

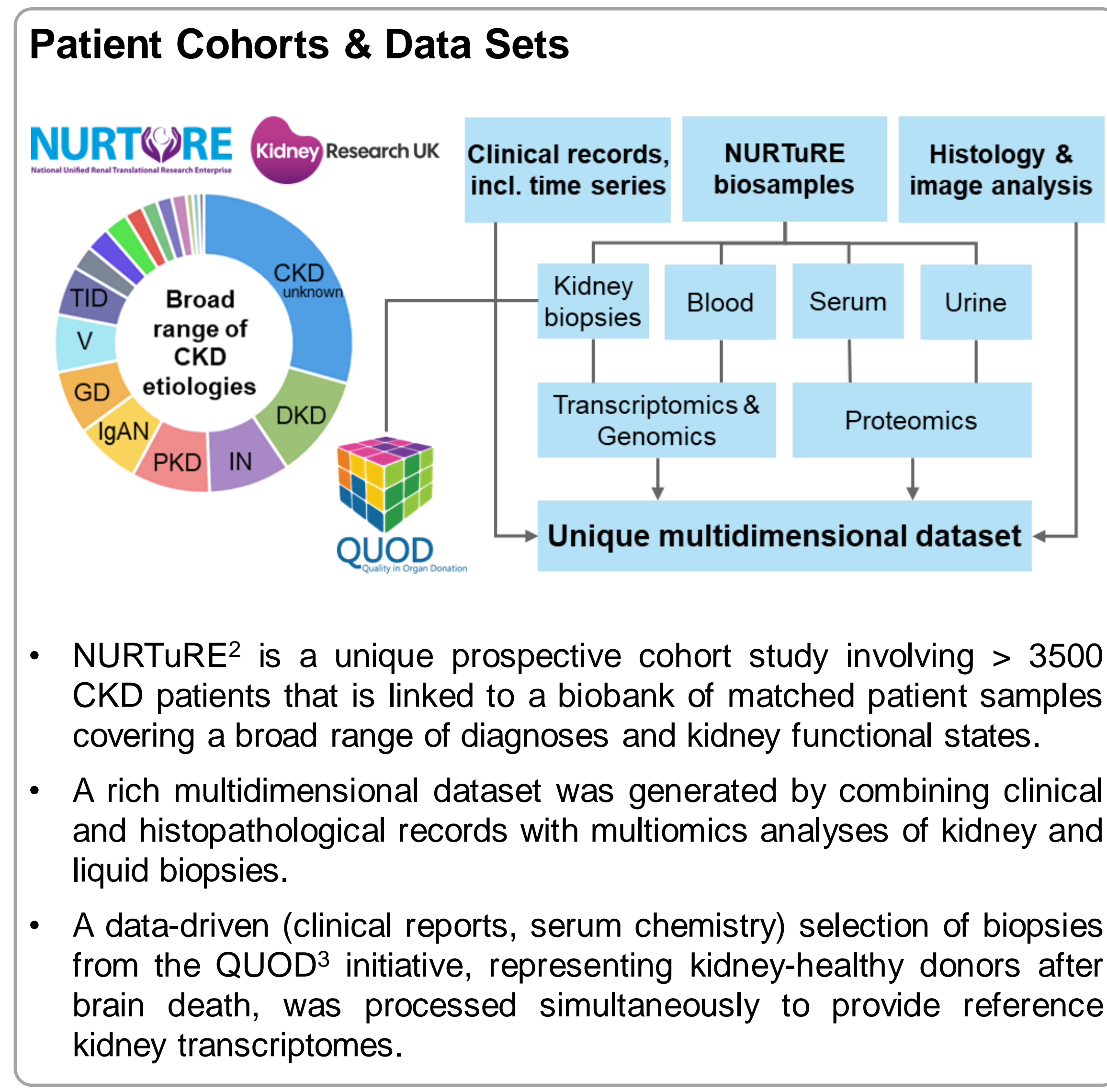
Unsupervised Characterization of the NURTuRE Cohort Reveals Gene Expression and Tissue Remodeling Dynamics along a Synthetic CKD Progression Axis

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Background

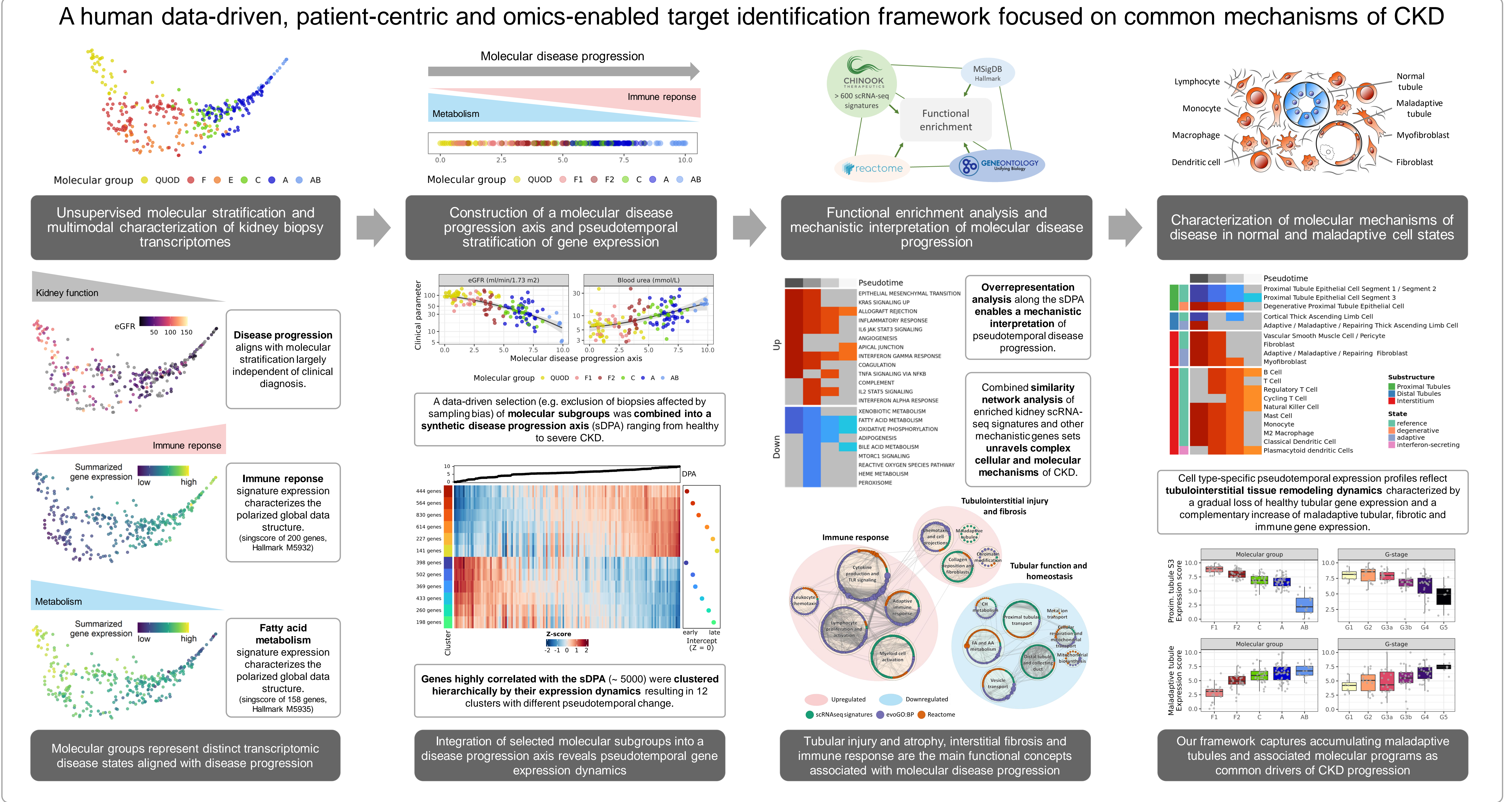
- Conventional stratification by clinical and histopathological phenotypes is insufficient to describe the heterogeneity of chronic kidney diseases (CKD). Recent advances in CKD classification¹ integrate real-world molecular, morphological and clinical data from large patient cohorts to improve mechanistic disease understanding.
- Here, we combined molecular groups identified by unsupervised characterization of the NURTuRE² and QUOD³ patient cohorts into a synthetic disease progression axis (sDPA) ranging from healthy to severe CKD, with the aim to explore gene expression and tissue remodeling dynamics along this pseudotime trajectory.

We will use this framework for a human data-driven, patient-centric and omics-enabled target identification focused on common cellular and molecular mechanisms of disease



Methods

- Unsupervised classification of NURTuRE kidney transcriptomes via self-organizing maps⁴ and characterization via PHATE⁵ dimensionality reduction inferred 5 groups with distinct molecular profiles that aligned with clinical and histopathological disease progression.
- A data-driven selection of QUOD (healthy, n = 36) and NURTuRE (CKD, n = 139) kidney biopsy transcriptomes (FFPE, RNA-seq) representative of molecular groups was combined into a synthetic disease progression axis (sDPA) via PHATE⁵ embedding.
- Groups of genes with similar expression dynamics were derived via local regression and hierarchical clustering enabling a pseudotemporal interpretation of gene expression dynamics along the sDPA.
- Gene set overrepresentation analysis based on > 600 manually curated kidney-focused scRNA-seq signatures and additional public sources (evoGO⁶, Reactome, Hallmark) was employed to support a mechanistic interpretation of molecular disease progression.



Conclusions and Outlook

- Unsupervised cohort characterization and multimodal data exploration enabled the careful selection and integration of disease-relevant biopsy transcriptomes into a molecular CKD progression axis. Pseudotemporal stratification of gene expression along this axis revealed groups of genes with shared expression dynamics corresponding to CKD tissue remodeling.
- Our framework captures major concepts of CKD progression, including but not limited to tubular injury and atrophy, interstitial fibrosis, inflammation and immune infiltration as reflected by the enrichment of curated scRNA-seq-derived cell type-specific signatures and other mechanistic gene sets.
- Importantly, our human data-driven and omics-enabled analysis provides translational evidence for an early accumulation of profibrotic and proinflammatory maladaptive cell tubular states reflecting failed repair as common drivers of CKD progression in this large patient cohort.

Chinook Therapeutics and Evotec joined forces for a patient-centric target identification supported by strong translational evidence to initiate drug discovery programs with a focus on tubular failed repair and cross-talk in the tubulointerstitial niche

References and Acknowledgement

- Bohnenpoll et al. A Systems Nephrology Framework for the Molecular Classification of Chronic Kidney Disease. *Nephrology Dialysis Transplantation*. 2022; 37:gfac114.004. **Follow QR codes for additional information.**
- NURTuRE - The National Unified Renal Translational Research Enterprise; <https://www.nurturebiobank.org>
- QUOD - The Quality in Organ Donation Initiative; <https://quod.org.uk/>
- Löffler-Wirth et al. oposSOM: R-package for high-dimensional portrayal of genome-wide expression landscapes on bioconductor. *Bioinformatics*. 2015;31(19):3225-3227.
- Moon et al. Visualizing structure and transitions in high-dimensional biological data. *Nat Biotechnol*. 2019;37(12):1482-1492.
- evoGO - An Evotec R package providing advanced functionality for performing a Gene Ontology (GO) enrichment analysis. <https://github.com/Evotec-Bioinformatics/evoGO>

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