Cancer Viewing Glasses for Fluorescence Image-Guided Cancer Surgery

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Disclosure

I do not have financial conflict of interest based on the materials presented.

http://www.molecularimagingcenter.org/
Outline

Challenges in oncologic surgery
Molecular approaches to light up cancer cells
Cancer viewing goggles
Conclusions

Optical imaging: a pesky orphan in radiology

- X-ray: an empire
- MRI: a mansion
- Nuclear imaging: a home
- Ultrasound: a room
- OI: cute but homeless!

Optical imaging: an orphan no more
Multiscale imaging reveals cancer complexity

Cancer – the enemy within

Uncontrolled cell growth and altered function

Oncologic surgery

Primary treatment method for most solid tumors
Challenges in the operating room

Where is the tumor?

Challenges in the operating room

Where is the sentinel lymph node; what is the status?

Challenges in the operating room

Is the surgical margin negative?
Net surgical outcome

Subjective decision; variable outcomes

Goal

• Eliminate guesswork

• Prevent local relapse

• Selectively kill cancer cells

The power of light
Strategy

Tag
Visualize
Eradicate

Tumor survival pathways

Adapted from Hanahan et al. Cell 2000, 100:57

Fluorescent molecular probes
An intractable proposition

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Universal cancer-targeting imaging agent and drug


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LS301 targets diverse tumors

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LS301 identifies spontaneous tumors

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Transgenic mouse MMTV-PyMT spontaneous breast cancer model
**LS301 identifies microscopic tumors**

![Image of microscopic tumors]

**LS301 selectively binds to human cancer tissue**

![Image of cancer tissue binding]

PDX breast cancer model

**Detection of invading tumor margins**

*Green Arrow: Invading Cancer Frontier*

*Red Circle: Blood Vessels*
Optical surgical guidance systems

- Non-ionizing radiation – suitable for OR
- High detection sensitivity – ideal for MI
- Real-time feedback – improves surgical decisions
- Detection of small cancer cells – minimize relapse
- Affordable – relative to other imaging methods

Fluorescence image guidance systems in clinic

Crowded operating room

**Goals:**
- Maximize spectral separation
- Maintain light output $>5$ mW/cm²
- Maintain surgical lights

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**Illumination module**
NIR light source

Supplies 5mW/cm² peak light output at 760 nm and 50 cm distance

Generation 2: Laser light source

10 mW/cm², 50 cm distance

Optical Fiber 780 nm (NA=0.39, 400μm)
Plano Convex Lens (20 mm)

5 degree Diffuser minimizes specular reflection

Imaging module

Goals:
- Signal detection
- Compact form-factor
- Autofocusing
Imaging module

Camera size: 22x26x34mm

Mini stepper: Motor to match working distance

Display module

Goals:
- High resolution, large field-of-view
- Compact and light-weight
- Ease of use

Processing module

Goals:
- Real-time image processing
- Generation of color-NIR images
- User-friendly operation

Specifications

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Specification</th>
</tr>
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<tbody>
<tr>
<td>NIR sensor quantum efficiency</td>
<td>36% at 810 nm</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>100-150x, 100x, 70x, 50x, 15x, and working distance = 900mm</td>
</tr>
<tr>
<td>Bandwidth</td>
<td>8-12.5 nm</td>
</tr>
<tr>
<td>Signal</td>
<td>50 nm (tem) + 155 nm (tissue) in 4NEM0</td>
</tr>
<tr>
<td>illumination</td>
<td>16 LED light, 760 nm, 750 nm, FWHM at 50 cm</td>
</tr>
<tr>
<td>Spatial resolution</td>
<td>320 um</td>
</tr>
<tr>
<td>Frame Rate</td>
<td>24 fps</td>
</tr>
<tr>
<td>Tumor Fluorescence Test</td>
<td>tumor (395 and 470 nm), MB = 1.2, 10ips, 50 cm</td>
</tr>
<tr>
<td>Depth detection limit</td>
<td>5 mm in tissue mimicking phantom, SBR &gt; 1.2, 24 fps, 50 cm</td>
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Detection/resection of multifocal tumors

White light

Fluorescence

Image-guided tumor resection

2nd module
Companion dog clinical trial

- Phase I: Standard of care tumor resection and ex vivo GAINS imaging
- Phase II: GAINS-guided tumor resection
- Histologic verification of margin status
- LS301 injected 24 h prior to surgery
- CVG detects canine tumors
- Intraoperative use
- Ex vivo tumor fluorescence
- LS301 specifically accumulates in canine tumors

Clinical trials

- Number of patients completed: 58
- Cancer types: breast, skin, liver
- Image guidance: sentinel lymph node, margin assessment, survey of surgical ROI
- Contrast agent: ICG
Human pilot study

Real-time visualization

SLN visualization in a Melanoma patient

SLN visualization in a BC patient

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
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<tbody>
<tr>
<td>Radionuclide</td>
<td>86.67 ± 0.27%</td>
</tr>
<tr>
<td>CVG</td>
<td>100%</td>
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</tbody>
</table>

11 BC patients
Partial mastectomy

Prediction of margin positivity

Hepatocellular carcinoma

- Leads to 600,000 mortalities annually
- Does not respond well to chemotherapy and radiotherapy
- Poor surgical outcome: 80% to 90% of cancer relapse
**Intra-hepatic arterial ICG injection**

- **Satellite tumors**
- **Multifocal primary tumors with non-defined boundaries**

**Summary**

- **Intraoperative**
- **Real-time**
- **High Sensitivity**
- **High Resolution**
- **Non-disruptive**
- **User-friendly**
- **Wide Usability**

**Viewing cancer complexity via imaging**

- **Phenotyping**
- **Omics**
- **Molecular Signatures**
- **Microenvironment**
- **Clonal Signatures**
Conclusions

- Developed a broad spectrum tumor-targeting NIR molecular probe
- Developed cancer vision goggles for image guided surgery
- Efforts toward multicenter clinical trials in progress

Collaborators

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- Shengkui Gao
- Ron Liang, PhD
- Dr. Nan Zhu, PhD
- Jeffrey Bryan, DVM
- Tony Mann, DVM
- Michael Lewis, PhD
- Zhao-You Tang, MD
- Jia Fan, MD, PhD
- Hui-Chuan Sun, MD
- Qing-Fei Yu, MD
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