Transcriptomic, epigenomic and spatial metabolomic cell profiling redefines regional human kidney anatomy

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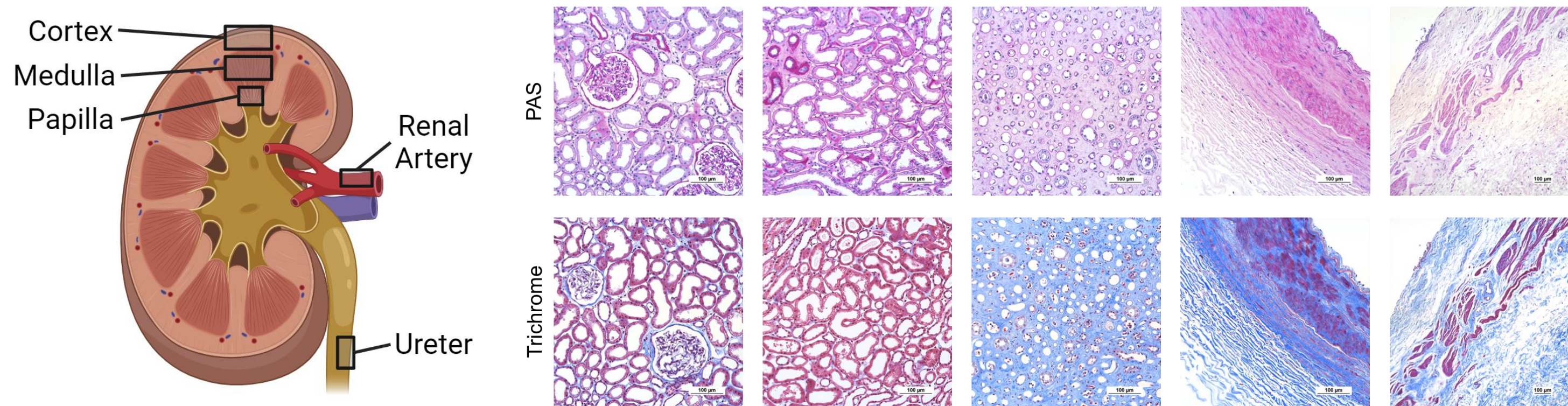
INTRODUCTION

Chronic Kidney Disease (CKD)

37 MILLION
MORE THAN **1 IN 7** US adults may have CKD.

ONLY **1 IN 10** adults with CKD **KNOW** they have CKD.

Human Kidney Anatomy

Cortex, Medulla, Papilla, Renal Artery, Ureter

PAS / Trichrome

Glomerulus, Cortex, Medulla, Papilla, DCT, PT, Loop of Henle (thick), Loop of Henle (thin)
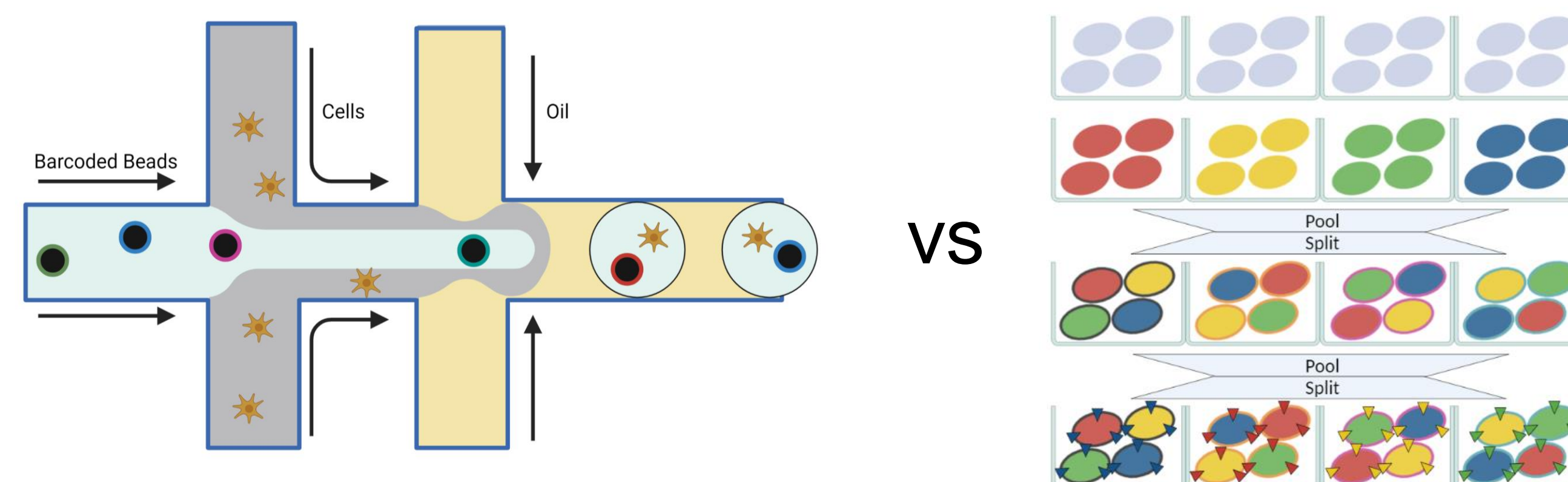
1. The **multimodal landscape** of human kidney has not been studied across major anatomic regions.
2. The **same** tubular epithelial cell type may be positioned within **distinct** anatomical regions. Do these cells possess a differential molecular signature when located in different regions?
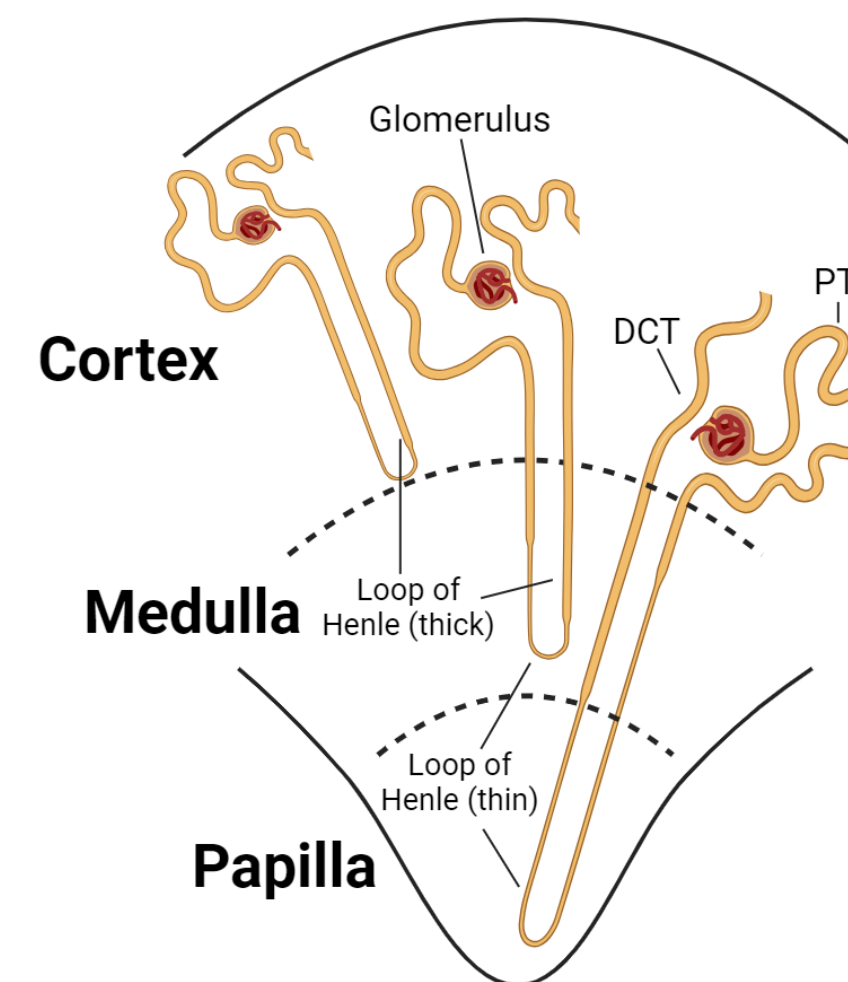
Single-cell Sequencing Methodology

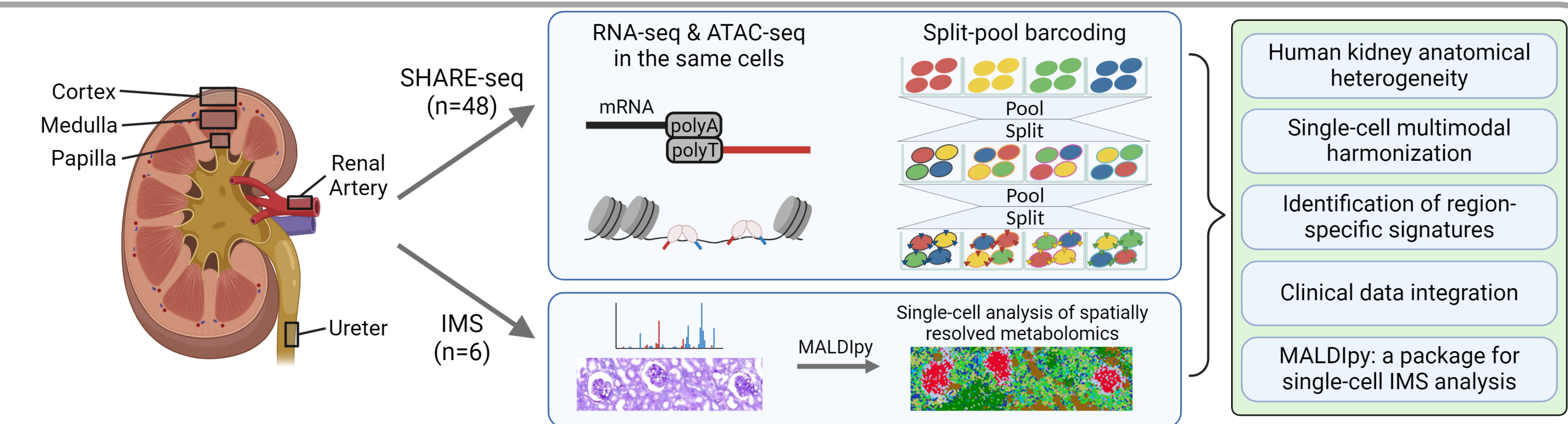Barcoded Beads, Cells, Oil   VS   Pool Split

- Current popular droplet microfluidics platforms have **limitations** including throughput, sample multiplexing ability and costs.
- We previously developed an optimized **split-pool barcoding**-based scRNA-seq method to study mouse kidneys with high throughput and low costs (Li et al. Cell Metabolism 2022)

- Transcriptomic profiling → Multiomics
- Mouse → Human kidneys

METHODS & WORKFLOW

We employed split-pool barcoding simultaneous RNA and ATAC-sequencing (**SHARE-seq**) and spatially resolved metabolomics (**MALDI-IMS**) to profile 54 human kidneys from different anatomical regions.
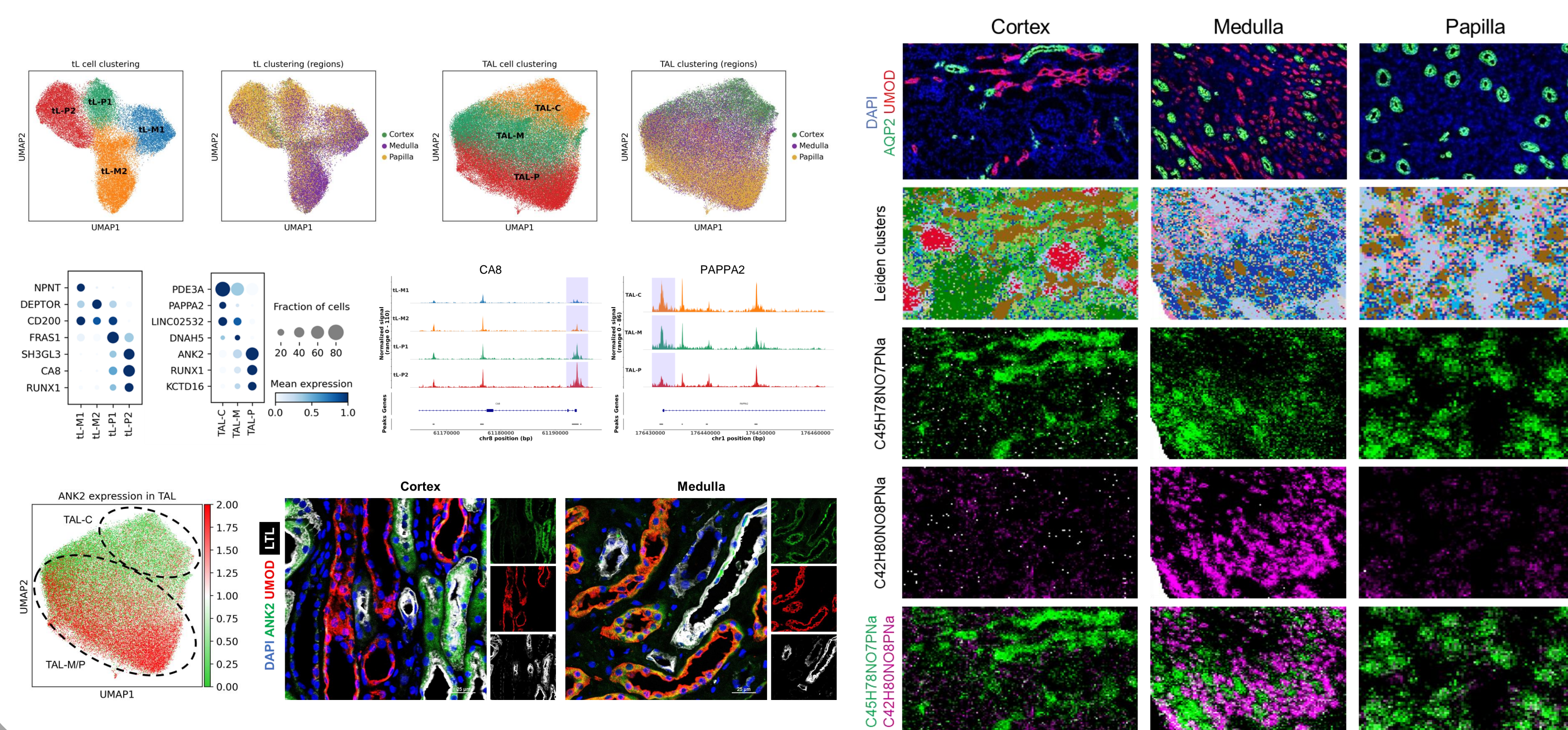

Cortex, Medulla, Papilla, Renal Artery, Ureter

SHARE-seq (n=48): RNA-seq & ATAC-seq in the same cells — Split-pool barcoding — mRNA polyA polyT — Pool Split

IMS (n=6): MALDIpy — Single-cell analysis of spatially resolved metabolomics

- Human kidney anatomical heterogeneity
- Single-cell multimodal harmonization
- Identification of region-specific signatures
- Clinical data integration
- MALDIpy: a package for single-cell IMS analysis

KEY HIGHLIGHTS

1. A multimodal & anatomically stratified human kidney atlas: 446,267 snRNA-seq + 401,875 snATAC-seq cells
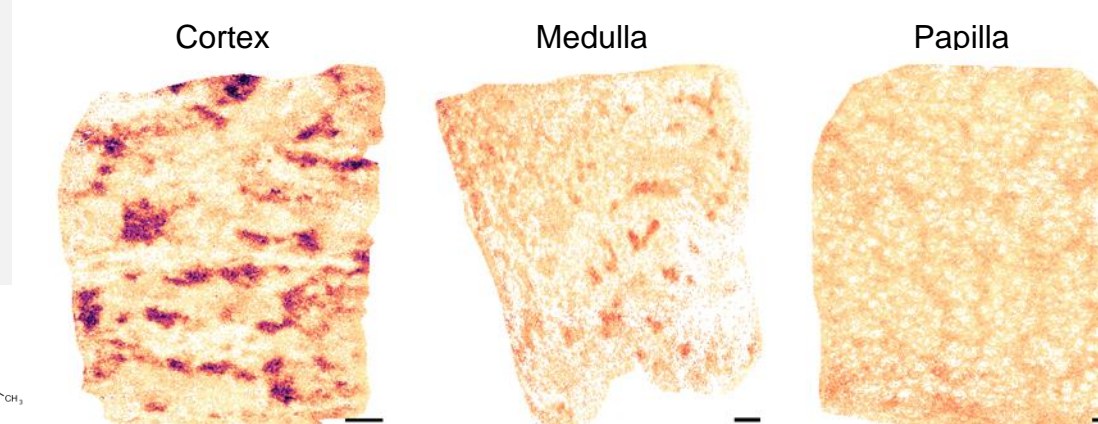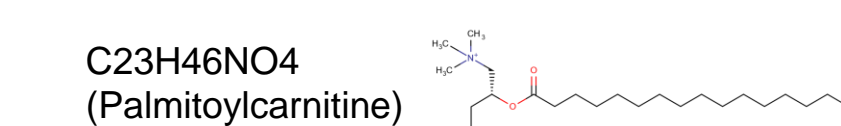

446,267 cells | RNA-seq   401,875 cells | ATAC-seq
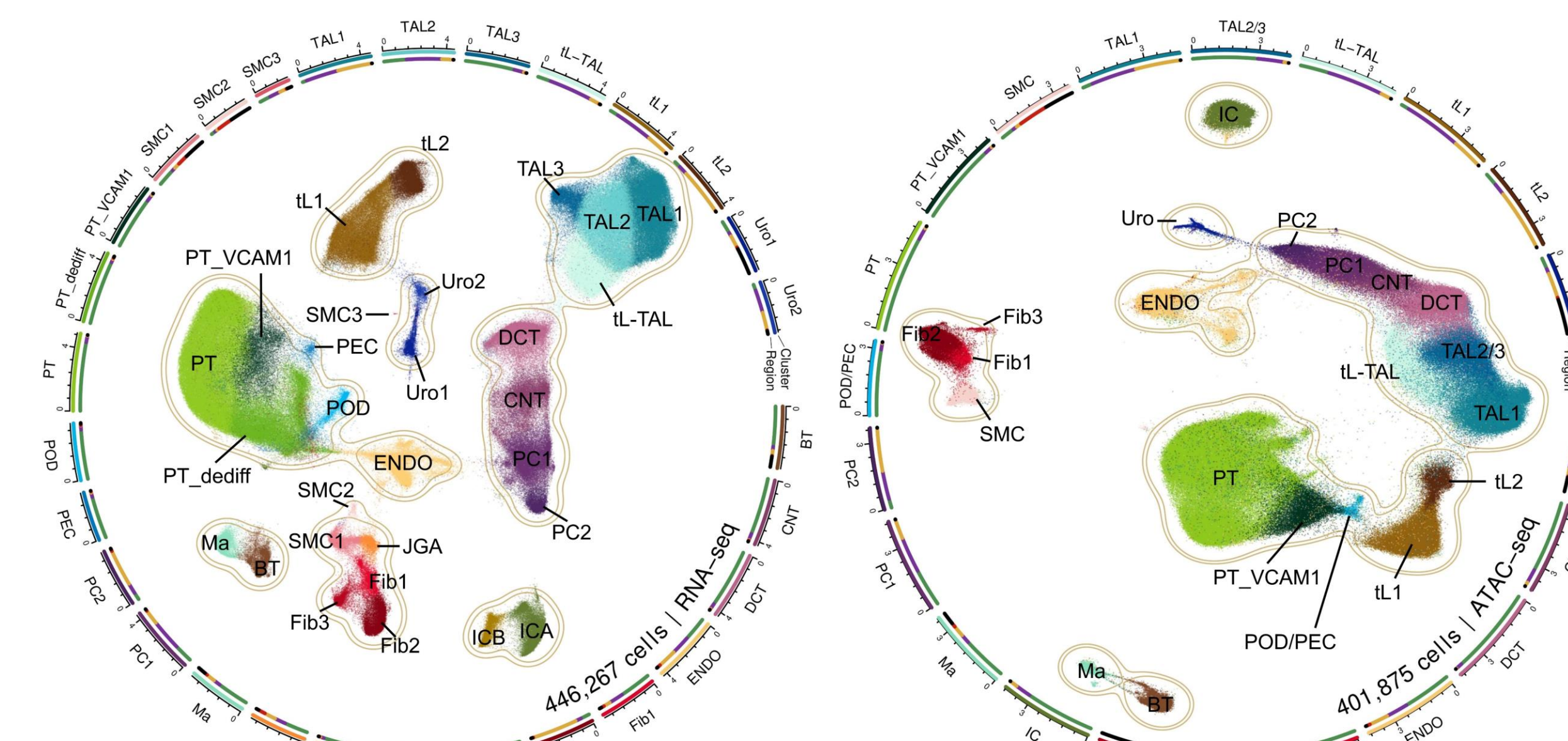
2. Developing MALDIpy as a package for IMS single-cell analysis & identification of metabolomic heterogeneity across kidney regions
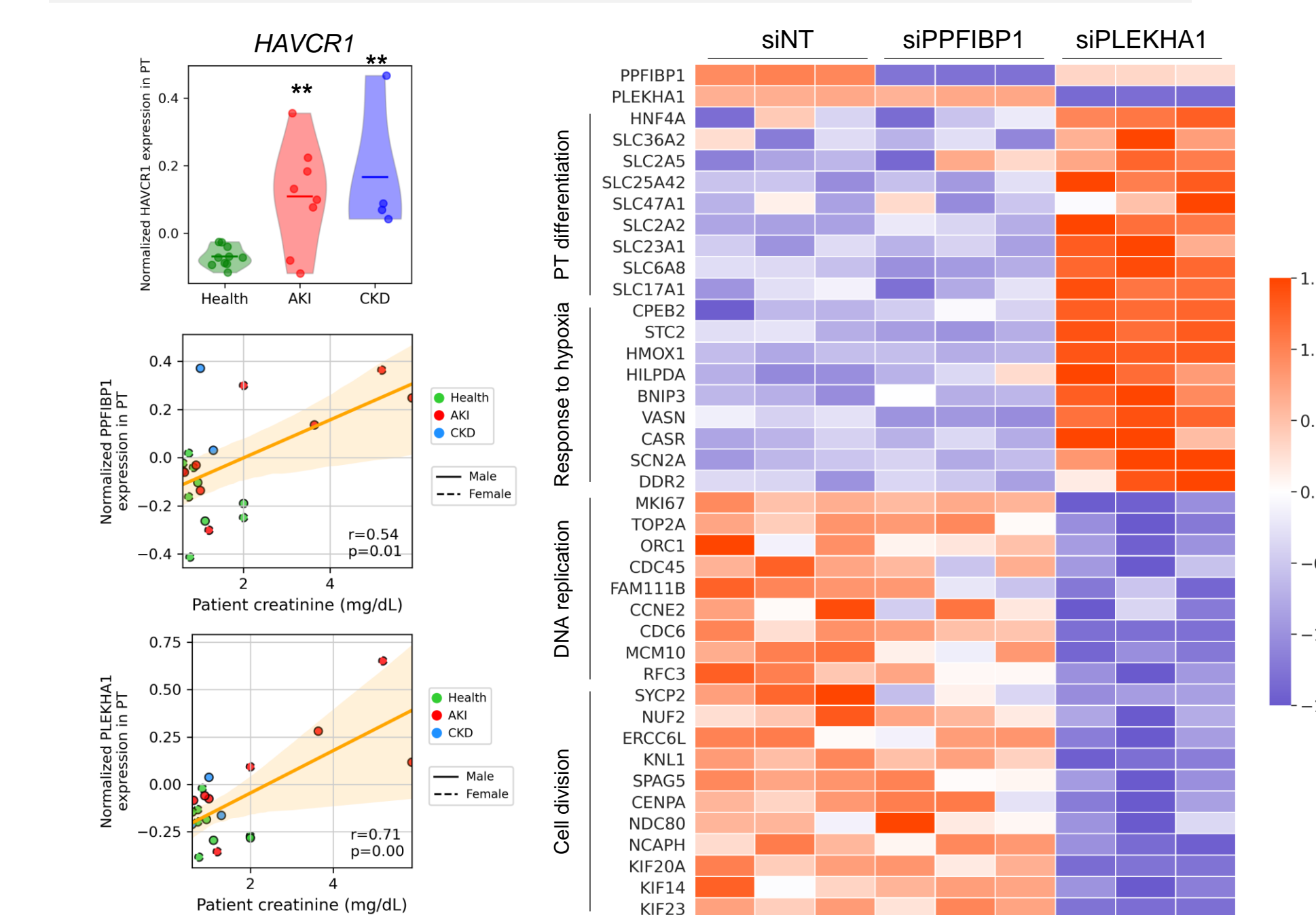

Cortex, Medulla, Papilla — Metabolomics Leiden clustering
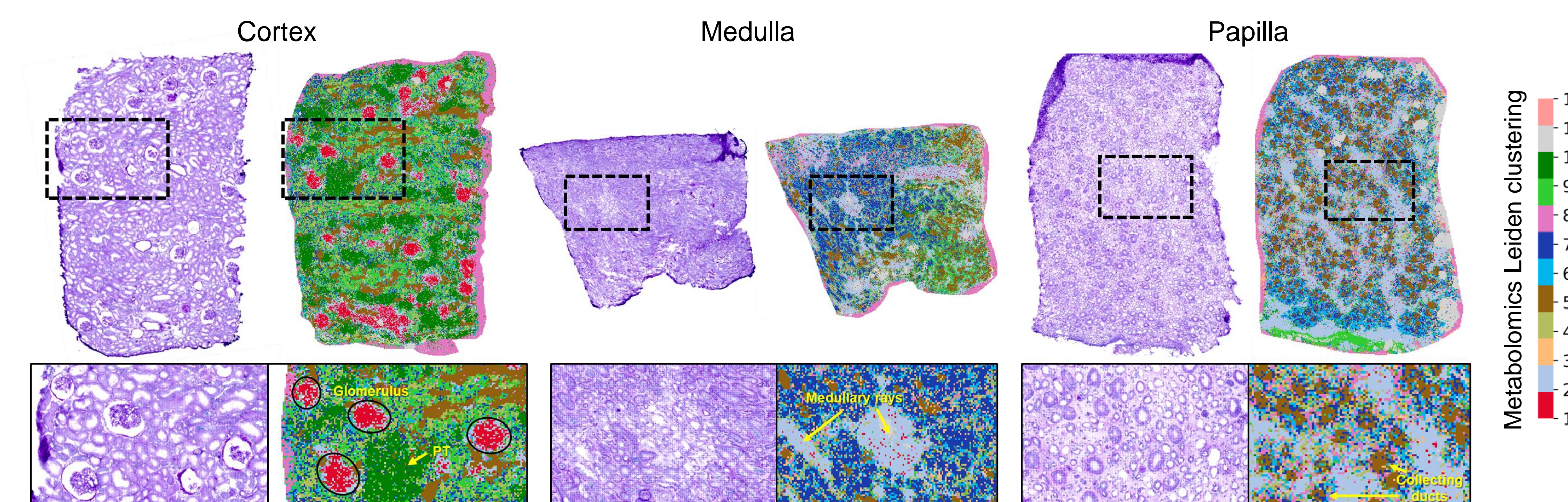
3. The same tubular epithelial cell type may have distinct transcriptomic, epigenomic and metabolomic signatures depending on anatomical regions.

tL cell clustering, tL clustering (regions), TAL cell clustering, TAL clustering (regions)

CA8, PAPPA2, ANK2 expression in TAL

Cortex, Medulla, Papilla

4. Characterization of proximal tubule lipid metabolism

Cortex, Medulla, Papilla

C23H46NO4 (Palmitoylcarnitine)

5. Integrating multiomics with clinical data

HAVCR1

siNT, siPPFIBP1, siPLEKHA1

CONCLUSIONS & ACKNOWLEDGEMENT

- SHARE-seq analyzes transcriptomes and open chromatin accessibility profiles of >400,000 cells from human kidney samples of different anatomical regions.
- MALDIpy is a package for IMS single-cell analysis allowing identification of kidney anatomical heterogeneity.
- The same kidney tubular cell types have distinct transcriptomic, epigenomic and metabolomic signatures depending on regional location.
- Clinical data integration identifies novel candidate genes in kidney disease progression.

The Humphreys Lab

DBBS Graduate Program