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Research Interests:

My group is using transgenic mouse models to study the mechanisms of human neurodegenerative diseases, particularly AD and PD. There are three broad areas of active interest. 1) Understanding the pathogenesis/progression of PD using alpha-synuclein and LRRK2 transgenic mouse models. 2) Mechanisms of amyloid-dependent neurodegeneration using transgenic mouse models of AD. 3) Pathologic interactions between genetic and environmental factors. While most cases of AD and PD are “sporadic”, the key assumption is that genetic lesions that cause classic forms of the relevant neurodegenerative diseases will cause neural abnormalities that are common between the genetic and sporadic forms of the disease. When used in conjunction with careful analysis of human subjects, invertebrate models, and cell culture models, we will be able to define mechanisms that are directly relevant to the pathogenesis and identify possible targets for therapeutic intervention. The models generated are also essential for cross-platform screening and validation of novel therapeutic approaches. My group has identified several robust biochemical, pathological and behavioral outcome measures in transgenic mouse models of AD and PD. These measures will be essential for in vivo preclinical evaluation of therapeutics.

Parkinson's Disease (PD)

Genetic and biochemical abnormalities of a-synuclein (a-Syn) and LRRK2 are directly relevant to the pathogenesis of PD. My group has contributed to the field by generating a human a-Syn transgenic (Tg) mouse model of a-synucleinopathy, characterizing the pathological abnormalities associated with the disease, and characterizing the cell biology of a-Syn. We are currently studying the role of protein folding pathways, mitochondrial abnormalities, oxidative stress, inflammation, and aberrant protein kinase regulation.

Alzheimer's Disease (AD)

My laboratory was first to describe progressive degeneration of monoaminergic (MAergic) neurons (5-HT, NE) in mouse model of AD. Significantly, degeneration 5-HT and NE systems is associated with human AD. Our findings will provide a platform to study the mechanisms of amyloid-dependent neurodegeneration *in vivo* and will provide an ideal *in vivo* model system to evaluate neuroprotective therapies. We are currently testing if the degeneration of 5-HT and

NE system participates in progression of amyloid pathology, progression of cognitive dysfunction, and development of non-cognitive abnormalities. Mechanistically, we are evaluating if abnormal BDNF signaling is involved in monoaminergic neurodegeneration.

Recent Publications:

Yan Y, She H, Gearing M, Colla E, **Lee M**, Shacka JJ, Mao Z. Regulation of Neuronal Survival Factor MEF2D by Chaperone-Mediated Autophagy. *Science*, 2009; 323:124-127.

Liu Y, Yoo MJ, Savonenko A, Stirling W, Price DL, Borchelt DR, Mamounas L, Lyons WE, Blue M, **Lee MK**. Amyloid pathology is associated with progressive monoaminergic neurodegeneration in a transgenic mouse model of Alzheimer's disease. *J Neurosci.* 2008 28:13805-14.

Wang J, Martin E, Gonzales V, Borchelt DR, **Lee MK**. (2008) Differential regulation of small heat shock proteins in transgenic mouse models of neurodegenerative diseases. *Neurobiol. Aging*, 29(4):586-97.

Martin Lj, Pan Y, Price AC, Sterling W, Copeland NG, Jenkins NA, Price DL, **Lee MK** (2006) Parkinson's Disease a-Synuclein Transgenic Mice Develop Neuronal Mitochondrial Degeneration and Cell Death. *J Neurosci.* 26:41-50.

Li W, West N, Colla E, Pletnikova O, Troncoso JC, Marsh L, Dawson TM, Jakala P, Hartman T, Price DL, **Lee MK** (2005) Aggregation promoting C-terminal Truncation of a-synuclein is normal cellular process and is enhanced by the familial Parkinson's disease-linked mutations. *Proc. Natl. Acad. Sci. USA.* 102: 2162-2167.

Li W, Lesuisse C, Xu Y, Troncoso J, Price, D, **Lee MK** (2004) Stabilization of a-Synuclein protein with aging and familial Parkinson's disease-linked A53T mutation. *J.Neurosci.* 24(33):9400-9409.

Lee MK, Stirling W, Xu Y, Xu X, Qui D, Mandir AS, Dawson TM, Copeland NG, Jenkin NA, Price DL (2002) Human a-Synuclein Harboring Familial Parkinson's Disease Linked Ala53Thr Mutation Causes Neurodegenerative Disease with a-Synuclein Aggregation in Tg Mice. *Proc. Natl. Acad. Sci. USA.* 99:8968-8973.

(For a comprehensive list of [recent publications](#), refer to PubMed, a service provided by the National Library of Medicine.)

Education:

- **BA Psychology** – Macalester College, St. Paul, MN, 1985
- **PhD Neuroscience** – University of Virginia, Charlottesville, VA, 1991
- **Postdoctoral Fellow** – The Johns Hopkins University of Medicine, Baltimore, MD, 1994

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