

MCKNIGHT BRAIN RESEARCH FOUNDATION (MBRF)
Meeting of the Research Committee
of the Board of Trustees

Monday, October 17, 2022
4:00 pm ET – 5:00 pm ET

Members Attending: Dr. Madhav Thambisetty, Chair; Dr. Patricia Boyle, Trustee;
Dr. Mike Dockery, MBRF Chair; Dr. Richard Isaacson, Trustee;
and Dr. Sue Pekarske, Trustee

Also Attending: Dr. Lee Dockery, Chair Emeritus; Ms. Melanie Cianciotto,
Corporate Trustee; Dr. Angelika Schlanger, Executive Director;
and Ms. Valerie Patmintra, Senior Communications Advisor

AGENDA

- | | | | |
|-------------------|----|---|------------------------|
| 4:00 pm ET | 1. | Call to Order/Roll Call | Dr. Madhav Thambisetty |
| ACTION | 2. | Approval of Minutes, October 21, 2021 | Dr. Madhav Thambisetty |
| | 3. | Updated Activity Timeline | Dr. Madhav Thambisetty |
| | 4. | Current Grants/Programs | Dr. Madhav Thambisetty |
| | | a. Status - MBRF Innovator Awards in Cognitive Aging and Memory Loss (AFAR) | |
| | | i. Overview of Review Committee Structure | |
| | | ii. Next Year's Program | |
| | | b. Status - MBRF Clinical Translational Research Scholarship in Cognitive Aging and Age-Related Memory Loss (ABF) | |
| | | i. Applications | |
| | | ii. Timeline | |
| | 5. | Pilot Grants – Leadership Council Update | Dr. Mike Dockery |
| | 6. | New Program Concepts | Dr. Madhav Thambisetty |
| | | a. Exploring Potential Alignment and Synergies with Like-Minded Funders | |
| | | i. Hevolution Foundation/AFAR New Investigator Awards in Aging Biology and Geroscience Research | |
| | | ii. Other Foundations/Funders | |
| ACTION | 7. | Adjourn | Dr. Madhav Thambisetty |

**MINUTES
MCKNIGHT BRAIN RESEARCH FOUNDATION (MBRF)
RESEARCH COMMITTEE
CONFERENCE CALL
October 21, 2021**

The Research Committee of the MBRF was called to order at 5:00 pm EST on October 21, 2021, by Dr. Madhav Thambisetty.

The following members were present:

Dr. Madhav Thambisetty, Chair of the Research Committee, Trustee
Dr. Patricia Boyle, Trustee
Dr. Mike Dockery, MBRF Chair
Dr. Richard Isaacson, Trustee

The following members were absent:

Dr. Sue Pekarske, Trustee

Others attending:

Dr. Lee Dockery, Chair Emeritus
Ms. Melanie Cianciotto, Corporate Trustee
Ms. Amy Porter, Executive Director

1. Call to Order

Dr. Thambisetty welcomed the members of the committee to the call.

2. Minutes of the July 6, 2021, Meeting

The minutes of the July 6, 2021, Research Committee Meeting (Attachment 1) were reviewed and approved as presented.

Action Item 1: The minutes of the July 6, 2021, Research Committee Meeting were approved as presented (Attachment 1).

3. Updated Activity Timeline

The committee reviewed the updated Activity Timeline (Attachment 2) for information.

4. Current Grants/Programs

a. Status – MBRF Innovators Awards in Cognitive Aging and Memory Loss

Dr. Thambisetty shared that good progress is being made. The AFAR Review Committee has been formed. Dr. Carol Barnes is unable to participate in the review committee due to a conflict. 9 applications were received and 7 applicants were invited to submit a full application.

b. Status – MBRF Clinical Translational Research Scholarship in Cognitive Aging and Age-Related Memory Loss

The meeting to review this year's applications has been scheduled for December 2, 2021. Dr. Boyle, Dr. Isaacson and Dr. Thambisetty will participate in the review committee.

c. Inter-Institutional Meeting Draft Program

The committee reviewed the Inter-Institutional Meeting Draft Program (Attachment 3) and provided feedback. Farah Lubin's name is spelled incorrectly on the program. It was noted that no update on the Brain Aging Registry is scheduled. Dr. Ron Cohen and Dr. Adam Woods are not on the program. The committee feels Dr. Woods' study of the impact of COVID-19, social isolation on cognitive, mental health of seniors is timely and consideration may be given to including it in the program. There is also no update from Dr. Bonnie Levin on the funded pilot grant on "Uncovering Risk Profiles of Deception and Mitigating Susceptibility to Scamming in Midlife and Older Age: A Novel Intervention Tool." Dr. Mike Dockery will reach out to Dr. Carol Barnes to share the feedback from the research committee.

Action Item 2: Dr. Mike Dockery will reach out to Dr. Carol Barnes to share the feedback from the research committee.

5. New Program Concepts/Requests

Dr. Thambisetty reminded the committee that the University of Miami submitted a request for \$3 million to endow a Neurocognitive Training Fund in Brain Health and Aging that was declined by the trustees at the July 28, 2021 meeting. At that time, Dr. Lee Dockery was asked to pursue conversations with UM about how they might proceed. The committee reviewed the "Investing in Our Future, The Evelyn F. McKnight Neurocognitive Clinical Scholar in Brain Health and Aging" request from the UM (Attachment 4) as well as the MBRF Funding for Endowments, Programs and Scholarships document (Attachment 5) and Dr. Dockery provided the committee with an overview of the conversations he and Ms. Porter had with the UM. After discussion, the committee made a motion to recommend to the full board that the request for \$250,000 to be paid over 5 years to fund The Evelyn F. McKnight Neurocognitive Clinical Scholar in Brain Health and Aging be supported with a requirement for the scholars to come through a national search and additional clarification of how UM may seek to retain these scholars when their training is complete.

Action Item 3: The committee recommends the full board supports the request for \$250,000 to be paid over 5 years to fund The Evelyn F. McKnight Neurocognitive Clinical Scholar in Brain Health and Aging with a requirement for the scholars to come through a national search and additional clarification of how UM may seek to retain these scholars when their training is complete.

6. Adjourn

Dr. Thambisetty asked if there was any further discussion. Hearing none, he called for adjournment of the meeting at 6:10 p.m. EST.

Summary of Action Items:

Respectfully Submitted,

Melanie A. Cianciotto
Corporate Trustee

Research Committee Activity Timeline
For the Period July 1, 2021, to December 31, 2022
Updated October 12, 2022

Duty (from Committee Charter)	Activity/Action	Outcome	Date	Comments
<i>"Encourage and assess research at the McKnight Brain Institutes (MBIs)"</i>	Review of the Annual Reports of the MBIs	Information for scientific review includes: scientific achievements, publications, presentations, collaborations	DONE February 5, 2020 DONE June 15, 2020 DONE Feb. 26, 2021 Annual Reports were reviewed by the Trustees on Feb. 9, 2022	Reviewers presented at Feb. 2021 Trustees Meeting. Follow up letters were written and sent to each of the MBIs. All Requests of MBIs have been addressed by MBIs. MBRF/MBI Task Force was established April 2021 to streamline Annual Report Recommendations. Recommendations were reviewed Oct 28, 2021 by Trustees. New Template was used for 2021 Annual Reports
	Review of all New Funding Requests from MBIs. Most Funding Requests should be reviewed by the Interventional Core Committee of the MBIs first.	UM submitted a request for \$200,000 for Neurocognitive Post-Doctoral Fellowship over the next two years Christian Agudelo, MD, was selected	October 23, 2019 Trustees voted to fund -- payable over two years. Position Start Date – July 2020	The notification letter mentioned that future funding should come from other sources (See "The Evelyn F. McKnight Neurocognitive Clinical Scholar in Brain Health and Aging" on page two)

		UA submitted a request for \$244,400 for UM's participation in the Precision Aging Demonstration Pilot	The proposal was reviewed and approved by the Trustees on Feb 5, 2020. The budget was revised and approved June 2020	Dr. Mike Dockery notified UA of the Trustees' approval. Trustees were notified of the revised budget and approved no-cost revisions
		A Funding Request "Centralized, telephone-based, computer-assisted...Spanish" for \$129,000 was submitted in April 2021 by Dr. Ron Lazar	Reviewed by Cmte in July and not recommended	This request was reviewed by the Trustees in July 2021 and was denied. Suggestion was provided to Dr. Lazar to work through MBI Core Committee if he chooses to resubmit.
		UM submitted a request for \$ 3 million to endow a Neurocognitive Training Fund in Brain Health and Aging. UM submitted a request for \$250,000 to co-fund a fellowship over 5 years – The Evelyn F. McKnight Neurocognitive Clinical Scholar in Brain Health and Aging"	July 1, 2021 October 2021 Research Cmte reviewed on October 21, 2021; Recommended funding; Trustees reviewed and approved funding October 28, 2021 Grant Notification Memorandum was dated Nov. 10, 2021	This request was denied by Trustees on July 28, 2021, but Dr. Lee Dockery was asked to pursue conversations with UM about how they might proceed. Dr. Dockery had several conversations and exchanges with UM with ideas for strengthening the program infrastructure. A memorandum notifying UM of the approval for funding the Evelyn F. McKnight Neurocognitive Clinical Scholar in Brain Health and Aging for a total of \$250,000 (\$50,000 over 5 years) to be matched by UM was sent by Dr. Mike Dockery to UM and agreed to and signed by Drs. Sacco and Rundek.

<i>"Encourage and assess research at the McKnight Brain Institutes (MBIs)" continued</i>	Review of Travel Award Fund: Originally established to fund research scholars and faculty to visit other McKnight institutions.	Few applications for travel. The funds allocated for travel have been used to fund the activities of focus groups: Epigenetics, MRI standardization and cognitive test battery working group	Reviewed at each Trustees' Meeting ON HOLD DUE TO UNIVERSITY TRAVEL RESTRICTIONS	Approved in 2009 In the amount of \$100,000 Approximately \$30,000 remains in the fund
	Inter-institutional Block Grants	Cognitive Aging Core Working Groups	N/A	5 Areas: Brain and Cognitive Health Cognitive Aging & Memory Cognitive Testing Battery Epigenetics MRI standardization
	Inter-institutional Block Grants	Bio-Informatics Core (Epigenetics)	Funding period: 9/1/2013-8/31/2015	Tom Foster, UF still lead scientist.
	Inter-institutional Block Grants	Neuroimaging Core	Funding period: 1/1/2015 to 12/31/2017 \$931,759.00	
	Inter-institutional Block Grants	Cognitive Assessment and Brain Registry Core	Funding period: 9/1/2015-8/31/2017 Request for another extension was approved at the Feb 5, 2020, Trustees' meeting.	No-cost Extension Request submitted for April 30, 2021. Trustees approved the extension.
	Review of Pilot Grants (Funding Requests and Progress Reports)	1)A Novel Invention Tool – Levin 2)Revitalizing Cognition in Older Adults – Bowers	1)Funding Period: 5/1/2018-4/30/2020 2)Funding period: 5/1/2018-4/30/2020	1)Funding for 2-years for total of \$120,000 2)Funding for 2-years for total of \$120,000

		3)Transcutaneous Vagal Nerve Stimulation and Cognition Training – Williamson/Alexander	3)Approved July 2019 Funding period: 10/1/2019-9/30/2021 Deadline was extended	No-cost Extension Request submitted and approved for April 30, 2021.
	Applications for 2021 Pilot Grants	5 Letters of Intent were Submitted	Request for no-cost Extension	3)Funding for 2-years for total of \$120,000
		3 Grants were approved	Research Cmte Reviewed LOIs for 2020 Jan. 29, 2021.	Trustees approved at their August 29, 2022 meeting
		With Dr. Gomes-Osman's subsequent departure from UM, the Core Committee recommended the next application in line to replace Dr. Gomes-Osman's. This was submitted by Dr. Sonya Kaur "Sleep Intervention..."	Feb. 26, 2021	Trustees approved 3 grants
			The Research Cmte did not recommend funding the next-in-line proposal in its July 2021 meeting	The Trustees denied funding and setting this precedent in its July 2021 meeting. Dr. Rundek was notified.
			"Reuniting the Brain and Body to Understand Cognitive Aging: The Nexus of Geroscience and Neuroscience" pilot grant August 2022	Interim Report submitted. Trustees reviewed and approved on August 29, 2022
	Checked RFA for 2022 before it was posted to be sure it stresses Junior Faculty. It does.	Drs. Lazar and Levin shared that only 1 LOI was received for 2022 funding cycle.	January 31, 2022 Leadership Council Meeting attended by Drs. Thambisetty and Mike Dockery and A. Porter	Several reasons for only 1 LOI were cited. The Leadership Council drafted a new RFA to address these reasons and broaden the scope of the research for Trustee review at their February meeting

			February 23, 2022 September 12, 2022	Dr. Mike Dockery, on behalf of the Trustees, responded to the LC and the members of the Core Committee that they did not wish to change the focus of the pilot grant program by changing the RFA Dr. Mike Dockery, on behalf of the Trustees, and Angelika Schlanger attended the Leadership Council meeting and asked the Council to follow up with the MBRF on the status of the Cognitive Aging and Memory Intervention Core Workgroup, in terms of its membership and plans to respond to the Memo from February 23, 2022.
<i>"Identify opportunities...to foster greater interest in cognitive aging and age-related memory loss (in the scientific community)"</i>	Research Partnership with the Foundation for NIH and the NIA. 1st cycle-2009, 2nd cycle-2014	Fund balance of \$1 million from 2nd five-year partnership returned to MBRF Report received on all FNIH/MBRF activities RFA posted: "Network for Identification, Evaluation, and Tracking of Older Persons with Superior Cognitive Performance for Age"	DONE August 2019 FNIH Report in October 2019 had an error. A corrected report resubmitted on Feb. 5, 2020.	History: Established 2009 \$5 M over 5 years from MBRF; match from NIA and partners was \$23 M for total of \$28 M (17 five-year grants funded) 2014 Partnership renewal funded one 5-year project for \$15 million with \$5 M from MBRF and \$10 M from NIA Valerie connected with Julie Wolf-Rodda and Molly Wagster on promoting STARRS study.

	3 rd cycle approved 2019 to begin Spring of 2020	FNIH Report submitted For information only	Posted Feb 2020; Deadline LOI Sept. 1; Application October 1, 2020 First payment was made to FNIH by March 31, 2021. Will continue until 2025 Dr. Molly Wagster will be attending the March 23-25 Inter-institutional Meeting at UA. The Trustees have invited her to present at their meeting on March 23, and to the idea of inviting the grantees for a video presentation. Discussion of inviting Dr. Julie Gerberding, FNIH, and Dr. Molly Wagster, NIA, to the MBRF Trustees Meeting on October 27, 2022, in Bethesda/DC area	NIA will provide \$14M to be pooled with MBRF \$5 M. A 2.8 Match. RFA was shared with Communications Working Group for posting and with Leadership Council. Two grants were provided from the Research Partnership ""Network for Identification, Evaluation and Tracking of Older Persons with Superior Cognitive Performance for their Chronological Age" to Dr. Thomas Perls, Boston University, and Dr. Emily Rogalski. Dr. Julie Gerberding, Julie Wolf-Rodda, FNIH, and Dr. Molly Wagster, NIA, plan to join the Trustees on Oct. 27, 2022
<i>"Identify opportunities...to foster greater interest in cognitive aging and age-related memory loss (in</i>	MBRF Innovators Awards in Cognitive Aging and Memory Loss	Program was Approved by the Trustees Potential administrative and/or funding partners were approached	October 14, 2020 December 2020 January 2021	AFAR Review Committee: Chair: Dr. Anna Maria Cuervo Members: Dr. Rafa de Cabo Dr. Thambisetty

<i>the scientific community)"</i>	The McKnight Brain Research Foundation committed \$4.5 million over the next five years to support outstanding mid-career scientists committed to researching the basic biological mechanisms underlying cognitive aging and memory loss.	American Federation of Aging Research (AFAR) was identified as an excellent partner organization. AFAR presented a proposal and draft contract for review Revised Agreement signed between AFAR and the MBRF	February 2021 July 15, 2021 August 2021 Mid Oct. 2021 Dec. 15, 2021 March 2022 August 2, 2022 September 19, 2022 October 2022	Dr. Boyle and Dr. Roz Anderson 2021 LOI Deadline – 9 LOIs Received LOI Review – 7 applicants asked to submit full application Application Deadline Award Announcement 2022 LOI Submission and review was eliminated due to the small number of applicants in 2021 Application Deadline Application Review – 4 applicants Award Announcement
	Reserve & Resilience Workshop 2019 Reserve & Resilience Workshop Pilot Grants 2020 Final Reserve & Resilience Workshop 2021	Over 300 Attendees (8 MBI researchers) Organizers requested \$30,000 to support (1 – 3) pilot grants	September 9 and 10th, 2019 Bethesda In-Person Meeting CHANGED TO VIRTUAL MTG September 14 and 15, 2020; Report Submitted Jan. 2021 Oct 31/Nov 1 Bethesda Meeting will be a hybrid – part virtual and part person. The program is posted on reserveandresilience.com.	This is an outcome from Cog. Aging Summit III held in 2017. Research Committee approved support in first and second years. Dr. Stern requested support for the Final R & R Workshop to take place Oct. 31/Nov. 1 in Bethesda. He did not request a specific amount but support MBRF provided last year was \$30,000. Committee supports recommendation to fund at no more than \$30,000.

			Of note, Jen Bizon and Tom Foster are panelists.	
<i>"Encourage young investigators in this area of research"</i>	McKnight Brain Research Foundation Clinical Translational Research Scholarship with American Academy of Neurology (AAN) and American Brain Foundation (ABF)	2021-2022 MBRF Reviewers are Dr. Boyle, Dr. Thambisetty, and Dr. Isaacson	Reviewers meet in Dec. Two Scholars are selected and alternates were identified. Awardees are notified in January. Funding starts July 1 of each cycle	<u>First Scholarships Awarded</u> January 2018 (McConnell, Albert) <u>Second Scholarships</u> Awarded January 2019 (Camargo, Sedaghat) <u>Third Scholarships</u> Awarded January 2020 (Baxter, Getz)
	McKnight Brain Research Foundation Clinical Translational Research Scholarship with American Academy of Neurology (AAN) and American Brain Foundation (ABF) (continued)		Edits to 2021 RFA were made and approved by Research Cmte. RFA was posted as of July 4, 2020, on AAN site. Advertising followed 2019 Plan for 2020 Award and begin in August, 2020. 8 applications for 2021 were received. October 14, 2020, Renewal for next five years was approved by the Trustees	<u>Fourth Scholarships</u> were Awarded in January 2021 to Dr. Wendy Yau Wai-Ying (Brigham and Women's) and Dr. Matthew Burns (UF) Dr. Reem Waziry (Publicly announced in April 2021 (Dr. Matthew Burns [UF] received a K-Award from NIA and had to decline the McKnight Scholarship.) <u>Fifth Scholarships</u> Advertising was conducted in August and September 5 Applications received Oct. 1. Review was in Dec. 2021

		Members of the 2022-23 Review Committee include Dr. Madhav Thambisetty and Dr. Patricia Boyle	2022-23 Deadlines September 1, 2022 Application Deadline November 3, 2022 Review Committee Meets January 2023 Notification of Recipients Spring 2023 Announcement of Recipients	Sixth Scholarships New 2022-23 RFA Draft was reviewed and has been posted and advertised - 9 applications being reviewed
<i>"Encourage young investigators..."</i> <i>Continued</i>	Poster Reception at 2019 Society for Neuroscience annual meeting (Chicago) MBRF/MBI Poster Reception 2020 Society for Neuroscience (SfN) annual meeting in DC October 24 – 28, 2020 canceled due to DC pandemic closing guidelines Society for Neuroscience will meet in San Diego Nov 12 - 16		October 20, 2019 August 29, 2022 September 5, 2022	First Poster Reception held in 2008. (50 submissions received) Sponsored by MBRF. Hosted by Directors of MBIs. Submissions open to researchers at MBIs and invited guests only MBRF Trustees Decided not to host the MBRF/MBI Poster session at the 2022 meeting. Dr. Mike Dockery updated the Leadership Council on Sept. 12, 2022 by Zoom. Dr. Mike Dockery wrote to the Leadership Council to ensure it will take place in 2023.

			September 1, 2022	Ms. Porter wrote to Dr. Molly Wagster to alert her that the poster reception will not take place this year.
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McKnight Brain Research Foundation Innovator Awards in Cognitive Aging and Memory Loss Committee Recommendations

The selection committee met September 19, 2022, to review the 2022 applications for the MBRF Innovator Awards in Cognitive Aging and Memory Loss. Four applications received a full review. Each of the 5 committee members was asked to review and rank the applications prior to the review meeting. Dr. Boyle was not able to attend the meeting due to illness but provided information on her top two choices. During the meeting, the four applications were discussed in detail. One application received low overall rankings and received a brief review. The committee further discussed the top three applications, which would all be highly fundable, however, taking into consideration the program's goals and intent to support one award focusing on clinical translational research and another award toward understanding basic biological mechanisms underlying cognitive aging and age-related memory loss, they recommended the following two applicants:

Tara Tracy, PhD, Assistant Professor, Buck Institute for Research on Aging: *"Role of KIBRA in Age-Related Memory Loss"*

Project summary (provided by the applicant): Synapse function in the brain is critical for memory and cognitive processing, and yet we have a poor understanding of the mechanisms underlying synapse dysregulation in aging. Researchers have linked synapse plasticity deficits and memory impairment in aging, however, *a major gap in our knowledge in the brain aging field* is that little is known about what factors make synapses more vulnerable to dysfunction in aging. In this proposal, we will address this critical barrier by determining how the KIBRA (Kidney/BRAin) protein affects age-dependent susceptibility to synaptic and memory decline. A polymorphism in the WWC1 gene that encodes KIBRA is linked to cognitive decline in aging in humans. However, previous work has focused primarily on the role of KIBRA at synapses in postnatal and young adult mice. Moreover, the role of KIBRA in synapse function has not yet been explored in human neuron models. Our proposed study would be the first to mechanistically dissect how KIBRA levels influence susceptibility to memory loss in aging and to characterize KIBRA function in human neurons. We anticipate that the successful completion of our proposed studies will establish key mechanistic insights into how KIBRA affect synaptic vulnerability to age-related memory loss. Delineating this mechanism of synapse decline would be transformative and guide the development a therapeutic approach to enhance KIBRA-signaling at synapses as a treatment for age-related memory loss.

There was overall agreement by the committee that Dr. Tracy is a strong candidate who has clear support from her institution. While this is predominantly a basic science application, the hypothesis is derived from observations in humans and the second aim will use human iPSC.

- New approach that has potential clinical applications, really fits the program
- Limited to one strain of mice
- Novel protein, niche in this area
- Some of the correlations in the preliminary data very striking

- Associating this protein with cognitive aging
- While there is a significant basic component, hypothesis originated in human studies
- IPSC model – a lot of enthusiasm currently and the candidate has extensive training/expertise on their use
- \$7 million in start-up, very good publications
- Electrophysiology – calls it memory but she's measuring electrophysiological pulses. Still is one step forward than most studies on this topic
- Environment great, ideas good, blend to techniques very strong

Emilie Reas, PhD, Assistant Professor, University of California, San Diego: *"The mediating role of bloodbrain barrier dysfunction in effects of systemic inflammation on brain microstructure and memory"*

Project Summary (provided by the applicant): Sporadic Alzheimer's disease (AD) is an untreatable neurodegenerative memory disorder that profoundly impacts quality of life and increases caretaker and financial burden. As age is the strongest risk factor for AD, targeting biological aging has been proposed as a promising therapeutic strategy to prevent AD. Notably, low levels of chronic inflammation that emerge with age are a common thread among most age-related disorders, prompting coinage of the term "inflammaging". While neuroinflammation is strongly implicated in AD pathogenesis, peripheral inflammatory factors have also been associated with neurodegeneration and cognitive impairment, suggesting that the neurophysiological changes promoting cognitive decline and dementia may, in part, be systemic in origin. A critical outstanding challenge to disentangling the role of systemic aging in neurodegeneration and dementia is characterizing the pathways by which peripheral inflammatory signals compromise neural function. The brain enjoys a privileged environment, uniquely protected by a semipermeable blood-brain barrier (BBB) that tightly orchestrates influx of blood-borne nutrients and immune factors, and efflux of metabolic products. While the BBB is essential for maintaining brain homeostasis, it becomes more permeable with age and dysfunctional in many neurological disorders including AD. Indeed, BBB damage may partially account for the pronounced contribution of vascular dysfunction to AD risk and the frequent co-existence of vascular and AD neuropathology. Peripheral inflammation has been linked to endothelial BBB damage, immune reactivity, and immune cell infiltration ⁶, suggesting that systemic inflammation may disrupt the neurovascular unit by impairing BBB function, with further vulnerability to a neuroinflammatory response for those with concomitant BBB breakdown related to vascular disease. The proposed project will leverage a multimodal approach integrating advanced diffusion and permeability MRI with biofluid and neuropsychological measures to test the hypothesis that peripheral inflammation is associated with accelerated microstructural brain aging and memory impairment, a process mediated by BBB breakdown. To probe the specificity of this pathway to AD pathophysiology, we will assess modifying effects of an AD polygenic hazard score (PHS) that has been previously validated as a sensitive marker of preclinical AD. Findings will help to fill a crucial piece of the AD puzzle by clarifying the link between systemic inflammaging and neurodegenerative changes underlying cognitive decline. Ultimately, results may help to guide therapeutic approaches to preserve brain health into later life and to optimize cognitive aging trajectories.

The committee is also recommending that Dr. Reas is supported.

- Great translational significance
- Lots of talk about inflammaging – also relevant to cognitive aging/neurodegenerative disease
- How inflammatory signals are translated across the blood brain barrier is largely unknown
- Investigating how abnormalities of blood brain barrier allow peripheral inflammatory signals to reach the brain
- Fairly large study, 150 participants
- Question is of great translational importance – enthusiastic about ranking this highly, particularly with lack of clinical/translational applications in last cycle
- Restriction spectral imaging
- Divergent trajectories of memory impairment
- Novelty is trying to relate to longitudinal changes in aging as well as abnormalities in the blood brain barrier
- ADRCs are measuring everything they can get their hands on and connecting it with brain aging
- This individual has the full heft of ADRCs
- Is this more ADRD focused or brain aging focused?
- Looking at cognitive aging as opposed to pathological aging
- Weaknesses – not as novel, and may not be able to create own niche
- Strengths – really looking at longitudinal changes in aging, important questions that need to be answer.

Dr. Thomas Longden was also considered a very strong candidate who could have been supported if funding were available. He uses unique technology and ask important questions. However, since Dr. Tracy, despite the basic biology focus, had a clearer potential translational value, her application received higher enthusiasm. AFAR will explore whether other funders would consider supporting this application.

2022 MBRF Innovator Awards Committee

Ana Maria Cuervo, MD, PhD, *Chair*

Albert Einstein College of Medicine

Rozalyn Anderson, PhD

University of Wisconsin, Madison

Patricia Boyle, PhD

Rush University

Rafael de Cabo, PhD

National Institute on Aging

Madhav Thambisetty, MD, PhD

McKnight Brain Research Foundation (Vice Chair)

Dear colleagues,

I am very happy to provide a few brief confidential comments to accompany the recommendations from AFAR in selection of the Innovator awardees for 2022. As the timeline for announcement of the awards is very short, the ideal procedure of discussing these recommendations in the Research Committee prior to presenting before the full BoT is not feasible. We will assess how we might be able to tweak the process to be able to do this in the following years. The remarks below are provided to give you a broader context of the discussion during the reviewer committee meeting on 9/19/2022.

You may recall that given the lack of any clinical translational applications last year, one of the changes we made to the RFA this year was to specifically state that we would make one award each to support projects in basic research and clinical translational work in cognitive aging and age-related memory loss. Please see the link below to the program announcement.

<https://www.afar.org/grants/mcknight-award>

Prior to discussion of the specific applications, I was given the opportunity to make some introductory remarks at the meeting of the review committee. I took this opportunity to emphasize that the MBRF would strongly prefer to support at least one application that had a clear clinical translational focus. I shared with the committee that my own approach to ranking the applicants was to divide them into a basic science and clinical translational pool so that I could identify the top ranked applicants in each category. There was considerable discussion within the committee about the pros and cons of this approach. It was clear that this was not the approach that the rest of the committee favored, and they had preferred to rank all applications irrespective of whether they were basic research or clinical translational in nature. We therefore reviewed the program announcement, and I highlighted the change to the RFA this year as below:

“One award will be made to support studies focusing on clinical translational research and another award toward understanding basic biological mechanisms underlying cognitive aging and age-related memory loss.”

This persuaded the committee to reconsider their ranking of the applications within two separate categories i.e. basic and clinical translational. I am happy to note that among the four applications received, there was one clearly clinical translational project that was considered worthy of support by the committee (**Emilie Reas, PhD, Assistant Professor, University of California, San Diego**: *“The mediating role of bloodbrain barrier dysfunction in effects of systemic inflammation on brain microstructure and memory”*). Dr. Reas’s lab page is here:

<https://neurosciences.ucsd.edu/research/labs/reas/index.html>

In 2018, she was awarded the
The Irene Diamond Fund/AFAR Postdoctoral Transition Awards in Aging.

It is noteworthy that the other awardee also focuses her research on a hypothesis that was originally derived from human genetic studies implicating the KIBRA gene in cognitive aging (**Tara Tracy, PhD, Assistant Professor, Buck Institute for Research on Aging**: *“Role of KIBRA in Age- Related Memory Loss”*). Hence while the research she proposes follows a basic science approach to understand how this gene may cause impairment in memory during aging, I would consider this project partly translational in nature. Dr. Tracy’s lab page is here:
<https://www.buckinstitute.org/lab/tracy-lab/>

There was considerable enthusiasm for the 3rd ranked applicant Dr. Thomas Longden and his work was considered innovative and potentially of high impact. This was however an entirely basic research approach towards understanding mechanisms of neurovascular coupling by pericytes and how this may contribute to age-related memory impairment. Given our stated preference to make only one award in the basic science category, his application did not rise to the top rank. AFAR will assess whether he could be supported by other funding mechanism(s) in their portfolio.

Thanks a lot.

Madhav

Hevolution Foundation/AFAR Partnership

“Hevolution Foundation and AFAR Announce New Investigator Awards in Aging Biology and Geroscience Research” – Press Release

<https://www.businesswire.com/news/home/20220830006038/en/Hevolution-Foundation-and-AFAR-Announce-New-Investigator-Awards-in-Aging-Biology-and-Geroscience-Research>

“Hevolution/AFAR New Investigator Awards in Aging Biology and Geroscience Research” – AFAR Grants Page

Link to grant in partnership with AFAR: <https://www.afar.org/grants/hevolution-new-investigator-awards>

Examples of other Foundations that have worked with AFAR and focus on aging/brain research include:

- **Gilbert Foundation - New Investigator Awards in Alzheimer’s Disease:**
<https://www.afar.org/news/afar-and-the-gilbert-foundation-announce-three-new-investigator-awards-for>
- **Glenn Foundation for Medical Research - "Breakthroughs in Gerontology (BIG)" Award:** <https://www.afar.org/grants/big>
- **Simon Foundation - Simons Collaboration on Plasticity and the Aging Brain:**
<https://www.simonsfoundation.org/grant/scpab-research-awards/>
- **John A. Hartford Foundation - Centers of Excellence in Geriatric Medicine and Geriatric Psychiatry Program):** <https://www.afar.org/news/afar-national-program-office-and-john-a-hartford-foundations-centers-of-ex> and [article](#). JAHF currently funds research around "[Age-friendly Health Systems](#)," "[Family Caregiving](#)" and "[Serious Illness and End of Life](#)."