

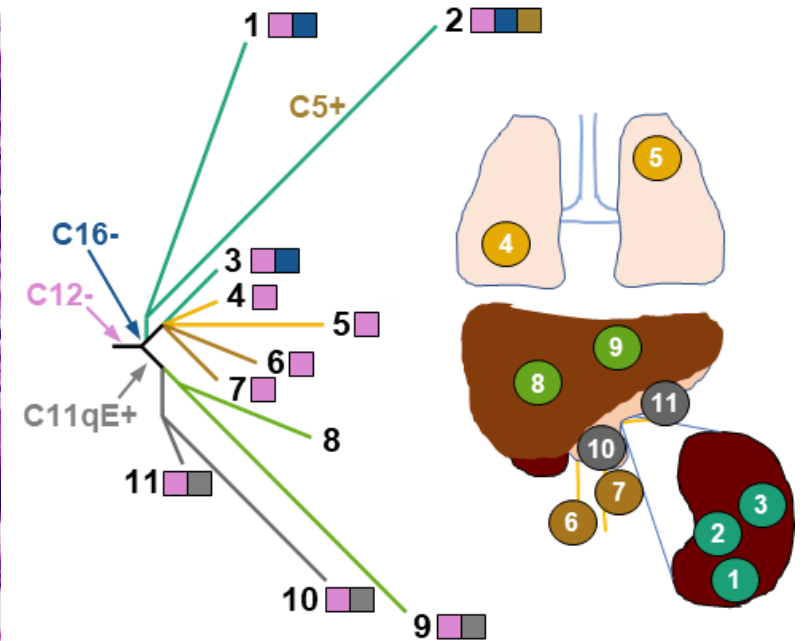
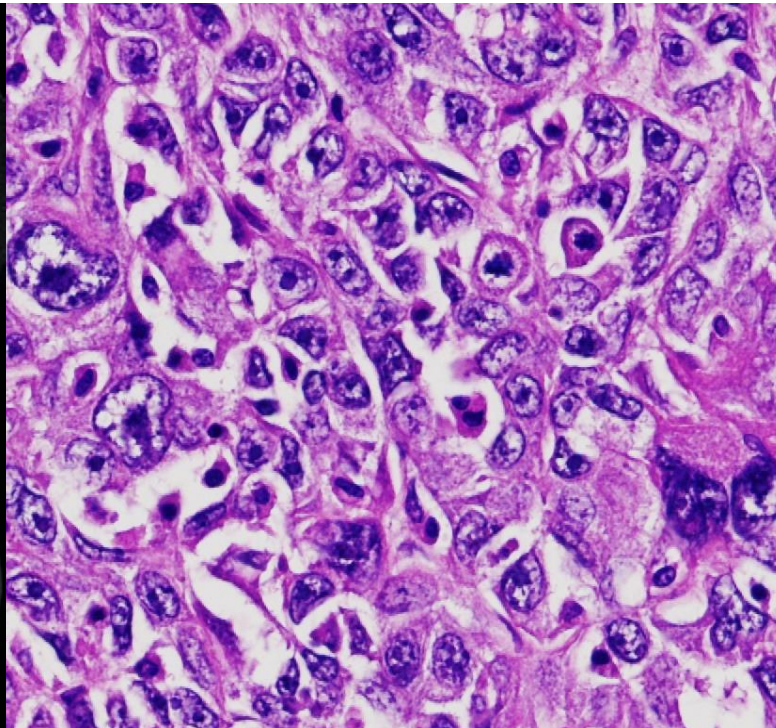
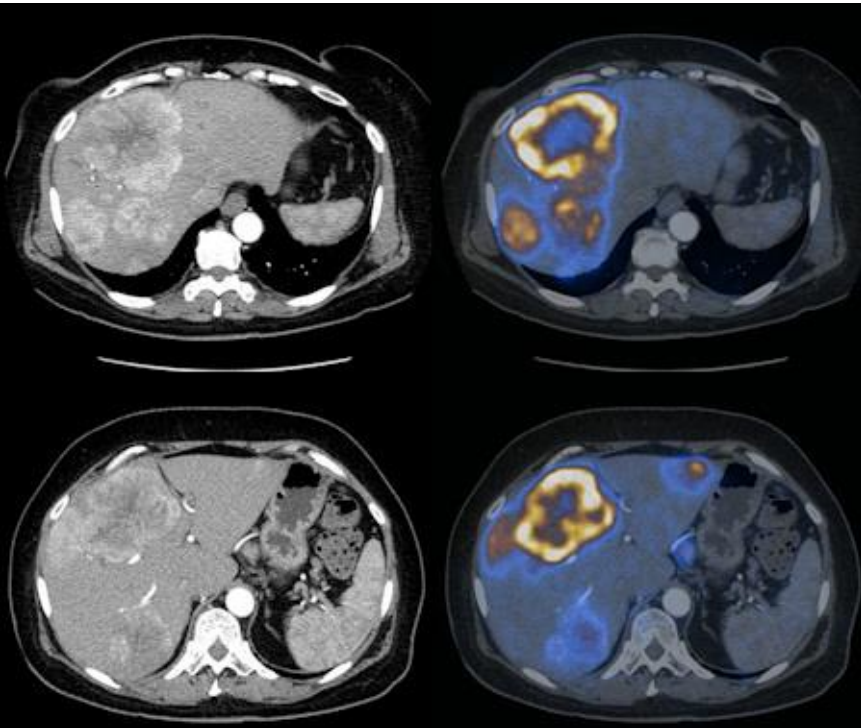
Cross-Species Functionalization of the RCC Genome

Giannicola Genovese, M.D., Ph.D.

Department of GU Oncology and Genomic Medicine

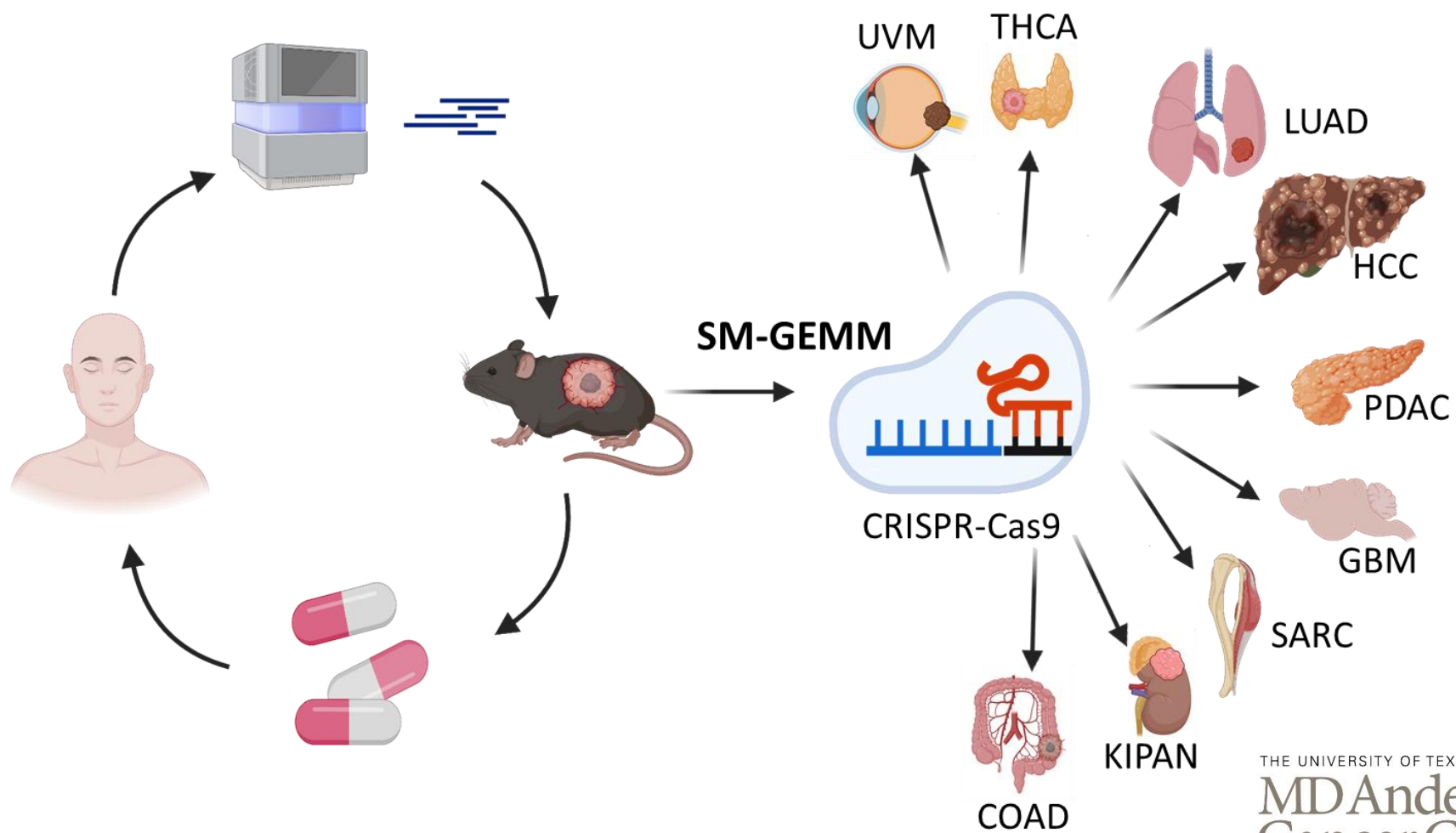
David H. Koch Center for Applied Research of Genitourinary Cancers

Division of Therapeutic Discoveries/TRACTION Platform

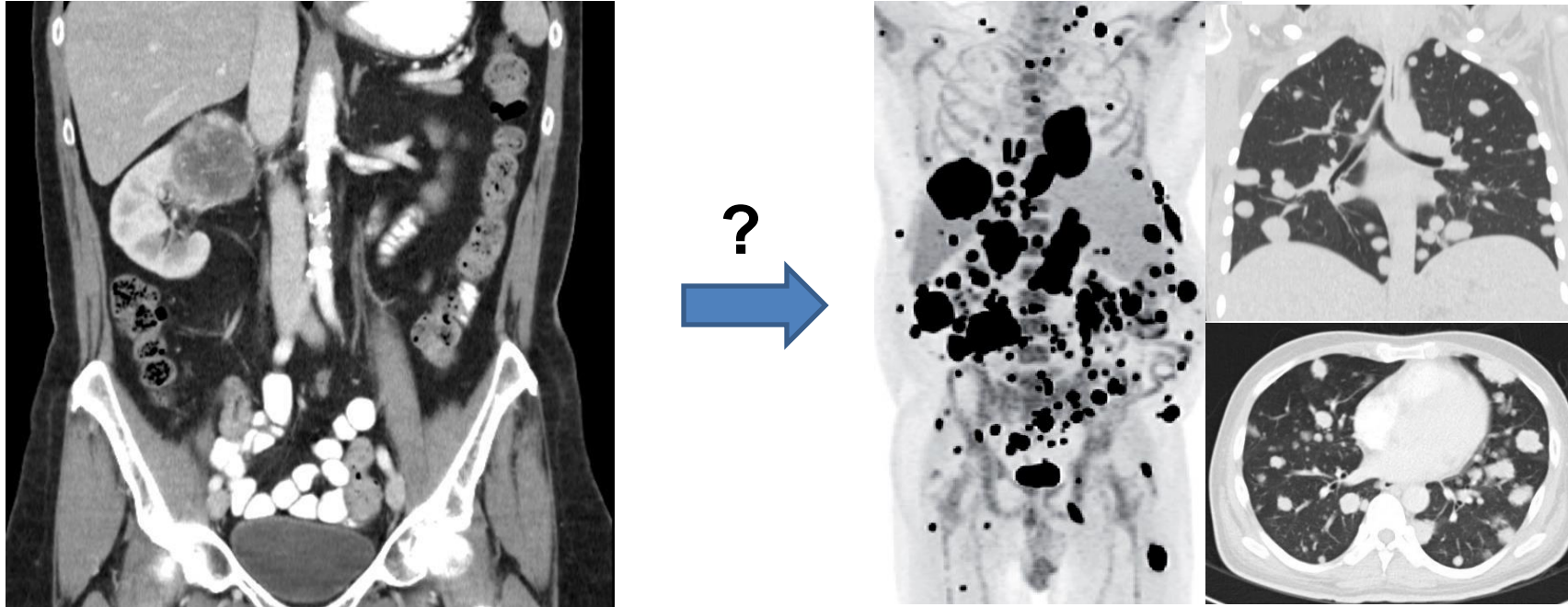


 ggenovese@mdanderson.org

In Vivo Functional Genomics



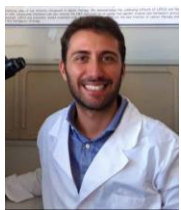
Clinical challenge: what drives metastasis in RCC



Radiopedia (2019)



**Federica
Carbone**



**Luigi
Perelli**



**Ralph
DeBerardinis**



**Divya
Bezwada**



Ari Hakimi



**Renzo
Di Natale**



**Yingbei
Chen**



Turajlic Lab

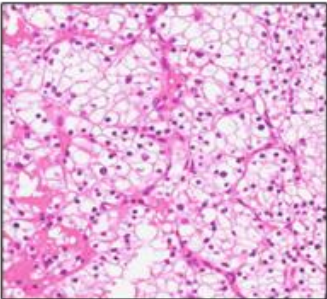
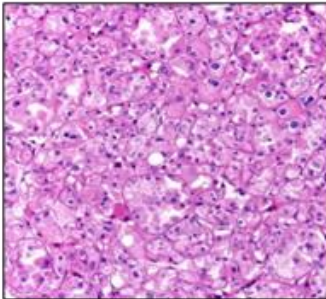
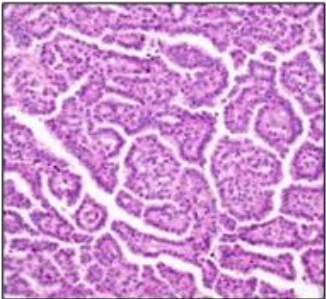
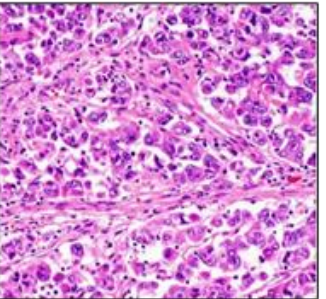
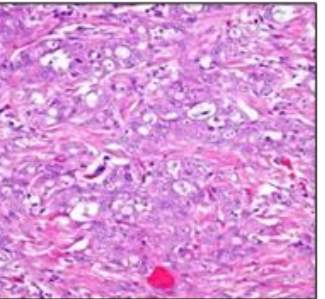
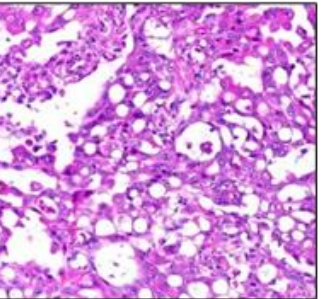
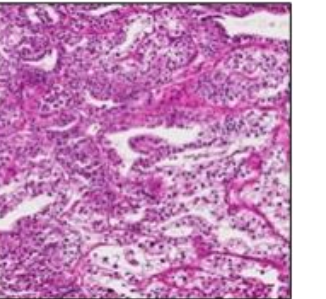


**Nizar
Tannir**

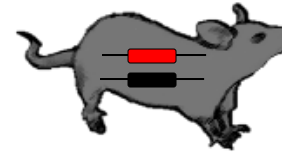
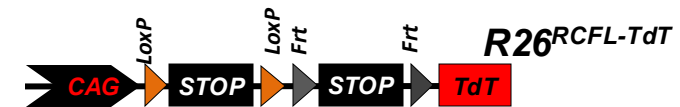


**Pavlos
Msaouel**

RCC subtypes by pathology/genetics

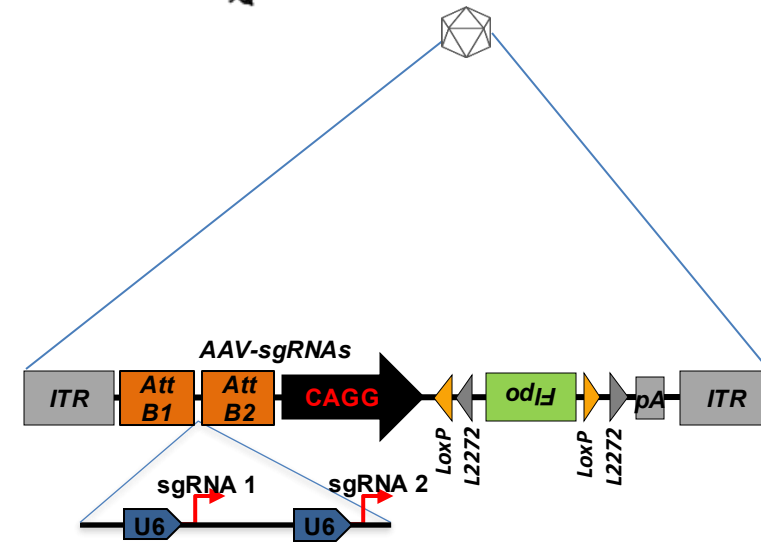
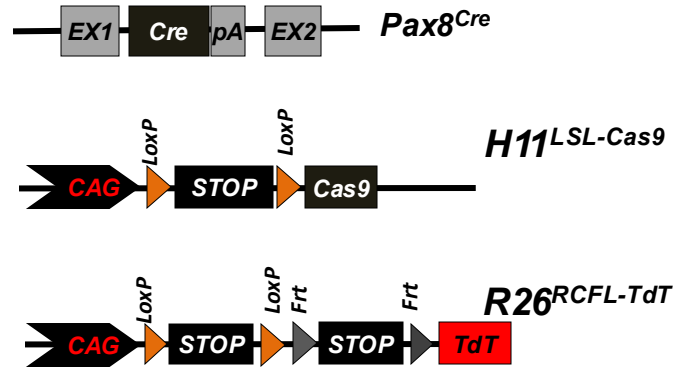
	Clear Cell RCC	Chromophobe RCC	Type I papillary RCC	Type II papillary RCC/HLRCC	Unclassified RCC/CDC	RMC/MRT	MiTF Translocation RCC
							
Incidence:	75%	5%	5%		~14%	<1%	~1%
Median Age:	62	58	62	62	50-55	28	31-49
Prognosis:	Good	Very good	Good	Poor	Very poor	Dismal	Often poor
Genetics:	<i>VHL</i> , 3p loss	<i>BHD</i> Aneuploidy	<i>c-MET</i>	<i>FH</i> , <i>NF2</i> , 9p loss	<i>NF2</i> , <i>SETD2</i> , <i>Trp53</i> <i>BAP1</i> , 9p loss	<i>SMARCB1</i> 22q loss	<i>TFE3</i> or <i>TFEB</i> translocation
Therapeutic targets:	HIF, VEGF, RTKs, mTOR	Surgery	<i>c-MET</i>	<i>FH</i> , Hippo-YAP	<i>Hippo-YAP</i>	<i>SMARCB1</i> 22q loss	<i>TFE3/PI3K/A</i> <i>KT/mTOR</i>

Generation of somatic mosaic models of RCC

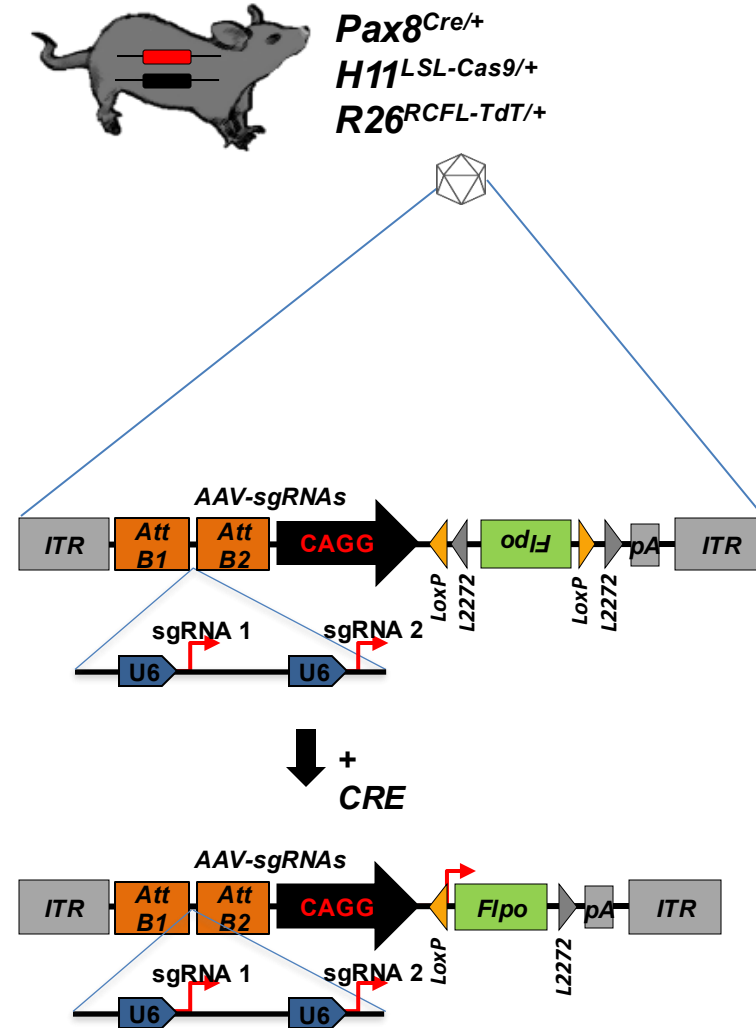
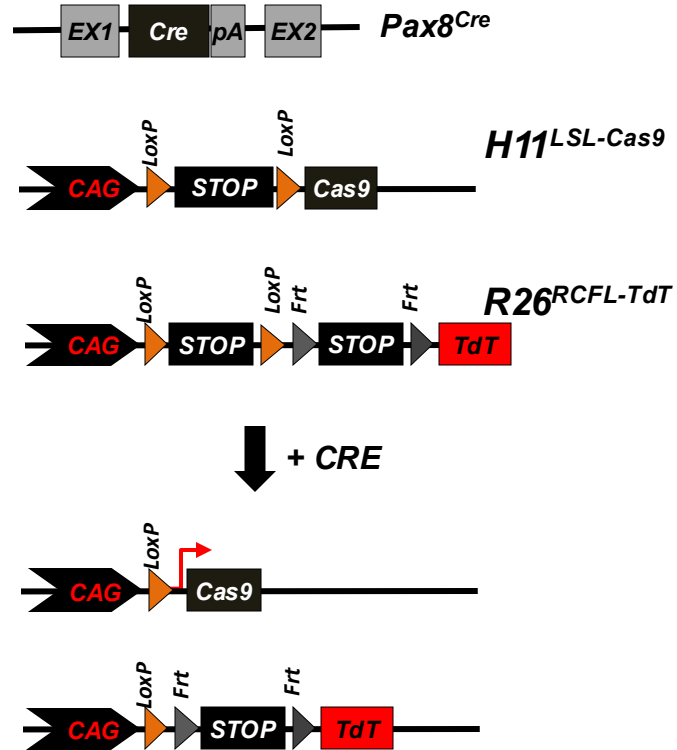


Pax8^{Cre/+}
H11^{LSL-Cas9/+}
R26^{RCFL-TdT/+}

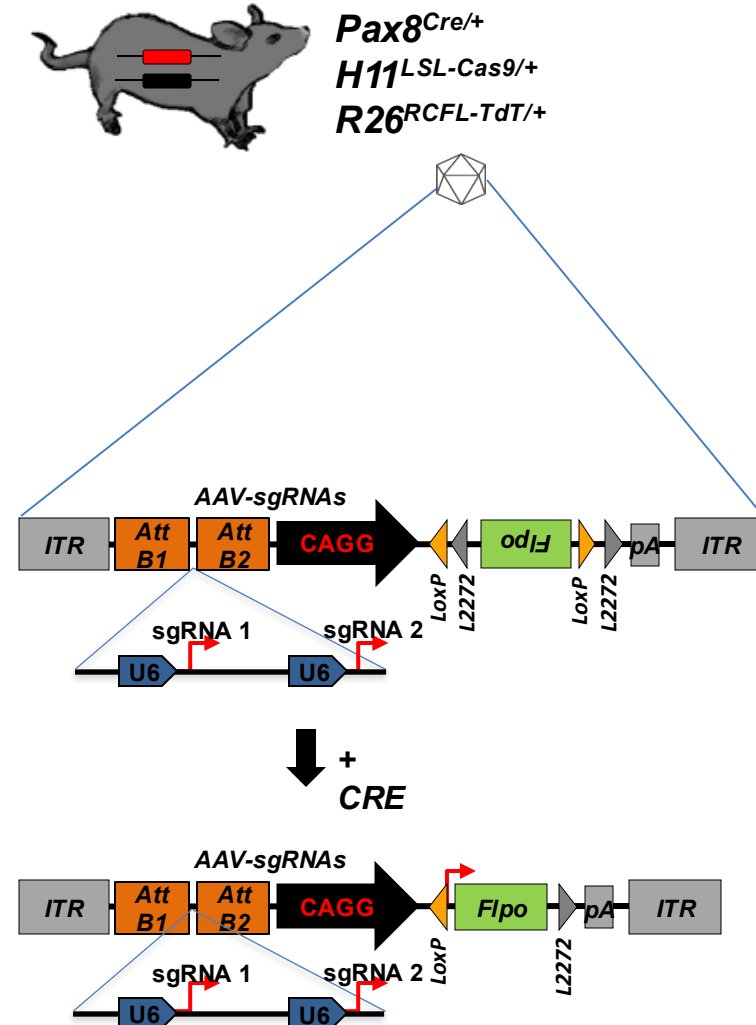
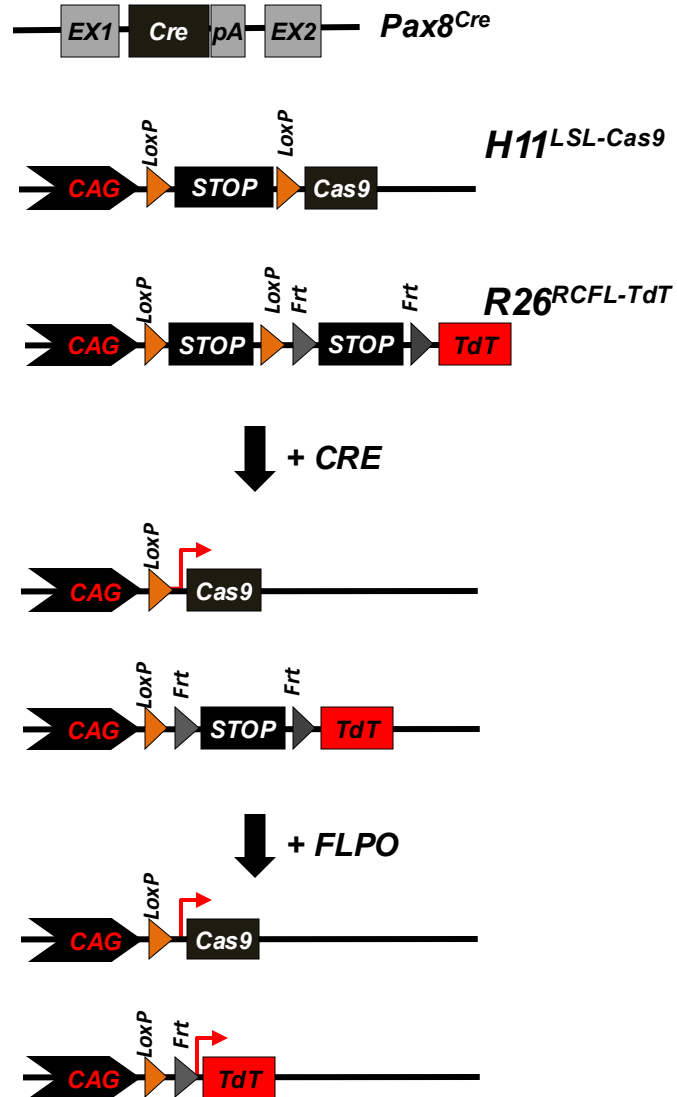
Generation of somatic mosaic models of RCC



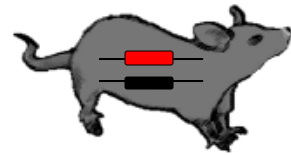
Generation of somatic mosaic models of RCC



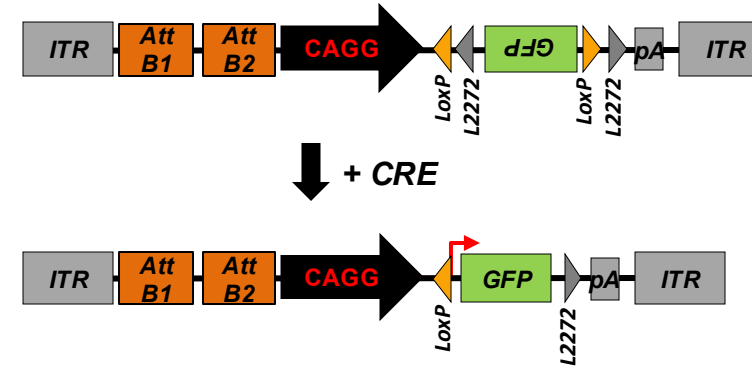
Generation of somatic mosaic models of RCC



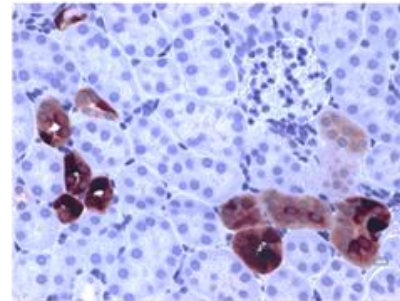
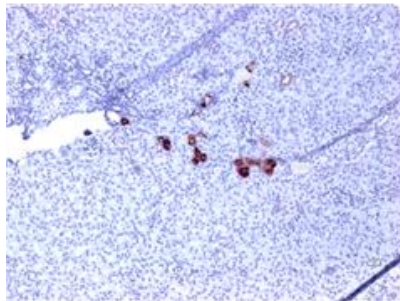
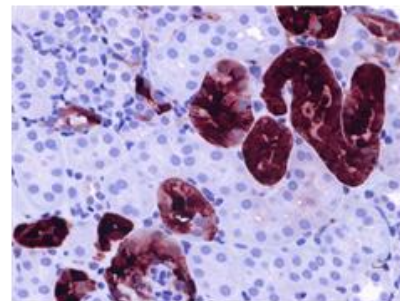
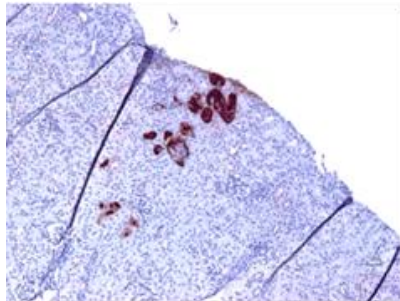
Generation of somatic mosaic models of RCC: specificity



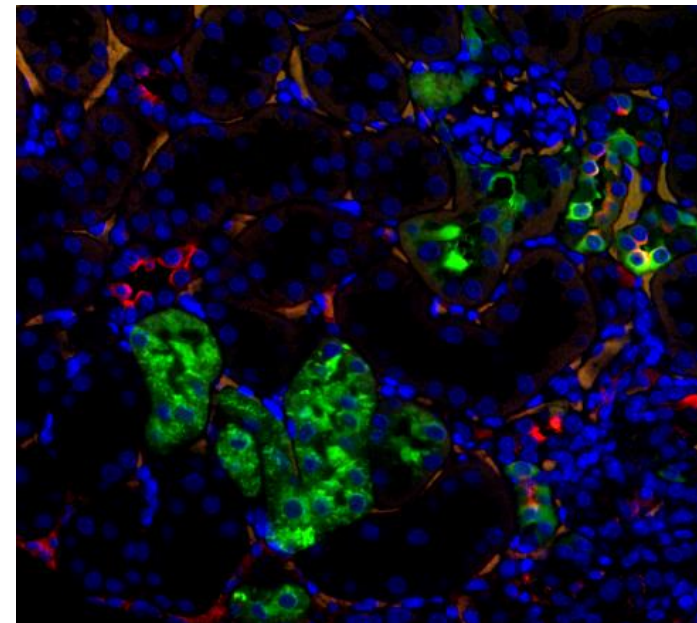
Pax8^{Cre/+}
H11^{LSL-Cas9/+}



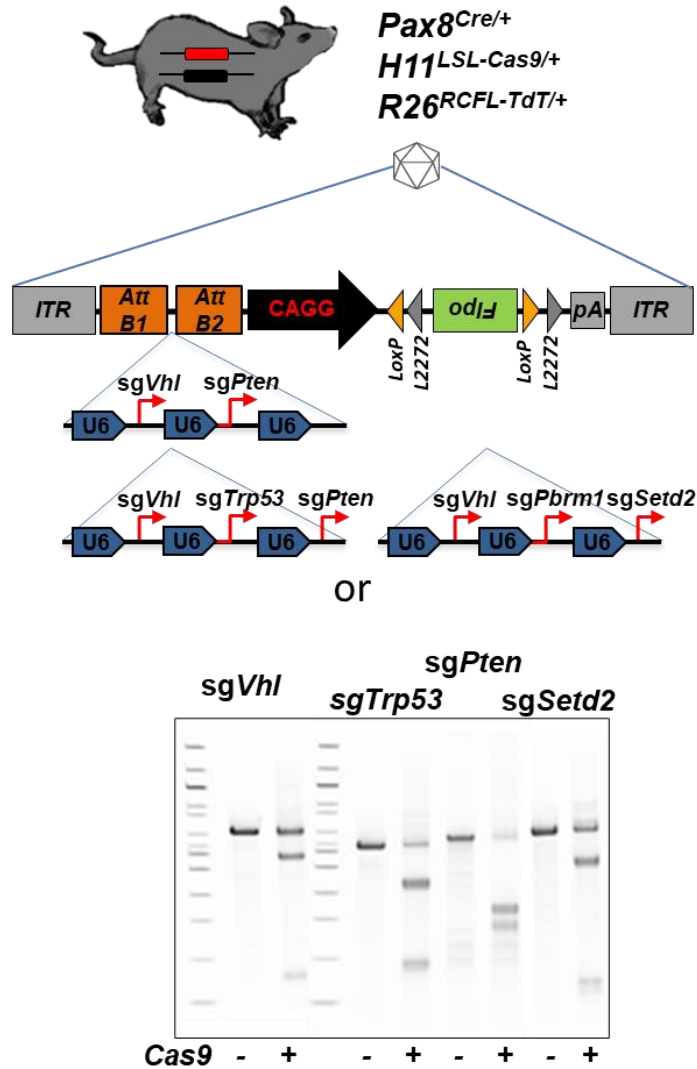
GFP



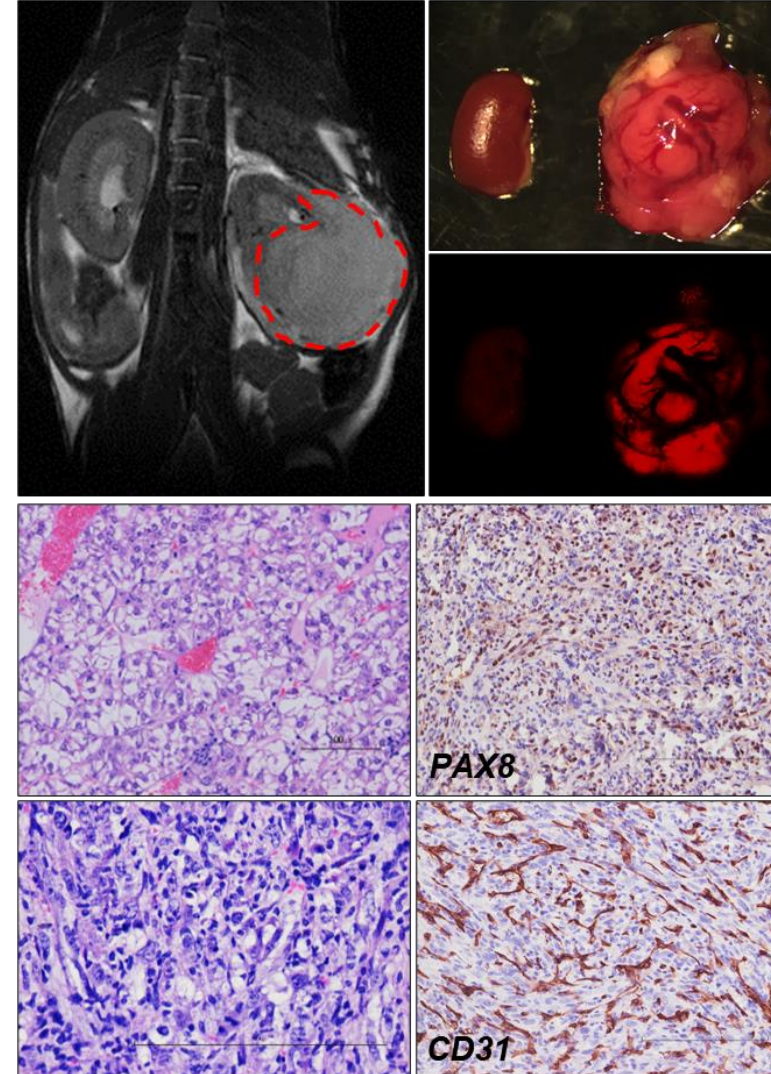
GFP/AQP2



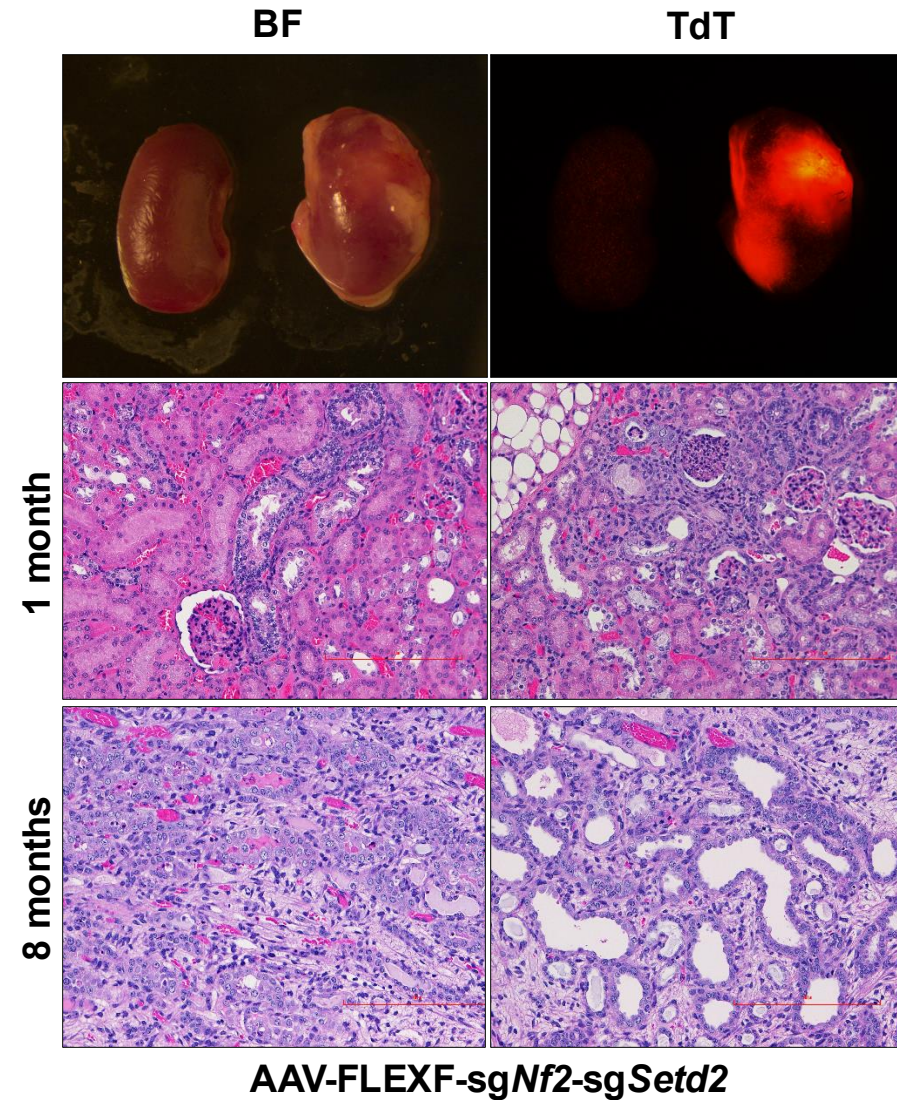
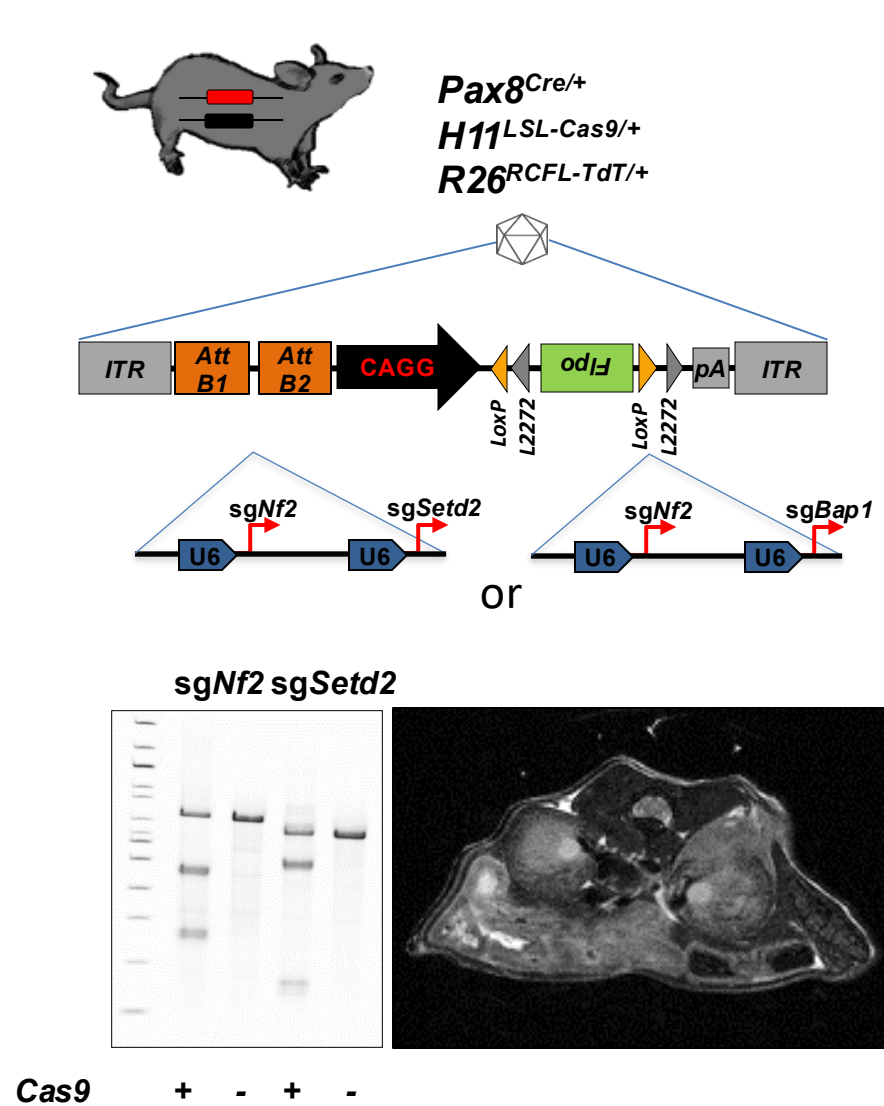
Mosaic ablation of *Vhl* drives ccRCC



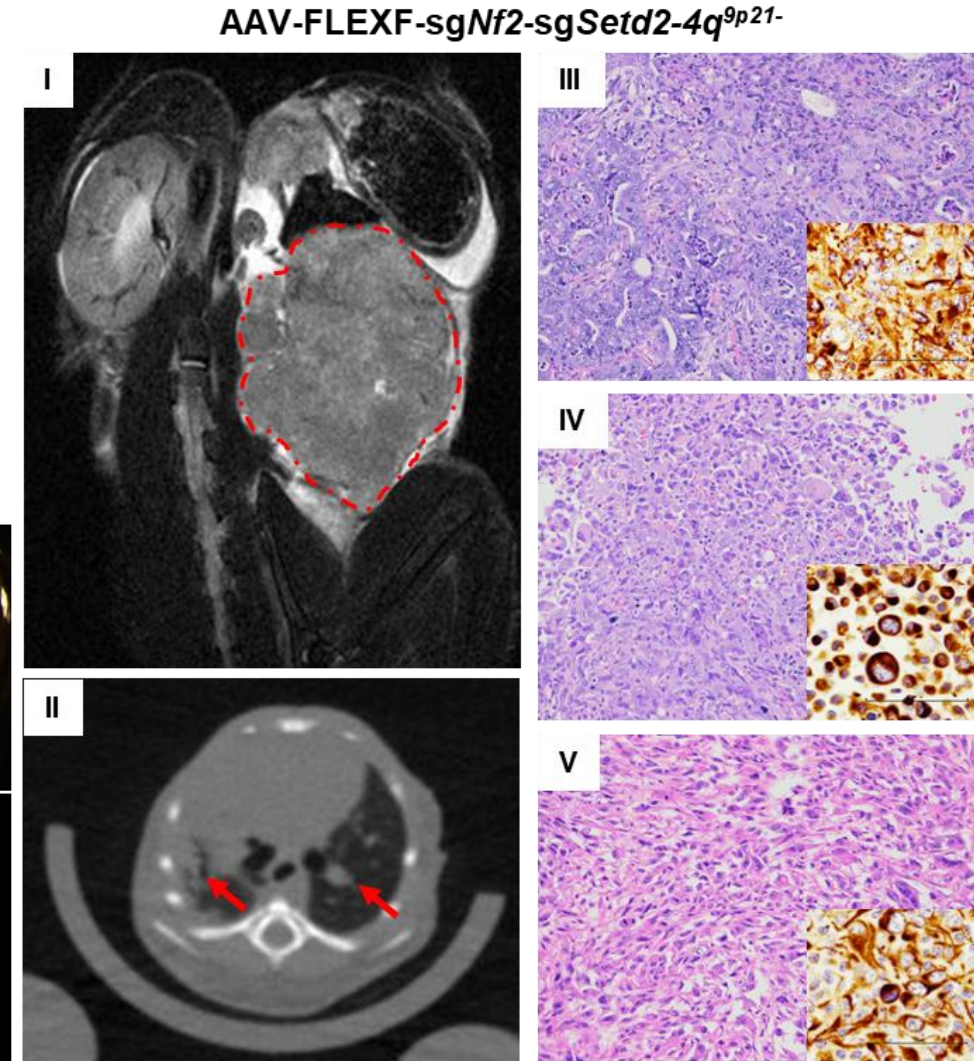
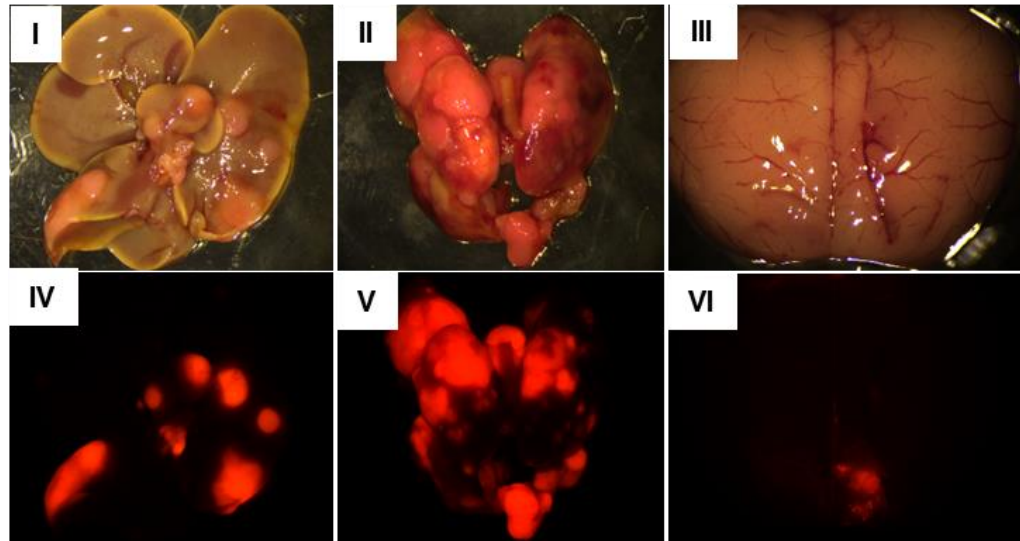
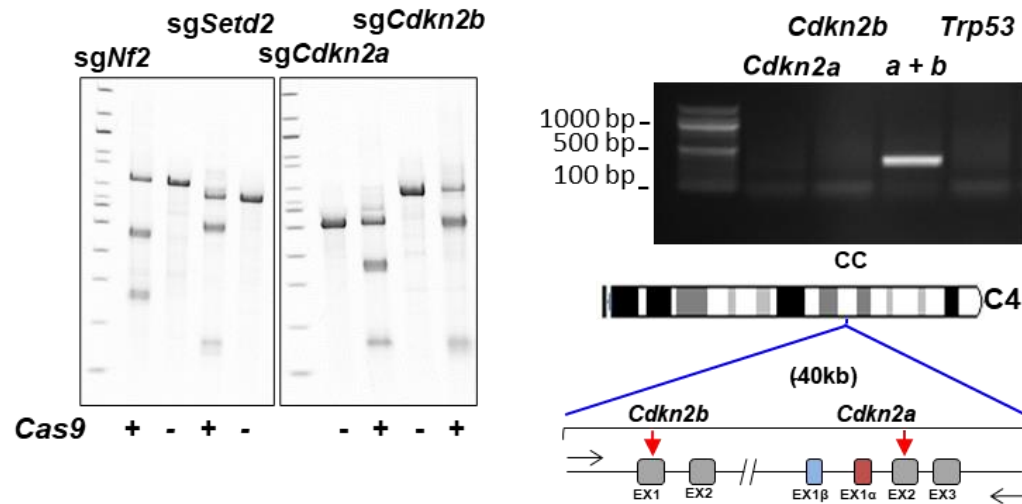
AAV-FLEXF-sgVhl-sgPten-sgTp53



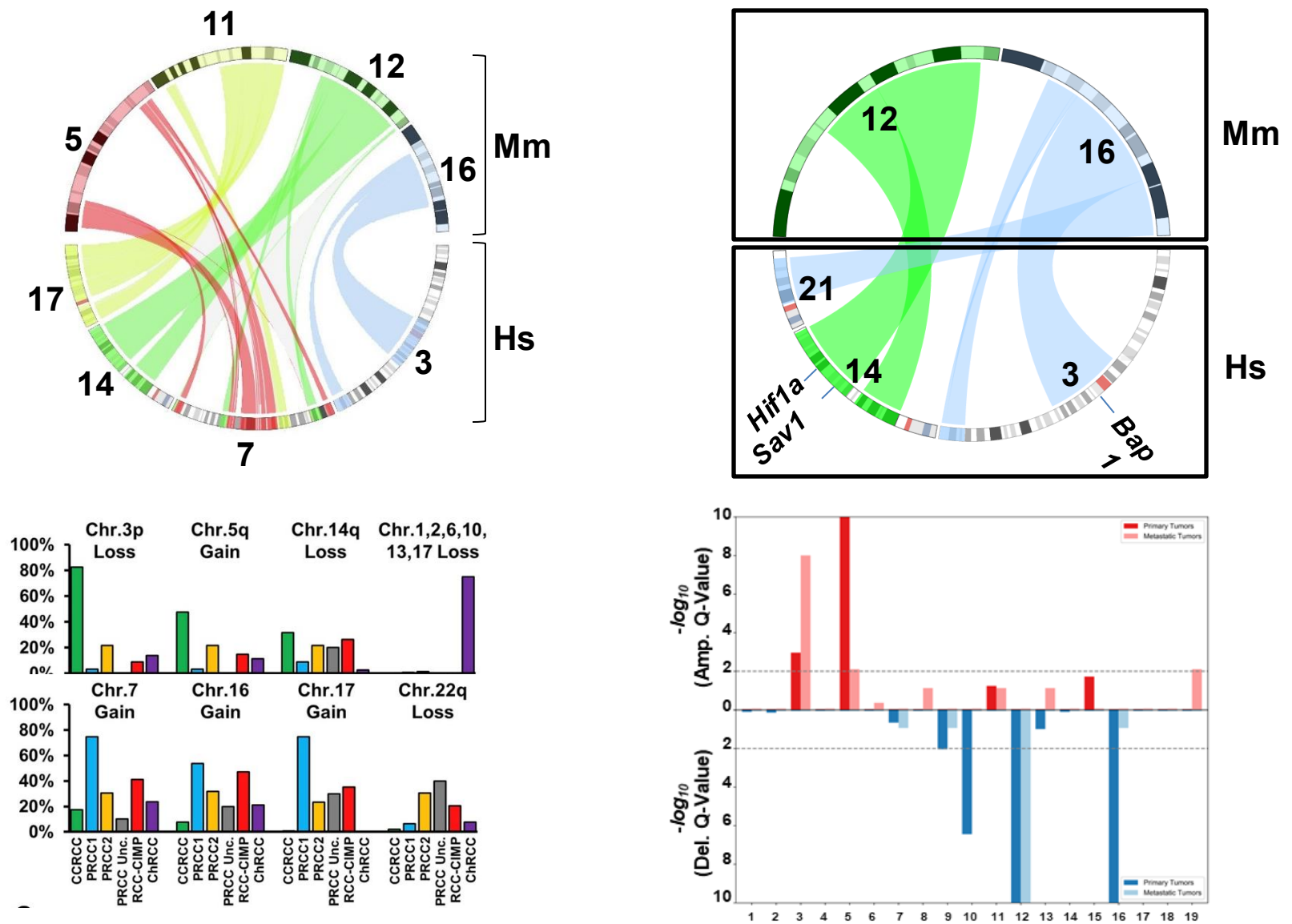
Mosaic ablation of *Nf2* drives tumors with tubular/papillary features



Key finding 1: somatic genetic ablation of 9p drives aggressive disease



Key finding 2: Cross-species convergent evolution



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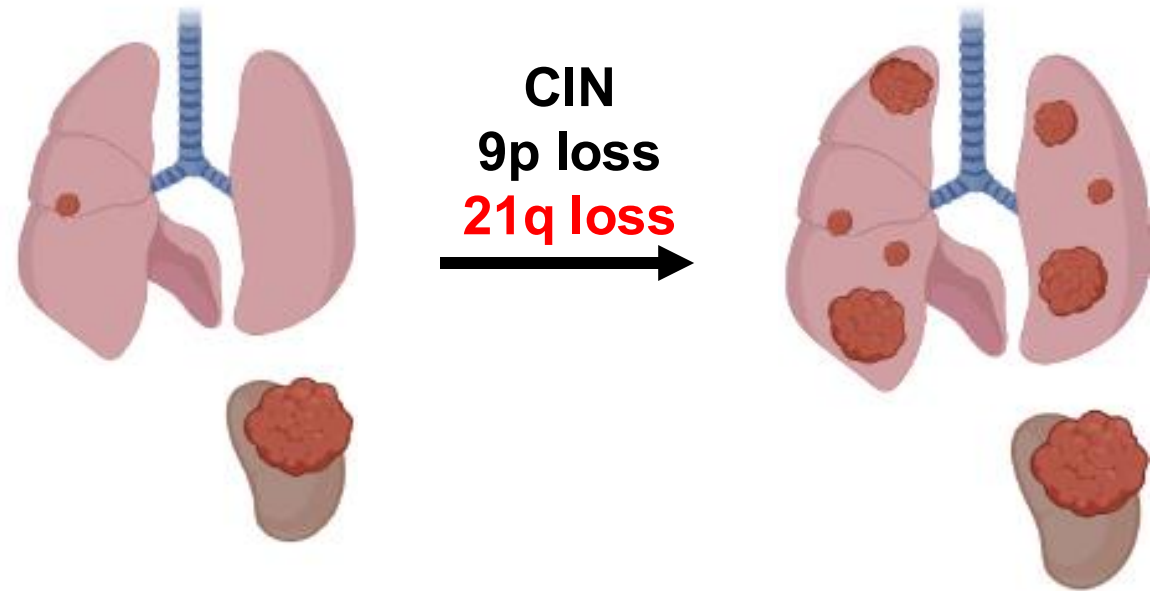
Interferon signaling promotes tolerance to chromosomal instability during metastatic evolution in renal cancer

[Luigi Perelli](#) ✉, [Federica Carbone](#), [Li Zhang](#), [Justin K. Huang](#), [Courtney Le](#), [Hania Khan](#), [Francesca Citron](#), [Edoardo Del Poggetto](#), [Tony Gutschner](#), [Hideo Tomihara](#), [Melinda Soeung](#), [Rosalba Minelli](#), [Sanjana Srinivasan](#), [Michael Peoples](#), [Truong Nguyen Anh Lam](#), [Sebastian Lundgren](#), [Ruohan Xia](#), [Cihui Zhu](#), [Alaa M. T. Mohamed](#), [Jianhua Zhang](#), [Kanishka Sircar](#), [Alessandro Sgambato](#), [JianJun Gao](#), [Eric Jonasch](#), [Giulio F. Draetta](#), [Andrew Futreal](#), [Ziad Bakouny](#), [Eliezer M. Van Allen](#), [Toni Choueiri](#), [Sabina Signoretti](#), [Pavlos Msaouel](#), [Kevin Litchfield](#), [Samra Turajlic](#), [Linghua Wang](#), [Ying Bei Chen](#), [Renzo G. Di Natale](#), [A. Ari Hakimi](#), [Virginia Giuliani](#), [Timothy P. Heffernan](#), [Andrea Viale](#), [Christopher A. Bristow](#), [Nizar M. Tannir](#), [Alessandro Carugo](#) ✉ & [Giannicola Genovese](#) ✉

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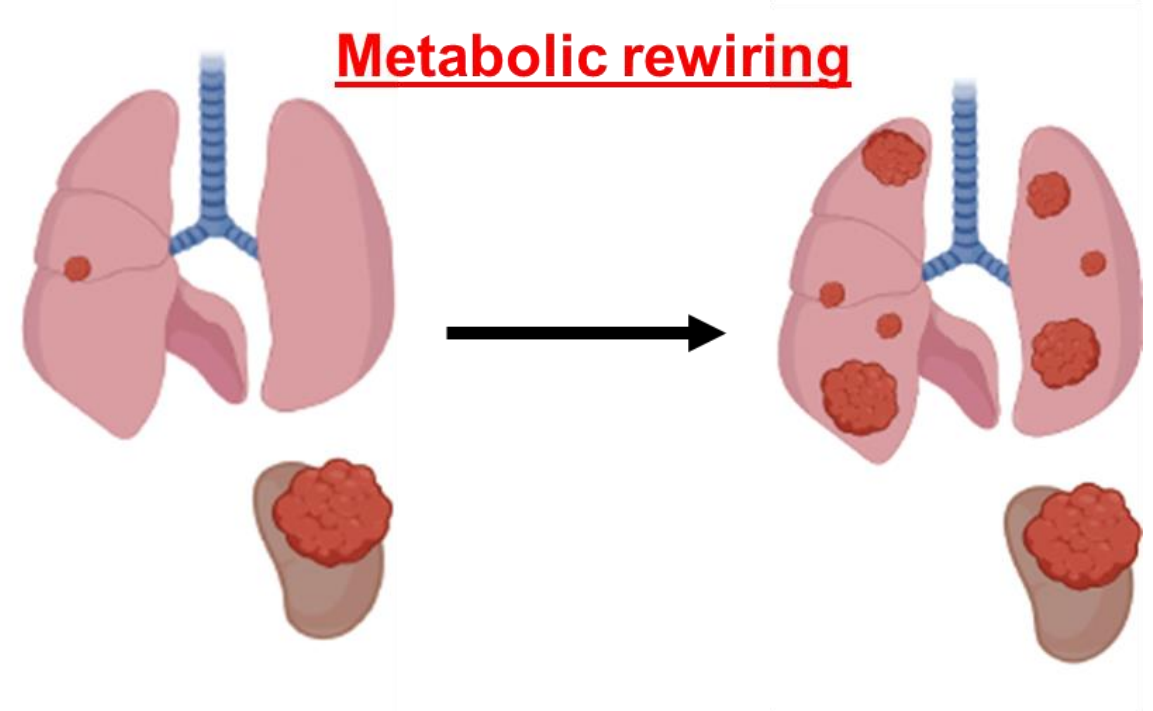
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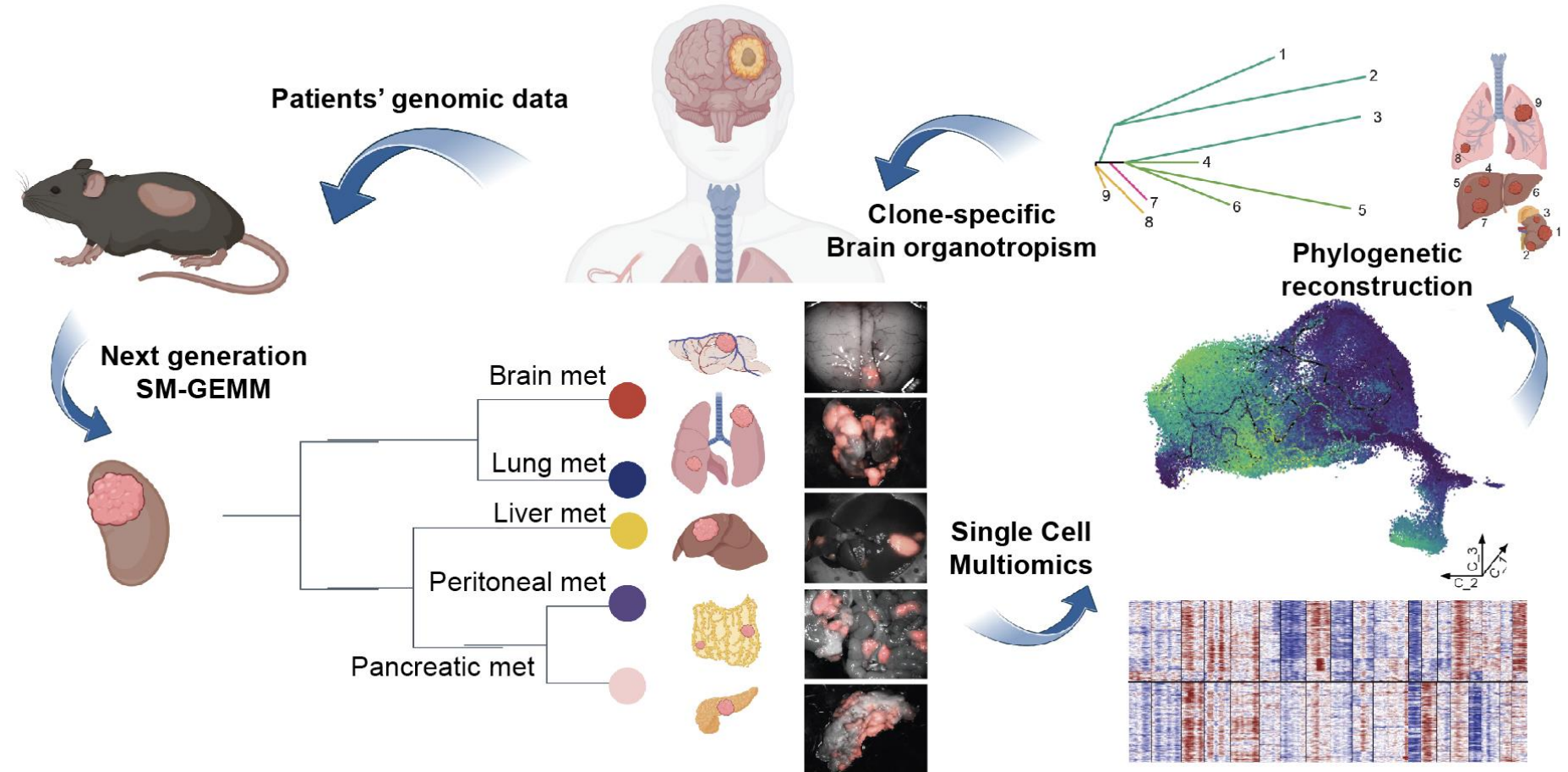
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Mitochondrial complex I promotes kidney cancer metastasis

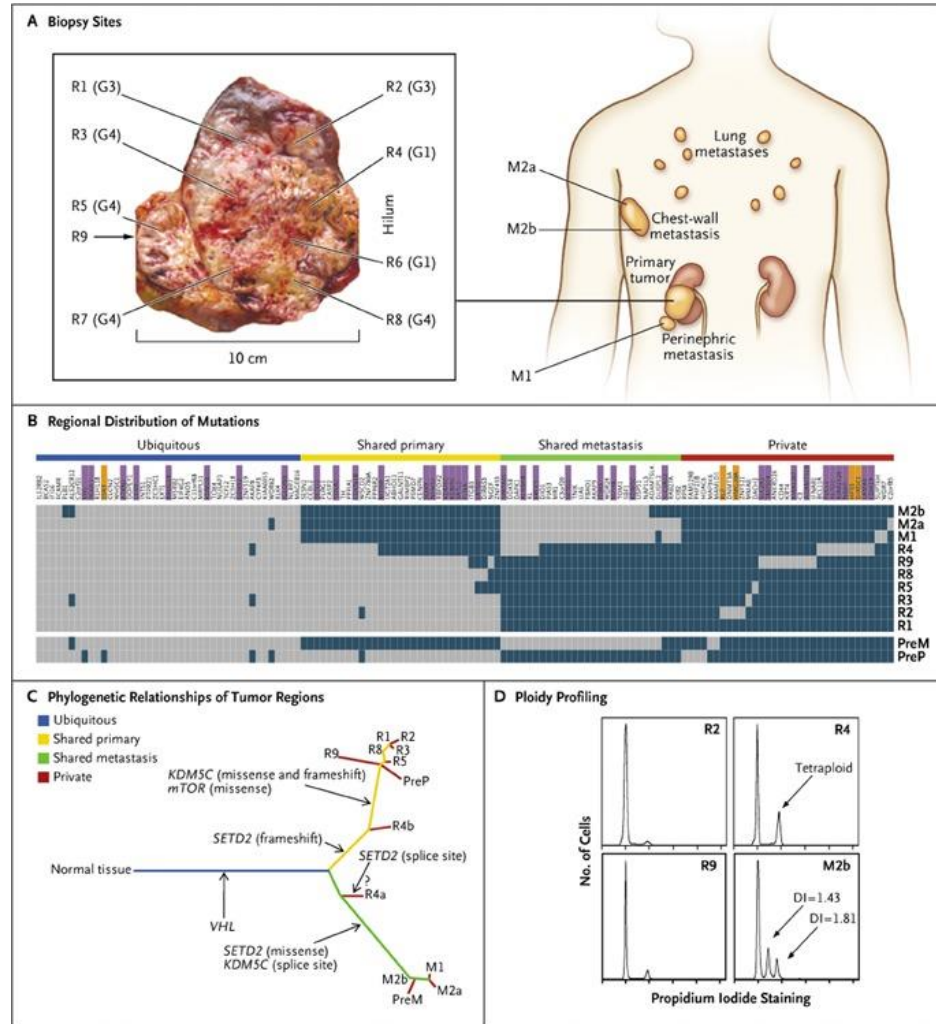
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Ongoing work: cross species characterization of metastatic organotropism

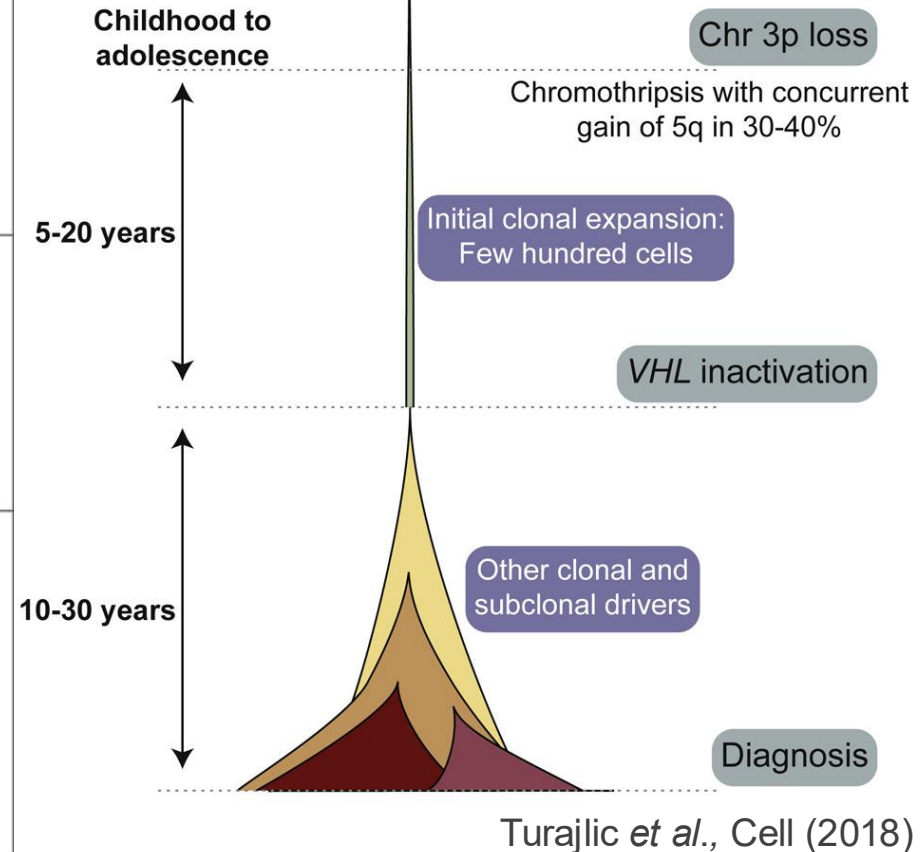


Challenges: branched evolution drives clonal diversity in RCC



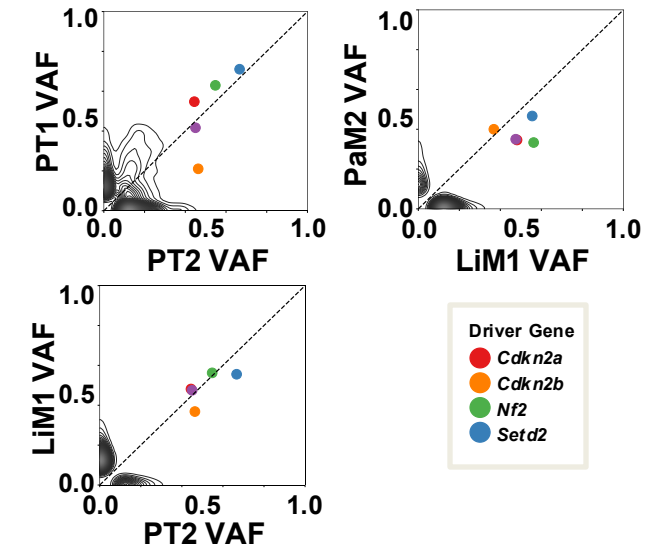
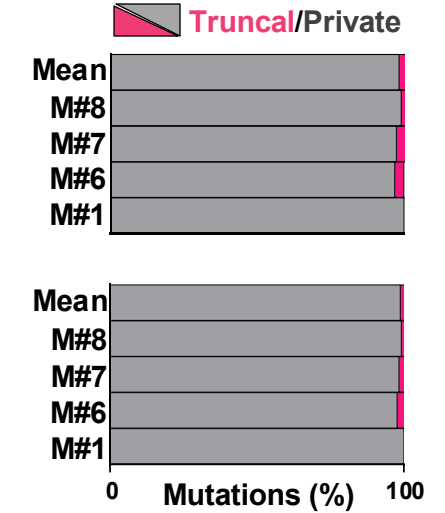
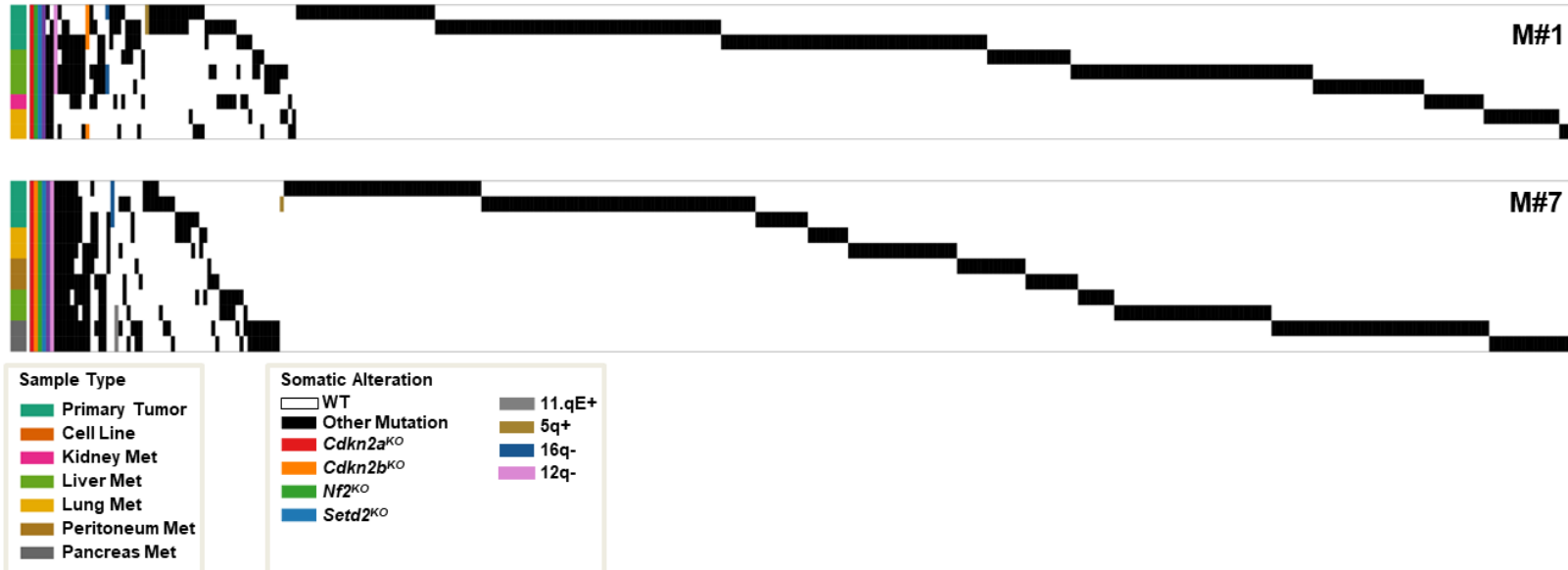
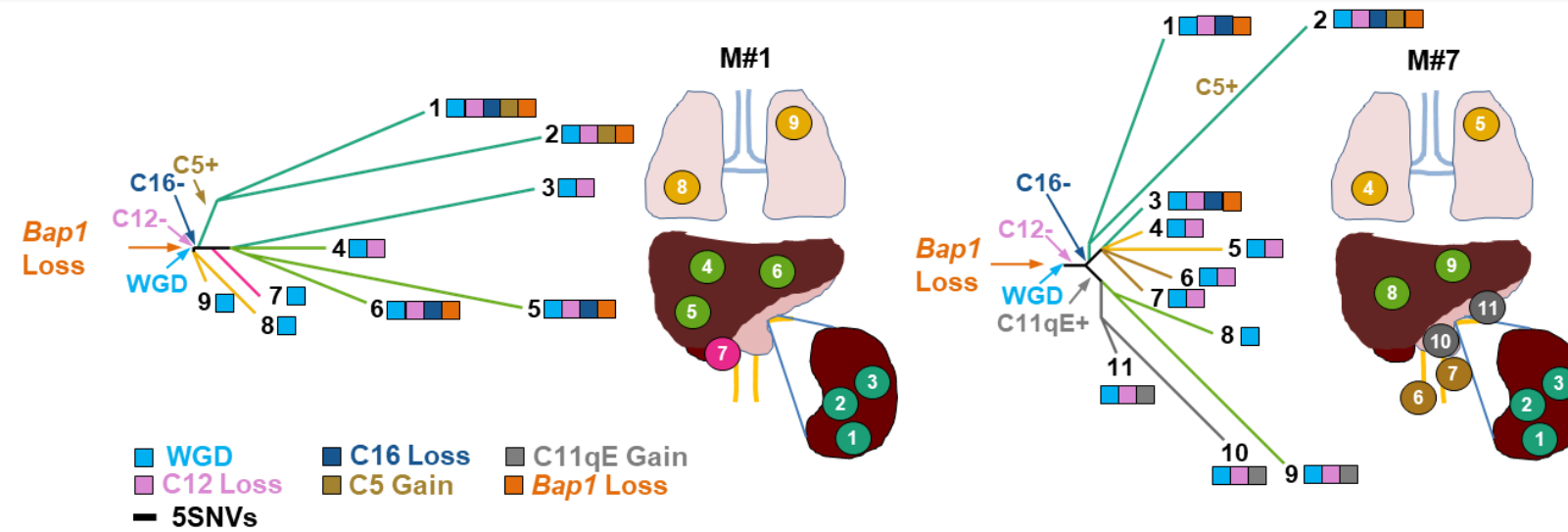
Gerlinger *et al.*, NEJM, 2012

Timeline for clear cell renal cell carcinoma

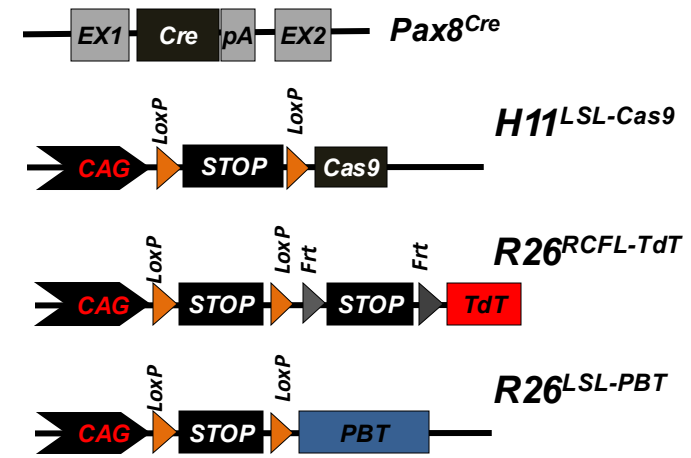
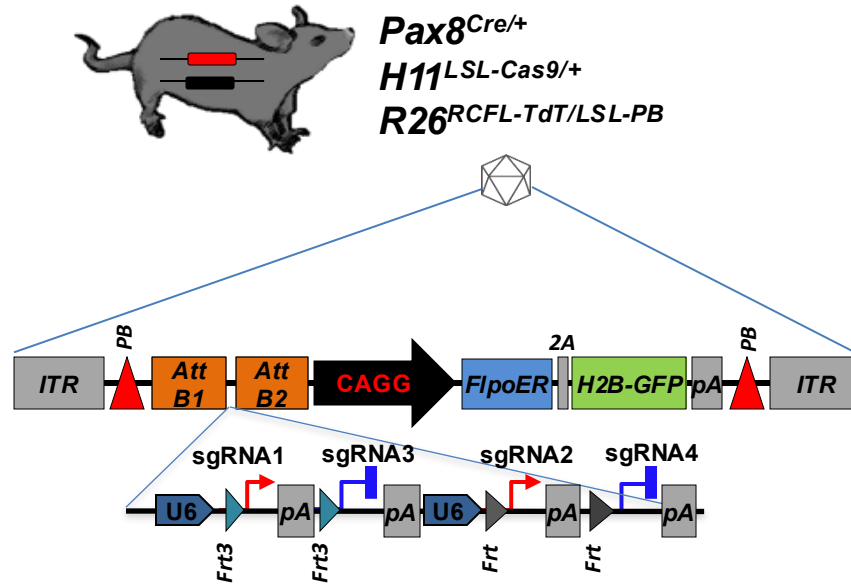


Turajlic *et al.*, Cell (2018)

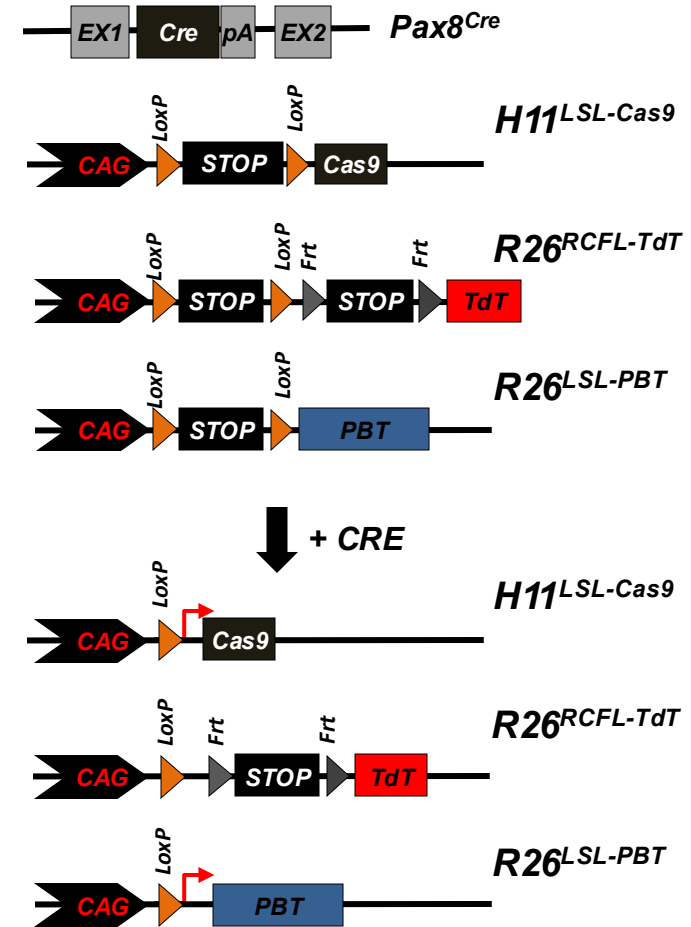
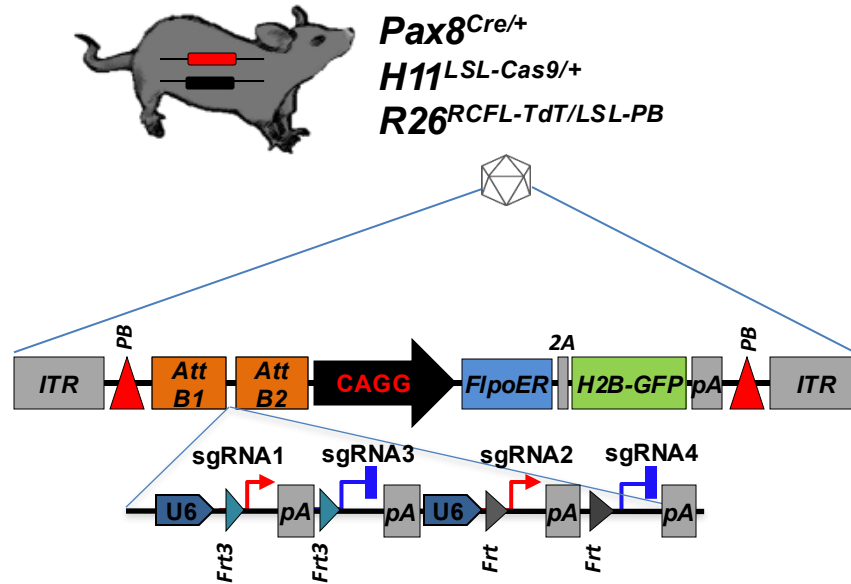
Evolutionary patterns of smGEMMs



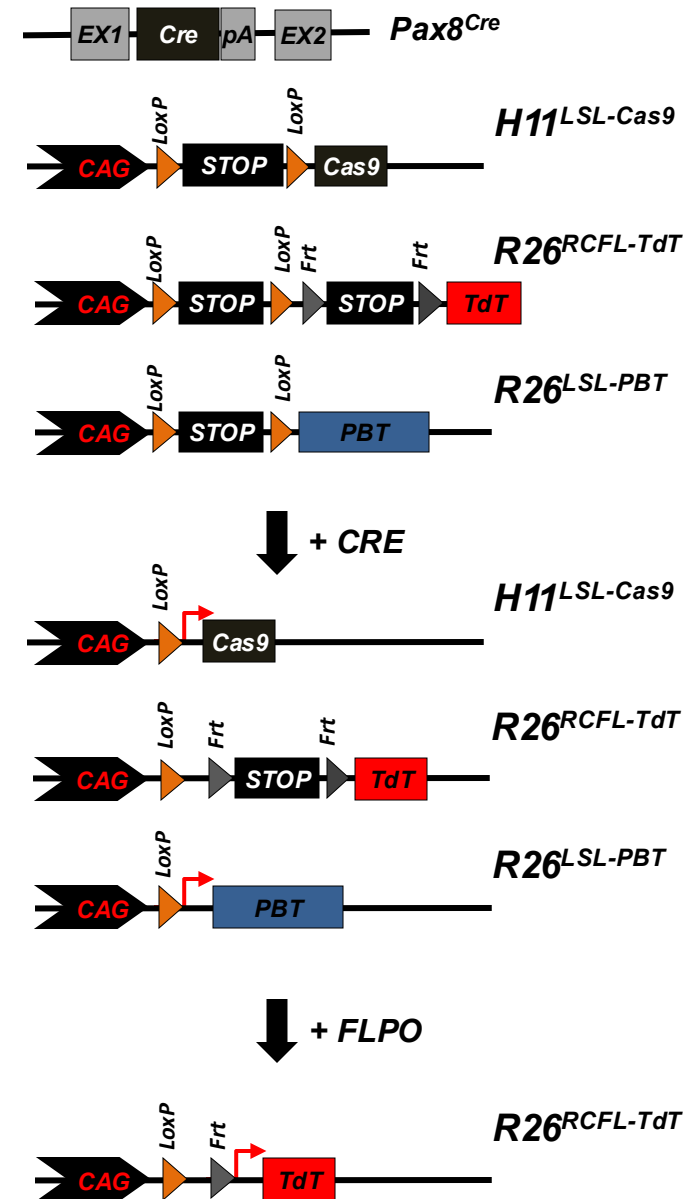
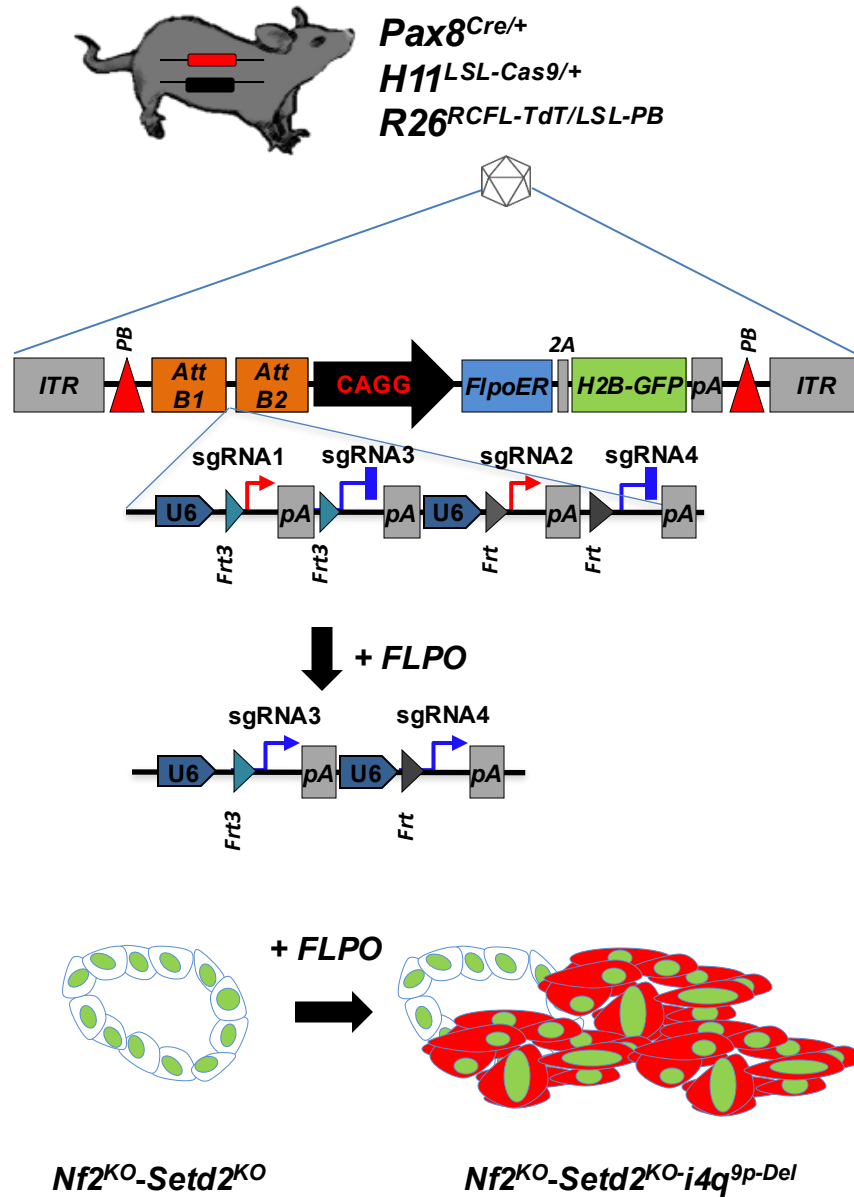
Second generation system: sequential mosaic model of RCC



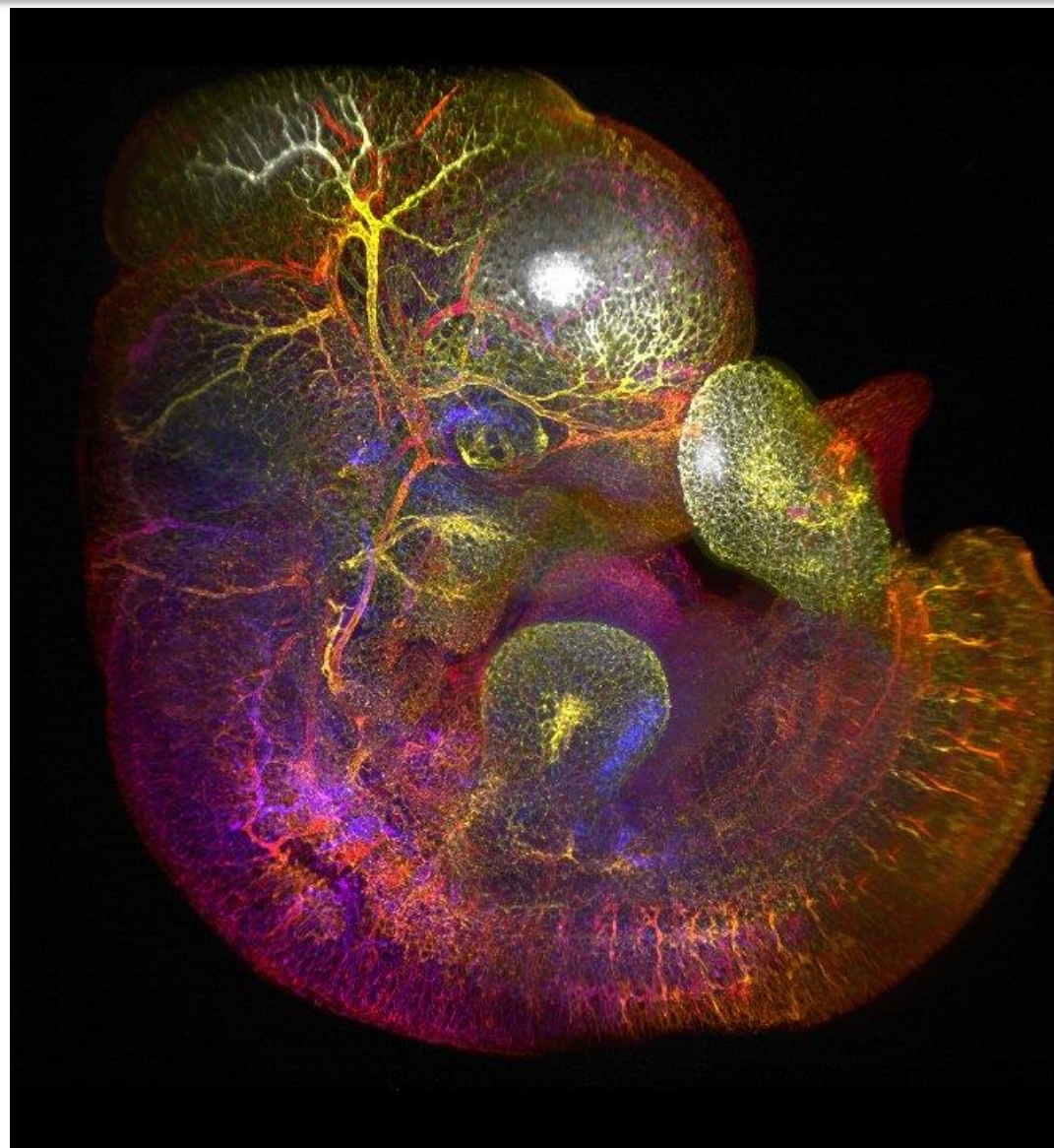
Second generation system: sequential mosaic model of RCC



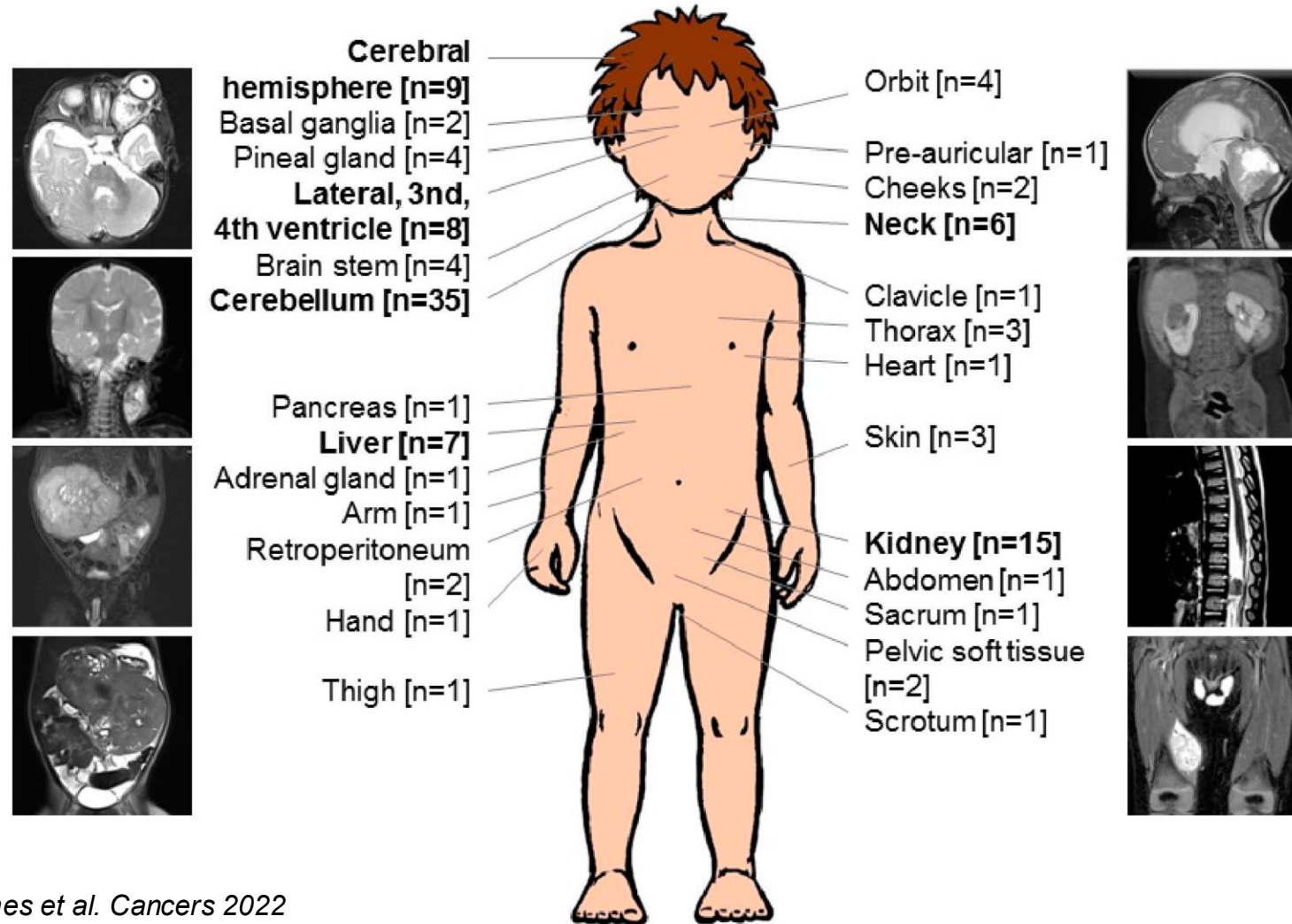
Second generation system: sequential mosaic model of RCC



Developmental Oncology Program

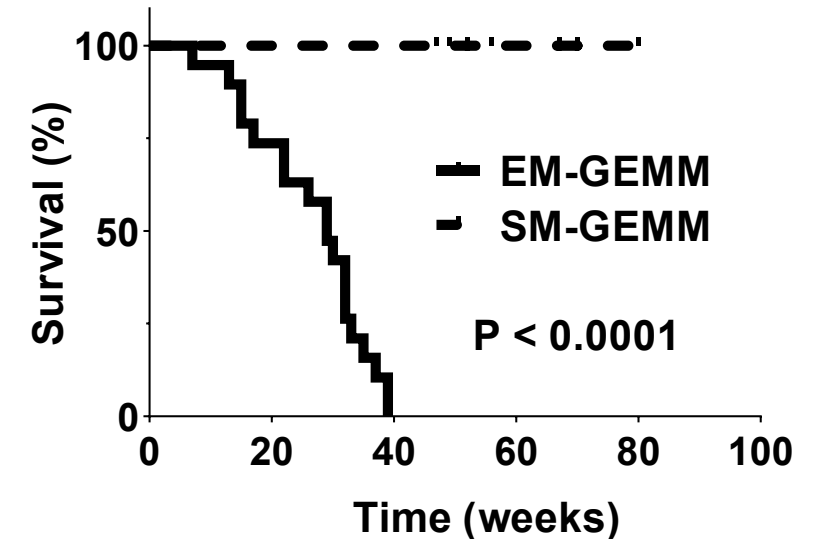
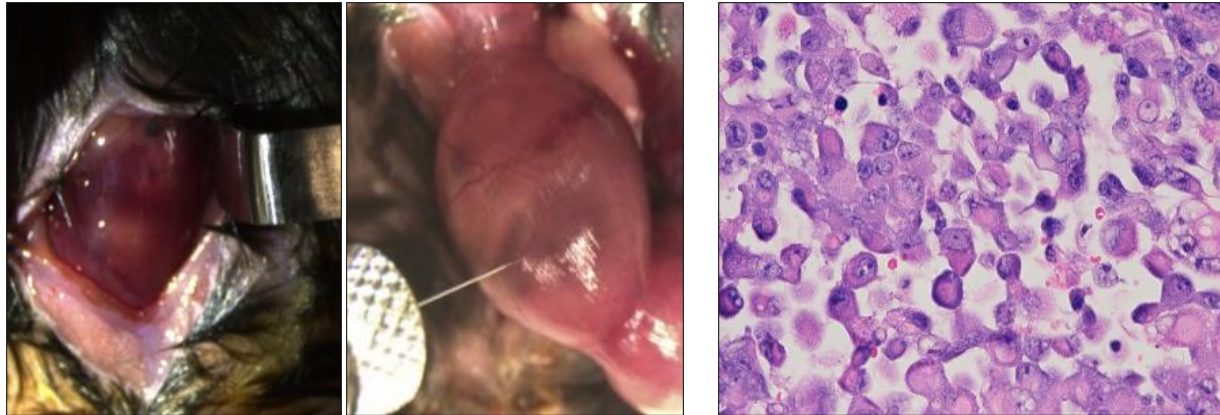
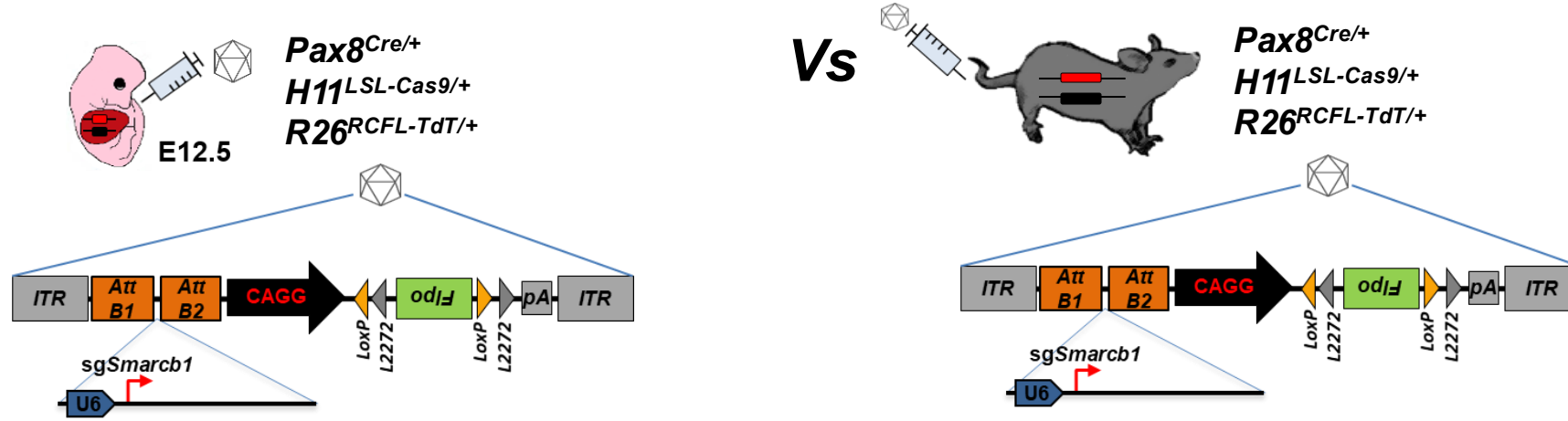


Rhabdoid predisposition syndrome and SWI/SNFopathies



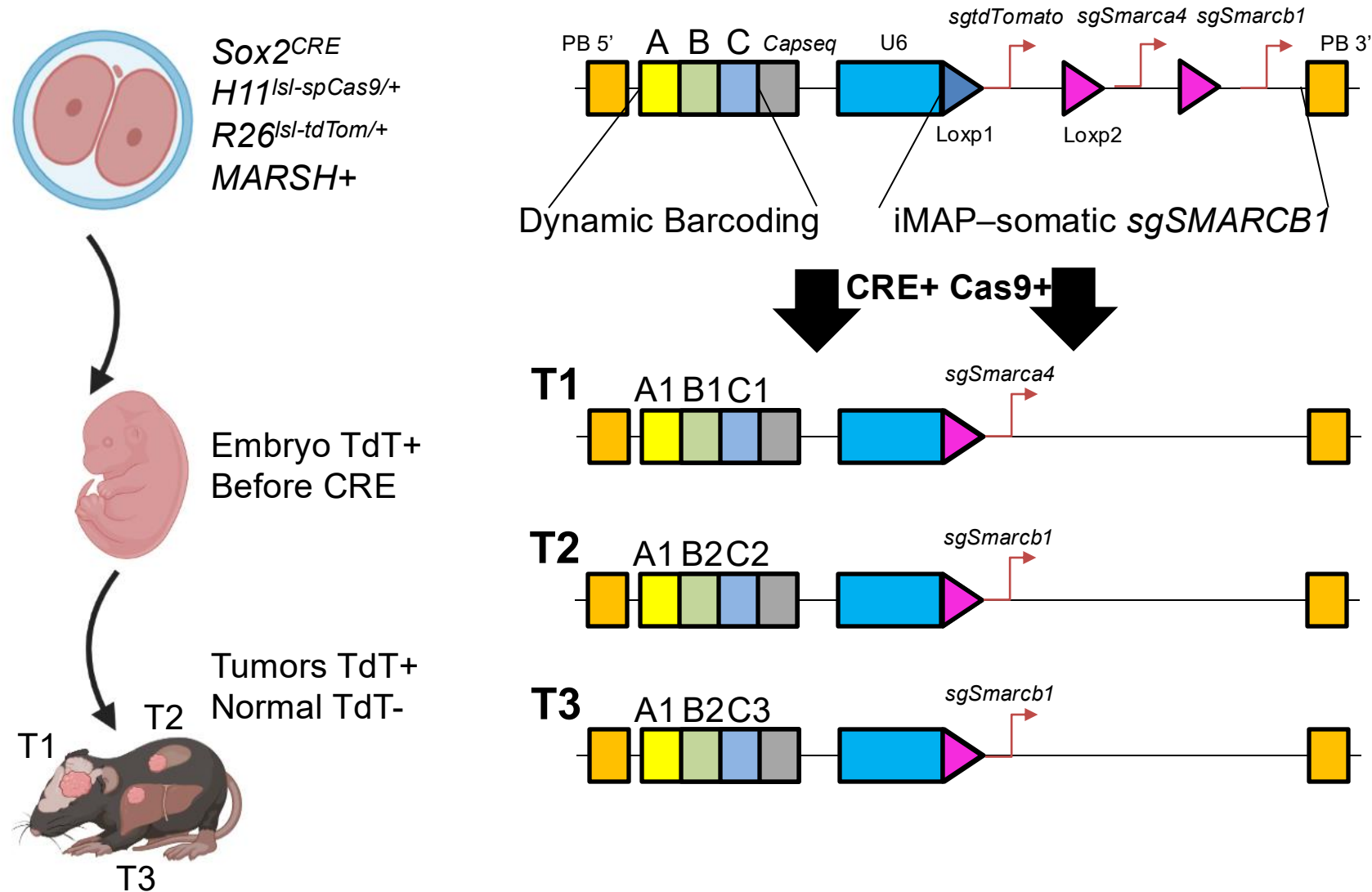
Nemes et al. Cancers 2022

Susceptibility to *Smarb1* knock-out

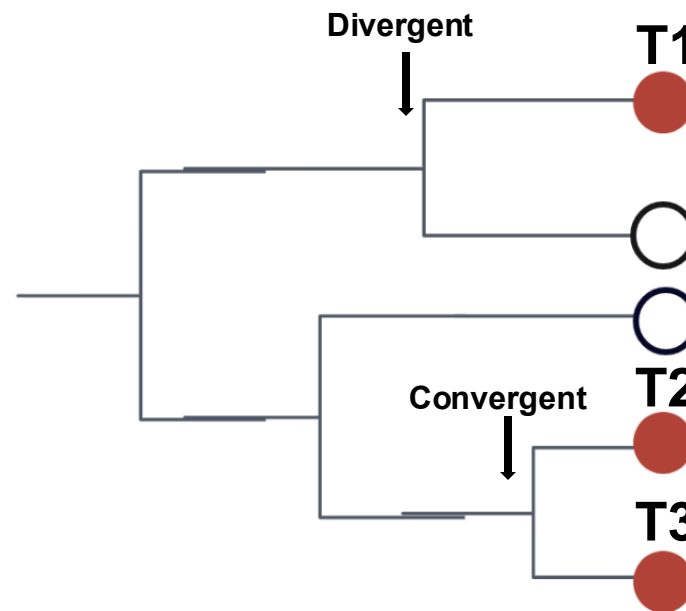
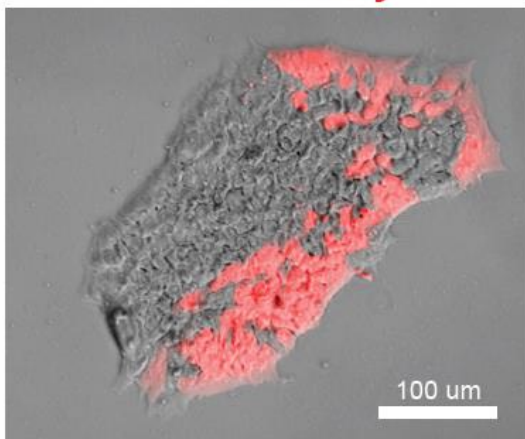
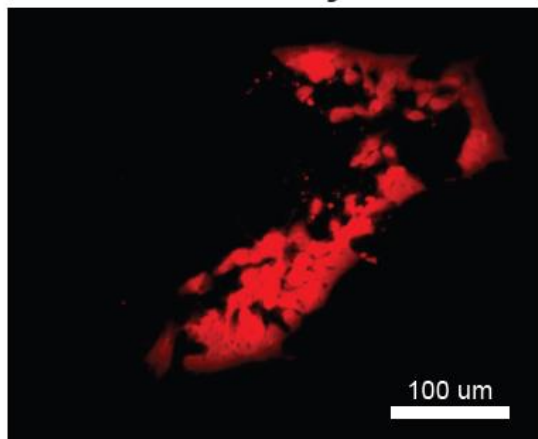
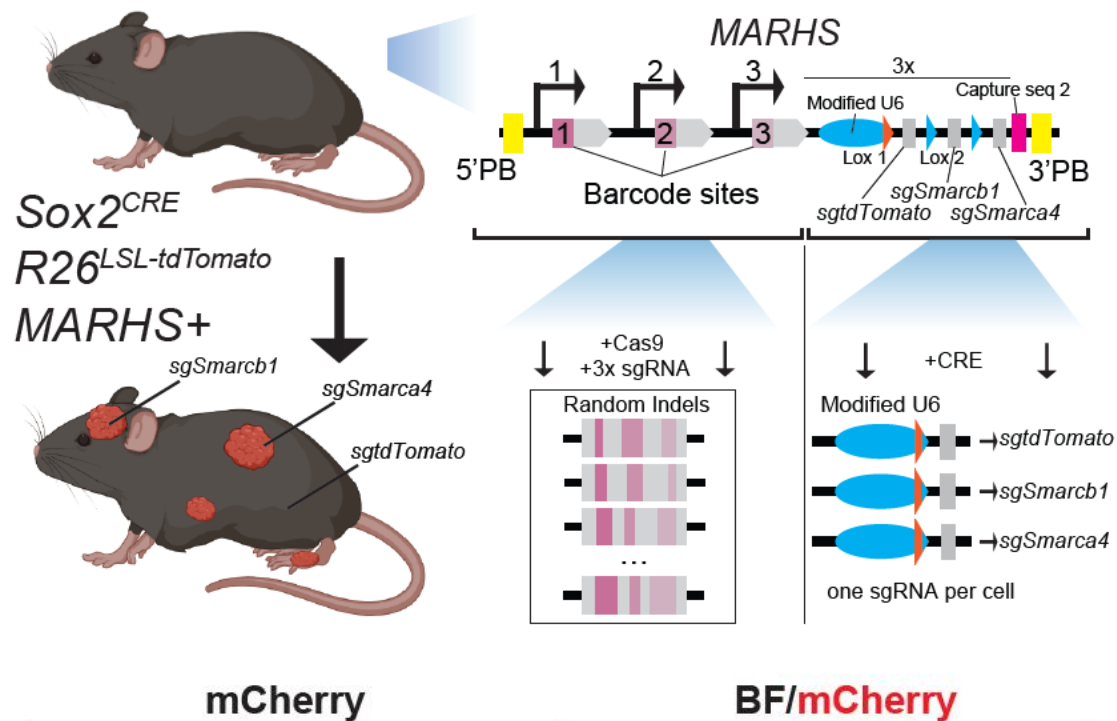


Carugo et al., *Cancer Cell* (2019)

A lineage tracing model of in utero genetic mosaicism



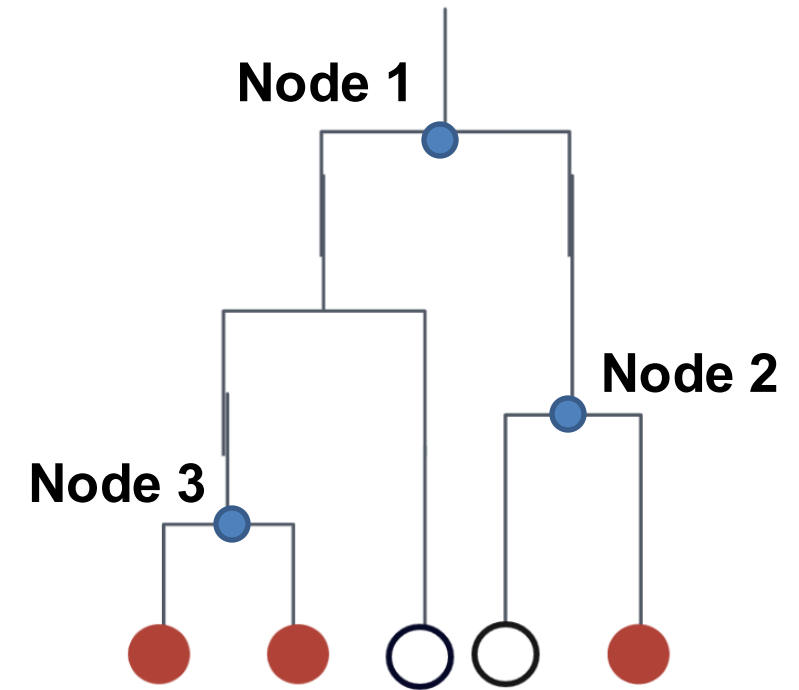
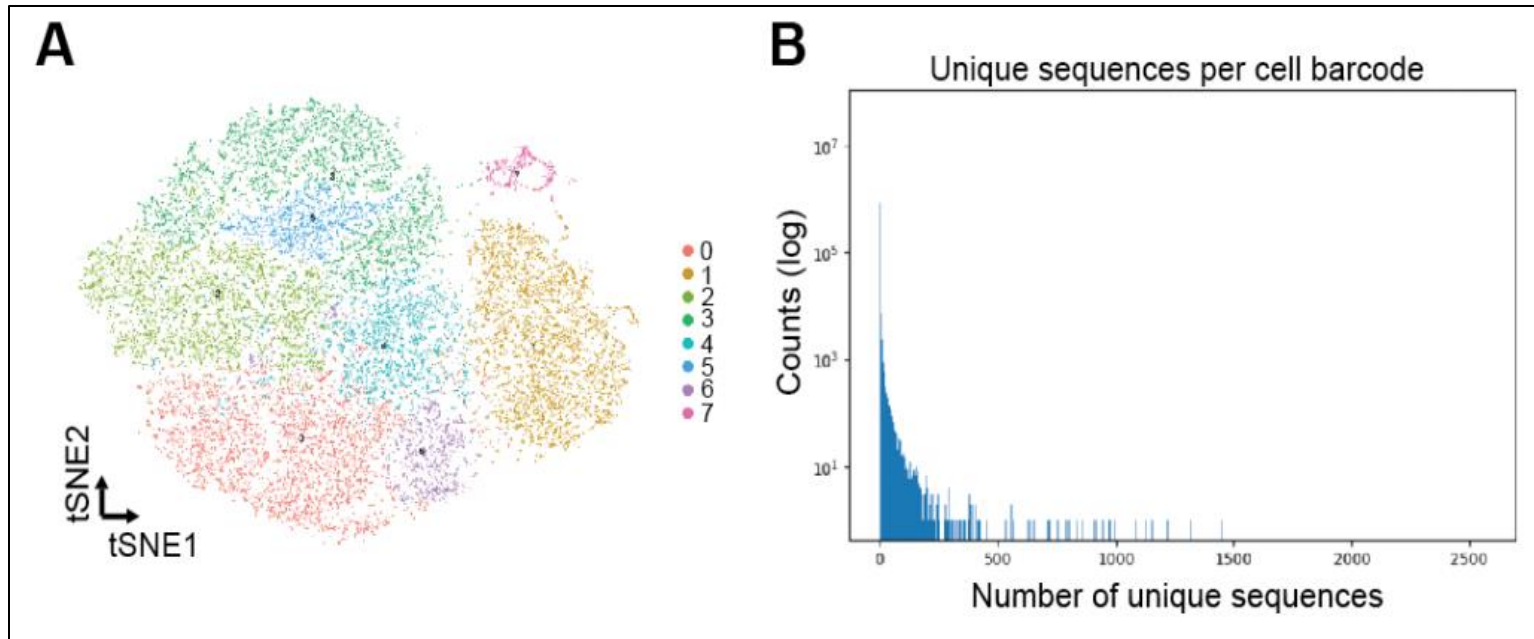
A lineage tracing model of *in utero* mosaic SWI/SNF alterations



Phylogenesis is calculated by:

- 1) Barcode indels
- 2) Indels generated by sgRNA
- 3) Secondary passenger or driver mutations
- 4) scRNA-seq transcriptomic analysis

A lineage tracing model of *in utero* mosaic editing



Thanks to Li Zhang

Genovese Lab

Luigi Perelli

Li Zhang

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