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High-energy pulsed tunable mid-infrared laser aids biomedical applications

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Longer wavelengths from a tunable laser improve performance for angioplasty, lithotripsy, and mass spectrometric protein analysis.

Lasers have many applications in biomedicine, including treatments for cardiovascular and gallbladder disease. However, nonselective removal of arteriosclerotic lesions, calculi (stones), and so on may cause unexpected damage to ambient normal tissue.\(^1,2\) Additionally, crushing calculi by laser lithotripsy is associated with high recurrence rates due to large residual fragments.\(^2\) Another laser-related difficulty involves an established method for analyzing proteins and other large molecules called time-of-flight mass spectrometry with matrix-assisted laser desorption/ionization (MALDI).\(^3-5\) Ultraviolet lasers are commonly used for MALDI. However, high fragmentation of molecules or low ionization efficiency can make analysis difficult for some analytes, such as insoluble membrane proteins.\(^6,7\)

Because many characteristic absorption bands originate in molecular vibrations in the mid-infrared (MIR) region, selective excitation or dissociation of molecules is possible using tunable MIR lasers. An MIR free-electron laser (FEL) can selectively remove cholesterol esters from arteriosclerotic lesions,\(^1\) finely crush calculi,\(^2\) and improve MALDI ionization efficiency.\(^5-9\) Although broad wavelength tunability (5–22 \(\mu\)m) and high average power (less than 30mW) of FELs are attractive for biomedical applications, the equipment is very large and expensive. This limits the use of FELs.

Recently, Kawasaki Heavy Industries Ltd. and RIKEN in Japan developed a high-energy pulsed solid-state tunable MIR laser.\(^10\) The laser has a tunable wavelength range of 5.5–10 \(\mu\)m, pulse duration of 5ns, and repetition rate of 10Hz. The MIR output is obtained by difference-frequency generation (DFG) between a Q-switched Nd:YAG (neodymium-doped yttrium-aluminum-garnet) laser and a tunable Cr:forsterite laser using two AgGaS\(_2\) crystals (see Figure 1). The wavelength of the Cr:forsterite laser is tuned by rotating the rear mirror of the optical resonator. Figure 2 shows the relationship between the pulse energy and wavelength for an MIR-DFG laser.

Here, we report preliminary results for a study in which we selectively removed atherosclerotic lesions from blood vessel samples using an MIR-DFG laser. We excised thoracic aortas from myocardial infarction-prone Watanabe heritable hyperlipidemic (WHHLMI) rabbits\(^11\) and a Japanese white rabbit for atherosclerotic and normal samples, respectively. The Institutional Animal Care and Use Committee approved this study, which was carried out according to the Guidelines of Animal Experimentation of Osaka University.

To measure infrared absorption spectra with a microscopic Fourier-transform infrared spectrometer, we first used a cryostat microtome to slice the aortas to a thickness of 5 \(\mu\)m. In measured spectra, the absorption peak at wavelength 5.75 \(\mu\)m originates in the C=O stretching vibration of the ester bond in cholesterol esters. This peak occurs only from atherosclerotic lesions (see Figure 3).

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Figure 2. Pulse energies are higher at shorter wavelengths in the MIR-difference-frequency generation (MIR-DFG) laser.

Figure 3. Typical infrared absorption spectra for the innermost layers of atherosclerotic and normal aortas. Notice the absorption peak at 5.75 µm from atherosclerotic lesions. (The spectrum for the atherosclerotic aorta is shifted for easier viewing.)

We focused the output of an MIR-DFG laser to a diameter of 140 µm using a ZnSe lens with a focal length of 100 mm and irradiated wet thoracic aortas from the inside. After laser irradiation, the aortas were sliced to a thickness of 10 µm with a cryostat microtome. We observed the cross-sections presented in Figure 4 with an optical microscope. Tuning the laser to 5.75 µm allowed selective removal of an atherosclerotic lesion without damaging normal tissue. However, tuning the laser to 6.09 µm resulted in penetration of both aortas.

Additionally, we have observed that crushing efficiency of human gallstones in laser lithotripsy and ionization efficiency in MALDI mass spectrometry depend on the MIR-DFG laser’s wavelength. Currently, we are investigating wavelength dependencies and optimal irradiation conditions.

Recent fabrication of hollow optical fiber enables transmission of both MIR and visible guide lasers. Combining an MIR-DFG laser with hollow optical fiber could be a safe tool for laser angioplasty and lithotripsy.

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