System for Image-Guided Tumor Resection

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Abstract

Two fluorescent phospholipid ether small molecules, CLR-1501 and CLR-1502, developed by Dr. Jamey Weichert's lab at the UW Madison School of Medicine and Public Health, are being proposed for use in tumor resection. The molecules accumulate preferentially in tumor cells; the fluorescence intensity ratio is 2.74:1 for glioblastoma tumor cells to normal brain cells for CLR-1501 [27]. This allows precise definition of tumor margins for accurate removal. As the extent of resection directly corresponds to patient outcome, the compounds will be a promising tool for the advancement of cancer surgery and prevention of recurrence. An imaging device capable of exciting the fluorescent molecules and displaying the feedback images is therefore needed to conduct clinical trials and later for use in conjunction with the molecules during tumor resection. The proposed device houses three small full CCD cameras with three LED lights, one emitting light in the 490-510 nm range (to excite CLR-1501), one emitting light in the 760-780 nm range (for CLR-1502), and one visible light LED for the standard reflected light image, inside a laparoscopic tube. The components will be integrated using a microcontroller connected to a computer running the open-source imaging software ImageJ. Control of the displayed video feeds will be hands-free.

Figure A [36]

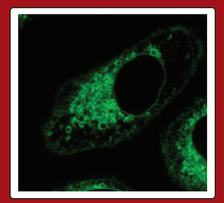


Figure C [28]

Motivation

Current cancer removal surgeries called resections, often result in incomplete removal of the cancerous tissue due to insufficient methods used for intraoperative assessment of tumors.

- Current assessments are based off medical imaging, palpation, and visual inspection of the cancerous mass.

Fluorescence image-guided surgery has undergone substantial growth recently and will be an integral tool in aiding surgeons during future procedures.

- CLR-1501 and 1502 provide more accurate tumor border definition and increased fluorescence intensity ratio compared to current competing drugs such as 5-ALA
- Imaging the combination of CLR-1501 and CLR-1502 provides a sense of tumor depth to surgeons
- CLR-1501 and 1502 cannot be used in surgery until custom imaging tools are developed

Current Devices

A device called the Fluobeam is capable of exciting fluorophores in the near infrared range and capturing images in the emissions

- The device is over 10 cm in diameter and therefore can only be used in open surgery
- The device only works with fluorophores in the infrared range, this is because in rared light and visible light can be easily seperated.

Capsule endoscopy is currently used to capture images of the digestive tract

- The capsules are approximately the size of a pill and house LEDs, a battery, a transmitter, and a camera. [24-25]

A dual-mode laparoscope that provides nearly simultaneous white light and high brightness fluorescence imaging of nerves using a single camera exists [20].

- This shows that it is possible to excite a fluorophore and capture visible light and fluorescent images using a single endoscope
- All optical components are housed in the exterior end of the endoscope, light is channeled through optical fibers in the laparoscopic tube
- Currently this product has only been produced as a prototype for use with a different fluorophore tagged compound

Background

Fluorophores are fluorescent chemical compounds which emit light at specific wavelengths visible to the human eye upon excitation. [1]

- Exposing a flurophore to its corresponding wavelength of excitation causes it to release at a higher wavelength
- The difference in excitation and emission wavelengths allows for separation of emitted fluorescence from the excitation light

Fluorophores are useful for tagging specific molecules which can aid in locating and removing tumors.

- Fluorescence labeling utilizes fluorophores by attaching them to other molecules such as proteins, amino acids, and peptides [2]
- Dr. Jamey Weichart's lab has developed two fluorescent phospholipid ether small molecules, CLR-1501 and CLR-1502
- They were created by incorporating fluorophores into the hydrophobic alkyl chain of CLR-1404 [8]
- Phospholipid ether analogs have the ability to accumulate preferentially in tumors. [7]

Endoscopes are medical imaging tools commonly employed in diagnostic and surgical procedures. Figure A shows a standard endoscope.

- They allow doctors to view the interior of a patient's body cavity through a very small incision
- A rigid or flexible tube houses optical fibers that feed a light source in and a visible image out to the CCD sensor
- Laparoscopes, a type of endoscope, refer to those used in minimally-invasive procedures
- Today's laparoscopes almost exclusively mount their CCD sensors at the external end of the endoscopic tube.

Design Criteria

The client requires a system capable of simultaneously illuminating and capturing a visible image while exiting fluorophores at two separate wavelengths and capturing two corresponding fluorescent images. This imaging will be performed inside a patient's body during minimally-invasive tumor resection procedures.

- Fluorophores need to be excited with light at wavelengths of 500 nm and 772 nm
- The surgeon needs visible light illumination on his work area within the body
- Cameras must capture fluorescence emissions at wavelengths of 520 nm and 790 nm
- Four high definition images need to be displayed at 30 frames per second: One visible light image, one 520 nm fluorescent light image, one 772 nm fluorescent light image, and a composite image of both fluorescent light images allowing for a sense of depth.
- The displays and imaging software should include a "hands free" interface
- All electronics must be housed in a safe, non-reactive rigid tube no more than 2 cm in diameter
- Must include the ability to clean the internal lens during procedures and a method for sterilization between procedures
- Must be durable, extremely reliable, lightweight, and portable
- Should interface easily with open-source imaging software such as ImageJ and be compatible with a regular desktop computer
- Needs to operate at low voltages to minimize risk to patient and user

Final Design

Three cameras and three light sources will be housed in a surgical-grade stainless steel tube, no more than 1.5 cm in diameter as shown in Figure C. [Figure D]

- CCD panel will be customer ordered to size with sufficient pixel density
- CCD panels must be capable of capturing 60 frames per second
- The quality of a CCD is measured in megapixels, which correlates to capacitor density on the CCD panel itself. •
- Theoretically, the CCD panels could be 9 millimeters squared, which would allow for a sensitivity of 6 megapixels based on a pixel size of 1.5 micrometers squared
- Lenses for the CCD Panels will need to be custom cut and ground to match the size of the CCD
- Custom built high pass optical filters are used to filter the light incident on the CCD panel
- With modern imaging software a mechanical shutter is not necessary.

All necessary light for excitation and illumination will be produced by LEDs [Figure D]

- A visible spectrum LED, a green LED, and a near-infrared LED will be housed within the tip of the endoscope
- The green and near-infrared LEDs will need custom low-pass optical filters.

The custom lens and light source will determine the field of view of the camera

- The larger the field of view, the lower the resolution of the image.
- Another limiting factor for this field of view is how large a section of tissue can be excited properly by our light sources.
- Future testing will decide what an appropriate field of view will be based on the image quality produced.

ImageJ software will be used to control the microcontroller which controls all the internal components

- The visible light image will be captured, followed by both fluorescent images
- To achieve a frame rate of 30 frames per second these captures must alternate at 60 hertz
- The captured images need to be compiled into four separate video feeds

Future Work

A photon budget analysis [35] needs to be completed in order to determine light source power and CCD sensitivity requirements.

- A set voxel of the compound will be analyzed
- Ratio of incident photons versus emitted photons is experimentally found
- A percent of photons are lost during each transmission through each optical component
- Signal to noise ratio at the CCD needs to allow for a quality image to be produced.

Fabrication of the a prototype must occur before testing can proceed

- Lenses and filters will have to be custom ordered or fabricated in house
- The CCD panels will have to be custom ordered
- A microcontroller along with wiring will have to be purchased to connect all component
- The microcontroller firmware and the ImageJ software need to be written to control all components
- All internal components will be housed within a stainless steel endoscopic tubing

A standardized testing protocol will written and executed on the prototype

- Initial component testing can take place without the components housed within the endoscopic tube
- Testing will check the effectiveness of the light sources and the quality of the produced images
- Program functionality and robustness will be evaluated
- Necessary modifications will be made to the design during each stage of testing.

Use in clinical trials with CLR-1501 and CLR-1502 will be the final goal for this product

- Final product consists of all components packed in a laparoscopic tube, must withstand vigorous stress testing
- User manual for the product will be written and reviewed
- All clinical trials will adhere to FDA and IACUC regulations
- A patent to protect the original ideas in this design will be strongly pursued

Figure D

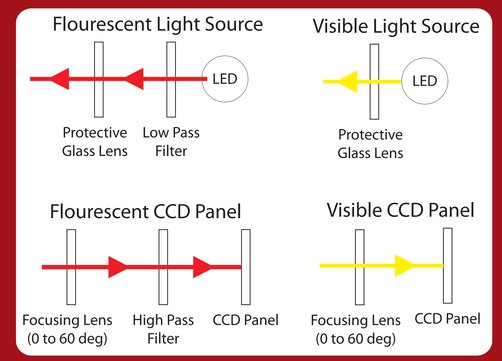
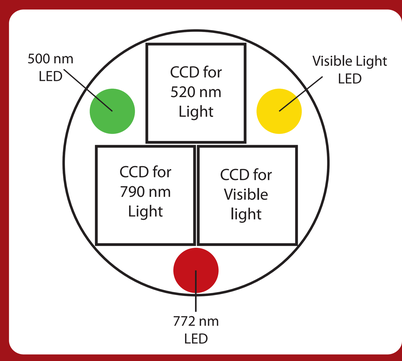


Figure C



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