Dementia is the loss of cognitive and intellectual functions, without impairment of perception that can be caused by a variety of disorders, the most common of which is Alzheimer’s disease. Dementia is characterized by decline in memory, disorientation, and impaired ability to make sound judgments. In dementia, the decline in cognitive ability interferes with daily life. It is important to distinguish progressive dementia caused by neurodegenerative diseases from conditions causing dementia-like symptoms that may be reversible.

Benefis Health System and McLaughlin Research Institute
Teaming Up Against Alzheimer’s Disease

Great Falls, Montana, is represented by one of the most iconic partnerships in American history: that of Lewis and Clark. Each man brought unique skills and talents to their exploration of the American west, and together they profoundly altered the course of our nation’s history. Now, more than 200 years later, the focus of scientific exploration in Great Falls has turned inward, to the geography and hidden networks of the human brain.

Alzheimer’s disease (AD) and related dementing disorders are major public health issues that will increasingly affect the wellbeing of our aging population and our community. According to the Alzheimer’s Association’s most recent report, it is estimated that 1 in 3 people will be suffering from AD or another dementing disease at the time of their death. These diseases place enormous emotional, physical, and financial stress on patients and their families, in addition to placing a tremendous strain on the health care system. Benefis Health System (BHS) and the McLaughlin Research Institute (MRI) are responding to the challenges posed by the increasing prevalence of diseases of the aging brain.

BHS is currently establishing the Grandview continuing care retirement community, which will include independent living units, as well as assisted living and memory support cottages. While the physicians and staff

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“I am proud to honor these inspiring American innovators. They represent the ingenuity and imagination that has long made this Nation great.”  –Barack Obama

Dr. Lee Hood with President Obama

MRI Advisors Honored by Scientific Awards

Dr. Leroy Hood, a founding member of McLaughlin Research Institute’s Scientific Advisory Committee, was awarded the National Medal of Science by President Obama at the White House on February 1, 2013. Dr. Hood received America’s highest scientific honor “For pioneering spirit, passion, vision, inventions, and leadership combined with unique cross-disciplinary approaches resulting in entrepreneurial ventures, transformative commercial products, and several new scientific disciplines that have challenged and transformed the fields of biotechnology, genomics, proteomics, personalized medicine, and science education.” Dr. Hood, who is director and president of the Institute for Systems Biology in Seattle, has presented many lectures at McLaughlin Research Institute and continues to collaborate with Institute scientists.

Dr. James Spudich, who served on MRI’s Scientific Advisory Committee and continues to work with McLaughlin Professor John Mercer, was one of three scientists honored by the 2012 Albert Lasker Basic Research Award for “discoveries concerning cytoskeletal motor proteins, machines that move cargoes within cells, contract muscles, and enable cell movements.”

The Lasker Awards are among the most respected science prizes in the world and frequently presage future recognition by the Nobel committee, so they have become popularly known as “America’s Nobels.”

Dr. Spudich studies molecular motors at Stanford University, but also has a lab at the National Center for Biological Sciences (NCBS) in Bangalore, India; Dr. John Mercer is currently on loan from MRI to NCBS to work with Dr. Spudich.

Lee Hood and Nobel Laureate David Baltimore (another Scientific Advisory Committee member) have been previously honored with Lasker Awards.

2012 Lasker Award winner
Dr. Jim Spudich

Artist Steve Seltzer Signs Prints for Biomedical Science

In 1928, the Great Falls Clinic commissioned renowned western artist O. C. Seltzer to produce a series of paintings that traced the development of Montana. The Rear Guard, a scene of bison, captures Montana before civilization; The Medicine Man honors its native culture; The Coming of the White Man and The Foothills Nester depict the inroads made by settlers. In honor of the Clinic’s 75th Anniversary, its doctors used Seltzer’s artwork to aid yet another stage of Montana’s development—emerging leadership in biomedical research.

The physicians donated the rights to their favorite of the pieces, The Medicine Man, to McLaughlin Research Institute in 1992, and a limited edition of 499 prints was produced. Income from the prints has assisted the Institute in recruiting additional scientists and purchasing specialized equipment.

Last fall Seltzer’s grandson, prominent Great Falls artist Steve Seltzer, signed and numbered the remaining prints. Funds raised from the sale of these prints will assist the Institute in supporting its mission to improve human health through innovative genetic research and education.

Each limited edition print (24” x 32”) is available on request for a contribution of $100 or more.

Check out our support page at www.mclaughlinresearch.org or call 406.454.6024

Dr. James Spudich

Dr. Leroy Hood with President Obama
As part of the international collaboration between the McLaughlin Research Institute, Stanford University and the new Institute for Stem Cell Biology and Regenerative Medicine (inStem) in Bangalore, India, Sherry Turner, a transgenic technician at MRI, traveled to Bangalore last fall to teach her skills to staff and students at inStem.

Sherry’s teaching stint came at the request of MRI’s Dr. John Mercer, who is on loan to inStem, where he is helping James Spudich of Stanford University establish a lab on molecular motors and heart failure. Dr. Spudich is a former member of MRI’s Scientific Advisory Committee and winner of the prestigious Lasker Award in 2012.

Sherry, who has worked with mice at MRI since 1989, taught technologies such as sperm cryopreservation and in vitro fertilization (IVF) to the inStem scientists so they can use transgenic mouse lines as models for human disease, as MRI does. She also taught the skills to the students so they will be able to resurrect their own frozen mouse lines for future research.

She spent one week establishing the technologies with the scientists and taught twelve students in a three-day course. Her teaching activities focused on IVF, harvesting embryos, raising stock mice, and freezing a mouse line with a gene of interest. She was excited by the results. “On the third day we looked at the embryos from the IVF we had done. We saw two-celled embryos, showing that there was fertilization and that the IVF worked. We used the sperm that was frozen on the first day to make sure that we could resurrect the strain.”

As Sherry explained, “Learning these methods will mean the lab won’t have to depend on receiving or sending live mice elsewhere, and it is much easier and cheaper to ship frozen sperm and embryos. Also, it is advantageous to have a person on site that serves as the transgenic technician and can do the mouse surgeries.”

During a recent presentation to MRI staff, Sherry described her experiences complemented with a colorful set of photos. “The highlight of my trip was spending time in Srinagar (in Kashmir) with the family of one of my students. We toured the area, seeing a glacier and the top of the ski slope at 13,054 feet. I saw mountaintops that seemed to go on forever. I caught four rainbow trout in a mountain pond and was the subject of many Indian tourists’ photos.”

I’ve been on four trips to Europe and the Middle East and this trip by far was the most exciting adventure. Every meal was an adventure since I didn’t have a clue what I was choosing to eat. I feel extremely blessed to have been able to experience the Indian culture.”
Parkinson’s Disease: Promising Developments in Cabin Lab

Dr. Deb Cabin explains her enthusiasm for a recent discovery in her laboratory at MRI.

My lab studies alpha-synuclein, a protein that is associated with Parkinson’s disease in humans. Parkinson’s appears to depend on a combination of a person’s genetic background and one or more environmental factors. One hypothesis is that a person with a susceptible genetic background, if exposed to some chemical in the environment, will develop Parkinson’s. It is possible that exposure to certain chemicals can increase the amount of alpha-synuclein protein in the brain, leading to disease.

Alpha-synuclein is similar in all the vertebrate species, and there are only a few differences between the mouse and the human alpha-synucleins (Fig 1). We are using these mouse-human differences to decipher how the human protein can cause Parkinson’s by generating alpha-synuclein variants in the lab.

We have several methods to test all our different versions of alpha-synuclein. The fastest test is to ask whether a version of alpha-synuclein can inhibit the growth of yeast, a single-celled organism that is widely used in biology research. Using this test, we found differences among several of our modified versions of alpha-synuclein, identifying some amino acids that affect the toxicity of the protein.

Next, we wanted to test the effects of these versions in the brains of mice. We can express human proteins in mice by a procedure called transgenesis, but making transgenic mice takes a long time and is expensive.

Fortunately, a recent finding from the University of Pennsylvania provided a quicker way of testing all our alpha-synuclein variants in the mouse brain. In that study, purifying alpha-synuclein protein, leaving it in a test tube until it took on a change in shape associated with disease, and then injecting it into a mouse brain caused pathology that spread from the injection site. This means that alpha-synuclein acts like a prion, the cause of chronic wasting disease, mad cow disease, and similar diseases in humans and other animals. Prions cause disease when a normal protein in the brain “misfolds,” or changes to a shape that is bad for neurons, and then that misfolded form spreads from neuron to neuron.

Given the expertise of the Carlson lab in studying prions, we were able to quickly begin using this method to test our different versions of alpha-synuclein. So far, we have results on the two variants that inhibited growth in yeast the most. One of these variants causes disease in our injected mice much more quickly than does the normal mouse alpha-synuclein protein. This means we have identified a part of the alpha-synuclein protein that is probably important in the misfolding process.

We have experiments planned to determine the misfolding rates of our alpha-synuclein variants, and we will see if those rates correlate with how quickly the variants cause the development and spread of brain pathology in mice (Fig 2).

Understanding how alpha-synuclein misfolds will be helpful in designing tests to analyze and screen drugs that will prevent the protein from taking on harmful shapes. Such drugs may work to prevent the spread of alpha-synuclein pathology through the brain in Parkinson’s disease.

Figure 1

Alignment of human and mouse alpha-synuclein proteins

<table>
<thead>
<tr>
<th>Human</th>
<th>Mouse</th>
</tr>
</thead>
<tbody>
<tr>
<td>A30P</td>
<td>A30P</td>
</tr>
<tr>
<td>E46K</td>
<td>E46K</td>
</tr>
<tr>
<td>A31T</td>
<td>A31T</td>
</tr>
</tbody>
</table>

- mutations that cause autosomal dominant Parkinson’s disease
- amino acid differences between human and mouse alpha-synucleins

Figure 2 – A Control nervous system tissue shows no response to injection of solution with no alpha-synuclein. B Severe reaction by astrocytes—Darkly stained cells demonstrate a condition called astrogliosis that appears upon insult to the nervous system. This is seen in mice injected with misfolded alpha-synuclein, not in the control mice. C Alpha-synuclein aggregates (arrowhead) are only seen in nervous systems of mice injected with misfolded alpha-synuclein. This aggregate is found far from the site of injection.
A Day in the Life of an MRI Scientist

Brenda Canine is a postdoctoral fellow in the Carlson lab at MRI, where she applies her engineering and pharmacology backgrounds to finding biomarkers to detect Alzheimer’s and prion diseases. Dr. Canine juggles five or six projects at a time.

The one I’m focusing on right now is called GPM6A, which seems to be an early indicator of prion disease.

**Data entry.** Roughly 50% of my time goes to data entry and analysis. I think interpreting data and finding something meaningful is probably one of the hardest things about research. In this high tech information-rich era, you have to be able to sift through an enormous amount of data and filter out all the noise. This is where my engineering background makes a difference. Much of what engineers do is take a bunch of data and model it, and the point is to have a product that works. When you bring that background to a research environment, it helps to see that while it’s always interesting to find something, if you can’t apply that in a meaningful way, all the data collection in the world won’t get you anywhere.

I’ve always wanted to be part of something where we’re effecting a change in something. Here at MRI we’re looking at the neurodegenerative diseases that are having a huge impact on lots of different families, and if we can understand what’s going on and maybe even find some new diagnostic or eventually a therapeutic for that, then that’s really exciting.

**Glow-in-the-dark mice?** Our live imaging system allows me to follow a live animal through the entire course of prion disease progression by taking images at every stage of the same animal. This is a helpful way to identify the genetic markers that indicate the early stages of the disease. [Dr. Canine’s images of mice, above, wearing miniature earmuffs to minimize ear-interference, are famous around the institute for their luminescent brains.]

**Nair for mice?** Problems will arise during imaging, so I have to solve those. Yesterday I was trying various methods of hair removal with the mice so the light signals from the imaging system will show up better. Another postdoc and I were trying shaving and plucking. Someone suggested Nair (a hair removal product), which is next on the list to try as long as we can get approval from our institutional animal care and use committee.

Through all this, Dr. Canine says, “You’re always thinking, making connections between projects.” She’s also communicating with collaborators at the Institute for Systems Biology in Seattle or the Prusiner and De Armond labs at UC San Francisco. And then there’s the constant job of looking for funding and writing grants to keep the work going and to keep your job. “It’s such a tough time for research funding,” Dr. Canine lamented. “That makes it a hard time to be a scientist, but I feel fortunate that I love my job.”

“"The work of a laboratory researcher takes a tremendous amount of planning, and multi-tasking is a valuable skill," she explains. "Every day is different. You have to be very flexible, ready to switch gears according to the outcomes of experiments. And experiments don’t work most of the time.”

**Here’s a glimpse of her typical day:**

**Pregnant mice?** The first thing I do in the morning is to check the mice breeders I’ve set up to see if there are any pregnancies. If there are, that means in two weeks I can get stem cells from the resulting embryos to start new stem cell cultures.

**Feed the stem cells.** I make stem cell culture models from the mouse embryos and grow them in an incubator. I need to feed them every couple of days and check them for contaminants. When they’re ready, I’ll infect them with prions and then look for proteins we’re interested in.
Educating Tomorrow’s Scientists, From Cut Bank to India

Last summer the reach of MRI’s education program extended across the country and beyond, from Berkeley to Boston, from Baylor to Brown University, and even from Cut Bank, MT to India.

Rafael Broh is a junior at Colorado College who learned about MRI from a prominent researcher and family friend in his hometown of Boston. He described his excitement about working in the Carlson lab over the summer. “I learned so many things, instead of reading and hearing about them,” he said.

“We’re performing the actual troubleshooting rather than the predetermined “cookbook” labs at school. It’s really neat to see what’s going on and not necessarily getting the expected result.”

In addition to Rafael, four college students from Montana, studying at UC Berkeley, Baylor University, and the University of Montana worked in MRI’s labs to solve scientific problems and learn what research is all about.

Four Great Falls High and C. M. Russell High School students also had the opportunity to test drive a career in research in those same labs, and four high school teachers learned alongside them. The teachers’ enthusiasm then stimulates interest in science among scores of students in their classrooms.

Allyson Hoof, a science teacher at Cut Bank High School and Rachael Newmiller, a Biology/Advanced Biology teacher at Chouteau High, spent last summer in research labs and will spend this summer working with other teachers at MRI to integrate their lab experience into the curriculum. One of the goals for the teacher internship program has been to attract teachers from the surrounding areas.

Last year was the first year MRI had teachers from rural communities apply to the program. Allyson is glad her participation in the program is offering rural students more exposure to the world of science. “I think we need to step it up a bit and not assume that the kids in our smaller school system won’t be interested in science careers,” she said. “Just letting them know that a place like MRI exists here is important; it’s pretty amazing.”

At the same time that the program drew in teachers from smaller schools outside Great Falls, it also attracted a teacher from India who was teaching underserved students on an Indian reservation in Grants, New Mexico. It was the unique combination of programs for high school students, high school teachers, and college students that attracted Kiran Satyavarapu to MRI’s education program.

“The students and teachers working together in the same lab is completely unique among programs of this kind,” he said. He would love to someday start a charter school for underprivileged students in India based on things he is learning in the U.S.

Rafael Broh

This two-year program for teachers has been funded by a six-year grant from the Howard Hughes Medical Institute (HHMI). This HHMI program will come to an end this summer. Teachers are still welcome to work in the research labs at MRI but will need to apply for their own funding from programs such as the M. J. Murdock Trust’s Partners in Science program. Interested teachers are encouraged to contact one of the principal investigators at MRI to request a sponsorship.

With the HHMI funding drawing to a close, the high school and college students will now be funded by generous philanthropy and the George & Sybil Upton Scholarship Fund, which has supported the college students in the past. Great Falls Public Schools Superintendent Cheryl Crawley, who attended the students’ presentations at the end of the summer, stressed the importance of continued funding for the program. “It’s amazing what an incubator this place is, and we need to keep growing it. We can’t ignore the pipeline if we want to continue to produce scientists in this country.”

One of those scientists-in-training is Great Falls High senior Jourdon Gudatis. He was engaged enough in his MRI summer project to complete the data collection as a volunteer during the fall school term. He used a live imaging system to monitor the progression of prion disease in a mouse. “After spending 12 years in the classroom just learning things – and very little of that time is spent doing real life applications – to be able to conduct real research that is going to contribute to the scientific community, that’s pretty sweet,” he said.
Ways of Giving to MRI
Charitable contributions made to MRI help fuel and sustain innovative, and collaborative research and education in our community. Your assistance can help support our research now so we can help patients in the future.

Together with our collaborators (Drs. Lee Hood, Brad Hyman, and Irv Weissman among them), we are building an unparalleled understanding of the processes causing degenerative brain diseases such as Alzheimer’s and Parkinson’s. Our vision for the future is to connect the research to clinical practice that will directly benefit dementia patients locally and nationally.

If you know someone suffering from Alzheimer’s or Parkinson’s disease, you will be glad to know biomedical scientists at McLaughlin Research Institute are working on research that may lead to treatments or a cure.

Consider funding research and education on Alzheimer’s, Parkinson’s and related brain disorders at the Institute through:
- Current gifts of stock
- Life insurance policies or other assets
- Memorial or Honor Designations
- Personal Will or Trust
- Cash Donations

For further details and how to apply for the M.J. Murdock Charitable Trust’s Partners in Science Program:
www.murdock-trust.org/grants/partners-science.php
Please visit:
www.mclaughlinresearch.org/education/science-teacher-program

Summer Internships for high school and college students begin Wednesday, June 12, 2013 and end Wednesday, August 14, 2013.

Past Events Since August 2012

8/21/12 Annual Biomedical Sciences Workshop
9/10/12 Tour: Kim Gillan & Press Announcement: Steve Bullock Campaign
9/12/12 Seminar: Nobuko Uchida PhD
Vice President, Stem Cell Biology; StemCells, Inc. Therapeutic Potential of Human Neural Stem Cells
10/18/12 Cascade County Legislative Open House
10/11/12 Seminar: Tara Spires-Jones, D-Phil
Assistant Professor of Neurology, Harvard Medical School; Assistant in Neuroscience, Massachusetts General Hospital. rTg4510 and rTGtauEC Models: Lessons about the Role of Tau in Neurodegenerative Disease
12/17/12 Seminar: J Riley McCarten MD
Medical Director and Staff Neurologist, Geriatric Research, Education and Clinical Center (GRECC), Minneapolis VA Health Care System; Medical Director, The Memory Clinic, University of Minnesota / N. Bud Grossman Center for Memory Research & Care (CMRC); Associate Professor, Department of Neurology, University of Minnesota Medical School Identifying Dementia in Primary Care

12/19/12 Lunch Meeting: Cascade County Elected Officials
1/17/13 Tour: Leadership Great Falls
1/22/13 Seminar: Joe Nadeau PhD
Pacific Northwest Diabetes Research Institute, Seattle. Mendel 2.0: Epigenetic Inheritance, Phenotypic Variation and Disease Risk
2/6/13 Tour: Fort Benton High School AP Biology
3/7/13 Seminar: Raghu Padinjat MB BS PhD
Associate Professor, National Centre for Biological Sciences, Bangalore, India. Regulation of Multiple Pools of P1(4,5) P2 in Neuronal Cells
3/27/13 Application deadline for summer student internships

To find out more about Institute events, including public lectures and seminars, please visit www.mclaughlinresearch.org or call 406.454.6024

MRI Upcoming Events
4/17/13 7pm Cameron Auditorium, Benefis Health System. Film screening: Rare, a mother’s quest for a cure for her daughter’s rare disease. Followed by a discussion on ethical issues in human clinical research led by Jeanne Chowning MS, Director of Education, Northwest Association for Biomedical Research
4/25/13 5:30pm Cameron Auditorium, Benefis Health System. Seminar: Karen Ashe PhD, Director, N. Bud Grossman Center for Memory Research & Care; Edmund Wallace & Anne Marie Tulloch Chairs in Neurology and Neuroscience, University of Minnesota Medical Center
8/14/13 Public Lectures: MRI Summer Student and Teacher Interns
of BHS Senior Services are dedicated to providing a wide range of care for elderly patients, scientists at MRI are successfully using mouse models to advance understanding of Alzheimer’s disease and similar disorders. These models, in combination with advances in genomics, systems biology, and stem cell science, can lead to new, pre-symptomatic diagnostic tools and therapies for patients.

Together, MRI and BHS are in a unique position to develop The Montana Center for Aging Research & Memory Care in Great Falls focused on Alzheimer’s disease and related disorders. This Center will provide enhanced diagnosis of early stage dementia, and, for interested individuals, the opportunity to participate in scientific studies and, eventually, clinical trials. Work toward the development of the Center is underway.

BHS has already begun implementation of standardized screens by BHS physicians for early signs of dementia, the logistics of record keeping, and estimation of numbers of patients over age 65 who might be interested in participating in scientific studies.

Even though there is no treatment for AD or other dementing disorders, patients and their families benefit from early diagnosis of the condition by having time to plan for the inevitable decline, by improving medication compliance resulting in fewer ER visits, and by utilizing the resources available through Benefis Senior Services.

MRI will expand ongoing work with Dr. Leroy Hood at the Institute for Systems Biology in Seattle using mouse models to identify disease-associated protein markers in the blood that could identify pre-clinical disease in people. MRI will also develop expertise in isolation of stem cells from patients and healthy volunteers to extend the collaborative studies with Dr. Irv Weissman at Stanford, and others, on use of human stem cell transplants in mice to understand disease mechanisms. MRI is actively seeking philanthropic and government support for these preliminary studies.

BHS and MRI share the goal of helping to understand, prevent, and treat neurodegenerative diseases that can accompany aging. The cooperative alliance between the two organizations is exciting and will meld each organization’s strengths to the direct benefit of patients now and in the future.

The Benefis Health System and the McLaughlin Research Institute collaboration, which may be the first of its kind between an independent research institute and a not-for-profit community health system, will address the growing problem of dementia in American seniors. In addition to advancing patient care and research, it will provide new jobs and educational opportunities to the Great Falls community.

Like the farming and ranching families across Montana, Benefis Health System and the McLaughlin Research Institute have deep roots and even deeper loyalties to the Great Falls community. The Montana Center for Aging Research & Memory Care will advance the missions of both organizations and, more importantly, will contribute to curing or preventing Alzheimer’s disease and other dementing illnesses.