

Gastroenterology and Hepatology

1. Staffs and Students (April, 2009)

Professor	Mamoru WATANABE
Associate Professor	Naoya SAKAMOTO (Department for Hepatitis Control), Ryuichi OKAMOTO (Department of Advanced Therapeutics in Gastrointestinal Diseases)
Junior Associate Professor	Kiichiro TSUCHIYA, Tetsuya NAKAMURA (Department of Advanced Therapeutics in Gastrointestinal Diseases), Sei KAKINUMA (Department for Hepatitis Control, April~), Makoto NAGANUMA (Department of Advanced Therapeutics in Gastrointestinal Diseases, June~), Akihiro ARAKI (Department of Endoscopic Diagnosis and Therapeutics, October~), Shinya OOKA (Department of Professional Development, April~)
Assistant Professor	Masakazu NAGAHORI, Shinji SUZUKI, Cheng-Hsin AZUMA, Teruji TOTSUKA, Takashi NAGAISHI(April~), Mina NAKAGAWA (Department for Hepatitis Control), Eriko OKADA (Department of Endoscopic Diagnosis and Therapeutics · October~),
Tokunin Assistant Professor	Yasuhiro NEMOTO (GCOE)
Hospital Staff	Yuki SAKURAI (April~), Toshimitsu FUJII (April~), Yuko OSAJIMA (April~), Tomoyuki ODAGAKI (April~), Hiroyuki MATSUMOTO (April~), Eiko OKAMOTO (April~),
Medical Fellow	Megumi TASAKA (April~), Michio ONIZAWA
Graduate Student	Michiko IWASAKI, Tamako SHINOHARA, Yuko KARAGAMA, Kako MISHIMA, Machi YAMAMOTO, Gouki SUDA, Junko AKIYAMA, Kaori ISHIGURO, Izumi ONOZUKA, Sea Bong HYUN, Mayumi UEYAMA, Masahiro SUZUKI , Yusuke FUNAOKAKA, Osamu YAMAJI, Shiro YUI, Takako WATANABE, Akiko KITADUME, Tomohiro MIZUTANI, Yoshihito KANO, Kei KIYOHASHI (April~), Sayuri NITTA (April~), Xiu ZHENG (April~)

2. Education Principles

We believe that the central role of clinical departments in the graduate school is to establish basis for the innovative medicine / medical treatment in the next generation. Basic research lead by clinical concepts, and development of novel therapeutics established upon basic research are both critically required to achieve our mission. Therefore, our primary goal is set to train highly educated and experienced clinician-researchers in the field of gastroenterology and hepatology.

In the clinical area, we pursue development and application of highly advanced technologies, including novel endoscopic procedures, for sophisticated diagnosis and treatment of gastrointestinal and liver diseases. In basic research, our principle is to achieve “clinical science”, a research evoked from various clinical problems, and also directed to launch innovative therapeutic procedures to the daily clinical practice. Based on these principals, we are running research projects to 1) develop novel therapy for refractory inflammatory bowel diseases, 2) prevent progression of liver failure in chronic hepatitis patients and 3) improve anti-cancer therapy for the treatment of gastrointestinal malignancies, by expanding our distinct basic research findings in the area of mucosal immunology, liver immunology, regenerative medicine and virology, to various clinical settings.

Moreover, we promote both intra- and inter-national exchanges of researchers, and provide good opportunities to study abroad. The final goal of our education is to promote students to become a well-developed clinician-researcher, and also a leading expert in the field of gastroenterology and hepatology.

3. Basic Research Projects

- Elucidating the pathophysiology of inflammatory bowel diseases and development of treatment by disease-specific immune-regulation.

- Development of novel therapeutics for inflammatory and allergic diseases based on gut-specific mucosal immune regulation.
- Basic research and clinical application of regenerative medicine in gastrointestinal diseases.
- Analysis of interferon-resistant hepatitis C virus.
- Comprehensive analysis of susceptibility genes for various gastrointestinal diseases.

4. Expert Areas in Clinical Practice

- Immune-regulation based treatment of inflammatory bowel diseases.
- Prevention of chronic hepatitis progression to hepatocellular cancer and liver failure, by virology-based treatment strategy.
- Clinical trial of innovative treatment for hepatocellular cancer.
- Diagnosis and treatment of small intestinal diseases by double-balloon enteroscopy.
- Advanced diagnosis and treatment of colonic diseases by colonoscopy.
- Development of minimally-invasive diagnostic modalities for gastrointestinal diseases (i.e. CT colonography).
- Improved chemotherapy for gastric and pancreatic malignancies.

5. Publications

1. Araki A, Tsuchiya K, Okada E, Suzuki S, Oshima S, Yoshioka S, Yoshioka A, Kanai T, Watanabe M: Single-operator double-balloon endoscopy (DBE) is as effective as dual-operator DBE. **J Gastroenterol Hepatol.** 24(5): 770-775, 2009
2. Chatterji U, Bobardt M, Selvarajah S, Yang F, Tang H, Sakamoto N, Vuagniaux G, Parkinson T, Gallay P: The isomerase active site of cyclophilin a is critical for hepatitis C virus replication. **J Biol Chem.** 284(25):16998-17005, 2009
3. Itsui Y, Sakamoto N, Kakinuma S, Nakagawa M, Sekine-Osajima Y, Tasaka-Fujita M, Nishimura-Sakurai Y, Suda G, Karakama Y, Mishima K, Yamamoto M, Watanabe T, Ueyama M, Funaoka Y, Azuma Cheng-Hsin, Watanabe M: Antiviral effects of the interferon-induced protein GBP-1 and its interaction with the hepatitis C virus NS5B protein. **Hepatology.** 50(6): 1727-37, 2009
4. Kakinuma S, Ohta H, Kamiya A, Yamazaki Y, Oikawa T, Okada K, Nakauchi H: Analyses of cell surface molecules on hepatic stem/progenitor cells in mouse fetal liver. **J Hepatol.** 51(1): 127-138, 2009
5. Kakinuma S, Nakauchi H, Watanabe M: Hepatic stem/progenitor cells and stem cell transplantation for the treatment of liver disease. **J Gastroenterol.** 44:167-172, 2009
6. Kamiya A, Kakinuma S, Yamazaki Y, Nakauchi H: Enrichment and clonal culture of progenitor cells during mouse postnatal liver development in mice. **Gastroenterology.** 137:1114-1126, 2009
7. Kim K, Kim KH, Ha E, Park JY, Sakamoto N, Cheong J: Hepatitis C virus NS5A protein increases hepatic lipid accumulation via induction of activation and expression of PPARgamma. **FEBS Letter.** 583(17):2720-2726, 2009
8. KuoTT, de Muinck EJ, Claypool SM, Yoshida M, Nagaishi T, Aveson VG, Lencer WI, Blumberg RS: N-Glycan Moieties in Neonatal Fc Receptor Determine Steady-state Membrane Distribution and Directional Transport of IgG. **J Biol Chem.** 284(13): 8292-300, 2009
9. Mizui T, Yamashina S, Tanida I, Takashima M, Takei Y, Ueno T, Sakamoto N, Ikejima K, Kitamura T, Enomoto N, Sakai T, Kominami E, Watanabe S: Therapeutic targeting of hepatitis C replication-associated autophagy by chloroquine. **J Gastroenterol.** (in press) , 2009
10. Murayama M, Okamoto R, Tsuchiya K, Akiyama J, Nakamura T, Sakamoto N, Kanai T, Watanabe M: Musashi-1 suppresses expression of Paneth cell-specific genes in human intestinal epithelial cells. **J Gastroenterol.** 44(3) 173-182, 2009
11. Nemoto Y, Kameyama K, Shinohara T, Sakamoto N, Totsuka T, Okamoto R, Tsuchiya K, Nakamura T, Sudo T, Matsumoto S, Watanabe M: Long-lived Colitogenic CD4+ Memory T Cells Residing Outside the Intestine Participate in the Perpetuation of Chronic Colitis. **J Immunol.** 183(8): 5059-5068, 2009
12. Nishimura-Sakurai Y, Sakamoto N, Mogushi K, Nagaie S, Nakagawa M, Itsui Y, Sekine-Osajima Y, Tasaka-Fujita M, Onuki-Karakama Y, Suda G, Mishima K, Yamamoto M, Ueyama M, Funaoka Y, Watanabe T, Chen CH, Kakinuma S, Tsuchiya K, Tanaka H, Enomoto N, Watanabe M: Comparison of HCV-associated gene expression and cell signaling pathways in cells with or without HCV replicon-cured cells. **J Gastroenterol.**(in press), 2009
13. Ohira M, Ishiyama K, Tanaka Y, Doskali M, Igarashi Y, Tashiro H, Hiraga N, Imamura M, Sakamoto N, Chayama K, Asahara T, Ohdan H: Adoptive immunotherapy with liver allograft-derived NK/NKT cells: a new paradigm for eliciting anti-hepatitis C virus response after liver transplantation. **J Clin Invest.** 119(11): 3226-3235, 2009

14. Oikawa T, Kamiya A, Kakinuma S, Zeniya M, Nishinakamura R, Tajiri H, Nakauchi H: Sall4 regulates cell fate decision of fetal hepatic stem/progenitor cells. **Gastroenterology**. 136:1000-1011, 2009
15. Okamoto R, Tsuchiya K, Nemoto Y, Akiyama J, Nakamura T, Kanai T, Watanabe M: Requirement of Notch activation during regeneration of the intestinal epithelia. **Am J Physiol Gastrointest Liver Physiol**. 296(1):G23-G25, 2009
16. Onizawa M, Kanai T, Totsuka T, Okamoto R, Tsuchiya K, Nemoto Y, Nagaishi T, Sakamoto N, Watanabe M: Signaling pathway via TNF α /NF κ B in intestinal epithelial cells may be directly involved in colitis-associated carcinogenesis. **Am J Physiol Gastrointest Liver Physiol**. 296(4): G850-859, 2009
17. Sakamoto N, Watanabe M: New therapeutic approaches to HCV. **J Gastroenterol**. 44(7): 643-649, 2009
18. Sakamoto N, Wu GY: Prospects for future therapy of hepatitis C virus infection. **Future Virology**. (in press) , 2009
19. Sekine-Osajima Y, Sakamoto N, Nakagawa M, Itsui Y, Tasaka M, Nishimura-Sakurai Y, Chen CH, Suda G, Mishima K, Onuki Y, Yamamoto M, Maekawa S, Enomoto N, Kanai T, Tsuchiya K, Watanabe M: Two flavonoids extracts from a herb, Glycyrrhizae radix, inhibit in-vitro hepatitis C virus replication. **Hepatology Res**. 39(1): 60-69, 2009
20. Tai AW, Benita Y, Peng LF, Kim SS, Sakamoto N, Xavier RJ, Chung RT: A functional genomic screen identifies cellular cofactors of hepatitis C virus replication. **Cell Host Microbe**. 5(3): 298-307, 2009
21. Takamiya R, Hung CC, Hall SR, Fukunaga K, Nagaishi T, Maeno T, Owen C, Macias AA, Fredenburgh LE, Ishizaka A, Blumberg RS, Baron RM, Perrella MA: High-mobility group box 1 contributes to lethality of endotoxemia in heme oxygenase-1-deficient mice. **Am J Respir Cell Mol Biol**. 41(2):129-35, 2009
22. Takazoe M, Matsui T, Motoya S, Matsumoto T, Hibi T, Watanabe M: Sargramostim in patients with Crohn's disease: results of a phase 1-2 study. **J Gastroenterol**. 44(6): 535-543, 2009
23. Takizawa H, Nishimura S, Takayama N, Oda A, Nishikii H, Morita Y, Kakinuma S, Yamazaki S, Okamura S, Tamura N, Goto S, Sawaguchi A, Manabe I, Takatsu K, Nakauchi H, Takaki S, Eto K. Lnk/Sh2b3 regulates integrin α IIb β 3 outside-in signaling in platelets leading to stabilization of developing thrombus in vivo. **J Clin Invest**. (in press) ,2009
24. Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, Nakagawa M, Korenaga M, Hino K, Hige S, Ito Y, Mita E, Tanaka E, Mochida S, Murawaki Y, Honda M, Sakai A, Hiasa Y, Nishiguchi S, Koike A, Sakaida I, Imamura M, Ito K, Yano K, Masaki N, Sugauchi F, Izumi N, Tokunaga K, Mizokami M: Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. **Nature Genetics**. 41(10): 1048-1050, 2009
25. Toma S, Yamashiro T, Arakaki S, Shiroma J, Maeshiro T, Hibiya K, Sakamoto N, Kinjo F, Tateyama M, Fujita J: Synergistic inhibition of intracellular hepatitis C virus replication by nelfinavir and interferon- α . **Journal of Viral Hepatitis**. 16(7): 506-512, 2009
26. Tomita T, Kanai T, Totsuka T, Nemoto Y, Okamoto R, Tsuchiya K, Sakamoto N, Ohteki T, Hibi T, Watanabe M: IL-7 Is Essential for Lymphopenia-driven Turnover of Colitogenic CD4⁺ Memory T Cells in Chronic Colitis. **Eur J Immunol**. 39(10): 2737-2747, 2009
27. Totsuka T, Kanai T, Nemoto Y, Tomita T, Okamoto R, Tsuchiya K, Nakamura T, Sakamoto N, Akiba H, Okumura K, Yagita H, Watanabe M: RANK-RANKL signaling pathway Is critically involved in the function of CD4⁺CD25⁺ regulatory T cells in chronic colitis. **J Immunol**. 182(10): 6079-6087, 2009
28. Wang SY, Tseng CP, Tsai KC, Lin CF, Wen CY, Tsay HS, Sakamoto N, Tseng CH, Cheng JC: Bioactivity-guided screening identifies a potent anti-hepatitis C virus compound pheophytin a from *Lonicera hypoglauca* Miq. **Biochem Biophys Res Commun**. 385(2):230-235, 2009