Preclinical Imaging @ Tübingen

Bernd J. Pichler

Department of Preclinical Imaging and Radiopharmacy
Eberhard Karls University of Tübingen
Tübingen, Germany
New Radiopharmacy
Our Facility
Our Facility
Sham vs. Therapy: PI3K

M24 Sham

M09 Therapy

days p.o. 16

days p.o. 20

23

27

30

16

20

23

27

30
Tumor growth: Sham vs. Therapy

\[ y = 0.992e^{0.1364x} \]
\[ R^2 = 0.8913 \]
\[ y = 3.552e^{0.0404x} \]
\[ R^2 = 0.7034 \]

\[ Y = A e^{Bx} \]

T-test → B (Sham) vs. B (Therapy): \( P = 0.00009 \)
Why PET/MRI

**MRI**
- high resolution
- high soft tissue contrast

**PET**
- high sensitivity
- target specific tracer

Added value by PET/MRI

In vivo PET/MR-Spectroscopy

In vivo PET/MR-Spectroscopy

- PET/MR-spectroscopy and $[^{11}\text{C}]$Choline-Tracer administration in VMDk mouse with brain tumor
- $[^{11}\text{C}]$Choline PET versus CSI (tCh)

- spatial extent does not quite well match (dotted lines)
- differentiation between carcinoma *in situ*/hyperplasia/solid tumor?
- maxima do not match

  possibility for complimentary information (high Cho metabolic rate vs. deposited choline)

  *H.F. Wehrl, et al.; Cancer Research; 2013*
In vivo PET/MR-Spectroscopy

In vivo PET/MR-Spectroscopy

Day 14

A. H&E

B. Tk 1

Day 18

E. H&E

F. Tk 1

I. CD 31

J. CD 31

Choline Metabolism studied by PET/MR

• **ex vivo correlation needed**: Histology and SIMS
• secondary ion mass spectrometry imaging (SIMS)

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*scanning ion beam*

*primary ions*  
e.g. 22 keV Au⁺

*tissue section*  
e.g. 12 µm on conducting slide

*ion lens*

*secondary ions and molecular ions*

*ablation at surface, typically 0.1 to 10 atoms per primary ion (10 Å)*

*molecular maps*

*m/z*
In vivo PET/MR-Spectroscopy/SIMS

Heterogeneous Pattern

<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>mean SUV [418.7]</td>
<td>665.3</td>
<td>0.14</td>
<td>0.45</td>
<td>0.65</td>
<td>1.26</td>
</tr>
<tr>
<td>hotspots SUV</td>
<td>1712.2</td>
<td>0.23</td>
<td>0.62</td>
<td>1.43</td>
<td>2.48</td>
</tr>
</tbody>
</table>
Phenotype Identification

- [18F]FDG < 3.9 TMR
- [18F]FDG 3.9 - 9.1 TMR
- [18F]FDG > 9.1 TMR
- ADC > 1009 $10^{-6}$ mm/s

- Solid acinar
- Cystic Hyperplasia
- Cystic Hyperplasia
- Solid nodular

<table>
<thead>
<tr>
<th>Population</th>
<th>[18F]FDG</th>
<th>ADC</th>
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<tbody>
<tr>
<td>solid nodular</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>cystic hyperplasia</td>
<td>-/+</td>
<td>+</td>
</tr>
<tr>
<td>solid acinar</td>
<td>++</td>
<td>-</td>
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</table>
Backwards Inference: Gaussian Distribution

Histology

Probability Map
Metastasis & Premetastatic Niche
Tracking of G-MDSC and TC

- Simultaneous tracking of Cy5-G-MDSC and Luciferase-tumorcells
  - intracardiac injection
  - orthotopic injection (mammary fat pad)
  - i.v. injection

G-MDSC: Granulocyte myeloid-derived supressor cells
G-MDSC in MMFP tumor d8 p.i.

“Butterfly”

Organs

G-MDSC systemic

Tumor cells MMFP
PET/MR in Neuro Research
Brain Function as a Result of Receptor Activation
[\textsuperscript{11}C]PIB – APP23 (I)

\(\beta\)-Amyloid

H&E

![Image](image.png)

**

\(n=6\)

**

\(BP_{\text{nd}}\)
$[^{11}\text{C}]$PIB – APP23 (II)

**Model**

$y = A_2 + \frac{(A_1 - A_2)}{1 + (x/x_0)^p}$

**Reduced Chi-Sqr**

7.2E-04

**Adj. R-Square**

0.996

<table>
<thead>
<tr>
<th>Value</th>
<th>Standard Error</th>
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<tr>
<td>B</td>
<td></td>
</tr>
<tr>
<td>A1</td>
<td>-0.00</td>
</tr>
<tr>
<td>A2</td>
<td>1.49</td>
</tr>
<tr>
<td>x0</td>
<td>21.10</td>
</tr>
<tr>
<td>p</td>
<td>8.48</td>
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<tr>
<td>EC20</td>
<td>18</td>
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<td>EC50</td>
<td>21</td>
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<tr>
<td>EC80</td>
<td>25</td>
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**n=5, *p<0.05, **p<0.01**

Department of

Preclinical Imaging and Radiopharmacy
rCBF (ASL) - APP23

- **p<0.01
- *p<0.05

Control vs Transgenic

<table>
<thead>
<tr>
<th>Time</th>
<th>Control</th>
<th>Transgenic</th>
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<tbody>
<tr>
<td>4 months</td>
<td>240</td>
<td>220</td>
</tr>
<tr>
<td>9 months</td>
<td>210</td>
<td>190</td>
</tr>
<tr>
<td>11 months</td>
<td>200</td>
<td>180</td>
</tr>
<tr>
<td>16 months</td>
<td>190</td>
<td>170</td>
</tr>
<tr>
<td>18 months</td>
<td>180</td>
<td>160</td>
</tr>
<tr>
<td>24 months</td>
<td>170</td>
<td>150</td>
</tr>
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</table>

n=5
Targeting Aspergillus Infection: Diagnosis & Treatment

The approach of the consortium is to develop new disease specific tracers based on monoclonal antibodies along with molecular imaging technologies PET/MR and microscopy.

Newly developed tracers shall then be functionalised by a combined labelling with radio-isotopes allowing diagnostic PET imaging but also radio-immuno-therapy, thus representing truly anti-infectious theranostics.

This would provide a framework for new tools in the management not only of this rare but life-threatening mycosis but principally also for other infectious hazards.
• **Invasive Aspergillosis**
  – *A. fumigatus* most prevalent airborne fungal pathogen
  – size of conidia: 2-3 µm → ability to reach lung alveoli
  – major cause of infectious morbidity and mortality in immunocompromised patients
  – bone marrow and organ transplants
Results – $[^{64}\text{Cu}]\text{DOTA-JF5}$

- strong uptake of $^{64}\text{Cu}$-DOTA-JF5 in the lungs of $A. \text{fumigatus}$ infected animals (indicated with the white arrows in Fig. 1)
- quantification of PET/MRI images shows a specific binding of $^{64}\text{Cu}$-DOTA-JF5 to $A. \text{fumigatus}$ infected lung tissue
- the ex vivo biodistribution strongly verifies the findings
Imaging of MMP/ROS
# Imaging of PNMs

<table>
<thead>
<tr>
<th></th>
<th>naïve mouse</th>
<th>depleted mouse (RB6-8C5)</th>
<th>stimulated mouse (G-CSF)</th>
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</thead>
<tbody>
<tr>
<td>PET</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Static** PET scans of naïve (left), Gr-1-depleted (middle) and G-CSF stimulated (right) mice 24h after *i.v.* $[^{64}\text{Cu}]$DOTA-RB6-8C5 tracer injection. Tracer accumulation was decreased in bones, LNs and spleens of PNM depleted mice and enhanced in G-CSF stimulated mice.
Molecular Imaging Targets

- **Caspase 3/7**
- **HK II**
- **18F-FDG**
- **18F-FET**
- **18F-FLT**
- **18F-FAZA**
- **18F-FMISO**
- **18F-Gln**
- **18F-ICMT11**
- **18F-Annexin 5**
- **18F-FASN**
- **18F-FASN-Inhib.**
- **SA-αL-Fuc**
- **18F-SA-αL-Fuc-Inhib.**

Fluorine-18 labeled compounds for imaging targets:

- **DNA Synthesis**
- **Protein Biosynthesis**
- **Glutaminolysis**
- **Trapping**
- **Nitroreductase**

**Tumor Cell**

**Blood Vessel**

**Perfusion**

**68Ga-NOTA-RGD-Peptide**

**αVβ3 Integrin**

**Lysosome**

**H+**

**FAP**

**Cancer Associated Fibroblast**

**64Cu-FAP-AB**

**FASN**
# Multiparametric Imaging

## Molecular - PET

<table>
<thead>
<tr>
<th>Target</th>
<th>Biomarker</th>
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<tbody>
<tr>
<td>Metabolism</td>
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</tr>
<tr>
<td>• Glucose</td>
<td>$^{[18F]}$FDG</td>
</tr>
<tr>
<td>• Aminoacid</td>
<td>$^{[18F]}$FET</td>
</tr>
<tr>
<td></td>
<td>$^{[11C]}$MET</td>
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<tr>
<td></td>
<td>$^{[18F]}$GLA</td>
</tr>
<tr>
<td>Fatty Acid</td>
<td>FASN</td>
</tr>
<tr>
<td>Stroma</td>
<td>$^{[64Cu]}$FAP</td>
</tr>
<tr>
<td>Proliferation</td>
<td>$^{[18F]}$FLT</td>
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<tr>
<td>Hypoxia</td>
<td>$^{[18F]}$FAZA</td>
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<tr>
<td></td>
<td>$^{[18F]}$FMISO</td>
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<tr>
<td>Angiogenesis</td>
<td>$^{[68Ga]}$RGD</td>
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<tr>
<td>Perfusion</td>
<td>$^{[15O]}$H$_2$O</td>
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<tr>
<td>Apoptosis</td>
<td>$^{[18F]}$4CMT11</td>
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<tr>
<td></td>
<td>$^{[18F]}$AnnexIn V</td>
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<tr>
<td>Senescence</td>
<td>$^{[18F]}$SA-aL-Fuc</td>
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</table>

## Morphological - MRI

<table>
<thead>
<tr>
<th>Target</th>
<th>Biomarker</th>
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<tbody>
<tr>
<td>Tissue contrast</td>
<td>$T_1$</td>
</tr>
<tr>
<td></td>
<td>$T_2$</td>
</tr>
<tr>
<td></td>
<td>Relaxation</td>
</tr>
<tr>
<td></td>
<td>$T_1$ map</td>
</tr>
<tr>
<td></td>
<td>$T_2$ map</td>
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<td>GD</td>
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## Functional - MRI

<table>
<thead>
<tr>
<th>Target</th>
<th>Biomarker</th>
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<tbody>
<tr>
<td>Oxygenation</td>
<td>BOLD</td>
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<tr>
<td>Diffusion</td>
<td>ADC</td>
</tr>
<tr>
<td>Perfusion</td>
<td>BOLD</td>
</tr>
<tr>
<td>Interstitial Pressure</td>
<td>XX</td>
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<tr>
<td>Metabolites</td>
<td>$^1$H Spectroscopy</td>
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## Hyperpolarized Imaging

<table>
<thead>
<tr>
<th>Target</th>
<th>Biomarker</th>
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<tbody>
<tr>
<td>Enzyme Activity</td>
<td>Lactate</td>
</tr>
<tr>
<td></td>
<td>Pyruvate</td>
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</table>
Towards Understanding Imaging Signals

- Metabolomics
- Proteomics
- Data Mining
- Clinical Relevance

Non-invasive PET/MR Imaging

Molecular -PET
Morphological-MRI
Functional-MRI

Hyperpolarized Imaging