



Biotechnet Meet-Up 2025: Biotech and Aging

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why some organs age faster than others

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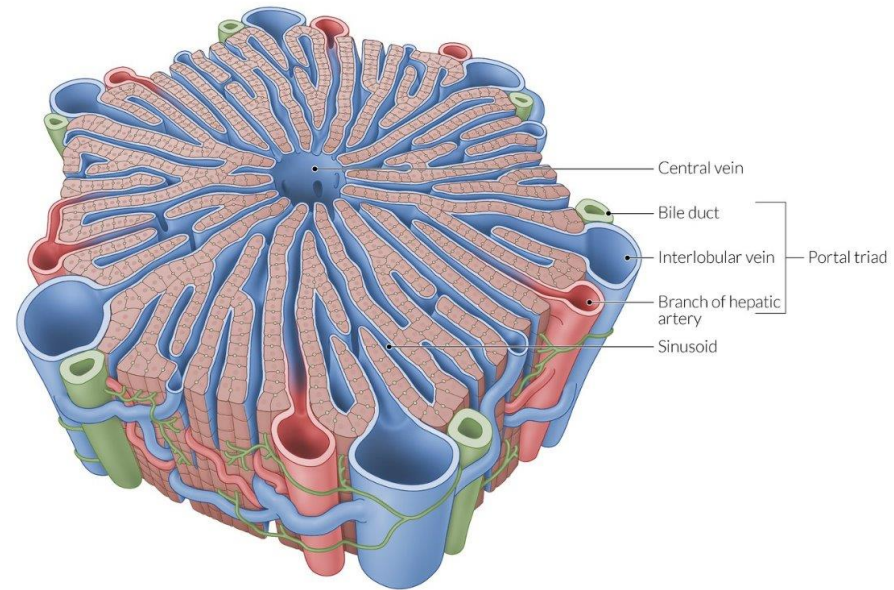
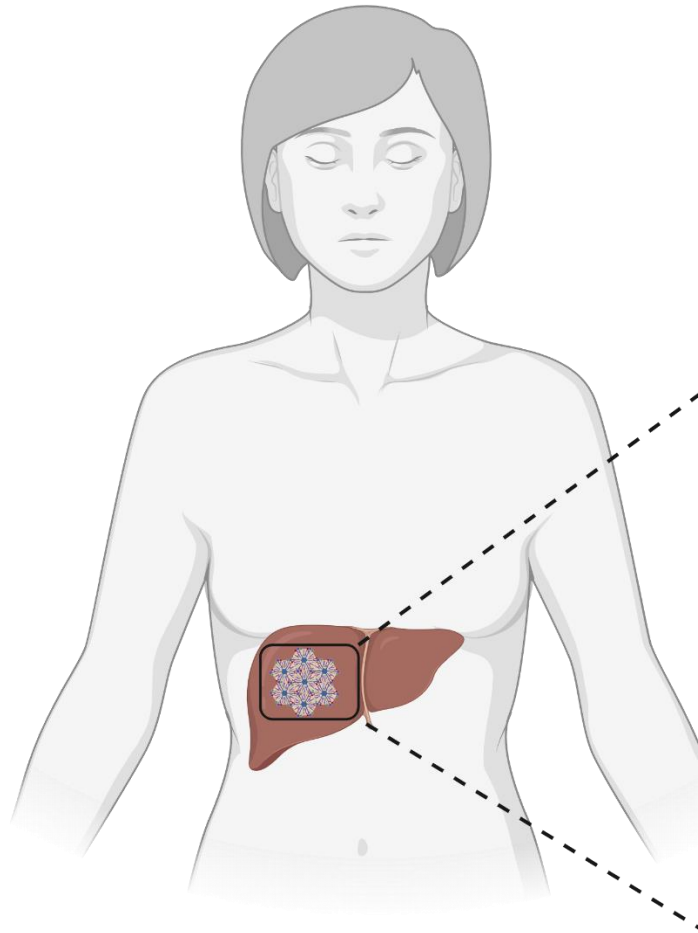
Deborah Stroka



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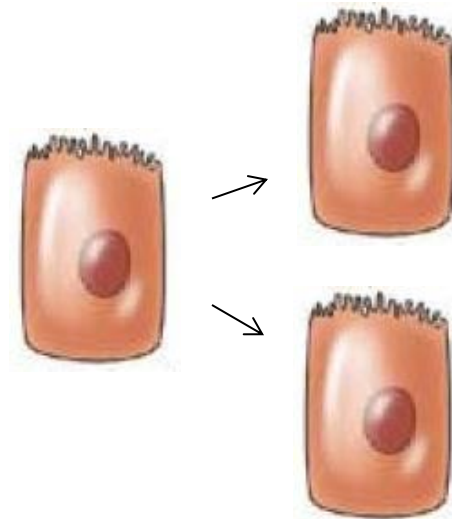
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Liver



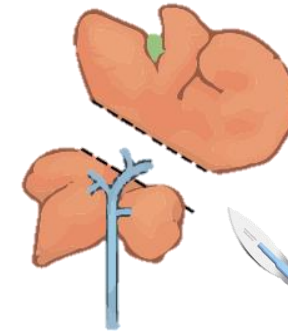
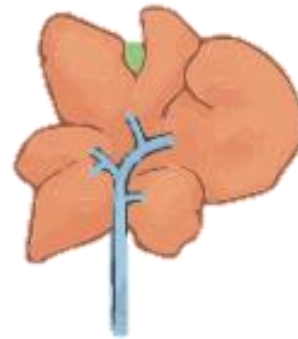
The Liver Regenerates (excellent organ to study)

hepatocytes re-enter cell cycle



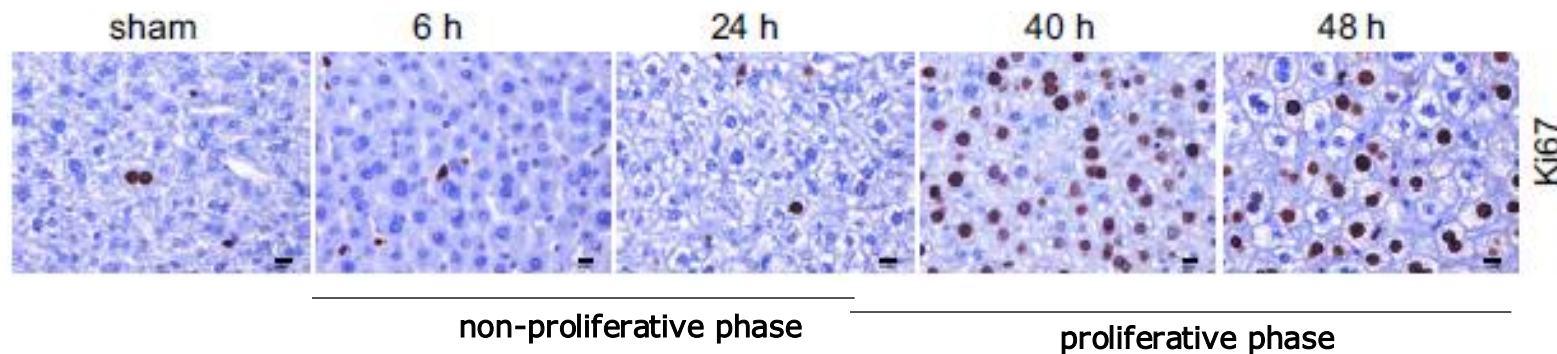
- sense lost or damaged tissue
- signaling cues to proliferate
- metabolic state
- replicate DNA

Mouse Liver is an Ideal Organ to Study DNA replication *in vivo*



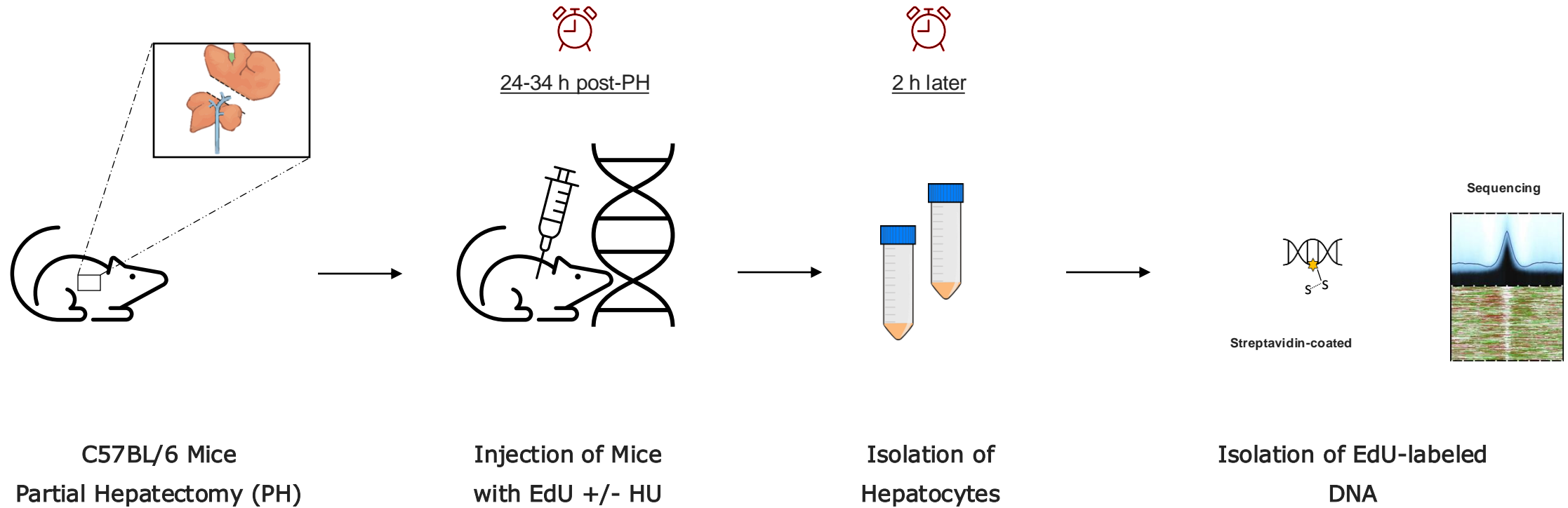
partial hepatectomy (PH)

Higgins & Anderson, 1931



Quiescent adult hepatocytes **synchronously** re-enter cell cycle after PH

Monitoring Origin Firing *in vivo*

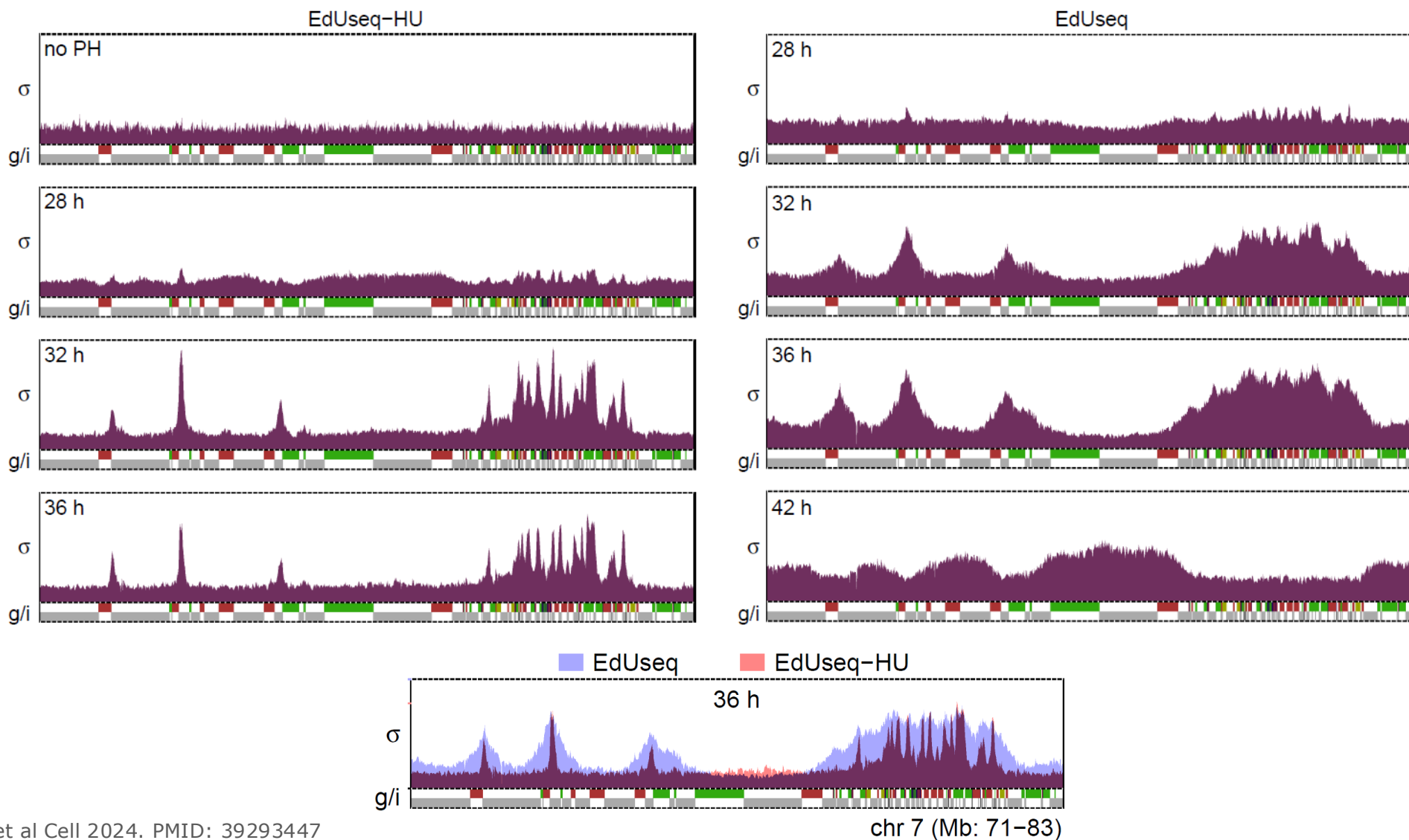


EdU: thymidine analog
HU: ribonucleotide reductase inhibitor



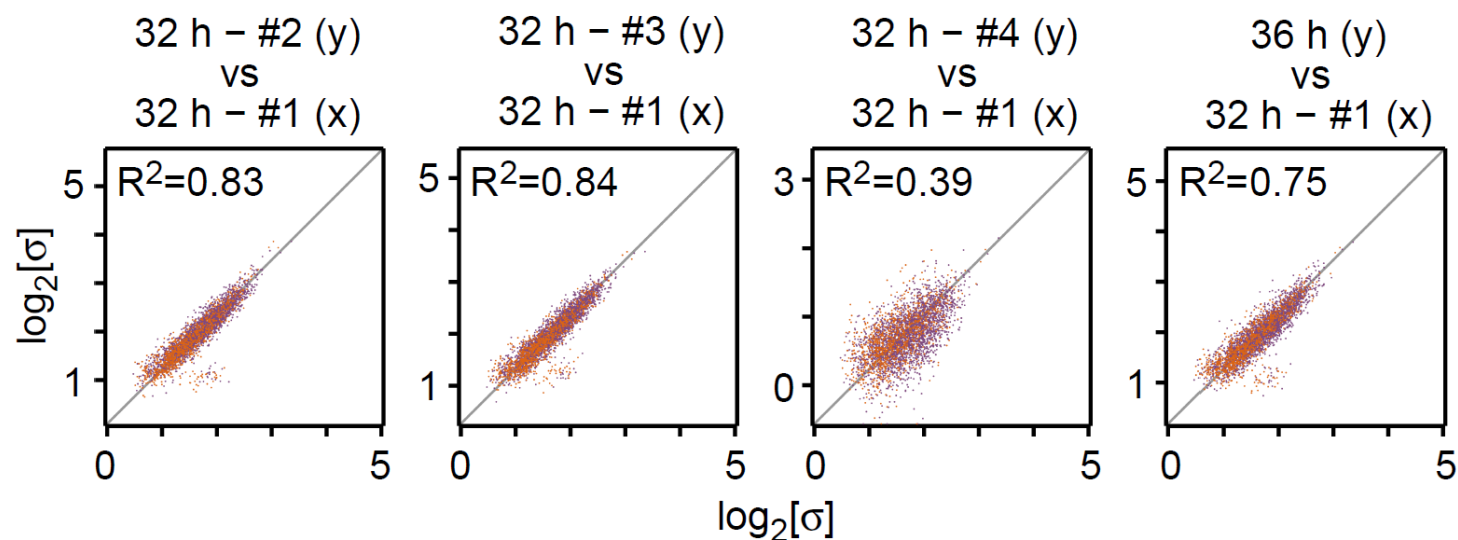
Origin Firing *in vivo*

Hepatocytes of Regenerating Livers of Young Mice



Origin Firing *in vivo*

Hepatocytes of Regenerating Livers of Young Mice

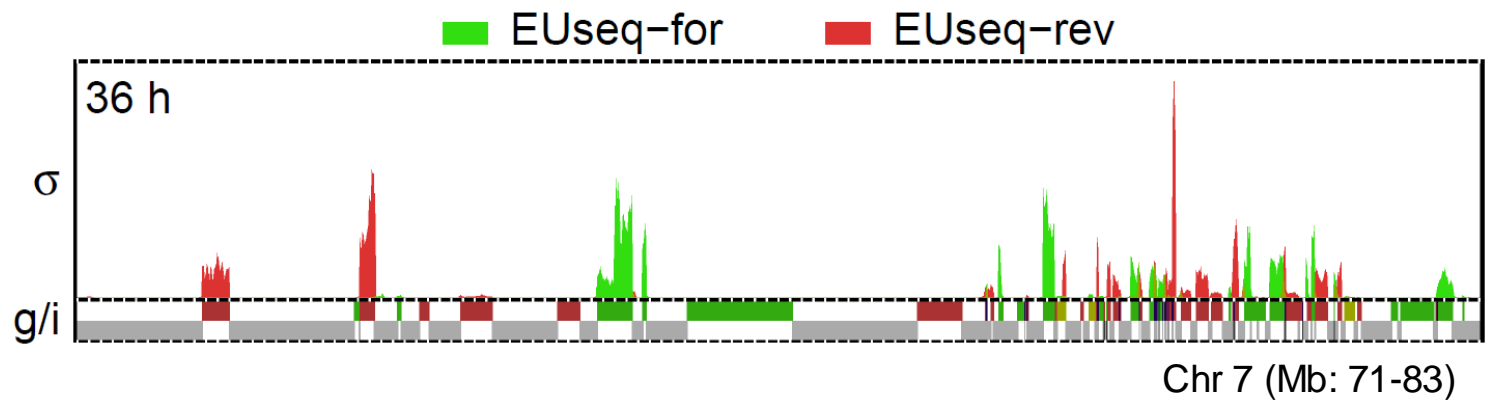


Reproducibility of Origin Firing Data
3,517 Origins identified by Peak-finding Algorithm

Nascent Transcription *in vivo*

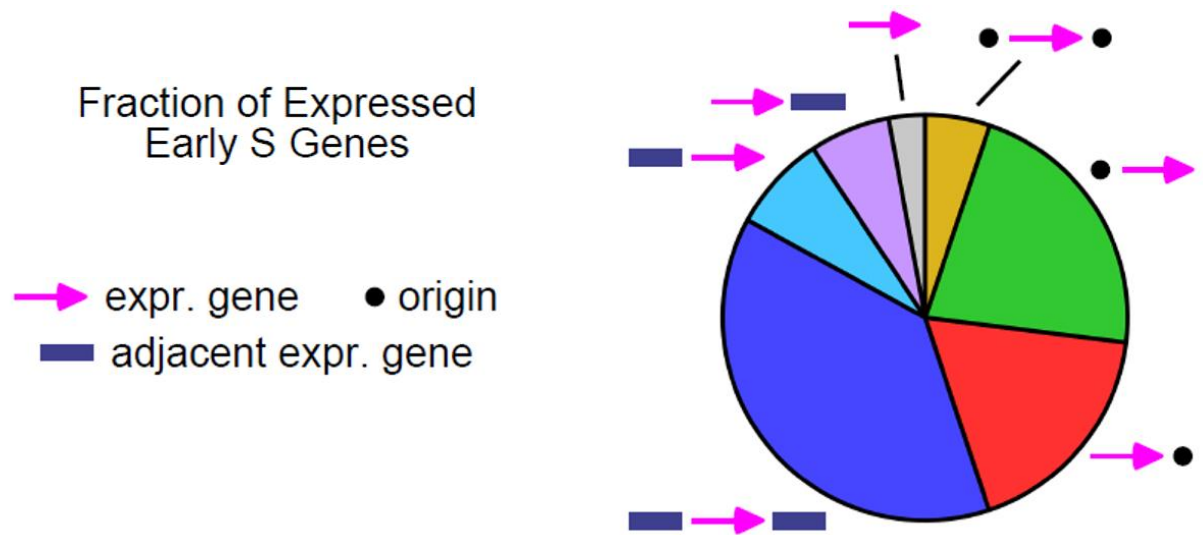
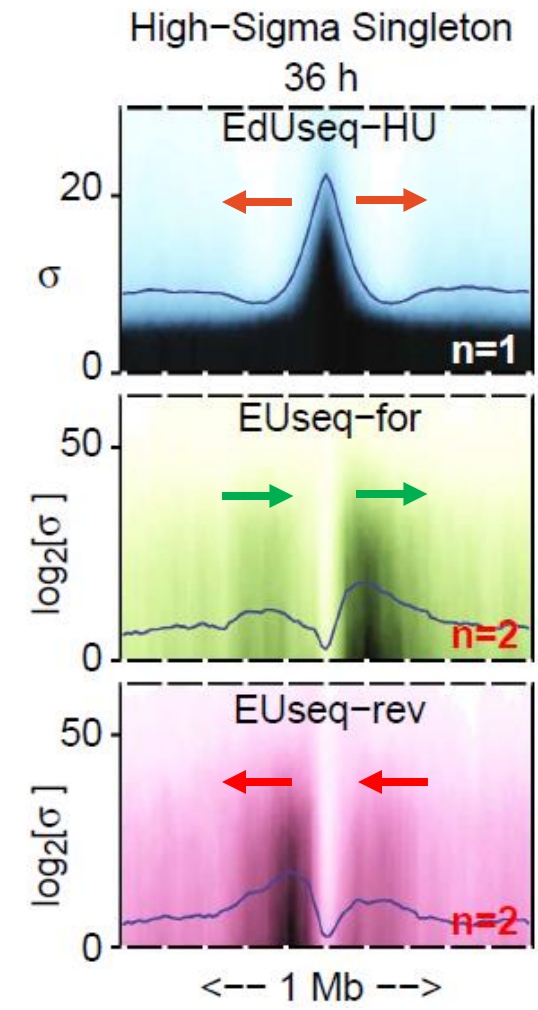
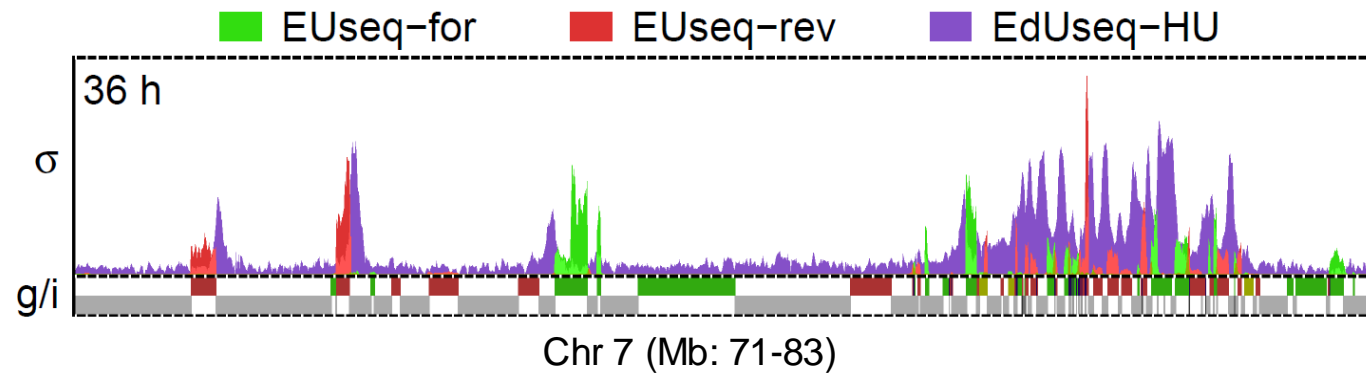


Partial Hepatectomy
↓
Injection of Mice with EU
↓
Isolation of Hepatocytes
↓
Sequencing of EU-labeled
RNA



Location of DNA Replication Origins

Origins are Intergenic, but near Expressed Genes



The Aged Liver

1. Changes in Liver Structure

2. Alterations in Detoxification

3. Changes in Metabolism

- lipid metabolism → fat accumulation in the liver (steatosis).
- glucose metabolism → insulin resistance and diabetes.

4. Increased Susceptibility to Disease

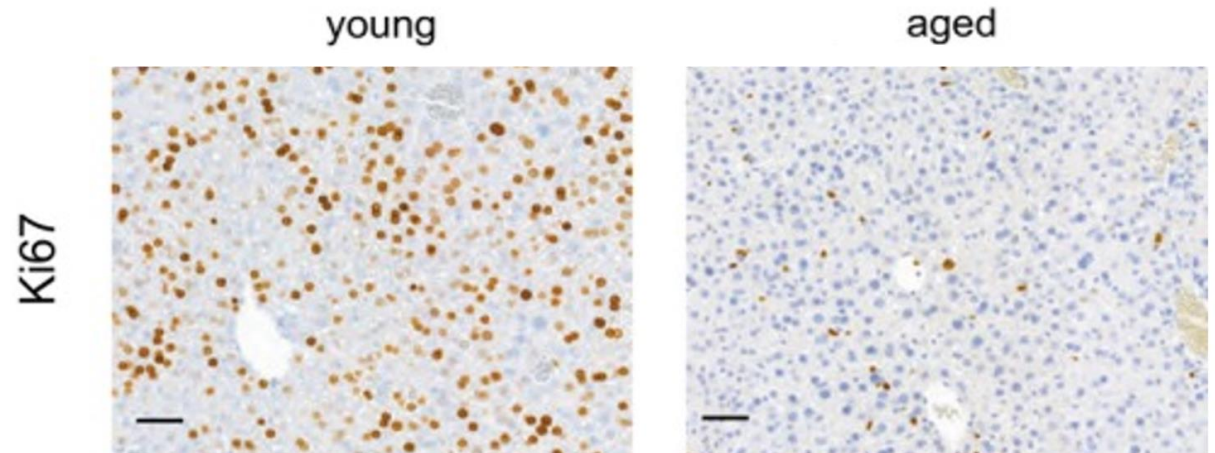
- prone to diseases
- less efficient immune response

5. Accumulation of Cellular Damage

- reactive oxygen species (ROS) and oxidative stress
- cellular senescence increases

6. Reduced Regenerative Capacity

Hepatocyte Proliferation is Impaired in Aged Mice following PH

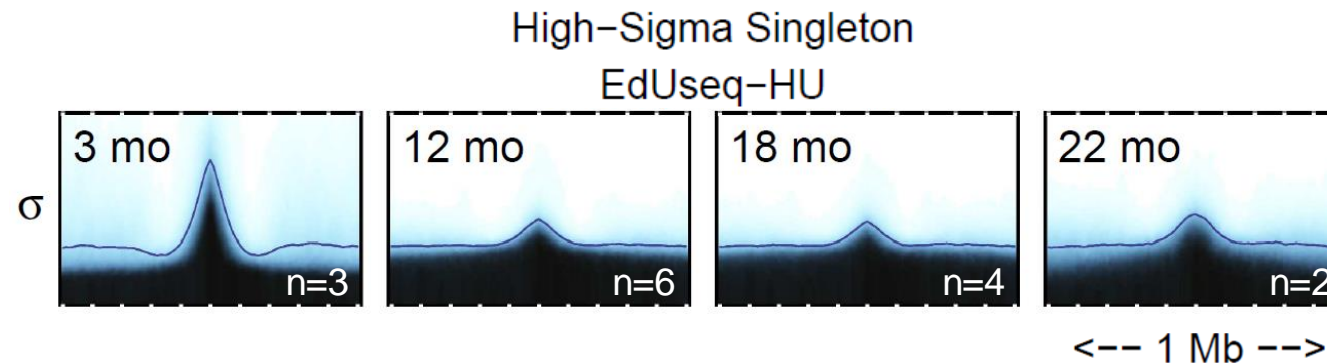
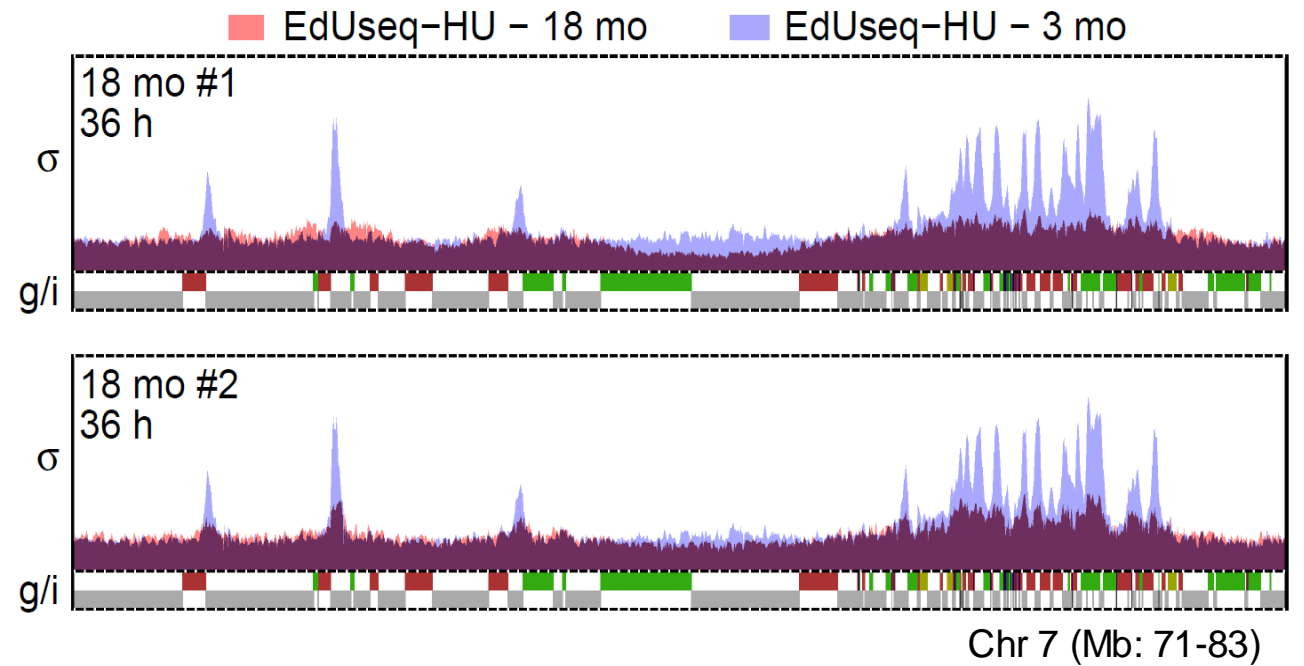


Loforese et al. EMBO Mol. Med. (2017)

“The loss of regenerative capacity is the most dramatic age-associated alteration in the liver”

Timchenko et al., 2009

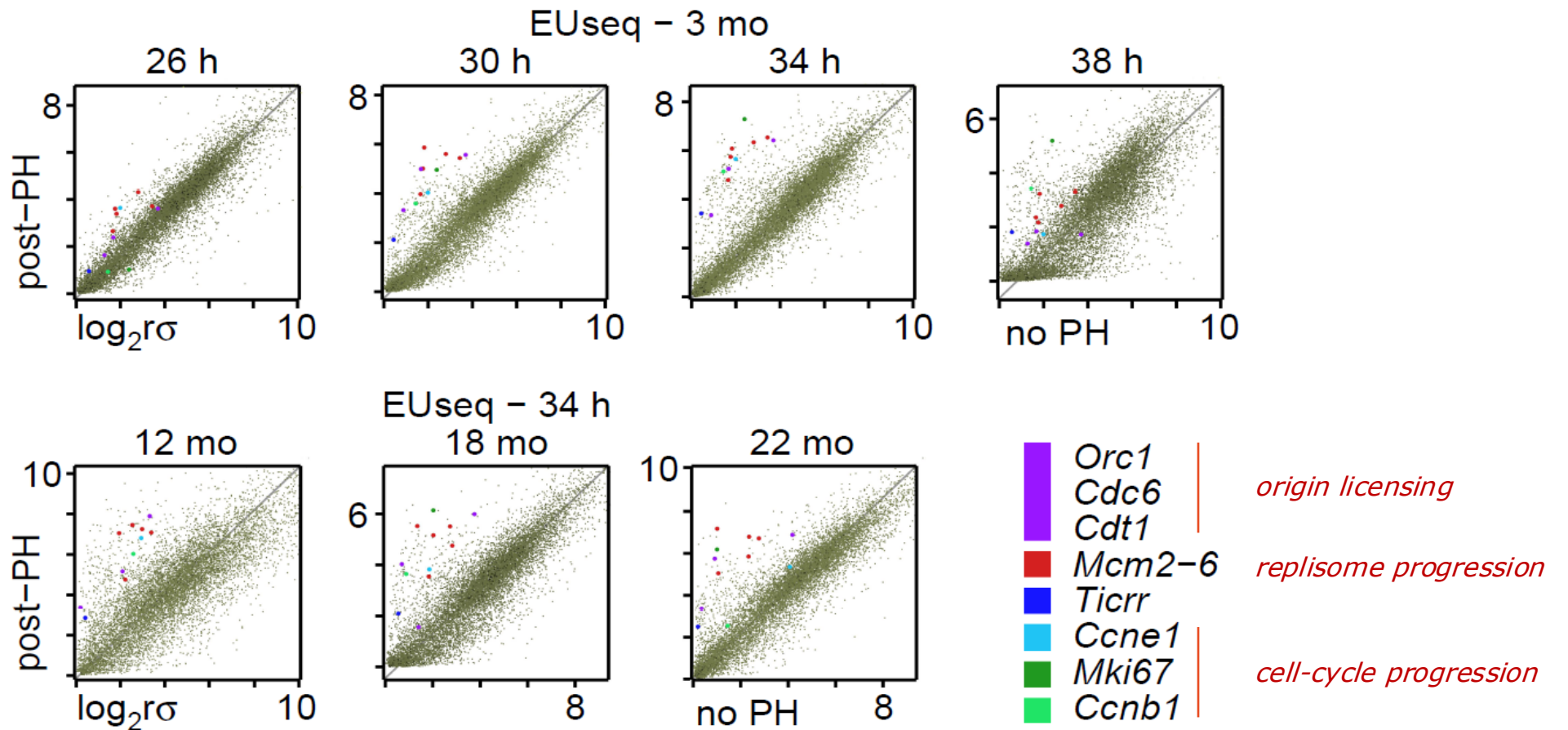
Reduced *in vivo* Origin Firing in Regenerating Livers of Aged Mice



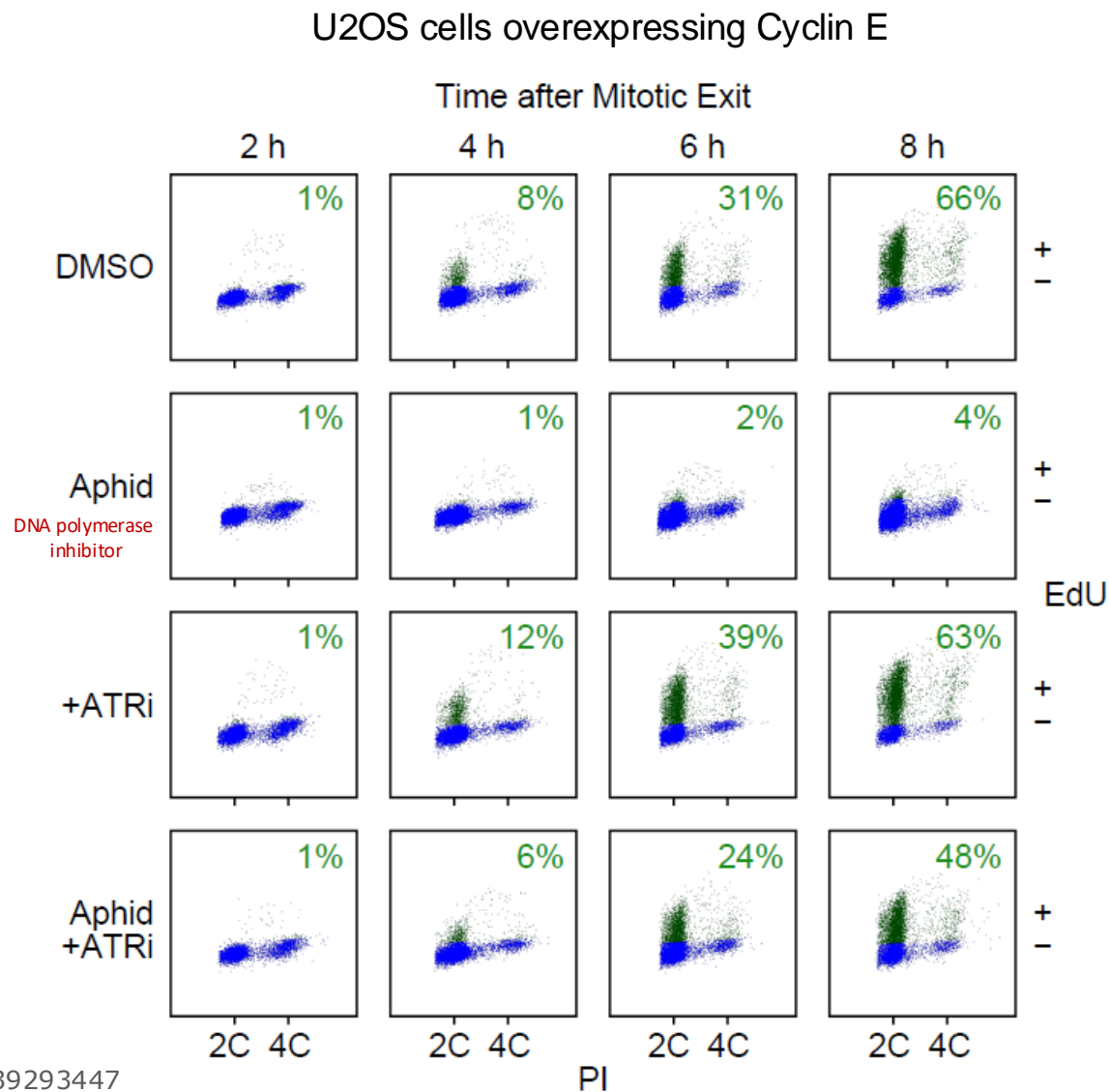
Reduced in vivo Origin Firing in Regenerating Livers of Aged Mice

no defect in induction of gene expression in aged mice

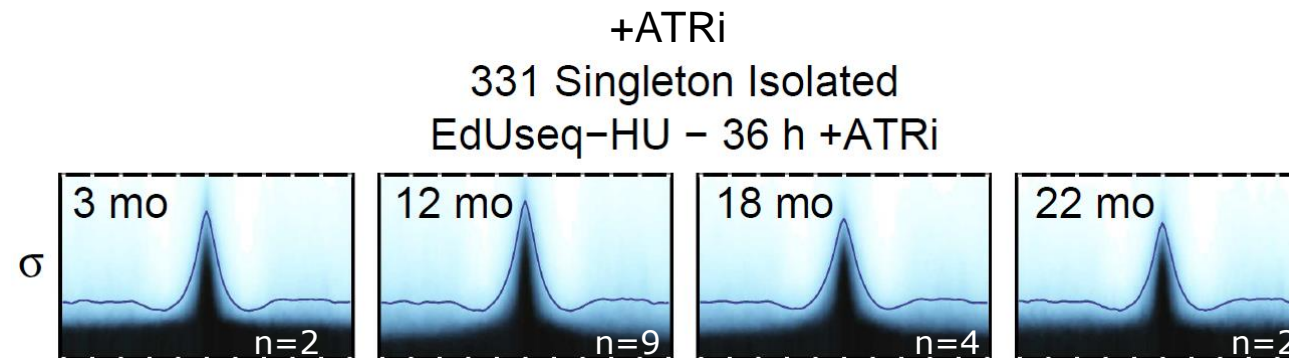
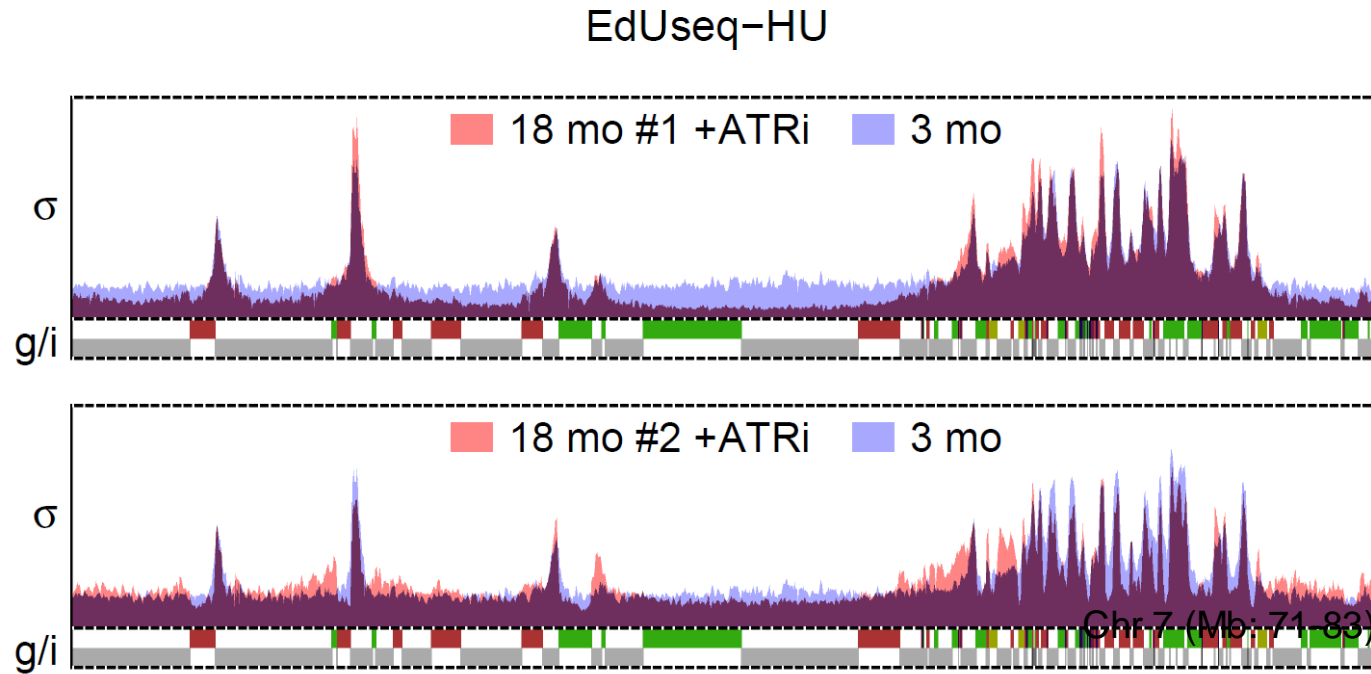
Nascent Transcription Data



ATR Suppresses Origin Firing in Cells that Experience DNA Replication Stress upon Entering S Phase



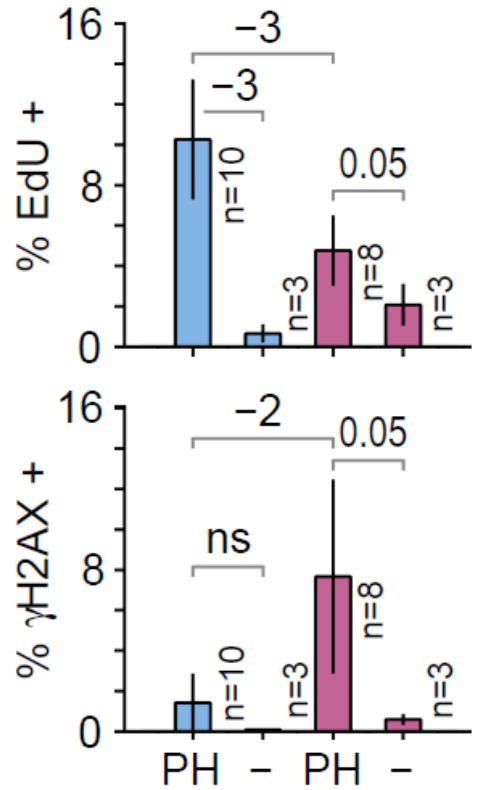
An ATR Inhibitor enhances the Efficiency of Origin Firing in Regenerating Livers of Aged Mice



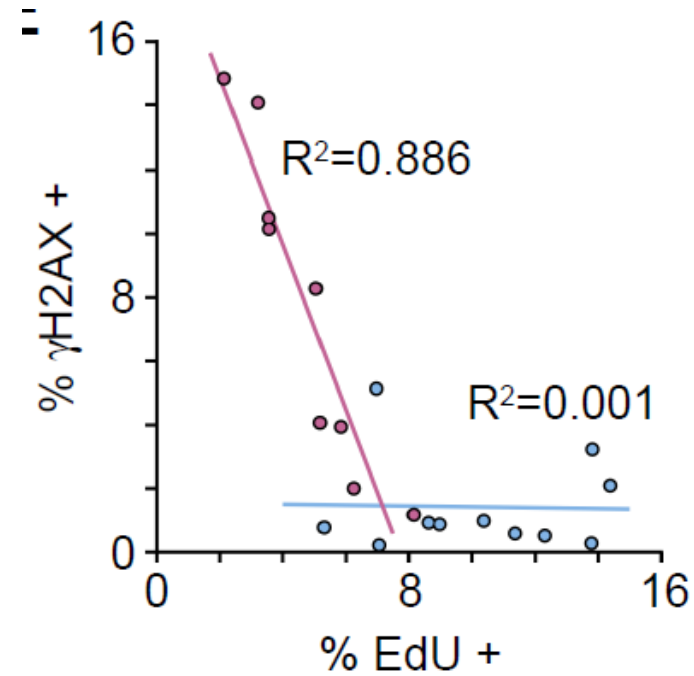
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Liver Regeneration in Aged Mice

Association with Induction of a DNA Damage Response



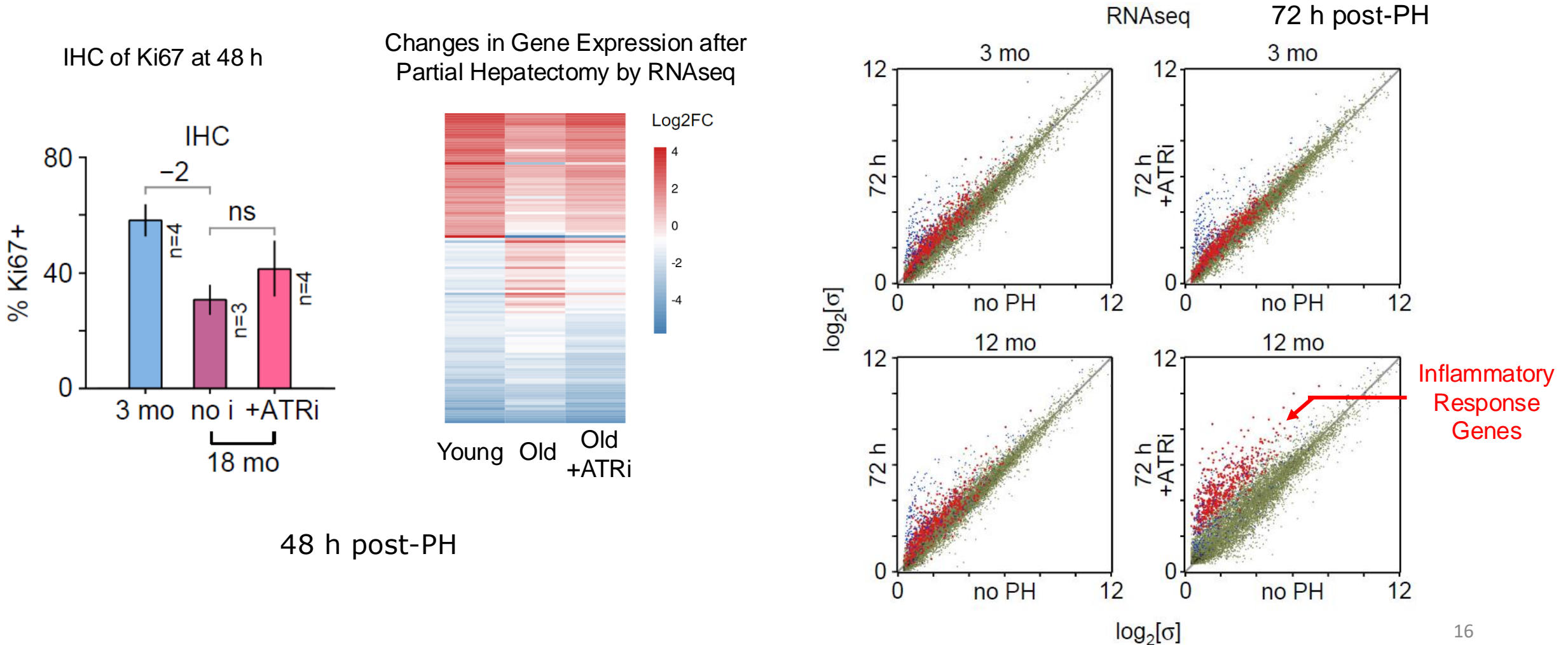
PH: partial hepatectomy



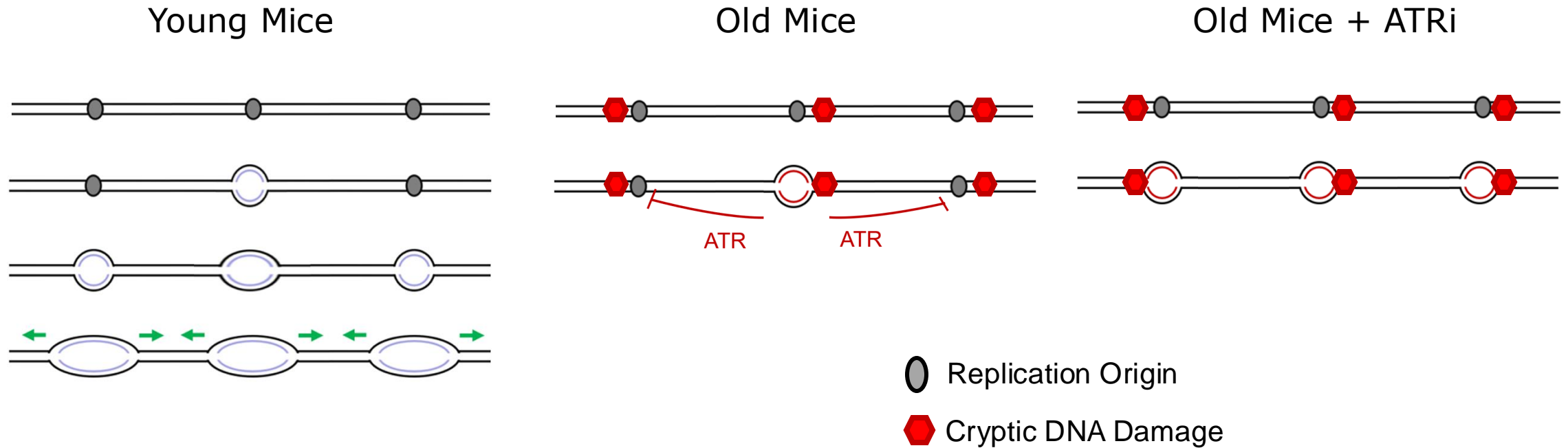
■ 3 mo ■ ≥12 mo

Liver Regeneration in Aged Mice

Partial Rescue by ATRi and Induction of an Inflammatory Response



Cryptic DNA Damage Model for Aging



Cause of cryptic damage?

- DNA interstrand crosslinks (ICL)
- aldehyde-DNA adducts
- oxidized bases
- abasic sites

Future Prospects

Approaches to Overcome Aging-Associated Defect in Liver Regeneration

- A. Combination of Agents to Suppress the Effects of the Stress Responses
- B. Induce Repair of the Cryptic DNA Damage, before stimulating Liver Regeneration

Relevance of these findings to other Organs

- A. Premature Aging?
- B. Aging-Associated Neurodegeneration?



Acknowledgements



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Giacomo Rossetti
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