UAB SCHOOL OF MEDICINE

Evelyn F. McKnight Brain Institute

April 2, 2013

Trustees
McKnight Brain Research Foundation

Dear Trustees:

I am writing to give you an update and summary concerning the McKnight Epigenetics Strategic Planning Meeting that occurred in New Orleans on January 8th and 9th 2013. In brief overview, the meeting was a great success and was very productive in outlining a Strategic Plan to allow the Evelyn F. McKnight Brain Institutes (UF, UM, UAB, UA) to collaboratively pioneer a comprehensive program to test an epigenetic hypothesis of cognitive aging. Please consider this document both a Progress Report for the Epigenetics Initiative thus far, and an initial request for financial support for establishing a new Evelyn F. McKnight Inter-Institutional Bioinformatics Core. Thus, for the first part of this letter I will provide a progress report, and attached to the letter is a Proposal and request for funding for the Bioinformatics Core, a resource to be shared collaboratively across all four Evelyn F. McKnight Brain Institutes.

You will recall that the idea of a McKnight Epigenetics and Cognitive Aging Initiative arose out of the last Inter-Institute meeting in Arizona, specifically based on discussions among the Institute Chairs and Directors and the Board at our annual morning get-together. With approval and funding from the Board, a subset of McKnight Investigators (under the loose direction of David Sweatt) decided to pursue discussing a broad collaborative initiative to propel discovery and advancement concerning the role of epigenetic mechanisms and processes in memory and cognitive aging.

Toward this end, on June 21-22 2012 David Sweatt went to Gainesville for a planning session with Tom Foster and Leonid Moroz (after extensive consultation with Carol Barnes) for beginning to outline ideas for the larger neuroepigenetics collaborative effort. This was essentially a brain-storming session that laid the groundwork to help focus the larger group's discussions that took place in the subsequent strategic planning meetings that this report covers. On August 13-15, 11 McKnight Investigators met in Gainesville to share ideas, with all Institutes represented. At this meeting we identified and developed points of potential productive interaction on epigenetic analytic methods for use in furthering our understanding of cognitive aging. Subsequently in January of this year the planning and implementation group (comprising most of the attendees of the UF meeting, plus a few highly invested and interested additional investigators) met in New Orleans to formulate a detailed plan for moving the epigenetics initiative forward. The meeting agenda and a list of participants is attached. The main output of the New Orleans meeting is the Proposal that is attached to this letter of update, specifically a proposal to catalyze discovery concerning a unifying hypothesis of epigenetics and cognitive aging, through the establishment of an inter-Institute bioinformatics core.

In brief, at the New Orleans meeting the participants identified the following strategic and logistical priorities to propel a collaborative Inter-Institute Epigenetics and Cognitive Aging Initiative and establish the

four Evelyn F. McKnight Institutes as the leading group nationally and internationally in the domain of the ***neuroepigenetics of aging***.

Strategic Priorities:

1. The study group concluded that scientifically a foundational discovery in the area of neuroepigenetics of aging would be an Epigenome-Wide Association Study (EWAS-Memory) to identify the epigenome-transcription interface and its disruption in aging. Achieving this breakthrough will require the establishment of a highly collaborative bioinformatics initiative, utilizing an inter-institute bioinformatics core available to all McKnight Institutes and physically located at the University of Florida and the University of Arizona.

2. Establish the shared Inter-Institute resource to provide a catalyst for discoveries in the area of epigenetics of cognitive aging. This is envisioned to be a "core without walls" to provide support for bioinformatic analysis of high-throughput DNA sequencing and epigenomics, bio-informatics, and cross-correlation of human and animal studies.

3. The effort will focus on novel epigenetic target discovery to provide a basis for development of innovative new therapeutics.

4. The inter-institute core initiative will have as priorities: propelling discovery through inter-Institute collaborations, McKnight mission-relevance, and high real-life therapeutic impact.

In summary, the Epigenetics Initiative meetings have been highly productive, focused, collaborative, and exceptionally innovative. The Initiative has identified a novel target area that will both propel new discoveries in cognitive aging and produce a high-profile scientific focal point with which the McKnight "brand" will be identified nationally and internationally. Innovative therapeutic approaches to cognitive enhancement in aging is a strong, viable target outcome for the initiative. With this background in mind, a specific proposal for the next stage of advancing the Evelyn F. McKnight Epigenetics and Cognitive Aging Initiative is described in the attached document.

Sincerely,

David Sweatt,
On behalf of all the participating Investigators

PROPOSAL

Evelyn F. McKnight Brain Institutes: Inter-Institutional Bioinformatics Core

Executive Summary

This proposal describes a plan of action for developing a shared collaborative resource, freely available to Investigators in each of the four Evelyn F. McKnight Brain Institutes (MBI's), that will allow cutting-edge epigenomic and bio-informatic analysis of DNA sequence-based datasets. The Inter-Institutional Bioinformatics Core will allow rapid, high-impact advances in our understanding of the role of epigenetic processes in cognitive aging, allowing the MBI's to take the leading role internationally in testing this major new unifying hypothesis for how cognitive decline occurs in aging.

In overview, this document will address the background and rationale for proposing this new Core, present an implementation and logistical plan, and describe the funding and resources needed.

Background and Significance

Epigenetic molecular mechanisms, specifically histone post-translational modifications and cytosine methylation of DNA, have recently been discovered to be critically important regulators of learning and memory. Two laboratories of two McKnight Chairs, Barnes and Sweatt, have been leading groups in moving these discoveries into the arena of cognitive aging. This initiative proposes to capitalize on these recent discoveries, by using whole-epigenome high-throughput screening approaches to identify new gene targets for potential drug development for enhancing memory formation in cognitive aging.

The impact of this work will likely extend greatly beyond cognition to the entire area of aging *per se*, as an emerging high-profile hypothesis in the broad area of organismal aging is the idea that epigenetics drives aging at the cellular level. Testing this hypothesis in the specific area of CNS and cognitive aging could allow a conceptual advance in this area, especially as related to DNA methylation and small non-coding RNAs. Thus, the scientific impact of studies of cognitive aging in our systems sill be quite high. The breadth of impact in terms of novel human therapeutics that might arise from these studies is also quite high, such therapies being relevant to almost everyone over the age of 70, and to anyone who aspires to live that long.

We propose to focus on the cognitive and CNS-based aspects of DNA chemical modification in memory for three reasons. First, understanding the role of gene methylation in *cognitive function* will have a great impact in terms of potential practical applications for augmenting human learning and memory, making this a priority area for drug development. Second, the discovery of a role for epigenetics in the ongoing function of the adult brain opens up a plethora of new possibilities for regulating memory capacity (positively and negatively) that need to be investigated. Third, understanding the role of gene transcriptional regulation in cognitive function is the long-standing expertise and focal point of many investigators operating at the Evelyn F. McKnight Brain Institutes, and is the area where we will be best able to make a rapid, profound, and meaningful impact.

What We Already Have

As one of the first steps in strategic planning for the Inter-Institute Epigenetics Initiative, we undertook a self-assessment of the relevant resources that are already available at the four MBI's, in order to gain a solid understanding of what potential already existed. The existing resources that will leverage the Inter-Institute

Core are *substantial*, encompassing scientific discoveries, technical infrastructure, and existing funding commitments. Regarding data and discoveries, as described above, McKnight Investigators already are recognized as leading the emergence of the new unifying behavioral epigenetic hypothesis of cognitive aging, laying a strong experimental foundation for the Initiative. (Although it should be noted that we are beginning to face significant competition for scientific leadership in this area from scientists at the NIA, Johns Hopkins, and the German Max Planck Institutes.) An impressive existing infrastructure of expertise and equipment is already in place at the four MBI's as well. One of the most impressive findings of our analysis of available resources was that ***among the four Institutes we already have all the necessary DNA sequencer infrastructure already in place***. Already-available DNA sequencing equipment and computational facilities that can be brought to bear on the Initiative from the four participating Universities are valued in the tens of millions of dollars. Specifically, among the 4 participating MBI's, resources already in place that will be utilized for the initiative include 3 supercomputers and 11 Next-Generation DNA nucleotide sequencer machines (8 Hi-Seq 2000's, 1 HiSeq 2500,1 dedicated Ion Proton, and 1 Ion Torrent). Finally, there is an appreciable pool of already-existing funding commitments that will leverage the Core Initiative, Thus, significant leveraging funds have already been obtained from government agencies that, while not funding cognitive aging projects *per se*, still allow for a great degree of amplification of the impact of the McKnight Epigenetics Initiative. In particular, the UAB group under the guidance of David Sweatt as PI, has recently obtained significant funding commitments from the Defense Advanced Research Project Agency (DARPA) in the area of epigenomics of memory, and for developing new nano-technological approaches to cognitive enhancement. These commitments consist of approximately $2,000,000 in pilot funding (for one year) already approved, and an invitation from DARPA to submit an additional proposal for approximately $3,000,000 in further funding over three years. In summary, the powerful existing infrastructure and relevant resources related to the MBI Inter-Institute Bio-Informatics Core will allow implementation of the Core with great rapidity, efficiency, and impact.

What We Need

Our analysis of available resources also made crystal-clear what is missing at all four MBI's – bio-informatics capacity. Bio-informatics is the emerging new scientific subdiscipline of using computational (i.e. computer-based) approaches to grapple with enormously large data-sets. The rapid recent progress in DNA nucleotide sequencing technology, driven by the human genome project, has made large-scale "next-generation" nucleotide sequencing achievable for the biomedical researcher at reasonable costs. However, compared to the ease of use and availability of the basic technological infrastructure for DNA sequencing, the capacity to analyze and interpret these huge datasets has become the rate-limiting factor in scientific progress in this exciting new area. Also, there is a pronounced shortage nationwide of trained bio-informaticians, the practitioners of these sorts of analyses. In our self-assessment process, it became clear to the participating MBI leadership that our lack of sufficient capacity for bio-informatic analysis is a significant bottleneck and impediment to our staying on the leading edge of investigating epigenetic mechanisms in cognitive aging.

For this reason, we propose to develop an inter-institutional shared resource, the Evelyn F. McKnight Inter-Institutional Bio-Informatics Core that will allow all four MBI's to collaboratively fill the existing void in this scientific area.

Implementation Plan

Overview

The Evelyn F. McKnight Inter-Institute Bio-informatics Core will provide the following services (see Figure 1), based on our self-assessment and strategic plan:

1. High-throughput epigenomic and mRNA sequencing analysis and technical support.
2. Top-flight bio-informatics, for both routine analysis and novel analytical techniques.
3. Shared data storage and rapid transfer of data and analyses between and among the four participating MBI's.
4. Supercomputer time for bio-informatic analysis.
5. Coordinated tissue sharing, both human and animal.
6. Cross-analysis of human and animal data regarding transcriptional dysregulation in aging.
7. Information on common standardized protocols in all these domains, for consistency across MBI groups.

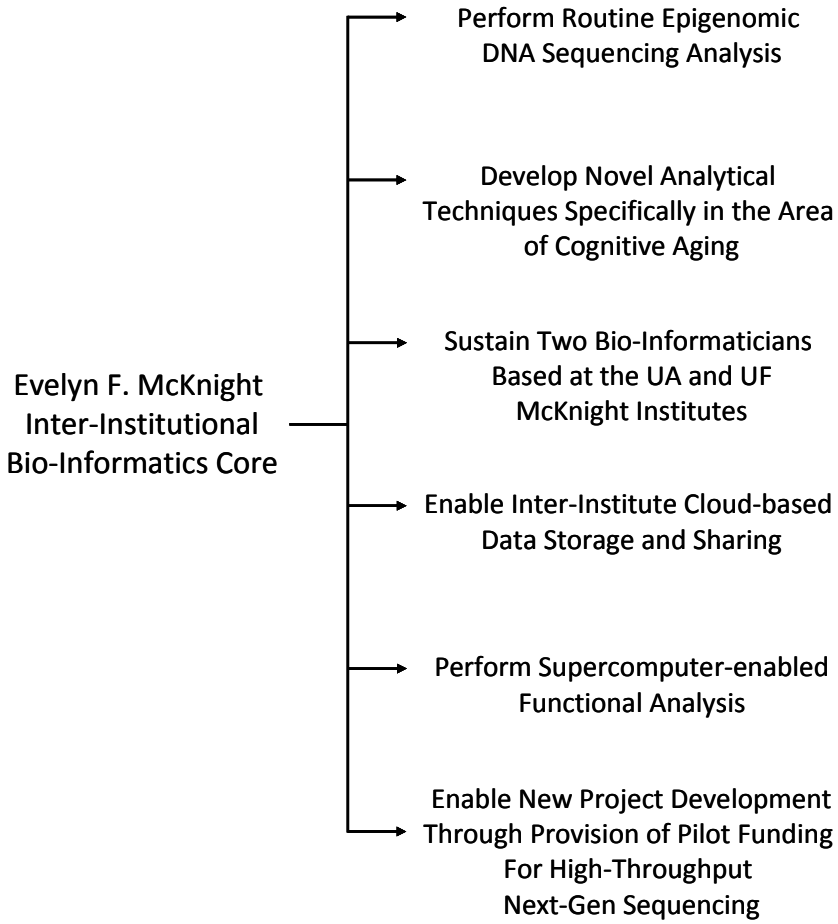

Figure 1

Logistical Considerations

1. Substantial leveraging of the initiative from individual research grants is highly likely. As described above there is already significant leveraging of the overall project in place at all four MBI's including both research funds and equipment infrastructure. At a minimum the initiative and associated shared resources will provide a basis for additional new applications for large collaborative Center-type grant applications in the future.

2. In terms of the shared resources (sequencing, bioinformatics, etc.) being allocated, strategic priorities #1 & #3 described in the cover letter (therapeutic and scientific impact, respectively) will be used to screen potential users at the various McKnight Institutes for eligibility to use the resources. A supervisory committee made up of senior Investigators from all four MBI's (specifically the McKnight Chairs: Barnes, Foster, Wright, and Sweatt) will be responsible for approving written requests for use of Core resources and analytical services.

3. There is a vitally important need that funds for reagent and next-generation sequencing costs be made available to McKnight Investigators that desire to do pilot projects in the area of the epigenetics of cognitive aging. This is a new area for many investigators, and one goal of the Initiative is to allow novel epigenetic approaches to be implemented in McKnight laboratories where these methodologies do not already exist. Expanding the number of McKnight laboratories that are pursuing the epigenetics of cognitive aging is an important component to linking these types of innovative studies to the McKnight "brand". For this reason the Inter-Institute Bioinformatics Core will also serve as a clearinghouse to review and fund new collaborative pilot projects in the area of epigenetics and cognitive aging. Overall, this component of the Core will allow McKnight Investigators new to the epigenomics field the opportunity to get their "foot in the door" regarding the use of these innovative approaches and technologies for studying cognitive aging.

Timeline and Budget

We are requesting 2 years of support in order to initialize the Inter-Institute Bioinformatics Core, at a total cost of $410,000 per year.

The budget will serve as seed funding with the plan being to secure long-term support for the Core from institutional leveraging, collaborative grants and/or fee-for-service utilization.

The cost breakout per year is as follows:

Personnel: $250,000
This will support two full-time bio-informaticians, one based at the University of Florida and one based at the University of Arizona. Office/lab space for these individuals will be provided by the host institutions, but each of the informaticians will serve all four MBI's. Care will be taken to distribute the work-load evenly across the two individuals, with each person having responsibility for projects originating at all four MBI's. In other words, we will deliberately distribute the job responsibilities so that *both* bio-informaticians interact with *all four* MBI groups – this will facilitate inter-Institute collaboration, communication, and cross-fertilization.

Data Storage: $50,000
Operation of the Core will require rapid transfer of very large quantities of data (the equivalent of entire human genome sequences, for example) between the Core and the participating Investigators physically

located at the various MBI's. To allow this, the Core will utilize Cloud-based data storage and sharing, the only practical means by which to transfer these amounts of data in a day-to-day working fashion. Costs for cloud-hosting the data files, the data sharing, etc., is requested.

Supercomputer Time: $10,000
The bioinformatics analyses provided by the Core, indeed the *raison d'être* of the Core, will require utilization of supercomputer time in order to process nucleotide sequence information in a timely fashion. Costs for supercomputer time will be offset significantly by using the supercomputer facilities already available at UF and UA, where investigators on-site can purchase supercomputer time at university-subsidized costs. (Indeed this is one rationale for having the two physical Core sites based at UF and UA.) Nevertheless, the Core will need to purchase supercomputer processor time and funds are requested for this purpose.

Pilot Project Funds: $100,000
As described above funding for reagent and sequencing costs will be requested via a written project proposal, and funding decisions made by a committee of senior scientists representing all four MBI's (Barnes, Foster, Wright and Sweatt as described above). It is important to note that the bioinformatics analysis of the resulting data will be free (i.e. no-cost) as part of the routine operation of the Core. However, some McKnight Investigators will need modest financial support to do the initial next-gen sequencing, in order to generate the actual epigenomics data that the Core will analyze for them. Thee data and resulting bioinformatic analyses will serve as the basis for initial publications in the area of epigenomics of cognitive aging, and also as preliminary results for NIH and DoD grant applications.

Concluding Remarks

The McKnight Chairs and McKnight Investigators that participated in the three scientific review and planning sessions that led to this proposal wish to thank the Board members of the Evelyn F. McKnight Brain Research Foundation for your steadfast support and for the opportunity to present this proposal for your consideration.

Sincerely,

David Sweatt,
On behalf of all the McKnight Epigenetics Initiative Working Group members:

<u>The University of Alabama at Birmingham</u>
David Sweatt, Ph.D., Professor and Evelyn F. McKnight Endowed Chair, Director, McKnight Brain Institute, Department of Neurobiology
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Scott Phillips, Ph.D., Assistant Professor, McKnight Brain Institute, Department of Neurobiology

The University of Arizona

Carol Barnes, Ph.D., Regents' Professor, Psychology, Neurology, Evelyn F. McKnight Chair for Learning and Memory in Aging, Director, Evelyn F. McKnight Brain Institute

Paul Coleman, Ph.D., Senior Scientist, Co-Director of J.L. Roberts Center for Alzheimer's Research, Affiliate, Evelyn F. McKnight Brain Institute

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