Karen Hsiao Ashe, M.D, Ph.D.

- **Staff Physician**, GRECC, Minneapolis VA Health Care System, Minneapolis, MN
- **Director,** N. Bud Grossman Center for Memory Research, University of Minnesota, Minneapolis, MN
- **Professor,** Department of Neurology, University of Minnesota, Minneapolis, MN
- **Edmund Wallace and Anne Marie Tulloch Chairs in Neurology and Neuroscience,** University of Minnesota, Minneapolis, MN

Research Interests:

For over 20 years I have been engaged in the study of the molecular genetics, biochemistry and molecular biology of prion diseases and Alzheimer's disease. My contributions are in three main areas: the genetics of human prion diseases; transgenic models of prion and Alzheimer's diseases; and the molecular basis of memory loss in Alzheimer's disease.

With my lab I created the Tg2576 transgenic mouse, which develops subtle memory problems and plaques composed of amyloid-beta protein. This mouse models the "pre-clinical" phase of Alzheimer's disease. During this phase, the disease processes are underway in the brain, but people do not yet notice symptoms. This model of Alzheimer's disease is studied around the world today. The work continued with the creation of other mouse models of neurodegenerative disease, including developing the rTg4510 mouse that models another biological sign of Alzheimer's: neurofibrillary tangles made of tau protein.

My current research focuses on:

1.) Finding markers in blood and cerebral spinal fluid that will let us detect Alzheimer's disease at its earliest stages, before people notice symptoms -- and before there is irreplacable loss of large numbers of brain cells.
2.) Creation of an improved mouse model of Alzheimer's disease that more completely recapitulates the course of the human disease, exhibiting plaques, tangles, memory loss, and massive death of brain cells.
3.) Increasing the understanding of the basic mechanisms of Alzheimer's disease at the molecular level so that an intervention in the process might be found to halt the progress of the disease, specifically focusing on Abeta*56 and Tau.
4.) Translation of safe and affordable compounds which have shown results in mouse models of Alzheimer's disease into a prevention strategy to reduce the incidence of the disease in humans through a collaboration of laboratory and clinical researchers.

My dream is to develop an effective, safe and affordable prevention for Alzheimer's disease.

Selected Publications:

Ashe, K.H. and Zahs, K.R.: Probing the biology of Alzheimer's disease in mice. *Neuron* 66:631-45, 2010.

Zahs, K.R. and **Ashe, K.H**.: "Too much good news!": Are Alzheimer mouse models trying to tell us how to prevent, not cure, Alzheimer's disease? ***Trends in Neurosciences*** 33: 381-389, 2010.

Lesné, S., Kotilinek, K., **Ashe, K.H.**: Plaque-bearing mice with reduced levels of oligomeric amyloid-β assemblies have intact memory function. *Neuroscience* 151:745-749, 2008.

Kotilinek, L.A., Westerman, M.A., Wang, Q., Panizzon, K., Lim, G.P., Simonyi, A. Lesné, S., Falinska, A., Younkin, L.H., Younkin, S.G., Rowan, M., Cleary, J., Wallis, R.A., Sun, G.Y., Cole, G., Frautschy, S., Anwyl, R., **Ashe, K.H.**: Cyclooxygenase-2 inhibition improves amyloid-β mediated suppression of memory and synaptic plasticity. ***Brain*** 131:651-664, 2008.

Ma, H., Lesné, S., Kotilinek, L., Steidl-Nichols, J.V., Sherman, M., Younkin, L.., Younkin, S., Forster, C., Sergeant, N., Delacourte, A., Vassar, R., Citron, M., Kofuji, P., Boland, L., **Ashe, K.H.**: Involvement of BACE1 in amyloid precursor protein-mediated enhancement of memory and activity-dependent synaptic plasticity. *Proc Natl Acad Sci (USA)* 104:8167-8172, 2007.

Lesné, S., Koh, M.T., Kotilinek, L., Kayed, R., Glabe, C.G., Yang, A., Gallagher, M., **Ashe, K.H**.: A specific amyloid-β protein assembly in the brain impairs memory. *Nature* 440:352-357, 2006.

SantaCruz, K., Lewis, J., Spires, T., Paulson, J., Kotilinek, L., Ingelsson, M., Guimaraes, A., DeTure, M., Ramsden, M., McGowan, E., Forster, C., Yue, M., Orne, J., Janus, C., Mariash, A., Kuskowski, M., Hyman, B., Hutton, M., **Ashe, K.H.**: Tau suppression in a neurodegenerative mouse model improves memory function. *Science* 309:476-81, 2005.

Ramsden, M., Kotilinek, L., Forster, C., Paulson, J., McGowan, E., SantaCruz, K., Guimaraes, A., Yue, M., Lewis, J., Carlson, G., Hutton, M., **Ashe, K.H**.: Age-dependent neurofibrillary tangle formation, neuron loss, and memory impairment in a mouse model of human tauopathy (P301L). *Journal of Neuroscience* 25:10637-10647, 2005.

Cleary, J., Walsh, D.M., Hofmeister, J.J., Shankar, G.M., Kuskowski, M.A., Selkoe, D.J., **Ashe, K.H**.: Natural oligomers of the amyloid-β protein specifically disrupt cognitive function. *Nature Neuroscience* 8:79-84, 2005.

Westerman, M., Cooper-Blacketer, D., Mariash, A., Kotilinek, L., Kawarabayashi, T., Younkin, L.H., Carlson, G., Younkin, S.G., **Ashe, K.H.**: The relationship between Aβ and memory in the Tg2576 mouse model of Alzheimer's disease. *Journal of Neuroscience* 22:1858-1867, 2002.

Kotilinek, L., Bacskai, B., Westerman, M., Kawarabayashi, T., Younkin, L.H., Hyman, B.T., Younkin, S.G., **Ashe, K.H.**: Reversible memory loss in a mouse transgenic model of Alzheimer's disease. *Journal of Neuroscience* [Rapid Communication] 22:6331-6335, 2002.

Kawarabayashi, T., Younkin, L.H., Saido, T.C., Shoji, M., **Ashe, K. Hsiao**, Younkin, S.G.: Age dependent changes in brain, cerebrospinal fluid, and plasma amyloid β protein in Tg2576 transgenic mouse model of Alzheimer's disease. *Journal of Neuroscience* 21:372-381, 2001.

Lim, G.P., Yang, F., Chu, T., Chen, P., Beech, W., Teter, B., Tran, T., Ubeda, O., **Ashe, K. Hsiao**, Frautschy, S.A., Cole, G.M.: Ibuprofen suppresses plaque pathology and inflammation in a mouse model for Alzheimer's disease. *Journal of Neuroscience* 20:5709-5714, 2000.

Chapman, P.F., White, G. L., Jones, M.W., Cooper-Blacketer, D., Marshall, V.J., Irizarry, M., Younkin, L., Good, M.A., Bliss, T.V.P., Hyman, B.T., Younkin, S.G., **Hsiao, K.K.**: Impaired synaptic plasticity and learning in aged amyloid precursor protein transgenic mice. *Nature Neuroscience* 2:271-276, 1999.

Holcomb, L., Gordon, M.N., McGowan, E., Yu, X., Benkovic, S., Jantzen, P., Wright, K., Saad, I., Mueller, R., Morgan, D., Sanders, S., Zehr, C., O'Campo, K., Hardy, J., Prada, C.-M., Eckman, C., Younkin, S., **Hsiao, K.K**., Duff, K.: Accelerated Alzheimer's type phenotype in transgenic mice carrying both mutant amyloid precursor protein and presenilin 1 transgenes. *Nature Medicine* 4:97-100, 1998.

Hsiao, K.K., Chapman, P., Nilsen, S., Eckman, C., Harigaya, Y., Younkin, S., Yang, F., Cole, G.: Correlative memory deficits, Aβ elevation, and amyloid plaques in transgenic mice. *Science* 274:99-102, 1996.

Hsiao, K.K., Borchelt, D.R., Olson, K., Johannsdottir, R., Kitt, C., Yunis, W., Xu, S., Eckman, C., Younkin, S., Price, D., Iadecola, C., Clark, H.B., Carlson, G.: Age-related CNS disorder and early death in transgenic FVB/N mice overexpressing Alzheimer amyloid precursor proteins. *Neuron* 15:1203-1218, 1995.

Hsiao, K.K., Scott, M., Foster, D., Groth, D.F., DeArmond, S.J., Prusiner, S.B.: Spontaneous neurodegeneration in transgenic mice with mutant prion protein. Science 250:1587-1590, 1990.

Hsiao, K.K., Baker, H.F., Crow, T.J., Poulter, M., Owen, F., Terwilliger, J.D., Westaway, D., Ott, J., Prusiner, S.B.: Linkage of a prion protein missense variant to Gerstmann-Sträussler syndrome. *Nature* 338:342-345, 1989.

Stahl, N., Borchelt, D. R., **Hsiao, K.K.**, Prusiner, S.B.: Scrapie prion protein contains a phosphatidylinositol glycolipid. *Cell* 51:229 240, 1987.

Selected Collaborations:
Grossman Center for Memory Research & Care, University of Minnesota, Minneapolis, MN
Institute for Therapeutics Discovery and Development**,** University of Minnesota, Minneapolis, MN
Institute for Translational Neuroscience, University of Minnesota, Minneapolis, MN
Department of Neuroscience, University of Minnesota, Minneapolis, MN
Department of Neurology, University of Minnesota, Minneapolis, MN
Department of Psychiatry, University of Minnesota, Minneapolis, MN
Veterinary Population Medicine, University of Minnesota, Minneapolis, MN
Biochemistry, Molecular Biology, and Biophysics, University of Minnesota, Minneapolis, MN
Mayo Clinic, Rochester, MN
Alzheimer's Disease Center, Rush University, Chicago, IL
Sahlgrenska University Hospital, Göteborg University, Sweden

Education:

- **AB Chemistry & Physics –** Harvard University, Cambridge, MA, 1975
- **Ph.D.–** Massachusetts Institute of Technology, Cambridge, MA, 1981
- **M.D. –** Harvard Medical School, Boston, MA, 1982
- **Postdoctoral Fellow –** in Neurology, University of California, San Francisco 1986-9

Honors:

- **MetLife Award for Medical Research** , 2005
- **Potamkin Award for Research in Pick's, Alzheimer's and Related Diseases**, 2006
- **Member, Institute of Medicine**, National Academies of the United States of America, 2009
- **Khalid Iqbal Lifetime Achievement Award**, Alzheimer's Association, 2010

Contact Information:

Voice:
Office: 612-467-4770
University of Minnesota Office: 612-625-0963

Email: hsiao005@umn.edu
Mail: Karen Ashe
GRECC (11G)
Minneapolis VA Medical Center
1 Veterans Dr.
Minneapolis, MN 55417