Animal Model Workshop

Tracking the functional consequences of *Vhl* / *Pbrm1* inactivation in adult mouse renal epithelium

Sakari Vanharanta, MD, PhD
Sigrid Jusélius Professor
Translational Cancer Medicine Program
University of Helsinki
Finland

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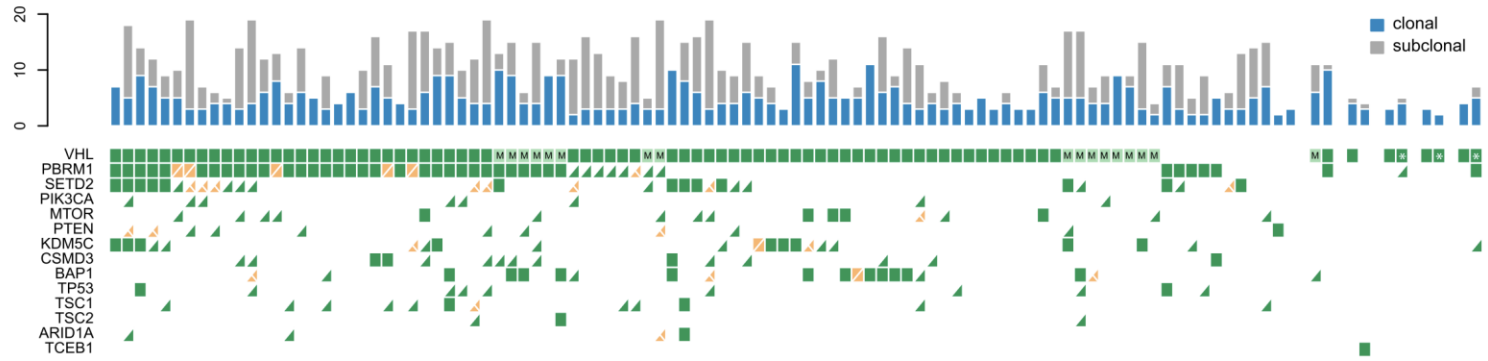
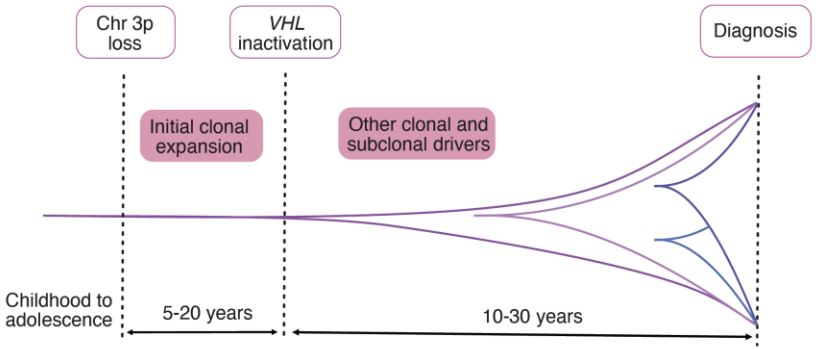
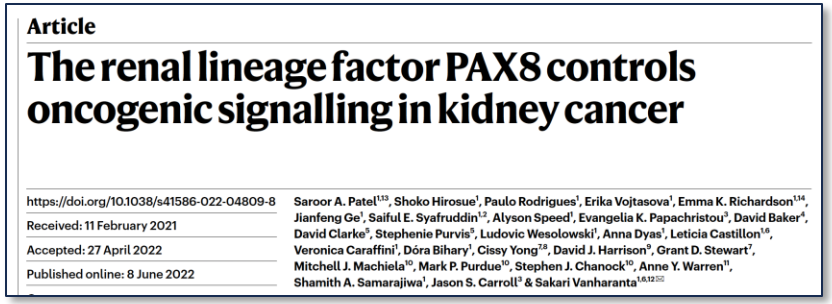
Slow progression and tissue-specific control of renal tumorigenesis



Turajlic et al. Cell 2018



Mitchell et al. Cell 2018



Article

The renal lineage factor PAX8 controls oncogenic signalling in kidney cancer

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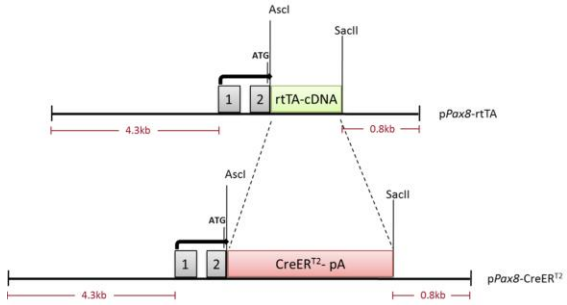
Saroor A. Patel[1,13], Shoko Hirosue[1], Paulo Rodrigues[1], Erika Vojtasova[1], Emma K. Richardson[1,14], Jianfeng Ge[1], Saiful E. Syafruddin[1,3], Alyson Speed[1], Evangelia K. Papachristou[3], David Baker[4], David Clarke[5], Stephenie Purvis[5], Ludovic Wesolowski[1], Anna Dyas[1], Leticia Castillon[1,6], Veronica Caraffini[1], Dóra Bihary[1], Cissy Yong[7,8], David J. Harrison[9], Grant D. Stewart[7], Mitchell J. Machiela[10], Mark P. Purdue[10], Stephen J. Chanock[10], Anne Y. Warren[11], Shamith A. Samarajiwa[1], Jason S. Carroll[3] & Sakari Vanharanta[1,6,12]

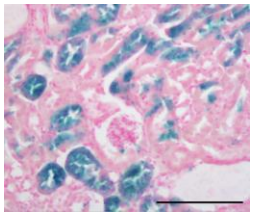
Patel et al. Nature 2022

The Pax8-CreER^{T2} transgenic line



- **Pax8-CreER^{T2}**
  - Tamoxifen-inducible Cre-activity
  - DNA from the *Pax8* locus (originally from *Traykova-Brauch et al. Nat Med. 2008*) engineered to contain the CreERT2-pA sequence
  - Microinjected into fertilised C57BL/6J embryos
  - chr6:62,912,590–62,912,610; GRCh38/mm10

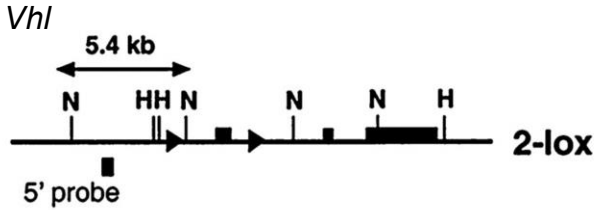
- **Pax8-CreERT2 x Rosa26R (lacZ)**
  - Beta-gal positivity in the kidney: **proximal and distal tubules and collecting ducts**
  - Other tissues negative (skin, fat, pancreas, stomach, small and large intestine, spleen, liver, bladder, genital tract, thymus, heart, lungs, muscle, salivary glands, thyroid, brain, and bone)



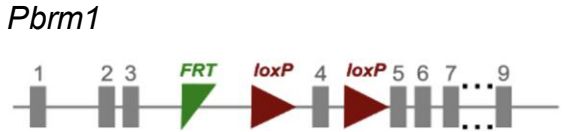
X-gal staining

Espana-Agusti et al. Plos One 2016

Conditional *Vhl*^{fl} and *Pbrm1*^{fl} alleles



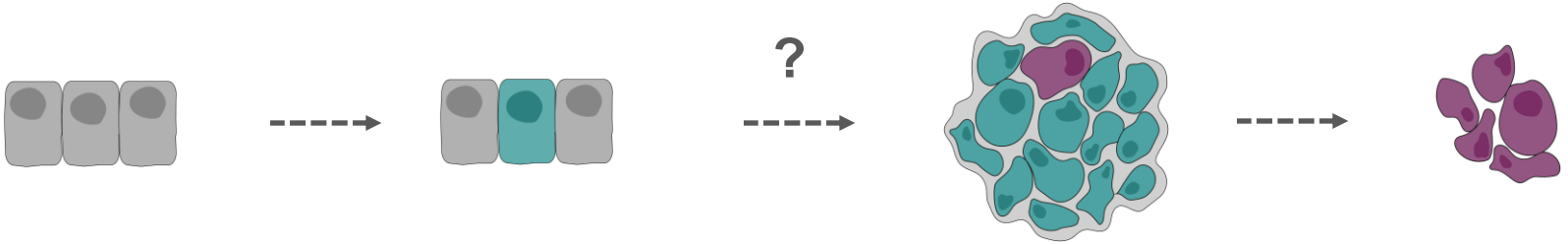
- **Vhl^{fl}**
  - *Vhl* exon 1 and promoter flanked by loxP sites
  - B6.129S4(C)-*Vhl*^{tm1Jae}/J from the Jackson lab
  - Originally from *Haase et al. PNAS 2001*
  - J1 ES cells, back-crossed to C57BL/6J mice

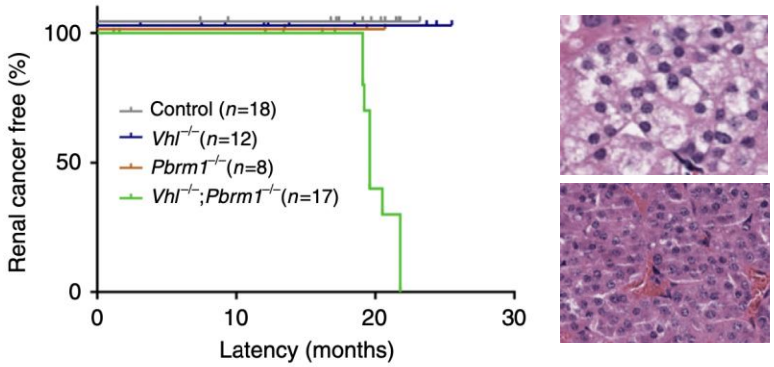


- **Pbrm1^{fl}**
  - *Pbrm1* exon 4 flanked by loxP sites
  - C57BL/6 N embryonic stem cells (*Skarnes et al. Nature 2011*)
  - Line from *Espana-Agusti et al. Nat Commun 2017*


Normal
Mutant
“normal”
Carcinoma
Metastasis
VHL-/-

What facilitates the early progression of carcinoma precursor cells?





Espana-Agusti et al. Nat Commun. 2017

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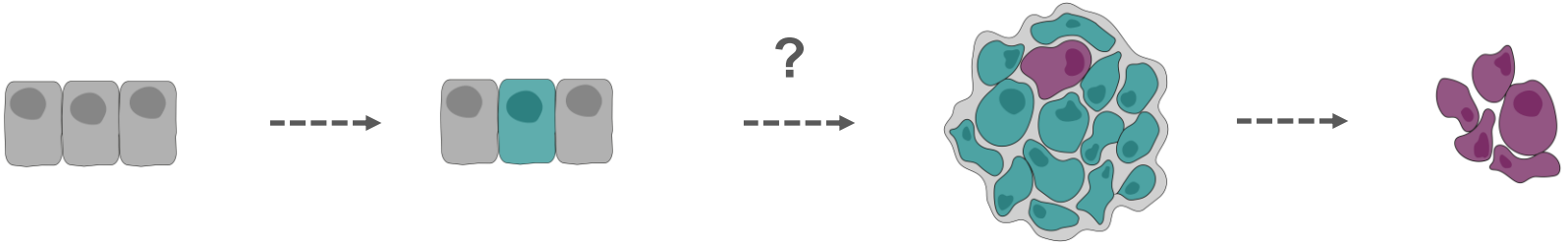
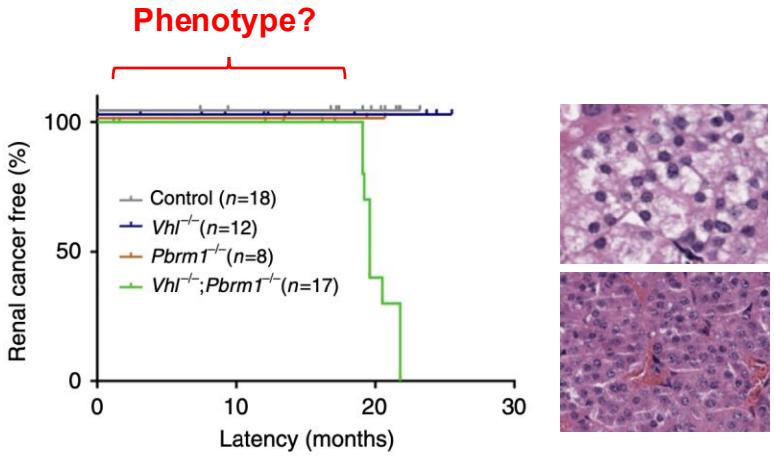
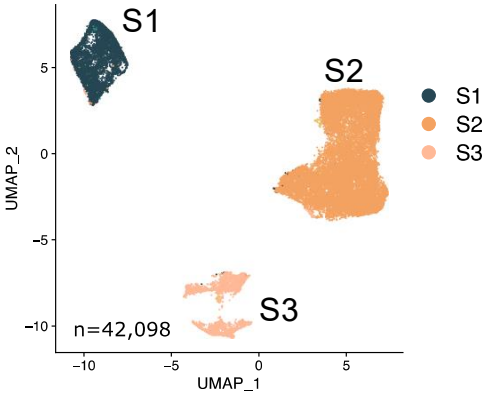




Espana-Agusti et al. Nat Commun. 2017

Delayed progression of renal epithelial cells upon *Vhl* and *Pbrm1* inactivation

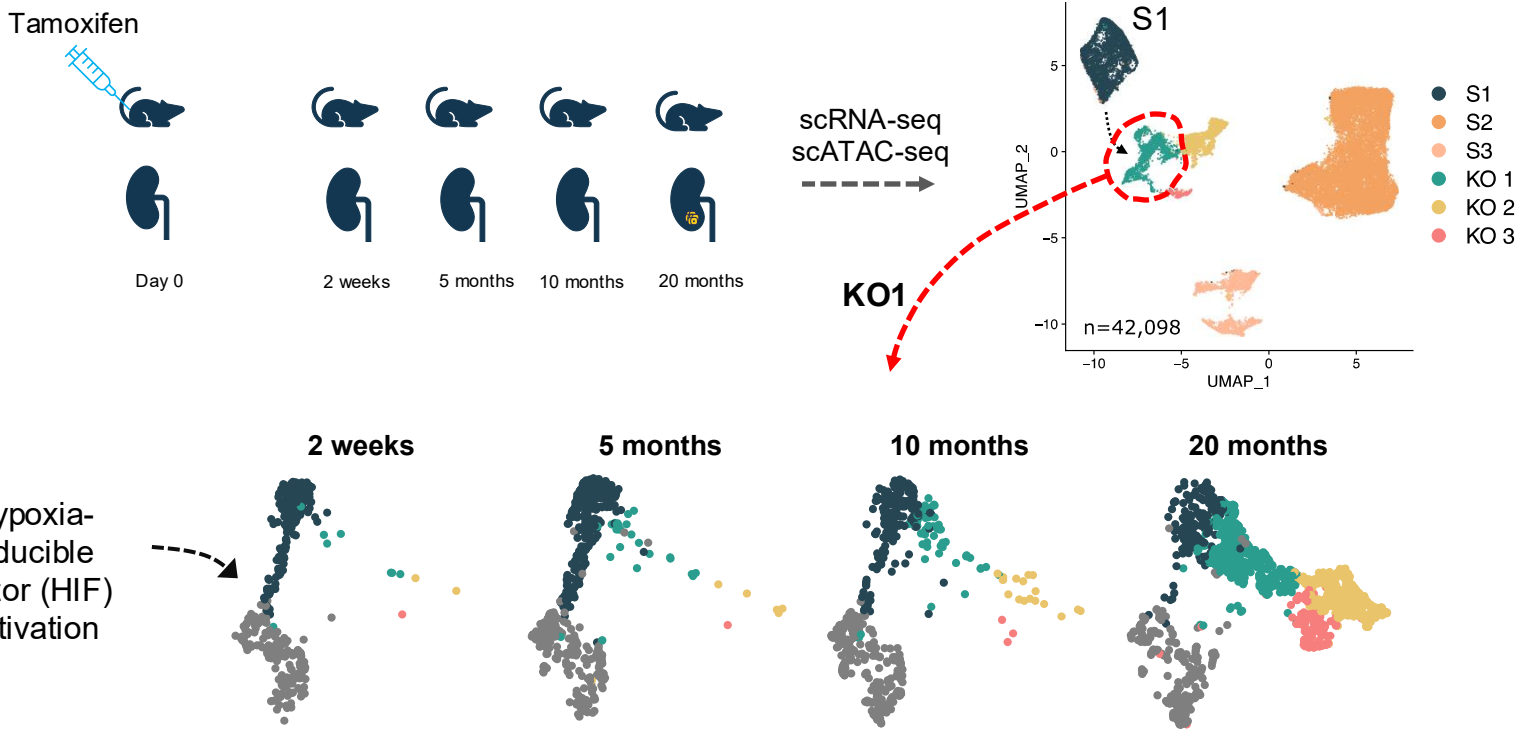
scRNA-seq
scATAC-seq



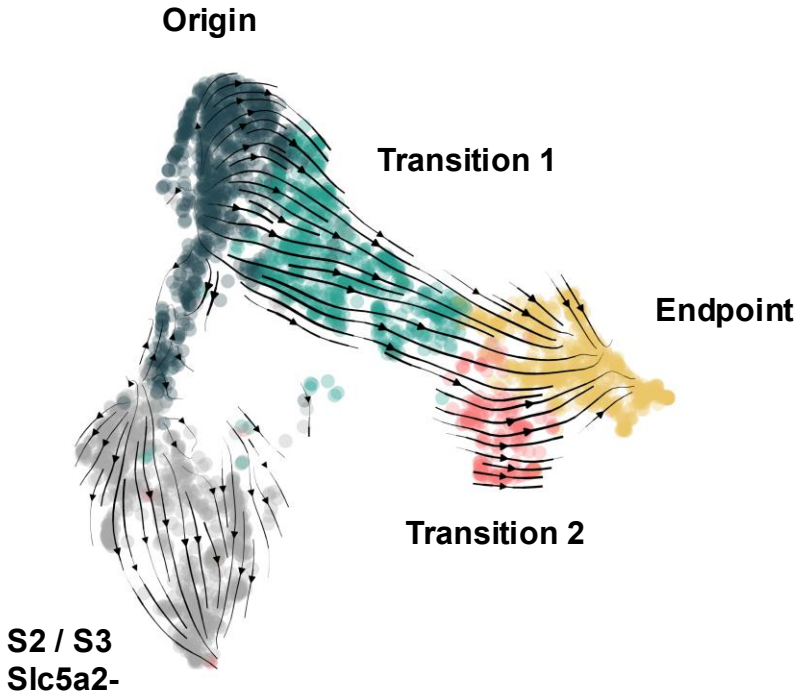
Proximal tubular epithelial cells only (in this plot)

Delayed progression of renal epithelial cells upon *Vhl* and *Pbrm1* inactivation

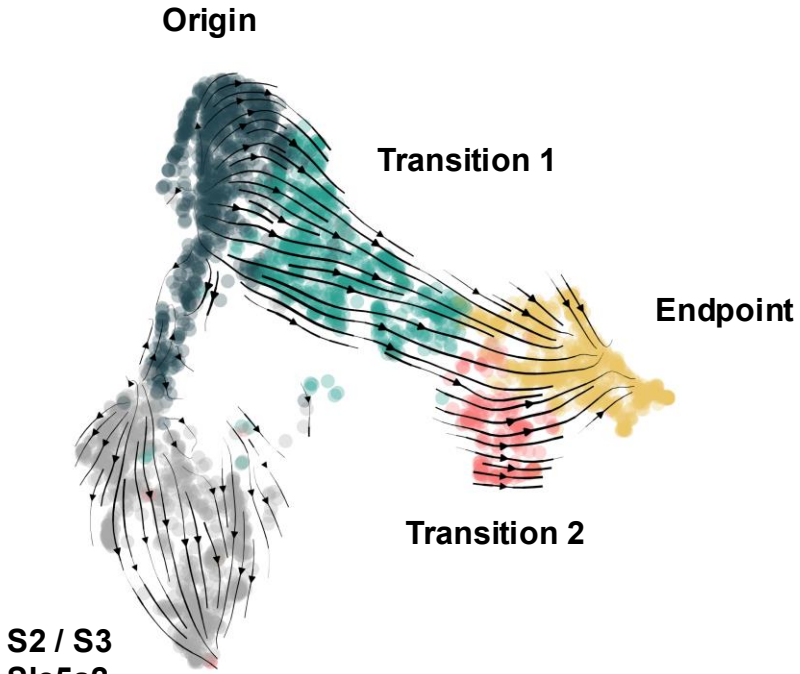
Delayed progression of renal epithelial cells upon *Vhl* and *Pbrm1* inactivation

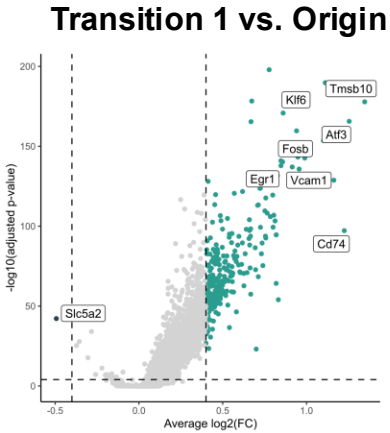


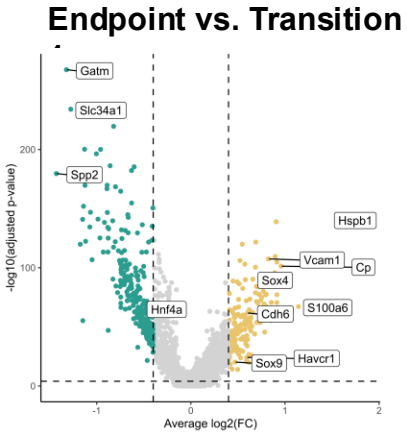
Transcriptional state transitions in early renal carcinogenesis



Transcriptional state transitions in early renal carcinogenesis







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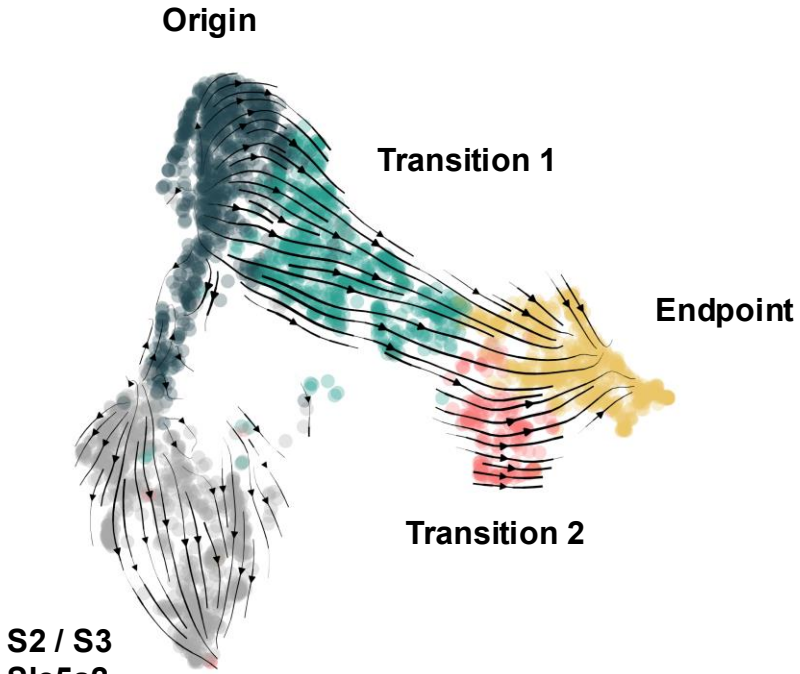
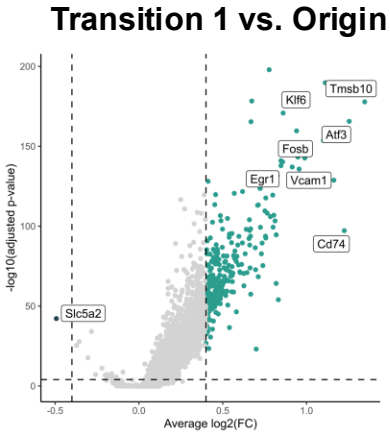
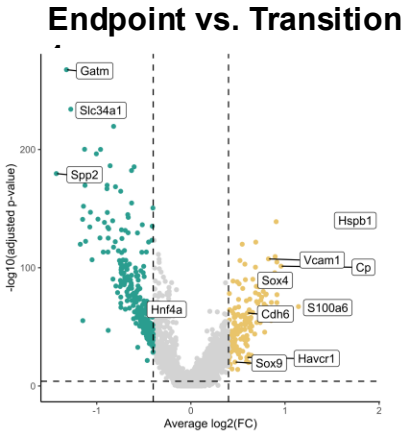
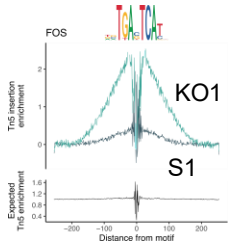
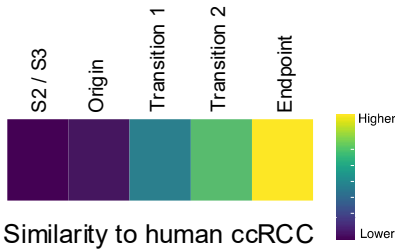








AP-1 footprint on chromatin (ATAC-seq)



Transcriptional state transitions in early renal carcinogenesis

KIM-1

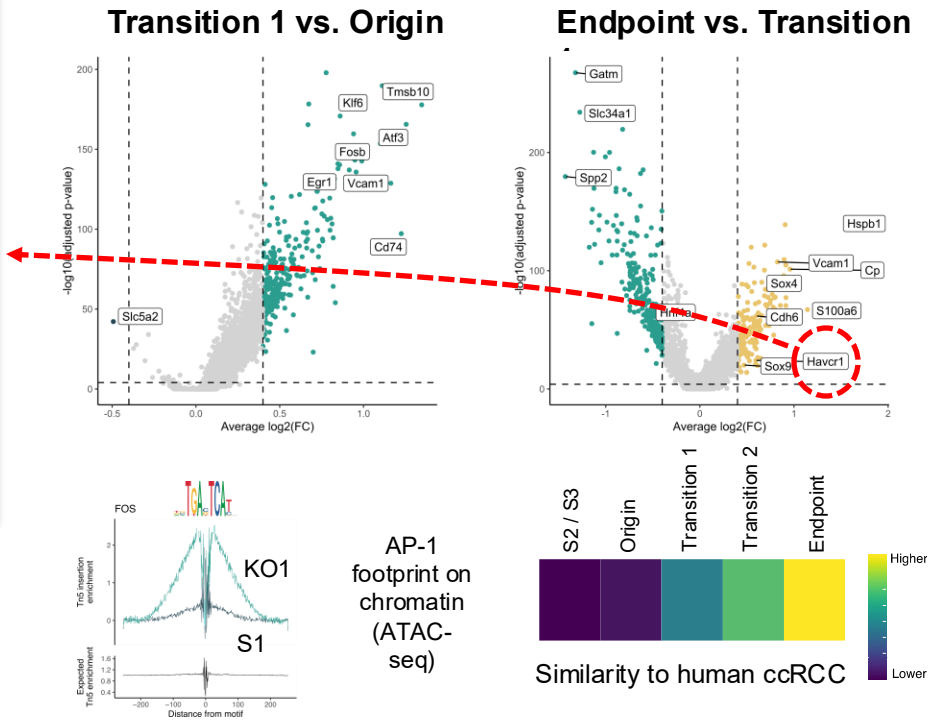
Precision Medicine and Imaging

Clinical Cancer Research

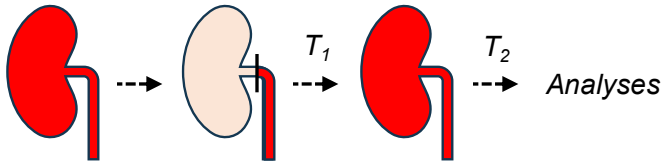
KIM-1 as a Blood-Based Marker for Early Detection of Kidney Cancer: A Prospective Nested Case–Control Study

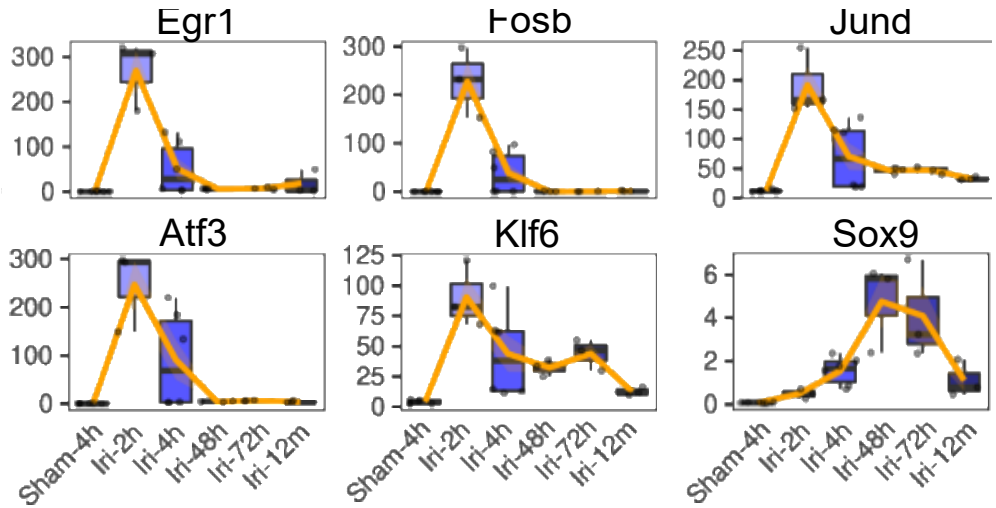
Ghislaine Scelo[1], David C. Muller[2], Elio Riboli[2], Mattias Johansson[1], Amanda J. Cross[2], Paolo Vineis[2], Konstantinos K. Tsilidis[2,3], Paul Brennan[1], Heiner Boeing[4], Petra H.M. Peeters[5], Roel C.H. Vermeulen[6], Kim Overvad[7], H. Bas Bueno-de-Mesquita[2,8,9,10], Gianluca Severi[11,12], Vittorio Perduca[11,12,13], Marina Kvaskoff[11,12], Antonia Trichopoulou[14], Carlo La Vecchia[14,15], Anna Karakatsani[14,16], Domenico Palli[17], Sabina Sieri[18], Salvatore Panico[19], Elisabete Weiderpass[20,21,22,23], Torkjel M. Sandanger[20], Therese H. Nøst[20], Antonio Agudo[24], J. Ramón Quirós[25], Miguel Rodríguez-Barranco[26,27], Maria-Dolores Chirlaque[27,28,29], Timothy J. Key[30], Prateek Khanna[31], Joseph V. Bonventre[32], Venkata S. Sabbisetti[32], and Rupal S. Bhatt[31]

Scelo et al. Clin Can Res 2018



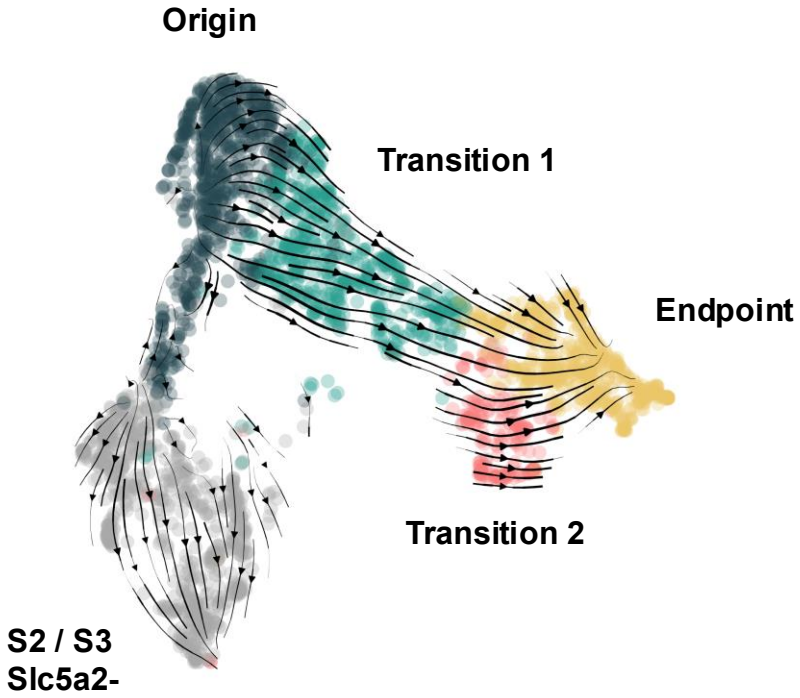
Transcriptional responses to renal injury

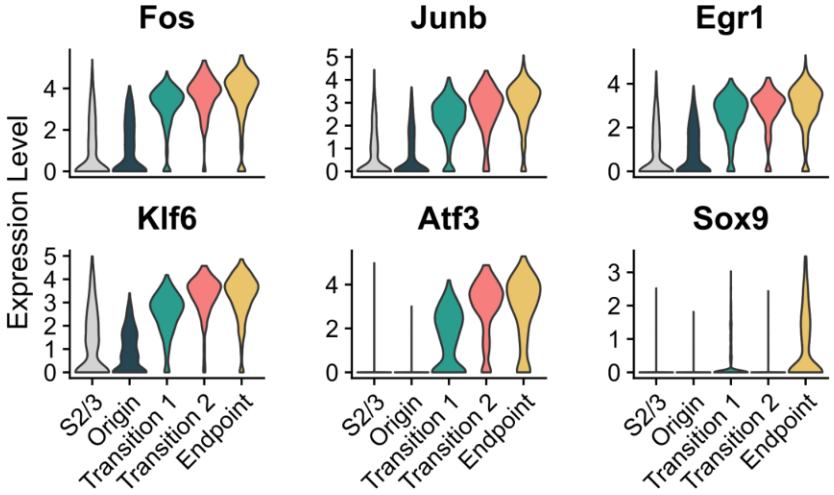




Liu et al. JCI Insight 2017

Renal injury markers along the KO1 trajectory

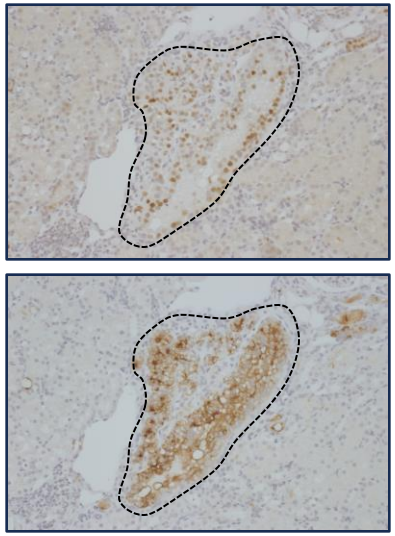




SOX9 expression in early *VHL* null renal lesions

SOX9

KIM1



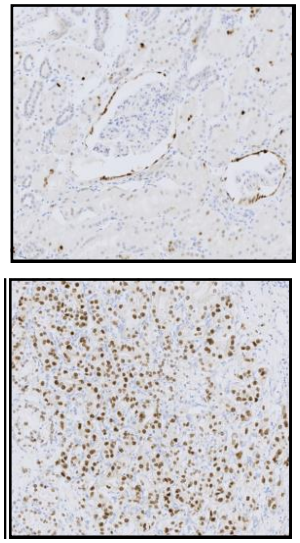
Pax8-CreERT^{2};
Vhl$^{fl/fl}$;Pbrm1$^{fl/fl}$

Mouse

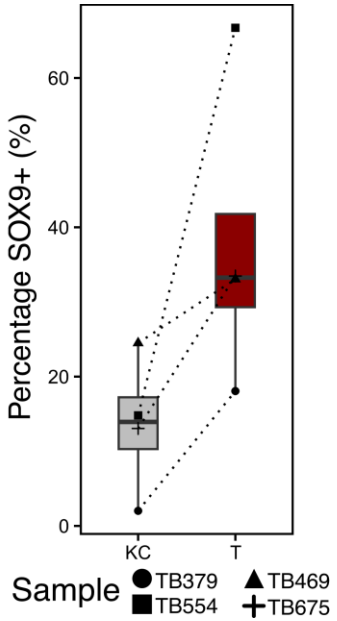
SOX9 – IHC

Normal

ccRCC



Early stage ccRCC –
VHL mutation carrier



Human

The Pax8-CreER^{T2};Vhl$^{fl/fl}$;Pbrm1$^{fl/fl}$ model

- Conditional inactivation of two commonly mutated ccRCC suppressors in adult mouse renal epithelium
- Cre activation not ubiquitous
  - Mutant cells within normal tissues
- Delayed phenotypic progression of renal epithelial cells with oncogenic mutations
  - Mimics delayed progression of *VHL* mutant cells in humans?
- Tissue repair-associated transcriptional state transitions mark early progression of *Vhl / Pbrm1*-mutant cells
  - Mediators of renal injury programs support renal cancer cell fitness

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HELSINGFORS UNIVERSITET
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iCAN

Research Council of Finland

Kidney Research UK
Funding research to save lives

MARIE CURIE ACTIONS

SIGRID JUSELIUS STIFTELSE

worldwide cancer research

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Supporting the best in medical research

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