COLOGNE GRADUATE SCHOOL OF AGEING RESEARCH

Characterising antibody immunity and ageing in a short-lived teleost

William John Bradshaw

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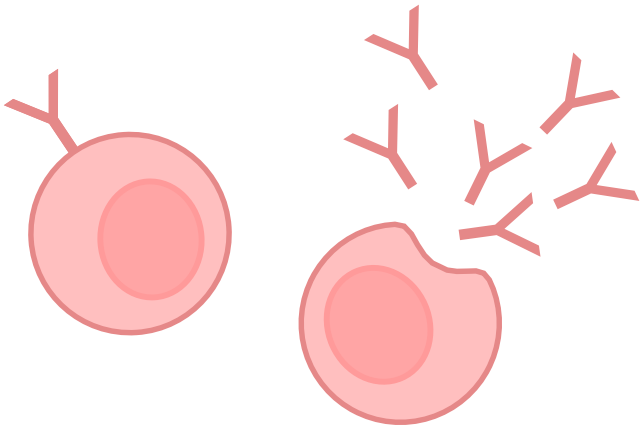
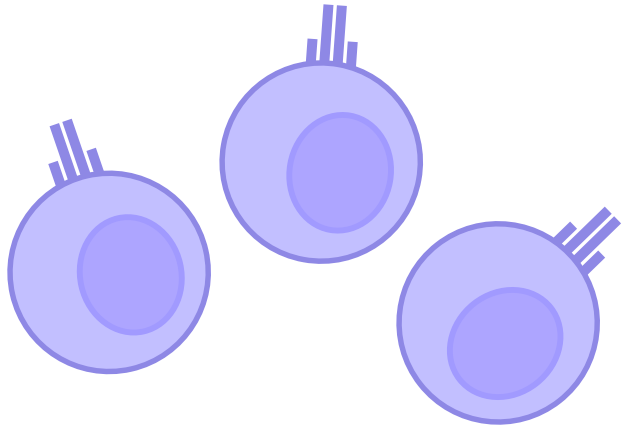
CECAD COLOGNE | MAX PLANCK INSTITUTE FOR BIOLOGY OF AGEING | Max Planck Institute for Metabolism Research | caesar center of advanced european studies and research | University of Cologne | UNIKLINIK KÖLN

Antibodies



T-cell receptors



B-cells

T-cells

Adaptive immune system

Ageing has major effects on human adaptive immunity

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- Reduced naïve B-cell output
- Fewer unique antibody sequences
- Decreased responsiveness to vaccination
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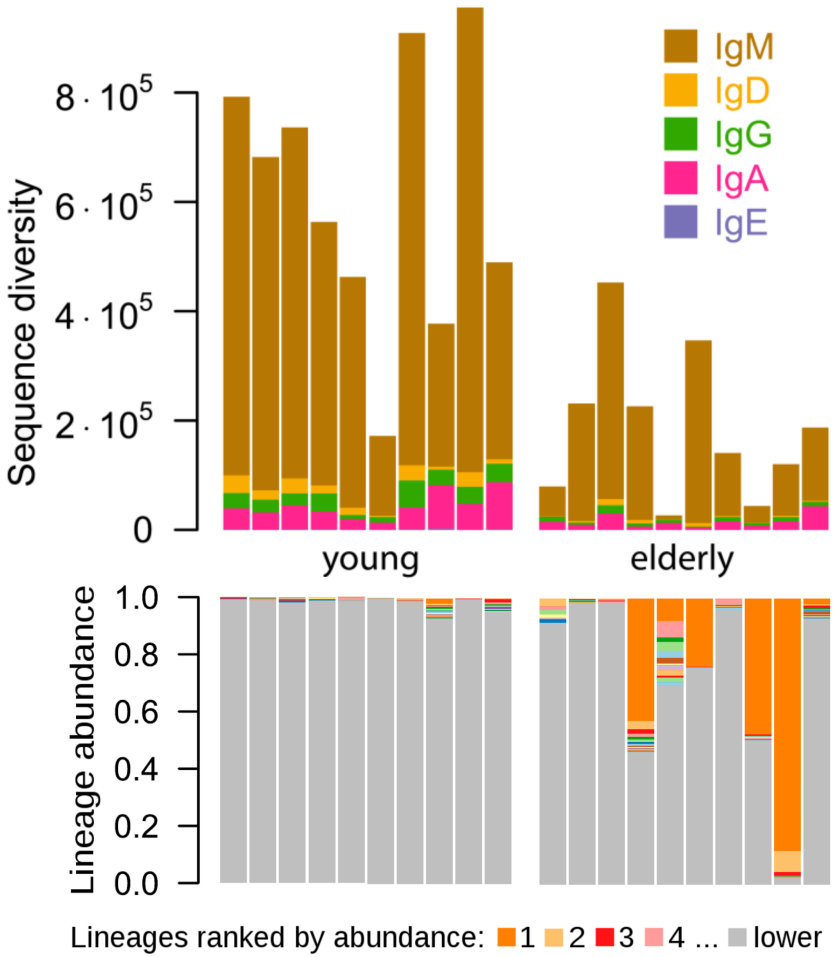

Adapted from de Bourcey et al., PNAS 2017

There's a lot we don't know about adaptive immune ageing

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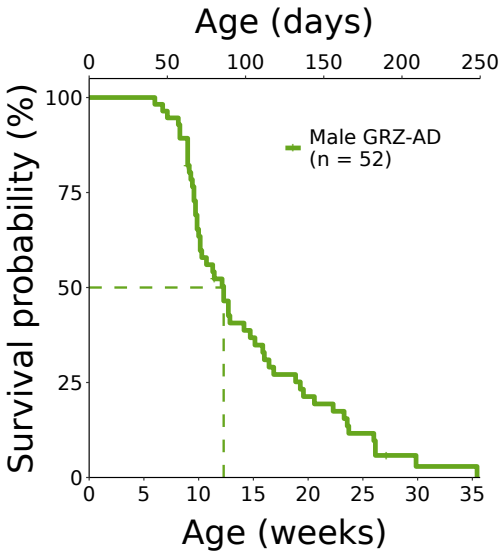
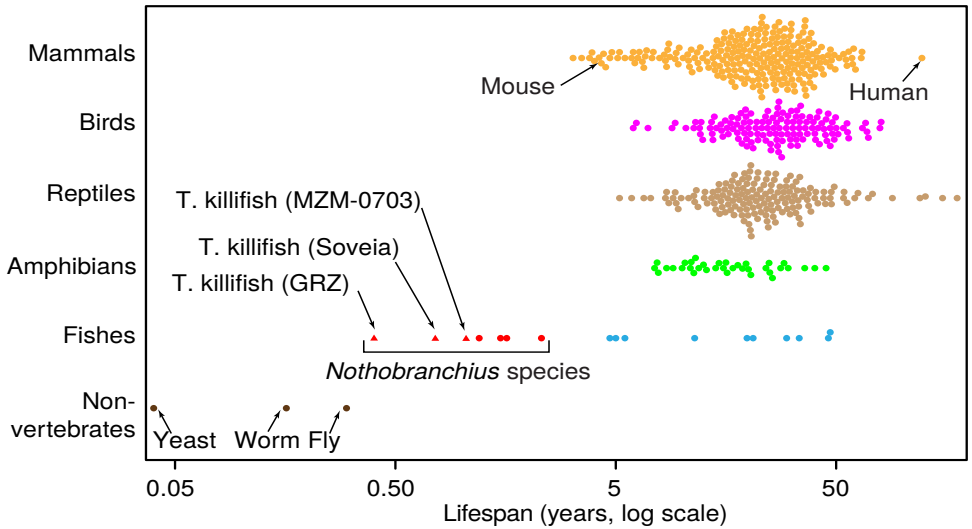
- Limited temporal resolution (typically just two time points)
- Nothing known about effect of anti-ageing interventions

The turquoise killifish as a model for antibody ageing





Valenzano et al., Cell 2015

- Shortest-lived vertebrate bred in captivity (median lifespan 12-16 wk)
- **Short-lived:** tractable for large, repeatable ageing experiments
- **Vertebrate:** possesses a mammal-like adaptive immune system

Understanding adaptive immune ageing in turquoise killifish

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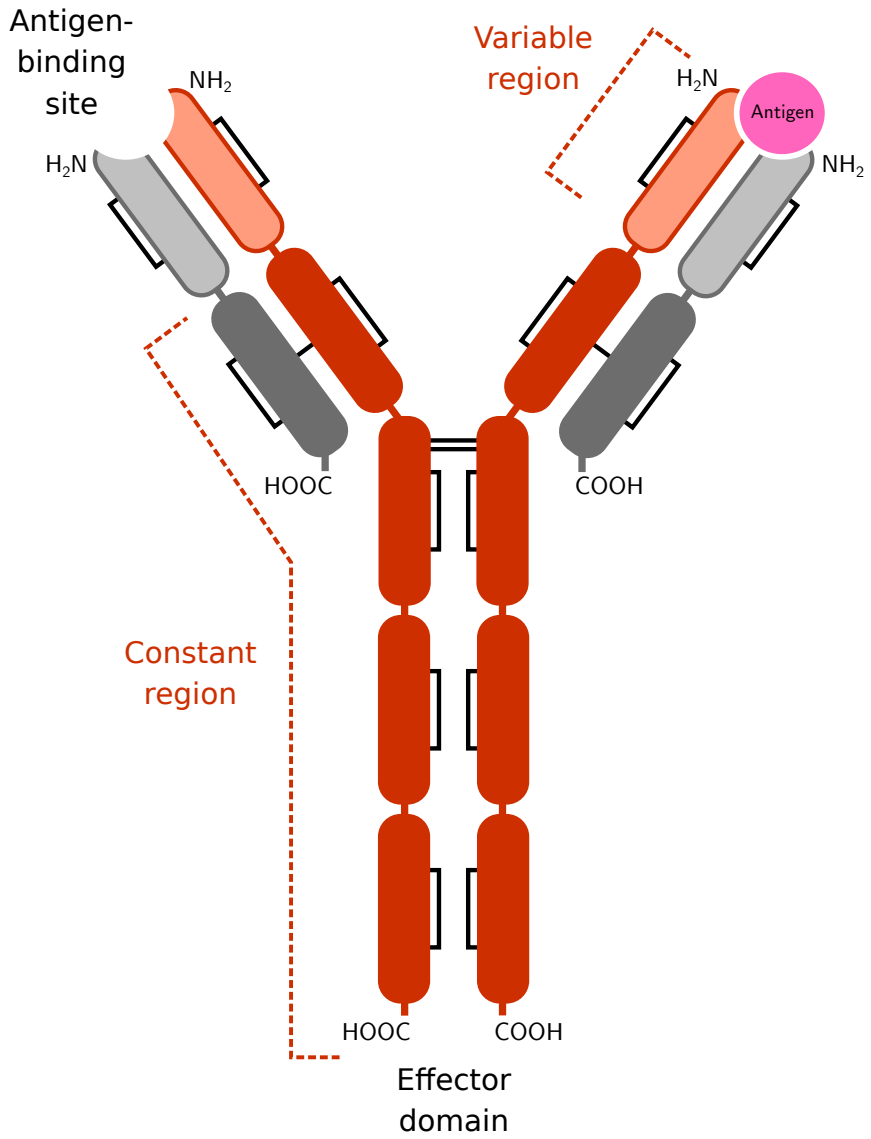

VDJ recombination and primary antibody diversity

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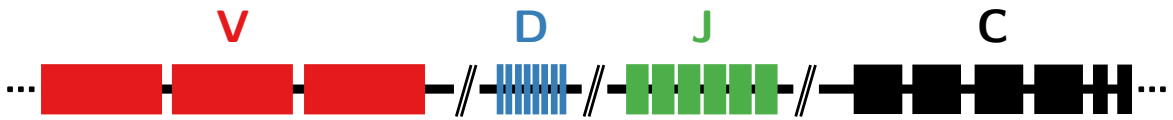
(i) Native state



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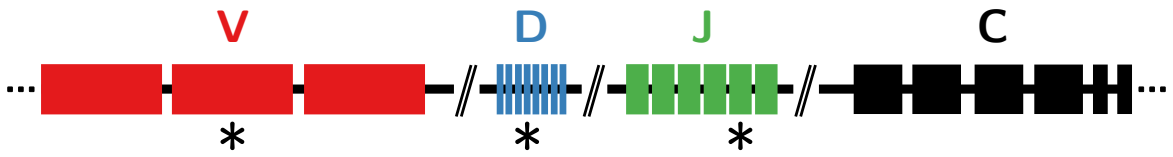

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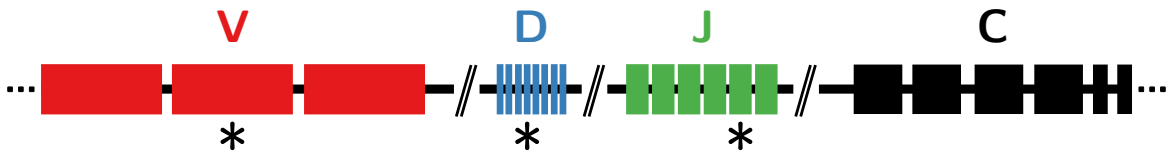

(ii) VDJ Recombination on the chromosome

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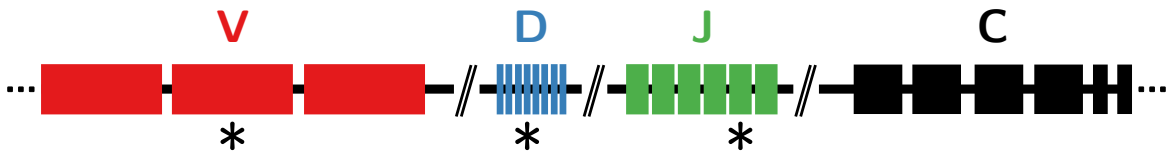

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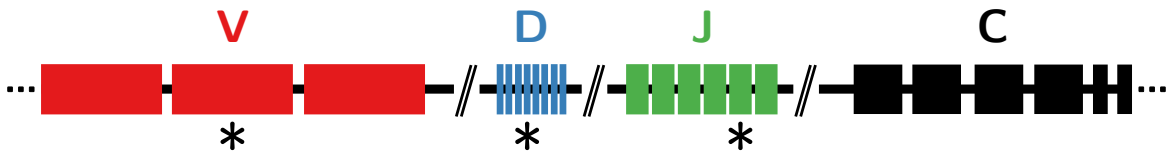
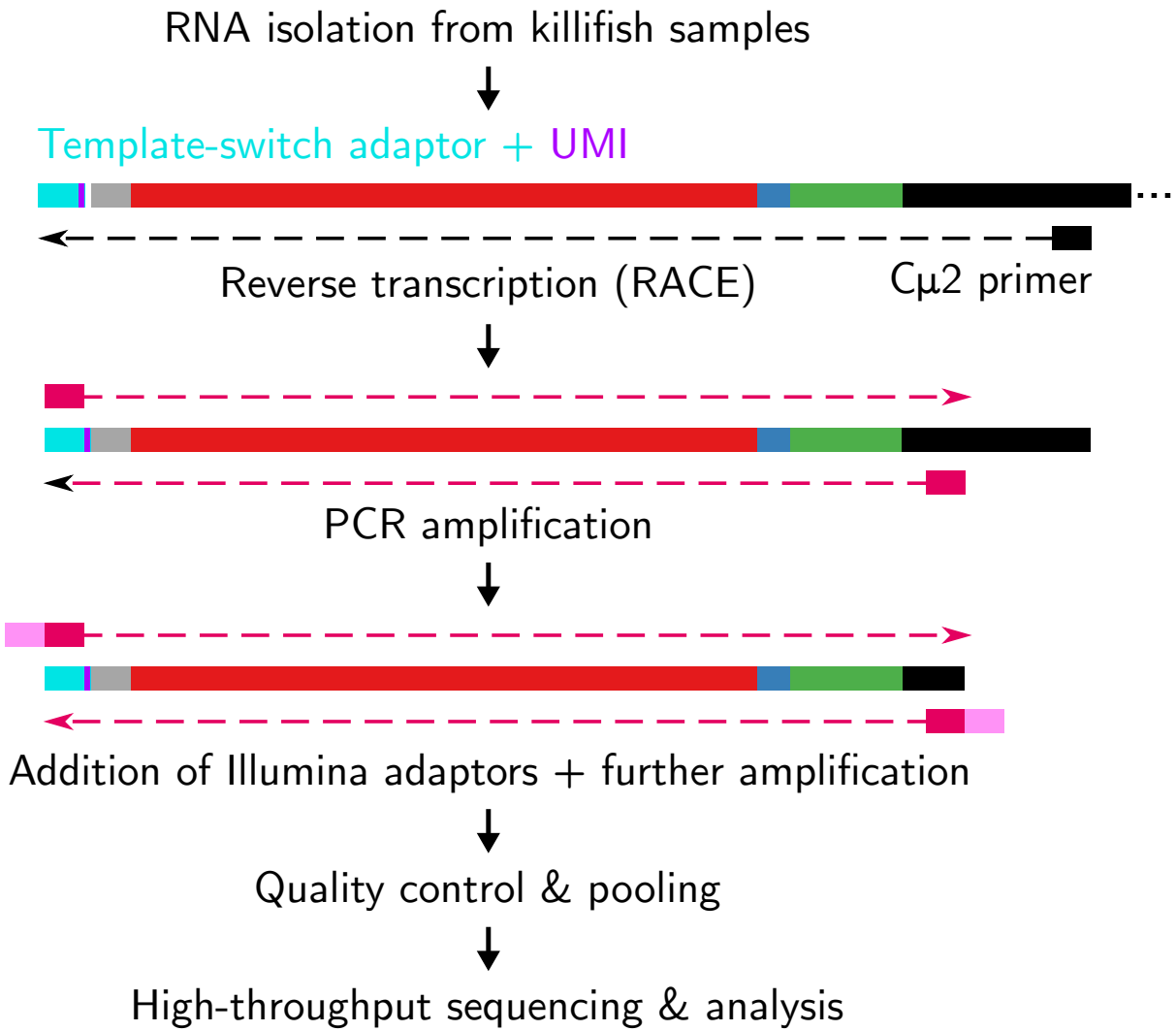


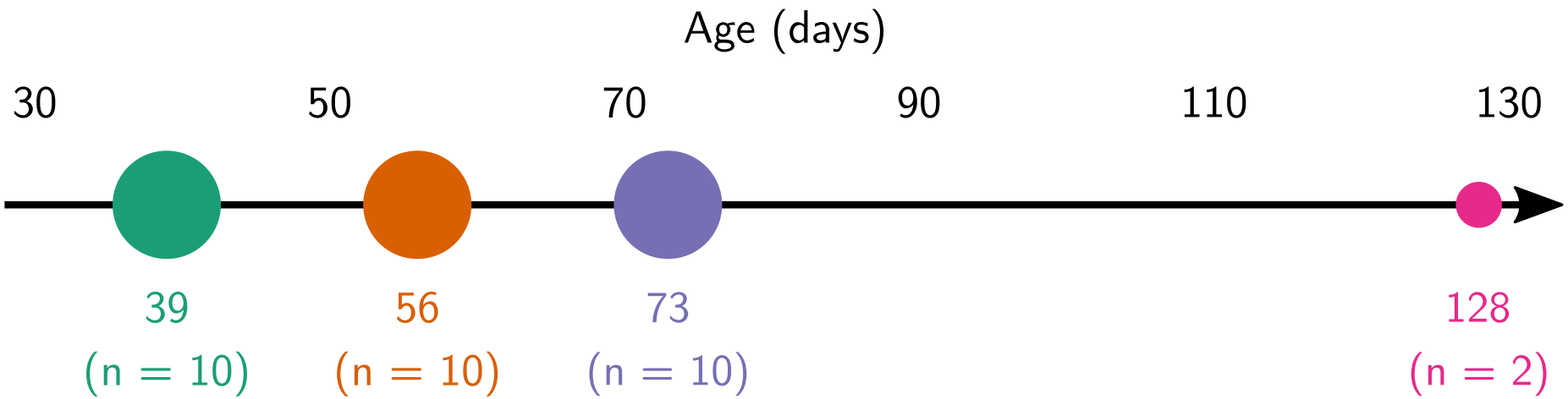
(ii) VDJ Recombination on the chromosome

(iii) Transcription and splicing

Immunoglobulin sequencing in the turquoise killifish



Sample design – killifish ageing study



Clonal antibody diversity

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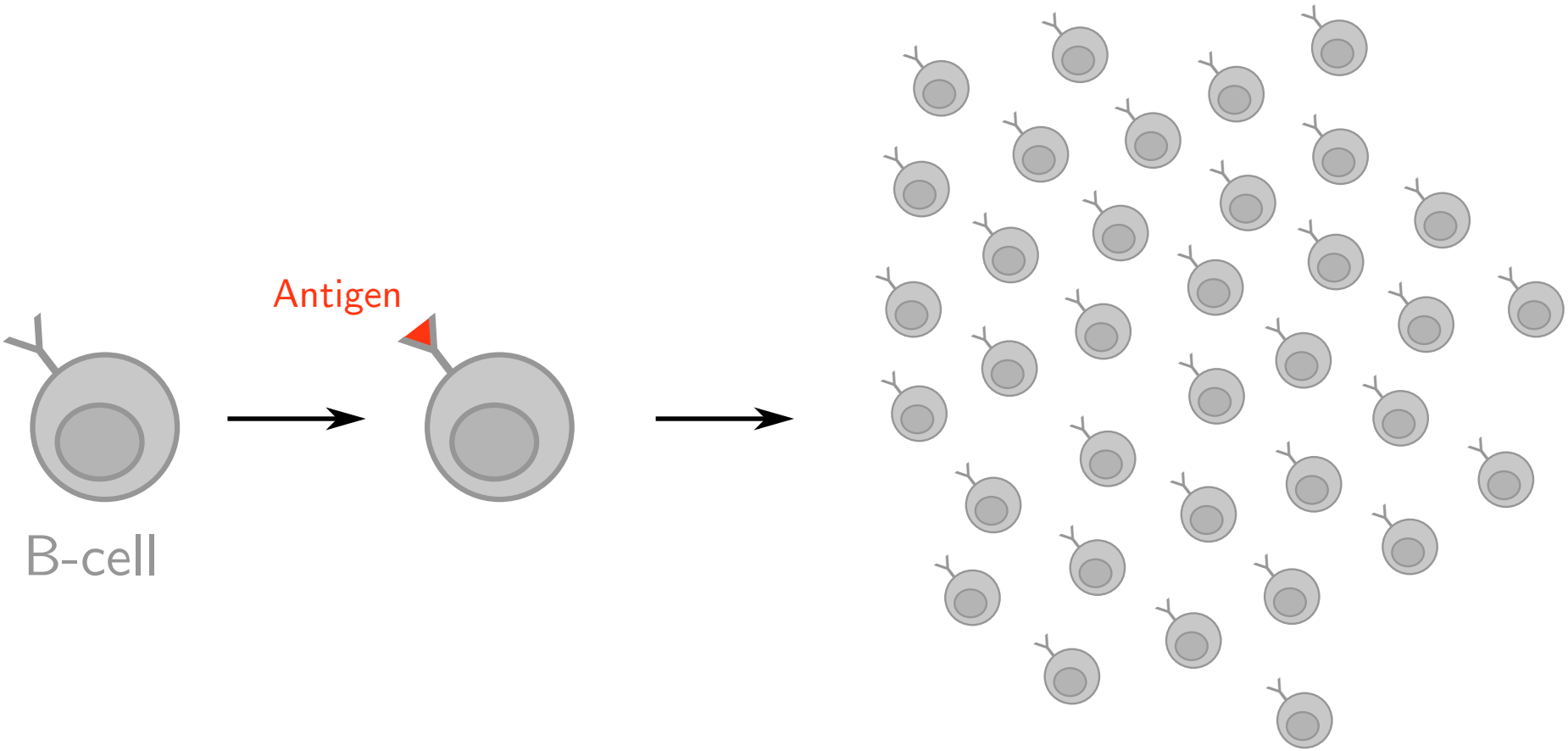

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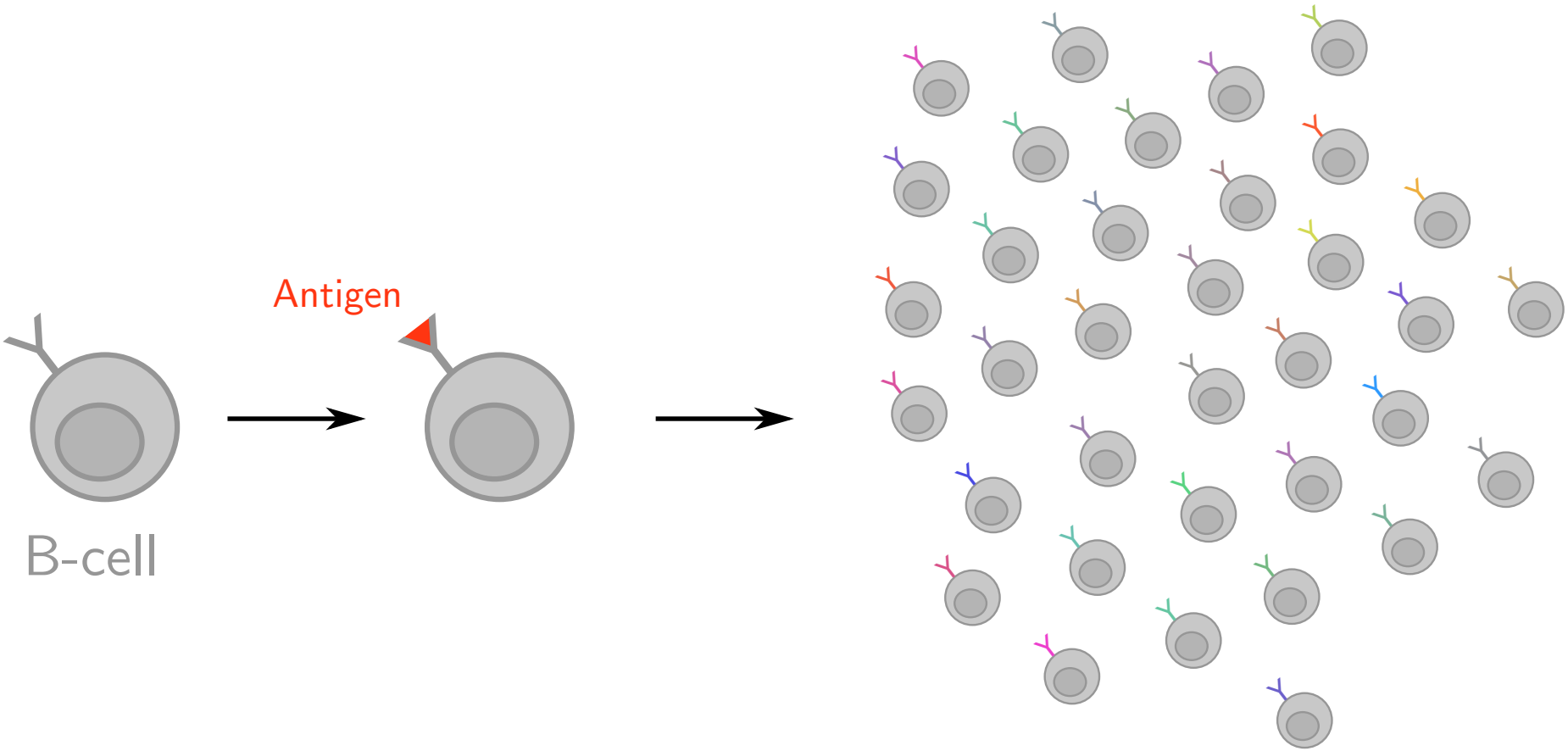

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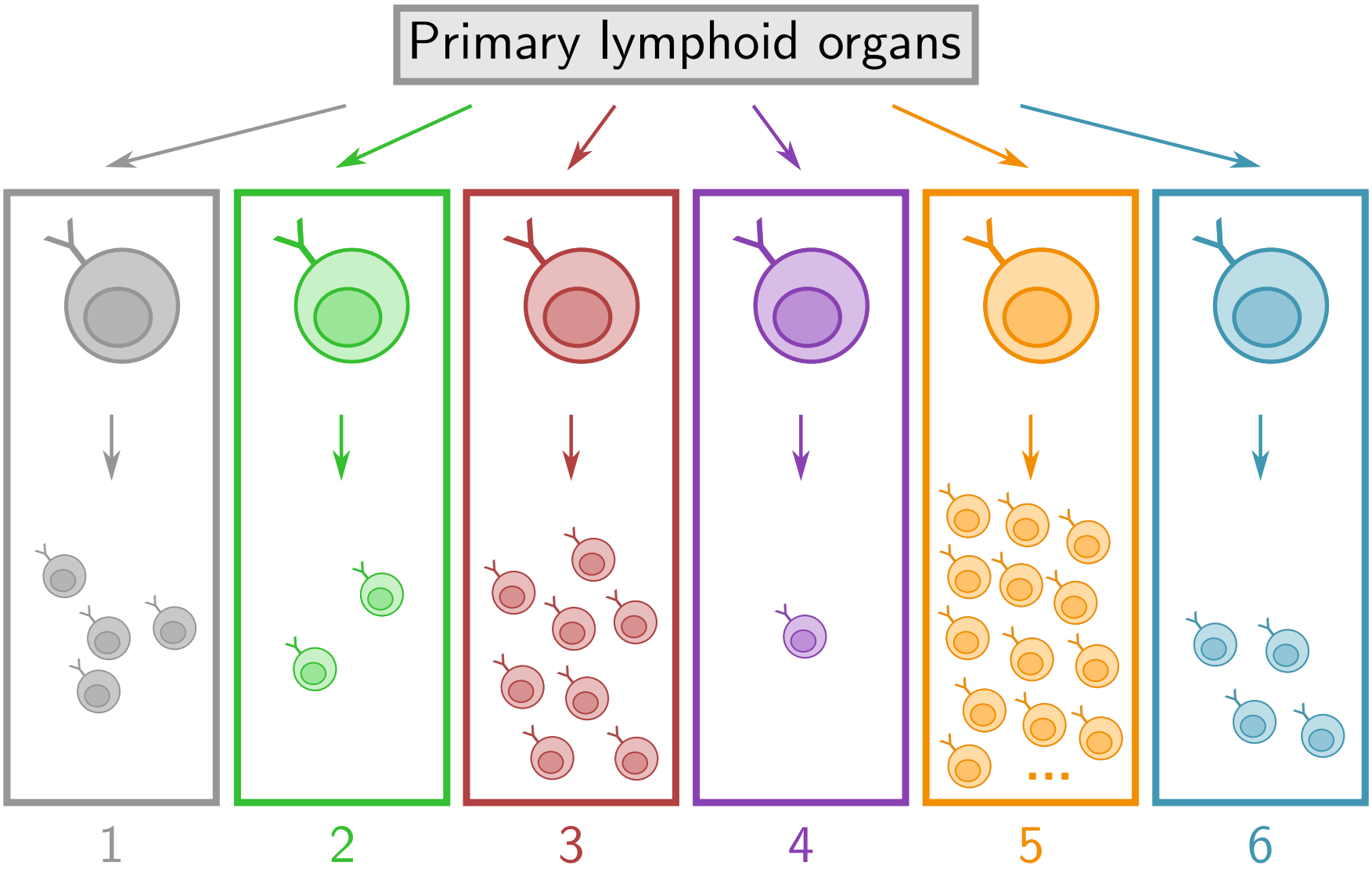
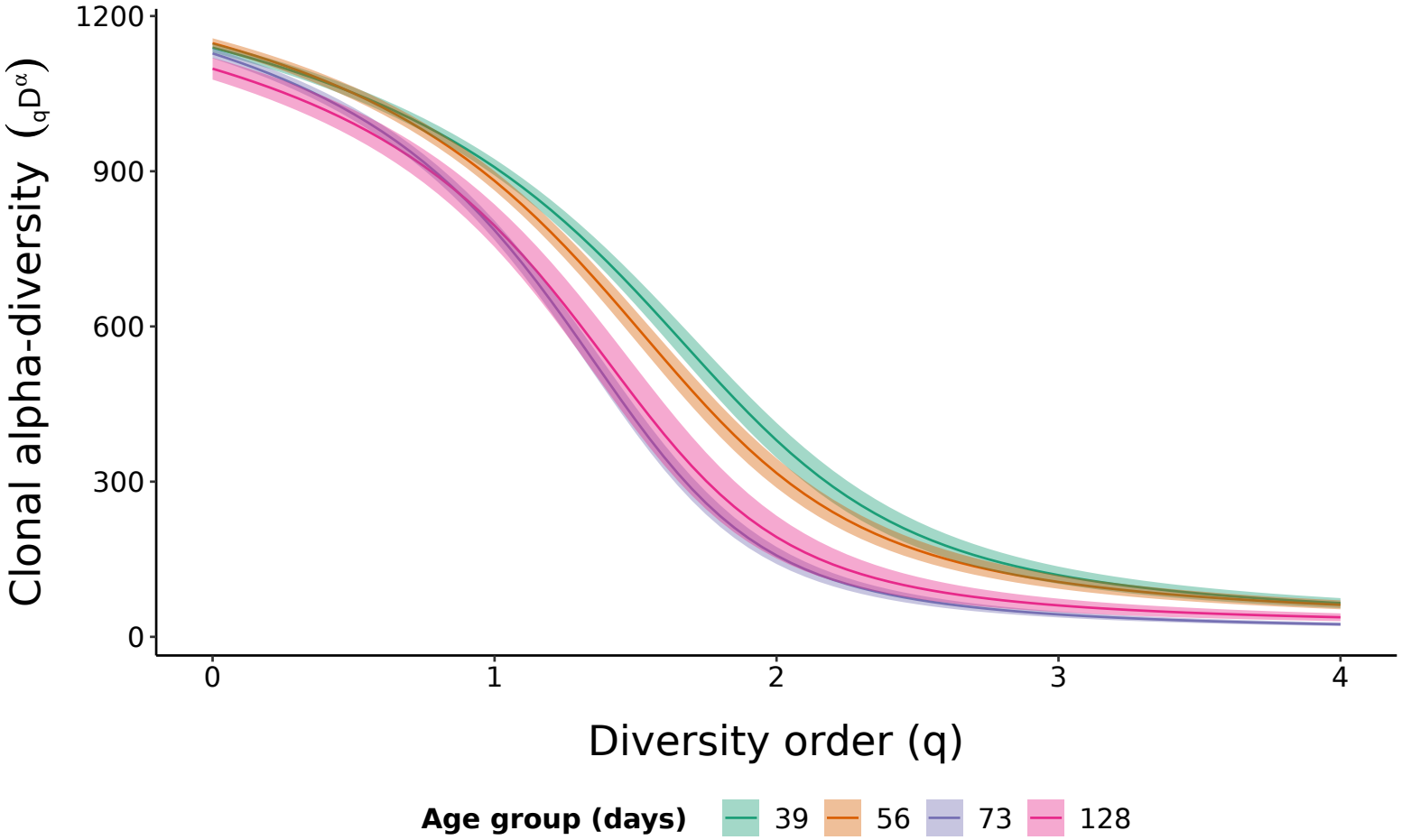
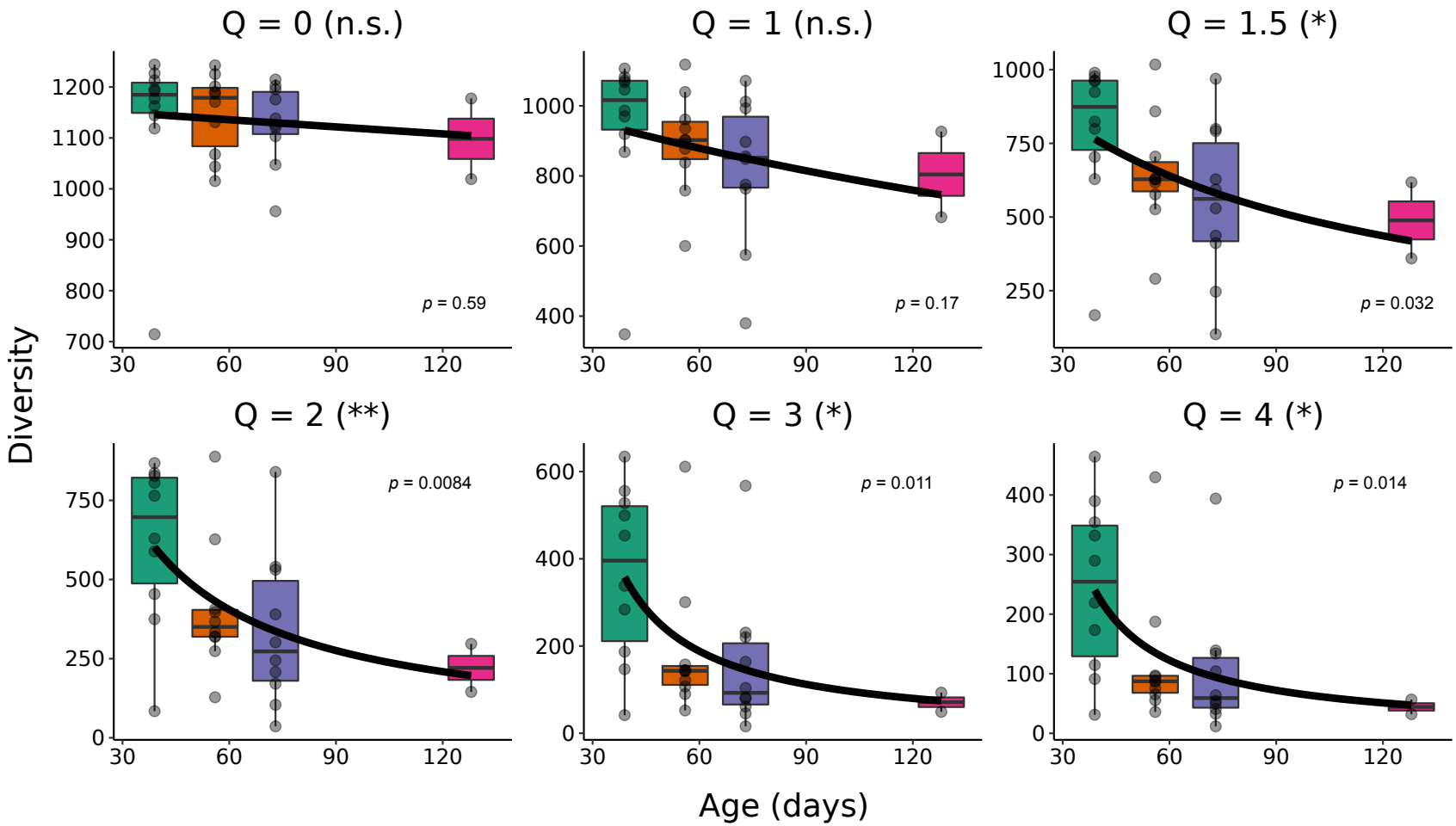


Clonal alpha-diversity in the killifish antibody repertoire

Clonal alpha-diversity in the killifish antibody repertoire declines with age



Clonal alpha-diversity in the killifish antibody repertoire declines with age at high diversity orders



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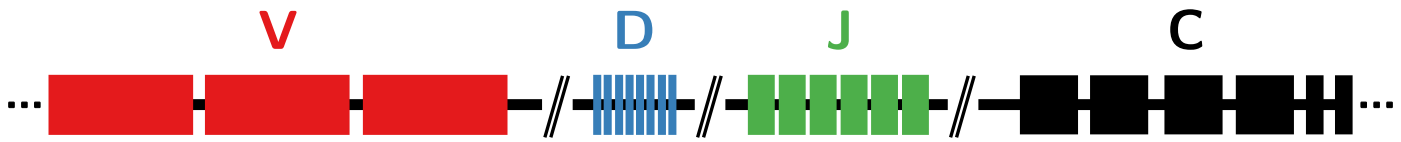

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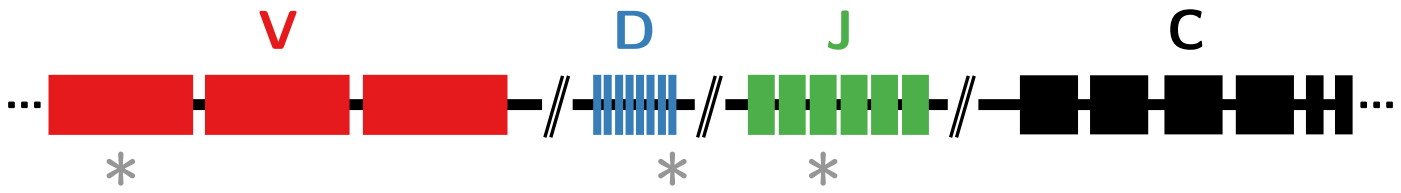
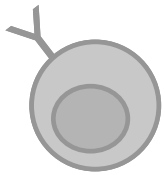


V2/J5



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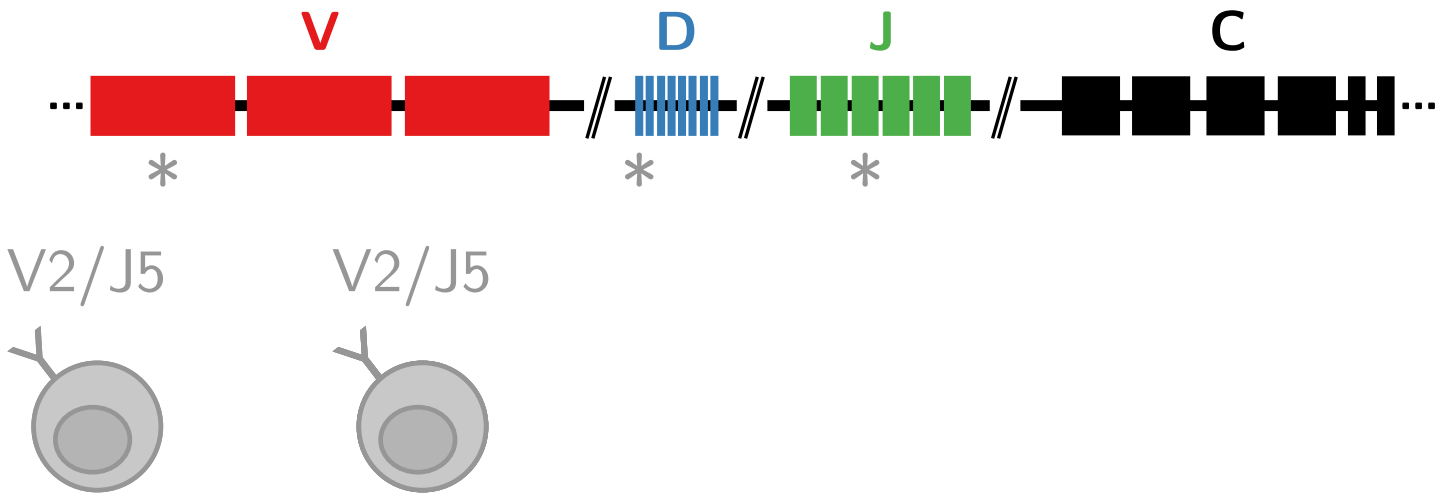

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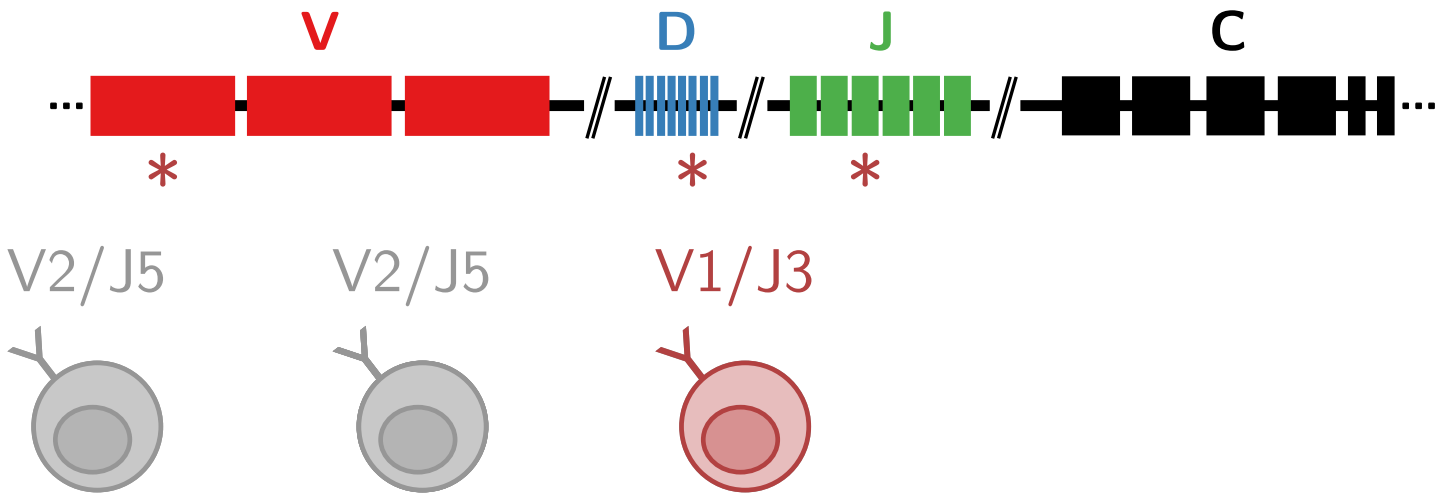

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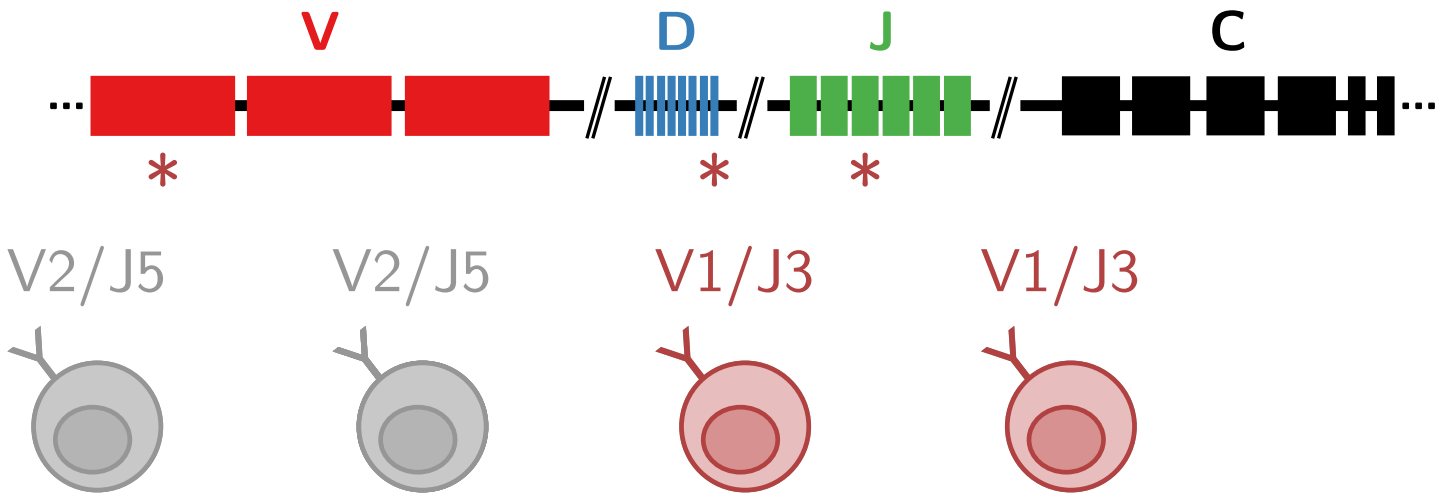

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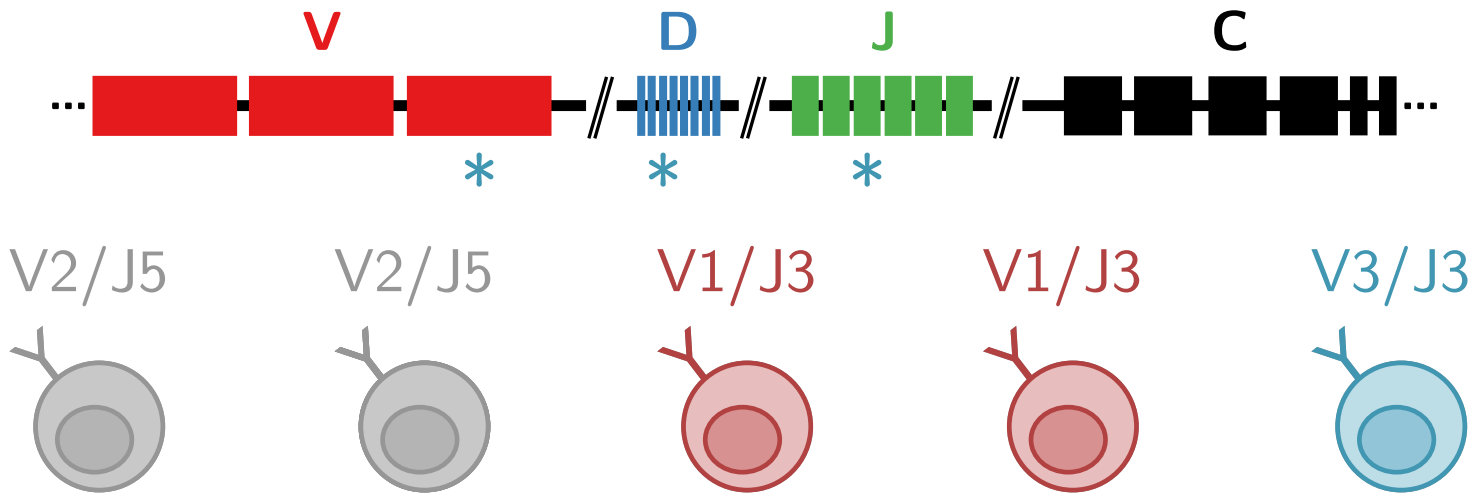

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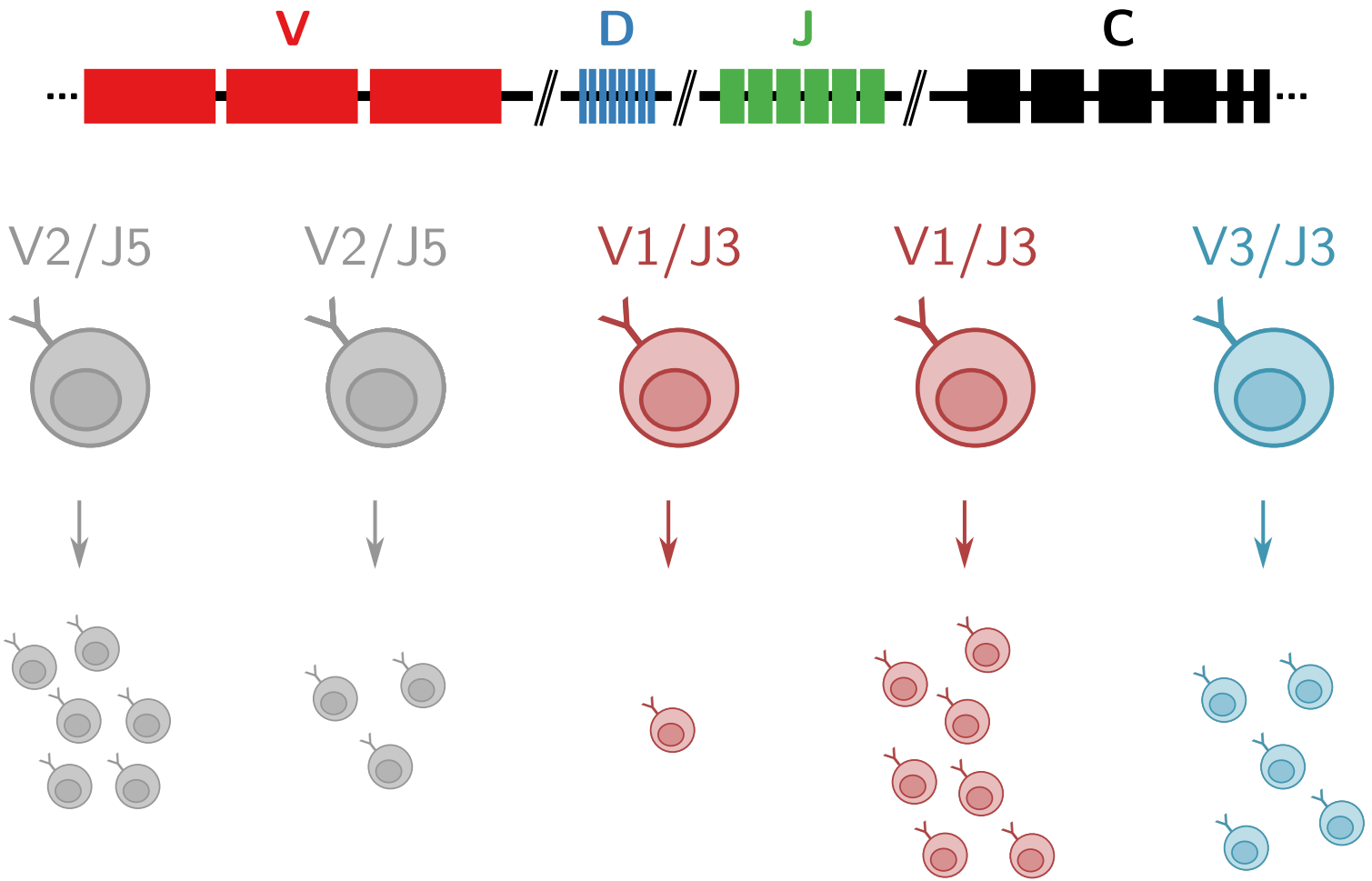

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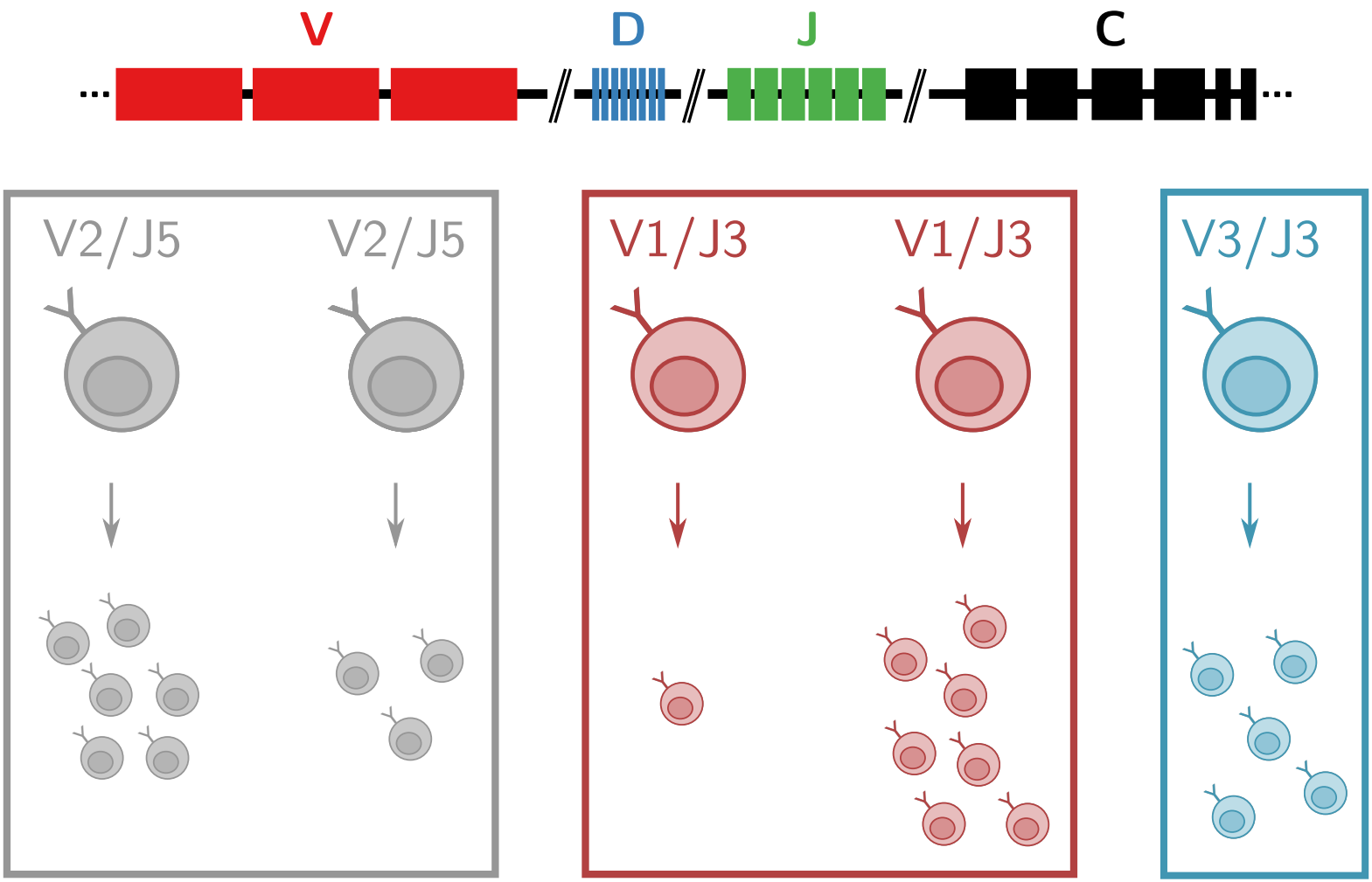
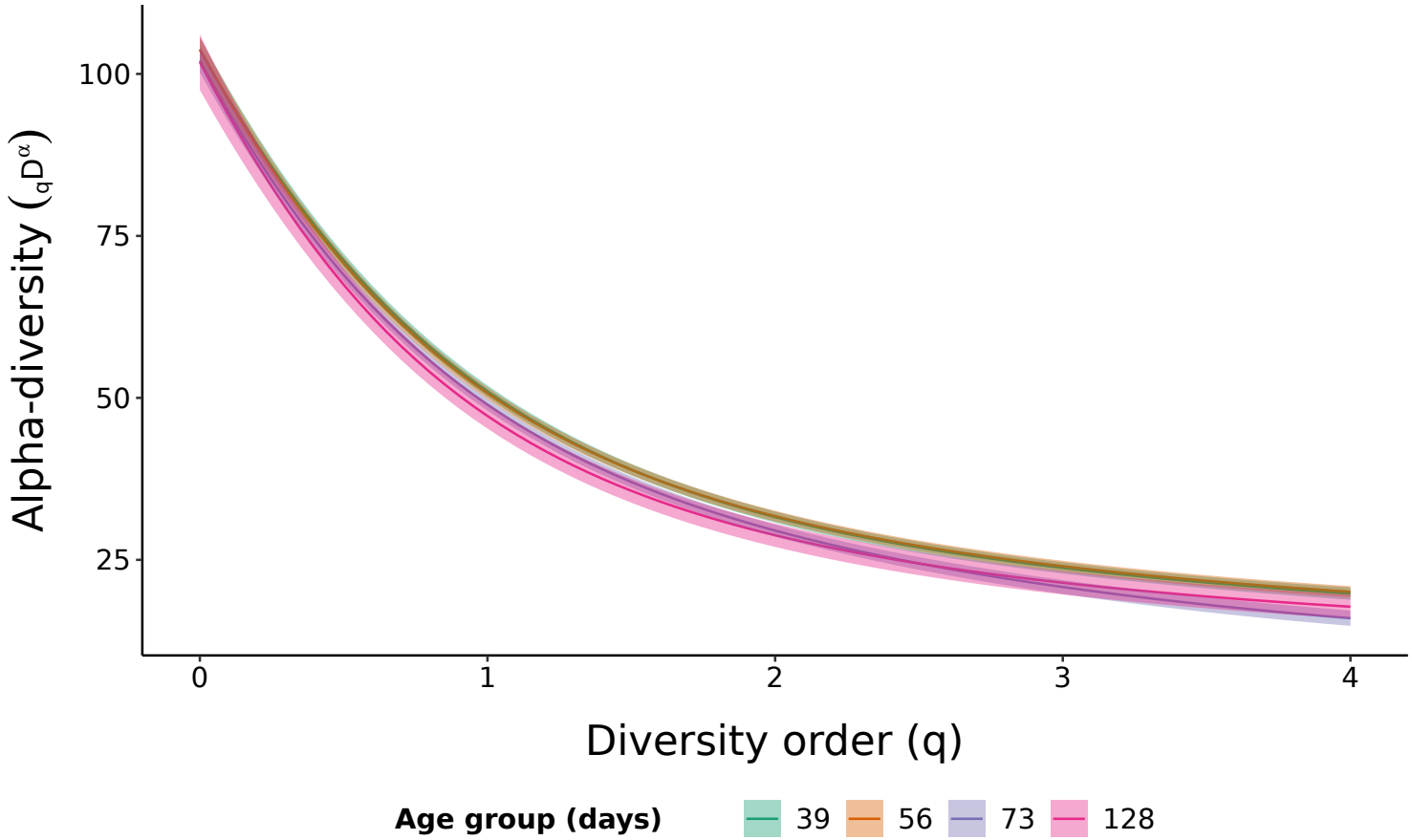


VJ alpha-diversity in the killifish antibody repertoire

VJ alpha-diversity in the killifish antibody repertoire **does not decline** with age



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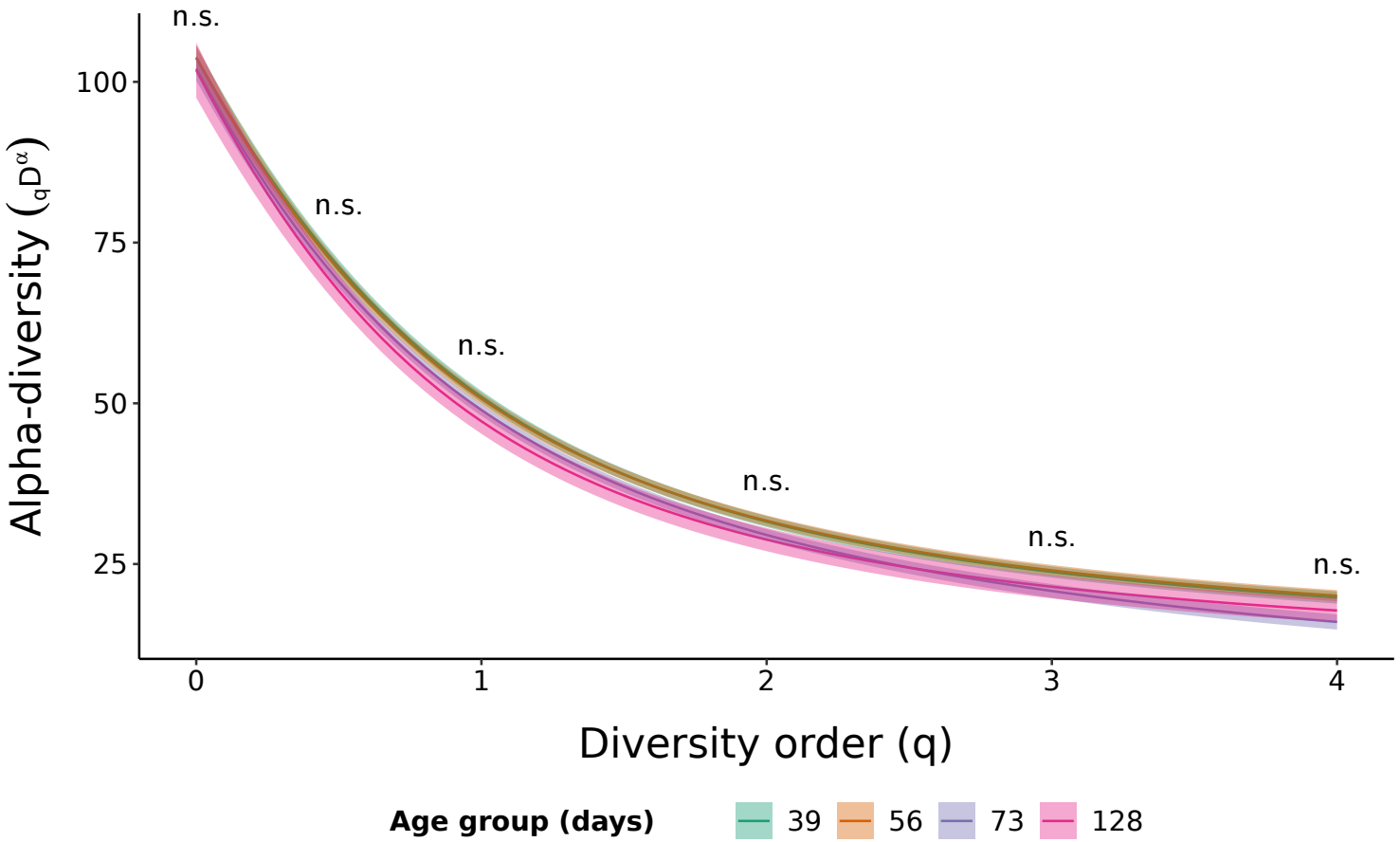

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- Why the difference?

VJ alpha-diversity of **large clones**

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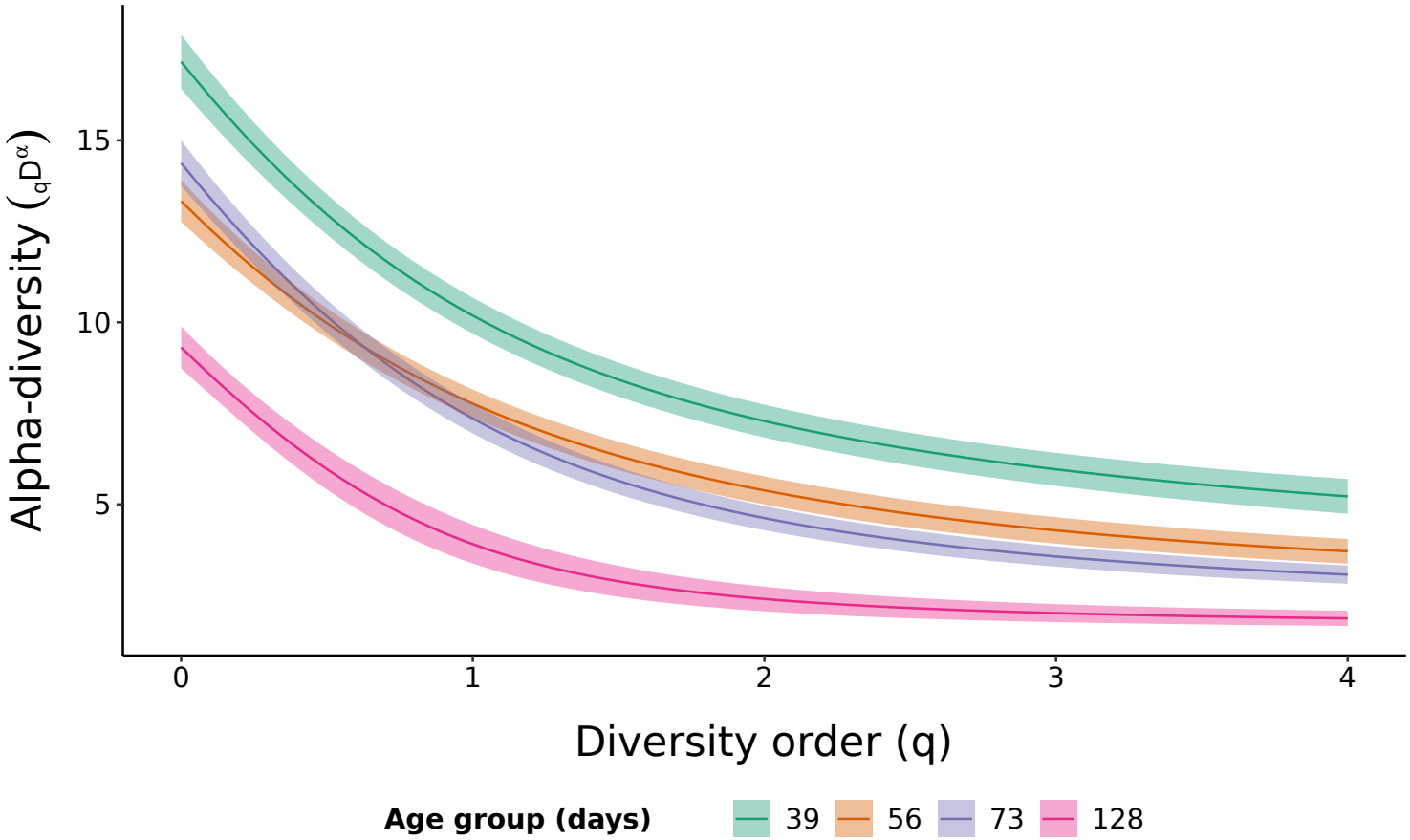

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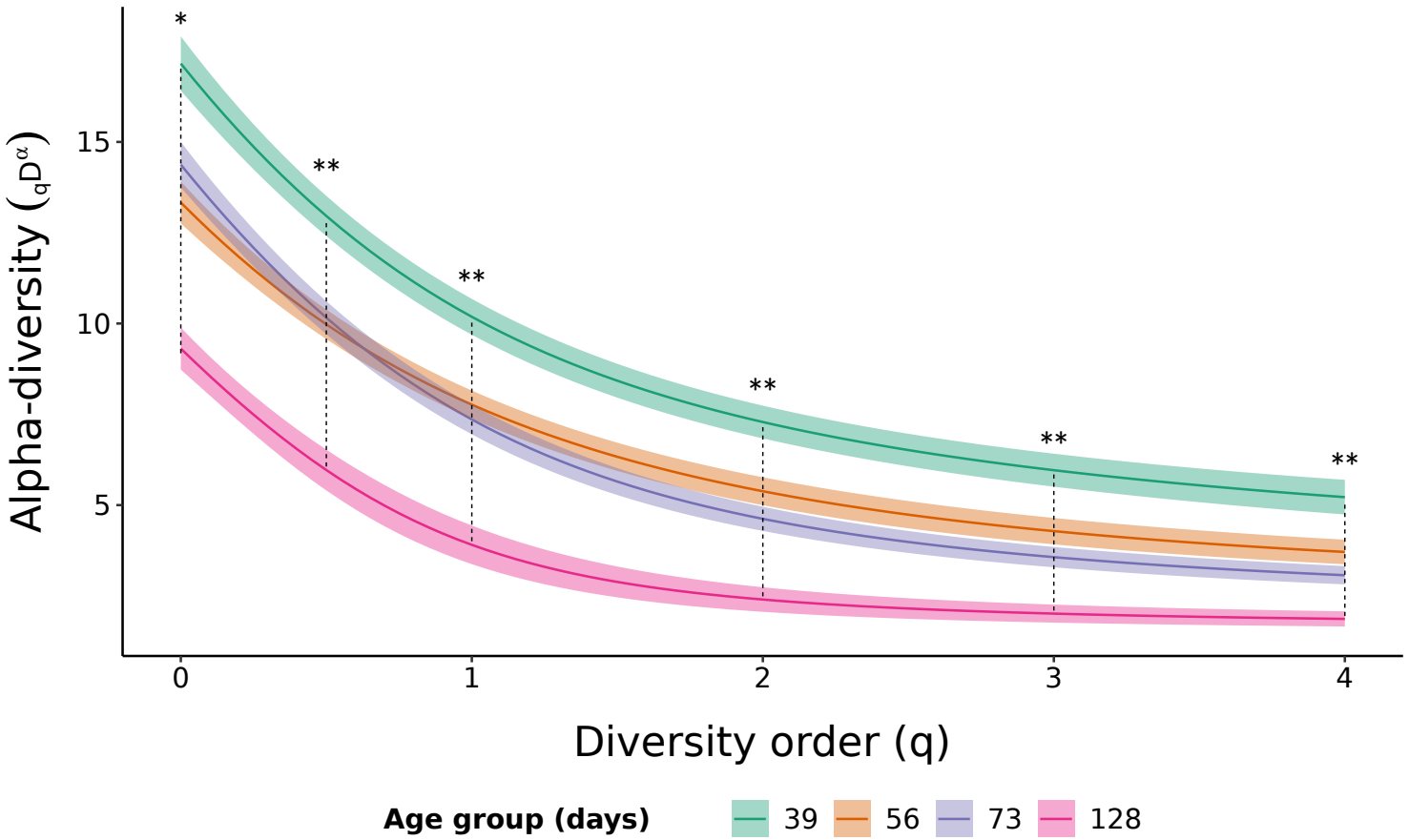
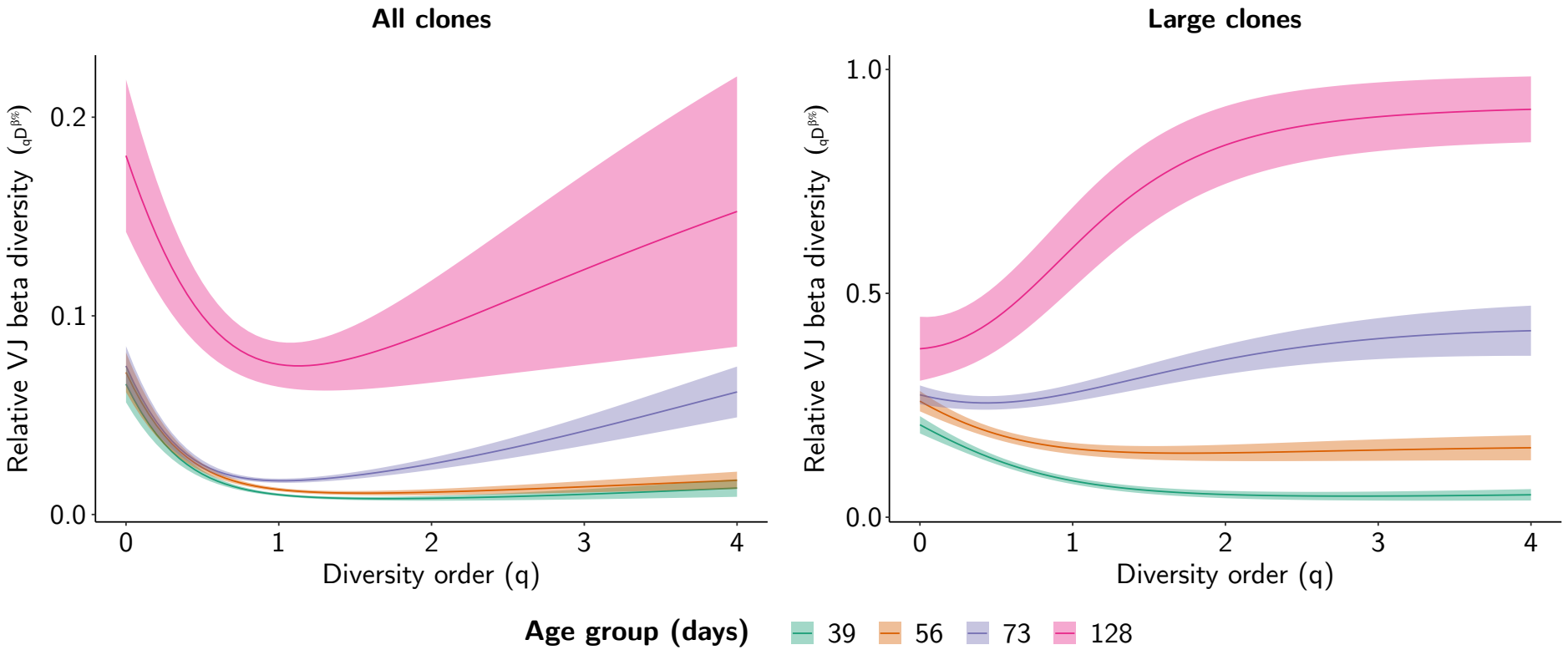


Killifish VJ repertoires become **more dissimilar** with age



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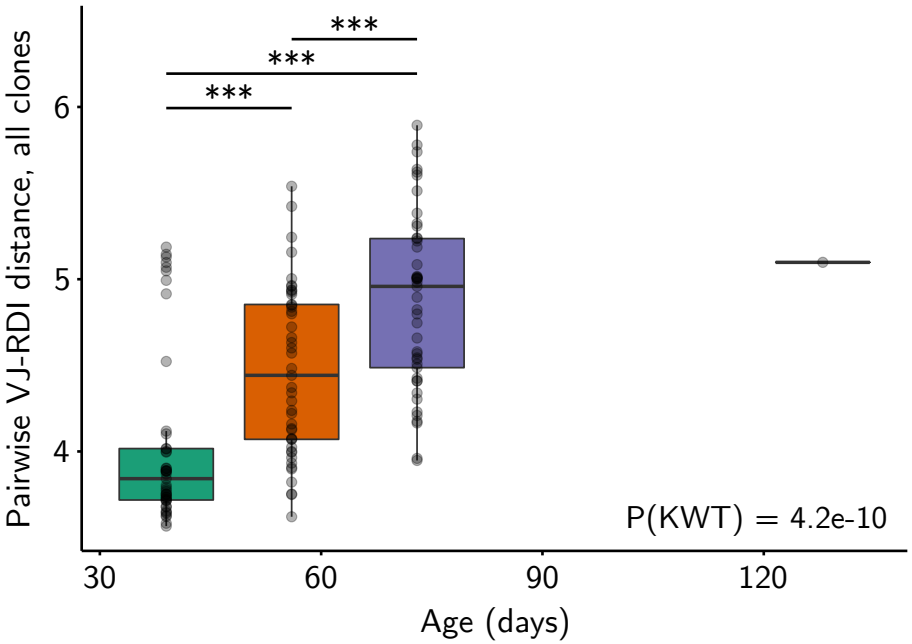

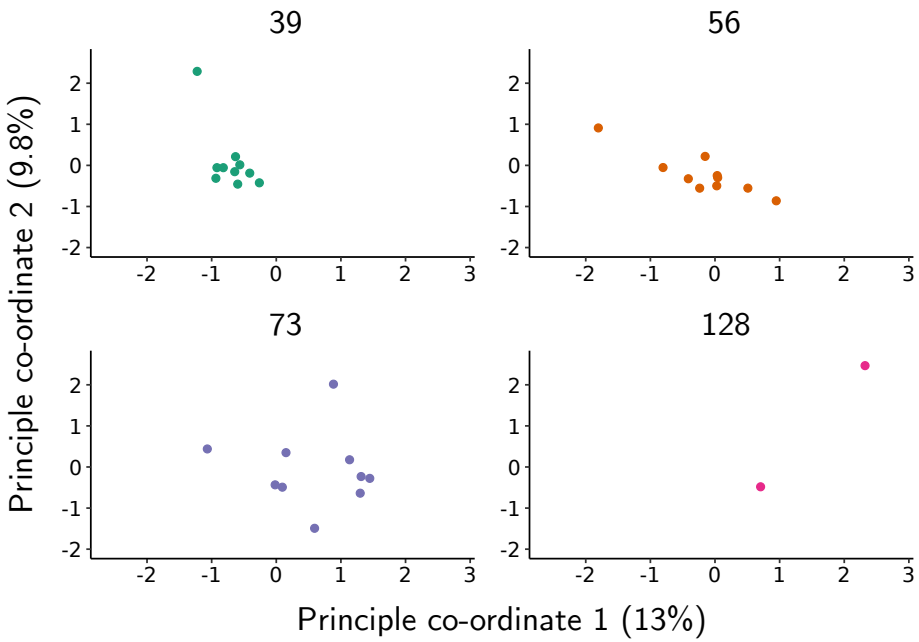

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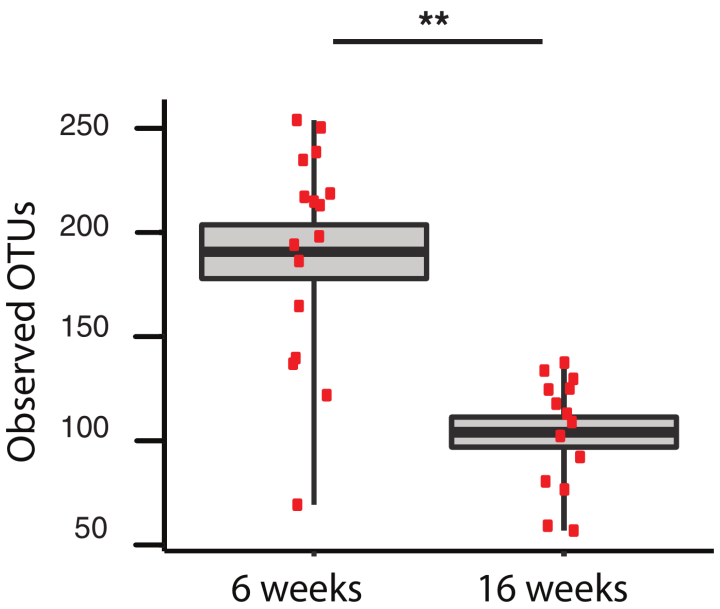
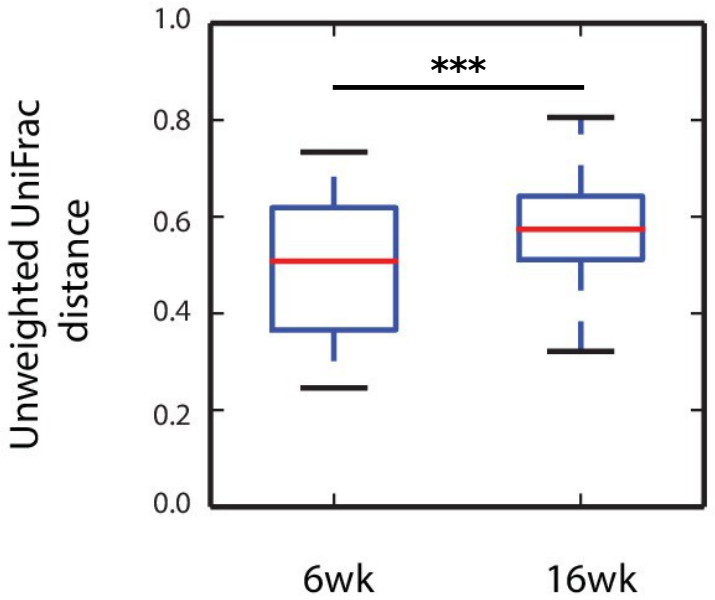
- V/J alpha diversity shows no change with age if all clones are included but a large decline in large clones
- Between-individual variation (beta diversity) in killifish repertoires increases with age

Killifish gut microbiota also show decreasing alpha- and increasing beta-diversity with age

Alpha diversity

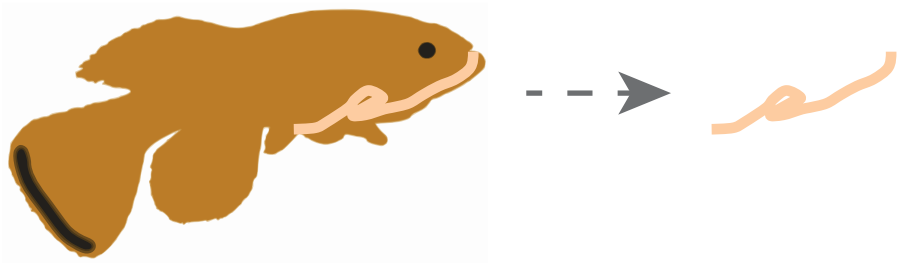


Beta diversity



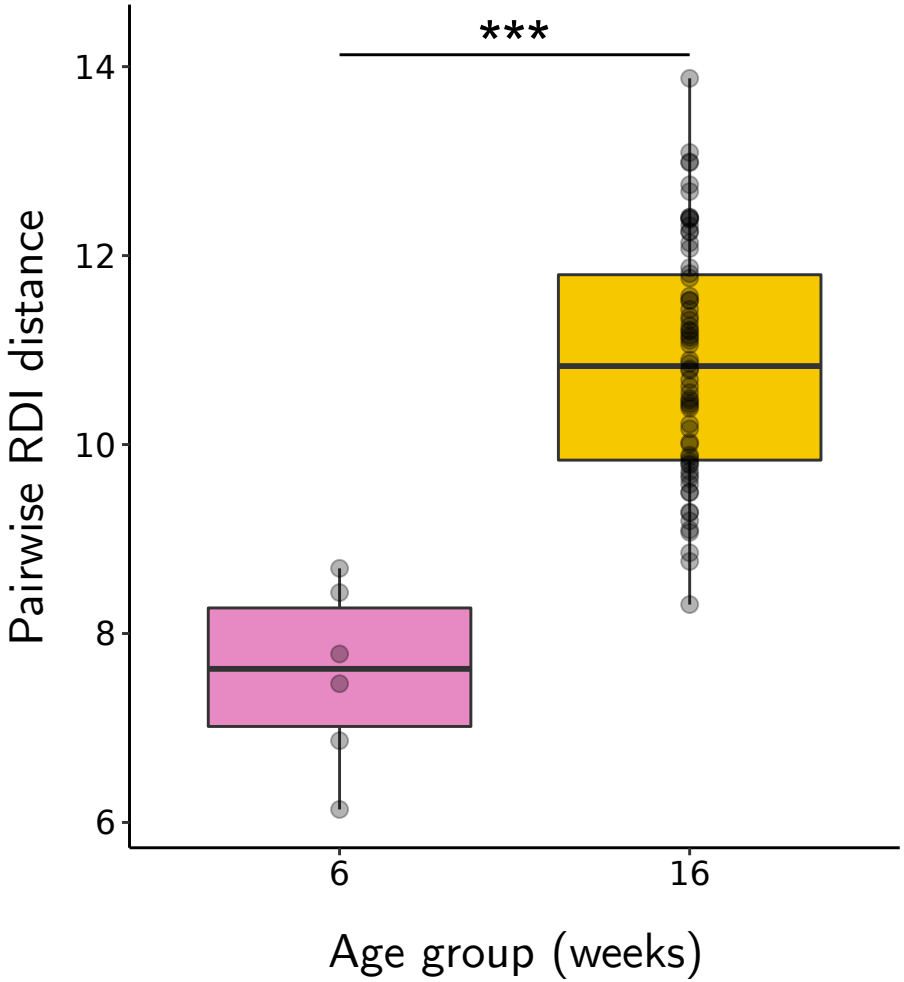
Smith et al., eLife 2017

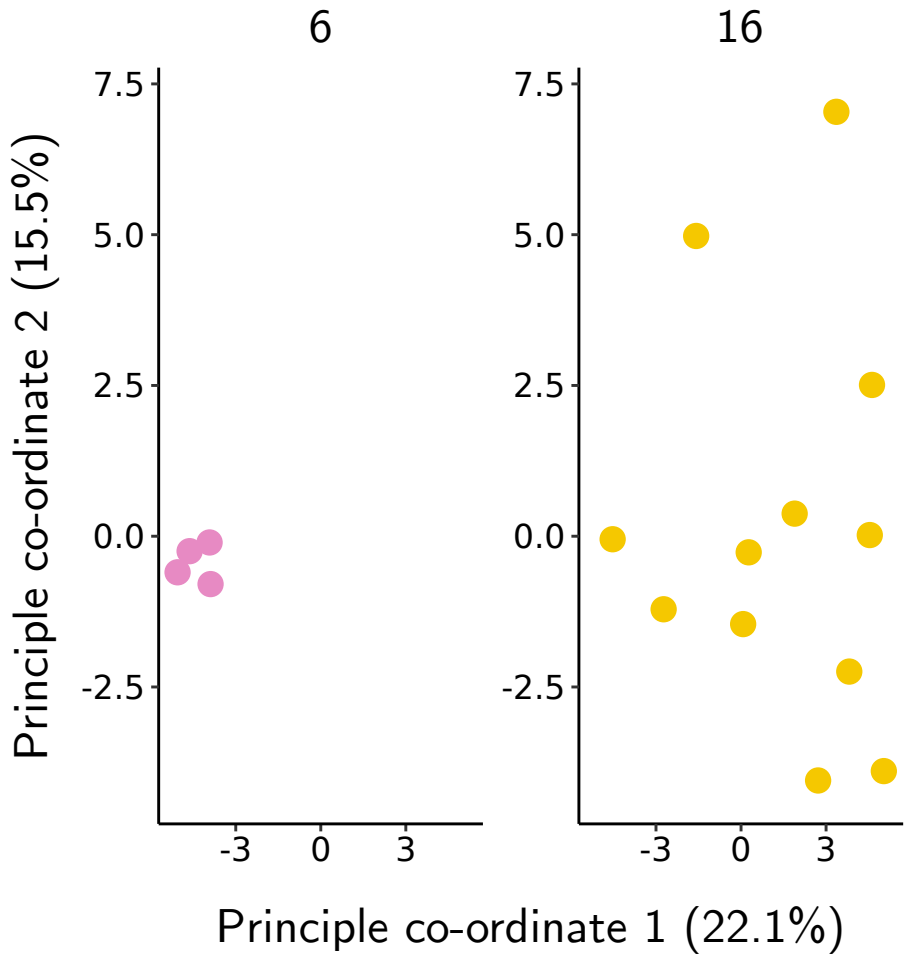
Sample design – gut repertoire study



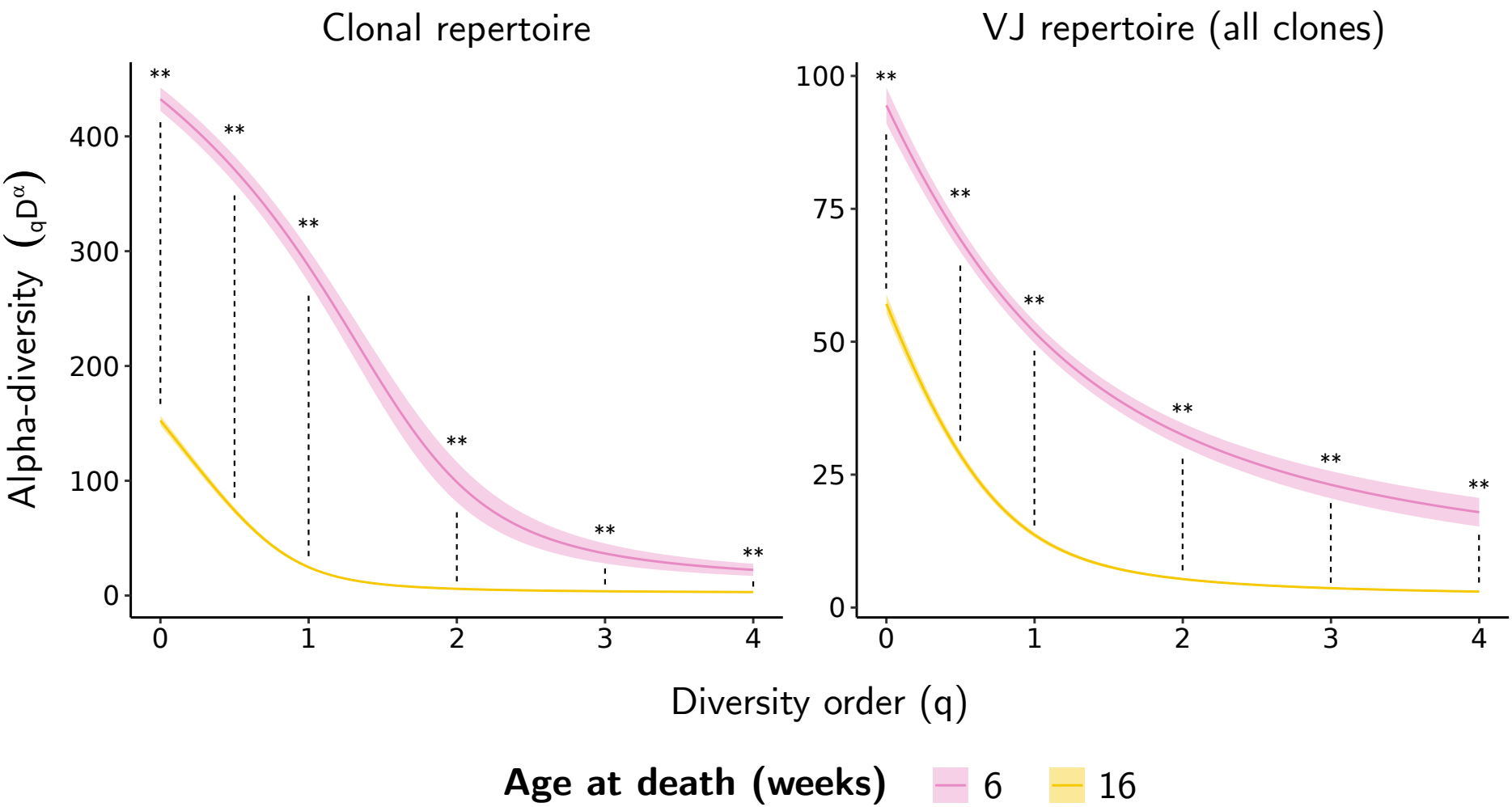
Samples collected for Smith et al., eLife 2017

Killifish gut repertoires become much more dissimilar with age





Gut repertoire alpha diversity declines dramatically with age in turquoise killifish



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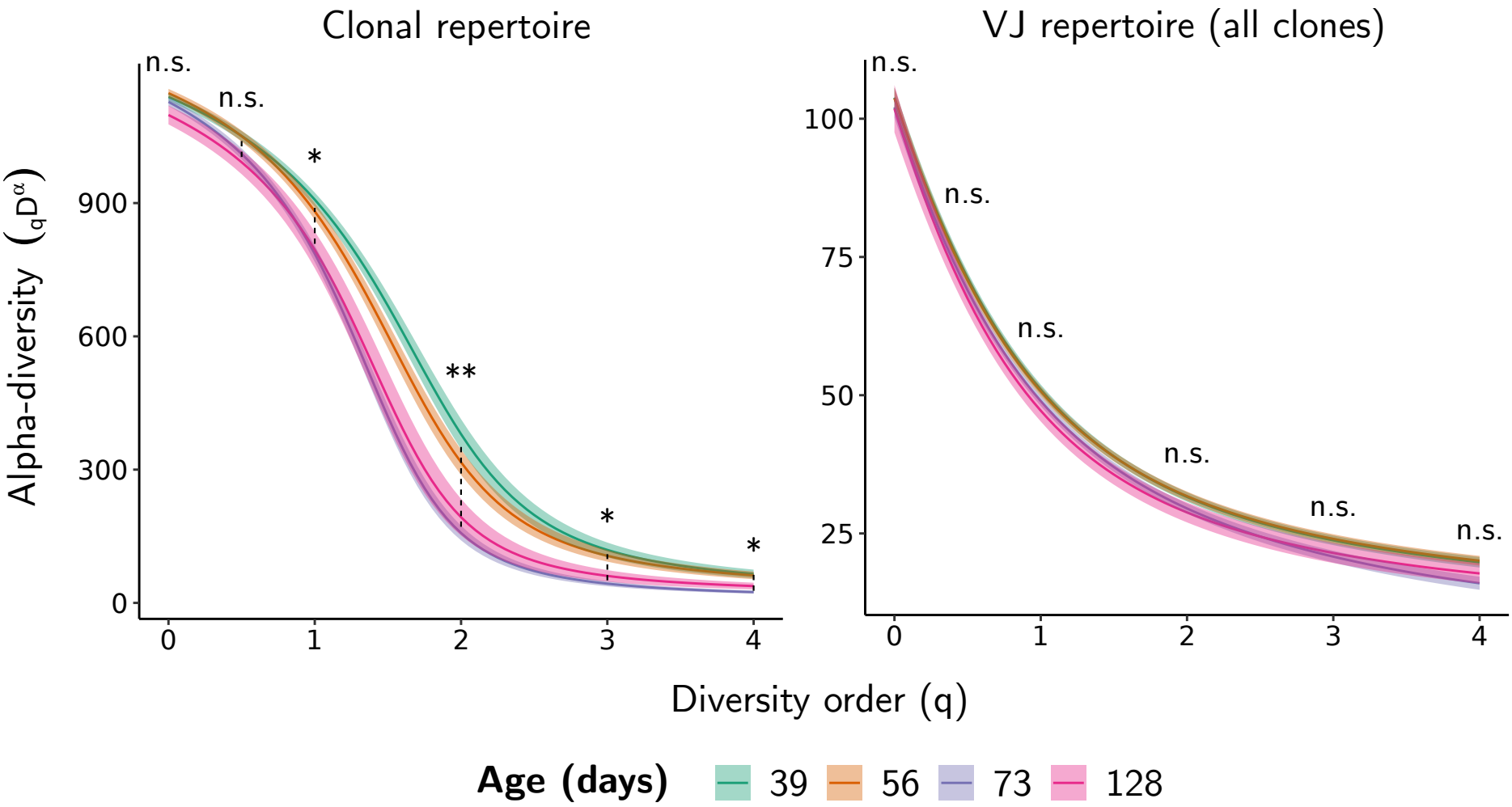

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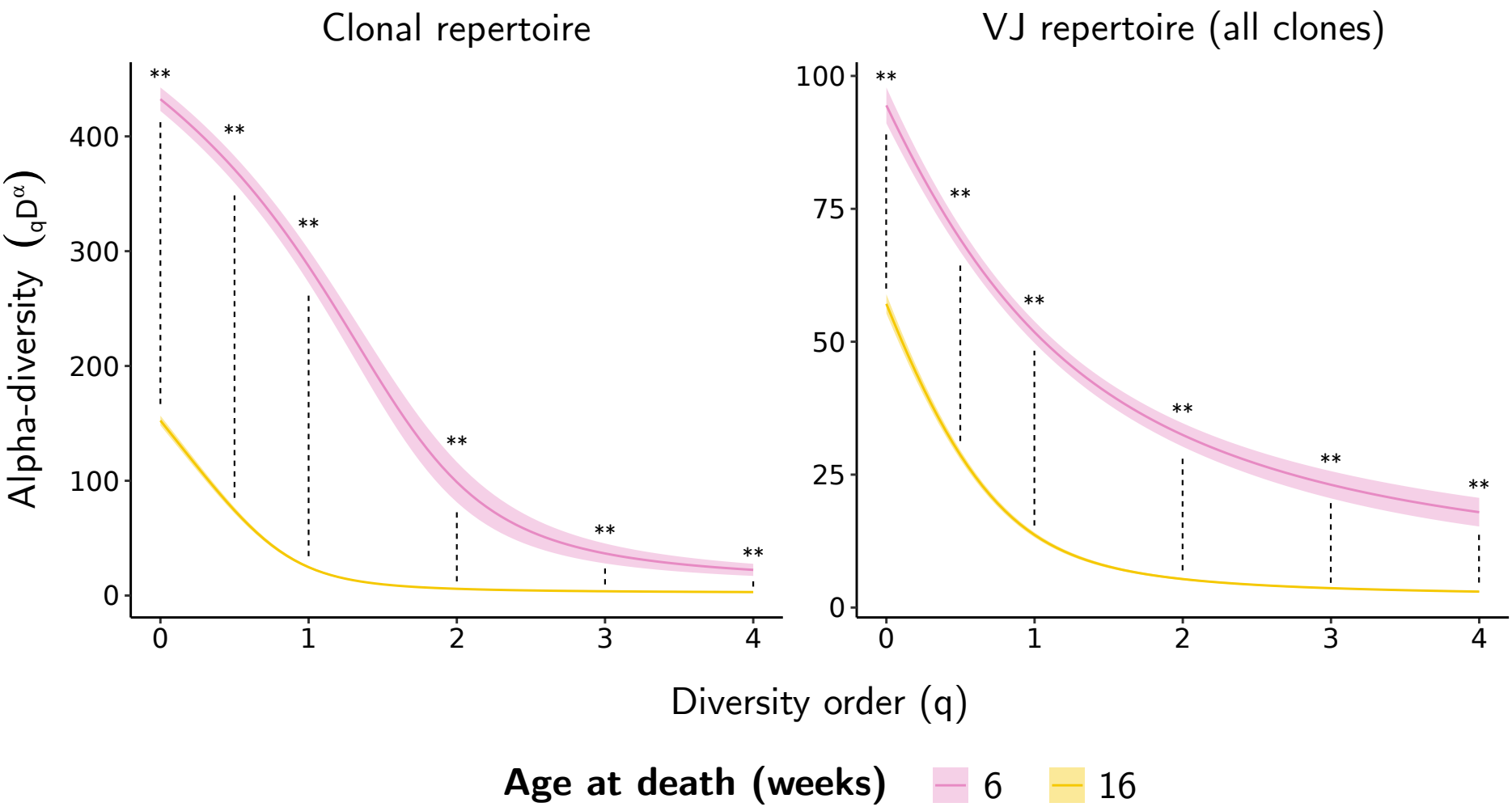

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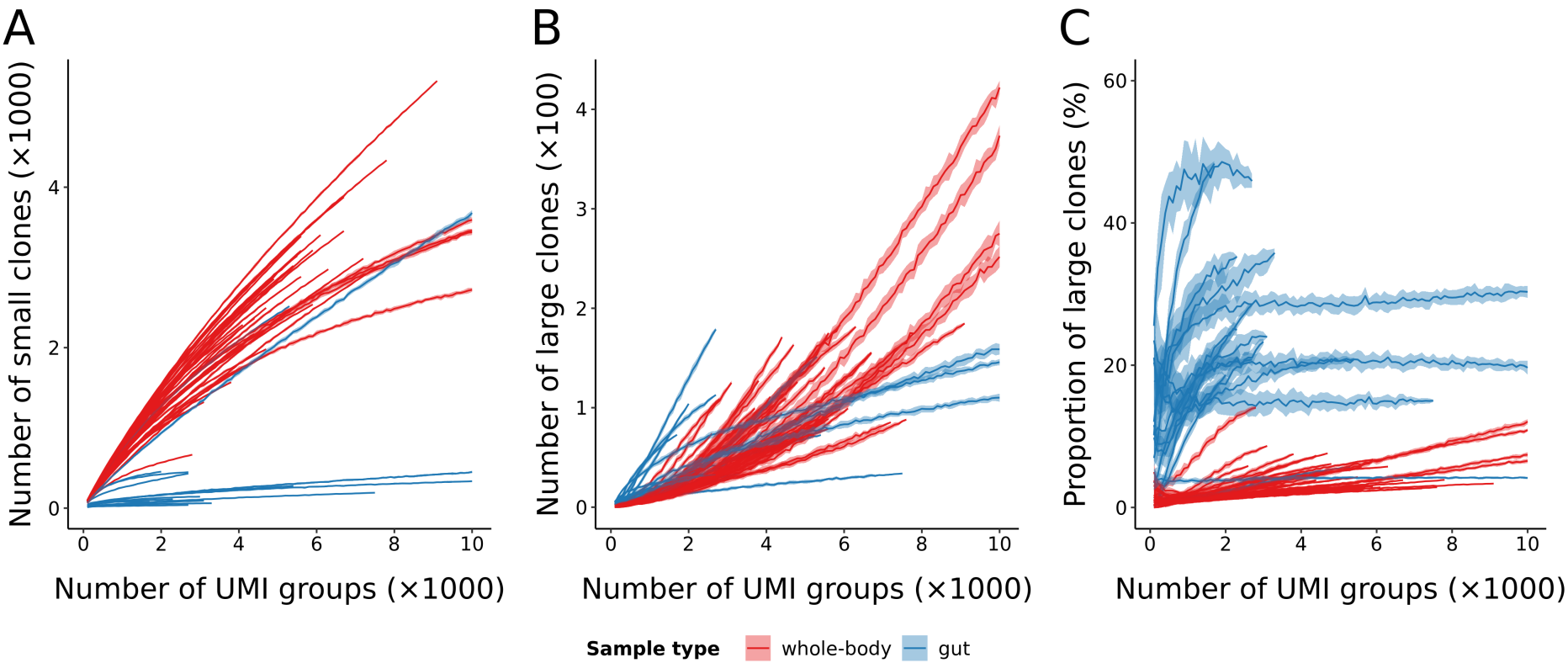
1. Difference in **environment**?
   - Intense antigen exposure from gut microbiota
   - Greater antigen exposure → more clonal expansion, less diversity
2. Difference in **clonal composition**?
   - Whole body includes primary lymphoid organs, intestine does not
   - → More small naïve clones in whole-body samples than gut samples
   - Larger clones more age-sensitive → stronger age effect in gut samples

Killifish gut repertoires contain fewer **small** clones than whole-body repertoires



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- Killifish intestinal samples show a much more dramatic decline in alpha-diversity with age than in the whole body
- Both gut and whole-body repertoires show an increase in beta-diversity with age

Acknowledgements

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Ray Cui
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Jenny Ostermann

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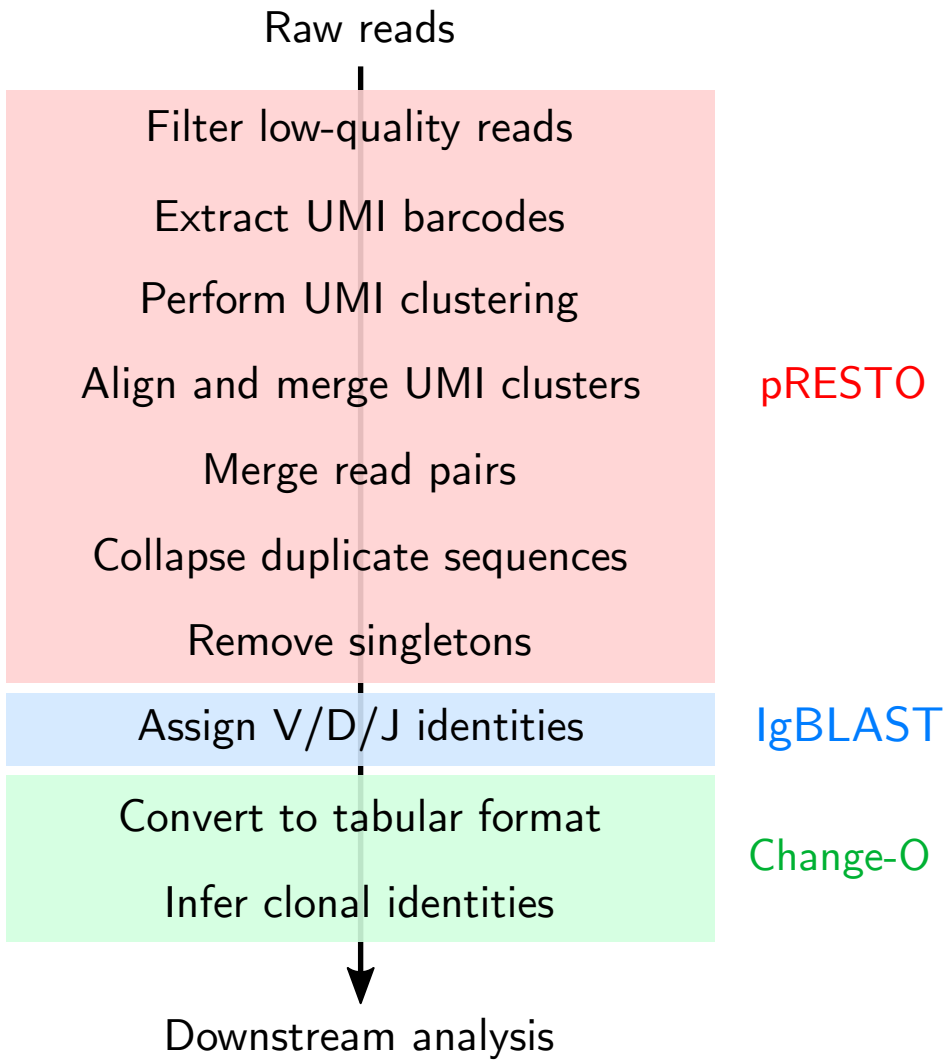
John Beausang

Kathrin Reichwald
Jason Vander Heiden
Quentin Marcou

Manolis Pasparakis
Andreas Beyer
Michael Lässig

Thank you!

Bioinformatics pipeline



The generative entropy of the naïve antibody repertoire does not change with age