



Animal Model Workshop

TFE3 Xp11.2 translocation RCC mouse model

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Session 4: Shades Beyond Clear: GEM Models of Rare Renal Cell Carcinomas



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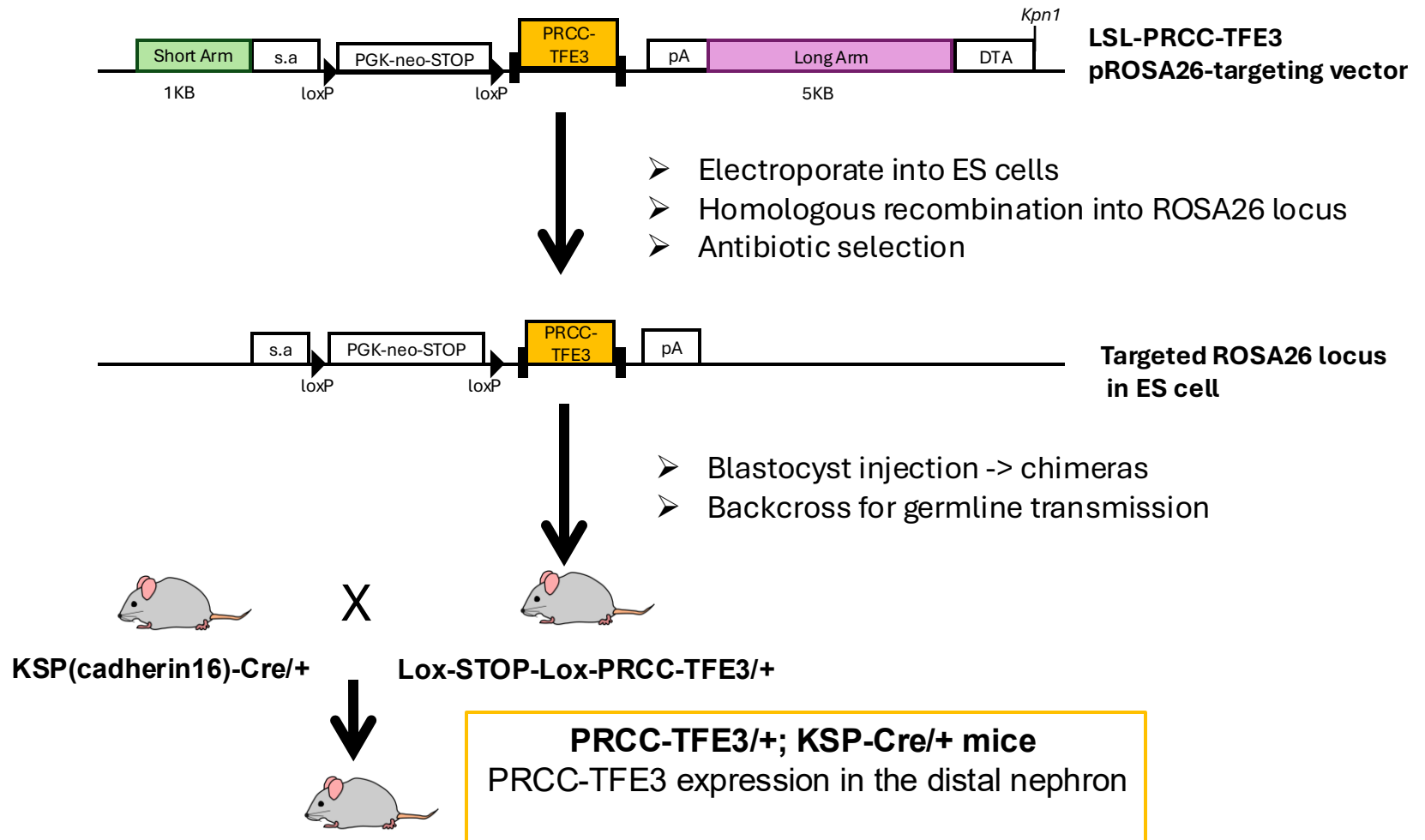
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Why develop a mouse model for TFE3 Xp11.2 tRCC?

- TFE3 Xp11.2 tRCC involved in 25-40% of pediatric RCC & 2-5% of adult RCC
- Xp11.2 rearrangements create oncogenic fusions with different partners (e.g. PRCC)
- TFE3 transcriptionally activates target genes involved in lysosome biogenesis, autophagy and metabolic pathways that drive tumor progression
- TFE3 tRCC is aggressive, can metastasize when small
- No effective therapy for advanced disease

NEED A MODEL FOR EVALUATING THERAPIES & MECHANISTIC STUDIES

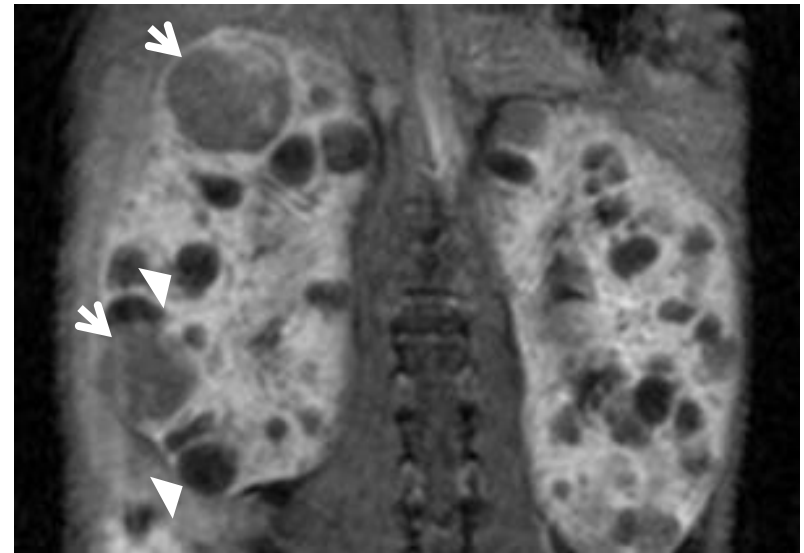
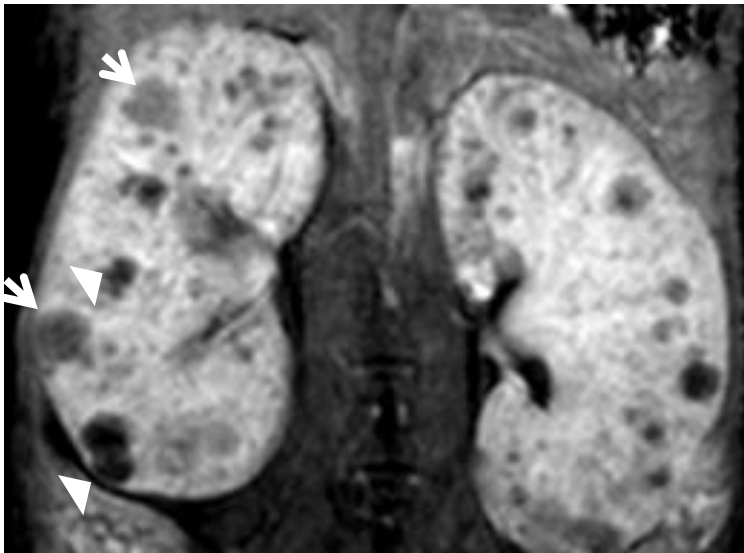
Generation of PRCC-TFE3/+; KSP-Cre/+ mouse model



Phenotype of PRCC-TFE3/+; KSP-Cre/+ mice

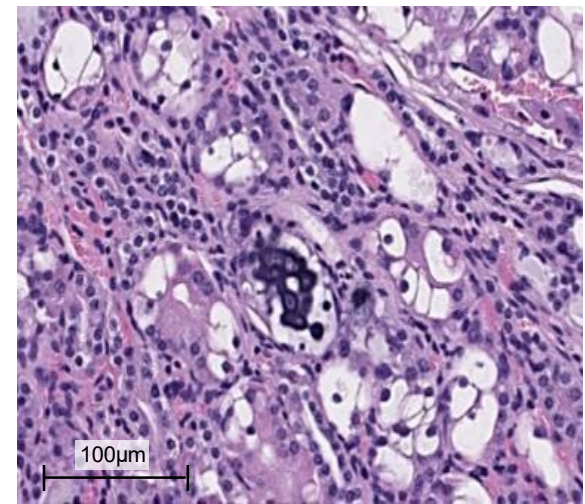
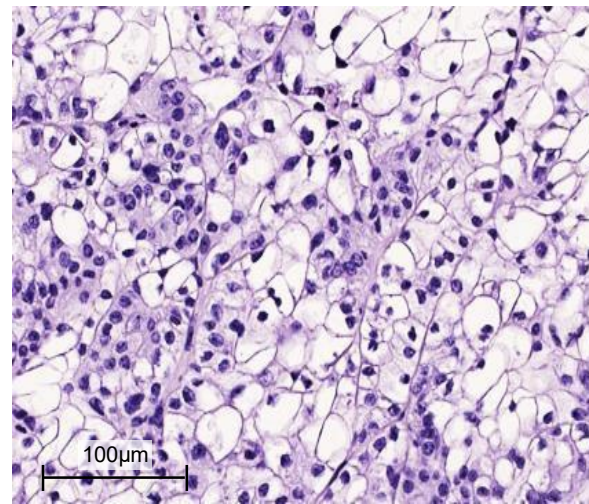
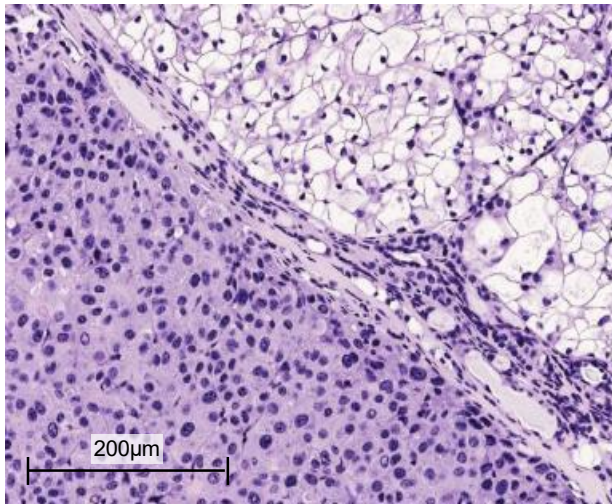
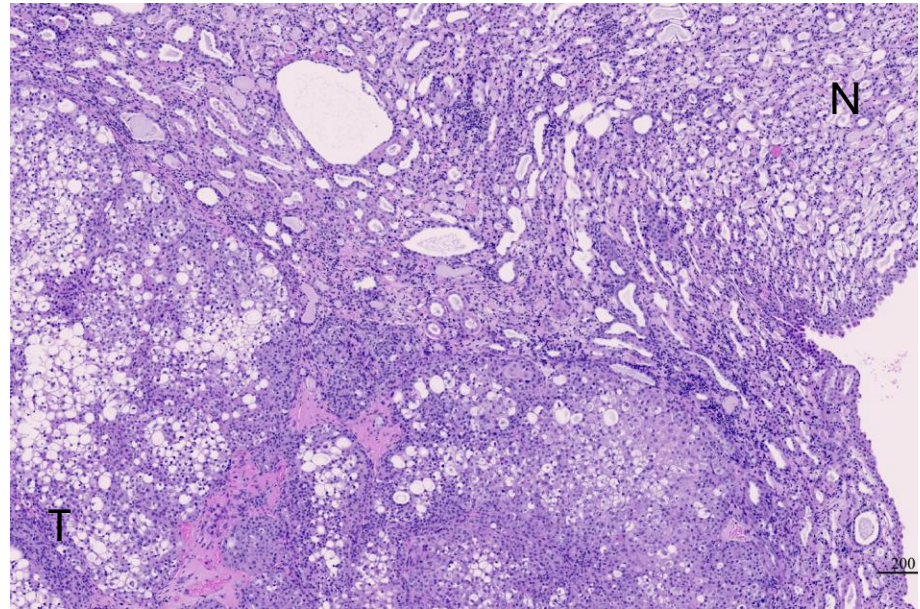
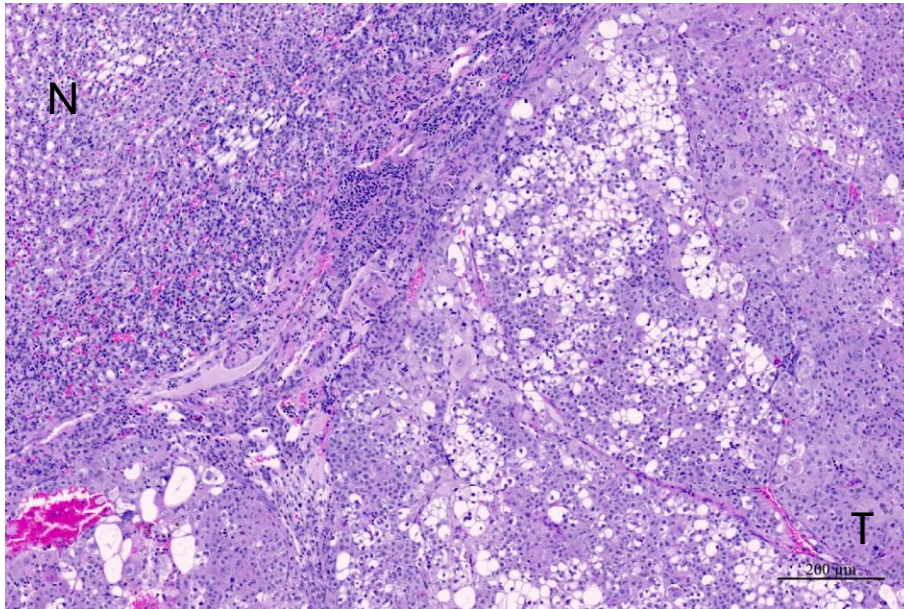
Multiple bilateral tumors and cysts are visible on imaging by 4 months of age

MRI with contrast of mouse at 7 (left) and 9 months(right) of age



Tumors and cysts display rapid growth rate (~3-fold increase in size)

Histology of PRCC-TFE3/+; KSP-Cre/+ kidney tumors



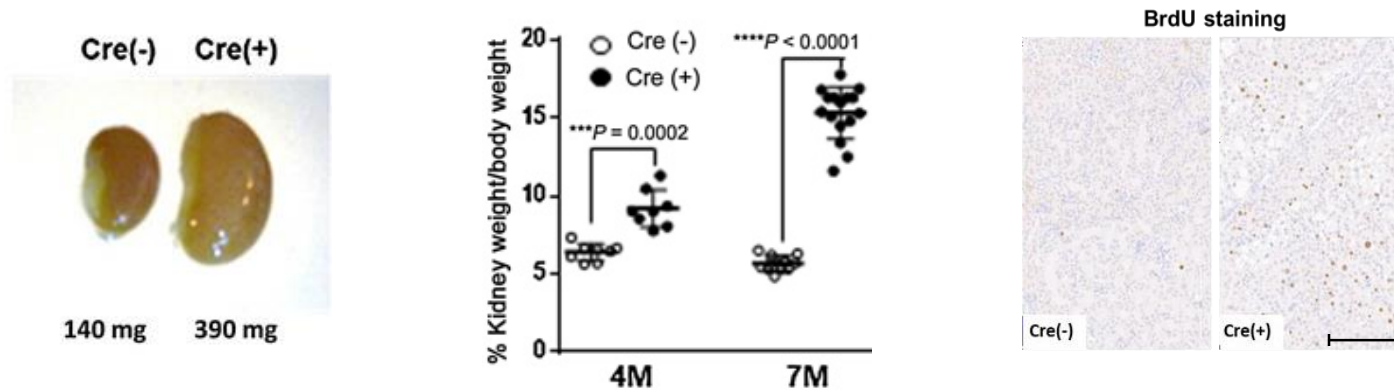
cells with eosinophilic cytoplasm

cells with large clear cytoplasm

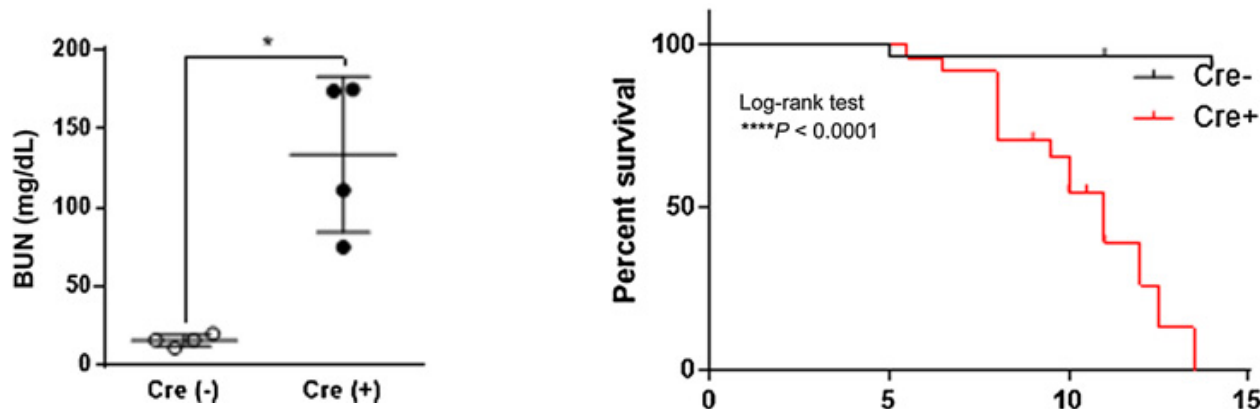
calcified psammoma body

Characterization of PRCC-TFE3/+; KSP-Cre/+ mice

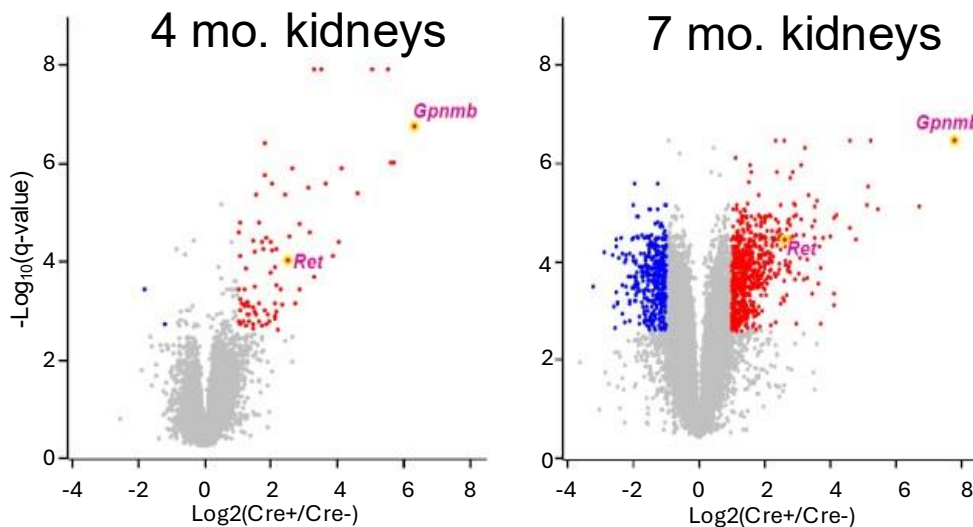
PRCC-TFE3/+;KSP-Cre/+ kidneys 2-3 fold heavier than littermate controls



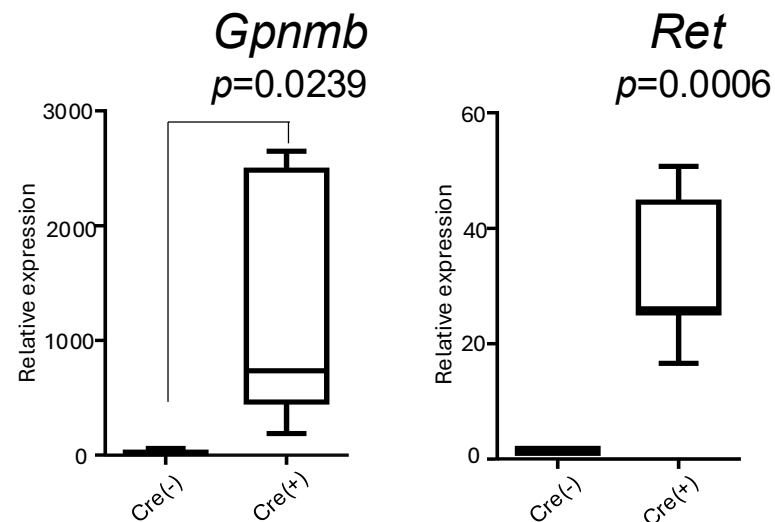
Shortened lifespan due to kidney failure (median 11 mo.)



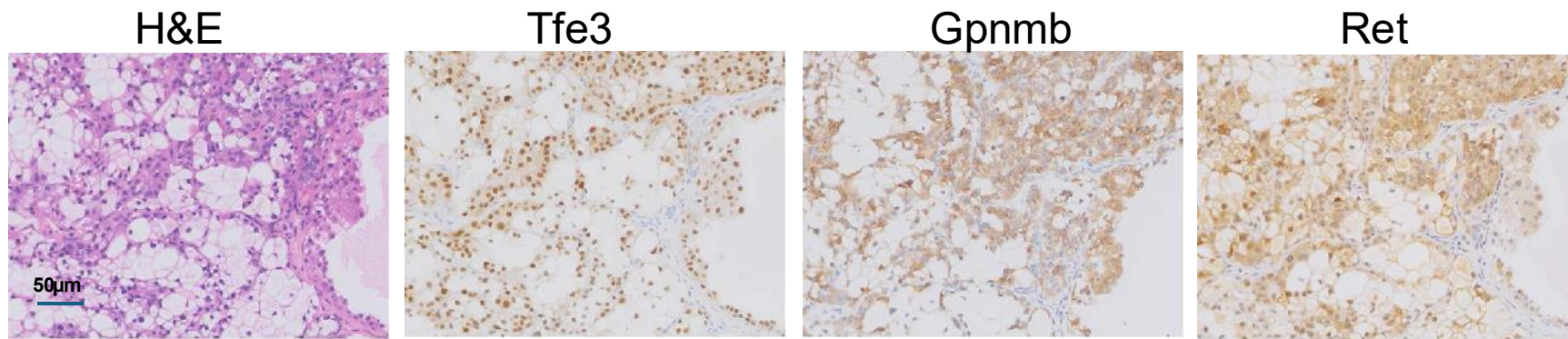
Gene expression analysis of PRCC-TFE3/+; KSP-Cre/+ kidneys identifies Tfe3 target Gpnmb and Ret proto-oncogene



Gene expression volcano plots display significantly expressed genes

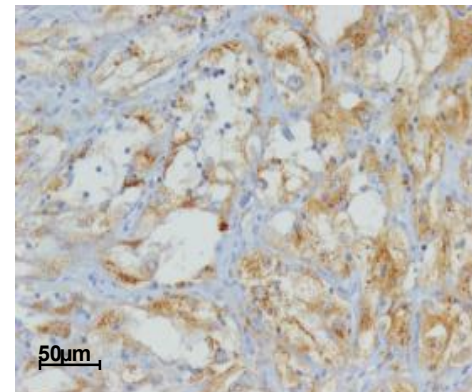
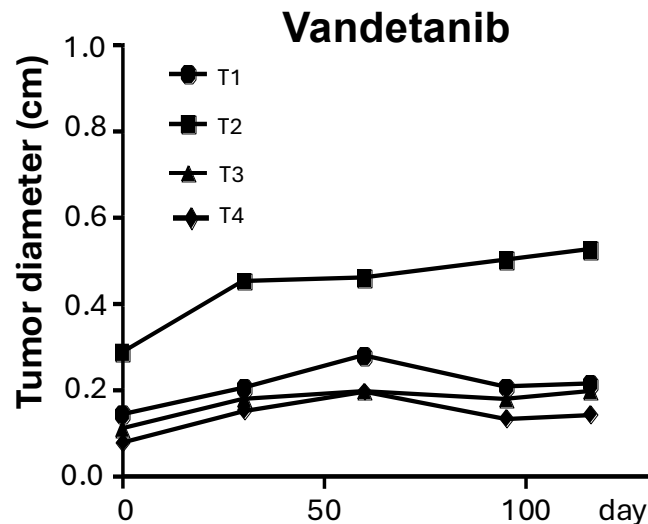
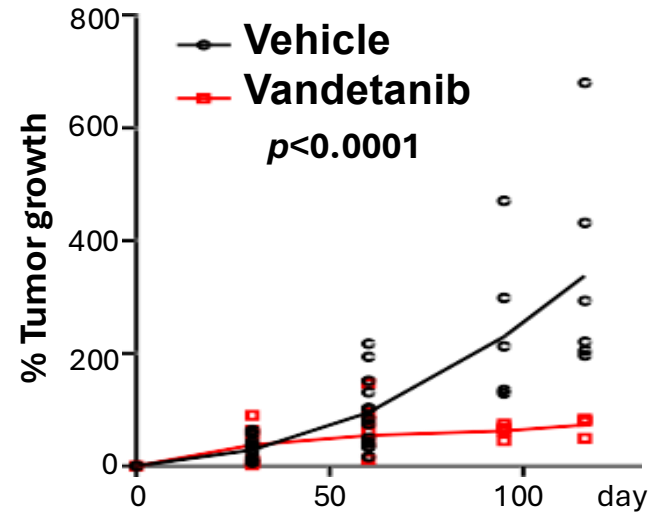
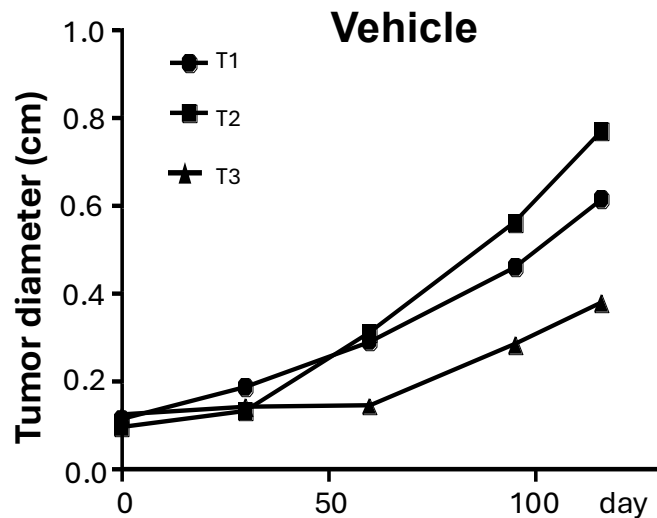


qPCR confirms *Gpnmb* & *Ret*



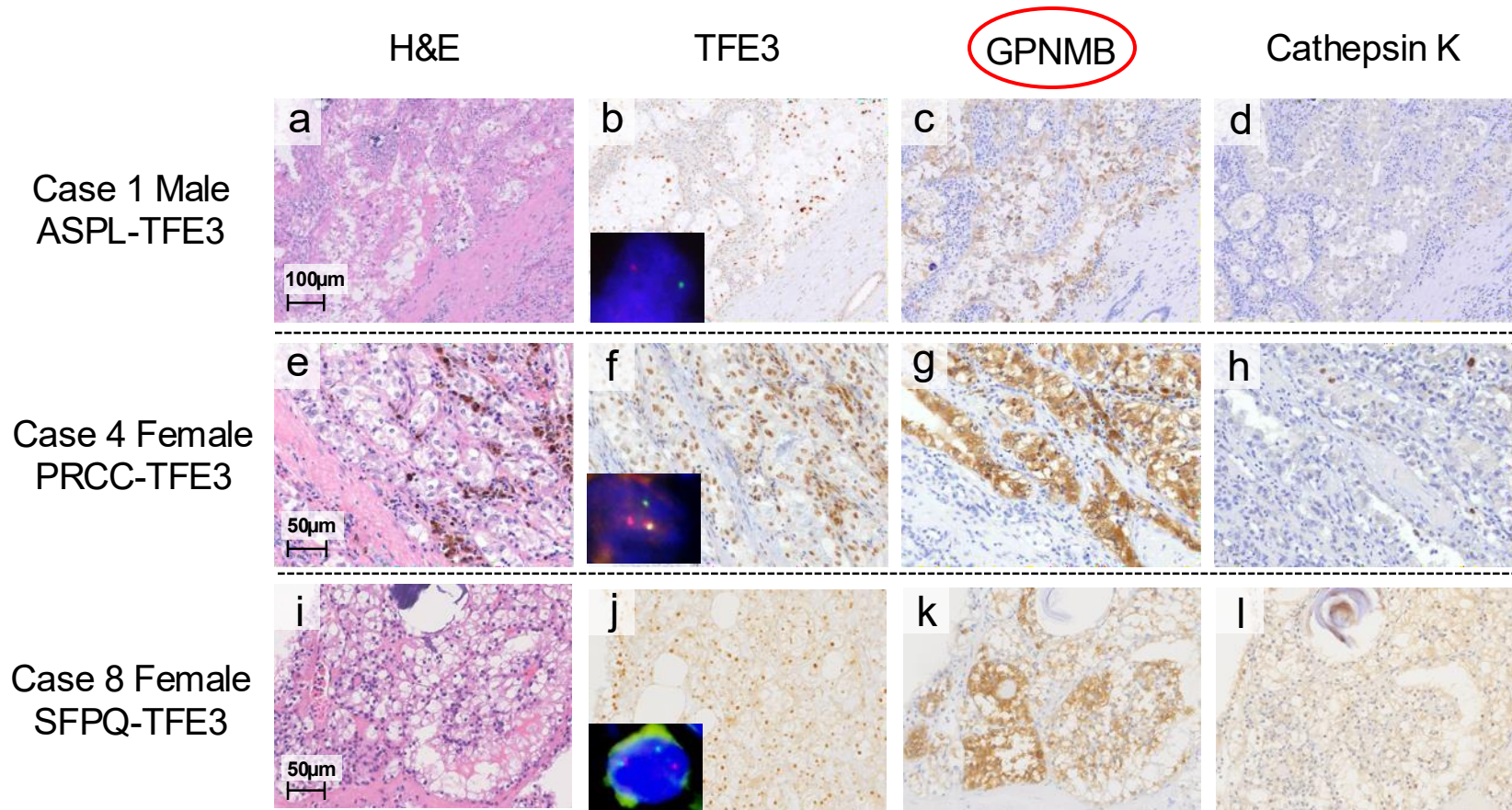
Nuclear Tfe3, Gpnmb and Ret protein expression in PRCC-TFE3/+;KSP-Cre+ kidneys by IHC

PRCC-TFE3/+; KSP-Cre/+ tumor response to RET/VEGFR inhibitor vandetanib (100mg/kg)

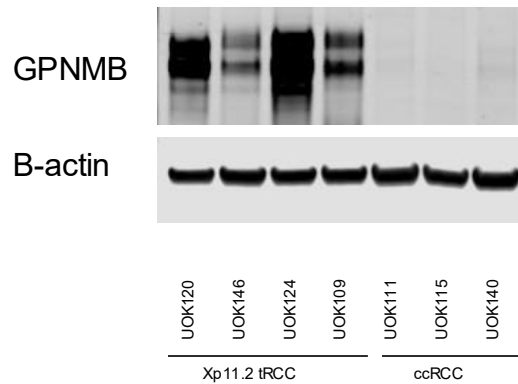


RET IHC on human TFE3-tRCC

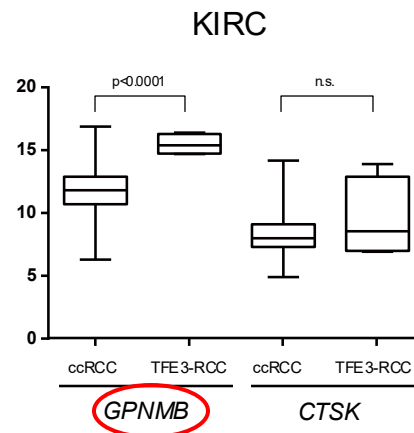
GPNMB, an improved diagnostic marker of TFE3 tRCC



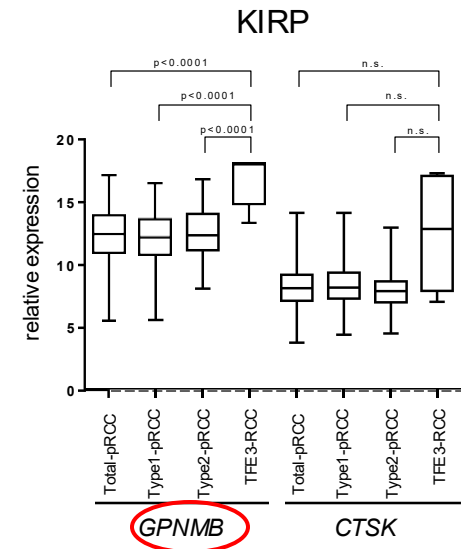
GPNMB, an improved diagnostic marker of TFE3 tRCC



GPNMB is expressed in TFE3 tRCC cell lines, but not in ccRCC lines



GPNMB is expressed in TFE3 tRCC but not ccRCC or pRCC (TCGA data) whereas CTSK shows no significant difference



Acknowledgements

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