ERS Annual Congress Vienna
1–5 September 2012

Postgraduate Course 13
AirPROM: patient-specific modelling and systems biology living labs workshop

Saturday, 1 September 2012
14:00–17:30
Room: Schubert 5
**The need and potential of patient-specific modelling**

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*United Kingdom*
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**Aims**

1. Define the current approaches to phenotyping airways disease
2. Describe what is meant by scales of disease
3. Describe our current knowledge of immunopathology across the scales of disease using asthma as an exemplar
4. Discuss the shortcomings of our current approaches to clinical integration of multi-scale data
5. Propose how systems biology and computational multi-scale modelling might add value to our understanding of disease and its potential in stratified/personalized medicine

**Summary**

The airways diseases asthma and chronic obstructive pulmonary disease affect over 400 million people world-wide and cause considerable morbidity and mortality. Airways disease costs the European Union in excess of €56 billion per annum. Current therapies are inadequate due to our incomplete understanding of the pathophysiology of these diseases and our lack of recognition of the enormous disease heterogeneity, such that our current ‘one size fits all’ approach is inappropriate. We need to fully characterise this heterogeneity in order to identify the ‘right target’ for the ‘right patient’ and measure the ‘right outcome’. To achieve this goal we need sufficient tools to predict disease progression or response to current or future therapies. Current diagnostic criteria based on the presence of airflow obstruction and symptoms do not integrate the complex pathological changes occurring within the lung, do not define different airway inflammatory patterns, nor do they define different physiological changes or differences in structure as can be defined by imaging. Over recent years there has been interest in describing this heterogeneity and using this information to sub-group patients into airway disease phenotypes. Most approaches to phenotyping have considered disease at a single scale and have not integrated information from different scales (e.g. organ-whole person, tissue-organ, cell-tissue and gene-cell) of disease to provide multi-dimensional phenotypes. Integration of disease biology with clinical expression is critical to improve understanding of this disease. When combined with bio-statistical modelling, this information may lead to identification of new drug targets, new end-points for clinical trials and targeted treatment for subgroups of airway disease patients. It is hoped this will ultimately improve COPD outcomes and represent a move towards personalised medicine. In this review, we will consider these aspects of multi-dimensional phenotyping in more detail.

**References**

1. Barker B, Brightling CE. Phenotyping the Heterogeneity of Chronic Obstructive Pulmonary Disease Clinical Science in press 2012
The need and potential of patient specific modelling

- 400 million people affected with asthma world-wide
- COPD third leading cause of death by 2030
- Airway disease costs EU >56 billion Euros/annum
The need and potential of patient specific modeling

- Validated models to predict airways disease progression and response to treatment
- Platform to translate patient-specific tools
- Personalised management of airways disease.

Towards Personalised Medicine

Asthma UK Asthma Audit 1999

Traditional Asthma Classification

- Aetiology
  - Extrinsic / Intrinsic asthma Rackemann 1927
  - Occupational asthma
  - Exercise induced asthma
  - Catamenal asthma
- Severity/Control
  - BTS
  - ATS Refractory
  - ERS 'Difficult' asthma
  - GINA
  - NAEPP III
- Pathology
- No uniformity
- Descriptive
- Focus on few dimensions of disease
- Patterns of Variable Airflow Obstruction
  - GINA
  - ATS Refractory
  - ERS 'Difficult' asthma
  - Indeterminant asthma
  - Intrinsic asthma
  - Variability asthma
Unravelling Complexity

“If you can not measure it, you can not improve it”.
Lord Kelvin

High Resolution Complex Phenotyping

Resolution

Granularity

Clinical
Symptoms
Signs
Lung function

Histopathology
Cellular assays
Imaging

Molecular
PGx
Genomics
Epigenomics
Proteomics

What is a Phenotype?

A phenotype is any observable characteristic that results from the genetic background as well as the influence of environmental factors and possible interactions between the two.
Airway Disease Domains

Inflammatory Phenotypes

Phenotyping Heterogeneity
Summary

INFLAMMATION PREDOMINANT
Late onset
Greater proportion of males
Few daily symptoms

Concordant disease

Discordant

Symptoms

OBESE FEMALE NON EOSINOPHILIC
High symptom expression

EARLY SYMPTOM PREDOMINANT
Normal BMI
High symptom expression

Discordant

Symptoms

NON-EOSINOPHILIC
Normal BMI
High symptom expression

Refactory Asthma

Cluster Specific Outcomes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Outcomes at 12 months</th>
<th>Study Group</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom predominant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in ICS Dose</td>
<td>+1428.57</td>
<td>-400</td>
<td>0.022</td>
</tr>
<tr>
<td>Severe exacerbation frequency</td>
<td>5.43</td>
<td>2.50</td>
<td>0.198</td>
</tr>
<tr>
<td>Number commenced on OCS</td>
<td>6 (85.7%)</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>
Cluster Specific Outcomes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Outcomes at 12 months</th>
<th>Study Group</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammation predominant</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Change in ICS Dose</td>
<td>Clinical Protocol N=15</td>
<td>Sputum management N=24</td>
<td></td>
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<tr>
<td></td>
<td>+753.33</td>
<td>+241.67</td>
<td>0.22</td>
</tr>
<tr>
<td>Severe exacerbation</td>
<td>3.53</td>
<td>0.38</td>
<td>0.002</td>
</tr>
<tr>
<td>frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number commenced on OCS</td>
<td>2 (13.3%)</td>
<td>9 (37.5%)</td>
<td>0.167</td>
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EARS SYMPTOM PREDOMINANT
Non-eosinophilic, typical BUT
greater symptom expression

OBESE FEMALE NON
EOSINOPHILIC high symptom expression

Specific Anti-eosinophil Therapy

Right Patient, Right Target, Right Outcome

Haldar
NEJM 2009
### Airway geometry: response to mepolizumab

<table>
<thead>
<tr>
<th>Siddiqui et al</th>
<th>Haldar et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy 2009</td>
<td>NEJM 2009</td>
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### At Exacerbations:

**Are there biological clusters?**

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### Study Outline

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Started</th>
<th>Withdrawn:</th>
<th>Other co-morbidities</th>
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<tbody>
<tr>
<td>156</td>
<td></td>
<td>4 died; 7</td>
<td></td>
</tr>
<tr>
<td>145</td>
<td></td>
<td>6 died; 5</td>
<td></td>
</tr>
<tr>
<td>133</td>
<td></td>
<td>2 died; 4</td>
<td></td>
</tr>
<tr>
<td>124</td>
<td></td>
<td>2 died; 5</td>
<td></td>
</tr>
<tr>
<td>116</td>
<td></td>
<td>2 died</td>
<td></td>
</tr>
<tr>
<td>115</td>
<td></td>
<td>2 died</td>
<td></td>
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</tbody>
</table>

Bafadhel et al AJRCCM 2011
Biological Clustering COPD Exacerbations

<table>
<thead>
<tr>
<th>Factor</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<tbody>
<tr>
<td>TNF α</td>
<td>0.80</td>
<td>-0.36</td>
<td></td>
</tr>
<tr>
<td>TNF R1</td>
<td>0.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF R2</td>
<td>0.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCL13</td>
<td>0.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCL17</td>
<td>0.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXCL10</td>
<td>0.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXCL11</td>
<td>0.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL 1B</td>
<td>0.89</td>
<td>-0.36</td>
<td></td>
</tr>
<tr>
<td>IL 5</td>
<td>0.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL 6R</td>
<td>0.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL 8</td>
<td>0.83</td>
<td></td>
<td></td>
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Bafadhel et al. AJRCCM 2011

Bacterial Exacerbation

AUC = 0.89
IL1B 125pg/ml:
90% sensitive
80% specific

Bacterial exacerbation if bacteria in stable state
OR 4.9 (2.4 to 9.9)

Predictors for Sputum Eosinophilia

AUC = 0.85
2% cut off 90% sensitivity, 60% specificity

Eosinophilic exacerbation if eosinophilic in stable state
OR 2.7 (1.3 to 5.7)
At Exacerbations:
Can biomarkers direct therapy?

COPD Exacerbations: Targeted Therapy

Targeted Corticosteroid Therapy at Exacerbation
Targeted Corticosteroid Therapy at Exacerbation

Complex Systems-homeokinesis

AirPROM- Airway Disease Predicting Outcomes Through Patient Specific Computational Modelling
CFD: Therapeutic Response

Small Airway: Structure-Function

Air Trapping: Expiratory CT
**Small airway obstruction in Asthma & COPD**

Hogg *et al*
NEJM 2004

**Airway Remodelling**

**Immunopathology Asthma versus COPD**
The need and potential of patient specific modeling

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Cell</th>
<th>Tissue</th>
<th>Organ</th>
<th>Patient</th>
</tr>
</thead>
</table>

Host Susceptibility
Impaired Innate immunity

PATHOGENS
Bacteria/ Viruses/ Moulds

POLLUTION & Physical Damage

ALLERGENS

PATHOGENS

Patient-Specific Multi-Scale Models

ORMDL3
Cantero-Recasens Hum Mol Gen 2010

Politi J Thero Biol 2010

Mahn 2009 PNAS

Personalised Healthcare / Target Identification
UP & Down the Scales
# Acknowledgements

<table>
<thead>
<tr>
<th>Air PROM</th>
<th>Wellcome Trust</th>
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<tr>
<td>MRC</td>
<td>Asthma Research Council</td>
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