ADDENDUM
TO THE MAY 2008 LETTER OF AGREEMENT
BETWEEN
THE FOUNDATION FOR THE NATIONAL INSTITUTES OF HEALTH, INC.
AND
THE MCKNIGHT BRAIN RESEARCH FOUNDATION

This Addendum is effective as of the last date of signature and supplements and amends the terms of the Letter of Agreement ("Agreement") that was fully executed on May 6, 2008, between the Foundation for the National Institutes of Health, Inc., a tax-exempt, not-for-profit Maryland corporation located at 9650 Rockville Pike, Bethesda, MD 20814 ("FNIH") and The McKnight Bram Research Foundation ("Donor").

The Agreement is supplemented to include the following language in addition to the Agreement's existing language:

Donor desires to extend its partnership with FNIH and the National Institutes on Aging (NIA) for the Research Partnership in Cognitive Aging for an additional five years, to support a new research initiative tentatively entitled, "Mechanisms of Cognitive Remediation in Older Adults" ("Program").

The goal of the Program (as described in Attachment C) is to develop biological and behavioral intentions for maintaining and enhancing cognitive function that are based on evidence of their ability to harness beneficial plastic changes in the aging brain, including intervention trials to remediate or prevent age- related decline.

The research areas to be funded through the Program are well-powered intervention trials to remediate or prevent age-related cognitive decline. Of particular interest are therapeutic approaches that aim to drive beneficial plasticity of the aging brain and require investigators to monitor plastic changes through behavioral and biological markers. The funded studies will use behavioral and biological markers and structural and functional imaging to investigate the mechanism of action, monitor plastic changes in the central nervous system caused by the intervention, and identify subgroups of participants who differ in their response to the intervention. Designed to advance the understanding of normal cognition and brain health m aging, this initiative will help to pave the way for development of definitive therapeutics that could be implemented in older adults. As outlined below and in Attachments C and D, the NIA will establish and coordinate the grant making program and will match the Donor's contribution, investing a total of at least $5 million in grant funds over the five year period

Subject to the terms of the Agreement, Donor will provide funding to FNIH to support the Program as set forth below, under the following terms:

a) *Payments* —Donor agrees to provide $5,000,000, payable in equal annual installments over five years according to the following schedule. The Donor's funding is conditioned upon NIA's investment of at least $5 million in grant funding in the research partnership over the five year period. Payment 1 is guaranteed. Subsequent payments will be forthcoming unless, no later than January 1 of the funding year, Donor advises FNIH that it has elected not to continue such funding:
   Payment 1: $1,000,000 due on or before July 1, 2014
   Payment 2: $1,000,000 due on or before July 1, 2015
   Payment 3: $1,000,000 due on or before July 1, 2016
   Payment 4: $1,000,000 due on or before July 1, 2017
   Payment 5: $1,000,000 due on or before July 1, 2018

b) *Use of funds* - FNIH shall use the funding provided by Donor solely for the purpose of funding the Partnership, except that the FNIH shall retain a fee of five percent (5%) of each payment, plus direct costs incurred for performing its services in connection with the Project.

NO CORRECTIONS TO PAGE 2, EXCEPT:

1. THE INSERTION OF Attachment C in section 2
2. THE INSERTION OF Attachment D in section 3
3. Add all of the names of the trustees of the Donor
    a. J. Lee Dockery, MD
    b. Michael L. Dockery, MD
    c. Nina Ellenbogen Raim, MD, JD
    d. Gene G. Ryerson, MD
    e. Robert M. Wah, MD
    f. Melanie A. Cianciotto, Corporate Trustee

SIGNATURES BEGIN ON THE FOLLOWING PAGE

Approved and Accepted for the McKnight Brain Research Foundation

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

10/23/2013
Date

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

10/23/13
Date

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

10/10/13
Date

Gene G. Ryerson, M.D.
Trustee, McKnight Brain Research Foundation

10/23/2013
Date

Robert M. Wah, M.D.
Trustee, McKnight Brain Research Foundation

23 OCT 2013
Date

Melanie A. Cianciotto
Corporate Trustee, McKnight Brain Research Foundation

10/23/13
Date

Approved and Accepted for the Foundation for the National Institutes of Health, Inc.

Charles A. Sanders, M.D.
Chairman

10/31/2013
Date

The McKnight Brain Research Foundation®

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

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

April 15, 2008

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

Dear Dr. Sanders,

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:

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. 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) 237-5907or 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-rodda@fnih.org. Other relevant FNIH contacts are:
   Julie Tune, Chief Financial Officer, jtune@fnih.org, 301-435-6246
   Charles Pucie, Communications Director, cpucie@fnih.org, 301-435-6248
   Shawn Neil, Development Systems Manager, 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

John G. Clarkson, M.D.
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.

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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

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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.

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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.

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Attachment C
Research Partnership in Cognitive Aging

Mechanisms of Cognitive Remediation in Older Adults

The following is a summary of the program concept, which was presented to and approved by the National Institute on Aging Advisory Council at its January 29-30, 2013 meeting.

Overview

Although only 13% of adults over the age of 65 have Alzheimer's disease (Alzheimer's Association, 2012), the vast majority of older adults will experience some deterioration in cognitive function as they age. Following up on recommendations generated by the 2007 Cognitive Aging Summit, in 2009, the NIA, in collaboration with the McKnight Brain Research Foundation (MBRF) and FNIH, released two RFAs: "Interventions to remediate age-related cognitive decline" (RFA-AG-09-009) and "Neural and Behavioral Profiles of Cognitive Aging" (RFA-AG-09-010). The RFAs drew a strong response. The eleven awards funded from the Profiles RFA have yielded new and exciting information about the plasticity of the aging brain. The six awards funded from the Interventions RFA implemented pilot-scale randomized clinical trials that capitalized on advances in cognitive aging interventions. Crucially, many of these trials also collected imaging and biomarker data that would potentially allow a much closer examination of the mechanism of action of the tested interventions. The promise of this approach was underlined by some of the recommendations from the 2010 Cognitive Aging Summit (Wagster et al., 2012) which pointed in particular to "increasing opportunities at the interface of basic and clinical science to enhance the clinical trial enterprise," "encouraging more integrative models of mechanisms for age-related decline/maintenance/adaptation," and "use of a uniform set of measures of cognition in both animal and human studies." The agenda and audio/video of the presentations are available at: http://www.nia.nih.gov/about/events/2011/cognitive-aging-summi-ii.

Stemming from these recommendations, the proposed initiative consists of an RFA soliciting one or possibly two well powered intervention trials to remediate or prevent age-related cognitive decline. In particular, investigators will be strongly encouraged to pursue therapeutic approaches that aim to drive beneficial plasticity of the aging brain and require the monitoring of plastic changes through behavioral and biological markers.

Applicants will be required to use state-of-the-art outcome measures including behavioral and biological markers and perform pre-/post-/maintenance structural and functional imaging. Three important reasons for the use of biomarkers and imaging are (1) to investigate the mechanism of action, (2) to monitor plastic changes in the CNS caused by the intervention, and (3) to identify subgroups of participants who differ in their response to the intervention. Furthermore, major trans-NIH efforts in measurement and instrument development recently have come to fruition, yielding products including the NIH Toolbox (Gershon et al., 2010) and PROMIS (Cella et al., 2010) that promise valid, state-of-the-art measures to increase the data yield from longitudinal studies and clinical trials. One other point that speaks to timeliness of this proposal is the possibility that FNIH can identify substantial cofounding for this initiative that would be available in FY2014. Overall, a far richer assortment of potential cognitive interventions and much improved instruments and measures to monitor cognitive maintenance or improvement, as well as improved tools to investigate their brain substrates are in place.

Clinical Trials

Through this partnership, NIA anticipates, in collaboration with the McKnight Brain Research Foundation and the FNIH, to release RFAs for clinical trial applications aimed at interventions to remediate age-related cognitive decline. The formation of multidisciplinary teams, that might not otherwise exist, will be encouraged with emphasis on definitive therapeutics that could be implemented in older adults. Applications submitted in response to this initiative will require reviewers with comprehensive expertise in cognitive aging, clinical trial design, measurement, and brain plasticity.

Objectives

The development of new cognitive interventions was a key recommendation made at the advisory meeting following the 2007 Cognitive Aging Summit, and enhancements in the properties of the interventions and conduct of the trials were top recommendations at the 2010 Cognitive Aging Summit advisory meeting, both supported by the NIA and the McKnight Brain Research Foundation, through the FNIH.

The objectives of these recommendations are (1) to improve our understanding of healthy aging and disease and disability among older adults. The rich measurement protocol required by this initiative, even in the absence of treatment effects, has the potential to advance the understanding of normal cognition and brain health in aging. The second and third objectives are (2) to reduce disease and disability and improve the health and quality of life of older adults; and, (3) to improve the understanding of Alzheimer's disease, other dementias of aging, and the aging brain by developing drug and behavioral interventions for treating these diseases, preventing their onset and progression, and maintaining health. The goal of the initiative is to develop biological and behavioral interventions for maintaining and enhancing cognitive function that are based on evidence of their ability to harness beneficial plastic changes in the aging brain. In addition, the development of biomarkers to assess impact of an intervention on cognitive and brain function is crucial.

ATTACHMENT D:

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 materials, both print and electronic, in much the same way as was done with MBRF's support of the October 2007 and 2010 Cognitive Aging Summits, and the previously funded research grants.

- NIA provided MBRF with the proposed concept clearance form and invited MBRF to participate in the January 29-30, 2013, NIA Advisory Council meeting.

- MBRF Trustees or other representatives will be invited to attend and participate in the public session at future NIA Advisory Council meetings.

- 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.

- FNIH will submit a copy of the grantee(s) research summary, which includes the abstract and public health relevance statement, provided by the grantees to NIA, to MBRF.

- Grantees will be asked to report on progress of their work; MBRF will be invited to attend these meetings.