# Special Lecture

**Date:** 15:00-17:00, October 20, 2016

**Place:** Room 407, Yifu Building, Peking University Health Science Center

**Speaker:** Richard J. Roman, Ph.D. Professor and Chair

Department of Pharmacology & Toxicology

The University of Mississippi Medical Center

**Title:** Role of 20-HETE in cerebral vascular dysfunction and the development of cognitive impairment and dementia with aging and hypertension

**Chair：** Jing-Yan Han, M.D., Ph.D.

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**Abstract：** Alzheimer's disease (AD) and vascular dementia (VaD) are the most common forms of dementia. There is no cure and current therapies are not that effective at delaying progression. The annual costs for the treatment of dementia exceeds $159 billion in the US and is projected to rise to $511 billion by 2040. There is increasing evidence suggesting that cerebral vascular dysfunction plays an important role in the development not only VaD, but also AD. Young hypertensive patients are generally protected from cerebral microcirculatory damage as hypertrophic inward remodeling and enhanced myogenic tone in cerebral arteries prevents transmission of pressure to the capillaries. This adaptive response shifts the range of CBF autoregulation to higher pressures and protects the brain from microbleeds and BBB leakage at the expense of increased susceptibility to ischemic injury. However, recent studies have indicated that this adaptation is impaired in elderly mice, and is associated with disruption of the BBB, glial activation, neuroinflammation and a decline in cognitive function. The factors and genes responsible for the loss of this adaptive vascular response remain to be determined.

In our previous work we found that 20-HETE, a lipid mediator, plays a critical role in the myogenic response and autoregulation of cerebral blood flow. 20-HETE levels increase following SAH and play an important role in cerebral vasospasm. 20-HETE also contributes to infarct size following cerebral ischemia. Variants in the CYP4A and 4F genes that produce 20-HETE have been linked the development of hypertension and stroke in man. More recently, we have found that functional variants of these genes are also linked to cognitive impairments in hypertensive elderly patients. We also discovered that the expression of CYP4A enzymes and the production of 20-HETE is reduced in Dahl salt sensitive rats. They exhibit impaired autoregulation of CBF and develop a cognitive impairment with aging and hypertension similar to that seen in elderly patients. To study the mechanisms involved, we generated a Dahl SS.CYP4A1 transgenic rats that restores the production of 20-HETE and CYP4A2 and 4A3 KO strains. We found that Dahl SS rats exhibit vascular remodeling, blood-brain barrier dysfunction, neurodegeneration and cognitive impairments following the development of hypertension. Upregulation of the formation of 20-HETE in CYP4A1 transgenic rats restores autoregulation of CBF and attenuates the development of the cognitive decline with aging and hypertension. These studies indicate that mutations in genes that produce 20-HETE may increase the susceptibility to the development of age and hypertension related cognitive impairments by altering transmission of pressure to the cerebral microcirculation.