Molecular imaging with MRI – Ready for prime time?

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Overview

1. Introduction
2. Iron oxide
3. Gadolinium
4. Fluorine
5. Discussion
Introduction
Molecular Imaging?

- Weissleder definition (Radiology 2001): **non-invasive** in vivo characterization and **measurement of biologic processes** at the cellular and molecular level.

- Current medical imaging approaches are mostly based on **anatomical changes** – a late stage of most diseases.

- Molecular imaging allows for the detection of altered cellular processes in vivo – much **earlier detection**, which will directly affect patient care.
How is it done?

1. Inject a particle that **specifically targets** a disease process.

2. **Wait** for the non-targeted remainder to clear out of the region.

3. Use **non-invasive imaging** to detect the particles.
How is it done?

- Needs high specificity or sensitivity, preferably both.

- Can be targeted actively (has binding ligand) or passively (taken up by certain cells)

Leuschner & Nahrendorf, Circ Res 2011
Iron Oxide
Iron Oxide

- Iron oxide core coated in dextran
- Comes in different sizes:
  - ultrasmall (~30nm, USPIO, Sinerem/Combidx)
  - small (~150nm, SPIO, ferumoxytol(Feraheme)/Endorem/Feridex)
- Perturbs magnetic field → MR signal loss → dark voids in images

Briley-Saebo et al., JACC 2011
Iron Oxide – Applications

- Pre-label stem cells in vitro
- Visualize correct injection of stem cells in infacted region
- Evaluate migration of stem cells
- Concerns exist with persistence of signal after cell death (Terrovitis et al., Circulation 2008)

Kraitchman et al., Circulation 2003
Iron Oxide - Overview

**Advantages**
- Extremely sensitive ("single cell")
- Approved for the clinic in several specific forms

**Disadvantages**
- Hard to quantify signal
- Signal voids easily confused with artifacts
- May be retained after cell dies
Gadolinium
Gadolinium-based particles

- Gadolinium ion with a shell ("chelate")
- Relaxes water faster $\xrightarrow{}$ positive contrast
- Less powerful, so need many per target particle
Gadolinium - Applications

- **Micelles** that targets macrophage scavenging receptor (MSR)
- Detect **inflammation** content in atherosclerosis.

Amirbekian et al., PNAS 2007
Gadolinium - Applications

- Elastin-binding contrast agent for atherosclerotic plaque
- Single Gd ion, but lots of elastin in a plaque

Makowski et al., Nat Med 2011
Gadolinium- Overview

**Advantages**

- Positive contrast
- Concentration is partially quantifiable

**Disadvantages**

- Signal is weak – high concentration or loading per particle needed
- Targeted particles challenging to translate to clinical setting
Fluorine-19
Fluorine-19

- Has 85% of sensitivity of $^1$H
- No occurrence in the body (or invisible for MRI)
- Need special coil/antenna, but works with normal scanner hardware
Perfluorocarbons (PFC)
Perfluorocarbons (PFC)

- Fluorine-carbon bond is strongest single organic bond: very stable, completely non-toxic
- FDA phase III as blood substitute
  >1 unit (450 ml) injected in humans

- Examples:
  - Perfluorooctylbromide (PFOB)
  - Perfluoro-15-crown-5-ether (CE)
  - Perfluoropolyether (PFPE)
PFC Preparation

- PFC both lipophobic and hydrophobic \( \rightarrow \) emulsion needed
- \(^{19}\)F concentration in emulsion: \(~3\text{M}\)

Slide courtesy of Ulrich Flögel, Univ Düsseldorf
**$^{19}$F MRI of Immune Cells**

- Inject perfluorocarbon emulsion
- Emulsion is **phagocytozed** by immune cells
- Immune cells travel to **site of inflammation**
- $^{19}$F Signal now **only** comes from site of inflammation
$^{19}$F MRI Visualization

Michelangelo
1504

Matthias Stuber
2011

Ruud van Heeswijk
2015

Fusion
Monitoring Inflammation

Temme et al., J Leukoc Biol 2014
Inflammation in Myocarditis

Macrophages

van Heeswijk et al., Circ Imaging 2013
Inflammation in Atherosclerosis

In Vivo Detection

Ex Vivo Confirmation

3D ex-vivo MRI Visualization

van Heeswijk et al., Radiology 2014
Inflammation in Atherosclerosis

van Heeswijk et al., Radiology 2014
Inflammation in Infarction

- Reperfused myocardium in rats
- Monitor immune cell recruitment over time
- Complementary to EGE, LGE and T₂*-weighted
- Observed reduced ¹⁹F in MVO regions

OPW=operational wound, MVO=microvascular obstruction

Ye et al., Circulation 2013
MRI of dendritic cells in stage-4 CRC patients

Ahrens et al. MRM 2014

Slide courtesy of Eric Ahrens, UC San Diego
Fluorine - Overview

**Advantages**
- No background signal → high specificity
- Signal ~ $^{19}$F quantity → quantification
- Inert, safe molecules → “easy” translation
- Good clearance from tissue once released → monitoring over time

**Disadvantages**
- Requires special hardware
- Low signal strength – requires larger concentrations of agent
Some Discussion
## Clinical Perspectives

<table>
<thead>
<tr>
<th>Probe</th>
<th>MRI technique</th>
<th>Type of contrast</th>
<th>Minimum number of detectable cells</th>
<th>Quantification of cell number?</th>
<th>Clinical trial approval?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gd³⁺ or Mn²⁺ labelling</td>
<td>T1-weighted ¹H MRI*</td>
<td>Positive</td>
<td>~10⁵</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>SPIO labelling</td>
<td>T2-weighted ¹H MRI⁺</td>
<td>Negative</td>
<td>1</td>
<td>No</td>
<td>Yes (in the Netherlands, China, Switzerland, Czech Republic, Israel, Poland and United Kingdom)</td>
</tr>
<tr>
<td>PFC labelling</td>
<td>¹⁹F MRI</td>
<td>Hot spot (also known as tracer)</td>
<td>10³–10⁵</td>
<td>Yes</td>
<td>Yes (in USA)</td>
</tr>
<tr>
<td>Metal-binding reporter genes</td>
<td>T2-weighted ¹H MRI⁺</td>
<td>Negative</td>
<td>10⁴</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CEST agents and reporter genes</td>
<td>¹H CEST MRI</td>
<td>Differential (can be colour encoded)</td>
<td>10⁴</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Ahrens & Bulte, Nat Rev Immunol 2013
Clinical Perspectives

- MR molecular imaging has opened up the **non-invasive detection** and monitoring of **molecular and cellular mechanisms** of cardiovascular diseases.

- Custom-made **antibody-targeted particles** face **translation challenges** with the regulatory bodies (FDA, EMA).

- An increasing number of particles has already been through or is **currently in clinical trials**.

- The future looks bright for molecular imaging! (or dark, if you are a fan of iron oxide)
Thank you for your attention!

Grant sponsors

• the Pierre Mercier Foundation
  the Swiss National Science Foundation

Thanks to colleagues at the CHUV in Lausanne

• The CardioVascular MR research center (CVMR, led by Prof. Matthias Stuber)
• The Center for Cardiac Magnetic Resonance (CRMC, led by Prof. Jürg Schwitter)

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