The 5th Leonard Berg Symposium was held at the Eric P. Newman Education Center, Washington University School of Medicine, on October 7-8, 2005. Over 200 scientists and clinicians from the US and several foreign countries gathered to learn about the latest research on risk factors and biological markers for early and preclinical Alzheimer’s disease (AD). A poster session featured 32 studies from labs around the globe and stimulated much interaction.

A highlight was a presentation from Symposium honoree, Dr. Leonard Berg. With support from his wife, Gerry, and daughter, Nancy, Dr. Berg shared his thoughts on the founding of the Memory & Aging Project (MAP) starting in the 1970’s, his gratitude to his family and many valued colleagues, and his hopes for the future. His remarks were a true highlight and brought tears of appreciation from many.

The Symposium was divided into four half-day sessions:
1. Risk Factors for Preclinical AD
2. Genetic Markers of AD
3. Antecedent Biomarkers
4. Neuroimaging

Visiting faculty presenters included Claudia Kawas, MD UC-Irvine; Kristine Yaffe, MD, UC-San Francisco; Laura Almasy, PhD, Southwest Foundation for Biomedical Research; Sherrilynne Fuller, PhD, University of Washington; Eric Larson, MD, University of Washington; Howard Schulman, PhD, SurroMed, Inc.; John Trojanowski, MD, University of Pennsylvania; and William Klunk, MD, University of Pittsburgh. Washington University presenters included John C. Morris, MD, William Landau, MD, former Chair of Neurology and longtime supporter of the Memory & Aging Project (MAP), enjoys the company of Leonard Berg, MD, founding director of the MAP and ADRC, and Symposium honoree (right).

There are so many people that I need to thank for their amazing dedication and long hours - people who believed in our project, people who have been instrumental in research and administration for all these years. Without all of you, the ADRC and our wonderful research would not have happened.

Leonard Berg, MD, 10/7/05

James Galvin, MD, Alison Goate, DPhil, Jeffrey Millbrandt, MD, Randy Buckner, PhD, and Mark Mintun, MD, Zaven Khachaturian, PhD, formerly with the National Institutes of Health and a key figure in the development of AD Center funding on a national level, and Dennis Selkoe, MD, Harvard University, were luncheon keynote speakers on Friday and Saturday, respectively. A special session on Friday afternoon recognized the 20th anniversary of the ADRC. Director, John C. Morris, MD, and NIA colleagues, Tony Phelps, PhD, and Marcelle Morrison-Bogorad, PhD, shared their reflections.

Former US Senator and longtime advocate for aging research, Thomas Eagleton (center), with ADRC Associate Director, Gene Johnson, PhD (left), and Norman R. Seay, Chair of the ADRC’s African American Advisory Board.

Visiting Scholars to the ADRC in 2005: John Yang, MD (Taiwan, far left), Lea Grinberg, MD (Brazil, center), Daniela Costardi, MA (Italy), and Ebru Karakoc, MD (Turkey, far right).

Founding director of the St. Louis Chapter of the Alzheimer’s Association and now National Office VP, Kathleen O’Brien, shares a light moment with ADRC Director, John Morris, MD.
New Booklet Stresses AD Prevention

A new free 28-page booklet from the National Institute on Aging (NIA) Alzheimer’s Disease Education and Referral Center (ADEAR) — Can Alzheimer’s Disease be Prevented? — provides the latest research findings on risk factors. It describes the ongoing search for prevention strategies and how heart disease, high blood pressure, diabetes and insulin resistance, and inflammation may affect development of Alzheimer’s disease (AD).

The booklet discusses intriguing new research from observational studies and discusses thought-provoking theories about the possible origins and development of AD. These findings and NIA’s continuing research programs are renewing hope that someday we will be able to delay the onset of AD, slow its progress, or even prevent it altogether.

The booklet can be viewed and ordered online at: www.alzheimers.org/pubs/PreventingAD/TOC.htm
You can also order copies by calling the ADEAR Center at 800-438-4380.

Helpful Resources on the Web

The ADEAR Center offers free e-mail alerts on AD-related news releases, clinical trials, & new publications. Sign up at www.alzheimers.org/maillist.htm

- Alzheimer’s Disease Education and Referral Center – www.alzheimers.org
- National Cell Repository for AD – http://ncrad.iu.edu
- National Alzheimer’s Coordinating Center – www.alz.washington.edu
- NIA AD Genetics Initiative – www.niageneticsinitiative.org
- Alzheimer’s Disease Cooperative Study – http://adcs.ucsd.edu
- Alzheimer’s Association – www.alz.org

In Her Own Words:

Ebru Karakoc, MD, a Neurologist from Hacetteppe University Medical Center, Ankara, Turkey, joined the ADRC as a Visiting Research Scholar in September. She will spend six months at the ADRC studying our clinical methods and researching neuropsychological and imaging data of persons with very early dementia.

I was born in a small city near Istanbul as the only child of my family. My medical interest started early in childhood with appreciation for my pediatrician. After completing my Bachelor’s degree with honor roll, I enrolled in Hacettepe University Medical School with scholarship. I am still working as a resident in Neurology at Hacettepe University and I am also now enrolled in a doctoral program at Institute of Neurological Sciences there. I married my husband, Ergun Dagloolu, a neurosurgeon, in 2000. He is currently part of a medical team helping earthquake survivors in Pakistan.

At home, I am part of a working group to develop a standardized neuropsychological test battery for the diagnosis of early dementia. Outstanding articles of Dr. John Morris and his colleagues enhanced my interest in learning the clinical evaluation of the ADRC. Thanks to Dr. Morris and the ADRC family for their warm and gentle welcome and opportunity for this fellowship!
New Hypothesis Links Brain Activity in Youth to AD Later in Life

Using five different medical imaging techniques to study the brain activity of 764 people, including those with Alzheimer’s disease (AD), those on the brink of dementia, and healthy individuals, Washington University (WU) researchers have found that the areas of the brain that young, healthy people use when musing or daydreaming are the same areas that fail in people who have AD.

On the basis of their data, the researchers are proposing a hypothesis that AD may be due to abnormalities in the regions of the brain that operate the “default state.” This is the term used to describe the cognitive state people defer to when musing or thinking to themselves.

Writing in the Aug. 24 issue of the Journal of Neuroscience, the researchers state that “the default activity patterns of the brain may, over many years, augment a metabolic- or activity-dependent cascade that participates in AD pathology.”

“The regions of the brain we tend to use in our default state when we are young are very similar to the regions where plaques form in older people with AD,” said the study’s lead author, Randy L. Buckner, associate professor of psychology in Arts & Sciences and a Howard Hughes Medical Institute (HHMI) investigator at WU.

The findings are important because they could help scientists and clinicians identify and understand the beginnings of what is probably a cascade of events that ultimately leads to Alzheimer’s.

The availability of powerful imaging techniques and the ability to merge different sets of imaging data through new bioinformatics and statistical methods enabled Buckner and his team to construct a picture of Alzheimer’s from molecular changes to the structural and functional manifestations of the disease.

In the process, the team unexpectedly observed that the regions of the brain that “light up” when humans slip into comfortable patterns of thought are the same as those that, later in life, exhibit the disabling clumps of plaque characteristic of Alzheimer’s.

That remarkable correlation, Buckner said, suggests that dementia may be a consequence of the everyday function of the brain. “The hypothesis is that the cascade of events that leads to Alzheimer’s begins at young adulthood,” said Buckner.

Scientists have long known that when the mind is not concentrated on a task — reading, engaging in conversation or solving a math problem, for example — it switches to a default mode, a state of mind where we may muse, daydream or retrieve pleasant memories. When a young person is asked to concentrate on a specific task, they are easily able to shut off the default mode — and the corresponding regions of the brain that run this mode.

With the help of powerful imaging technologies such as positron emission tomography and magnetic resonance imaging, scientists, including Buckner’s HHMI team, have begun to map the activity of the brain in its different states, including the default state. Among the observations they are making is that when a person who has clinical AD is asked to concentrate on a specific task, the default mode actually becomes more active — rather than showing less activity, as it would in a young, healthy adult.

The default state, according to Buckner, is characterized by metabolic activity in specific regions of the brain, notably the posterior and cortical regions. “These regions were active in the default states in young adults and also showed amyloid (plaque) deposition in older adults with AD,” the researchers wrote.

"The key insight is that brain activity and metabolism are not uniform across the brain," Buckner said. "When we looked at people on the cusp of dementia, we saw a loss of brain tissue in the regions we predicted it would occur," based on their observations of metabolism.

Insight from the study may help explain why the memory systems of the human brain are vulnerable. "We appear to use memory systems often in our default states," Buckner said. "This may help us to plan and solve problems. Maybe it helps us be creative. But it may also have metabolic consequences."

The newfound correlation may also have future clinical implications, because Alzheimer’s is typically diagnosed when it is too late to intervene. To develop and administer effective treatments, clinicians will need to figure out ways to detect the disease in its earliest stages, said William E. Klunk, M.D., Ph.D., associate professor of psychiatry at the University of Pittsburgh and a co-author of the Journal of Neuroscience paper.

"You have to get to this pathology before it has its biggest effect, before it has done its damage," said Klunk, who has developed techniques for imaging the amyloid plaques in AD patients. (cont. on p. 4)
New Hypothesis (continued)

Klunk said the findings suggest there is now the potential to begin to trace the patterns of the disease and develop methods to detect it before the clinical symptoms set in.

Buckner emphasized that the notion of a causative relationship between everyday metabolic functions of the brain and Alzheimer's remains a hypothesis. However, new studies may help "show if amyloid (plaque) deposition is really dependent on metabolism. Moreover, looking to see if the phenomenon varies or is the same among many individuals will be required to firm up the link between brain metabolism in early life and Alzheimer's pathology later in life.

In addition to Buckner and Klunk, the study authors include Abraham Z. Snyder, Benjamin J. Shannon, Gina LaRossa, Rimmon Sachs, Anthony F. Fotenos, Yvette I. Sheline, John C. Morris and Mark A. Mintun, all of Washington University; and Chester Mathis of the University of Pittsburgh.

Support the ADRC

Want to make a holiday or memorial gift? You may support our research, education and service goals by joining the Friends of the ADRC. Members of the Friends are entitled to attend periodic Friends Receptions featuring presentations on research findings from Dr. John C. Morris, Director of the ADRC, and other investigators, and also receive free admission to various ADRC-sponsored conferences. Friends are encouraged to make an annual gift in support of the ADRC.

Donations from Friends support both the infrastructure upon which the ADRC depends, as well as specific research and educational projects of the Center. Private donations help to fund promising pilot research projects (i.e., small projects to test out new ideas), educational conferences such as the Leonard Berg Symposium series, the training of medical students and fellows, and other worthwhile projects.

To join, simply call (314-286-241) or e-mail (adrcfriends@abraxas.wustl.edu) the Friends Coordinator.

Molecular drug pump may help reduce risk of Alzheimer's

By Michael Purdy

A molecule that has long been an obstacle to cancer chemotherapy and drug treatments for brain disorders may soon become an ally in the fight against Alzheimer's disease, according to researchers at Washington University School of Medicine in St. Louis and the University of Rochester. The Journal of Clinical Investigations will publish their results online on Oct. 20.

In studies in genetically modified mice, scientists found that the molecule, P-glycoprotein (Pgp), accelerates clearance from the brain of amyloid beta (A-beta) peptide, the primary component of the plaques that are the hallmark of Alzheimer's disease.

According to scientists, the new link is potent and intriguing enough to suggest several potential follow-up studies, including investigations of how pharmaceuticals might affect Alzheimer's risk by altering Pgp activity levels.

"We would never claim that Pgp activity is the single critical causative factor in Alzheimer's disease, just like there isn't any single cause of heart attacks, hypertension or cancer," says author David Holtzman, M.D., the Andrew B. and Gretchen P. Jones Professor and head of the Department of Neurology. "But our evidence suggests that it may be one of the more significant risk factors so far identified."

Scientists are already familiar with a variety of drugs that can promote and suppress Pgp activity. The new connection may, for example, explain a puzzling study that suggested the antibiotic rifampin could slow the decline of patients with mild to moderate Alzheimer's.

"That result didn't seem to be linked to the drug's antibiotic properties, and now we have a much more appealing explanation: rifampin is a known inducer of Pgp activity," says co-author David Piwnica-Worms, M.D., Ph.D., professor of molecular biology and pharmacology and of radiology at Washington University. "Researchers will likely be evaluating this drug and other known Pgp promoters as potential ways to reduce risk."

Several drugs regularly prescribed over extended periods of time are also known to suppress Pgp activity. These drugs include some calcium channel blockers, immune suppression drugs and anti-depressants. Such compounds may need to be reevaluated for potential effects on long-term risk of Alzheimer's disease.

Scientists emphasized that the pharmaceuticals that suppress Pgp have confirmed medical benefits, while their potential to increase Alzheimer's risk is still tentative and unconfirmed. They strongly urged against any thought of stopping a prescription on the basis of their study alone.

When German scientists published in vitro evidence in 2000 that Pgp might transport A-beta, the labs of Holtzman and Piwnica-Worms independently read the findings. Pgp is one of several molecular transporters that form the blood-brain barrier, a layer of cells that strictly limits the ability of many types of molecules—including many drugs—to enter the brain via the circulatory system.

"Everything that's in the spaces between the cells of the brain can get out (to the blood stream) passively, but the A-beta peptide appeared to be getting out of the brain at a high speed that was consistent with it being helped out of the brain by other mechanisms," he explains.

Meanwhile, Piwnica-Worms' lab had spent more than a decade studying Pgp's role in resistance to chemotherapy. "When tumor cells make Pgp, they can use it to pump cancer chemotherapy agents out of themselves and increase their chances of surviving the chemotherapy," explains Piwnica-Worms.

John R. Cirrito, a fellow in Holtzman's lab, contacted Piwnica-Worms about the potential overlap, and the two labs combined their expertise to study whether Pgp transports A-beta out of the brain. This work continues.
Sleep disturbances are common in older adults. Transient insomnia, lasting 5-7 days, is usually the result of environmental stress, and typically doesn’t require treatment. If treatment is given, no more than 2-3 doses are usually necessary. Chronic insomnia is characterized by sleep disturbance lasting longer than 1 month. Older adults are particularly vulnerable for sleep changes due to normal physiologic changes in the sleep cycle with age. Normal sleep progresses through four stages. Stages 1 and 2 are lighter stages, while stages 3 and 4 are deeper, more restful stages. In the elderly, substantially less time is spent in stages 3 and 4, and some data suggests that these stages may completely disappear in extreme old age. Insomnia can also be caused by situational, medical, and psychiatric factors such as major life events, pain conditions, respiratory disorders, Cardiovascular (CV) disorders, anxiety, and drug use.

### Treatment

Sleep Hygiene can be an effective alternative to drug therapy, and this should be considered first in persons suffering from insomnia. Sleep hygiene consists of alterations to one’s daily routine that provide for more restful sleep. Persons suffering from insomnia should avoid daytime naps, caffeine, nicotine and alcohol. Drinking large quantities of liquid or eating a heavy meal within a few hours before bedtime are not recommended. It is important to develop a bedtime ritual and keep a consistent schedule each day. Regular exercise and physical activity during the day, as well as relaxation techniques in the evening, can alleviate sleep difficulties. Make the bedroom a comfortable environment by preventing extreme temperatures, loud noises, and removing illuminating clocks. For more information on sleep and aging, visit NIH Senior Health at http://nihseniorhealth.gov/sleepandaging/toc.html.

A special contribution from Dana Asaro, Pharm.D. Candidate, St. Louis College of Pharmacy.

### FDA Approved Medications for Sleep

<table>
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<tr>
<th>Drug Name</th>
<th>Medication Type</th>
<th>Side Effects</th>
<th>Dosing</th>
<th>Comments</th>
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<tr>
<td><strong>Ambien</strong></td>
<td>A non-benzodiazepine sedative-hypnotic medication for the short-term treatment of insomnia</td>
<td>Drowsiness, amnesia, dizziness, headache, nausea, diarrhea.</td>
<td>10mg p.o. h.s. (In elderly patients dose should be reduced to 5mg HS)</td>
<td>Normally preserves deep sleep of stages 3 and 4. Schedule IV controlled substance.</td>
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<tr>
<td><strong>Sonota</strong></td>
<td>A short-acting, non-benzodiazepine sedative-hypnotic shown to decrease the time to sleep onset</td>
<td>Headache, dizziness, somnolence</td>
<td>10mg p.o. h.s. (In elderly patients dose should be reduced to 5mg HS)</td>
<td>Shown to decrease time to sleep onset. Less likely to have rebound insomnia or withdrawal. Schedule IV controlled substance.</td>
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<tr>
<td><strong>Lunesta</strong></td>
<td>A non-benzodiazepine sedative-hypnotic indicated for chronic treatment of insomnia</td>
<td>Headache, diarrhea, dyspepsia, dry mouth, dizziness.</td>
<td>2-3mg p.o. h.s. (In elderly patients dose should be reduced to 1-2 mg HS)</td>
<td>Indicated to decrease sleep latency and improve sleep maintenance. First indicated for treatment of chronic insomnia. Withdrawal possible Schedule IV controlled substance.</td>
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<tr>
<td><strong>Rozerem</strong></td>
<td>Targets the melatonin receptor. Approved for the treatment of insomnia due to prolonged sleep onset</td>
<td>Headache, somnolence, fatigue, dizziness, nausea. May cause decreased testosterone and/or increased prolactin levels in some individuals.</td>
<td>8mg p.o. h.s. (Avoid taking with or after a high fat meal)</td>
<td>Indicated for the treatment of insomnia characterized by difficulty with sleep onset. Not a controlled substance.</td>
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### Controlled Substances Schedule:

I—High abuse potential, no medical use (eg, Heroin)
II—High abuse potential, severe dependence risk, limited medical use (e.g., Methamphetamine)
III—Moderate abuse potential, medical use (eg, Vicodin)
IV—Some abuse potential but less than I-III (eg, Darvocet)
V—Lowest abuse potential of the group (eg, Robitussin AC)
Rx—No documented abuse potential, but requires prescription.

### Abbreviations:

- p.o. = By Mouth
- h.s. = At bedtime

### Notes:

Other approved treatments for insomnia include some antihistamines, tricyclic antidepressants, benzodiazepines, and hypnotics. In addition there are several marketed herbal products for sleep aid, such as melatonin and valerian root. The safety and efficacy of these products have not been determined.
On June 24, the ADRC hosted the 2nd Annual Regional CME Conference, entitled “Providing Quality Dementia Care: The Critical Role of the Primary Care Clinician”, in partnership with five sister Alzheimer’s Disease Centers from the following institutions: Rush University (RU), University of Michigan (UM), Indiana University (IU), University of Kentucky (UKY), and Northwestern University (NU).

Over 160 area physicians and other health professionals attended this informative and enjoyable event.

Faculty Presenters:
Julie Schneider, MD (RU)
John Morris, MD (WU)
William Markesbery, M.D., (UKY)
Martin Farlow, MD (IU)
Judith Heidebrink, MD, MS (UM)
Darby Morhardt, MSW (NU)
Stephanie Rohlfs-Young, MSW, Alzheimer’s Association, St. Louis
Charles Crecelius, MD, PhD (WU)
David Holtzman, MD (WU)

Attendees Appreciated Most:
- Great mix of theory & practice!
- Focus on patient + family + medical team interactions
- Adequate time given to topics - not rushed
- Candid response from speakers about their practice of Diagnosis and Treatment
- Great panel discussion at end

The 3rd Annual Regional CME Conference will take place in Lexington, KY, on May 17, 2006. Contact Dr. David Wekstein for information: dwekstein@aging.coa.uky.edu

On Thursday, November 3rd, the sweet fruits of 15 months of collaborative effort were realized with the St. Louis debut of For Pete’s Sake, a play by Cleveland playwright, DaNine K. Ward. This free public event featured a “Meet the Playwright” and dessert reception, a private reception to educate local physicians about AD, and a dramatic reading by actors from the St. Louis Black Repertory Company. Ms. Ward and Darlyne Redd, Minority Recruiter for the Cleveland ADRC, which commissioned and first produced the play in 2003, shared their reflections with the 800-strong audience.

Playwright, DaNine K. Ward, & her husband, Terrance, enjoy the performance.

The St. Louis Chapter of the Alzheimer’s Association jointly sponsored the program with the ADRC. The Delta Sigma Theta Sorority and Mound City Medical Forum were co-sponsors, and a number of other organizations helped promote the event. The program was very well received and was capped off with a standing ovation. A large number of attendees (n = 363) completed a brief survey prior to the performance. Findings: 81% Female, 77% African American, 48% current/former caregivers, and 50% interested in helping with research.

Left to right: John C. Morris, MD, ADRC Director; Consuelo Wilkins, MD, WU Physician and President, Mound City Medical Forum; Dorothy Edwards, PhD, ADRC Investigator; & special guest speaker, Patrick Griffith, MD, Meharry Medical College, Nashville, Tennessee.
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<th>Enrollment Ongoing</th>
<th>Study Coordinator</th>
<th>Angela Oliver, MSN, RN</th>
<th>Angela Berry, MSN, RN</th>
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<th>Christy Tomison, MSN, RN</th>
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<td>Information Table – Active Clinical Trials through the MAP-ADRC (Fall 2005)</td>
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Notables

**Steve Balsis**, a student in the Aging and Development Program in the Psychology Department won an award for student research at the annual meeting of the American Psychological Association in Washington, DC, August 2005. His project, conducted through the ADRC, was titled “Personality Change Precedes Clinical Diagnosis of Dementia of the Alzheimer Type.” It was published in 2005 in the Journal of Gerontology: Psychological Sciences.

**Alison Goate**, D.Phil., the Samuel and Mae S. Ludwig Professor of Genetics in Psychiatry, and professor of genetics and of neurology, will receive the Carl and Gerty Cori Faculty Achievement Award on December 3rd. In addition, Dr. Goate recently received a $200K, 5-year grant as part of a National Institute on Aging effort to start a Genetics Consortium for Late Onset AD.

**David Johnson**, PhD, Research Associate, published his first 1st-authored paper as part of the ADRC research team—entitled Verbal and visuospatial deficits in dementia with Lewy bodies—in the October 2005 issue of the journal Neurology. John C. Morris, MD, and James E. Galvin, MD, were co-authors.

**John Heuser**, MD, Professor of Biophysics and ADRC-affiliated investigator, was inducted recently as a new Fellow of the American Academy of Arts and Sciences and also named the Bernard Katz Honorary Lecturer of the Biophysical Society, with the opportunity to deliver the keynote address at their annual meeting in Salt Lake City in Feb, 2006.

On November 19th, ADRC Director and Friedman Distinguished Professor of Neurology, **John C. Morris**, MD, was honored with the Zealot Award by the Monsanto Family YMCA at their 5th Annual Tuxedo & Tennis Gala. Dr. Morris was the recent recipient of the 2005 Physician-Scientist Lifetime Achievement Award from the Barnes-Jewish Hospital Foundation. Finally, he was recently named a “St. Louis Healthcare Hero” by the St. Louis Business Journal.

**Eugene M. Johnson**, PhD, ADRC Associate Director and Professor of Molecular Biology & Pharmacology, reports that the neurotrophic factor he discovered with WU colleagues Drs. Jeff Milbrandt, Paul Kotzbauer, Pat Lampe, recently entered into Phase 1 clinical trials for the treatment of Parkinson's disease. The factor is administered via gene therapy and, if proven effective, would provide another avenue for treatment of this devastating disease.