PROGRESS REPORT
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Division of Biomedical Technology

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A project laboratory is set in NEXT Medical Device Innovation Center, National Cancer Center (NCC) Hospital East, which is equipped with common research facilities of TUS and NCC. Proper research staff members of the laboratory (cross appointment assistant professors) are also affiliated to both TUS and NCC. By the direct collaboration between academic researchers and medical doctors, we are developing innovative medical devices for realizing "hyper-assisted medical care" that assists medical care with "abilities beyond human skill".

1. Laparoscopic Near-infrared Hyperspectral Imaging System

Cancer is a leading cause of death, with surgical resection being a critical treatment. Minimally invasive surgery (MIS) has grown, necessitating advanced support systems for safer operations. Near-infrared (NIR) light penetrates deeper into tissues and provides detailed molecular information. This study developed an NIR-Hyperspectral Imaging (HSI) laparoscope using a supercontinuum light source and Acousto-Optic Tunable Filter for rapid wavelength switching, aiming for high-speed NIR-HSI during surgery.

A laparoscopic NIR-HSI system using a custom rigid endoscope and an optical system centered on an acousto-optic tunable filter and SC light source are developed. We investigated its performance by measuring light intensity, spectral performance, and resolution. Ex vivo SWIR-HSI imaging was conducted on pig arterial, mesentery,

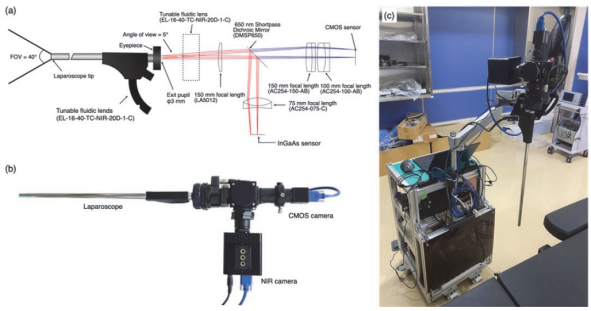

Figure 1. Diagram of an optical system of the laparoscope using a visible camera and picture of the laparoscope system using visible camera.

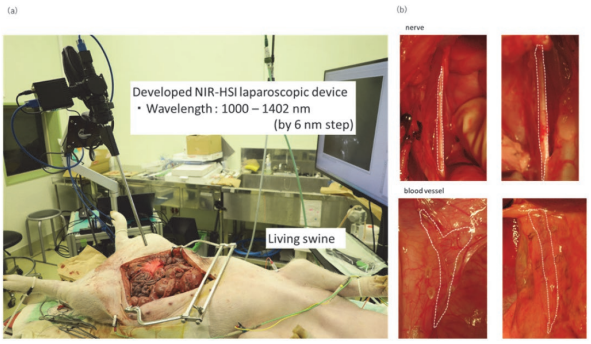

Figure. 2 (a) NIR-HSI setup under in vivo evaluation. Visible image of captured tissue of nerve (b) and artery (c).

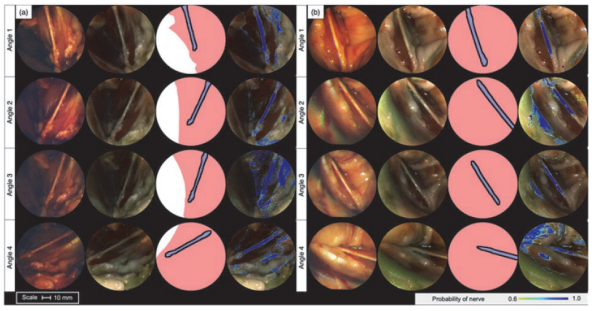

Figure 3. Four-angle images of in vivo exposed nerves in two locations of the lower abdomen (a) and (b). From left to right: visible pseudo-color image (R: 700 nm, G: 604 nm, and B: 556 nm), near-infrared pseudo-color image (R: 1036 nm, G: 1282 nm, B: 1372 nm), annotation image, and overlay image in the visible image with classified pixels.

and nerve tissues, followed by in vivo imaging to identify nerves and blood vessels in deep tissue. Data processing involved pixel calibration and machine learning for tissue identification. A three-layer neural network was trained using leave-one-out cross-validation. The model's accuracy was assessed through specificity, sensitivity, and overall accuracy metrics.

The device showed varying light intensities across different wavelengths, with peak intensity around 18 mW near 1064 nm. Accurate spectral separation was confirmed for wavelengths beyond 1000 nm. Ex vivo imaging distinguished blood vessels, fat, and nerves with high accuracy. In vivo imaging on an anesthetized pig used machine learning to segment exposed nerves and non-exposed blood vessels. Visible and near-infrared pseudo-color images were created for analysis. Fig. 3 shows images of exposed nerves (2 locations) captured and classified by the NIR-HSI laparoscopic system from 4 different angles. Each pixel was classified into two classes by nerve and other tissue, and exposed nerves were detected as TP across all scenes. On the other hand, there were also confirmed situations where there were more FPs depending on the angles. The overall accuracy, recall, and specificity for the exposed nerves were 88.4%, 68.7%, and 89.1%, respectively. We developed a laparoscopic NIR-HSI system with an acousto-optic tunable filter and SC light source. The device effectively distinguished blood vessels and nerves in both ex vivo and in vivo conditions.

2. Development of 490–1600 nm hyperspectral imaging system based on flexible fiberscope

Herein, we report the world's first flexible fiberscope system that can perform hyperspectral imaging (HSI) from 490–1600 nm. The spectroscopy method uses a super continuum light source and an acousto-optic tunable filter to output a specific wavelength at 6 nm intervals. The HSI of the six resin samples were obtained and classified using a neural network under four wavelength ranges. The highest performance was achieved for the 1000–1600 nm range, with accuracy of 99.0%, recall of 94.6%, and specificity of 98.8%. The proposed system has potential applications in the medical and industrial fields for noninvasive component analysis.

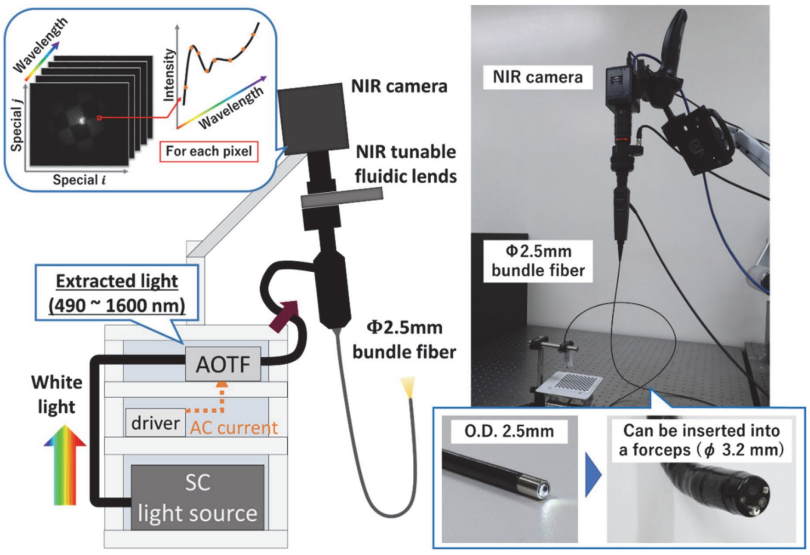

Figure. 4. Schematic and image of the as-developed VIS-NIR (Visible–Near Infrared) HSI (Hyperspectral Imaging) fiberscope device. AOTF: Acousto-Optic Tunable Filter; SC light source: Supercontinuum light source.

3. Development of bimodal over-1000 nm (OTN) near infrared (NIR) fluorescence and magnetic resonance (MR) imaging probe for breast cancer detection

One of the research missions of the division is the development of bimodal over-1000 nm (OTN) near infrared (NIR) fluorescence and magnetic resonance (MR) imaging probe for breast cancer detection. In addition to the development to the last year, we've reported the following two studies.

(1) *Influence of Carboxyl Group Ratios on the Design of Breast Cancer Targeting Bimodal MR/NIR-II Imaging Probe from PLGA@Gd-DOTA@PEG Micelles Conjugating Herceptin*

We developed a small MRI/NIR-II probe to target HER2 (tetanucleotide) breast cancer cells. The probe is composed of PLGA-b-PEG micelles encapsulated NIR-II, and Gd-DOTA is conjugated at the border of PLGA/PEG. Herceptin was then conjugated to carboxyl residues of PLGA-b-PEG chains. We examined the influence of carboxyl group ratios on the probe property stability and Herceptin concentration and the binding affinity to HER2(+) cells corresponding to the −COOH ratios. The binding assays demonstrated that the optimal surface ratio of −COOH is 5%, which is less affected by fluorescence reduction and which exhibited the highest antigen-capturing activity.

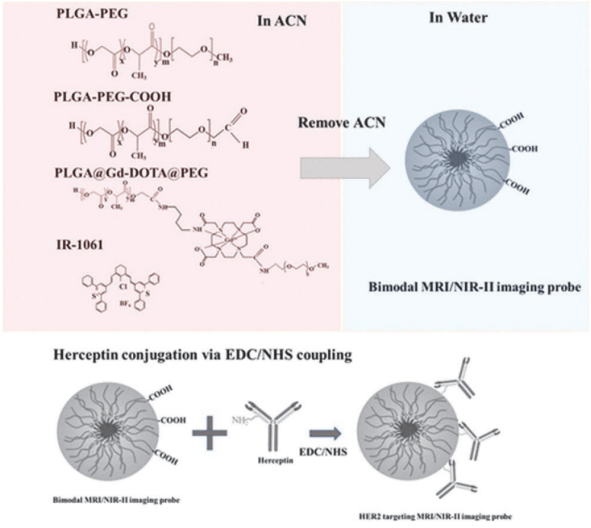

Figure 5. Schematic illustration of bimodal imaging probe development and Herceptin conjugation

(2) *Enhancing near-infrared fluorescence intensity and stability of PLGA-b-PEG micelles by introducing Gd-DOTA at the core boundary*

Micelles have been extensively used in biomedicine as potential carriers of hydrophobic fluorescent dyes. Their small diameters can potentially enable them to evade recognition by the reticuloendothelial system, resulting in prolonged circulation. Nevertheless, their lack of stability in physiological environments limits the imaging utility of micelles. In particular, when a dye sensitive to water, such as IR-1061, is encapsulated in the micelle core, the destabilized structure leads to interactions between water and dye, degrading the fluorescence. In this study, we investigated a method to improve micelle stability utilizing the electrical effect of gadolinium (Gd3+) and tetraazacyclododecane tetraacetic acid (DOTA), introduced into the micelles. Three micellar structures, one containing a poly(lactic-co-glycolic acid)- block-poly(ethylene glycol) (PLGA-b-PEG) block copolymer, and two other structures, including PLGA-b-PEG with DOTA or Gd-DOTA introduced at the boundary of PLGA and PEG, were prepared with IR-1061 in the core. Structures that contained DOTA at the border of the PLGA core and PEG shell exhibited much higher fluorescence intensity than probes without DOTA. With Gd3+ ions at the DOTA center, fluorescence stability was enhanced remarkably in physiological environments. Most interesting is the finding that fluorescence is enhanced with increased Gd-DOTA concentrations. In conclusion, we found that overall fluorescence and stability are improved by introducing Gd-DOTA at the boundary of the PLGA core and PEG shell. Improving micelle stability is crucial for further biomedical applications of micellar probes such as bimodal fluorescence and magnetic resonance imaging.

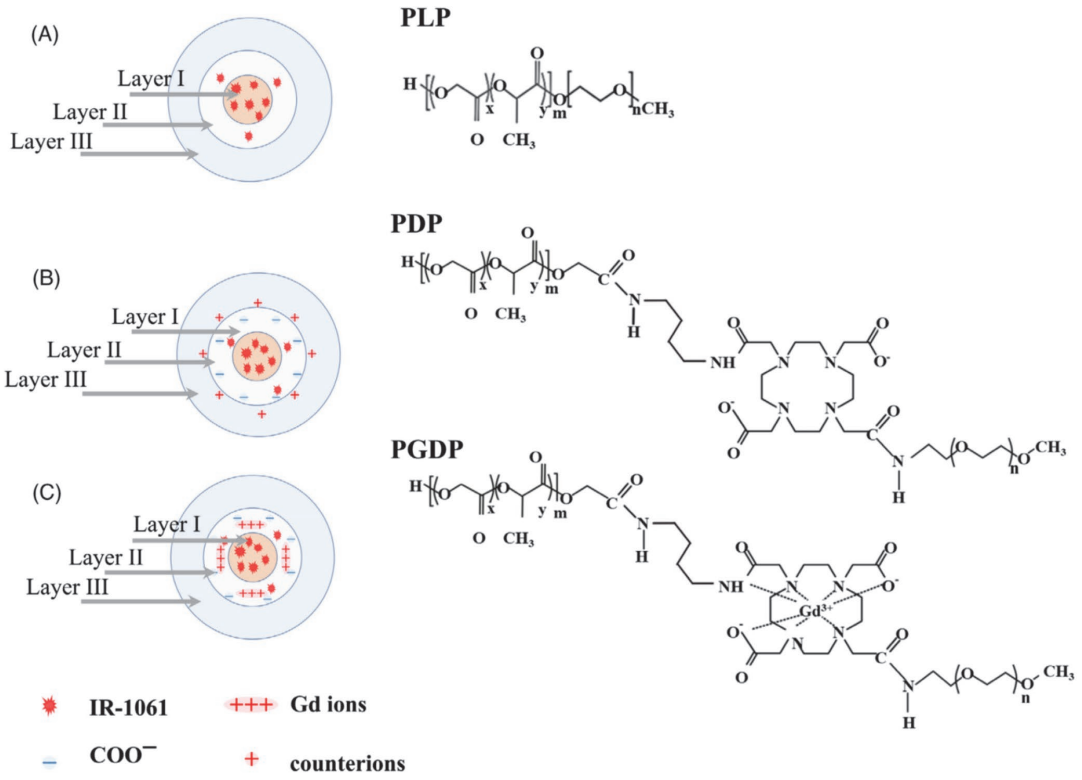

Figure 6. Illustration of IR-1061 molecules distributed inside the micelles throughout the inner core (layer I), the border of PLGA/PEG (layer II), and the outer shell of PEG. When DOTA was introduced at the border of PLGA/PEG, a double electrical layer was formed between the COOH groups and counter ions. In the case of Gd-DOTA, a double electrical layer was formed between COOH and Gd3+ ions at the center of adjacent DOTA molecules.

4. Circulating Tumor Cell Capture by Microfluidic Devices

As a major factor of metastases, circulating tumor cells (CTC), which are leaking from primary tumor into peripheral blood, has attracted large attention. It is assumed that CTC reaches distant organs along the blood circulation and subsequent growth will cause the metastasis. If we could capture CTCs, useful knowledge can be obtained for novel treatments. Previous studies indicate that CTCs are generally larger and harder than leukocytes, and we have developed deterministic lateral displacement (DLD) microfluidic devices for separating large cells from peripheral bloods. However, we have been struggling with the clogging of microchannels. Finally, we managed to solve it by condensing DNA in the blood, and we have successfully conducted CTC concentration experiments from the blood of cancer patients continuously over 40 times . Our next challenge is to improve the concentration efficiency. Selection based solely on size has not been able to prevent the contamination of larger white blood cells. Therefore, we were considering utilizing specific adsorption to attach white blood cells to the walls of the microchannel. However, it was found that simply flowing cells slowly through the microchannel does not result in specific adsorption. Since the cell surface is not smooth, it is assumed that antigens located in the recesses do not come into contact with the antibodies on the wall. We have examined a microfluidic device as shown in Figure 7, aiming to press cells against the wall. We observed that stronger the pressure against the wall, the more the specific adsorption was promoted, and we are working on further optimization.

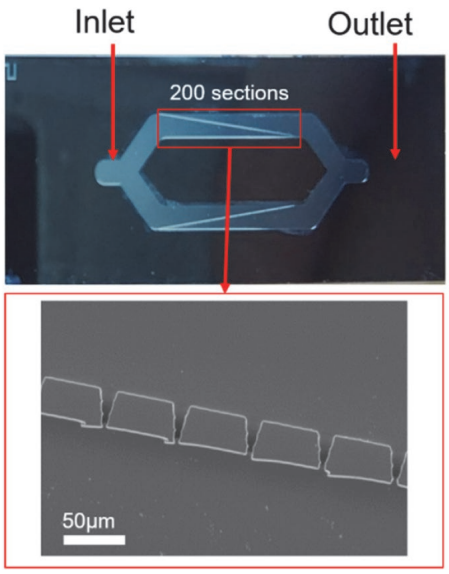

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Figure 7. Prototype microfluidic device for elimination of white blood cells. Cells are sucked at slits in the figure, and are pressed onto the channel walls around the slits. Larger pressure showed rapid specific adsorption.

Publications

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6. Fukushima R, Takamatsu T, Sato K, Hern?ndez-Guedes A, Callic? G, Okubo K, Umezawa M, Yokota H, Soga K, Takemura H, 'Detection of exposed nerves in two individuals in vivo and unexposed nerves ex vivo with near-infrared hyperspectral laparoscope,' 2024 IEEE/SICE International Symposium on System Integration (SII), (2024) 19-24.