UAB SCHOOL OF MEDICINE

*Evelyn F. McKnight Brain Institute*

Trustees
McKnight Brain Research Foundation

Dear Trustees:

I am writing to give you a brief update and summary concerning the McKnight Epigenetics Strategic Planning Meeting that occurred recently. In brief overview, the meeting was a great success and was very productive in terms of beginning to outline 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 and an initial request for financial support for a follow-up implementation meeting to be held in New Orleans in Dec 2012 or Jan 2013.

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 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 meeting that this report covers.

On August 13-15, 11 McKnight Investigators met in Gainesville to share ideas, with all Institutes represented. The meeting agenda and a list of participants is attached. At this meeting we identified and developed points of potential productive interaction on epigenetic analytic methods for understanding cognitive aging.

In summary, 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. Establish a 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 high-throughput DNA sequencing and epigenomics, bio-informatics, and cross-correlation of human and animal studies.

2. The effort should focus on epigenetic target discovery to provide a basis for development of novel therapeutics.

3. Scientifically a foundational discovery in the area of neuroepigenetics of aging will be an Epigenome-Wide Association Study (EWAS-Memory) to identify the epigenome-transcription interface and its disruption in aging.

4. The initiative should have as priorities: Inter-Institute collaborations, McKnight mission-relevance, and high real-life therapeutic impact.

**Logistics:**

1. Substantial leveraging of the initiative from individual research grants is highly likely. At a minimum the initiative and associated shared resources will provide a basis for new applications for large collaborative Center-type grant applications.

2. In terms of the shared resources (sequencing, bioinformatics, etc.) being allocated, strategic priorities #2 & #3 (therapeutic and scientific impact, respectively) will be used to screen potential users at the various McKnight Institutes for eligibility to use the resources.

3. The shared resource will provide:

high-throughput epigenomic and mRNA sequencing analysis and technical support
top-flight bio-informatics, for both routine analysis and novel analytical techniques
shared data storage
supercomputer time
coordinated tissue sharing, both human and animal
cross-analysis of human and animal data regarding transcriptional dysregulation in aging
common standardized protocols in all these domains, for consistency across groups.

The group proposed a follow-up meeting to occur within a few months in New Orleans (as mentioned above) that would have as its agenda the following deliverables:

1. A detailed plan for moving the epigenetics initiative forward.

2. To update each other on our scientific discoveries in the area.

3. To update each other on potential funding avenues that can leverage the initiative.

4. To conceptualize a jointly authored paper on this topic.

In **summary**, 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 could 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.

Cheers,

David Sweatt,
On behalf of the participating Investigators