Gas-Filled Liposomes as Ultrasound Contrast Agents for Blood Pool, Thrombus-Specific and Therapeutic Applications

Evan C. Unger1,2, Thomas P. McCready2, DeKang Shen3, GuanLi Wu3, Robert H. Sweitzer1, and Qiu Wu2

1University of Arizona Health Sciences Center, Department of Radiology, Tucson, Arizona 85724
2ImaRx Pharmaceutical Corp., 1635 E. 18th Street, Tucson, Arizona 85719

Abstract: We have developed phospholipid-coated microbubbles as ultrasound contrast agents. By incorporating ligands into the vesicle surface, targeted contrast agents have been prepared. Encouraging results have been obtained with thrombus-specific microbubbles for diagnosis and detection of thrombosis. These thrombus-specific microbubbles increase the rate of sonothrombolysis and accelerate clot lysis. A variety of different drugs have been incorporated into microbubbles. Site-specific drug release is obtained in the insonation region.

BACKGROUND

High-molecular-weight, insoluble gases, such as fluorocarbons, are being used as ultrasound contrast agents. Coating materials are necessary to stabilize the microbubbles for clinical use as ultrasound contrast agents. Our group has developed phospholipid-coated microbubbles with varying properties for specific applications. MRX-115 consists of phospholipid-coated perfluoropropane microbubbles with a mean size of about 2.5 microns in diameter and a concentration of about $1.5 \times 10^9$ particles per ml. MRX-115 has finished Phase III clinical trials for ventricular function, and at the time of preparation of this abstract, the contrast agent was well along in Phase III myocardial perfusion and Phase III radiology clinical trials. Encouraging results have been obtained for detection of myocardial infarct. MRX-115 (also developed as DMP 115 by licensee, The DuPont Merck Pharmaceutical Company) is a blood pool contrast agent designed to have minimal interaction with serum proteins or any biological receptors.

TARGETED CONTRAST AGENTS

We have incorporated a variety of targeting ligands into gas-filled phospholipid vesicles. Many different lipid bioconjugates can be incorporated into the lipid layer of the gas-filled vesicles. MRX-408 consists of perfluorobutane microbubbles bearing oligopeptides targeted to the GPIIbIIIa receptor of activated platelets. In vitro studies of ultrasound imaging with MRX-408 show that the agent binds the thrombus and elicits a strong harmonic response (Figure 1). Microbubbles are known to lower the cavitation threshold and accelerate the rate of sonothrombolysis. Compared to nontargeted microbubbles, targeted microbubbles increase the rate of sonothrombolysis. MRX-408 has improved detection of clots in canine models of thrombosis in arteriovenous grafts, vena cava, peripheral arterial, left atrial, and left ventricle thrombosis. This contrast agent may have applications not only for improving detection of thrombosis, but also in conjunction with high-energy ultrasound in sonothrombolytic therapy.

A wide variety of other targeted ultrasound contrast agents may also be developed for improving diagnosis of different diseases as well as for ultrasound-mediated delivery of bioactive materials.

THERAPEUTIC APPLICATIONS: ACOUSTICALLY ACTIVE CARRIERS

Ultrasound is known to destroy microbubbles. Ultrasound is readily transmitted and focused into the vasculature and soft tissues. We have developed a variety of acoustically active carriers for drug delivery (Figure 2). Different drugs can be incorporated into gas and fluorocarbon carriers with sufficient acoustic impedance mismatch from tissues and fluids to accomplish drug release upon exposure to ultrasound. Targeting moieties can also be incorporated into the surface of acoustically active carriers. Potential exists for an ultrasound contrast agent to be employed for both diagnosis and treatment.
Intensity of Backscattering from a Blood Clot Post Treatment

**FIGURE 1**

**FIGURE 2.** Four different types of acoustically active carriers (each is filled with gas).

**PATENT REFERENCES**
