

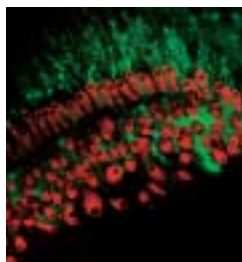


NEUROLINK

News from The Montana Neuroscience Institute Foundation

Spring 2005

At the Edge of Hearing Montana Neuroscience Institute Researchers Explore Cochlear Implants and Gene Therapy



"Green fluorescent protein expression in support cells (green) of mouse cochlea. Hair cells are stained red."

Translational research, or research that bridges bench neuroscience with new treatments in clinical medicine, is at the heart of the mission of The Montana Neuroscience Institute. MNIF-based researchers Dave Poulsen, Peter VonDoersten, and Diana Lurie are three scientists working to realize that vision.

Through a unique collaboration, Poulsen, Director of the MNIF Molecular Medicine Laboratory, VonDoersten, a neuro-otologist, and Lurie, a University of Montana neuroscience researcher, are using lab-based gene therapy techniques and specialized surgical procedures to design a highly innovative gene therapy application that could have a profound impact on the treatment of hearing loss. Using a special cochlear implant device, genes could potentially be effectively delivered directly to delicate support cells in the inner ear.

Inside the cochlea of the ear, there are small hair cells that move when sound waves create motion, and through that motion, they tell the neurons to send messages to the brain, causing us to be able to hear. Hair cell loss is common with age and is associated with hearing loss. Hair cells, once lost, cannot regenerate themselves. Thus, the therapy being designed by Poulsen and VonDoersten is directed at delivering a gene therapy directly into the support cells of the ear to grow new hair cells. If the experiments being done in animals work, trials could then be developed to test this technique in humans.

The gene therapy technique Poulsen has developed involves using a common virus called Adeno-Associated Virus (AAV). This virus does not cause any symptoms, but serves as a vehicle to carry genes to specific areas in the body where they might be needed. The genes that are then carried by the virus are specially designed in the laboratory to address particular diseases, such as in this case, hearing loss.



Dave Poulsen and Peter VonDoersten in the MNIF Molecular Medicine Laboratory at St. Patrick Hospital and Health Sciences Center.

About the Montana Neuroscience Institute Foundation

Founded in 1998, The Montana Neuroscience Institute Foundation (MNIF) is a unique collaborative partnership between St. Patrick Hospital and Health Sciences Center and The University of Montana. The mission of the Institute is to promote the integration of neuroscience research and patient care to help those afflicted with diseases of the nervous system.

The MNIF conducts basic, clinical and translational research covering a wide spectrum of neurological diseases. Through a strong affiliation with the NIH Center of Biomedical Excellence in Structural and Functional Neuroscience (COBRE CSFN) at The University of Montana, the MNIF is involved in many collaborative projects between physicians and neuroscientists, all working on many areas of brain cell function and disease. In addition, the MNIF houses a molecular medicine laboratory, where translational research is being conducted every day to develop new gene-therapy based treatments for neurological diseases. The Institute also features an active clinical trials program to study new approaches, devices and medications for neurological disease.

Governed by a Chairman and Board of Directors, the MNIF operates as a not-for-profit 501c3. Founding member **Nick Chandler, MD**, is Chair of the Board of Directors, and is a practicing neurosurgeon. In-house staff include **Dave Poulsen, PhD**, Director of the Molecular Medicine Laboratory; **Cindi Laukes, MA**, Clinical Research Manager; **Pamela Meck, RN**, Research Nurse Specialist; **Carol Lemieux, LPN**, Part-time Clinical Research Coordinator; and **Cindy Poulsen**, Program Assistant. The MNIF also regularly contracts and collaborates with many physicians and scientists outside of the Institute to design and conduct a wide spectrum of clinical and neuroscience projects.

The MNIF Board of Directors includes **Richard Bridges, PhD**, Founding MNIF Member and Director of the NIH COBRE CSFN; **Lilian Calderon-Garciduenas, MD, PhD**, Assistant Professor in the Department of Biomedical and Pharmaceutical Sciences at The University of Montana; **George Dennison**, President of The University of Montana; **Timothy Descamps, CPA**, Executive Director of



The Montana Neuroscience Institute is housed on the third floor of the beautiful Broadway Building adjoining St. Patrick Hospital and Health Sciences Center.

The International Heart Institute of Montana Foundation; **Daniel Dwyer**, Vice President for Research and Development at The University of Montana; **Vernon Grund, PhD**, Chair of Biomedical and Pharmaceutical Sciences at The University of Montana; **Diana Lurie, PhD**, Founding MNIF Member and Associate Professor in the Department of Biomedical and Pharmaceutical Sciences at The University of Montana; **Randale Sechrest, MD**, Director of the Montana Spine Center; **Rob Velin, PhD**, a neuropsychologist with Montana Neurobehavioral Specialists; **Peter VonDoersten, MD**, a neuro-otology surgeon with Rocky Mountain Eye and Ear Center in Missoula; and **Steve Witz**, President of St. Patrick Hospital and Health Sciences Center.

Visit our website at www.umt.edu/mnif

Clinical Trials at the MNIF

The Montana Neuroscience Institute is currently involved in several clinical trials, including a study of a medication for the pain that lingers after someone has had a case of shingles, two studies using an alternative to surgery for treatment of narrowed carotid arteries, a study of a medication for chronic pain, and a study for the treatment of acute stroke. In addition, the Institute is conducting an ongoing project to characterize many types of brain and spinal tumors. The type of clinical trials being conducted at the Institute changes regularly, and we welcome calls or emails from all interested people. Many of our studies are advertised in the newspaper, or can be accessed through local neurologists, neurosurgeons, and other referring physicians.

If you are interested in learning more about our ongoing or future trials, please feel free to contact our Clinical Research Nurse Specialist Pamela Meck at 406/329-2664, or our Clinical Research Manager Cindi Laukes at 406/329-5663.

The staff of The Montana Neuroscience Institute would like to thank and acknowledge the neurosurgeons and staff of Neurological Associates, P.C. for their encouragement, daily kindnesses, and generosity of spirit.

Guest Article: Insomnia - What It Is and How to Treat It

Excerpts from an article by Julie Hergenrather, Ph.D., A.C.T., Montana Neurobehavioral Specialists

What is insomnia? Insomnia is a widespread problem affecting between 15% and 30% of the adult population. In primary insomnia, the individual has difficulty falling asleep, staying asleep, wakes too early in the morning, or experiences poor quality sleep. Often, the individual reports an inability “turning off thoughts,” chronic restlessness, frustration, discouragement, worries about daily functioning, irritability, and an overall dissatisfaction and unhappiness. Not surprisingly, research reveals that people with primary insomnia work hard to sleep and worry quite a bit about the consequences of not sleeping. Like a negative feedback loop, however, the effort and worry actually contribute to one’s inability to fall and stay asleep. This emotional distress triggers physical arousal, which serves to only heighten one’s wakefulness.

What treatments are available for primary insomnia? Primary insomnia can be successfully treated in the short term with hypnotics (sleeping pills), and many doctors prescribe medication to help with sleep. Unfortunately, once the patient

discontinues use of medication, the symptoms of insomnia often return. This is because while sleeping pills effectively promote sleep, they don’t treat the cause of the sleep disturbance.

Cognitive Behavior Therapy for Primary Insomnia Cognitive Behavior Therapy (CBT) is a short-term behavioral and psychological intervention found to be particularly effective in treating primary insomnia. People with sleep problems learn to identify the factors, behavioral, environmental and thought-related, which contribute to the sleep problem. Therapy focuses on changing the thinking and behavioral patterns that keep one locked in the dysfunctional sleep cycle. Learning skills that improve overall sleep ensures that, unlike medication, the changes are more permanent. And, if insomnia recurs for some reason, the individual can implement these skills to return the sleep pattern to normal. In CBT, the therapist and client collaborate, setting specific goals, monitoring progress and devising targeted interventions. Typically, fewer than 6 sessions are required to treat insomnia. □

Oligoastrocytoma Case Study, Cont.

Oligoastrocytoma is a heterogeneous primary brain tumor that is composed of both oligodendroglial cells and astrocytic cells. They are rare tumors with an incidence of approximately 1 per 1 million in the U.S. population. They are graded according to the World Health Organization (WHO) classification as either grade II (low grade) or Grade III (anaplastic). They typically occur in young adults with a mean age at presentation of 35-45 years with a slight male predominance. 90% of patients present with seizures. Most tumors are located supratentorially in the frontal (57%) or temporal(30%) lobes of the brain.

Favorable prognostic factors include age < 40 years at presentation, tumor size <6 cm, lower histologic tumor grade, high preoperative patient performance status, extent of surgical resection, and lack of tumor enhancement on preoperative imaging. The presence of TP53 genetic mutations is predictive of poor survival.

Initial evaluation of patients with oligoastrocytoma includes CT and MR imaging. The typical CT appearance of these tumors is that of an area of low attenuation in the frontal or temporal lobe with minimal mass effect, little or no surrounding brain edema, and no contrast enhancement. Intratumoral calcifications may be present. MR imaging reveals a lesion that is hypointense on T1 sequences and hyperintense on T2 and FLAIR images. 50% of tumors will enhance with gadolinium contrast agent.

Treatment options include surgery, radiation therapy, and chemotherapy. Initial biopsy is recommended of all suspected low grade gliomas to rule out other lesions that may not require aggressive treatment such as cortical dysplasias or neuronal tumors. Surgery with the aim of gross total resection is recommended, and can usually be accomplished with minimal morbidity with modern techniques of intraoperative computer image guidance, functional MRI imaging, and cortical mapping via awake craniotomy or motor cortex stimulation. Postoperative radiation treatment is recommended for patients with Grade III tumors, subtotal tumor resection, age >50, and preoperative tumor enhancement on MR imaging. In younger patients with Grade II tumors where total resection is accomplished, radiation treatment is deferred until the time of tumor recurrence or progression. Because of the oligodendroglial component of these tumors, chemotherapy with either oral temozolomide or a regimen of up to six cycles of procarbazine, lomustine, and vincristine can be very effective, and

can be used in either Grade II or III tumors. The literature reports median survival times of 7-14 years from diagnosis. Five and ten year survival rates for Grade II tumors average 60% and 30% respectively, with figures of 45% and 15% for the grade III tumors.

The future holds promise for brain tumor patients. Cutting edge neurosurgical techniques like those described above will continue to be refined and developed. Newer chemotherapy agents are in development and even early clinical trials. Researchers in the burgeoning field of Molecular Medicine such as MNIF's Dr. Poulsen are striving for novel gene-therapy based approaches to diagnosis and treatment of brain tumors.

TP53 mutations serve as a predictive marker for poor survival in patients with astrocytomas.

Gliomas are a group of rare, slow growing tumors that can be divided into 3 different classifications: astrocytomas, oligodendrogliomas and oligoastrocytomas. Certain tumor types, such as oligodendrogliomas, are more sensitive to chemotherapeutic agents and typically have a better prognosis compared to astrocytomas. Therefore, determining the type of tumor can be valuable in defining treatment and prognosis. Tumor types are typically diagnosed based on their shape and structural characteristics. However, astrocytomas, oligodendrogliomas and oligoastrocytomas do not show great differences in their structural characteristics and therefore differentiating between them can be quite troublesome. However, different tumors may express different genes and recent studies (Okamoto et al., 2004; and Stander et al., 2004) have indicated that gliomas can be differentiated on a genetic bases. For example, about 50% of oligodendrogliomas carry a chromosomal deletion mutation and only 7% contain a point mutation within the *TP53* gene. In contrast 50% of astrocytomas carry a *TP53* mutation but only about 15% have specific chromosomal deletion mutations. These types of studies are valuable in that they help to focus efforts on the development of more targeted therapeutic treatments and lead to better diagnostic tools for defining treatment and prognosis. – *Dave Poulsen, Ph.D., Director, MNIF Molecular Medicine Laboratory*

Focus on Children

Two researchers from the Department of Biomedical and Pharmaceutical Sciences at The University of Montana are studying ways in which pollutants and metals in our environment may be affecting the children of Montana. Controlled studies involving children often provide the critical data necessary for establishing future guidelines for the health protection of children in our communities.

Associate Professor Diana Lurie, in collaboration with MNIF research staff and the Bonner school system, is currently studying the effect that exposure to lead has on auditory processing in children. Lurie has a long-standing interest in the auditory system and factors that cause impairments in auditory function. Lurie is also a collaborator on the auditory translational research project. (cover story)

Assistant Professor and MNIF Board Member Lilian Calderón-Garcidueñas is currently conducting research on children in Missoula to study the impact of air pollution and particulate matter on the heart rate variability of children. Animal studies have provided clear warnings that long term exposure to pollutants may have lasting and irreversible effects.

Because research on the cardiovascular effects of chronic exposures to air pollutants in children is currently very limited, there is a strong need for further research in this area. Calderon is testing a cohort of Missoula children to look for variations in heart rate that can be traced to specific air particulate exposures.



The Montana Neuroscience Institute Clinical Research Clerkship

The Montana Neuroscience Institute supports a 30-day clinical research rotation for PharmD students from The University of Montana Skaggs School of Pharmacy who are interested in learning more about clinical research in the hospital. During this rotation, students create and design a full clinical trial protocol, learn about the ethical issues involved in clinical research, attend a meeting of the committee that reviews all human subjects research for safety, and attend various clinical activities related to the clinical areas of their specific protocols.

Congratulations are in order to the seven PharmD candidates who have completed the MNIF rotation to date: Whitney Whidhalm, Kris Jensen, Marisa Clarke, Jeremy Otteson, Brian Galbreth, Barbara Arnold and Ben Rush. Their clinical projects have ranged from designing clinical trials related to metabolic syndrome, to trials involving imaging agents for depression, to treatments for addiction, to comparisons of treatments for post-surgical infection.

Research clerkship preceptor, Cindi Laukes, is enthusiastic about the program. "The research clerkship benefits everybody involved. The students are able to benefit from the clinical exposure and research expertise of hospital clinicians and MNIF research staff, the MNIF benefits from the pharmacology expertise of the students, and The University of Montana is able to offer a valuable clinical research clerkship experience to their PharmD students."

Giving to the MNIF

Your donation to the MNIF will help us to continue vital neurological research being done by physicians and scientists at the Institute and to be able to continue to provide excellent, free public educational programs. Due to the Foundation's 501c3 status, all donations are tax-deductible. For further information, or to make a donation and specify the intended purpose of your gift, please contact Cindi Laukes at 406/329-5663. She will be happy to direct you to the appropriate individuals who can then assist you with the details of your individual giving process.

Montana Neuroscience Institute Public Lecture Series

PET Brain Imaging: Understanding Depression

John Gerdes, Ph.D. Tuesday, February 15 6:30-7:30PM

Neurological Illness and Care Giving at Home: Successful Strategies

Chad O'Lynn, Ph.D., R.N. and Pamela Meck, R.N.
Tuesday, March 22 6:30-7:30PM

Age-Related Macular Degeneration: A Fight for Sight

Brian Sippy, M.D., Ph.D. Tuesday, April 19 6:30-7:30PM

CNS Stem Cells & Alzheimer's Disease

George Carlson, Ph.D. Tuesday, May 17 6:30-7:30PM

The Many Facets of Managing Chronic Pain

Randale Sechrest, M.D., LeeAnn Bradley, PharmD, and Patrick Johnson, Ph.D.
Tuesday, Sept. 20 6:30-7:30PM

Your Brain and the Air You Breathe: Chronic Health Effects of Air Pollution

Lilian Calderón-Garcidueñas, M.D., Ph.D.
Tuesday, Oct. 18 6:30-7:30PM

Contemporary Stroke Therapy in 2005: Focus on Carotid Artery Disease

Mark Sanz, M.D. Tuesday, Nov. 15 6:30-7:30PM



All lectures are free and open to the public. They are held in the Broadway Building Conference Center St. Patrick Hospital and Health Sciences Center, 500 W. Broadway in Missoula Montana. For more information contact: Cindi Laukes at 329-5663 or visit our website www.umt.edu/mnif and click on Public Lecture Series.

Other Upcoming Events

11th Annual Montana Neurosurgery Symposium

Every summer, the MNIF hosts The Montana Neurosurgery Symposium at Chico Hot Springs, a western-style resort near Yellowstone Park. Neurosurgeons from around the country attend to learn about state-of-the-art developments in neurosurgery. The symposium also features exhibitors from neurosurgical device companies. This year's symposium will be held July 31-August 4. For more information, contact Program Assistant Cindy Poulsen at 406/329-5733.

Montana Neuroscience Retreat

Every spring, neuroscience faculty from The University of Montana and Montana State University, along with scientific advisory faculty, representatives from N.I.H., graduate students and clinicians, meet for two days at Seeley Lake to present and discuss their latest research. This retreat provides an exciting forum for the exchange of cutting-edge neuroscience developments in Montana. This year's meeting will be held June 3-5. For more information, contact Kate Stewart at 406/243-4334.

Topics in Neurosurgery Oligoastrocytoma: A Case Study

Nick Chandler, M.D.

Clinical History

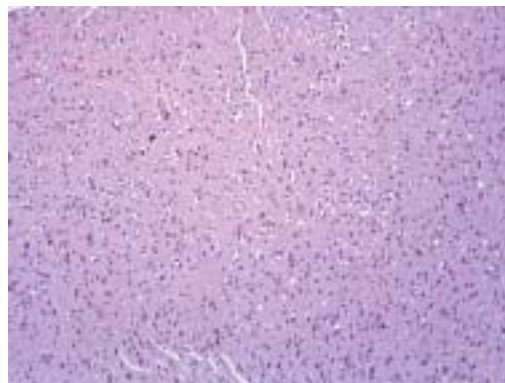
A 35 year-old woman presented with a new onset focal motor seizure characterized by unilateral onset in the left lower extremity and spreading to involve all four extremities *without* loss of consciousness. She presented to the Emergency Department where a CT scan of the head revealed a frontal lobe mass just above the corpus callosum, accounting for the bilateral focal motor seizures. Subsequent MRI evaluation revealed a mass lesion in the posterior frontal lobe localized to the right cingulate gyrus and extending upwards into the supplementary motor area. It exhibited uniform hypointensity on T1 images and no contrast enhancement. It was hyperintense on T2 and FLAIR sequences with mild surrounding edema. Anticonvulsant therapy was initiated with good subsequent seizure control.



She underwent an image-guided frameless stereotactic biopsy which revealed the tumor to be a low grade oligoastrocytoma (WHO Grade II). She was returned to the OR a week later for resection. MR Image-guidance and intraoperative electrophysiologic motor cortex mapping were utilized

and resulted in safe, gross total resection of the lesion. Extent of resection was confirmed with early postoperative MR imaging. The patient suffered transient postoperative deficits characterized by left ideomotor apraxia which resolved completely.

Pathologic Findings



Microscopic section of the tumor showing an infiltrating glioma with both oligodendroglial and astrocytic cell differentiation.



Preoperative T1 Gadolinium-enhanced sagittal Magnetic Resonance image showing a hypointense, non-enhancing mass lesion in the cingulate gyrus, extending upward into the supplementary motor area.

MR Images



Postoperative T1 Gadolinium-enhanced MR image showing the extent of surgical resection. The area of bright signal intensity represents blood products and debris in the tumor resection cavity.