Image-Guided Surgery using Invisible Near-Infrared Fluorescent Light

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Disclosures

• This talk describes the off-label use of indocyanine green and methylene blue, two NIR fluorophores that are FDA-approved for other indications.

• The FLARE™ imaging system is investigational only and not approved for the indications shown.

• All intellectual property is owned by the Beth Israel Deaconess Medical Center, a teaching hospital of Harvard Medical School. As inventor of the FLARE™ technology, Dr. Frangioni may someday receive royalties if products are ever commercialized.

• None of the technology is licensed at the present time.

• I have no real or deferred equity interest, or any other interest, in any company.

• I do not consult for any company.
Objectives

- To teach the fundamental optics underlying near-infrared fluorescence imaging.

- To describe the fundamentals of imaging system design and NIR fluorescent contrast agent clinical translation.
Outline

I. Principles of Invisible Near-Infrared Light
II. NIR Fluorescence Surgical Imaging System Design
III. NIR Fluorescent Contrast Agents
IV. Clinical Translation of Devices & Contrast Agents
VI. Summary and Future Directions
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Near-Infrared Light and Biomolecules

Tissue Attenuation as a Function of Wavelength

**Skin** (Rayleigh-Type, i.e., Wavelength-Dependent Scatter)

- Absorbance
- Scatter
- Total

**Breast** (Mie-Type, i.e., Non-Wavelength-Dependent Scatter)
Sensitivity Curve of the Human Eye under Well-Lit (Photopic) or Poorly-Lit (Scotopic) Conditions

Photopic

Scotopic
Near-Infrared (700-900 nm) Fluorescent Light

- Invisible to the human eye, so no alternation of the surgical field (no learning curve)
- Safe at the fluence rates used
- Relatively high transmission through tissue (mm depths easy, 1 cm depths very hard)
- Relatively low autofluorescent “background”
- Exogenous NIR contrast agents permit high sensitivity detection of “targets” *in vivo*
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FLARE™ Imaging Technology

Designed with the principles of oncologic surgery in mind:

• Real-time image-guided resection of tumors

• Real-time image-guided avoidance of nerves, blood vessels, glands, etc.

• Simultaneous imaging and superimposition of above with surgical anatomy
FLARE™ Imaging System Filter Design

(Chroma Sputtered Filters, 4-5 logs at boundaries, ≥ 98% transmission)
An Optical Imaging Platform for Image-Guided Surgery

- **800 nm NIR Camera**
- **700 nm NIR Camera**
- **800 nm-848 nm Band-pass**
- **794-900 nm**
- **689-725 nm Band-pass**
- **700 nm NIR Camera**
- **650-794 nm Band-pass**
- **400-650 nm Band-pass**
- **Color Video Camera**
- **Fluorinert Cooling Plate**
- **High-Power White/NIR 1/NIR 2 LED Light Source**
- **Dichroic #1**
- **Dichroic #2**
- **Image Intensifier**
- **Lens Motors**
- **Color Video**
- **Fluorescence 700 nm**
- **Fluorescence 800 nm**
- **Excitation Light Module**
  - **White**: 400-650 nm
  - **670 nm**: 656-678 nm
  - **760 nm**: 745-779 nm
- **Surgical Field**

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**Color Video**
**700 nm Fluorescence**
**800 nm Fluorescence**
**Color/NIR or Ratiometric Merge**
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Clinically-Available NIR Fluorophores

700 nm Fluorescence

Methylene Blue

Ureter imaging
Bile duct imaging
Cardiac perfusion imaging
Insulinoma

M.W. 320

800 nm Fluorescence

Indocyanine Green

NIR angiography
Perforator flap mapping
Sentinel lymph node mapping
Intraluminal imaging

M.W. 776
Methylene Blue and Indocyanine Green in Swine

Methylene Blue (Single IV Injection, 1 mg/kg, 5 min wait)

Ureters

Bile Ducts

Indocyanine Green (Single IV Injection, 2 mg, 2 hr wait)

Bile Ducts

Matsui et al, Surgery, in press
Two-Channel Assessment of Lymph Nodes and Sentinel Lymph Nodes in Swine

Two-Channel Simultaneous Assessment of Intravascular Thrombi and Blood Flow in Pig using a Stop-Motion Gating System

Tanaka et al., J Thor Cardiovasc Surg, 2009
Gioux et al., J Biomed Optics, 2009
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### Orders of Magnitude in Drug (Contrast Agent) Dosing

<table>
<thead>
<tr>
<th>Modality</th>
<th>“Typical” Intravenous Human Dose (g)</th>
</tr>
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<tbody>
<tr>
<td>CT</td>
<td>75 cc of 930 mM solution = 56 g</td>
</tr>
<tr>
<td>MRI</td>
<td>15 cc of 500 mM solution = 7 g</td>
</tr>
<tr>
<td>Optical (NIR)</td>
<td>5 cc of a 1 mM solution = 5 mg</td>
</tr>
<tr>
<td>SPECT</td>
<td>20 mCi (10,000 Ci/mmol) = 2 μg</td>
</tr>
<tr>
<td>PET</td>
<td>20 mCi (10,000 Ci/mmol) = 2 μg</td>
</tr>
</tbody>
</table>

- 2 Regular Strength Tylenol = 600 mg
- FDA definition of micro-dosing = 100 μg

[Eligible for eIND](#)
Methylene Blue for Tumor Resection (Insulinoma)

Winer et al, Ann Surg Onc, in press
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Image-Guided Surgery using Invisible NIR Fluorescence

• FLARE™ imaging technology was designed with the principles of oncologic surgery in mind:
  
  Color Video: Surgical anatomy  
  NIR Channel #1: Resection of malignant cells  
  NIR Channel #2: Avoidance of normal structures

• Multiple imaging systems are now available, and are sure to improve over the next 5 years

• Indocyanine green and methylene blue are available now for certain (off-label) applications

• Next-generation contrast agents will lag by 2 to 5 years, however optimized agents already validated pre-clinically. Unfortunately, patience is required
FLARE™ Imaging Network

Beth Israel Deaconess Medical Center, Boston
  Bernard Lee, M.D.
  Samuel Lin, M.D.

Brigham & Women’s Hospital, Boston
  Yolonda Colson, M.D., Ph.D.

Dana-Farber Cancer Institute, Boston
  Susan Troyan, M.D.

Leiden University Medical Center, The Netherlands
  Alex Vahrmeijer M.D.
  Cornelius van de Velde, M.D.

University of Basel, Switzerland
  Marcus Zuber, M.D.

Hokkaido Univ Hospital, Sapporo, Japan
  Eiichi Tanaka, M.D., Ph.D.
  Satoshi Kondo, M.D.
Acknowledgements (Presented Data)

Frangioni Laboratory (BIDMC):
  Hak Soo Choi    Alan Stockdale
  Sylvain Gioux  Summer Gibbs-Strauss
  Vida Kianzad   Eiichi Tanaka
  Aya Matsui     Rafiou Oketokoun
  Joshua Winer

BIDMC: Bernie Lee    Susan Troyan

BWH: Yolonda Colson  Frederick Chen

GSU: Maged Henary    Gabor Patonay
   Lucjan Strekowski
Acknowledgements (Funding)

R01-CA-115296 (BRP)
R01-EB-005805
R01-CA-134493
R21/R33-EB-000673
R21/R33-CA-88245
R21-CA-110185
DOE DE-FG02-01ER63188
CIMIT Awards (4)
Doris Duke Charitable Foundation
GE Healthcare
GE Global Research
CaPCURE
Center for Molecular Imaging
at the
Beth Israel Deaconess Medical Center

Seeing is Curing™

Frangioni Laboratory:
www.frangionilab.org

Longwood Small Animal Imaging Facility:
www.longwoodsaif.org
Relevant Reviews


