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Primary Research Interest:	Neurology
Description of Research:	<p>Tumor necrosis factor-like weak inducer of apoptosis (TWEAK) is a member of the tumor necrosis factor superfamily that acts via binding to a cell surface receptor known as fibroblast growth factor-inducible 14 (Fn14). We hypothesize that during cerebral ischemia the interaction between TWEAK and Fn14 regulates the permeability of the neurovascular unit (NVU). We propose that during cerebral ischemia the binding of TWEAK to Fn14 in the endothelial cell-basement membrane-astrocyte interface results in the following sequence of events: i) increase in the expression of NF-κB-inducible leukocyte-endothelial cell adhesion molecules and chemokines with infiltration of inflammatory cells into the abluminal side of the NVU, ii) increase in inflammatory cell-derived MMP-9 activity, and iii) MMP-9-mediated increase in the permeability of the NVU with development of cerebral edema. In the last Aim of this proposal we will study whether inhibition of TWEAK-Fn14 binding with Fn14-Fc decoy delivered to the endothelial cell-basement membrane-astrocyte interface with a nanocarrier protects the barrier function of the NVU during ischemic conditions.</p>
Relevance to VA:	<p>Stroke is one of the leading causes of mortality and a leading cause of morbidity in the USA. Unfortunately, there is evidence indicating that the morbidity and mortality due to stroke are higher among USA Veterans, particularly those of the Southern states. Thus, research in cerebral ischemia may lead to the development of an effective therapeutic strategy aimed at decreasing the deleterious impact of this conditions in the Veteran's population.</p>