Medical Engineering Laboratory

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General Summary

The Medical Engineering Laboratory provides new and essential techniques for developments of medicine. There are 2 key technologies in our laboratory: ultrasound and polymer nanoparticles. 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 departments, both in our university and hospitals and others. For the other key technology, polymer nanoparticles, we have applied polymeric micelles to drug delivery systems (DDSs). Recently, we have also applied a polymeric micelle carrier system to a magnetic resonance imaging (MRI) contrast agent. In particular, we have studied the polymeric micelle MRI contrast agent for the diagnosis of acute ischemic stroke. The polymeric micelle carrier system has become a great system for diagnosing and treating ischemic stroke.

Research Activities

Medical application of ultrasound

We have applied transcranial ultrasound for the sonothrombolysis of acute ischemic stroke. For this condition, injection of tissue plasminogen activator (t-PA) within 4.5 hours of onset is the only effective thrombolytic therapy. Therefore, safe and effective technology to enhance the therapeutic effects of t-PA would be highly beneficial. We have shown that transcranial ultrasound for sonothrombolysis can enhance the thrombolytic activity of t-PA and increase the recanalization rate. However, although the recanalization rate is increased, other groups have shown that standing waves at an ultrasound frequency of 300 kHz is associated with a high risk of brain hemorrhage. Therefore, we have applied ultrasound at a medium frequency, 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 a medium frequency. We have found that our modulation method, which involves periodic selection of random ultrasound frequencies, 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. We have also developed a novel medical device that can detect blood clots in the carotid artery.

Polymeric micelle drug carrier systems

Self-assemblies of synthetic polymers, polymeric micelles, have been actively developed for drug targeting. Yokoyama, the director of this laboratory, is an international pioneer in the development of polymeric micelle targeting systems. Currently, 4 formulations of

polymeric micelle anticancer drugs are undergoing clinical trials in Japan, Europe, and the United States. We are trying to establish 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 diseases. We have shown that this MRI contrast agent has the ability to target solid tumor sites and exhibits high signal intensity in extremely small solid tumors. We have been studying a novel application of the MRI contrast agent for brain ischemic stroke. In a 3-hour middle cerebral artery occlusion (MCAO) model, the MRI contrast agent quickly showed high signal intensity within part of the ischemic hemisphere. The high signal intensity area did not appear on diffusion-weighted images or T2-weighted images. Furthermore, the image obtained with the MRI contrast agent was not obtained with a conventional low-molecular-weight MRI contrast agent. These findings indicate that the MRI contrast agent we developed might be used to assess the hemorrhage risk of ischemic stroke. The MRI contrast agent must be further optimized to be suitable of this purpose. Therefore, the polymeric micelle carrier system will be useful in both the diagnosis and treatment of brain ischemic stroke. This is our new and valuable challenge.

We have been studying polymeric micelle-related immune responses. The phenomenon exhibits specificity for polyethylene glycol (PEG), which is used for block copolymer. The PEG-specific antibody (anti-PEG immunoglobulin M) is generated when either polymeric 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 polymeric micelles and PEGylated liposomes possess PEG and generate anti-PEG antibodies, the polymeric micelles exhibited little or no change in behavior after priming. We further evaluated the effect of the anti-PEG antibody on the behaviors of both polymeric micelles and PEGylated liposomes. We found that both carriers generated nearly the same numbers of antibodies; however, although the injected dose includes nearly the same number of PEG chains, polymeric micelles were 10 times as numerous as PEGylated liposomes. Five to 10 anti-PEG antibodies can bind to a 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 through the use of synchrotron radiation (at the Super Photon Ring 8 Gigaelectronvolt facility, Hyogo Prefecture, Japan). The precise measurement accurately detects the inner core structure of polymeric micelles, and we have shown a correlation between the characteristics of polymeric micelles and their biological behavior, in particular, their pharmacokinetic behavior.

Publications

Sanada Y*[1]*, Akiba I*[1]*, Sakurai K*[1]*, Shiraishi K, Yokoyama M, Mylonas E*[2]*, Ohta N*[2]*, Yagi N*[2]*, Shinohara Y*[3]*, Amemiya Y*[3] *(*[1]*Univ Kitakyushu,* [2]*JASRI,* [3]*Univ Tokyo). Hydrophobic molecules infiltrating into the poly (ethylene glycol) domain of the core/shell interface of a polymeric micelle: evidence obtained with anomalous small-angle X-ray scattering. *J Am Chem Soc.* 2013; **135:** 2574-

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Review and Books

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