Of mice and medicine

How a U researcher’s quest for a better model of Alzheimer’s disease could speed up progress toward a cure

When Karen Hsiao Ashe, M.D., Ph.D., talks about her almost 30 years of Alzheimer’s disease (AD) research, she always credits the mice.

How else to study this devastating disease of the brain, which gradually robs people of their memories and their ability to complete even the simplest tasks? Mice, so closely linked genetically to humans, offer scientists hope for modeling the disease.

But to study this frustratingly elusive disease in mice, you first have to create a mouse that gets Alzheimer’s disease. And that’s no easy feat.

Such monumental challenges don’t faze Ashe, who is widely known as an international superstar in the world of Alzheimer’s research. At the University of Minnesota, she leads the N. Bud Grossman Center for Memory Research and Care and holds the Edmund Wallace and Anne Marie Tulloch Chairs in Neurology and Neuroscience; in the wider world of medicine, she has won too many awards to list, the most recent of which is a 2015 Zenith Fellows Award from the Alzheimer’s Association.

Ashe was first catapulted onto the international stage in 1996 when she successfully created a mouse that exhibited the memory loss associated with AD. That mouse line became the most widely used AD research model in the world.
U scientist aims to close the knowledge gap about Alzheimer’s with a five-year, $1.5 million NIH grant

With funding tighter than ever, grants from the National Institutes of Health (NIH) are becoming increasingly difficult to get. In 2013, only 17.5 percent of scientists who applied for the NIH’s basic research grant, the “R01,” were funded. So when University of Minnesota assistant professor of neuroscience Sylvain Lesné, Ph.D., got word that he was one of the chosen few last fall, it was cause for celebration.

“Our objective with this grant is to understand the role of a particular protein—typically associated with Parkinson’s disease—in Alzheimer’s,” says Lesné, who started working with Karen Hsiao Ashe, M.D., Ph.D., in 2002 as a postdoctoral research associate and now is an Institute for Translational Medicine.

Now, following many more breakthroughs, Ashe is absorbed in her quest for what she calls “iMouse,” named with a nod to the inspirational design of Apple products, she says. iMouse will offer a much more complete model of the disease, reflecting all that researchers have learned about the physical characteristics of AD over the years.

“Once we successfully achieve iMouse,” explains Ashe, “we will begin experimenting with a variety of safe and affordable compounds to try to prevent neuron loss. Once we can prevent neuron loss in iMouse, the next step would be to consider testing the most promising compounds in humans.”

Scientists have been using mice to study diseases for decades, but creating a mouse that develops a particular disease is tough. As Ashe explains it, the traditional method—inserting human Alzheimer’s genes into the mouse’s genome—yields unpredictable results: In 25 years, Ashe has been able to create 10 distinct mouse models.

A better mouse
Now, however, the game has changed.

The U’s Michael Koob, Ph.D., an associate professor in the Department of Laboratory Medicine and Pathology, has developed a new process that allows scientists to insert a particular gene into exactly the same spot in the mouse genome every time. Given the right genetic “recipe,” Koob can create new mouse models with unparalleled speed and certainty. For Ashe, that means she can now make 10 distinct mouse models in just one year.

“This process should ultimately benefit all mouse model research,” says Koob, “because our approach is reproducible—every mouse will be exactly the same.”

Adds Ashe: “This new technology could enable me to be more productive in the last quarter of my career than in the first three quarters combined.”

**The critical challenges**

Alzheimer’s already hits Americans hard, and future projections look dismal. Consider the grim facts:

- AD cannot be prevented, cured, or slowed;
- More than 5 million Americans have AD, and that number is expected to reach 14 million by 2050;
- AD is the 6th leading cause of death in the United States; and
- Last year, Alzheimer’s cost the United States $214 billion.

Through painstaking work, Ashe and her team are at the forefront of the worldwide
effort to conquer this disease, but, she says, four major problems remain to be solved.

“We have yet to determine what causes Alzheimer’s, and we need to create a more complete mouse model of the disease,” she explains. “We also need to discover safe, cheap, and effective drugs for intervention, and, finally, we need to establish platforms for affordable clinical prevention trials.”

Again, it’s a daunting picture. But Ashe is chipping away. In 2011, she led an effort to create the Twin Cities Consortium for Alzheimer’s Research, or T-CAR, a coalition of seven major health care organizations that now share resources and expertise and will ultimately provide a platform for her to reach tens of thousands of people for prevention trials.

Two kinds of support

Ashe has deep gratitude for the philanthropists who have supported her work; she cites Beverly Grossman, who pledged $5 million in 2007 to establish the Grossman Center in honor of her husband, who then was suffering from the disease. He died in 2010.

“The funds are indispensable, yes,” says Ashe, “but more than that, Beverly has also given her love and personal encouragement, which has meant so much to me.”

Now, what Ashe calls “another amazing, strong woman” has joined Team Ashe. Karin Moe, whose husband, Robert, was diagnosed with Alzheimer’s disease in 2009, recently committed substantial funds to help Ashe reach the next stage in the fight: finding a means of preventing AD.
“Karen is such a forward-looking researcher, so creative in her thinking and, I believe, really on the leading edge of this research,” says Moe. “My children and I have seen firsthand how painful this disease can be, how it’s caused my husband to become lost from himself. I’m happy I found someone like Karen to support.”

“Karin is one of my angels,” says Ashe. “She gives me her heart, in addition to her funds.” Ashe hopes to finish work on iMouse by 2017 and identify safe and affordable preventive compounds by 2025.

“This is hard, time-consuming work,” she says, “and in the past it’s taken 10 years to answer one question at a time. So, if we work hard, I believe prevention could be within our grasp 10 years from now.”