Leveraging Humanized Mice to Map Kidney Cancer Immune Evasion Mechanisms

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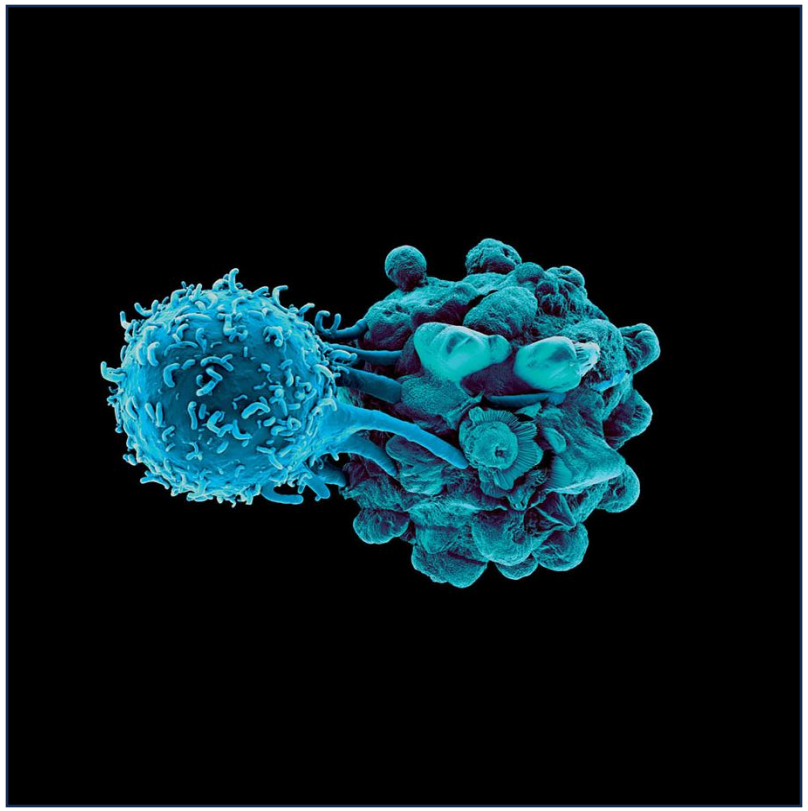
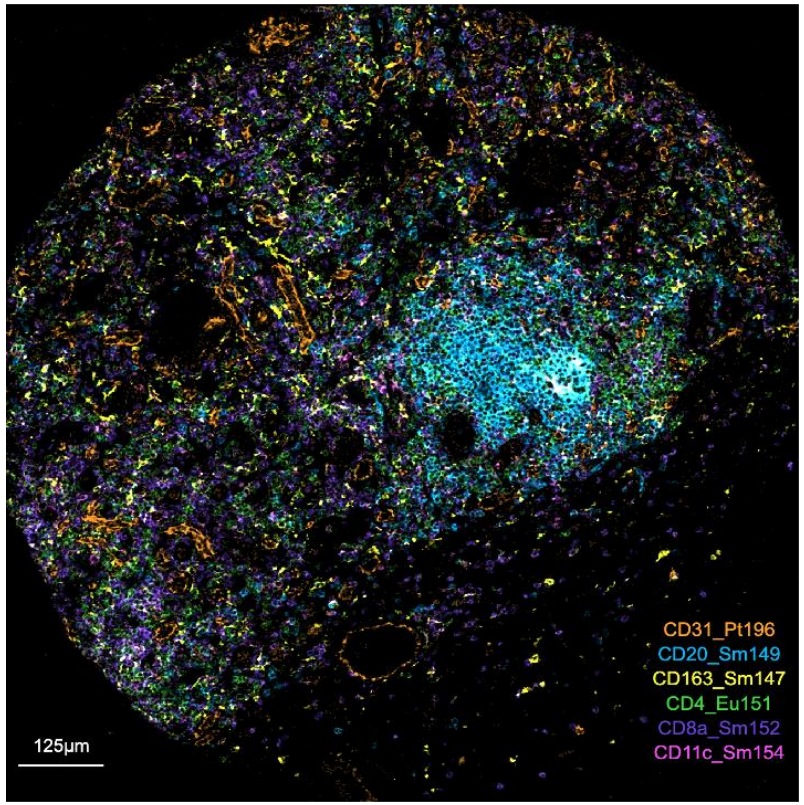
How do kidney cancers evade killing by the immune system?



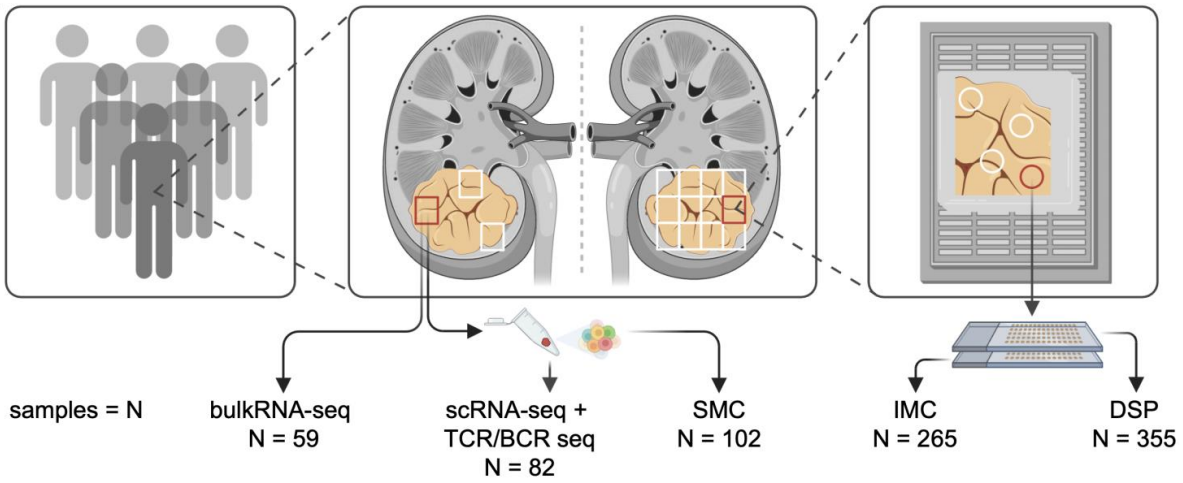
Intrinsic



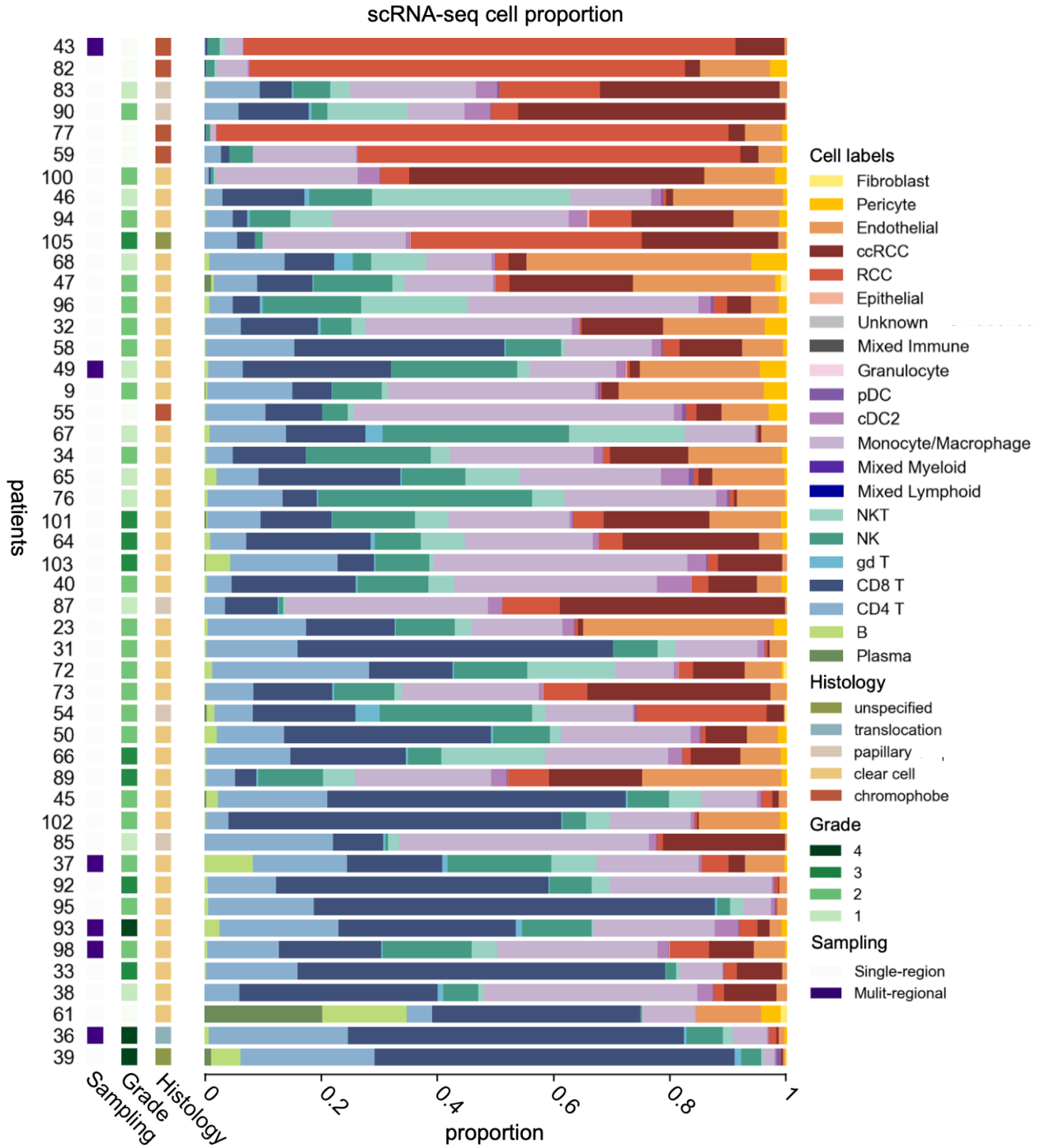
Extrinsic

Novel immunotherapeutic targets

Problem:
Heterogeneity in immune composition =
Different *evasion mechanisms*



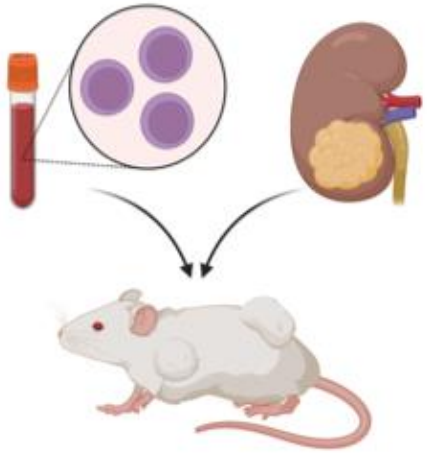
Models that capture heterogenous immune cell composition



Modeling Immune Heterogeneity Using Humanized PDXs

Laurie Ailles PhD
Senior Scientist
Princess Margaret

CD34+ Stem Cells **Human RCC tumor**



Triple immunodeficient background
e.g. **NOG**, NSG, NCG

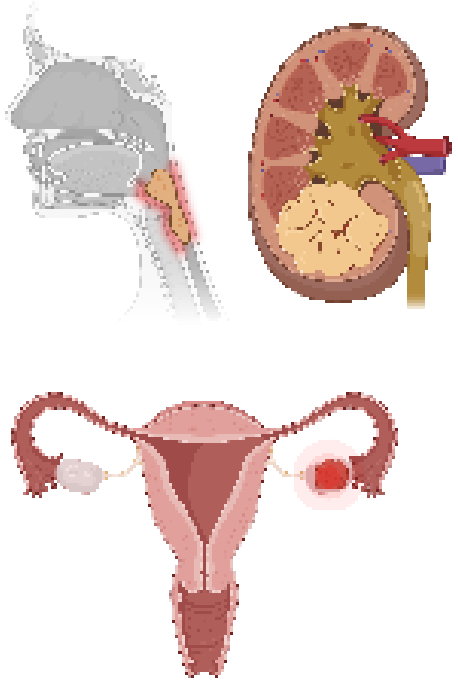
EXL - Myeloid Enhanced*
**IL-3, GM-CSF expressing*

Pros:

- PDX retains genetics of patient tumor
- Myeloid cell infiltration
- Broad tumor engraftment
- Long-term lifespans (> 12 months)

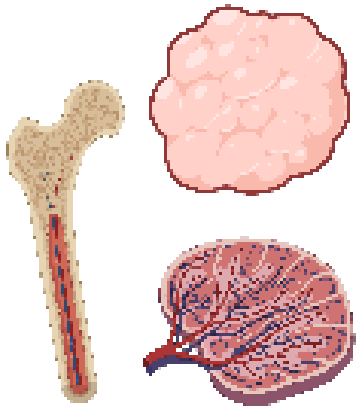
Faithful representation of the primary tumor?

Modeling Immune Evasion Using Humanized Patient-Derived Xenografts

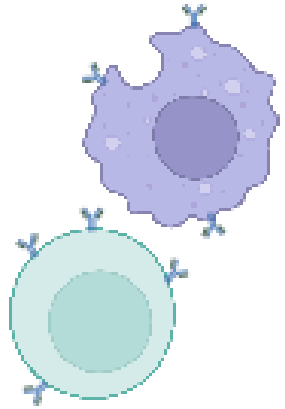


n = 16 samples from
HNSCC
Ovarian Cancer
Renal Cell Carcinoma

Primary tumour samples
implanted into
humanized mice
(n = 88 mice)



Samples collected from
Bone Marrow (n = 88),
Spleen (n = 88),
PDX (n = 59)



Single-cell suspensions
analyzed with Cytometry by
Time-of-Flight (CyTOF)

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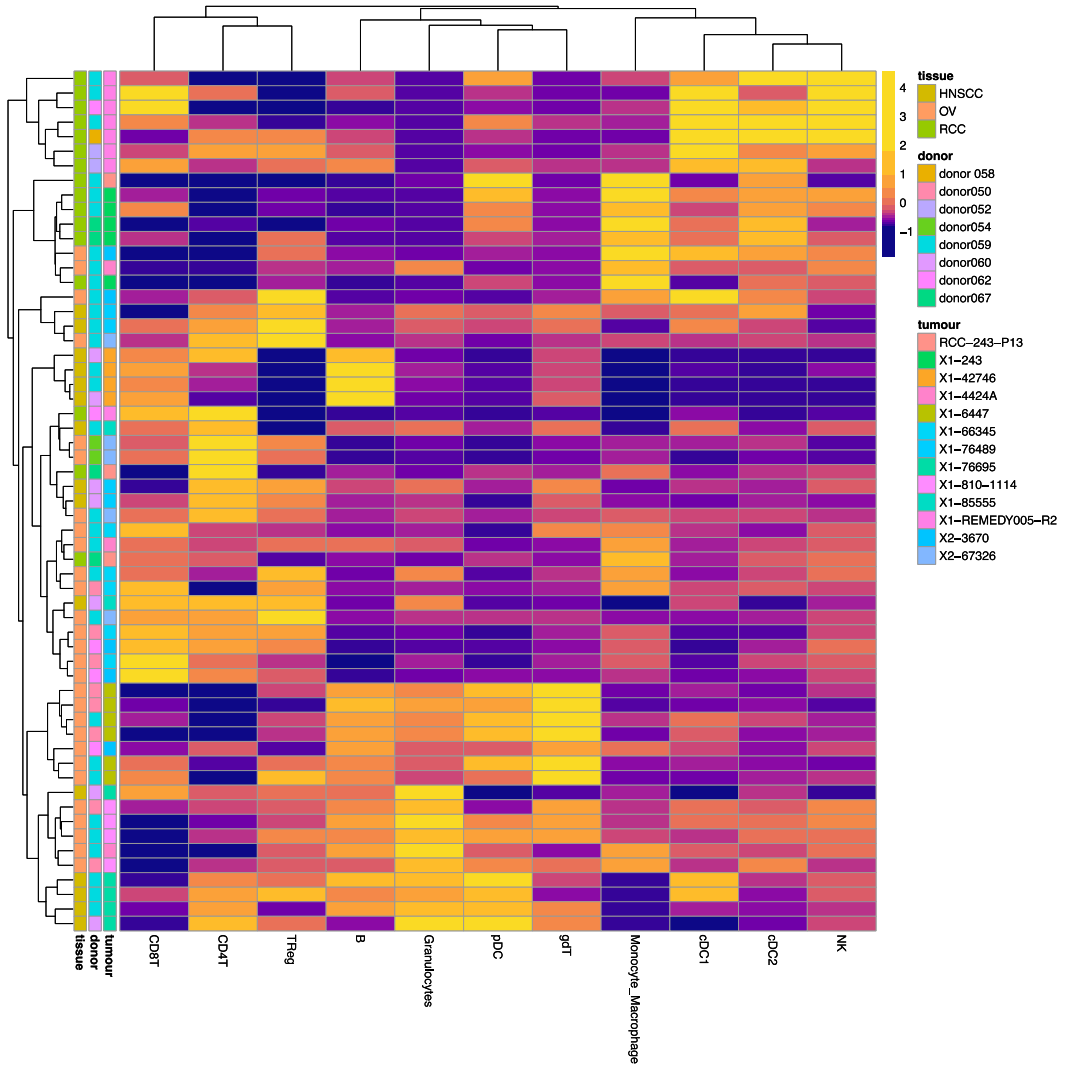
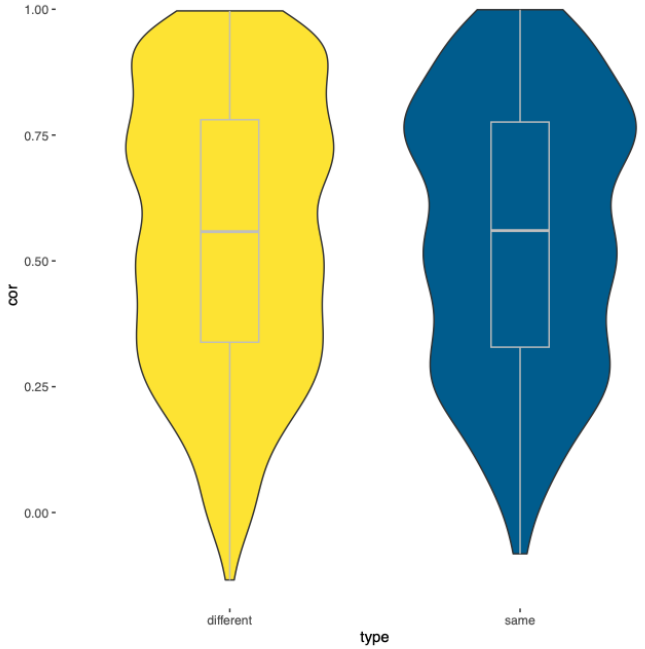
Bernd Bodenmillar Lab

Tumor Intrinsic Factors Drive Immune Composition of Humanized PDXs

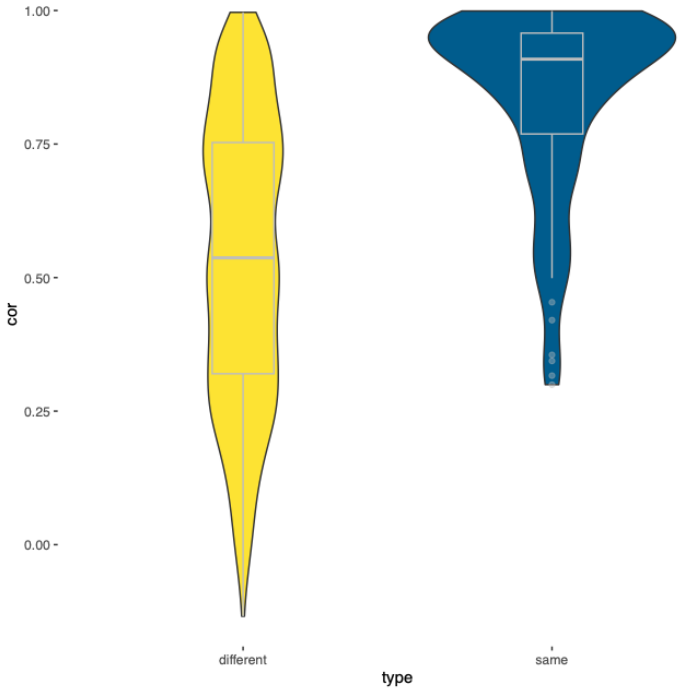
PDX tumor immune composition



Donor HSC ID

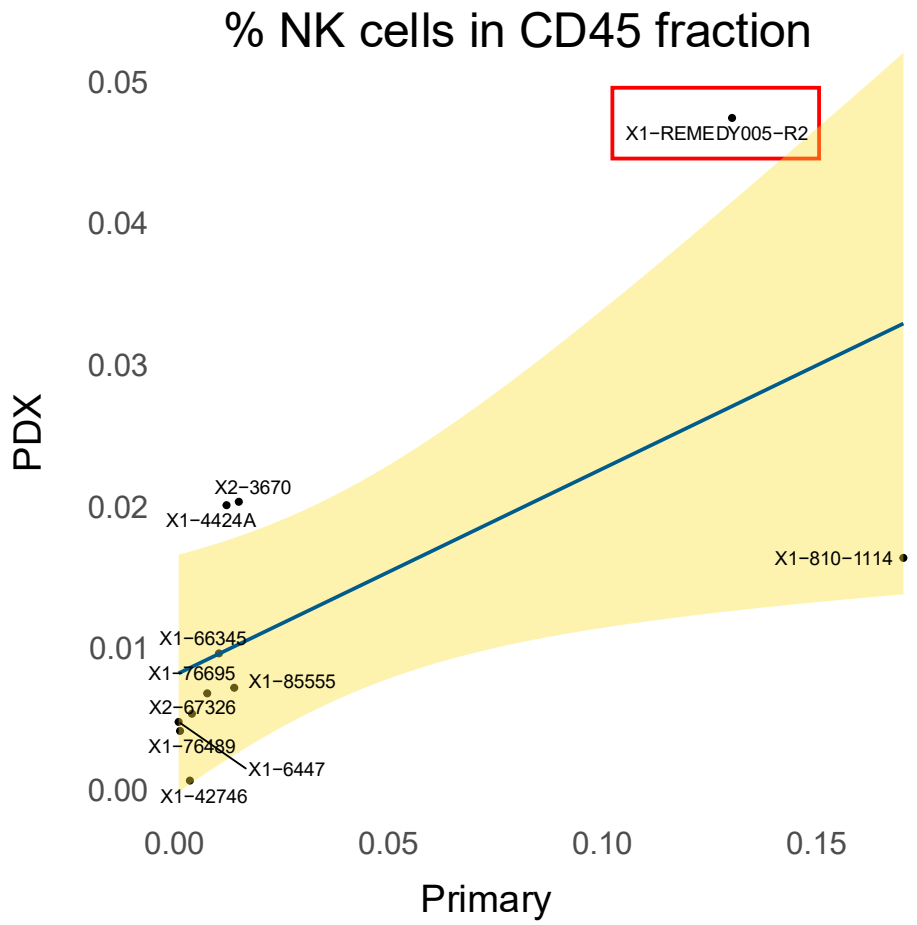


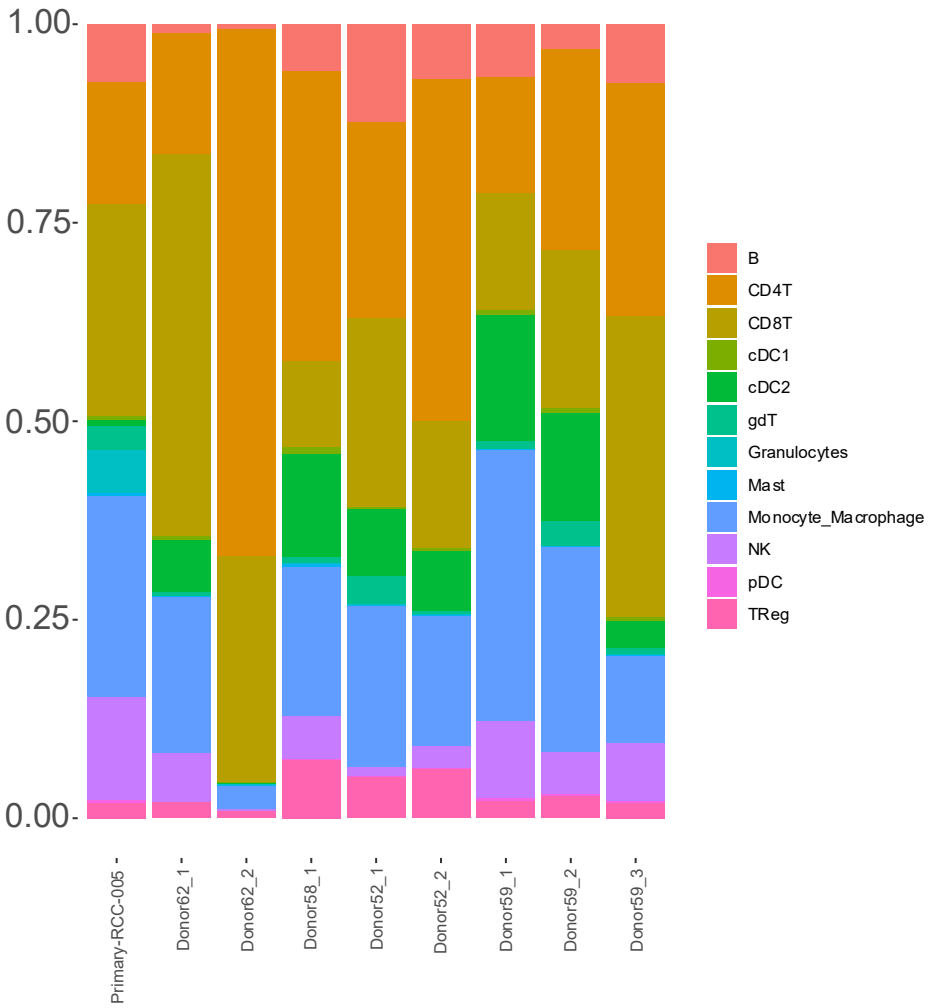
Tumor ID



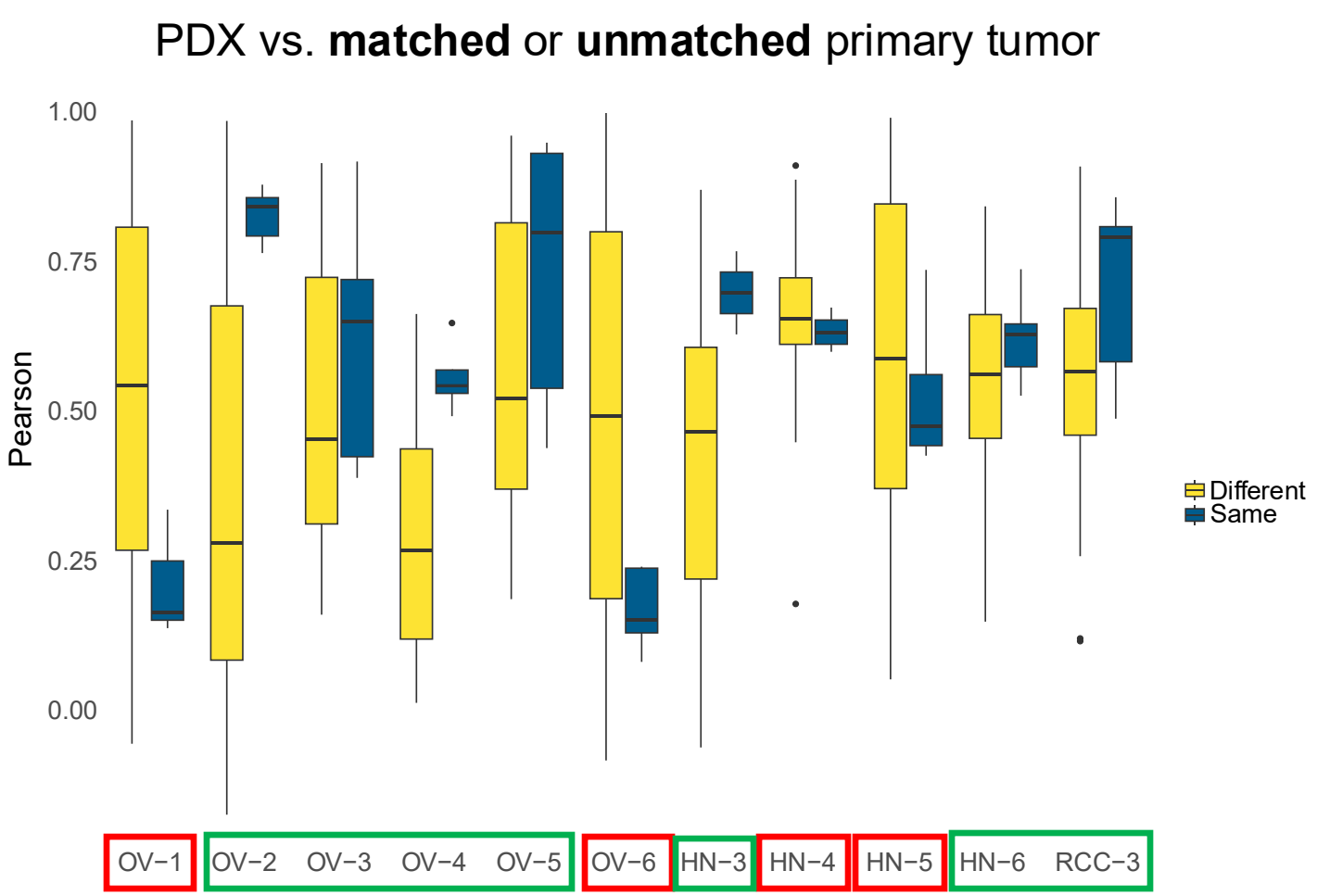
Tumor ID drives immune composition

Humanized PDXs Variably Capture Primary Tumor Immune Phenotype





Humanized PDXs Variably Capture Primary Tumor Immune Phenotype

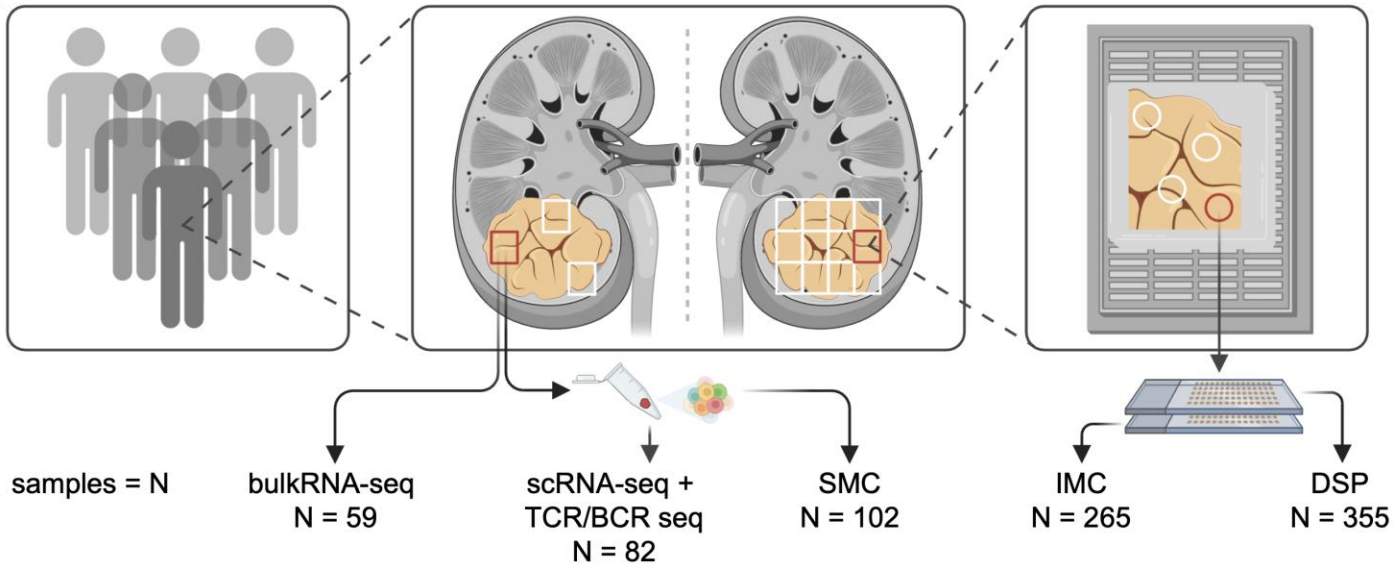


Cons:

- Lower overall immune infiltration
- Not all models reflect primary tumor
- Allo- immune response
- Unknown functional status

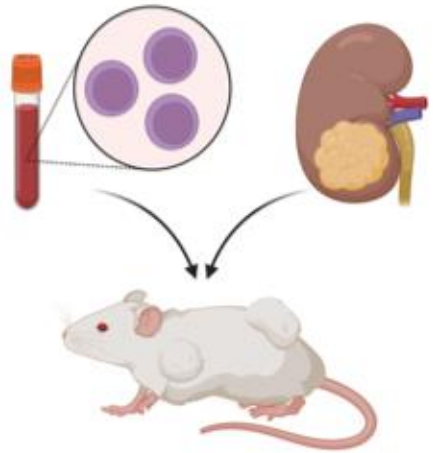
Myeloid rich primary tumors associated with failure

Modeling Multicellular Niches Using Humanized Patient-Derived Xenografts



- Single-cell genomics
- HLA-transgenics/BLT model
- ***In vivo* CRISPR screens**

N = 109 viably banked
(16 PDX established)



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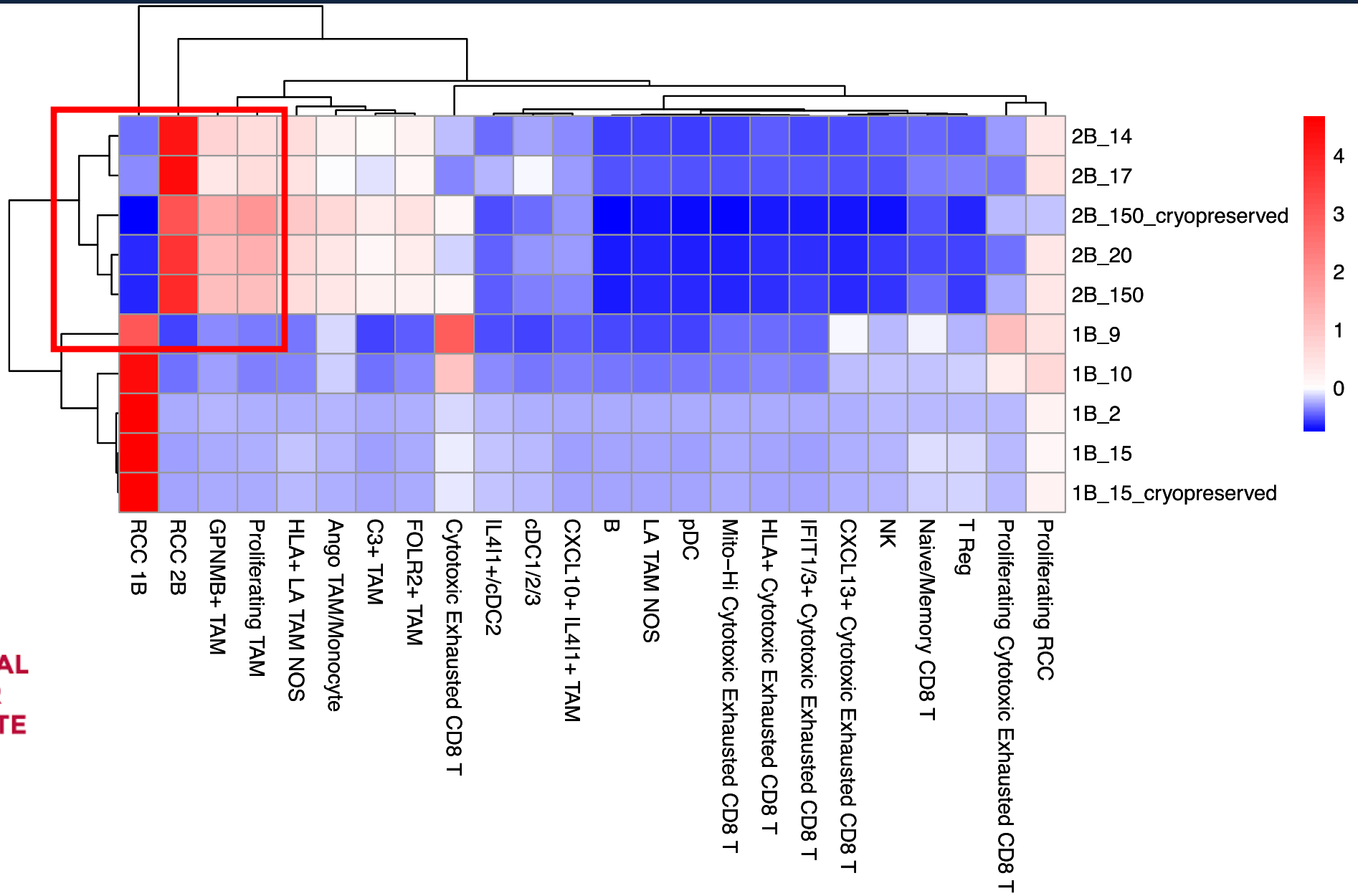
RRCRC RÉSEAU DE RECHERCHE SUR LE CANCER DU REIN DU CANADA
NIH NATIONAL CANCER INSTITUTE
Anna-Liisa Farquharson Chair Kidney Cancer
UHN Biospecimen Services

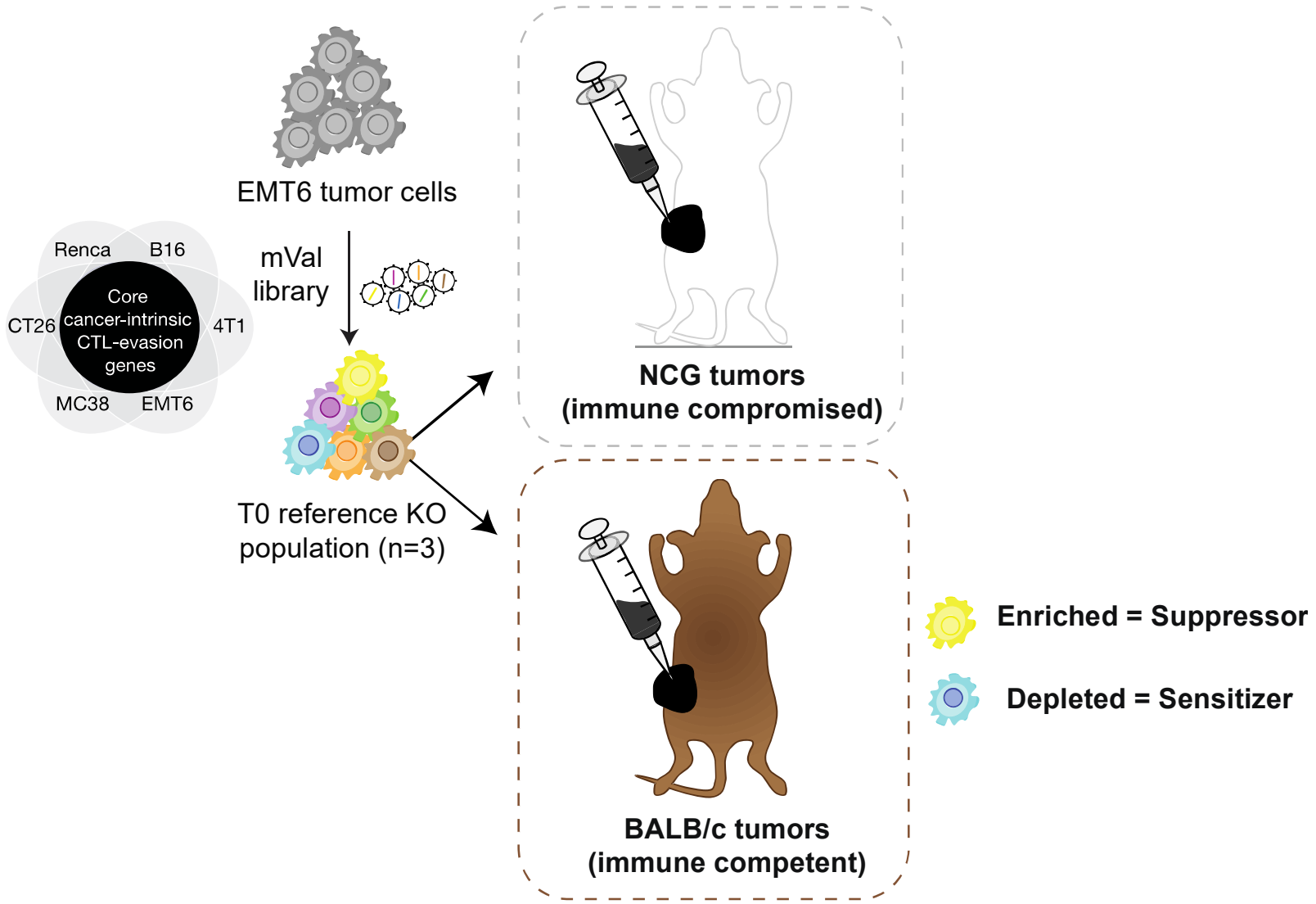
Humanized Mouse scRNAseq Data

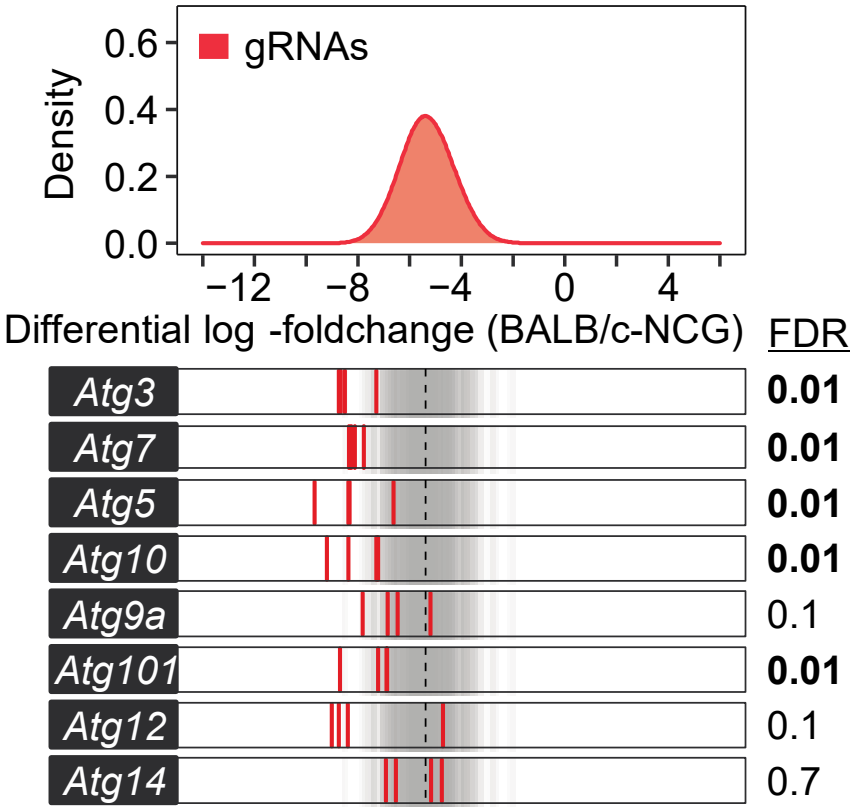
Marston Linehan

NIH NATIONAL CANCER INSTITUTE



In Vivo CRISPR screens



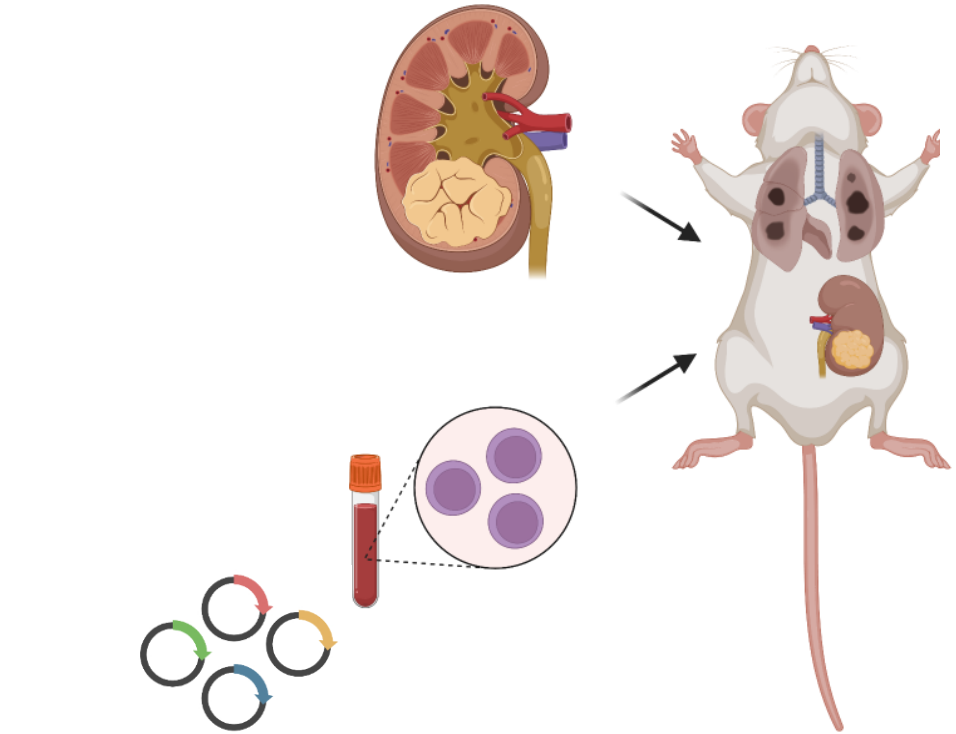


Lawson & Sousa *et al. Nature*, 2020

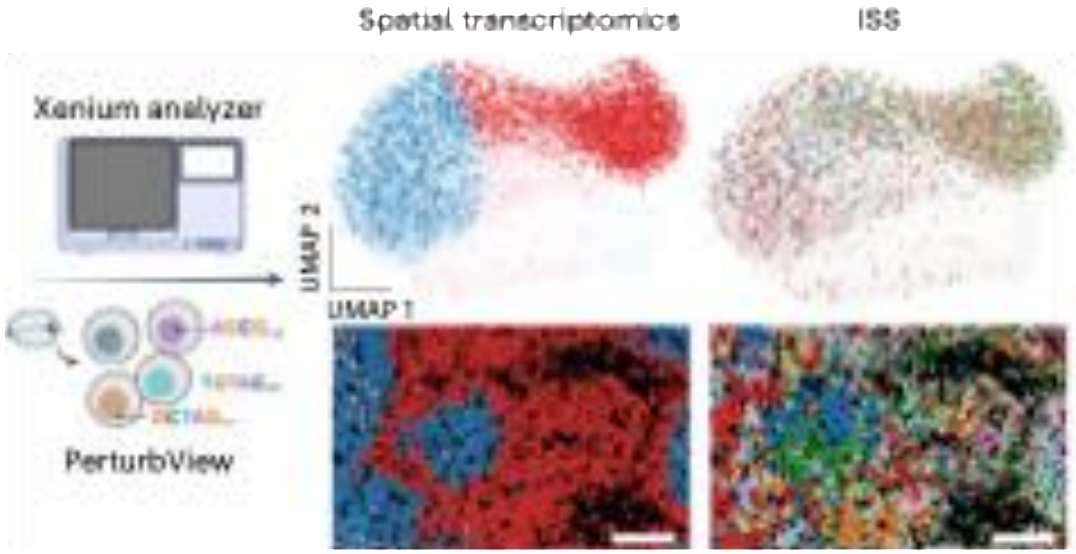
In vivo CRISPR screens to dissect immune evasion mechanism

Cancer intrinsic targets

Therapeutic cell targets



TME targets



Kudo *et. al.* 2024

Perturbview – couples gRNA (genotype) to multicellular niche (phenotype)