



# Characterising antibody immunity and ageing in a short-lived teleost

William John Bradshaw

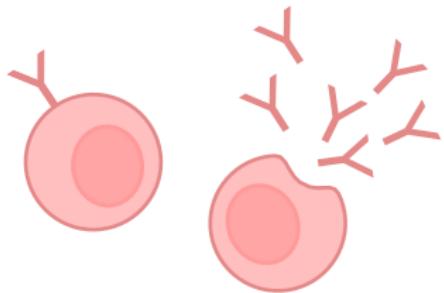
6th June 2019



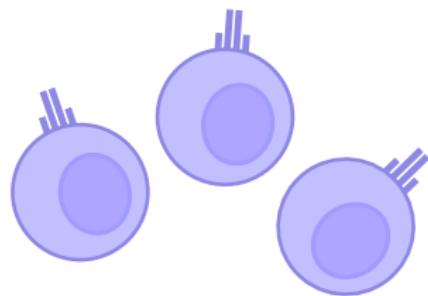
University of Cologne



Antibodies



T-cell receptors



B-cells

T-cells



Adaptive immune system

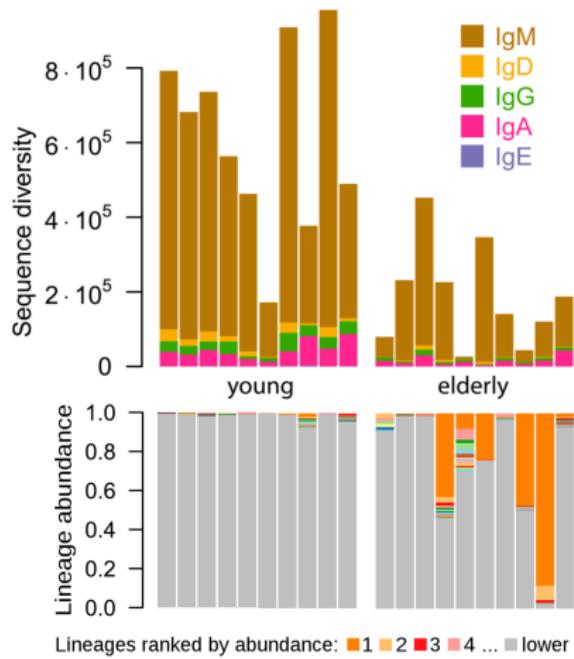
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- Impaired antibody quality
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Adapted from de Bourcey et al., PNAS 2017

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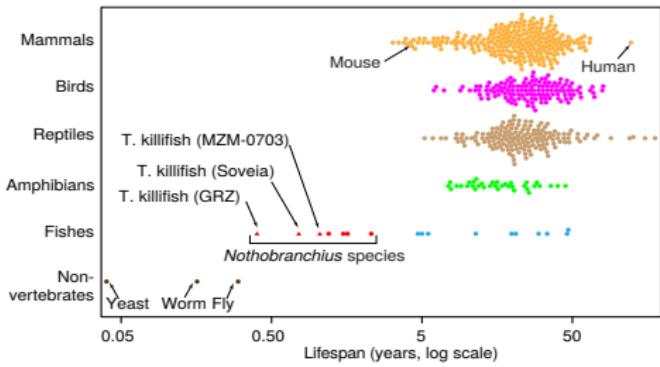
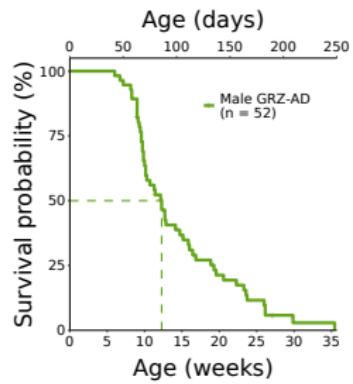
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- Limited temporal resolution (typically just two time points)

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

- Nothing known outside humans and mice
- Almost all data comes from peripheral blood
- No spatial resolution (different organs)
- 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

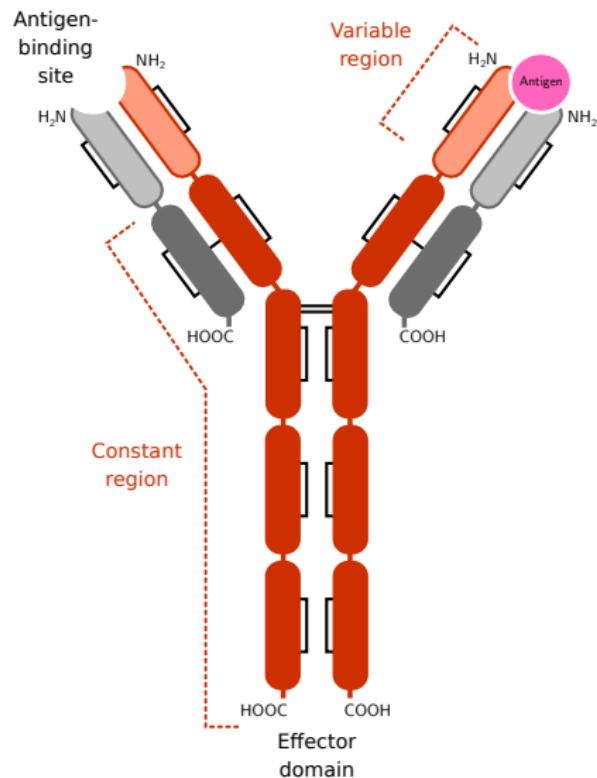


Valenzano et al., Cell 2015

- 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

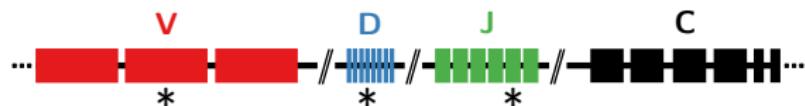
# VDJ recombination and primary antibody diversity

## (i) Native state



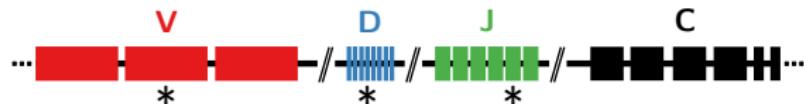
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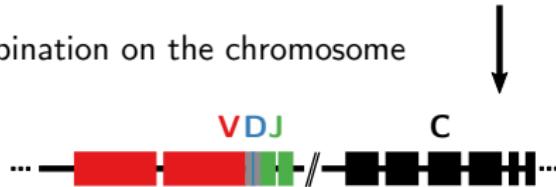


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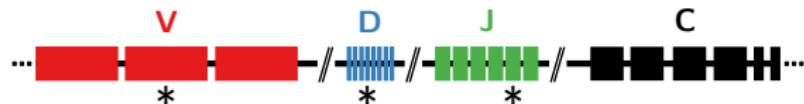


(ii) VDJ Recombination on the chromosome

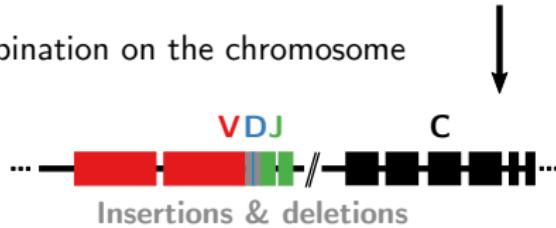


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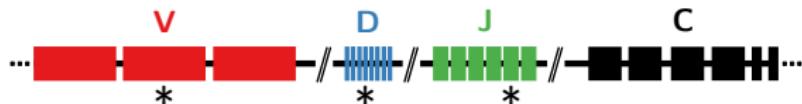


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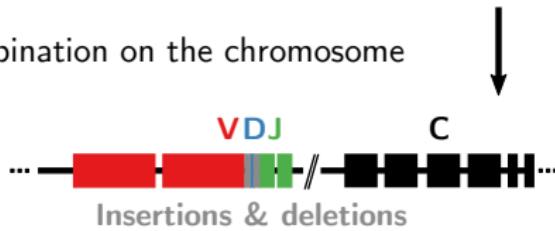


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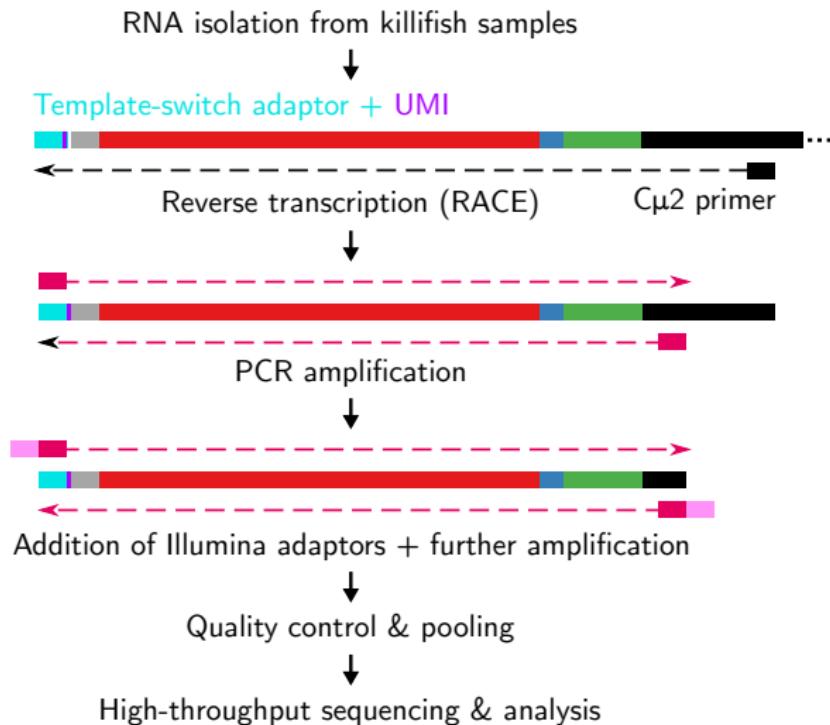
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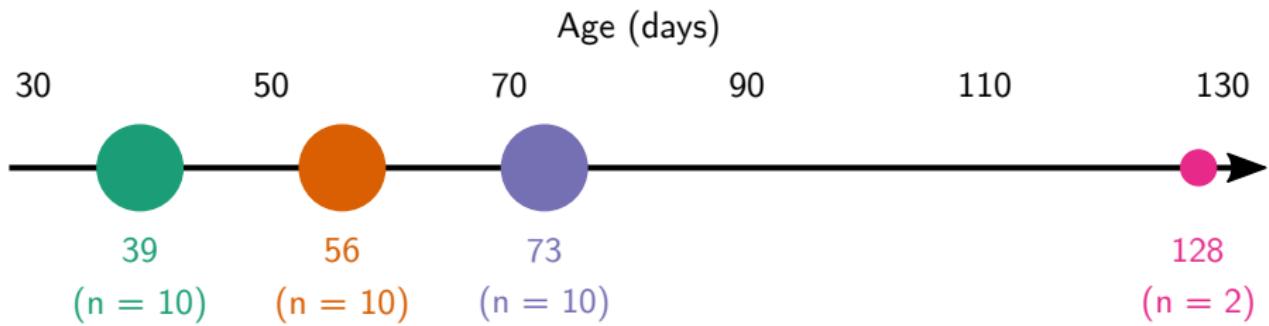
(iii) Transcription and splicing



# Immunoglobulin sequencing in the turquoise killifish

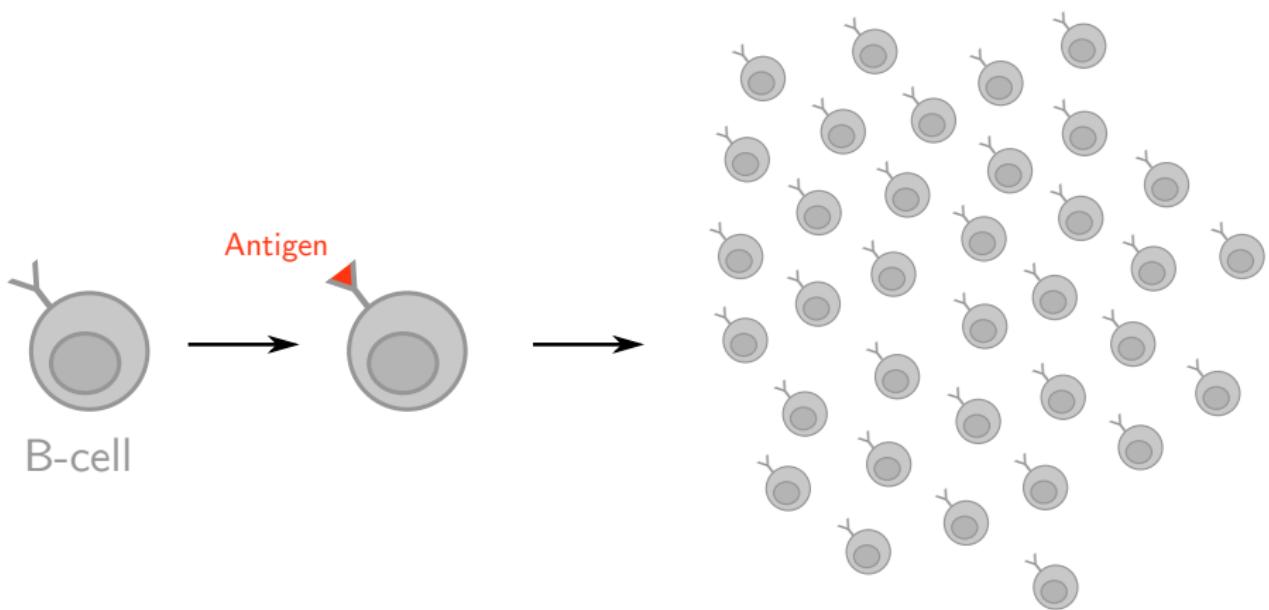


# Sample design – killifish ageing study

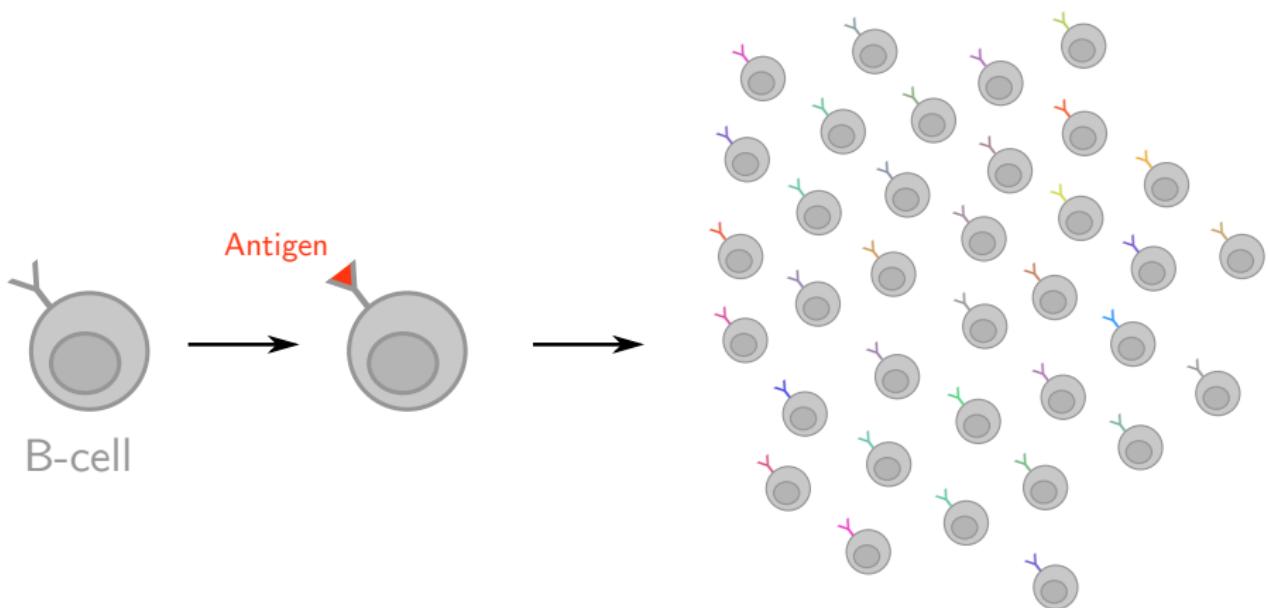


# Clonal antibody diversity

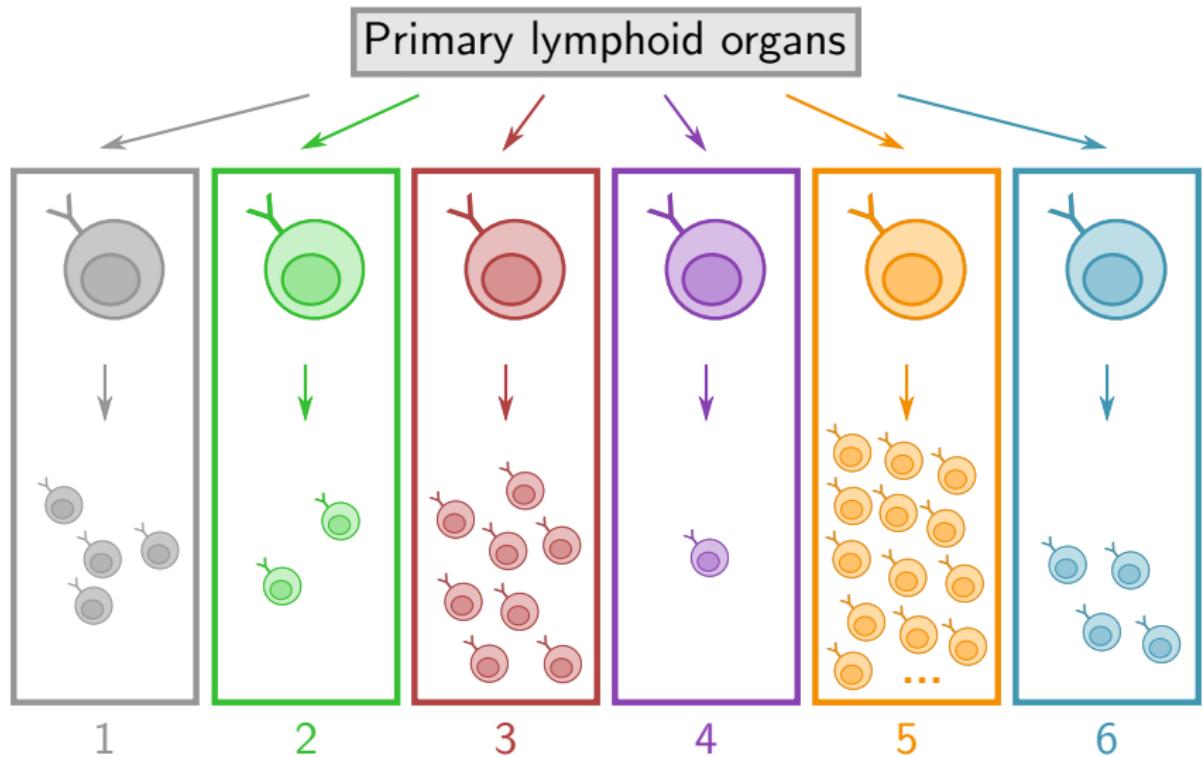
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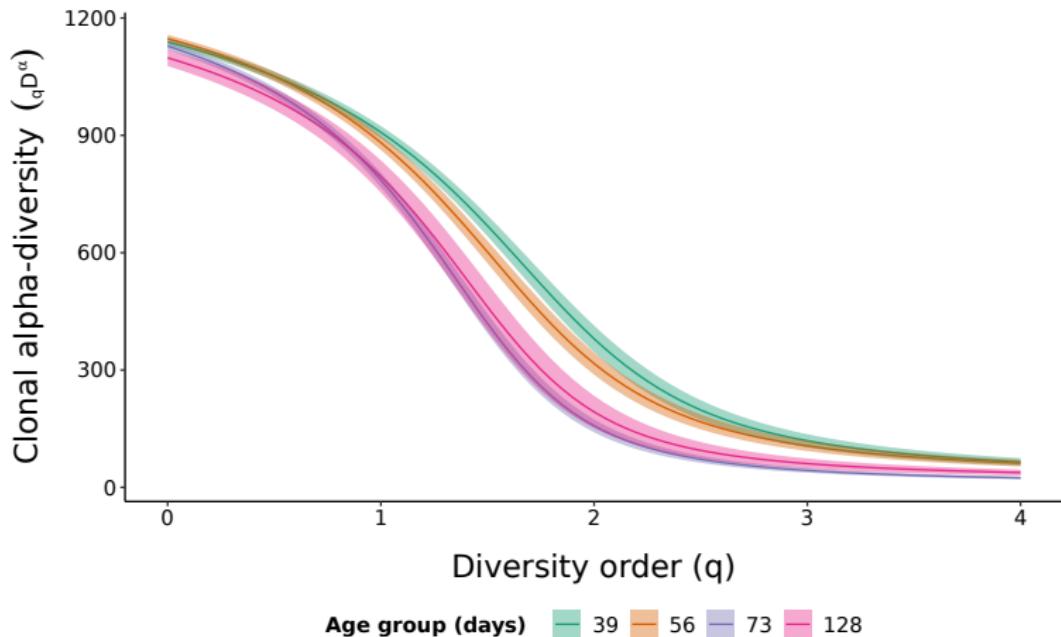


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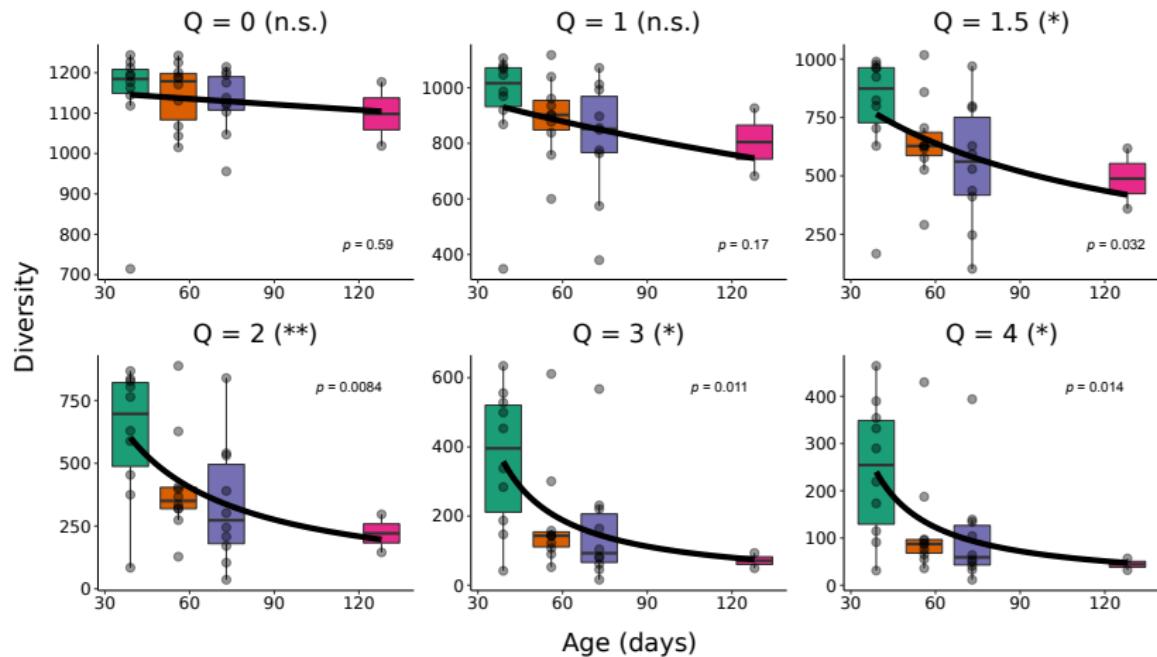


# Clonal alpha-diversity in the killifish antibody repertoire

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



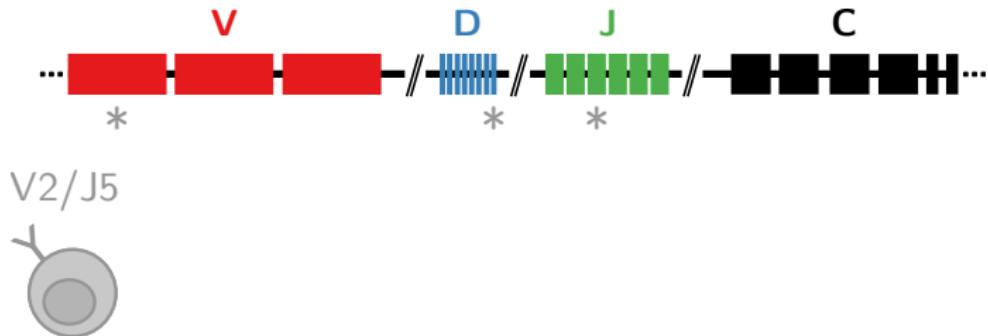
# Clonal alpha-diversity in the killifish antibody repertoire declines with age at high diversity orders



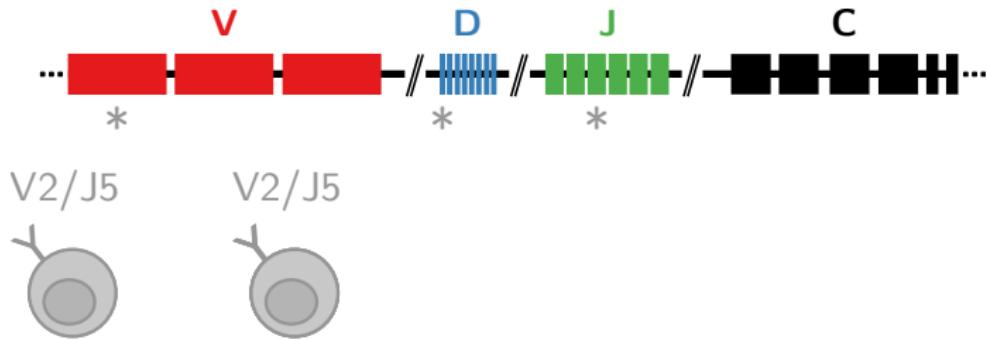
# VJ alpha-diversity in the killifish antibody repertoire



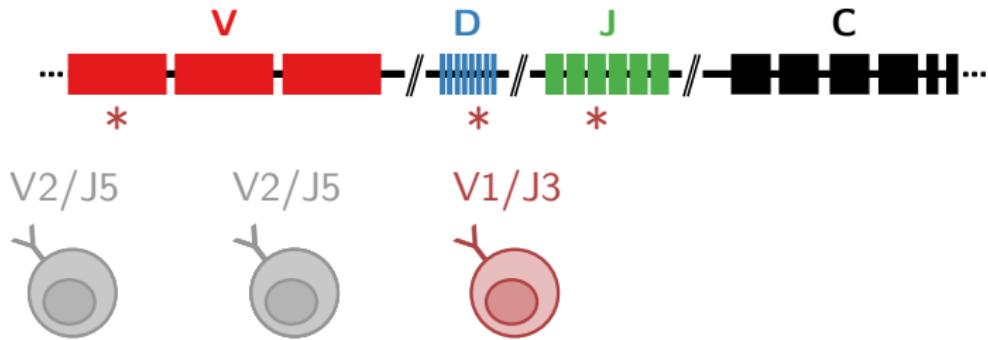
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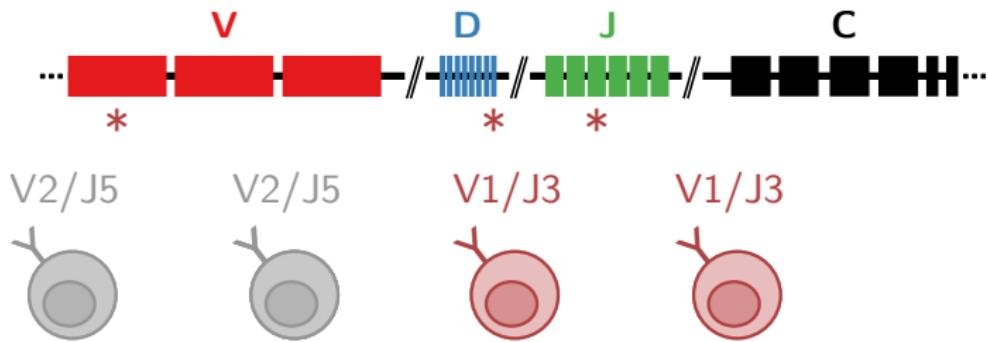
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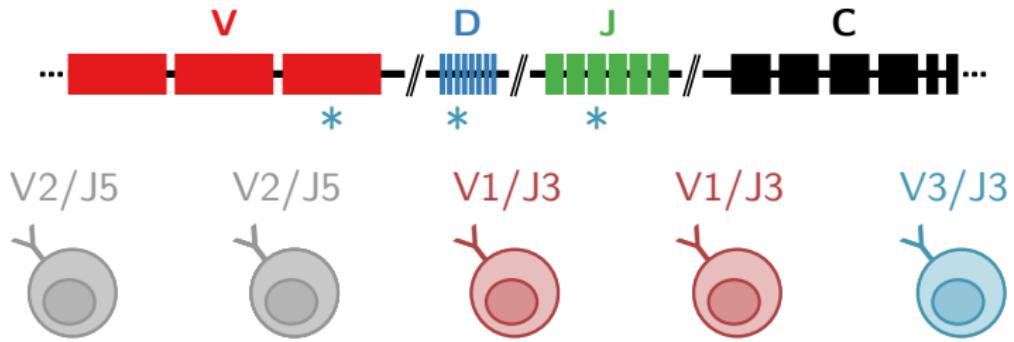
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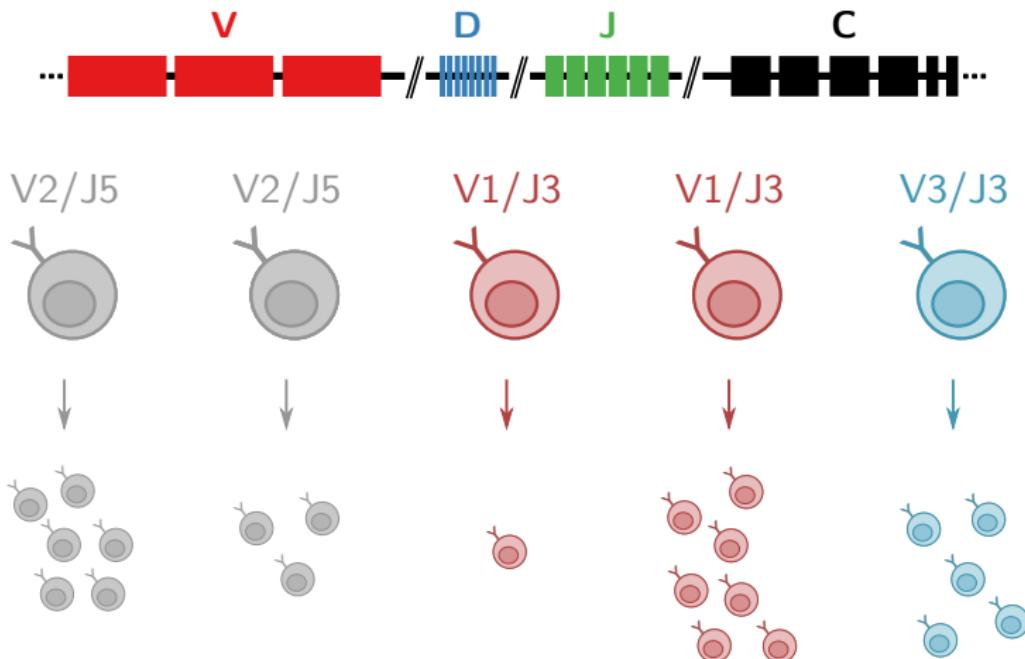
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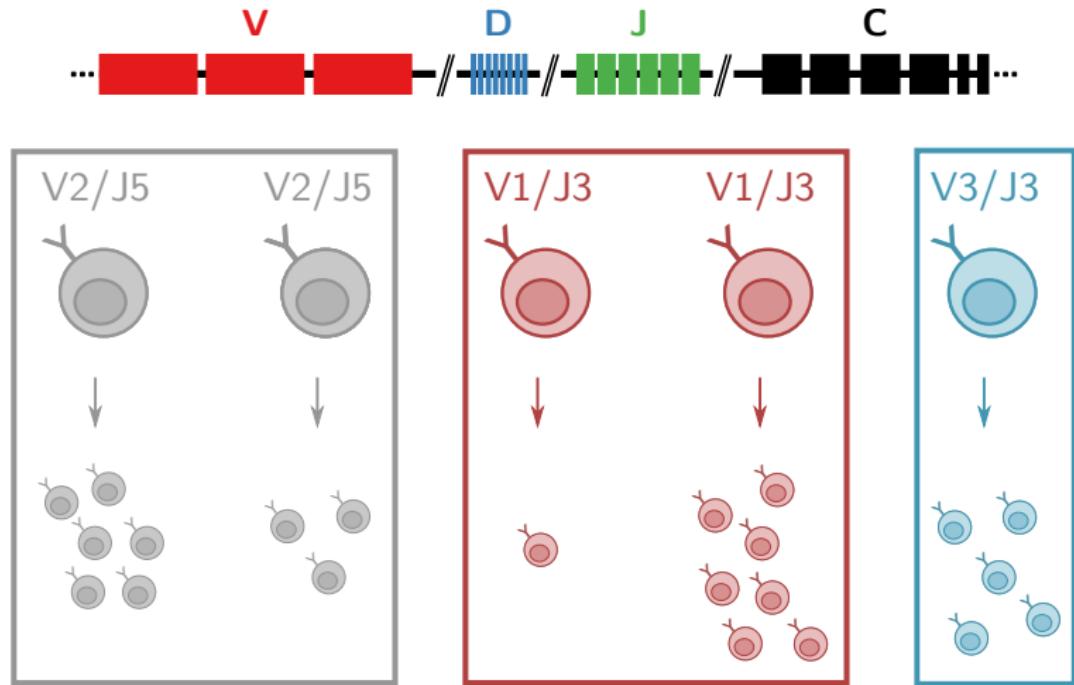
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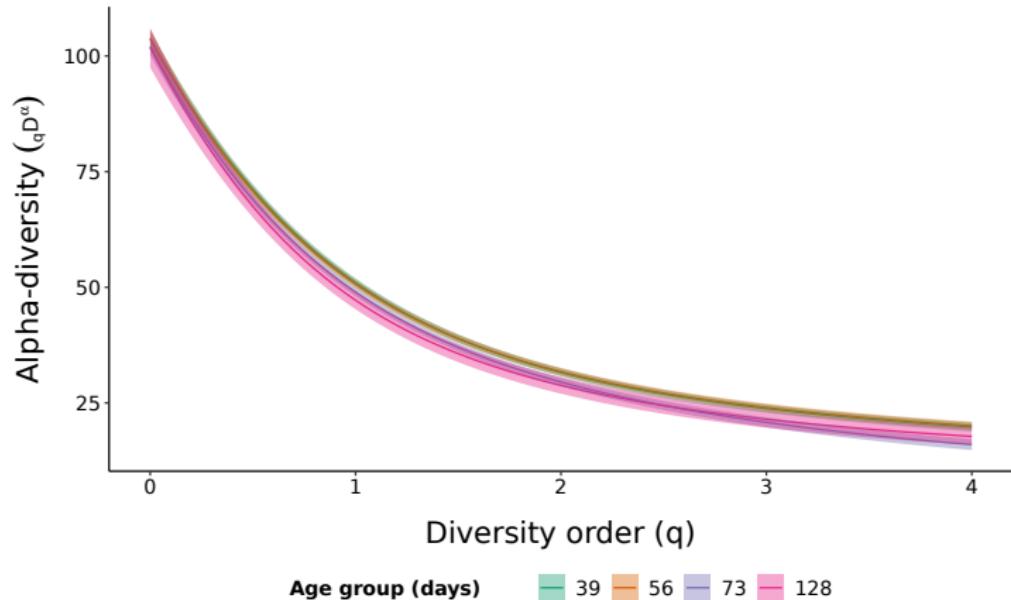


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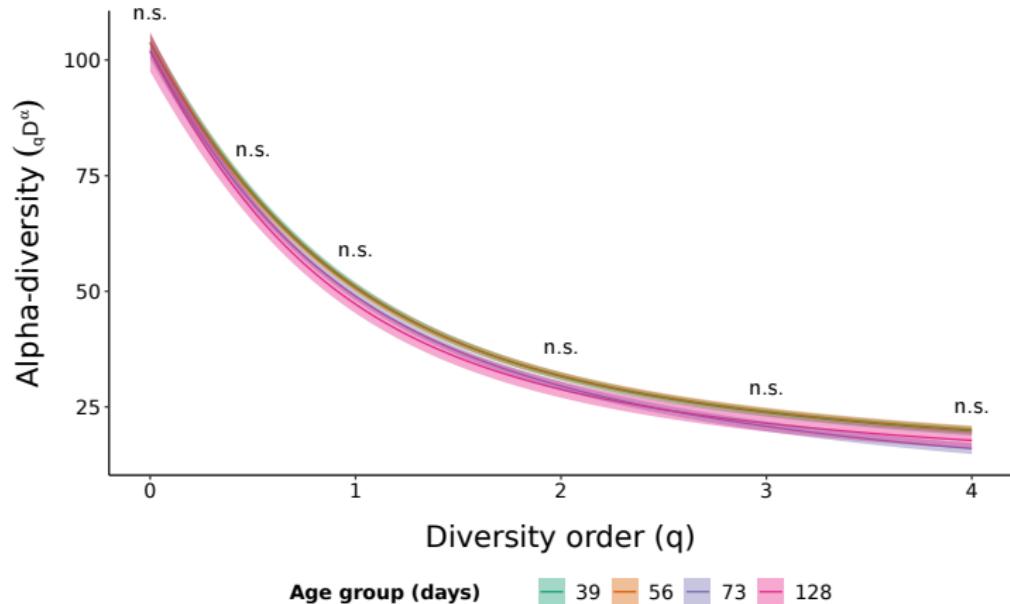


# VJ alpha-diversity in the killifish antibody repertoire

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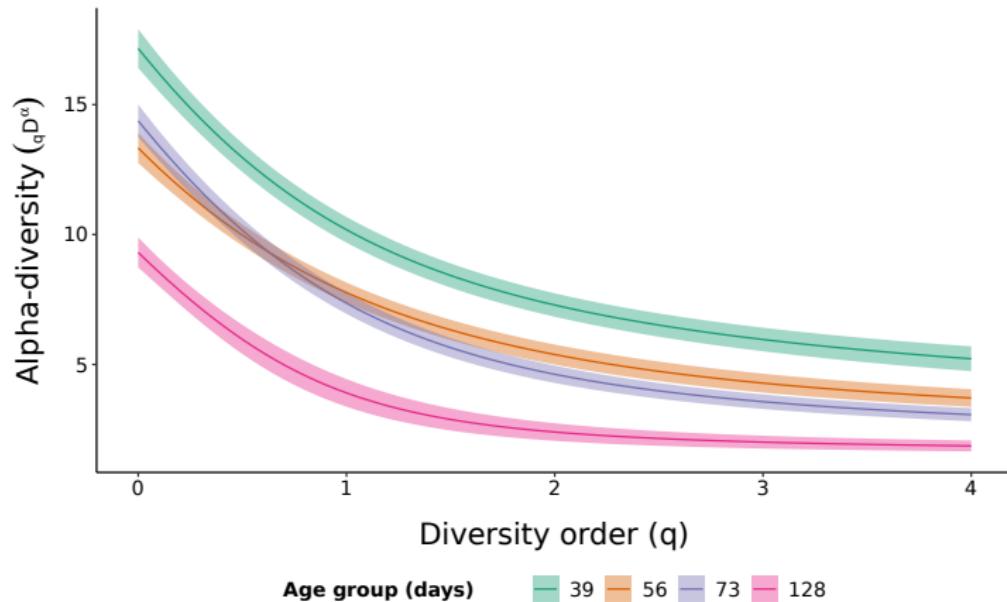
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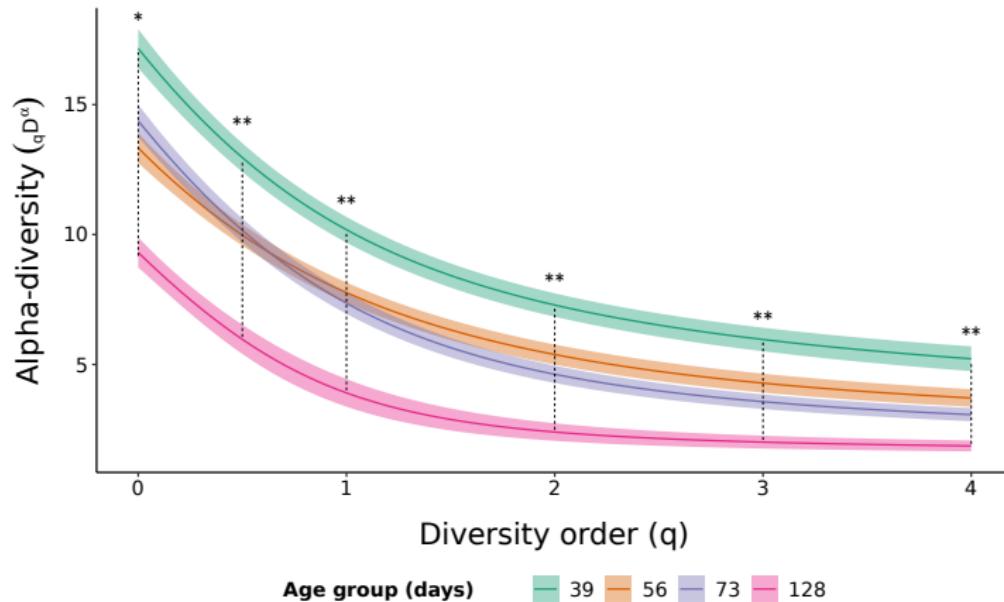
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- **No** (V/J diversity)
- Why the difference?

# VJ alpha-diversity of large clones

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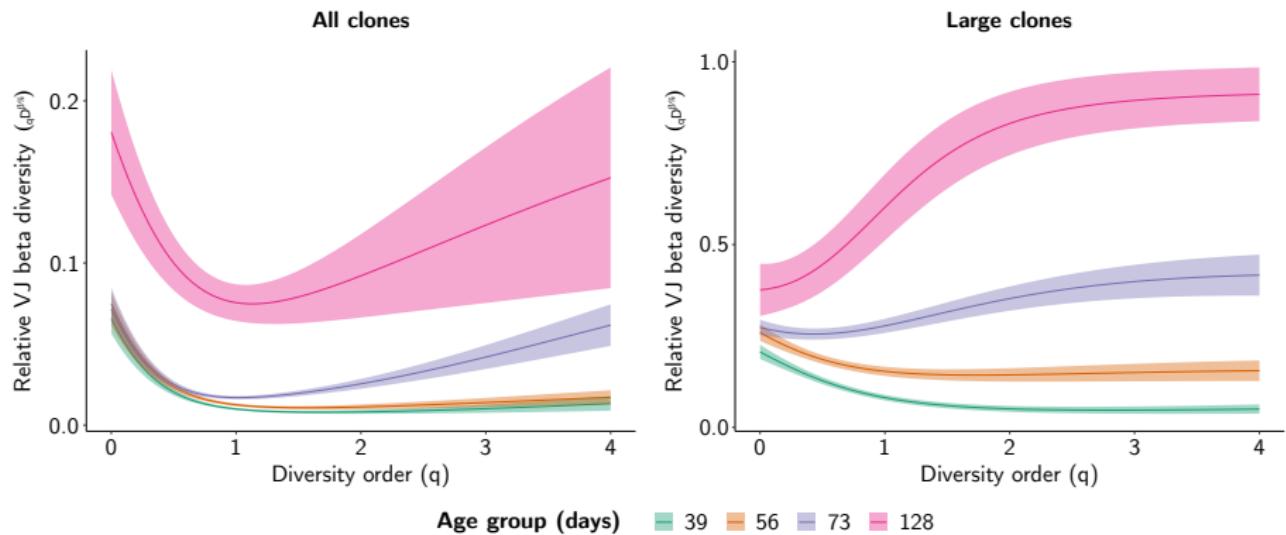


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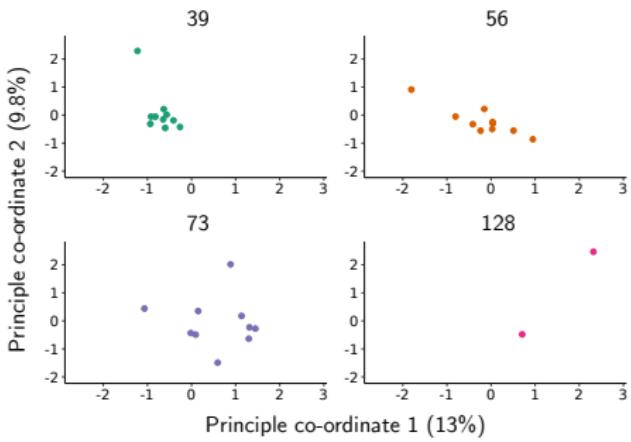
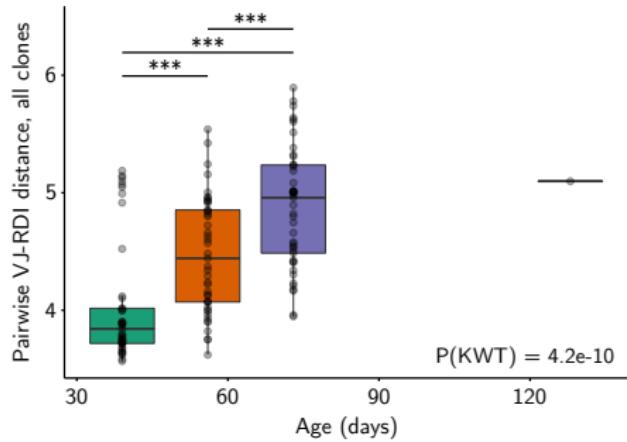




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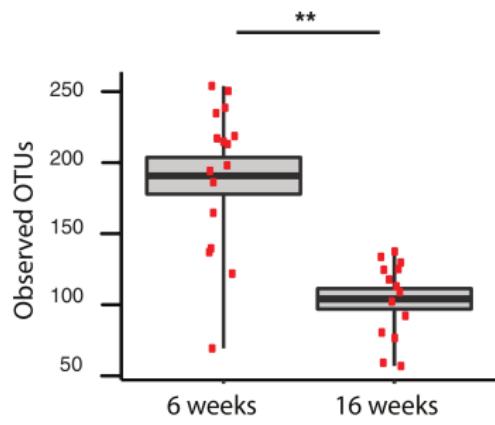
- Antibody repertoires sampled from whole-body killifish samples show a progressive decline in clonal alpha diversity at high (but not low) diversity orders
- V/J alpha diversity shows no change with age if all clones are included but a large decline in large clones
- Between-individual variation (beta diversity) in killifish repertoires increases with age



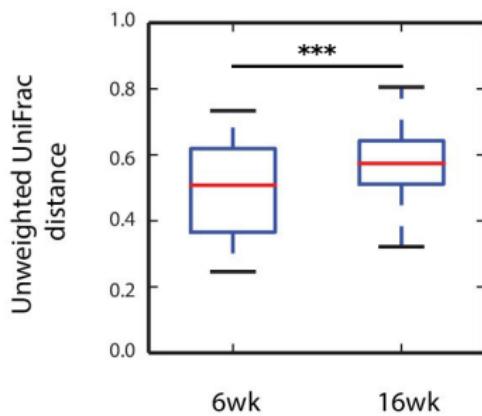
# Killifish gut microbiota also show decreasing alpha- and increasing beta-diversity with age



**Alpha diversity**

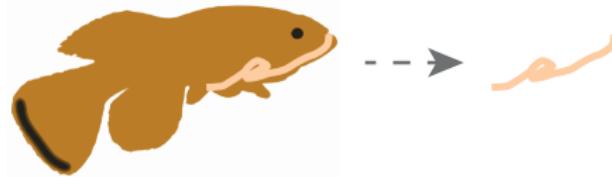
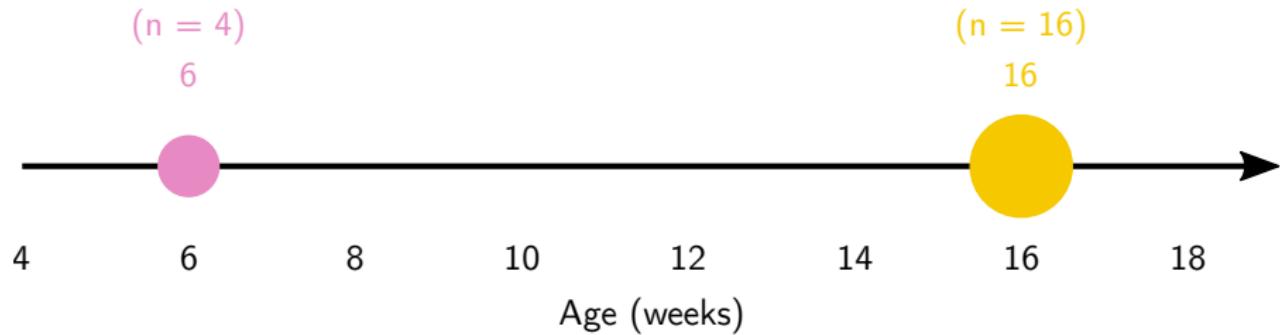


**Beta diversity**



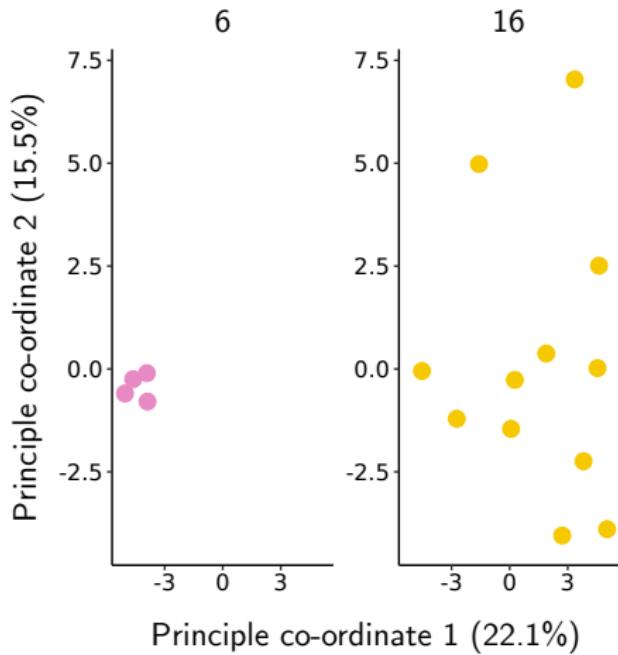
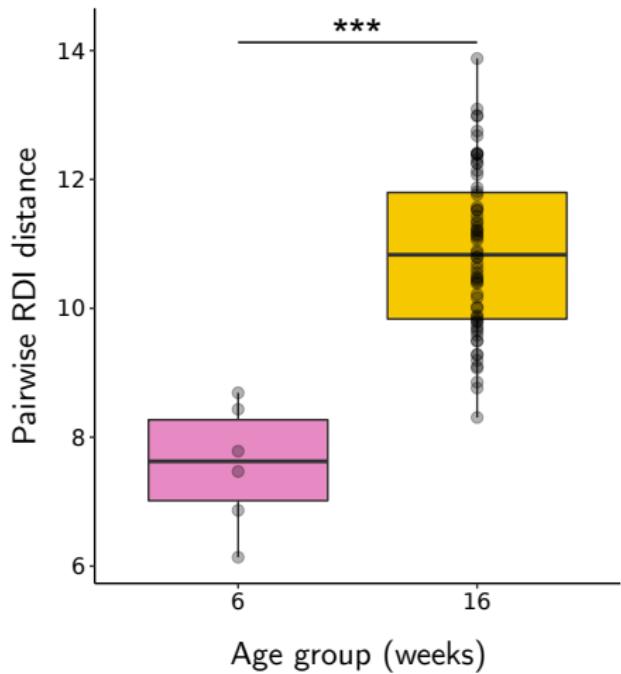
Smith et al., eLife 2017

# Sample design – gut repertoire study

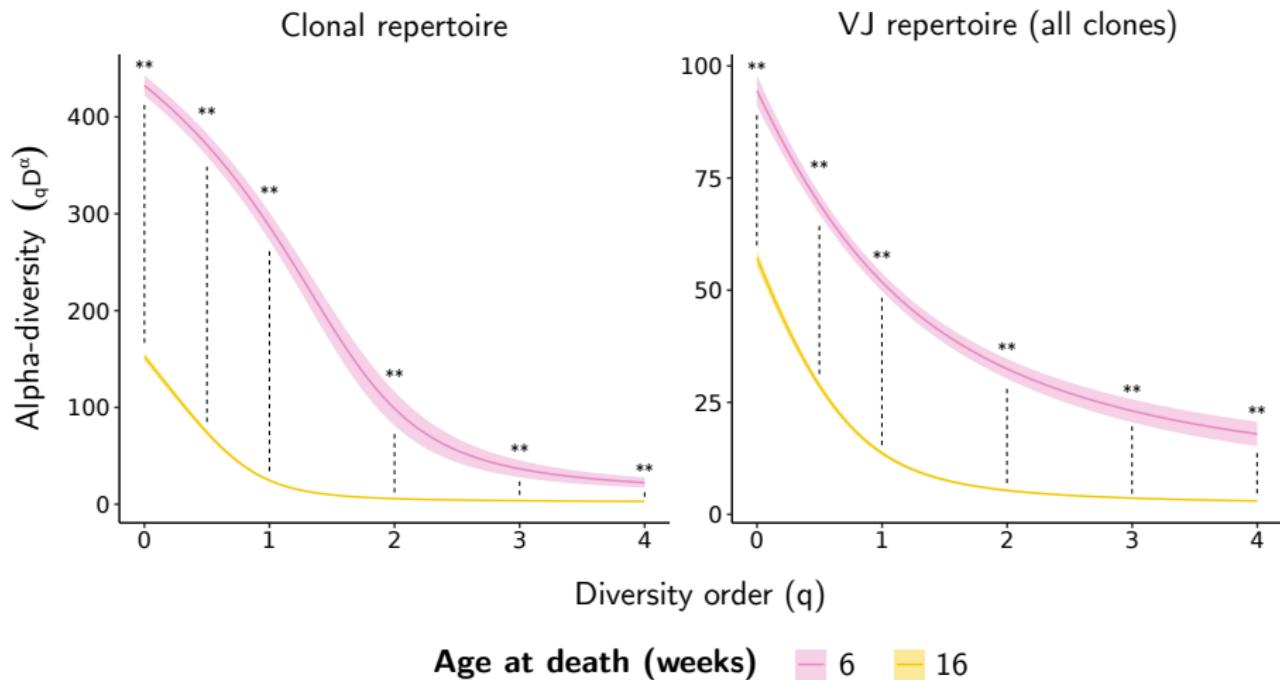


*Samples collected for Smith et al., eLife 2017*

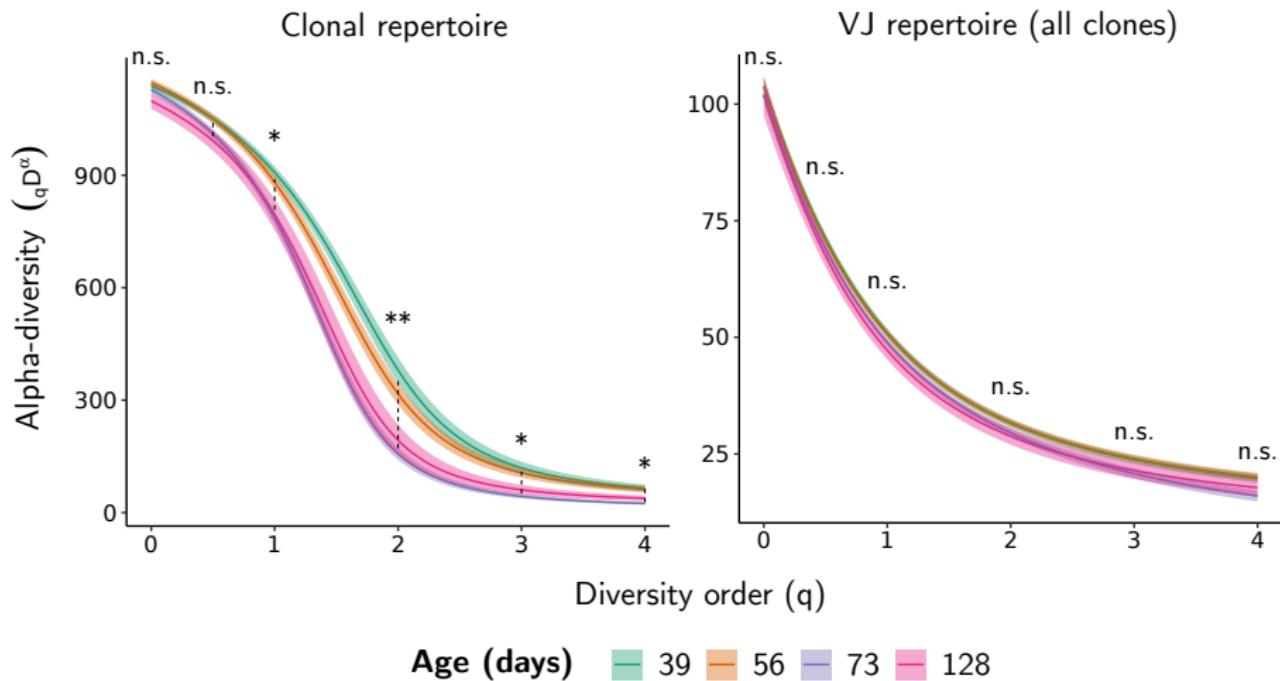
# Killifish gut repertoires become much more dissimilar with age



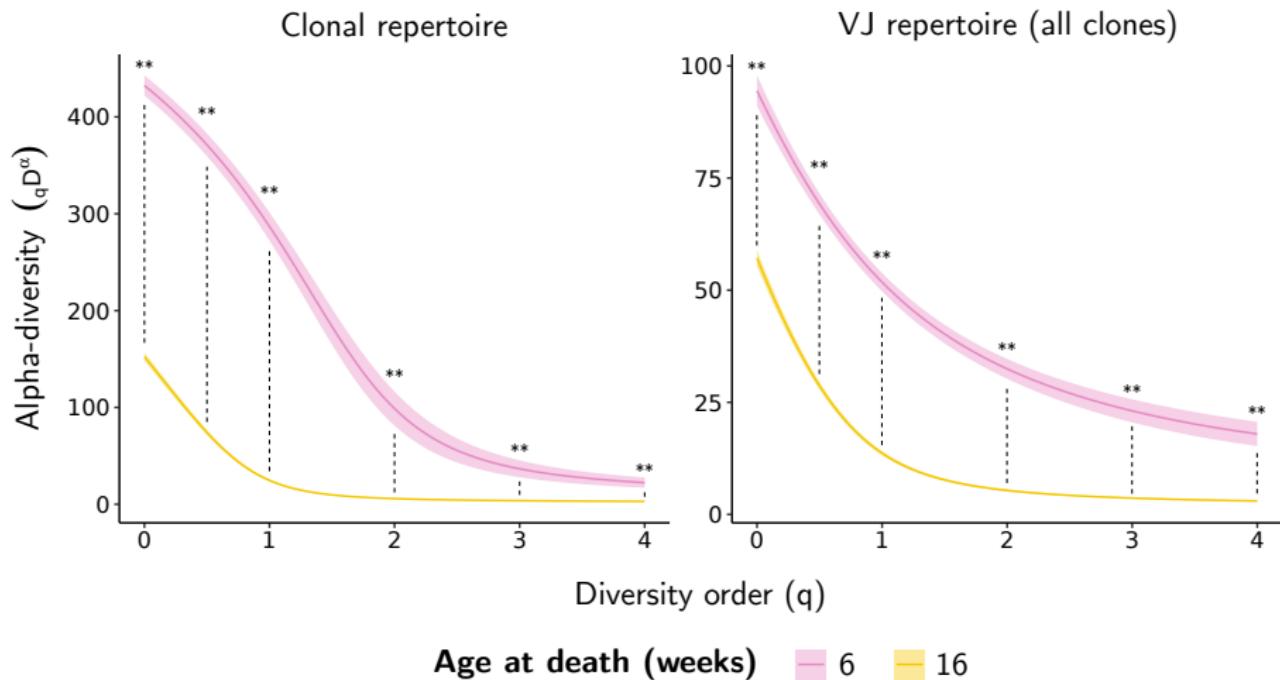
# Gut repertoire alpha diversity declines dramatically with age in turquoise killifish



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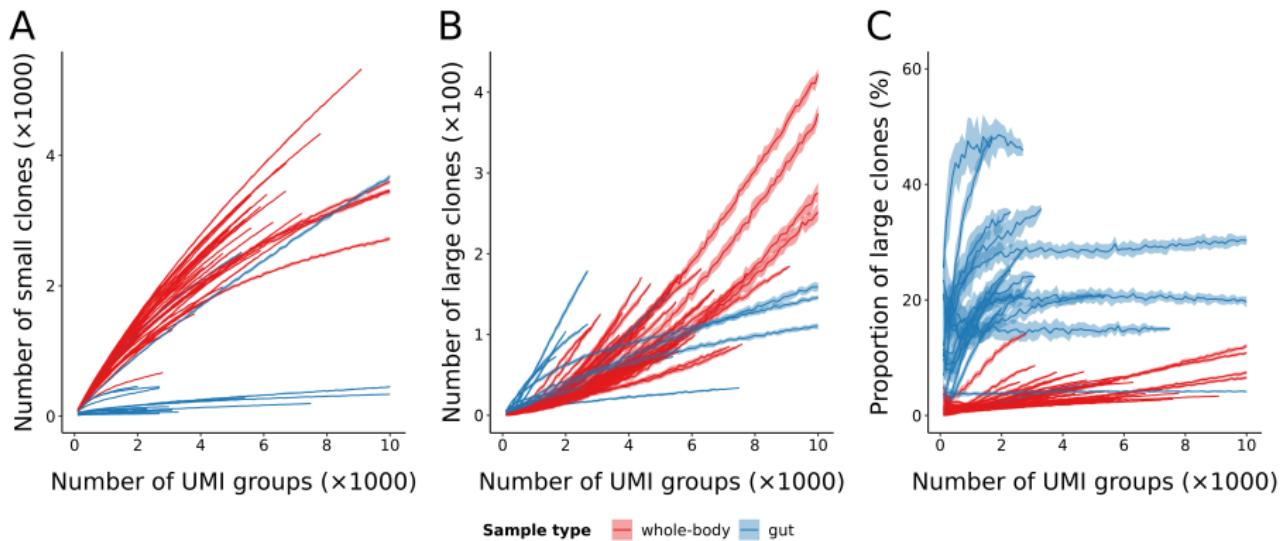
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## 2. Difference in **clonal composition**?

- 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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Aleksandra Walczak  
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John Beausang



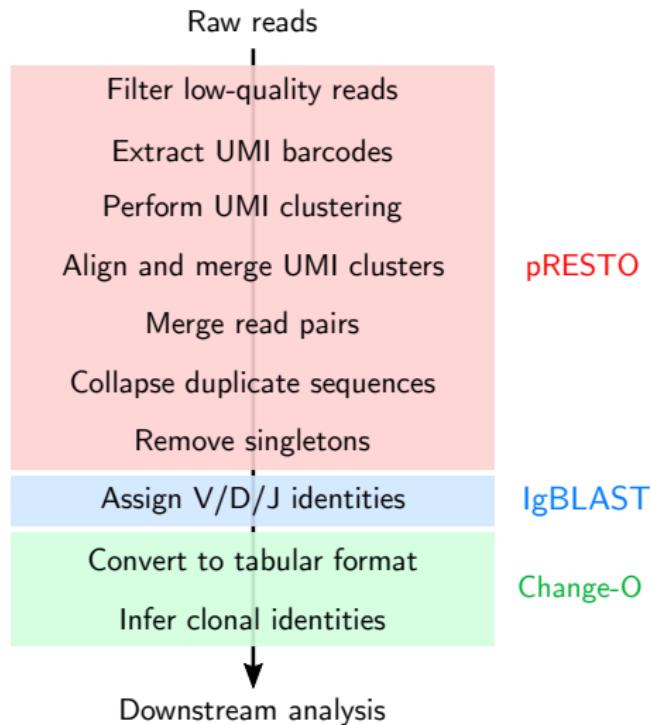
Kathrin Reichwald  
Jason Vander Heiden  
Quentin Marcou

Manolis Pasparakis  
Andreas Beyer  
Michael Lässig

# Thank you!

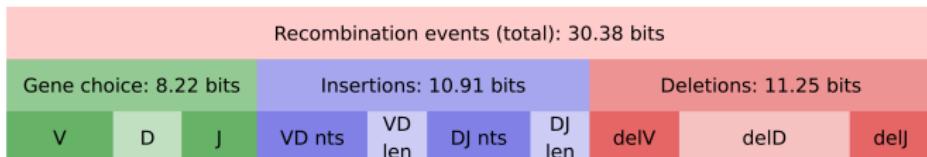


# Bioinformatics pipeline

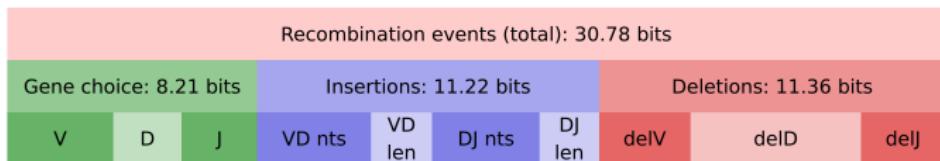


# The generative entropy of the naïve antibody repertoire does not change with age

Age (days) = 39



Age (days) = 56



Age (days) = 73

