Rupture of a cerebral aneurysm causes subarachnoid hemorrhage (SAH). Primary treatment for the patients who survived the initial rupture is prevention of second rupture. Even if the aneurismal obliteration, by either surgical or endovascular interventions, is successful, many complications follow. Neurological deterioration due to delayed cerebral ischemia (DCI) is a major consequence responsible for the mortality/morbidity of SAH and resists, in many patients, to the currently recommended therapies. Multiple factors seem to contribute to DCI. This exploratory project will test our hypothesis that combination of betaine and fenofibrate may be a potential candidate for preventing DCI after SAH.

We previously reported that lipid normalizing drug fenofibrate at an appropriate dose significantly elevates superoxide dismutase levels in mouse brain microvessels [1]. In addition, fenofibrate attenuates superoxide production and protein oxidation in ischemic brain, and subsequent infarct formation in mice subjected to focal cerebral ischemia [1,2]. Moreover, we have shown that fenofibrate dramatically inhibits the elevations of cellular adhesion molecules after intracerebral LPS injection [3]. The adhesion molecules are deteriorating factors in microcirculation. Thus, fenofibrate may be effective in preventing DCI after SAH. On the other hand, fenofibrate has been shown to elevate plasma homocysteine level. High level of homocysteine is harmful to most of the brain cell types and plasma homocysteine level is considered as a risk factor for cerebrovascular diseases. Betaine is clinically used to lower homocysteine. Thus, betaine may pronounce the beneficial effect of fenofibrate on the brain microvessels.

The hypothesis will be tested in aging mice that will receive injection of blood into the prechiasmatic cistern. This mouse SAH model has been reported to induce spasm in the cerebral arteries accompanied by neuronal death [4]. This study will be the first testing betaine and fenofibrate, either alone or together, for improving outcomes after SAH.

