

Institute of Clinical Medicine and Research

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General Summary

The Institute of Clinical Medicine and Research conducts research with a focus on clinical applications as its basic approach. In 2006, the Institute thus conducted medical research associated with clarifying the etiology, diagnosis, and treatment of intractable diseases. As such, we carried out research on the relationship between oxidative stress and disease, including an analysis of the effects of oxidative stress on carcinogenesis, the role of reactive oxygen species (ROS) in physiological and pathological conditions (which was detected *in vivo* using a sensing system developed in collaboration with the Tokyo University of Science), and the usefulness of antioxidant agents. We have also performed basic research into cancer therapies, including the enhanced antitumor effect of 5-fluorouracil (5-FU) with photoactivated dihydropyrimidine dehydrogenase (DPD)-small interfering (si)RNA transfection, prevention of liver metastasis by NK-4 gene transduction, magnetically enhanced drug delivery systems, and the development of immunotherapy using fusions of dendritic cells and cancer cells. Additionally, we have carried out studies to define the pathological conditions underlying hyperlipidemia and heart disease, to clarify the actions of anesthetics against substances associated with pain, to prepare nanoparticles containing poorly insoluble drugs using an innovative procedure, and to define the pathological conditions underlying viral diseases.

Research Activities

Liver disease and oxidative stress

1. Comprehensive RNA gene expression analysis of the contribution of oxidative stress in chronic liver disease: Our group investigated how ROS produced in oxidation-reduction (redox) reactions would affect the pathogenesis of fulminant hepatitis and oncogenesis in chronic liver disease, using an animal model with persistent exposure to ROS and comprehensive RNA gene expression analyses. Based on our experiments, we are now analyzing whether the findings can be applied clinically.
2. Development of a novel antioxidant agent: A candidate agent, which was developed by a venture capital company, was investigated as a novel antioxidant in an animal model. A patent application has been submitted.

Role of reactive oxygen in ovulation

Immunohistochemical detection of markers for oxidative stresses in the ovulating ovary: ROS containing superoxide are believed to play a role in ovulation. We have recently confirmed production of superoxide by using a specific sensor for it in the ovulating

ovary. This year, we observed localization of oxidative stresses by using several markers for it (8-hydroxydeoxyguanosine, 4-hydroxynonenal, and hexanoyl-lysine). We observed heavy oxidative stresses in the theca interna and the theca externa and concluded that these stresses are involved in formation of stigmata as the ovum exits during ovulation.

Basic research for development of cancer therapy

1. The enhanced antitumor effect of 5-FU with the photo-activated DPD-siRNA transfection: We devised photosensitive nanoparticles by which the delivery of DPD-siRNA to gastric cancer lesions can be enhanced. 5-FU is the most widely used chemotherapeutic agent for gastrointestinal cancers; however, DPD strongly decomposes and inactivates 5-FU. To overcome these difficulties, we developed an efficient DPD-siRNA transporter through photochemical internalization.
2. The prevention of liver metastasis by NK-4 gene transduction using novel lipid nanoparticles: We developed a novel lipid-nanoparticle vector that selectively delivers the NK-4 gene to liver. NK-4 binds to the c-Met receptor without activation and competitively antagonizes hepatocyte growth factor c-Met-mediated biological activities. Moreover, NK-4 inhibits angiogenesis by blockade of basic fibroblast growth factor and vascular endothelial growth factor.
3. Magnetically enhanced drug-delivery system: We devised magnetic nanoparticles as an active targeted drug-delivery system. Through the use of a magnetic field these nanoparticles outperformed present drug-delivery systems. We are now investigating the therapeutic potential of these nanoparticles in tumor-bearing mice.

Trial for preparation of nanoparticle

An innovative procedure for preparing lipid nanoparticles for poorly water-insoluble drugs: We developed a safe and simple method of preparing lipid nanoparticles using a novel grinding mill. The greatest advantage of this method is that it does not require a harmful organic solvent. Moreover, with this method, we could obtain smaller, more-uniform nanoparticles than with current methods.

Analysis of hepatitis virus in liver disease

Analysis of the pathogenesis of chronic viral hepatitis and the development of treatment: We are aiming to improve the efficacy of antiviral treatment for chronic viral infection by analyzing viral kinetics and applying a new clinical protocol in collaboration with the Division of Gastroenterology and Hepatology, Kashiwa Hospital.

Publications

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