Surface-Enhanced Raman Spectroscopy (SERS) for Intraoperative Brain Tumor Imaging and Photothermal Therapy

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SCIT seminar, October 05, 2017
Background: Intraoperative Detection of Brain Tumors

- Intraoperatively it is difficult to distinguish the exact margin between brain tumors and the adjacent normal brain tissue.
- Residual cancer cells result in tumor recurrence.
- Resection that includes normal brain tissue can result in neurological deficits.
- Developing intraoperative methods to better delineate brain tumor margins.
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Background: Surface Enhanced Raman Spectroscopy (SERS)

Raman

- Raman intensity proportional to:
  - laser power density,
  - target analyte conc.

= bulk analyte

= chemi/physisorbed surface analyte

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Background: Intraoperative Raman Spectroscopy in Humans

Background: Intraoperative Raman Spectroscopy in Humans

Background: In Vivo Evaluation of Multiplexing Different NPs

- High sensitivity
- Multiplexing
Background: Intraoperative Surface Enhanced Raman Spectroscopy

Aims, Significance & Study Design

Silica coated gold Nanoparticles
NIR fluorescent dye
Poly (ethylene glycol)

Nanoparticles injection into brain tumor
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- Silica coated gold Nanoparticles
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Nanoparticles injection into brain tumor

Raman spectroscopy/imaging

Raman Laser

Laser

Raman scattering

Intensity (a.u.)

Raman Shift / cm⁻¹
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Nanoparticles injection into brain tumor

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Raman spectroscopy/imaging

Laser

Raman Laser

Raman scattering

Heat

Photothermal therapy
Methods: Tumor Implantation and Bioluminescent Imaging
(U87 Brain Tumor Cells)

4 weeks after implantation
Methods: Preparation of the Nanoparticles

(a) Gold Raman active layer
   Silica
   Nanoparticles
   PEG-maleimide

(b) PEG coated Raman Nanoparticles

(c) PEG-maleimide + Thiolated nanoparticles (NP) → PEG Stabilized PEG coated nanoparticles (NP)

Stanford University
Department of Radiology
School of Medicine
Results: Nanoparticles Characterizations

Hydrodynamic size: 149.5nm
Polydispersity index: 0.063

Zeta potential: -27.2mV

Raman spectrum

Intensity (a.u.)

Counts (a.u.)

Raman signal intensity (a.u.)

Intense: 800, 1000, 1200, 1400, 1600, 1800 cm⁻¹
Results: Mouse brain MRI

(T2-weighted, U87 tumor)
Results: Intratumoral Diffusion of the Raman Nanoparticles

*(NPs volume and concentration ~ 2 µL & 1 nM)*
1) Nanoparticles infusion

Silica coated gold nanoparticles
Poly (ethylene glycol)

2) Raman spectroscopy/imaging

Raman Laser
Laser
Raman scattering

Brain tumor
Normal Brain
Leaky blood vessels
Tumor

Intensity (a.u.)
Raman Shift / cm⁻¹
800 1200 1600
## Summary:

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Tumor</th>
<th>Dog’s weight (kg)</th>
<th>Nanoparticles concentration (nM)</th>
<th>Nanoparticles volume (mL)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Oligodendroglioma</td>
<td>8.7</td>
<td>0.5</td>
<td>8.7</td>
</tr>
<tr>
<td>2</td>
<td>Psammomatous Meningioma</td>
<td>24.7</td>
<td>0.5</td>
<td>24.7</td>
</tr>
<tr>
<td>3</td>
<td>Fibrolastic Meningioma</td>
<td>20.3</td>
<td>0.5</td>
<td>20.3</td>
</tr>
</tbody>
</table>
Dog Frontal Lobe Meningioma post-contrast T1 MRI and histology:

- **Pre-Operative**
- **Post-Operative**

Anterior (ventral) tissue

Posterior (dorsal) tissue

Histology of the tumor tissue (H&E)

Whorls and Psammoma bodies (center) and dura mater (left, right, bottom)
SEM at a tissue section, showing nanoparticles embedded in tumor tissue:
Elemental Analyses Using Electronic Microscopy:

Electron beam on the nanoparticles
Nanoparticles delivered to tumor

Tumor tissue surface

Si peak
Gold peak
Conclusions & Future Directions

• Surface enhanced Raman spectroscopy shows potential for simultaneous detection and ablation of brain tumors
• Nanoparticles systematic design appears to help their uniform intratumoral diffusion in brain microenvironment
• These are proof of concept data that require further investigation for clinical translation
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