



Animal Model Workshop

Mouse Models of TSC and Chromophobe RCC

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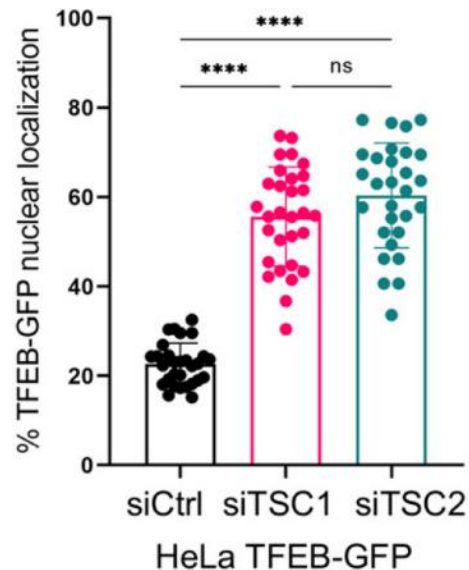
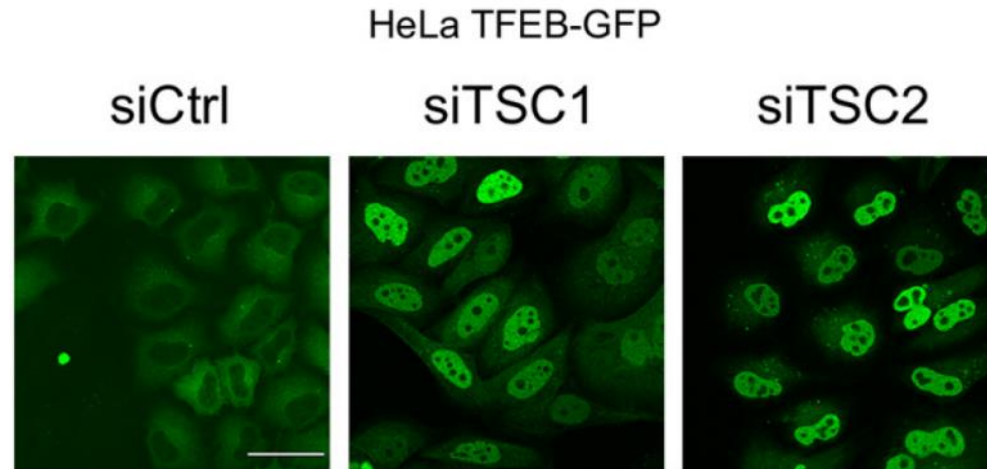
September 11-13, 2025



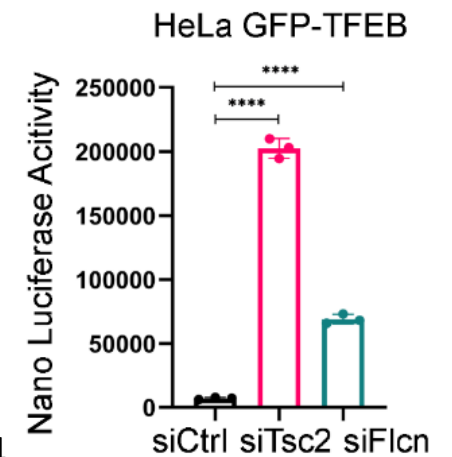
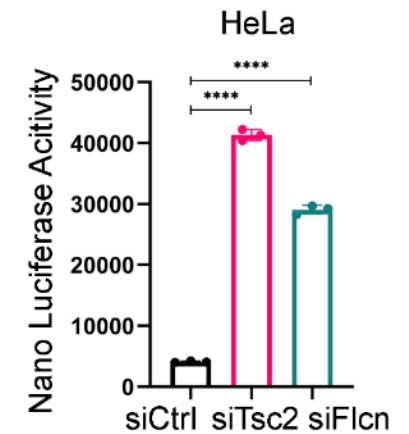
Outline

- TFEB activates mTOR and mediates renal disease in TSC
- New Tsc2 mouse model (unpublished)
 - Chromophobe-like tumors

TFEB and TFE3 localize to the nucleus in Tsc1/2 deficient cells (despite high mTORC1 activity)



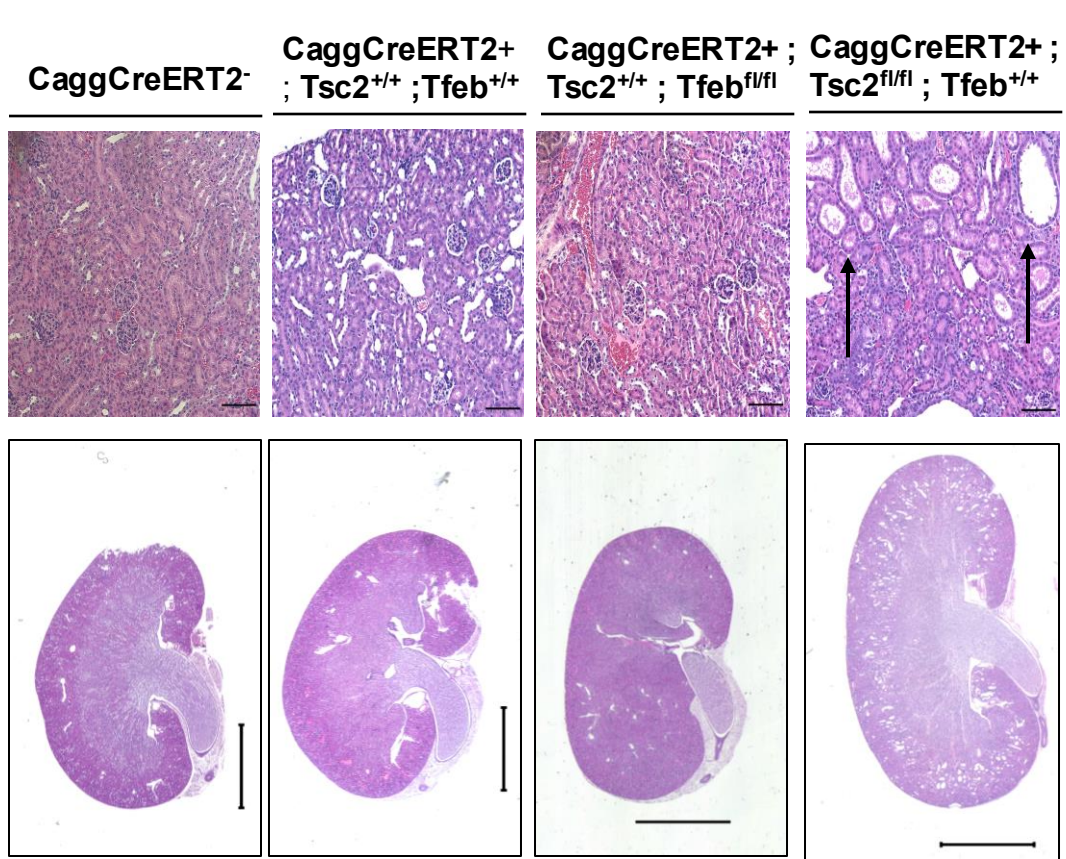
GPNMB Promoter activity



Alesi N, Khabibullin D, Ballabio Henske Nat Comm 2024
Asrani K, Lotan T, Nat Comm 2022
Pena-Llopis S, Brugarolas J, EMBO J 2011

10% FBS
siRNA for 72 hours

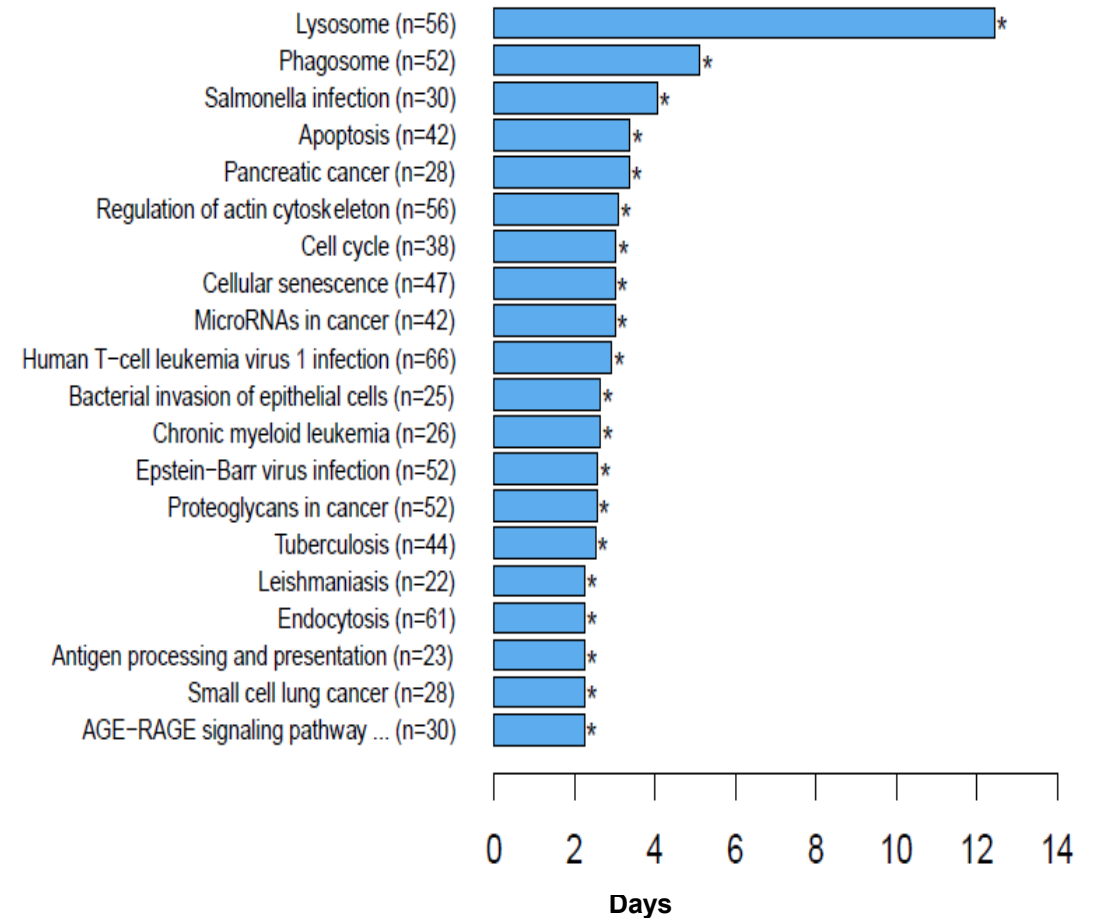
TFEB knockout normalizes renal pathology in CAGGCreERT2⁺; Tsc2^{fl/fl} mice.



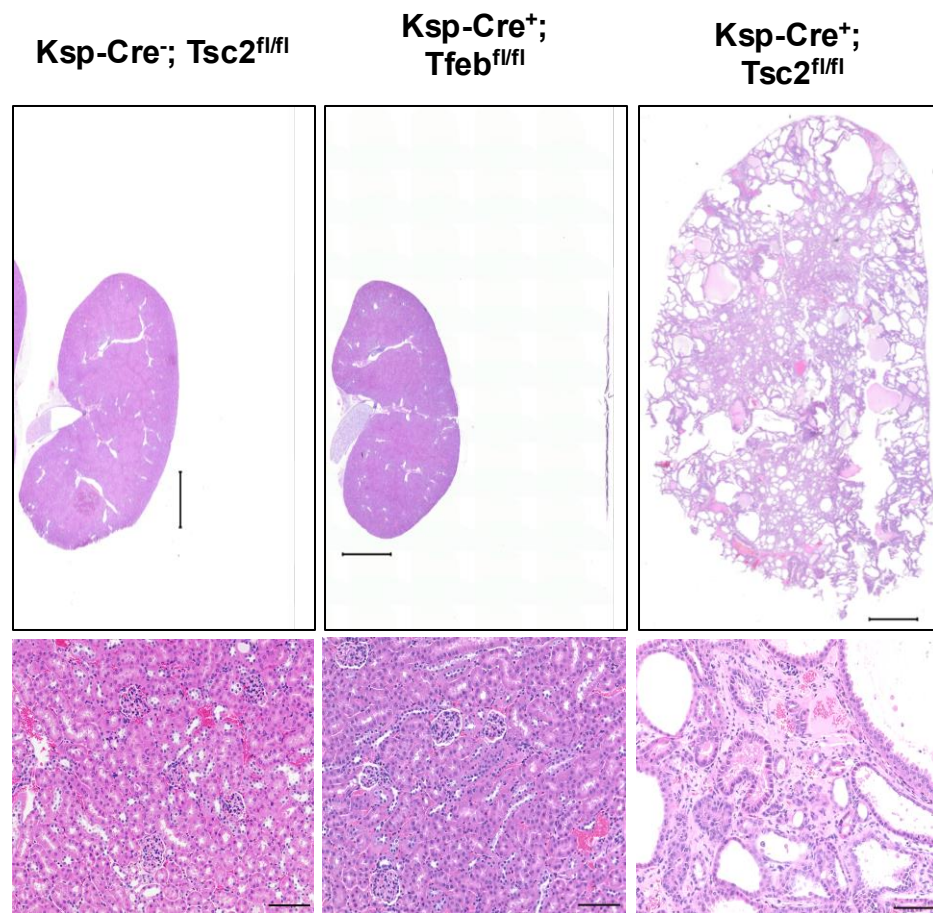
Tamoxifen injected day 1-3 to lactating mothers

30days

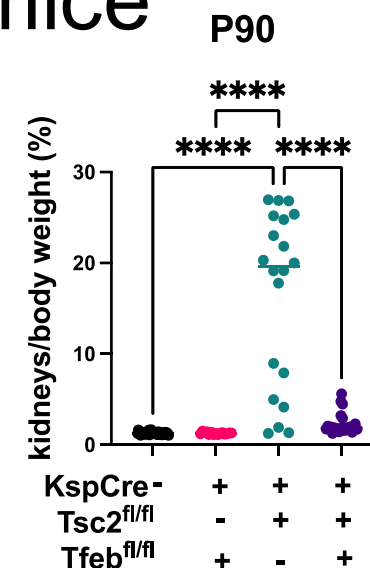
b CagGCreERT2⁺;Tsc2^{fl/fl} vs. CagGCreERT2⁺ (Upregulated pathways)



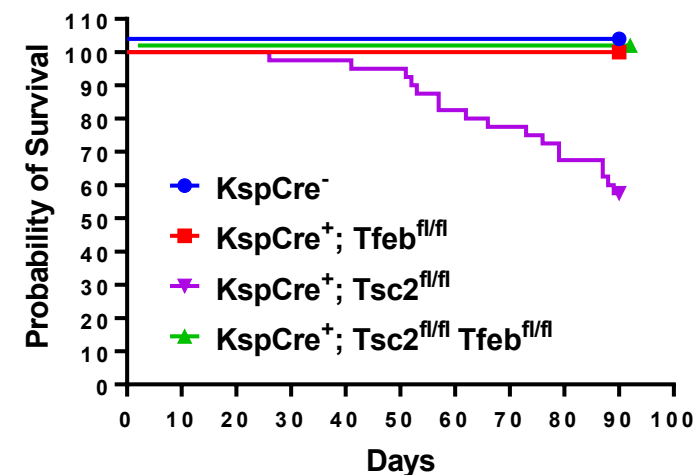
TFEB is required for renal pathology in kidney-specific Tsc2-knockout mice



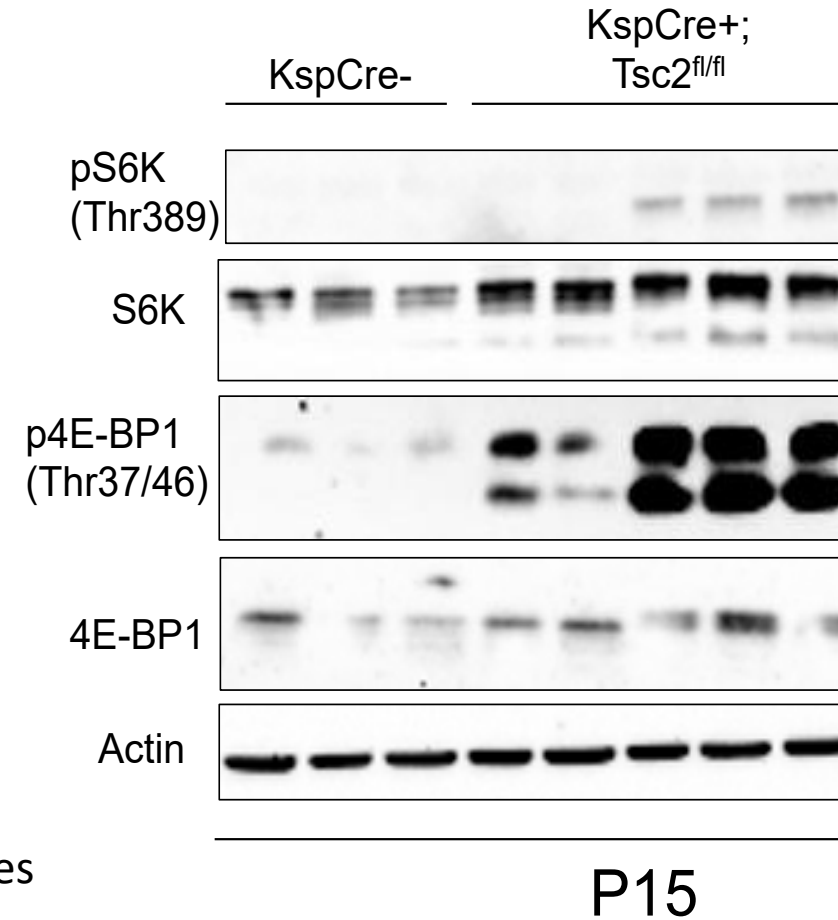
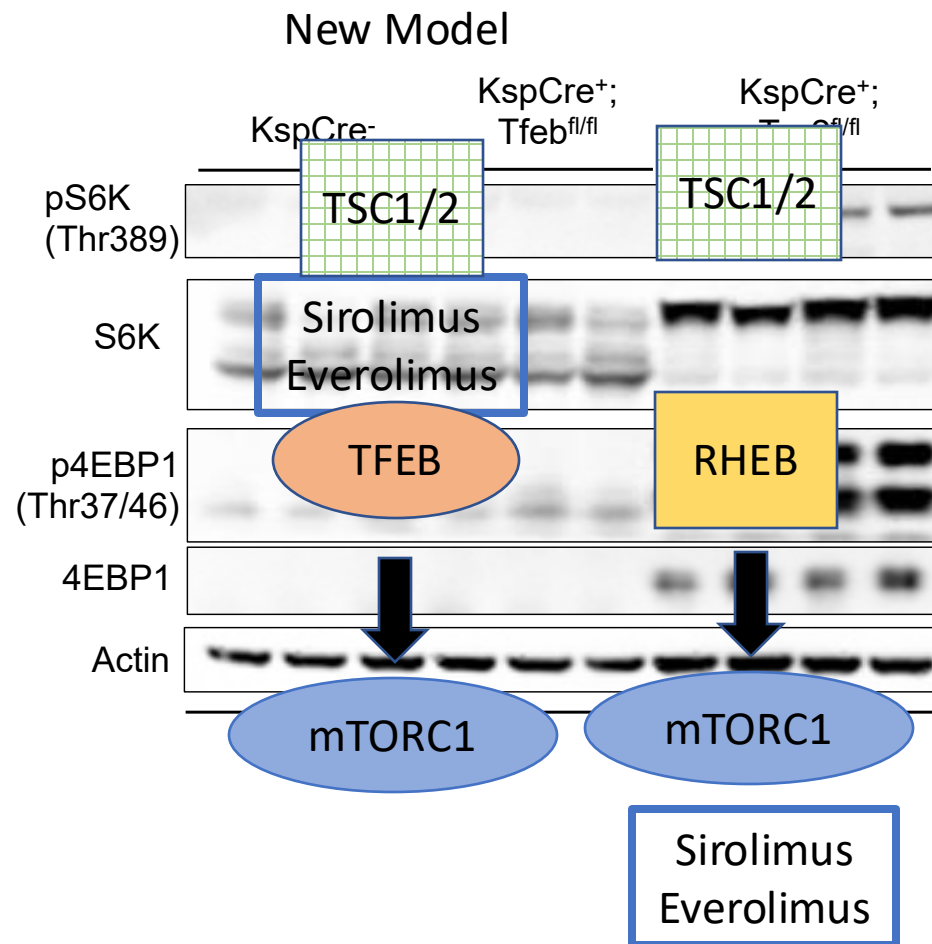
P90



Survival



TFEB mediates mTORC1 hyperactivation in TSC



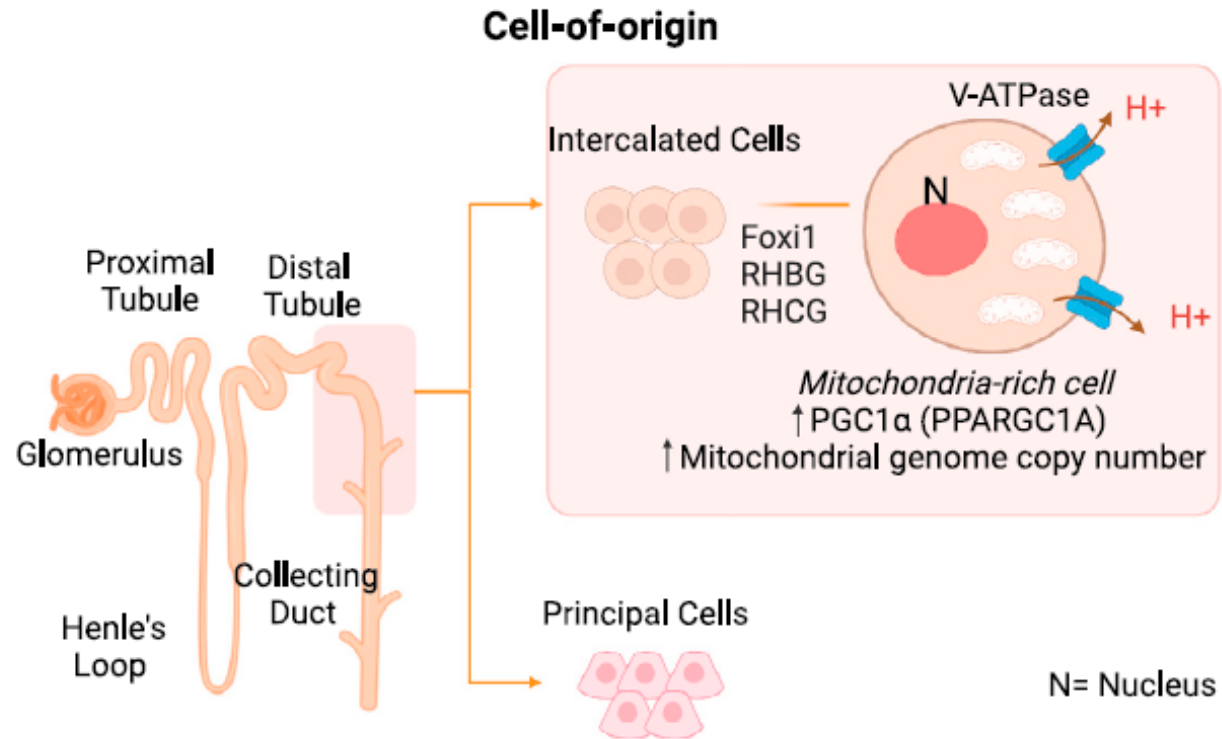
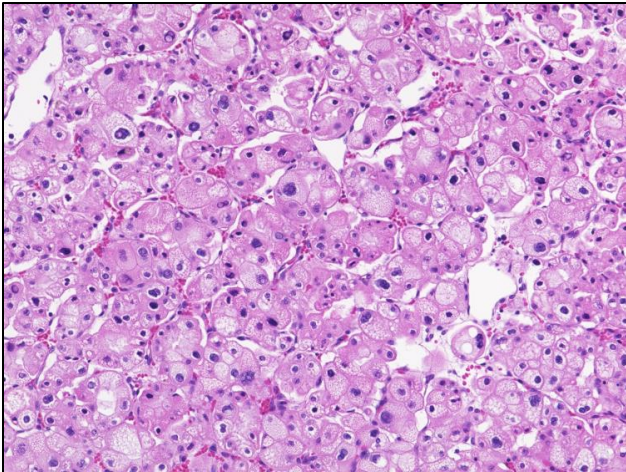
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TFEB deletion normalizes kidneys in two Tsc2 models
- New Tsc2 mouse model (unpublished)
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Chromophobe RCC arise from Renal Intercalated Cells & Occur in Tuberous Sclerosis Complex and Birt Hogg Dube syndrome

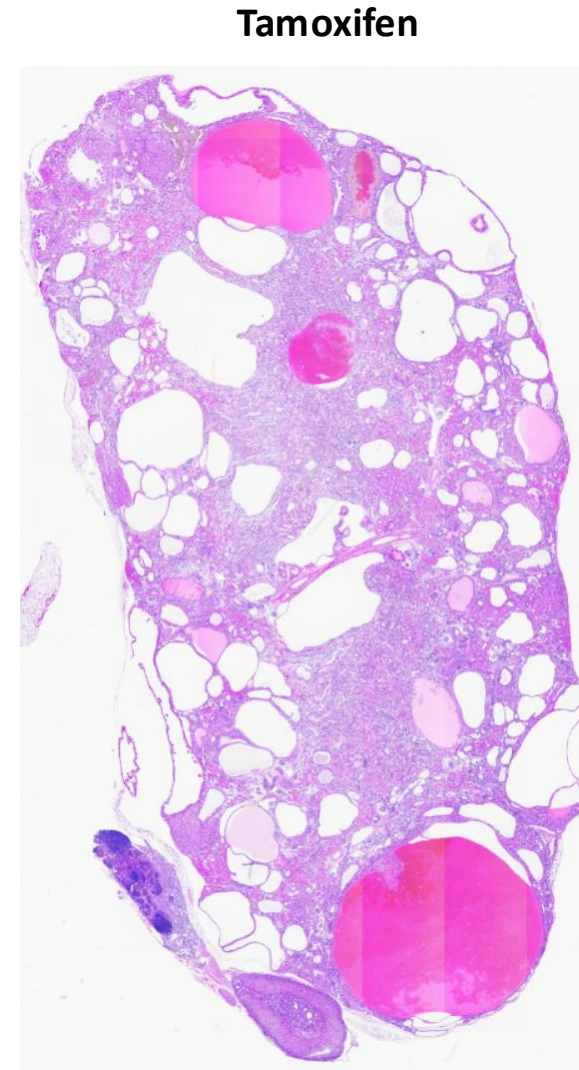
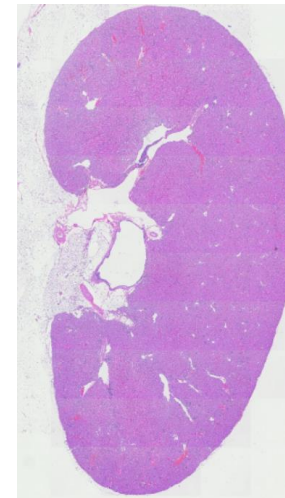
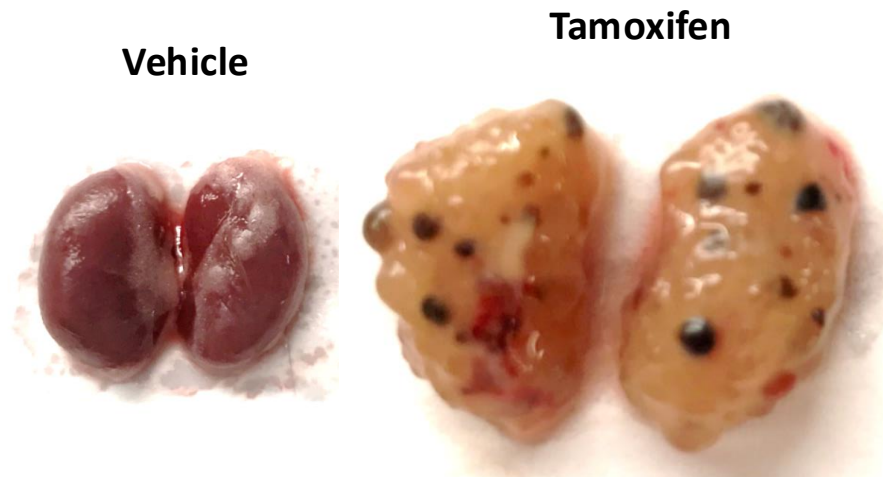
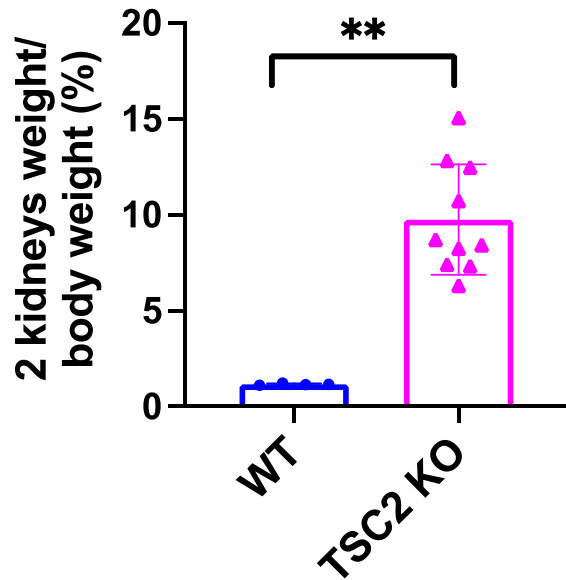
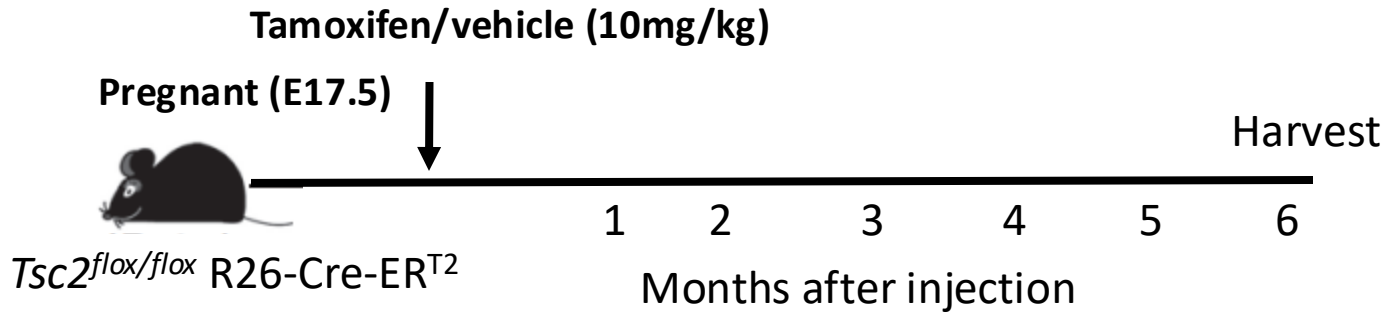
Renal Cell Carcinoma

Chromophobe
Hybrid Oncocytic-Chromophobe



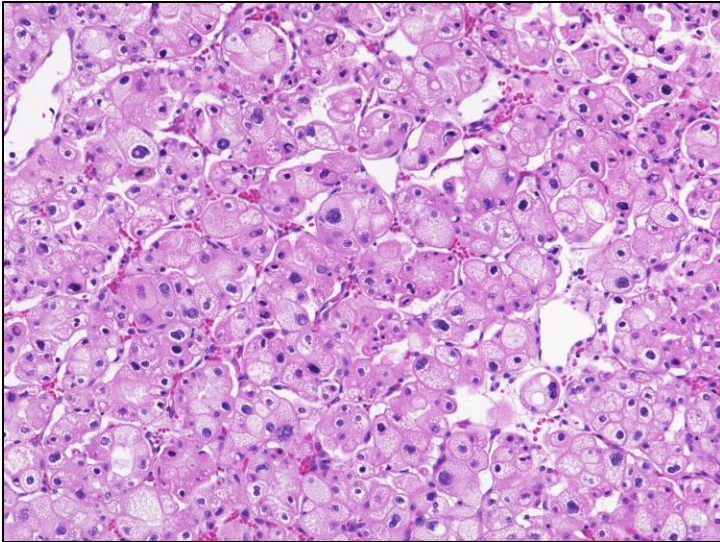
Henske, Cheng, Hakimi, Choueiri, Braun, Cancer Cell, 2023
Labai, Shukla, Choueiri, Henske, Braun JCO 2025

Rosa26 Cre+ Tsc2^{fl/fl} mice: Solid and Cystic Renal Tumors

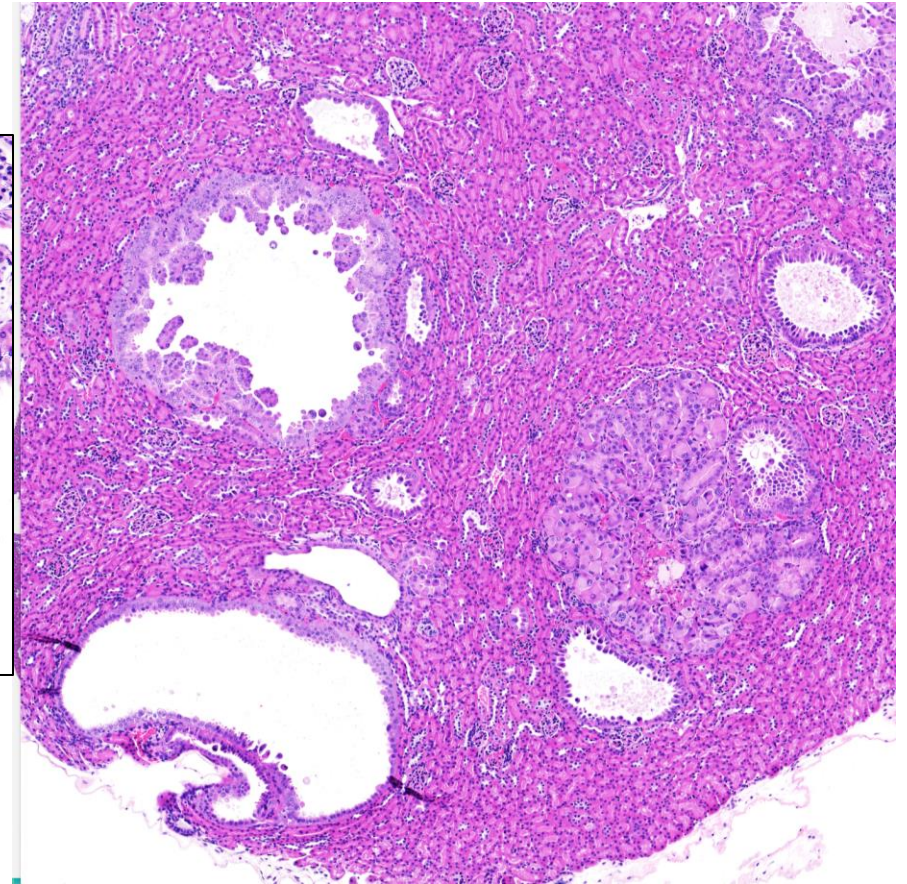
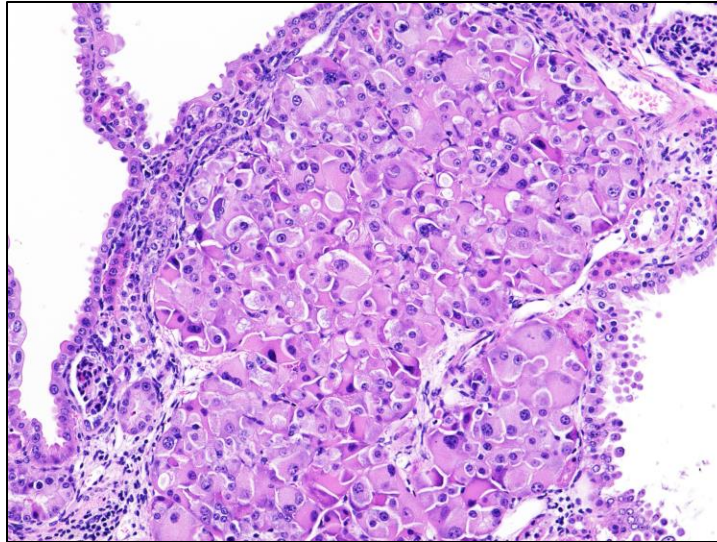


Rosa26 Cre+ Tsc2^{fl/fl} mice: Solid and Cystic Renal Tumors

Human Chromophobe



Tsc2 KO kidney tumors



Summary

- TFEB activates mTOR and mediates renal disease in TSC
TFEB deletion normalizes kidneys in two Tsc2 models
New model: **TFEB is primary activator of mTORC1 in TSC**
- New Tsc2 mouse model with chromophobe-like tumors