Department of Laboratory Medicine

Senya Matsufuji, *Professor*
Ken Kaito, *Professor*
Tomokazu Matsuura, *Professor*
Kenichi Sugimoto, *Associate Professor*
Setuko Akizuki, *Assistant Professor*
Akihiro Ohnishi, *Professor*
Hiroshi Yoshida, *Professor*
Hironari Sue, *Associate Professor*
Midori Kono, *Assistant Professor*
Masato Suzuki, *Visiting Professor*

General Summary

The members of our department performed studies about clinical laboratory medicine, with a focus on their individual specialties, as shown in the following *Research Activities*. Our study of the measurement of host interleukin 28B single nucleotide polymorphisms for predicting the effects of treatment with interferon for chronic hepatitis C could contribute to advanced medical care. Our new method of high-performance liquid chromatography (HPLC) to determine cholesterol levels of lipoproteins was listed in the insurance publication by the Ministry of Health, Labour and Welfare.

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 evaluated the status of a methicillin-resistant *Staphylococcus aureus* outbreak in an affiliated hospital through molecular analysis (the phage open reading frame typing method and pulsed-field gel electrophoresis).
2. We performed assays of interleukin 28B single nucleotide polymorphisms to predict the effect of interferon in patients with hepatitis C infection. This assay was useful for deciding whether to perform antiviral therapy, continue treatment, or discontinue treatment.
3. In the field of microbial examination, we studied extraction conditions of multiple blood cultures and the effects of clinical judgments and the analysis of molecular typing of toxin A-negative, toxin B-positive *Clostridium difficile* isolated from nosocomial outbreaks and published the results.

Clinical chemistry

1. Oral tegafur/uracil therapy has been indicated for patients with hepatocellular carcinoma (HCC) and is often used as a single-agent treatment. However, how treatment efficacy is related to fluorouracil (5-FU) metabolic enzymes is unclear. We investigated genetic polymorphisms of the 5-FU metabolic enzymes in Japanese patients with HCC. We examined 2 genetic polymorphisms of the metabolic enzymes cytochrome P450 2A6 and dihydropyrimidine dehydrogenase in 58 Japanese patients with hepatitis C virus-seropositive HCC. To measure efficacy, we investigated genetic polymorphisms of the variable number of tandem repeats of thymidylate synthase and classified the geno-

types as high- or low-expression types. Our results suggested that only 13 of 58 patients with HCC (22.4%) tested would respond positively to treatment with oral tegafur/uracil. Therefore, when administering oral 5-FU to patients with HCC, it is important to consider 3 genetic polymorphisms (cytochrome P450 2A6, dihydropyrimidine dehydrogenase, and thymidylate synthase) associated with 5-FU metabolic enzymes.

2. Our principal research interests are to clarify the pathophysiology of atherosclerosis in relation to impaired lipoprotein metabolism and oxidized low-density lipoprotein and to develop a method of assessing cardiovascular disease risk including the application of our HPLC method to determine cholesterol levels of lipoproteins. We published the following studies.

1) The HPLC method we developed can correlate intermediate-density lipoprotein cholesterol level to Framingham risk score in Japanese men (Int J Cardiol 2013; 168: 3853-8).

2) Pleiotropic effects of hydroxymethyl glutaryl coenzyme A reductase inhibitors (statins) on oxidized lipoproteins are divergent, and pitavastatin can markedly decrease malondialdehyde-low-density lipoprotin/apolipoprotein B while atorvastatin can decrease oxidized high-density lipoprotein/apolipoprotein A1 (Atherosclerosis 2013; 226: 161-4).

In addition, the significant associations of lipoprotein(a)-cholesterol to triglyceride-rich lipoprotein cholesterol, high-density lipoprotein cholesterol and Framingham risk score were found and reported in the accomplishment paper of a Ministry of Education, Culture, Sports, Science and Technology Research Grant. In the meantime, remuneration reimbursement of medical treatment for HPLC lipoprotein analysis was approved by the Ministry of Health, Labour and Welfare.

3. This study was performed to investigate whether the fasting ^{13}C-glucose breath test (FGBT) is useful as a convenient and highly sensitive clinical test for evaluating hepatic insulin resistance. The area under the curve until 360 minutes of the ^{13}C excretion kinetic curve of the FGBT reflects the efficiency of energy production in the liver. The FGBT is a novel glucose metabolism test that can be used conveniently and safely to evaluate the balance of glucose metabolism in the liver. This test has excellent sensitivity for diagnosing alterations in hepatic glucose metabolism, particularly hepatic insulin resistance. (Supported by a Ministry of Education, Culture, Sports, Science and Technology-Supported Program for the Strategic Research Foundation at Private Universities, 2011-2015) (performed in collaboration with the National Defense Medical College and the Department of Internal Medicine, The Jikei University)

Clinical hematology

Pathological significance of helper T type 1 lymphocytes in patients with aplastic anemia; Activated T cells play an important role in aplastic anemia (AA). We investigated helper T type 1 (Th1) (interferon γ) and helper T type 2 (Th2) (interleukin 4) lymphocytes in patients with aplastic anemia treated with immunosuppressive therapy. We found that Th1 cells were significantly fewer and that the Th1/Th2 ratio was significantly lower in responders than in nonresponders. These results suggest that measurement of Th1 and Th2 provide important clinical information for the treatment of aplastic anemia.

Clinical pathology

Precisely which cell types, such as hepatic stellate cells (HSCs) in the parenchyma or myofibroblasts in the portal area, contribute most to portal fibrosis, especially in chronic viral hepatitis, remains unclear. Clarifying the characteristics of cells that contribute to portal fibrosis is necessary to determine the mechanism of portal fibrogenesis and to develop a therapeutic target for portal fibrosis. This study examined whether HSCs positive for both lecithin : retinol acytransferase and cellular retinol-binding protein 1 contribute to portal fibrosis in viral hepatitis. This study provided evidence that functional HSCs that coexpress both lecithin : retinol acytransferase and cellular retinol-binding protein 1 and continue to maintain the ability to store vitamin A contribute in part to the development of portal fibrogenesis and parenchymal fibrogenesis in patients with viral hepatitis. (Supported in part by grants from the High Technology Research Center Project for Private University; The Jikei University Research Fund; the Program for Promotion of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation; the Japan Society for the Promotion of Science Core-to-Core Program, A. Advanced Research Networks; and the Research on the Innovative Development and the Practical Application of New Drugs for Hepatitis B provided by the Ministry of Health, Labour and Welfare of Japan, 2012-13).

Clinical psychiatry

We reported on a patient with epilepsy induced by a specific situation and showed a peculiar clinical course. Furthermore, we examined serum concentrations of new antiepileptic drugs during pregnancy. A study was performed to prevent the recurrence of depression in patients with epilepsy. We plan a clinical study of the management of pregnancy in women with epilepsy.

Clinical physiology

An animal study suggested that prepubertal-onset exercise might help adults maintain long-term body weight reduction and increased energy metabolism after the cessation of exercise.

Addition

We performed studies of the effects of nonspecific materials which gave them to blood data. First we reported the effect of a nonspecific material for measuring tacrolimus with the Affinity Column Mediated Immunoassay (ACMIA) method and studied the effects of a nonspecific material for subsequent measurement of squamous cell carcinoma antigen (SCC).

Publications

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