Molecular Imaging (MI)

• Molecular imaging can be defined as the in vivo characterization and measurement of biological processes at the cellular and molecular level.

• Molecular imaging has become an important tool for pre-clinical as well as clinical research across a broad range of disciplines, including oncology, cardiology, neurology, psychiatry, and pharmacology.

• MI shows particular promise as a means to accelerate the transfer of laboratory discoveries into clinical practice and the implementation of personalized, molecularly targeted medicine.

Molecular Imaging Techniques

- MI can be performed with many different imaging modalities, including CT, MRI, ultrasound, optical imaging and nuclear medicine techniques.

- Except for MRI spectroscopy and diffusion weighted MR imaging all MI techniques depend on the use of exogenous probes to provide imaging signal or contrast.

- FDG PET-CT is currently one of the most validated and clinically useful MI techniques.

Molecular Imaging Targets

- **Hypoxia**
  - FMISO
  - FAZA
  - Cu-ATSM
  - BOLD

- **Glucose metabolism**
  - $^{18}$F-FDG
  - glucoCEST

- **Amino acid transport/synthesis**
  - $^{11}$C-methionine
  - F-DOPA
  - $^{18}$F-FET

- **Apoptosis**
  - $^{18}$F-ML-10

- **Angiogenesis**
  - CT perfusion
  - DCE MRI

- **Tumour heterogeneity**
  - Textural analysis

- **Cell membrane synthesis**
  - $^{18}$F/$^{11}$C - choline

- **Cell metabolism**
  - MRS

Molecular Imaging Techniques

- X-ray based imaging: CT perfusion
- Ultrasound: Doppler and contrast-enhanced US
- Nuclear Medicine: Scintigraphy, PET
- Magnetic Resonance Imaging: dynamic contrast enhanced (DCE MRI), diffusion-weighted (DW MRI), MR spectroscopy, hyperpolarized MRI
- Optical Imaging: bioluminescence, near infra-red imaging
CT Imaging

**Strengths:**
- Excellent anatomical resolution
- Quick and widely available
- Provides size measurement used in RECIST

**Weaknesses:**
- Ionizing radiation
- Tumour size changes are “last thing” to occur with successful or unsuccessful treatment
- Lack of specific contrast agents
CT Perfusion

- CT perfusion enables measurement of blood flow characteristics through dynamic CT acquisitions following IV contrast administration.

- Can easily be integrated into routine CT imaging protocols.

- Can be used for predicting early response to treatment and monitoring tumour recurrence after therapy.
Ultrasound Based Imaging

- **Strengths**
  - No ionizing radiation
  - Reasonably good resolution
  - Relatively inexpensive
  - Widely available

- **Weaknesses**
  - Limited depth of penetration
  - Limited quantitative information
  - Lack of specific contrast
Contrast-enhanced US assessment of Sunitinib treatment in renal carcinoma
Nuclear Medicine techniques

• Strengths
  • Low quantities required (tracer)
  • Quantitative
  • Can evaluate deep structures
  • Wide range of tracers available
  • Readily combined with CT and MRI
  • Reproducibility understood

• Weaknesses
  • Ionizing radiation
  • Radiotracers expensive and may not be widely available
  • Short half-life of some agents make it logistically challenging
Molecular Imaging with $^{18}$F-FDG

- $^{18}$Fluorine-FDG is a non-specific biomarker of glycolytic metabolism

- Relies on the Warburg effect of differential cell glycolysis in target tissues

- Increased $^{18}$F-FDG uptake exhibited by malignant cells but inflammatory or infective conditions can mimic malignancy – a well-recognized ‘pitfall’
Indications for PET-CT

- Wide range of indications for PET-CT have good evidence that patients benefit from improved disease assessment often resulting in altered management or improved outcomes.

- Comprehensive list of oncological and non-oncological applications of PET-CT and key evidence is available in Guidelines produced by the Intercollegiate Standing Committee on Nuclear Medicine in the United Kingdom (latest version published in December 2013).

PET-CT – Evolving Clinical Applications

• Despite the emergence of PET-MRI the role of PET-CT in initial and subsequent patient management will continue to expand over the next decade.

• Applications in oncology will be refined by standardizing image acquisition, reconstruction and analysis and internationally accepted treatment response criteria will become routine.

• Highly specific PET imaging probes to determine whether therapeutic targets are expressed will become more widely available in the clinical arena.
PET-CT – Evolving Clinical Applications

- Radiotherapy planning
- Treatment response assessment
- Non-FDG tracers
- Cardiac PET-CT
- Neurological PET-CT
- Infection/Inflammation
Radiotherapy Planning
Metabolic Response in Lymphoma
PET Tracers of Interest in Oncology


The Leeds Teaching Hospitals NHS Trust
New gold standard for neuroendocrine tumour imaging

1 month time difference

$^{111}$In-Octreotide

$^{68}$Ga-Octreotate PET
$\alpha_\nu \beta_3$ integrin imaging with $^{18}$F-RGD to predict/monitor anti-VEGF therapy

18F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: a prospective clinical trial

Nikhil V Joshi, Alex T Vesey, Michelle C Williams, Anoop SV Shah, Patrick A Calvert, Felicity H M Craighead, Su Ern Yeah, William Wallace, Donald Salter, Alison M Fletcher, Edwin J R van Beek, Andrew D Flapan, Neal G Uren, Miles WH Behan, Nicholas L M Cruden, Nicholas L Mills, Keith A A Fox, James HF Rudd, Marc R Dweck*, David E Newby*

Summary
Background The use of non-invasive imaging to identify ruptured or high-risk coronary atherosclerotic plaques would represent a major clinical advance for prevention and treatment of coronary artery disease. We used combined PET and CT to identify ruptured and high-risk atherosclerotic plaques using the radioactive tracers 18F-sodium fluoride (18F-NaF) and 18F-fluorodeoxyglucose (18F-FDG).

Methods In this prospective clinical trial, patients with myocardial infarction (n=40) and stable angina (n=40) underwent 18F-NaF and 18F-FDG PET-CT, and invasive coronary angiography. 18F-NaF uptake was compared with histology in carotid endarterectomy specimens from patients with symptomatic carotid disease, and with intravascular ultrasound in patients with stable angina. The primary endpoint was the comparison of 18F-fluoride tissue-to-background ratios of culprit and non-culprit coronary plaques of patients with acute myocardial infarction.
Neurological imaging

Early diagnosis of dementia – which patients with Mild Cognitive Impairment (MCI) do you treat?

- Anti-amyloid drugs treated (top) versus controls (bottom) - $^{11}$C PIB

Rinne et al. *Lancet Neurology* 2010
## Alzheimer’s Disease Guidelines 2011

<table>
<thead>
<tr>
<th>Category</th>
<th>Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biomarkers of Aβ accumulation</strong></td>
<td>1. Abnormal tracer retention on amyloid PET imaging</td>
</tr>
<tr>
<td></td>
<td>2. Low CSF Aβ42</td>
</tr>
<tr>
<td><strong>Biomarkers of neuronal degeneration or injury</strong></td>
<td>3. Elevated CSF tau (total and phosphorylated tau)</td>
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<tr>
<td></td>
<td>4. Decreased FDG uptake on PET</td>
</tr>
<tr>
<td></td>
<td>5. Atrophy on structural MR imaging</td>
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</table>
FDG PET-CT imaging in infection and inflammation

<table>
<thead>
<tr>
<th>Major indications</th>
<th>Clinically useful, but without sufficient evidence base</th>
<th>Usefulness of $^{18}$F-FDG imaging is unclear</th>
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</thead>
<tbody>
<tr>
<td>Sarcoidosis</td>
<td>Infection of intravascular devices, pacemakers, etc.</td>
<td>Diabetic foot infections</td>
</tr>
<tr>
<td>Peripheral bone</td>
<td>AIDS-associated opportunistic infections</td>
<td>Joint prosthesis infections</td>
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<tr>
<td>osteomyelitis</td>
<td>Assessment of metabolic activity in TB</td>
<td>Vascular prosthetic infections</td>
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<tr>
<td>Suspected spinal</td>
<td></td>
<td>IBD</td>
</tr>
<tr>
<td>infection</td>
<td></td>
<td>Endocarditis</td>
</tr>
<tr>
<td>Fever of unknown</td>
<td></td>
<td>?Others</td>
</tr>
<tr>
<td>origin (FUO)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasculitides</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

66 F. Raised inflammatory markers and weight loss

Extensive mural FDG uptake (more than liver) involving the aorta, subclavian arteries, carotid arteries, common iliac and external iliac arteries consistent with a large vessel vasculitis, eventually diagnosed as TA

Large vessel vasculitis (Takayasu’s)
Magnetic Resonance Imaging

• Strengths
  • Relatively widely available
  • Resolution is good and can be excellent
  • Many pulse sequences available
  • Can provide physiological information
  • Variable contrast agents (nodal/vascular)

• Weaknesses
  • Predominantly anatomical in many applications
  • Pulse sequences are not well-standardized across manufacturers or institutions
  • Reproducibility is not yet well characterized
  • Cost
  • NSF (severe complication in patients with poor renal function and repeated Gadolinium dosing)
Functional applications of MRI to predict and detect tumour response

- Dynamic contrast enhanced (DCE)-MRI
- Diffusion Weighted (DW)-MRI
- MR spectroscopy (cellular metabolism)
- Blood oxygenation level dependent (BOLD)-MRI (hypoxia)
Dynamic Contrast Enhanced-MRI

- Provides a semi-quantitative assessment of blood flow
- Potential marker of angiogenesis
Diffusion Weighted-MRI

• Apparent Diffusion Coefficient (ADC) can be used as a marker for prediction and early detection of response to concurrent chemoradiotherapy

• An increase in ADC after treatment indicates a substantial decrease in restriction of water diffusion within the extracellular space
• A change in ADC is associated with increased number of apoptotic cells and loss of cellularity during apoptosis-induced cancer therapy

• Reduced cell density and enlarged extracellular space due to apoptosis or necrosis – suggests successful treatment
Breast Cancer – Response to chemo

Baseline

1st cycle (7 days)

4th cycle (5 days)

Before surgery
Hyperpolarized MRI

- Hyperpolarization involves “activation” of the MR tracer prior to injection

- Hyperpolarization enhances the signal > 100,000 times compared to normal

- $^{3}$Helium MRI for lung imaging and $^{13}$Carbon labelled metabolites for cancer imaging are the most studied to date
Hyperpolarized $^3$Helium MRI

Conventional MRI of the chest
Signal Source is $H_2O$
Lung tissue not visualized

Helispin™ MRI of the chest
Signal Source is $^3$He gas
Major airways and air spaces visualized
Hyperpolarized $^{13}$Carbon MRI

- $^{13}$Carbon - stable and magnetically active isotope

- Signal frequency specific to chemical environment and identifies the compound

- MRI spectroscopy measures biochemical "fingerprint" of tissue at cellular level

- Multiple potential clinical applications
Real-Time Molecular Imaging with $^{13}$C-Pyruvate
Optical Imaging

• **Strengths**
  - Very sensitive to small numbers of molecules
  - Semi-quantitative (attenuation effects)
  - Some use in operating theatre and superficial organ assessments
  - Excellent pre-clinical tool

• **Weaknesses**
  - Not easily scalable to humans, at least for deep structures due to light absorption
  - Limited specific contrast agents (but they can be made)
Horizon Gazing

- Functional parameters such as tumour perfusion and texture derived from CT images providing indices of vascularization and angiogenesis will be used to further refine diagnostic, prognostic, intermediate endpoint and predictive biomarkers.

- Greater emphasis will be placed on integration of clinical, biological and functional imaging data to improve accuracy.

- Software advances will facilitate segmentation of MI data and extraction of additional biomarkers.

- Hardware advances will reduce cost and increase availability of different tracers.
Quantitative Imaging in Cancer

- Marked heterogeneity in genetic properties of different cells in the same tumour is typical and reflects ongoing intra-tumoral evolution.

- Evolution within tumours is governed by Darwinian dynamics, with identifiable environmental selection forces that interact with phenotypic properties of tumour cells in a predictable and reproducible manner.

- Imaging is uniquely suited to measure temporal and spatial heterogeneity within tumours that is both a cause and a consequence of this evolution.

Gatenby RA et al. Radiology 2013; 269: 8-15
Imaging Tumour Heterogeneity


The Leeds Teaching Hospitals NHS Trust
PET-CT perfusion

Metabolic-flow relationships in primary breast cancer: feasibility of combined PET/dynamic contrast-enhanced CT

Ashley M. Groves · Gordon C. Wishart · Manu Shastry · Penelope Moyle · Sharon Iddles · Peter Britton · Mathew Gaskarth · Ruth M. Warren · Peter J. Ell · Kenneth A. Miles

Received: 4 June 2008 / Accepted: 19 August 2008
© Springer-Verlag 2008
PET-MR the next step?
## Multi-parametric on-treatment imaging

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>MR-T2</th>
<th>DW-MR</th>
<th>DCE-MR</th>
<th>FDG PET-CT</th>
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</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>GTV=3.9cm³</td>
<td>GTV=6.4cm³</td>
<td>ADC=1.3x10⁻³mm²s⁻¹</td>
<td>PF=65(ml/min/100ml)</td>
<td>SUVmax=14.8</td>
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<tr>
<td></td>
<td>(image)</td>
<td>(image)</td>
<td>(image)</td>
<td>(image)</td>
<td>(image)</td>
</tr>
<tr>
<td><strong>Fraction 11</strong></td>
<td>GTV=2.4cm³</td>
<td>GTV=6.2cm³</td>
<td>ADC=1.4x10⁻³mm²s⁻¹</td>
<td>PF=75(ml/min/100ml)</td>
<td>SUVmax=10.9</td>
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<td></td>
<td>(image)</td>
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<td>(image)</td>
<td>(image)</td>
<td>(image)</td>
</tr>
<tr>
<td><strong>Fraction 21</strong></td>
<td>GTV=2.1cm³</td>
<td>GTV=2.1cm³</td>
<td>ADC=1.8x10⁻³mm²s⁻¹</td>
<td>PF=116(ml/min/100ml)</td>
<td>SUVmax=6.2</td>
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<td></td>
<td>(image)</td>
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</tbody>
</table>

Subesinghe et al. BMC Cancer 2015; 15:137

The Leeds Teaching Hospitals NHS Trust
% change in anatomical and functional parameters during radiotherapy in comparison with baseline measurements

![Graph showing % change in various parameters during radiotherapy in comparison with baseline measurements. The parameters include CT volume, MR volume, DWI volume, SUVmax, ADC value, and Plasma Flow. The graph compares baseline measurements from #11 and #21.](image_url)
Conclusions

• FDG PET-CT is the most established MI technique and has revolutionised cancer imaging in recent years

• Other MI techniques and new tracers show great promise for helping to personalize therapy in the future

• MI applications related to cardiovascular, neurological and rheumatological disorders are increasing in clinical practice

• Validation of imaging biomarkers and integration with patient specific factors will advance clinical accuracy and utility of MI in the emerging era of precision medicine – a fertile ground for further research