

Tumor Plasticity and Immunity in Prostate and Renal Cell Carcinoma

Insights from Syngeneic Organoid Models



Animal Model Workshop

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Yale School of Medicine and Yale Cancer Center

Session 8: Organoid Models



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September 11-13, 2025

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Seminar Outline

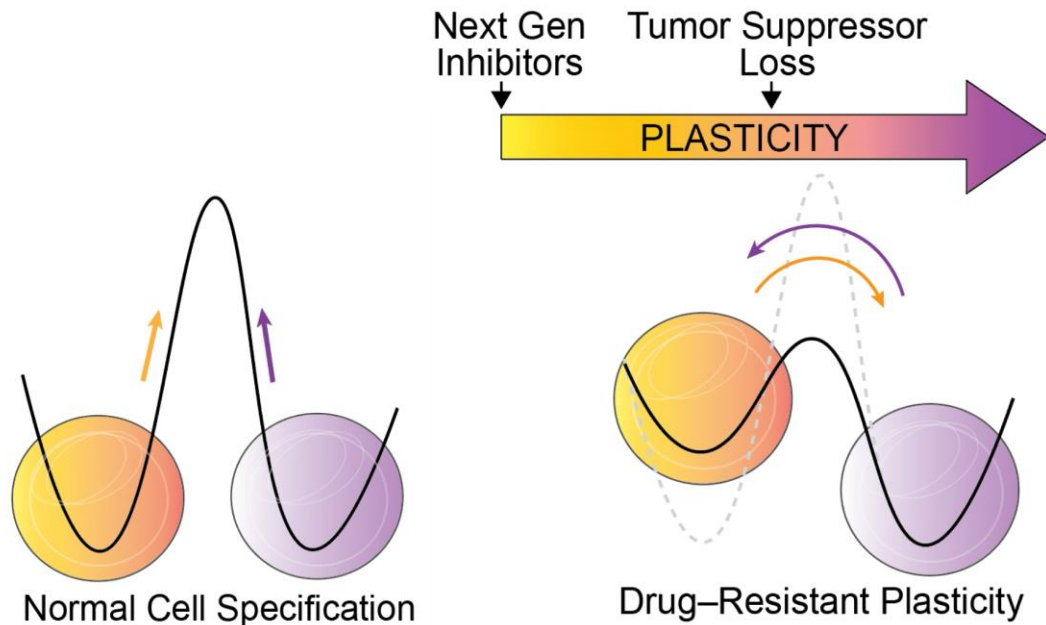
- Insights from using murine organoids as a functional tool for prostate cancer
- Development of murine organoid for RCC modeling
- Proof of principle studies for non–ccRCC
- Future development of ccRCC with *Vhl* loss



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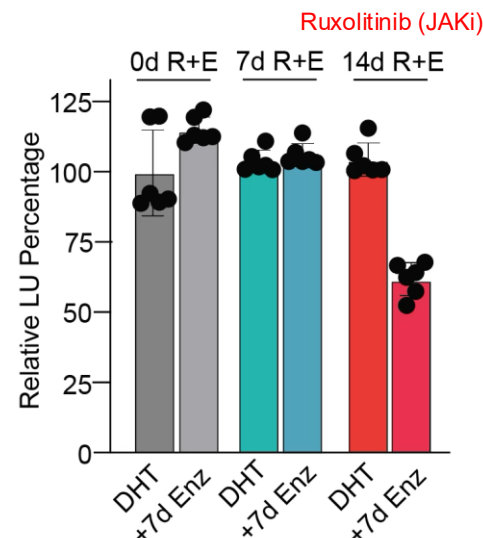
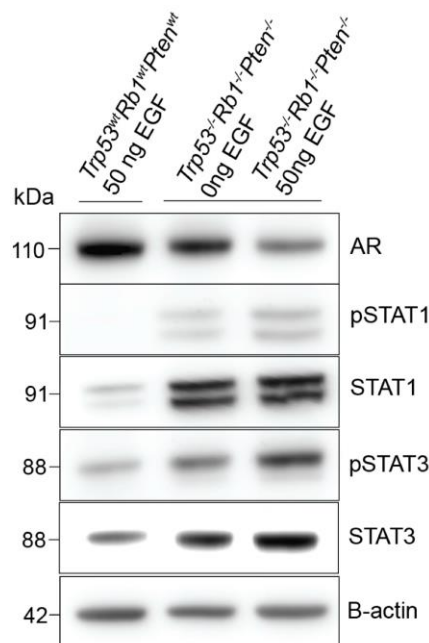
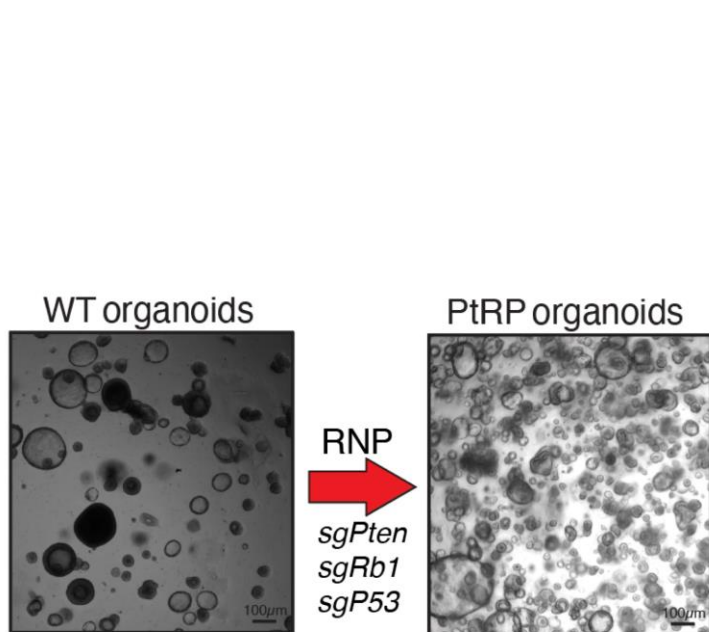
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Organoid Models in Prostate Cancer Reveal Mechanisms of Lineage Plasticity



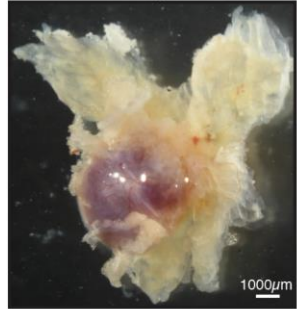
- Lung, prostate, and gastric tumors can transform into neuroendocrine carcinomas — ~10 to 15% of treatment-resistant patients
- Associated with poor prognosis and overall survival of ~6–12 months

Co-Inhibition of JAK/STAT in PtRP Prostate Organoids Leads to Re-sensitization of ARPIs



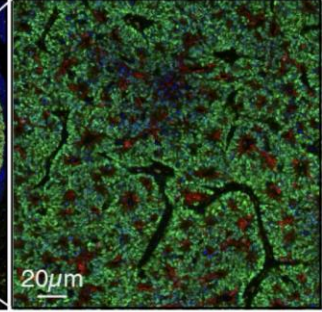
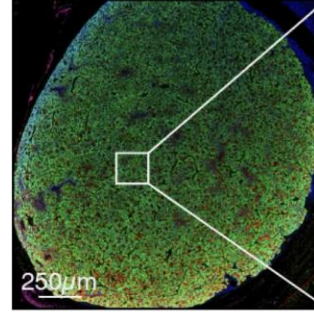
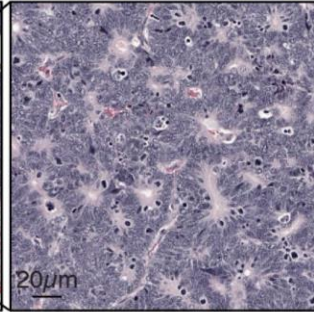
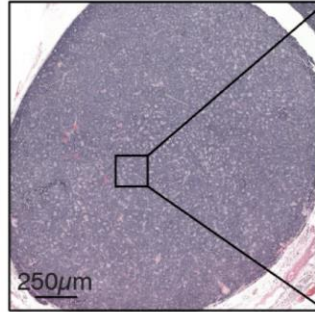
JAK/STAT–High Prostate Organoids Require *In Vivo* Environment for Transformation

PtRP Orthotopic Transplant



~4–5 months

NEPC



DAPI ASCL1 NEUROD1 CK8 CK5 AR



Is it feasible to utilize adult murine kidney organoids for ex vivo CRISPR editing and generation of syngeneic RCC tumors?



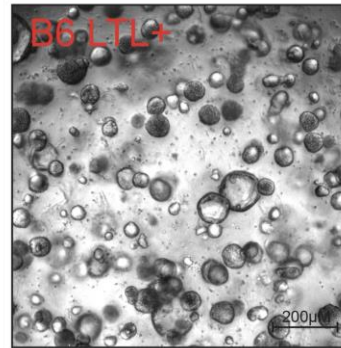
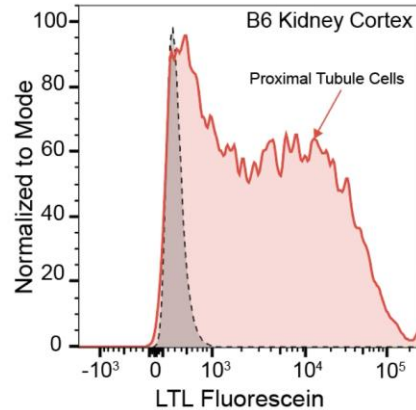
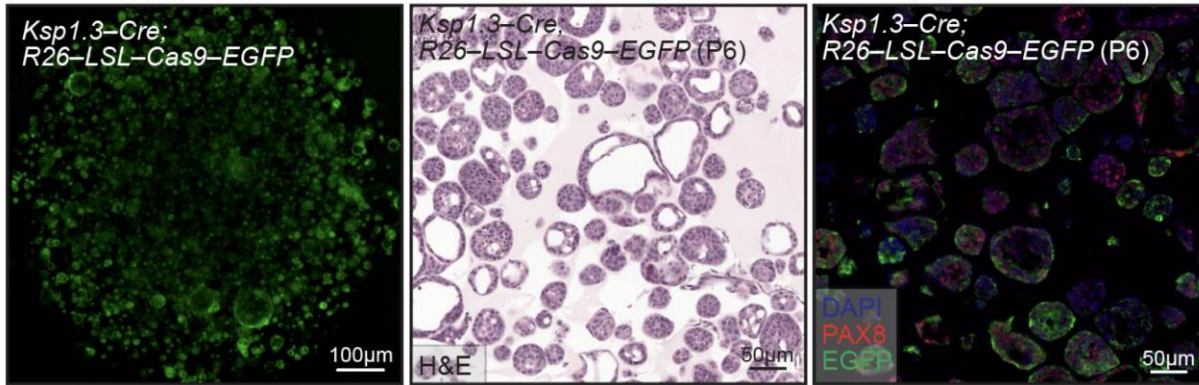
- GEMM models have long latency and require multi-alleles
- *Ex vivo* generation and propagation of native renal tubular cells
- Rapid editing of multiple alleles
- Development of orthotopic syngeneic tumors



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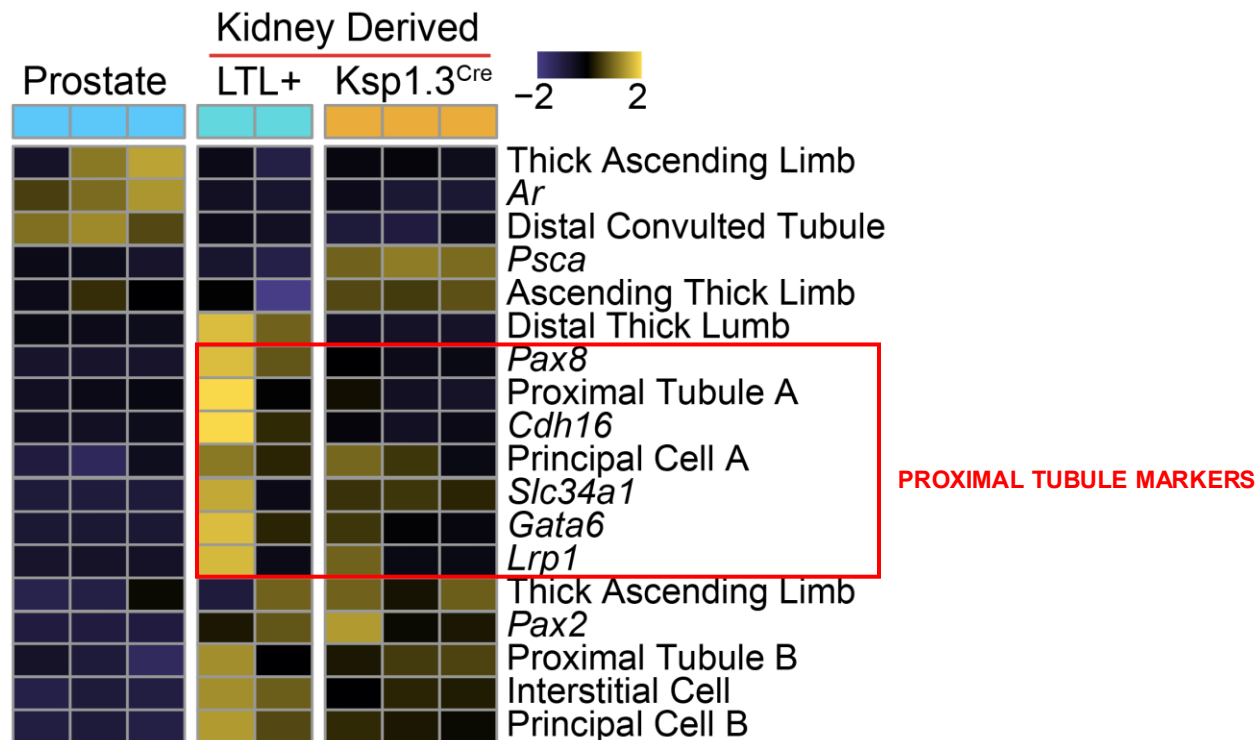
Selective Isolation and Culturing of Murine Kidney Organoids



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LTL+ Organoids Retain Markers of Proximal Tubular Cells

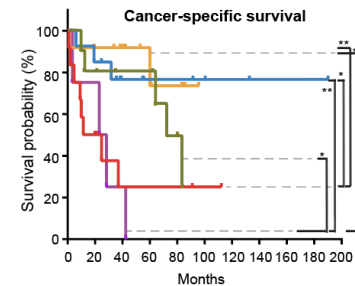
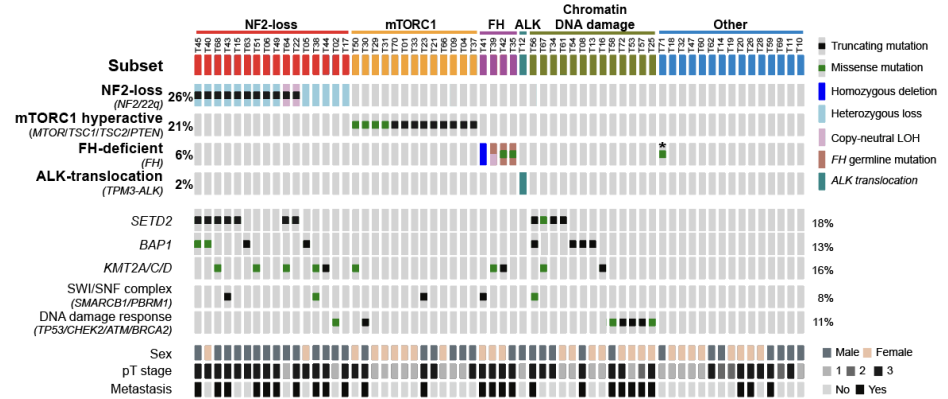


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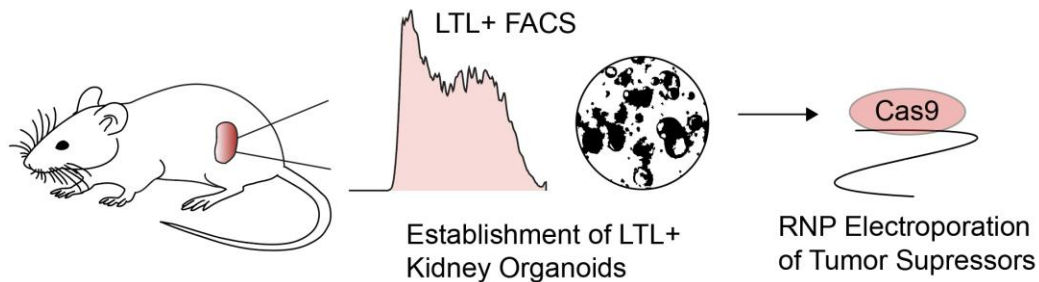
Figure 1 Schematic of the genetic strategy for generating Pax8-Cre mice and the resulting lung cancer model. The top panel shows the generation of Pax8-Cre mice using a loxP-flanked STOP cassette (LoxP-STOP-Cas9) and a loxP-flanked STOP cassette (LoxP-STOP-Luc). The middle panel shows the generation of Pax8-Cre mice using a loxP-flanked STOP cassette (LoxP-STOP-Cas9) and a loxP-flanked STOP cassette (LoxP-STOP-Luc). The bottom panel shows the generation of Pax8-Cre mice using a loxP-flanked STOP cassette (LoxP-STOP-Cas9) and a loxP-flanked STOP cassette (LoxP-STOP-Luc).



Chen et al. *Nature Communications*. 2016
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Generation of Allelic Series of Non-ccRCC Organoids



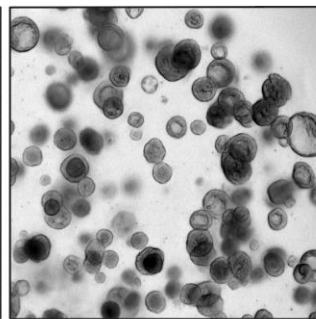
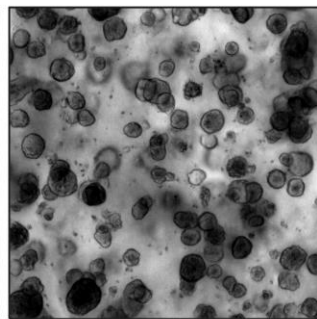
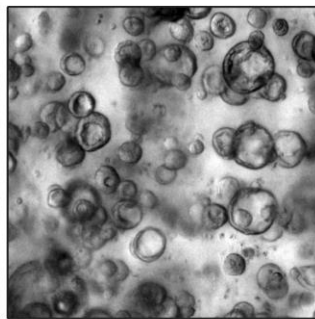
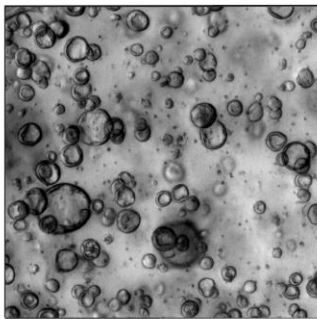
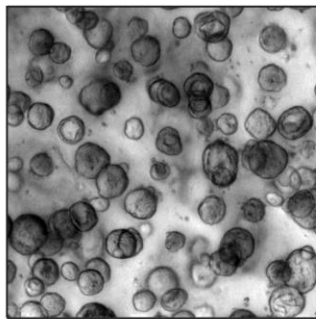
Nf2^{-/-} (CN)

Setd2^{-/-} (CS)

Fh^{-/-} (CF)

Setd2^{-/-}; *Nf2*^{-/-} (CSN)

Fh^{-/-}; *Nf2*^{-/-} (CFN)



B6 LTL⁺ *Cdkn2a*/b^{-/-}

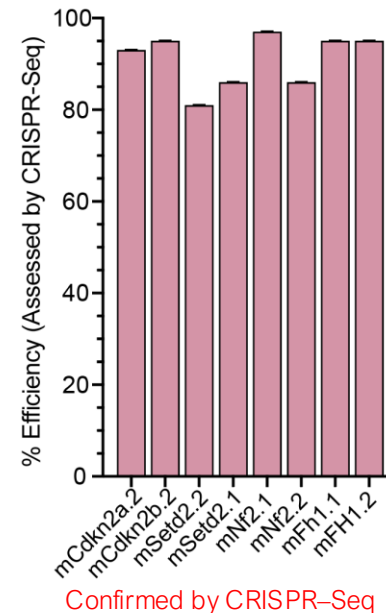
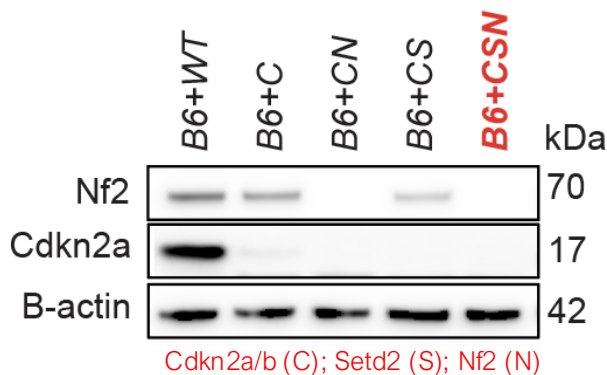
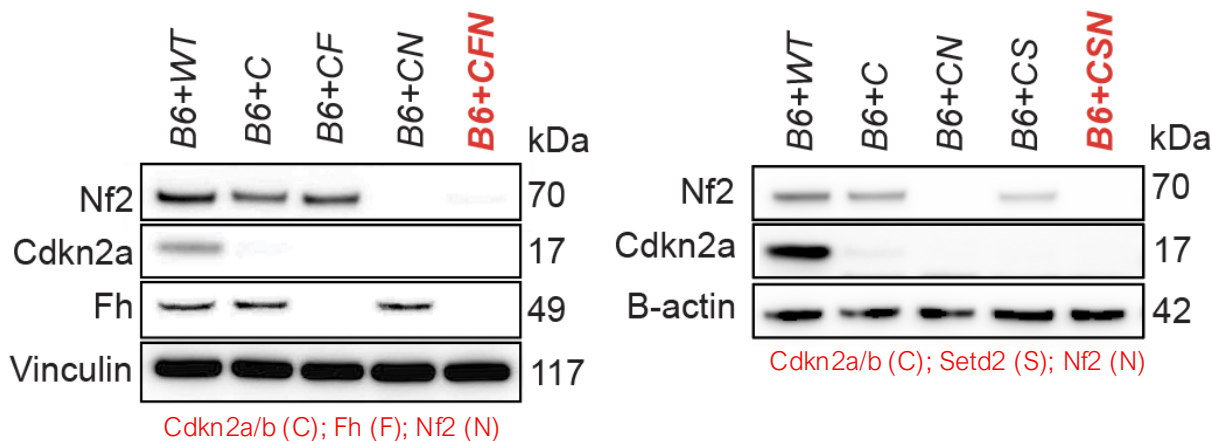


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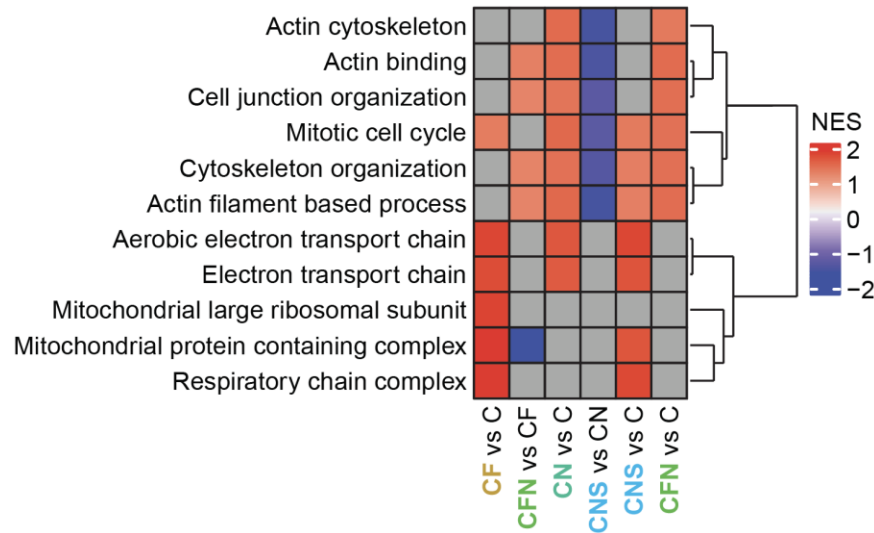
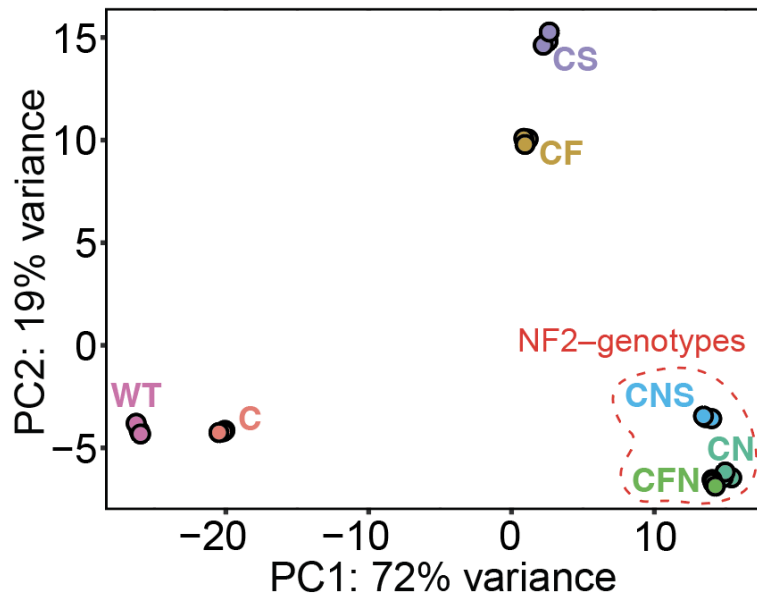
Ex vivo editing using Cas9–RNP for generation unclassified NF2 and FH RCC organoids



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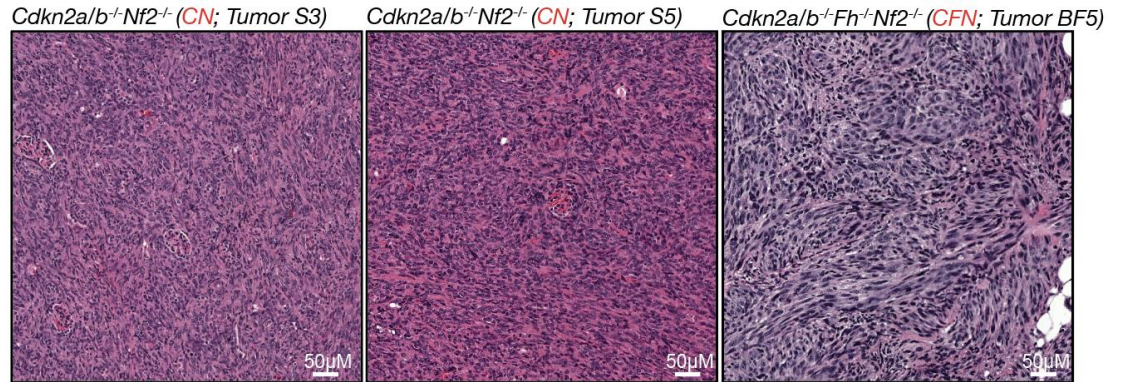
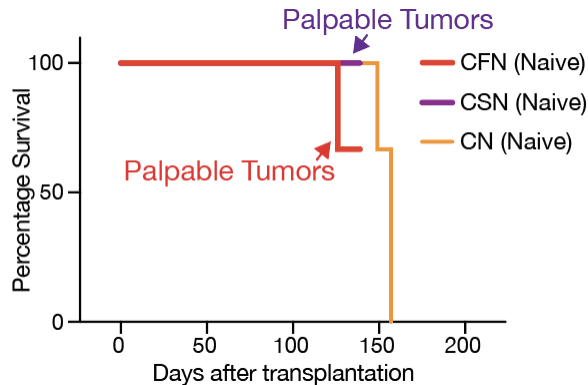
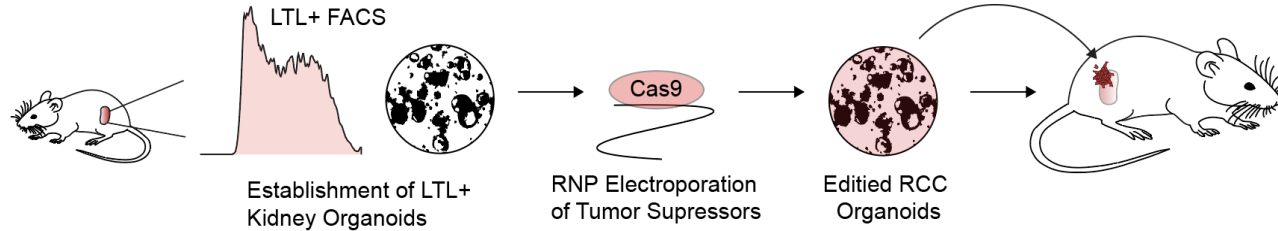
RCC organoids group by genomic loss of tumor suppressors



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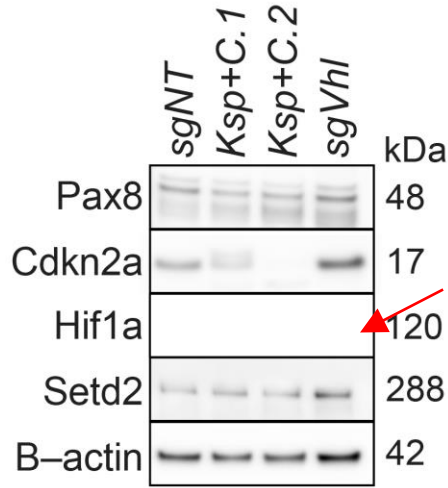
Highly penetrant tumors form in B6 syngeneic hosts



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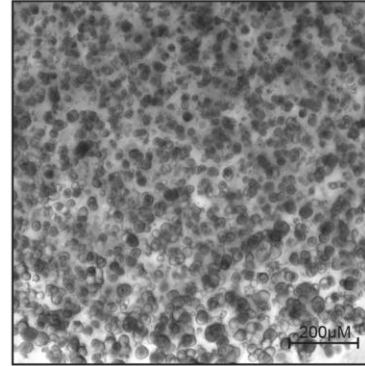
Future ongoing efforts development around Vhl loss – CRISPR–deletion of murine *Vhl* leads to senescence



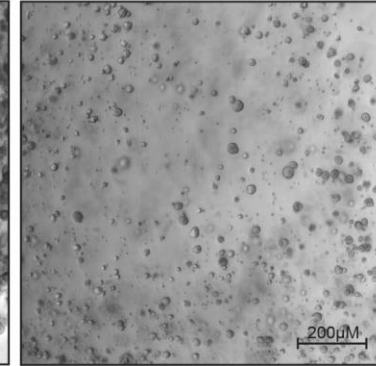
VHL loss mediates senescence

Shown previously by Young et al, *Nature Cell Biology*, 2008

Ksp1.3-CreER; Vhl^{fl/fl}
PBS



Ksp1.3-CreER; Vhl^{fl/fl}
4-OHT



No viable cells on next passage

Inducible strategies to overcome *Vhl* loss *in vivo*



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Ongoing Work

- Isogenic CRISPR–Cas9 screens: NF2 and FH–deficient RCC lines.
- Tumor and TME characterization of NF2 and FH–deficient tumors with and without anti–PD1.
- Ongoing development of inducible *Vhl* loss ccRCC syngeneic organoid models.



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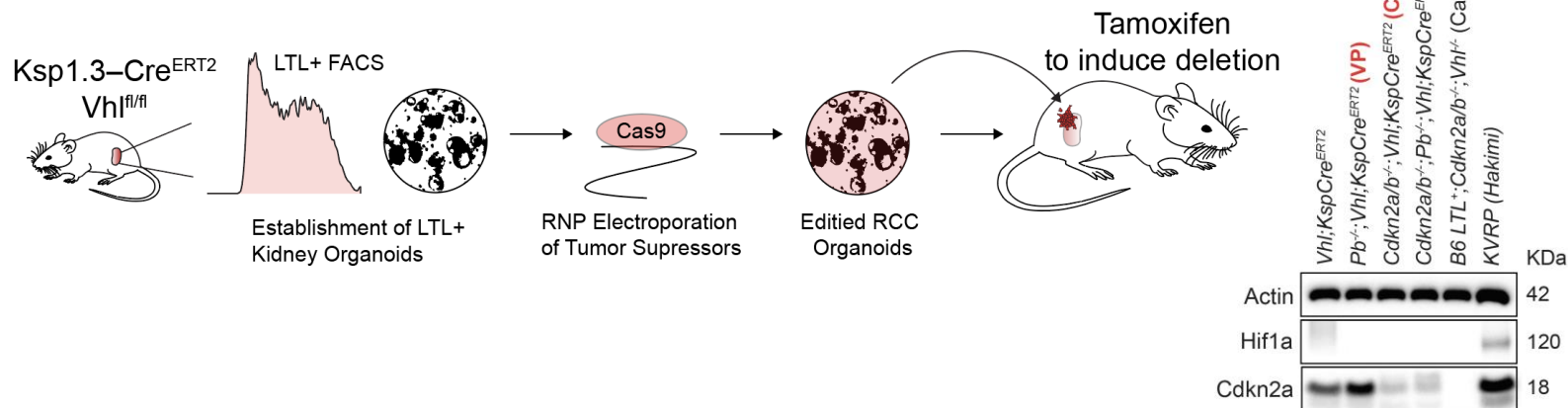


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Generation of inducible *in vivo* Vhl-loss in B6 mice with RNP CRISPR mediated deletion of co-occurring genes



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