Somatic Mouse Models in Kidney Cancer

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September 11-13, 2025

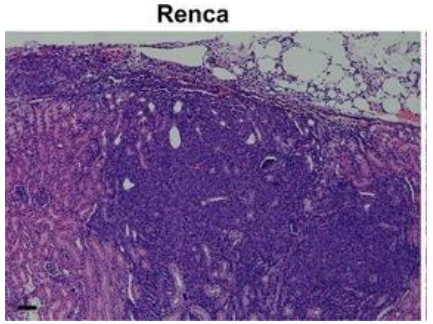
Why Somatic/Syngeneic Models

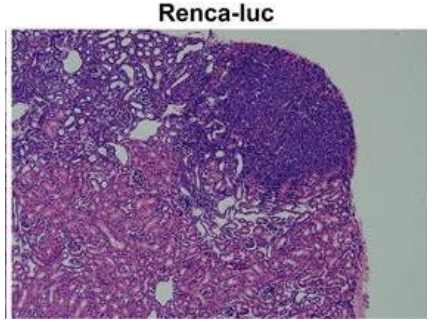
- Genetically engineered mouse models (GEMMs) are valuable for genotype–phenotype relationships and for evaluating new therapeutic concepts in a range of tumor types, however:
  - **Germline intercrossing is resource-intensive**, limiting modeling of tumor genotypes and large-scale studies
  - **Modeling tumor–host genetics requires excessive intercrosses**, making it cumbersome and inefficient
  - **Long latency** for tumors formation
  - **Cystic renal disease** limits outcomes assessment
  - Lack of **metastatic** models
- Patient Derived xenograft, can better reflect humans tumor complexity but:
  - **Lack of immune system:** PDXs require immunodeficient mice, preventing interrogation of immune–tumor interactions and limiting immunotherapy studies.
  - **Engraftment bias:** Not all patient tumors successfully engraft; more aggressive subtypes are overrepresented, skewing results.
  - **Time and cost**: Establishing and expanding PDX lines is slow and resource-intensive, delaying preclinical testing.
  - **Genetic drift**: Over passages, PDXs can accumulate mouse-specific adaptations or diverge from the patient's original tumor.
  - **Stroma replacement**: Human stromal components are gradually replaced by murine stroma, altering the tumor microenvironment.
  - **Limited scalability**: Difficult to model large patient cohorts or perform high-throughput studies due to cost and engraftment variability.
  - **Logistical hurdles:** Reliance on fresh patient tissue and immunodeficient animals increases complexity.

Feature	PDX (Patient-Derived Xenograft)	GEMM (Genetically Engineered Mouse Model)	Syngeneic or Somatic Model
Pros	• Retain human tumor genetics & heterogeneity • Clinically relevant, patient-derived • Useful for targeted therapy testing • Captures intra-/inter-tumor variability	• Tumors arise de novo in immunocompetent host • Models natural initiation & progression • Compatible with immune studies (incl. immunotherapy) • Highly reproducible & scalable	• Fully immunocompetent host (intact immune system) • Rapid, inexpensive, and reproducible • Widely used for immunotherapy testing • Scalable for large cohorts/high-throughput
Cons	• Require immunodeficient mice (no immune studies) • Engraftment bias toward aggressive tumors • Time-consuming & costly • Human stroma replaced by mouse stroma • Genetic drift over passages • Limited scalability	• Time/resource-intensive breeding & crosses • Limited tumor genotype spectrum • Less human-relevant heterogeneity • May not capture late-stage/metastatic disease	• Tumors are murine, not human (limited clinical relevance) • Do not reflect patient tumor heterogeneity • Faster growth kinetics than human cancers • Limited translational predictive value
Best Used For	• Testing targeted therapies • Capturing patient heterogeneity • Translational drug development	• Mechanistic studies of tumor initiation • Genetics-driven hypotheses • Immunocompetent modeling	• Immunotherapy screening • Rapid, scalable preclinical studies • Cost-effective high-throughput testing

RENCA Syngeneic Model in Kidney Cancer

- Origin:
  - Derived in 1973 from a spontaneous renal cortical adenocarcinoma in BALB/c mouse.
  - Maintained as a transplantable murine cell line.
  - Histology resembles poorly differentiated renal carcinoma.
- Uses:
  - Widely used in preclinical immuno-oncology (checkpoint inhibitors, vaccines, adoptive T cells).
  - Metastasis models: subQ (local growth), orthotopic (kidney + metastasis), IV/intracardiac (experimental metastasis).
  - Drug testing platform for chemotherapy, targeted therapy, and immunotherapy.
  - Studying angiogenesis, tumor–immune interactions, microenvironment.
- Problems:
  - Murine origin – lacks human RCC genetics (no VHL/HIF alterations).
  - Aggressive growth kinetics, less clinically relevant timelines.
  - Histology does not fully mimic human clear cell RCC.
  - Limited translational predictability – effective preclinical therapies often fail clinically.
  - Restricted to BALB/c strain.





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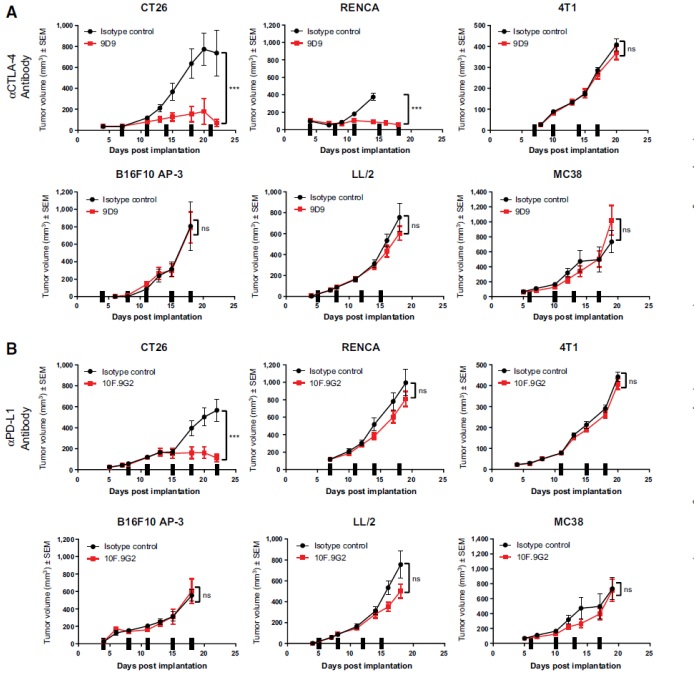
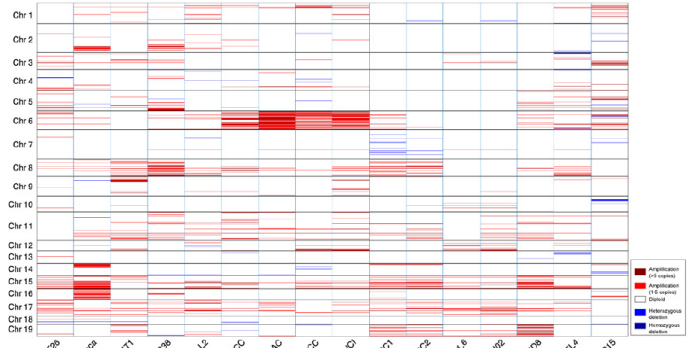
Research Article

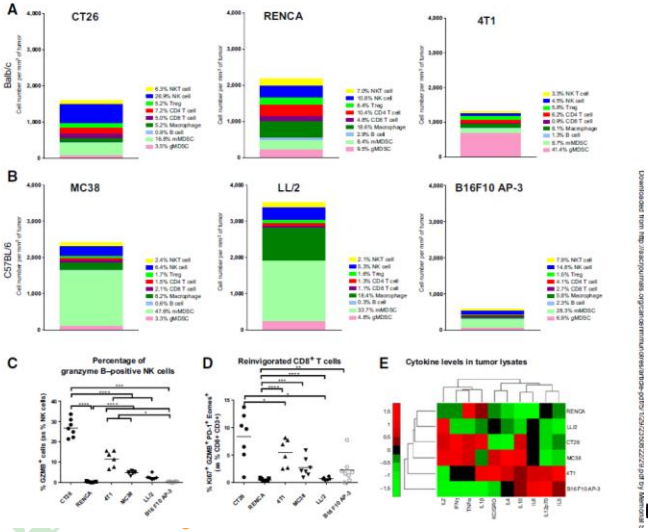
Cancer Immunology Research

Rational Selection of Syngeneic Preclinical Tumor Models for Immunotherapeutic Drug Discovery

Suzanne I.S. Mosely[1], John E. Prime[1], Richard C.A. Sainson[1], Jens-Oliver Koopmann[1], Dennis Y.Q. Wang[2], Danielle M. Greenawalt[3], Miika J. Ahdesmaki[2], Rebecca Leyland[1], Stefanie Mullins[1], Luciano Pacelli[1], Danielle Marcus[1], Judith Anderton[1], Amanda Watkins[1], Jane Coates Ulrichsen[1], Philip Brohawn[4], Brandon W. Higgs[4], Matthew McCourt[1], Hazel Jones[1], James A. Harper[1], Michelle Morrow[1], Viia Valge-Archer[1], Ross Stewart[1], Simon J. Dovedi[1], and Robert W. Wilkinson[1]







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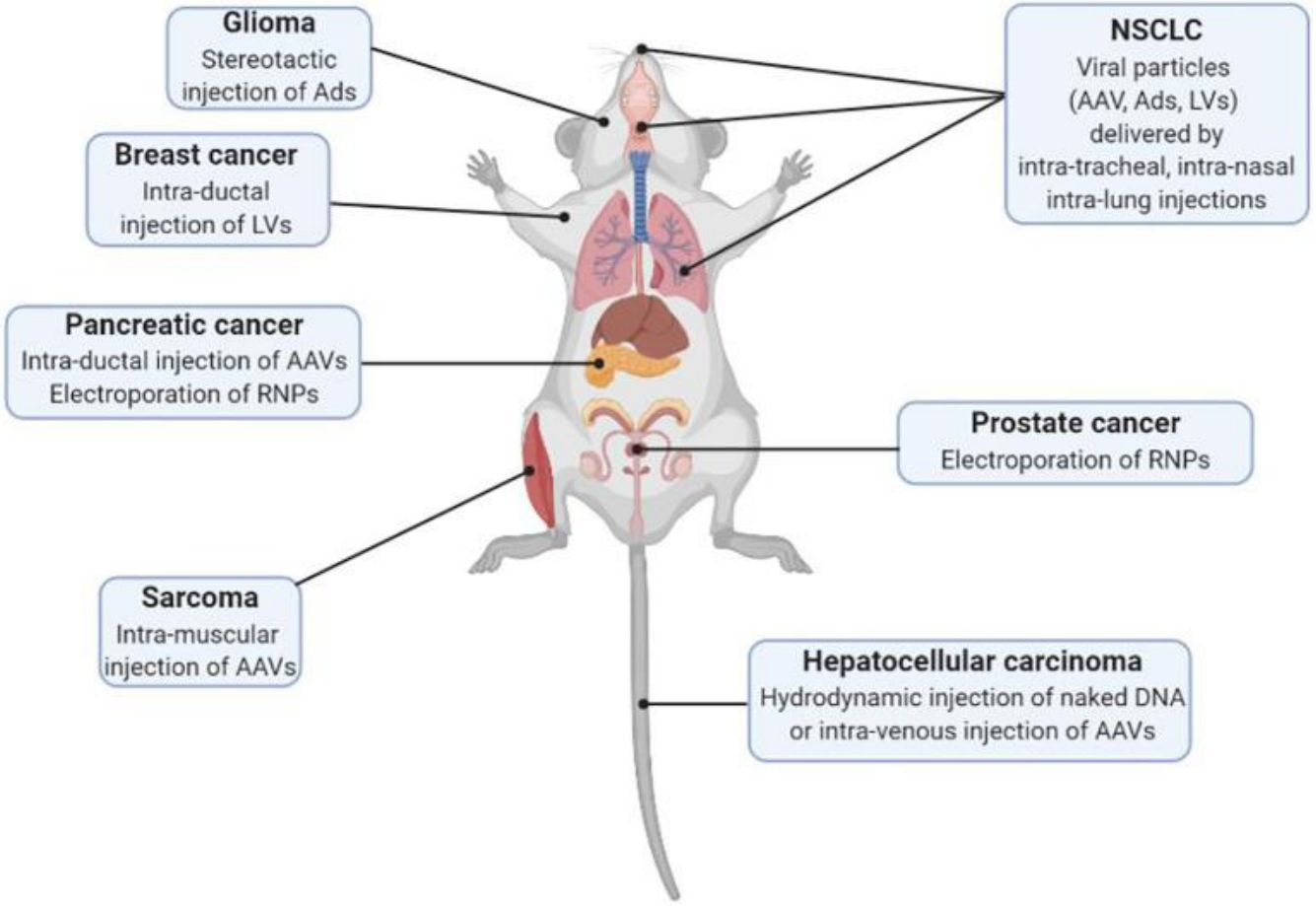
Techniques for somatic models

- **Tumor Cell Line Derivation**
  - **Source:** Tumors are induced in mice (chemically, virally, or genetically) and tumor cells are harvested to establish **murine cancer cell lines**.
  - **In vivo editing**
  - **Ex vivo editing**
  - **Key Point:** Once established, these lines can be propagated indefinitely and used across experiments.



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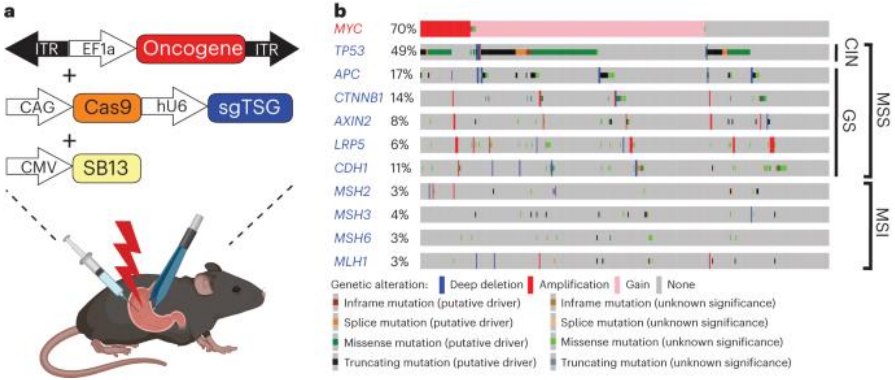
Lima et al Front Onc 2021

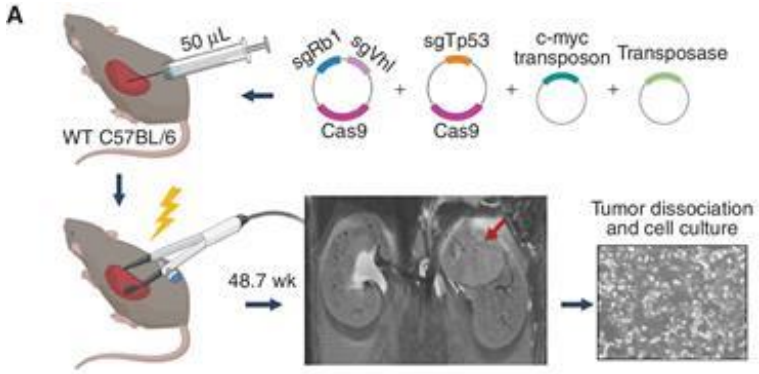
Ex-vivo engineering

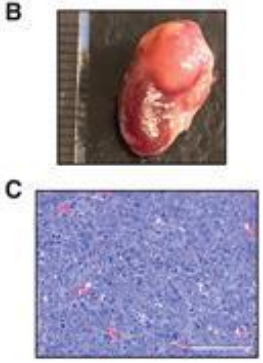
- **Genetically Defined Murine Tumors Transplanted**
  - Tumor cells can be **engineered ex vivo** (e.g., CRISPR/Cas9, shRNA, transposon) to introduce specific oncogenes or delete tumor suppressors.
  - Modified tumor cells are then transplanted into syngeneic hosts.
  - **Advantage:** Models specific driver mutations in an immunocompetent setting.

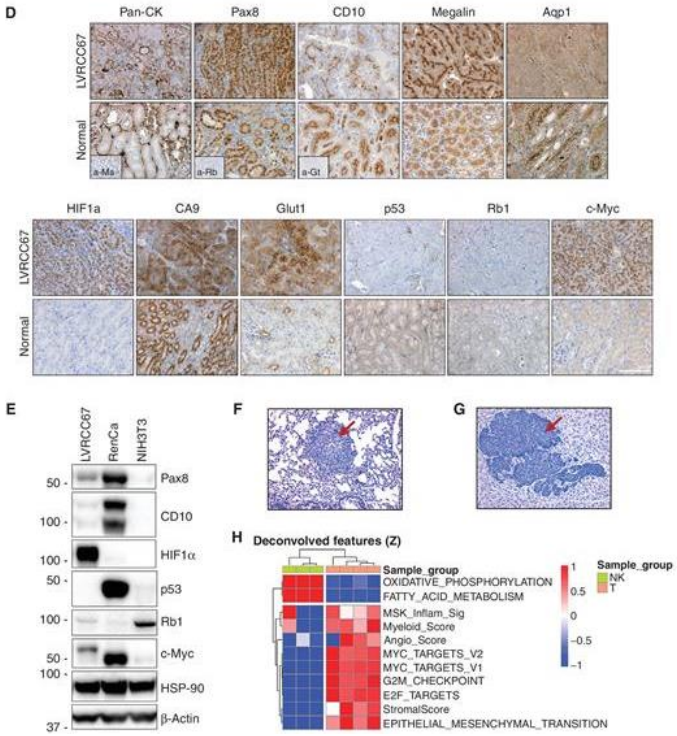


Leibold et al *Nat Cancer* 2024

LVRCC







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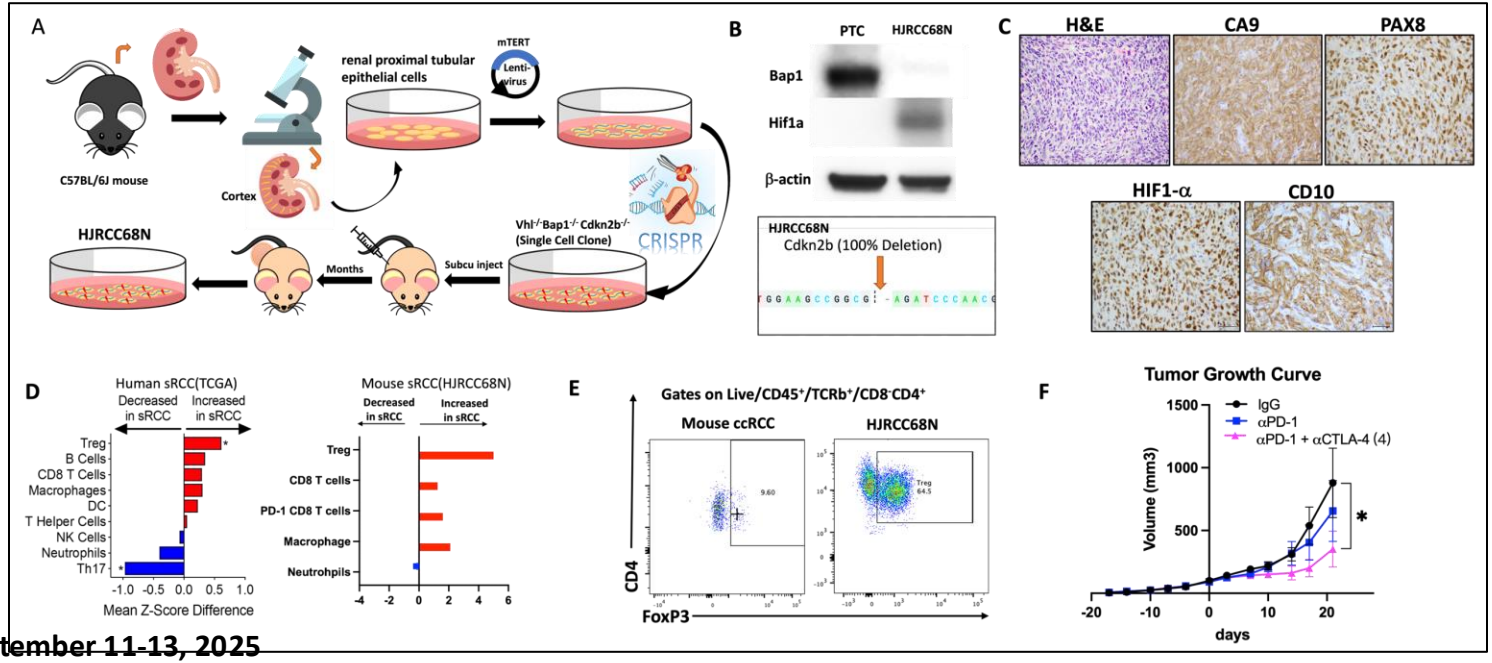
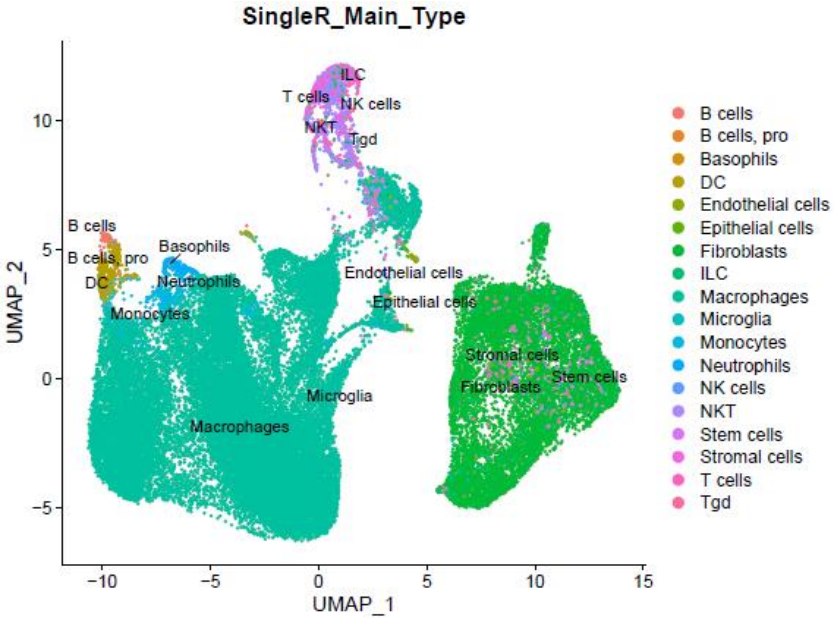
Rappold, Voung et al Canc Disc 2022

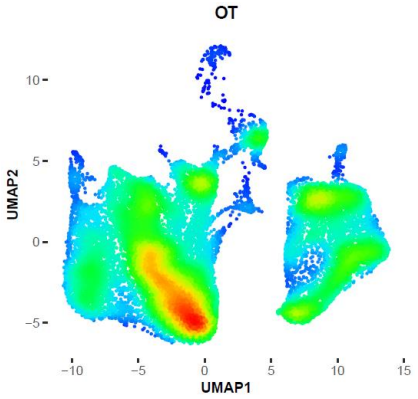
Editing cell of origin ev-vivo

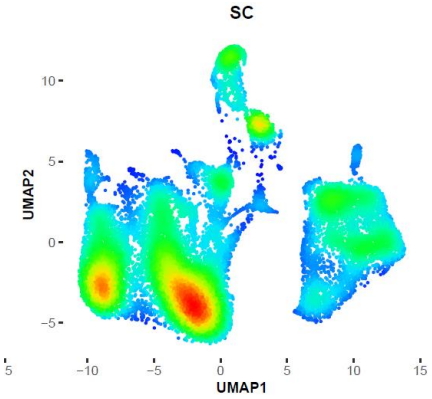


Hui et al *Unpublished*

Location of implantation can impact TME

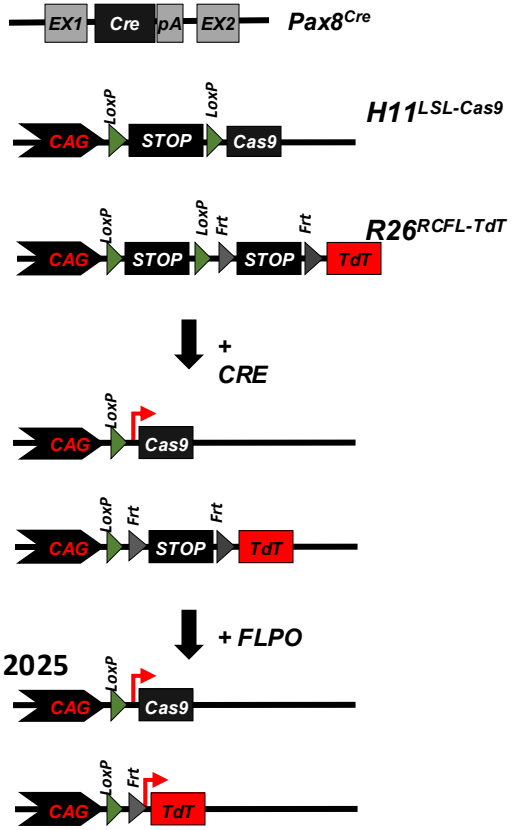


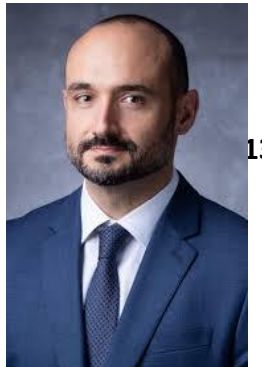




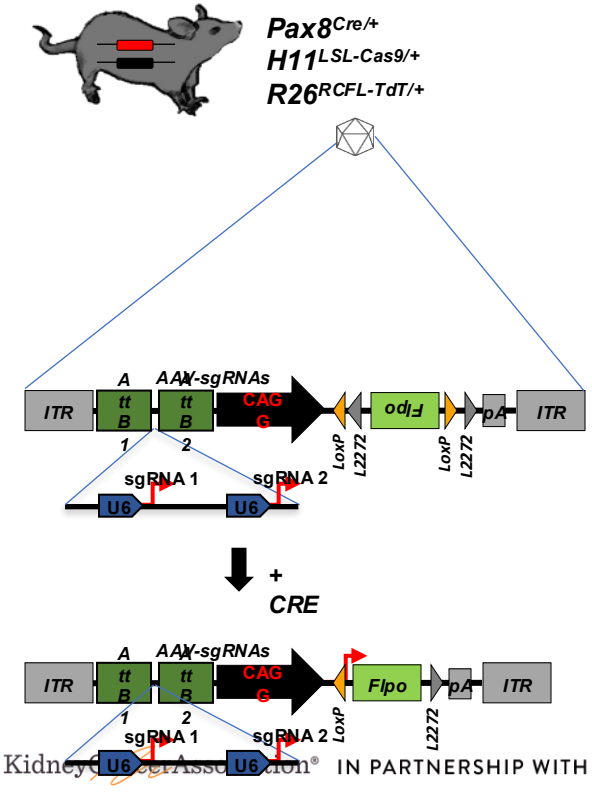
KidneyCancerAssociation® IN PARTNERSHIP WITH UTSouthwestern Medical Center Kidney Cancer Program

Generation of somatic mosaic models of RCC





13, 2025



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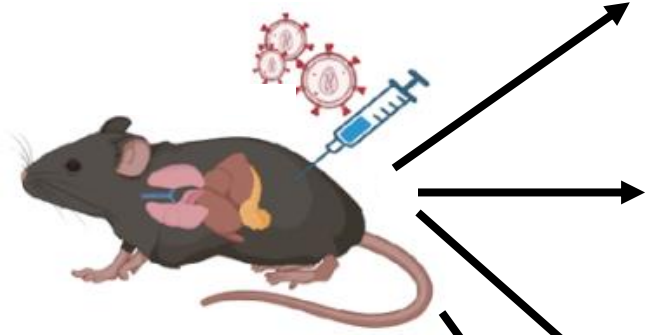
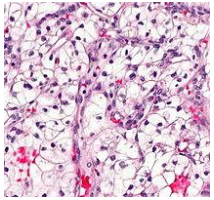
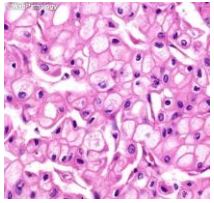
RCC subtypes by pathology/genetics



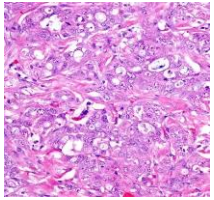
$Pax8^{Cre/+}$
$H11^{LSL\text{-}Cas9/+}$
$R26^{RCFL\text{-}TdT/+}$



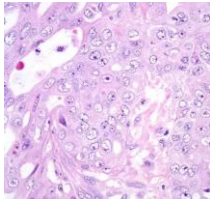
Vhl^{KO}-$Setd2^{KO}$-$Cdkn2a/b^{KO}$
Vhl^{KO}-$Bap1^{KO}$-$Cdkn2a/b^{KO}$
Vhl^{KO}-$Tp53^{KO}$-$Pten^{KO}$



$Tp53^{KO}$-$Pten^{KO}$



$Nf2^{KO}$-$Setd2^{KO}$-$Cdkn2a/b^{KO}$
$Nf2^{KO}$-$Bap1^{KO}$-$Cdkn2a/b^{KO}$
$Nf2^{KO}$-$Tp53^{KO}$-$Cdkn2a/b^{KO}$
Fh^{KO}-$Cdkn2a/b^{KO}$



$Smarcb1^{KO}$-$Tp53^{KO}$-$Cdkn2a/b^{KO}$

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Conclusion

- Somatic mouse models offer flexible options for rapid drug testing
- Allow for immunocompetent studies enabling assessment of TME
- Can be customized by genotypes
- Are limited by mouse genetics and inherent differences in human/mouse immunity