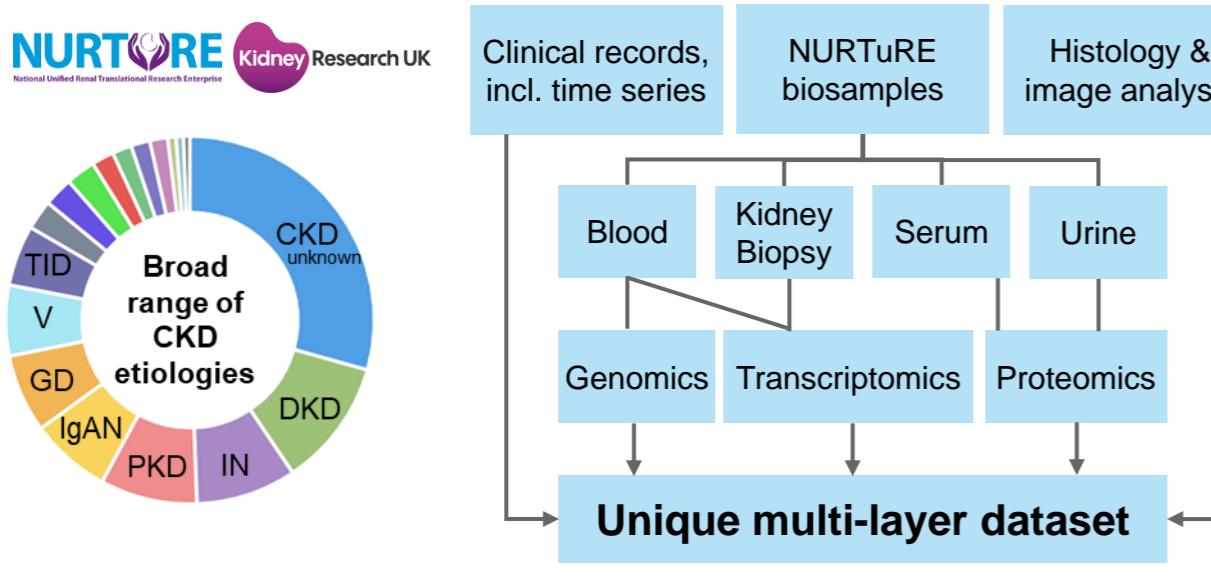

A Systems Nephrology Framework for the Molecular Classification of CKD

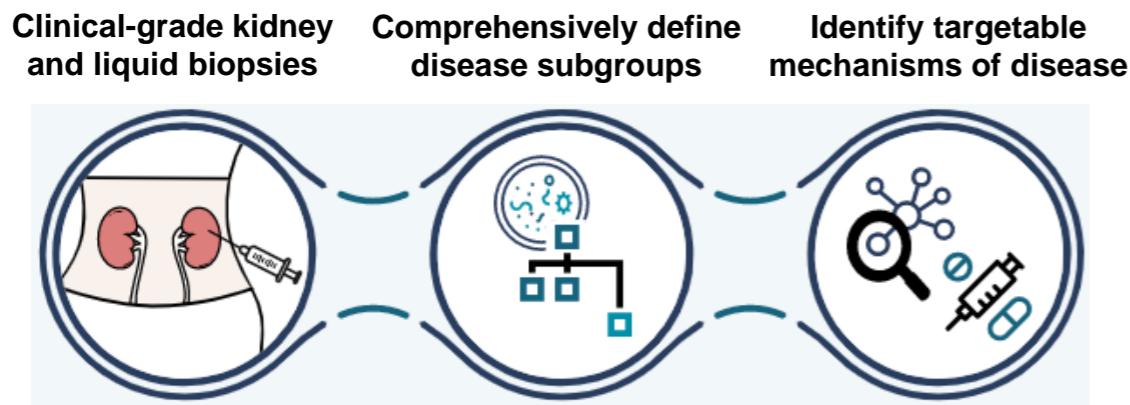
Tobias Bohnenpoll, Eric Olson, Mykola Dergai, Jennifer Cox, Simone Romoli, I-Ju Lo, Johannes Pospiech, Krishan Vishnolia, Mark McConnell, Marvin Gunawan, Michaela Bayerlová, Nicolette Honson, Niklas Michel, Nikolas Stroth, Olivier Radresa, Philipp Skroblin, Priyanka Kohli, Seamus Ragan, Shenshen Lai, Steven Bromidge, David Powell, Uwe Andag and Andrew King

A systems nephrology framework for the molecular classification of CKD

Integration of real-world clinical, morphological and molecular data



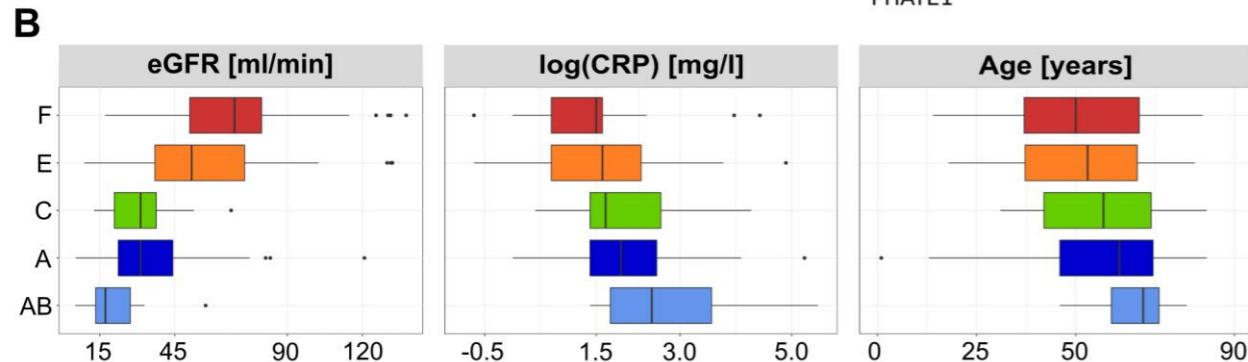
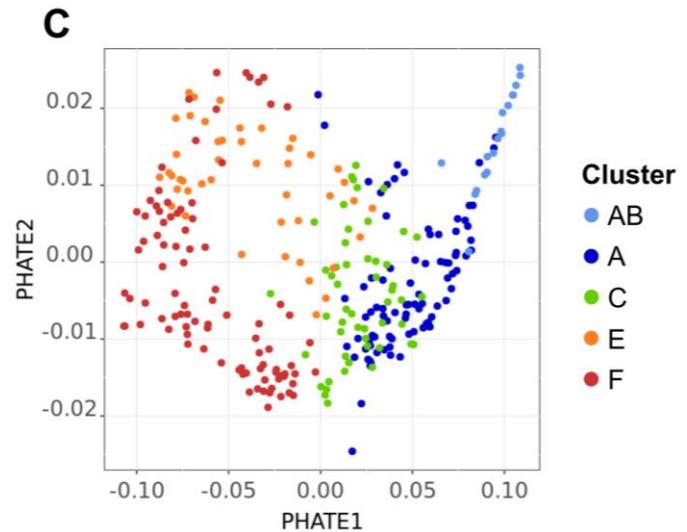
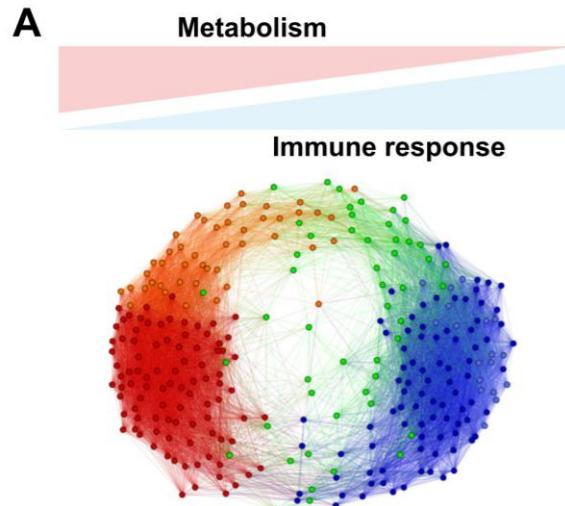
- Conventional stratification by clinical and histopathological phenotypes is insufficient to describe the heterogeneity of chronic kidney diseases (CKD)
- Integration of intra-renal molecular and morphological features with clinical outcomes is required to drive discovery of disease-modifying therapies
- The NURTURE biobank comprises matched patient samples from a broad range of diagnoses and kidney functional states, that are associated with rich clinical data



We aim to generate mechanistic disease understanding for a patient-centric, integrated target and biomarker discovery that will enable the development of novel precision treatments

Unsupervised analysis reveals molecular similarities and transitions that align with disease progression

Definition of molecular clusters and disease trajectories from biopsy transcriptomes



- Unsupervised clustering of kidney transcriptomes via self organizing maps¹ inferred 5 groups with distinct molecular landscapes (F, E, C, A and AB) that were generally consistent with molecular clusters previously described for CKD²
- Correlation of metagenes reveals a highly polarized global data structure resulting from strong opposing metabolic and immune signatures (Figure A)
- Molecular stratification aligns with clinical disease progression, but can not be fully explained by conventional parameters (Figure B)
- PHATE³ dimensionality reduction suggests molecular similarities and transitions that can be interpreted as molecular disease trajectories (Figure C)

Molecular stratification aligns with disease progression irrespective of clinical diagnosis, reflecting common cellular and molecular mechanisms of disease

1) Loeffler-Wirth H, Kalcher M, Binder H (2015). "oposSOM: R-package for high-dimensional portraying of genome-wide expression landscapes on Bioconductor." *Bioinformatics*.

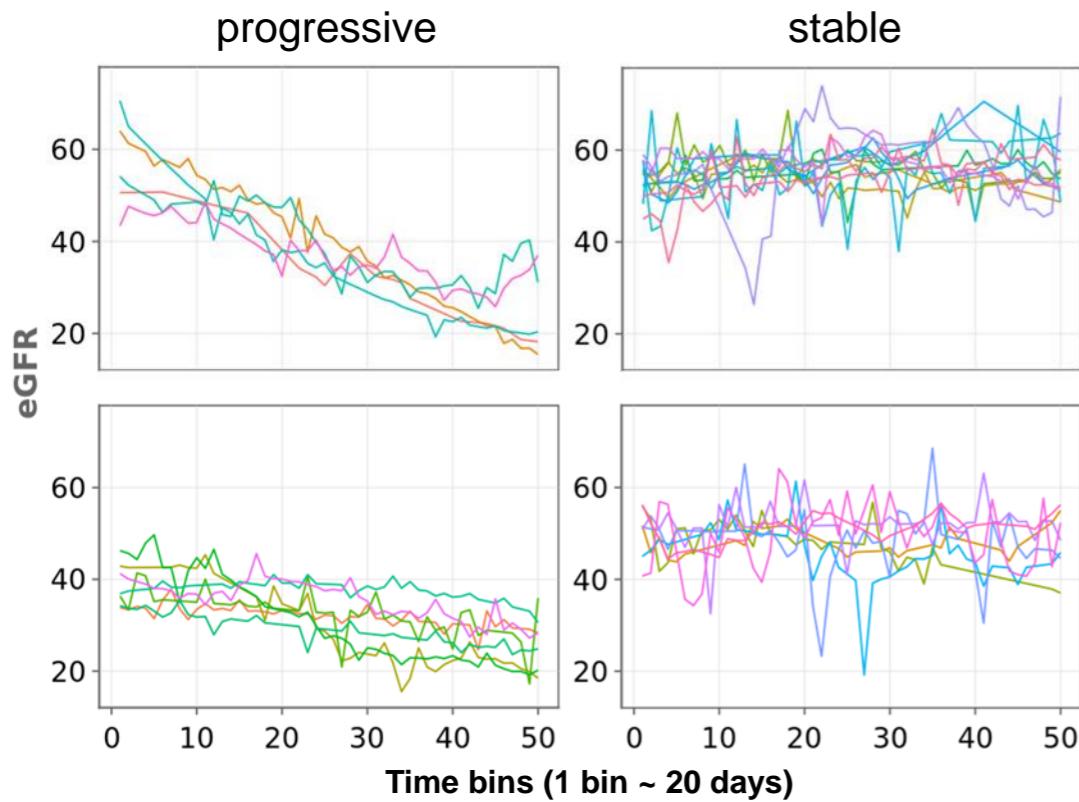
2) Reznichenko A, Nair V, Eddy S et al. (2021). "Molecular Stratification of Chronic Kidney Disease" *medRxiv*. doi.org/10.1101/2021.09.09.21263234

3) Moon K, van Dijk D, Wang Z et al. (2019). "Visualizing structure and transitions in high-dimensional biological data" *Nature Biotechnology*.

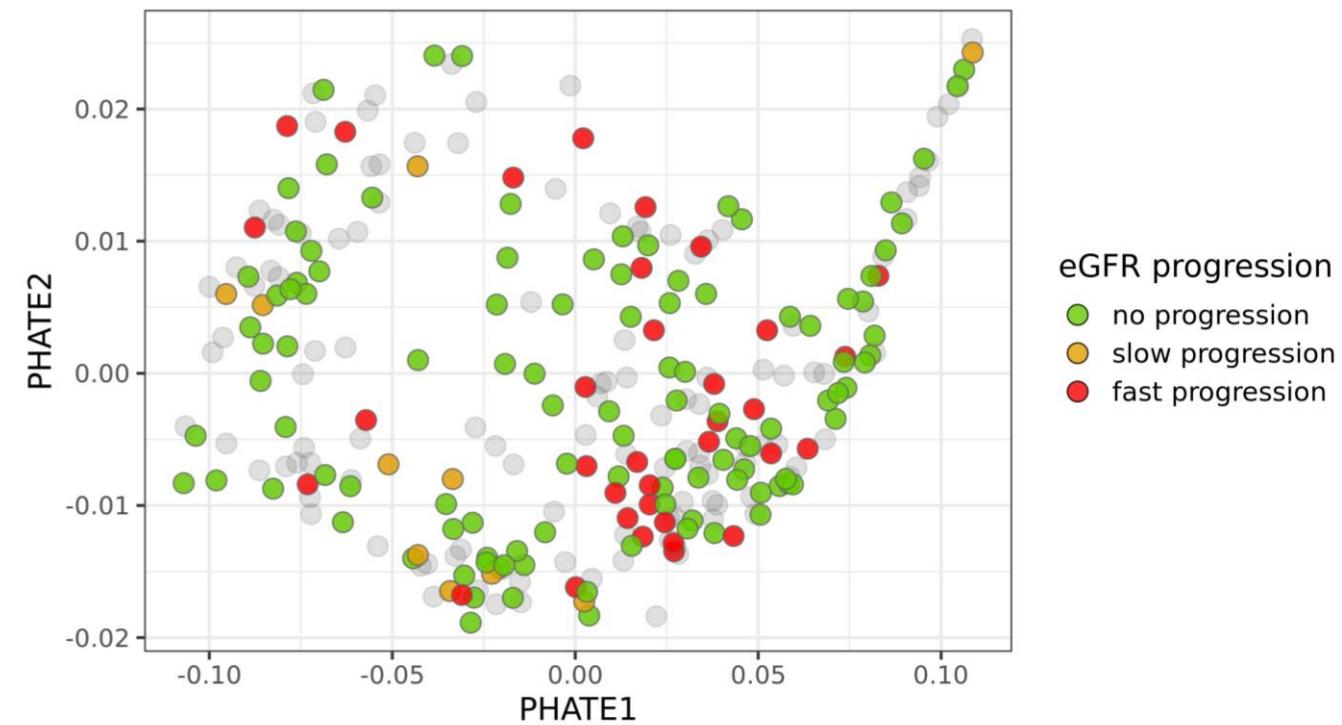
Disease progression rates are non-randomly distributed across molecular clusters and disease trajectories

Integration of eGFR time series

Patient stratification based on longitudinal eGFR decline (representative examples)



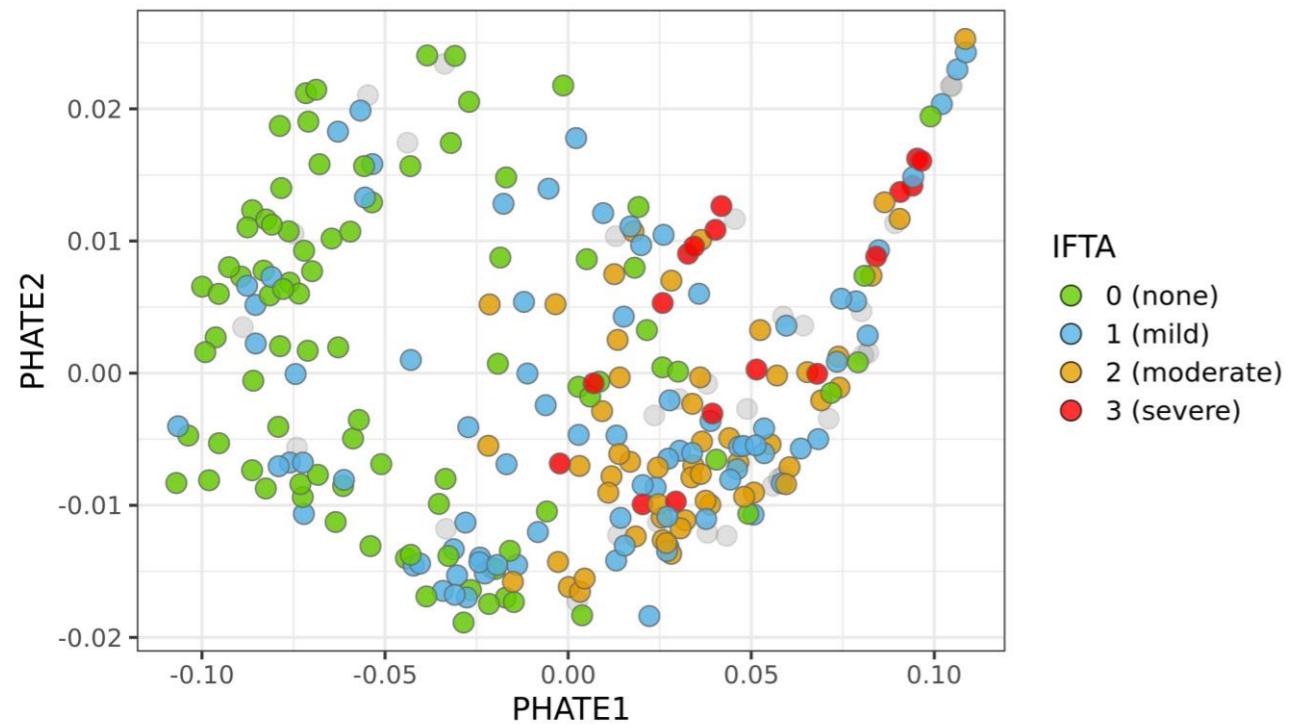
Molecular clusters C and A are enriched for patients with progressive disease



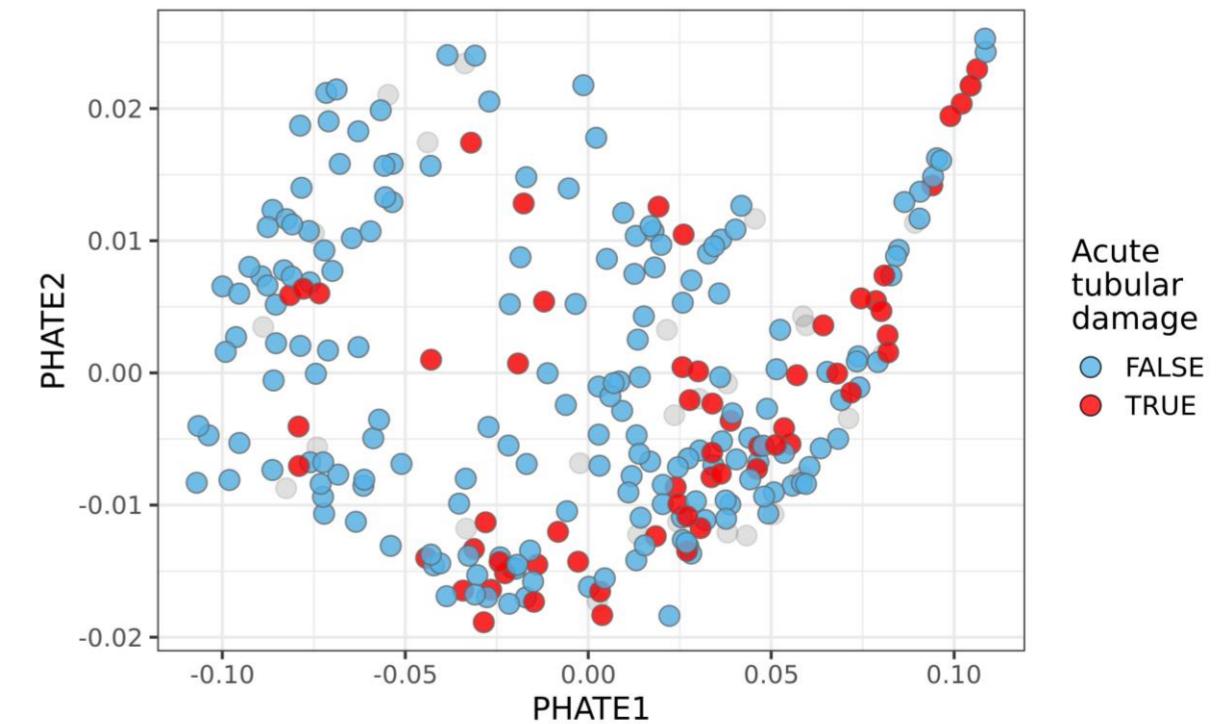
Morphological risk factors are non-randomly distributed across molecular clusters and disease trajectories

Integration of free-text histopathology records

Interstitial fibrosis and tubular atrophy (IFTA) gradually increases with molecular disease progression



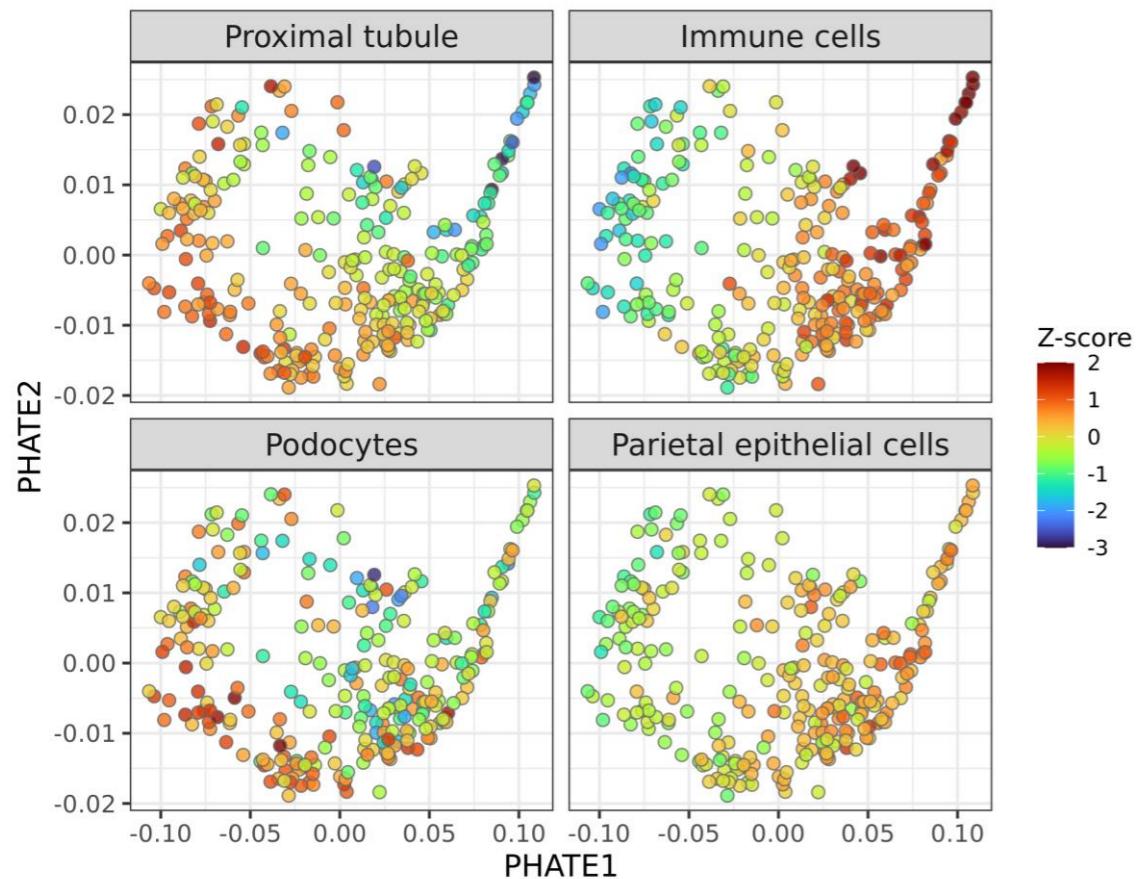
Acute tubular damage highlights clusters of patients with active disease



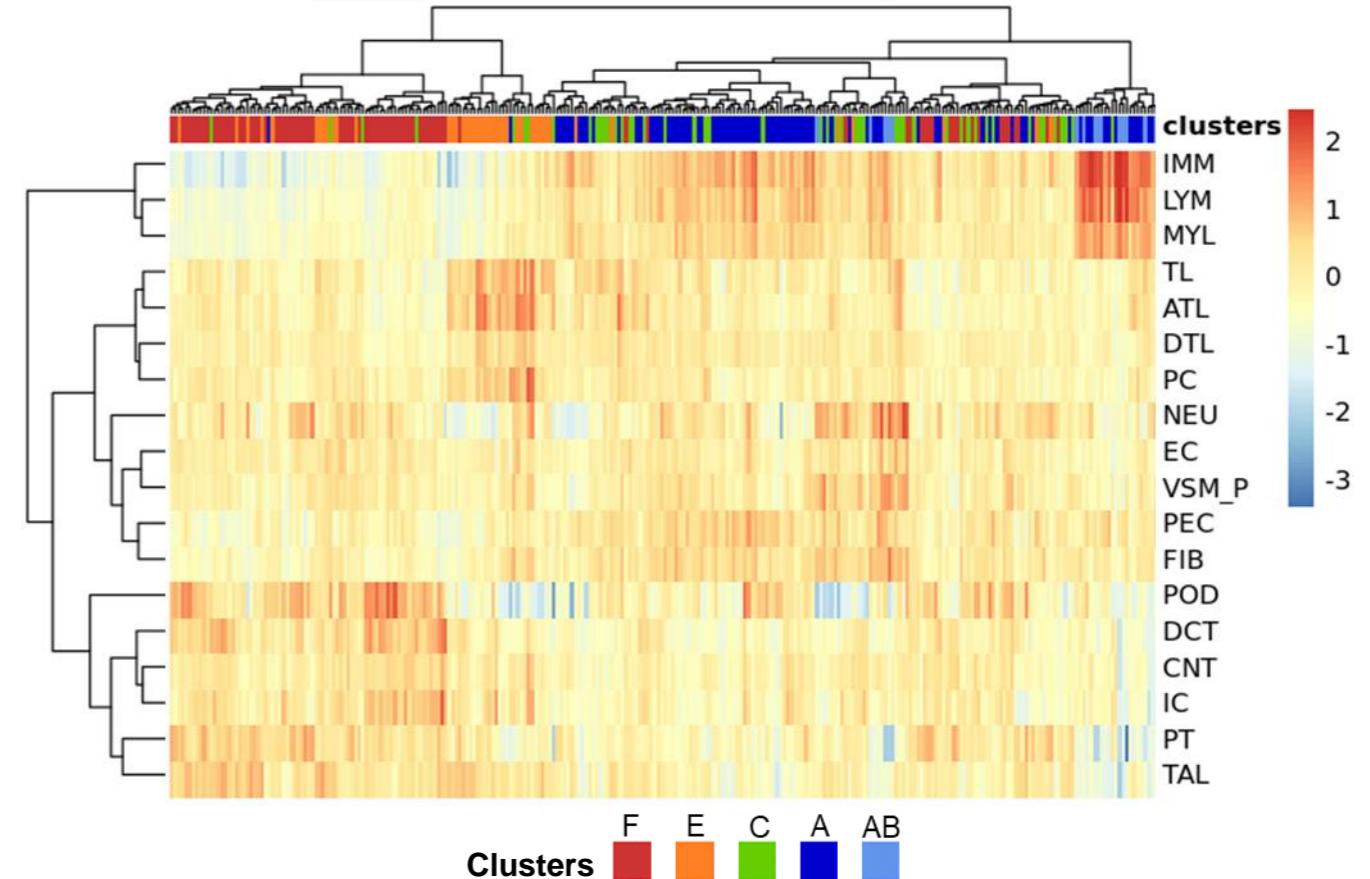
Molecular stratification captures tissue remodeling dynamics in CKD

Exploration of cell type signatures across molecular clusters and disease trajectories

Changes in signature expression indicate tissue remodeling dynamics



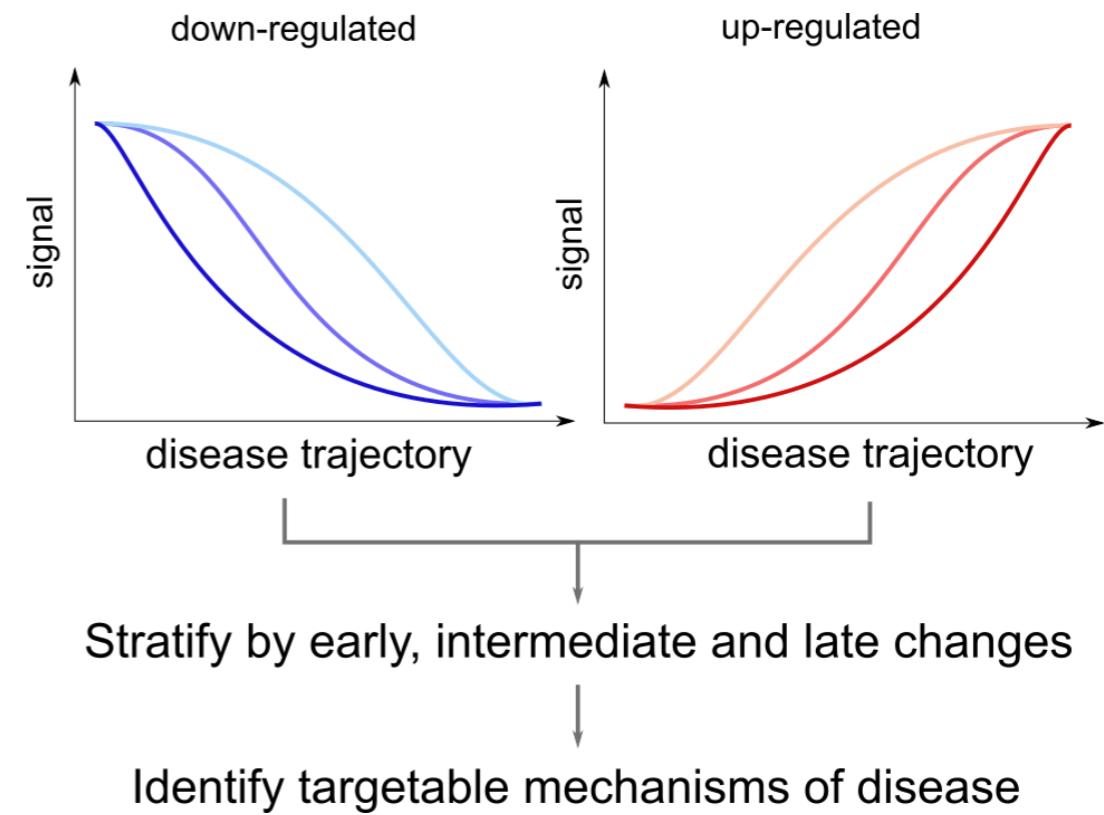
A cell-centric map of NURTuRE biopsy transcriptomes



Summary and Outlook

- Unsupervised characterization of NURTuRE kidney transcriptomes inferred 5 clusters with distinct molecular landscapes (F, E, C, A and AB)
- Molecular stratification aligned with clinical and histopathological parameters of disease progression
- Dimensionality reduction suggested transitions between molecular clusters that can be interpreted as pseudotime disease trajectories
- Careful characterization of gene expression and tissue remodeling dynamics along these trajectories will reveal cellular and molecular mechanism of CKD that unfold over years and decades

Gene expression and tissue remodeling dynamics along molecular disease trajectories



#RESEARCHNEVERSTOPS

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