21st century disease models
Case study: COPD and severe asthma

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Worldwide prevalence of inflammatory lung diseases

- Asthma
- CF
- COPD
- Other

- ~500 Million
- 300 Million
- 210 Million
- 70,000

Donnelly & Rogers 2008
Severe asthma and COPD: the problem

• Current treatments are insufficient
• All disease is not the same –
  • heterogenous diseases with distinct phenotypes

• Improve understanding of severe asthma and COPD subtypes
• Consider an individual’s characteristics before diagnosis and management plans are given
U-BIOPRED project: Hypothesis generation

Knowledge management platform

\[ \text{Handprint of severe asthma} \]
Consensus clustering on clinical features

- **Cluster 1**: Moderate-to-severe asthma; well-controlled; medium to high dose ICS
- **Cluster 2**: Severe asthma; Late onset asthma; smoker or ex-smoker; airflow obstruction; high dose ICS
- **Cluster 3**: Severe asthma; Oral corticosteroid-dependent; airflow obstruction; high dose ICS
- **Cluster 4**: Severe asthma; Female; obese; frequent exacerbations; high dose ICS

49 different clustering analysis performed
Consensus clustering on clinical features

Smoking (cluster 2) vs non-smoking (cluster 3) of airflow obstruction

- **Pathway analysis of cell transcriptomics**
  Regulation of actin cytoskeleton (\textit{ITGB1, FN1, ACTN2})
  Fibronectin matrix formation (\textit{ITGB1, FN1})

- **Differentially-expressed proteins in supernatants**
  LYN: src non-receptor lyn tyrosine kinase
  FUT5: Fucosyltransferase 5
Relationship between sputum inflammatory pattern and the 3 transcriptomic modules

**Eosinophil predominant asthma:**
- TM1 & TM3 subtype

**Mixed granulocytic asthma:**
- TM1 & TM2 subtype

![Graph showing the relationship between sputum inflammatory pattern and the 3 transcriptomic modules with Eosinophil predominant asthma and Mixed granulocytic asthma subtypes.]
Relationship between sputum inflammatory pattern and the 3 transcriptomic modules

Linked to OXPHOS and ageing and specific macrophage subtypes
TAC3 cluster also enriched in COPD patients

TAC1 enrichment predicts ICS responders in GLUCOLD patients
### Summary of Transcriptome Modules in asthma from sputum analysis

<table>
<thead>
<tr>
<th></th>
<th><strong>TAC 1</strong></th>
<th><strong>TAC 2</strong></th>
<th><strong>TAC 3</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanisms</strong></td>
<td>‘T-2 associated’</td>
<td>‘Inflammasome’</td>
<td>‘Mitochondrial’</td>
</tr>
<tr>
<td></td>
<td>Epithelial driven</td>
<td>Macrophage driven</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td><strong>Sputum inflammation</strong></td>
<td>Eosinophilic/Mixed</td>
<td>Neutrophilic/Mixed</td>
<td>Eosinophilic/Paucigranulocytic</td>
</tr>
<tr>
<td><strong>Microarray</strong></td>
<td>IL33R, TSLPR, CCR3, IL3RA</td>
<td>IFN &amp; TNF superfamily, CASP4</td>
<td>Metabolic genes</td>
</tr>
<tr>
<td><strong>GSVA</strong></td>
<td>Th2/ILC2</td>
<td>NLPR3/DAMP-associated</td>
<td>Th17; OXPHOS; ageing</td>
</tr>
<tr>
<td><strong>Protein (Somalogics)</strong></td>
<td>IL-16, Periostin, Serpin peptidase inhibitor 1, ADIPOQ</td>
<td>TNFAIP6, MIF, Tyrosine kinase src</td>
<td>Cathepsin B, G</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td>Severe asthma; Highest nasal polyps and OCS use; Severe airflow obstruction</td>
<td>Moderate-to-severe asthma Mild airflow obstruction</td>
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</tr>
</tbody>
</table>
Summary of Transcriptome Modules in asthma from sputum analysis

Specific genes characterise each TM and subgroup

TM clustering in sputum used to define blood biomarkers
*(IL5RA, VEGFA; GCG, PLA2G2A; CD55, TGFB1, CD22)*

Biomarker tests for molecularly targeted therapies are the key to unlocking precision medicine
TDA analysis of 22 clinico-pathological clusters in asthma (including sputum cells)

1. Mild asthma, predominantly steroid-naive, Th2-high, pauci-granulocytic
2. Well-controlled asthma, eosinophilic
3. Moderately severe asthma, high eNO, Th2-/Th17-high
4. Moderately-severe asthma, nasal polyposis, salicylate-sensitive
5. Severe asthma, atopic, older, obese, high type-2 cytokines and mast cell mediators
6. Severe asthma, frequent oral corticosteroids, obese, non-atopic, predominantly female, high mast cell mediators

0. Healthy participants

John Smith

Ratko Djukanovic & Jim Schofield
Can new models help redefine phenotypes and test drugs?

Mice models not predictive

Transcriptomic analysis of lung tissue from cigarette smoke induced emphysema murine models and human COPD show shared and distinct pathways

Jeong H. Yun$^{1,2}$, Jarrett Morrow$^1$, Caroline A. Owen$^{2,3}$, Weiliang Qiu$^1$, Kimberly Glass$^1$, Taotao Lao$^1$, Zhiqiang Jiang$^1$, Mark A. Perrella$^{2,4}$, Edwin K. Silverman$^{1,2}$, Xiaobo Zhou$^{1,2,*}$, Craig P. Hersh$^{1,2,*}$

*contributed equally

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Schematic of Bronchosphere Culture

Plus stiffening agent
NHBE Bronchosphere Development

Day 1
- Single basal cells

Day 3
- Merging Spheroids
- Start of Mucous secretion

Day 12
- Inner lumen
- Basal Ring
- Start of Vacuole Formation

Day 18
- Mucous
- Inner lumen
- Basal Ring

Basal Cells
- Spheroids
- Intermediate Spheroid
- Bronchosphere

Basal cell marker positive (P63\(^+\), NFG\(^+\) and ITGA6\(^+\))

NHBE C
- AHBEC
- CHBEC

Vacuole
- 63µM
- Inner lumen
- Start of Vacuole Formation

Basal Ring
- 85µM

Vacuole
- 35µM
- Undifferentiated Spheroid
NHBE Bronchosphere Development

Basal cell marker positive (P63+, NFGR+ and ITGA6+)

NHBECHBE

Basal cell marker positive (P63+, NFGR+ and ITGA6+)

NHBECHBE
Gene Expression During Bronchosphere Development

Representative staining of bronchosphere sections- α-tubulin (cilia), goblet cell (MUC5AC and DAPI (nucleus) from day 2-17 (NHBE) and 8-23 (CHBE) to show luminal development. Bronchospheres replicate features of human airway lumen.
Bronchotubules/organoid formation

ASM, fibroblasts or stem cells. Tubules contract with acetylcholine. Stiffness essential as maintains structure – allows time to produce own matrix.

Tank Guney, Sharon Mumby, Sean Ojo
The future

• Precision medicine is a rapidly developing field in respiratory medicine

• Integration of large datasets over time can:
  • refine patient subsets,
  • indicate mechanisms to enable targeted therapy

• Analysis at the target site important for subphenotyping patients before examination of blood biomarkers

• Better models for mechanistic studies and PoC drug studies

• Need to translate to point of care
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UCB
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SME’s
Aerocrine
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Synairgen
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Patient organisations
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Netherlands Asthma Foundation

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