



McKNIGHT BRAIN RESEARCH FOUNDATION

Preserving memory, enhancing life

From: Mike Dockery, MD, MBRF Chair

Sent: February 22, 2022

To: Bonnie Levin, PhD and Ronald M. Lazar, PhD

cc: **Former and Current Members of the McKnight Brain Research Foundation Inter-Institutional Cognitive Aging and Memory Interventional Core:** Tatjana Rundek, MD, PhD; Lee Ryan, PhD; Gene E. Alexander, PhD; Ronald A. Cohen, PhD; Kristina M. Visscher, PhD; Adam J. Woods, PhD
Members of the Leadership Council (not listed above): Carol Barnes, PhD; Ralph L. Sacco, MD; Todd Golde, MD, PhD; Stephen DeKosky, MD; Thomas Foster, PhD; Jennifer Bizon, PhD; David G. Standaert, MD, PhD; Eric D. Robeson, MD, PhD
MBRF Trustees: Madhav Thambisetty, MD, PhD; Patricia Boyle, PhD; John E. Brady, MD; Allison Brashear, MD, MBA; Richard Isaacson, MD; Sue Pekarske, MD; Lee Dockery, MD; Melanie Cianciotto; Amy Porter

Subject: RFP for the Pilot Grant Program

Thank you for the timely submission of the request to modify the language in the Announcement and the Request for Proposals (RFP) for the Inter-Institutional Pilot Grant Program supported by the McKnight Brain Research Foundation (MBRF) through the Cognitive Aging and Memory Intervention (CAMI) Core Committee. The reasons provided for the request were to increase the number of applicants by broadening the appeal to younger investigators by considering proposals with more basic science research as a pathway to developing proposals for clinical intervention. The isolation imposed by the pandemic has also restricted collaborative relationships and ability to perform traditional clinical interventions virtually.

At the February 9, 2022, trustees' meeting, the suggested modifications to the RFP, generated the review of the purpose for which the CAMI Core was created, and the history of the pilot grants awarded through the program were discussed.

Attached for your review is a copy of the justification for the creation of the CAMI Core by the members of the Clinical Translational Working Group followed by the description of the Proposal to establish Inter-Institutional CAMI Core.

The trustees were very impressed with the work of the members of the Clinical Translational Working Group and the vision stated below.

Our vision is to create a high-profile, nationally recognized Cognitive Aging and Memory Intervention Core, which would serve as an interventional hub for the four MBIs and complement the existing Brain Aging Registry, Cognitive Core, and Epigenetics Core. It would help to facilitate promising multisite pre-clinical and clinical interventions, with high potential for public impact and access.

The Trustees were also impressed with the described infrastructure and strategy for implementation and management of the CAMI CORE which predicted enduring success. The vision was also thought to be in perfect alignment with Mission and Purpose of the MBRF "...to support research of the brain principally

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Dr. Bonnie Levin
Dr. Ronald Lazar
Page two

intended for clinical application". As a result, the trustee unanimously approved the proposal at the trustees meeting at the July 16, 2016, meeting.

The trustees have great confidence of the past and current leadership of the CAMI Core which led to the trustees making the decision in the past to not accept unsolicited proposals and will only consider proposal recommended by the CAMI Core Committee.

After extended discussion, and in agreement with some of the barriers in submitting proposals, the trustees did not approve the suggested wording change of the RFP, because it changed the entire concept of the CAMI Core and the reasons for the MBRF support and approval. The trustees ask members of the CAMI Core committee consider the following suggestions.

1. Considering the many negative influences of the pandemic may soon improve, let's give more time and reevaluate in the future
2. Extend the current deadline to May 15, 2022
3. Revise the header of the current RFP to be more descriptive with removal of all abbreviations
4. Extensive publication throughout the McKnight Brain Institutes through the leadership council and at the upcoming 13th Inter-Institutional meeting
5. Reconstitute the committee membership to include retired members and current members and resume a more intensive committee oversight

In the meantime, the trustees convey our collective appreciation to you and the other members of the CAMI Core committee for your efforts and commitment in helping the CAMI Core fulfill its purpose and achieve its intended success.

With best wishes,

Michael L. Dockery, MD
MBRF Chair

McKnight Brain Institute Inter-Institutional Meeting

Clinical Translational Working Group Meeting Minutes and Summary

Tucson, Arizona

April 27th, 2016

Attendees: Tatjana Rundek, Xiaoyan Sun, Bonnie Levin, Katalina Fernandez-McInerney, Stacy Merritt, Monica Chawla, Asta Haberg, Ron Cohen, Adam Woods, Yenisel Cruz-Almeida and Kimberly Sibille

Meeting Commencement

The group began by re-introducing the members in attendance. In addition, Yenisel Cruz-Almeida and Kimberly Sibille attended remotely via conference call. The proceedings from the first meeting in Miami were reviewed and the action items from that meeting discussed. An agenda was put forward for the current meeting which included: 1) working group mission, 2) working group name, 3) relationship to the Cognitive Brain Health Working Group, 4) primary future goals for the group, and 5) goals for this meeting. From this discussion, 3 items emerged as primary topics of discussion: 1) the generation of a review paper on clinical translation for cognitive aging, 2) generation of a white paper that would delineate the structure/objectives of the working group and proposal for a new McKnight Core focused more specifically on clinical intervention and education for cognitive aging, 3) create a collaborative network and inventory of key intervention resources within the McKnight Institutes.

General Discussion

Plans resulting from the Miami Working Group meeting were reviewed. This included the major areas of interest among faculty, including biomarkers, cognitive training, neuromodulation, pharmacological approaches, sensory loss in visual and auditory systems, meditation, mindfulness, exercise, socializing, decision-making, nutrition and sleep. This discussion led to consideration of the Cognitive Brain Health Working Group, which met earlier that day. The group concluded that the other Working Group was more focused on establishing parallel animal and human paradigms. The consensus of our Working Group was that the mission that we had originally intended was different and focused on clinical translation; i.e., translating human, pre-clinical, experimental, and preliminary findings to clinical applications for cognitive aging. At this meeting, the group concluded that its focus should be primarily on intervention and education.

Name Change:

Given this focus and the planned direction of the Cognitive Brain Health Working Group, a decision was made to rename our Working Group to the **McKnight Clinical Intervention and Education Working Group**.

Mission:

The group reached agreement that the mission of the McKnight Clinical Intervention and Education Working Group is to advance clinical science and practice directed at combating cognitive aging. A primary objective is the implementation and facilitation of interventions aimed at prevention, amelioration, and slowing of age-related cognitive decline and also approaches to enhance cognitive

and functional capacity in older adults. A second major objective is the education and dissemination of knowledge to the public, health care providers, and researchers in the field.

Plan of Action Identified:

- 1) Short-term plan for review paper
- 2) Need to develop a longer-term plan
- 3) Need to identify what is currently being done in this area across the institutes
- 4) Need to prioritize areas of intervention on which the group would focus
- 5) Determine the requirements for establishing and maintaining a Clinical Intervention and Education Core

Review Paper:

The group decided a short-term objective would be the creation of a review paper on clinical interventions for cognitive aging. Work had been done by Drs. Sibille, Cruz-Almeida, and Rudnick on an initial outline for this purpose. The group decided to consider recent review papers written by faculty of the University of Florida CAM/IOA, including Drs. Woods, Cohen, Sibille, Cruz-Almeida, et al. that focused more broadly on successful aging. We discussed journal options. Dr. Rudnick suggested the possibility that Neurology may have interest in this review. The decision was made that she would prepare a one-page summary of the paper and circulate this to the group. Based on this summary, Dr. Rudnick will approach the editor of Neurology to gauge interest in the review and report back to the group.

Long-term Plan:

The group concluded that it was essential to lay out its mission and long-term objectives in a white paper for presentation to the McKnight Leadership Board and the Trustees. This white paper should specify the mission and rationale for this future core. It should also delineate key steps in establishing this core. It was decided that Drs. Woods and Cohen would lead the preparation of the white paper and circulate a draft to the group.

Pressing Needs for Core Development:

The group identified several types of information that needed to be acquired in order to determine the feasibility and also direction of the core. In this regard, the group concluded that it was necessary to survey each institute to obtain information regarding the interest, expertise, and clinical intervention research being conducted by investigators at each institute. Secondly, it is necessary to determine available resources for clinical interventions and each institute. Third, developing a database and collaborative network across institutes to meet the goals of the core. Fourth, further investigation regarding educational and dissemination resources currently in place at each institute, as well as future needs for this core objective.

With respect to the above plan, the following key points were raised in discussion:

Pressing need to translate basic science to techniques for older adults that can be done cost-efficiently, effectively, easily, in the home and in primary care settings.

Clinical Translation is needed across institutions that can translate basic science into techniques for older adults to prevent MCI, enhance cognition and reverse effects of cognitive decline in older adults.

Identify existing interventions being done at each center and create a type of clearinghouse. Ask each institute to create a list of their interventions.

A subset of data already compiled at each institution could be studied such as translating basic science to cognitive training.

One idea is to look at how working memory re-training translates into other cognitive domains. Another is to identify the correlation between poor physical function and increased inflammation.

There is clinical translational work being done at UF that may provide biomarkers. Dr. Bowers conducted a study involving cognitive training and exercise that was done at The Village retirement community in Gainesville.

Would the McKnight basic scientists be willing to approach this 'Core' when their data is ready to set up Phase I and II trials?

Educate community on meditation, mindfulness, exercise, socializing, decision making, nutrition and sleep.

Determine how to disseminate this information. One idea is to have trainees rotate at each MBI.

Organize an infrastructure for rapid clinical translation.

The aging community at large needs public information on preventing and possibly reversing the effects of cognitive decline. We need to identify public health concerns in the elderly population such as cognitive decline, nutrition, weight loss, diabetes, heart failure, exercise, sleep, aging and driving, polypharmacy, etc.

The key point is to find a way to translate the science faster and make it available to the public now, not several years later. The aging community needs/wants accessible interventions that are simple and can be done at home and primary care settings that will help them now. Early intervention detections are also needed.

Summary Action Plan

- Drs. Woods and Cohen will create a 1-2 page white paper for the Trustees to gauge their interest in creating a "McKnight Clinical Intervention and Education Core". The goal is to first set up an infrastructure to identify interventions at each MBI. The working group is not requesting support at this point. **By June 17th**
- Dr. Rundek will draft a 1-page paper based on the outline presented in the meeting and circulate to the group for review. The intention is to send it to the *Neurology* editor who Dr. Rundek knows. **By June 23rd**
- Based on response to the white paper, move forward with initial steps in developing a collaboration network to include all 4 McKnight institutes and an inventory to available intervention and education resources.

Workgroup Meeting Adjourned.

Cognitive Aging and Memory Intervention Core

White Paper

The Clinical Translational Workgroup met for the second year in Tucson at the annual inter-institute MBI meeting. As noted in the minutes of that meeting, an action plan was developed with specific goals over the coming year. The first issue addressed was the overarching focus of this group and whether clinical translation adequately captured its intent. A decision was made that the name of the workgroup should be changed to reflect a primary focus on the need for clinical interventions to combat cognitive aging and memory loss. Accordingly, a name change was suggested: **Cognitive Aging and Memory Intervention Workgroup**.

The workgroup concluded that a primary objective should be to develop the MBRF Clinical Intervention Core that would dovetail with and leverage findings from the MBRF cognitive, neuroimaging, and epigenetic cores. This core would promote inter-institute initiatives directed at rapid clinical translation of interventions for alleviating cognitive aging and memory decline in older adults. As an initial step, the workgroup concluded that a white paper should be produced that would outline a proposal to be presented to the MBRF trustees and leadership. This proposal would specify the mission and scope of the Core, and also identify specific objectives.

Our vision is to create a high-profile, nationally recognized Cognitive Aging and Memory Intervention Core, which would serve as an interventional hub for the four MBIs and complement the existing Brain Aging Registry, Cognitive Core, and Epigenetics Core. It would help to facilitate promising multisite pre-clinical and clinical interventions, with high potential for public impact and access.

The core would be comprised of faculty from the four McKnight Brain Institutes, under the leadership of the five investigators listed below:

UM: Dr. Tatjana Rundek

UF: Dr. Adam Woods (contact PI), Dr. Ronald Cohen,

UA: Dr. Gene Alexander

UAB: Dr. Virginia Wadley

Background and Significance

The MBRF has sponsored a block grant to create an inter-institute Brain Aging Registry, which currently contains neuroimaging and cognitive assessment cores. These cores are in the process of recruiting and studying 200 older adults (≥ 85 years). The rationale for this effort was to establish a registry of neuroimaging and cognitive data on people who are aging successfully without evidence of neurodegenerative disease. This registry will yield unique normative data on age-associated cognitive function and neuroimaging brain indices. This cross-institutional collaboration leverages different resources, interests, and expertise available at each of the institutes. The Brain Aging Registry is yielding data that cannot be feasibly obtained at one site. The goal is to provide an essential infrastructure to facilitate subsequent extramural research projects by investigators across the four MBIs, biomarker development, new neuroimaging, and assessment approaches for this population. It is also envisioned that the Brain Aging Registry would facilitate the rapid implementation of interventions via pilot studies and subsequent clinical trials focused on preventing and treating age-related cognitive decline.

To begin to address these longer-term objectives, the Clinical Translational Workgroup was formed and convened at the Miami annual MBI meeting in 2015. At that meeting, considerable discussion was directed at areas of expertise, interest, and potential inter-institute research. A large number of topic areas were identified. It was decided, that following the meeting, the workgroup would organize these topics and consider how it might move forward.

There was a also discussion of the workgroup generating a manuscript (review/position paper) that would highlight the topic and intervention domains, current evidence from clinical research on these interventions, and future directions.

At the second meeting in Tucson, a decision was made to focus the efforts of the group specifically on clinical interventions for combating cognitive aging. The workgroup decided on a new name to reflect this change: Cognitive Aging and Memory Intervention Core. The workgroup outlined ways in which an inter-institute MBI initiative could serve to achieve these goals. These objectives and their rationale are outlined below.

Core Objectives:

Phase 1 Core Goals

1. Collaborative intervention research network development.

The core will work to develop an overall research network for facilitation of cognitive intervention studies. The research network will focus on connecting MBI investigators with resources and other researchers who may facilitate the overall success of MBI-investigator-led interventions for cognitive aging. It will also work to integrate pre-clinical intervention investigators with clinical researchers to facilitate the translation process. In many ways, this is the purpose of the McKnight Inter-Institute meeting. Furthermore, the publicly available Annual Reports provide much of this information. The network developed by the core will leverage the success of these meetings and collected information to help investigators with logistical planning for execution of interventions to maximize the speed of translation and clinical implementation of promising cognitive aging interventions.

2. Identify current MBI intervention studies for cognitive aging.

The core will survey investigators across the four MBIs to generate a list of ongoing interventions targeting cognitive aging. This will be facilitated through email and direct contact with MBI investigators across the four sites and will be led at each site by the Core investigators at each institution. Information will be collated across sites at UF and distributed to the Core members, Trustees, and MBI investigators. This will facilitate knowledge of ongoing intervention efforts across MBI sites and the Trustees, as well as enable collaboration between MBI investigators.

3. Identify current MBI pre-clinical intervention studies with promise for clinical translation.

The core will survey investigators at the four MBIs to generate a list of pre-clinical interventions with potential for translation to cognitive aging trials. This will be facilitated through email and direct contact with MBI investigators across the four sites and will be led at each site by the Core investigators at each institution.

4. Identify promising new pre-clinical and clinical cognitive aging interventions.

The core will also survey the literature and trends in cognitive aging to identify promising new cognitive aging interventions that could be implemented at MBI sites. The Core members will identify promising studies, circulate these studies among members, and meet to discuss feasibility, potential impact, and issues preventing implementation or translation

5. Identify Inter-Institute Resources.

The core will survey the facilities and investigators at the four MBIs to generate a list of intervention resources available, as well as contact persons for those resources, across the four sites. This will be facilitated through email and direct contact with MBI investigators across the four sites and will be led at each site by the Core investigators listed at each institution. Information will be collated across sites at UF and distributed to the Core members, Trustees, and MBI investigators. This will facilitate knowledge of existing resources across MBI sites and facilitate collaboration between MBI investigators on interventions.

6. Prioritization of inter-institute intervention studies.

The core will work to prioritize ongoing and upcoming inter-institute intervention studies that could benefit from core support. We will specifically focus on studies that will utilize more than one MBI site. These studies will receive support in the form of assistance with logistical planning, identification of resources for intervention success, connection with MBI investigators that will complement the intervention team, and facilitation of access to necessary resources. The core will also work with investigators to identify issues and obstacles for translation or trial implementation and help to form a plan to address and overcome these issues.

Phase 1 Logistics.

Goals 1-5: To achieve Goals 1-5, the core will start by organizing information within the annual reports relative to cognitive aging and memory interventions. This information will be used to contact investigators engaged in cognitive aging and memory interventions in person (rather than using survey methods) and to collect relevant information to expand the body of resources available. The annual reports will be supplemented by the in-depth knowledge of the PIs at each site regarding interventions underway at their institution. The UF Cognitive Aging and Memory Clinical Translational Research Program (Cohen/Woods) will provide Phase 1 support through commitment of 25% of Ms. Joy Johnson's (CAM Administrative Assistant) effort for Core coordination and resource organization. She will extract relevant intervention information from the McKnight Annual Reports and directly contact investigators at the four sites.

Goal 6: To achieve Goal 6, the Core will hold bi-monthly conference calls to review collected information and prioritize inter-institute intervention studies. Prioritization will be based on committee decision. The committee will consist of the 5 PIs listed in the proposal, representing all sites. Committee meetings will increase to weekly frequency once goals 1-5 are complete. Priority will be given to studies with high potential for rapid translation and immediate impact on cognitive aging and memory in the older adult community. Candidate interventions include, but are not limited to:

- Meditation
- Cognitive training
- Pharmaceutical
- Nutraceutical
- Non-invasive brain stimulation
- Sensory Loss – vision, hearing
- Physical Activity
- Sleep
- Pain reduction
- Social cognition

Phase 1 Timeline:

Goals 1-5: Completed within 3 months of approval

Goal 6: Prioritization will be completed within 5 months of approval

Total completion time of Phase 1: 5 months

Preliminary Phase 2 Core Goals

The aforementioned goals represent what is referred to collectively as Phase 1 goals. The plan provided is intended to lay the groundwork for Phase 1. In the future, after successful implementation of Phase 1 goals, we would like to aim for a second phase of core development that would directly facilitate the rapid translation of pre-clinical or novel clinical findings through administration of pilot interventions administered across the four sites. At this time, resources are not requested for Phase 2, but we feel it important to outline the full intended scope of the Core. Prior to initiation of Phase 2, an appropriate support request and detailed plan will be submitted to the MBRF Trustees for consideration. We outline the initial overall plan for Phase 2 below.

1. Establish an online MBI-investigator-accessible database for aforementioned resources and investigator lists from Phase 1.

This resource would provide MBI investigators with a central repository for MBI site facilities sections (for grant submissions), lists of investigators and affiliated resources/specialties, and MBI-accessible resources across sites, as well as lists of ongoing interventions at MBI sites. This resource would be a central feature for facilitation of collaboration and multi-site trials.

2. Cognitive Aging and Memory Intervention Proposal Invitation and Generation.

Upon completion of intervention prioritization, the top 10 priority interventions for cognitive aging and memory with strong potential for rapid translation, immediate impact, and potential for initiation across more than one MBI site will be invited to submit proposals for consideration by the Core, and ultimately by the MBRF leadership group and MBRF Trustees. Ideally, the Core would invite proposals by MBI investigators on either an annual or bi-annual basis following the procedures outlined above. Proposals will include:

1. Abstract – no more than 30 lines
2. Statement of feasibility for rapid translation and immediate impact – no more than 30 lines
3. Specific aims – 1 page
4. Research Strategy – 6 pages
5. Human Subjects Section (including inclusion/exclusion criteria, data safety monitoring plan (DSMP) and/or data safety monitoring board plans (DSMB), and other relevant materials
6. Budget
7. Facilities and Resources (with a specific focus on inter-institute resources utilized)

3. Determination of requirements, logistics, and funding for prioritized pilot project.

Based on proposals submitted, the Core will meet via weekly conference calls to review proposals and work with investigators to 1) identify potential barriers to success, 2) generate a logistical plan for study completion, 3) generate timelines, and 4) maximize use of relevant MBI resources. Proposals will be submitted to the MBRF leadership group and the MBRF Trustees following this process. Decisions about funding allowable/feasible for study facilitation and execution would be determined in collaboration with MBRF prior to request of Phase 2 funds.

4. Pilot intervention project initiation.

Upon selection of project(s), pilot interventions will be initiated. The Phase 2 proposal, in follow-up to the current Phase 1 proposal, will outline reporting structures for initiated studies, study progress monitoring, projected budgetary needs, etc. We plan to request annual or bi-annual progress reports from studies and hold monthly conference calls with study teams to continue ongoing study facilitation and logistical support throughout the project period. Another key component of the Phase 2 application will involve establishing an interval for proposal invitation or RFA release, if the latter format is preferred.

Phase 2 Logistics: Based on the prioritization of research projects, the workgroup would meet to consider the needs for initiating the projects that have the highest priority and request formal submissions for further consideration. Coordination and review will be done by weekly conference calls. These projects will be presented to the MBRF leadership group and also to the MBRF trustees for consideration. A programmer/web-design expert will be hired to build, populate, and optimize the online database for MBI investigators.

Phase 2 Timeline: After the initial Phase 1 period (approximately 5 months). Proposals will be requested and sent for consideration by the MBRF Board within 5 months of prioritization and selection. Invited investigators will have 3 months to prepare proposals. The Core will have two additional months to formulate study facilitation plans and implementation strategies. The online database will take approximately 3-6 months to build, populate, and implement and would run in parallel to other portions of Phase 2. Total completion time of phase 2: 6 months.

Table 1. Timeline		Months										
	Goals:	1	2	3	4	5	6	7	8	9	10	11
Phase 1	Collaborative intervention research network development	█	█	█								
	Identify <u>current</u> MBI intervention studies for cognitive aging	█	█	█								
	Identify <u>current</u> MBI pre-clinical intervention studies with promise for clinical translation	█	█	█								
	Identify promising <u>new</u> pre-clinical and clinical cognitive aging interventions	█	█	█								
	Identify inter-institute resources	█	█	█								
	Prioritization of inter-institute intervention studies					█						
Phase 2	Establish online-accessible database for Phase 1 resources						█	█	█	█	█	█
	Intervention proposal invitation and generation						█	█	█			
	Determination of requirements, logistics, and funding for prioritized pilot project								█	█	█	
	Pilot intervention project initiation											█

Proposed Cognitive Aging and Memory Intervention Core
 At this time, we do not request funding support from the MBRF. Rather, we seek to establish the Core and receive approval to proceed with the outlined plan in Phase 1. At a later date,

we would then submit Phase 2 for approval to facilitate future goals of pilot support, newsletter development, and resource database development.

No support is requested at this time. Over the coming year, we will evaluate the resources required for advancing Phase 1 and Phase 2. Funds may be requested in the future based upon identified needs for developing these Core initiatives.

We are requesting five months to establish Phase 1 of the Core. During this period, we will submit a request outlining Phase 2 goals and funding requests for consideration by the Trustees.

Personnel

Faculty: As noted above, percent effort is not requested for the Multiple Principal Investigators comprising the core.

Core Coordinator: Effort is not requested at this time. The UF CAM (Cohen/Woods) will provide Phase 1 support through commitment of 25% of Ms. Joy Johnson's (CAM Administrative Assistant) effort for Core coordination and resource organization.