Biomedical Research Advisory Group: Draft Strategic Plan for Neuroscience

Executive Summary

- Neuroscience is at a historic juncture, where the understanding of basic principles at a molecular, cellular, and physiological level will begin to have substantial influence on the treatment of neurologic and psychiatric disease.

- Sustained progress will require not only the 'translation' of a few ripe ideas toward clinical application, but also a substantial increase in the number of neuroscientists at Harvard and fundamentally improved communication between researchers doing primarily 'basic' and 'disease-applied' research. Both communities are very strong at Harvard (including HMS, the associated medical institutions, and FAS), but communication is not optimal.

- We recommend the creation of a physical center (a Neuroscience Institute) for bringing together a core interdisciplinary group, which will include members of the existing HMS Department of Neurobiology, researchers from the medical institutions, and a significant number of additional faculty recruited by the new Neuroscience Institute. This core group should consist of researchers, across the spectrum from basic to applied research, who have particular interest in bridging the cultures. The Institute should also have a 'big tent' approach to including 'affiliates' across the Harvard community.

- Researchers of the Neuroscience Institute should have a mandate to bring the entire Harvard neuroscience community together for intellectual interaction and collaboration. Although there should be occasional gatherings of the whole community, smaller topical meetings will have the most impact. Just as we require members of the graduate programs to teach, we should require (and create incentive for) investigators at the Institute to organize topical symposia or informal discussion groups that span the Harvard community. These meetings would serve an educational role (for M.D. and Ph.D. students, postdocs, residents, and faculty) and provide opportunities for cross-fertilization and collaboration.

- Producing real improvement in the culture of interaction between diverse investigators will require committed and active leadership, as well as resources to enable meetings and collaborations and to create incentives for these interactions.

- The cross-cultural and educational activities of the Neuroscience Institute would complement the strong existing PhD Program in Neuroscience.

- The physical space of the Neuroscience Institute could be initially allocated and paid for with contributions of faculty and resources from the existing Departments. Ultimately the Institute should have resources that can be used to recruit new faculty in coordination with existing Departments.

The Neuroscience strategic planning discussion group (see Appendix for membership) discussed the existing strengths of the overall neuroscience enterprise at Harvard University, some of the ways that Harvard neuroscience has not reached its full potential, the situation in clinical neurology and psychiatry, and opportunities for basic neuroscience to have more impact in human disease. One specific proposal arose from this discussion: to create a new Harvard Neuroscience Institute that brings together in one building neuroscientists from a number of Harvard departments and affiliated hospitals.

Neurology has been famous in decades past as a clinical specialty with great diagnostic power and limited clinical tools. This is changing, as new treatments have been developed for a variety of disorders, but progress has been frustratingly slow. Similarly, psychiatry is moving into a new era in which many mental disorders can be understood in terms of neurodevelopmental failures or mutation of specific synaptic proteins or misregulation of brain circuits, but the gap between understanding and treatment is still large. This is partly due to the complexity of the problem: We must understand not only how the aberrant function of a protein affects the behavior of individual neurons, but also the consequences for the operation of complex neural circuits and ultimately sensation, action, and thought. Solving the problem and curing these disorders will require a concerted approach involving multiple approaches, and many investigators working at different levels of integration.

At the same time, basic neuroscience research has exploded in the past 40 years. The Society for Neuroscience now has 38,000 members and its annual meeting showcases a breathtaking diversity of research in the field. The promise of neuroscience has begun to permeate other parts of the culture, with new disciplines of neuroeconomics, neuroethics, and even neurotheology acknowledging the importance of an understanding of brain function in nearly all aspects of daily life. In addition, basic research is providing new insights into a wide range of diseases involving the nervous system, including neurodegeneration, stroke, chronic pain, autism, epilepsy, fear, addiction, obesity, and sleep disorders. Yet at Harvard and elsewhere, a surprising disconnect exists between basic and translational neuroscience. In considering this problem, we began by assessing the current state of Harvard neuroscience.

Current state of neuroscience at Harvard

Strengths

Neuroscience research at Harvard and its affiliates is very strong. The HMS Department of Neurobiology, the first such department in the country, has been home to four Nobel Laureates (David Hubel, Torsten Wiesel, Rod MacKinnon and Linda Buck) who did significant portions of their work here. It has trained the scientists who went out to start outstanding neurobiology departments at other institutions. Although the Department has had eras of strength and weakness, it is now one of the leading departments in the world. The Department has 25 members who run active laboratories. Seven are at affiliated hospitals (Children's, DFCI, or MEEI) and 18 are on-Quad.

Similarly, the Center for Brain Science (CBS) at the Cambridge campus has unified a number of outstanding neuroscientists in several departments, with a focus on understanding the structure and function of brain circuits. Some of the Cambridge-based CBS neuroscientists will be soon brought together in the new Northwest Building.

Other HMS Quad departments as well as the Harvard-affiliated hospitals and institutions are home to many more neuroscientists, some very basic and some more translational. A preliminary list of Harvard University NeuroScience (HUNS) faculty identified more than 150

neuroscience laboratories across the Harvard community. These are particularly concentrated in hospital-based departments of Neurology and Psychiatry, but also found in Genetics, Psychology, and other departments.

Overall, the current Harvard neuroscience faculty has very substantial national visibility. Twelve are members of the *Neuron* editorial board, one is the Editor-in-Chief of the premier *Journal of Neuroscience*, 8 are HHMI Investigators, 3 are past presidents of the Society for Neuroscience, and 3 have been Young Investigator Awardees of the Society for Neuroscience. Twenty-eight have received one or more awards from the McKnight Endowment Fund for Neuroscience. Eight are members of the NAS and 6 are members of the IOM.

Education in neuroscience occurs vigorously at the undergraduate, graduate and professional levels. In the MD curriculum, two superb second-year courses have received numerous teaching awards: The *Human Neural Systems and Behavior* course for HMS MD students and the *Introduction to Neuroscience* course for HST Program MD students. Both teach the basic function of the nervous system with reference to human neurological and psychiatric disorders.

The graduate level is covered by the Program in Neuroscience, which is based in the Division of Medical Sciences but functions as a University-wide PhD program. Participating faculty are widespread: at HMS Neurobiology as well as other Quad departments, at all HMS-affiliated hospitals, and at FAS. The core courses are taught mostly by the HMS Neurobiology faculty with increasing participation by FAS neuroscience faculty; additional topical courses are offered by faculty throughout the Harvard community. Participation in teaching is a requirement for faculty membership in the Program. The Program in Neuroscience has a strong educational program and an outstanding reputation. It attracts top applicants and enrolls over 50% of those offered admission. Students in the Program regularly compete with great success for outside fellowships and honors.

Undergraduate education in neuroscience has been strong for many years but has gained even more emphasis through the recent creation of the Neurobiology concentration in the life sciences. Teaching in the undergraduate courses is done mainly by FAS neuroscience faculty, with substantial participation of teaching fellows from the graduate Program in Neuroscience.

Weaknesses

Integration

It has been suggested that science at Harvard is less than the sum of its parts. Although we feel this charge may be unduly severe, it is true that neuroscience at Harvard is not sufficiently integrated to make the most of the strength and breadth of the overall enterprise. The problem is primarily geographical, in that these 150+ laboratories are dispersed among institutions separated by a river and as much as 10 miles distance. There is even difficulty in fully integrating neuroscientists along Longwood Avenue, where the largest number of neuroscience laboratories reside. The problem is cultural as well, in that no one department or institution is perceived as or serves as a unifying base for all of Harvard neuroscience. Finally, there is some sense of a two-tier system within the Harvard medical community in which scientists outside of the basic science departments have felt excluded. Differences in hard money support between Quad and off-Quad faculty no doubt contribute to this; an additional factor is a sense of exclusion lingering from the HMS Neurobiology's early days; and there has been insufficient outreach effort until recently.

A significant challenge for the next few years will be to integrate the greater Harvard community more effectively. Under the leadership of Kathy Buckley, Associate Provost for

Science, a Neuroscience Coordinating Committee had been meeting regularly to find ways to bridge the institutional and geographical barriers, and to agree on priority goals for programs that could be presented to HUSEC. In November 2007, it held a Harvard University NeuroScience retreat, which was open to all 150 faculty and was very successful. Another HUNS retreat, with even broader outreach to include more faculty at Childrens', BIDMC, BWH, Dana Farber, MGH, and McLean, will be held in Spring 2008.

These efforts, while a useful start, will not themselves be adequate to fully integrate the neuroscience community and meet the challenge of understanding and treating complex neurological disorders. We feel there should be a new culture of interaction that is maintained by regular meetings and a new physical center where Harvard neuroscientists can come together to apply new understanding of brain development and function to the development of therapies and cures for treating neurological disorders.

Translation

The explosion of research in neuroscience and the resulting understanding of proteins, synapses and circuits in the brain should be revolutionizing treatment of neurological and psychiatric disease. We believe that certain areas of research are ripe for application to clinical problems; these might include spinal cord regeneration, multiple sclerosis, and reward pathways underlying addiction. Other neurological and psychiatric diseases--such as schizophrenia, neurodegenerative disorders, and movement disorders--involve complex pathways that will require many years of basic science to elucidate, yet it is not too soon for basic scientists and clinicians to be looking for common ground.

Yet we lack good coordination between this wealth of basic neuroscience and clinical-translational efforts at Harvard. A part of the problem is again geographical. A neurologist at the Brigham with a specific clinical interest might never meet a scientist at MGH East who is doing research relevant to that disorder, much less have opportunity for convenient collaboration. A secondary problem is cultural, in that scientists and clinicians have not developed a tradition of seeking each other out. The result is a significant failure to capitalize on new and exciting translational opportunities.

Opportunity: A Harvard Neuroscience Institute

Our group felt that the solution to the problem is two-fold. One part is to bring together, in physical proximity, a critical mass of investigators that span the spectrum from basic research to disease-applied and translational research. The complexity and range of modern neuroscience requires that investigators working with diverse tools and at multiple levels of organization (molecules to cells to brains) can interact in close proximity. The second part – necessary both because the Harvard neuroscience community is too large to be located in one building and because it should not be cut off from the other elements of the Harvard research and clinical communities – is to improve communication and collaboration among the neuroscientists across the basic-to-clinical spectrum.

Both of these goals might be accomplished by an Institute that we refer to here as a Harvard Neuroscience Institute (HNI). The exact name, organization and governance remain to be decided, but we identified a number of important characteristics.

The Harvard Neuroscience Institute should collect a core group of Harvard neuroscientists in a common location. These could be initially drawn from relevant neuroscience researchers at the affiliate hospitals and from HMS Neurobiology. Ideally the Institute would have funds to

recruit additional faculty who would have appointments in one of the member Departments, in coordination with those Departments. This is important as it would allow the recruitment of scientists in emerging areas (e.g. stem cell biology, human genetics, bioengineering) that are currently under-represented in the Harvard neuroscience community. The Institute would eventually comprise 30-40 resident laboratories in order to create a critical mass for interaction.

The HNI mission should be explicitly translational. Not all laboratories will be working directly on disease, but collectively the research should have significant potential to impact treatment of neurological and psychiatric disease. This would make its mission complementary to that of the Center for Brain Science, which has a more basic focus. Ties between HNI and CBS should be strong, though, as there is substantial relevance of each area to the other.

Assembly of the Neuroscience Institute need not draw faculty away from thriving departments at HMS, hospitals or affiliates; instead these institutions could place investigators in a common host building with space paid for by the home institution—what we might call a "condo" model. Resident investigators will have affiliation with their home institution and scientific affiliation with others working on similar problems. The Institute should be large enough to support a number of core facilities (e.g. imaging and molecular biological resources) that serve resident neuroscience laboratories as well as other laboratories in the Harvard Community. Also, experience at Harvard shows that mere juxtaposition of laboratories will not be enough to improve communication. Substantial effort – from leadership and from the resident laboratory heads – will be needed to bridge the cultures and create real community.

Importantly, placement of these investigators in a common building must not cut their ties to and interaction with their home institutions. The flow of people and ideas between the home institution and the host HNI must remain bidirectional, or the advantage of bringing people together is lost. For investigators with clinical responsibilities in their home institutions, the movement will occur naturally; for basic neuroscientists it may be more difficult, but strategies like maintaining offices and perhaps even laboratories in each place may preserve ties. We hope that a bidirectional movement will also help bring ideas from other fields into the Institute; that resident investigators' collaborations in other areas like genomics, physics, imaging and bioengineering will create some cross-pollination.

The second key element needed to make Harvard an optimum center for neuroscience research is improved outreach and communication. The Harvard Neuroscience Institute must not be limited to the resident laboratories but must serve as a center for all interested Harvard neuroscientists. An explicit part of the HNI mission should be to organize affinity or special-interest groups that meet periodically to talk and exchange ideas. Existing models are seminars and journal clubs in the LAM-TSC Seminar Series, the Division of Sleep Medicine, the Harvard NeuroDiscovery Center, and the Center for Hereditary Deafness, which draw membership from all the Harvard institutions and meet at roughly monthly intervals. We propose, first, a large expansion in the number of such groups, but we recognize, second, that such groups must be self-assembling and fluid rather than organized from the top down. Important new areas of science cannot be predicted by a director or executive committee and so groups should be encouraged to assemble spontaneously. The role of HNI is both to facilitate such organization and to provide a physical location that is conducive to meeting. A small conference center with an auditorium of ~150 seats would be an essential component of HNI. Moreover, it will be an explicit responsibility of investigators in resident HNI laboratories to help organize and manage meetings in their areas. They may not always be the directors of such groups but they will have a role in promoting them. Obviously, these affinity groups are natural catalysts for new funding in the form of training grants, program project grants, and core grants. It would also be

valuable for the HNI to have seed grant money to help truly new collaborations evolve to the point of attracting such outside funding.

As a home for meetings of these special interest groups, HNI will naturally become a home base for all of Harvard neuroscience, a place where all investigators feel welcome. Cores that serve the entire community will draw faculty, students, and postdocs into interactions based on common technologies. Guest office space or carrels would allow off-Longwood visitors to work for a few hours between teaching and meetings. By being explicitly inclusive of those outside the walls of the Institute, we think HNI will go a long way towards eliminating the sense of a two-tier system within the Harvard medical community.

The Harvard Neuroscience Institute will also have an educational mission, which will complement the Harvard Program in Neuroscience, the very successful cross-university PhD program. Instead, HNI could be a focus for courses or programs that grow out of the affinity-group meetings. The Tuberous Sclerosis group, for instance, might organize a minicourse or reading group for students, postdocs, residents and faculty who have an interest in that area and who need to know the basic neuroscience relevant to the disorder. Again, the role of HNI will be to facilitate such courses and to provide a location.

Location and Governance

As Harvard Medical School is the hub of the medical/translational research enterprise and also at the heart of the greatest concentration of neuroscience researchers, it makes sense for the HNI to be an HMS entity, with a Director appointed by the Dean of HMS. The Director would necessarily consult with an Executive Committee comprising representatives of each of the affiliated medical institutions and FAS. Any plan to create improved interactions among neuroscientists, both within the HNI and across Harvard, will require a strong and committed Director.

The HNI should also ideally be sited in the Longwood area, as close as possible to the existing concentrations of neuroscience researchers (located on the Quad and on Blackfan Circle). Identifying a specific location for the Harvard Neuroscience Institute is beyond the scope of this committee and will require consideration of many logistical and financial factors. However we noted the existence of two buildings that already have elements of the condo model. The Harvard Institutes of Medicine at 4 Blackfan Circle presently has neuroscience investigators from Brigham & Women's Hospital, and some uncommitted floors. It has a good conference space on the first floor. The new Center for Life Sciences Boston at 3 Blackfan Circle will house neuroscientists from Children's and BIDMC; it also has uncommitted floors. Both are centrally located. Eventually, a building that could house more laboratories is desirable; it might be located adjacent to the HMS Department of Neurobiology if the Harvard School of Public Health is partially relocated to Allston. If the enterprise is as exciting to the public as it is to us, it would represent a substantial philanthropic opportunity.

In summary, we suggest that a new institution organized along these principles will serve both to integrate Harvard Neuroscience and to promote the flow of basic neuroscience research into clinical applications. Organized as a condo model and drawing on existing laboratories, it could be less expensive than substantially expanding HMS Neurobiology or creating an entirely new center. Serving both as a critical mass of resident laboratories and a center for nonresident members, it will help make neuroscience at Harvard much more than the sum of its parts.

Appendix

As an extension of the Biomedical Research Strategic Planning process, Gary Yellen and Michael Greenberg convened a meeting of some leaders in Harvard Neuroscience on January 30, 2008.

Invited were

Robert Brown (MGH)
David Corey (HMS)
Michael Greenberg (Children's)
Frances Jensen (Children's)
Josh Sanes (CBS; FAS)
Clif Saper (BIDMC)
Dennis Selkoe (BWH)
Chris Walsh (BIDMC/CH)
Gary Yellen (HMS)
Anne Young (MGH).

All but Drs. Selkoe and Young were able to attend the initial meeting. Subsequently a preliminary draft proposal (prepared by Yellen, Greenberg, and Corey) was circulated to all of the group by email, with comments incorporated into this draft. Additional revisions were made in response to the discussion at the Critical Areas of Research subgroup.