

Institute of Clinical Medicine and Research

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General Summary

The Institute of Clinical Medicine and Research always conducts research with a focus on clinical applications. In 2007, the institute performed medical research related to the etiology, diagnosis, and treatment of intractable diseases. As part of this research, we examined the relationship between oxidative stress and disease, including the effect of oxidative stress on hepatocarcinogenesis, the role of reactive oxygen species (ROS) in physiological and pathological conditions, and the usefulness of antioxidant agents. Additionally, we have performed studies to define the pathological conditions underlying hyperlipidemia and heart disease, to clarify the action of anesthetics against substances associated with pain, to prepare nanoparticles for poorly soluble drugs using innovative procedures, and to define the pathological conditions underlying viral diseases.

Research Activities

Liver disease and oxidative stress

1. Comprehensive RNA gene expression analysis of hepatocarcinogenesis in oxidative stress-induced chronic liver damage: Our group investigated how oxidative stress conditions influence oncogenesis in chronic liver damage, using an animal model of persistent exposure to ROS and comprehensive RNA gene expression analyses.
2. Development of a novel antioxidant agent: The effect of bovine lactoferrin on oxidative stress-induced chronic liver damage was investigated in an animal model. We have clarified the mechanism of lactoferrin action and have developed a novel drug delivery system, including intestine-dissolved and PEGylated types. An international patent application for this system has been submitted.
3. Analysis of the pathogenesis and development of treatment in chronic hepatitis C virus infection: We are aiming to improve the efficacy of antiviral treatment for chronic hepatitis C virus infection by analyzing viral kinetics and applying clinical protocols, including randomized controlled trials, in collaboration with the Division of Gastroenterology and Hepatology, Kashiwa Hospital.

Ovulation inhibition due to removal of peripheral blood phagocytes

ROS containing superoxide are involved in ovulation. We have recently used a specific superoxide sensor to confirm production of superoxide and have used immunohistochemical studies to localize DNA and lipid peroxides in the ovulating ovary. Phagocytes, such as neutrophils and macrophages, are thought to be sources of ROS involved in ovulation. This year, we have started to examine whether removal of

peripheral blood phagocytes inhibits ovulation, to examine the source of ROS involved in ovulation.

The development of a magnetic drug delivery system for cancer

The desired performance of cancer treatment has not been achieved with conventional drug delivery systems. To overcome this problem, since 2006 we have developed novel magnetic nanoparticles that include anticancer agents. Moreover, we have developed strong magnets to accumulate these nanoparticles at tumor lesions. This work has been supported by Industrial Technology Research Grant Program 08C46049a in 2008 from New Energy and Industrial Technology Development Organization (NEDO) of Japan, the Takeda Science Foundation in 2007 and the Tsuchiya Foundation in 2006.

The development of molecular prevention of metastasis of colon cancer

The hepatocyte growth factor analogue NK-4 strongly inhibits angiogenesis and tumor metastasis. To prevent colon cancer from metastasizing to the liver, since 2006 we have investigated the effect of the oligomannose-coated lipid nanoparticles that contain the NK-4 gene.

Clinical microbiology

DNA diagnosis of clinical mycosis was established with the mycotic universal sequence and applied to infectious tissues. The minimum inhibitory concentration of a *Pseudomonas aevuginosa* was measured with an oxygen potential electrode system, which was applied clinically.

The dioxin chemical structure was proposed for anti-inflammatory, antiproliferative agents from the aspect of the resistance mechanism of the thermophilic bacterium *Bacillus midousuji*.

Publications

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