PRECISION MEDICINE: TOWARDS A MECHANISTIC DEFINITION OF KIDNEY DISEASE

Matthias Kretzler, MD
Div. Nephrology / Internal Medicine
Computational Medicine and Bioinformatics
University of Michigan Medical School
Disclosures

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• NephCure, Eli Lilly, Goldfinch Bio, Retrophin, Elpidera, Boehringer-Ingelheim (Neptune)
• Eli Lilly, Astra-Zeneca, NovoNordisc, Gilead, Jansen (Renal Pre-Competitive Consortium (RPC2))

• Patent: “Biomarkers for CKD progression” (encompassing urinary EGF as biomarker of CKD progression)
The challenge in kidney disease

CKD, AKI, Nephrotic Syndrome:

- Descriptive disease categorization describing a recognizable clinical picture = phenotype
- But driven by multiple pathogenetic mechanisms

- Problems of ‘mixed bag’ diseases:
  - Unpredictable disease course and response to therapy and
  - Non-targeted therapies of one size fits all
  - Glomerular disease therapies as ‘art of trial and error’
Description of Kidney Failure
anno 1760

'Die Urinbeschau'
Unknown master
Lower Rhine valley, ca. 1760

KDIGO
The challenge in kidney disease

• Descriptive disease categorization with multiple pathogenetic mechanisms
  – Problems of ‘mixed bag’ diseases:
    • Unpredictable disease course and response to therapy
    • Medicine as an ‘art of trial and error’

• Shift in our disease paradigms:
  – Mechanism based patient management
    • Define the disease process active in our patients
      – Define molecular disease causality
      – Base prognosis on specific disease process
      – Target therapy to interfere with the mechanism currently active in patients
Precision Medicine: Molecular Disease Definition

Deep Clinical & Molecular Phenotyping

Prospective cohort studies

Multiscalar Data Integration

Clinical Phenotype
Histology
Genome
Transcriptome
Proteome
Metabolome

Patient-level Pathway Activity

Patient profiling
Non-invasive surrogate markers
Outcome prediction

Poor outcome patients
Good outcome patients
Targeted therapies
Molecular Mechanism for Kidney Diseases

Comprehensive profile

- **Clinical profile:** clinical data
- **Morphologic profile:** Kidney biopsy (first, initial, repeat)
- **Molecular profile:** non-invasive biomarkers, gene expression maps, genetic analysis obtained and integrated

Predict

1. Response to standard of care
   - Progression Biomarkers

2. Clinical Trial
   - Predictive Biomarkers for targeted therapy selection
   - Dynamic (target engagement) Biomarkers monitoring treatment response

Identify

3. Target identification and development
   - Develop repurposing trials
   - Match drugs with pathways in individual patients
   - Identify targets for *de novo* drug development
Structure Function Pathway Network in early DKD

Inflammatory signatures

Metabolic signatures

Nair et al. 2018
**Dynamic mapping of regulatory pathways: Jak-Stat pathway**

<table>
<thead>
<tr>
<th>Tubulointerstitial compartment</th>
<th>Early DN</th>
<th>Progressive DN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (LD+MCD): n=11</td>
<td>Early DN: n=22</td>
<td>Control (LD+MCD): n=7</td>
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<tr>
<td>Cytoplasm</td>
<td></td>
<td>Prog. DN: n=11</td>
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<tr>
<td>Nucleus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glomerular compartment</th>
<th>Early DN</th>
<th>Progressive DN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (LD+MCD): n=12</td>
<td>Early DN: n=24</td>
<td>Control (LD+MCD): n=8</td>
</tr>
<tr>
<td>Cytoplasm</td>
<td></td>
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**Key**
- **Red**: Up-regulation
- **Green**: Down-regulation
- **Light Green**: Differential regulation

*Berthier et al., Diabetes. 2009;58:469*
Phase II trial of Jak 2 inhibition in diabetic kidney disease

Baricitinib, oral JAK2 inhibitor, efficacy in RA and Psoriasis

=> Repurposed in Diabetic Kidney Disease

• RCT by Eli Lilly in DN:
  • Clinical inclusion criteria selected to enrich for patients with high activity of Jak-Stat pathway
  • Primary outcome:
    • Change in urine ACR from baseline to 24 weeks
• Reductions in 24-hour UACR were observed at 3 and 6 months (Figure 3).

Tuttle et al. NDT, 2018
Target Engagement Biomarkers

• Based on molecular analysis downstream biomarkers of Jak/Stat activation were assessed

• Improvements relative to placebo seen for:
  – Inflammatory biomarkers including:
    • Urinary IP-10 (CXCL10)
    • CCL2
Urine IP-10 (CXCL10) (pg/mg/creat)

Abbreviations: IP-10=urinary interferon gamma-induced protein-10; LSM=least squares mean; SE=standard error
Note: Mixed model repeated measures analysis of log-transformed data with results back transformed.
*p-value <0.05 for comparison to baseline. ^p-value <0.05 for comparison to placebo.
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KDIGO
The Nephrotic Syndrome Study Network

The Nephrotic Syndrome Study Network Consortium (NEPTUNE), U54-DK-083912, is a part of the National Institutes of Health (NIH) Rare Disease Clinical Research Network (RDCRN), supported through a collaboration between the Office of Rare Diseases Research (ORDR), NCATS, and the National Institute of Diabetes, Digestive, and Kidney Diseases. Additional funding and/or programmatic support for this project has also been provided by the University of Michigan, the NephCure Kidney International and the Halpin Foundation.
Targeted Therapies for Glomerular Diseases

- Clinical Phenotyping
- Histology
- Molecular Profiling
- Genomics
Molecular Driven Disease Stratification: FSGS-MCD gene expression cluster
Ward's (Minimum variance) + (Nonnormalized data)

Validation in independent ERCB cohort

Cluster 1
Cluster 2
Cluster 3

GFR 104
94
69

71/202 genes sign. Upregulated – concordant with NEPTUNE genes that differentiated cluster 3 there (125/131 also upregulated)

Mariani et al. bioRxiv
Gene expression based stratification of NEPTUNE FSGS/MCD cohort

Mariani et al. bioRxiv
Cluster Based Outcomes

Complete Remission of Proteinuria

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Number at Risk</th>
<th>Complete Remission</th>
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</thead>
<tbody>
<tr>
<td>Cluster = 1</td>
<td>49</td>
<td>30 23 17 12 7</td>
</tr>
<tr>
<td>Cluster = 2</td>
<td>34</td>
<td>16 8 6 3 1</td>
</tr>
<tr>
<td>Cluster = 3</td>
<td>27</td>
<td>20 15 15 10 6</td>
</tr>
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Composite of 40% loss of baseline eGFR and ESRD

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<tr>
<th>Cluster</th>
<th>Number at Risk</th>
<th>Kaplan-Meier survival estimates</th>
</tr>
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<tbody>
<tr>
<td>Cluster = 1</td>
<td>50</td>
<td>45 39 34 26 18</td>
</tr>
<tr>
<td>Cluster = 2</td>
<td>39</td>
<td>34 30 23 18 9</td>
</tr>
<tr>
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Kaplan-Meier survival estimates

Mariani et al. bioRxiv
309 probesets $q<0.01$ plus **FC>2** uploaded to IPA, all up-regulated, 1st FSGS/MCD batch

**Transcriptional Networks in Cluster 3 vs 1+2**

**Other Upstream Regulators:**
- IFN-G
- TGFB1
- IL1-B
- IL4
- IL6
- STAT1
- PPARA
- IL10

**FONT trial:**
- Adalimumab in FSGS
- *Trachtman H.*, *et al.*
- 2010

**KDIGO**
Causal analysis TNF activation network differentially regulated in cluster 3

This network explains 523 of 1712 (30.5%) transcriptional changes (FC>1.5, q≤0.05) in an analysis of cluster 3 vs cluster 1 and 2 patients.
TNF activation score delineates cluster 3 from clusters 1 and 2

ANOVA p-value (across clusters): 2.61E-29
N=124
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https://kidneyhealthgateway.com/
Defining Kidney Disease from the Tissue Level for CKD and AKI
Kidney Precision Medicine Project (KPMP)

Goal: Understand and treat human kidney disease

Ethically and safely obtain research kidney biopsies
  • Patient partners engagement core
  • Ethical framework; experienced biopsy teams

Interrogate biopsies using state of art technologies that provide information from molecular to cellular

Curate, integrate, and visualize data for Kidney Tissue Atlas
  • Phenotype critical cell and tissue compartments with RNA-protein-lipid-epigenetic markers
  • Integrate with clinical data to identify cell state and activated pathways
  • Determine diagnosis, sub-groups prognosis, and targets for individualized therapy

=> Establish novel assays for AKI and CKD for molecular patient stratification

Courtesy of R. Star, NIDDK
Kidney Precision Medicine Project workflow

Ethically and safely obtain kidney biopsies.
Learn from biopsies. Find markers.
Evaluate markers on biopsies.
Find cell pathway markers; tie to Patient outcomes.
Create Kidney Tissue Atlas.

Courtesy of R. Star, NIDDK
Bring standardized kidney nomenclature into current Ontology development

- A Disease Ontology is a system of standardized definition and relationships, which are both human and machine readable:
  - Should enable integrated search capabilities for **data and metadata in clinical, pathology and molecular domains** and be fully FAIR (Findable, Accessible, Interoperable, Reusable) compliant

- Benefits:
  - Logical definition of related components and relations
  - Computer understandable
  - Automatically infer AKI status by computer
  - Standardization, interoperable

- Challenges:
  - Community consensus is required
  - Challenge from text definition to ontology definition
HPO (Human Phenotype Ontology)

• HPO text definition of AKI (HP_0001919):
  o “Sudden loss of renal function, as manifested by decreased urine production, and a rise in serum creatinine or blood urea nitrogen concentration (azotemia).”

• Example: one KDIGO AKI definition: “Increase in serum creatinine (SCr) by \( \geq 0.3\, \text{mg/dl} \) within 48 hours”

• Define in ontology as necessary and sufficient condition:
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