

Distinguished Lecture Series in Physiology



Physiology and Membrane Biology

University of California, Davis

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Departments of Neurology, Anatomy & Neurobiology,
And Neurosurgery

“Enter the Matrix: Novel Stroke and Vascular Dementia Therapeutic Targets”

Ischemic stroke is a worldwide leading cause of death and morbidity with few therapeutic options. Indeed, despite the advent of thrombolytic therapy (tissue plasminogen activator (tPA)) for acute stroke and mechanical thrombectomy for emergent large vessel occlusion, improvement in clinical outcomes has lagged. The focus of research in my lab is the development of novel neuroprotective and neuroreparative stroke therapies derived from the brain's response to ischemic injury. Along these lines, we have determined that a small protein fragment of the extracellular matrix heparan sulfate proteoglycan perlecan, termed domain V (DV), is acutely and persistently elevated in the brain after experimental and human stroke. Prevention of this increase in mouse transient middle cerebral artery occlusion (MCAo) results in larger infarcts, diminished angiogenic neurorepair and worse functional outcomes suggesting that this post-stroke DV generation is of consequence. Mice treated acutely (within 24 hours) or in a delayed (7 days) fashion with human recombinant DV (intraperitoneal administration), have smaller brain infarcts, enhanced angiogenesis, enhanced neurogenesis and significantly improved functional outcomes. Furthermore, astrocytic responses appear to be acutely enhanced and chronically suppressed. Further analysis identified a specific endothelial cell receptor, alpha5beta1 integrin, to be responsible for most of DV's therapeutic benefits. Intriguingly, mice with endothelial cell selective knockdown of alpha5beta1 integrin are profoundly resistant to ischemic stroke, potentially via enhanced stability of their blood-brain barrier after MCAo. Furthermore, new results suggest that pharmacologic blockade of the alpha5beta1 integrin after experimental stroke in wild type mice may also be significantly beneficial. Lastly, we have begun to expand these observations in experimental stroke to experimental models of vascular dementia including bilateral carotid artery stenosis (Chronic cerebral hypoperfusion) and a mouse that develops significant amyloid brain deposition and diabetes (db/AD).

Genome Auditorium
Thursday, May 26, 2016
11:00 a.m.

Host: Martha O'Donnell meodonnell@ucdavis.edu