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
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.
NURTuRE IgAN Cohort Characterization and Data Availability

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

<table>
<thead>
<tr>
<th>Data Sources</th>
<th>Data type</th>
<th>Source</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical data</td>
<td>UK Renal Registry</td>
<td></td>
<td>205</td>
<td></td>
</tr>
<tr>
<td>SNP array</td>
<td>Blood</td>
<td></td>
<td>199</td>
<td></td>
</tr>
<tr>
<td>Whole Exome Sequencing</td>
<td>Blood</td>
<td></td>
<td>197</td>
<td></td>
</tr>
<tr>
<td>RNA-Seq</td>
<td>Blood</td>
<td></td>
<td>179</td>
<td></td>
</tr>
<tr>
<td>Histopathology report (MEST-C)</td>
<td>Biopsy</td>
<td></td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>RNA-Seq</td>
<td>Biopsy</td>
<td></td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Olink Proteomics</td>
<td>Serum</td>
<td></td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Immunoglobulin isotypes (Gd-1gA1, IgA, IgG, IgM)</td>
<td>Serum</td>
<td></td>
<td>69</td>
<td></td>
</tr>
</tbody>
</table>

- 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

**Overlap of serum proteins significantly correlated with kidney function metrics**

- 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.

**Highlight Select Targets with Significant Correlation**

<table>
<thead>
<tr>
<th>Significance Threshold:</th>
<th>Correlation</th>
<th>&gt;=0.3; -log10(adjusted p-value) &gt;=1.3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APRIL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BAFF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ET1</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Kidney function by MEST-C score

<table>
<thead>
<tr>
<th>Feature</th>
<th>log10(UACR) p-value</th>
<th>log10(UPCR) p-value</th>
<th>log10(eGFR) p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesangial cellularity</td>
<td>0.0006</td>
<td>0.0187</td>
<td>0.6182</td>
</tr>
<tr>
<td>Endocapillary proliferation</td>
<td>0.0239</td>
<td>0.0221</td>
<td>0.6430</td>
</tr>
<tr>
<td>Segmental glomerulosclerosis</td>
<td>0.0820</td>
<td>0.0841</td>
<td>0.6828</td>
</tr>
<tr>
<td>Tubular atrophy/interstitial fibrosis</td>
<td>0.1606</td>
<td>0.3698</td>
<td>0.0096</td>
</tr>
<tr>
<td>Crescents</td>
<td>0.0017</td>
<td>0.0110</td>
<td>0.4962</td>
</tr>
</tbody>
</table>

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.

## Kidney function by MEST-C score

- **T** (Tubular atrophy/interstitial fibrosis)
  - **T0**: 0-25%
  - **T1**: 25%-50%
  - **T2**: > 50%

- **M** (Mesangial cellularity)
  - **M0**: 0-50%
  - **M1**: > 50%

- **E** (Endocapillary proliferation)
  - **E0**: no hypercellularity
  - **E1**: any hypercellularity

- **C** (Crescents)
  - **C0**: 0
  - **C1**: 0-25%
  - **C2**: > 25%

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

Proteinuria is associated with mesangial cellularity (**M**), endocapillary proliferation (**E**) and crescents (**C**).
A Preclinical Model Derived Atrasentan Response Signature* is Correlated with Kidney Function

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

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

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.

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
The Kidney Atrasentan Response Score is Correlated with Serum Proteins

45 serum protein are strongly correlated ($r \geq 0.60$) with the kidney atrasentan signature score

- 700 serum Olink proteins are correlated with the kidney atrasentan response signature score – 45 proteins are strongly correlated ($r \geq 0.60$)

- 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
Summary and Future Plans

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
Thank You!

To all members of the Chinook-Evotec Strategic Partnership…

… and all contributors of the NURTuRE Consortium!

Elaine Davies, Director at Kidney Research UK

Prof. Moin Saleem
University of Bristol

Prof. Maarten Taal
University of Nottingham