for primer-specific amplification biases



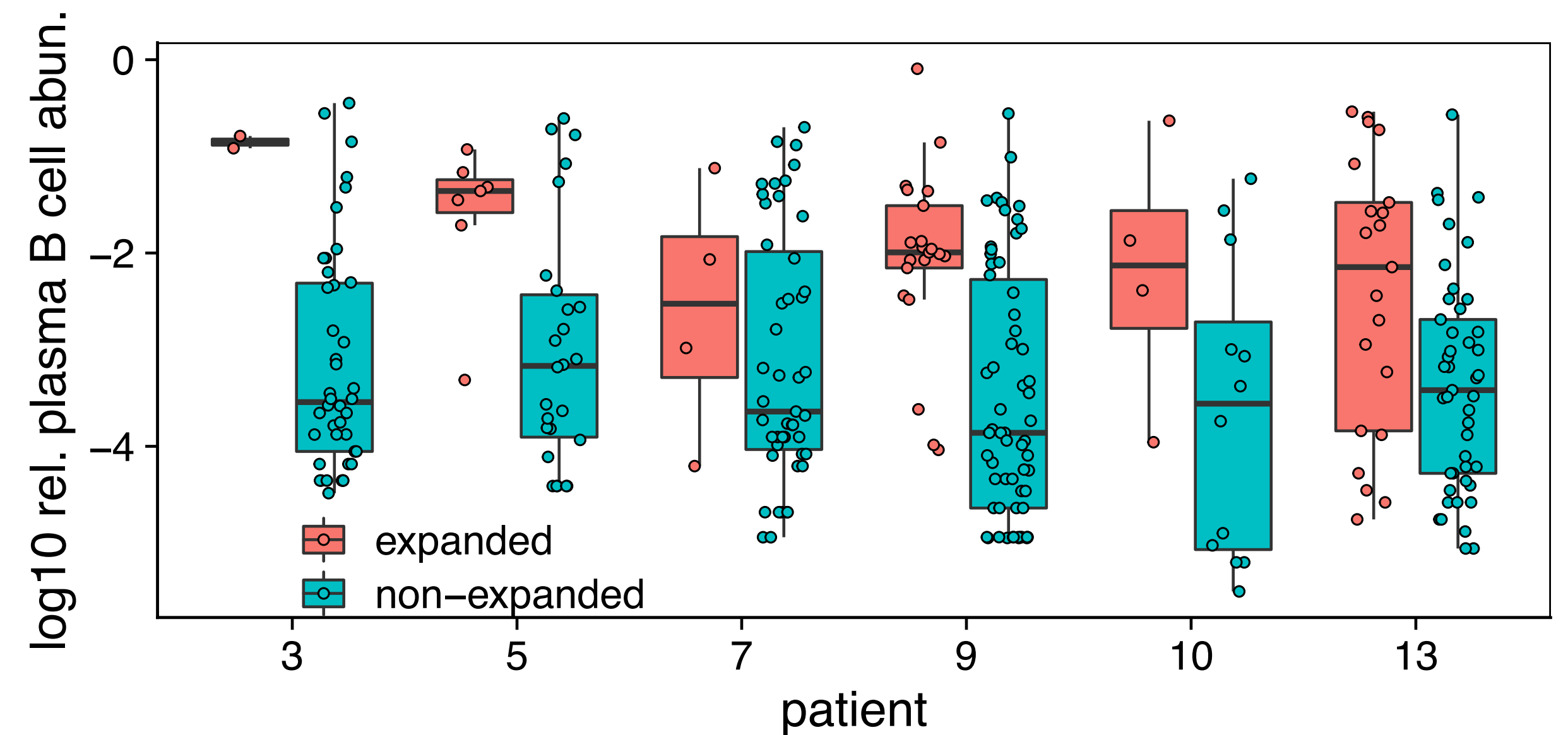
# Clonal dynamics in response to SARS-CoV-2

- Clonal expansion for **up to 15% of lineages**

**an order of magnitude too large! Why?**

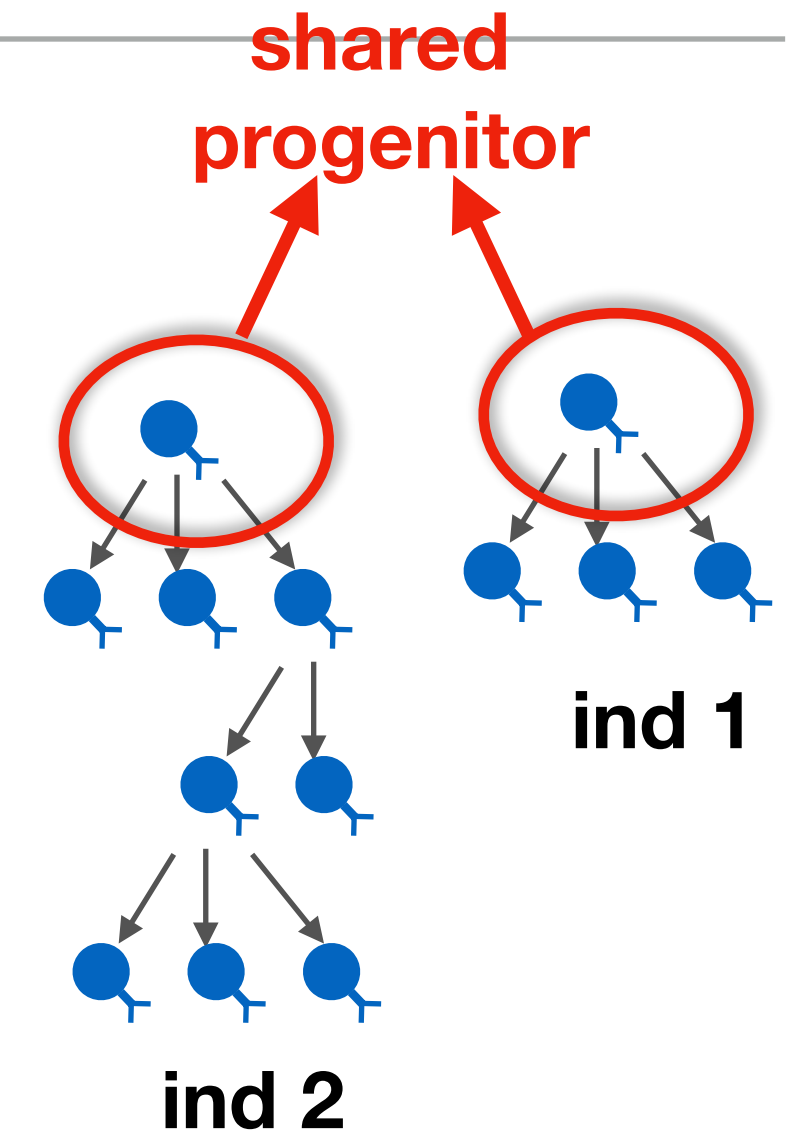
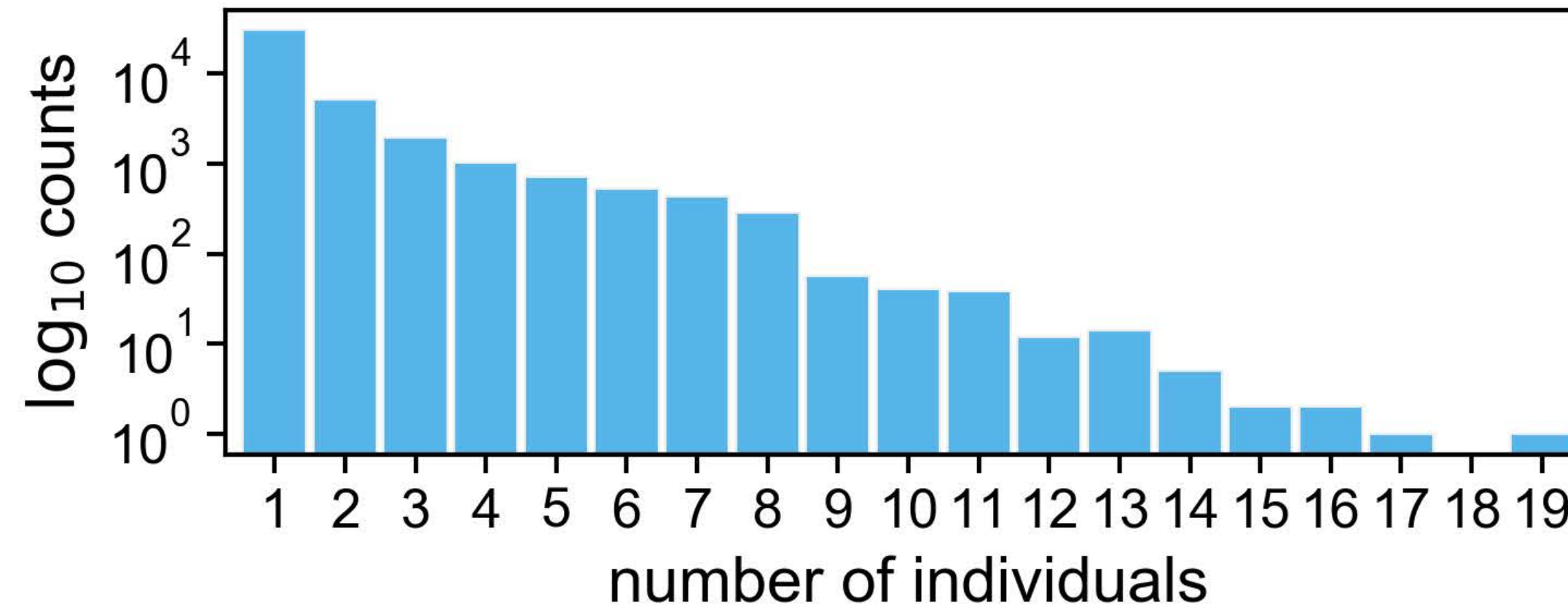


- Over-abundance of plasma B-cells in expanded lineages (**reassuring**)



# Sharing of B-cells among patients

Sharing of B-cell clonal lineages is ubiquitous.

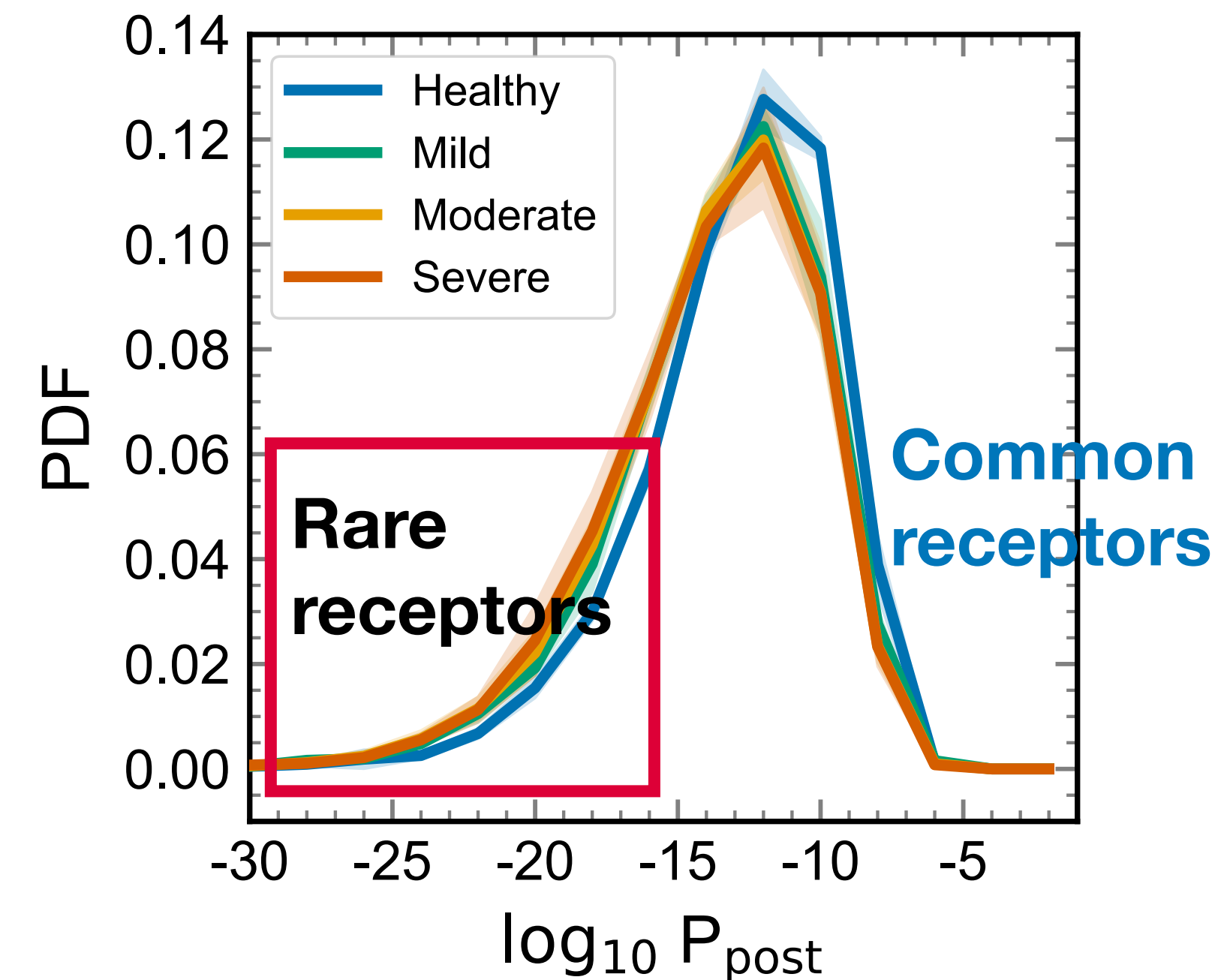


## Should we be surprised?

Yes **only** for **rare** BCRs  
(*public vs. private repertoire*)

## Compute sharing probability:

$P_{\text{share}}$  = probability to find a BCR in X inds, given its  $P_{\text{post}}$



*For T-cell sharing*, see: Pogorelyy et al; eLife 2018

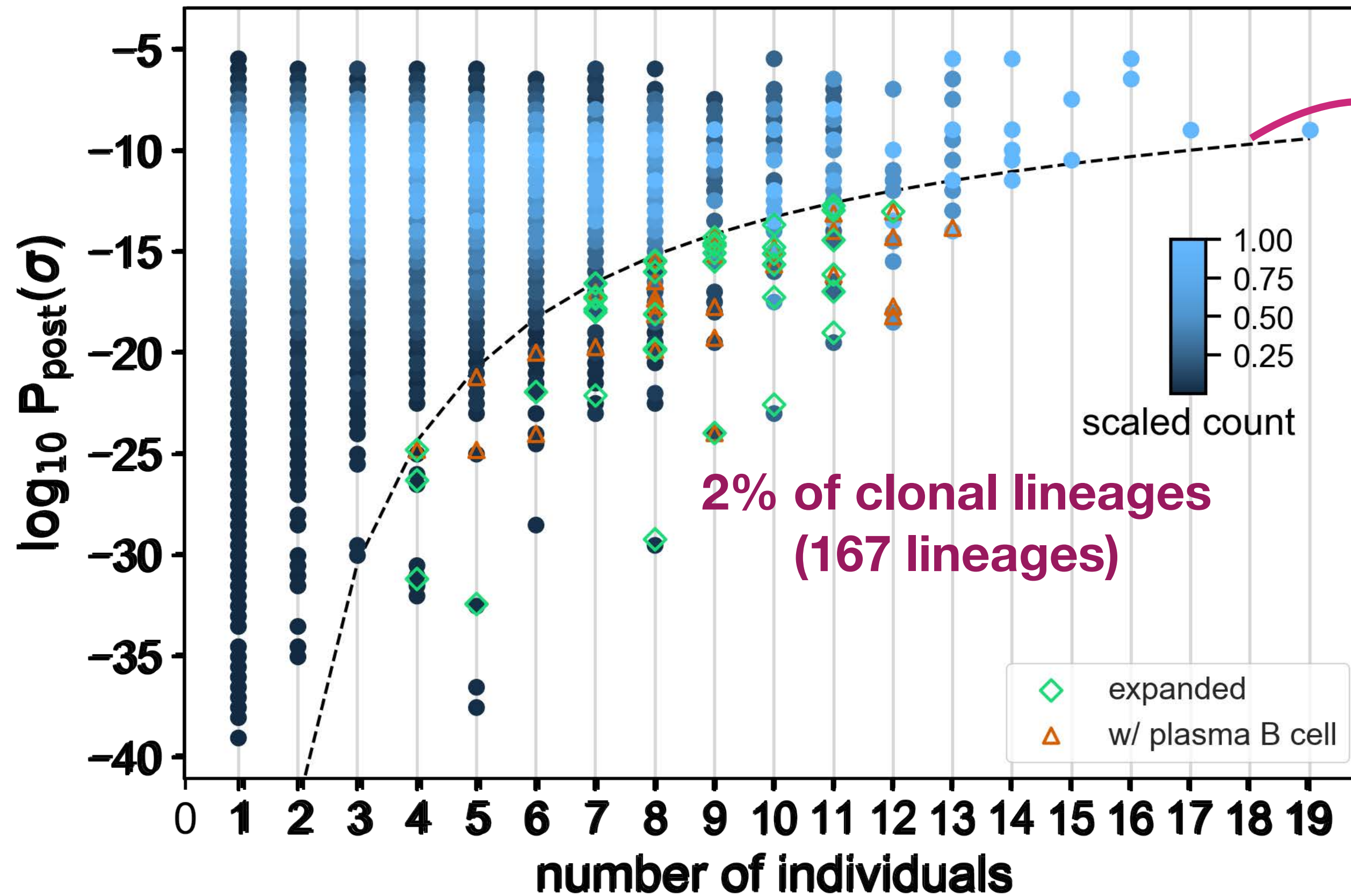
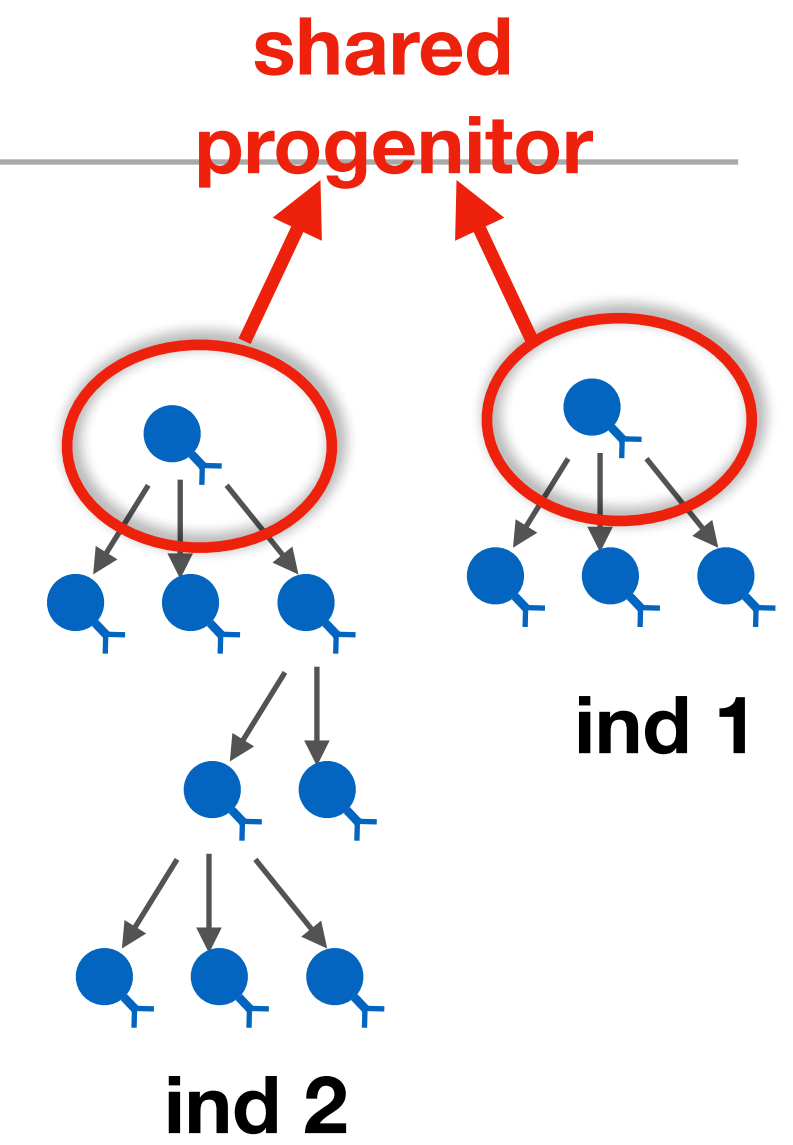
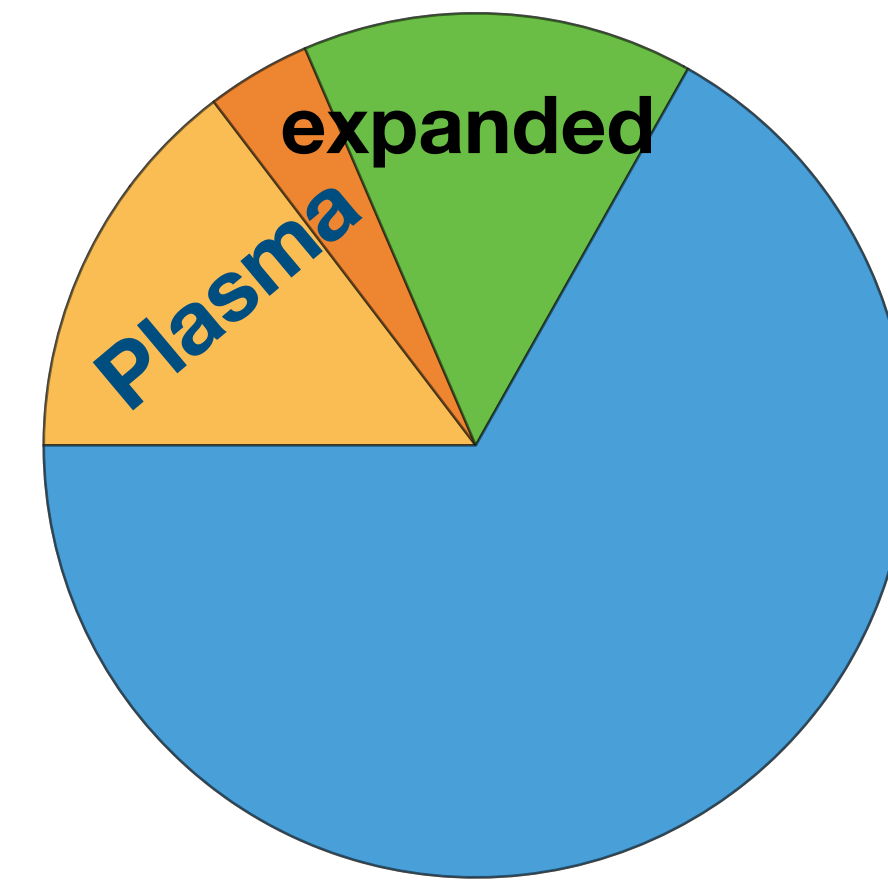


# Sharing of B-cells among patients

38 rare shared **expanded** lineages

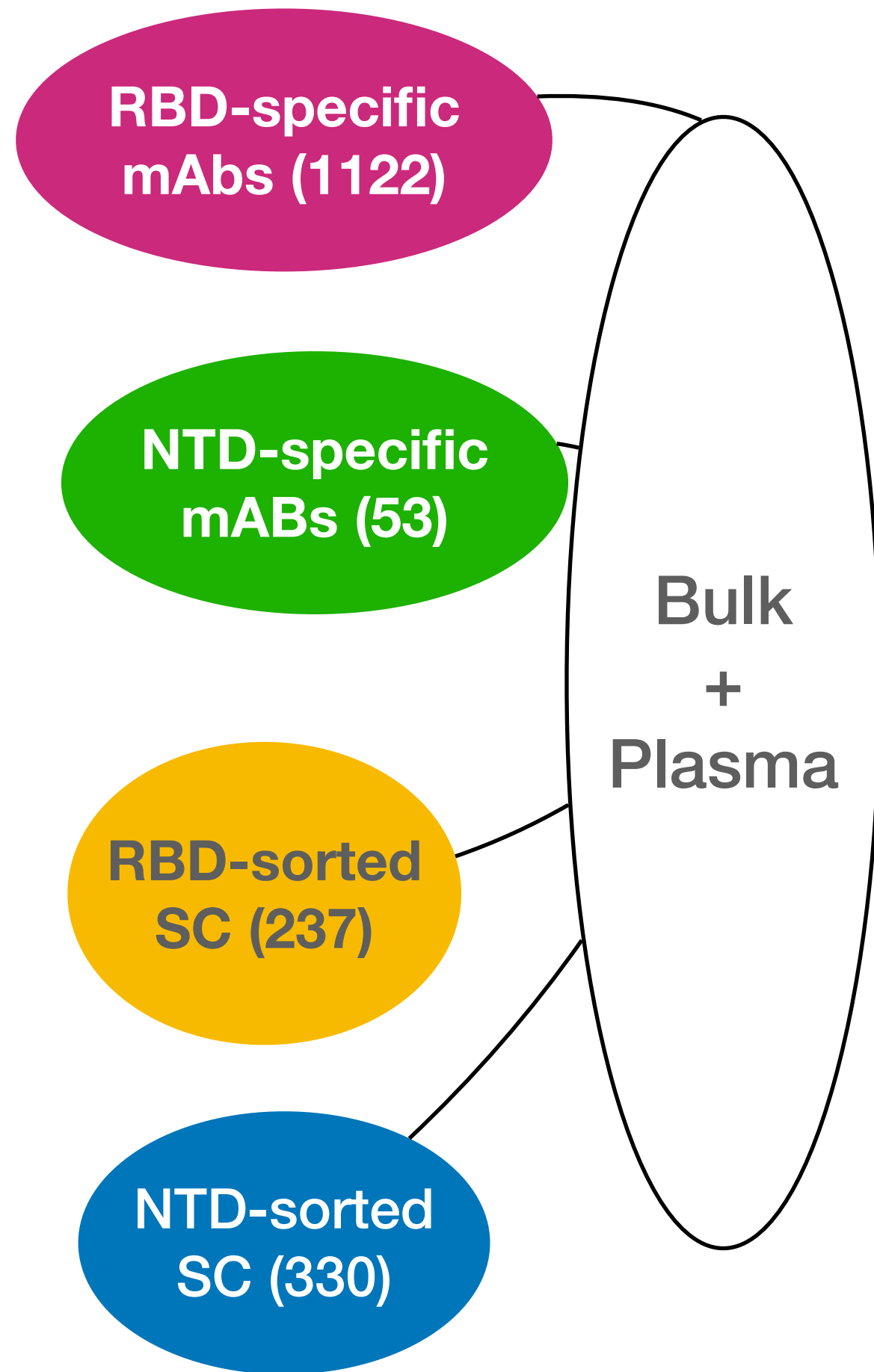
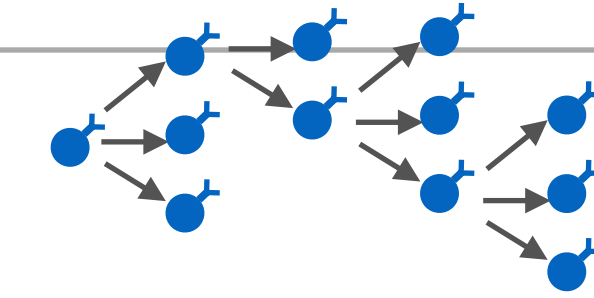
30 rare shared lineages, **with plasma**

**Candidates for response !!!**

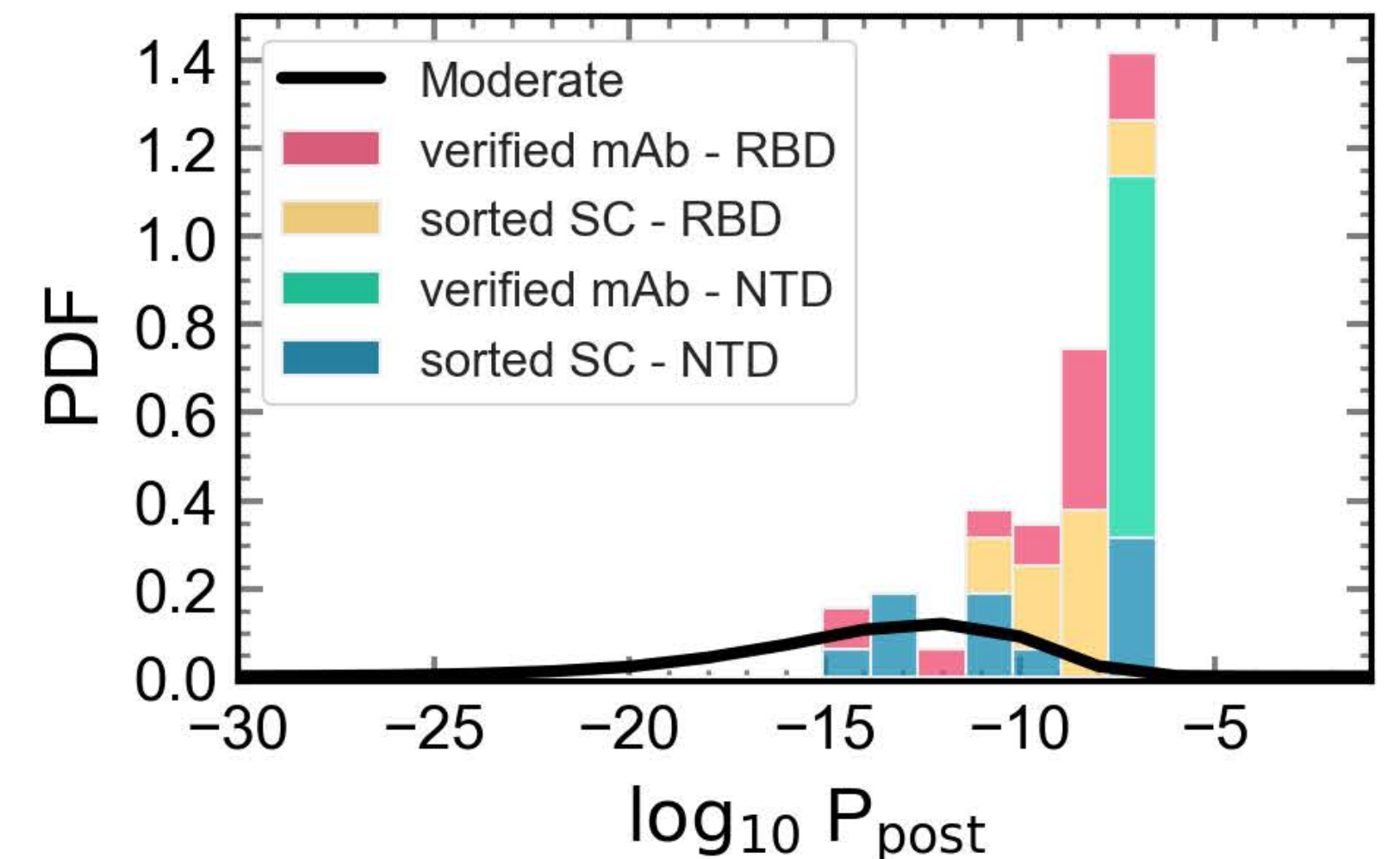
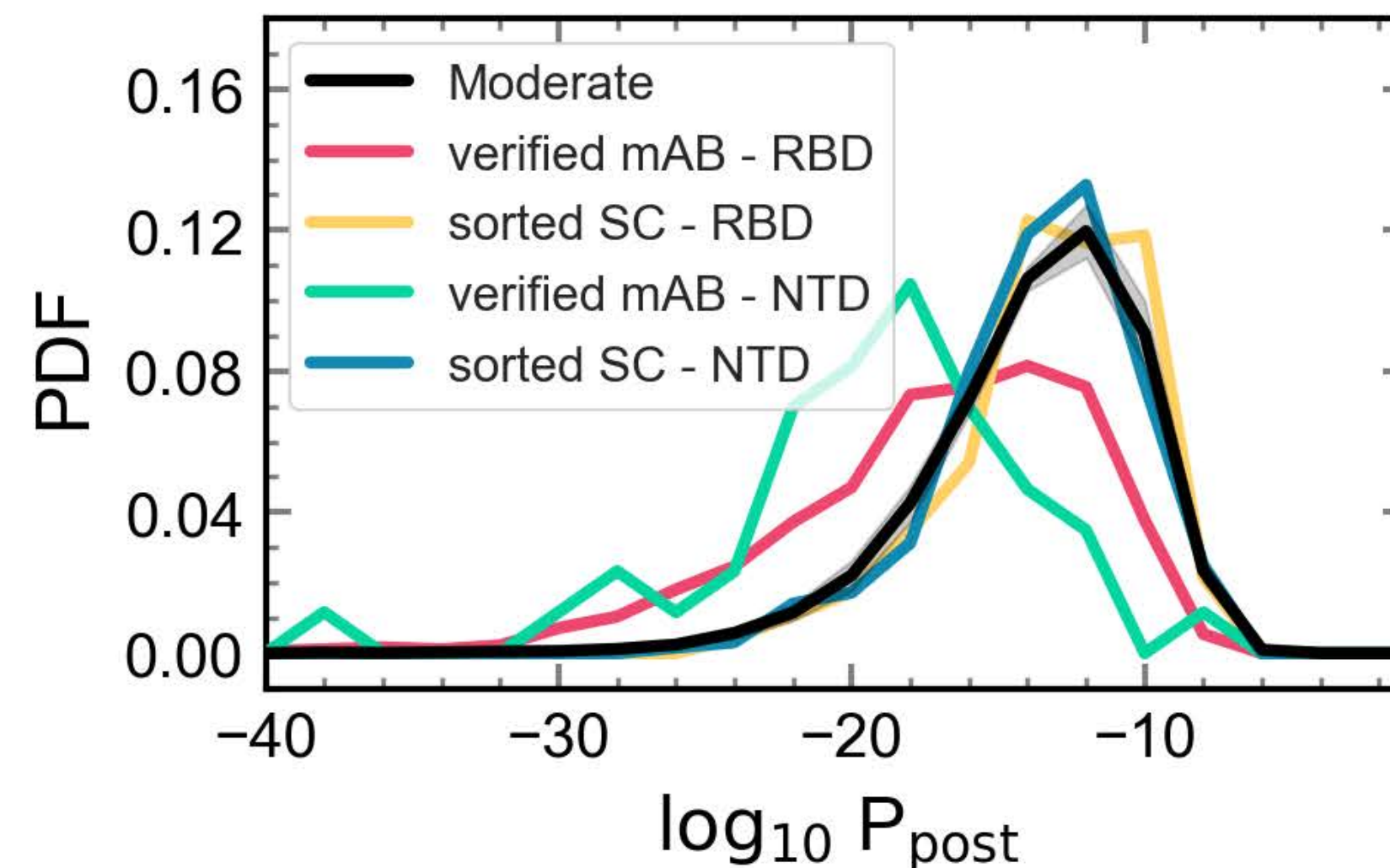
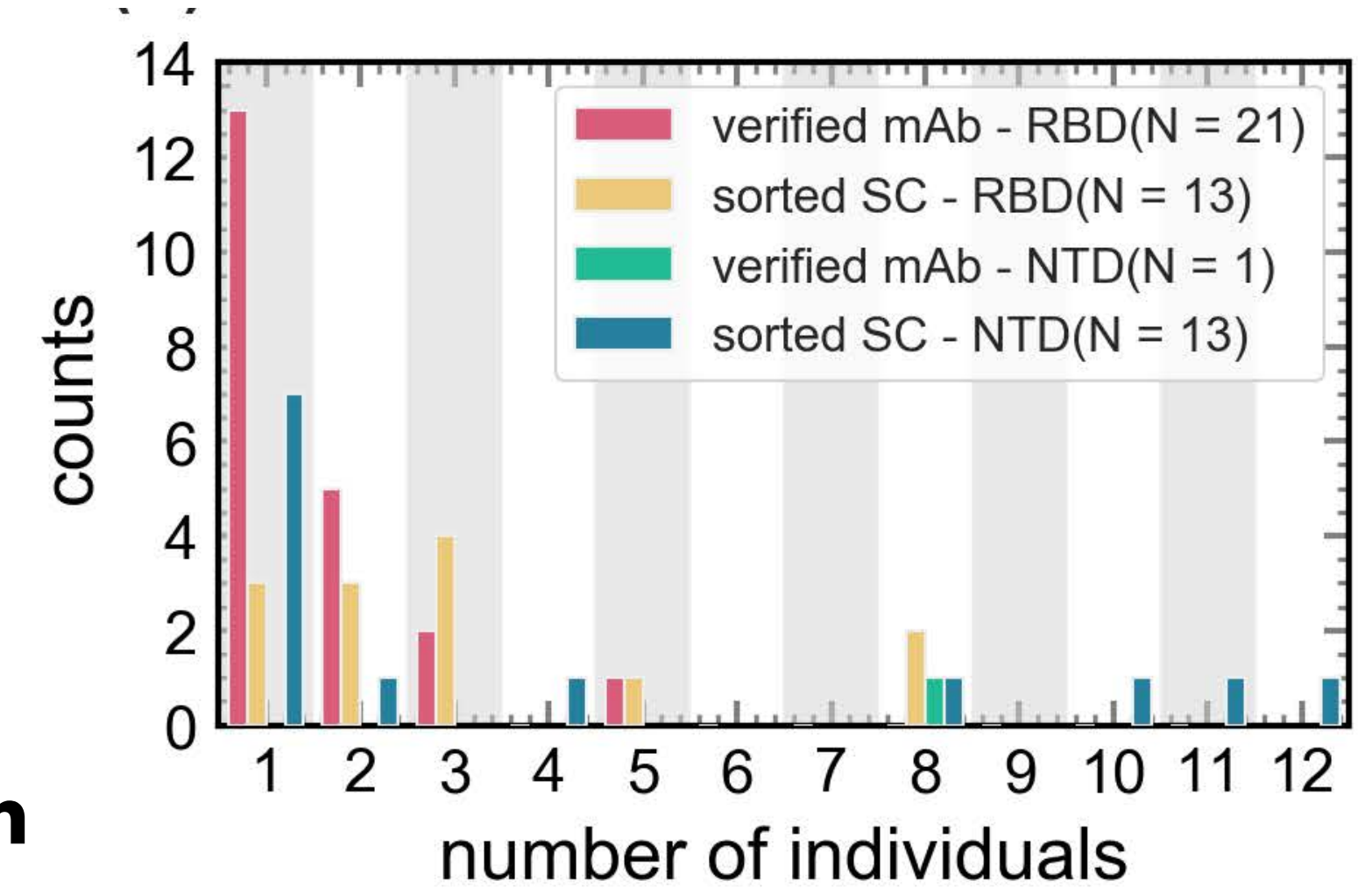


# specific responses to SARS-CoV-2

lineage clustering to map functional data (**single cell and mAbs**) to repertoires



- Sharing of epitope sorted receptors (**13+13**)
- Sharing of verified mAbs (**21+ 1**)
- Verified mAbs tend to be rare
- Repertoire-mapped mAbs **are very common**





# Summary

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- i. **Dynamics** useful in characterizing acute (& chronic) repertoire responses
- ii. **Sharing** is *mostly* not so surprising. *Put a number on it.*
- iii. **Bulk + Plasma** is powerful in assessing response
- iv. Moving beyond simple statistics: combining **functional data** with repertoires

Dynamics of B-cell repertoires and emergence of cross-reactive responses in COVID-19 patients with different disease severity

Montague et al; medRxiv 2020.07.13.20153114

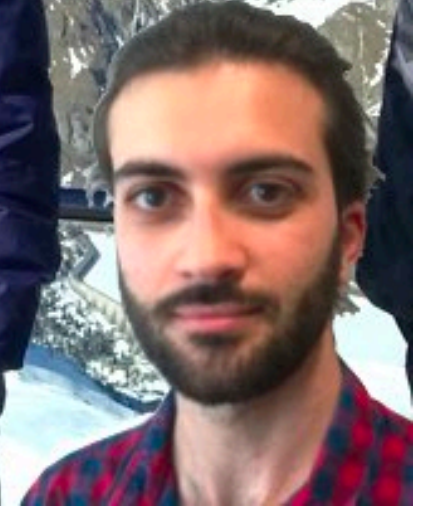
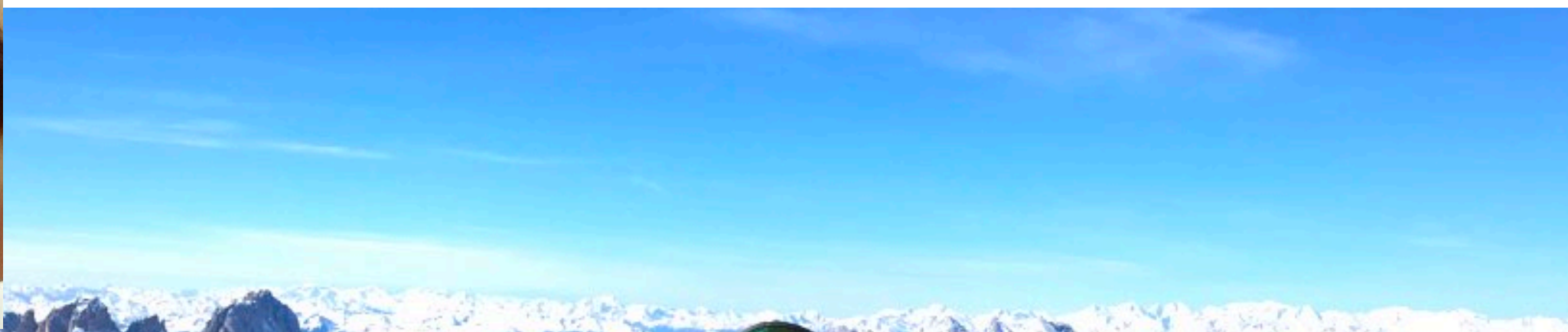


StatPhysBio/covid-bcr



**Group (left : right)**

Kjertan van Driel  
Andrew Ivanov  
**Zach Montague**  
Colin LaMont  
**Giulio Isacchini**  
Oskar Schnaack  
AN  
Mike Pun  
Vincent Balerdi  
Mari Torii-Karsh



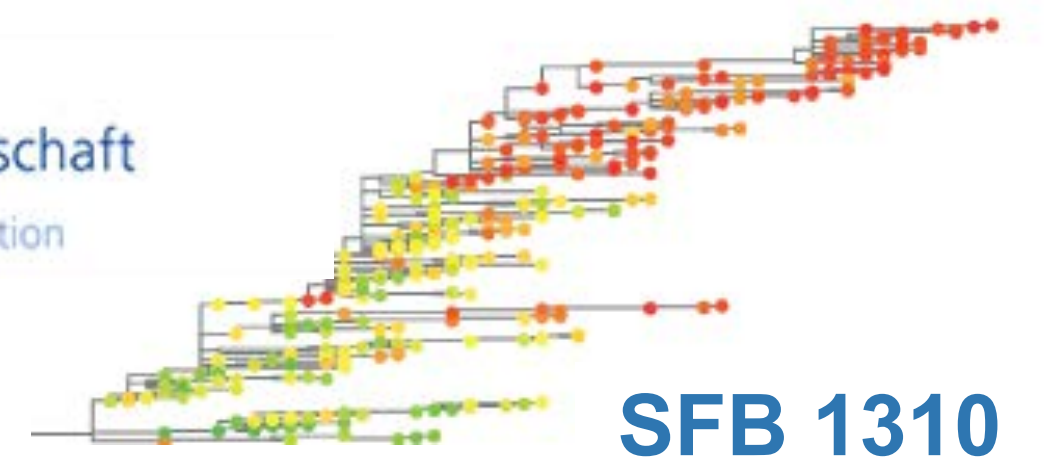
**Collaborators**

**Chris Mok (Uni Hong Kong)**  
**Tomas Lv (Uni Hong Kong)**  
**Nicholas Wu (UIUC)**  
**William DeWitt (UW)**  
Aleksandra Walczak (ENS)  
Michael Lässig (Uni Köln)  
Sid Goyal (U Toronto)  
Vijay Balasubramanian (UPenn)

Florian Klein (Uni Köln)  
Josh Plotkin (UPenn)  
Ceyhun Eksin (Texas A&M)  
Yannick Rondelez (ESPCI)  
Luca Peliti (SMRI)  
Thierry Mora (ENS)  
Marta Luksza (Mnt. Sinai)  
**Jakub Otwinowski (Dyno Therapeutics)**



Predictability in Evolution



**SFB 1310**