Organoids as scalable models for splice modulation therapy development in Alport Syndrome

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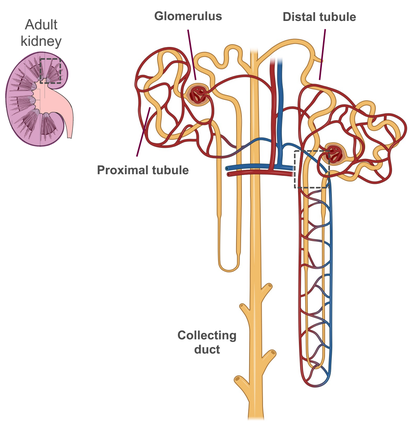
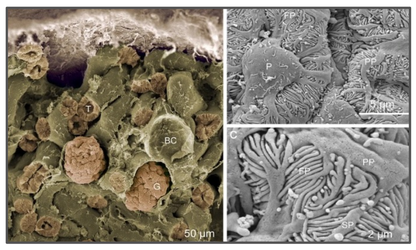
Introduction and Objective

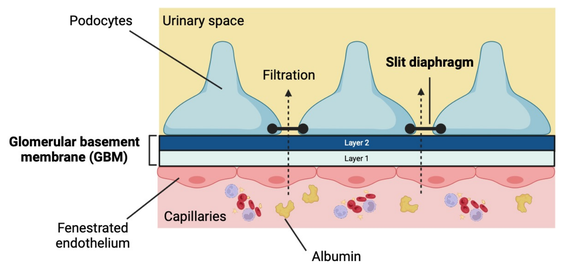
X-linked Alport syndrome (XLAS) is a hereditary glomerulopathy arising from genetic mutations in the *COL4A5* gene, encoding the α5 chain of the collagen IV [α5(IV)] in the glomerular basement membrane (GBM).

In a study on a cohort of **19 patients** with clinically proven XLAS, we identified deep-intronic variants responsible for the aberrant splicing events (17/19) using a **targeted RNA sequencing approach**.

The objective of this study is to develop a robust *in vitro* model for XLAS to characterize the disease and to test different therapeutic approaches including ASO therapy.

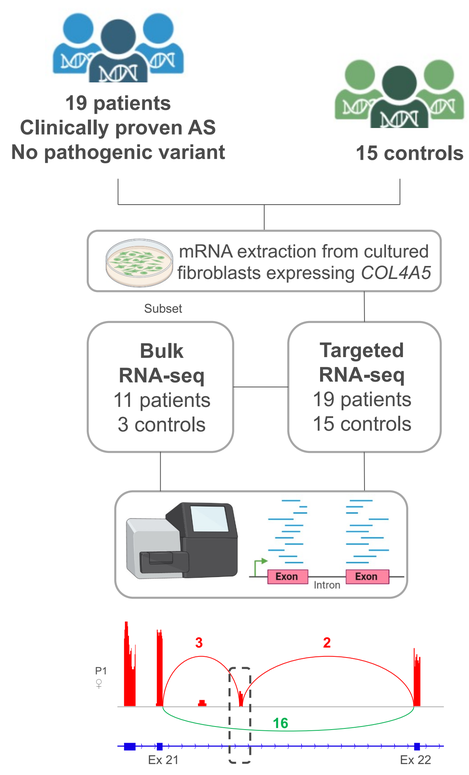


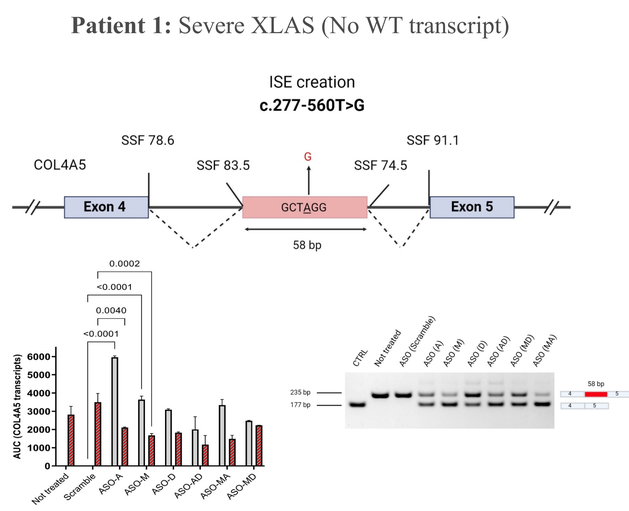


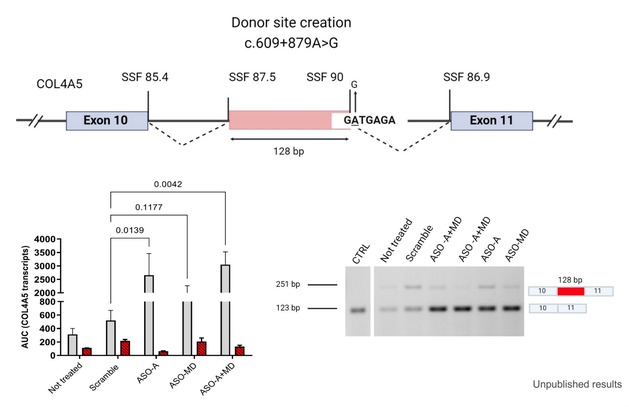


Andres et al., 2023; Naylor RW et al. Nat Rev Nephrol, 2021

Genetic Diagnosis – Splicing Variants





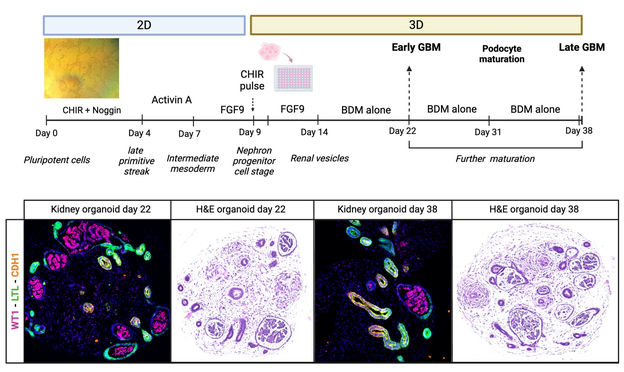


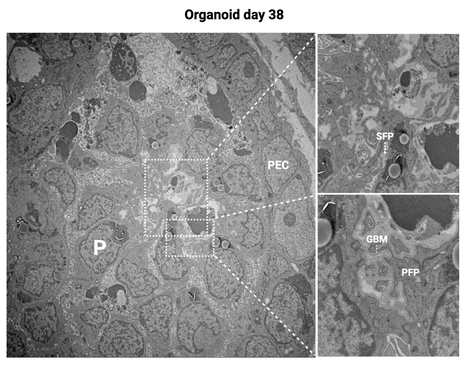
Boisson et al., Kidney International, 2023.

Unpublished results

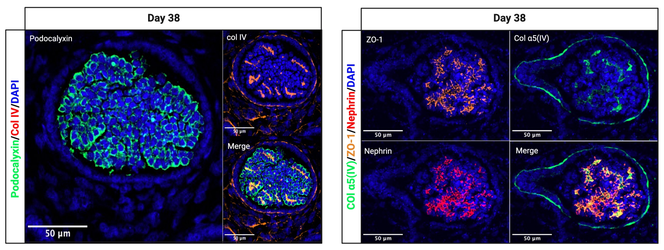
XLAS Organoid Model

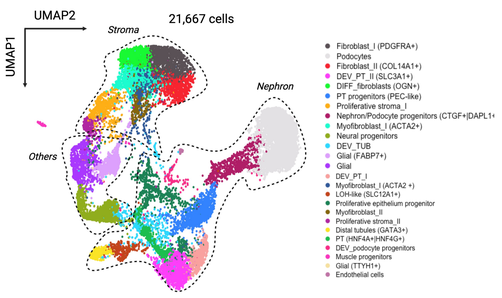
Kidney organoids recapitulate basement membrane assembly



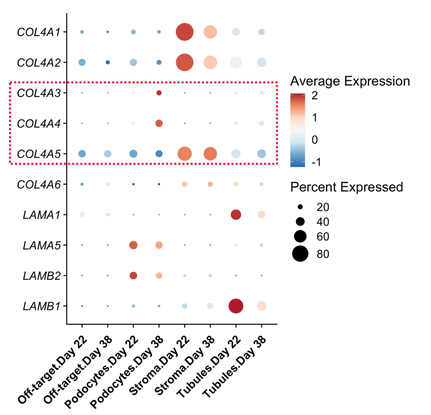


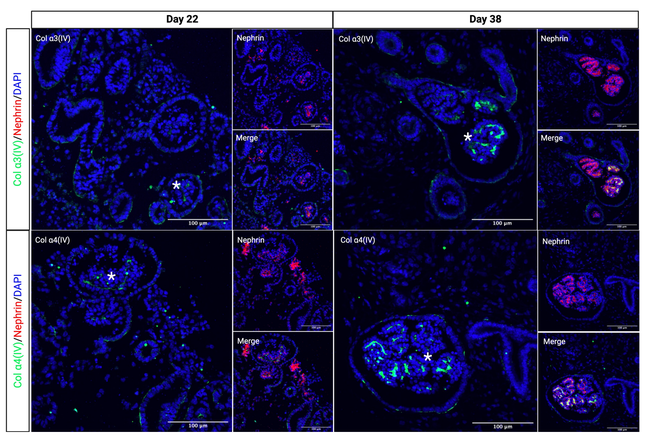
Podocytes in kidney organoids are polarized

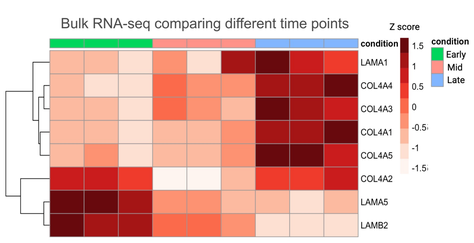


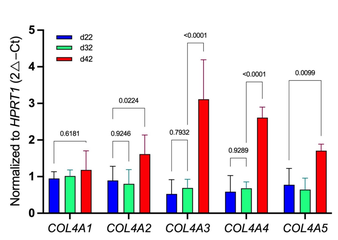


Prolonged organoid culture is essential for maturation of the GBM collagen network







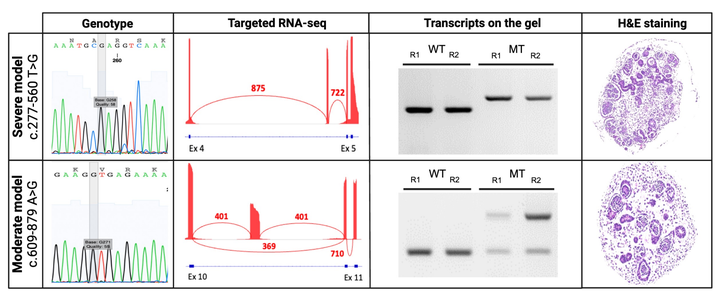


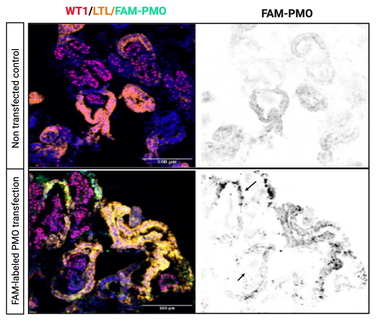
Multi-omics analysis of kidney organoids at different time points revealed ECM protein (specially collagens and laminins) expression dynamics

Hassan Saei et al,. Under review. 2025

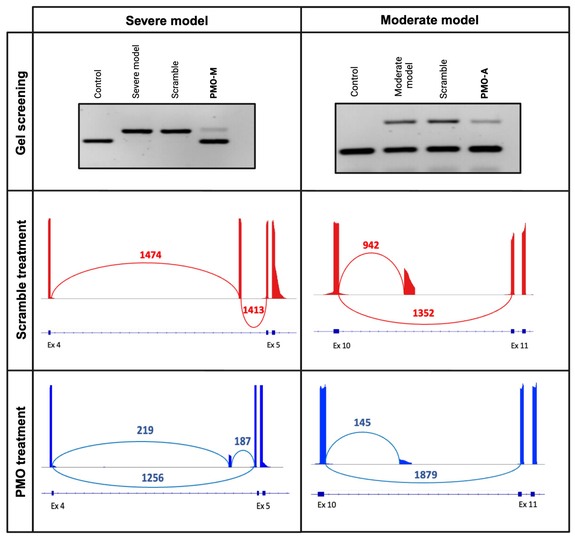
Splice Modulation Therapy Development

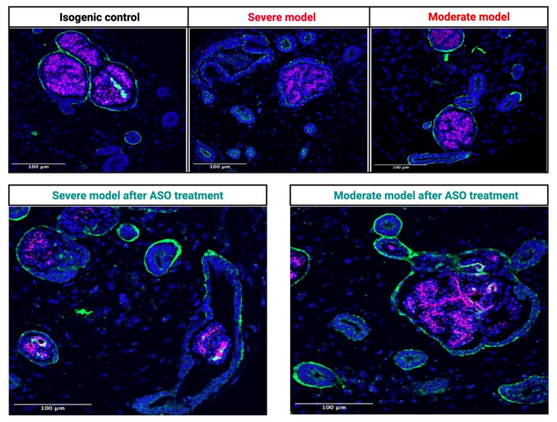
Kidney organoids carrying patient variant showed aberrant *COL4A5* splicing

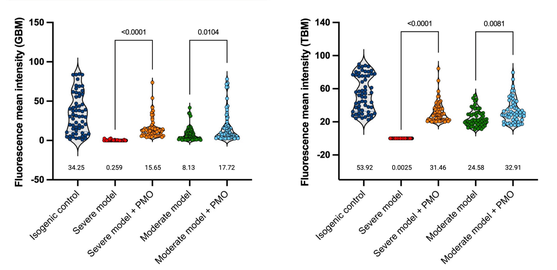




ASO treatment reinstates collagen IV assembly in organoid models of XLAS



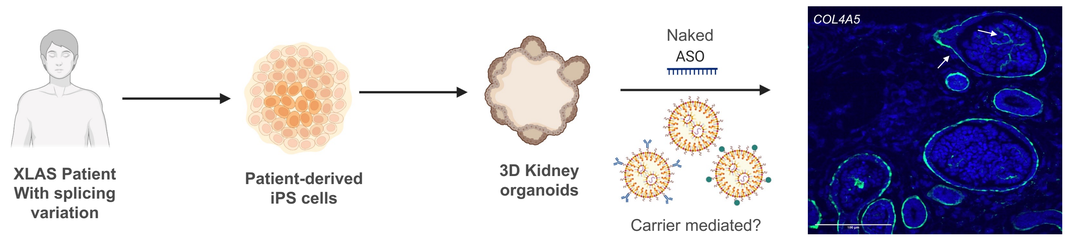




The severe model showed a complete absence of wild-type *COL4A5* transcript, which was significantly restored at both mRNA and protein levels following ASO transfection in organoids

Hassan Saei et al,. Under review. 2025

Organoids Enable Scalable Development of Tailored Therapies



- We optimized antisense oligonucleotide (ASO) treatment in a kidney organoid model to develop splice modulation therapy
- Kidney organoids serve as a scalable platform to develop and test personalized therapies