Personalised Medicine: Promise to Practise

Professor Tariq Sethi
King’s Health Partners
Personalised Medicine

- Phenotyping of patients to allow individual decisions about a patient’s diagnosis, treatment, and prognosis.
Construct to Develop Personalised Medicine

Clinical Phenotype

Physiological and or Radiological Characterisation of phenotype

Validation of marker and or determination of therapeutic response in population

Biologic or molecular characterisation of phenotype

+/- Development of therapy
A Genotype Specific Drug to Treat Cystic Fibrosis

- Ivakaftor is an iconic example of personalised medicine.
- The most common CF gene gating mutation is G551D.
- Gating failure mutations prevent the Cl channel opening.
- Ivakaftor potentiates the gating activity of CFTR in gating mutation.

- 1,200 CF patients in the US, 466 patients in the UK have G551D mutation.
- $300,000/patient/year
Target Therapies For Non-Small Cell Lung Cancer

- EGFR TK
- K-RAS
- EML 4-ALK
- MET amplification
- ErB2 Amplification
- PIK3CA
- B-raf
- ErB2
- Unknown
• ~4% of NSCLC patients - 9,000/yr in U.S. and 1,500 in UK have a fusion gene *EML4 & ALK* resulting in constitutive kinase activity

• The kinase activity of the fusion protein is inhibited by crizotinib.

• Crizotinib shrinks or stabilises 90% tumours carrying the *ALK* fusion. Tumours shrunk ≥30% in 57% of patients, costing $113,000/patient/yr

• The U.S. FDA approved crizotinib to treat late-stage NSCLC expressing ALK gene. Approval required a companion diagnostic molecular test
• DEVICE: Abbott Vysis® clinically established platform- FISH
• Utilises FFPE tissue sections
• Interpretation can be made on a minimum of 50 tumour cells, cut-off: positive defined as $\geq 15\%$ of cells exhibiting ALK gene fusion
Lung Cancer Heterogeneity

- EGF-R
- T790M
- PIK3CA
- EGF-R
- T790M
- PIK3CA
- EGF-R
- T790M
- PIK3CA
- EGF-R
- T790M
- PIK3CA
Galectin-3 in Fibrosis

- 30-32Kda protein binds β-galactosides via C-terminal carbohydrate binding domain

<table>
<thead>
<tr>
<th>Normal</th>
<th>Fibrotic</th>
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<tbody>
<tr>
<td>Liver</td>
<td></td>
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<tr>
<td>Kidney</td>
<td>Hepatitis C cirrhosis</td>
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<tr>
<td>Lung</td>
<td>Chronic pyelonephritis</td>
</tr>
<tr>
<td></td>
<td>Usual intersitial pneumonitis (UIP)</td>
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Serum Galectin-3 in patients with IPF.

**Graph 1:**
- X-axis: Control, Stable, Acute, COPD
- Y-axis: [galectin-3] ng/ml
- Data points indicate statistical significance:
  - Control: * (p < 0.05)
  - Stable: ** (p < 0.01)
  - Acute: *** (p < 0.001)

**Graph 2:**
- X-axis: Time (months)
- Y-axis: [galectin-3] ng/ml
- Data points show a decrease in [galectin-3] over time in IPF patients, with COPD patients showing a different trend.
Galectin-3, a Marker of Cardiac Fibrosis Predicts Incident Heart Failure in the Community

- The cumulative incidence of heart failure increases at higher galectin-3 quartiles.
The BG Medicine Galectin-3 assay

- Used in conjunction with clinical evaluation to stratify patients diagnosed with heart failure.
- Measures Galectin-3 in serum or plasma by ELISA using purified mouse anti-human galectin-3 IgG₁ on microtiter plates.
Novel Galectin-3 inhibitor TD139

TD139
Chemical Formula $C_{28}H_{30}F_2N_6O_8S$
Molecular Weight 648.6

Kd = 7nM
Galectin-3 inhibition blocks fibrosis.

Control

Galectin-3 Inhibition

Liver

Kidney

Lung

Collagen µg

Days

* + TD139
COPD

- Heterogeneous disease

- COPD drugs cost the NHS £350M/year - QUALY £120,000-170,000

- Prescribing to correct phenotypes would reduce QUALY cost to £7,000

- Phenotyping may also identify those at risk of developing rapid decline in lung function and co-morbidities such as Lung Cancer and Cardiovascular disease for early intervention
Where to search for biomarkers in COPD?

- Physiological Measurements
- Imaging
- Blood, sputum, urine, BAL and bronchial biopsies
  - Cellular Biomarkers
  - Proteins
  - Genetics
  - Metabolomics
  - Microbiota
- Exhaled air
Eosinophils may predict response to bronchodilators and steroids.

WBC and neutrophils are associated with persistent systemic inflammation, frequent exacerbations and mortality.

COPD patients with baseline plasma fibrinogen > 3.3 g/L had faster FEV1 decline and an increased risk of hospitalisation.

Plasma fibrinogen is likely to be the 1st biomarker qualified for use in drug development.

An increase in exhaled NO in patients with COPD correlates with increased eosinophils, increased bronchodilator and steroid response.
Broad Phenotypes in COPD

• (1) “overlap” or mixed COPD-asthma (25-30%);
  Hx of asthma/atopy or wheeze, eosinophilic inflammation,
  & high exhaled [NO] - respond to bronchodilators/IC.

• (2) frequent exacerbator; (12% >2 or exacerbations/yr, 23% had none)
  Airway and systemic neutrophilic inflammation, systemic
  manifestations, obesity, CVS disease, diabetes.

• (3) emphysema hyperinflation.
  Destruction of alveoli, loss of elastin, expiratory flow limitation,
  air trapping but no increased exacerbation

• Chronic bronchitis is a modifying factor of the main phenotypes.
Treatment Paradigm in COPD

Sputum Eosinophilia, FeNO
Sputum Neutrophilia
Sputum Neutrophilia and frequent exacerbators
Oxidative stress frequent exacerbations
Emphysema/small airways disease
Reversible Airway Obstruction
Chronic sputum, air trapping

- Inhaled Steroids
- CXCR-2 inhibitors
  - Macrolides
  - N-acetyl cysteine
- MMP inhibitors
  - Bronchodilators
  - Anticholinergics
Genes Associated with COPD Phenotypes

- Airflow limitation (eg, CHRNA3/5, IREB2, HHIP, FTO);
- Emphysema (eg, CHRNA3/5, BICD1);
- Exacerbation frequency (eg, HHIP);
- BMI (eg, HHIP, FTO);
Search for Biomarkers in a Heterogeneous Disease
Conclusion

• Single genetic diseases offer a great opportunity to develop personalised medicine and companion diagnostics.

• In polygenetic diseases biomarkers may target existing therapies more effectively and identify patients for early intervention.

• Precise clinical, physiologic and imaging phenotyping and appropriate tissue sampling that reflects the disease is crucial to the development of personalised medicine.

• Simple phenotyping may still have a dramatic impact.