Institute of Clinical Medicine and Research

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General Summary

The aim of our research is to fill the gap between clinical medicine and fundamental medicine and to shorten the time needed for discoveries to go from bench to bedside. We are proud to report that during the last few years we have made good progress in the development of a drug delivery system using nanotechnology. We also made progress in gene technology, especially in the treatment of hepatitis C virus (HCV) infection and liver cancer. In the field of lipid metabolism related to atherosclerosis, we succeeded in measuring lipoprotein A, a atherosclerotic lipoprotein, with our newly developed ion-exchange chromatography.

Research Activities

Functional analysis of oxidative stress-induced liver carcinogenetic genes

Our comprehensive gene expression profiling analysis has identified candidate genes associated with oxidative stress-induced liver carcinogenesis in an animal model with naturally occurring hepatotumorigenesis. We are now analyzing the function of the gene signatures in the process of liver carcinogenesis and the mechanism of tumorigenesis.

Transporter gene in the treatment of chronic HCV infection

Pegylated interferon plus ribavirin combination therapy is the standard of care (SOC) treatment for chronic HCV infection. In the SOC treatment, exposure of HCV to ribavirin in hepatocytes is critical for virus eradication. Ribavirin is transported into hepatocytes by cell membrane transporters. We are investigating the function of transporters and the association of single nucleotide polymorphisms of the gene with treatment response.

Comprehensive gene expression profiling analysis of microRNA/messenger RNA in liver tissue

We are profiling and analyzing the expression of microRNA/messenger (m) RNA in the liver tissue of patients with chronic HCV infection who would receive SOC treatment. We are analyzing whether the microRNA/mRNA candidates can be associated with treatment response in chronic HCV infection. When the candidates affect the treatment outcome, the function of the microRNA/mRNA will be investigated in detail.

The temporal and spatial manipulation of "basket-type organic/inorganic-hybrid structure" as a future theranostic nanomedicine

Free manipulation of the movement of drugs with remote controlled light/magnetism/ultrasound used in cutting-edge medical technology is expected to be a next-generation technology. Remotely manipulating the speed and position of nanoparticles, which are mineral capsules that respond to various types of physical energy and are filled with organic drugs, will lead to an innovative technology that allows "pinpoint and perfectly timed" diagnosis and treatment.

We aim for the realization of innovative nanomedicine in which we can remotely control the accumulation, release, and effects of drugs by using nanosized capsules that efficiently convert light, magnetic, and ultrasonic energies. This is unprecedented research in which we can apply Japan's world-leading nanotechnology to medicine. It will allow highly sensitive, rapid diagnosis and highly effective treatment that is gentle to the body for incurable diseases and for diseases that are difficult to diagnose. The realization of medical care that is gentle to the weak, such as elderly persons, will contribute to the promotion of a long and healthy life, reduced healthcare costs, and the development of the healthcare industry. Moreover, because this technology can precisely control the behavior of drugs, it can be applied to wide areas, such as pharmacology and biotechnology.

Studies of lipid metabolism and atherosclerosis

The relationship between diet and the incidence of cardiovascular disease among Japanese was investigated exhaustively through large-scale cohort studies in Japan, and results were published in the *Journal of Atherosclerosis and Thrombosis*. Effects of carbohydrate co-feeding with lipids on postprandial hyperlipidemia were investigated with measurement of serum level of apolipoprotein B48. An incubation study using bacteriophages was performed to examine the antiviral effects of plasma fractions, and the antiviral fraction was extracted from human plasma. We developed a new high-performance liquid chromatography (HPLC) method for measuring lipoprotein A (published in the *Journal of Lipid Research*). By measuring very low density lipoprotein cholesterol with this HPLC, we proved the benefit of therapeutic exercise for reducing remnant lipoproteins. Effects of astaxanthin on triglycerides, high-density lipoprotein, and adiponectin were investigated, and the results were reported at the annual scientific meeting of the Japanese Society of Clinical Nutrition.

Publications

Tsubota A, Fujise K, Namiki Y, Tada N. Peginterferon and ribavirin treatment for hepatitis C virus infection. *World J Gastroenterol* 2011; **17:** 419–32.

Aizawa M, Tsubota A, Fujise K, Sato K, Baba M, Takamatsu M, Namiki Y, Ohkusa T, Tajiri H. Overlap/switch to adefovir monotherapy for lamivudine-resistant patients who responded to combination therapy: a pilot controlled study. *Intern Med* 2010; **49:** 1067–72.

Fuchigami T[1], Kawamura R[1], Kitamoto Y[1], Nakagawa M[2], Namiki Y ([1]Tokyo Inst Tech, [2]Tohoku Univ). Ferromagnetic FePt-nanoparticles/polycation hybrid capsules designed for a magnetically guided drug delivery system. *Langmuir* 2011; **27:** 2923–8. Epub 2011 Feb 3.

Yoshida H, Shimizu M, Ikewaki K, Taniguchi I, Tada N, Yoshimura M, Rosano G, Dahlof B, Mochizuki S; Jikei Heart Study group. Sex differences in effects of valsartan administration on cardiovascular outcomes in hypertensive patients: findings from the Jikei Heart Study. *J Hypertens*

2010; **28:** 1150–7.
Yoshida H, Ishikawa T, Suto M, Kurosawa H, Hirowatari Y, Ito K, Yanai H, Tada N, Suzuki M. Effects of supervised aerobic exercise training on serum adiponectin and parameters of lipid and glucose metabolism in subjects with moderate dyslipidemia. *J Atheroscler Thromb* 2010; **17:** 1160–6.
Yanai H, Kaneko H, Yoshida H, Tada N. A significant association between impaired glucose metabolism and polymyalgia rheumatica. *J Atheroscler Thromb* 2010; **17:** 1108–9.
Yanai H, Tomono Y, Yoshida H, Tada N. Therapeutic application of diacylglycerol oil for the metabolic syndrome (in Japanese). *Rinsho Byori* 2010; **58:** 39–44.
Hirowatari Y, Yoshida H, Kurosawa H, Shimura Y, Yanai H, Tada N. Analysis of cholesterol levels in lipoprotein(a) with anion-exchange chromatography. *J Lipid Res* 2010; **51:** 1237–43.
Koido S, Homma S, Hara E, Namiki Y, Takahara A, Komita H, Nagasaki E, Ito M, Ohkusa T, Gong J, Tajiri H. Regulation of tumor immunity by tumor/dendritic cell fusions. *Clin Dev Immunol* 2010; **2010:** 516768.
Fujise K, Tatsuzawa K, Kono M, Hoshina S, Tsubota A, Niiya M, Namiki Y, Tada N, Tajiri H. A mutation of the start codon in the X region of hepatitis B virusDNA in a patient with non-B, non-C chronic hepatitis. *World J Hepatol* 2011; **3:** 56–60.
Sasaki T, Hiki Y, Nagumo S, Ikeda R, Kimura H, Yamashiro K, Gojo A, Saito T, Tomita Y, Utsunomiya K. Acute onset of rheumatoid arthritis associated with administration of a dipeptidyl peptidase-4 (DPP–4) inhibitor to patients with diabetes mellitus. *Diabetol Int* 2010; **1:** 90–2.