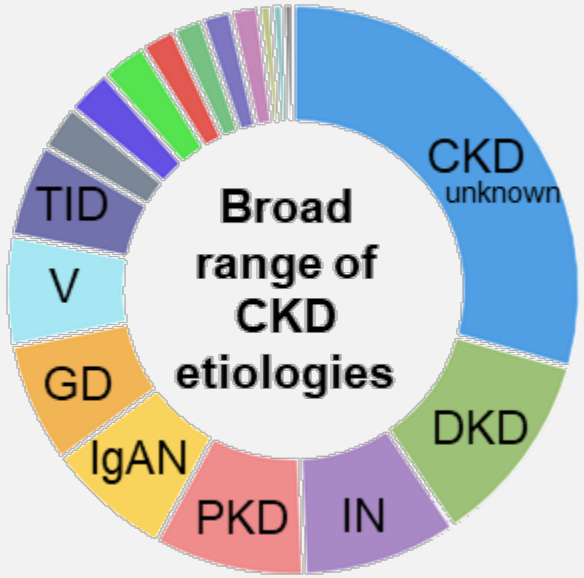
A Multi-Omics Approach to IgA Nephropathy Characterization in the NURTuRE Cohort Enables Precision-Based Treatment Approaches

N. Eric Olson, Jennifer Cox, I-Ju Lo, Seamus Ragan, Niklas Michel, Johannes Pospiech, Michaela Bayerlova, Simone Romoli, Taher Sathaliya, Tobias Bohnenpoll, Nikolas Stroth, Olivier Radresa, Andrew King, and Uwe Andag

FR-OR60, Glomerular Diseases: From Bench to Bedside [OR1300-1]

ASN Kidney Week, November 4, 2022

The NURTuRE Consortium Dataset



The NURTuRE biobank comprises matched patient samples from a broad range of diagnoses and kidney functional states that are associated with rich clinical data from over **3,500** subjects

Integration of intra-renal molecular and morphological features with clinical outcomes is required to drive discovery of disease-modifying therapies

https://www.nurturebiobank.org

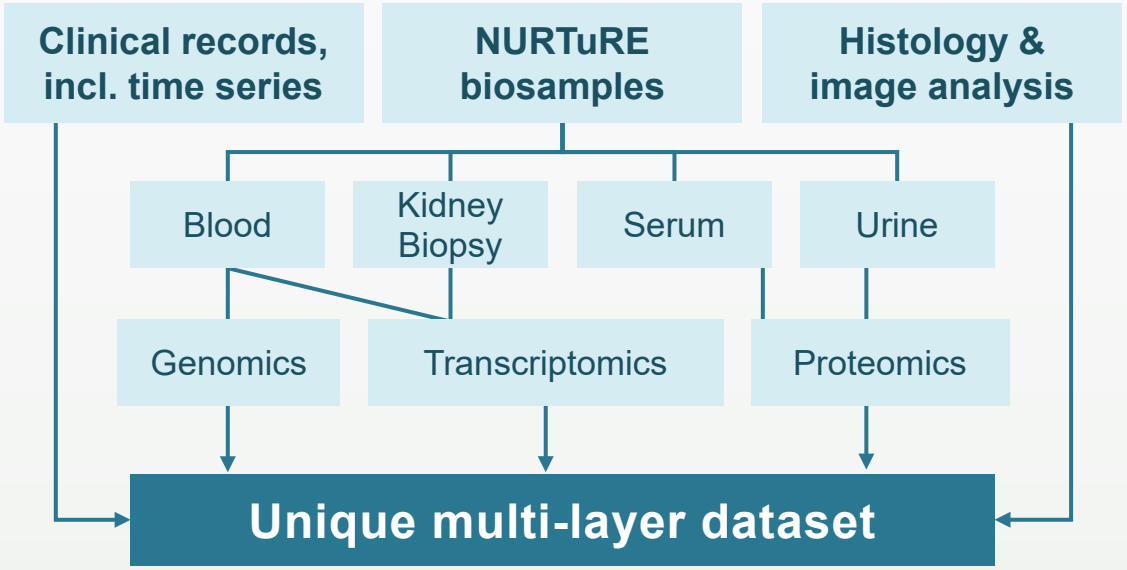
Figure (upper left) adapted from Kidney Precision Medicine Project, accessed 4 May 2022, https://www.kpmp.org/about-kpmp

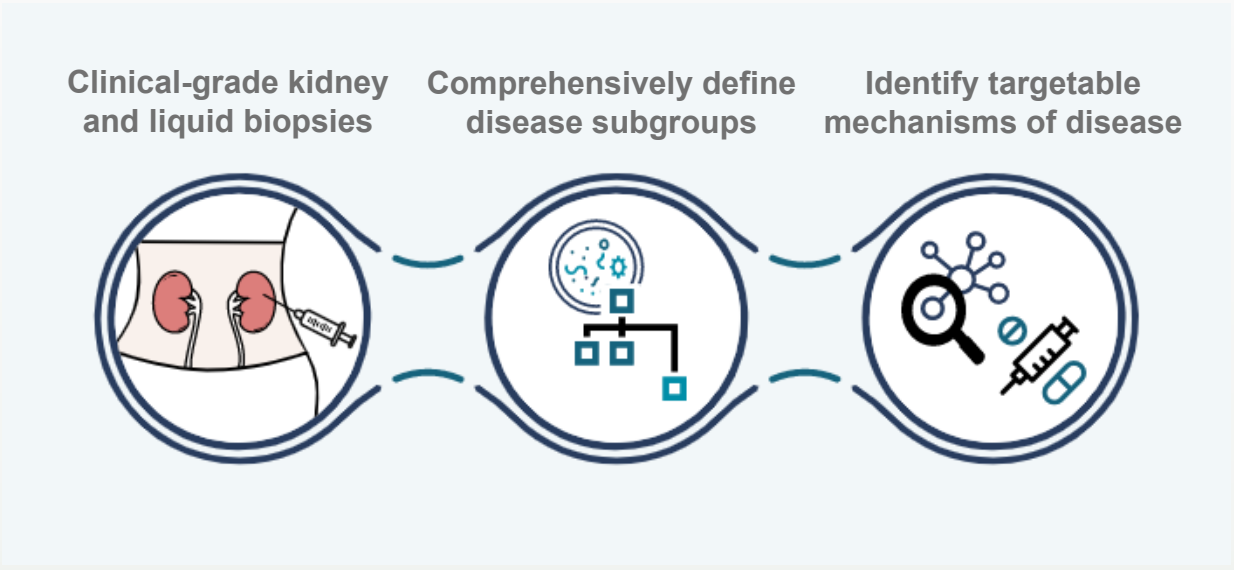
Integration of Real-World Clinical, Morphological and Molecular Data

KIDNEY WEEK 2022
Nov. 3–6 | Orlando, FL

Project Aims:

- The aim of this project is to use a multi-omics approach to the characterization of IgAN in the NURTuRE cohort, integrating clinical, histological, transcriptomic and serum proteomic data to gain deeper insights into patient stratification and disease biology.
- These learnings will be applied to clinical studies evaluating atrasentan, an endothelin receptor A antagonist, and BION-1301, an anti-APRIL antibody, for the treatment of IgAN.





https://www.nurturebiobank.org
Figure (lower left) adapted from Kidney Precision Medicine Project, accessed 4 May 2022, https://www.kpmp.org/about-kpmp

evotec
CHINOOK THERAPEUTICS

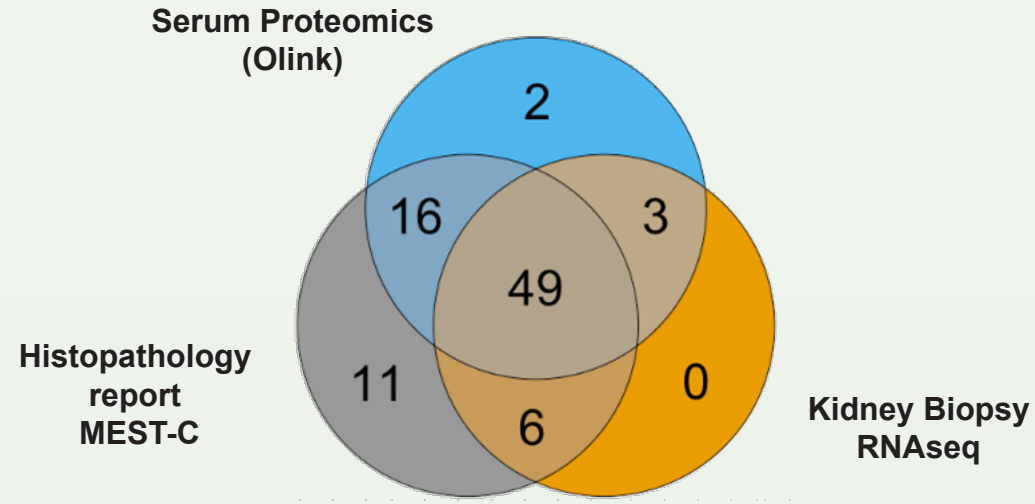
NURTuRE IgAN Cohort Characterization and Data Availability

KIDNEY WEEK 2022
Nov. 3-6 | Orlando, FL

Multi-dimensional characterization of patient samples enables a deeper understanding of disease mechanisms and outcomes

Data Sources

Data type	Source	n	%
Clinical data	UK Renal Registry	205	
SNP array	Blood	199	
Whole Exome Sequencing	Blood	197	
RNA-Seq	Blood	179	
Histopathology report (MEST-C)	Biopsy	82	
RNA-Seq	Biopsy	58	
Olink Proteomics	Serum	70	
Immunoglobulin isotypes (Gd-IgA1, IgA, IgG, IgM)	Serum	69	

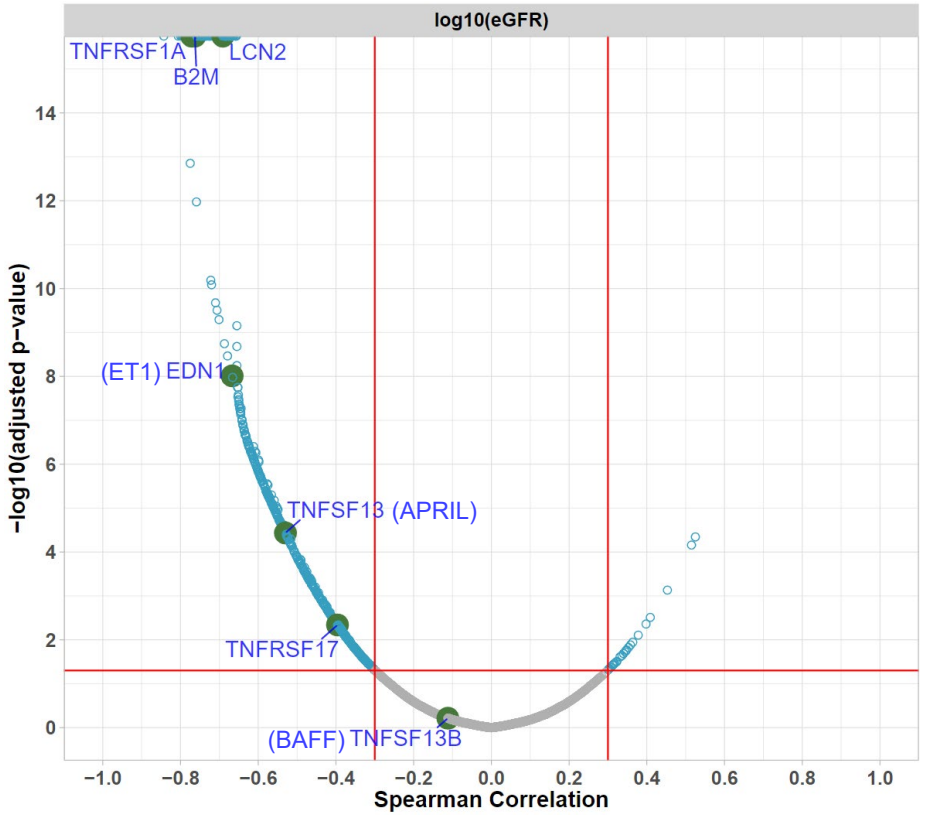


- There is substantial overlap for many of the data types available for the NURTuRE IgAN cohort
- A set of 70 subjects with targeted serum proteomics and a set of 49 subjects having kidney RNA-seq gene expression data, MEST-C scores and targeted serum proteomics (Olink) was used for these analyses

Serum Proteins Show Strong Relationship with Kidney Function

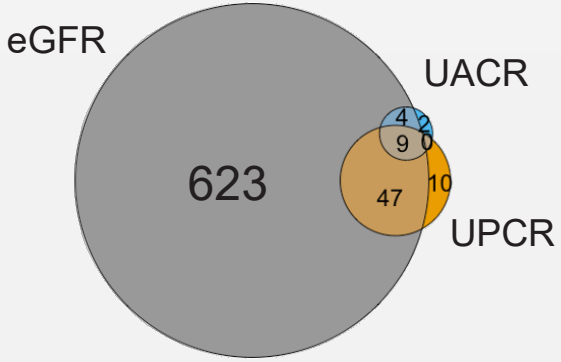
KIDNEY WEEK 2022
Nov. 3-6 | Orlando, FL

OLink serum proteomics correlation with kidney function metrics

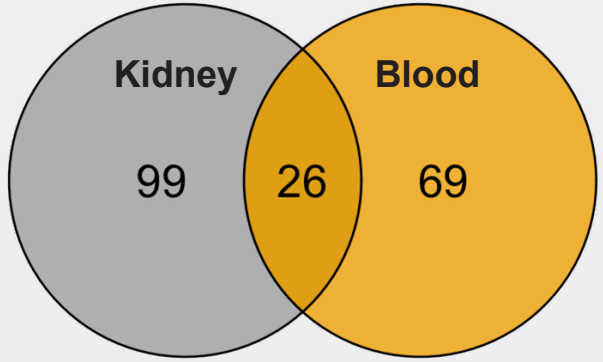


Highlight Select Targets with Significant Correlation
Significance Threshold: | Correlation | >=0.3; -log10(adjusted p-value) >=1.3

Overlap of serum proteins significantly correlated with kidney function metrics



25% of the 683 eGFR associated serum proteins are correlated with kidney or blood RNAseq



- eGFR, UACR, and UPCR were tested for relationship with 2,666 serum proteins (Olink) from 71 NURTuRE IgAN patients
- eGFR showed the strongest relationship, with 683 proteins significantly correlated
  - APRIL (TNFSF13) is strongly (r = -0.585, p = 2E-7) correlated with eGFR and is correlated with UPCR (r =0.336 , p = 0.02)
  - BAFF (TNFSF13B) is not significantly correlated with eGFR, UACR or UPCR
- Of 683 proteins correlated with eGFR, 125 and 95 are correlated with RNA from kidney and blood RNAseq, respectively
  - The kidney RNAs tended to be expressed in tubules

evotec
CHINOOK THERAPEUTICS

Histopathology MEST-C Features Differ in Relationship to eGFR and Proteinuria

KIDNEY WEEK 2022 Nov. 3–6 | Orlando, FL

Kidney function by MEST-C score

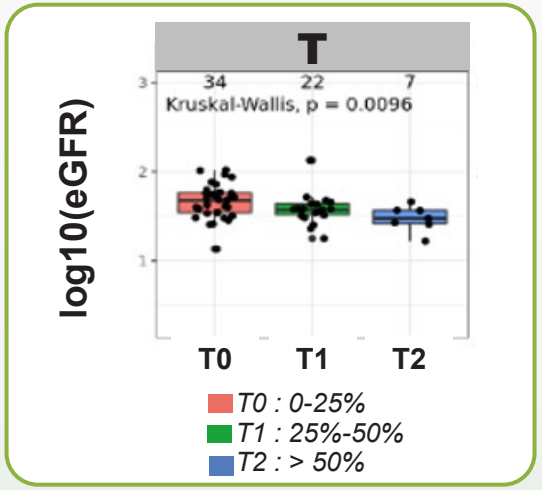
	Feature	log10(UACR) p-value	log10(UPCR) p-value	log10(eGFR) p-value
M	**M**esangial cellularity	**0.0006**	**0.0187**	*0.6182*
E	**E**ndocapillary proliferation	**0.0239**	**0.0221**	*0.6430*
S	**S**egmental glomerulosclerosis	*0.0820*	*0.0841*	*0.6828*
T	**T**ubular atrophy/interstitial fibrosis	*0.1606*	*0.3698*	**0.0096**
C	**C**rescents	**0.0017**	**0.0110**	*0.4962*

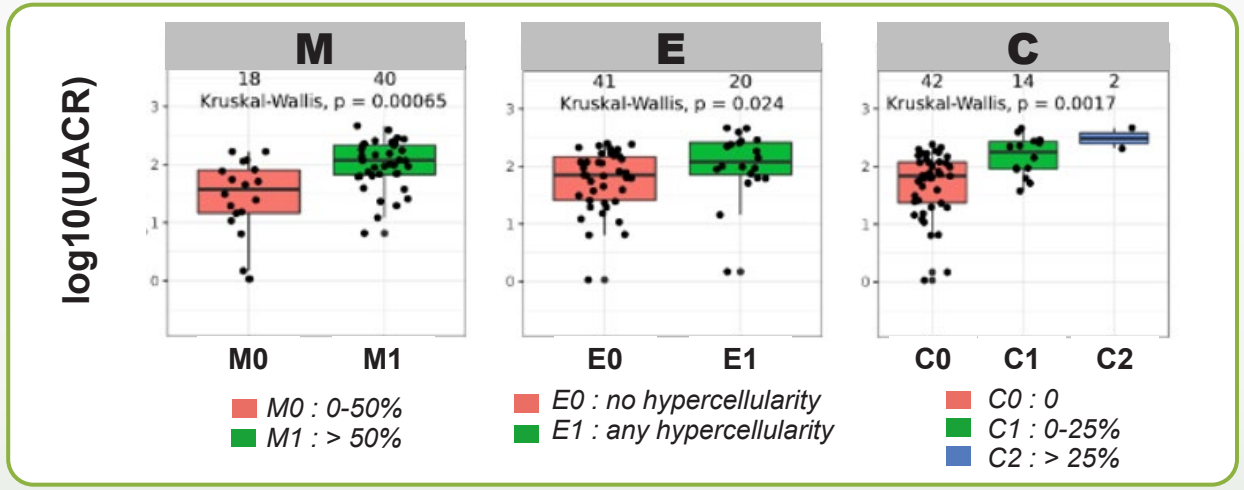
Kidney function (eGFR) is associated with the **T** component of the **MEST-C** score

Proteinuria (UACR, UPCR) is associated with the **M**, **E** and **C** components of the **MEST-C** score

eGFR is associated with tubular atrophy/interstitial fibrosis (**T**)

Proteinuria is associated with mesangial cellularity (**M**), endocapillary proliferation (**E**) and crescents (**C**)



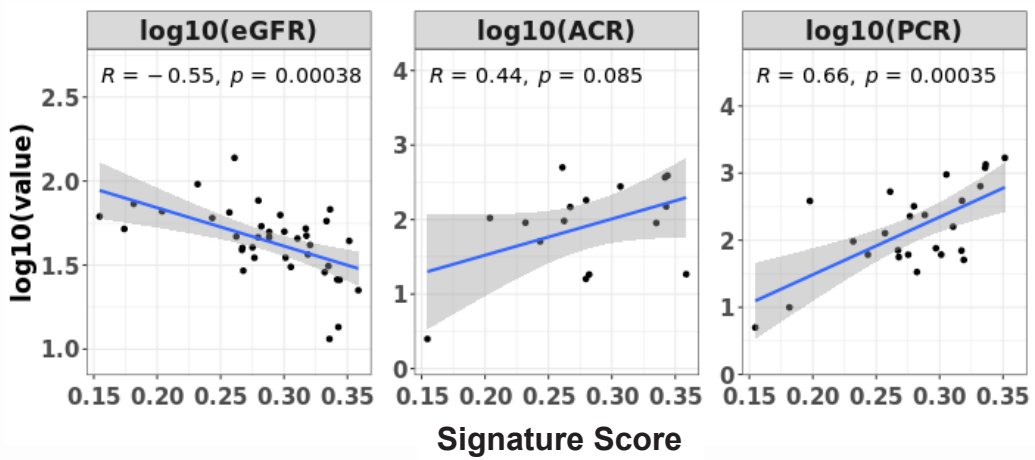


evotec CHINOOK THERAPEUTICS

A Preclinical Model Derived Atrasentan Response Signature* is Correlated with Kidney Function

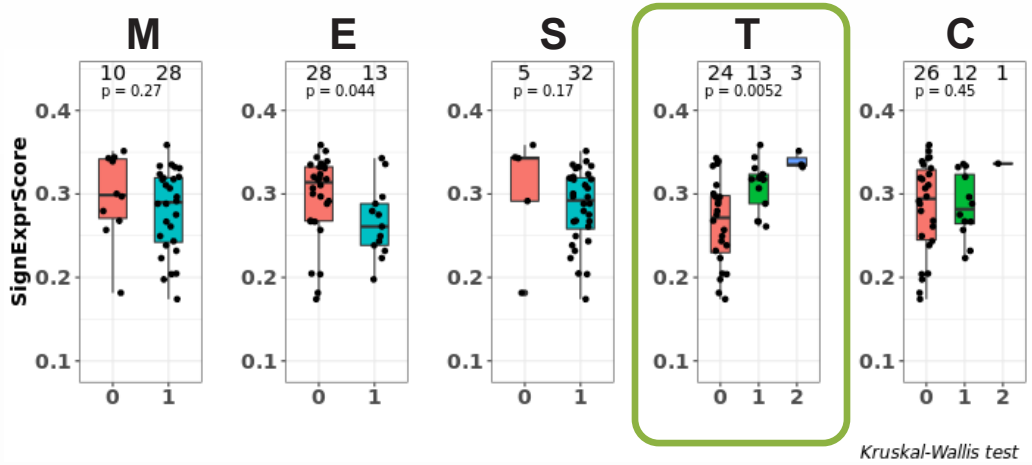
KIDNEY WEEK 2022
Nov. 3–6 | Orlando, FL

The atrasentan signature score from kidney biopsies is correlated with kidney function in the IgAN cohort



A 31-gene atrasentan response signature score was calculated using the gene expression data from kidney biopsies for the IgAN cohort. This score was correlated (spearman correlation test) with log10 eGFR, UACR and UPCR.

Increased atrasentan signature score is associated with tubular atrophy and interstitial fibrosis



A 31 gene atrasentan response signature derived from Failed Repair proximal tubule cells in the gddY IgAN model is significantly correlated with eGFR and UPCR in the IgAN cohort

The signature score is significantly higher in samples from subjects with an elevated T score

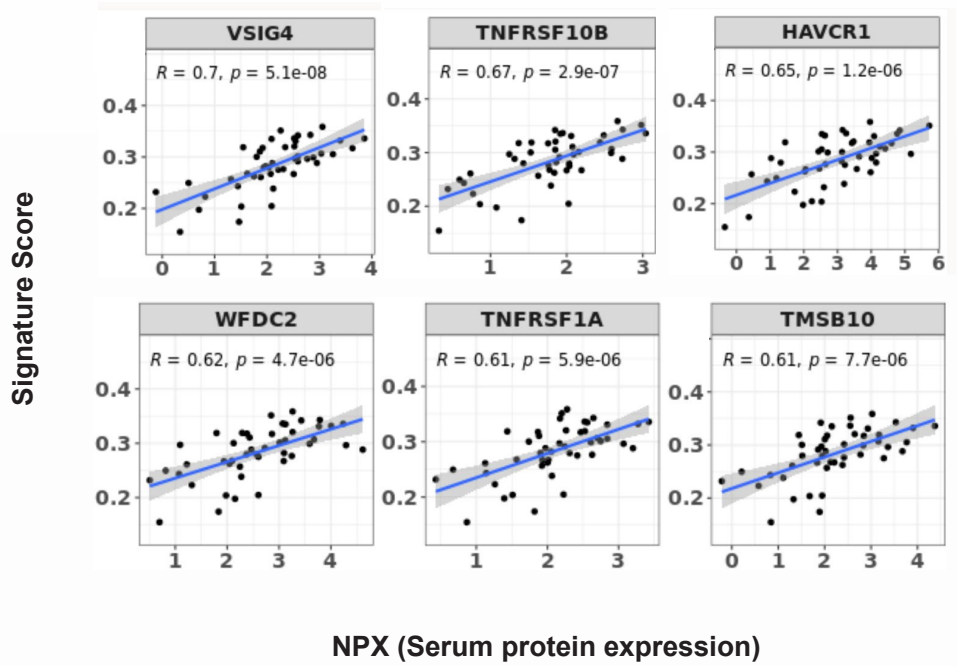
** See poster TH-PO419 for details*

evotec CHINOOK THERAPEUTICS

The Kidney Atrasentan Response Score is Correlated with Serum Proteins

KIDNEY WEEK 2022
Nov. 3-6 | Orlando, FL

45 serum protein are strongly correlated (r >= 0.60) with the kidney atrasentan signature score



- 700 serum Olink proteins are correlated with the kidney atrasentan response signature score – 45 proteins are strongly correlated (r >= 0.60)
- Urine proteomic analysis is being performed on matched urine samples and will be used to identify urine proteins that are correlated with the atrasentan response score
- Serum or urine proteins may provide non-invasive surrogate biomarkers for assessing the atrasentan response signature in patients

evotec
CHINOOK THERAPEUTICS

Summary and Future Plans

KIDNEY WEEK 2022
Nov. 3–6 | Orlando, FL

Key observations

- Over 600 serum proteins that were inversely correlated with eGFR were identified
- Kidney function (eGFR) is associated with the **T** component of the **MEST-C** score while proteinuria (UACR, UPCR) is associated with the **M**, **E** and **C** components
- A failed repair proximal tubule atrasentan response signature derived from atrasentan treated gddY mice is correlated with kidney function in the IgAN cohort
- 45 serum proteins showed a strong correlation with the kidney atrasentan response score

Future steps

- Urine proteomics will be performed on matched urine samples from the NURTuRE IgAN cohort and used to identify urine biomarker for atrasentan signature score
- Non-invasive surrogate biomarkers for the atrasentan response signature will be measured in atrasentan trials

Goals

- **To validate non-invasive surrogate biomarker strategy that can be used in clinical trials for atrasentan in IgAN and other indications**
- **Assess the association of APRIL levels with baseline IgAN patient characteristics and kidney transcriptomics in support of patient stratification for BION-1301**

evotec CHINOOK THERAPEUTICS

Thank You!

KIDNEY WEEK 2022
Nov. 3–6 | Orlando, FL

To all members of the Chinook-Evotec Strategic Partnership…

CHINOOK™ THERAPEUTICS

evotec

… and all contributors of the NURTuRE Consortium!

biocentre The centre for biomedical services
HUG Hôpitaux Universitaires Genève
Kidney Research UK
RR
University of Birmingham
University of Bristol
University of Nottingham UK | CHINA | MALAYSIA

NURTURE
National Unified Renal Translational Research Enterprise

ucb Inspired by patients Driven by science.
Kidney Research UK
AstraZeneca Health Connects Us All
evotec
abbvie
TRAVERE THERAPEUTICS

Elaine Davies,
Director at Kidney Research UK

Prof. Moin Saleem
University of Bristol

Prof. Maarten Taal
University of Nottingham