Using human transcriptomics to identify infectious disease agents

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Host-Pathogen Genomics

- Meningococcal
- Kawasaki
- Influenza
- TB
- RSV
- Dengue

**Human Genomics**
- Case control and family

**Host - Pathogen**
- Patient expression profiles
  - *In vitro* modeling

**Pathogen Genomics**
- Genome sequencing
- Pathogen discovery
Disease Models
Patient Cohorts

Humans
ChIP defined Transcription networks (NFκB, PPARγ etc)

Pathogens
Virulence mutations
Strain specific host response pathways

Disease Models
Functional evaluation of genetic variants Human and/or Pathogen

GWAS
Expression
Host response pathways

Functional SNPs

Population based Prognosis

Sequencing
Detection
Evolution
Transmission

Modulation of host response compounds / drugs / siRNA

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Modulation of host response compounds / drugs / siRNA
Global gene expression profiling identifies new therapeutic targets in acute Kawasaki disease

Long Truong Hoang¹, Chisato Shimizu², Ling Ling³, Ahmad Nazri Mohamed Naim¹, Chiea Chuen Khor¹, Adriana H Tremoulet², Victoria Wright³, Michael Levin³, Martin L Hibberd¹* and Jane C Burns²*

### A. Upregulated Canonical Pathway

<table>
<thead>
<tr>
<th>Pathway</th>
<th>GLM</th>
<th>Z test</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-10 Signaling</td>
<td>7.35</td>
<td>9.72</td>
</tr>
<tr>
<td>Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses</td>
<td>6.17</td>
<td>7.47</td>
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<tr>
<td>TREM1 Signaling</td>
<td>5.45</td>
<td>11.05</td>
</tr>
<tr>
<td>IL-8 Signaling</td>
<td>5.31</td>
<td>7.24</td>
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<tr>
<td>Granulocyte Adhesion and Diapedesis</td>
<td>5.20</td>
<td>5.91</td>
</tr>
<tr>
<td>Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis</td>
<td>4.07</td>
<td>8.29</td>
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<tr>
<td>Gai Signaling</td>
<td>4.05</td>
<td>5.56</td>
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<tr>
<td>Acute Phase Response Signaling</td>
<td>4.26</td>
<td>7.76</td>
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<tr>
<td>Hepatic Fibrosis / Hepatic Stellate Cell Activation</td>
<td>4.18</td>
<td>7.99</td>
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<tr>
<td>iNOS Signaling</td>
<td>4.03</td>
<td>6.00</td>
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<tr>
<td>Toll-like Receptor Signaling</td>
<td>4.03</td>
<td>7.02</td>
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<tr>
<td>Production of Nitric Oxide and Reactive Oxygen Species in Macrophages</td>
<td>3.45</td>
<td>7.71</td>
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<tr>
<td>Leukocyte Extravasation Signaling</td>
<td>3.43</td>
<td>5.67</td>
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<tr>
<td>IL-6 Signaling</td>
<td>3.29</td>
<td>7.82</td>
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<tr>
<td>NF-κB Signaling</td>
<td>3.13</td>
<td>6.82</td>
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### B. Downregulated Canonical Pathway

<table>
<thead>
<tr>
<th>Pathway</th>
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<th>Z test</th>
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<tbody>
<tr>
<td>EIF2 Signaling</td>
<td>42.50</td>
<td>41.83</td>
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<tr>
<td>Regulation of eIF4 and p70S6K Signaling</td>
<td>15.01</td>
<td>13.10</td>
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<tr>
<td>mTOR Signaling</td>
<td>14.18</td>
<td>15.15</td>
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<tr>
<td>B Cell Development</td>
<td>5.07</td>
<td>7.59</td>
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<tr>
<td>Antigen Presentation Pathway</td>
<td>3.51</td>
<td>8.04</td>
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<tr>
<td>Role of NFAT in Regulation of the Immune Response</td>
<td>3.08</td>
<td>12.34</td>
</tr>
<tr>
<td>Altered T Cell and B Cell Signaling in Rheumatoid Arthritis</td>
<td>3.00</td>
<td>4.89</td>
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<tr>
<td>iCOS-iCOSL Signaling in T Helper Cells</td>
<td>2.58</td>
<td>16.85</td>
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<tr>
<td>p70S6K Signaling</td>
<td>2.37</td>
<td>1.91</td>
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<tr>
<td>Cytotoxic T Lymphocyte-mediated Apoptosis of Target Cells</td>
<td>2.24</td>
<td>8.53</td>
</tr>
<tr>
<td>OX40 Signaling Pathway</td>
<td>2.14</td>
<td>9.03</td>
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<tr>
<td>Histamine Biosynthesis</td>
<td>2.05</td>
<td>1.51</td>
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<tr>
<td>Nur77 Signaling in T Lymphocytes</td>
<td>1.89</td>
<td>9.08</td>
</tr>
<tr>
<td>Calcium-induced T Lymphocyte Apoptosis</td>
<td>1.75</td>
<td>14.31</td>
</tr>
<tr>
<td>Allograft Rejection Signaling</td>
<td>1.43</td>
<td>6.64</td>
</tr>
</tbody>
</table>
Gene network analysis

Module-trait relationships

- N genes

Gene dendrogram and module colors

Module colors:
- 

- MEmagenta
- MEblack
- MEbrown
- MEgreenyellow
- MEPink
- MEcyan
- MEblue
- MESalmon
- MEMidnightblue
- METan
- M EGreen
- METurquoise
- MEGrey

- Time
- Sex
- HAI
- Ethnic group
- Age

Correlation coefficients:

- 0.12 (0.1)
- 0.018 (0.8)
- 0.006 (0.9)
- 0.049 (2.5)
- 0.047 (2.5)
- 0.065 (0.4)
- 0.15 (0.3)
- -0.042 (0.6)
- -0.047 (0.5)
- -0.022 (0.9)
- 0.11 (0.1)
- 0.056 (0.4)
- -0.012 (0.9)
- -0.071 (0.3)
- -0.029 (0.7)
- 0.061 (0.3)
- 0.14 (0.05)
- -0.032 (0.7)
- -0.029 (0.7)
- -0.007 (0.9)
- 0.14 (0.05)
- 0.052 (0.5)
- 0.0036 (1)
- -0.029 (0.7)
- 0.0047 (0.9)
- 0.032 (0.7)
- -0.28 (1e-04)
- -0.07 (0.3)
- 0.13 (0.07)
- -0.007 (0.9)
- -0.22 (0.062)
- -0.12 (0.1)
- -0.082 (0.2)
- -0.0022 (1)
- 0.0048 (0.9)
- 0.017 (0.8)
- 0.17 (0.02)
- 0.016 (0.8)
- -0.0022 (1)
- 0.041 (0.6)
- -0.45 (0e-11)
- -0.1 (0.2)
- -0.1 (0.2)
- 0.15 (0.03)
- 0.0863 (0.9)
- -0.23 (0.002)
- -0.0019 (1)
- -0.016 (0.8)
- -0.01 (0.9)
- -0.024 (0.7)
- 0.0056 (0.9)
- 0.018 (0.8)
- 0.053 (0.4)
- 0.0017 (1)
- -0.072 (2.2)
- 0.079 (0.5)
- -0.544 (0.5)
- 0.12 (0.1)
- 0.019 (0.8)
- -0.064 (0.4)
- 0.1 (0.2)
- 0.019 (0.8)
- -0.03 (0.7)
- 0.0021 (1)
- 0.033 (0.7)
The IL 1 pathway is unusually active in KD
A

B

C

D
Figure S5: Performance of the 59-transcript 1 s.e elastic net signature by illness day at sample collection in validation set.
Diagnosis of Childhood Tuberculosis and Host RNA Expression in Africa

TB diagnosis by Host response array

<table>
<thead>
<tr>
<th>Table 3. Diagnostic performance of the TB/OD disease risk score and the Xpert MTB/RIF® in the Kenyan validation cohort.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DRS based on the 51 transcript TB vs OD signature</strong></td>
</tr>
<tr>
<td><strong>TB vs. Other Diseases – HIV + &amp; HIV- combined</strong></td>
</tr>
<tr>
<td>Area under ROC curve (95% CI)</td>
</tr>
<tr>
<td>(82.3 - 94.9)</td>
</tr>
<tr>
<td>Sensitivity, % (95% CI)</td>
</tr>
<tr>
<td>(68.6 - 94.3)</td>
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<tr>
<td>Specificity, % (95% CI)</td>
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<tr>
<td>(74.6 - 92.7)</td>
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<tr>
<td><strong>Culture Negative TB vs. Other Diseases – HIV + &amp; HIV- combined</strong></td>
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<tr>
<td>Area under ROC curve (95% CI)</td>
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<td>(58.7 - 79.7)</td>
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<tr>
<td>Sensitivity, % (95% CI)</td>
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<tr>
<td>(27.3 - 56.8)</td>
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Are we missing a lot of TB diagnosis?
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