Speaker: Stefan-M. Pulst, MD, Dr. med.

Title: Degenerative Ataxias: From Genes to Therapies

Biographical Information:
Dr. Pulst is Professor and Chair of Neurology at the University of Utah in Salt Lake City. He received his neurological training at the Medizinische Hochschule Hannover in Germany and in the Longwood Program at Harvard Medical School in Boston. He did his postdoctoral fellowship with Earl Mayeri at UCSF working on peptidergic neurotransmission in *Aplysia*. His research focuses on inherited diseases of the nervous system with an emphasis on spinocerebellar ataxias and Parkinson disease. Recently, his work has branched out into the genetic epidemiology of neurological diseases using the Utah Population Database. Work in his laboratory has been funded by grants from the National Institutes of Health, the CDMRP, and the National Ataxia Foundation. He currently serves on the editorial boards of *Nature Reviews Neurology, Journal of Molecular Neuroscience, Neurogenetics, Cerebellum, and Experimental Neurology*. He has edited several books on Neurogenetics, the Genetics of Movement Disorders, and most recently on the Ataxias and Spastic Paraplegias. Dr. Pulst has been active in the AAN since 1991 beginning with service on the Education Committee. He later served on the Science Committee, which he chaired from 2006 to 2011. He is now on the AAN Board of Directors and chairs the AAN Meeting Management Committee.

Talk Description:
Despite their name, the dominant spinocerebellar degenerative ataxias (SCAs) result in neuronal degeneration not only in cerebellar neurons, but in other systems as well. DNA repeat mutations constitute the majority of genetic changes in the SCAs, with many mutations leading to expansion of a polyglutamine (polyQ) domain in the respective proteins. Although SCAs belonged to the vanguard of positionally cloned neurodegenerative disease genes in the 1990’s, only now are these discoveries providing deeper understanding necessary for therapeutic development. In this lecture, I will focus on SCA2, a disease that is not only characterized by cerebellar ataxia and slow saccadic eye movements, but that can also present as L-DOPA-responsive parkinsonism or as a motor neuron disease. We have taken two different approaches to developing therapeutics, pathway- and gene-directed strategies. Based on the abnormal interaction of mutant ataxin-2 protein with the inositol triphosphate receptor, which results in increased calcium release from intracellular stores, we have identified compounds normalizing intracellular calcium homeostasis. In the second strategy, we have identified novel 2’-O-methoxyethyl phosphorothioate antisense-oligonucleotides (MOE-ASOs) that down-regulate expression of ATXN2 and thus target the initiating event in SCA2. These ASOs can reach diverse regions of the CNS after injection into the lateral ventricle of the mouse including cerebellum and brainstem and may thus make this strategy applicable to other neurodegenerative diseases as well.