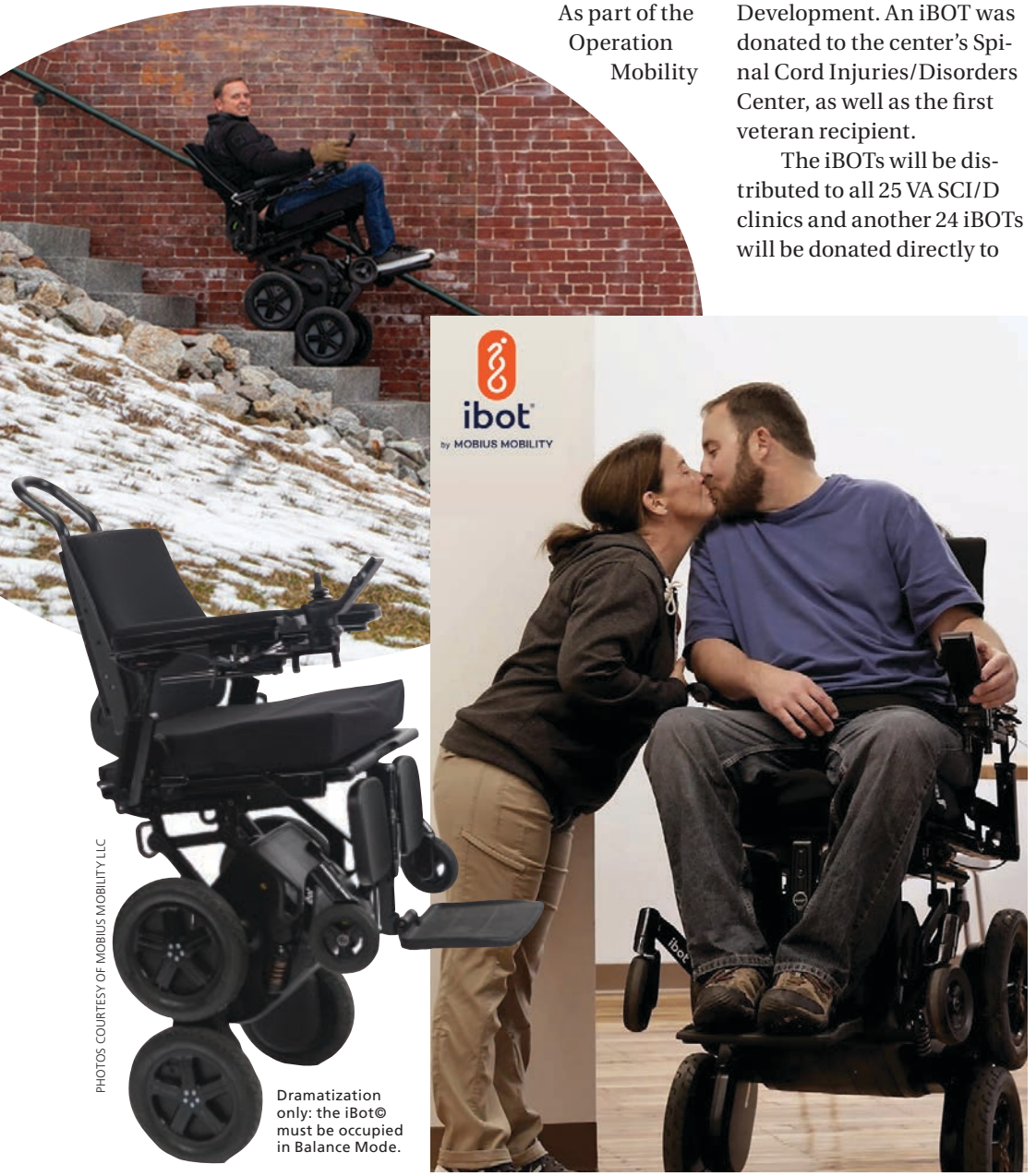
VA Receives iBOT Delivery

The Department of Veter-ans Affairs (VA) accepted a donation of 50 iBOT Personal Mobility Devices from manufacturer Mobius Mobility LLC, on May 27 to help veterans with spinal-cord injuries regain their autonomy.

The iBOT increases users' mobility by allowing them to independently elevate, interact at eye level, climb stairs and traverse varied terrain.

As part of the Operation Mobility Tour kickoff, Acting Deputy Secretary of Veterans Affairs Carolyn Clancy, MD, welcomed the first donation at the VA East Orange Medical Center in New Jersey from Dean Kamen, inventor of the iBOT and president of DEKA Research and Development. An iBOT was donated to the center's Spinal Cord Injuries/Disorders Center, as well as the first veteran recipient.

The iBOTs will be distributed to all 25 VA SCI/D clinics and another 24 iBOTs will be donated directly to veterans — as appropriately determined by the local SCI/D clinic — based on need, a clinical assessment and prescription.



PHOTOS COURTESY OF MOBIUS MOBILITY LLC

Dramatization only: the iBot© must be occupied in Balance Mode.

Promising ALS Therapy

Research on a potential therapy for amyotrophic lateral sclerosis (ALS) that's taking place in a University at Albany chemistry lab in New York is showing promising results.

Inspired by a mentor with ALS, Li Niu, a chemistry professor and researcher who is also affiliated with University at Albany's RNA Institute, has used his expertise as a biochemist and neurochemist to work on a National Institutes of Health-funded project aimed at developing a class of RNA molecules or RNA aptamers (molecules that bind to a specific target molecule) as potential drug candidates designed to block the death of the motor neurons that connect the brain to muscles.

"We're focusing on a particular group of receptors that are uniquely expressed in the brain and spinal cord, called glutamate receptors, which are responsible for things like memory, learning and are indispensable for brain development," says Niu.

There are several theories regarding glutamate receptors in ALS that

are helping to guide the research, says Niu. Some have to do with the amount or a higher activity level of the receptors, while another theory is that an abnormal receptor form is generated in motor neurons and these receptors, which are channel proteins, allow more calcium to get into the cells. This is a problem, says Niu, because too much calcium in a neurological context causes neurodegeneration and cell death; this is the theory from which his lab primarily works.

Working with many current and past graduate and undergraduate students in his lab, as well as an ALS physician and researcher at the University of Tokyo School of Medicine, Niu is developing RNA aptamers that aim to regulate the glutamate receptor activities and prevent calcium from getting into and accumulating inside the cells. His partner lab in Japan has been testing these RNA aptamers on an ALS mouse model, and the results thus far are promising. One of the RNA aptamers Niu developed is shown to be effective in stopping motor neuron cell death and rescuing dying neurons — and the animals are showing improved motor function following the aptamer treatment. The aptamer is not only effective, but it also does not cause any side effects when it is injected directly into the spinal cord.

"Before we bring the drug candidate forward for human trials, we have to do more testing," Niu says. "If we can confirm these are safe and do not induce side effects, we are hoping to receive funding to launch clinical trials to see whether we can bring this treatment forward."

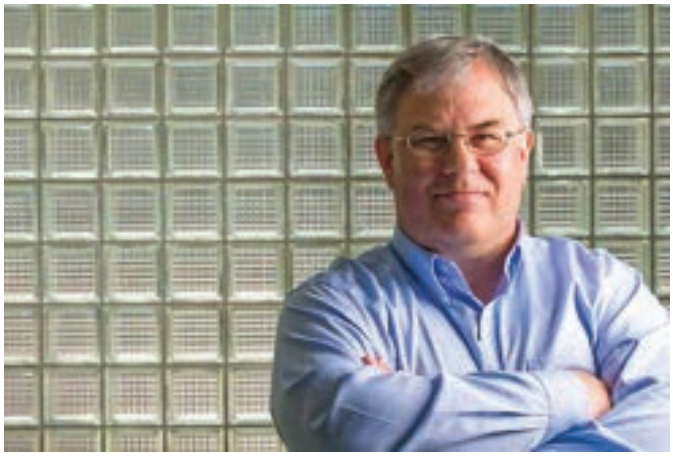
Metabolite Effects On MS

A new University of California, Irvine (UCI)-led study finds low serum levels of the sugar called N-acetylglucosamine (GlcNAc) are associated with progressive disability and neurodegeneration in multiple sclerosis (MS).

The study, done in collaboration with researchers from Charité – Universitätsmedizin Berlin, Germany, and the University of Toronto, Canada, is titled Association of a Marker of N-Acetylglucosamine With Progressive Multiple Sclerosis and Neurodegeneration. The study was published in *JAMA Neurology* in May.

The study suggests that GlcNAc, which has been previously shown to promote remyelination and suppress neurodegeneration in animal models of MS, is reduced in serum of progressive MS patients and those with worse clinical disability and neurodegeneration.

"We found the serum levels of a marker of GlcNAc was markedly reduced in progressive MS patients compared to healthy controls and patients with relapsing-remitting multiple sclerosis," says Michael Demetriou, MD, PhD, FRCP(C), professor of neurology, microbiology and molecular genetics at UCI School of Medicine and senior author on the paper.



COURTESY OF UNIVERSITY OF CALIFORNIA, IRVINE SCHOOL OF MEDICINE

Michael Demetriou, MD, PhD, FRCP(C), professor of neurology, microbiology and molecular genetics at the University of California, Irvine School of Medicine, is a senior author on a new study that found low serum levels of the sugar called N-acetylglucosamine (GlcNAc), are associated with progressive disability and neurodegeneration in multiple sclerosis.

"Lower GlcNAc serum marker levels correlated with multiple measures of neurodegeneration in MS, namely worse expanded disability status scale scores, lower thalamic volume and thinner retinal nerve fiber layer," says first study author Alexander Brandt, MD, adjunct associate professor of neurology at the UCI School of Medicine. "Also, low baseline serum levels correlated with a greater percentage of brain volume loss at 18 months."

GlcNAc regulates protein glycosylation, a fundamental process that decorates the surface of all cells with complex sugars. Previous preclinical, human genetic and ex vivo human mechanistic studies revealed that GlcNAc reduces proinflammatory immune responses, promotes myelin repair and decreases neurodegeneration. Combined with the new findings, the data suggest that GlcNAc deficiency may promote progressive disease and neurodegeneration in patients with MS. However, additional human clinical studies are required to confirm this hypothesis.

"Our findings open new potential avenues to identify patients at risk of disease progression and neurodegeneration, so clinicians can develop

and adjust therapies accordingly," says Michael Sy, MD, PhD, assistant professor in residence in the Department of Neurology at UCI and a co-author of the study.

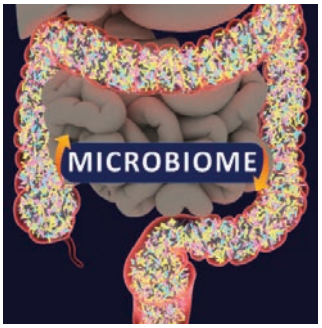
Changes In Gut Microbiome

For the first time, researchers at The Ohio State University have used metagenomics sequencing to identify changes in gut bacteria and viruses that occur after spinal-cord injuries (SCI) in mice.

Metagenomics allows researchers to better understand how the functions of diverse microbes and viruses relate by studying the collective DNA from a sample site, in this case, the gut microbiome of SCI-injured mice.

The study findings were published online in May in *mSystems*, an open-access journal published by the American Society for Microbiology.

"This is the first time that metagenomics has been applied in spinal-cord injury to characterize the persistent imbalance of the gut's microbial community, also known as gut dysbiosis," says Phillip Popovich, PhD, professor and chair of the department of neuroscience and executive director of the Belford Center for Spinal Cord Injury at The Ohio State University College of Medicine. "We're trying to better understand the gut microbiome and its potential health impact on people with spinal-cord injury, such as metabolic disease, cardiovascular dysfunction, decreased immune function, fatigue and mental health issues."



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During the study, researchers performed SCIs on the fourth thoracic spine (T4) or 10th thoracic spine (T10) in mice, then compared the results to mice receiving spinal surgeries without SCI, also known as "sham injuries."

Researchers found that SCI affects many different bacteria and viruses: some increase, some decrease and some are virtually depleted by the injury. Using metagenomic sequencing, scientists evaluated how SCI affects bacteria, archaea, fungi and viruses, and then predicted the functional consequences associated with these changes in the gut's microbial ecosystem.

Metagenomic analyses were performed on fecal samples from the mice that were collected at baseline and three weeks post-injury or post-surgery. The researchers discovered these results after SCI:

- The relative abundance of several beneficial bacteria decreased, while potentially pathogenic bacteria increased.
- Microbial genes encoding proteins for tryptophan, vitamin B6 and folate biosynthesis — the essential pathways for central nervous system function — were reduced.
- Viruses of beneficial bacterial hosts decreased, while viruses of pathogenic bacterial hosts increased.

"We're learning how the different levels of spinal-cord injuries will have distinct effects on the gut and the microbiome," says Popovich. "Although the microbiomes and viromes changed in all mice with spinal-cord injuries, some changes were notably enhanced in mice with higher level spinal injury. These findings are the first steps to developing therapies and treatments for humans in the future."

Study Looks At Sex, Genotype

Earlier this year, researchers at the University of Kentucky (UK) published the first study to focus on how genotype and sex differences in the human population may impact the response to treatment strategies for spinal-cord injuries (SCI).

Although many studies have previously examined treatment strategies that are effective at restoring function after experimental SCI, there is currently a lack of successful translation of these strategies from animal models to the SCI population. This led to the group's hypothesis that there may be factors in the human population, such as sex and genetic background, which alter individuals' ability to respond positively to treatments.

Lydia Strattan, a graduate student in the UK Department of Neuroscience, says to address this, the team utilized spinally injured male and female mice that express the human APOE gene.

"There are three versions of this gene and one version, known as e4, is infamous for being closely associated with the development of Alzheimer's disease and negative outcomes after traumatic brain injury," Strattan says. "However, APOE's impact on recovery after SCI has remained understudied. Therefore, we examined how the different variants of APOE influence the response to a promising therapeutic strategy known as intermittent hypoxia, which is currently in clinical trials for improving respiratory function

after SCI. We found that both APOE genotype and sex impacted the manner in which spinally injured mice respond to intermittent hypoxia treatment."

Ultimately, the study found that females that express the e4 allele of APOE had a negative response to intermittent hypoxia, indicating that treatment strategies may not be equally effective or beneficial for all individuals. This phenomenon could contribute to the historical difficulty of translating SCI therapeutics from the bench to the bedside.

> "Our results could help pave the way for personalized medicine in SCI and enhance the translational potential of treatments that improve functional recovery and, consequently, quality of life for injured individuals." — **Lydia Stratton**

When therapeutics are tested pre-clinically, they are typically evaluated for efficacy in a homogenous animal population. For example, rodent studies of SCI are often conducted in either males or females — not both — with similar genetic backgrounds. Since the data from this new study shows that both sex and APOE genotype can influence how individuals respond to treatment strategies, the researchers hope it emphasizes the importance of considering the human population's diversity when developing treatments pre-clinically.

"Our results could help pave the way for personalized medicine in SCI and enhance the translational potential of treatments that improve functional recovery and, consequently, quality of life for injured individuals," Stratton says.

Contributor: Hillary Smith/University of Kentucky. ■