

Department of Internal Medicine

Division of Gastroenterology and Hepatology

Masayuki Saruta, *Professor*
Atsushi Hokari, *Associate Professor*
Kazuhiko Koike, *Assistant Professor*
Kan Uchiyama, *Assistant Professor*
Akiyoshi Kinoshita, *Assistant Professor*
Tsunekazu Oikawa, *Assistant Professor*

Shigeo Koido, *Professor*
Tomohisa Ishikawa, *Associate Professor*
Seiji Arihiro, *Assistant Professor*
Yuichi Torisu, *Assistant Professor*
Makoto Mitsunaga, *Assistant Professor*

General Summary

In 2016, our department reorganized into laboratories on the basis of organs and established new groups: the Gastrointestinal tract group, the Liver group, Biliary-pancreatic group, and Tumor group. The Gastrointestinal tract group aims to elucidate the pathophysiology of inflammatory bowel diseases, represented by ulcerative colitis (UC) and Crohn's disease, and to establish biomarkers and therapeutic methods. The Liver group copes with viral and alcoholic liver damage and carcinogenesis and works to elucidate the pathophysiology of autoimmune hepatitis and primary cholangitis caused by autoimmune disorder. The Biliary-pancreatic group attempts to establish highly specialized diagnostic methods and treatment techniques for the early diagnosis of pancreatic cancer and to clarify the mechanism of pancreatic cancer development. The Tumor group considers the safe use of chemotherapy and tries to elucidate the mechanism of unexpected side effects mediated by the immune mechanism.

Research Activities

Alimentary Tract

1. Prostaglandin E-major urinary metabolite: a reliable marker for endoscopic remission in patients with UC

We analyzed 92 patients and observed a significant difference in prostaglandin E-major urinary metabolite (PGE-MUM) between the groups that achieved endoscopic remission and pathological remission and those who did not. There was no difference in the area under the curve between PGE-MUM, fecal calprotectin, and immunological fecal occult blood in determining the achievement of each evaluation item, indicating usefulness comparable to existing biomarkers.

2. Examination of characteristics of gastrointestinal primary malignant lymphoma

We analyzed 182 patients and found them to have malt lymphoma (49.4%), diffuse large B-cell lymphoma (28.9%), follicular lymphoma (14.5%), mantle cell lymphoma (3.0%), Burkitt lymphoma (1.8%), and T-cell lymphoma (2.4%).

3. Examination of biological malignancy analyzed from positive rate of vascular invasion in patients with resected gastrointestinal neuroendocrine tumor

4. Examination of irregular irregularity change of gastric mucosa newly generated after *Helicobacter pylori* eradication

We evaluated 352 cases and classified the posteradication changes into “the easy group” (49.7%), “the unchanged group” (24.7%), and “the difficult group” (25.6%) based on the ease of endoscopic observation. “The difficult group” included about ¼ of cases, indicating that gastric cancer might be difficult to detect.

5. Molecular imaging of cancer and development of therapeutic method using imaging as a guide

6. Randomized trial of vitamin D supplementation to prevent seasonal influenza and upper respiratory infection in patients with inflammatory bowel disease

Although vitamin D supplementation did not prevent influenza, upper respiratory inflammation was significantly prevented ($P = 0.042$). However, the disease activity of symptomatic UC was significantly worsened ($P = 0.02$).

7. Randomized trial of the prevention of colorectal tumor development by whey protein

8. Investigation of the effects of genetic polymorphisms of thiopurine S-methyltransferase (*TPMT*), inosine triphosphatase (*ITPA*), and nudix hydrolase 15 (*NUDT15*) on the pharmacokinetics of azathioprine: Measurement of intermediate metabolite thioinosine nucleotide.

9. Examination of the significance of pretreatment analysis of the genes *NUDT15*, *TPMT*, *ITPA* to prevent side effects with thiopurine preparation

10. Study of the relationship between insoluble excretion of pH-dependent 5-aminosalicylic acid formulation and UC relapse

11. Randomized trial of the efficacy of indigo naturalis (*qing-dai*) in UC

Liver

1. The development of targeting therapy for cancer stem cells in liver cancers: We have reported that dual-specificity tyrosine-regulated kinase 2 (DYRK2) knockdown enhances the tumor growth of liver cancer cells. Conversely, adenovirus-mediated overexpression of DYRK2 inhibits cell proliferation and tumor growth and induces apoptosis both *in vitro* and *in vivo*. Furthermore, we found that patients with liver cancer and low DYRK2 expression had a significantly shorter overall survival. The findings that DYRK2 regulates proliferation and apoptosis of cancer cells suggests that DYRK2 expression is a promising predictive marker of the prognosis and that stabilized or forced expression of DYRK2 is a potential target when treating liver cancer.

2. Clinical analysis of the long-term outcomes of combined ursodeoxycholic acid and bezafibrate therapy in ursodeoxycholic acid-refractory primary biliary cholangitis patients and identify prognostic factors

Combination therapy significantly improved transaminase, biliary enzymes, and serum immunoglobulin M; reduced liver-related death and liver transplantation; and contributed to long-term prognosis.

3. Study on long-term prognosis of autoimmune hepatitis

4. Immunohistochemical study of hepatic infiltrating lymphocytes of autoimmune hepatitis: Comparison between typical cases and centrilobular zonal necrosis cases

5. Current status and treatment of liver disease patients in super-aging society (multi-center study)

6. Study of frailty in a super-aging society

Gall bladder and Pancreas

1. Construction of a surveillance strategy using endoscopic ultrasonography by enclosing patients with intraductal papillary mucinous neoplasia for early diagnosis of pancreatic cancer
2. Clinical study of long-term management of autoimmune pancreatitis
3. Study of the relationship between intestinal flora and oxidative stress in pancreatic cancer
4. Qualitative evaluation of non-alcoholic fatty pancreas by endoscopic ultrasonography
5. Examination of localized pancreatic atrophy findings as predictors of pancreatic cancer onset
6. Current status and treatment of patients with pancreatic diseases in a super-aging society
7. Combining WT1 dendritic cell vaccine and standard chemotherapy for advanced pancreatic cancer (Phase I clinical trial)

Chemotherapy

1. Systemic chemotherapy for colorectal cancer
We investigated the therapeutic effects and side effects of drug changes on 3 available kinds of fluorinated pyrimidine preparations.
2. Systemic chemotherapy for elderly patients
3. Management of thrombosis and systemic chemotherapy for patients with cancer

Publications

Yokoyama-Mashima S, Yogosawa S, Kanegae Y, Hirooka S, Yoshida S, Horiuchi T, Ohashi T, Yanaga K, Saruta M, Oikawa T, Yoshida K. Forced expression of DYRK2 exerts anti-tumor effects via apoptotic induction in liver cancer. *Cancer Lett.* 2019 Jun 1; **451**: 100-109. doi: 10.1016/j.canlet.2019.02.046. Epub 2019 Mar 6. PMID: 30851422.

Nishimura T, Mitsunaga M, Ito K, Kobayashi H, Saruta M. Cancer neovasculature-targeted near-infrared photoimmunotherapy (NIR-PIT) for gastric cancer: different mechanisms of phototoxicity compared to cell membrane-targeted NIR-PIT. *Gastric Cancer.* 2020 Jan; **23**(1): 82-94. doi: 10.1007/s10120-019-00988-y. Epub 2019 Jul 13. PMID: 31302791.

Nishimura T, Mitsunaga M, Sawada R, Saruta M, Kobayashi H, Matsumoto N, Kanke T, Yanai H, Nakamura K. Photoimmunotherapy targeting biliary-pancreatic cancer with humanized anti-TROP2 antibody. *Cancer Med.* 2019 Dec; **8**(18): 7781-7792. doi: 10.1002/cam4.2658. Epub 2019 Nov 1. PMID: 31674732; PMCID: PMC6912056.

Sawada R, Arai Y, Sagawa Y, Nagata Y, Nishimura T, Noguchi M, Amano K, Arihiro S, Saruta M, Homma S. High blood levels of soluble OX40 (CD134), an immune costimulatory molecule, indicate reduced survival in patients with advanced colorectal cancer. *Oncol Rep.* 2019 Nov; **42**(5): 2057-2064. doi: 10.3892/or.2019.7304. Epub 2019 Sep 6. PMID: 31545443.

Ishimoto U, Kinoshita A, Hirose Y, Shibata K, Ishii A, Shoji R, Yokota T, Iwaku A, Mizuno Y, Koike K, Saruta M. The efficacy and safety of nab paclitaxel plus gemcitabine in elderly patients over 75 years with unresectable pancreatic cancer compared with younger patients. *Cancer Chemother Pharmacol.* 2019 Sep; **84**(3): 647-654. doi: 10.1007/s00280-019-03895-2. Epub 2019 Jun 22. PMID: 31230157.

Ishikawa M, Iwasa S, Nagashima K, Aoki M, Imazeki H, Hirano H, Shoji H, Honma Y, Okita N, Takashima A, Kato K, Saruta M, Boku N. Retrospective comparison of nab-paclitaxel plus ramucirumab and paclitaxel plus ramucirumab as second-line treatment for advanced gastric cancer focusing on peritoneal metastasis. *Invest New Drugs.* 2020 Apr; **38**(2): 533-540. doi: 10.1007/s10637-019-00822-3. Epub 2019 Jul 2. PMID: 31264067.

Saruta M, Park DI, Kim YH, Yang SK, Jang BI, Cheon JH, Im JP, Kanai T, Katsuno T, Ishiguro Y, Nagaoka M, Isogawa N, Li Y, Banerjee A, Ahmad A, Hassan-Zahraee M, Clare R, Gorelick KJ, Cataldi F, Watanabe M, Hibi T. Anti-MAdCAM-1 antibody (PF-00547659) for active refractory Crohn's dis-

ease in Japanese and Korean patients: the OPERA study. *Intest Res.* 2020 Jan; **18**(1): 45-55. doi: 10.5217/ir.2019.00039. Epub 2020 Jan 30. PMID: 32013314; PMCID: PMC7000638.

Ito Z, Kan S, Bito T, Horiuchi S, Akasu T, Yoshida S, Kajihara M, Hokari A, Saruta M, Yoshida N, Kobayashi M, Ohkusa T, Shimodaira S, Okamoto M, Sugiyama H, Koido S. Predicted Markers of Overall Survival in Pancreatic Cancer Patients Receiving Dendritic Cell Vaccinations Targeting WT1. *Oncology.* 2019; **97**(3): 135-148. doi: 10.1159/000500359. Epub 2019 Jun 19. PMID: 31216557.

Kajihara M, Koido S, Kanai T, Ito Z, Matsumoto Y, Takakura K, Saruta M, Kato K, Odamaki T, Xiao JZ, Sato N, Ohkusa T. Characterisation of blood microbiota in patients with liver cirrhosis. *Eur J Gastroenterol Hepatol.* 2019 Dec; **31**(12): 1577-1583. doi: 10.1097/MEG.0000000000001494. PMID: 31441799; PMCID: PMC6844652.

Nagata Y, Sawada R, Takashima A, Shoji H, Honma Y, Iwasa S, Amano K, Kato K, Hamaguchi T, Shimada Y, Saruta M, Boku N. Efficacy and safety of pemetrexed plus cisplatin as first-line chemotherapy in advanced malignant peritoneal mesothelioma. *Jpn J Clin Oncol.* 2019 Dec 18; **49**(11): 1004-1008. doi: 10.1093/jcco/hyz104. PMID: 31287877.

Saeki C, Takano K, Oikawa T, Aoki Y, Kanai T, Takakura K, Nakano M, Torisu Y, Sasaki N, Abo M, Matsuura T, Tsubota A, Saruta M. Comparative assessment of sarcopenia using the JSH, AWGS, and EWGSOP2 criteria and the relationship between sarcopenia, osteoporosis, and osteosarcopenia in patients with liver cirrhosis. *BMC Musculoskelet Disord.* 2019 Dec 26; **20**(1): 615. doi: 10.1186/s12891-019-2983-4. PMID: 31878909; PMCID: PMC6933666.

Yoshida S, Ito Z, Suka M, Bito T, Kan S, Akasu T, Saruta M, Okamoto M, Kitamura H, Fujioka S, Misawa T, Akiba T, Yanagisawa H, Sugiyama H, Koido S. Clinical Significance of Tumor-Infiltrating T Cells and Programed Death Ligand-1 in Patients with Pancreatic Cancer. *Cancer Invest.* 2019; **37**(9): 463-477. doi: 10.1080/07357907.2019.1661427. Epub 2019 Sep 18. PMID: 31490702.

Yokoyama H, Masaki T, Inoue I, Nakamura M, Mezaki Y, Saeki C, Oikawa T, Saruta M, Takahashi H, Ikegami M, Hano H, Ikejima K, Kojima S, Matsuura T. Histological and biochemical evaluation of transforming growth factor- β activation and its clinical significance in patients with chronic liver disease. *Heliyon.* 2019 Feb 16; **5**(2): e01231. doi: 10.1016/j.heliyon.2019.e01231. PMID: 30815603; PMCID: PMC6378908.

Ide D, Saito S, Ohya TR, Nishikawa Y, Horie Y, Yasue C, Chino A, Igarashi M, Saruta M, Fujisaki J. Colorectal endoscopic submucosal dissection can be efficiently performed by a trainee with use of a simple traction device and expert supervision. *Endosc Int Open.* 2019 Jun; **7**(6): E824-E832. doi: 10.1055/a-0901-7113. Epub 2019 Jun 12. PMID: 31198847; PMCID: PMC6561769.

Yamane D, Feng H, Rivera-Serrano EE, Selitsky SR, Hirai-Yuki A, Das A, McKnight KL, Misumi I, Hensley L, Lovell W, González-López O, Suzuki R, Matsuda M, Nakanishi H, Ohto-Nakanishi T, Hishiki T, Wauthier E, Oikawa T, Morita K, Reid LM, Sethupathy P, Kohara M, Whitmire JK, Lemon SM. Basal expression of interferon regulatory factor 1 drives intrinsic hepatocyte resistance to multiple RNA viruses. *Nat Microbiol.* 2019 Jul; **4**(7): 1096-1104. doi: 10.1038/s41564-019-0425-6. Epub 2019 Apr 15. PMID: 30988429; PMCID: PMC6588457.

Kawamoto H, Hara H, Araya J, Ichikawa A, Fujita Y, Utsumi H, Hashimoto M, Wakui H, Minagawa S, Numata T, Arihiro S, Matsuura T, Fujiwara M, Ito S, Kuwano K. Prostaglandin E-Major Urinary Metabolite (PGE-MUM) as a Tumor Marker for Lung Adenocarcinoma. *Cancers (Basel).* 2019 Jun 3; **11**(6): 768. doi: 10.3390/cancers11060768. PMID: 31163629; PMCID: PMC6627988.

Shimodaira S, Yanagisawa R, Koya T, Hirabayashi K, Higuchi Y, Sakamoto T, Togi M, Kato T Jr, Kobayashi T, Koizumi T, Koido S, Sugiyama H. In Vivo Administration of Recombinant Human Granulocyte Colony-Stimulating Factor Increases the Immune Effectiveness of Dendritic Cell-Based Cancer Vaccination. *Vaccines (Basel).* 2019 Sep 19; **7**(3): 120. doi: 10.3390/vaccines7030120. PMID: 31546936; PMCID: PMC6789603.

Koya T, Date I, Kawaguchi H, Watanabe A, Sakamoto T, Togi M, Kato T Jr, Yoshida K, Kojima S, Yanagisawa R, Koido S, Sugiyama H, Shimodaira S. Dendritic Cells Pre-Pulsed with Wilms' Tumor 1 in Optimized Culture for Cancer Vaccination. *Pharmaceutics.* 2020 Mar 28; **12**(4): E305. doi: 10.3390/pharmaceutics12040305. PMID: 32231023.

Ikeda H, Watanabe T, Atsukawa M, Toyoda H, Takaguchi K, Nakamuta M, Matsumoto N, Okuse C, Tada T, Tsutsui A, Yamashita N, Kondo C, Hayama K, Kato K, Itokawa N, Arai T, Shimada N, Asano T, Uojima H, Ogawa C, Mikami S, Ikegami T, Fukunishi S, Asai A, Iio E, Tsubota A, Hiraoka A, Nozaki A, Okubo H, Tachi Y, Moriya A, Oikawa T, Matsumoto Y, Tsuruoka S, Tani J, Kikuchi K, Iwakiri K, Tanaka Y, Kumada T. Evaluation of 8-week glecaprevir/pibrentasvir treatment in direct-acting antiviral-naïve noncirrhotic HCV genotype 1 and 2-infected patients in a real-world setting in Japan. *J Viral Hepat.* 2019 Nov; **26**(11): 1266-1275. doi: 10.1111/jvh.13170. Epub 2019 Aug 9. PMID: 31278795.

Nakano K, Kawachi H, Chino A, Kita M, Arai M, Ide D, Saito S, Yoshimizu S, Horiuchi Y, Ishiyama A, Yoshio T, Hirasawa T, Tsuchida T, Fujisaki J. Phenotypic variations of gastric neoplasms in familial adenomatous polyposis are associated with endoscopic status of atrophic gastritis. *Dig Endosc.* 2020 May; **32**(4): 547-556. doi: 10.1111/den.13512. Epub 2019 Oct 31. PMID: 31411765.

Chino A, Kawachi H, Takamatsu M, Hatamori H, Ide D, Saito S, Igarashi M, Fujisaki J, Nagayama S. Macroscopic and microscopic morphology and molecular profiling to distinguish heterogeneous traditional

serrated adenomas of the colorectum. *Dig Endosc.* 2019 Dec 12. doi: 10.1111/den.13603. Epub ahead of print. PMID: 31833094.

Nakagawa R, Muroyama R, Saeki C, Oikawa T, Kaise Y, Koike K, Arai J, Nakano M, Matsubara Y, Takano K, Hirata Y, Saruta M, Zeniya M, Kato N. CD4⁺ T cells from patients with primary biliary cholangitis show T cell activation and differentially expressed T-cell receptor repertoires. *Hepatol Res.* 2019 Jun; **49**(6): 653-662. doi: 10.1111/hepr.13318. Epub 2019 Feb 26. PMID: 30690835.

Higashiyama M, Tomita K, Sugihara N, Nakashima H, Furuhashi H, Nishikawa M, Inaba K, Wada A, Horiuchi K, Hanawa Y, Shibuya N, Kurihara C, Okada Y, Nishii S, Mizoguchi A, Hozumi H, Watanabe C, Komoto S, Yamamoto J, Seki S, Miura S, Hokari R. Chitinase 3-like 1 deficiency ameliorates liver fibrosis by promoting hepatic macrophage apoptosis. *Hepatol Res.* 2019 Nov; **49**(11): 1316-1328. doi: 10.1111/hepr.13396. Epub 2019 Jul 12. PMID: 31250532; PMCID: PMC6916176.

Takajo T, Tomita K, Tsuchihashi H, Enomoto S, Tanichi M, Toda H, Okada Y, Furuhashi H, Sugihara N, Wada A, Horiuchi K, Inaba K, Hanawa Y, Shibuya N, Shirakabe K, Higashiyama M, Kurihara C, Watanabe C, Komoto S, Nagao S, Kimura K, Miura S, Shimizu K, Hokari R. Depression Promotes the Onset of Irritable Bowel Syndrome through Unique Dysbiosis in Rats. *Gut Liver.* 2019 May 15; **13**(3): 325-332. doi: 10.5009/gnl18296. PMID: 30602220; PMCID: PMC6529174.

Kato K, Shimada N, Atsukawa M, Abe H, Itokawa N, Matsumoto Y, Agata R, Tsubota A. Single nucleotide polymorphisms associated with elevated alanine aminotransferase in patients receiving asunaprevir plus daclatasvir combination therapy for chronic hepatitis C. *PLoS One.* 2019 Jul 10; **14**(7): e0219022. doi: 10.1371/journal.pone.0219022. PMID: 31291311; PMCID: PMC6619746.

Nishikawa Y, Chino A, Ide D, Saito S, Igarashi M, Takamatsu M, Fujisaki J, Igarashi Y. Clinicopathological characteristics and frequency of multiple rectal neuroendocrine tumors: a single-center retrospective study. *Int J Colorectal Dis.* 2019 Nov; **34**(11): 1887-1894. doi: 10.1007/s00384-019-03405-z. Epub 2019 Oct 19. PMID: 31630212.

Motoi Y, Ito Z, Suzuki S, Takami S, Matsuo K, Sato M, Ota Y, Tsuruta M, Kojima M, Noguchi M, Uchiyama K, Kubota T. FADS2 and ELOVL6 mutation frequencies in Japanese Crohn's disease patients. *Drug Discov Ther.* 2019; **13**(6): 354-359. doi: 10.5582/ddt.2019.01081. PMID: 31956234.

Teratani T, Tomita K, Furuhashi H, Sugihara N, Higashiyama M, Nishikawa M, Irie R, Takajo T, Wada A, Horiuchi K, Inaba K, Hanawa Y, Shibuya N, Okada Y, Kurihara C, Nishii S, Mizoguchi A, Hozumi H, Watanabe C, Komoto S, Nagao S, Yamamoto J, Miura S, Hokari R, Kanai T. Lipoprotein Lipase Up-regulation in Hepatic Stellate Cells Exacerbates Liver Fibrosis in Nonalcoholic Steatohepatitis in Mice. *Hepatol Commun.* 2019 Jun 6; **3**(8): 1098-1112. doi: 10.1002/hep4.1383. PMID: 31388630; PMCID: PMC6671781.

Reviews and Books

Takakura K, Oikawa T, Nakano M, Saeki C, Torisu Y, Kajihara M, Saruta M. Recent Insights Into the Multiple Pathways Driving Non-alcoholic Steatohepatitis-Derived Hepatocellular Carcinoma. *Front Oncol.* 2019 Aug 13; **9**: 762. doi: 10.3389/fonc.2019.00762. PMID: 31456946; PMCID: PMC6700399.

Takakura K, Kawamura A, Torisu Y, Koido S, Yahagi N, Saruta M. The Clinical Potential of Oligonucleotide Therapeutics against Pancreatic Cancer. *Int J Mol Sci.* 2019 Jul 6; **20**(13): 3331. doi: 10.3390/ijms20133331. PMID: 31284594; PMCID: PMC6651255.