Averting the devastating effects of stroke

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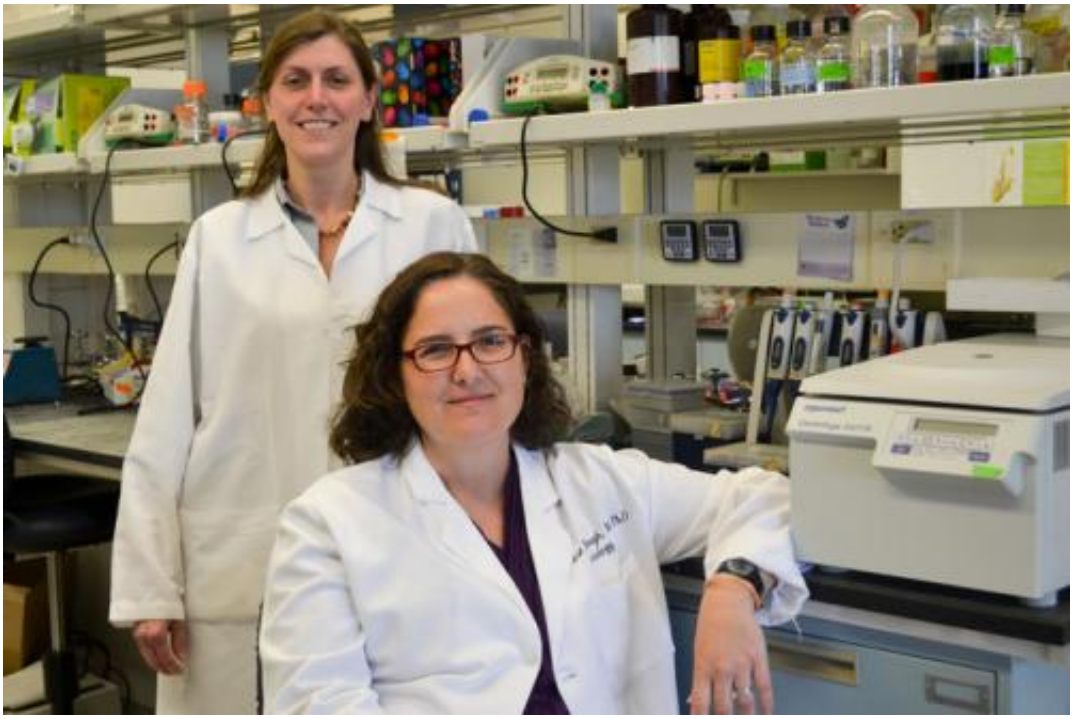

Drs. Louise McCullough (seated) and Lauren Sansing are studying ways to prevent the devastating injuries to the body caused by stroke, a leading cause of serious long-term disability. Credit: Carolyn Pennington/UConn Health Center Photo

(Medical Xpress)—Researchers at the University of Connecticut Health Center are studying ways to prevent the devastating injuries to the body caused by stroke, a leading cause of serious long-term disability.

One American dies from stroke, sometimes called a "brain attack," every

four minutes. More than five times that many people survive a stroke, and for them, the physical damage it causes can be enormous.

"Stroke often doesn't kill you, but some patients say they would have rather died than be left with severe disability and not be able to care for themselves," says Dr. Louise D. McCullough, professor of neurology and neuroscience and director of stroke research. "People can often be disabled from their stroke. They need assistance with feeding and sometimes can't get out of bed. Many can't speak or communicate, and this is very isolating. And now we're seeing an increasing number of stroke survivors as our population ages."

There are two types of stroke. Ischemic strokes, which account for the vast majority, happen when clots block the blood vessels to the brain and cut off blood flow. Hemorrhagic strokes happen when the wall of a blood vessel breaks and blood leaks into the surrounding brain. Signs of either type of stroke include sudden numbness or weakness of the face or arm or leg, especially on one side of the body, as well as sudden confusion, difficulty speaking or understanding, trouble seeing or walking, dizziness or loss of balance, and/or a sudden severe headache.

McCullough's research focuses on ischemic stroke. This type of stroke can be treated in an emergency room with "clot-busting" medication called tissue plasminogen activator (tPA), which helps reduce damage to the brain. But tPA can be effective only if given within a few hours of a stroke, and many people don't immediately realize they are having a stroke and don't seek help right away. In addition, some people can't receive tPA because of other health issues.

"Nationwide, only 5 to 8 percent of people who have a stroke get tPA effectively," she says. "So we've been limited in treatment. We've never been able to find a drug to protect the brain after stroke. Reperfusion (restoring the blood flow using tPA) is less useful because the brain is

already damaged."

So McCullough's research involves studying factors such as what contributes to brain injury after a stroke and how it might be reversed. Because women tend to do worse than men in terms of survival and disability, she also is studying the role that hormones play in stroke risk and recovery.

Much of the understanding about stroke and its treatment has stemmed from research in men, but not all of those findings can benefit women, she points out. "Stroke is different in women – how we present, how we respond to drugs, how we recover. Women have a higher risk of stroke, a slower recovery and more cognitive problems. We need to understand the sex differences on a cellular level. For example, cell death occurs by different pathways in the two sexes. We're trying to figure out why the biology is different and whether that's important to therapy."

In addition, women and men respond differently to different types of drugs. McCullough points to basic aspirin as an example of this. In women, a daily dose of aspirin can help prevent stroke but seems to have no impact in preventing heart disease. In men, the opposite is true.

Interestingly, McCullough also has found a correlation between social factors and stroke. In a study funded by the National Institutes of Health (NIH), McCullough is using mouse models to understand the role that social isolation might play in ischemic stroke.

"We've found that isolation is as big a risk factor for having a stroke as hypertension (high blood pressure)," she explains. "We also found that if we induce a stroke in a mouse that is isolated from others, the stroke is 40 percent bigger. And three days after a stroke, a mouse that is placed with others does better than a mouse that is alone. So now we're saying that with hospitalized patients, maybe we should put someone who has

had a stroke in a room with, say, someone who has had a hip replacement."

McCullough earned her medical degree and Ph.D. from UConn's School of Medicine. She completed an internship, residency and fellowship at Johns Hopkins University in Baltimore before returning to Connecticut after her father, a physicist, suffered a disabling stroke. She hopes her research will help people like her father as well as future generations, including her four children ranging in age from 7 to 13, whose framed artwork covers larger portions of the walls in her office than do the smaller certificates honoring her with Best Doctor awards and Outstanding Teacher recognition.

In a nearby office, Dr. Lauren Hachmann Sansing, assistant professor of neurology, is looking at stroke in another way. Her research focuses on hemorrhagic stroke, the type that results from a ruptured blood vessel in the brain. "This type of stroke is devastating," she explains. "It affects two million patients a year, and only 50 percent survive it. People may become paralyzed, unable to speak and unconscious due to the mass of blood within the brain."

This intracerebral bleeding induces an immune reaction in the body in which white blood cells (leukocytes) travel to the brain in response to the injury. Unfortunately, this does further harm by causing brain swelling and actually worsens the cell death caused by the stroke. Sansing has obtained an NIH K08 grant – funds awarded to support the research of new physician-scientists – to study how this immune reaction can be prevented.

"Using a mouse model, we are measuring and quantifying how many leukocytes travel to the brain and how we could block them using certain anti-inflammatory drugs, such as arthritis drugs that target this cell population," Sansing says. "We are working to determine which

pathways are active in patients after a stroke, and we think we are onto something. We're using drugs already tested in humans, with good safety data, and so we already know the dosing. If we find efficacy in animal models, we can go right to safety in human studies."

Working to understand and treat this secondary wave of injury after a stroke is an interesting mix of the neurology and immunology courses that Sansing enjoyed as a student. She completed undergraduate studies at Cornell University, her medical degree at SUNY Stony Brook School of Medicine, and a master's in translational research (which involves converting scientific discovery into health improvement) at the University of Pennsylvania, where she also completed an internship, residency and fellowships in vascular neurology and translational medicine.

"We're hopeful about our work," Sansing says. "But there have been many, many treatments for stroke that have worked in animal models but failed to improve outcomes in patients. With the evolution of biomarkers studies and the ability to study proteins and activation in patients, we have a lot of insights into what we should go after as potential targets. Dr. McCullough and I have a large biobank of samples from stroke patients who have donated blood samples to help us study the disease. These samples help ensure that what we study in our animal models is important in our patients."

Both McCullough and Sansing are involved in active research while also seeing patients, and they say their studies are greatly benefitted by doing both. "It's like a big puzzle," Sansing explains. "We create a model, study it, go back to patients, then go back to research. Our overall goal is to someday say we have a new treatment that can make a difference in people's lives."