Genomics, Proteomics, Transcriptomics
– a Systems Biology Approach to CKD

Rainer Oberbauer
What is 'Omics'?

- Neologism ‘omics’ informally refers to a field of study ending in -omics, such as genomics or proteomics.

- All constituents considered collectively
What is Systems Biology?
Large scale EU Project - €16 Mio
2010-2015

<table>
<thead>
<tr>
<th>Project Number 1</th>
<th>241544</th>
<th>Project Acronym 2</th>
<th>SysKID</th>
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**General information**

<table>
<thead>
<tr>
<th>Project title 3</th>
<th>Systems biology towards novel chronic kidney disease diagnosis and treatment*</th>
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<tbody>
<tr>
<td>Starting date 4</td>
<td>01/01/2010</td>
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<td>Duration in months 5</td>
<td>60</td>
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<td>Call (part) identifier 6</td>
<td>FP7-HEALTH-2009-single-stage</td>
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<tr>
<td>Activity code(s) most relevant to your topic 7</td>
<td>HEALTH-2009-2.4.5-2: Cellular and molecular mechanisms of the development of chronic kidney disease (CKD)</td>
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<td>Free keywords 8</td>
<td>chronic kidney disease, diabetic nephropathy, diagnostic assays, therapy regimes, omics experiments, systems biology, functional genomics, patient outcome, clinical data repositories</td>
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*R. O.4/33

* Focus on diabetes and hypertension as the major drivers of CKD
25 SysKid Partners

SysKid Collaborative Project
Systems Biology towards Novel Chronic Kidney Disease Diagnosis and Treatment
What is SysKid?

DM II  CKD  normo -> micro  micro -> macroalbuminuria

- biopsies
- blood
- serum
- urine
- clinical data

- SNPs, DNA
- Transcriptomics, mRNA
- Transcriptomics, miRNA
- Proteomics, Metabolomics

Computational Systems Biology

In-vitro models
In-vivo models

SysKid

Collaborative Project
Systems Biology towards Novel Chronic Kidney Disease Diagnosis and Treatment
What is SysKid?

- Applied Clinical Research
- Epidemiology and Systems Biology
- Molecular Research
- Development Partners
SysKid – Biomarker shortlist proposed

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Name</th>
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<tbody>
<tr>
<td>LCN2 (NGAL)</td>
<td>Lipocalin 2</td>
</tr>
<tr>
<td>FGF23</td>
<td>Fibroblast growth factor 23</td>
</tr>
<tr>
<td>SERPINE1 (PAI-1)</td>
<td>Serpine peptidase inhibitor, clade E, member 1</td>
</tr>
<tr>
<td>VCAN (CSPG2)</td>
<td>Versican</td>
</tr>
<tr>
<td>CTGF</td>
<td>Connective tissue growth factor</td>
</tr>
<tr>
<td>CCL2 (MCP-1)</td>
<td>Chemokine ligand 2</td>
</tr>
<tr>
<td>APOA1</td>
<td>Apolipoprotein A1</td>
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Genomics
about us

Mission Statement

23andMe's mission is to be the world's trusted source of personal genetic information.

A Snapshot of Team 23andMe

67% of us have a family history of cancer
2007: 23andMe introduces the first Personal DNA test. Unlock the secrets of your own DNA.
Allele frequencies and effect sizes of genetic variants in human diseases - GWAS

Le, Y, Shiffman D, Oberbauer R. MMB 2010 (in press)
Sample size/power in GWAS

OR=1.25, α=10^{-8}

Sample Size

Le, Y, Shiffman D, Oberbauer R. MMB 2010 (in press)
GWAS and CKD

Kottgen A et al. Nat Genet. 2010 May;42(5):376-84
Systems biology of kidney injury

Laser Capture Microdissection Of Donor Kidneys

DNA Microarrays

Quantitative PCR

Data Mining

Target Gen Definition

Antisense Nucleotide Design & Synthesise

In vitro POC

In vivo POC

R.O.15/33
Glomeruli isolated from live and deceased donor kidney biopsies

Transcripts are specific for deceased and live donor kidney compartments
Unsupervised Cluster Analysis of Donor Kidney Biopsies

Histogenomics of deceased donor kidneys (n=82)

Systems Biology and omicsNET

Physical Interactions

SEMantic Annotation Terms

Gene Expression Patterns

Subcellular LOCalization

Level
Protein
RNA
Gene
Protein

... extendable

PI
GEP
SEM
LOC

Label

R.O.20/33
Inflammation networks in cadaveric donor organs

Inflammation in Deceased Donor Kidney Biopsies

ICAM-1

VCAM-1

ELAM-1

DGF

PGF

Schwarz et al Transplantation 2001:71:1666-72
A Multicenter Double-Blinded RCT of Deceased Organ Donor Pre-Treatment with Corticosteroids for the Prevention of Postischemic Acute Renal Allograft Failure

Current Controlled Trials Registration #: ISRCTN78828338

Sponsor: FWF P15679, €350k 3yrs
Sample size estimation

Event rate
close group = 24%

Computed sample size to half event rate:

Donor sample size

\[ N^* = \frac{N}{1 - LFU/NU} \]

= 176(1/0.92)² ≈ 207
# Demography of the 274 donors & 458 recipients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Steroid</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of donors</td>
<td>137</td>
<td>137</td>
<td>na</td>
</tr>
<tr>
<td>Donor age (years)</td>
<td>47.1 (15.1)</td>
<td>48.5 (14.0)</td>
<td>0.452</td>
</tr>
<tr>
<td>Donor sex (f/m)</td>
<td>62/74</td>
<td>57/76</td>
<td>0.652</td>
</tr>
<tr>
<td>Last creatinine of donor (mg/dl)</td>
<td>0.89 (0.29)</td>
<td>0.90 (0.39)</td>
<td>0.840</td>
</tr>
<tr>
<td>Vasopressors used (n/y)</td>
<td>22/114</td>
<td>12/121</td>
<td>0.078</td>
</tr>
<tr>
<td>Multiorgan donors (n/y)</td>
<td>106/30</td>
<td>94/39</td>
<td>0.173</td>
</tr>
<tr>
<td>Number of recipients</td>
<td>239</td>
<td>219</td>
<td>na</td>
</tr>
<tr>
<td>Recipient age (years)</td>
<td>49.6 (14.4)</td>
<td>49.2 (13.9)</td>
<td>0.753</td>
</tr>
<tr>
<td>Recipient sex (f/m)</td>
<td>76/162</td>
<td>77/142</td>
<td>0.465</td>
</tr>
<tr>
<td>Transplant number (1/2/3/4/5)</td>
<td>204/23/8/2/1</td>
<td>194/21/4/0/0</td>
<td>0.505*</td>
</tr>
<tr>
<td>Cold ischemic time (hours)</td>
<td>16.9 (13.4)</td>
<td>16.9 (15.2)</td>
<td>0.995</td>
</tr>
<tr>
<td>PRA latest (%)</td>
<td>6 (17)</td>
<td>4 (12)</td>
<td>0.172</td>
</tr>
<tr>
<td>Sum of HLA mismatches</td>
<td>3 (1)</td>
<td>3 (1)</td>
<td>0.379</td>
</tr>
<tr>
<td>Immunosuppression (CNI/else)</td>
<td>223/15</td>
<td>205/14</td>
<td>0.969</td>
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<tr>
<td>Induction therapy (none/antiCD25/ATG)</td>
<td>143/83/12</td>
<td>126/86/7</td>
<td>0.437</td>
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</table>
Steroid treatment suppressed inflammation
Primary study end point - DGF

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<th>Placebo</th>
<th>p-value</th>
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<tr>
<td>% Pts requiring dialysis</td>
<td>65/13/22</td>
<td>63/12/25</td>
<td>0.700</td>
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<tr>
<td>during the first 7 days</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(0/1/&gt;1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of dialysis</td>
<td>154/32/18/28/2/4</td>
<td>137/27/27/18/8/2</td>
<td>0.115</td>
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<tr>
<td>during the first 7 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0/1/2/3/4/5)</td>
<td></td>
<td></td>
<td></td>
</tr>
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Creatinine Trajectories

\[ p = 0.955 \]

![Graph showing creatinine trajectories over days after transplantation with two lines representing Steroids and Placebo groups. The p-value indicates no significant difference between the groups.](image-url)
miRNA regulation of kidney injury (FWF P21436 - €250k 2010-2012)

DICER

code for a complex cellular phenotype by silencing of target mRNAs
Differential regulation of miRNAs in delayed graft function – several target genes (miRANDA)

B1 (light grey) = Banff 1
B2 (grey) = Banff 2
DGF (yellow) = delayed graft function
PBx (blue) = Management biopsies
Antisense DNA/siRNA

Antisense DNA/siRNA

Oberbauer R et al. PNAS, 1996, 93:4903-4906
Antisense DNA/siRNA

Oberbauer R et al. PNAS, 1996, 93:4903-4906
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