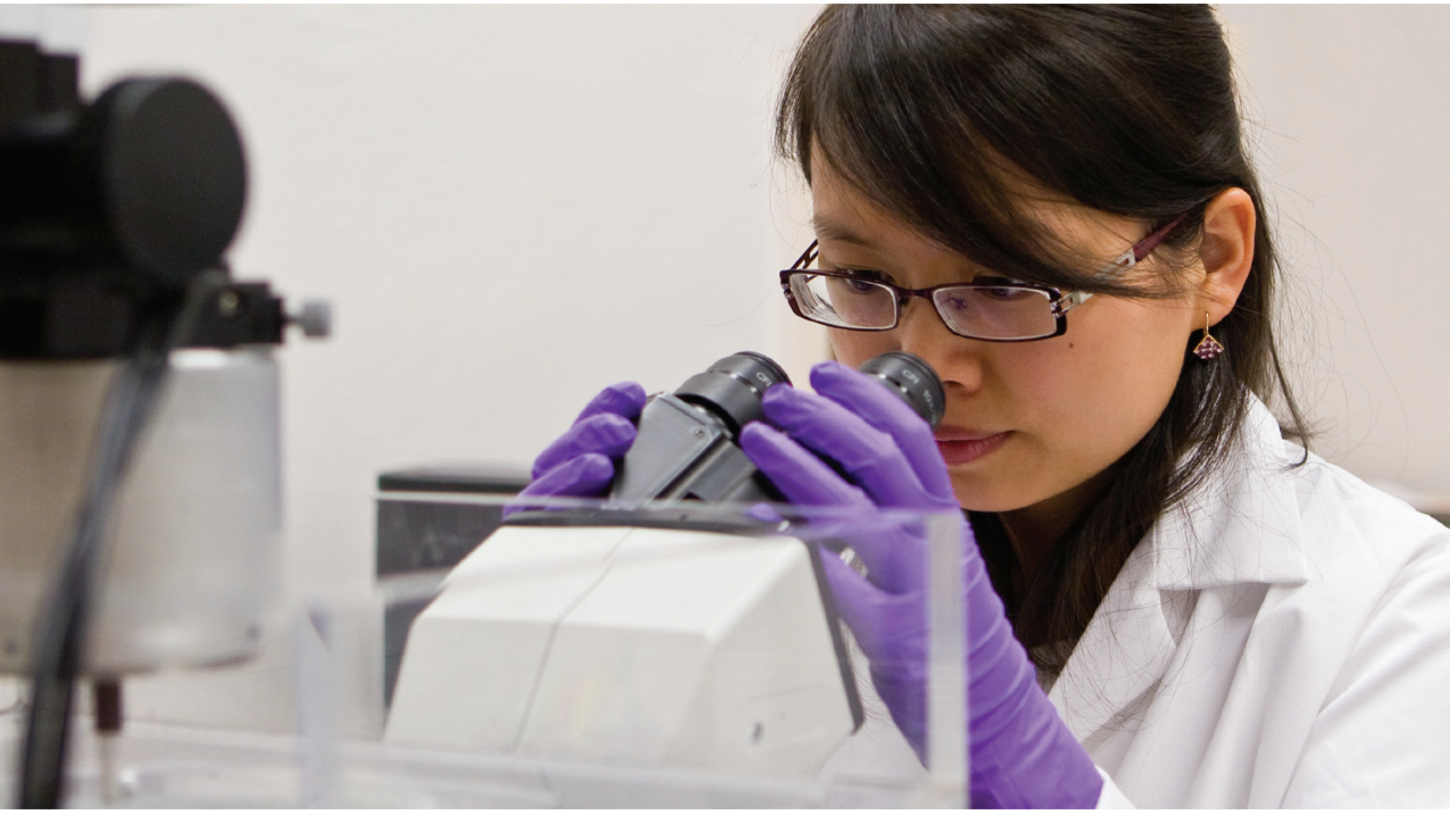
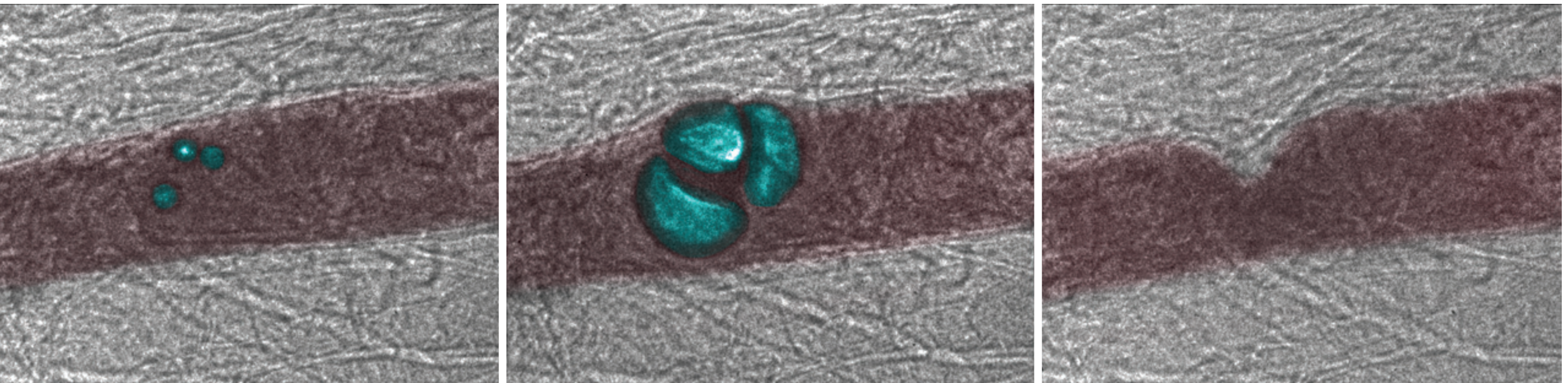
HUGE DISCOVERY IN TINY BUBBLES

Ultrasound contrast agents are extremely small gas bubbles. They increase the efficiency of diagnostic ultrasound imaging, such as echocardiography, because the microbubbles act as echo chambers when ensonified by an acoustic signal.

Advances in ultrasound imaging have reached a level where even a single microbubble —about one micron in size—can be imaged. Research is now exploring the possibility of targeting ultrasound contrast agents to site-specific regions of the body and using them to carry therapeutic agents. Acoustically activated microbubbles alter the shape of cell membranes and can increase vascular permeability, which may enhance local delivery of drugs or genes. But high acoustic pressures can damage vessels. The interaction between the microbubble and the vessel wall is very important, yet not well understood, so a research team at the Center for Industrial and Medical Ultrasound devised experiments to capture high-speed microphotographs of single microbubbles ensonified in tiny vessels.





Ultra Small, Ultra Fast

Microbubbles are made in the lab by mixing several different lipids together in a buffered electrolyte solution saturated with a perfluorocarbon gas. After mixing, the lipids form a thin (a few nanometers) protective shell around the gas to form the microbubble and prevent the gas from escaping. Ultrasound contrast agent microbubbles have a diameter of about 2–3 microns, with about 99% of the bubbles in the range of 1–10 microns. In a single milliliter vial there might be one hundred million microbubbles.

To stage a microbubble/microvessel experiment, a microscope is coupled with an extremely fast-exposure camera capable of 50-nanosecond acquisition times. A high-intensity flash lamp coupled to a fiber optic light path is required to generate enough photons to create a photographic image. The tissue samples must be transparent so that microbubbles in the blood vessel can be observed. Finally, the synchronization of optical and acoustic systems has to be precise so that the acoustic phase is known exactly at the time point where each high-speed image is acquired.

Expand, Contract, Collapse

To understand the interaction between a bubble and the surrounding tissue, consider a sinusoidal pressure wave. As the acoustic pressure goes negative, the microbubble expands under the tensile pressure and it continues to expand until the pressure turns positive, forcing the microbubble to contract. When the bubble contacts the vessel wall, the wall may dilate, but it also hinders the bubble from expanding much further.

Our high-speed microphotographs confirm that blood vessels do indeed dilate as the microbubbles push against them. But even more amazing is that when a microbubble collapses, the vessel wall is pulled inward, probably due to fluid rushing into the bubble void. This invagination effect is more dramatic than dilation and may be the dominant mechanism for increasing vascular permeability and/or tissue damage.

Technology Commercialization

The contributions of these discoveries to the ultrasound research and therapy communities are great, but one component of these novel experiments has commercial potential as well. Ultrasound contrast agents are being developed to target specific diseases. It is thus important to understand their protective shell's properties because the shell stabilizes the bubble and is the surface on which specific targeting ligands must adhere. The CIMU team has developed a light-scattering technique to indirectly characterize the shell by monitoring the bubble's oscillation when subjected to ultrasound. The observed dynamics are compared to a model where the shell viscosity and shear modulus are the fitting parameters. A patent application has been filed for this technology with the objective of developing an integrated system to characterize the microbubble size distribution and the shell properties together.

Top-Flight Student Research

Bioengineering doctoral student Hong Chen's thesis is based on these novel experiments. Research advisor Thomas Matula is very pleased with her work. "She has excelled in conducting these extremely difficult experiments—imaging micron-sized bubbles on nanosecond timescales to show the mechanical interaction of a microbubble in a constraining blood vessel with surrounding tissues." Her work won the student poster competition when presented in Beijing at the 2008 IEEE Ultrasonics, Ferroelectrics, and Frequency Control Society meeting.

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