

## **Novel Mechanism of Atherosclerotic Plaque Rupture: Zooming in on the Genesis of Microcalcifications**

Principal Investigator: Elena Aikawa, MD, PhD, Brigham and Women's Hospital

Co-Investigators: Joshua D. Hutcheson, PhD, Brigham and Women's Hospital  
Frederick J. Schoen, MD, PhD, Brigham and Women's Hospital

Rupture of vulnerable atherosclerotic plaques is the leading cause of myocardial infarct and stroke. Classically, atherosclerotic plaque vulnerability has been attributed to a reduction of collagen in the fibrous cap; however, recent studies have identified microcalcifications in the collagenous fibrous cap that contribute to biomechanical plaque failure. Calcifying matrix vesicles released by cells (e.g., smooth muscle cells, macrophages) within the plaque contribute to the formation of microcalcifications, but the mechanisms of microcalcification genesis are unknown. A major limitation in the field, which hinders current clinical practice and research progress, is the inability to identify and visualize the early processes that lead to microcalcifications. To overcome this limitation, we will use super-resolution imaging available at the HCBI along with a near-infrared calcium tracer to visualize the nucleation of microcalcifications within our recently developed controllable three-dimensional collagen hydrogel system that recapitulates the fibrous cap. We will then extend these analyses to samples of human atherosclerotic plaques to connect our in vitro model findings to pathological in vivo processes. Overall, this approach will address areas of pathology that cannot be addressed using current technologies applied in clinical practice and provide new insights into the pathobiology of plaque rupture. The long-term goal of the project is to develop a simple imaging tool that can be used by pathologists to diagnose rupture prone plaques.