22.561 Final Project

$^{19}$F Magnetic resonance imaging of perfluorooctanoic acid encapsulated in liposome for biodistribution measurement

Magnetic Resonance Imaging

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Motivation and Challenges

Visualization of the tissue distribution of perfluorooctanoic acid (PFOA, C$_7$F$_{15}$COOH) by $^{19}$F-MRI for pharmacological studies of similar compounds (many applications; toxicity)

Wide-range distribution of chemical shifts of $^{19}$F-containing metabolites $\rightarrow$ molecular imaging and tissue function evaluations

$^{19}$F-MRI for image contrast enhancement

- No background $\rightarrow$ $^{19}$F signal is the contrast for $^1$H-MR image (anatomy)
- $^{19}$F has the next highest MR sensitivity (83% of $^1$H)

Challenges intrinsic to $^{19}$F-MRI

- $^{19}$F has Long T1 $\rightarrow$ long acquisition time; Short T2 $\rightarrow$ signal attenuation
- Chemical shifts of $^{19}$F NMR $\rightarrow$ chemical shift image artifacts (although preferred to trace the metabolism)
- Signal can only be obtained from the agents retained in tissue $\rightarrow$ SNR is the major concern for $^{19}$F-MRI
Solution – Chemical Shift Selected Fast Spin-Echo

Chemical shift artifacts

$\rightarrow$ chemical shift selected RF pulse

Short T2

$\rightarrow$ Spin Echo (SE) to preserve the signal

Long T1 $\rightarrow$ Fast Spin Echo (FSE) to shorten acquisition time

Multiple phase-encoding steps with a single excitation (90° RF) and multiple echoes (180° RF), # of echoes per TR = echo train length (ETL)

Acquisition time reduced proportional to ETL

Effective echo time (TE) = maximum TE / ETL

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Chemical Shift Selection

9.4T (376.2 MHz)
TR = 0.2 s, 128 scans

The $^{19}$F NMR spectra in the female mouse stomach and liver were measured 0.4 and 2.7 h after the administration of the PFOA-liposome solution, respectively.

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- Chemical shift between -CF$_3$ group and other -CF$_2$ groups > 35 ppm (10 times that of fat and water $^1$H) $\rightarrow$ frequency difference $\sim$14 kHz
- Chemical shift selection was able to eliminate chemical shift artifacts.
- Only -CF$_3$ signal was excited $\rightarrow$ no the signal intensity modulation by J-coupling caused by adjacent $^{19}$F atoms
\textbf{\textsuperscript{19}F Relaxation Times}

In vivo and in vitro relaxation times of the CF\textsubscript{3} signal of PFOA

<table>
<thead>
<tr>
<th>Standard deviations in parentheses</th>
<th>PFOA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(T_1) (ms)</td>
</tr>
<tr>
<td>In vivo</td>
<td>140 (20)</td>
</tr>
<tr>
<td>In excised liver</td>
<td>300 (30)</td>
</tr>
<tr>
<td>In PFOA-liposome</td>
<td>400 (40)</td>
</tr>
<tr>
<td>In ethanol</td>
<td>1900 (100)</td>
</tr>
</tbody>
</table>

- \(T_1\) by Inversion Recovery \(\rightarrow\) double dynamic range
- \(T_2\) by Carr-Purcell-Meiboom-Gill (CPMG) \(\rightarrow\) refocusing pulse error corrected at even echoes
- \(T_2\) of water \(^1\text{H}\) \(\sim\) several tens to hundreds of ms; \(T_2\) of -CF\textsubscript{3} group of PFOA \(<\) 10 ms \textit{in vivo}
  
  Short \(T_2\) in liposome probably due to high solution viscosity

- Both \(T_1\) and \(T_2\) of -CF\textsubscript{3} of PFOA were shortened \textit{in vivo}
  
  Molecular motion of PFOA restricted, especially the -CF\textsubscript{3} group
In Vitro $^{19}$F-MRI of PFOA-Liposome Solution – Parameter Optimization for In Vivo $^{19}$F-MRI

ETL = 2 in (b) more effective than ETL = 4 in (c)

- [PFOA] = 5.4 mM; Effective TE = 1 ms
- For ETL = 4, last two echoes at 3, 4 ms
- T2 of $-\text{CF}_3$ of PFOA in solution = 2.3 ms

Maximum TE value constrained by T2, increase ETL to reduce effective TE

- More $180^\circ$ RF pulses per TR
- Requires strong and rapidly switching gradients
- Under instrumental constraints, ETL = 2 was used as the optimal value for in vivo $^{19}$F-MRI.

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In Vivo $^{19}$F-MRI

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1 mL PFOA-liposome solution orally administered to mice with fasting for 4 hr

9.4T (376.2 MHz); Chemical shift selection: Gaussian pulse, 9kHz band width; TR = 0.15 s; Effective TE = 1 ms; ETL = 2; 64 x 16 data points; FOV = 8cm x 4cm; No slice selection; Acquisition time = 12min

PFOA initially in the mouse stomach → at 1 hr, began to distribute into the liver → at 2.7 hr, PFOA mostly transferred to the liver
PFOA Tissue Distribution Quantification by $^{19}$F-NMR

Mice were sacrificed after $^{19}$F-MRI and the organs were excised and cut into pieces for $^{19}$F-NMR.

$^{19}$F-NMR signal intensity of -CF$_3$ of PFOA from different organs was measured and calibrated by signal from benzene solution of trifluoroacetamide (CF$_3$CONH$_2$) for quantification.

The lowest concentration of PFOA that $^{19}$F-MRI was able to visualize was estimated from the images $\rightarrow \sim 1$ µmol PFOA / g tissue

Assume tissue density = 1g/mL $\rightarrow \sim 1$ mM of PFOA $\ll \sim 100$M of water $^1$H

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Concentration (µmol/g tissue)</th>
<th>Percent dose (%/g tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>1.74 (± 0.41)</td>
<td>32.0 (± 8.6)</td>
</tr>
<tr>
<td>Plasma</td>
<td>0.74 (± 0.01)</td>
<td>13.6 (± 0.2)</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.30 (± 0.05)</td>
<td>5.5 (± 0.9)</td>
</tr>
<tr>
<td>Lung</td>
<td>0.27 (± 0.02)</td>
<td>5.0 (± 0.4)</td>
</tr>
<tr>
<td>Intestine</td>
<td>0.25 (± 0.08)</td>
<td>4.6 (± 1.5)</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.15 (± 0.03)</td>
<td>2.8 (± 0.6)</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.14 (± 0.01)</td>
<td>2.5 (± 0.2)</td>
</tr>
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Conclusions

• Tissue distribution of PFOA was successfully traced by $^1$H and $^{19}$F-MRI, the latter of which used chemical shift selected fast spin-echo method.

• It was necessary to administer PFOA at high concentration of 100 mg (0.19 mmol)/kg body weight, corresponding to 20 times the dose using radiolabel method. $\rightarrow$ major challenge for $^{19}$F-MRI is SNR

• Contrast agents that elongate T2 and shorten T1 are desirable.
Questions?

• Would you use ETL = 3 or 4 for \textit{in vivo} $^{19}$F-MRI since T2 = 6.3ms instead of 2.3ms?

• If the acquisition time is 12 min (0.2 hr) and PFOA is moving, what actual states do the images at 0.4, 0.6, 1.0 hr ... represent?

• Is FSE is the optimal sequence for $^{19}$F-MRI?

• How to make use of all the $^{19}$F nuclei in PFOA instead of -CF$_3$ only since the concentration of PFOA is the limiting factor?