Division of Medical Engineering

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General Summary

The Medical Engineering Laboratory provides new and essential techniques for developments of medical treatment. There are 2 key technologies in our laboratory: ultrasound and polymer nanomedicine. We have developed sonothrombolysis for treating acute ischemic stroke. For this project for acute ischemic stroke, we have collaborated closely with clinical departments and basic science laboratories, both in our university and hospitals and others. For the other key technology, polymer nanomedicine, we have applied polymer micelles carrying various drugs, such as anticancer drugs and diagnostic drugs, for cancer treatment and acute ischemic treatment. We have applied a polymeric micelle system to a magnetic resonance imaging (MRI) contrast agent for the diagnosis of cancers and acute ischemic stroke. The polymeric micelle carrier system has a great potential for therapy when it is combined with the diagnosis of cancers and acute ischemic stroke.

Research Activities

Medical application of ultrasound

We have applied transcranial ultrasound for the thrombolysis of acute ischemic stroke (sonothrombolysis). For this condition, tissue plasminogen activator (t-PA) treatment within 4.5 hours of the stroke onset is the only effective thrombolytic therapy. Therefore, a safe and effective technology to enhance the therapeutic effects of t-PA would be highly beneficial. We have shown that transcranial ultrasound for thrombolysis can enhance the thrombolytic activity of t-PA and increase the recanalization rate. Although the recanalization rate is increased, other groups have shown that standing waves at an ultrasound frequency of 300 kHz induced a high risk of brain hemorrhage. Therefore, we have applied ultrasound at a medium frequency (500 kHz), which possess a greater thrombolytic effect than the standard diagnostic frequency (2 MHz) and is safer than a frequency of 300 kHz. However, we should evaluate the hemorrhage risk of transcranial ultrasound at 500 kHz. We have found that our modulation method, which involves periodic selection of random ultrasound frequencies in the range of 400 to 600 kHz, reduces standing waves. We have developed an instrument that can determine the effect of sonothrombolysis through the absorption of blood clots. With this instrument, we have obtained sound intensity-dependent clot lysis with t-PA treatment.

Polymeric micelle drug carrier systems

Self-assembly nanoparticulates have been actively examined for drug targeting. Professor Yokoyama, the director of this laboratory, is an international pioneer in the development of self-assemblies of synthetic block copolymers and polymeric micelles for anticancer drug targeting systems. Currently, 4 formulations of polymeric micelle anticancer drugs

are undergoing clinical trials in Japan, Europe, and the United States. We are working to develop the next generation of novel technology based on the polymeric micelle carrier systems.

We have developed a new polymeric micelle MRI contrast agent for the diagnosis of solid tumor. We have shown that this MRI contrast agent possesses the ability to target solid tumor tissues and exhibits high signal intensity in small solid tumors. We have been studying a novel application of the MRI contrast agent for acute ischemic stroke. In a 3-hour middle cerebral artery occlusion (MCAO) model, the MRI contrast agent quickly showed high signal intensity within part of ischemic core in the hemisphere. The high signal intensity area did not completely overlap with the high signal intensity ischemic core where both diffusion-weighted images and T_2-weighted images provided high contrast. Furthermore, the images obtained with the MRI contrast agent were not obtained with a conventional low-molecular-weight MRI contrast agent. Because the image provided a damaged area of the blood-brain barrier where hemorrhage might occur after treatment with t-PA, the polymeric micelle MRI contrast agent system has a great potential to assess the hemorrhage risk of ischemic stroke. The MRI contrast agent must be further optimized to be suitable for this purpose. We proved that polymeric micelle carrier system delivers into the ischemic hemisphere beyond the blood-brain barrier; therefore, the polymeric micelle carrier system will be useful in both the diagnosis and treatment of acute ischemic stroke. This is our new and valuable challenge.

We have been studying synthetic polymer-related immune responses. The phenomenon exhibits specificity for poly(ethylene glycol) (PEG), which is used for a polymeric micelle drug carrier. The PEG-specific antibody (anti-PEG IgM) is generated when either PEG-PBLA micelles or PEGylated liposomes are intravenously injected. However, we have found that the behaviors of polymeric micelles are very different from those of PEGylated liposomes, although both nanoparticulates possess PEG. The polymeric micelles exhibited little or no change in pharmacokinetics in the presence of anti-PEG immunoglobulin M, whereas PEG liposomes exhibited drastic change in pharmacokinetics. We further evaluated the effect of the anti-PEG antibody on the behaviors of both polymeric micelles and PEGylated liposomes. We found that a limited number of anti-PEG IgM molecules had been generated after the priming. In contrast, polymeric micelle particles were 10 times as numerous as PEGylated-liposome particles, although the injected dose includes nearly the same number of PEG chains. We found 10 anti-PEG antibodies can bind to each PEGylated liposome, and antibody-PEGylated liposome complexes rapidly accumulate in the liver and spleen. Therefore, the polymeric micelle carrier systems have significant advantages for drug targeting in terms of the generated immune response.

We have tried to measure the inner core characteristics of polymeric micelles by means of synchrotron radiation (at the Super Photon Ring 8 Gigaelectronvolt facility, Hyogo Prefecture, Japan). The precise measurement accurately determined the inner core size of polymeric micelles, and we have shown a correlation between the structural characteristics of polymeric micelles and their in vivo and in vitro behaviors, in particular, their pharmacokinetics.

Publications

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