Department of Innovative Interventional Endoscopy Research

Hisao Tajiri, *Professor*　　Masato Mitsunaga, *Assistant Professor*

General Summary

This department was established in April 2015, aiming at new methods of endoscopic diagnosis and treatment and the development of apparatuses, with the purpose of supporting and teaching the standardization of endoscopic medicine in domestic and foreign facilities.

Research Activity

Endoscopic submucosal dissection (ESD), which was developed in Japan, has been followed by various improvements to conduct examinations safely, promptly, and accurately. Subsequently, new minimally invasive endoscopic treatments, such as endoscopic full-thickness resection and endoscopic treatment applying robotic technology, are being developed. As Japan's society ages, less-burdensome, minimally invasive endoscopic treatments significantly contribute to patients. While social demand for endoscopic medicine is growing, new methods should be used for endoscopic treatment and the development of instruments.
This department plays a role in developing educational structures for endoscopy for physicians in Japan, other Asian countries, Russia, the Middle East, and South America.

Development of supporting devices for ESD and clinical evaluation
Recently, there has been a shift from open surgery to laparoscopic surgery, a minimally invasive method to reduce the patients' burden reduces and increase quality of life. In addition, for early gastrointestinal cancers, oral and transanal endoscopic therapy is being performed more often with flexible endoscopes. However, a problem of oral and transanal endoscopic therapies, such as ESD, is that they are safely performed by only skilled physicians. Existing surgical instruments are electric scalpels, which pierce the forceps at an entrance 2.8 mm in diameter to penetrate a flexible endoscope, which moves only to-and-fro. Lifting affected parts and cutting open the inside while a fiberscope is operated are extremely difficult with all these devices. The endoscopic system, which can be operated by a surgeon's freely moving right and left hands, has long been expected, and bending, elastic forceps have been researched and developed all over the world. However, these forceps are not practical because the smallest ones are still 4 mm in diameter and cannot be inserted in the forceps channel (2.8 mm) of the existing elasticity endoscope. An article specially made to order is expensive. Because present flexible endoscopes are expensive, efforts must be made to develop ones that can be used economically on a daily basis. Because the forceps's outlet of commercially available flexible endoscope is 3 mm in diameter, a flexible forceps 2.6 mm in diameter must be inserted. Hashizume et al. have

succeeded in the trial manufacture of the world's first flexible flexure forceps 2.6 mm in diameter (Nakadate R, et al. Endoscopy 2015; 47(9): 820–4). This medical device might achieve practical economic use. Furthermore, to increase utility and decrease costs, 2 control sticks are equipped to the fixed base so it can be manipulated stably, and the grip of a flexible scope and its console are placed so that they can be reached and conducted at the same time by a single endoscopist. The flexible endoscopes can be removed any time manual manipulation is necessary. Because they are robotic devices not requiring motors, they are close to their practical application. We organized "A study group for ESD supporting devices" in 2015 and have been repeating animal studies of *in vivo*, *ex vivo*, for technology development so that ESD for the stomach, esophagus, and colon can be conducted with this device without stress.

Endoscopic optical molecular imaging for cancer

Molecularly targeted therapies, such as monoclonal antibodies, have recently been widely used to treat various types of cancer and have improved outcomes. The use of molecularly targeted medicine for patients with cancer generally depends on the level of molecular expression in the targeted tumor; therefore, a method of companion diagnosis must be developed when a molecularly targeted therapy is developed. Histological testing and genetic testing are usually used for companion diagnosis; however, the necessary time can delay the start of an appropriate therapy. We have developed methods of molecular target-specific fluorescence cancer imaging by using cancer-specific monoclonal antibodies and optical fluorescence probes for real-time companion diagnosis. In this study, we attempted to develop a method for optical molecular imaging of cancer with a laser-equipped endoscope system (LASEREO; FujiFilm Corp., Kanagawa, Japan) and molecular targeted-fluorescence probes which enables us to diagnose molecular expression in a real-time manner. We examined *in vitro* detectability of fluorescence probes, Alexa Fluor488-conjugated trastuzumab, fluorescein, and a cresyl violet solution. To improve signal detectability, the endoscope system was modified from the default settings by changing the output of laser units (410 and 450 nm) and image-processing algorisms. We were able to see the signals of AF488-trastuzumab and fluorescein with the naked eye; however, contrary to our expectations, none of 3 probes were able to detect through the endoscope system. In the case of cresyl violet, the excitation laser was not suitable for signal detection. In summary, we need to optimize the image processing of the endoscope system to detect fluorescence signals for further studies.

Publications

Toyoizumi H, Imazu H, Ikeda K, Mori N, Kanazawa K, Chiba M, Ang TL, Tajiri H. A novel second-generation multibending backward-oblique viewing duodenoscope in ERCP. *Minim Invasive Ther Allied Technol.* 2015; **24:** 101–7.

Saijo H, Tatsumi N, Arihiro S, Kato T, Okabe M, Tajiri H, Hashimoto H. Microangiopathy triggers, and inducible nitric oxide synthase exacerbates dextran sulfate sodium-induced colitis. *Lab Invest.* 2015; **95:** 728–48.

Horimatsu T, Sano Y, Tanaka S, Kawamura T, Saito S, Iwatate M, Oka S, Uno K, Yoshimura K, Ishikawa H, Muto M, Tajiri H. Next-generation narrow band imaging system for colonic polyp detection: a prospective multicenter randomized trial. *Int J Colorectal Dis.* 2015; **30:** 947–54.

Goda K, Dobashi A, Yoshimura N, Kato M, Aihara H, Sumiyama K, Toyoizumi H, Kato T,

Ikegami M, Tajiri H. Narrow-band imaging magnifying endoscopy versus Lugol chromoendoscopy with pink-color sign assessment in the diagnosis of superficial esophageal squamous neoplasms: A randomised noninferiority trial. *Gastroenterol Res Pract.* 2015; **2015:** 639462.

Saito Y, Saito S, Oka S, Kakugawa Y, Matsumoto M, Aihara H, Watari I, Aoyama T, Nouda S, Kuramoto T, Watanabe K, Ohmiya N, Higuchi K, Goto H, Arakawa T, Tanaka S, Tajiri H. Evaluation of the clinical efficacy of colon capsule endoscopy in the detection of lesions of the colon: prospective, multicenter, open study. *Gastrointest Endosc.* 2015; **82:** 861-9.

Ito K, Mitsunaga M, Arihiro S, Saruta M, Matsuoka M, Kobayashi H, Tajiri H. Molecular targeted photoimmunotherapy for HER2-positive human gastric cancer in combination with chemotherapy results in improved treatment outcomes through different cytotoxic mechanisms. *BMC Cancer.* 2016; **16:** 37.

Ito K, Mitsunaga M, Nishimura T, Kobayashi H, Tajiri H. Combination photoimmunotherapy with monoclonal antibodies recognizing different epitopes of human epidermal growth factor receptor 2: an assessment of phototherapeutic effect based on fluorescence molecular imaging. *Oncotarget.* 2016; **7:** 14143-52.

Reviews and Books

Tamai N, Takeuchi Y, Tajiri H. Second-generation autofluorescence imaging for colorectal neoplasia. *Dig Endosc.* 2015; **27** Suppl 1: 46.

Tanaka S, Kashida H, Saito Y, Yahagi N, Yamano H, Saito S, Hisabe T, Yao T, Watanabe M, Yoshida M, Kudo SE, Tsuruta O, Sugihara K, Watanabe T, Saitoh Y, Igarashi M, Toyonaga T, Ajioka Y, Ichinose M, Matsui T, Sugita A, Sugano K, Fujimoto K, Tajiri H. JGES guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. *Dig Endosc.* 2015; **27:** 417-34.

Muto M, Hayashi T, Goda K, Tajiri H, Inoue H, Arima M, Arima H, Tada M. Overview. In: Muto M, Yao K, Sano Y, editors. Atlas of endoscopy with narrow band imaging. Tokyo: Springer Japan; 2015. p. 33-48.

Ezoe Y, Muto M, Goda K, Ikegami M, Tajiri H. Atlas of nonneoplastic lesions. In: Muto M, Yao K, Sano Y, editors. Atlas of endoscopy with narrow band imaging. Tokyo: Springer Japan; 2015. p. 53-77.

Muto M, Inoue H, Morita S, Monma K, Yano T, Katada C, Goda K, Tajiri H, Fujiwara J. Atlas of neoplastic lesions. In: Muto M, Yao K, Sano Y, editors. Atlas of endoscopy with narrow band imaging. Tokyo: Springer Japan; 2015. p. 79-129.