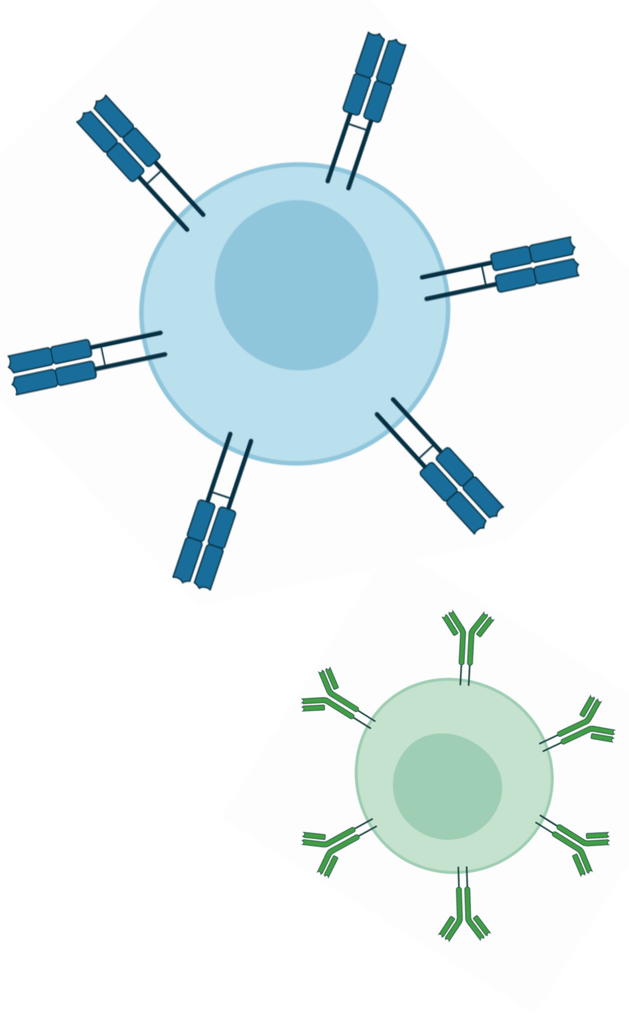
Intro to immune repertoire sequencing and analysis

Maggie Russell

TFCB 2024

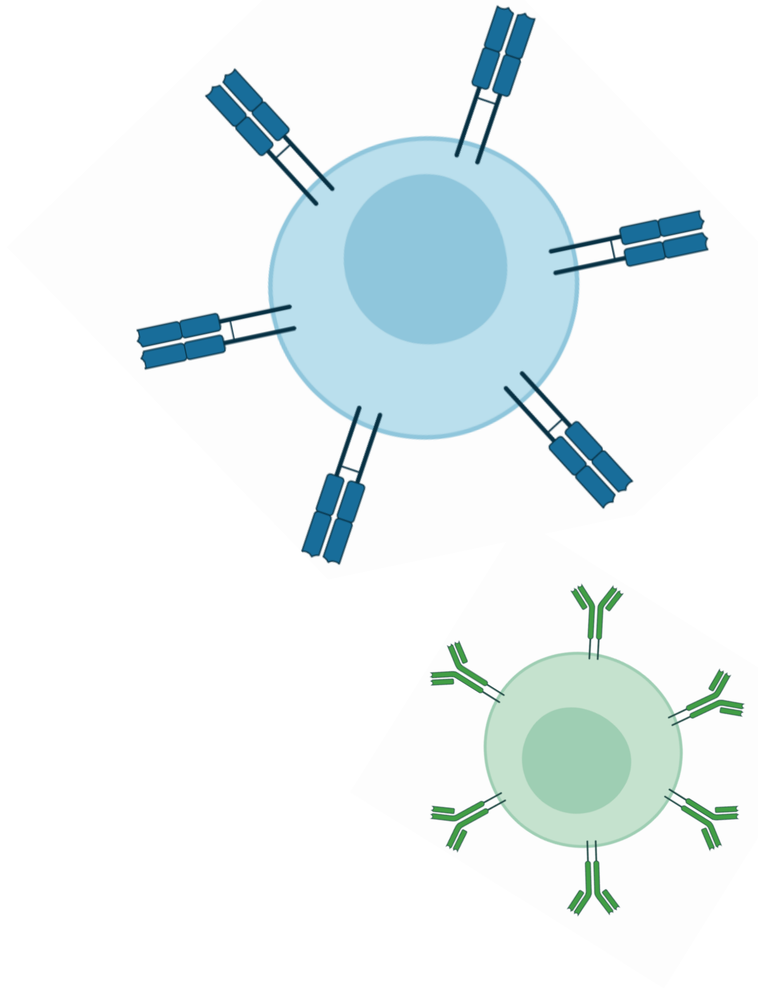
Lecture goals:

1. learn about immune repertoire sequencing
2. familiarize with immune repertoire data
3. work through an example analysis



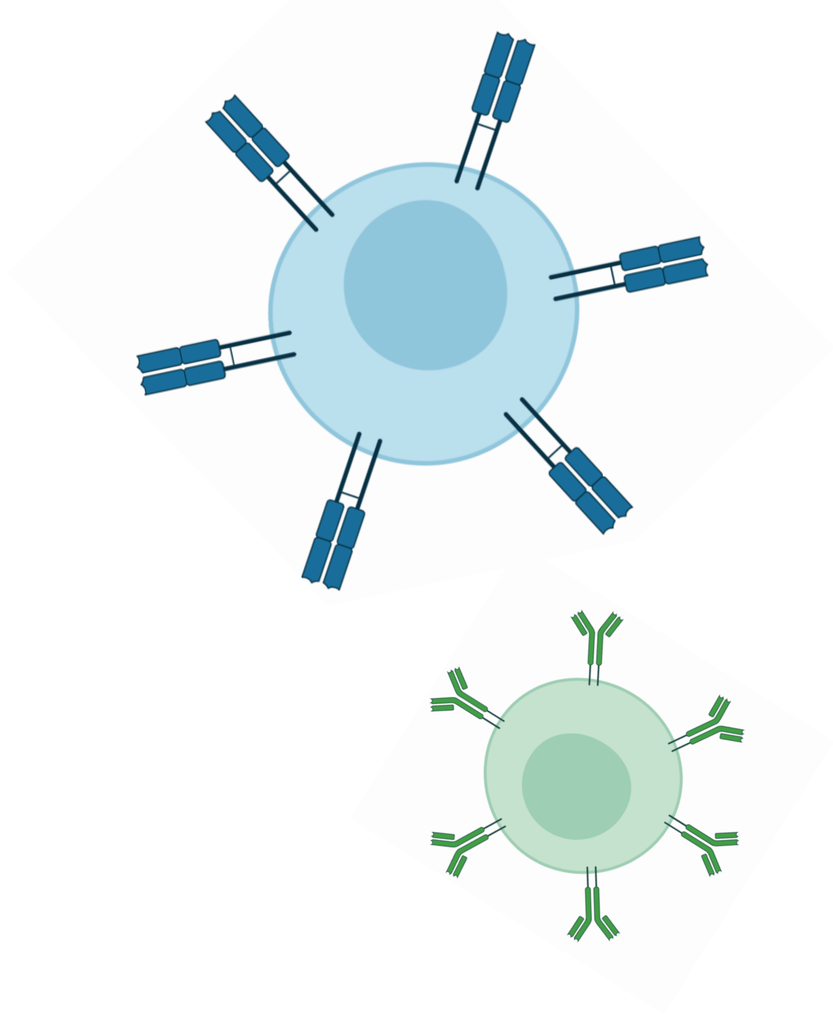
Lecture goals:

1. learn about immune repertoire sequencing

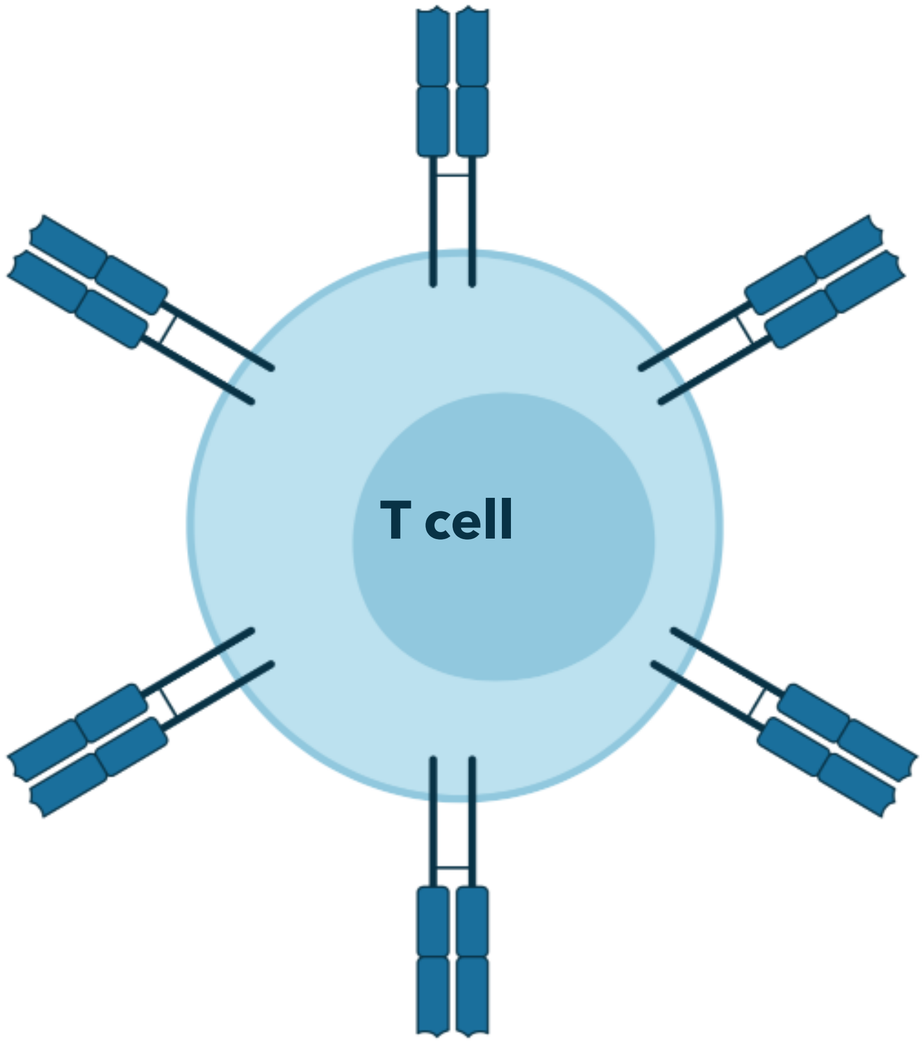


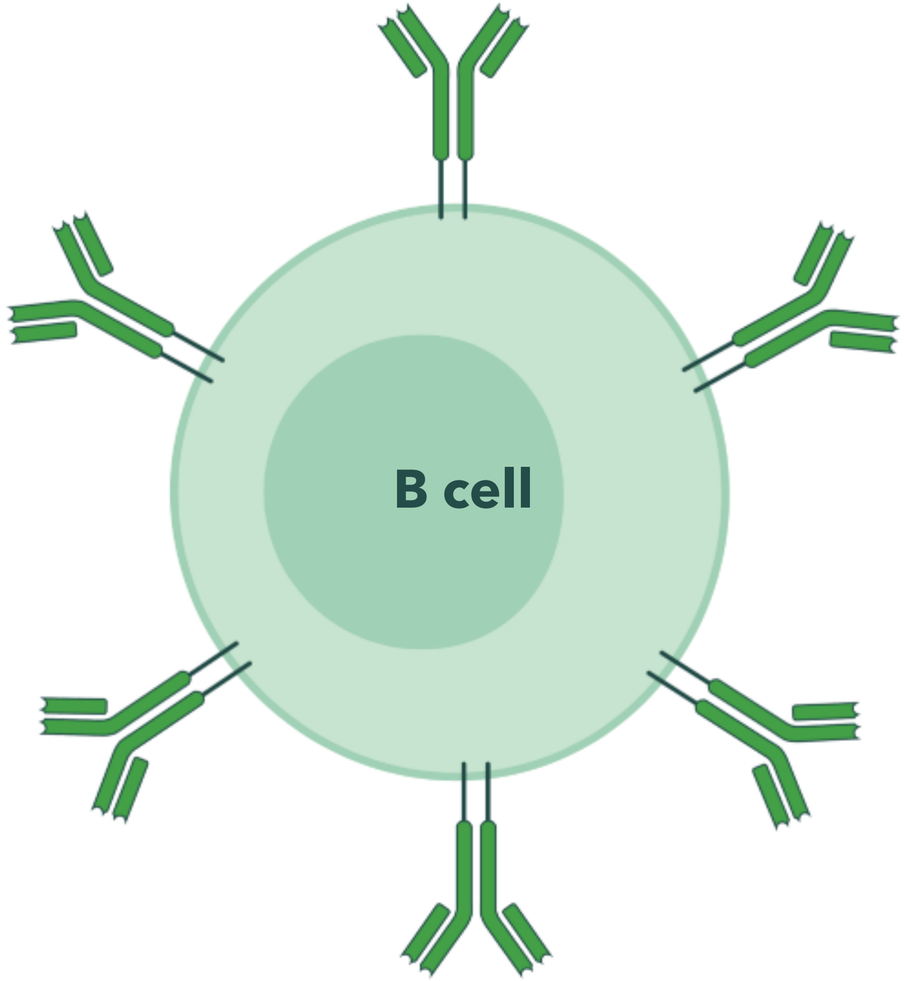
Lecture goals:

1. learn about immune repertoire sequencing
    - **what are immune repertoires?**

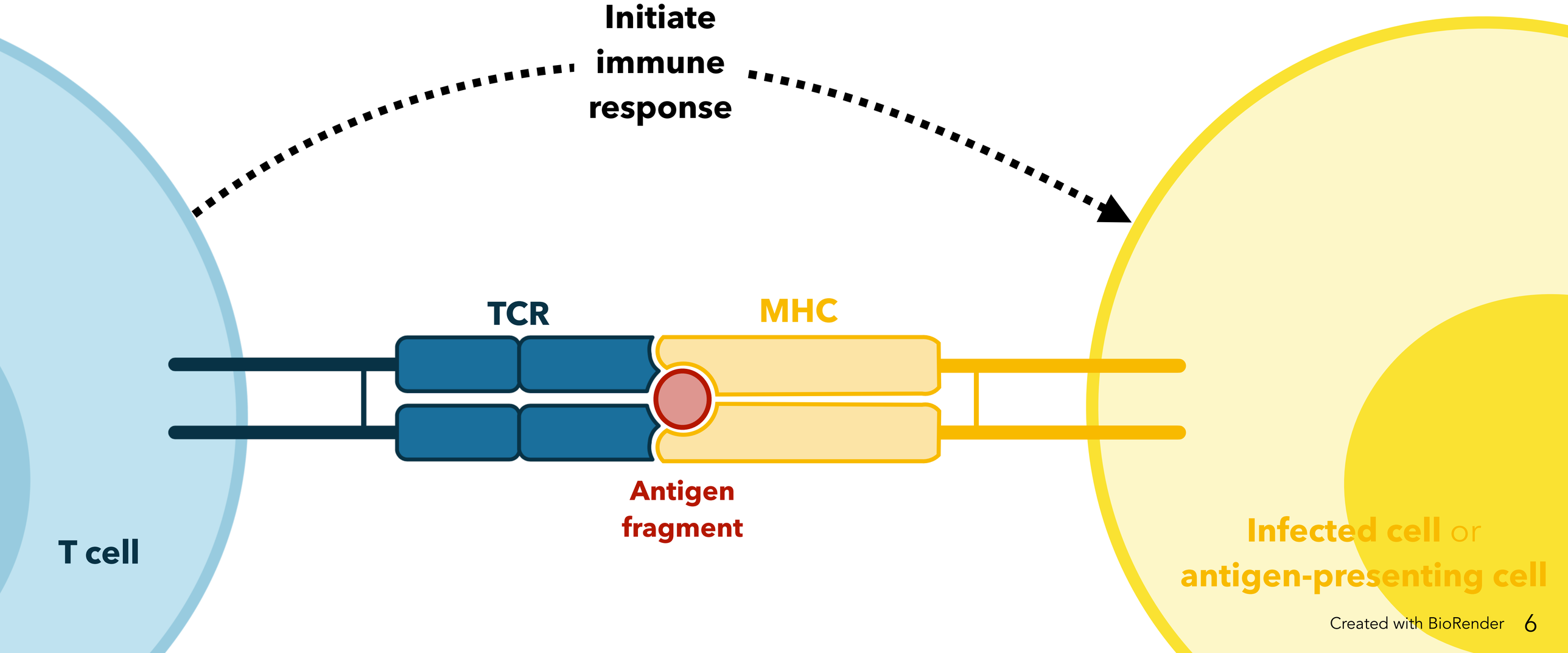


Adaptive immunity is essential for defending against pathogens

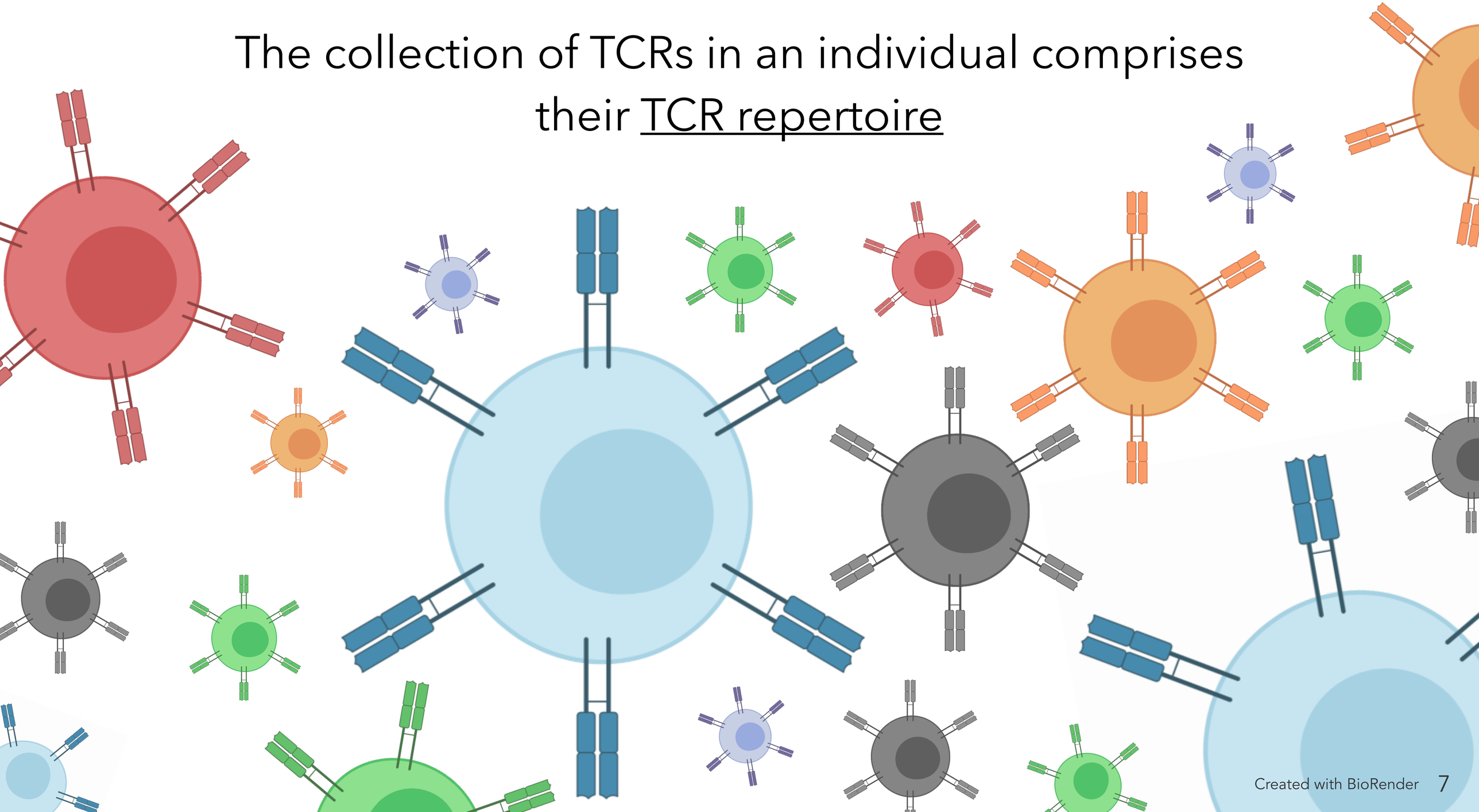




T cell receptors recognize antigen fragments bound to MHC



The collection of TCRs in an individual comprises their TCR repertoire



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1. learn about immune repertoire sequencing
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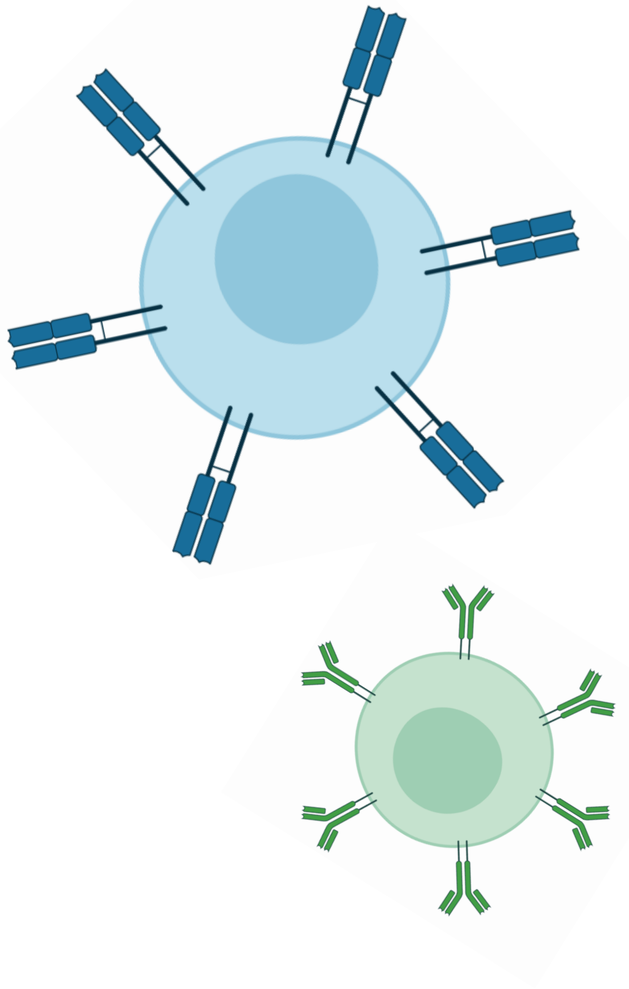
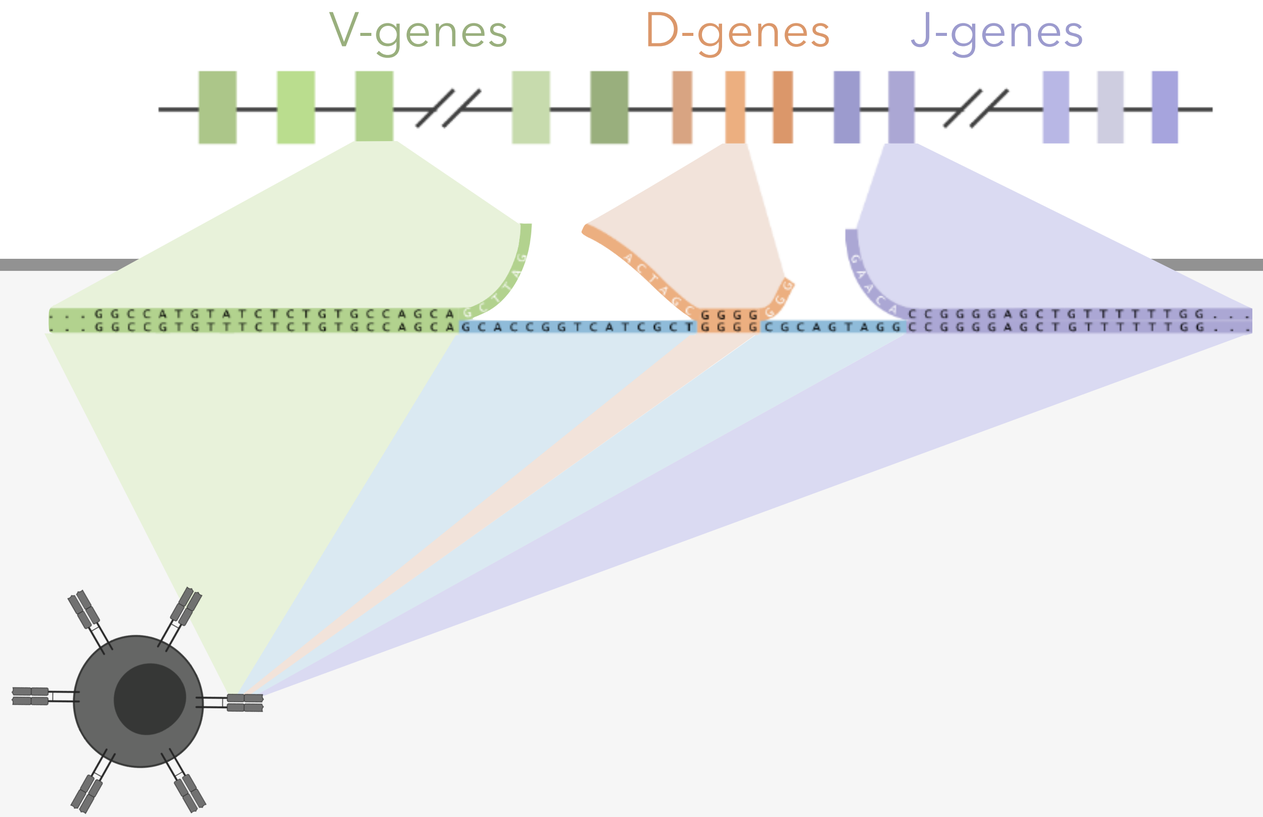
    - **how are they formed?**



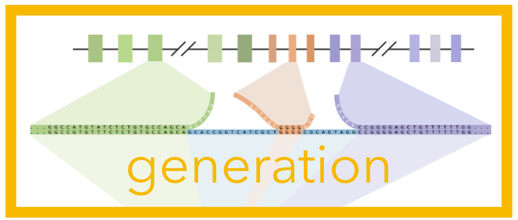
Repertoire composition is influenced by generation, selection, and exposures

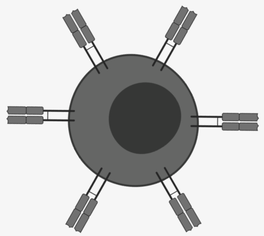
Let's use a water pipe as an analogy for TCR repertoire formation…

Repertoire composition is influenced by generation, selection, and exposures



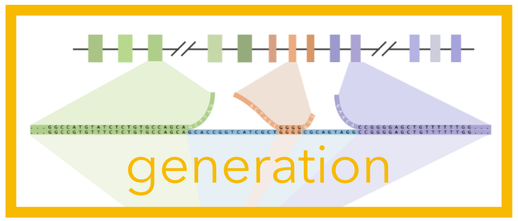
Repertoire composition is influenced by **generation**, selection, and exposures





modified from Murugan et. al *PNAS* 2012
Created with BioRender

Repertoire composition is influenced by **generation**, selection, and exposures



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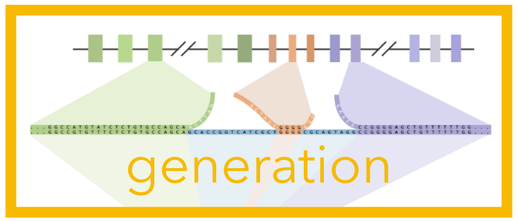

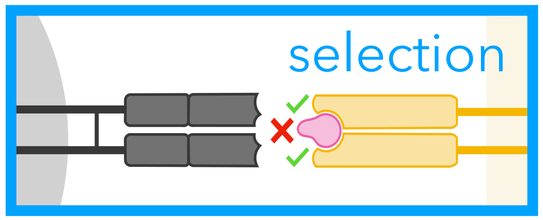

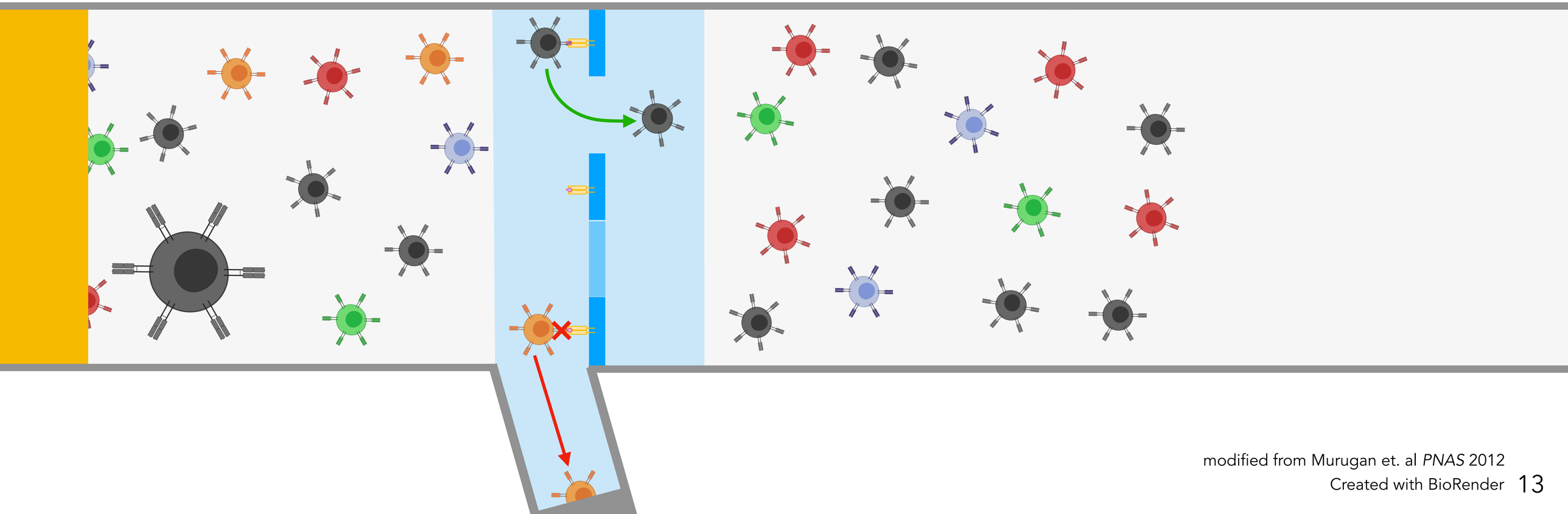

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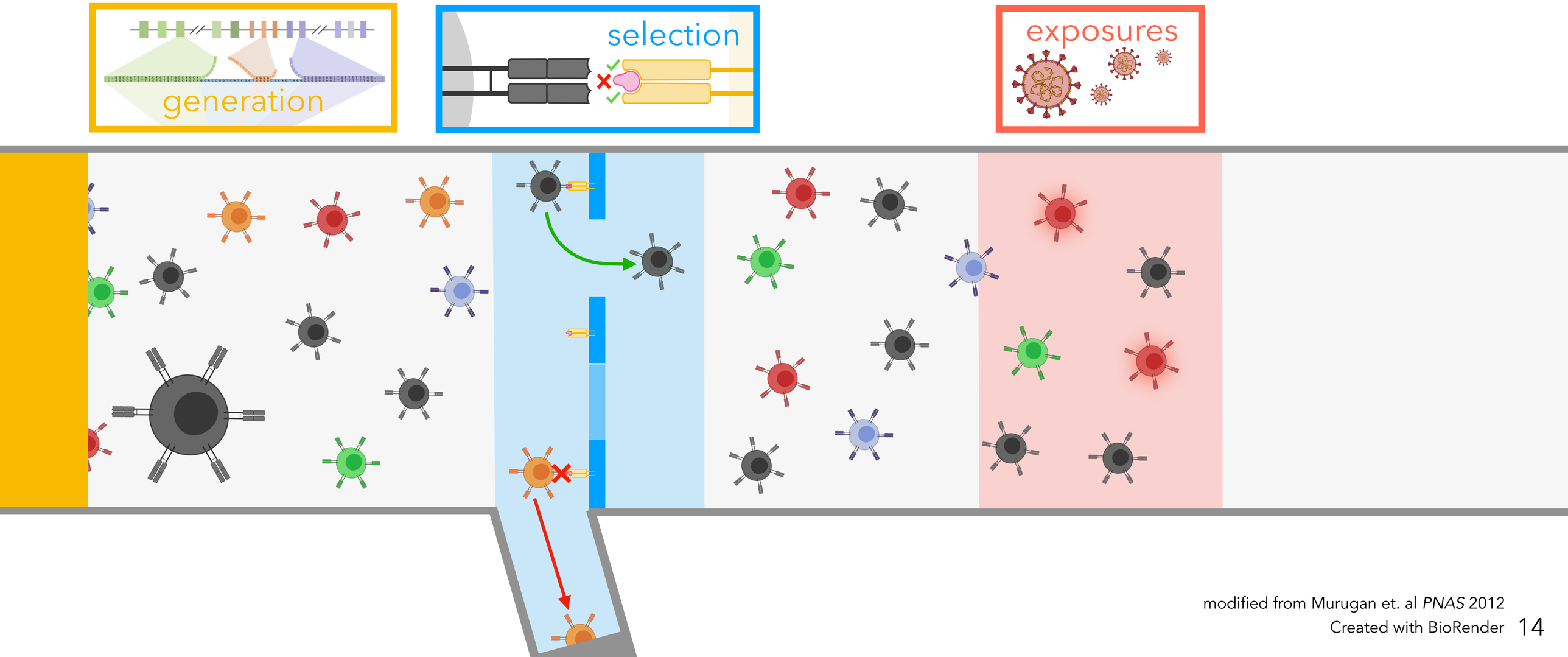
Created with BioRender

Repertoire composition is influenced by generation, selection, and **exposures**



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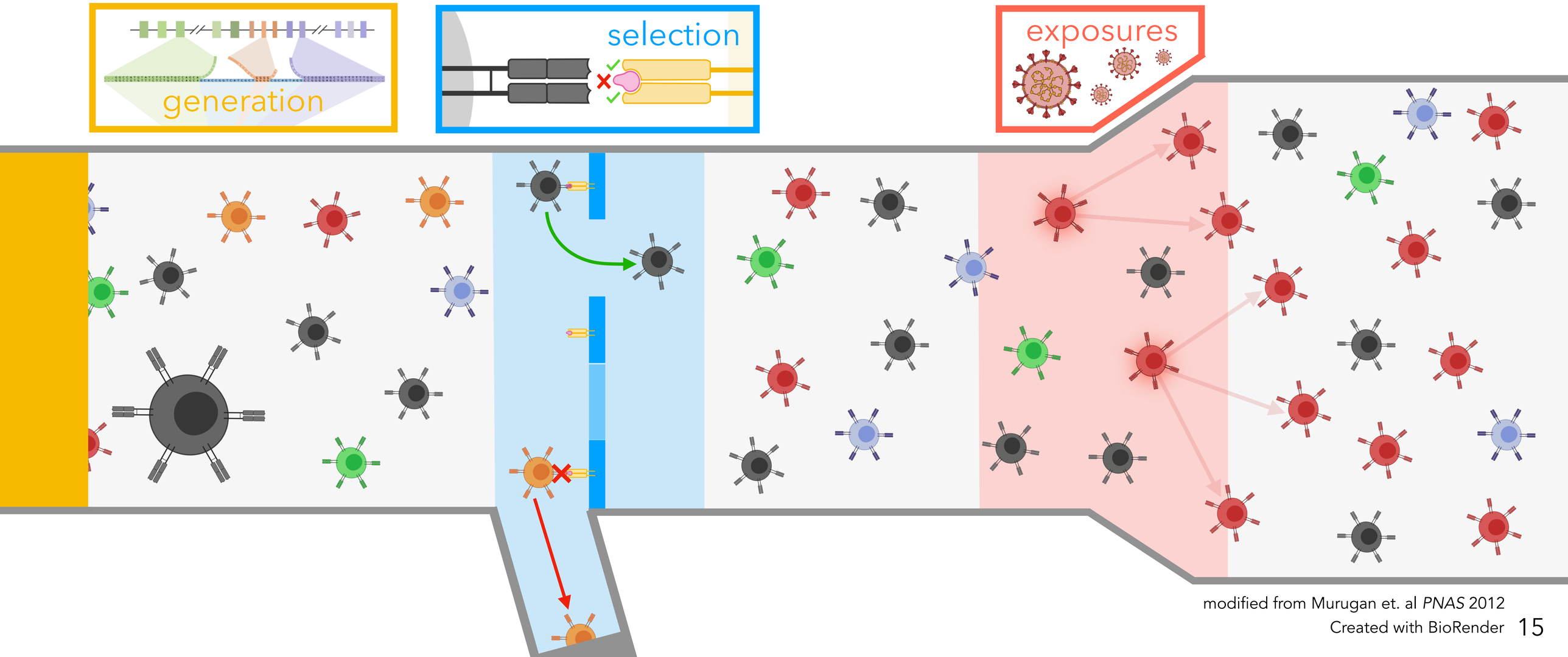

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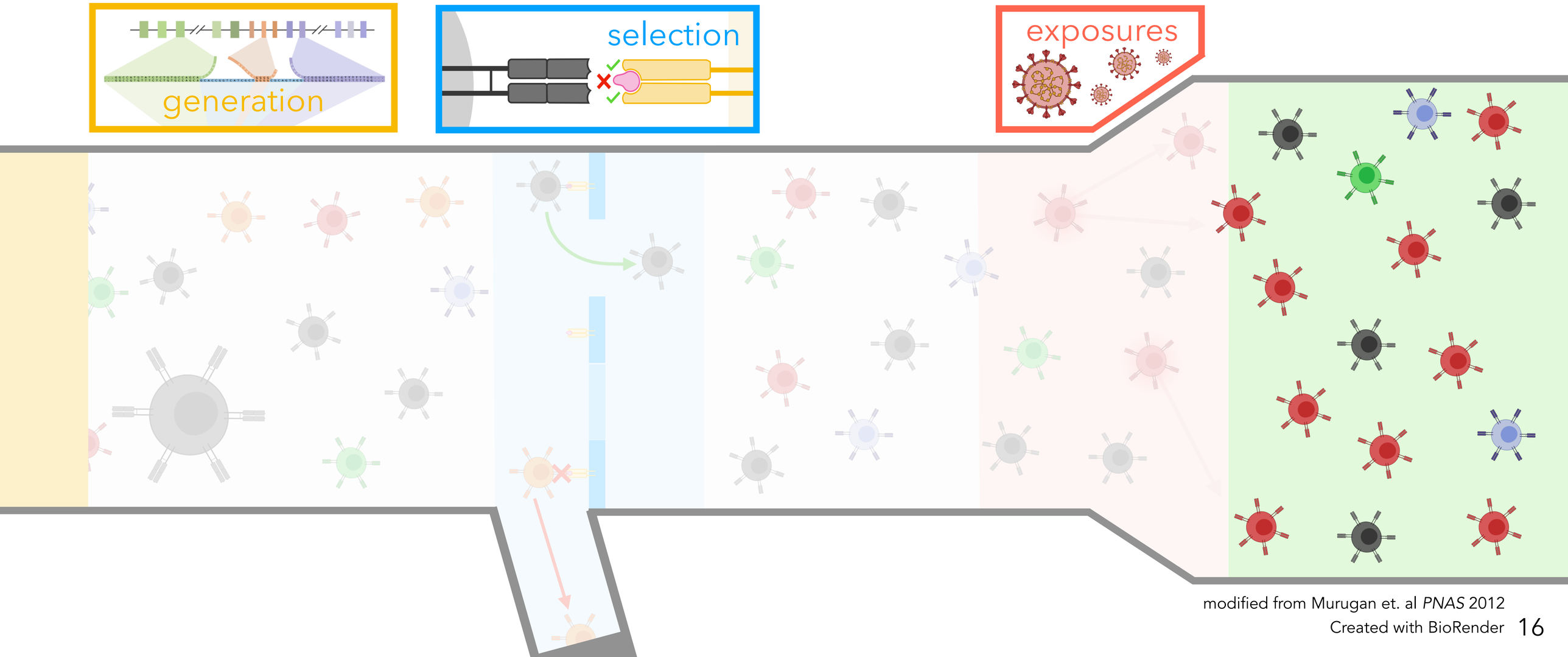
We can sample a **repertoire** using sequencing



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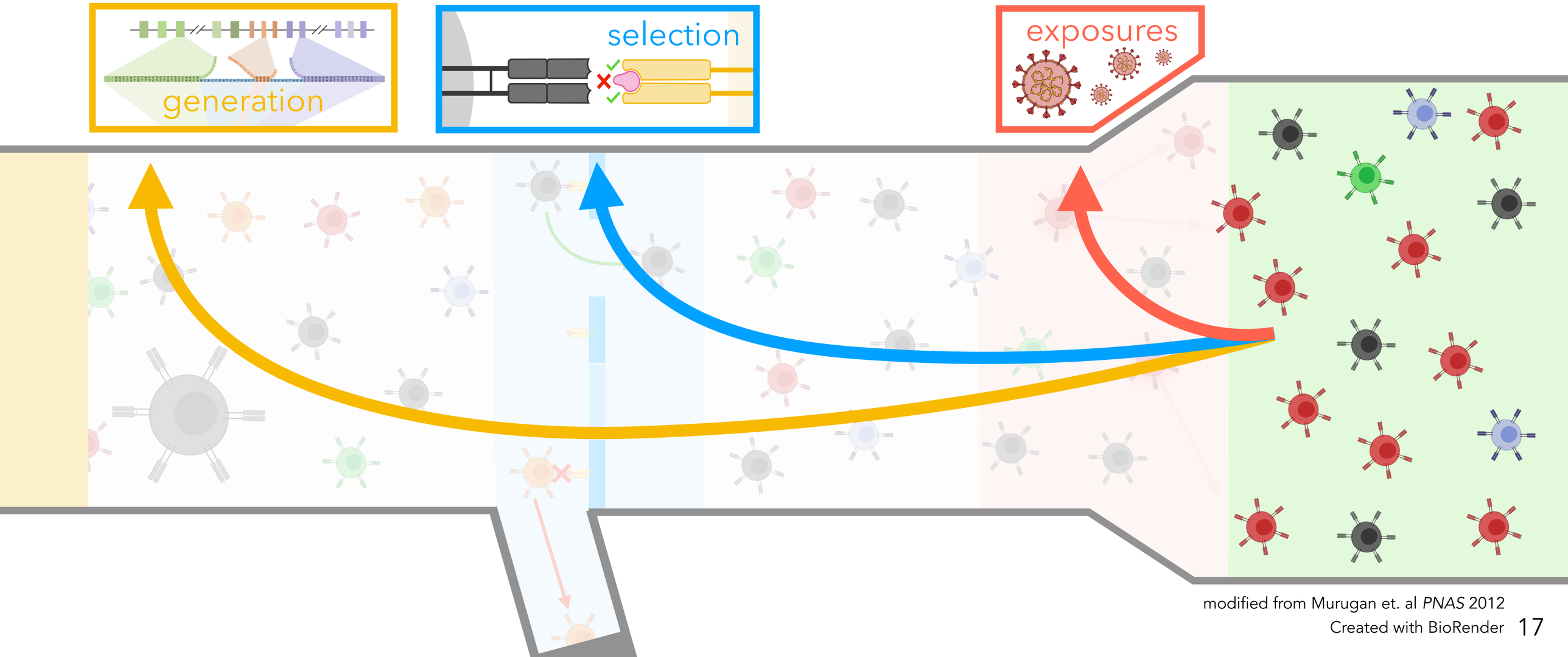
We can use **repertoire *statistics*** to infer previous dynamics



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Lecture goals:

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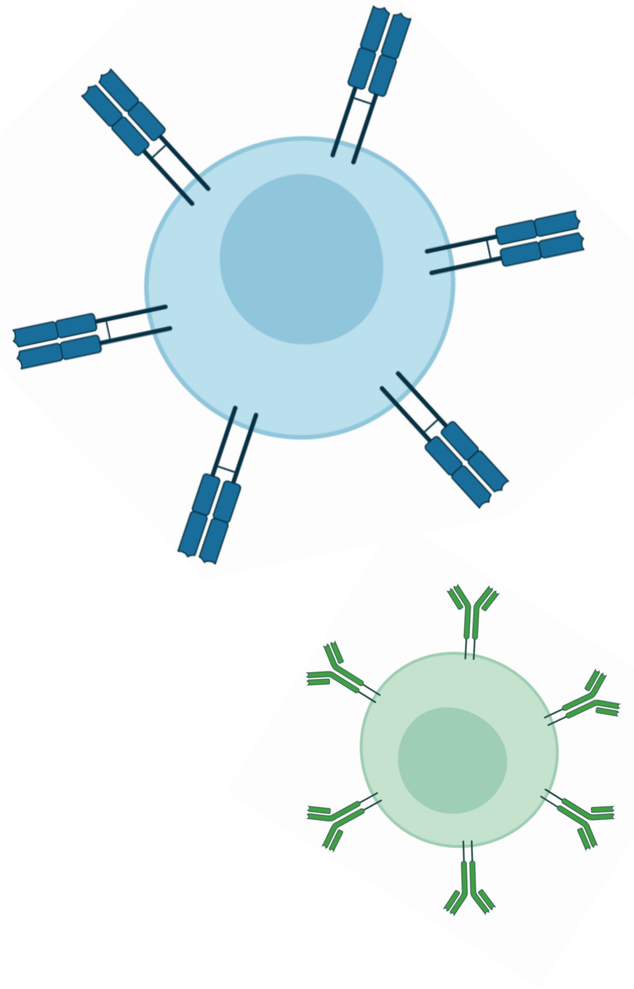
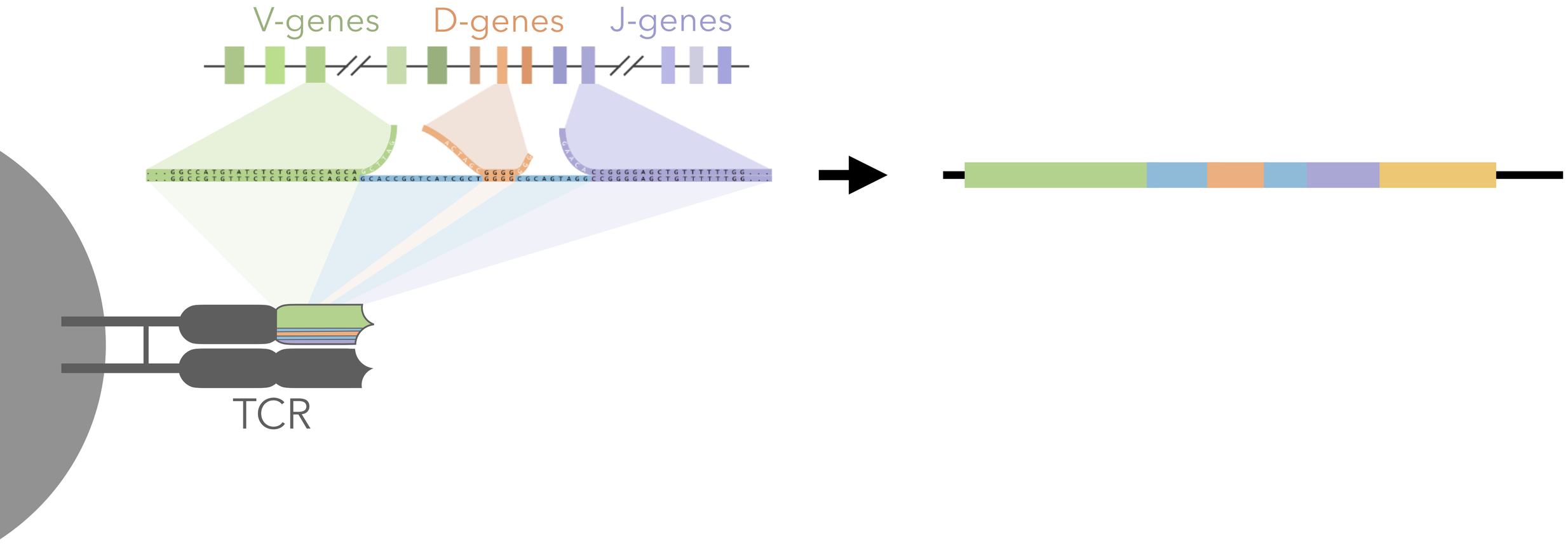
    - what are immune repertoires?
    - how are they formed?
    - **how are they sequenced?**



Sequencing is designed to capture the **most variable region**



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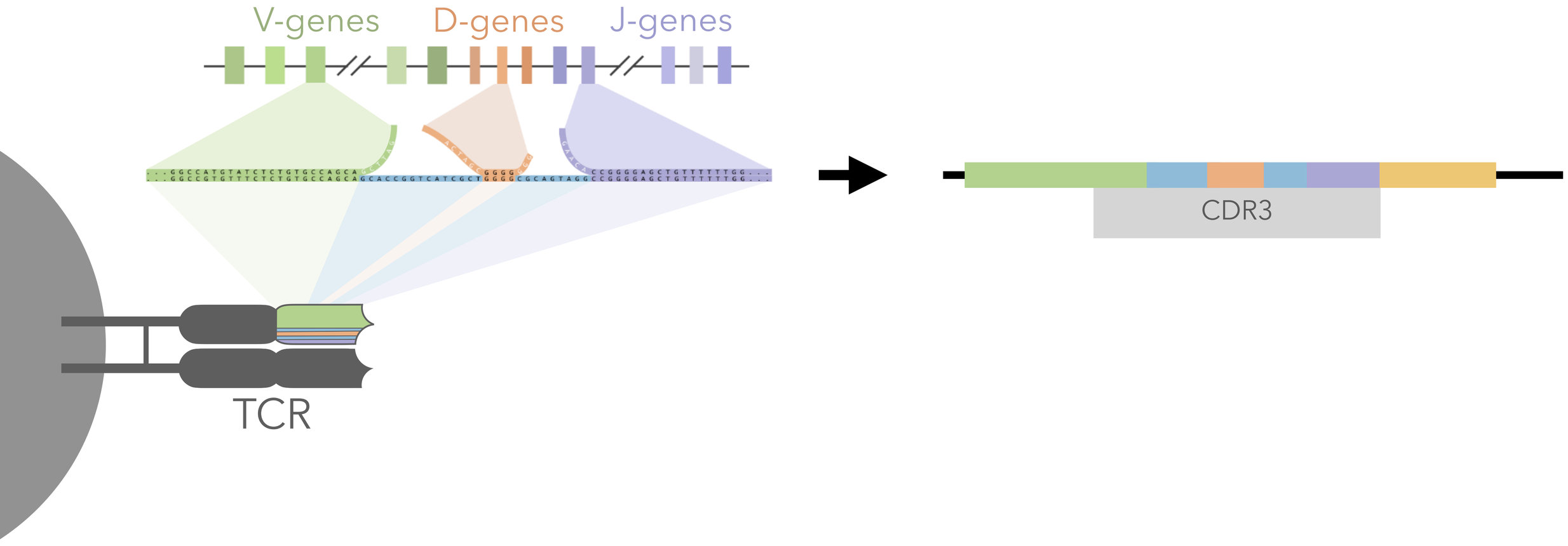

Both **bulk sequencing** and **single-cell sequencing** are possible

	Bulk	**Single-cell**
Sample size *(e.g. total # of sampled cells)*		
Repertoire coverage *(e.g. proportion of total repertoire sequenced)*		
Chain pairing *(e.g. each receptor consists of two protein chains)*		
Cost		

Both **bulk sequencing** and **single-cell sequencing** are possible

	Bulk	**Single-cell**
Sample size *(e.g. total # of sampled cells)*	**Large**	**Small**
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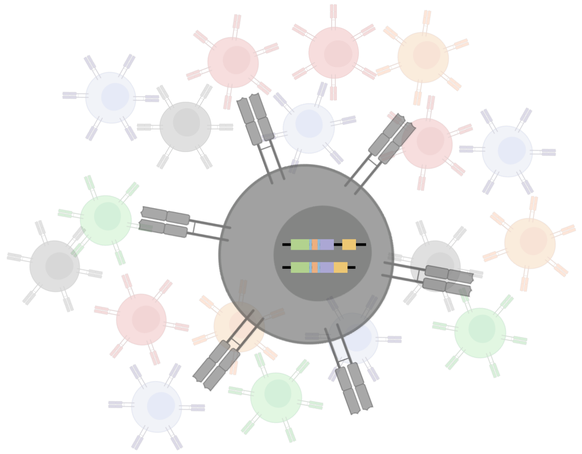
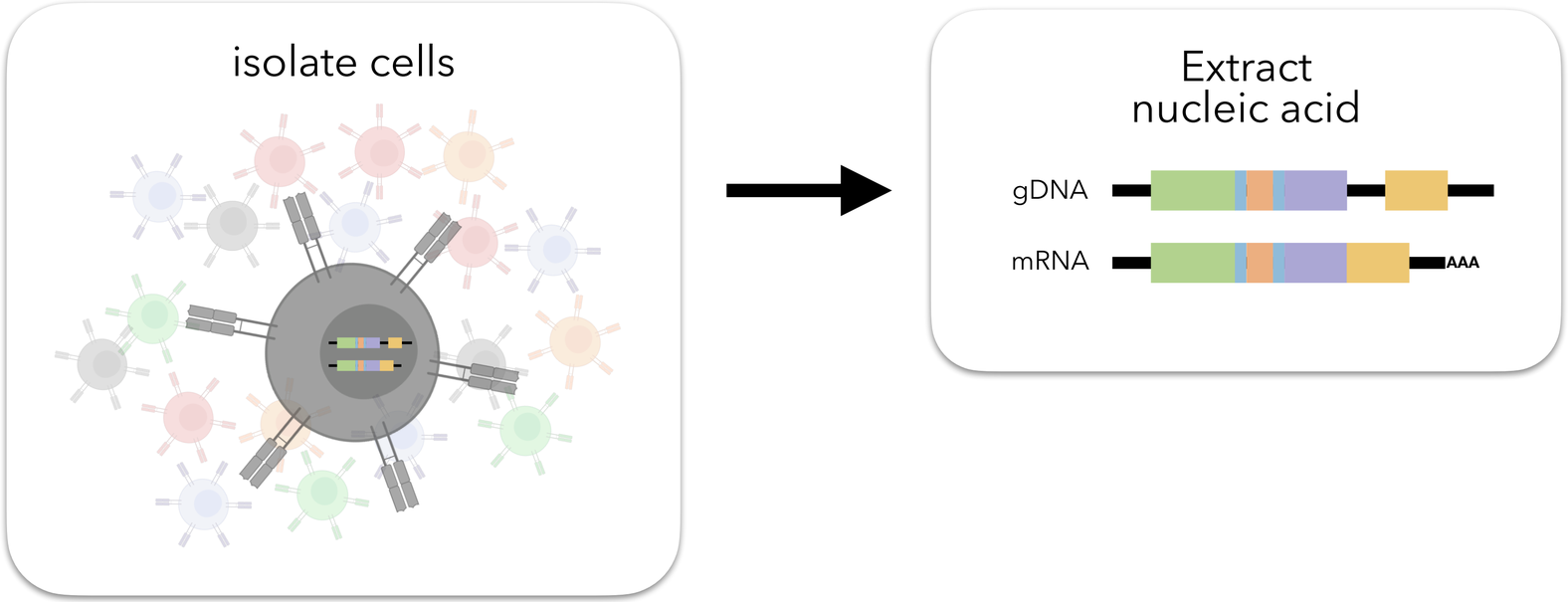
Bulk repertoire sequencing overview

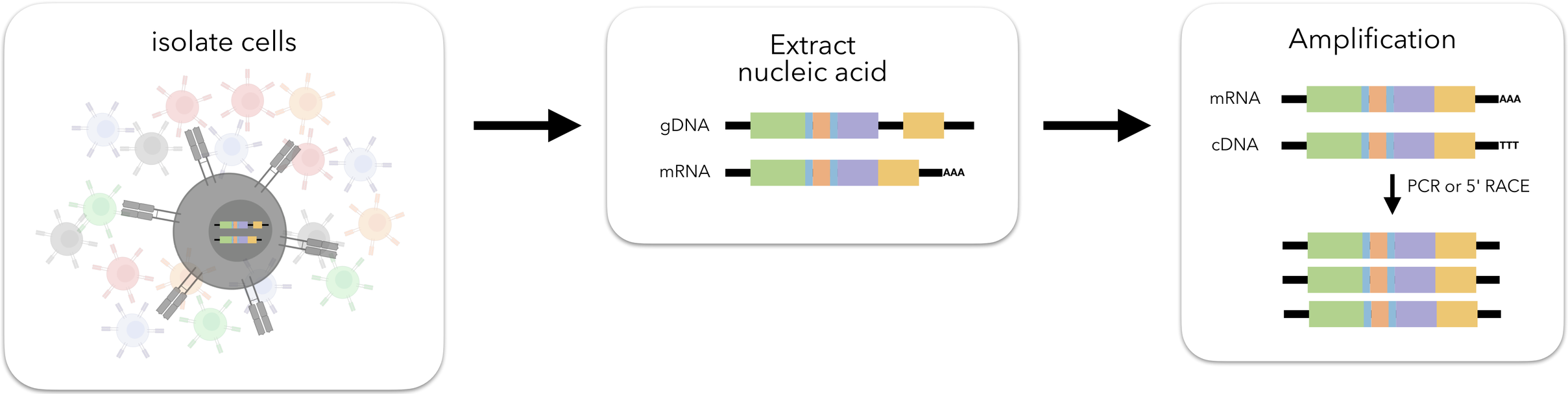
isolate cells



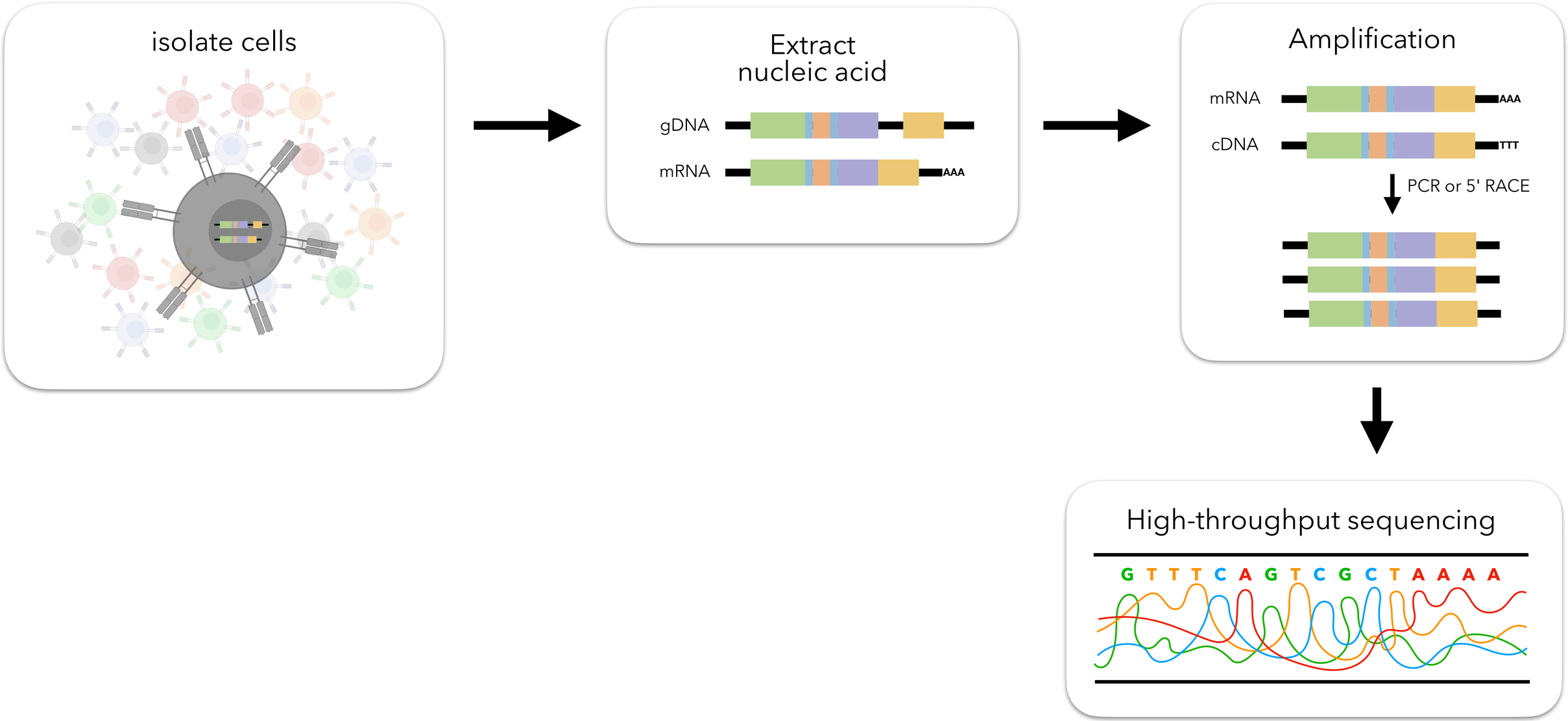
Bulk repertoire sequencing overview



Bulk repertoire sequencing overview



Bulk repertoire sequencing overview



Bulk repertoire sequencing overview

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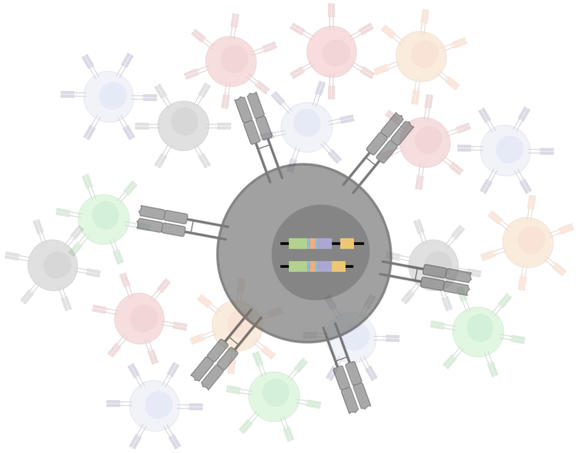
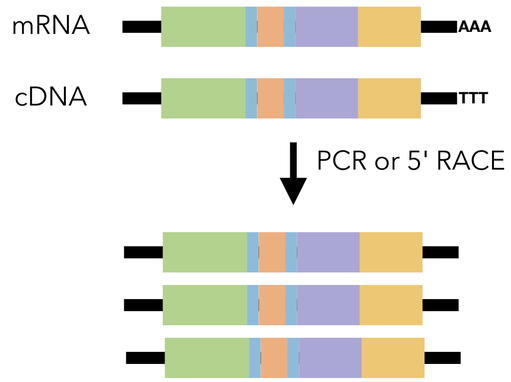
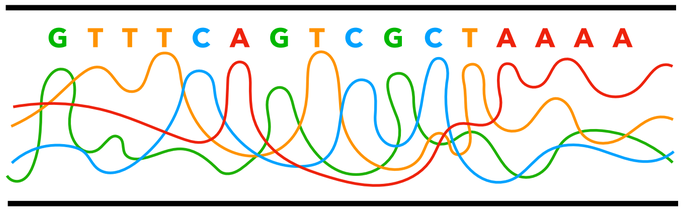


Extract nucleic acid

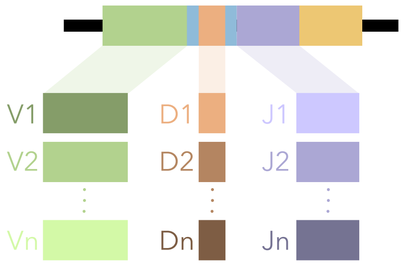
Amplification



High-throughput sequencing



Data preprocessing

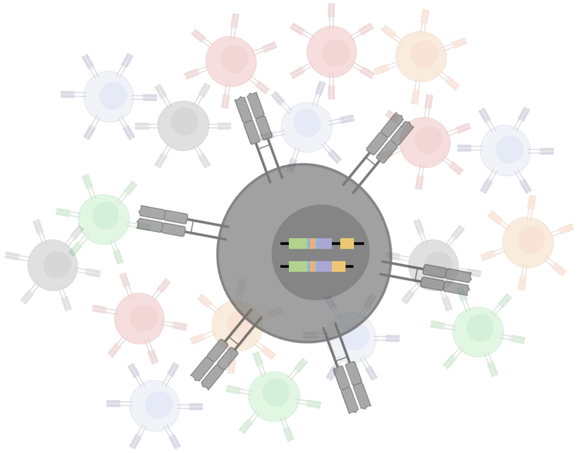


(filtering, alignment, annotation, etc.)

e.g. IGoR, MiXCR, IgBLAST, etc.

Bulk repertoire sequencing overview

isolate cells



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nucleic acid

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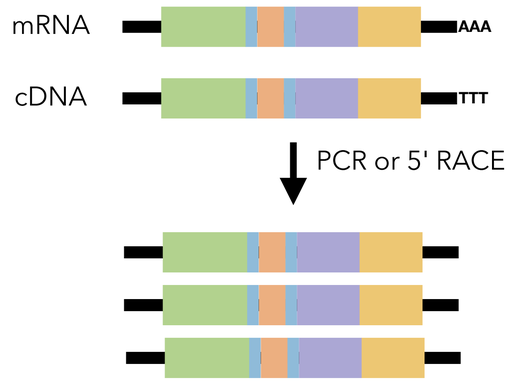

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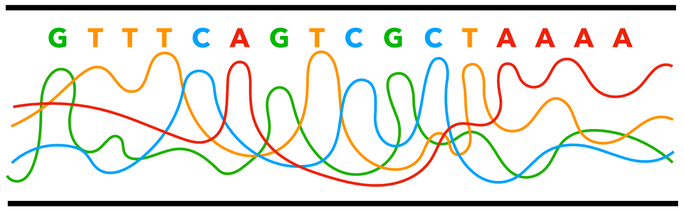

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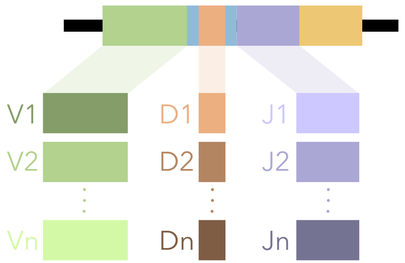

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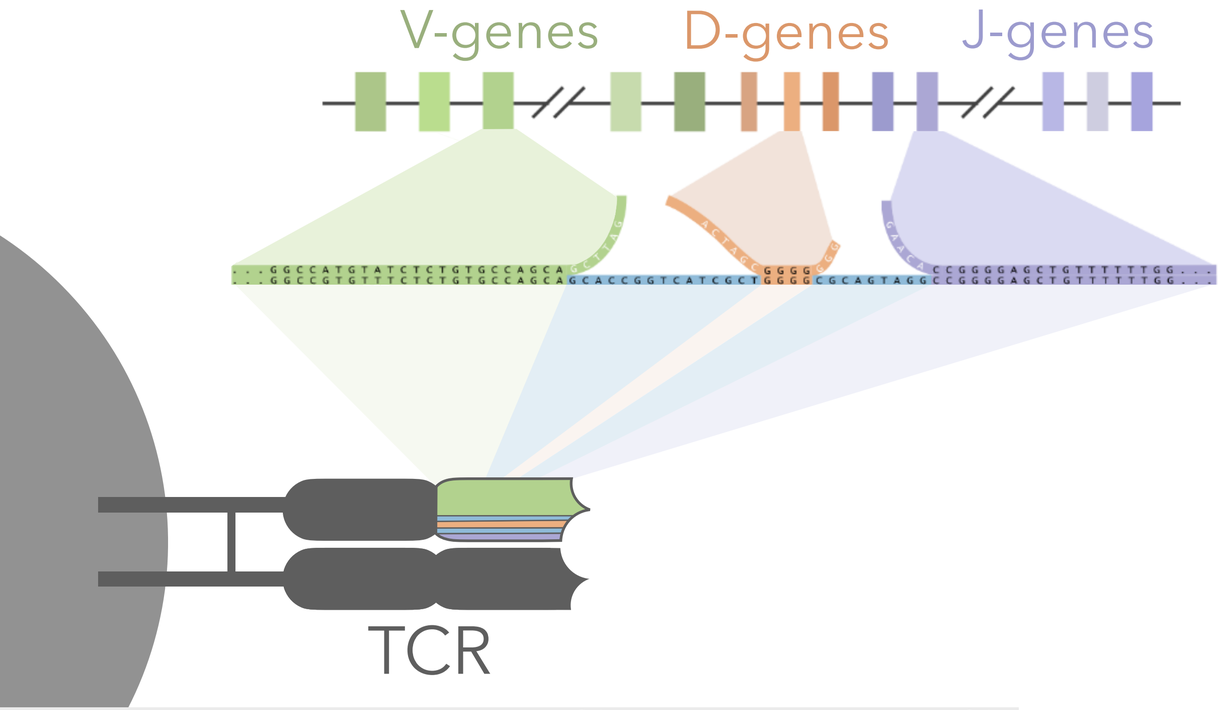
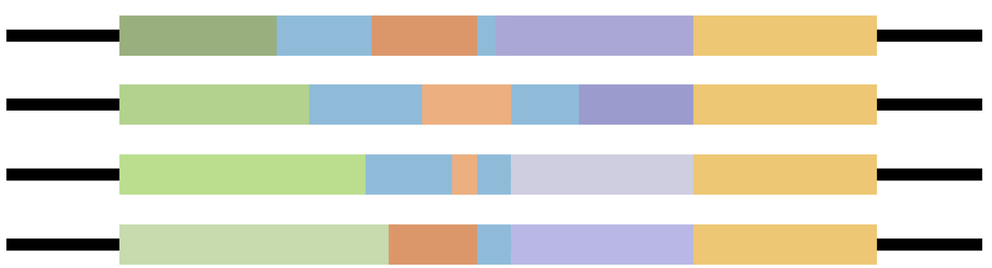
e.g. IGoR, MiXCR, IgBLAST, etc.

Data analysis

Processed **bulk repertoire sequencing** example output





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<chr>	<chr>
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TGCGCCAGCAGCTTGGCAGAGACCCAGTACTTC	CASSLAETQYF
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TGTGCCAGCAGCTTAAATCTGGTGAGGTACGAGCAGTACTTC	CASSLNLVRYEQYF
TGTGCCTGGTCAGGGGGCCCAAACACTGAAGCTTTCTTT	CAWSGGPNTEAFF
TGTGCCACCGAACGAGGGCCCCAAGAGACCCAGTACTTC	CATERGPQETQYF
TGTGCCAGCATAGCGGGAGGTGAGCAGTTCTTC	CASIAGGEQFF
TGTGCCTGGAGCTCCCTCCCTGGCGGGGAGAACAATGAGCAGTTCTTC	CAWSSLPGGENNEQFF
TGTGCCAGCAGTTATCAGGTCACTGAAGCTTTCTTT	CASSYQVTEAFF
TGTGCCAGCGGCCCAGGGCTCGGATACAATCAGCCCCAGCATTTT	CASGPGLGYNQPQHF
TGTGCCAGTGCGGGATTCTATGGCTACACCTTC	CASAGFYGYTF

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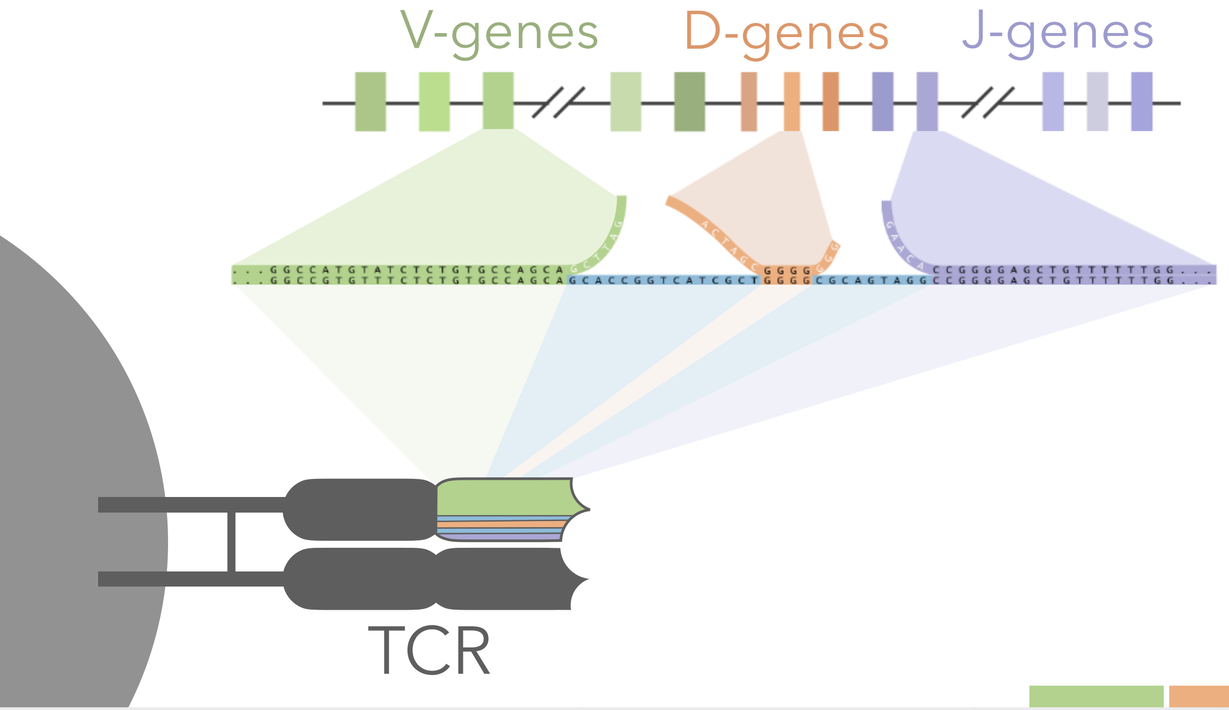

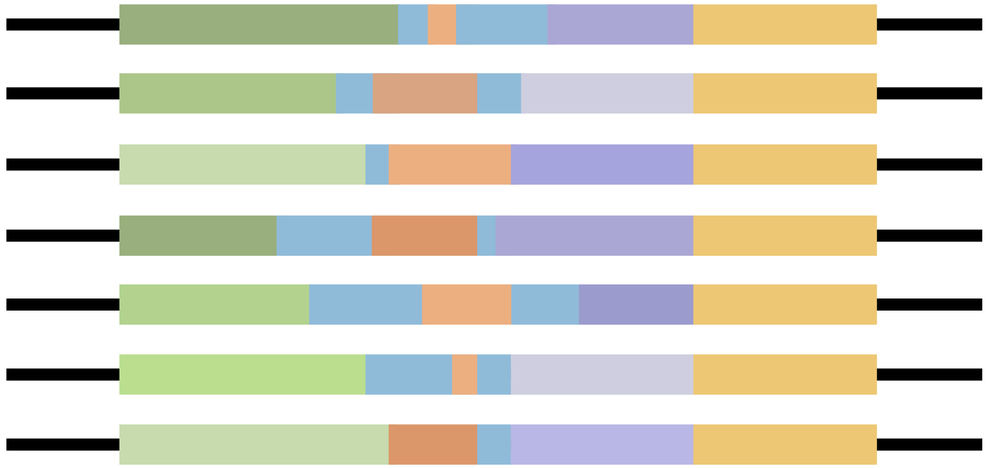

cdr3_nucseq	cdr3	v_gene	d_gene	j_gene
<chr>	<chr>	<chr>	<chr>	<chr>
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TGCGCCAGCAGCTTGGCAGAGACCCAGTACTTC	CASSLAETQYF	TRBV5-1*01	TRBD1*01	TRBJ2-5*01
TGCGCCAGTCGAGCGGCGAGCTCCTACAATGAGCAGTTCTTC	CASRAASSYNEQFF	TRBV5-1*01	TRBD2*01	TRBJ2-1*01
TGTGCCAGCAGCTTAAATCTGGTGAGGTACGAGCAGTACTTC	CASSLNLVRYEQYF	TRBV7-2*01	TRBD2*02	TRBJ2-7*01
TGTGCCTGGTCAGGGGGCCCAAACACTGAAGCTTTCTTT	CAWSGGPNTEAFF	TRBV30*01	TRBD1*01	TRBJ1-1*01
TGTGCCACCGAACGAGGGCCCCAAGAGACCCAGTACTTC	CATERGPQETQYF	TRBV2*03	TRBD1*01	TRBJ2-5*01
TGTGCCAGCATAGCGGGAGGTGAGCAGTTCTTC	CASIAGGEQFF	TRBV28*01	TRBD2*02	TRBJ2-1*01
TGTGCCTGGAGCTCCCTCCCTGGCGGGGAGAACAATGAGCAGTTCTTC	CAWSSLPGGENNEQFF	TRBV30*01	TRBD2*01	TRBJ2-1*01
TGTGCCAGCAGTTATCAGGTCACTGAAGCTTTCTTT	CASSYQVTEAFF	TRBV6-6*02	TRBD1*01	TRBJ1-1*01
TGTGCCAGCGGCCCAGGGCTCGGATACAATCAGCCCCAGCATTTT	CASGPGLGYNQPQHF	TRBV5-5*01	TRBD2*02	TRBJ1-5*01
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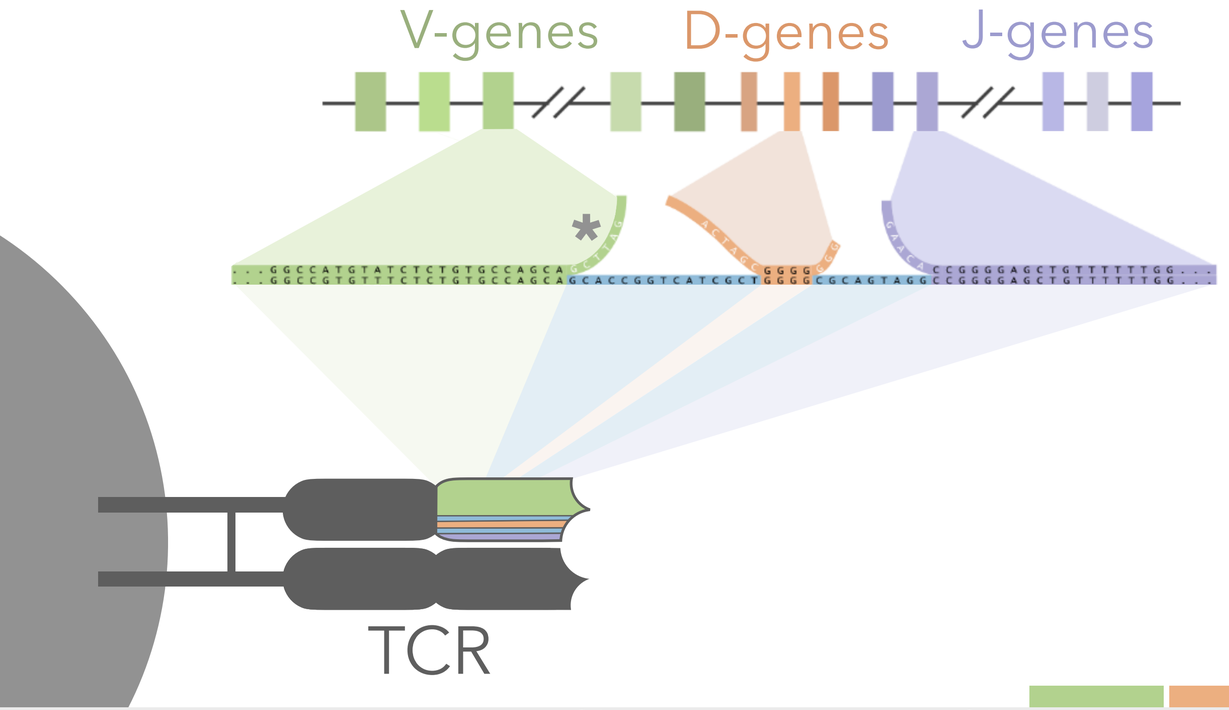
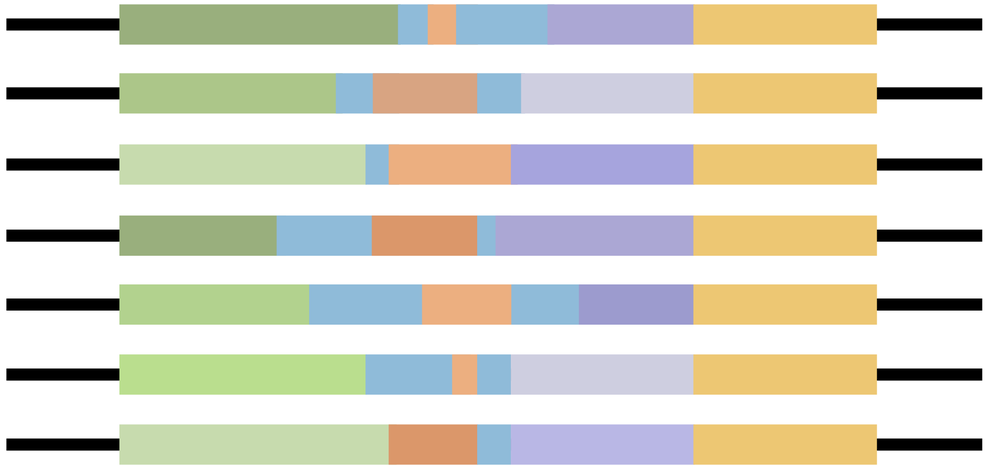
Processed **bulk repertoire sequencing** example output





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TGTGCCAGCAGCTTAAATCTGGTGAGGTACGAGCAGTACTTC	CASSLNLVRYEQYF	TRBV7-2*01	TRBD2*02	TRBJ2-7*01	2
TGTGCCTGGTCAGGGGGCCCAAACACTGAAGCTTTCTTT	CAWSGGPNTEAFF	TRBV30*01	TRBD1*01	TRBJ1-1*01	5
TGTGCCACCGAACGAGGGCCCCAAGAGACCCAGTACTTC	CATERGPQETQYF	TRBV2*03	TRBD1*01	TRBJ2-5*01	10
TGTGCCAGCATAGCGGGAGGTGAGCAGTTCTTC	CASIAGGEQFF	TRBV28*01	TRBD2*02	TRBJ2-1*01	7
TGTGCCTGGAGCTCCCTCCCTGGCGGGGAGAACAATGAGCAGTTCTTC	CAWSSLPGGENNEQFF	TRBV30*01	TRBD2*01	TRBJ2-1*01	3
TGTGCCAGCAGTTATCAGGTCACTGAAGCTTTCTTT	CASSYQVTEAFF	TRBV6-6*02	TRBD1*01	TRBJ1-1*01	4
TGTGCCAGCGGCCCAGGGCTCGGATACAATCAGCCCCAGCATTTT	CASGPGLGYNQPQHF	TRBV5-5*01	TRBD2*02	TRBJ1-5*01	7
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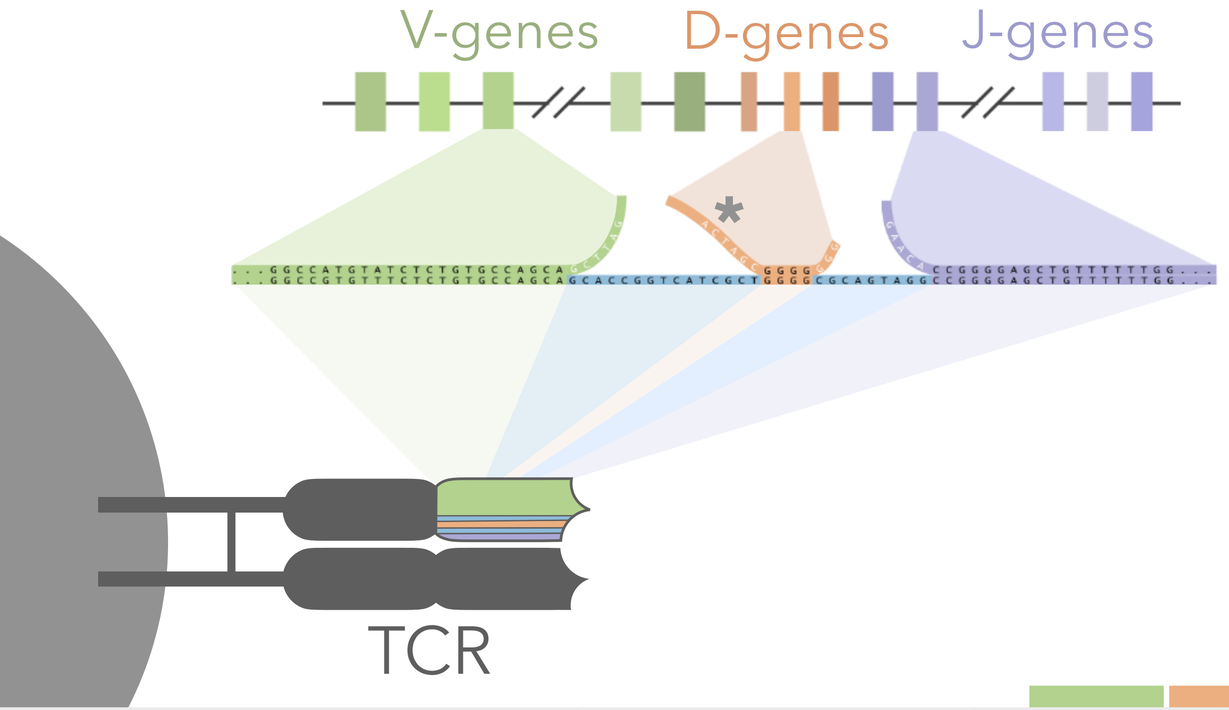
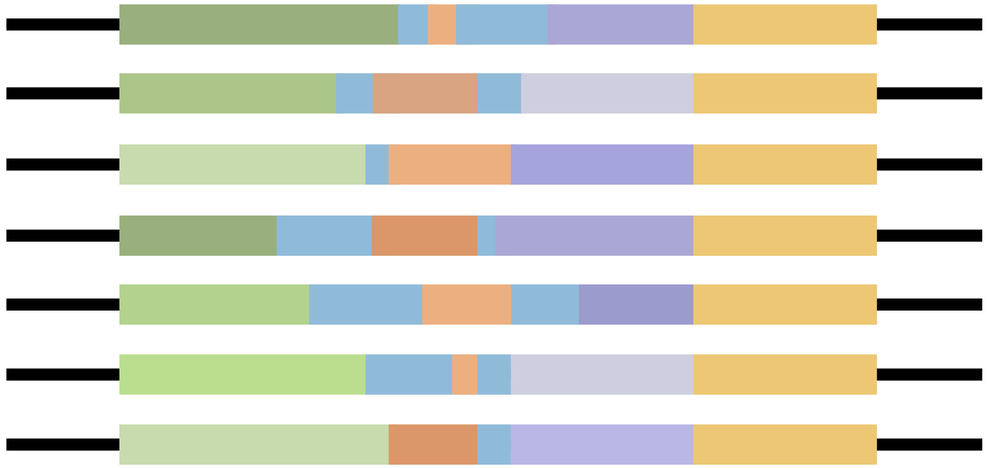
Processed **bulk repertoire sequencing** example output





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TGTGCCTGGTCAGGGGGCCCAAACACTGAAGCTTTCTTT	CAWSGGPNTEAFF	TRBV30*01	TRBD1*01	TRBJ1-1*01	5	4
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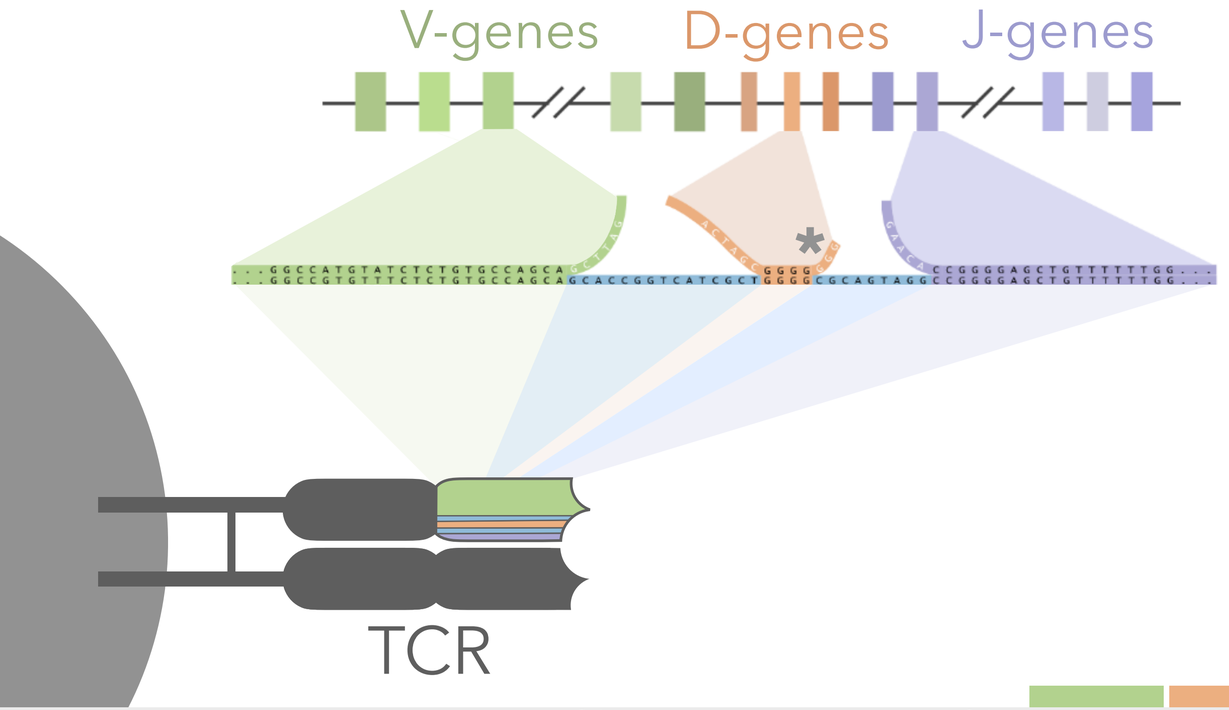
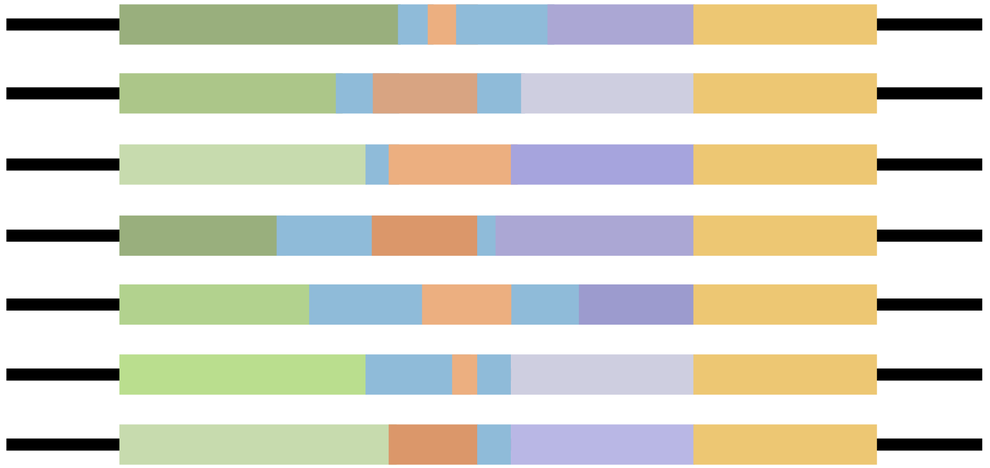
Processed **bulk repertoire sequencing** example output





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TGCGCCAGTCGAGCGGCGAGCTCCTACAATGAGCAGTTCTTC	CASRAASSYNEQFF	TRBV5-1*01	TRBD2*01	TRBJ2-1*01	9	6	5
TGTGCCAGCAGCTTAAATCTGGTGAGGTACGAGCAGTACTTC	CASSLNLVRYEQYF	TRBV7-2*01	TRBD2*02	TRBJ2-7*01	2	11	1
TGTGCCTGGTCAGGGGGCCCAAACACTGAAGCTTTCTTT	CAWSGGPNTEAFF	TRBV30*01	TRBD1*01	TRBJ1-1*01	5	4	0
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TGTGCCAGCATAGCGGGAGGTGAGCAGTTCTTC	CASIAGGEQFF	TRBV28*01	TRBD2*02	TRBJ2-1*01	7	6	3
TGTGCCTGGAGCTCCCTCCCTGGCGGGGAGAACAATGAGCAGTTCTTC	CAWSSLPGGENNEQFF	TRBV30*01	TRBD2*01	TRBJ2-1*01	3	7	3
TGTGCCAGCAGTTATCAGGTCACTGAAGCTTTCTTT	CASSYQVTEAFF	TRBV6-6*02	TRBD1*01	TRBJ1-1*01	4	4	5
TGTGCCAGCGGCCCAGGGCTCGGATACAATCAGCCCCAGCATTTT	CASGPGLGYNQPQHF	TRBV5-5*01	TRBD2*02	TRBJ1-5*01	7	12	0
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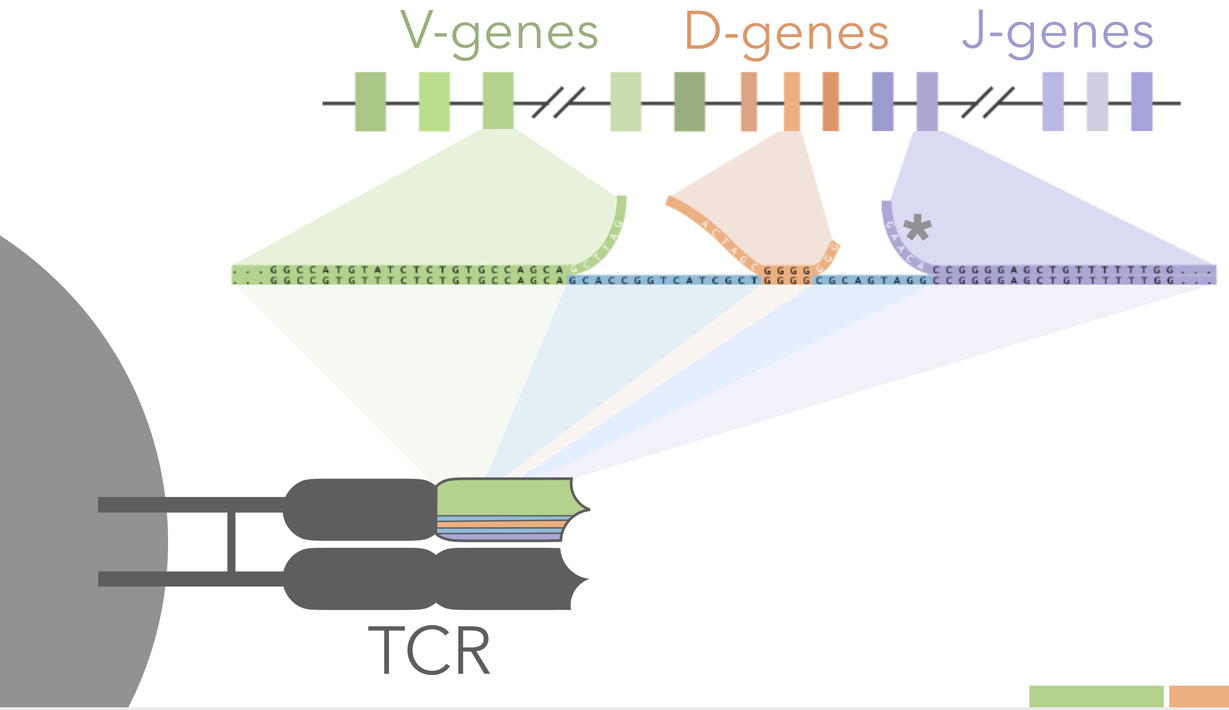
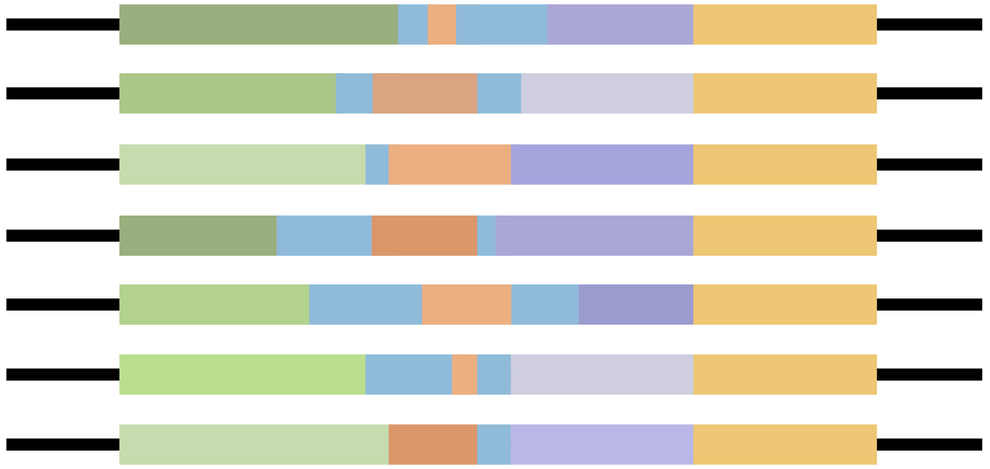
Processed **bulk repertoire sequencing** example output





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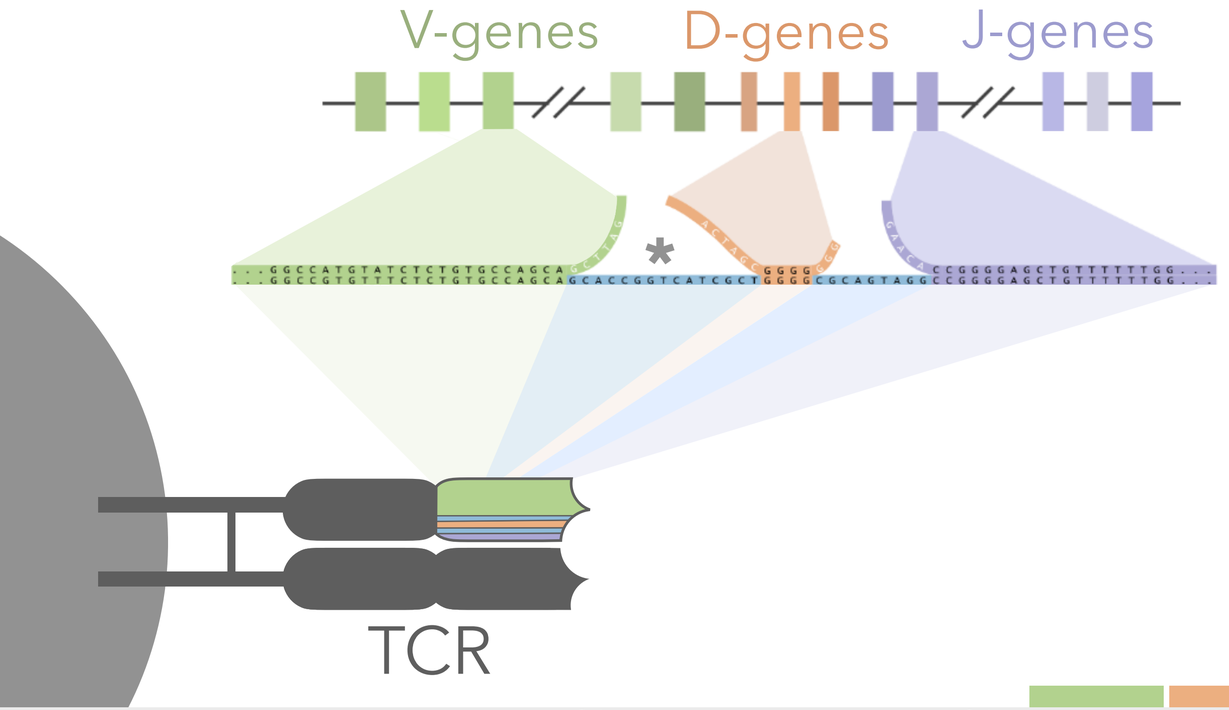
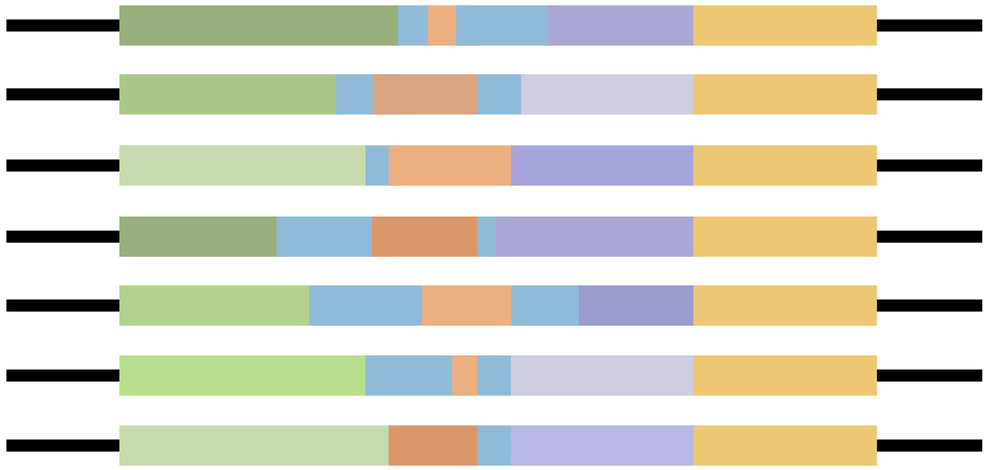
TGCGCCAGTCGAGCGGCGAGCTCCTACAATGAGCAGTTCTTC	CASRAASSYNEQFF	TRBV5-1*01	TRBD2*01	TRBJ2-1*01	9	6	5	0
TGTGCCAGCAGCTTAAATCTGGTGAGGTACGAGCAGTACTTC	CASSLNLVRYEQYF	TRBV7-2*01	TRBD2*02	TRBJ2-7*01	2	11	1	4
TGTGCCTGGTCAGGGGGCCCAAACACTGAAGCTTTCTTT	CAWSGGPNTEAFF	TRBV30*01	TRBD1*01	TRBJ1-1*01	5	4	0	2
TGTGCCACCGAACGAGGGCCCCAAGAGACCCAGTACTTC	CATERGPQETQYF	TRBV2*03	TRBD1*01	TRBJ2-5*01	10	5	3	1
TGTGCCAGCATAGCGGGAGGTGAGCAGTTCTTC	CASIAGGEQFF	TRBV28*01	TRBD2*02	TRBJ2-1*01	7	6	3	9
TGTGCCTGGAGCTCCCTCCCTGGCGGGGAGAACAATGAGCAGTTCTTC	CAWSSLPGGENNEQFF	TRBV30*01	TRBD2*01	TRBJ2-1*01	3	7	3	5
TGTGCCAGCAGTTATCAGGTCACTGAAGCTTTCTTT	CASSYQVTEAFF	TRBV6-6*02	TRBD1*01	TRBJ1-1*01	4	4	5	4
TGTGCCAGCGGCCCAGGGCTCGGATACAATCAGCCCCAGCATTTT	CASGPGLGYNQPQHF	TRBV5-5*01	TRBD2*02	TRBJ1-5*01	7	12	0	3
TGTGCCAGTGCGGGATTCTATGGCTACACCTTC	CASAGFYGYTF	TRBV6-1*01	TRBD1*01	TRBJ1-2*01	9	7	2	4

Processed **bulk repertoire sequencing** example output





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TGCGCCAGCAGCTTGGCAGAGACCCAGTACTTC	CASSLAETQYF	TRBV5-1*01	TRBD1*01	TRBJ2-5*01	2	9	0	4	0	
TGCGCCAGTCGAGCGGCGAGCTCCTACAATGAGCAGTTCTTC	CASRAASSYNEQFF	TRBV5-1*01	TRBD2*01	TRBJ2-1*01	9	6	5	0	4	GTCG
TGTGCCAGCAGCTTAAATCTGGTGAGGTACGAGCAGTACTTC	CASSLNLVRYEQYF	TRBV7-2*01	TRBD2*02	TRBJ2-7*01	2	11	1	4	8	AATCTGGT
TGTGCCTGGTCAGGGGGCCCAAACACTGAAGCTTTCTTT	CAWSGGPNTEAFF	TRBV30*01	TRBD1*01	TRBJ1-1*01	5	4	0	2	1	T
TGTGCCACCGAACGAGGGCCCCAAGAGACCCAGTACTTC	CATERGPQETQYF	TRBV2*03	TRBD1*01	TRBJ2-5*01	10	5	3	1	7	CCGAACG
TGTGCCAGCATAGCGGGAGGTGAGCAGTTCTTC	CASIAGGEQFF	TRBV28*01	TRBD2*02	TRBJ2-1*01	7	6	3	9	1	T
TGTGCCTGGAGCTCCCTCCCTGGCGGGGAGAACAATGAGCAGTTCTTC	CAWSSLPGGENNEQFF	TRBV30*01	TRBD2*01	TRBJ2-1*01	3	7	3	5	11	CTCCCTCCCTG
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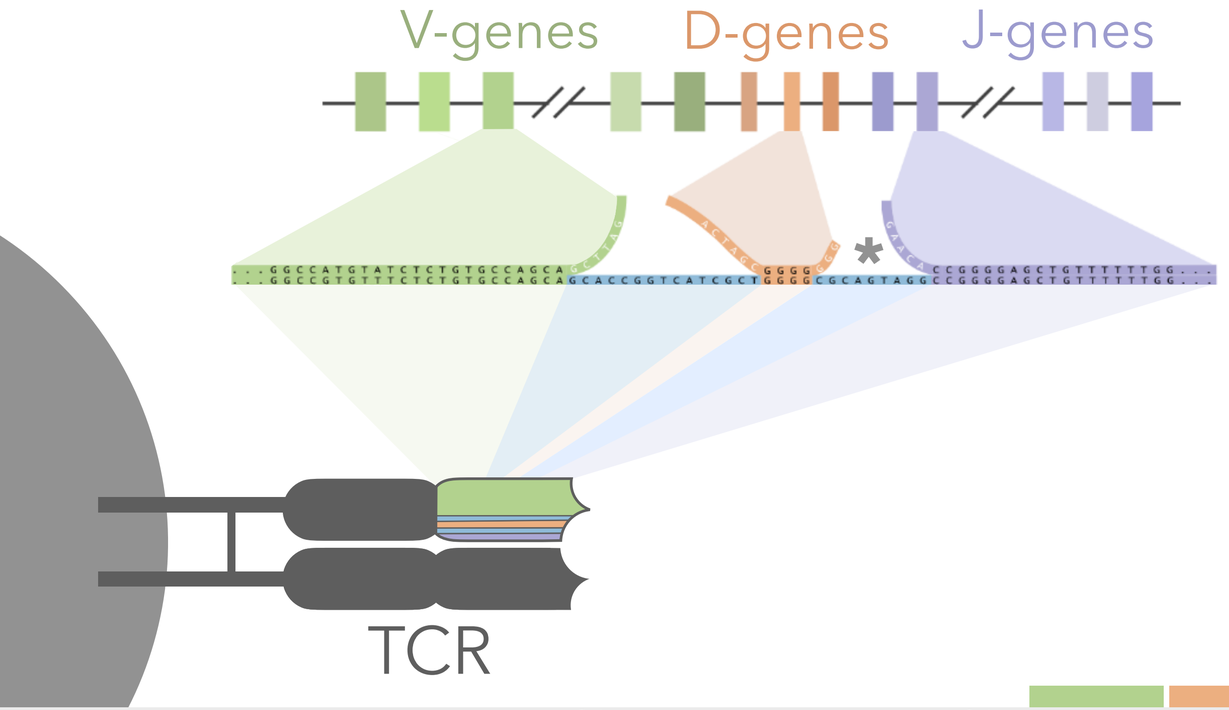
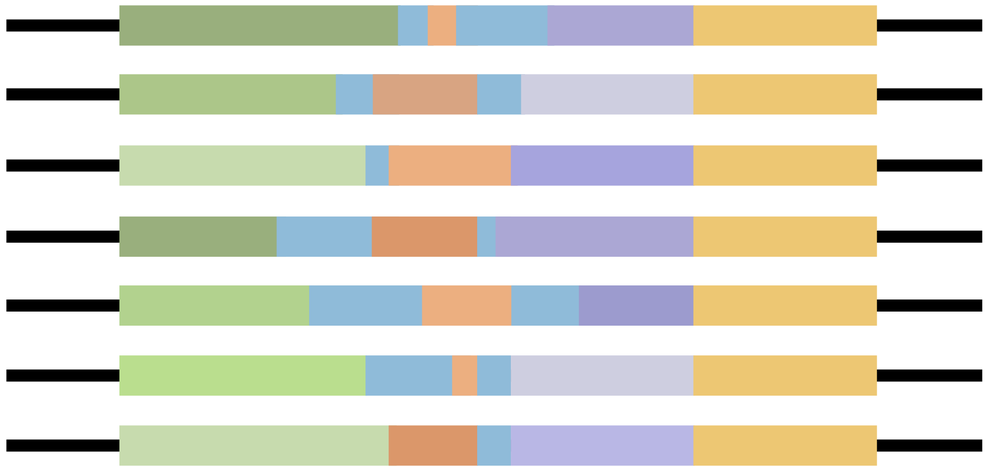
TGTGCCAGTGCGGGATTCTATGGCTACACCTTC	CASAGFYGYTF	TRBV6-1*01	TRBD1*01	TRBJ1-2*01	9	7	2	4	3	TGC

Processed **bulk repertoire sequencing** example output





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TGCGCCAGCAGCTTGGCAGAGACCCAGTACTTC	CASSLAETQYF	TRBV5-1*01	TRBD1*01	TRBJ2-5*01	2	9	0	4	0	0		
TGCGCCAGTCGAGCGGCGAGCTCCTACAATGAGCAGTTCTTC	CASRAASSYNEQFF	TRBV5-1*01	TRBD2*01	TRBJ2-1*01	9	6	5	0	4	2	GTCG	GC
TGTGCCAGCAGCTTAAATCTGGTGAGGTACGAGCAGTACTTC	CASSLNLVRYEQYF	TRBV7-2*01	TRBD2*02	TRBJ2-7*01	2	11	1	4	8	0	AATCTGGT	
TGTGCCTGGTCAGGGGGCCCAAACACTGAAGCTTTCTTT	CAWSGGPNTEAFF	TRBV30*01	TRBD1*01	TRBJ1-1*01	5	4	0	2	1	3	T	ACC
TGTGCCACCGAACGAGGGCCCCAAGAGACCCAGTACTTC	CATERGPQETQYF	TRBV2*03	TRBD1*01	TRBJ2-5*01	10	5	3	1	7	2	CCGAACG	CC
TGTGCCAGCATAGCGGGAGGTGAGCAGTTCTTC	CASIAGGEQFF	TRBV28*01	TRBD2*02	TRBJ2-1*01	7	6	3	9	1	2	T	GG
TGTGCCTGGAGCTCCCTCCCTGGCGGGGAGAACAATGAGCAGTTCTTC	CAWSSLPGGENNEQFF	TRBV30*01	TRBD2*01	TRBJ2-1*01	3	7	3	5	11	3	CTCCCTCCCTG	AGA
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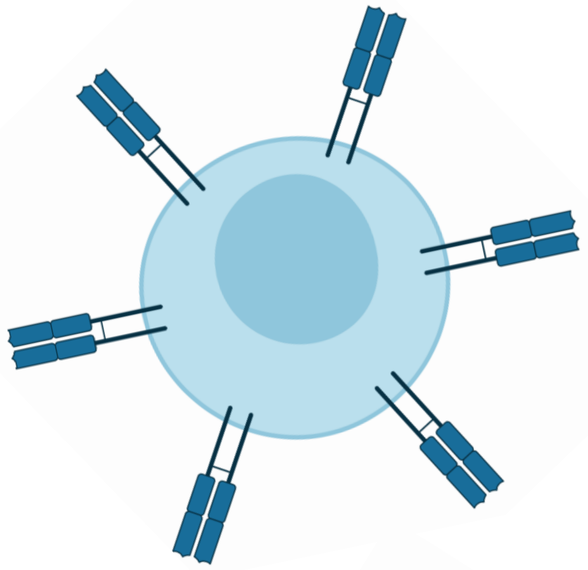
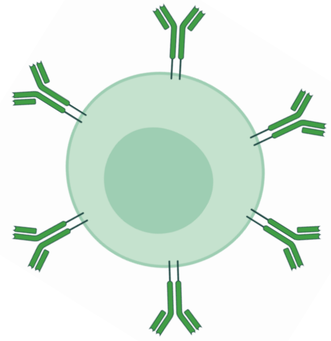
TGTGCCAGCGGCCCAGGGCTCGGATACAATCAGCCCCAGCATTTT	CASGPGLGYNQPQHF	TRBV5-5*01	TRBD2*02	TRBJ1-5*01	7	12	0	3	5	8	GGCCC	ATAGGCTC
TGTGCCAGTGCGGGATTCTATGGCTACACCTTC	CASAGFYGYTF	TRBV6-1*01	TRBD1*01	TRBJ1-2*01	9	7	2	4	3	3	TGC	TTA

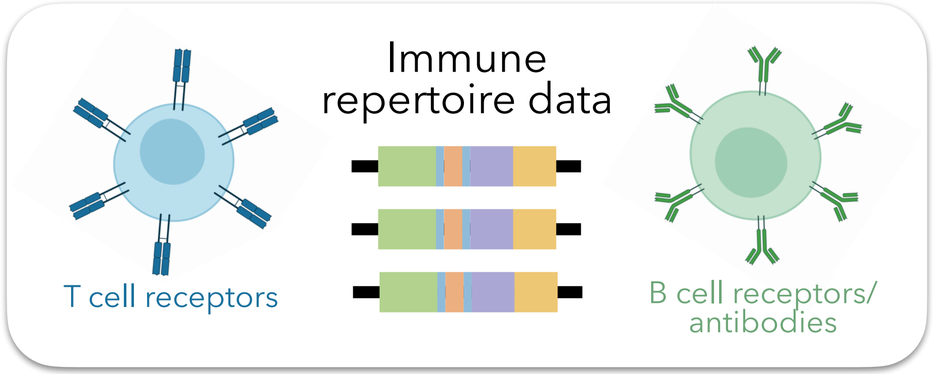
Lecture goals:





1. learn about immune repertoire sequencing
    - what are immune repertoires?
    - how are they formed?
    - how are they sequenced?
    - **what are some common areas of repertoire analysis?**

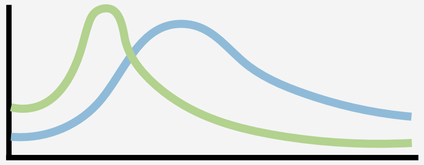
Immune repertoire analyses often focus on diversity, architecture, evolution, or convergence



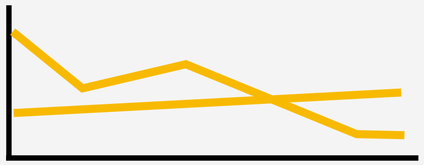
Immune repertoire analyses often focus on **diversity**, architecture, evolution, or convergence

Underlying mechanisms of diversity generation

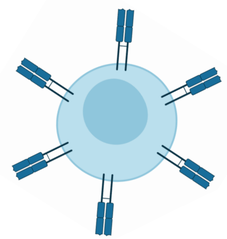
probabilistic sequence annotation



recombination statistics to learn about generation and selection

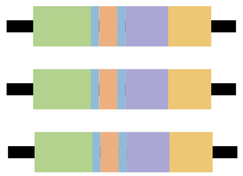


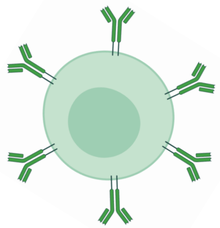
clonotype diversity dynamics



T cell receptors

Immune repertoire data

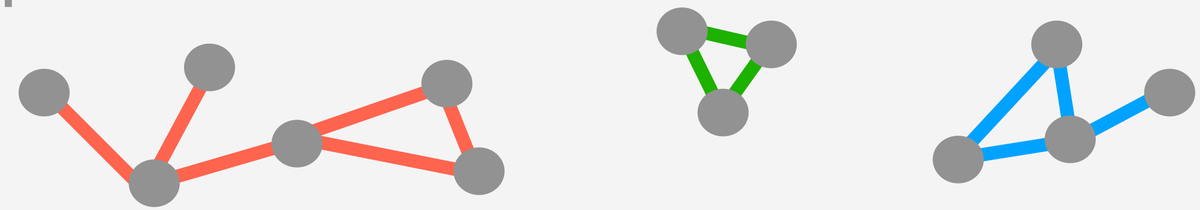




B cell receptors/ antibodies

Immune repertoire analyses often focus on diversity, **architecture**, evolution, or convergence

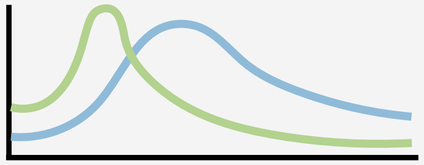
Repertoire architecture



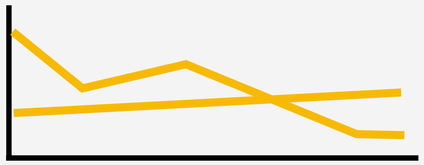
defining antigen recognition breadth using network analysis

Underlying mechanisms of diversity generation

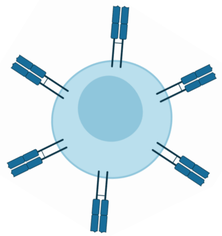
probabilistic sequence annotation



recombination statistics to learn about generation and selection



clonotype diversity dynamics



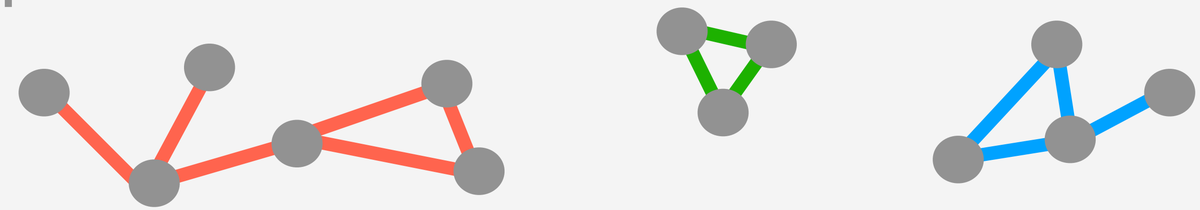
T cell receptors

Immune repertoire data

B cell receptors/ antibodies

Immune repertoire analyses often focus on diversity, architecture, **evolution**, or convergence

Repertoire architecture



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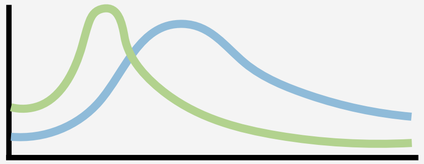

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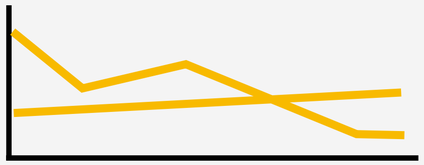
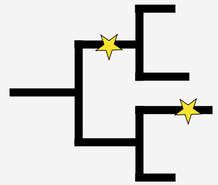
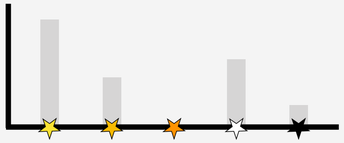


clonotype diversity dynamics

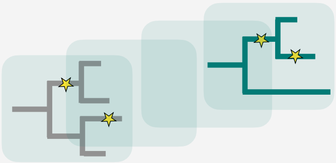
Antibody evolution



reconstruction of phylogenetic trees



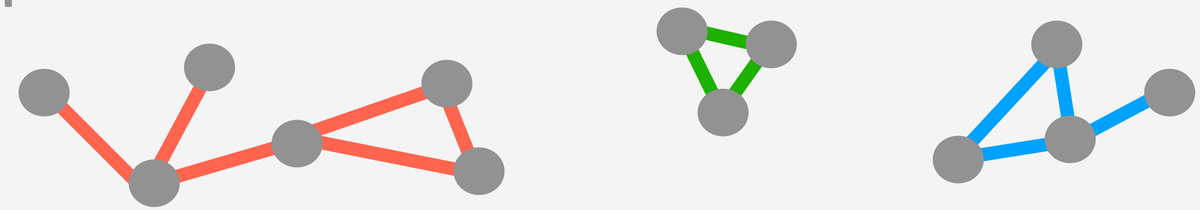
inferring mutation statistics



simulating antibody repertoire evolution

Immune repertoire analyses often focus on diversity, architecture, evolution, or **convergence**

Repertoire architecture



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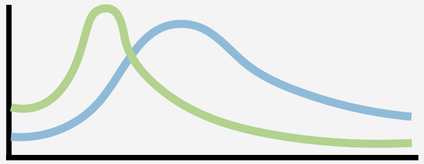

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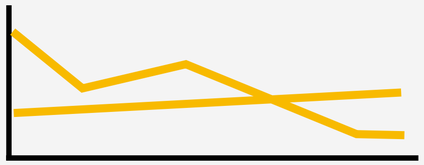

clonotype diversity dynamics

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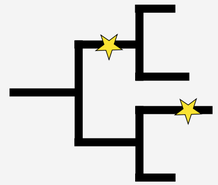

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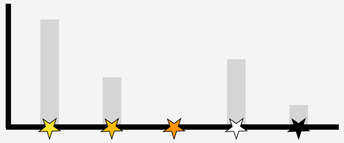

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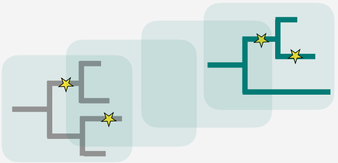
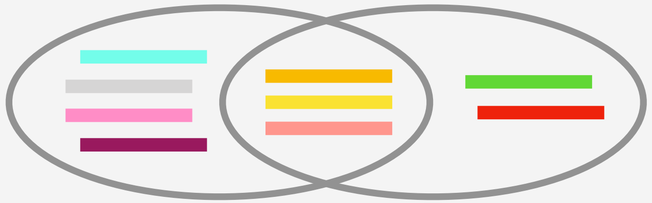


simulating antibody repertoire evolution

Molecular convergence



exploring cross-individual sequence similarity and convergence

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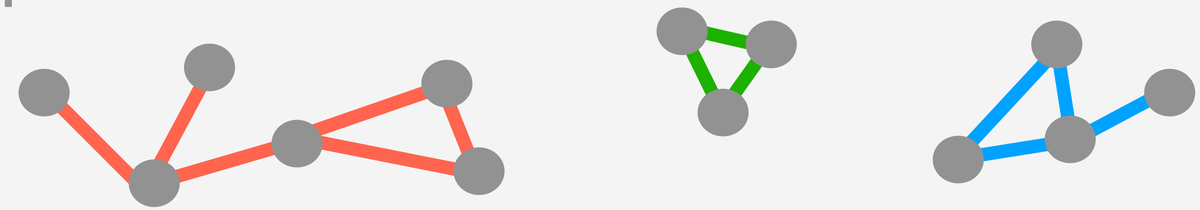

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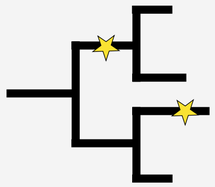

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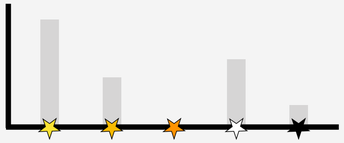

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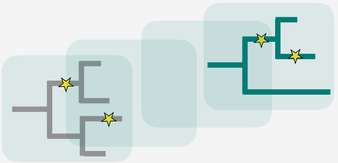

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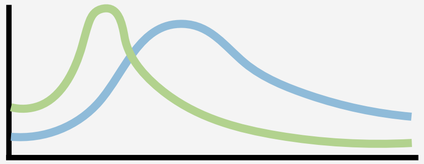

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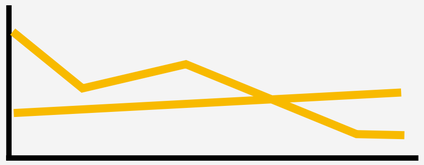

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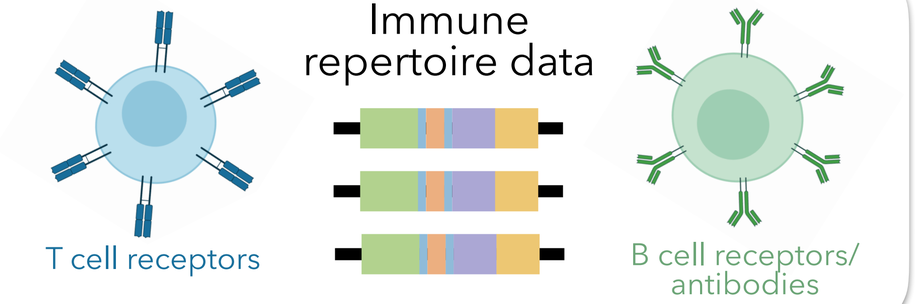

Molecular convergence

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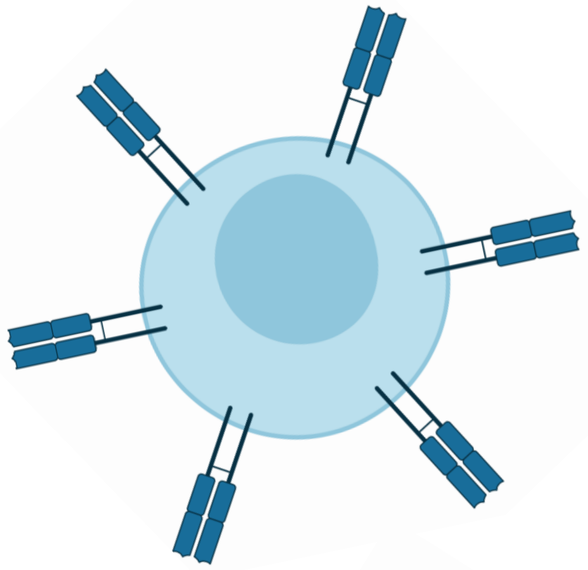
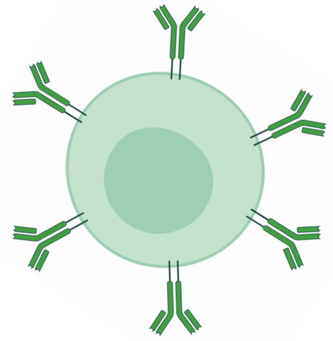
Lecture goals:





1. learn about immune repertoire sequencing
    - what are immune repertoires?
    - how are they formed?
    - how are they sequenced?
    - what are some common areas of repertoire analysis?
2. familiarize with immune repertoire data
3. work through an example analysis