Michael Kavanaugh, PhD, Director of the Center for Structural and Functional Neuroscience at the University of Montana since 2003, is McLaughlin Research Institute’s new director.

“Mike Kavanaugh’s scientific expertise, energy, and desire will make for a powerful leader of this long-historied Montana science institution,” said Dr. Leroy Hood, a longtime member of McLaughlin’s Scientific Advisory Committee and, among many other superlative titles, a winner of the National Medal of Science for his outstanding contributions to science and medicine.

As the fourth scientist/director to head the Institute in its 62 years, Kavanaugh joins a small, prestigious group including Carlson, Jack Stimpfling, and Ernst Eichwald.

Dr. Kavanaugh has had a long relationship with MRI. His Center for Structural and Functional Neuroscience has worked as a partner with McLaughlin over many years. He has attended annual science workshops at MRI and has presented his own research alongside MRI faculty, scientific advisory committee members, and other scientists.

“I’ve known him for ages,” said George Carlson at the time of Kavanaugh’s hiring. “I think he’ll be excellent.”

Dr. Kavanaugh studies the electrical signals between neurons, which is a very important aspect of any neurological disease.

“His work with electrophysiology, which records neuron activity in the brain, brings a new strength to the Institute,” Carlson said.

Dr. Kavanaugh’s research is focused on expanding the understanding of signaling processes in both healthy and diseased brains, with the goal of providing new approaches to treat neurodegenerative diseases, stroke, and brain injury.

“I see the addition of my work to the Institute as expanding on the research that has been going on here for a long time,” Dr. Kavanaugh said.

“I want to say how happy I am to be joining the McLaughlin Research Institute as director,” he said, “and how grateful I am to George Carlson for his stewardship over the past 28 years. He set a high standard of scientific rigor at MRI, and maintaining that is my top priority for the future. Next is making sure that the very talented scientists and staff of the Institute have the resources necessary to fulfill our research mission. This is an extraordinary time in the history of brain research - advances in neurophysiology, imaging, and genetics are providing scientists and physicians with exciting new tools and approaches to understand and cure neurological diseases.”

Dr. Kavanaugh came to the University of Montana in 2003 from the Oregon Health Sciences University (OHSU) School of Medicine, where he had been on the faculty for a decade. Before that, he received a PhD in Biochemistry from OHSU and was a postdoctoral fellow at the Vollum Institute there. He did his undergraduate studies at Washington University in St. Louis.
He has served on Neuroscience, Biophysics and Fellowship Review panels for the National Institutes of Health and is the recipient of research awards including a Klingenstein Fellowship in Neuroscience and a senior Wellcome Fellowship from Oxford University.

“In addition to its mission in research,” Dr. Kavanaugh said of MRI, “the Institute has a longstanding tradition of mentoring and encouraging young people by providing opportunities to get hands-on experience in science. Some of the eminent researchers on our Scientific Advisory Committee were influenced by their early experiences at MRI, and I want to continue and even expand our programs in outreach, and explore possibilities for partnerships with the University system and hospitals throughout the state.”

“I’m gratified to have the confidence and support of a dedicated and talented Board of Directors. I also feel very lucky to be able to rely on the advice of an extraordinary Scientific Advisory Committee—a group of truly visionary scientific leaders. The next 60 years is going to be a great journey for MRI.” McLaughlin celebrated its 60th anniversary in 2014.

Dr. Kavanaugh’s research is centered on electrical signaling in the brain and the roles of transporters and receptors in this process. Neurons communicate with one another by releasing different types of chemical messengers called neurotransmitters that transmit signals across a synapse, from one neuron to another.

Glutamate is the most common neurotransmitter in the brain, and when it binds to receptors it activates electrical signals that underlie fundamental processes ranging from visual perception to learning and memory. After activating receptors, neurotransmitters are cleared away by selective transporters, ending the signal.
Dr. Kavanaugh’s research focuses on transporters. He and his collaborators were first to identify the human genes encoding glutamate transporters, and to determine how these reuptake proteins work. Disruptions in glutamate transport and signaling are involved in many neurological disorders such as Alzheimer’s disease, epilepsy, and stroke.

His lab has recently identified the transporter for D-serine, an unusual neurotransmitter that works together with glutamate to activate NMDA receptors, a subclass of receptors involved in learning and memory. Recent findings suggest that mutant forms of this transporter cause cognitive and neurodevelopmental delays in children, and his group is working on developing new drugs that may provide a potential therapy.

They are also working to identify a transporter for neurotransmitters called endocannabinoids; an endocannabinoid-selective reuptake inhibitor could potentially reduce or eliminate the need for opiate use for pain relief. Endocannabinoids are naturally occurring molecules in the brain involved in processes including pain, mood, appetite, and memory; they activate the same receptors that cannabis does.

Dr. Irving Weissman of Stanford University’s Institute for Stem Cell Biology and Regenerative Medicine and chair of MRI’s Scientific Advisory Committee said, “Mike Kavanaugh brings to the McLaughlin Research Institute not only a first class research program in neurobiology—how brain cells communicate—but also a commitment to community service and making opportunities for young Montanans in high school and college to learn how information is obtained by becoming experimental scientists.”

Dr. Kavanaugh is no stranger to Great Falls; his wife, Larkin Bates Kavanaugh, grew up in Great Falls, where her parents still live. Her father is Leonard Bates and her mother is Janice Driver. The Kavanaughs have two sons.

Dr. Kavanaugh will maintain an appointment as professor at the University of Montana. He is an avid outdoorsman and enjoys mountaineering, skiing and, in the tradition of MRI, fly-fishing.

“It’s terrific to have Mike at the helm. He’s such a capable guy, who is already opening new doors for MRI to partner with other institutions and usher us into an exciting new era,” said Randy Gray, chair of McLaughlin’s Board of Directors.
Pre-clinical Changes Found in Huntington’s Disease Study

Huntington’s disease research at MRI has found early gene expression changes that occur well before signs of the disease appear, with the potential for identifying new targets for drug therapies. The results were published in the highly regarded journal Human Molecular Genetics in March 2017 by MRI’s Postdoctoral Research Associate Dr. Andrea Grindeland, her mentor Dr. George Carlson, and their collaborators. The extensive collaborative study involved a number of high profile scientists and institutions, many hundreds of transgenic mice from various strains, and several years of experiments and analysis.

As Dr. Grindeland points out, “Understanding this early part of the disease progression could make a big difference. Early is always better, regarding potential therapies, before neuron loss happens.” According to Dr. Carlson, “These results could be among the first documented pre-inflammatory changes in a neurodegenerative disease.”

Huntington’s disease is a genetic degenerative brain disease that attacks both a person’s physical and mental abilities, usually beginning between ages 30 and 50. Every child of a parent with HD has a 50/50 chance of carrying the genetic mutation that causes the disease. Huntington’s became better known in the U.S. when it struck legendary folk musician Woody Guthrie in the 1950s; he died from it in 1967.

Huntington’s belongs to the same class of protein misfolding disorders studied at MRI as Alzheimer’s and other dementias, Parkinson’s, and the traditional prion diseases. The diseases are distinguished from one another by the particular variety of protein whose misfolding causes the disease to spread through the brain in a cascade of dying neurons. The protein that misfolds in HD is called the huntingtin protein.

Dr. Grindeland is co-first author of the paper. She worked in former MRI director George Carlson’s lab for six years and has now begun work for his successor, Mike Kavanaugh. Her large role on this project included experimental design of mouse models and their production, microdissection of different brain regions, and assessing localization of the huntingtin protein to the cell nucleus.

Dr. Grindeland shares lead authorship of the paper with two young scientists training at the Institute for Systems Biology (ISB), Seth Ament and Jocelynn Pearl, who performed the computational analyses. Leading Huntington’s disease experts Marcy MacDonald and Vanessa Wheeler from Harvard Medical School’s Massachusetts General Hospital are senior co-authors, as are systems biology pioneer Leroy Hood and Nathan Price, both from ISB, and Dr. Carlson, now at the University of California, San Francisco, whose mouse genetics and prion disease expertise brought the group to him and MRI.

Other institutions partnering in the collaboration included Johns Hopkins University, University of Maryland School of Medicine, and the University of Washington. The CHDI Foundation, which works to discover drugs that delay the progression of Huntington’s, learned about the project and provided funds that allowed the study to be expanded.

Dr. Jeff Carroll at Western Washington University was another collaborator on the project. Dr. Carroll is prominent among Huntington’s researchers, and he spoke about his unique perspective on HD research at MRI in 2015. He studies the disease because his grandmother and mother died from it, and he carries the inherited genetic mutation that means he, too, will succumb to Huntington’s unless a way to prevent disease progression is discovered.

The group looked at the expression of genes in very young mice. Most HD research is done on older mice, after the progression of the disease is more advanced. Looking at the very early mice allowed the scientists to look at more subtle deviations in cellular functions that reflect the disease process, such as mislocalization of the huntingtin protein to the cell nucleus, and to identify possible mechanisms of the disease. The end result amounted to a signature for the disease “involving hundreds of differentially expressed genes and changes in diverse molecular pathways,” according to the paper.

“It was a really exciting project,” Dr. Grindeland said. “We all brought our different strengths to this huge, grand project. I thought it was cool that we could link gene expression with some of the early biochemical changes seen in young mutant mice,” she said.
George Carlson Maintaining Lab at MRI

When Dr. George Carlson resigned as director of McLaughlin Research Institute in December to accept a position as visiting professor at the University of California, San Francisco’s Institute for Neurodegenerative Diseases, he maintained an appointment as Affiliate Professor at MRI.

He oversees a couple of ongoing projects in his McLaughlin lab remotely, and there are others on the horizon.

In his new position, he is also fostering collaborations between UCSF’s Institute for Neurodegenerative Diseases and MRI.

Dr. Carlson has joined McLaughlin’s Scientific Advisory Committee, through which he will remain involved in the oversight of MRI’s research mission along with his esteemed colleagues: Irving Weissman (Chair), David Baltimore, David Cameron, Neil Copeland, Jeffrey Frelinger, Leroy Hood, and Nancy Jenkins.

MRI Plans Clinical Research Site

McLaughlin Research Institute is making plans to establish a site for clinical research into the treatment and prevention of Alzheimer’s disease at its facility in Great Falls.

The project will focus on clinical studies of genetic, metabolic, and behavioral factors that may influence the onset, progression, and prevention of Alzheimer’s disease. The clinical site will make use of existing space in the facility and will complement MRI’s current basic research focus, which will continue in the laboratories.

“We’re excited about this new project that will usher McLaughlin into the era of translational research – applying what is learned in the lab to patients in a clinical setting – and will more directly affect people’s lives,” Director Michael Kavanaugh said. “We will leverage our basic research strength and provide a unique resource in Montana to enhance brain health through outreach and education.”

In collaboration with MRI’s partners from the Institute for Systems Biology and the Easton Center for Alzheimer’s Disease Research at UCLA, McLaughlin plans to participate as a trial site in a multi-arm study.

The ultimate goal of the project is to develop approaches to prevent or delay the onset and progression of Alzheimer’s disease.

Growing evidence suggests that a complex set of molecular interactions is involved in Alzheimer’s disease. Although effective treatments are still lacking, recently published and unpublished studies from systems biology groups, including MRI’s collaborators, have provided preliminary data suggesting new approaches that may slow or potentially reverse the disease progression. However, there is a pressing need for rigorous clinical trials to evaluate these systems approaches involving multiple factors.

Longtime MRI Scientific Advisory Committee member Leroy Hood pioneered the field of systems biology. It involves the computational and mathematical modeling of complex systems of biological components.

Systems biology also relates to research Dr. Kavanaugh’s lab has carried out on the neurophysiology of learning and memory and the biochemical changes in the human brain that occur in early Alzheimer’s disease.

According to Dr. Hood, “This project is a natural outgrowth of the research strength of McLaughlin and its focus on neurodegenerative diseases, and I’m excited about our collaboration.”

Dr. Hood played a major role in the Human Genome Project, and since then has turned to applying the genetic information it made available to improve human health through predictive, preventive, personalized and participatory medicine. He calls this P4 medicine, the clinical face of systems biology.

Other partners in the project to date include Translational Health Sciences at the University of Washington; Department of Psychiatry and Behavioral Sciences at the University of Washington School of Medicine; Montana Chapter, Alzheimer’s Association; CostCare Family Practice Clinic of Missoula; Providence Health & Services and the Montana University System.

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Summer Interns Study Mouse Brains

Sophia Skwarchuk, now a senior at Flathead High School in Kalispell, and Lindsay Martinez, a sophomore at Princeton University, spent the summer of 2016 at MRI studying elderly mouse brains for signs of dementia.

Under the direction of associate research scientist Dr. Andrea Grindeland in George Carlson’s lab, the two students worked with transgenic mice engineered with a human form of a protein called tau to develop frontotemporal dementia. Tau, associated with Alzheimer’s and other dementing diseases, shows up in the brain in the form of neurofibrillary tangles.

As Lindsay and Sophia explained to the audience at their presentation in August, these mice have none of the plaques associated with Alzheimer’s, although MRI does have mice with plaques, too. The elderly mice, at 20 months old, were older than most mice studied at MRI or elsewhere.

The students’ main objective was to determine whether the transgenic mice were expressing the human tau, and if so, in which parts of their brains. They did find that the mouse brains they studied expressed the human tau in some unexpected portions of the brain, which raised some questions.

They explained that their experiment for the summer fit into the overall question of what makes a good model for humans with Alzheimer’s. One of the lab’s goals has been to make a better mouse model for Alzheimer’s in order to test drugs to stop brain cells from dying.

“My experience at McLaughlin was very meaningful because it showed me the complexity of lab research that is impossible to grasp without being actively involved in it,” Sophia said of the internship. “I am so grateful to have had this opportunity and it helped me better understand what I want to pursue in the future!”

Lindsay was glad to be able to gain experience in her area of interest while home in Great Falls after her first year at college. “I was lucky to have the opportunity to be involved in a research project this summer which has as a goal developing a better mouse model for human Alzheimer’s disease.”

See the adjacent article on the Montana Science Teachers Award to learn more about MRI’s education program.

The 2016 summer internship program was supported by the George & Sybil Upton Scholarship Fund and generous donations from Mr. Howard Bethel, Ms. Judy Birch, Mr. & Mrs. Donald Dirks, and The Windmill Foundation.
McLaughlin Research Institute’s scientists, collaborators, and staff are dedicated to biomedical research focused on neurodegenerative brain diseases such as Alzheimer’s, Parkinson’s, and Huntington’s. Our vision for the future is to connect research in the lab to clinical practice that will directly benefit dementia patients.

In order to fuel and sustain this important work, we rely on private charitable contributions.

Unrestricted gifts provide flexibility and support for the Institute’s current operating budget. This helps bridge the gap between research revenue and the core research and support costs of operating an independent research facility. Gifts can be made to support research, the summer student program, clinical research, the endowment, and special projects as well.

For more information, please go to our website: mclaughlinresearch.org and click on Support MRI and then Ways to Give.

Your gift will help us continue our proud tradition of improving human health through innovative genetic research and education.

If you have any questions, please call Ginny Abbott, Development Director, at 406.452.6208.

Thank you for your thoughtful consideration.
It’s a New Era at McLaughlin Research Institute

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