

## Endowed Departments

### Department of Innovative Interventional Endoscopy Research

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#### General Summary

This department was established in April 2015, with the aims of establishing new methods of endoscopic diagnosis and treatment and developing new apparatuses and with the purposes of supporting and teaching to standardize endoscopic medicine in Japan and in foreign facilities.

#### Research Activities

Endoscopic submucosal dissection (ESD), which was developed in Japan, has been followed by various improvements for safety, promptness, and accuracy. Following ESD, new minimally invasive endoscopic treatments, such as endoscopic full thickness resection and endoscopic treatment applying robotic technology, are being developed. Minimally invasive endoscopic treatments, which are less of a burden to patients, make a substantial contribution. As the social demands for endoscopic medicine grow, new endoscopic treatment methods and new instruments are being developed. This department plays several roles, such as performing relevant research studies and developing new educational methods for training physicians to perform endoscopy in Japan, other parts of Asia, Russia, the Middle East, and South America.

#### *Endoscopic optical molecular imaging for cancer*

Molecular targeted therapies, such as monoclonal antibodies, were widely used for various cancers recently, leading to improve patients' outcomes. Photoimmunotherapy (PIT) is a new class of molecular targeted cancer theranostics, which employs monoclonal antibody conjugated to a photosensitizer, IR700, that is activated by focal near-infrared (NIR) light irradiation leading to necrotic cell death by cell membrane rupture where antibody-IR700 conjugates binds to target membrane proteins specifically. A global phase 3 clinical trial of PIT for recurrent head and neck cancer patients has been conducted utilizing anti-EGFR monoclonal antibody, cetuximab-IR700 conjugate. We have recently developed a new type of PIT agents targeting VEGFR-2 expressed on vascular endothelium in a tumor. VEGFR-2 expressing NCI-N87 tumors were successfully treated with VEGFR-2-targeting DC101-IR700 conjugate and NIR light by damaging microvessels in the tumors. As VEGFR-2 is upregulated in many types of solid cancers, this method may be considered as being applicable to various types of cancers. Here, we tried to examine the feasibility of endoscopic molecular imaging of inducible murine colon cancer with DC101-IR700 in DSS-treated Apc/min<sup>+</sup> mice. In contrast to cell line derived xenograft

models, the tumor lesions of this mouse possess the histological complexity and heterogeneity. DSS-treated mice were monitored for 2 weeks to obtain the recovery of colitis, then endoscopic examination was performed under anesthesia. Pediatric fiberoptic bronchoscope was used as mouse colonoscopy, and distal side of the colonic mucosa was examined with white light imaging as well as IR700 fluorescence imaging. Tumor lesions were successfully detected both imaging methods. Additionally, pathological examination revealed that tumor lesions were adenocarcinoma. We plan to examine a treatment effect in response to endoscopic NIR-PIT by using this model to prove a concept of endoscopic molecular theranostics.

#### *Development of automatic insertion endoscope equipment*

We are developing a motorized spiral enteroscope. This enteroscope is unique because it incorporates a user-operated motor to rotate the power spiral tube, which is mounted on the endoscope's insertion tube and relies primarily on the pleating of the small bowel onto the scope with minimal pushing.

Representatives from Japan, Europe, and the United States repeated experiments in vivo and in vitro with medical device manufacturers, and clinical trials were conducted for the first time in Europe. As a representative of Japan, Tajiri was in charge of animal experiments and has participated as an advisor to clinical trials in Europe. This instrument has been available in Europe since 2018. In 2019, Tajiri gave advice to preparing application materials to Pharmaceuticals and Medical Devices (PMDA) for introducing the instrument to Japan, as well as being responsible in shared writing the educational English textbook for its global diffusion. Since the motorized spiral enteroscope needs less procedure time compared to the conventional scope, we anticipate that this technology will be applied to colonoscopy in the near future and revolutionize endoscopic medicine.

#### *Endoscopic Research utilizing Japan Endoscopy Database (JED) and AI*

Japan Endoscopy Database (JED) Project, started in 2015, started the operation of the automatic registration and is in the process of making data entry mandatory at all facilities, with the support of nearly 1,450 educational facilities. JED Institute was established on 1 March, 2018, and Tajiri has served the first President. Activities of operation and deployment related to JED project are conducted and collected data is analyzed, then given feedback to medical institution to improve the quality of endoscopy and standardize the technology. Japan Agency for Medical Research and Development (AMED) is conducting joint research with National Institute of Informatics (NII), as public offered research project, progressing the research of endoscopic image diagnosis using AI. In 2019, we conducted joint research to evaluate the quality of medicine and the practicality of ensuring safety focusing on unique AI research such as "deviation monitoring during screening", which solves the urgent problems that the endoscopists need in clinical scene. Since collecting large amounts of data matters, it is desired to construct a system fostering study mind to cooperate in collecting data, reducing the burden for the work and facilitating verification of AI. Japanese technology of GI endoscopy is a world-class proud, that precise manufacturing environment and the dexterity of endoscopists of this country has accomplished. By combining Japanese technology with AI, which is quite advanced,

innovation never before is convinced to be possible.

#### *Educational Activity*

Since 2014 the Japan Gastroenterological Endoscopy Society has been leading hands-on courses in China, and in 2019, Tajiri visited Peking, Dairen and Zunyi, where Tajiri gave lectures and performed therapeutic manipulation with animal models and live demonstrations. In addition, new hands-on courses have been conducted in Cambodia and Mongolia in 2019. The young physicians being trained made remarkable progress in early cancer detection and diagnosis and endoscopic treatment. In Russia, Vietnam, Myanmar, and Indonesia, we have been conducting similar activities. Hands-on courses have already been held in rural regions of Japan. Tajiri visited and will visit the regions directly, to improve the environment for facilities, responsible for community medicine, to standardize endoscopic diagnosis and treatment. Tajiri will continue to conduct these supportive activities.

#### *Inspection/Evaluation*

Remarkable results have been achieved up to the clinically applicable in the research of molecular diagnosis of cancer using fluorescence probe and development of endoscopic molecular theranostics. The development of devices to realize endoscopic molecular theranostics is in progress. As the first President of JED Institute, Tajiri is promoting close joint research with related parties to bring about innovation never before, by combining advanced GI endoscopy technology with AI in Japan.

#### **Publications**

**Uemura N, Oda I, Saito Y, Ono H, Fujisaki J, Matsushashi N, Ohata K, Yahagi N, Yada T, Satoh M, Tajiri H, Inomata M, Kitano S.** Efficacy and safety of 0.6% sodium alginate solution in endoscopic submucosal dissection for esophageal and gastric neoplastic lesion: A randomized controlled study. *Dig Endosc.* 2019 Jul; **31**(4): 396-404. doi: 10.1111/den.13352. Epub 2019 Mar 18. PMID: 30667557; PMCID: PMC6850280.

**Nakamura M, Watanabe K, Ohmiya N, Hirai F, Omori T, Tokuhara D, Nakaji K, Nouda S, Esaki M, Sameshima Y, Goto H, Terano A, Tajiri H, Matsui T; J-POP study group.** Tag-less patency capsule for suspected small bowel stenosis: A nationwide multicenter prospective study in Japan. *Dig Endosc.* 2020 Mar 25. doi: 10.1111/den.13673. Epub ahead of print. PMID: 32215959.

#### **Reviews and Books**

**Tajiri H, Dinis-Ribeiro M.** How I inspect the stomach. *Gastrointest Endosc.* 2019 Jun; **89**(6): 1106-1108. doi: 10.1016/j.gie.2019.02.003. Epub 2019 Apr 3. PMID: 30952478.

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**Tanaka S, Kashida H, Saito Y, Yahagi N, Yamano H, Saito S, Hisabe T, Yao T, Watanabe M, Yoshida M, Saitoh Y, Tsuruta O, Sugihara KI, Igarashi M, Toyonaga T, Ajioka Y, Kusunoki M, Koike K, Fujimoto K, Tajiri H.** Japan Gastroenterological Endoscopy Society guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. *Dig Endosc.* 2020 Jan; **32**(2): 219-239. doi: 10.1111/

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**Inoue H, Shiwaku H, Kobayashi Y, Chiu PWY, Hawes RH, Neuhaus H, Costamagna G, Stavropoulos SN, Fukami N, Seewald S, Onimaru M, Minami H, Tanaka S, Shimamura Y, Santi EG, Grimes K, Tajiri H.** Statement for gastroesophageal reflux disease after peroral endoscopic myotomy from an international multicenter experience. *Esophagus*. 2020 Jan; **17**(1): 3–10. doi: 10.1007/s10388-019-00689-6. Epub 2019 Sep 26. PMID: 31559513; PMCID: PMC6976544.

**Ishihara R, Arima M, Iizuka T, Oyama T, Katada C, Kato M, Goda K, Goto O, Tanaka K, Yano T, Yoshinaga S, Muto M, Kawakubo H, Fujishiro M, Yoshida M, Fujimoto K, Tajiri H, Inoue H; Japan Gastroenterological Endoscopy Society Guidelines Committee of ESD/EMR for Esophageal Cancer.** Endoscopic submucosal dissection/endoscopic mucosal resection guidelines for esophageal cancer. *Dig Endosc*. 2020 May; **32**(4): 452–493. doi: 10.1111/den.13654. PMID: 32072683.