

April 15, 2008

Charles A. Sanders, M.D.  
Chairman  
Foundation for the National Institutes of Health  
9650 Rockville Pike  
Bethesda, MD 20814

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*Established by  
Evelyn F. McKnight  
to Alleviate Memory Loss  
in the Aging.*

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Dear Dr. Sanders,

**Trustees**

*John G. Clarkson, M.D.  
Miami, FL*

*J. Lee Dockery, M.D.  
Gainesville, FL*

*Michael L. Dockery, M.D.  
Charlotte, NC*

*Nina Ellenbogen Raim, M.D., J.D.  
Miami Beach, FL*

*SunTrust Bank  
Orlando, FL*

This letter of agreement ("Agreement") sets forth the terms under which the McKnight Brain Research Foundation ("MBRF") will provide funding in support of a Research Partnership in Cognitive Aging ("Partnership"), a research grant-making program to be conducted with the National Institute on Aging ("NIA"), through a public-private partnership coordinated by the Foundation for the National Institutes of Health, Inc. ("FNIH"). The two areas of research are described in attachment A.

The MBRF is aware that the purpose of FNIH, pursuant to 42 U.S.C. § 290b, is to support the NIH in its mission and advance collaboration among universities, industry, and other non-profit organizations. Collaboration through FNIH will allow MBRF to build on the outcomes of the October 2007 Cognitive Aging Summit by committing financial resources to the Partnership in support of peer-reviewed research grants in two of the areas identified as an outcome of the Summit: 1) Interventions to Remediate Age-Related Cognitive Decline (as described in Attachment A), and 2) Neural and Behavioral Profiles of Cognitive Function in Aging (as described in attachment A). As outlined below and in attachments A and B, NIA will establish and coordinate the grant-making program and will match the MBRF's contribution, investing a total of at least \$5 million in grant funding over the five-year period.

MBRF desires to support the Partnership by providing funding to FNIH as set forth below, under the following terms.

1. **Funding:**

- a. *Payments* – MBRF agrees to provide \$5,000,000, payable in equal annual installments over five years. MBRF's funding is conditioned upon NIA's investment of at least \$5 million in grant funding in this research partnership over the five-year period. The installments from MBRF shall be payable on the following schedule:

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*Payment 1: July 1, 2009*  
*Payment 2: July 1, 2010*  
*Payment 3: July 1, 2011*  
*Payment 4: July 1, 2012*  
*Payment 5: July 1, 2013*

b. *Use of funds* – FNIH shall use the funding provided by MBRF solely for the purpose of funding the Partnership, except that the FNIH shall retain a fee of five percent (5%) of each payment to cover its costs associated with administering and overseeing the Program.

c. *Time and place of payment.* All payments shall be delivered by MBRF to:

Ms. Amy McGuire Porter  
Executive Director  
Foundation for the National Institutes of Health  
9650 Rockville Pike  
Bethesda, MD 20814

or sent via electronic transfer to:

SunTrust Bank  
1445 New York Avenue, NW  
Washington, DC 20005  
Account number: 209004037  
Routing number: 055002707  
For the account of the Foundation for NIH.

2. **Content and Administration:** FNIH will provide funds to the NIA for use in funding the Partnership, consistent with the agreement in place between NIA and FNIH. MBRF acknowledges and agrees that NIA will establish and coordinate the grant-making program and will have responsibility for and control over the solicitation, funding, and administration of any contracts or agreements related to the Partnership. The Partnership concept and grant making areas agreed to are described in Attachment A.
3. **Donor Involvement and Recognition:** As a partner in the research grant program, MBRF will be involved with and acknowledged for its partnership with NIA and the FNIH in a number of ways, as outlined in Attachment B.

In addition, FNIH will work with MBRF to appropriately acknowledge MBRF in all widely disseminated public print or electronic communications regarding the Partnership and on the Foundation's web site, [www.fnih.org](http://www.fnih.org). FNIH agrees to share drafts of such communication with MBRF for review and comment prior to their public availability or dissemination. It is understood that MBRF will share drafts of all widely disseminated public print or electronic communications regarding the Partnership, including news releases, with FNIH for review and comment prior to public availability or dissemination.

4. **Cognitive Aging Summit II:** MBRF agrees to jointly support, subject to agreement with NIA, a second Cognitive Aging Summit, to be held in 2010.
5. **Responsible Personnel:** Teresa W. Borcheck, Corporate Trustee, will represent the MBRF as the primary contact and can be reached at (407) 237-5907 or [teresa.borcheck@suntrust.com](mailto:teresa.borcheck@suntrust.com).

Julie Wolf-Rodda, Director, Partnership Development, will serve as the primary FNIH contact and can be reached at 301.402.6027 or [jwolf-rodde@fnih.org](mailto:jwolf-rodde@fnih.org). Other relevant FNIH contacts are:

Julie Tune, Chief Financial Officer, [jtune@fnih.org](mailto:jtune@fnih.org), 301-435-6246

Charles Pucie, Communications Director, [cpucie@fnih.org](mailto:cpucie@fnih.org), 301-435-6248

Shawn Neil, Development Systems Manager, [sneil@fnih.org](mailto:sneil@fnih.org), 301-594-9865

6. **Disposition of Unused Funds:** Should the Partnership terminate prematurely, FNIH shall return to MBRF all uncommitted funds or in keeping with MBRF wishes and at the discretion of the FNIH Board of Directors, redirect them to another FNIH project or purpose.
7. **Disclosures:** MBRF's support and participation in the Partnership may be disclosed at any time by FNIH subject to prior approval of the MBRF.
8. **Donor's Business:** MBRF's funding of the Partnership is not in any way conditioned upon any present or future business relationship between MBRF and FNIH.
9. **Entire Agreement:** The terms of this Agreement shall be construed according to the laws of the State of Maryland. This Agreement shall supersede any previous understandings or agreement, written or otherwise. This Agreement may only be amended by a written instrument signed by both parties.

Please indicate acceptance of this grant and certification that these funds will be used in support of the indicated Partnership by having an authorized representative of FNIH sign the duplicate originals of this letter. After the letter has been signed, please return one original to MBRF for our files.

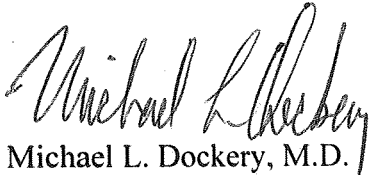
Sincerely,



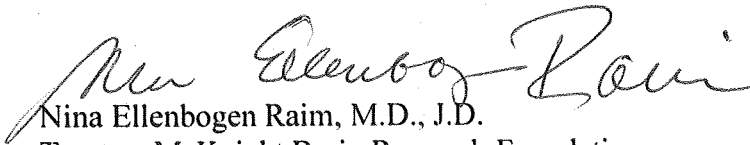
J. Lee Dockery, M.D.  
Trustee, McKnight Brain Research Foundation



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Trustee, McKnight Brain Research Foundation



Michael L. Dockery, M.D.  
Trustee, McKnight Brain Research Foundation



Nina Ellenbogen Raim, M.D., J.D.  
Trustee, McKnight Brain Research Foundation



Teresa W. Borcheck  
Corporate Trustee, McKnight Brain Research Foundation

Attachments

ACCEPTED AND AGREED to this 6th day of MAY, 2008.

FOUNDATION FOR THE NATIONAL INSTITUTES OF HEALTH, INC.

By: 

Name: Charles A. Sanders, M.D.

Title: Chairman

Tax ID No: 52-1986675

## ATTACHMENT A:

### Research Partnership in Cognitive Aging Grant Making Program Overview

#### Introduction

The Cognitive Aging Summit, held in Washington D.C. in October 2007, showcased the cutting edge research into the understanding and treatment of age-related declines in cognitive function, highlighting the importance to society of maintaining healthy brain function into older age. Two days of scientific presentations attended by 250 participants were followed by a half day Executive Session to further discuss scientific opportunities and needs. The primary objective of the Executive Session was to develop recommendations for future research directions. The recommendations can be distilled into some major themes:

- Acceleration of the development and testing of interventions
- Movement toward personalized interventions, “personalized medicine,” for maintenance of cognitive health
- Investigation of ways to enhance adherence to interventions
- Characterization of behavioral and neural aging to create a taxonomy or “gold standard” for both behavioral and neural profiles of successful aging. Such characterizations will be important for designing and assessing interventions.
- Encouragement of multidisciplinary training programs
- Encouragement of multidisciplinary and interdisciplinary research teams. Idea of having a network or consortium of investigators across university settings
- Development and/or expansion of methodologies for data analytic approaches, including dynamic modeling

Promising areas that could be developed with most expediency and that would incorporate all four themes include (1) preliminary research on promising interventions, particularly ones that incorporate a multi-faceted, or combinatorial approach and (2) the development of gold standards for behavioral and neural profiles of healthy aging. Both of these research directions will necessitate multidisciplinary approaches in order to be successful. It is anticipated that a secondary benefit of pursuing these research directions will be the development or expansion of dynamic modeling and data analytic approaches in order to appropriately interpret the data generated.

In partnership with the McKnight Brain Research Foundation, the National Institute on Aging would develop a grant making program supporting research in these areas, as described below.

### **Interventions to Remediate Age-related Cognitive Decline**

Age-related-cognitive decline will affect many older individuals and may have an impact on their independence and vitality. At the Cognitive Aging Summit, a vibrant discussion occurred on the prospects for implementing interventions that might prevent, reduce or reverse the course of age-related cognitive decline. Feedback from participants focused on the need for moving forward on investigation of promising, new intervention strategies, both singly and in combination, to establish initial levels of efficacy of the proposed interventions and to lay the groundwork necessary to plan full-scale clinical trials. Some drug clinical trials are under way, but it is clear that behavioral (exercise, social engagement, stress reduction, enhancement of self-efficacy), environmental, technological, dietary and dietary supplement, and community-based approaches also have considerable promise. The National Institute on Aging (NIA) and the National Institute of Nursing Research support the largest randomized clinical trial of cognitive training interventions (ACTIVE) that has achieved some positive results. Recent NIA-supported clinical trials also show that there are short-term beneficial effects of aerobic exercise on brain volume and cognitive function.

There is a clear need for a coordinated research program to develop new, more effective interventions and to identify which treatments or combination of treatments would be most effective for maintaining cognitive health in the long-term. Although many interventions have positive effects on memory and cognition, the underlying mechanisms for these treatments are unclear and there is considerable uncertainty about why some individuals do or do not respond to specific interventions. New analytic strategies offer the promise of being able to target interventions to individuals, significantly enhancing efficacy and efficiency. An equally important and complementary need is the determination of the most cost effective method(s) of introducing these interventions and facilitating adherence and therefore maintenance of cognitive improvements.

### **Neural and Behavioral Profiles of Cognitive Function in Aging**

Most people experience some deterioration in cognitive function as they age. The biological and psychological bases for selective loss of such functions as attention, memory, and executive skills are not, however, fully understood. With the aging of the U.S. population, maintenance of cognitive health into late old age is becoming more important for older workers and retirees, while the range of late-life outcomes is becoming more diverse. Given the economic and social devastation of cognitive decline and dementing illnesses and the NIH mandate to examine means of maintaining cognitive health, it has become imperative to better understand the neural, physiological, and behavioral profiles of healthy aging and to better discriminate these profiles from pathological or abnormal ones. At the recent Cognitive Aging Summit, current knowledge on age-related changes in cognition and brain function was highlighted and current knowledge gaps and opportunities for research were identified. Perhaps foremost among the identified

**ATTACHMENT A: Page 2 of 3**

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challenges and gaps was the stated need to develop “gold standard” profiles for brain health and cognitive function across the lifespan.

We know surprisingly little about what the longitudinal pattern of brain health and cognitive function should look like. It seems reasonable to assume that a healthy older brain should look like a younger brain, but existing research indicates that maintenance of brain health and cognitive function with age may require adaptive processes that differ from those seen in younger individuals, at least for certain cognitive domains and the brain regions that support them. It is not clear, however, if these changes truly represent positive compensatory mechanisms or whether they simply reflect the aging process. We have made progress in our goal to distinguish healthy from unhealthy cognitive aging, but the data has largely been generated by looking at the extremes of the continuum. For example, we are not yet able to distinguish individuals who may be developing Alzheimer’s disease but are presymptomatic from those who will not go on to develop the disease. Postmortem examination of the brain for diverse pathologies remains the gold standard for diagnosis of Alzheimer’s disease and other neurodegenerative diseases. Better differentiation of these individuals while living and a better understanding of how different pathologies and age-related changes contribute to decline in specific behavioral functions are crucially important for rational development of therapeutics. Further research at all relevant levels, including molecular, cellular, neuroanatomical, physiological, and behavioral, would help define profiles that characterize healthy cognitive aging. For example, exploitation of molecular tools using animal models to differentiate components of cognitive processes, such as encoding, consolidation and retrieval in memory, would allow the interrogation of where age-related changes occur. Another important goal would be the identification of specific types of brain cells and their molecular profiles that are vulnerable to the aging process. All of these approaches will increase our understanding of brain aging and aid in the identification of targets for future therapeutics. Research in this area also could lead to the development of biomarkers that could be included in a wide variety of research projects, including large scale longitudinal studies, which would further advance our understanding of the causes of age-related cognitive change and help guide treatment of cognitive decline or maintenance of cognitive function with increasing age. In addition to longitudinal approaches, studying the brain health and behavioral profiles of the oldest old who have successfully lived past 90 without developing dementia may provide an especially useful opportunity to test some of the theories of adaptation, compensation, and cognitive reserve.

**ATTACHMENT A: Page 3 of 3**

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## **ATTACHMENT B:**

### **Research Partnership in Cognitive Aging Opportunities for MBRF Involvement and Recognition**

As a partner in the Project, MBRF will be involved with and acknowledged for its partnership with NIA and the FNIH in a number of ways, including:

- MBRF will be broadly and publicly acknowledged as a partner with NIA in making these grant awards on the RFA and on other materials, both print and electronic, in much the same way as was done with MBRF's support of the October 2007 Cognitive Aging Summit.
- When NIA publishes the Request for Applications (RFA) for public comment, MBRF will be specially invited to have input.
- After the public comment period, the RFA will be reviewed by NIA's Advisory Council (probably at its May 2008) meeting. MBRF Trustees or other representatives will be invited to attend that meeting and the meeting materials will be provided to MBRF Trustees or other representatives.
- When it is possible for NIA to make information about the awards public, MBRF will be notified simultaneously with the public announcement of the award recipients.
- MBRF will be permitted to review the comments on the applications selected to receive an award, after the announcements are made public.
- Grantees will be asked to report on progress of their work; MBRF will be invited to attend this meeting.

**ATTACHMENT B: Page 1 of 1**

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