

## Department of Laboratory Medicine

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### General Summary

Research projects in our department in 2008 were concerned with clinical physiology, clinical microbiology, clinical chemistry, clinical biochemistry, hematology, cardiology, clinical cell biology, and clinical psychiatry. Research achievements in each division are described below.

### Research Activities

#### *Clinical physiology*

We investigated whether regular exercise in the early stage of growth (5 to 20 weeks of age) prevents the over-accumulation of visceral fat mass and other risk factors for metabolic syndrome in adolescent (46 weeks of age) Otsuka Long-Evans Tokushima fatty (OLETF) rats. The rats exercised voluntarily every day using a rotary wheel. This study found that regular exercise in the early stage of growth in OLETF rats prevents the increase in body weight and the over-accumulation of the subcutaneous and visceral fat masses and also maintained lower levels of triglycerides in the serum and liver as measured at 46 weeks of age. These results suggest that regular exercise in childhood prevents the incidence of lifestyle-related diseases, such as obesity, diabetes, and hypertension, in middle age.

#### *Clinical microbiology*

DNA diagnosis for mycosis was performed with a basic morphological study to assist the Microbiology section of the Central Laboratory and the Rhinosinusitis division of the Department of Otolaryngology. The polymerase chain reaction (PCR) allowed a test for epidemiological studies that was faster, simpler, and less expensive than pulse field gel electrophoresis.

The treatment of infectious waste zoonoses in an experimental animal laboratory was investigated with observation and questionnaires. Guidelines for waste management involving the H1N1 influenza virus were studied with the Ministry of the Environment.

#### *Clinical chemistry*

1. Pharmacogenetics of hepatobiliary ATP-binding cassette transporters in hepatocellular carcinoma

An important hepatic function is the biliary and sinusoidal secretion of endogenous and exogenous substances (e.g., drug, xenobiotics), which can protect against the accumula-

tion of various mutagens and carcinogens. This function is maintained by a drug transporter system that comprises mainly ATP-binding cassette (ABC)-transporter proteins. Therefore, genetic mutations of these proteins may impair this protective system that prevents the accumulation of hazardous compounds and may lead to hepatocellular carcinoma (HCC). We analyzed the genetic polymorphisms of efflux ABC transporters in apical (canalicular) membranes and basolateral membranes in hepatocytes using DNA samples obtained from hepatitis C virus—seropositive patients with HCC (n=58), and compared allele and haplotype frequencies with those in a group of healthy volunteers (n=61). The risks of acquired HCC were analyzed as morbidity odds ratios. We searched for 11 single nucleotide polymorphisms (SNPs) in efflux ABC transporters (multidrug resistance—associated protein [MRP]2, bile salt export pump [BSEP], breast cancer resistance protein [BCRP], multidrug resistance [MDR]1, MRP1, and MRP3) to identify HCC susceptibility genes. No significant association was found in any single SNP during single gene testing. However, some haplotypes in the MRP1 and BSEP genes significantly differed between patients with HCC and healthy volunteers. Further, the risk of HCC was increased by the SNP combinations of 3435C>T in MDR1 and 825T>C in MRP1, of 3435C>T in MDR1 and a CTCT deletion in BSEP, and of 825T>C in MRP1 and a CTCT deletion in BSEP, because the morbidity odds ratios ranged from 3.8 to 4.5. These results suggest that combinations of several SNPs and haplotypes in efflux ABC transporters increase the risk of hepatocarcinogenesis and lead to the development of HCC in patients with chronic hepatitis. Because the precise mechanism of how ABC transporters are involved in the development of HCC remains obscure, further studies are warranted.

#### *Clinical biochemistry*

We investigated and clarified the following.

1. Current issues of the remnant lipoprotein assay were highlighted by a high-performance liquid chromatography (HPLC) method we developed (reported in *Lipids in Health and Disease*, 2008).
2. The lipoprotein profiles of patients undergoing hemodialysis were investigated in detail with HPLC (reported in *Annals of Clinical Biochemistry*, 2008).
3. The clinical significance of malondialdehyde-modified low-density lipoprotein, a novel clinical use of the measurement of oxidized low-density lipoprotein, was assessed (reported in presentations and special seminars at annual meetings of the Japan Circulation Society, the Japanese Society of Laboratory Medicine, and the Japanese Society of Clinical Chemistry).
4. The beneficial effects of astaxanthin on triglycerides, high-density lipoprotein, and adiponectin were clarified (reported at annual meeting of the Japanese Society of Clinical Nutrition).

#### *Hematology*

1. The transcription—reverse transcription concerted reaction in detecting *Mycobacterium tuberculosis*

We examined the presence of *Mycobacterium tuberculosis* in 84 samples with the

transcription—reverse transcription concerted (TRC) method, PCR, and liquid culture. The rate of agreement between the TRC method and PCR was 97.6%, and that between TRC and liquid culture was 96.4%. The discrepancy was observed in a few samples but disappeared with cryopreservation of the samples. In such samples, the detection time of the internal control was also prolonged. Therefore, we could find the false-negative phenomenon by paying attention to such prolongation. These results indicate that TRC is a satisfactory system for *Mycobacterium tuberculosis* and could be introduced to clinical use.

### *Cardiology*

We have studied catheter intervention for atrial fibrillation (AF). To eliminate AF, segmental ostial catheter ablation (SOCA) has been performed to electrically isolate the pulmonary veins from the left atrium. Our purposes are to improve the method of SOCA and to increase the cure rate of AF. This year we made 3 findings related to AF.

1. Dormant reconnection of the pulmonary vein as an unusual cause of recurrent AF
2. Characteristics of the confluent inferior pulmonary vein
3. Hypoxemia in the inferior pulmonary vein is dependent on obesity.

### *Clinical cell biology*

1. Immunohistochemical study of lecithin retinol acyltransferase in hepatic stellate cells in liver diseases
2. The <sup>13</sup>C-glucose breath test for the diagnosis of insulin resistance
3. Development of a bioartificial liver using the radial-flow bioreactor
4. Ultrasonic molecular imaging for the diagnosis of small cancers
5. Plasma examination of the transforming growth factor  $\beta$ -activating reaction for the diagnosis of liver damage

### *Clinical psychiatry*

A retrospective study is under way to clarify the clinical significance of the 6-Hz spike and wave on electroencephalography. We reported the characteristics of patients with epilepsy compelled to withdraw from society and reported on a patient with abnormal, likely epileptic, behavior during sleep. Premonitory signs and symptoms as epileptic prodromes were studied. In addition, a study was started on the first-line choice of psychotropic drugs for the treatment of epilepsies with psychiatric symptoms.

## **Publications**

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