NIA Press Releases Featuring NIA-Funded ARRA Research Projects

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- ***http://recovery.nih.gov/stories/ucsf_genetics.php***
- ***http://recovery.nih.gov/stories/posterday2009.php***

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Recovery Funds Advance Alzheimer's Disease Research

November 23, 2009

American Recovery and Reinvestment Funds are being used to promote the national research efforts to better understand, diagnose and treat Alzheimer's disease. The National Institute on Aging (NIA), part of the National Institutes of Health, has targeted promising areas of research in granting the awards, such as new and ongoing studies to identify additional risk factor genes associated with Alzheimer's, improve diagnostic tools, find biomarkers, develop therapies, conduct clinical trials and explore preventive measures.

"We are delighted to announce the award of Recovery Act funds to many dedicated, hardworking scientists committed to advancing scientific discovery into Alzheimer's disease and cognitive impairment," said NIA Director Richard J. Hodes, M.D. "Over the next two years, the recipients will use this unprecedented boost in research funds to help reach our ultimate goal of understanding age-related cognitive decline and reducing the individual and societal burden of this devastating disease."

More than 100 Alzheimer's or Alzheimer's-related research grants were awarded under the Recovery Act. The full list of NIH grants can be found at *http://grants.nih.gov/recovery/*. The grants featured here highlight how these funds will expand research. Some of the funding will advance the work of existing NIA initiatives that benefit from large-scale collaborative, interdisciplinary research:

The Neuroimaging Initiative – Identifying brain changes before symptoms appear

The Alzheimer's Disease Neuroimaging Initiative (ADNI) will receive $24 million in stimulus funds—half from the NIA and half contributed by the NIH Office of the Director—to further groundbreaking research to establish neuroimaging and biomarker measures. These funds will enable researchers—and ultimately practicing physicians—to track changes in the living brain as older people transition from normal cognitive aging to amnestic mild cognitive impairment (MCI), in which individuals have a memory deficit but generally retain other cognitive abilities, and from MCI to Alzheimer's disease. ADNI, a research partnership supported primarily by the NIA with private sector support through the Foundation for NIH, seeks to find neuroimaging and other biological markers that can be used to detect Alzheimer's disease progression and measure the effectiveness of potential therapies.

The original ADNI involved the study of 800 people who ranged from normal to those with late-stage MCI or overt Alzheimer's disease. This new grant expands the scope of ongoing research under ADNI by allowing for the enrollment of participants at an earlier stage of MCI, when symptoms are milder. Furthermore, the funding for this new grant will allow ADNI investigators to extend the length of the original study to better assess changes in individuals over time. All of the participants will have neuroimaging scans and blood and cerebrospinal fluid analyses to look for changes in the brain.

The overall impact of the added funding will be increased knowledge of the sequence and timing of events leading to MCI and Alzheimer's disease and development of better clinical and imaging/fluid biomarker methods for early detection and for monitoring the progression of these conditions. This will facilitate clinical trials of treatments to slow disease progression and will ultimately contribute to the prevention of Alzheimer's disease. Just this year, ADNI made a significant step forward in developing a

test to help diagnose the beginning stages of Alzheimer's disease sooner and more accurately by measuring levels of two biomarkers—tau and beta-amyloid proteins—in cerebrospinal fluid.

"Researchers and clinicians need imaging and biomarker tools to detect and understand the very earliest signs of pathology that cause changes in the brain some 10 to 20 years before any clinical symptoms of cognitive impairment or Alzheimer's may appear," said ADNI Principal Investigator Michael Weiner, M.D., of the San Francisco Department of Veterans Affairs Medical Center and the University of California, San Francisco. "This grant will help us in our goal of establishing a panel of biomarkers that predict those at risk of developing the disease and also reveal which therapies may be effective in treating the disease or preventing its progression."

The grant was awarded to the Northern California Institute for Research and Education, a nonprofit research foundation affiliated with the San Francisco VA Medical Center. ADNI is the largest public-private partnership on brain research under way at the NIH. In addition to the NIA, the federal ADNI partners are the National Institute of Biomedical Imaging and Bioengineering, also part of NIH, and the U.S. Food and Drug Administration, another agency of the U.S. Department of Health and Human Services.

The AD Genetics Consortium and more – Identifying genes affecting risk for late-onset Alzheimer's

A grant of more than $5.4 million will add 3,800 Alzheimer's patients and an equal number of people free of the disease to a previously funded study by the Alzheimer' Disease Genetics Consortium (ADGC). Gerard Schellenberg, Ph.D., University of Pennsylvania School of Medicine, Philadelphia, leads the consortium, which aims to identify the additional risk factor genes for late-onset Alzheimer's disease. All of these study participants are currently enrolled in the NIA-funded national network of 29 Alzheimer's Disease Centers. When added to the samples from other sources, this will make available one of the largest collections of samples to perform genome-wide association studies (GWAS) in an effort to identify the susceptibility and protective genes influencing the onset and progression of late-onset disease. The large number of DNA samples brought together in this study may enable the researchers to detect genes whose individual effects in the disorder may be small but may still play a role.

The ADGC will use research infrastructures previously established by NIA to store and make available to qualified researchers DNA samples, datasets containing a wealth of information about participants, and genetic analysis data. The combined resources will allow scientists also to search for genes associated with a number of traits associated with Alzheimer's, as well as for genes related to cognitive decline.

"This funding will bring us closer to identifying the elusive genetic variations that contribute to overall risk and development of late-onset Alzheimer's disease," said Marcelle Morrison-Bogorad, Ph.D., director of the NIA Division of Neuroscience. "With this large sample size and the rapid DNA sample and data sharing, there are tremendous opportunities for defining new disease pathways that could lead to the development of new therapies."

Additionally, $4.7 million in Recovery Act funds will be used for another important study—a GWAS project examining cognitive decline in older African-Americans. Denis Evans, M.D., of Rush University Medical Center in Chicago, will collect and analyze the DNA of 4,140 elderly African-Americans enrolled in NIA-funded aging studies already taking place in Chicago and Indianapolis. Data from this analysis will also be shared with the ADGC to help identify risk factor genes for cognitive decline and late-onset Alzheimer's. The study will assess the associations of over 900,000 genetic markers with other co-morbidities, including stroke and high blood pressure.

Another $820,000 in Recovery Act funds will advance Alzheimer's genetics research by developing methods for identifying combinations of genes that might influence age-related risk of AD. The role of different forms of translocase of outer mitochondrial membrane (TOMM40), a gene that makes a protein thought to play a role in disease onset, will be studied by Allen Roses, M.D., of the Duke University School of Medicine in Durham, N.C.; Roses discovered the link between the apolipoprotein E (APOE)-epsilon 4 gene and increased risk for late-onset Alzheimer's disease. This new study will investigate whether particular variants of TOMM40 that tend to co-occur with the APOE3 gene also interact with that gene, and if this interaction plays a role in the age of disease onset.

Additional Recovery Act research opportunities

Other studies made possible by the Recovery Act range from clinical trials to epigenomic studies to translational research:

- Drug, exercise clinical trials – A clinical trial exploring whether low doses of an anti-epileptic seizure drug, levetiracetam, can improve memory and affect brain function in people with MCI will be conducted with $1.2 million in support. Michela Gallagher, Ph.D., of Johns Hopkins University, Baltimore, will use functional MRI to visualize activity in the hippocampus—a brain area that becomes overactive in MCI patients—while the clinical trial participants receiving either the drug or a placebo engage in memory tasks. In another trial, researchers will examine how exercise training, cognitive training, or a combination of both, might impact immune and inflammatory biomarkers and cognitive health in older adults with MCI. The randomized trial, under a $1 million grant to David Lowenstein, Ph.D., of the University of Miami, will examine a broad array of outcomes and will include Hispanic and non-Hispanic volunteers.
- Epigenetics /translational research – A $1 million grant will support a study exploring whether changes in histone acetylation (an epigenetic, or non-genetic factor that causes genes to behave differently) are one way in which a variety of life experiences may influence the risk of developing age-related cognitive decline and dementia. David Bennett, M.D., of Rush University Medical Center, Chicago, will use brain tissues from the NIA-funded Memory and Aging Project and the Religious Orders Study to examine this question. Another epigenomics grant of $819,000 will be used in translational research to test whether overexpressing histone deacetylase (HDAC1) with small molecule probes in the brain may demonstrate therapeutic potential for Alzheimer's and stroke patients. Li-Huei Tsai, Ph.D., of Massachusetts Institute of Technology, Boston, will lead the study, which seeks to find out whether abnormal regulation of the protein may play a role in neurological disorders.

Recovery Act Funding Seeks to Help Understand Basic Secrets of Aging

November 23, 2009

The National Institute on Aging (NIA), part of the National Institutes of Health, today announced two major awards to advance exciting areas of basic research on aging. Grants for studies to determine the potential healthy aging effects of rapamycin, a compound involved in regulating cell growth, and to understand the causes of protein misfolding—when a protein is either not formed correctly or damaged afterwards—that lead to age-related disease are made possible through American Recovery and Reinvestment Act funding. These grants are part of the $5 billion that President Obama announced Sept. 30 on the National Institutes of Health campus.

"This is a remarkable time in aging research. Our knowledge about the basic biology of aging has grown rapidly in recent years, and the studies supported with Recovery Act funds provide a wonderful opportunity to build on what we know in some key areas," said NIA Director Richard J. Hodes, M.D. "These studies, at the cellular level, will increase our understanding of some of the basic biological processes that occur with passage of time."

Study in Mice to Determine Possible Healthy Effects of Rapamycin

NIA has awarded $5.2 million over the next two years to the University of Texas Health Science Center in San Antonio to determine the effects of rapamycin on the health of mice.

"In a recent study, a team of researchers reported that rapamycin extended the median and maximal lifespan of mice, when the drug was fed to the mice beginning in middle age. With Recovery Act funding, we can more quickly follow up on these exciting and provocative findings," said Felipe Sierra, Ph.D., director of NIA's Division of Aging Biology.

Rapamycin—an inhibitor of the mTOR pathway that helps to regulate cell growth and proliferation and that is used to help suppress the immune system in people undergoing organ transplant—is one of many compounds being studied for effects that might be similar to those of calorie restriction. Calorie restriction, very low calorie but nutritious diets that have been tested in laboratory animals and on a limited basis in humans, has been found to have variety of positive effects on health and longevity. Despite these findings, calorie restriction may not be practical or safe for most people.

The study, led by Arlan Richardson, Ph.D., will seek answers to three questions:

1. How does rapamycin affect models of age-related human diseases in mice?
2. How does rapamycin affect normal physiology?
3. By what mechanisms does rapamycin work?

"Under normal circumstances, it took over 10 years of research to demonstrate that caloric restriction retarded age-related diseases and increased healthspan. However, Recovery Act funding will allow us to determine in two years if rapamycin can retard or reduce age-related diseases and improve quality of life in mice," said Richardson.

The team will test rapamycin's effects on multiple models of Alzheimer's disease, atherosclerosis, cardiovascular disease, Parkinson's disease, kidney disease and cancer. In addition, investigators will look

at rapamycin's effects on the physiology and behavior of healthy mice, focusing special attention on the response to infection, metabolism, movement and cardiac function.

Study to Develop New Technologies to Monitor Protein Folding

NIA has awarded $1 million to Northwestern University in Evanston, Ill., and the Salk Institute in La Jolla, Calif., and $1 million to The Scripps Research Institute in La Jolla, to develop new technologies—biosensors—that will monitor aging and age-related disease by focusing on protein folding.

The proper folding of proteins in cells, or proteostasis, is important for health. Like a three-dimensional puzzle, sections of a protein naturally fold into shapes and then arrange themselves to align to each other to produce the final active protein. A protein's function in the body depends on these folding patterns. If a protein is formed incorrectly or becomes damaged and then misfolds, it disrupts the pattern. As a consequence, the protein does not perform its normal function or cannot be properly disposed of by cellular machinery. These problems and consequences on cellular proteostasis may lead to disease.

"Scientists already know that proper protein folding may be affected by age. Protein misfolding inhibits the body's ability to respond to environmental and/or physiological stresses and cues and could lead to age-related diseases like Alzheimer's or Parkinson's. This Recovery Act funding provides an opportunity to better understand the role of proteostasis and the aging environment in which protein misfolding occurs," said NIA's Sierra.

The Recovery Act funding will also support the development of the Proteostasis Aging Sensor Consortium (PASC) comprised of five investigators, representing leaders in the fields of protein folding, human cell biology and aging. The highly complementary skill sets of these investigators will create synergy to implement these new technologies within the time frame of the Recovery Act funding.

The researchers from Northwestern University led by Richard Morimoto, Ph.D., and from the Salk Institute led by Andrew Dillin, Ph.D., will develop new tools to detect protein misfolding first in a worm model and then in mammalian tissue culture cells. Researchers from The Scripps Research Institute led by William Balch, Ph.D., Jeffery Kelly, Ph.D., and Rockland Wiseman Ph.D., will use some of the tools developed by the Northwestern and Salk teams as well as their own to test protein misfolding in different compartments of mammalian cells in culture and in mice. The five investigators established the PASC to coordinate collaboration in the design, test and use of all the tools designed to follow protein folding and misfolding in cells.

"Aging is highly complex, involving multiple and variable metabolic and biochemical parameters. These studies could lead to first-in-class biosensors that would detect key features of the aging environment and its response to stress and disease," said Richard Morimoto, Ph.D., principal investigator and professor of biochemistry, molecular biology and cell biology at Northwestern University. "Ultimately, biosensors aim to enable researchers to monitor disease progression and the response to therapeutic intervention in real time."

What Can Prevent Walking Disability in Older People?

Recovery Act Funds Support Large-Scale Clinical Trial to Test Specific Exercise Program

November 4, 2009

The National Institute on Aging (NIA), part of the National Institutes of Health, today announced the award of $29.5 million in grant support over the next two years to determine whether a specific physical activity program can stave off disability in older people. The funding will begin the Lifestyle Interventions and Independence for Elders—LIFE— trial, the largest ever undertaken to prevent mobility disability among older people who are at risk of losing their ability to walk and to live independently in the community. The grant is being awarded to the University of Florida's Institute on Aging in Gainesville.

The first two years of the six-year, eight-site LIFE trial are being funded through the American Recovery and Reinvestment Act. The grants are part of the $5 billion that President Obama announced Sept. 30 on the NIH campus.

"There is a lot of evidence indicating that exercise can help in preventing diseases, such as diabetes, among older people. But we do not know whether and how a specific regimen might prevent walking disability in older people who are at risk of losing mobility," said NIA Director Richard J. Hodes, M.D. "This research is critically important at a time when the population is aging and new interventions should be sought to keep people healthy and functioning in the community longer."

At eight sites around the country, LIFE will involve 1,600 people aged 70 to 89, who at the start of the study meet its criteria for risk of walking disability, defined as the inability to walk a quarter of a mile or four blocks. About 200 participants will be enrolled at each of the study sites, which include the University of Florida; the University of Pittsburgh; Northwestern University School of Medicine in Chicago; Stanford University in Palo Alto, Calif.; Pennington Biomedical Research Center in Baton Rouge, La.; Yale University in New Haven, Conn.; Tufts University in Boston and Wake Forest University School of Medicine in Winston-Salem, N.C. Wake Forest will also coordinate the data management and analysis.

"Limitations in walking ability compromise independence and contribute to the need for assistive care," said Evan C. Hadley, M.D., director of NIA's Division of Geriatrics and Clinical Gerontology, whose program is overseeing the trial. "Older people with impaired walking are less likely to remain in the community, have higher rates of certain diseases and death, and experience a poorer quality of life. A successful intervention might help prevent these bad outcomes."

"We know that many older people have chronic health problems that affect their ability to walk," said Jack Guralnik, M.D., Ph.D., chief of the NIA's Laboratory of Epidemiology, Demography and Biometry and co-principal investigator of the study. "Arthritis, muscle weakness and poor balance can all affect how well and how far a person can walk. And, some older people have all of these problems. We will test the LIFE intervention in this population to see how it works in a real-world setting."

Study participants will be randomly assigned to one of two groups. One group will follow a structured intervention consisting of walking at moderate intensity, stretching, balance and lower extremity strength training; the control group will participate in a health education program. The participants will be followed for about three years. Researchers will evaluate whether, compared to health education, the physical activity intervention reduces the risk of major walking disability, serious fall injuries and

disability in activities of daily living, and whether it improves cognitive function. They will also assess the cost-effectiveness of the intervention.

“This will be the largest randomized controlled trial to prevent major mobility disability ever conducted in older persons who are at high risk of losing their physical independence,” said Marco Pahor, M.D., director of the University of Florida’s Institute on Aging and study principal investigator. “Typically, this population is excluded from large trials, and from this perspective the LIFE study is unique.”

NIA Extends Research on Health, Economics of Older Americans

Recovery Act Funds Will Enhance Long-Term Research Project

October 29, 2009

The National Institute on Aging (NIA), part of the National Institutes of Health, today announced the award of four grants totaling more than $19 million over the next two years to expand the Health and Retirement Study (HRS), the nation's premier long-term study and data resource on the combined health, economic, and social factors influencing the well-being of Americans over age 50.

The awards, made possible through the American Recovery and Reinvestment Act, are part of the $5 billion that President Obama announced Sept. 30 on the NIH campus. They will supplement the cooperative agreement between the NIA and the University of Michigan in Ann Arbor, which conducts the study.

"Since it began in 1992, the HRS has provided a wealth of information on the physical and economic health of older Americans," said NIA Director Richard J. Hodes, M.D. "With this infusion of Recovery Act funds, we can augment the quality of the data we are collecting, expand minority participation in the study cohort and add genetic analysis to the study."

The awards focus on data collection in four crucial areas:

- Enroll approximately 3,000 new participants, through the addition of more than 1,000 African-American and more than 1,000 Hispanic individuals. More than doubling the current oversampling of minority adults between the ages of 51 and 61 in the study will improve the statistical power of HRS data on the sources of disparities in health and economic status.
- Repeat collection of biomarker and psychosocial data in 2010 through face-to-face interviews with about 9,200 participants, from whom such data were first collected in 2006. This will enable researchers to analyze changes in these measures over time and link changes to other life circumstances and health events.
- Conduct genome-wide scans of previously collected saliva samples from approximately 13,000 participants. As a result, researchers will be able to perform multiple association studies to identify potential genetic risks and influences on a broad range of health conditions as well as social and behavioral aspects of normal aging. Researchers also will be able to better understand the environmental contexts in which genetic risk and protective factors are expressed.
- Conduct pilot research on methods for diagnosis of dementia, cognitive impairment without dementia or normal cognition for individuals in a subsample of 120 HRS participants age 70 or older. This will extend the methods of the 2001–2003 Aging, Demographics and Memory Study supplement to the HRS and set the stage for a better understanding of trends in the prevalence, causes and outcomes of dementia in the United States.

Integral to the success of the proposed expansion in the minority cohort, the Social Security Administration (SSA) has increased its longstanding support of the HRS, providing an additional $3 million of non-Recovery Act funds over the next two years. These funds provide support for the interviews of the new minority sample expansion. SSA's participation will also include linkages to pension and earnings data for these new members of the HRS, contributing to the enhancement of a valuable research data resource.

"We are gratified by the commitment of the Social Security Administration to the enlargement of the Health and Retirement Study's minority sample," said Richard Suzman, Ph.D., director of NIA's Division of Behavioral and Social Research, who was instrumental in conceptualizing and starting the study. "This will allow for more in-depth analyses of minority population data, which is critically important at a time when the older population is becoming more diverse."

Suzman also highlighted the opportunities for cutting-edge analyses that will be afforded as a result of the Recovery Act funding.

"We are excited by the potential for transforming social and behavioral science by adding genetic information to such a large, national longitudinal study," Suzman said. "The ability to link genetic information with social, psychological and economic data should result in much deeper understanding of how we age."

"The HRS is an outstanding partnership between government and academic research, and these new funds will create exciting new opportunities for the thousands of researchers who make use of this great resource," said David Weir, Ph.D., of the University of Michigan and principal investigator of the HRS. "We also expect to see new additions to the more than 10,000 researchers who have already registered to use the data and the more than 1,000 authors and co-authors who have published more than 1,400 publications and dissertations. HRS's success has become a role model for studies in over 20 countries who are now part of a remarkable international collaborative agenda of research on aging."

The HRS, now in its 17th year, follows more than 22,000 people over the age of 50, collecting data every two years, from pre-retirement to advanced age. To keep the study fully representative of the population over age 50, the HRS regularly adds new groups to the survey sample. The study provides data about these older Americans to help address the challenges and opportunities associated with population aging in the United States. The study's unique combination of data allows for better understanding of the nature of health and well-being in later life.

The 2007 NIA publication, "Growing Older in America: The Health and Retirement Study," summarizes 15 years of HRS findings and is available at *www.nia.nih.gov/ResearchInformation/ExtramuralPrograms/BehavioralAndSocialResearch/HRS.htm*. The HRS Web site, *http://hrsonline.isr.umich.edu*, provides more information on the study as well as an online bibliography of publications using the HRS data.