Clinical imaging investigations: PET, CT and MRI

Philip S. Murphy, Ph.D.
Clinical Imaging
Medicines Development
GlaxoSmithKline, UK

philip.s.murphy@gsk.com
AIMS OF DEVELOPING LUNG IMAGING FOR DRUG DEVELOPMENT

• **Develop sensitive, localised markers of lung inflammation**
  – Enable small, rapid POC or pre-POC studies
  – Evaluation of disease modulation within 3-6 months
  – Demonstration that drug is delivered and engaging with the target
  – Interrogation of drug mechanism

• **Superiority over FEV1-based studies in terms of:**
  – De-risking subsequent development; trial cost

• **Translatable**
  – Establish linkage or highlight discordance between the clinical condition and experimental models

• **Development of methods applicable across indications**
  – For example, methods able to define deviation from normal lung function in COPD, fibrosis

• **Deliver endpoints that are relevant to outcome or symptomatology**
ISSUES WITH IMAGING BIOMARKER DEVELOPMENT AND APPLICATION

• Imaging studies can be complex and costly
• Many previous studies performed in small subject numbers at a single centre
  – are the studies sufficiently representing heterogeneous disease?
  – how well will these methods perform in a multi-centre setting?
  – need to repeat such studies to optimise methodology performance
• Methodological and biological variability typically not established
• Limited correlation with other measurements – e.g. histology
• Limited correlation with outcome or symptomatology
ATTRIBUTES OF AN IDEAL IMAGING BIOMARKER

• Linkage to mechanism
• Accessible across multiple trial centres
• Clinically meaningful/linkage to outcome and symptoms
• Acceptable study implementation cost
• Manageable radiation dose or no radiation dose
IMAGING-BASED BIOMARKERS FOR STUDYING PHARMACOLOGY IN THE LUNG

- Molecular/cellular aberrations
  - Inflammation
- Structure
  - Airway structure
  - Emphysema
- Function
  - Ventilation/perfusion
  - Lung mechanics
- Clinical symptoms
  - Symptomatology
IMAGING-BASED BIOMARKERS FOR STUDYING PHARMACOLOGY IN THE LUNG

molecular/cellular aberrations

structure

inflammation

airway structure

emphysema

function

ventilation/perfusion

lung mechanics

clinical symptoms

symptomatology

Graph:

\[ y = 0.0007x + 0.1374 \]
IMAGING THE LUNG WITH PET

- FDG accumulates in activated neutrophils (Jones et al., JNM, 2002).
- Initial work highlighted elevated $[^{18}\text{F}]$-fluorodeoxyglucose uptake in COPD subjects vs. control (Jones et al., ERJ, 2003).
- $[^{18}\text{F}]$-FDG-PET may provide a localised marker of lung inflammation to evaluate novel therapies.
- Challenges:
  - Uptake of FDG in the lung is low
  - FDG uptake is variable in control and disease
  - Complex dynamic scanning protocol
  - Methodology improvements are required

From Chen et al, J Appl Physiol 2006;100:1602

Courtesy of Dr. Delphine Chen, Washington University, St. Louis
Reproducibility of positron emission tomography-measured $[^{18}\text{F}]$fluorodeoxyglucose uptake as a measure of the lung inflammatory burden in chronic obstructive pulmonary disease


American Thoracic Society Annual Meeting
May 18, 2011

Courtesy of Dr. Delphine Chen, Washington University, St. Louis
Methods: Study Design

Visit: Screen
Procedures: PFTs

Visit 1
Procedures: FDG-PET + PFTs

Visit 2
Procedures: FDG-PET

Visit 3
Procedures: FDG-PET + PFTs

10 Patients characterized at screen by: (+8 healthy volunteers)
- GOLD Stage (2 or 3)
- Lung function indices (FEV₁, FVC, FEV₁/FVC, DL₅₀) and lung volumes (TLC, IC, RV)
- Smoking history
- St. George’s Respiratory Questionnaire
- BODE Index
- Clinical COPD Questionnaire
- Chronic Respiratory Questionnaire

*Courtesy of Dr. Delphine Chen, Washington University, St. Louis*
Methods: Image Acquisition

• PET imaging
  – CTI ECAT EXACT HR+ scanner
  – ~10 mCi $[^{18}F]$FDG i.v.
  – Dynamic scan acquisition over 60 min
  – Blood sampling

• PET data analysis
  – ROIs over whole lungs on 8-12 slices/subject
  – *Uptake rate constant* - $K_i$ by Patlak graphical analysis, normalized for intercept (initial volume of distribution of FDG, $K_{iN}$)

*Courtesy of Dr. Delphine Chen, Washington University, St. Louis*
Sample Patlak plot

COPD Patient

\[ K_i \div \text{Intercept} = K_{iN} \]

\[ y = 0.0007x + 0.1374 \]

\[ K_{iN} = 0.0064 \]

Ki – influx constant

amount of accumulated tracer in relation to the amount of tracer that has been available in plasma

Courtesy of Dr. Delphine Chen, Washington University, St. Louis
Results: PET Variability Over Time

Healthy Volunteer

<table>
<thead>
<tr>
<th>Visit</th>
<th>1-7 days</th>
<th>4-6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>0.000</td>
<td>0.002</td>
</tr>
<tr>
<td>Visit 2</td>
<td>0.002</td>
<td>0.004</td>
</tr>
<tr>
<td>Visit 3</td>
<td>0.004</td>
<td>0.006</td>
</tr>
</tbody>
</table>

COPD*

<table>
<thead>
<tr>
<th>Visit</th>
<th>1-7 days</th>
<th>4-6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Visit 2</td>
<td>0.002</td>
<td>0.004</td>
</tr>
<tr>
<td>Visit 3</td>
<td>0.004</td>
<td>0.006</td>
</tr>
</tbody>
</table>

- *p<0.05 between groups but not between visits within each group
- Average within-subject standard deviation
  - COPD: 0.0012 (28%)
  - Healthy: 0.0009 (32%)
- ICC
  - COPD: 0.4
  - Healthy: 0.27
- Solid and dotted gray lines represent mean±SD of all healthy volunteer measurements
**Preliminary Sample Power Calculations Using FDG-PET as the Outcome Measure**

- For a within-subjects placebo-controlled trial, with power = 0.8 and alpha = 0.05:
  - N=10 allows detection of a change in $K_{iN}$ in COPD patients back to the mean of healthy volunteers
  - N=33 allows detection of change in $K_{iN}$ in COPD patients halfway back to the mean of healthy volunteers

*Courtesy of Dr. Delphine Chen, Washington University, St. Louis*
SUMMARY: IMAGING THE LUNG WITH PET

- PET imaging in the lung is challenging, limited FDG uptake limits sensitivity
- FDG-PET is well-characterised in COPD and believed to provide a marker of activated neutrophils
- Enhanced methodologies are likely to help:
  - optimal application of PET/CT:
    - PET vs. HRCT correlations
    - use of HRCT to define PET analysis regions should improve measurement sensitivity
  - respiratory correction methods
- Alternative tracers likely to become important
  - $^{[11]}$C-PK11195 for studying macrophages (Jones et al., ERJ, 2003)
  - $^{[18]}$F-fluoro-L-proline for evaluation of pulmonary fibrosis (Wallace et al., JNM, 2002)
IMAGING-BASED BIOMARKERS FOR STUDYING PHARMACOLOGY IN THE LUNG

molecular/cellular aberrations

structure

inflammation

airway structure

emphysema

ventilation/perfusion

lung mechanics

clinical symptoms

symptomatology
DEFINING LUNG STRUCTURE WITH HRCT

- Extensive application of HRCT, exploiting the latest generations of multi-slice CT scanners combined with advanced image analysis tools
- A shift from high-quality diagnostic images to patient-level quantitative CT in COPD:
  - airway wall measurements
  - emphysema mapping
- Extensive diagnostic application across multiple lung disorders
- Increasing evidence that CT provides phenotypic information (COPDgene.org; eclipse-copd.com)
- Longitudinal studies ongoing to evaluate how CT and other parameters can define disease progression
- Further work required to understand reversibility of different CT parameters in response to different interventions
IMAGING-BASED BIOMARKERS FOR STUDYING PHARMACOLOGY IN THE LUNG

- molecular/cellular aberrations
- inflammation
- airway structure
- emphysema
- ventilation/perfusion
- lung mechanics
- symptomatology
- structure
- clinical symptoms

MRI
An array of lung assessments are available:
- pulmonary hemodynamics, parenchymal structure and motion, measurements with hyperpolarised gas, oxygen transfer

Lung is an unfavourable environment for MRI: low tissue density; complex gas-solid interfaces; extensive motion.

MRI should focus where specific attributes offer advantages relative to other methods (vs. a ‘poor CT scan’):
- Dynamic scanning without ionising radiation dose; sensitivity of MR signal to oxygen

**Perfusion/microvascular permeability** - image the lungs during injection of intravenous contrast

**Lung motion** - rapid serial scanning with MRI can interrogate parenchymal motion, studying altered mechanics in disease

**Lung function** – serial scanning during oxygen delivery enables the study of gas delivery and transport (methods have been operationalised by BiOxyDyn).
LUNG MOTION: Previous MRI Work

Grid-tagging
Chen, Q. et al.
Magn Reson Med 2001; 45: p.24-8

Registration of breath-hold images
Sundaram, T.A. & Gee, J.C.
Med Image Anal 2005; 9: p.524-7

Morgan et al., ERS, 2011, Courtesy of Prof. Geoff Parker, The University of Manchester
Morgan et al., ERS, 2011, Courtesy of Prof. Geoff Parker, The University of Manchester
Methods – Local Lung Motion

Expiratory vector field

Morgan et al., ERS, 2011, Courtesy of Prof. Geoff Parker, The University of Manchester
Results – Local Lung Motion

HEALTHY VOLUNTEERS

COPD PATIENTS

Morgan et al., ERS, 2011, Courtesy of Prof. Geoff Parker, The University of Manchester
OXYGEN-ENHANCED MRI BASICS

- Increased concentration of paramagnetic O₂ in blood:
  - reduced T1
  - increase in signal intensity using T1-weighted MR

VENTILATION
(1) Delivery of oxygen to alveoli
(2) Diffusion into pulmonary capillaries

PERFUSION
(3) Perfusion

O₂, CO₂, alveolus, oxygenated blood, deoxygenated blood.
Oxygen-enhanced MRI

10 min on $O_2$

Baseline $T_1$ map

$\Delta PO_2$

time

Air  O$_2$  Air

$+ A \text{ novel physiological model, derived by Naish & Parker (ISMRM 2010)}$

$> \text{ maps of } \log_{10} V/Q \text{ generated}$

Hubbard et al., ERS, 2011, Courtesy of Prof. Geoff Parker, The University of Manchester
log V/Q maps

Healthy

Moderate COPD

log V/Q histograms

Hubbard et al., ERS, 2011, Courtesy of Prof. Geoff Parker, The University of Manchester
log V/Q histograms

Healthy

Severe COPD

Hubbard et al., ERS, 2011, Courtesy of Prof. Geoff Parker, The University of Manchester
Based on reproducibility assessment: Minimum group sizes to detect a 50% change in IQR V/Q is 14.

> Increased heterogeneity in COPD

Hubbard et al., ERS, 2011, Courtesy of Prof. Geoff Parker, The University of Manchester
SUMMARY: IMAGING THE LUNG WITH MRI

- MRI can provide multiple insights into lung function, multiple measurements within one examination
- Although complex, imaging protocols can be standardised and endpoints quantified
- Multiple follow-up scans can be conducted without radiation dose concerns
- Where such methods can be optimally used in drug development remains an open question:
  - which indications are such methods most relevant?
  - which methods can define treatment response – what is reversible?
  - what timescales?
IMAGING-BASED BIOMARKERS FOR STUDYING PHARMACOLOGY IN THE LUNG

- molecular/cellular aberrations
- inflammation
- airway structure
- emphysema
- ventilation/perfusion
- lung mechanics
- clinical symptoms
- symptomatology

fMRI
STUDYING SYMPTOMS WITH FUNCTIONAL BRAIN IMAGING

• Functional brain imaging with fMRI is a well established research tool across neuroscience disciplines.

• Just like application to pain, fMRI has the ability to define neural correlates of symptoms such as dyspnea.

• Functional imaging can be performed during experimental induction of a breathing challenge.

• Could this be used to develop drugs that could mediate the central response of dyspnea? or define symptomatic relief generally? or generally promote understanding of this symptom?

• More data required to assess whether the approach can define therapeutic intervention.


-Banzett et al., The affective dimension of laboratory dyspnea: air hunger is more unpleasant than work/effort, Am J Respir Crit Care Med., 177, 1384-1390, 2008.


Evans et al., ATS, 2011
The neural dynamics of air hunger perception
SUMMARY

• Multiple methods exist to probe drug delivery, interaction with target and then functional, structural and symptomatic consequences

• Some methods are well-established and continue to evolve (e.g. HRCT), some very nascent lung methodologies have growing potential (e.g. PET)

• Methods continue to develop:
  – Higher resolution, methods to reduce radiation dose burden esp. with HRCT
  – Greater temporal resolution to study lung dynamics
  – Image analysis methods reduce measurement variability and enable consistent derivation of study endpoints

• Methods such as MRI applied to lung are complex and need to be ‘operationalised’ to enable robust multi-site application.

• Translatability is variable but most clinical CT, PET and MRI methods can be conducted in small species

• Where these methods can be optimally applied in drug development will likely evolve
Acknowledgements

• Delphine Chen, University of Washington
• Bill Vennart, Pfizer R&D
• Gary Pitcairn, Pfizer R&D
• Geoff Parker, University of Manchester and BiOxyDyn Limited