



Animal Model Workshop

KVPR GEMM

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Human Oncology and Pathogenesis Program

MSKCC

9/11/2025

September 11-13, 2025

Session #:Topic



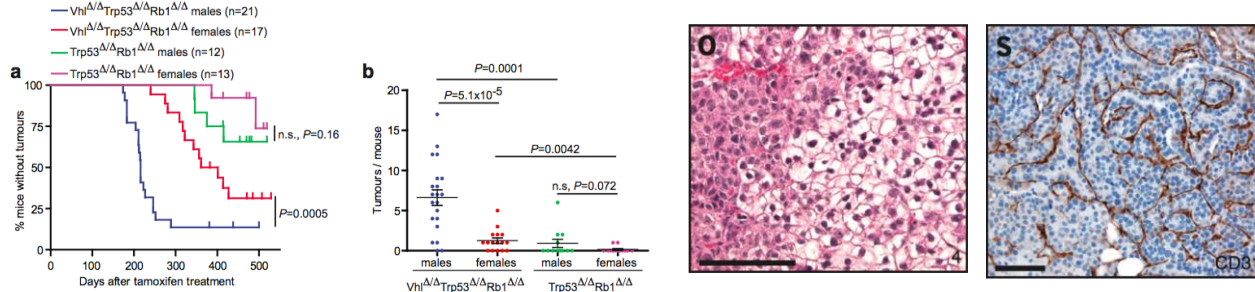
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Please add the session number and session title from the agenda

KVpR GEM model

Vhl^{fl/fl} p53^{fl/fl} Rb1^{fl/fl} Ksp-1^{Cre-ERT2} GEMM
(Frew I at al., Nature Medicine 2017)



- Overall 82% develop grade 3-4 ccRCC tumors at 25-61 wks (>9 mo spread)
- Male ~87% 25-40 wks (6-10mo onset, 3.6mo spread) and more tumors/mouse
- Female ~70% 35-61 wks (6.4mo spread)
- Histological and molecular characteristics similar to human ccRCC
- Range of therapeutic response to sunitinib and everolimus
- No aneuploidy or large regions of CNA, but 55 regions of focal CNA found.
- Have 161 vs 50 SNVs per tumor in humans
- No Mets
- Other common ccRCC mutations (PBRM1, BAP1, SETD2) not detected
- Mixed background (50% FVB.129P2, 25% C.129S, 25% B6.Cg)

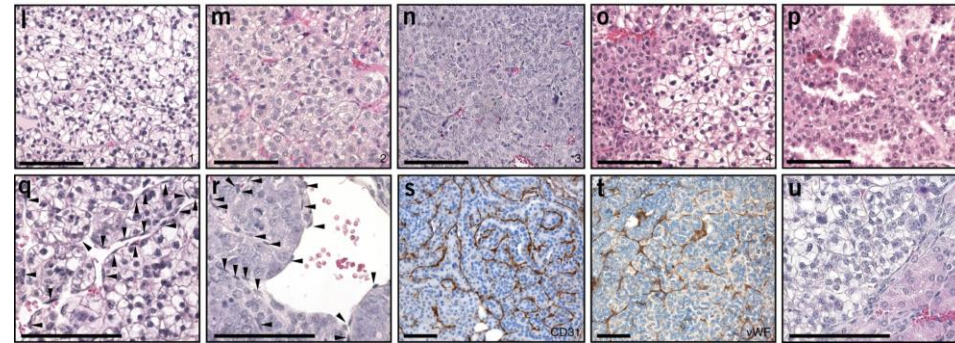
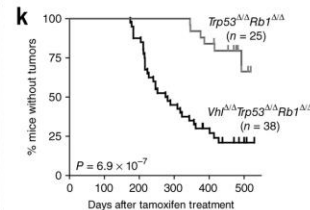
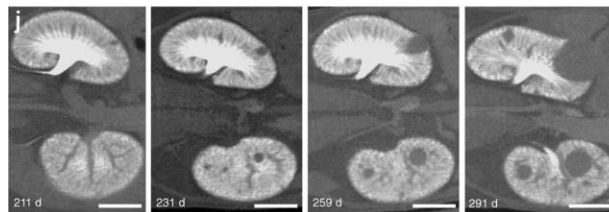
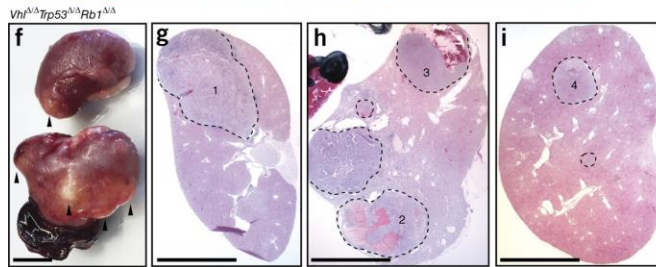
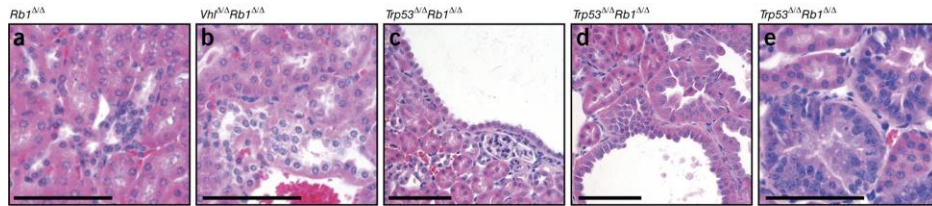
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Renal epithelial cell-specific co-deletion of *Vhl*, *Trp53* and *Rb1* permits the evolution of ccRCCs.

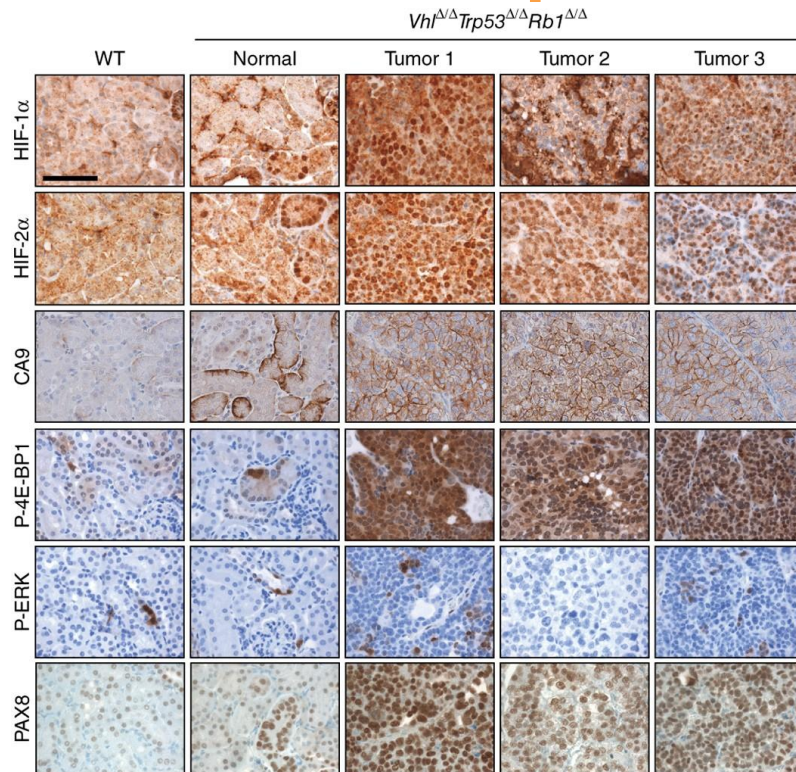


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Frew al., Nature Medicine 2017

ccRCCs in $Vhl^{\Delta/\Delta}Trp53^{\Delta/\Delta}Rb1^{\Delta/\Delta}$ mice exhibit HIF- α and mTORC1 pathway activation.



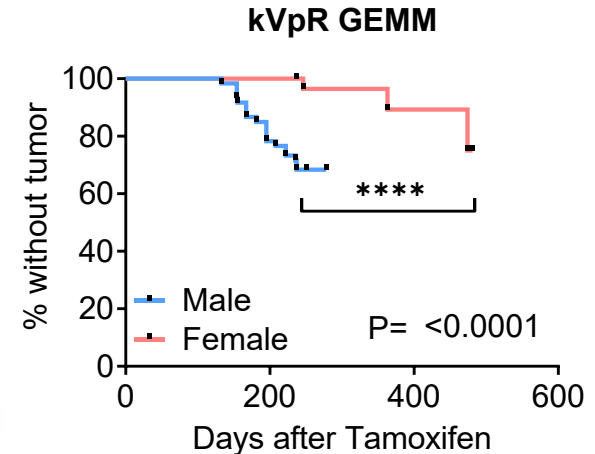
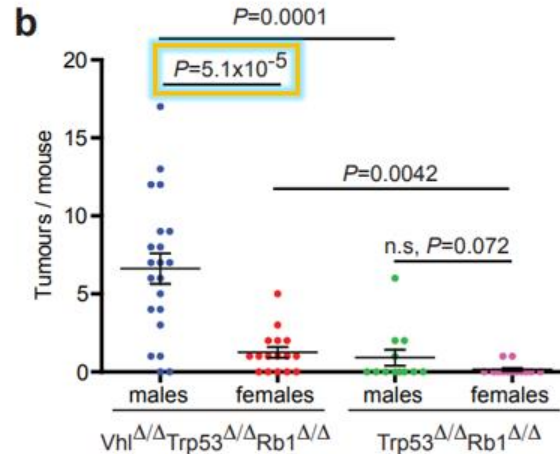
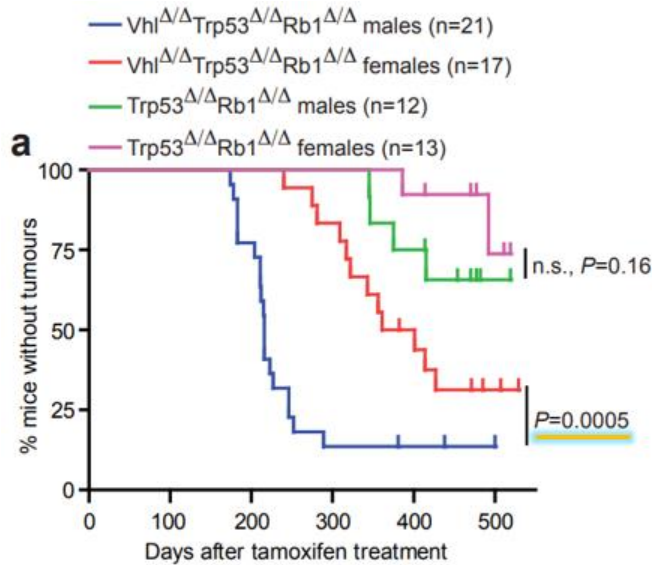
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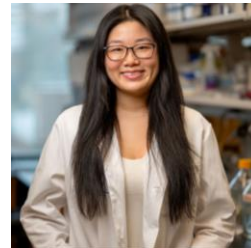
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Gender disparity in penetrance and latency

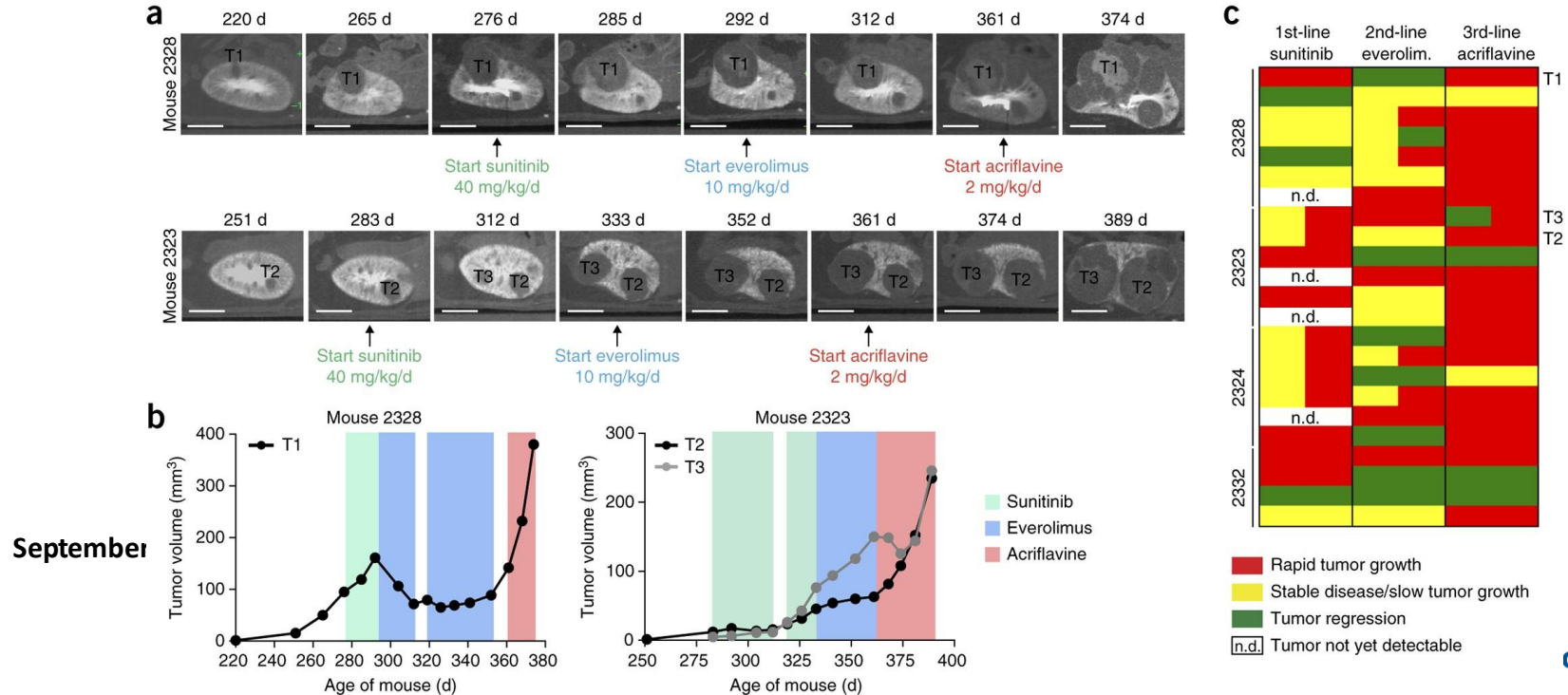


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Frew al., Nature Medicine 2017



ccRCCs in $Vhl^{\Delta/\Delta}Trp53^{\Delta/\Delta}Rb1^{\Delta/\Delta}$ mice exhibit varying patterns of therapeutic sensitivity and resistance

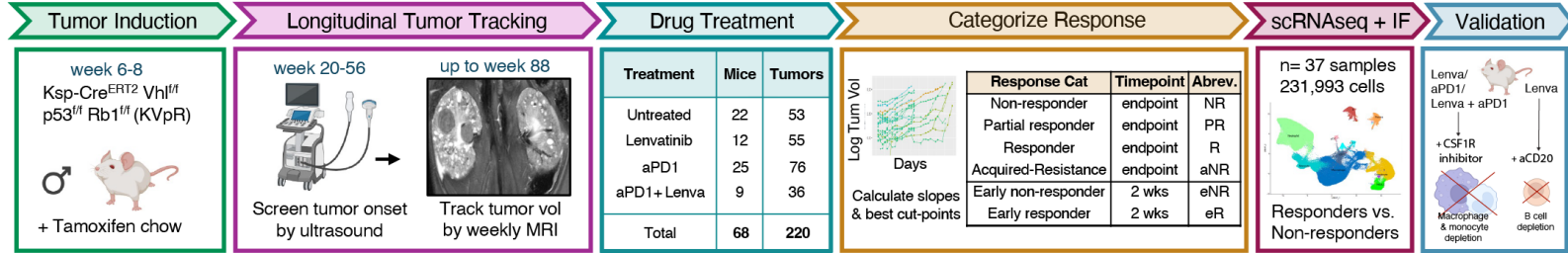


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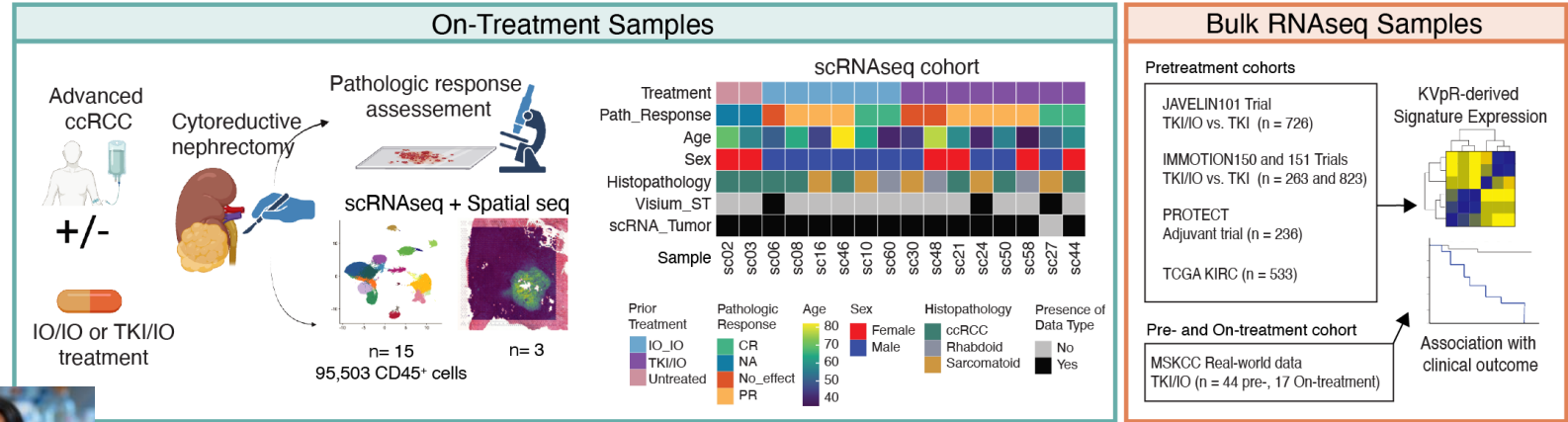
Study Overview

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Preclinical



Clinical



Important credits: **David Kuo**, Andrew Cornish, Yash Khandwala, Hui Jiang



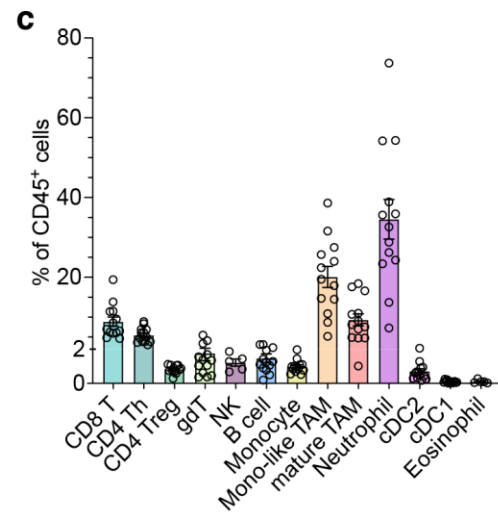
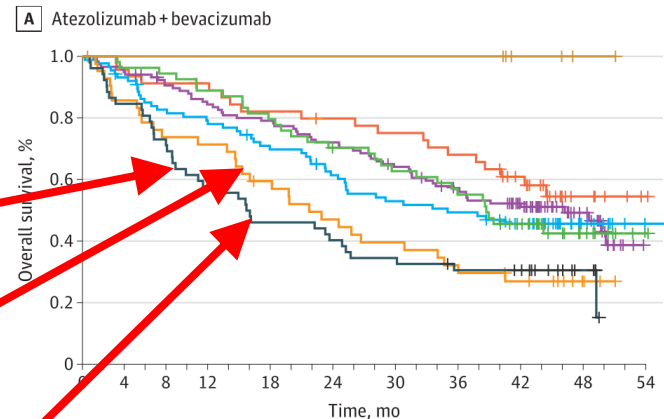
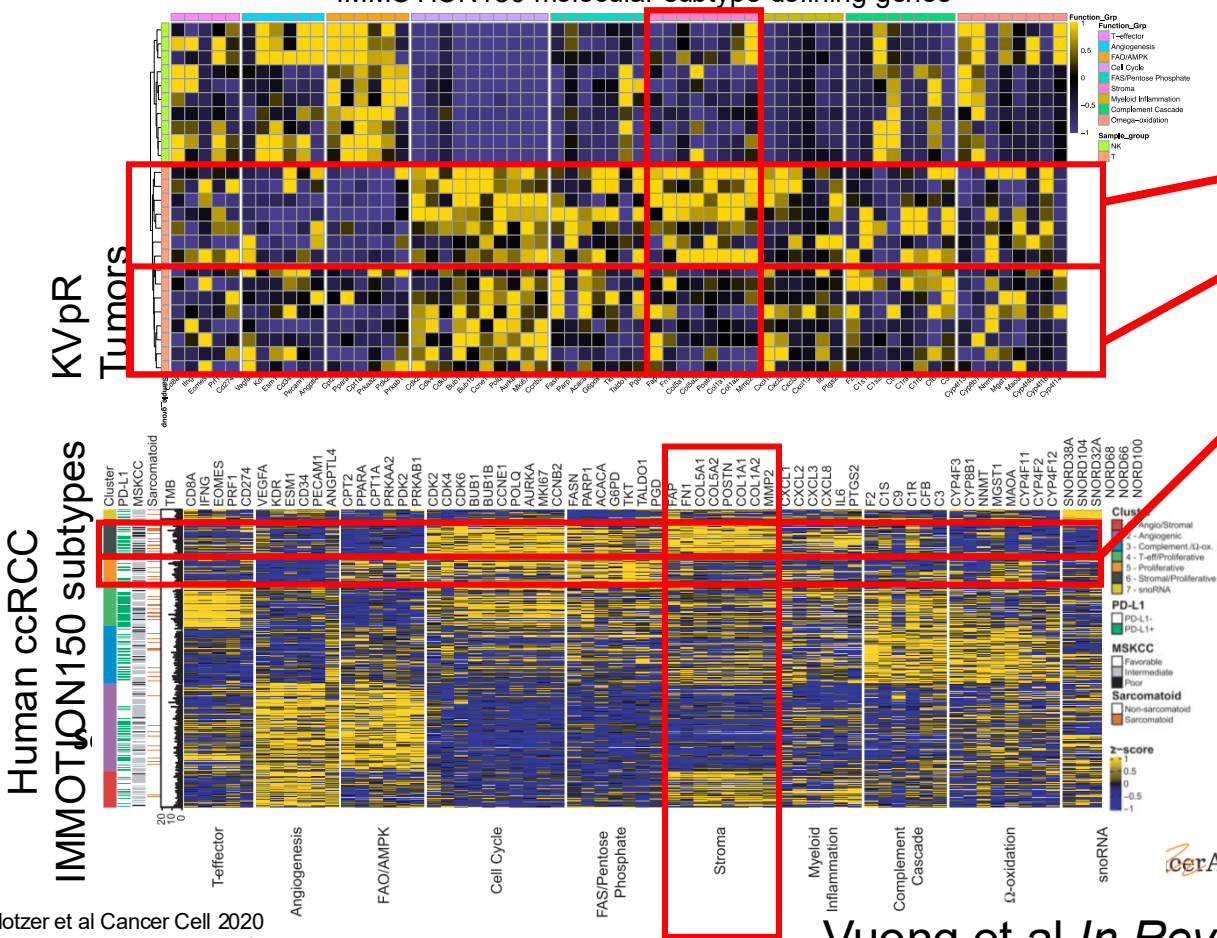
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KVpR tumors resemble treatment-refractory human molecular subtypes of human ccRCC

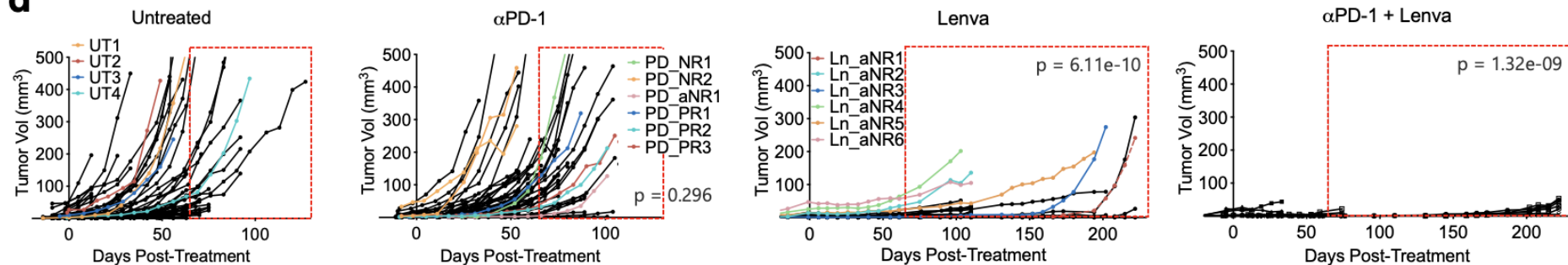
IMMOTION150 molecular subtype defining genes



Vuong et al *In Revision*

KVpR model response to therapies mirrors humans

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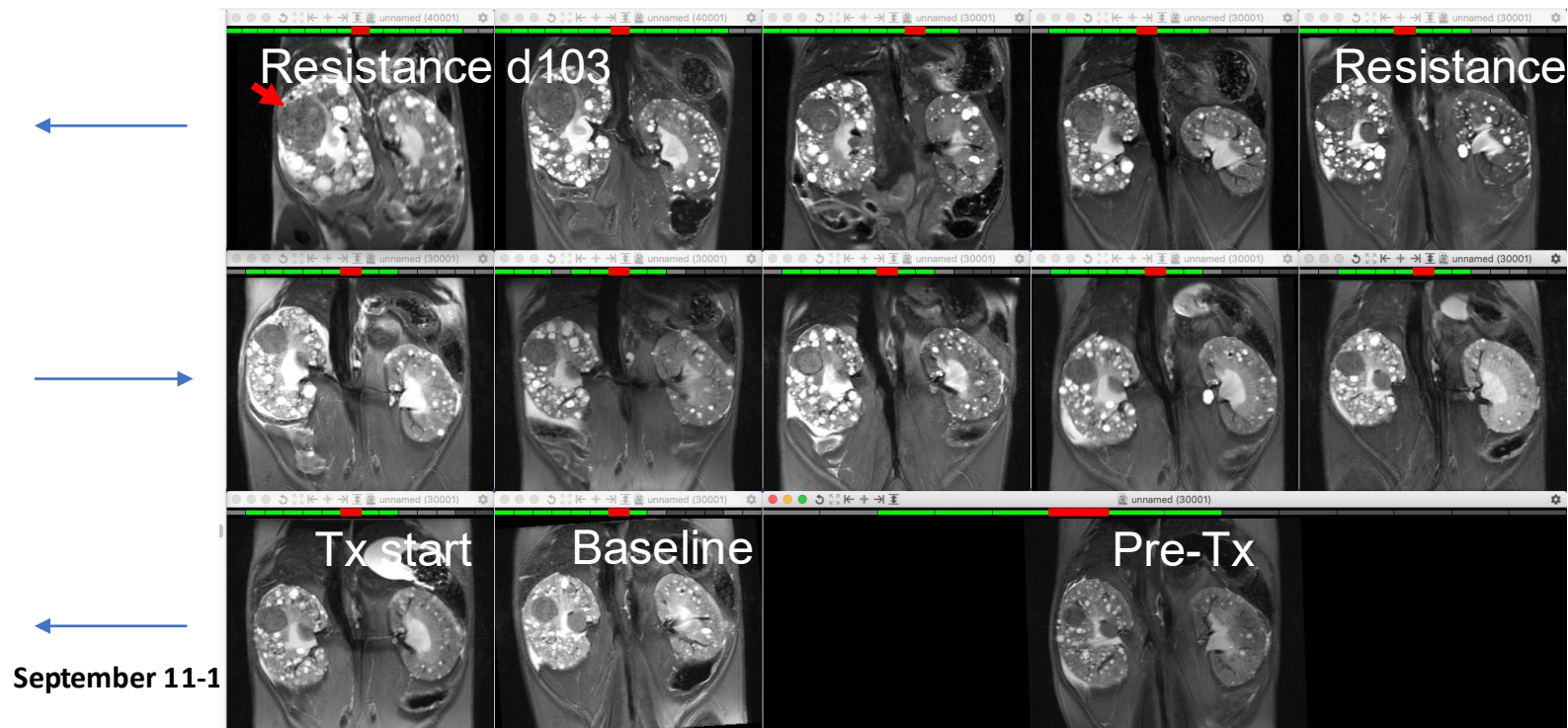
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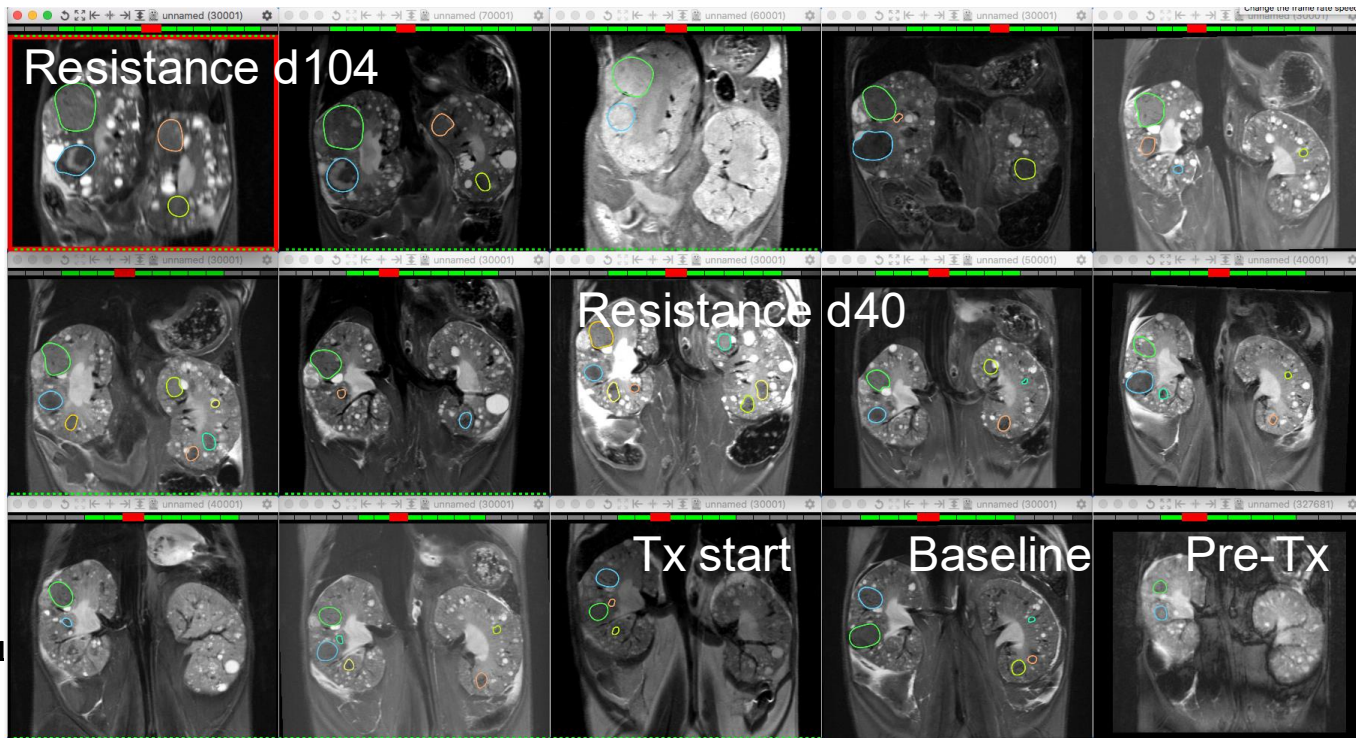
m40RT2 – Lenvatinib Acquired resistance



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m38RT1 – Lenvatinib Acquired resistance



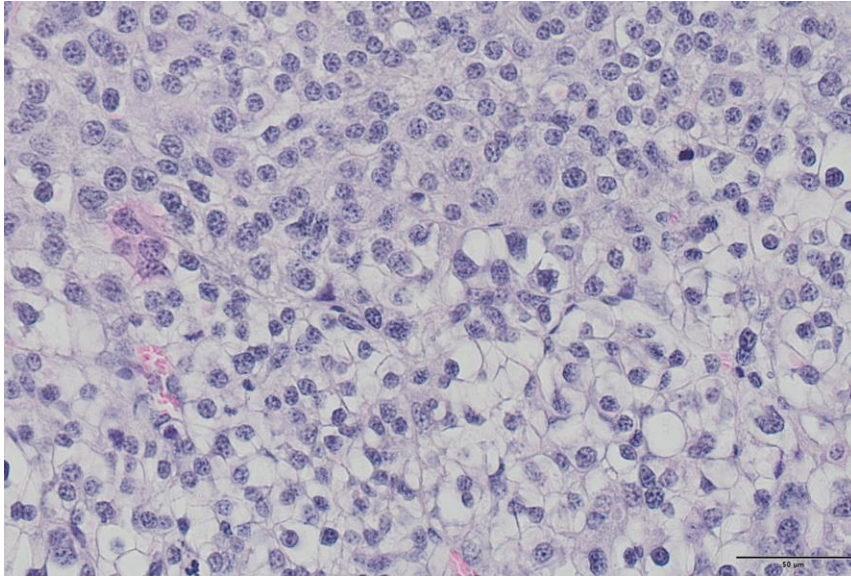
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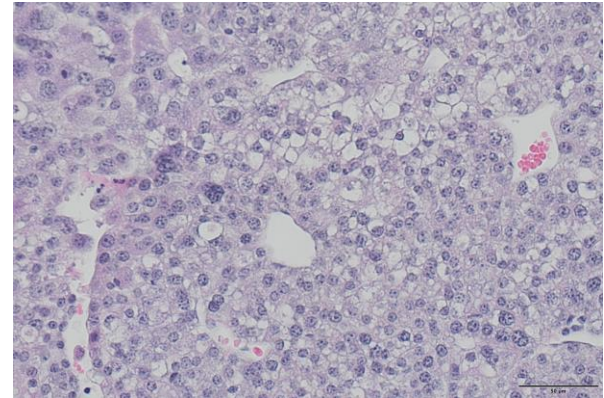
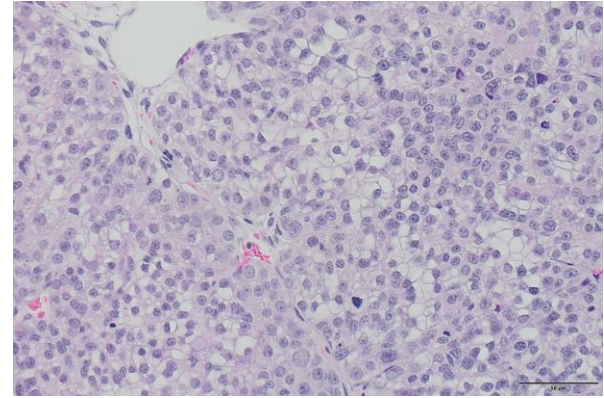
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Transition regions



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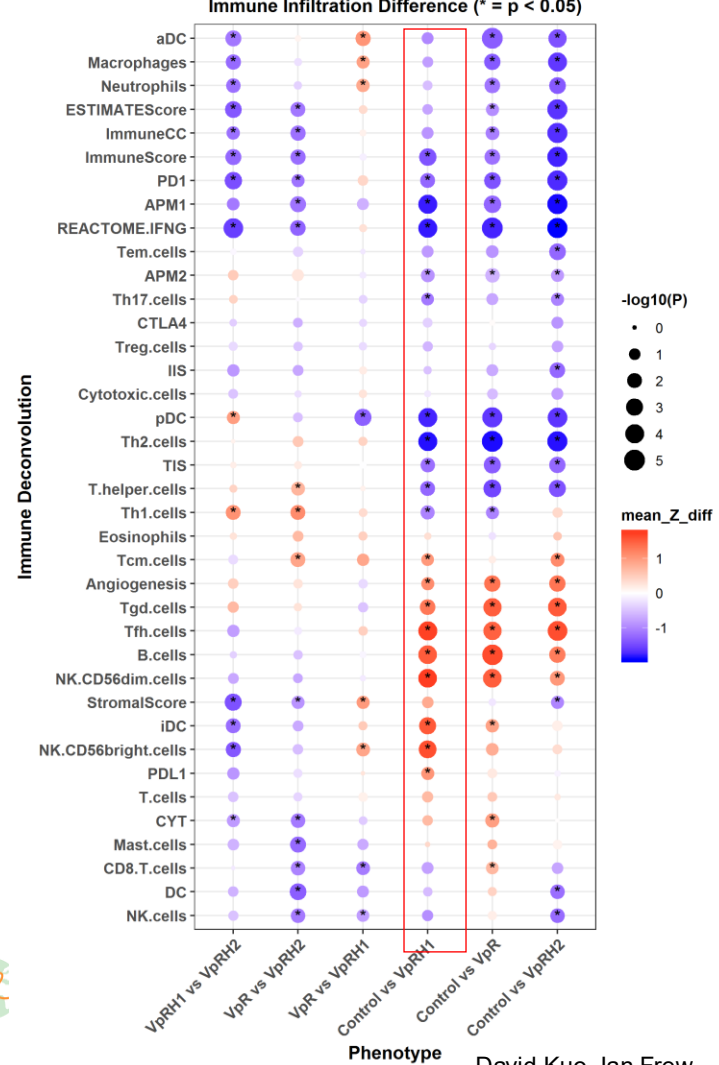
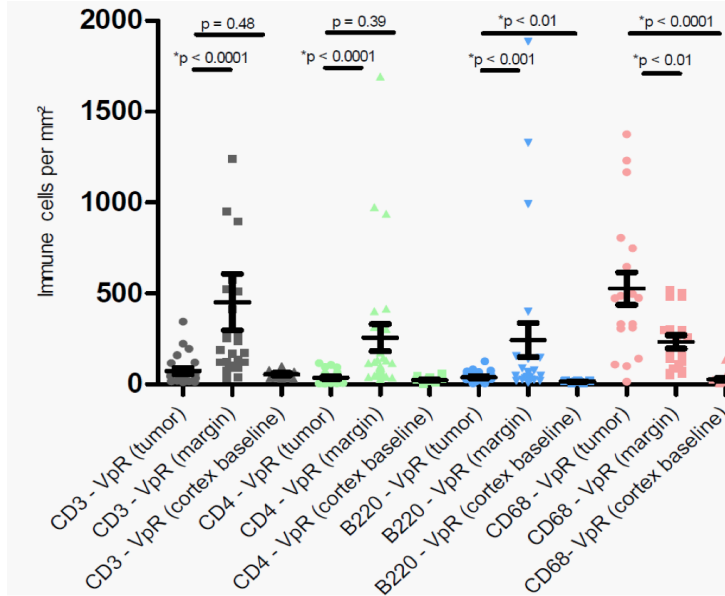


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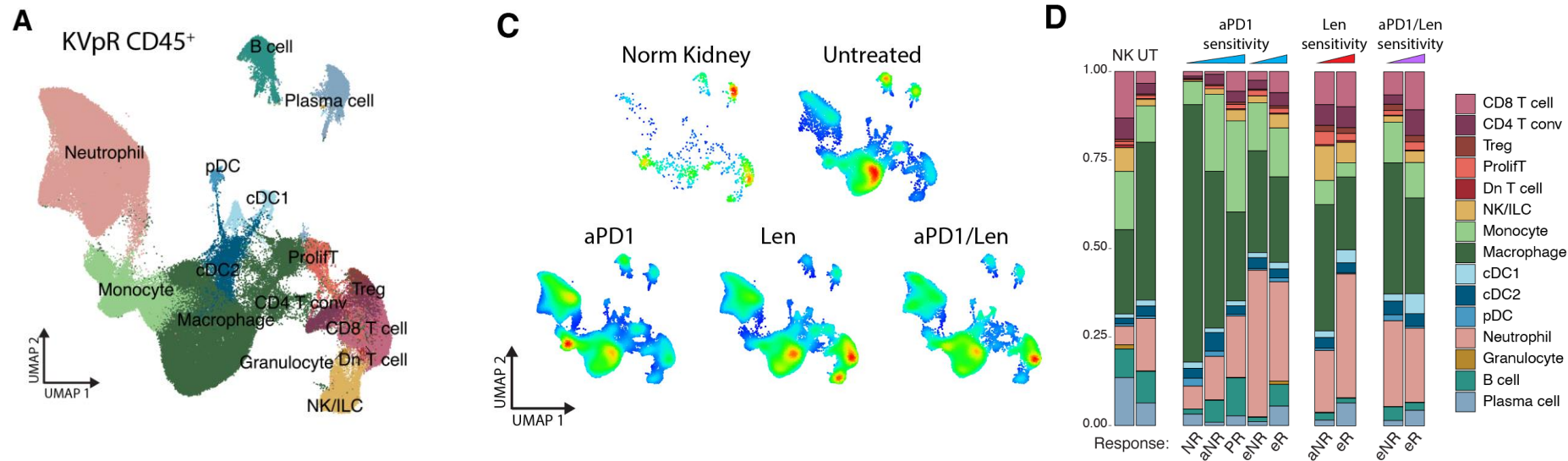
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KVpR tumor immune infiltrates

- RNAseq (11 tumors, 9 NK): lower angiogenesis, more macrophage and overall immuneScore and TIS but lower CD8 T cells
- IHC: T- and B-cells enriched in margins, high macrophage infiltration throughout.
- **But no response to anti-PD-1/anti-CTLA-4! (6-8mice/group, over 20 tumors each imaged by MRI; Frew group)**

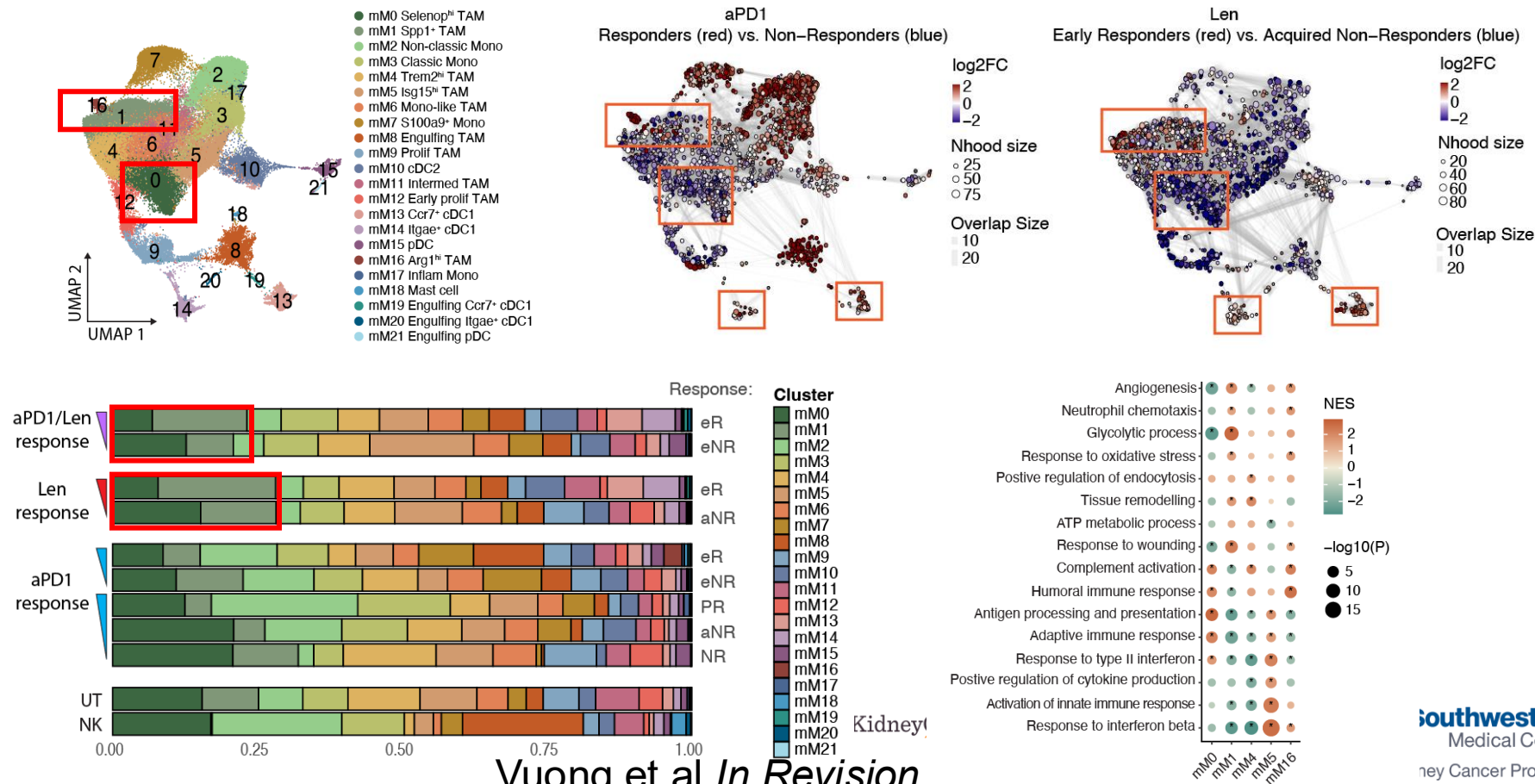


ICB and TKI differentially modulate the TME in mice

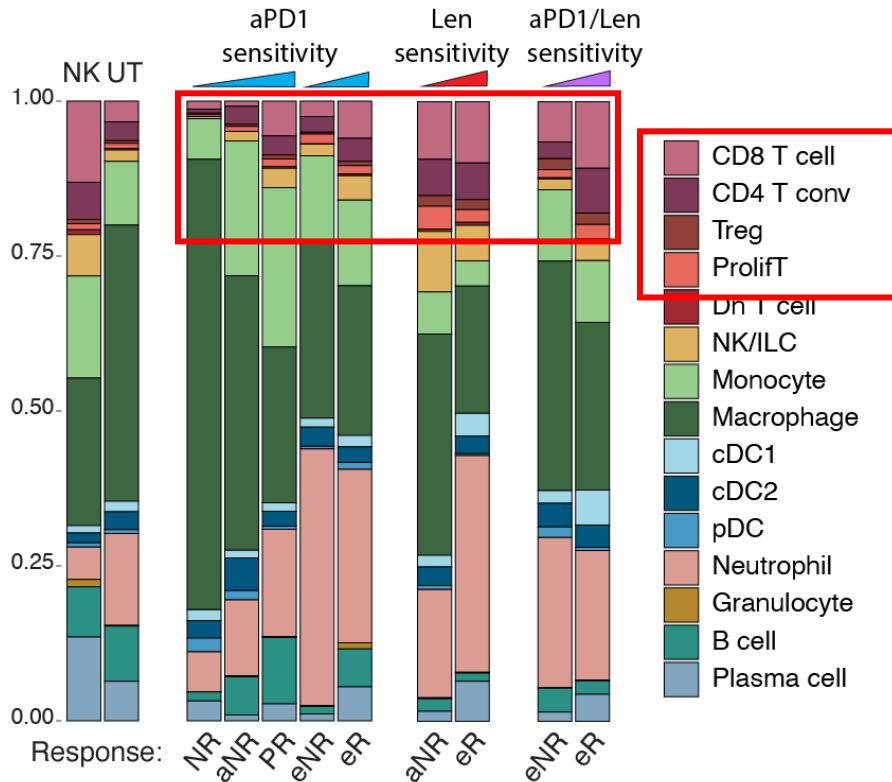


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SPP1+ TAMs distinguish true vs. pseudohypoxia and are associated with TKI response in mice



Total CD45+ cells



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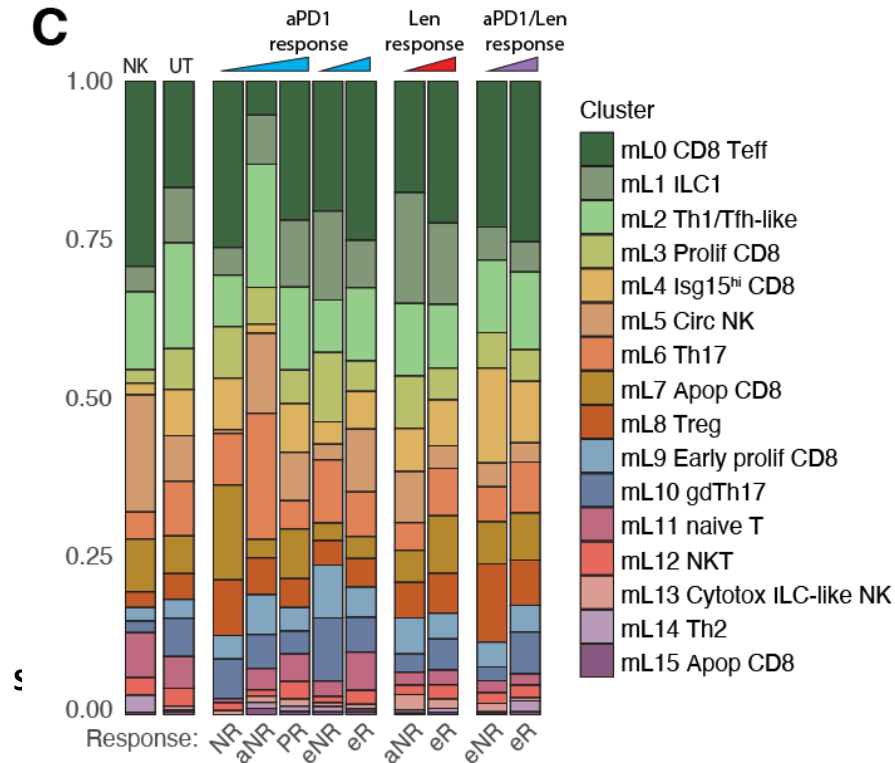
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Partnership with

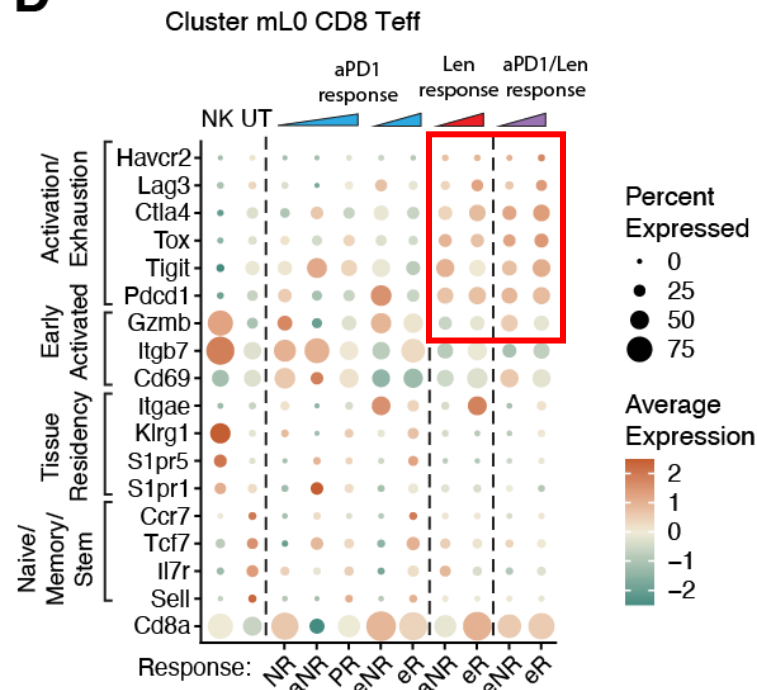
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TKI promotes CD8 T cell exhaustion in mice

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Conclusion

- KVPR model likely representative of Tp53 myeloid subset
- Strong response to Lenva opportunities for studying acquired resistance
- Synergizes with PD1
- Male predominance for tumor formation (opportunities to model similar human findings)
- Does not metastasize, with long latency and mixed background

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