The treatment of neurodegenerative diseases is difficult because of multiple etiologies and the interplay of genetics and environment as precipitating factors. In the case of amyotrophic lateral sclerosis (ALS), we have knowledge of a handful of genes that cause disease when mutated. However, drugs to counteract the effect of genetic mutations have not yet been found. One of the causative genes, Cu, Zn-superoxide dismutase (SOD1) is responsible for about 10-15% of the genetically linked autosomal dominant disease. Our rationale was that compounds that reduce expression of the mutant protein would be beneficial to slow onset and/or disease progression. We screened candidate compounds using a cell-based in vitro assay for those that reduce mutant SOD1 (G93A) protein expression. This led to the discovery of 2-[3-iodophenyl)methylsulfanyl]-5pyridin-4-yl-1,3,4-oxadiazole, a known protein kinase inhibitor that decreases G93A-SOD1 expression in vitro and in the brain and spinal cord in vivo. However, this compound has a biphasic dose response curve and a potential toxophore which limits its therapeutic window for chronic disease such as ALS. Therefore, we designed and tested a focused library of analogs for their ability to decrease SOD1 expression in vitro. This exercise resulted in the identification of a lead compound with improved drug-like characteristics and activity. It is currently undergoing further preclinical testing. In the course of testing another agent for efficacy in the G93A-SOD1 mouse we unexpectedly found that ACTH (Acthar gel, Questcor) also decreased the expression of mutant SOD1 in the transgenic mouse spinal cord and brain. Acthar gel significantly delayed onset of disease in the mouse and trended toward slowing of disease progression. Acthar gel is currently used for treatment of multiple sclerosis, infantile spasms, and other conditions. Thus, two different agents have been found with the potential for treating SOD1 mutant-linked ALS. Development of small molecules and other agents that reduce the expression of etiologically relevant toxic proteins is a strategy that may also be extended to familial ALS linked to gain of function mutations in other genes.

Biography

Thomas Lukas has obtained PhD from Rutgers University, Chemistry (1979) and Postdoctoral Fellowship from Rockefeller University, Biochemistry (1980). His research interests involve using a systems biology approach to discover mechanisms of neurodegenerative diseases. This systems biology approach uses proteomics, genomics, and metabolomics data from both animal models of disease and patient derived cells/tissues to investigate disease mechanisms and discover new therapeutics. These methods are currently being applied to amyotrophic lateral sclerosis (ALS) Cayman’s ataxia, Friedrich’s ataxia, as well as hearing loss due to chemical and/or environmental insults.

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