



Neurosciences News

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

Connecting the dots

With donors' support, University researcher pursues the causes of neurodegeneration behind Parkinson's and Alzheimer's

Don't be mistaken: Parkinson's and Alzheimer's are distinct neurodegenerative diseases. Both involve the death of neurons, but the primary cells affected are different.

In Parkinson's disease, most of the killed-off cells are responsible for physical movement. The disease's most common symptoms, therefore, are motor-related: tremors, stiff muscles, poor balance, and difficulty walking, sitting, or standing.

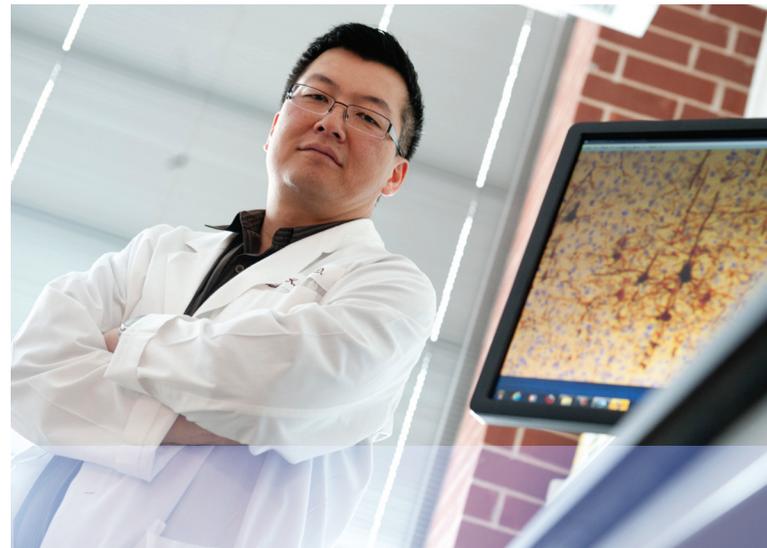
In Alzheimer's disease, the destroyed cells are mainly responsible for memory and cognitive skills. Thus, the disease's key characteristic is gradual cognitive decline, including a devastating loss of memory.

But the two conditions—the most common neurodegenerative illnesses in the United States—do share some hallmark features. Dementia occurs in up to 80 percent of people who have Parkinson's disease. And many people with Alzheimer's lose motor function, including their ability to walk, especially toward the end of the illness.

In fact, as scientists learn more about Parkinson's and Alzheimer's, they're discovering that the diseases' pathological pathways in the brain have much more in common than was previously believed. One of those commonalities is the abnormal behavior of the alpha-synuclein protein.

continued on page 2

Photo by Scott Strebbe



Hoping to identify better therapies, Michael K. Lee, Ph.D., examines how neurons affected by Parkinson's and Alzheimer's diseases die.

Gift supports integrative mental health treatment **page 4**

U named one of five sites for Parkinson's biomarker study **page 5**

New gene-sequencing technology leads to answers faster **page 7**

Connecting the dots *(continued from cover)*

Through his renowned research on this protein, University of Minnesota neuroscientist Michael K. Lee, Ph.D., is deepening our understanding of how neurons die in both Parkinson's and Alzheimer's diseases.

This novel work is pointing to new avenues of therapies that may one day slow or even stop the progression of these two debilitating diseases, which together affect as many as 6 million Americans.

"In both Parkinson's and Alzheimer's, the brain just starts dying off," says Lee, who is codirector of the Center for Neurodegenerative Diseases, part of the Institute for Translational Neuroscience at the University. "We need to stop that if we're going to have an impact on the progression of the diseases. We have to go beyond just trying to treat the symptoms and get to the underlying processes."

"I have several family members on my mother's side who died with severe dementia, and David's father had Parkinson's disease with severe dementia," says Susan Plimpton, who leads a neurosciences development advisory committee for the University of Minnesota Foundation.

Lee's research "just hit on all cylinders, so to speak, for us," she adds. "It has the possibility of leading to some important discoveries that might help prevent or manage these diseases more effectively than we do today."

Today, someone in the United States develops Alzheimer's disease every 68 seconds. By 2050, experts are projecting, there will be one new case every 33 seconds—or nearly 1 million new cases per year.

Source: Alzheimer's Association

When a protein turns toxic

Alpha-synuclein is a major constituent of Lewy bodies, the abnormal protein clumps that have long been known as a hallmark of Parkinson's disease. The protein also becomes abnormal in Alzheimer's disease. Its precise role in the brain and in the pathology of these diseases is unclear, however.

One of the places alpha-synuclein resides in neurons is an area outside of the nucleus known as the endoplasmic reticulum (ER). The ER functions like an assembly line, synthesizing and "packaging" proteins into folded shapes that enable them to perform specific functions in the cell. If the folding of the proteins is not done correctly, however, the proteins become useless—or, worse, toxic.

Usually, nature takes charge and fixes the problem proteins. Those that are unfolded or

David and Susan Plimpton understand on a personal level the need to better understand Alzheimer's and Parkinson's diseases.



Photo by Jim Bovin

A personal interest

Susan and David Plimpton understand on a personal level the urgent need for such research, which is why the couple has made a gift to support Lee's work. Susan, a former consumer marketing executive, and David, a semi-retired internal medicine physician (and 1966 University of Minnesota Medical School alumnus), also have set aside additional funding for the research in their estate plans.

misfolded are “caught” and either re-folded or destroyed by proteins called chaperones before they can harm the cell. But as the brain ages, incorrectly folded alpha-synuclein molecules may gather into small toxic clumps called oligomers. Over time, the oligomers may form even bigger clumps, an outcome that can “gum up the entire assembly line of the cell,” says Lee.

The “stressed” ER tries to clean up trouble-making proteins by sending out more chaperones, but if that response is inadequate, explains Lee, “the cell activates a self-destruct mechanism that leads to its death.”

In 2012, Lee and his colleagues were the first to report an association between high levels of alpha-synuclein oligomers and the breakdown of the ER. They found this association both in mouse neurons and in neurons in postmortem human brains.

“We observed it in Parkinson’s disease,” says Lee. “But what we found may also have relevance for Alzheimer’s disease.”

That’s because research suggests that ER stress—the condition triggered by these accumulating toxic clumps—is involved in Alzheimer’s disease as well as in Parkinson’s disease.

Further evidence

To test whether the association he found between ER stress and alpha-synuclein oligomers is an important factor in the death of neurons, Lee teamed up with researchers at Johns Hopkins University to treat mice that model human Parkinson’s disease with salubrinal, an experimental drug that protects cells against chronic ER stress.

“We found that the treated mice were able to survive [without symptoms] for a much longer time,” he says.

In yet another experiment, this time conducted with researchers at the Brain Mind Institute in Lausanne, Switzerland, Lee’s colleagues gave salubrinal to rats that model human Parkinson’s

and that have dopamine neurons targeted for death from alpha-synuclein. (Dopamine is a brain chemical critical for coordinating movement, and the loss of dopamine neurons is the major reason for the onset of Parkinson’s.) Once again, the salubrinal dramatically reduced the toxic effects of the alpha-synuclein protein.

About 50,000 Americans are diagnosed with Parkinson’s disease each year, though some researchers believe the true prevalence of the disease is much higher. Parkinson’s affects about 50 percent more men than women.

Source: National Institute of Neurological Disorders and Stroke

Although salubrinal may one day become a good candidate for neurodegenerative therapies, it’s not currently approved for use in humans. Lee and his colleagues are testing other promising drugs, including one already used to treat high blood pressure, in animal models to see whether those compounds also will relieve ER stress.

Lee emphasizes that although the findings from his lab suggest new therapeutic targets, the research is at an early stage. Still, he’s hopeful.

“We need to have a better understanding of the underlying reason the symptoms of Parkinson’s and Alzheimer’s diseases occur,” he says, “so that we can actually help people live longer and have a better quality of life. It’s a big issue—and one that affects not only the individuals who have the disease, but their families as well.”

A more hopeful future

Company's gift supports integration of psychotherapy treatments for adolescents and young adults facing mental illness



It seems that psychotherapy research has taken a backseat to pharmaceutical research in recent years. After all, it's comparatively easy to quantify the effectiveness of pharmaceuticals: count the milligrams, measure the drug in the blood, and then correlate the data to an outcome.

S. Charles Schulz, M.D., head of the University of Minnesota Medical School's Department of Psychiatry, and Stephen Setterberg, M.D., president of PrairieCare, a Twin Cities psychiatric treatment services company, say that they're concerned by this trend.

But psychotherapy research has "progressed tremendously over the past 10 to 20 years," Setterberg says, "and there is quite a bit of empirical support now for a variety of the psychotherapy approaches that are commonly used." He believes psychotherapy should play a bigger role in psychiatric practice in general.

"I think that something very precious is lost without that dimension of practice," he says.

This belief led Setterberg to commit \$200,000 to the University to support research in integrative treatment methods, especially those involving psychotherapy, for adolescents and young adults. Setterberg, who received his undergraduate and medical school degrees from the University, says

that he hopes the Integrative Treatment Research Fund he's creating through his company will help to improve the lives of young people living with mental illness.

PrairieCare's focus on children and adolescents is one reason that the gift is targeted to youth mental health. Another is Setterberg's belief in the importance of early intervention.

"Brain development is very intensive throughout childhood and adolescence, even up to age 25 or so," he says. "Because of this, effective psychological and behavioral interventions with younger people are both more likely to show results and to have lasting benefit."

PrairieCare is an official training site for child psychiatry fellows and medical students at the University, a relationship that Setterberg says he feels brings the excellence of the University into his organization.

"The gift is a kind of reciprocity for that," he says. "It's a reflection of how we value that relationship."

Schulz says the potential impact of the work that will be funded by PrairieCare's gift is significant.

"It can lead us to provide better care," he says. "We know that the need to better understand how to best treat children and adolescents, how to best structure and utilize the psychosocial treatments, is crucial. I'm just delighted with our affiliation with PrairieCare and its generosity."

With better diagnosis and treatment methods in mind, U takes part in study to identify biomarkers for Parkinson's disease

Parkinson's disease, a movement disorder that affects the central nervous system, is diagnosed in more than 50,000 Americans every year. Yet there is no test for diagnosing it or for predicting its progression.

The University of Minnesota is participating in a new research study called BioFIND that's focused on identifying Parkinson's disease biomarkers to ultimately help find better ways of diagnosing and treating the condition.

The University is one of five sites chosen by the Michael J. Fox Foundation for Parkinson's Research for this groundbreaking two-year study.

A biomarker is a substance, process, or characteristic that is associated with the risk or presence of a disease, or one that changes over time with disease progression. Reliable and consistent biomarkers allow scientists to predict, diagnose, and monitor diseases and can be used to help determine which medications work and which do not.

There is currently no known Parkinson's biomarker, according to Paul Tuite, M.D.,

principal investigator for the University's portion of BioFIND and an associate professor in the Department of Neurology. That's why, he says, even though there have been numerous drug trials for Parkinson's disease in the past 10 to 20 years, the current crop of drugs being tested doesn't appear to be stopping or reversing damage to the central nervous system; instead, today's drugs help to manage symptoms.

Tuite says BioFIND is a particularly promising study because it involves collecting and analyzing spinal fluid, which, because it surrounds the brain and other parts of the central nervous system, could provide a host of useful information.

Tuite and his colleagues plan to focus their work on the presence of antioxidants, DNA variants, and various proteins in the blood and spinal fluid of study participants, who will include both Parkinson's patients and healthy volunteers. And he's optimistic about the road ahead.

"The goal is to help better diagnose patients, better predict their course," Tuite says.



Paul Tuite, M.D., leads the U's portion of a study funded by the Michael J. Fox Foundation for Parkinson's Research.

IRA charitable giving opportunity extended for 2013

Thanks to recent legislation, you can benefit from a popular tax-advantaged giving option again this year.

Make a gift of up to \$100,000 directly from your IRA to the University of Minnesota Foundation (UMF) to support brain, nerve, and muscle research at the University of Minnesota before December 31, 2013, and you can avoid paying federal income tax on the amount of your gift.

These rules apply to IRA charitable rollovers in 2013:

- Only IRAs are eligible (other types of retirement accounts are not).
- You must be age 70½ or older at the time you make your gift.

- Your gift must come directly from the IRA custodian to UMF.
- You can give up to \$100,000 from your IRA to one or more qualified charities in 2013 (and if your spouse has a separate IRA, you can each give up to \$100,000).
- Your gift must be outright; it cannot be used to fund a charitable gift annuity or charitable remainder trust.

While you will not be able to claim a charitable deduction for your IRA rollover gift, you won't owe federal income tax on any amount up to \$100,000 that you distribute to a qualified charity.

To learn more, contact Jennifer White of the University of Minnesota Foundation at 612-625-8676 or whit0559@umn.edu.

Epilepsy care options expand through integration of physician groups

The epilepsy programs of MINCEP® and University of Minnesota Physicians have integrated, expanding epilepsy care options for patients throughout Minnesota.

Founded at the University in 1964, MINCEP was the first comprehensive epilepsy center in the United States and has since served as a model for epilepsy centers across the world. It is designated as a Level 4 epilepsy center by the National Association of Epilepsy Centers.

With MINCEP's return to the University, the integrated MINCEP and UMPPhysicians team is a regional leader in the field. The partners are bringing the best of two worlds together to provide comprehensive epilepsy care, including:

- Exceptional patient experiences and outcomes through coordinated care and advanced capabilities, specifically in pharmacology, diagnostics, and surgery;
- Specialized programs for unique patient populations, such as children and older adults; and
- Expanded medical research opportunities through the University's state-of-the-art facilities.

Learn more at www.umphysicians.org/Clinics/mincep.

Two U foundations merge

The Minnesota Medical Foundation and University of Minnesota Foundation have merged to create a single foundation, operating as the University of Minnesota Foundation.

The combination of these two foundations will enhance support of excellence at the University, provide even greater efficiencies, and better serve University donors.

For more information, contact us at 612-624-3333 or 800-775-2187.



Retraining the brain

The University of Minnesota's Brain Plasticity Laboratory helps kids and adults recover from stroke and other disabling conditions. Read the new *Medical Bulletin* article, featuring 16-year-old violinist and stroke survivor Tiffany Cowan, at www.give.umn.edu/mb/BrainPlasticity.



Photo by Scott Strebbe



The Line Up

News from the Bob Allison Ataxia Research Center

New gene-sequencing technology gives patients answers faster and at a much lower cost

When Apple, Inc., cofounder Steve Jobs paid \$100,000 to have his DNA sequenced in a bid to outrun the pancreatic cancer that ultimately claimed his life, he was just one of 20 people in the entire world to have had it done.

But for the general public, the benefits of DNA sequencing—which has been both time-consuming and costly—have remained largely unattainable. Until now.

A new technology called next-generation sequencing (NGS), previously used in research studies but rarely for clinical diagnostic tests, is now being used in clinics affiliated with the University of Minnesota. It can test large numbers of very specific genes simultaneously and at a significantly reduced cost.

Already at the University of Minnesota Ataxia Center, NGS is helping clinicians diagnose dozens of forms of rare ataxias.

“The big technical advance is the capability of focusing the sequencing power,” says Matthew Bower, M.S., C.G.C., the Ataxia Center’s genetic counselor. “Rather than distributing it across 3 billion letters of the genome, you can focus it on a set of target genes.”

As Bower explains it, this targeting allows for a considerably shorter “diagnostic odyssey” for patients. In the past, diagnoses were ruled out one gene at a time, a process that for some patients would take decades. Using NGS, the process typically takes about two to three months.

NGS makes gene sequencing more accessible, too. The process once cost \$1,000 to \$2,000 per gene, and with tens of thousands genes in



A diagnosis that once could take decades now typically takes about two to three months, says genetic counselor Matt Bower, M.S., C.G.C.

Photo by Jim Bovin

the human genome, the price was far out of reach for most people. But NGS typically costs between \$1,500 and \$4,000 total, Bower says, depending on how many genes are analyzed.

“We’re looking at hundreds of genes for the price of what it used to cost to look at a single gene,” he says.

Ataxia Center director Khalaf Bushara, M.D., says many of his patients are glad to have a definitive diagnosis, even if there’s no clear-cut treatment option. That’s particularly true if there’s a hereditary component to their disease, he says.

“They want to plan to have kids. Is it dominant or recessive?” he says. “Some patients just want to know.”

NGS is being used at other University-affiliated specialty clinics that treat patients for inherited genetic diseases and cancers, as well, says Bower, including the ophthalmology, otolaryngology, pediatrics, hematology-oncology, and blood and marrow transplant clinics.

Does psychosocial distress elevate your risk of stroke?



Susan Everson-Rose,
Ph.D., M.P.H.

Older Americans dealing with high levels of psychosocial distress are at higher risk for stroke, according to a University of Minnesota study.

Psychosocial distress is broadly defined as internal conflicts and external stress that prevent a person from self-actualization and connecting with others. It can include depression, stress, and a negative outlook.

For this study, University researchers followed more than 4,000 people aged 65 and older through the Chicago Health and Aging Project. They measured psychosocial distress using four indicators: perceived stress, dissatisfaction with life, neuroticism, and depressive symptoms.

Those people who had the most psychosocial distress had three times the risk of dying from

stroke and a 54 percent increased risk of being hospitalized for the first time compared with those who had the least amount of distress in their lives. The risk of distress also climbed with age.

The research, published in the American Heart Association journal *Stroke*, noted that the impact of psychosocial distress on stroke risk did not differ by race or gender.

“People should be aware that stress and negative emotions often increase with age,” says lead researcher Susan Everson-Rose, Ph.D., M.P.H., associate director of the Medical School’s Program in Health Disparities Research. “Family members and caregivers need to recognize [that] these emotions have a profound effect on health and that it’s important to pay attention when older people complain of distress.”

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