New Technique Offers Dynamic Study of Proteins Involved in AD

By Gila Z. Reckess

ADRC researchers in collaboration with researchers at Eli Lilly and Co. have developed a new technique that dynamically studies proteins in the fluid between brain cells, called interstitial fluid, known to be related to Alzheimer's disease.

Using this new technique in mice, the team discovered that the relationship between levels of a key molecule involved in Alzheimer's disease, amyloid-beta (ABeta), in interstitial fluid and cerebrospinal fluid changes as the disease progresses. Cerebrospinal fluid, the fluid that cushions and surrounds the brain, is a main focus in diagnosing and possibly treating Alzheimer's disease.

"We now have a way to measure a pool of ABeta that previously could not be evaluated," said graduate student John R. Cirrito. "Using this new approach, we were able to identify another difference between young mice that have not yet developed Alzheimer's-like changes and those that have developed Alzheimer's-like brain changes, which provides a new opportunity to explore the development of this disease."

Cirrito is first author of the study, published in the Oct. 1 issue of The Journal of Neuroscience. The principal investigator is David M. Holtzman, M.D., the Andrew B. and Gretchen P. Jones Professor of Neurology and head of the Department of Neurology, the Charlotte and Paul Hagemann Professor of molecular biology and pharmacology.

A key step in the development of Alzheimer's disease is the formation of sticky, senile plaques in the brain, composed primarily of clumps of ABeta. Although these plaques are believed to form at least in part in the spaces between brain cells, there previously was no way to selectively extract and measure levels of ABeta in interstitial fluid.

Cirrito and his colleagues developed an unique microdialysis technique to measure two key forms of ABeta. The team confirmed that in cerebrospinal fluid, Abeta 42 levels decrease as the disease progresses, whereas Abeta 40 remains unchanged. Surprisingly, they discovered a different pattern in interstitial fluid: Abeta 42 remains constant while Abeta 40 increases.

"ABeta that ends up in the cerebrospinal fluid comes from interstitial fluid, so you'd expect the two compartments to communicate," Cirrito said. "We were surprised to find they were not correlated in young mice. There apparently is a shift during aging and/or during plaque development that affects how ABeta is moved between the two compartments because levels of ABeta do correlate in older, plaque-ridden mice."

The team found it takes about twice as long for the soluble pool of brain ABeta to break down in mice with Alzheimer's-like brain plaques than in young mice without plaques. However, the baseline concentration of ABeta in old and young mice was not significantly different, which may suggest that another, previously unidentified mechanism is involved in the development of Alzheimer's plaques.

"The difference in the elimination rate may turn out to be an extremely important finding," Holtzman said. "This finding and technique should assist us in determining how other molecules involved in ABeta metabolism influence Alzheimer's disease as well as be useful in developing new diagnostic and treatment strategies."

Nationwide Study Seeks Families with 2 or More Siblings Living with Alzheimer's Disease

The Washington University ADRC is joining a nationwide effort to identify 1,000 families with 2 or more siblings with late-life Alzheimer's disease (AD) to participate in a major research study, the Alzheimer's Disease Genetics Study. The goal of the study is to speed the search for risk-factor genes that increase the risk of developing AD later in life.

The AD Genetics Study is sponsored by the National Institute on Aging (NIA), part of the National Institutes of Health in the U.S. Department of Health & Human Services, and is supported by the Alzheimer's Association, the nation's largest private health organization dedicated to advancing AD (see p 3)
The 4th Leonard Berg Symposium was held at the Chase Park Plaza Hotel on September 19-20, 2003. This biennial symposium is sponsored by the ADRC in honor of founding director and professor emeritus of neurology, Leonard Berg, M.D.

This year’s symposium focused on neuroimaging techniques to identify the earliest signs of Alzheimer’s pathology in the brain. A distinguished faculty of experts presented their findings to an international audience of 230—the largest Berg Symposium yet. In addition, thirty academic posters showcased some of the best research in this area right now.

The Symposium was divided into three segments based on imaging technique: (1) Structural, (2) Functional, & (3) Molecular.

The first series of talks showcased techniques to measure how brain structures, such as the hippocampus, change in shape and volume as the disease progresses. These techniques will be important for diagnostic purposes and for tracking rates of decline in persons with probable AD.

The second series of talks showed how functional deficits associated with memory loss and AD can be identified using special fMRI scans that measure the metabolism of brain cells in certain areas.

The final talks focused on the early detection of AD pathology (especially plaques) in living individuals before any signs of memory loss appear! We know now that AD pathology starts in the brain years before symptoms. Molecular imaging holds the promise of diagnosing people before significant brain damage occurs and initiating treatment (when available) to prevent the disease altogether.

Visit http://alzheimer.wustl.edu to learn more.

**Notables**

**Eugene M. Johnson**, Jr., Ph.D., the Norman J. Stupp Professor of Neurology and professor of molecular biology and pharmacology and co-director of the Alzheimer’s Disease Research Center in the School of Medicine, was honored on September 30, 2003, with the Carl and Gerty Cori Faculty Achievement Award.

Long time ADRC Investigator, **David M. Holtzman**, M.D., has been named the Andrew B. and Gretchen P. Jones Professor of Neurology and head of the Department of Neurology at Washington University School of Medicine in St. Louis. Holtzman also will continue as the Charlotte and Paul Hagemann Professor of Neurology and as professor of molecular biology and pharmacology. The appointment took effect Oct. 1, 2003. Holtzman succeeds David B. Clifford, M.D., professor of neurology and the Melba and Forest Seay Professor of Clinical Neuropharmacology in Neurology, who served as head of the department during the search for a permanent replacement for Dennis W. Choi, M.D., Ph.D., now executive vice president of neurosciences at Merck Research Laboratories.

In May, 2003, Harvey A. and Doris-mae Friedman, benefactors of Washington University and the Center for Aging, funded a new Friedman Award — given to non-physicians who have made "outstanding contributions to patient-oriented research on aging." This award was presented for the first time to **Mary A. Coats**, MSN, research instructor in neurology and co-director of the Memory and Aging Project.

**HORIZONS** is the newsletter of the Alzheimer’s Disease Research Center (ADRC) — a research program in the Department of Neurology, Washington University School of Medicine, funded by grants from the National Institute on Aging and private donations. The ADRC supports and promotes interdisciplinary research on Alzheimer’s Disease. The Memory & Aging Project (MAP) — the clinical research arm of the ADRC — provides expert clinical assessments of cognitive functioning in normal aging and dementia.

**Alzheimer’s Disease Research Center**
4488 Forest Park Ave., Suite 130
St. Louis, MO 63108
ADRC (314) 286-2881; MAP (314) 286-2683
www.adrc.wustl.edu / adrcedu@abravas.wustl.edu

**John C. Morris**, M.D., Co-Director, ADRC, & Director, MAP
**Eugene M. Johnson**, Ph.D., Co-Director, ADRC
**David M. Holtzman**, M.D., Associate Director, ADRC
**Martha Storandt**, Ph.D., Assoc. Dir. & Psychometric Core Leader
**Daniel W. McKeel**, M.D., Neuropathology Core Leader
**Alison Goate**, D.Phil., Genetics Core Leader
**Randy L. Buckner**, Ph.D., Imaging Core Leader
**J. Philip Miller**, M.A., Biostatistics Core Leader
**Dorothy F. Edwards**, Ph.D., Minority Satellite Leader
**Thomas M. Meuser**, Ph.D., Education Core Leader &
Editor of the HORIZONS Newsletter
AD Genetics Initiative
(continued from page 1)

research and providing information and support to those affected by the disease. The Study will be conducted by NIA-funded AD research centers around the country.

Researchers will create a large bank of genetic material, cell lines, and data from families with multiple members with late-onset AD, which scientists can then use in their quest to discover the risk-factor genes that contribute to late-onset AD, the most common form of the disease. Discovery of risk-factor genes will help illuminate the underlying disease processes of AD, open up novel areas of research, and identify new targets for drug therapy.

“Discovery of risk-factor genes is essential for understanding the causes of late-onset AD and for developing effective treatments and prevention strategies,” said Dr. Alison Goate, Genetics Core Leader for the ADRC. “Families who have been affected by this devastating disease understand the urgency of finding the causes of AD, and how to stop it.”

To be eligible to participate in the study, families must have at least 3 members who can donate blood, including:

- 2 siblings (brothers or sisters) who developed AD after age 60, and
- Another family member over age 50 who may have memory loss OR a family member over age 60 who does not have any memory loss.

Participation involves a neurological examination or collection of medical records and the donation of a blood sample, which will be made into a cell line (a family of cells grown in the laboratory) that will enable the participant’s DNA to be available to qualified scientists over many years. Medical, demographic, and family history information also will be collected.

Unaffected family members also may be asked to participate. The cell lines and DNA will be stored at a centralized repository at Indiana University – the National Cell Repository for AD (NCRAD).

There is no cost for those who join the study. To ensure broad participation, study coordinators will make alternative arrangements for participation if people eligible to take part are not located near a designated study site.

An important part of the study is the confidential treatment of the genetic information collected from participants. Researchers will not be able to identify samples on an individual level. While clinical, demographic and family history information about the participants will be available to researchers, this information will also be free of unique identifiers. Coded data on the blood sample will be stored in a secure computer at the NCRAD. Detailed discussion of informed consent documents will outline for participants how the study will be conducted and how data will be protected at each site and at the cell repository.

To participate in the study, families should contact NCRAD toll-free at 1-800-526-2839 by e-mail alzstudy@iupui.edu. Information is also available through the study Web site, www.ncrad.org, or by calling 314-747-2981.

About 90 percent of people with AD have the late-onset (also called “late-life”) variety, which strikes people age 65 and older. There is no obvious inheritance pattern with late-onset AD, but researchers have identified one “risk-factor” gene, the ε4 variant of apolipoprotein E (apoE). This discovery has opened up many important avenues to understanding the biological and environmental interactions that may be important to the development of late-onset AD. While scientists have drawn significantly closer to identifying at least four regions of chromosomes where other risk-factor genes might be, researchers have strongly recommended that further collection and analysis of larger sample sets are needed to root out these genes.


Key brain structure changes over time

By the time a person begins to experience symptoms of Alzheimer’s disease (AD), several brain structures already are dotted with the plaques and tangles that characterize the illness. John G. Csernansky, M.D., the Gregory B. Couch Professor of Psychiatry, and his team at the Conte Center are working to identify changes in brain structures as early as possible in the course of the disease — at a time when it might soon be possible to halt its progress before people become severely impaired.

Reporting online and in an upcoming issue of the journal *NeuroImage*, this team has identified changes in the brain that appear to distinguish AD from healthy aging. Because learning and memory are greatly affected by AD, the team focused on a structure important for learning and memory: the hippocampus, a seahorse-shaped structure deep inside the brain.

"In AD, presumably brain structures have a normal size and shape until the disease cascade begins," said Dr. Csernansky. "Changes in hippocampal shape represent early evidence of damage to a part of the brain that previously was normal. Those changes in shape happened as patients were first showing symptoms of Alzheimer's disease, so that provides strong evidence the shape changes we observed in the hippocampus may be actually causing at least some of the symptoms of AD." (Excerpts of article by Jim Dryden, WUSM Record, 10/10/03)
Memantine Approved for Late Stage Alzheimer’s Disease

Memantine was approved by the United States Food and Drug Administration (FDA) on October 17, 2003. It should be on pharmacy shelves in January 2004 under the brand name Namenda®. Memantine works by partially blocking the brain chemical, glutamate. Excess glutamate has been shown to be harmful to nerve cells. In the pivotal study reviewed by the FDA, subjects with moderate to severe Alzheimer’s disease showed benefit from memantine when compared to placebo. The group that took memantine deteriorated less in their ability to conduct basic daily activities like toileting and feeding than the group that took the placebo. The dose that was tested was 10mg in the morning and 10mg in the evening.

It is not known if memantine alone is effective treatment in people with mild to moderate Alzheimer’s disease. Memantine showed no additional benefit when tested in subjects with mild to moderate Alzheimer’s disease who were also taking one of the three commonly prescribed Alzheimer’s medications (Aricept®, Reminyl®, or Exelon®). The results of a study using memantine alone in patients with mild to moderate Alzheimer’s disease have not yet been released.

Memantine is initiated at a low dose with several weekly dose increases to reach the target dose of 10mg twice a day to minimize the occurrence of side effects. The most commonly reported side effects of the drug were headache, constipation, confusion, and dizziness.

A helpful fact sheet about memantine (Namenda®) is available for downloading on the Alzheimer’s Association website: http://www.alz.org/ResourceCenter/FactSheets/FSMemantine.pdf
Driving Performance Declines with Dementia and Age

By Gila Z. Reckess

In one of the first studies to track driving performance over time in older adults, researchers at Washington University in St. Louis found that driving abilities predictably worsened in individuals with early Alzheimer’s disease and, to a lesser extent, in older adults without dementia. The findings will appear in the October 2003 issue of the Journal of the American Geriatrics Society.

“As we expected, people with dementia, generally in the mild stages, declined faster than the nondemented individuals,” says senior author Janet M. Duchek, Ph.D., associate professor of psychology and of occupational therapy. “But it is very interesting that there also was decline in some of our nondemented participants. This is a preliminary study, but it suggests that testing individuals with mild dementia every six months can be useful to identify those who become unsafe.”

Alzheimer’s disease is the most common cause of dementia in older adults and affects about 4.5 million Americans. Affected individuals experience memory difficulties and problems with attention and eventually lose the ability to perform complicated tasks like driving.

But according to co-author John C. Morris, M.D., principal investigator of the Alzheimer’s Disease Research Center and the Harvey A. and Dorismae Hacker Friedman Distinguished Professor of Neurology, it’s impossible to predict driving performance based solely on whether a person has been diagnosed with dementia. That’s why the research team, which also included Linda Hunt, Ph.D., formerly at the School of Medicine and now at Flathead Valley Community College in Mont., and David B. Carr, M.D., associate professor of medicine, developed an extensive, 45-minute, in-traffic driving test called the Washington University Road Test.

“Appropriate testing is important,” Morris says. “For individuals who still drive safely, it can be reassuring and help them remain independent. It also can be used to follow individuals to detect the development of unsafe driving behaviors and intervene, hopefully before there is an actual crash or other problem.”

In a study published by Hunt and the team in 1997, 41 percent of individuals with mild Alzheimer’s disease failed the driving test, compared with only 14 percent of those with very mild dementia and 3 percent of nondemented participants.

The current study details longitudinal findings with the same group of participants. The team administered the road test every six months to the individuals who passed the test the first time and then compared the time it took each group to go from “pass” to “fail.”

As expected, the mild Alzheimer’s group declined the fastest, followed by the very mild dementia group. Surprisingly, performance in the non-dementia group also declined over time, though at a slower rate than the other two groups.

In addition, when data from all three groups was combined, increased age alone appeared to be a risk factor in driving performance.

"While the majority of the nondemented people we tested remained very safe drivers, as we followed them, more and more became unsafe," Morris says. "Age-related changes other than dementia likely contribute to driving performance and should be further investigated in larger groups of older adults."

Duchek and Morris emphasize the need to educate physicians and families about the importance of detecting changes that may impair an individual’s driving performance. Signs that should raise concern include an inability to maintain speed or to stay in one lane while driving, hesitating at turns or becoming lost, particularly in familiar areas.

“One of the features of dementia is that individuals lose insight and may not recognize that they are becoming unsafe,” Morris explains. “We must increase public awareness about driving issues in demented persons.”

To learn more about ADRC-sponsored driving research and for links to helpful resources, visit http://alzheimer.wustl.edu. Click on Special Topics in the Education pull-down menu.

ADRC to Train Rural Clinicians in How to Assess & Counsel Demented Drivers

ADRC Education Core Leader, Dr. Tom Meuser, and ADRC Investigator, Dr. David Carr, will lead a National Institute on Aging and National Highway Traffic Safety Administration funded project to educate rural clinicians on dementia and driving issues.

Impaired older drivers pose a significant safety hazard to themselves, their family members and others on the road. Family members and law enforcement officials look to medical professionals for expert advice when an older adult is suspected of having a dementing disorder that may impair driving ability. A series of six evidence-based workshops will be held across eastern and central Missouri starting in December 2003 to address this need and equip health professionals to manage this challenge effectively in the future.

Call Dr. Tom Meuser at 314-286-2882 for more information.
New Model of Alzheimer’s Enzyme May Help Refine Future Treatments

By Gila Z. Reckess

An international team of scientists led by researchers at Washington University School of Medicine in St. Louis have found that the enzyme largely responsible for the development of Alzheimer’s disease may work in a different way than previously thought.

“We’re very excited to provide more insight into how this bizarre process takes place,” says principal investigator Raphael Kopan, Ph.D., professor of medicine and of molecular biology and pharmacology. “The more we understand the way this enzyme works, the easier it will be to design better and more intelligent approaches to tweaking the enzyme to do what we want.”

The results are published online in the early edition of the Proceedings of the National Academy of Sciences and appear in the Oct. 28 print edition. The study was an international collaboration between researchers at the School of Medicine, Merck and Co. Inc., University of Tokyo, Harvard Medical School, University of Tennessee at Memphis, and the K.U. Leuven and Flanders Interuniversity Institute for Biotechnology in Belgium.

The results focus on gamma-secretase, an enzyme that clips a long protein called amyloid precursor protein (APP), which results in fragments that accumulate as brain plaques. The plaques are a hallmark of Alzheimer’s disease, making inhibition of gamma-secretase activity a main objective for new Alzheimer’s drugs.

Kopan and colleagues previously found the enzyme also is required for another protein called Notch to function. Notch helps produce many cell types and, using a thymus organ culture model system, Kopan’s team found gamma-secretase inhibitors had the potential to interfere with production of key immune cells.

“Ideally, the next generation of drugs will be able to prevent gamma-secretase from triggering production of plaques without interfering with the enzyme’s role in Notch signaling,” Kopan says. “That goal is made easier with every additional glimpse into how the enzyme works.”

The team’s latest findings, which suggest that gamma-secretase may contain multiples of one subunit, are a step in that direction.

To confirm the enzyme cleaves both APP and Notch, Kopan’s team first examined whether the two compete with each other for the enzyme’s attention in culture cells. They did indeed find evidence of competition: Notch cleavage was significantly stunted after the addition of C99, the piece of APP upon which gamma-secretase acts. The opposite also was true: In the presence of Notch fragments, there was significantly less production of ABeta40, one product of APP cleavage.

The team also ranked each of seven different gamma-secretase inhibitors in order of its ability to interfere with cleavage of Notch or APP. The rankings were the same for both proteins. Six of the inhibitors also had an identical effect on Notch and APP.

Together, these findings suggest gamma-secretase cleaves both APP and Notch and treats them interchangeably — rather than distinguishing between the two, it simply clips whichever it runs into first. The presence of either protein can therefore influence gamma-secretase’s effect on the other.

Next, the team examined how the same enzyme is responsible for clipping each molecule at two separate sites. A breakthrough came from observing the activity of a particular mutation in Notch that is protected from gamma secretase cleavage. As expected, Kopan’s team found that this fragment does not compete with C99. Surprisingly, though, it did bind to the enzyme.

According to Kopan, enzymes can either have one site where they interact with molecules or have separate cutting and binding sites. This study suggests that gamma-secretase belongs to a class of enzymes where, in addition to the active site (which is in limited supply and therefore leads to competition between APP and Notch), there also are “binding” sites, where molecules can latch onto the enzyme without competing with each other and without becoming subject to cleavage.

“The active site is like a mouth — it chews whatever it touches but can only chew one thing at a time,” Kopan explains. “The other site is like a hand — it’s used for holding, and doesn’t interfere with the ability of the mouth to chew another object. Maybe one molecule acts as the “hand” serving a meal to the “mouth,” which is located on another molecule.”

The researchers tested this theory in several ways. Gamma-secretase is a large, complex enzyme composed of four proteins. At its core is a molecule called presenilin. Kopan’s team found that antibodies designed to find a tag on one presenilin molecule also could latch onto a different presenilin molecule with a different tag. This implies the two molecules are located close to each other.

Kopan’s team confirmed the molecules’ close proximity to each other by creating an irreversible chemical bond between the two molecules using a small inhibitor molecule designed by Merck and Co. in England.

“The data generated by our colleagues at Merck shows conclusively that there are two presenilin molecules in very tight proximity to each other,” Kopan says. “But we still can’t differentiate how (next page)
Alzheimer’s Enzyme

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the catalytic core of gamma-secretase, the "mouth" of the enzyme, is organized and whether it functions as a single entity or at the interface between two molecules.”

To further investigate the complex organization and function of the enzyme, the researchers examined the effects of presenilin mutations found in people who develop the early, genetically linked form of Alzheimer’s disease. They reintroduced mutated presenilin proteins from Alzheimer's disease patients to cultured cells missing both presenilin molecules. The mutant proteins failed to completely restore gamma-secretase activity, but the cells still produced Aβ42, the product of APP cleavage that accumulates to form brain plaques. In fact, some even resulted in production of more Aβ42 than when only normal presenilin molecules were present.

Kopan’s team hypothesized that perhaps the mutated presenilin molecules influence production of Aβ42 by gamma-secretase activity by interacting with each other differently than do normal molecules, even though they themselves cannot efficiently clip APP or Notch. If a mutated presenilin molecule could be developed that is completely incapable of performing the active functions of gamma-secretase on its own and yet still is capable of increasing production of Aβ42, it would confirm that the enzyme has a functional unit at the interface between two presenilin proteins and suggest that familial forms of Alzheimer’s disease are caused by inter-molecular interactions between mutant and normal proteins.

The team was able to observe that exact phenomenon; however, the finding was fleeting and, thus far, has not been reproducible.

“There are many reasons why this experiment shouldn’t work, and yet for a short while it did,” Kopan says. "Perhaps some component in the experimental conditions that allowed this to happen has changed; however, we don’t fully understand what those key variables are and therefore have lost the ability to replicate the result. Our hope is that by publishing this study and proposing this experimental approach we will inspire other scientists to try different pairs of mutations or to develop better experiments while we continue to work on ours.”

Dr. Kopan’s research is funded by the Alzheimer’s Association and NIH.

Supporting AD Research

The Alzheimer’s Disease Research Center at Washington University is funded by grants from the National Institute on Aging. Although we are not “needy” per se, we do have specific financial needs associated with our research, education and community outreach efforts. Private donations help us expand our federal mandate to meet important needs such as:

- Supporting our Postdoctoral Research Fellowship Program,
- Allowing us to underwrite innovative pilot research projects to develop preliminary data for formal grant applications;
- Supporting informative community education (e.g., Leonard Berg Symposium series);
- Allowing creative community and academic partnerships to further knowledge and service.

And the list goes on ….

Your Gift

If you would like to make a financial contribution, either as a gift or tribute to a loved one with AD, you may send us your donation by making your check payable to the Alzheimer’s Disease Research Center and mailing it to:

Executive Director
Washington University ADRC
4488 Forest Park Blvd., Suite 130
St. Louis, MO 63108

Or, you may call us at (314) 286-2881 to speak personally with a member of our staff for information about making a donation.

If you are making a tribute donation and would like others to know about it, we will send a notification letter to a brief list of individuals. Include a note with the names and addresses of persons you would like to be notified.

Thank you for your support!

Special Video on Alzheimer’s Disease

Reflections on Memories Lost

The Washington University Alzheimer’s Disease Research Center (ADRC) and the St. Louis Black Repertory Company have produced a 30-minute video for families on recognizing the early warning signs of Alzheimer’s disease and next steps in arranging a medical evaluation and obtaining other assistance.

Actors from the Black Rep portray characters from a book by Lisa Snyder entitled Speaking our Minds: Personal Reflections from Individuals with Alzheimer's, Henry Holt Publishers, 1999. Medical commentary is provided by Dr. John C. Morris, Washington University Professor of Neurology. The video includes information on free services in the St. Louis area.

Call 314-286-0930 to order your VHS copy today! Quantities are limited and will be distributed on a first come, first serve basis.
New Faces at the Memory and Aging Project

ADRC Principal Investigator, Dr. John C. Morris (center), is joined by ADRC Fellows Dr. Kyung Yoon Eah from S. Korea and Dr. Maria Behrens from Chile. Both are working on one-year fellowships focusing on AD research and clinical care.

Psychologist and gourmet coffee drinker, Dr. David Johnson, joined the ADRC team in August, 2003. As an expert in statistics and study design, Dave will consult on existing and new projects, while also pursuing his own independent research projects. Dave replaces Dr. Kim Powlishta who left to take a faculty position at SLU.

Teri Gorsage joins the ADRC front office team after many years working in business. Welcome Teri!

The Memory and Aging Project Psychometrics Team, coordinated by Denise Maue Dreyfus, MA (2nd from left), administers tests of memory and other cognitive skills to participants in the MAP. All are new to their current positions in the past year. They are: Jacque Neuwoehner (left), Elise Clerkin (2nd from right), and Amy Samborsky Knapp (right).

Pamela Jackson, BSN, RN, joined the MAP in August as a new nurse clinician. In addition to her nursing responsibilities, Pamela will play an important role in minority outreach and education. Welcome Pamela!