

## Department of Laboratory Medicine

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### General Summary

The main studies were accomplished by 2 large-scale projects: the Research on the Innovative Development, provided by the Ministry of Health, Labour and Welfare of Japan, and the Practical Application of New Drugs for Hepatitis B, provided by the Japan Agency for Medical Research and Development. We performed studies to connect experimental medicine with clinical medicine.

### Research Activities

#### *Clinical microbiology*

1. Several clinically isolated, previously unidentified bacterial strains were identified though gene sequencing of polymerase chain reaction-amplified 16S ribosomal RNA. We attempted to characterize the differentiation of methicillin-resistant *Staphylococcus aureus* at the strain level using whole-cell matrix-assisted laser desorption ionization-time of flight mass spectrometry. We observed the congruence of mass spectrometry-based clustering and pulsed-field gel electrophoresis (established typing method) clustering.
2. We developed cell lines that produced hepatitis B virus in episomal for evaluating the antiviral action of new compounds.
3. We studied the biofilm formation ability of *Staphylococcus epidermidis*.

#### *Clinical chemistry*

1. We accumulated the case for studies, including patients with diabetes mellitus and diabetic complications. In addition, we measured serum pentosidine concentrations and endogenous secretory receptors for advanced glycosylation endproducts (AGEs). Hypoglycemic treatment reduced GA levels, glycation sites of albumin, and AGE levels with or without complications of diabetes mellitus. Keeping GA levels low would prevent the formation of AGE and may prevent the progression of diabetic complications.
2. We published an article about the performance of the latest version of our high-performance liquid chromatography lipoprotein cholesterol measurement system, which has been covered by health insurance since July 2013. A study to determine the high-density lipoprotein function of cholesterol efflux with stable isotope and to assess the risk of atherosclerosis has been supported by a research grant from the Ministry of Education, Culture, Sports, Science and Technology, and the fundamental method is currently being established. The collaborative study results of statin-related adverse events for glucose

metabolism and renal function were published in *Atherosclerosis* (2015; 241: 409–18). The preventive effects of astaxanthin, a member of the xanthophyll class, on the impairment of glucose and lipid metabolism and blood pressure control was published in *Marine Drugs* (2016; 14(2).pii: E35).

3. We developed the fasting  $^{13}\text{C}$ -octanoic acid breath test as a technique to noninvasively evaluate the  $\beta$ -oxidation of the liver.  $^{13}\text{C}$ -octanoic acid is absorbed from the jejunum and is transferred to the liver via the portal vein. In the liver  $^{13}\text{C}$ -octanoic acid passes through the mitochondrial outer membrane without contribution of carnitine and is oxidized by  $\beta$ -oxidation. We can evaluate the beta-oxidation of the liver if we measure  $^{13}\text{CO}_2/^{12}\text{CO}_2$  in exhaling gas.

#### *Clinical oncology*

Ruxolitinib successfully decreased the burden of the mutant *V617F* allele of the Janus kinase 2 gene (*JAK2*). The burden of the *JAK2\*V617F* was measured in patients treated with ruxolitinib, an inhibitor of tyrosine kinase subtypes JAK1 and JAK2. In a patient with continuous ruxolitinib treatment, the mutant allele burden was initially 72.4% but then decreased through 59.2% and 53.7% to 52.9%. However, in a patient who had stopped receiving ruxolitinib, no change was observed. A cytogenetic response with a decrease in the burden of mutant allele *JAK2\*V617F* was observed after treatment with ruxolitinib.

#### *Clinical psychiatry*

We attempted interpretation based on Neojacksonism (from French psychiatrist Henri Ey) about the patients who presented the psychotic symptoms associated with epilepsy. Furthermore, we reported changes in serum concentrations of antiepileptic drugs (especially new ones) while patients with epilepsy were pregnant. We performed a study about preventing depression from recurring in patients with epilepsy. We examined the safety and efficacy of psychotropic drugs in several forms of psychosis associated with epilepsy.

#### *Clinical physiology*

In an examination in phases of menstruation we performed a basic examination of the walk analyzer.

#### *Clinical immunology*

A main theme of our research is the study of nonspecific reactions in the inspection of immunity. This year, we studied the nonspecific reactions in the measurement of SCC and the syphilis *Treponema pallidum* antibody.

#### *Clinical cell biology and pathology*

1. Hepatic stellate cells store vitamin A as a form of retinylester through an enzymatic activity of lecithin:retinol acyltransferase. The upregulation of the retinoic acid receptor  $\alpha$  gene (*RARA*) at the posttranscriptional level and the subsequent upregulation of the cellular retinol-binding protein I gene (*CRBPI*) at the transcriptional level make a feedback loop toward the recovery of vitamin A-containing lipid droplets within the activated

hepatic stellate cells.

2. Using human liver biopsy specimens, we examined the stainability of transforming growth factor- $\beta$  latency-associated protein of transforming growth factor- $\beta$  degradates, which was a fibrogenesis marker of nonalcoholic steatohepatitis/nonalcoholic fatty liver disease.

## Publications

**Shrestha R<sup>1,2</sup>, Tatsukawa H<sup>3</sup>, Shrestha R<sup>1,4</sup>, Shibashi N<sup>5</sup>, Matsuura T, Kagechika H<sup>2</sup>, Kose S<sup>1</sup>, Hitomi K<sup>3</sup>, Imamoto N<sup>1</sup>, Kojima S<sup>1,2,4</sup>** (<sup>1</sup>RIKEN, <sup>2</sup>Tokyo Med Dent Univ, <sup>3</sup>Nagoya Univ, <sup>4</sup>Tokyo Inst Tech, <sup>5</sup>KOWA Company Ltd). Molecular mechanism by which acyclic retinoid induces nuclear localization of transglutaminase 2 in human hepatocellular carcinoma cells. *Cell Death Dis.* 2015; **6**: e2002.

**Hara M<sup>1</sup>, Inoue I<sup>1</sup>, Yamazaki Y<sup>1</sup>, Kirita A<sup>1</sup>, Matsuura T, Friedman SL<sup>2</sup>, Rifkin DB<sup>3</sup>, Kojima S<sup>1</sup>** (<sup>1</sup>RIKEN, <sup>2</sup>Icahn Sch Med Mount Sainai, <sup>3</sup>New York Univ Sch Med). L<sup>59</sup>TGF- $\beta$  LAP degradation products serve as a promising blood biomarker for liver fibrogenesis in mice. *Fibrogenesis Tissue Repair.* 2015; **8**: 17.

**Abe H, Aida Y, Seki, N, Sugita T, Tomita Y, Nagano T, Itagaki M, Sutoh S, Nagatsuma K, Itoh K, Matsuura T, Aizawa Y.** Aldehyde dehydrogenase 2 polymorphism for development to hepatocellular carcinoma in East Asian alcoholic liver cirrhosis. *J Gastroenterol Hepatol.* 2015; **30**: 1376-83.

**Sato M<sup>1</sup>, Hikita H<sup>1</sup>, Hagiwara S<sup>1</sup>, Sato M<sup>1</sup>, Soroida Y<sup>1</sup>, Suzuki A<sup>1</sup>, Gotoh H<sup>1</sup>, Iwai T<sup>1</sup>, Kojima S<sup>2</sup>, Matsuura T, Yotsuyanagi H<sup>1</sup>, Koike K<sup>1</sup>, Yatomi Y<sup>1</sup>, Ikeda H<sup>1</sup>** (<sup>1</sup>Univ Tokyo, <sup>2</sup>RIKEN). Potential associations between perihepatic lymph node enlargement and liver fibrosis, hepatocellular injury or hepatocarcinogenesis in chronic hepatitis B virus infection. *Hepatol Res.* 2015; **45**: 397-404.

**Sugita T, Amano K, Nakano M, Masubuchi N<sup>1</sup>, Sugihara M<sup>1</sup>, Matsuura T** (<sup>1</sup>Daiichi Sankyo Co., LTD). Analysis of the serum bile Acid composition for differential diagnosis in patients with liver disease. *Gastroenterol Res Pract.* 2015; **2015**: 717431.

**Manita D, Hirowatari Y, Yoshida H.** A rapid anion-exchange chromatography for measurement of cholesterol concentrations in five lipoprotein classes and estimation of lipoprotein profiles in male volunteers without overt diseases. *Ann Clin Biochem.* 2015; **52**: 638-46.

**Inada K, Matsuo S, Tokutake K, Yokoyama K, Hioki M, Narui R, Ito K, Tanigawa S, Yamashita S, Tokuda M, Shibayama K, Miyanaga S, Sugimoto K, Yoshimura M, Yamane T.** Influence of the concomitant use of heparin on the effects of warfarin during catheter ablation for atrial fibrillation. *Heart Vessels.* 2016; **31**: 397-401.

## Reviews and Books

**Arai Y, Matsuura T, Matsuura M** (Teikyo Univ), **Fujiwara M** (Jpn Red Cross Med Ctr), **Okayasu I** (Kitasato Univ Sch Med), **Ito S** (IDAC Theranostics), **Arihiro S.** Prostaglandin E-major urinary metabolite as a biomarker for inflammation in ulcerative colitis: Prostaglandins revisited. *Digestion.* 2016; **93**: 32-9.

**Kishimoto Y, Yoshida H, Kondo K.** Potential anti-atherosclerotic properties of astaxanthin. *Mar Drugs.* 2016; **14**: E35.