Gulbenkian Institute for Molecular Medicine

LISBOA UNIVERSIDADE DE LISBOA

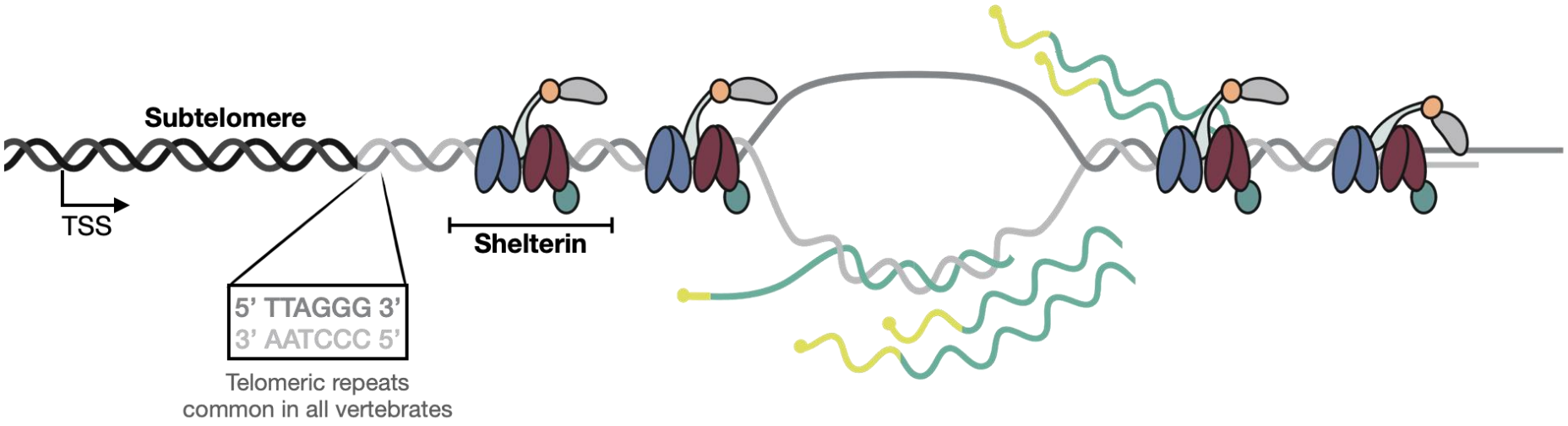
Faculdade de Medicina

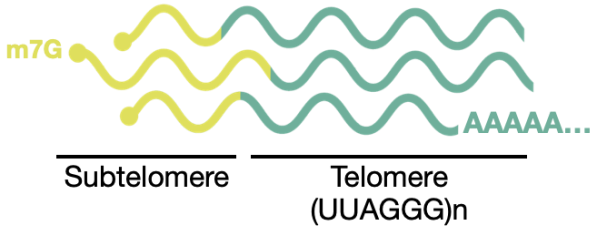
Characterization of the long noncoding RNA TERRA in a vertebrate

TRIAD

April 28th, 2025

Telomeric repeat-containing RNA





- Transcribed by RNA pol II from multiple chromosome ends
- In humans, two classes of subtelomeric promoters have been identified
- Heterogeneous in length
- m7G cap, but only a fraction is poly-adenylated

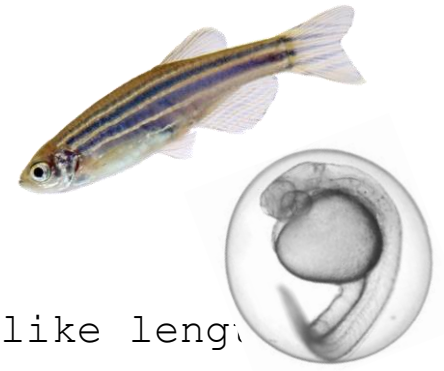
TERRA is an **essential component** of telomere biology

e.g., telomere elongation and protection

But…

What are the roles of TERRA in **complex processes** at the organismal level (aging or cancer insurgence)?

Study TERRA in **zebrafish**



- Characterized development
- Sequenced genome
- Heterogeneous telomeres of human-like leng

  Cayuela et al., Frontiers in Cell and Developmental Biology, 2019
  Carneiro et al., Disease Models & Mechanisms, 2016
  Alcaraz-Pérez et al., Nature Communications, 2014

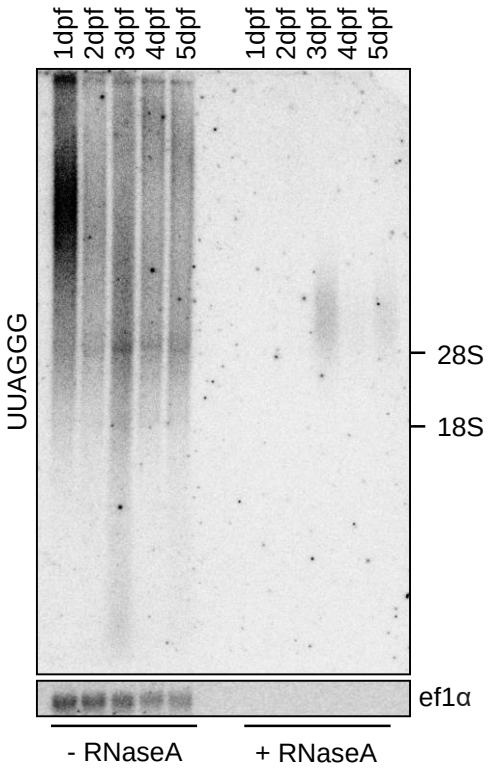
- Telomeres shorten with age both in high- and low-proliferative tissues

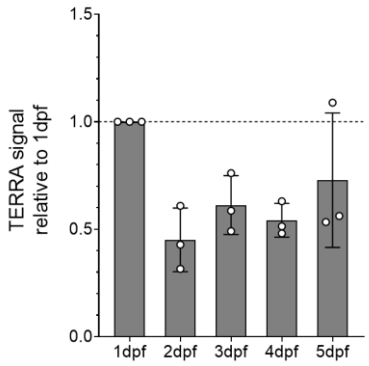
  Carneiro et al., PLoS Genetics, 2016

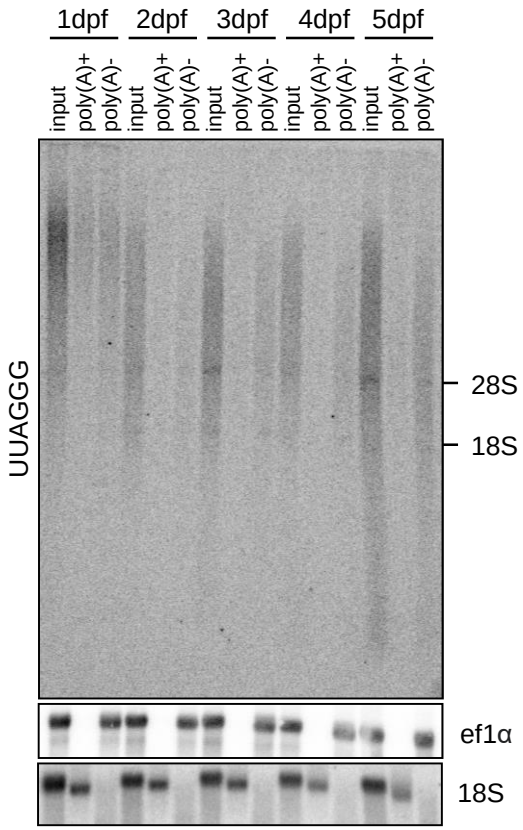
- Telomerase activity decreases with age

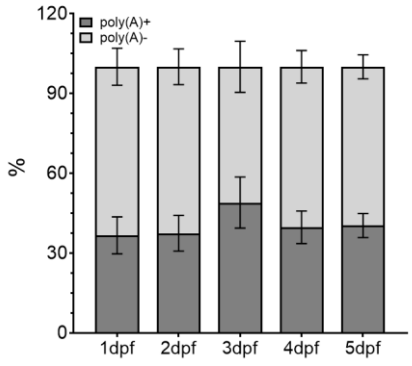
  Anchelin et al., PLoS ONE, 2011
  Kishi et al., Experimental Gereontology, 2003

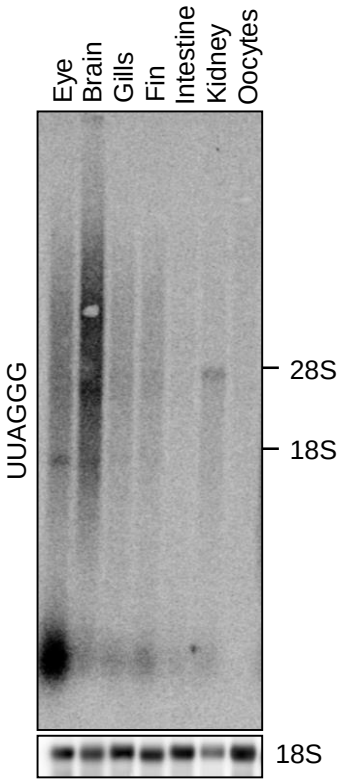
TERRA in physiological conditions

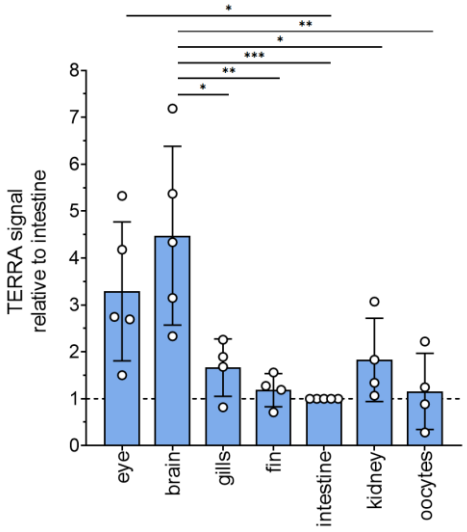




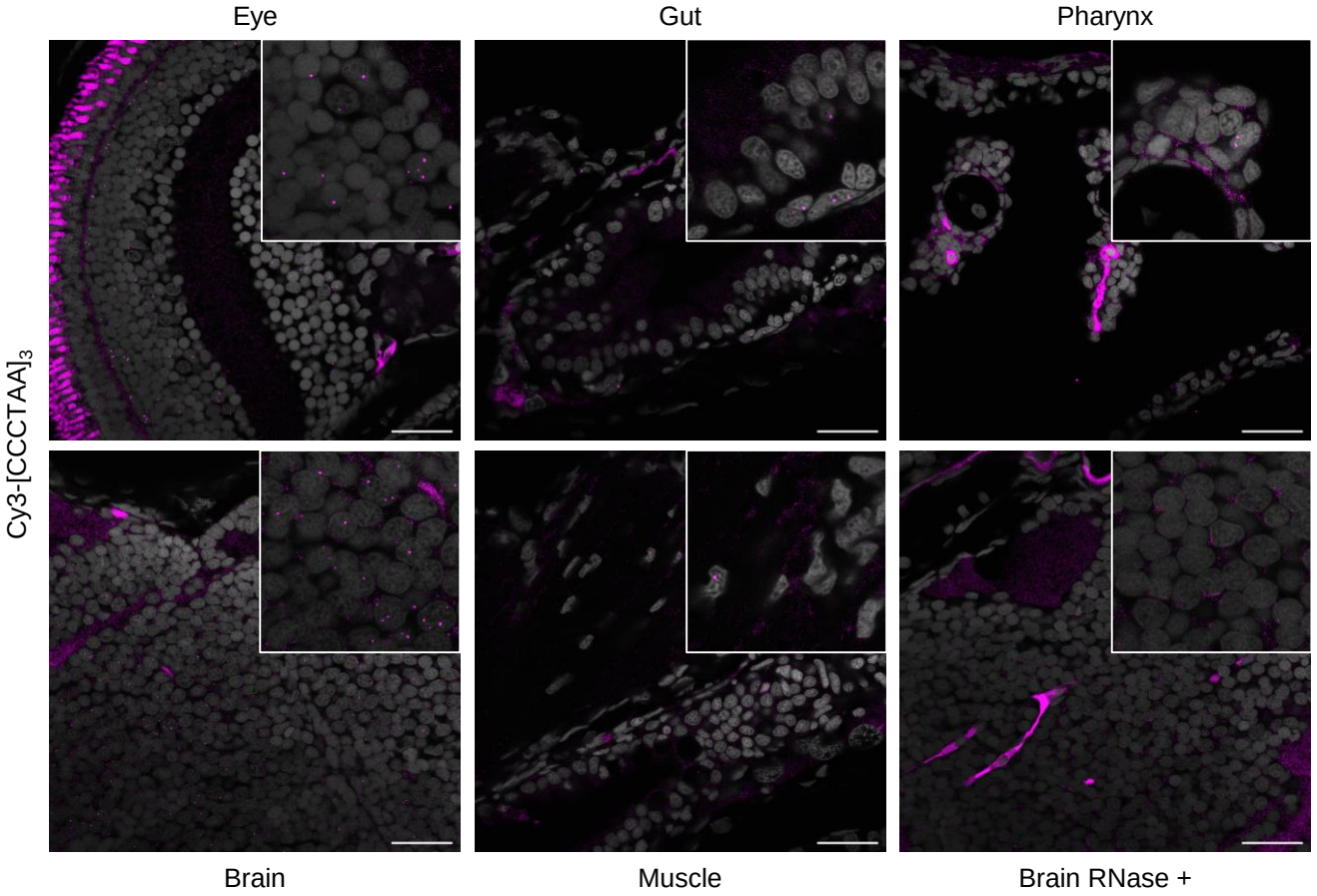


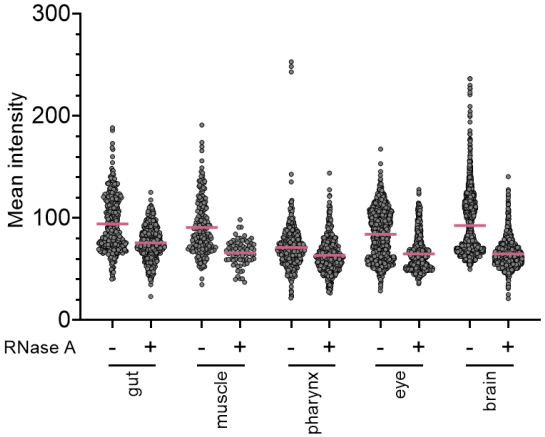






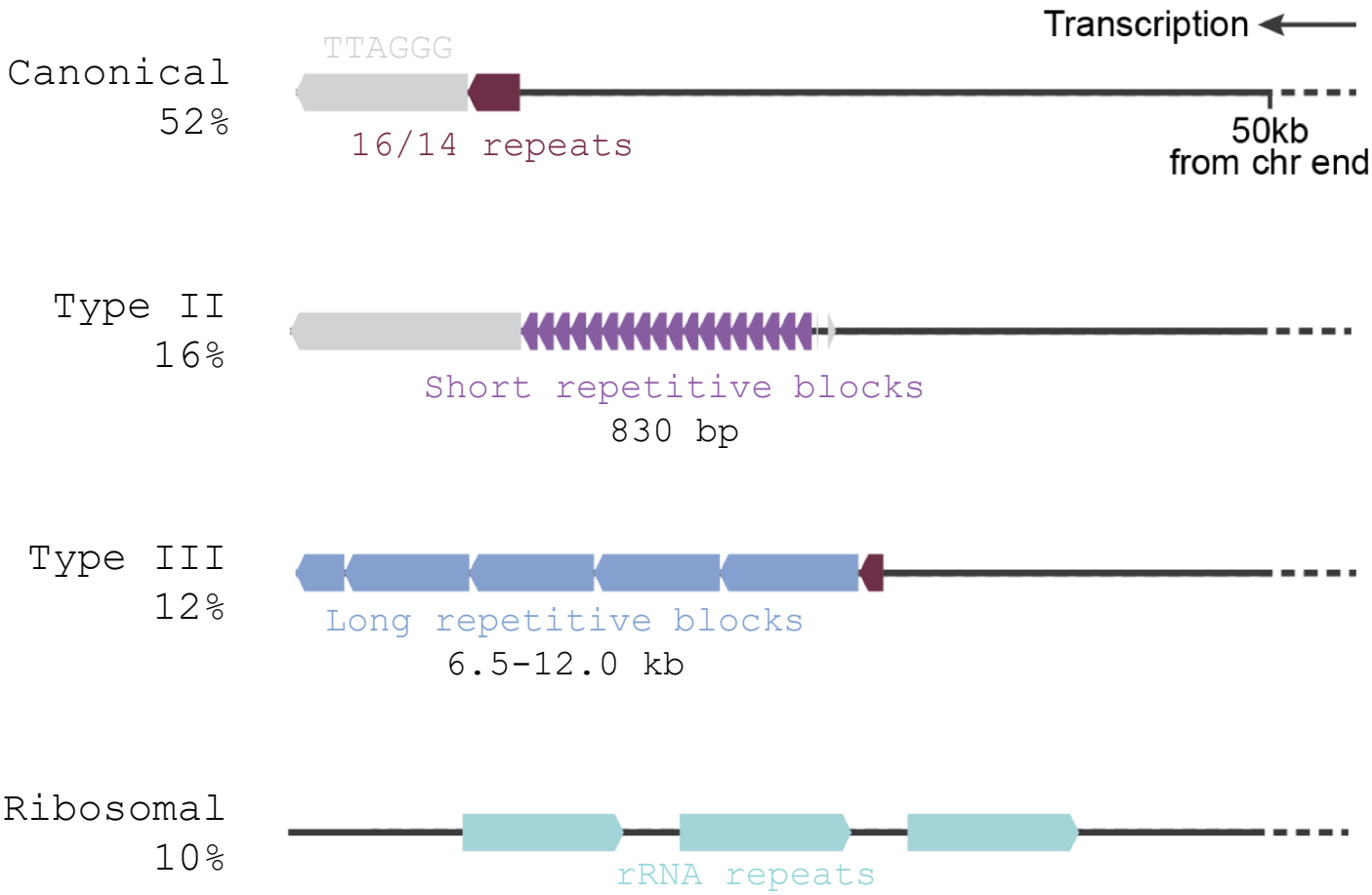
TERRA in physiological conditions





Organization of zebrafish chromosome ends and their contribution to TERRA

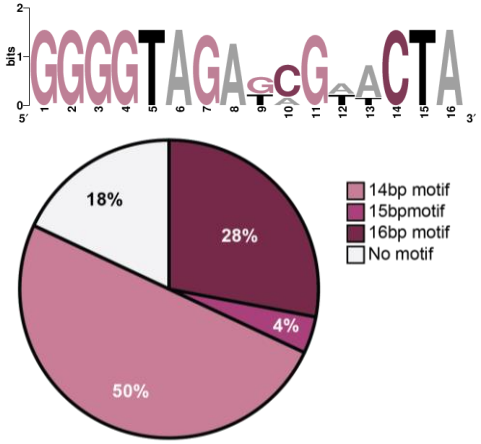
Four main classes of chromosome ends identified:



In some cases, oriented in the same direction of TERRA transcription

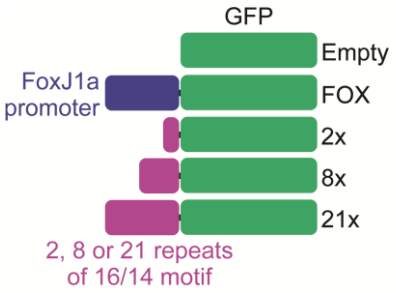
Organization of zebrafish chromosome ends and their contribution to TERRA

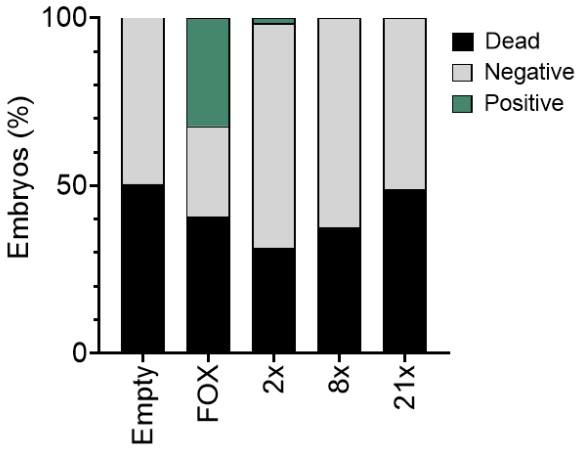
16/14 repeats

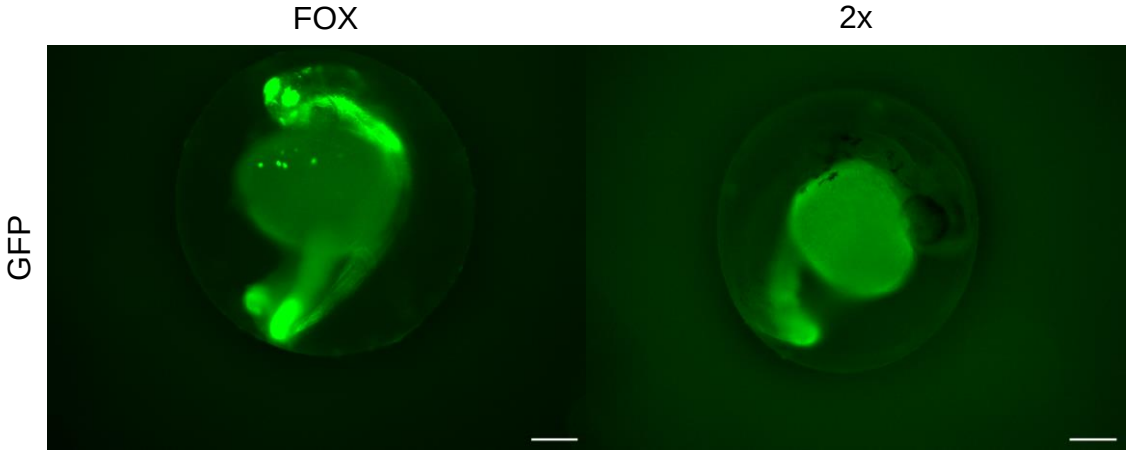


The 16-bp motif corresponds to a CpG island

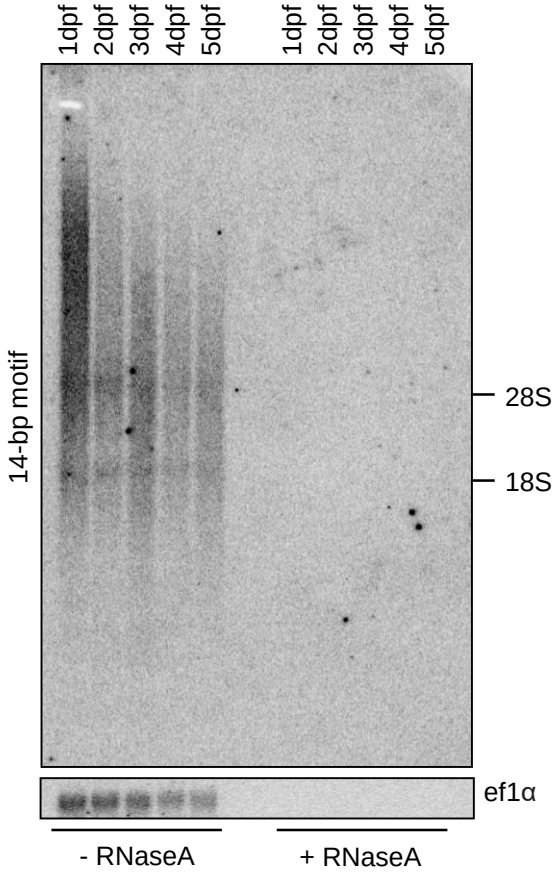
TERRA promoter?

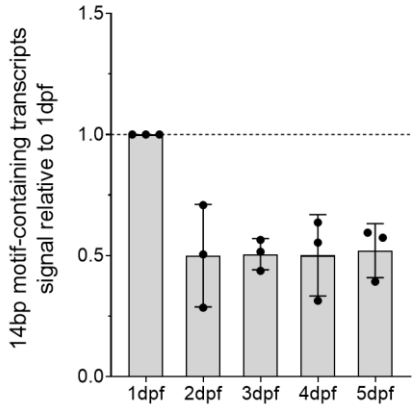


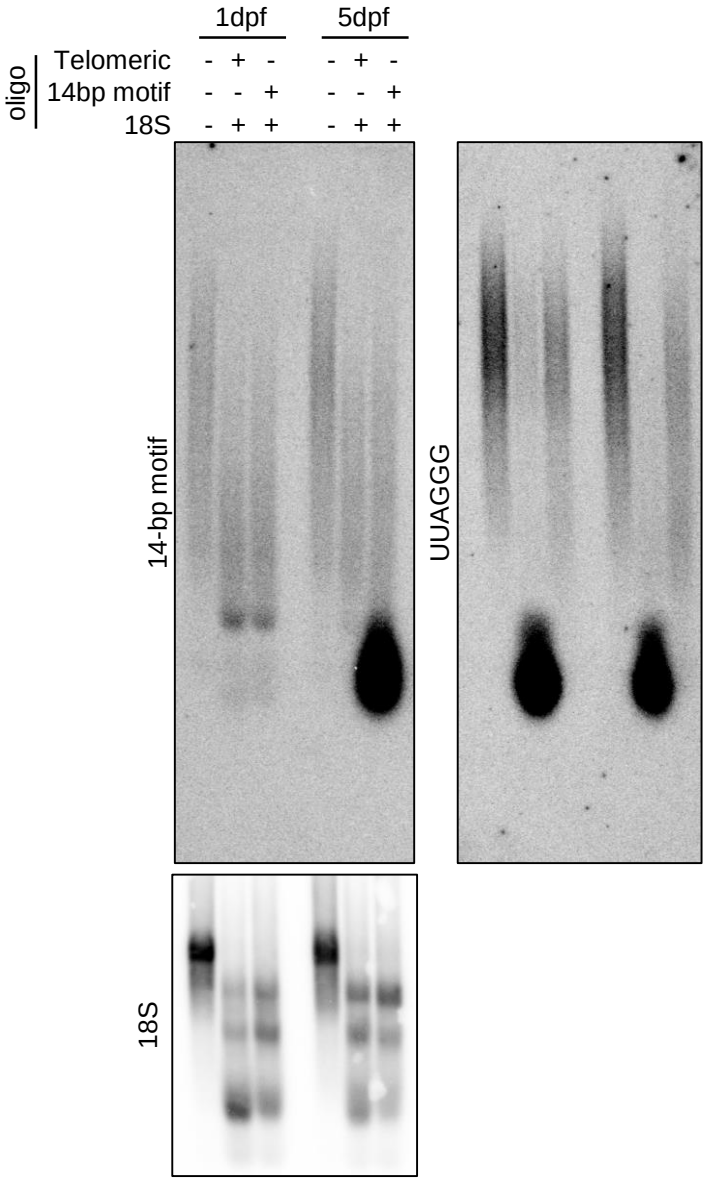




Organization of zebrafish chromosome ends and their contribution to TERRA







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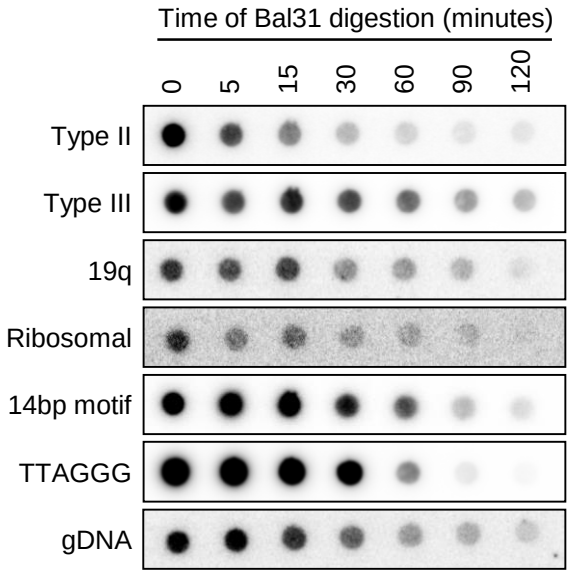
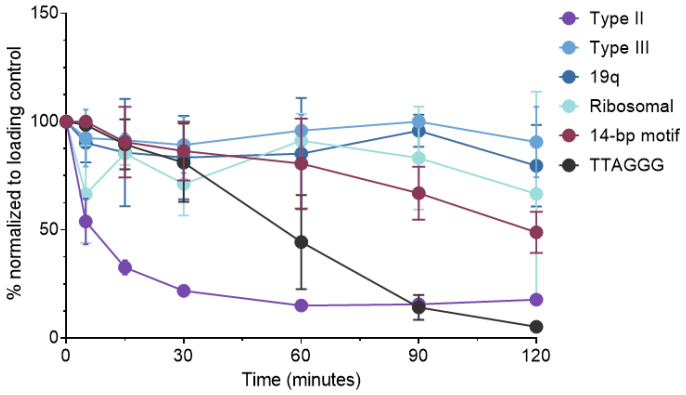
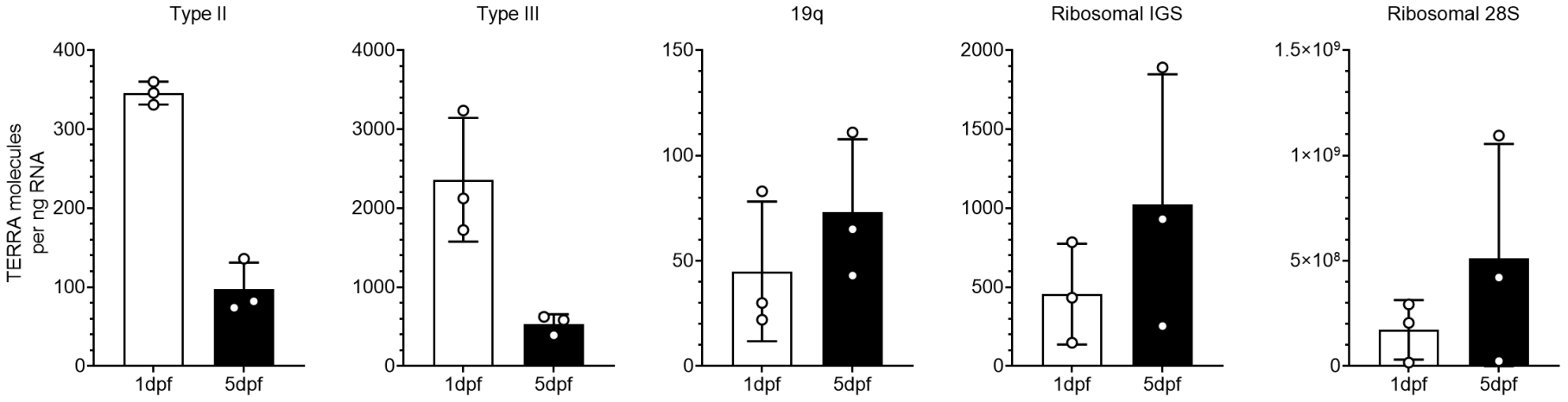




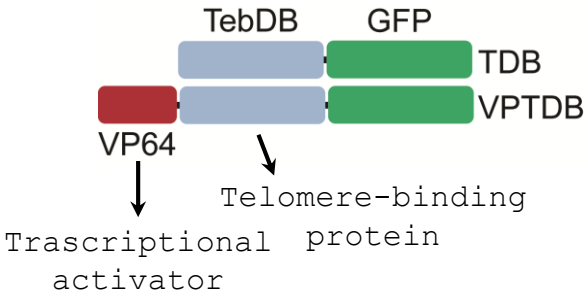


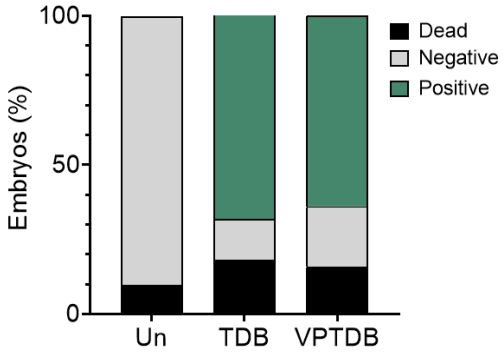
Summary 1

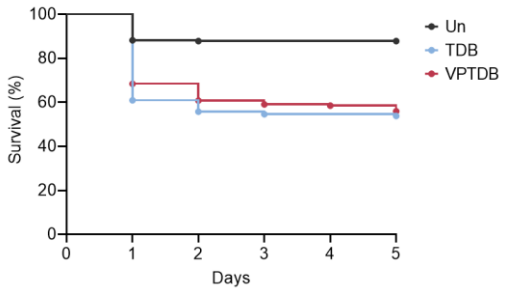
- TERRA is transcribed at different stages of zebrafish life, both at **embryonic stages and adulthood**
- TERRA molecular features (length and polyadenylation profile) are **evolutionary conserved**
- Higher TERRA levels are detected in tissues of **neuronal origin**

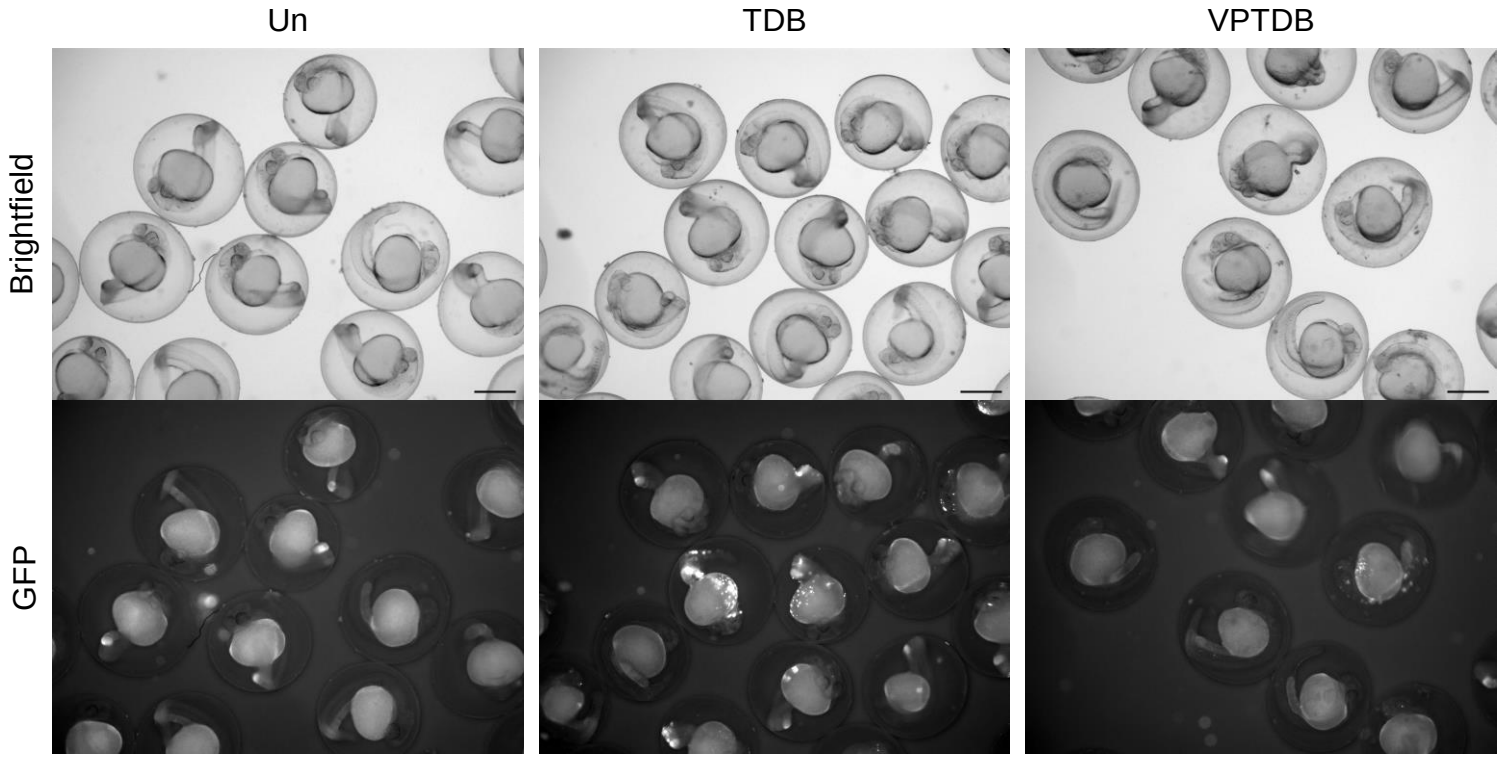
- A tandem repeat (**16/14 repeats**) different from the canonical TTAGGG is also present and transcribed
- TERRA transcription initiates in the subtelomeric tract, giving rise to **different TERRA species** like in humans

Establishment of model with enhanced TERRA transcription









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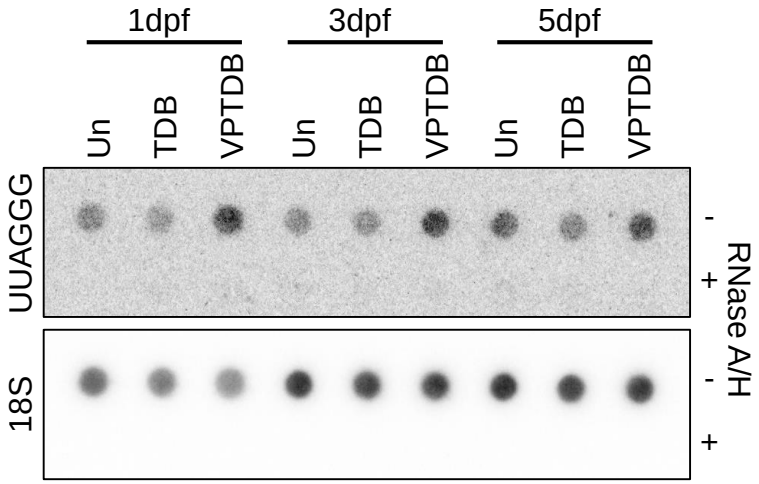
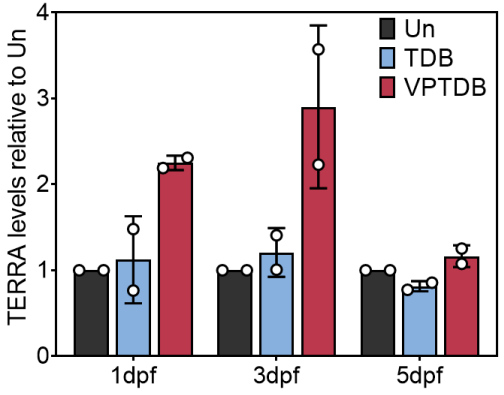
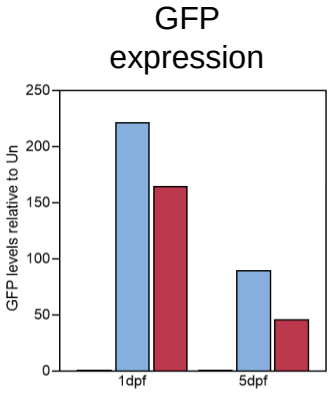
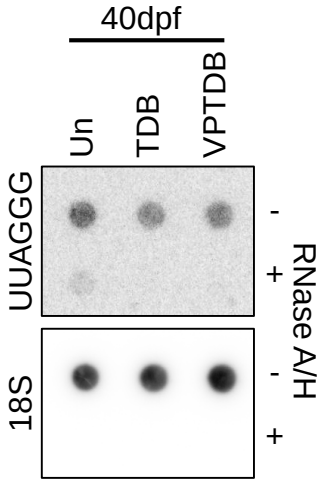
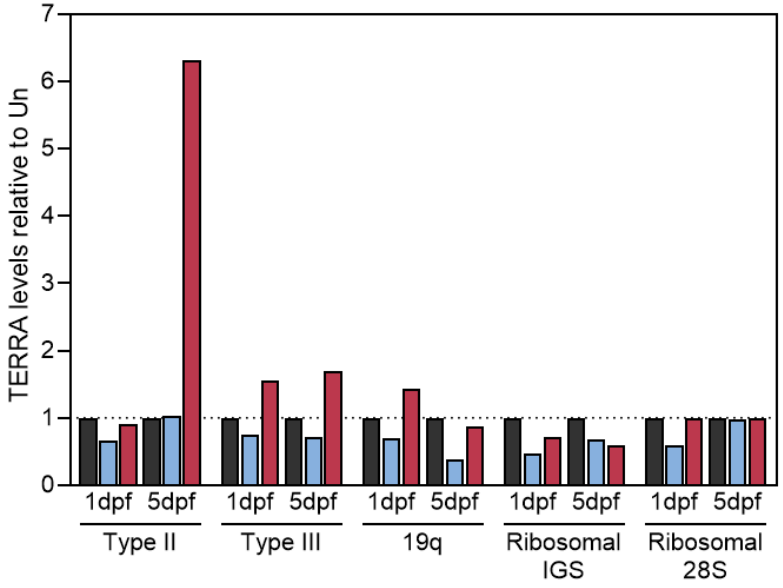


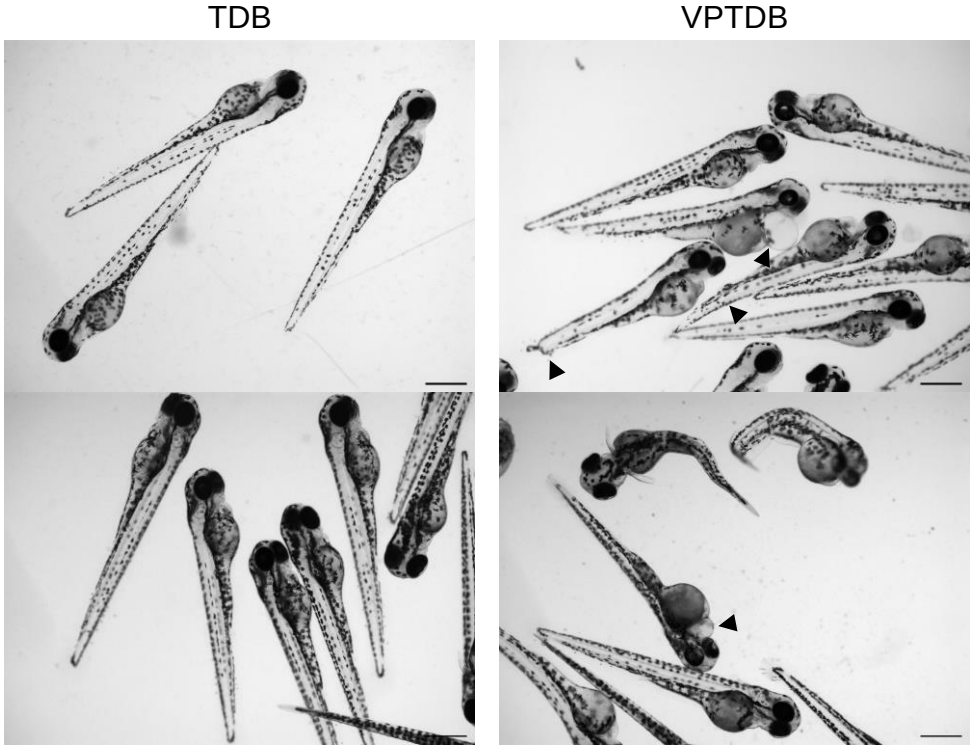


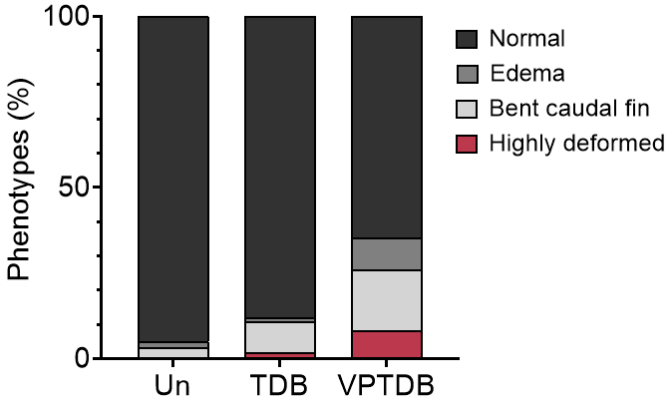






Effects on enhanced TERRA transcription on zebrafish development





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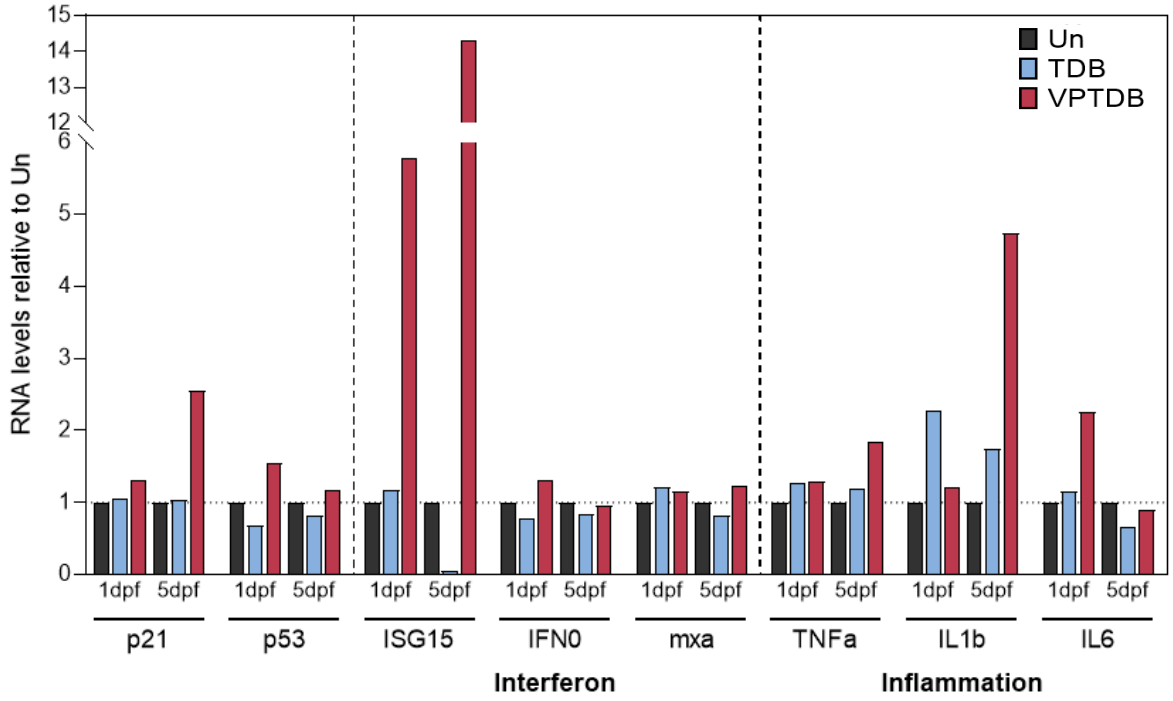
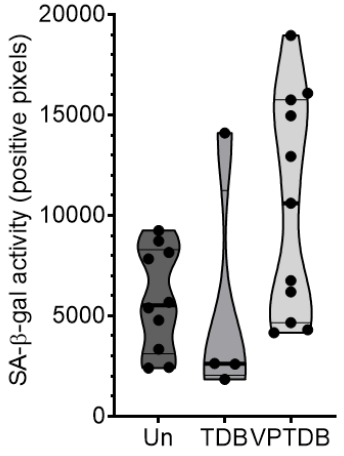




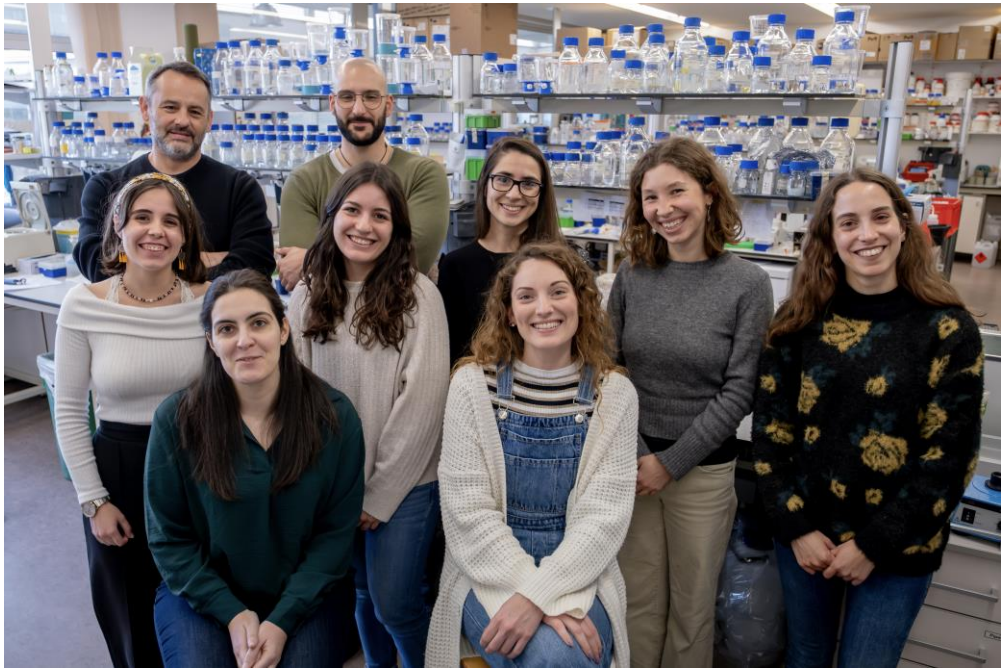
Summary 2

- **VPTDB-injected fish** represent a good system to induce TERRA transcription in zebrafish starting at its subtelomeric promoter
- An initial boost in TERRA expression is sufficient to cause **abnormal development** in zebrafish embryos
- Fish with induced TERRA transcription show signs of **premature aging** (edemas and curved caudal fin)
- Induced TERRA transcription caused **interferon response and inflammation**

Outlook:

1. Is telomeres length affected by TERRA overexpression?
2. What are the downstream effectors?
3. Are specific organs/tissues more affected than others?
4. Activating TERRA transcription in a tissue specific manner would cause a systemic effect?

Thank you!



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