Read-through therapeutics reduce cystogenesis in a novel cohort of CRISPR base edited ADPKD organoids

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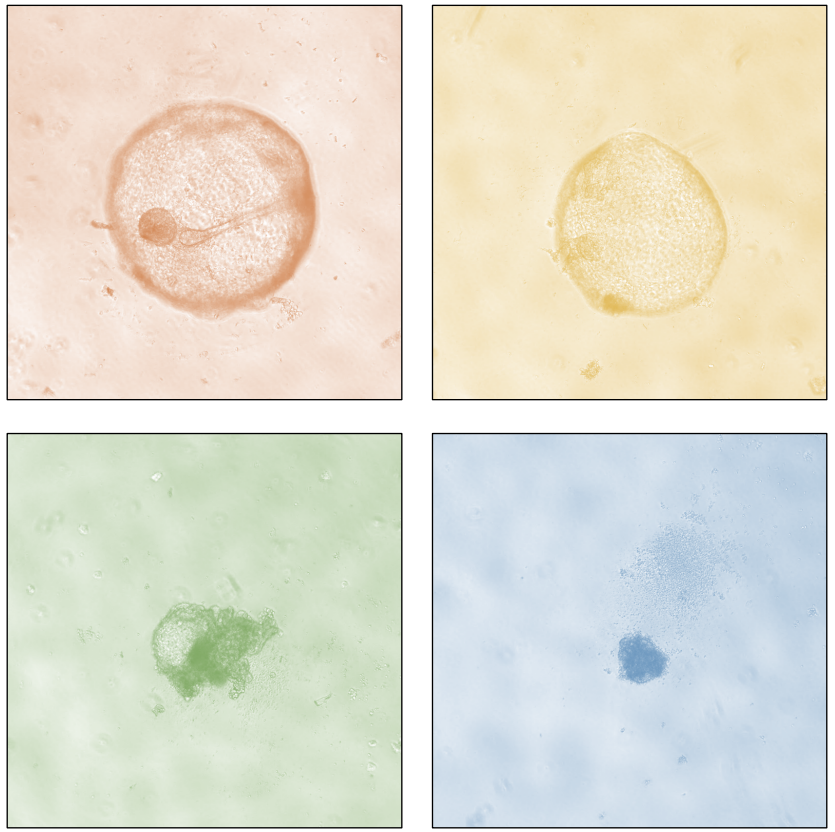
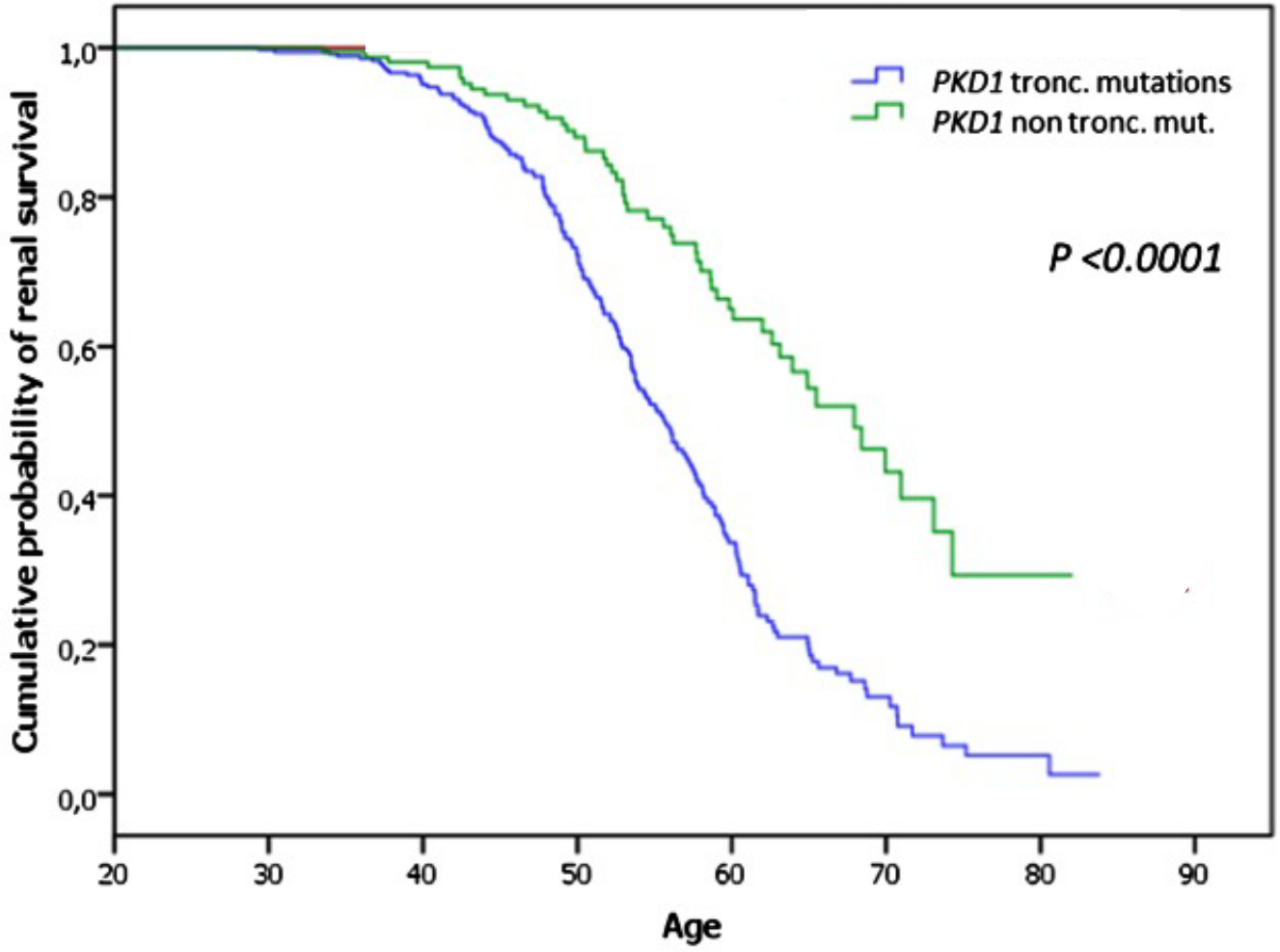


Nonsense mutations are severe and common in PKD



Cornec-Le Gall et al. *JASN* 2013

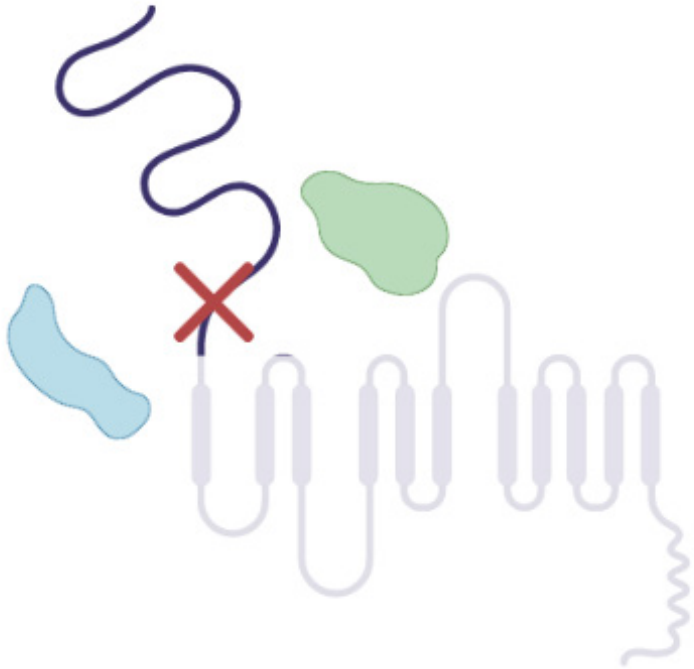
ADPKD Mutation Database:

38% of *PKD1* disease-causing mutations are nonsense mutations

50% of *PKD2* disease-causing mutations are nonsense mutations

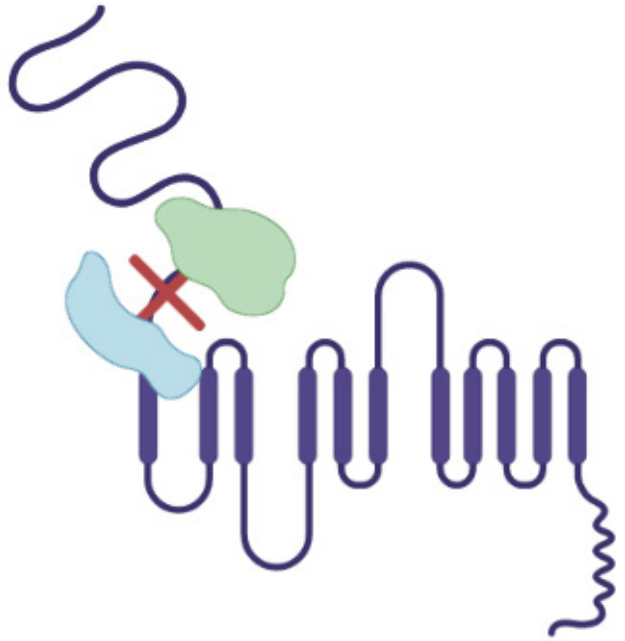
Novel compounds read-through premature stop codons

Untreated



Disengaged -> Truncation

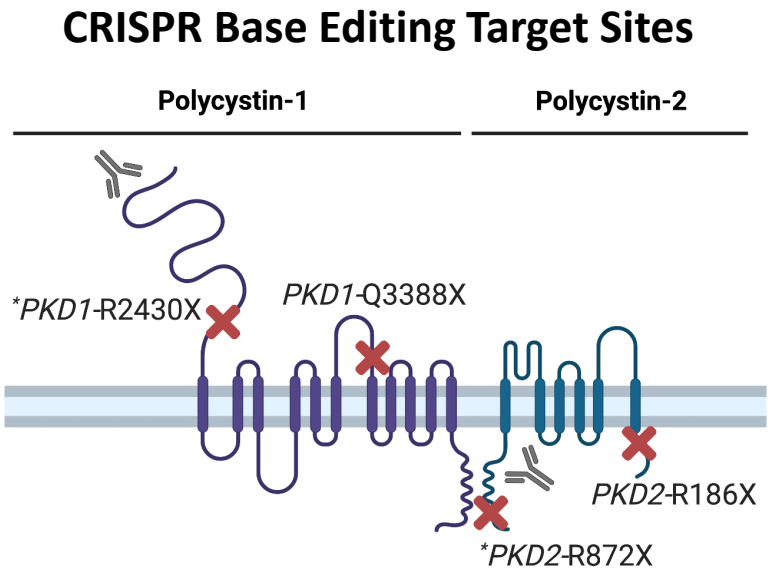
Treated

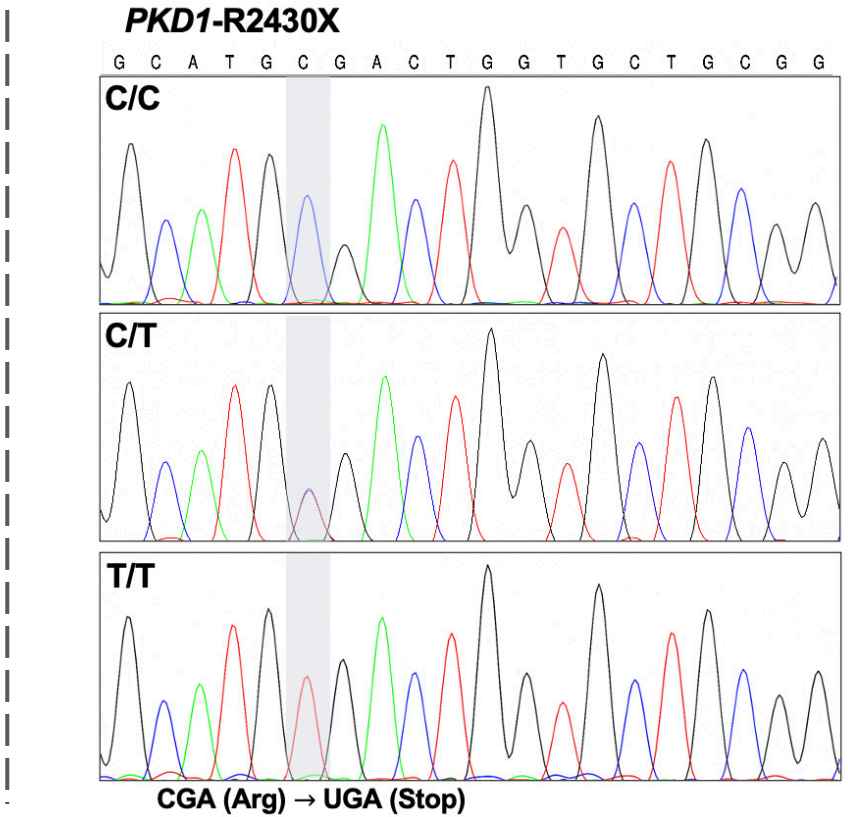


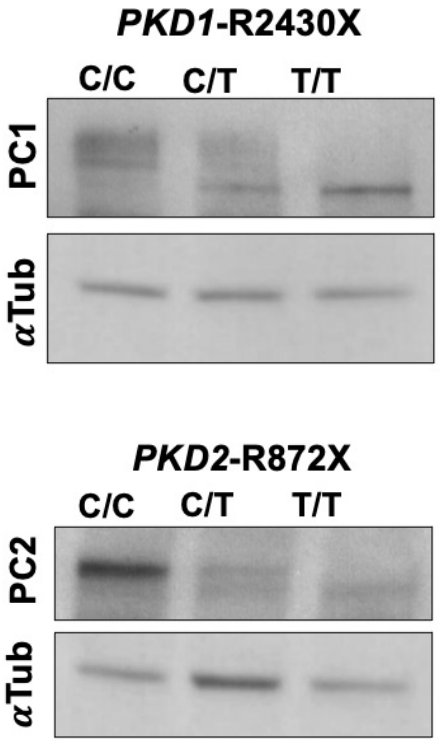
Engaged -> Read Through -> Full Length

Existing animal and kidney organoid models lack mutations amenable to read-through

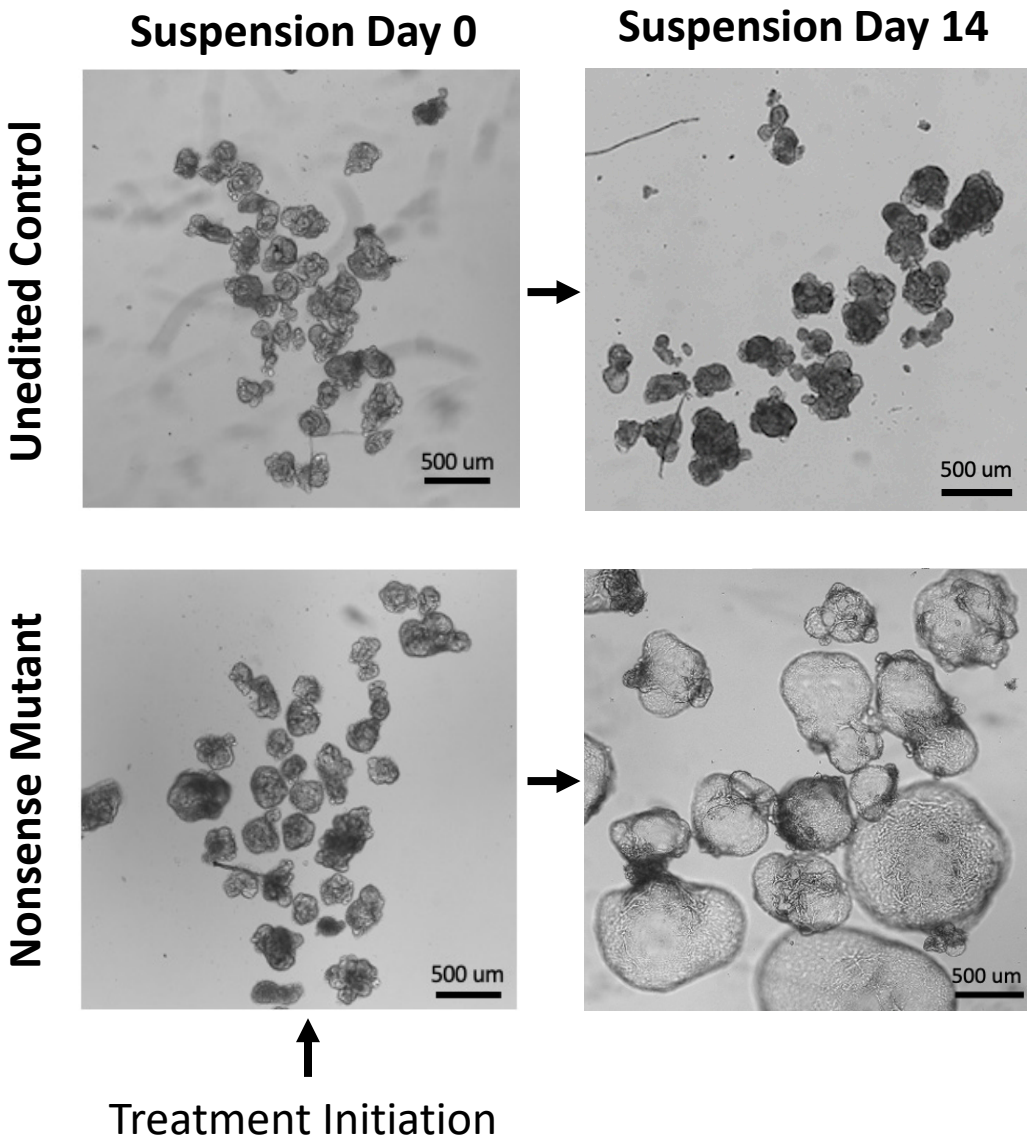
Nonsense PKD mutations can be modeled in hPSCs

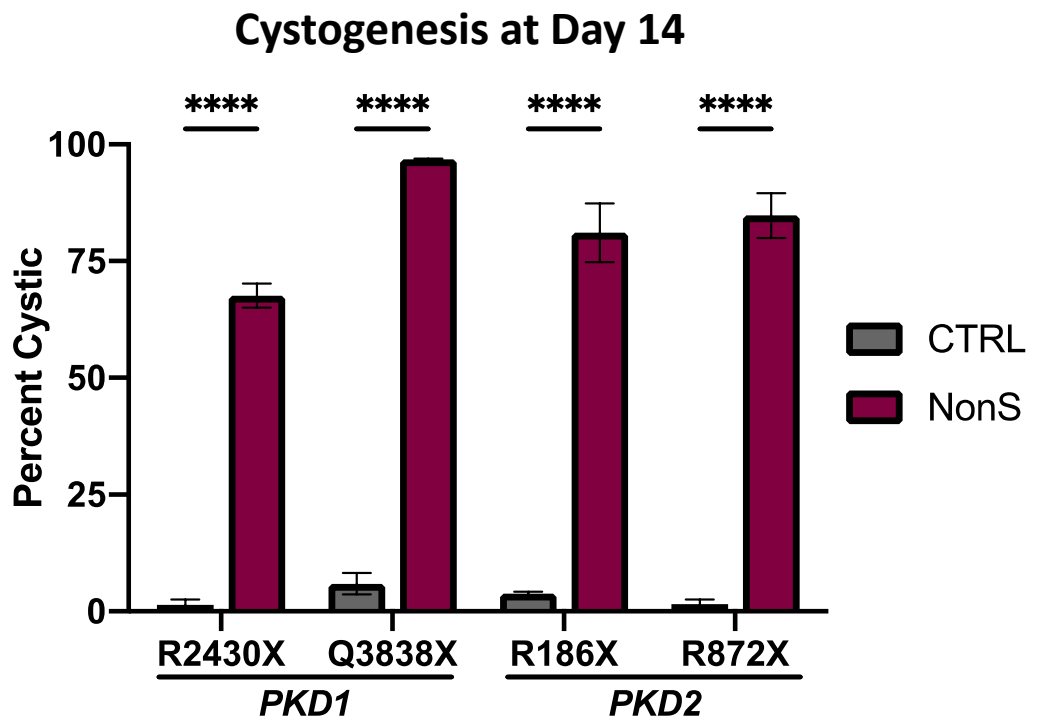




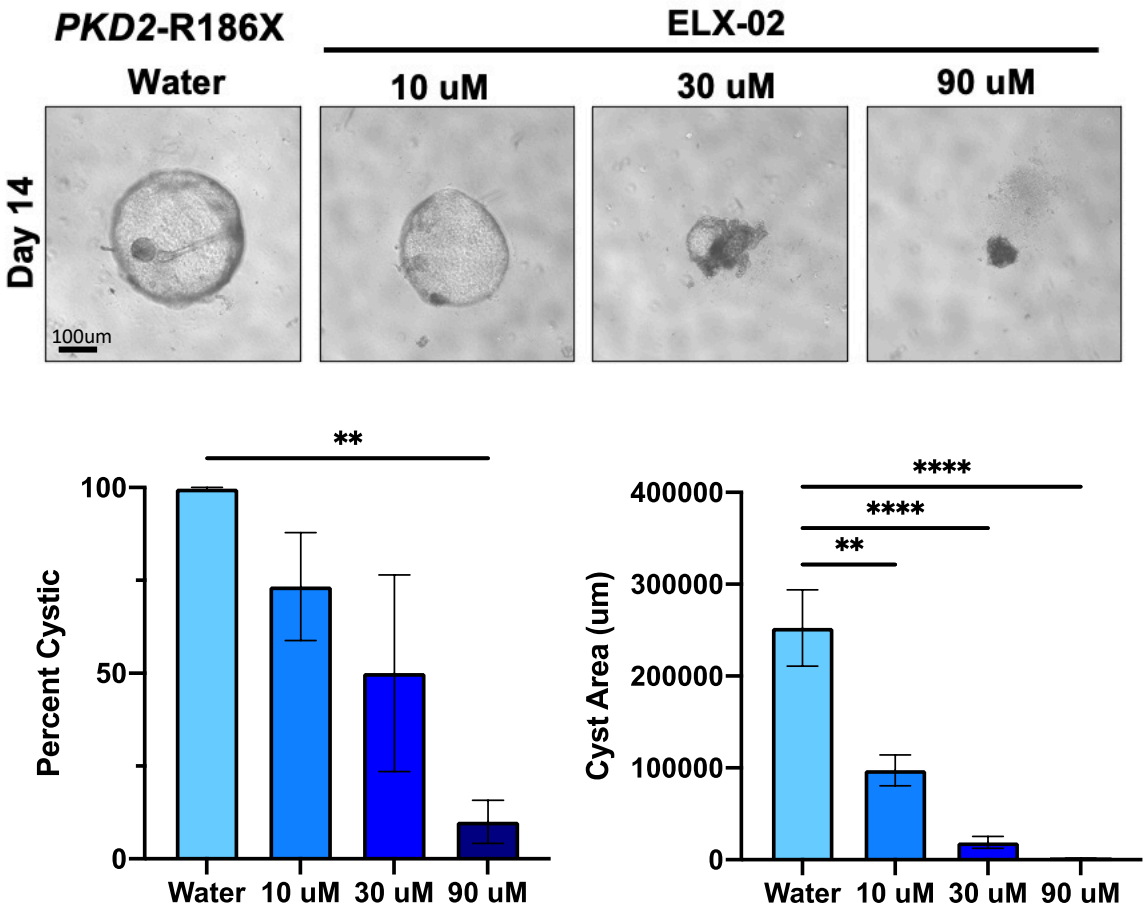


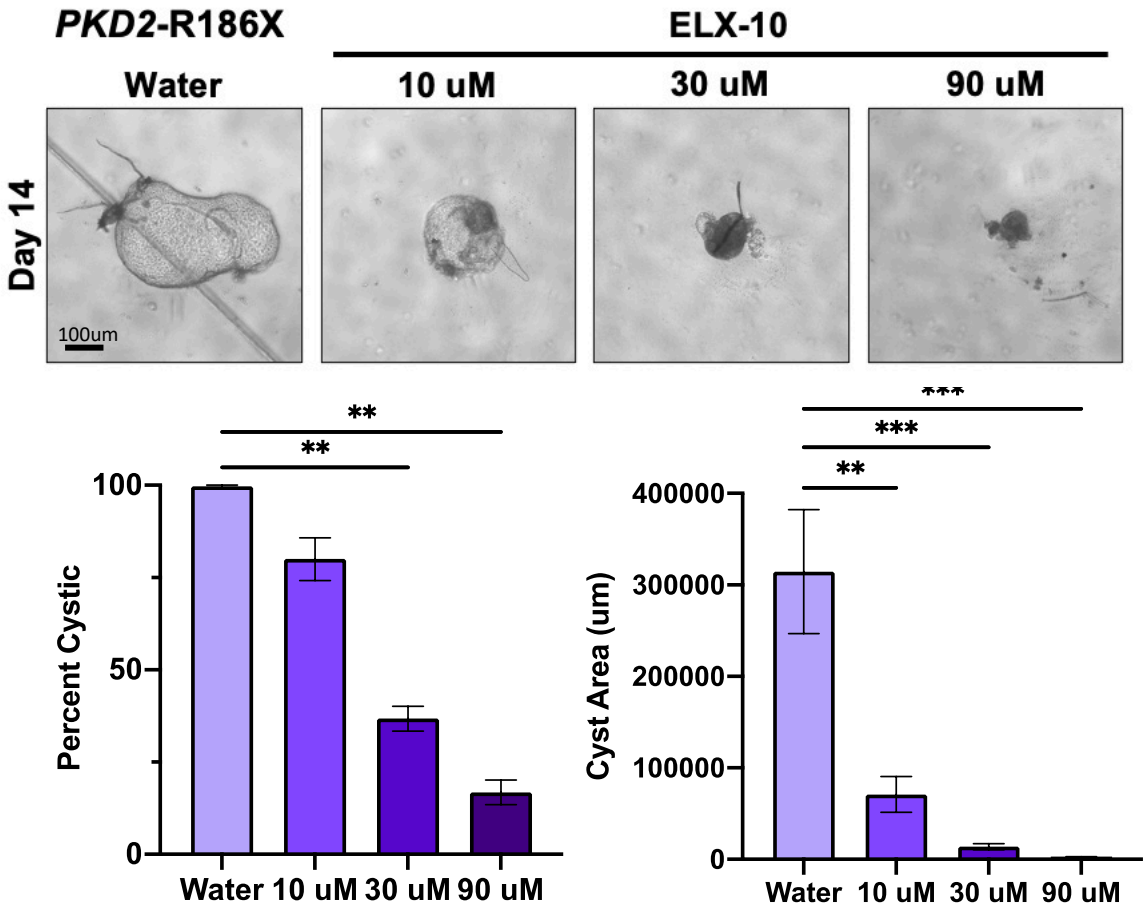
Nonsense kidney organoids form PKD-specific cysts



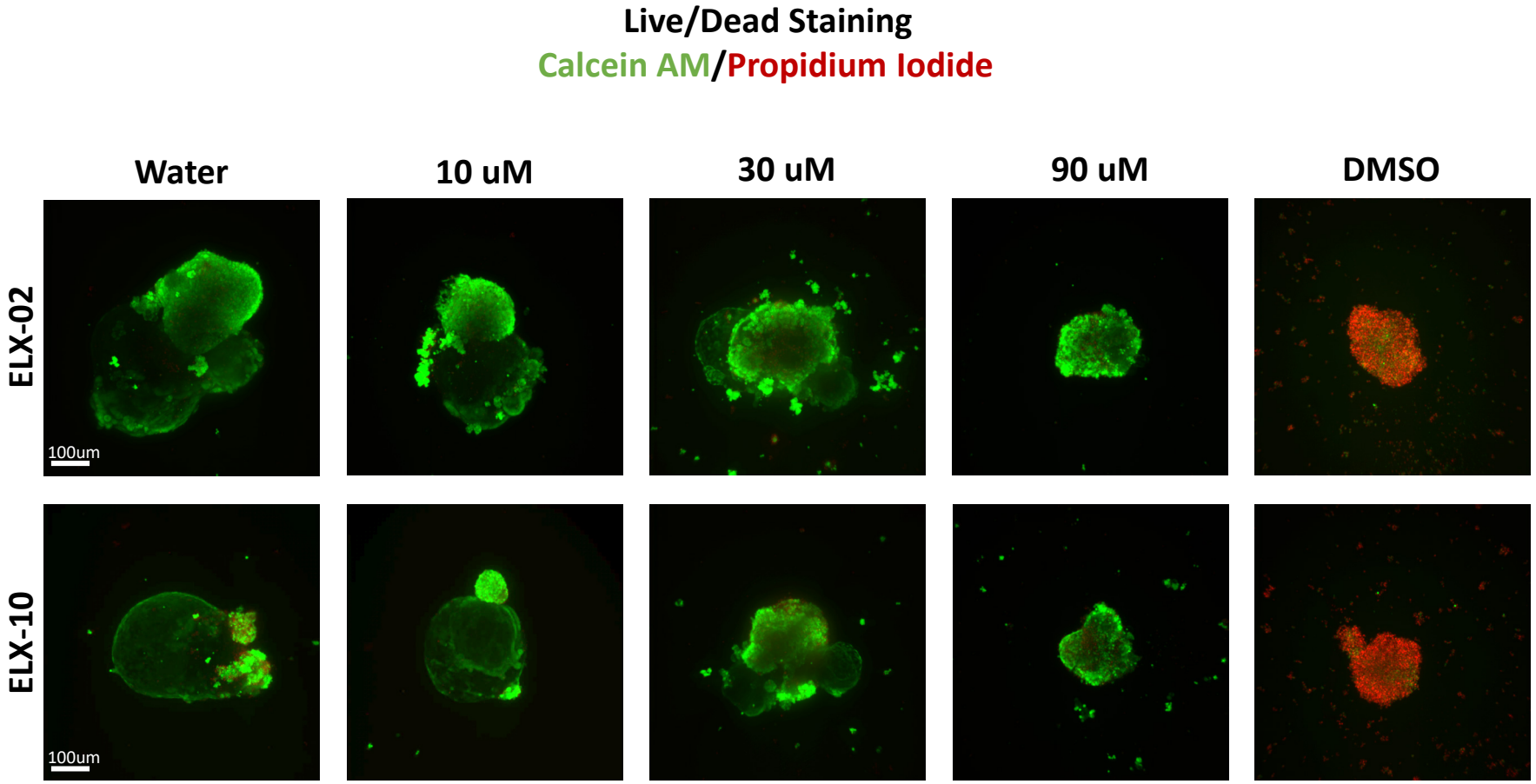


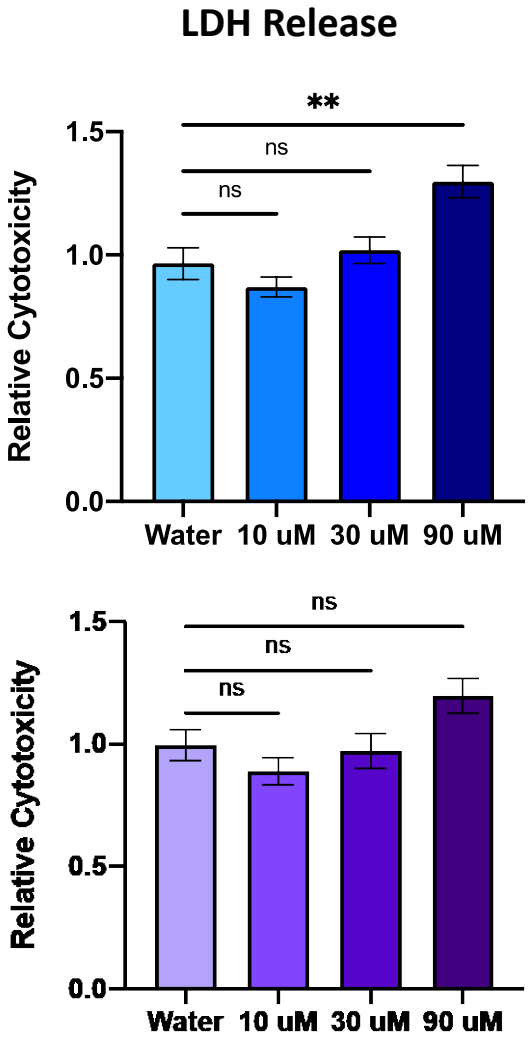
Nonsense read-through prevents PKD cystogenesis





Read-through is not associated with cytotoxicity

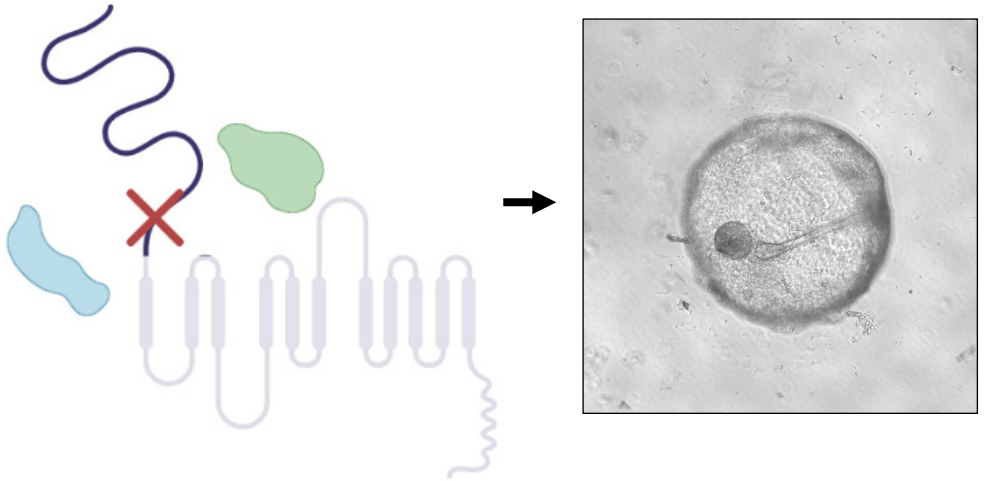




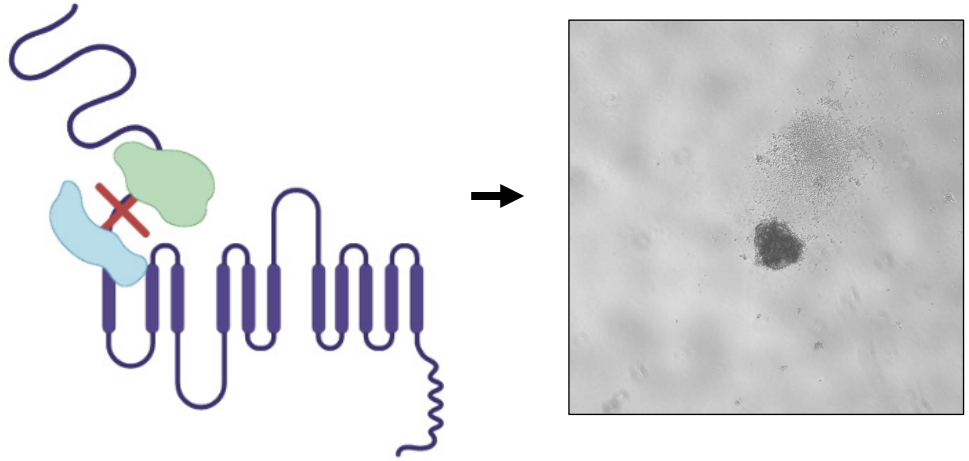
Conclusions & Future Directions

- Established CRISPR base edited ADPKD organoid cohort with patient targeted nonsense mutations
- Demonstrated read-through as a viable therapeutic approach for reducing cystic burden
- Future work will aim to determine efficacy in vivo

Untreated



Read-Through Compound Treated



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