

# Disclosures

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# Integrated multi-omics in animal and observational human datasets provides insights into potential molecular mechanisms and biomarkers for atrasentan

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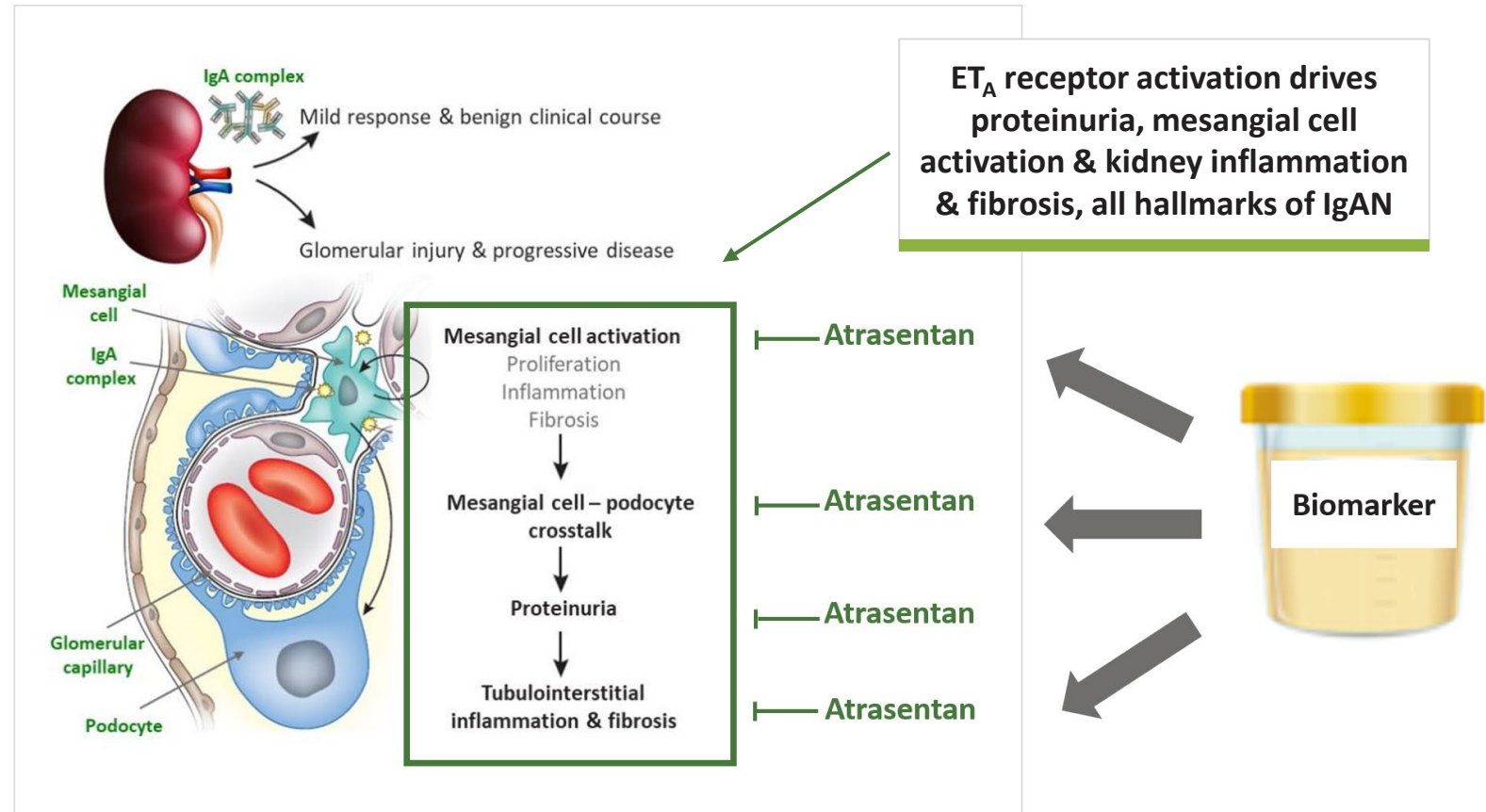
# Identifying, characterizing and validating an atrasentan response signature in animal models

*Insights into atrasentan's mechanism of action*

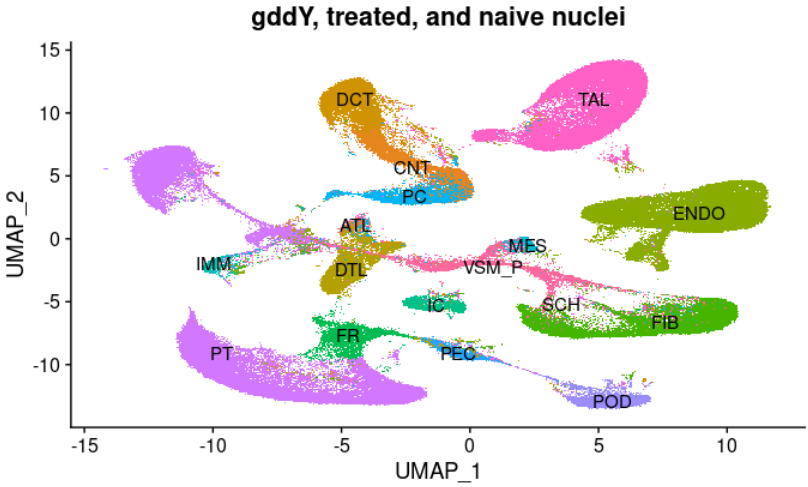
## Atrasentan Blocks Central Drivers of IgAN Pathogenesis

**Approach:** Apply translational cellular & in vivo models to investigate potential impact of atrasentan on key mechanisms of IgAN pathogenesis

**Goal:** identify gene signature and non-invasive biomarkers to differentiate MOAs in IgAN

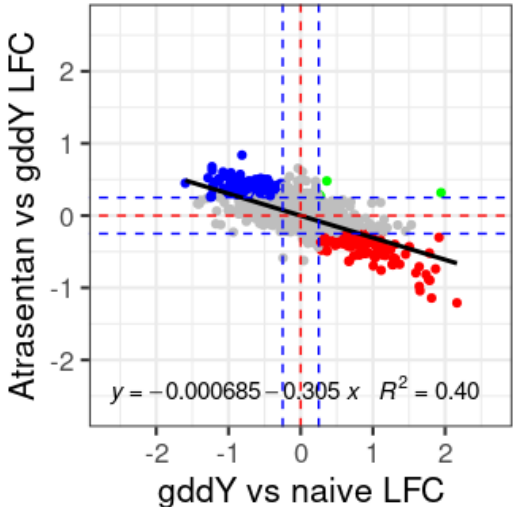


# An atrasentan response signature derived from preclinical models



~150,00 nuclei were isolated and sequenced from naïve, gddY and gddY + atrasentan mice

- A cluster of cells corresponding to failed repair proximal tubules (FR-PTEC) was highly expanded in the gddY mice compared to naïve mice
- FR-PTEC showed the largest response to atrasentan as measured by number of differentially expressed genes.
- A 31 gene signature (Atra\_31) was derived from the genes that were increased in gddY and decreased by atrasentan in the FR-PTEC cells.
- The signature score was also found to be decreased by atrasentan in the anti-Thy1.1 model of Mesangio-proliferative Glomerulonephritis



### FR PTEC are a source of chemokines and cytokines for immune cells and fibroblasts

FR PTEC to FIB

FR PTEC to IMM

Putative relationships for key FR PTEC ligands and corresponding receptors on potential target cell types

- Pro-inflammatory and profibrotic effects on fibroblasts may be mediated through Tnf and Tgfb2 signaling from FR PTEC.
- FR PTEC may play a key role in recruitment of immune cells through their expression of Ccl2.

# NURTuRE disease cohort characterization and data availability

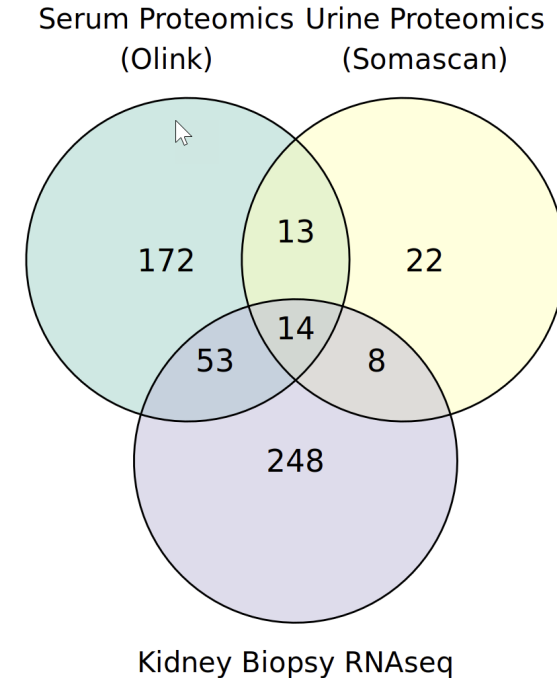
## Project Aims:



Conduct an analysis of patient-matched kidney biopsies and biofluids from the NURTuRE cohort with the aim to identify non-invasive biomarkers associated with the atrasentan response signature score

### NURTuRE Disease Cohort Data Availability

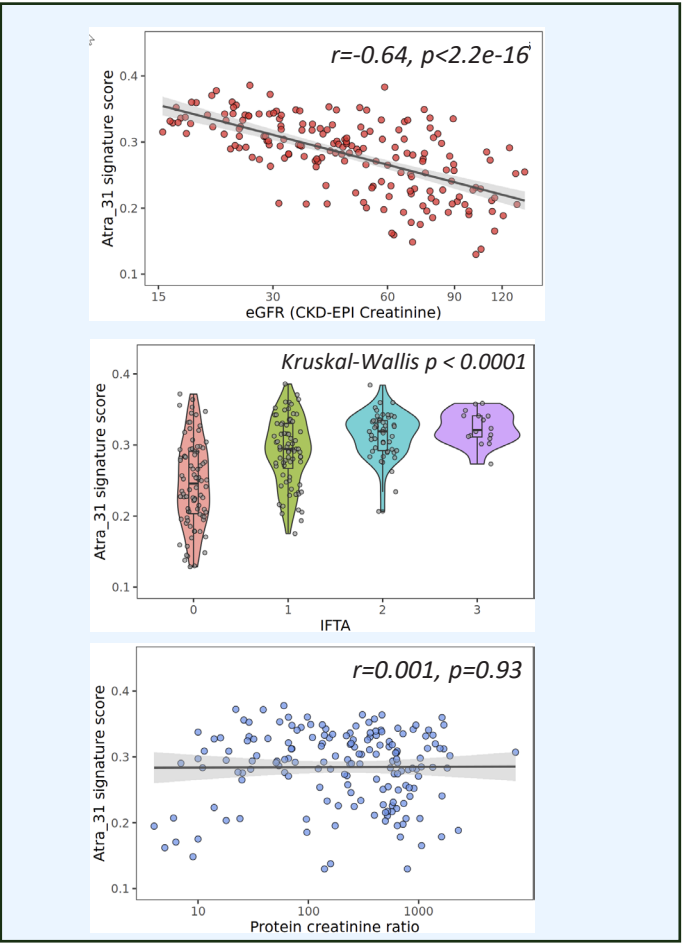
Data type	Source	n	%
Clinical data	UK Renal Registry	3518	<div style="width: 100%; height: 10px; background-color: #0056b3;"></div>
SNP array	Blood	3468	<div style="width: 100%; height: 10px; background-color: #0056b3;"></div>
Whole Exome Sequencing	Blood	3122	<div style="width: 95%; height: 10px; background-color: #0056b3;"></div>
RNA-Seq	Blood	4111	<div style="width: 100%; height: 10px; background-color: #0056b3;"></div>
RNA-Seq	Biopsy	332	<div style="width: 10%; height: 10px; background-color: #0056b3;"></div>
Olink Proteomics	Serum	252	<div style="width: 5%; height: 10px; background-color: #0056b3;"></div>
Somascan Proteomics	Urine	57	<div style="width: 1%; height: 10px; background-color: #0056b3;"></div>



- There is substantial overlap for many of the data types available for the NURTuRE disease cohort
- 67 subjects with serum proteomics and biopsy rna-seq and 22 subjects with both urine proteomics and biopsy RNAseq were used for analysis

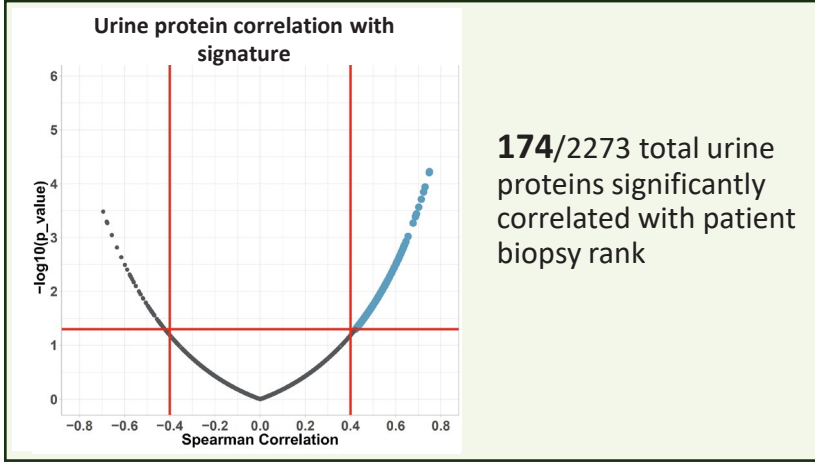
# Biomarker discovery strategy in the NURTuRE cohort

**1** Signature score is correlated with eGFR and IFTA

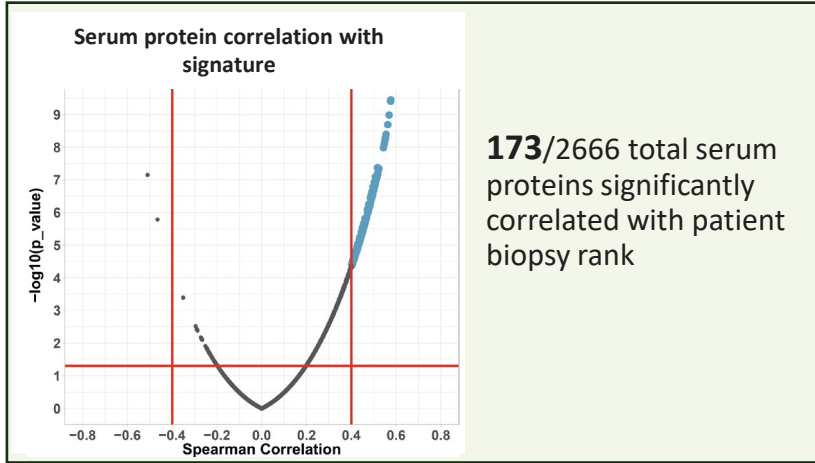


Urine (Somascan)

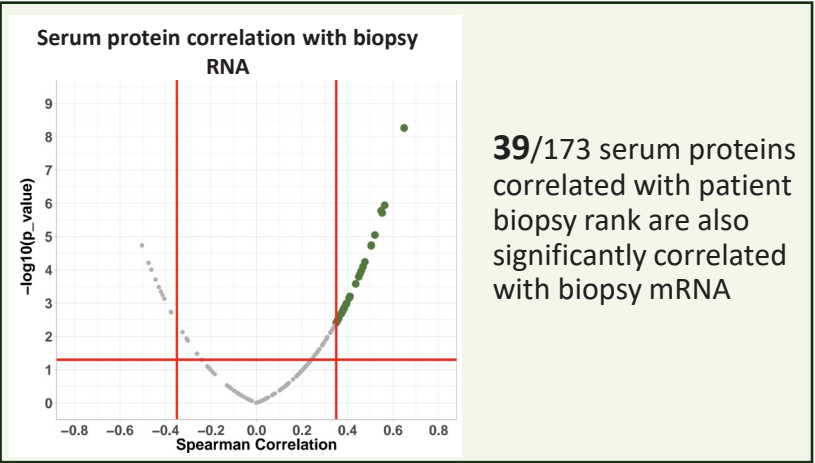
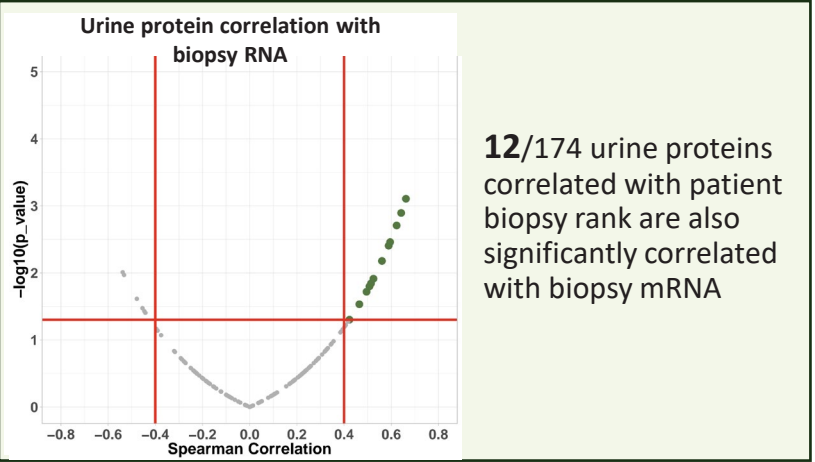
**2** Correlation of biofluid proteins with patient biopsy score



Serum (Olink)

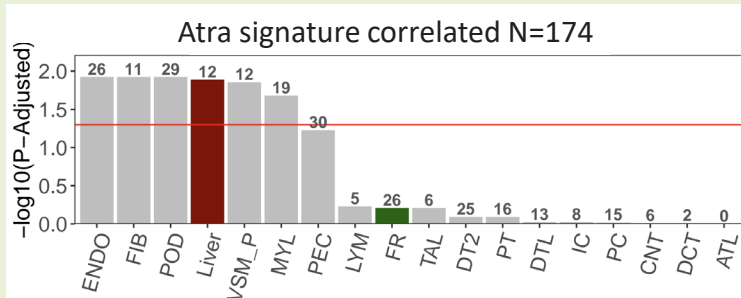


**3** Correlation of biofluid proteins with patient biopsy mRNA expression

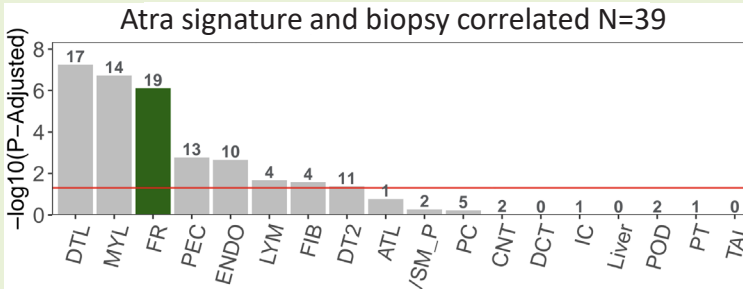
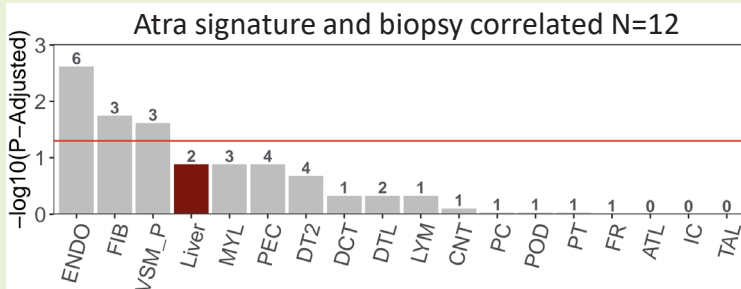
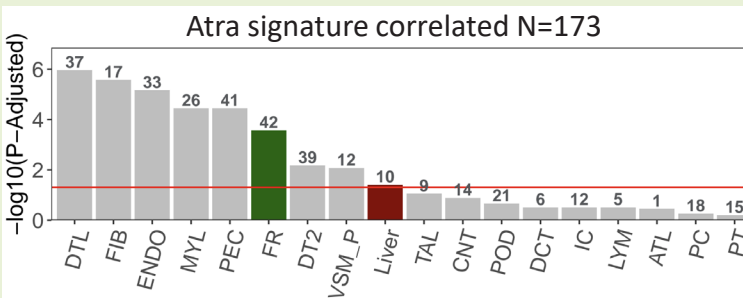


# Serum proteins are enriched for proteins expressed by failed repair tubules

A) Urine Proteins – enrichment for kidney cell type markers



B) Serum Proteins – enrichment for kidney cell type markers



## Cell type Enrichment Analysis

Cell type genesets for 17 cell types derived from scRNA-seq data (GSE171314)

Significant genes for each cell type from FindAllMarkers (padj < 0.05)

Liver specific gene set derived from Human Protein Atlas RNA data (enriched in only liver)

- Serum showed an enrichment for FR proteins compared to urine
- Including biopsy correlation reduced enrichment for liver associated proteins
- FR expressed protein identified in urine
  - 26 correlated with biopsy score
  - 1 also correlated with biopsy gene expression
- FR expressed proteins identified in serum
  - 42 correlated with biopsy score
  - 19 also correlated with biopsy gene expression

# Summary and future plans

## Key observations

- A gene signature associated with atrasentan response in failed repair cells was identified in the gddY mouse model of IgAN
- Proteins associated with the gene signature score in patient biopsies were identified in urine and serum samples
- A subset of proteins that were also correlated with gene expression in the biopsies were identified and were enriched for proteins associated with the tubules
- Serum proteins had a stronger enrichment for tubular proteins than urine

## Future steps

- Assess relationship between candidate proteins and signature score in a larger set of subjects for the NURTuRE cohort
- Assess effects of atrasentan treatment on proteins levels in urine and serum in subjects from the AFFINITY trial
  - Are signature-associated proteins reduced by atrasentan treatment?

## Goals

- **To identify non-invasive biomarkers associated with specific cellular responses that will enable precision treatment in CKD**



# Thank You!

To all members of the  
Chinook-Evotec  
Strategic Partnership...



... and all contributors of the  
NURTuRE Consortium!



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