



Neurosciences News

A publication for those who support brain, nerve, and muscle disease research, education, and care at the University of Minnesota

Of mice and medicine

How a U of M 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.

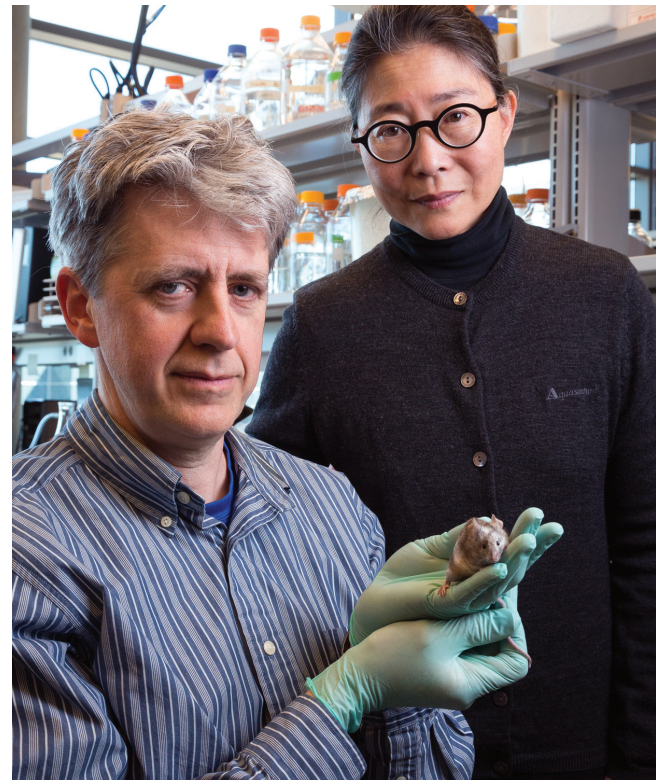
But to study this frustratingly elusive disease in mice, you first have to create a mouse that gets Alzheimer's disease. And that's no easy feat.

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

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Photo by Brady Willette



U scientist Michael Koob, Ph.D., has developed a more efficient way to create mouse models, speeding up the Alzheimer's research of Karen Hsiao Ashe, M.D., Ph.D.

Computer games show promise for treating schizophrenia **page 5**

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After a difficult diagnosis, dad still dreams of the slopes **page 7**

Of mice and medicine *(continued from cover)*

mouse that exhibited the memory loss associated with AD. That mouse line became the most widely used AD research model in the world.

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.”



Philanthropist Karin Moe (fourth from left) has personally experienced the impact Alzheimer's disease has on a family after her husband, Bob, was diagnosed in 2009.

A better mouse

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.

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.

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 "RO1," 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 Neuroscience Scholar at the Grossman Center.

Lesné hypothesizes that this protein, called alpha-synuclein, may play a significant role in Alzheimer's disease (AD).

"One of the reasons we haven't been successful in coming up with treatments for Alzheimer's," he says, "is because we still don't understand well enough how the disease develops and progresses. Projects like this one help reduce that knowledge gap and will ultimately allow us to identify possible treatments."

Lesné is already making strides toward identifying how this protein alters memory in mice, and in the future he hopes to test compounds designed to slow the protein's effects. His ultimate goal is to get new treatments into clinical trials.

"The hope is that we can lessen the severity of this disease and offer people with AD a better lifestyle," he says.

Sylvain Lesné, Ph.D.

Photo by Scott Strebler

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."

Nurturing success

Stroke Research Center internship program offers U students a special research opportunity



Afshin Divani, Ph.D., believes in wasting no time when a new class of medical students walks through University doors. As an assistant professor of neurology and neurosurgery, he's partial to the neurosciences, and he constantly looks for new ways to spark a similar passion in soon-to-be doctors.

"It makes sense to reach out to first-year medical students, to get them excited about neurology and stroke research early on," says Divani.

He started with a simple idea: to create an internship program at the U's Stroke Research Center to bring two or three students into the lab to do hands-on research. Internships, however, do not pay for themselves, and that's where Divani really proved his mettle.

Divani's enthusiasm is infectious, so it's not surprising that companies like Lake Region Medical, Covidien (recently acquired by Medtronic), and HealthEZ all stepped up to sponsor the internship opportunity for students.

Mario Hevesi, who was in his first week of medical school when he started talking with the outgoing Divani, is one of those students.

Afshin Divani, Ph.D., in black, has a father's pride in his Stroke Research Center interns.

"Dr. Divani is unique in the way he interacts with students," says Hevesi, now a third-year medical student. "He is so open and willing to take us on. And research opportunities like this are almost nonexistent."

Through his internship, for example, Hevesi has worked on developing a microwire that can be used to induce a stroke in mice, with the purpose of testing treatments to speed recovery. He is also one of several students who have already received national awards for their work with the program.

"Doing an internship like this matters hugely," Hevesi says, "because, more and more, medical students are expected to have a hand in research so they can better understand what's happening in their field."

And although Divani's level of commitment to students can be taxing at times, he's not backing off: "For me, the best reward is seeing these students succeed."

Support through a lifetime—and beyond

Your annual gifts to support brain, nerve, and muscle disease research, education, and care at the University of Minnesota make a real difference to patients and their families. Did you know that you can continue to make a difference after your lifetime by including the University of Minnesota Foundation in your estate plan? Here are three ways to continue your support:

- Leave a specified dollar amount or a percentage of your estate to the University of Minnesota Foundation through your will or living trust.

- Name the University of Minnesota Foundation as a beneficiary of your retirement plan account or a life insurance policy.
- Arrange a gift that will provide payments to you or others.

For more information, please contact Catherine McGlinch of the University of Minnesota Foundation at 612-626-5456 or mcgra022@umn.edu.

Brain games

Computer programs show promise for treating schizophrenia

At the University's day treatment program for people who have schizophrenia, young 20-somethings now spend part of their therapy time one-on-one with a computer.

"What we know now," explains S. Charles Schulz, M.D., executive medical director of the U's Department of Psychiatry, "is that cognitive problems are a part of schizophrenia. We can successfully treat the disease—the hallucinations, the paranoia, the delusions—but the person still has these very troubling cognitive deficits, and that's what these computer activities are designed to help."

He's talking about difficulties with attention, problem solving, memory, social cognition (recognizing emotion in people's faces, knowing how to start and end casual conversations), and visual tracking.

About two years ago, the Wells Family Fund of the Minneapolis Foundation donated 10 computers and the necessary software to allow day treatment staff to offer cognitive remediation therapy as part of the program.

"There is research going back to the early '90s that confirms that cognitive outcomes can improve," says Aimee Murray, Psy.D., assistant professor at the U, who works in the day treatment program.

Anecdotal evidence at the U indicates that these computer "brain games" really do help. Patients work through the games, getting positive reinforcement as they advance to higher levels.

There are separate games for each cognitive skill. In one game, the player runs a hot dog stand in a large arena and is challenged to accurately figure inventories, track income, research past event attendance—in other words, take the cognitive skills they've been working on in other computer activities and apply them to real-life problems.

This type of cognitive remediation therapy has a successful history in people who have traumatic brain injuries, Murray says, but has only recently been adopted to help people who have schizophrenia.

"We've come such a long way," says Schulz, "and we see every day just how much people with psychotic disorders can accomplish with proper support. Improving cognitive deficits can help people succeed in school, in their jobs, and in their personal relationships. There's a lot of hope here."



The pursuit of Parkinson's

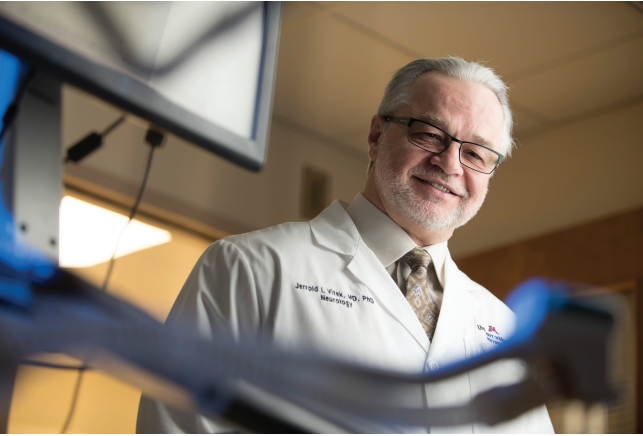


Photo by Scott Streble

Jerrold Vitek, M.D., Ph.D.

“Parkinson’s patients are a bit like snowflakes,” says Jerrold Vitek, M.D., Ph.D., head of the Department of Neurology and director of the University’s Neuromodulation Research Center. “No two are alike. The symptoms can vary

greatly from one patient to another—as can the effectiveness of the treatments available to them.”

So it only makes sense that researchers are pursuing Parkinson’s on many fronts. At the University of Minnesota, experts in neuroscience, magnetic resonance imaging, sleep science, and drug development are among the cadre of scientists striving to enhance the overall understanding of Parkinson’s, develop more effective treatments, and contribute to the development of a cure.

Vitek, for instance, and Noam Harel, Ph.D., associate professor of radiology at the U’s Center for Magnetic Resonance Research (CMRR), are using imaging technologies to map patient-specific 3-D brain models that will facilitate more precise placement of the electrodes used in deep brain

stimulation (DBS) surgery. DBS delivers electrical charges to a very precise area of the brain to mitigate and, in some cases, eliminate the motor symptoms of Parkinson’s disease.

Also working to improve life for people who have Parkinson’s disease are:

Colum MacKinnon, Ph.D., director of the University’s Movement Disorders Laboratory, who is shedding light on one of the more puzzling symptoms of Parkinson’s disease: freezing of gait, which affects about 70 percent of people in the advanced stages of Parkinson’s;

Sleep expert **Michael Howell, M.D.**, who is investigating a rare sleep disorder known as REM behavior disorder (RBD), which is often a precursor to Parkinson’s;

Liqiang Chen, Ph.D., of the University’s Center for Drug Design, who with his team has been developing compounds that could lead to suitable drugs for treating the disease; and

Paul Tuite, M.D., who was the U’s principal investigator for BioFIND, a two-year study funded by the Michael J. Fox Foundation for Parkinson’s Research, aimed at identifying reliable and consistent biomarkers for Parkinson’s, which could lead to better methods of diagnosing and treating the condition.

Read more at z.umn.edu/MBparkinsons.



Photos by Stephanie Dunn

10 years
of baseball and
philanthropy

Thank you for celebrating award winners from the Minnesota Twins community while raising critical funds for lifesaving research and care related to brain, nerve, and muscle disorders at the University of Minnesota at the 10th annual Diamond Awards, held January 22 at Target Field. The event has raised more than \$2.6 million since its inception.

View the photos from this year’s event at www.minnesotadiamondawards.org.



The Line Up

News from the Bob Allison Ataxia Research Center

Dreaming of the slopes

All Mark Buermann really wants is to ski with his family.

A Boy Scouts activity with his son forced Buermann to get on the slopes again in 2007 after a 15-year break. They both loved the experience so much that the next year, the whole Buermann family went skiing together in northern Minnesota.

"I'll never forget it because I thought this was something our family could enjoy for the rest of our lives," Buermann says.

But the following year, he was diagnosed with progressive muscular atrophy, which often develops into amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. "It really hit home that one of the activities I thought would bring our family closer together was no longer possible," he says.

Today, for the sports-loving Buermann—who now gets around with either a cane, walker, or power wheelchair—skiing again with his family seems like a distant hope.

ALS is a progressive, degenerative brain disease that attacks the neurons that control voluntary muscle movements. It causes muscle weakness that makes even simple daily tasks like brushing teeth and getting out of bed difficult. Today there is no known cure.

"Living with ALS is like having a cloud surrounding you every minute of the day," Buermann says. "Everything you do, everything you think about, everywhere you go, you have this cloud. ... It's very difficult to keep moving forward."

Even so, Buermann says that actually being diagnosed by University of Minnesota neurologist David Walk, M.D., in 2008, almost seemed like a relief. It certainly was traumatic for him and his family, but at least they had an answer—and a road map for moving on.

"The care at the University of Minnesota is professional," Buermann says. "There's no sugar-coating. It's caring. It's very

Photo by Stephanie Dunn



After a difficult diagnosis, Mark Buermann (seated) and his family, kids Derek and Laura and wife Linda, advocate for ALS research.

informative. It's a coordinated effort with so many specialists, and it's all done at one time."

Gratitude for that care is just one reason that Buermann wants to help advance ALS research.

When his disease forced him to retire early, Buermann, now just 53, felt boredom and depression setting in. Then Walk suggested that he get involved with the ALS Association. Last year Buermann was elected to the organization's board of directors for the local chapter, which serves Minnesota and the Dakotas.

He's proud to be an advocate for the ALS Association and to spread the word about what the U is doing to advance research.

"It's very important to me to know that the University of Minnesota is at the forefront of trying to find a cure, not only for ataxia and ALS but other neurological diseases," he says.

Buermann, after all, is holding out hope that he'll be able to ski with his family again.

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Training your brain

Research by University of Minnesota biomedical engineers shows that people who practice yoga and meditation long term can learn to control a computer with their minds faster and better than people who have little or no experience with yoga or meditation.

The research, published online in the journal *TECHNOLOGY*, could have major implications for people who are paralyzed, have lost limbs, or have brain diseases such as ALS or cerebral palsy. In these people, where brain function remains intact, they must find ways to bypass muscular control to move a wheelchair, an artificial limb, or other devices.

Study participants, who wore a high-tech cap over the scalp that picked up brain activity, were asked to move a computer cursor across the screen by imagining left or right movements.

Those with yoga or meditation experience were twice as likely to complete a brain-computer interface task by the end of 30 trials and learned three times faster than their counterparts for the left-right cursor movement experiments.

“There has been a lot of attention on improving the computer side of the brain-computer interface but very little attention to the brain side,” says lead researcher Bin He, Ph.D., who directs the U’s Institute for Engineering in Medicine. “This comprehensive study shows for the first time that looking closer at the brain side may provide a valuable tool for reducing obstacles for brain-computer interface success in early stages.

“Our ultimate goal,” he adds, “is to help people who are paralyzed or have brain diseases regain mobility and independence.”

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