California Institute of Technology
Visiting Committee for the Division of
Biology and Biological Engineering

April 7, 2016

TO: Thomas F. Rosenaum, President
Sonja and William Davidow Presidential Chair and
Professor of Physics

Edward M. Stolper, Provost
Carl and Shirley Larson Provostial Chair and
William E. Leonhard Professor of Geology

Stephen L. Mayo
William K. Bowes Jr. Leadership Chair,
Division of Biology and Biological Engineering and
Bren Professor of Biology and Chemistry

FROM: Richard H. Scheller
Chief Scientific Officer and Head of Therapeutics
23andMe
Visiting Committee co-Chair

Phillip A. Sharp
Institute Professor
Massachusetts Institute of Technology
Visiting Committee co-Chair

Enclosed is the final written report summarizing the findings and recommendations developed by the Visiting Committee for Caltech's Division of Biology and Biological Engineering in response to the meetings held on February 29, March 1 and March 2, 2016. While a number of the recommendations have evolved somewhat in the writing and editing process, we do not believe you will find any substantive change in the issues covered in the committee's discussion with you on March 2. The committee has no desire to restrict the contents of the report and leaves to you the decision on how best to disseminate this information to the faculty and other interested parties.

On behalf of the members of the Visiting Committee, we would like to express our appreciation to Dr. Mayo and the faculty and staff of the division for providing us with a wonderfully hospitable and honest environment in which to do our work. We hope you find the results of our efforts to be beneficial and useful.

c: Members of the BBE Visiting Committee

California Institute of Technology

Report of the Visiting Committee for the Division of Biology and Biological Engineering

February 29 – March 2, 2016

2016 VISITING COMMITTEE MEMBERS

Richard Scheller
Chief Scientific Officer and Head of Therapeutics
23andMe
Caltech Trustee
Committee co-Chair

Phillip Sharp
Institute Professor
Massachusetts Institute of Technology
Committee co-Chair

Brigitte Bren, Esq.
Caltech Trustee

Peggy Cherng
Co-Chairman
Panda Restaurant Group
Caltech Trustee

Naren Gupta
Managing Director
Nexus Venture Capital
Caltech Trustee

David Haussler
Distinguished Professor, Biomolecular Engineering
University of California, Santa Cruz
HHMI Investigator

Wendell Lim
Professor of Cellular and Molecular Pharmacology, Biochemistry and Biophysics, and Pharmaceutical Chemistry
University of California, San Francisco
HHMI Investigator

Richard Merkin
Founder and Chief Executive Officer
Heritage Provider Network
Caltech Trustee

Ken Moore
Gordon and Betty Moore Foundation
Caltech Trustee

Bill Rastetter
Biotechnology Entrepreneur
Caltech Trustee

Carla Shatz
Sapp Family Provostial Professor of Biology and Neurobiology and David Starr Jordan Director of Bio-X
Stanford University

Marc Stern
Chairman
The TCW Group, Inc.
Caltech Trustee

Introduction

The Visiting Committee for the Division of Biology and Biological Engineering (BBE) met at the California Institute of Technology on February 29, March 1, and March 2, 2016.

During the course of its review, the Visiting Committee had the opportunity to meet with undergraduate students, graduate students, postdoctoral scholars, assistant professors, tenured faculty, and, separately, with female tenured faculty. While the committee received many suggestions about how to improve the Caltech experience, the overall satisfaction with Caltech was universal.

Not only was this satisfaction manifested in absolute terms, but benchmarked against two somewhat objective criteria, it was also quite positive in relative terms. First, two members of the Visiting Committee, Carla Shatz and Marc Stern, were on the Visiting Committee when the division was last reviewed in 2006. The satisfaction of the various constituents was considerably more positive now than at that time. Secondly, the third-party members of the Visiting Committee who regularly review similar organizations, including in some instances their own, felt the level of satisfaction at Caltech was significantly higher than what they found in comparable organizations.

There seemed to be prevalent feelings that Dr. Mayo is doing a very good job as division chair and that he is a strong and effective advocate for BBE both within and outside the Caltech community. (This feedback was provided to the committee despite the committee's concerted efforts to elicit criticism or concerns.) General confidence was expressed that decisions were made fairly, without bias, and in the context of weighing difficult competing interests. Attempts to encourage cooperation and coordination within the departments were generally supported, and the annual offsite BBE retreat was frequently cited as a very effective community-building activity. Dr. Stolper's "birthday coffees" with faculty members were mentioned as a very successful example of the Administration's attempts to keep the lines of communications open.

Campaign Priorities

The BBE faculty provided the committee with campaign white papers for four programmatic initiatives, all of which require substantial funding:

1. Vision for Caltech Neuroscience
2. Caltech Center for Biological Circuit Design: a vision for a new integrated systems and synthetic biology initiative at Caltech
3. Center for Environmental Microbial Interactions ("Microbiology")
4. Caltech Center for Translational Sciences and Health Technology Committee Report

The first three of these campaign themes are being driven by BBE; the fourth is an Institute-wide initiative. Success in garnering support for these campaign initiatives will have a profound effect on the health, growth and relevance of BBE at the new frontiers of biology and biological engineering. Each of these four initiatives will share benefits from campaign success: facilities, instrumentation and other Infrastructure, and graduate student fellowships.

The biological circuit design and microbiology initiatives are more embryonic than neuroscience; however, all three are important BBE initiatives. Each is worthy of funding to drive growth, and each is led by visionary, passionate and strong faculty members. To the extent that campaign funding is less than ideal, or that funding comes in over a period of years rather than in a more steady flow, BBE will have to make hard decisions about the allocation of funds and other resources among these efforts. Any such prioritization of resources should be developed in close partnership with the BBE faculty and Dr. Mayo. To ensure forward progress, continued transparency and trust should be the hallmarks of any such discussions. In addition, the campaign emphasis on neuroscience (as it was described by the division to the Visiting Committee) did not appear to have been shared effectively with the BBE faculty at-large. The committee did not perceive a general understanding among the faculty of how the new funds would be spent, raising some concern that the division's future direction could be led by donor preferences rather than by strongly defined BBE priorities.

The following sections of the report provide additional details about specific campaign-related themes, as they relate to BBE.

Graduate Student Fellowships

The ability to provide graduate student fellowships from divisional and institutional resources is increasingly important in the recruiting of the very best graduate students, particularly in light of the decline in NIH funding. Two of BBE's key competitors provide three years (MIT) and four years (Stanford) of central funding for incoming graduate students before their support becomes the responsibility of their faculty advisors. Prospective students are sophisticated enough to appreciate the risk of underfunded graduate fellowships. The endowment of fellowships for all graduate students for three years is one of Caltech's institutional campaign priorities, and the Visiting Committee endorses this effort and celebrates the success already accomplished toward achieving this goal.

Neuroscience

Neuroscience is a strong campaign theme in a field where Caltech has an extraordinary history. There are two strong traditions at Caltech in the neurosciences. The first traces its history back to the 1980s when Carver Mead, John Hopfield and Richard Feynman started an extremely influential program at Caltech dubbed Computation and Neural

Systems (CNS). Now, 30 years later, when computing technology is finally catching up with this vision, the early CNS ideas are bearing fruit. Google recently purchased a London company, DeepMind, for an estimated $600 million based on their success in applying these early ideas in the area of Machine Learning. IBM has made a significant investment in building what are known as neuromorphic systems, computing platforms whose architecture more reflects the organization of the human brain than conventional computing devices. Devices performing brain-like computation are becoming a part of our everyday lives. The second rich tradition in neurosciences traces its history even further back to renowned faculty such as Roger Sperry and Seymour Benzer. Wide ranging new developments in physiology, genetics, and molecular biology, have enhanced our ability to look directly at brain circuits and measure their activity. Thus there is an unprecedented opportunity to come full circle and understand complex human behaviors in terms of molecules, cells and circuits. Caltech, with its exceptional base in scientific and engineering talent, is well positioned to marry these themes in a highly influential initiative.

To remain a great institution, Caltech must continue to support the evolution of neuroscience at all levels, and the Visiting Committee was very encouraged that this theme has been selected as one of the Institute's campaign priorities. However, this is a highly competitive area and the neuroscience concept that was presented to the Visiting Committee lacked crispness and failed to communicate the inherent excitement of this topic. To succeed in this key fundraising endeavor, the question, "Why Caltech?" needs to be much more clearly delineated. The question "What can the envisioned Neuroscience Institute do for Society?" should be explicitly addressed despite the assertion by faculty that the study of the brain is itself sufficient reason to create an institute. This topic does not need to address issues of clinical neuroscience, which are best left to medical centers. Instead, the faculty leaders should "imagine the future" and better convey their excitement in presentations.

In addition to the above, more general, comments, the Visiting Committee also observed that, from an outsiders' perspective, the two neuroscience groups mentioned above do not appear to be coordinated. We feel that there is a missed opportunity here. The committee heard that the CNS program and the BBE neuroscience groups are on good terms: with faculty from the two programs collaborating with one another and students at all levels moving fluidly between the programs. However, the Visiting Committee found this separation to be somewhat peculiar, since both computation and neuroscience themes run across the entire gamut from molecules to computer science to neuroengineering. Caltech, with its small population, should take the opportunity to include all relevant fields in its neuroscience program and synthesize a unified vision that will enable the Institute to be special in a very competitive environment. Building on Caltech's great early traditions and explaining how both computation and molecular biology, including self-organizing molecular systems, molecular cell circuits, and cellular systems behavior, will allow us to understand the brain at a profound new level.

In light of the above comments, the Visiting Committee believes that some additional introspection by the neuroscience faculty (in collaboration with their CNS colleagues) is required to better define the uniqueness of neuroscience at Caltech. In the course of these efforts, they could think about questions such as:

- How can Caltech's special strengths make unique contributions to the field of neuroscience? Why Caltech, as opposed to the competition at other institutions (some of which also have significant strengths in neuroscience, engineering and computation)?
- What are the implications of Caltech's strengths in quantitative fields, in electrical engineering, in physics to neuroscience?
- Does computational strength provide connections horizontally (across species) in neurobiology? And vertically: from synapse to circuit to brain?
- What contributions will neuroscience at the interface with computer science make to "neuromorphic machines"?
- Are there uniquely strong opportunities at Caltech at the interface of brain high-resolution functional imaging and big data? And what about the interface of the human brain with engineered brain constructs, e.g., non-invasive brain/machine interfaces?
- How will the cellular and molecular neuroscientists interact with, contribute to, and benefit from the computational neuroscientists?

In summary, the Visiting Committee believes the neuroscience campaign theme needs more work on "messaging" and "marketing." The current "pitch" sounds a bit like "science for science's sake"—and for very pragmatic reasons, it might be better to cast the story as "neuroscience for society's sake" to attract donor interest. In addition, the split between neuroscience and CNS is confusing when viewed from the outside—and perhaps some consideration should be given to merging these two programs into a single cohesive community. Both of these efforts should build on Caltech's special history and relationship to neuroscience.

Caltech Center for Biological Circuit Design

Caltech is uniquely positioned to contribute to the elucidation and understanding of the design principles of cellular regulatory circuits. In the view of the Visiting Committee, this makes the Caltech Center for Biological Circuit Design a highly appropriate campaign theme for the Institute. Caltech's scholarly and transformational work in seeking to understand biological systems addresses biomedical challenges and is leading to revolutionary applications. Caltech's unique community of world leaders with expertise in cellular and molecular circuits is generating strong, meaningful ties that are crossing the boundaries between physics, engineering, and computer science. This

work is facilitated by the Institute's small size, its uniquely collaborative research tradition, and the group's strong synergy with systems neuroscience, Caltech's emerging work in translational sciences and health technology and other applied initiatives that are percolating at Caltech. Caltech cannot be passive and miss these opportunities: it must provide the support needed to retain the community and the intellectual leaders in this area, while providing the facilities, instruments, and space needed to support the existing group and to recruit new faculty in these areas.

Center for Environmental Microbial Interactions

The Center for Environmental Microbial Interactions (CEMI) was established in 2012 and has become a leader in multiple important areas spanned by three divisions BBE, CCE and GPS. Understanding microbes is critical in several ways. First, they serve as critical model systems in a number of areas of science including biochemistry and cell biology. Second, interactions within microbial communities and between microbes and their hosts are poorly understood. For example, symbiotic relationships between microbes and plants underlie the nitrogen cycle and an understanding of this process is critical to future developments in agriculture. Investigations of the interactions between microbes and the animal hosts, including humans has become one of the most important and interesting areas of modern biology. Finally engineering microbes will likely be important in solving global societal problems.

Caltech has a tremendous opportunity to enhance its leadership in this area by including CEMI in the current fundraising campaign, and the committee strongly supports this proposal.

Center for Translational Sciences and Health Technology

President Rosenbaum commissioned a committee to put forward a vision for Caltech to increase its impact on improving human health. The emphasis of this committee's report centers on how Caltech, which does not have a medical school, can foster the translation of basic medical science discoveries. As a consequence of its deliberations, the committee recommended establishing a Center for Translational Sciences and Health Technology at Caltech. The requirements for space, personnel, governance, etc., for such a center are clearly presented in the committee's report, as are the mechanisms for implementation.

Since this is an Institute-wide initiative, it was initially not on the schedule for the Visiting Committee. However since the establishment of a translational sciences center at Caltech would clearly affect many BBE faculty members, the committee requested a briefing on this topic.

The vision for a Translational Sciences and Health Technology Center at Caltech (as described in the report of the committee appointed by the president) is the most

nascent of the initiatives discussed with the Visiting Committee. Since Caltech does not have a medical school, its approach to translational science and health technology needs to be uniquely creative. The success of translational science is based on three distinct elements:

1. the science,
2. the bridge to the clinic, and
3. the clinic.

At Caltech, BBE and other divisions provide the science, and the medical centers with which Caltech has established partnerships (e.g., UCLA or City of Hope) provide the clinic. The envisioned Translational Sciences and Health Technology Center would provide the entrepreneurial culture and learning, subject matter experts in translational subjects, and "incubator space" that would create the bridge to the clinic. (Models for such an entity exist within Johnson&Johnson, Illumina and the UC system's QB3.)

The unique strength of the biotechnology industry in the U.S. has come from the three distinct funding sources that have been available to entrepreneurs who are seeking to do translational science: the NIH, venture capital and NASDAQ. Generally, the most difficult transition for researchers to navigate successfully is from academic science (supported by the NIH) to a venture-backed start-up. In the therapeutic field, it is difficult to find venture capital funding for programs that are still years from the clinic. Incubators can help bridge this gap. Incubator tenants typically move to independent facilities upon closing their first or Series A financing from venture sources. In the interim, each incubator company might run with a staff of 4 to 8 scientists/technical staff using shared facilities and instrumentation. An initial Center might have bench and instrumentation space to support 50 to 75 "wet lab" personnel—and might grow from there given demand and success for the model.

Due to its lack of proximity to venture capital, Caltech's location in Pasadena poses a challenge to successful translational work. Travel and time create barriers to finding investment opportunities, which are more readily available to researchers at institutions located in the Bay Area. As Caltech's translational science work matures, and the Center begins to take form, special emphasis must be placed on establishing strong personal relationships with select venture capital funds in order to foster communication, due diligence and investment. Payback to Caltech from successful ventures would come primarily in the form of equity that would become liquid upon successful sale or IPO (some emphasis might be placed on royalties but only for the more near-term commercial opportunities).

The success of Caltech's efforts to establish a Center for Translational Sciences and Health Technology will be contingent upon the Institute's ability to communicate its vision for the Center's societal and health benefits in a way that will inspire philanthropists to provide essential resources. The Center may well be the entity that

creates the critical link between Caltech's science and engineering (which can seem impenetrable to the outsider) and relevant and tangible human applications.

In summary, the Visiting Committee views the creation of a translational sciences center as a positive and important step for Caltech and agrees with the priorities and the mechanisms for its implementation. At this time, however, it is unclear how the center would be funded. The Visiting Committee believes that the BBE priorities for the current campaign should remain the new building described to the committee at this meeting and the initiatives presented by the BBE faculty. The Caltech Center for Translational Sciences and Health Technology should be a separate initiative.

Space Needs

The physical study of biological systems at a gene and molecular biology level is a recent development and the field is expanding in societal importance. This expansion is physically visible on the Caltech campus by the addition of the Broad Center in 2002. Since that time, outstanding faculty at Caltech have initiated new fields of research that hold high promise for contributing to the solution of major future challenges. These range from the understanding of:

- how thought, memory, emotion and decision-making impact education and social behavior (e.g., aggression);
- cell circuits and systems, which allow researchers to design cells with new functionality; and
- the complexity of the microbiome and its impact on the atmosphere, geosphere and hydrosphere, thus allowing better control of climate change.

Each of these initiatives is led by distinguished faculty and particularly in the latter two areas, faculty who will be leaders at Caltech for decades to come.

The coalescence of bioengineering into biology and the development of collaborations between faculty in geology, biology, and other disciplines is exciting and is fostering important new developments at Caltech. The organic growth of these initiatives at the Institute has been stimulated by the recruitment and support of junior faculty over a period of several decades. Further, the momentum of these initiatives is at an inflection point as they begin to gain national and international recognition. Therefore, it is imperative for Caltech's future research in the life sciences that the cell circuit and systems and microbiome programs receive increased institutional support from the upcoming campaign. The Visiting Committee was informed of campaign objectives for these initiatives to acquire major endowments, on the order of $20-30 millions, and permanent funding of fellowships for graduate students. As mentioned earlier in this report, the Committee strongly endorses the goal to firmly establish these new

initiatives with their future promise of critical scientific discoveries and societal benefits. The third initiative in neuroscience is an outstanding program at Caltech with historical roots that are decades old. The current state of neuroscience is also discussed elsewhere in this report.

The Visiting Committee considers it imperative that the campaign achieve its objective of raising funds for the new Caltech biological sciences building (costing on the order of $200 million). The committee believes that the proposed building is essential to the success of Caltech's efforts to consolidate the neuroscience programs and to expand the cell systems and circuits and microbiome initiatives. The current neuroscience faculty is distributed across the campus, some in buildings that are a century old. These aged facilities do not facilitate collaboration and, because the room designs are inflexible, they are generally inefficient and not particularly conducive to the conduct of modern biological science. Over the past decade, the neuroscience program at Caltech has lost four distinguished faculty, three to other institutions and the fourth to an untimely death. The current faculty are excellent with a good mixture of seniority and expertise and they are actively engaged in the process of recruiting colleagues. It is likely that these recruitments will further strengthen relationships to the theoretical and computation community on campus as well as to the engineering community to further imaging of neurosystems at subcellular and even atomic levels in alert animals. The new space will facilitate this recruitment as well as the retention of current faculty.

The Visiting Committee was shown the proposed design and location of the new building that would open the campus to Del Mar Boulevard on the north and allow future expansion of the space available for life science researchers to at least one adjacent building. It has been 14 years since the addition of the Broad Center at Caltech and with the obvious growing importance of biological sciences across the campus and the transformational initiatives in progress, the Administration's statement that the new building has the highest construction priority in the campaign is strongly endorsed by the Visiting Committee.

Overall, BBE's facilities span the range from relatively new to recently renovated to antiquated and not up to current safety standards (e.g., lacking fire sprinklers and proper ventilation). Growth of BBE in faculty, students and postdocs will require not only the proposed new building but additional space that is configured (or reconfigured) to support modern biological research. While the new building may be forthcoming, there is apprehension at the division level that BBE may be required to relinquish current space and thus fail to benefit from the resulting increased square footage. The envisioned Translational Sciences and Health Technology Center will certainly require Caltech to provide a home for this effort that is in addition to the contemplated new building.

Another critically important space-related element is the instrumentation and other infrastructure that must be provided both for the new building and for any newly

renovated space. Given the rapid obsolescence of equipment, and the frequent need for maintenance, calibration and repair, the Visiting Committee encourages BBE to incorporate an endowment fund specifically allocated for instrumentation into the funding plan for the new building. Along similar lines, the division should examine the need for "methods centers" where trained personnel provide complex and/or specialized assays or other support for researchers who encounter an unfamiliar method on the critical path to research progress. It would be worth knowing how frequently research productivity in the division is hampered by the lack of state-of-the-art equipment and methods.

Gender Equity and Implicit Bias

BBE has achieved an admirable gender balance among faculty and PhD students since the Visiting Committee last met in 2006. Women comprise 31% of the BBE faculty, comparable to faculty at other institutions that have made concerted efforts to increase gender diversity. Even more promising, fully half of the junior faculty members are women. This percentage of junior faculty is the future of BBE and bodes well for faculty composition at Caltech. Among PhD students, the number is 50%+ women, which again is excellent and an accurate reflection of the overall applicant pool for graduate school. The Chair, Steve Mayo, and faculty in the division deserve kudos for these advances. Moreover, President Rosenbaum's clearly articulated commitment to diversity creates a very strong and supportive framework for continued growth and advancement in this critical area. The issue of faculty diversity in the context of underrepresented minorities continues to be difficult to solve, and the Visiting Committee is aware that this problem is of special concern to Dr. Mayo.

Despite, or perhaps because, women faculty feel that the climate for rational discourse about gender equity and diversity has improved, all of the senior BBE faculty women (with one absentee) requested a last-minute meeting with the Visiting Committee to discuss an issue of concern existing in the division. The issue can perhaps best be identified as one of unintentional or implicit bias, but it reveals a disturbing legacy of attitudes and culture towards women faculty at Caltech that would benefit from more work and attention—despite serious ongoing efforts. The women senior faculty members described a faculty meeting in which a search committee presented two top candidates (both female) to the entire division for consideration. These candidates had already been thoroughly vetted by the committee. Unfortunately, negative comments made by several senior faculty members at the faculty meeting were not as constructive or fact-based or process-oriented as would be appropriate and expected in a scholarly and collegial discussion of candidate qualifications. The discussion was derailed and the committee's decision itself was questioned. This incident was one of several, including a female graduate student report to the Visiting Committee concerning a faculty member's remark that was also quite unacceptable in today's workplace. These incidents underscore the fact that each of us comes to every conversation loaded with

implicit biases. Implicit bias is real and has been extensively documented in the scientific literature (e.g. Mahzarin Banaji at Harvard). The Visiting Committee urges the division—and indeed Caltech as a whole—to become more educated and cognizant about this topic so as to elevate the level of discourse.

Writing and Communication

The desire for more training in writing and communication was an issue raised by several of the groups with whom the committee met.

- Graduate Student Writing

  Young faculty expressed disappointment in the quality of graduate student writing, and at the same time, the graduate students expressed disappointment in the lack of training in grant writing. They noted that although Caltech has a writing center, this resource is good for advice on writing style and grammar, but it is not very helpful for the strategic and logical issues encountered in scientific writing, particularly grant writing. A potential solution that is common practice at other peer institutions is to have a workshop course linked to the writing of NSF graduate fellowships, guided by faculty and senior graduate students.

- Postdocs and Young Faculty

  Postdocs looking for faculty positions and young faculty expressed interest in opportunities to receive more training in speaking, giving chalk talks, and writing grants. Many sought this kind of input based on informal networks of faculty that they know. It could be helpful to create a more formal structure for providing this type of coaching to these young community members for whom communication skills are particularly critical.

Postdoctoral Scholars

The Visiting Committee encourages the division, and the Institute, to think more broadly about the postdoctoral scholar community at Caltech. At a minimum, steps should be taken to ensure that all postdoctoral scholars are paid at least the NIH scale for the first three years of their residency. BBE postdocs who remain at Caltech beyond three years should be moved to a research ladder scale that is consistent with that of the other academic divisions. The committee also received feedback from postdocs that they believe that it would be very beneficial if Caltech were to provide increased assistance as they undertake their search for suitable faculty positions.

Summary

While all institutions have areas for improvement, the Visiting Committee is impressed with the progress that has been made within BBE and the broader life sciences community at Caltech. As discussed in our report, the relatively small size of Caltech and the lack of a medical school present both challenges and unique opportunities for the Institute. At some larger organizations if a program or two is not world class it is not necessarily critical to the overall success of the institution. At Caltech this is not the case. The main imperative must be that each of the initiatives is absolutely world class in its vision and execution.

The Visiting Committee believes that BBE has an exciting vision for the future. With appropriate support from the Institute's Administration, Caltech will remain a leader in the life sciences in the 21st century, indeed a century that many believe will be recorded in history as THE CENTURY OF LIFE SCIENCE.