Dr. Ed Thorp

According to recent findings in humans and experimental rodents, a major feature of advanced, rupture-prone atherosclerotic plaque is defective clearance of apoptotic cells. Apoptotic cell death, in the absence of efficient phagocytic clearance (efferocytosis), promotes post-apoptotic necrosis, which contributes to inflammation and plaque disruption.

We recently discovered that in-vivo, mice engineered with an inactivating mutation of the cell surface receptor MERTK, exhibit reduced efferocytosis effeciency in murine lesions and exacerbated key features of plaque vulnerability, including necrotic core expansion. *In-vitro*, MERTK inactivation is also promoted by inflammatory stimuli that trigger the activity of proteases. These proteases specifically cleave MERTK, rendering it dysfunctional. Importantly, our preliminary data indicate that proteolytic cleavage of MERTK also occurs in advanced atherosclerotic plaque from humans.

To determine if MERTK proteolysis is associated with increased atherosclerotic progression in humans, we will in collaboration determine if increased levels of the MERTK proteolytic fragment, i.e., soluble-MER (solMER), are positively correlated with plaque necrosis in human atherosclerotic surgical specimens. Towards determining the prognostic value of solMER levels in plaque, we will also in collaboration work towards generating solMER-specific antibodies for non-invasive molecular imaging.

This overall concept presents an opportunity for novel therapeutic strategies directed against progression of inflammation and atherothrombosis, namely through the identification of biomarkers that gauge *in-vivo* efferocytosis efficiency and future modalities aimed at restoration and augmentation of defective efferocytosis.