Development of Photoacoustic Probes for the Detection of Nitric Oxide

Christopher J. Reinhardt and Jefferson Chan

Photoacoustic imaging is an emerging technique that utilizes optical excitation and acoustic detection for acquiring high-resolution images deep within tissue (centimeter depths). The development of activatable probes furthers the utility of this technology by enabling the non-invasive detection of specific stimuli within live-animal models. In particular, we are interested in nitric oxide, a free-radical signaling molecule involved in both acute and chronic inflammatory responses. Importantly, the biological implications of nitric oxide depend significantly on its timing, location, and concentration. To this end, we have developed a series of small-molecule activatable photoacoustic probes, or acoustogenic probes, for nitric oxide. Each compound responds rapidly to nitric oxide with a significant hypsochromic shift. Selective irradiation of the probe and the nitric oxide-derived product enables both turn-on and ratiometric imaging. The initial generation probe was successfully applied to the detection of endogenous nitric oxide in a murine lipopolysaccharide-induced inflammation model, however it lacked the requisite sensitivity to image nitric oxide within cancer. To overcome this limitation, the photophysical properties have been tuned to optimize the probe's sensitivity, ultimately enabling the detection of endogenous nitric oxide in a 4T1 mouse model of breast cancer. Current efforts are focused on improving pharmacokinetics, developing multimodal analogs for fluorescence and photoacoustic imaging, and applying the probes to understand the role of nitric oxide in tumor progression.