# Shortened Telomeres Impact Liver Regeneration in Mice

**Michael Y. Hu**[1,2], Mark A. Tigue[1], Melissa M. Rowe[1], Klaus H. Kaestner[1]

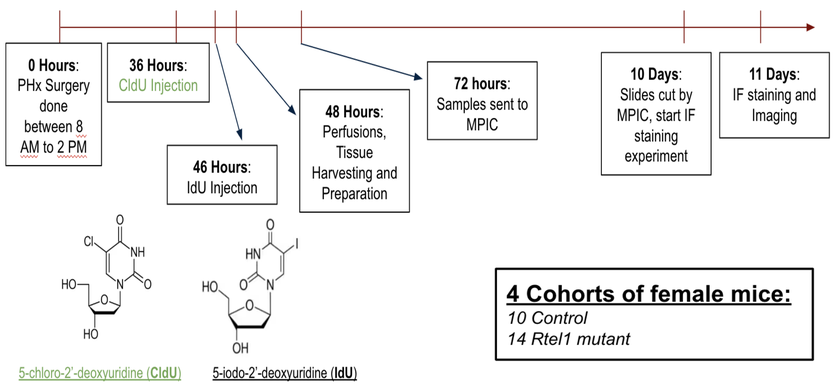
[1]Department of Genetics; University of Pennsylvania, [2]College of Arts and Sciences Class of 2026; University of Pennsylvania

## Introduction

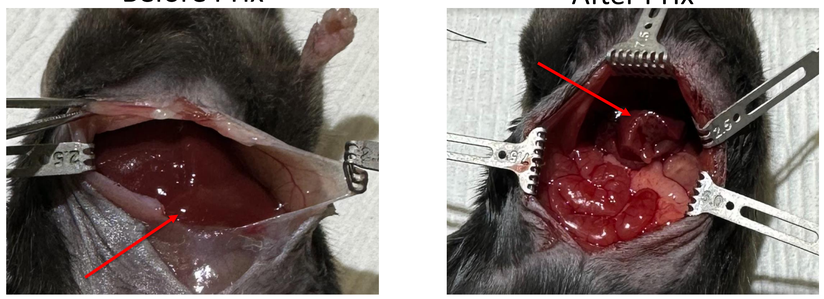
Telomeres, or the ends of linear chromosomes, consist of a short sequence (TTAGGG in humans and mice) repeated thousands of times and are complexed with shelterin proteins that protect chromosome ends and are thus critical for maintaining genomic integrity. The *Mus Musculus* C57BL/6 mouse has telomeres about 5 times longer than those of humans. Interestingly, the *Mus Spretus* mouse has 5-fold shorter telomeres than *Mus Musculus*, similar to the telomere length in humans. The Kaestner lab has recently generated an engineered C57BL/6 "telomouse" with human-length telomeres by introducing into *Mus Musculus* a single amino acid variation in the helicase 'Regulator of telomere elongation 1' (RTEL1) identified in *Mus Spretus*. These RTEL1 mice are fertile and overtly healthy.

The mammalian liver can regenerate following multiple forms of injury. Strikingly, following partial hepatectomy (PHx), where two-thirds of the liver is surgically resected, the remaining lobes of the mouse liver grow to compensate for the excised liver sections within one-week post-surgery. However, the extremely long telomeres of *Mus Musculus* do not become critically short following only a couple cell divisions. Here, we asked the question whether the shortened telomeres of *Rtel1* mice limit cell proliferation during short-term liver regeneration.

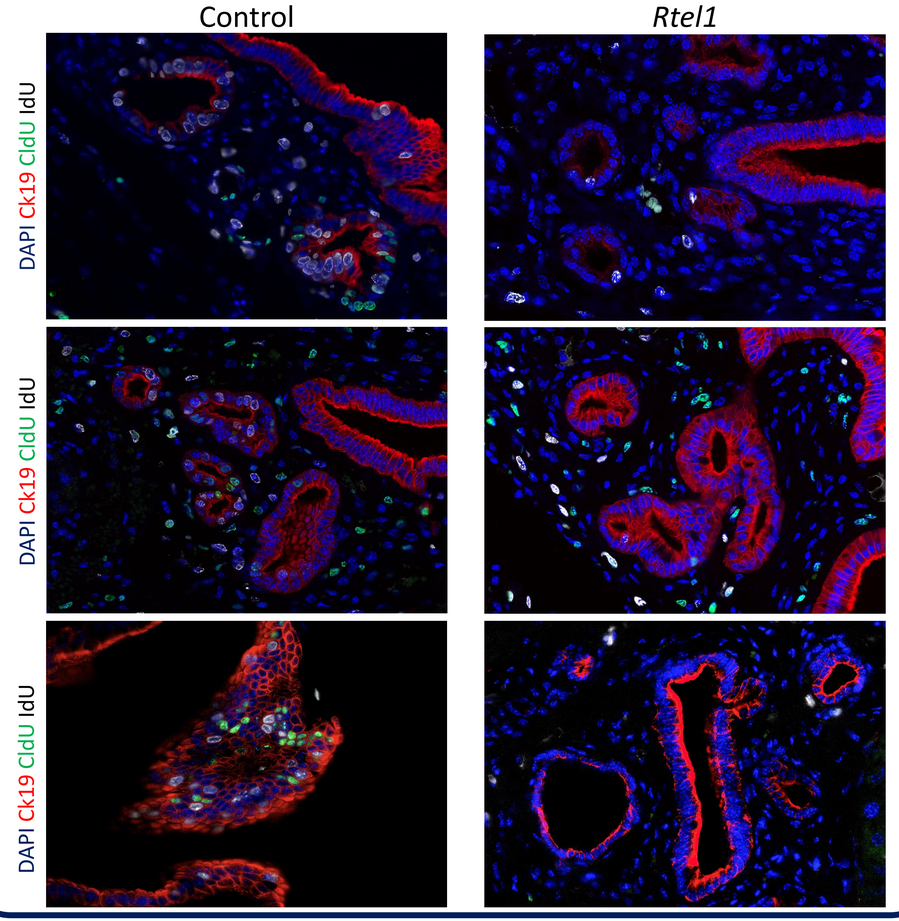
## Experimental Workflow



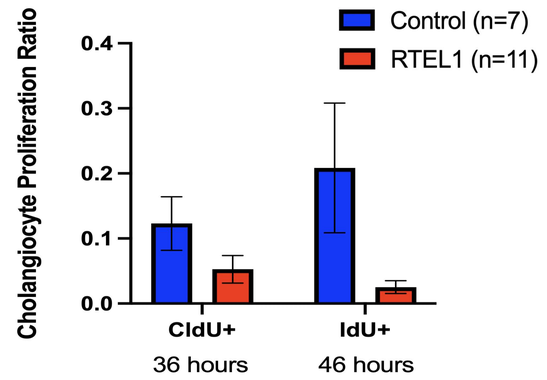

## Partial Hepatectomy (PHx) Surgical Procedure




## Representative Immunofluorescent Imaging Results




## Data Quantification




## Conclusion

- Cholangiocytes in *Rtel1* mutant mice exhibit less proliferative capacity than control mice during liver regeneration.
- Control mice exhibit significant proliferation rate at the 36 hours time point, and the rate further increased at the 46 hours time point.
- In contrast, *Rtel1* mutant mice display decreased cholangiocyte proliferation rate at the 36 hours time point and further decreased at the 46 hours time point.

## Future Experiments

- ALP/GGT tests for markers of cholestasis
- Hepatocyte staining for HNF4$\alpha$ and quantification of hepatocyte replication
- Sirius Red staining for fibrosis

## Funding

- NIH Grant funding to Dr. Kaestner
- Fall 2022 Goldfeder Family Undergraduate Research Grant to M.Y.H
- USSP Program: R25-DK066028