HARVARD UNVERSITY

daVinci Initiative for Physical Biology

Probing living systems through the lens of physics and engineering

daVinci Group

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PhD Track in Engineering and Physical Biology*

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The Harvard University daVinci Center Initiative for Physical Biology:

Viewing Living Systems Through the Lens of Physics and Engineering

[www.physicalbiology.fas.harvard.edu]

I. OVERVIEW

Intellectual rationale. For the past 50-100 years, biology at the molecular and cellular levels has been viewed primarily as the aggregate sum of a large number of individual events and the interactions amongst them. A group of ~25 members of the Faculty of Arts and Sciences have recently come together as the daVinci Group (below) on the basis of their shared belief that the next round of fundamental advances in the life sciences will emerge by viewing biological processes in a very different way: as manifestations of the fundamental principles that apply to all types of systems non-biological and biological. By this view, life can be described not in terms of collections of diverse specific molecular and cellular details but in a more unifying and fundamental way as the manifestation and implementation of basic physical laws and universal principles of engineering and physics. It may not be too extreme to suggest that the next major breakthrough, analogous to the discovery and elucidation of the structure of DNA, will come from this new approach. We characterize this approach as "viewing biological processes through the lens of physics and engineering" and describe the corresponding discipline by the term "Physical Biology".

Specific areas of research. From an engineering/physics perspective, a particular phenomenon may reflect the operation of chemical, electrical and/or mechanical processes. Our challenge is to determine how these basic physical effects have been brought together in biological systems. From this perspective, biological phenomena can be grouped into three major categories: mechanics and dynamics; patterns and collective behaviors; and transport, signalling and communication. Future da Vinci Center research will span all of these areas, in ways that cannot currently be

predicted. Importantly, however, the daVinci Center will focus on processes at the molecular and cellular levels and thus micro- and nano-scale biology.

Long term goal. Physical Biology is a just-emerging area of intense scientific interest throughout the world. The ultimate goal of the daVinci Center is to make Harvard University *the* place to be in this area, with innovative new thinking and research taking place immediately, and revolutionary new ideas emerging from the daVinci Center and its alumni 25 years hence.

To achieve these goals, the daVinci Center will pursue a unique research and educational philosophy. At present, nearly all research at the life sciences/physical sciences interface occurs by collaborations between scientists in the two areas. The aim of the daVinci Center, instead, will be to create and collect a new generation of scientists who can work comfortably and simultaneously in both areas. Furthermore, progress in Physical Biology, as in all experimental sciences, will be limited by the emergence of new methodologies. An overriding conceptual theme of the daVinci Center will be the development of innovative new ways of measuring physical and mechanical forces and effects in living cells. We also note that, in all of its endeavors, the daVinci Center will place a very high priority on imaginative and creative thinking. This priority is reflected in the choice of Leonardo daVinci as a namesake. It also follows the well-known dictum of Albert Einstein that "imagination is more important than knowledge".

Core elements of the daVinci Center initiative are specifically designed to address these priorities: (i) a new track for PhD training designed to train young scientists in this approach (Engineering and Physical Biology, or "EPB"); (ii) an International Scholar Center designed to make Harvard a focal point for world-wide scientific interchange in Physical Biology; (iii) new faculty appointments, initially to energize and then to develop this area; (iv) community-use facilities that foster faculty research in development of new approaches as well as making generally available current cutting-edge technologies in which daVinci Group faculty are world-wide experts; (v) outreaches to undergraduates, to non-EPB PhD students and to Harvard and non-Harvard faculty; and (vi) a set of elements designed specifically to promote intra-community interactions.

The daVinci Group. The daVinci Center initiative draws its strength from its founding community, the daVinci Group. Current daVinci Group faculty represent a

significant amount of intellectual capital drawn from the FAS basic science departments of Molecular and Cellular Biology (MCB), Organismic and Evolutionary Biology (OEB), Physics, Chemistry and Chemical Biology (CCB), and the Division of Engineering and Applied Sciences (DEAS):

H. Berg (MCB/Physics), M. Brenner (DEAS), J. Dumais (OEB), F. Engert (MCB), N. Francis (MCB); R. Gaudet (MCB); G. Guidotti (MCB); N.M. Holbrook (OEB); J. Hutchinson (DEAS), D. Jeruzalmi (MCB), N. Kleckner (MCB), R. Kolter (HMS), L. Mahadevan (DEAS/OEB/HMS), T. Maniatis (MCB), E. Mazur (Physics/DEAS), V. Murthy (MCB), D. Nelson (Physics/DEAS/MCB), M. Prentiss (Physics), A. Samuel (Physics), H. Stone (DEAS), Zhigang Suo (DEAS), D. Weitz (DEAS/Physics), G. Whitesides (CCB) and Xiaowei Zhuang (CCB/Physics). Many of these faculty are already working actively at the life sciences/physical sciences interface via inter-daVinci Group collaborations. Full titles are given below; for scientific credentials and research interests, see [www.physicalbiology.fas.harvard.edu]. We note that daVinci Group faculty are diverse not only with respect to their scientific interests but with respect to professional stage (15 senior and 9 junior faculty) and gender (18 men and 6 women).

The da Vinci Group is a self-assembled community. It was nucleated by scientific interactions between Professors Hutchinson (DEAS) and Kleckner (MCB), which also led to a joint course given by Stone, Brenner and Hutchinson (DEAS) plus Kleckner, Guidotti and Jeruzalmi (MCB) [ES210]. The Group *per se* came to full fruition during the past academic year. We met for two highly-successful one-day "retreats", one in September and one in June, each comprising a series of short talks. The June retreat involved nearly 75 people including both faculty and students (for Program and selected photographs of the event see [www.physicalbiology.fas.harvard.edu]). Concomitantly, the daVinci Group formulated and successfully initiated a new PhD program in Engineering and Physical Biology, or "EPB" (described in detail below) and developed the current daVinci Center initiative. In the upcoming year, activities of the daVinci Group will be expanded to include a "monthly lunch" of short research talks, a series of interactions centered around the new graduate program, and any activities involved in furthering the emergence of The daVinci Center for Physical Biology.

***Perspective*.** The daVinci Group represents a considerable amount of intellectual capital and "star power". The formulated intellectual mission of the daVinci Center represents a far-sighted view of the future of Physical Biology which, as far as we are aware, is unique among physical biology initiatives throughout the world. The daVinci Center initiative will unite these two strengths, with the unique resources of FAS basic science faculty coalescing around a fundamental interdisciplinary area of enormous importance and great future potential. Properly supported, the Harvard University daVinci Center has the potential to be the *creator* of what we anticipate to be the next new wave to emerge from the life sciences/physical sciences interface.

Key Components of the Initiative.

1. A new track for PhD training: Engineering and Physical Biology (EPB). A cornerstone of daVinci Center activities will be a new track for PhD training, in Engineering and Physical Biology (EPB). The future of Physical Biology lies in its young people. By focusing effort and attention on the best and brightest PhD students, The daVinci Center will come to be known as the founding source for this emerging field. Funding for this Program is an essential component of The daVinci Center initiative.

EPB will be a small, highly selective program whose goal is to train a new generation of scientists that embody the philosophy of The daVinci Center: they wish to view living systems through the lens of physics and engineering and they are prepared to do so by working effectively in both the life sciences and the physical sciences. Applicants may have their primary undergraduate training in either area. Program components combine flexibility with rigor, place a high priority on independence and imagination, and emphasize extensive individual student-faculty interactions. The daVinci Group faculty will serve as the training faculty of EPB and will also provide an intellectual and sociological community for EPB students.

EPB has just this spring become a reality, through combined efforts of the daVinci Group, Venky Narayanamurti (Dean of the Division of Engineering and Applied Sciences and of Physical Sciences), Doug Melton (Chairman of the Life Sciences Resources Council), Peter Ellison and Theda Skocpol (Past and Present Deans of the Graduate School of Arts and Sciences) and Christopher Walsh (Chairman, Harvard Integrated Life Sciences ("HILS")). Students will enter EPB via three host Departments: Physics, MCB and DEAS. The program will be small and highly selective, with five students admitted each year. The first students will apply

for admission in December, 2005 and will matriculate in September, 2006. For detailed program description see [www.physicalbiology.fas.harvard.edu]. A flyer advertising the EPB program is appended below (see front and back sides).

While we are excited at the prospect of beginning this new training program, the current arrangement is unsatisfactory in two respects. First, to properly fulfill its mission, it would be more suitable for students to be free to pursue the special goals of this interdisciplinary program without having to simultaneously satisfy the requirements of admitting Departments. One possible solution to this problem would be for EPB to become an independent degree-granting entity (Higher Degrees in Engineering and Physical Biology). Second, at present, the EPB Program is funded on a shoestring budget which is quite inadequate to the task (below). As a small effort to improve this situation, the daVinci Group recently submitted an application to a recently-announced HHMI-NIBIB Interface Initiative which provides funds to help in program emergence. The EPB proposal was one of only two proposals, among many from the University, approved by the Provost's Office. However, even if successful, HHMI-NIBIB funding will only go a small way towards supporting EPB. Some progress in this direction is likely to be achievable via an NIH training grant, for which EPB can apply once there are several years of a successful "track record". However, even NIH funding would not support the EPB program at the necessary level. Thus: funding for the daVinci Center must begin with an appropriate, stable funding stream for EPB.

Funding will be required in the following specific areas: (i) student tuition and stipends; (ii) administrative assistance; (iii) development and distribution of program information for recruiting purposes; (iv) student laptop computers; (v) support for an innovative laboratory course that is a key pedagogical element of the program (professional personnel, supplies and equipment) and (vi) an annual symposium that involves presentations by every student as well as outside guest lectures. Additionally, the EPB Program will require (i) space for student desks; (ii) social interaction space; and (iii) the associated laboratory course.

2. International Scholar Center. Scientists throughout the world are intrigued by the potential of Physical Biology as an emerging discipline; indeed, some of the most intense activity takes place outside of the United States (details below). We want the Harvard daVinci Center to be an international focus of activity in this area - a Mecca for Physical Biology to which people will travel from all over

the world, analogous in some respects to the Princeton University Institute for Advanced Studies. This goal will be supported by several program components:

The centerpiece of the International Scholar Center will be annual funding for three visiting senior scholars ("Harvard daVinci Fellows", analogous to Neiman Fellows in the field of journalism or Guggenheim Fellows in several areas). Support will include salary, housing and travel expenses as well as funds for laboratory expenses; office space must also be available. One or two of these positions could include a required teaching component. The presence of these visiting scholars will greatly enrich both the intellectual and pedagogical life of the University without the special burdens imposed by permanent faculty positions. it will also provide a *de facto* mechanism for identifying and recruiting new faculty for the daVinci Center.

The International Scholar Center will also have fellowships for younger scientists from other countries: each year, ~3 one-year internships for post-doctoral "sabbaticals" and 3-5 graduate student summer internships. Additionally, the daVinci Center can host summer interns, e.g. from Germany, France and Turkey, who are required to visit an institution in another country as part of their graduate training. These students come fully funded but need an administrative and intellectual "home".

3. New Faculty. A total of ten positions (junior plus senior) to be filled over a period of ~12 years, in coordination with existing Departments, in a "tri-modal" temporal program.

There is an immediate need for 2-3 new faculty whose interests match the goals of the daVinci Center. This initial burst of hiring will serve four purposes. First, it will energize and improve the existing community of the daVinci Group. Nearly all current faculty work primarily on either the life sciences or physical sciences side of the interface and the community; we need new faculty who are closer to being truly interdisciplinary. This will essentially jump-start the initiative by adding interesting new faculty in, or closer to, the new area of interest. Second, it will help meet a crucial need for teaching at the life sciences/physical sciences interface at both the graduate (above) and undergraduate (below) levels. Third, it will announce to the world that Harvard University is a major player in this area, with a resulting increase in our ability to attract the very best scientists at both the faculty and student levels.

Once this critical nucleation step occurs, new faculty should be added very gradually, perhaps at the rate of one per year, for the next several years. In the latter several years, the rate of hiring should increase, perhaps to two per year. The

reason for this approach is that physical biology is a just-emerging field. As a result, the number of highly qualified young scientists is very small at present but will increase progressively with time. We need to be positioned to capture the rare special scientist at any time and to capture the emerging generation of scientists in this area a few years hence.

In accord with the emerging nature of the field of Physical Biology, strong emphasis will be placed on hiring of junior faculty and relatively young senior faculty. We currently envision that the ten FTEs will be "new positions", i.e. that they will not come out of the allocations of existing Departments or the DEAS but will be "in addition" to current allocations.

4. Laboratory Support Facilities. The daVinci Center will require a communal infrastructure facility to further the research efforts of daVinci Center faculty and also to facilitate "crossover research" by faculty wishing to explore new disciplines.

Infrastructure required to further ongoing research is, to some extent, unknown; specific needs will evolve as the field progresses. However, a central overall theme of the daVinci Center will be the development of new ways to measure physical and mechanical forces in living cells (and in biologically-related materials outside of cells) and infrastructure needs will reflect this goal. As but one possible example, a major challenge for the field is merging of force-imposition devices (e.g. magnets) with detection devices (e.g. high resolution fluorescence microscopes). The former have been optimized for physical studies while the latter have been optimized for biological studies. What is needed is a way to integrate the two technologies. Additionally, the daVinci Center facility should provide community access to already-developed approaches, particularly those in which daVinci faculty offer special expertise, e.g. for single molecule analysis (Prentiss, Zhuang), laser surgery (Mazur), soft lithography and micro- and nanofabrication (Whitesides), rheology and light scattering (Weitz) and physical biochemical studies of macromolecules (Guidotti, Kleckner, Berg). In both of these aspects, infrastructure development will depend heavily on the daVinci group's talented theorists (Stone, Nelson, Brenner, Hutchinson, Mahadevan and Suo). The daVinci facility should also include items which permit scientists in the physical sciences to carry out biological studies (e.g. growth chambers for bacteria, yeast, mammalian cells and basic equipment needed for molecular methodologies).

A communal facility of the envisioned type would benefit the entire Harvard scientific community, particularly in Cambridge, but also elsewhere in the University. It would also function synergistically with the EPB laboratory course and with any undergraduate courses that might develop in the future. The daVinci Center infrastructure facility would coordinate its efforts with, and be complementary to, other related facilities in Cambridge (e.g. CNS, MRSEC, the Rowland Institute and the MCB and CBS imaging centers).

5. Initiatives for undergraduates and non-daVinci graduate students and faculty. Important options for education at the undergraduate level can piggy-back on EPB/daVinci efforts at early stages in several ways including (a) a "Special Concentrations" in Engineering and Physical Biology and (b) inclusion of a limited number of qualified undergraduates in EPB graduate courses. Additionally, the daVinci Center will directly promote undergraduate research in Physical Biology by providing ~10 summer fellowships for Harvard undergraduates for research in this area. These fellowships will have flexible terms that can include funds for travel abroad and academic year earnings supplements as appropriate to the particular student. In the longer term, as additional faculty become available to assume teaching responsibilities, more significant undergraduate components will be added. In this regard it is important to note that several current daVinci Group faculty are also reknowned teachers of undergraduates (e.g. Stone in DEAS, Prentiss and Mazur in Physics, Whitesides in Chemistry, and Berg and Guidotti in MCB.)

The main thrust of the daVinci Center with respect to graduate education will be the EPB Program (above). Additionally, however, daVinci Center would also offer ~5 two-month summer fellowships for Harvard PhD students who are not already engaged in cross-disciplinary studies but wish to venture into the "other" world. PhD students in physics/engineering could experience biological research while PhD students in biology could experience life in the world of physics and engineering. Such experiences should facilitate integratation of more young people into the area of physical biology at the post-doctoral and eventual faculty stages.

A small number of summer stipends and/or research support would also be available for faculty, from Harvard and elsewhere, to permit investgation across the life sciences/physical sciences interface (e.g. for physical scientists who recognize the biological imperative and wish to explore in this area, either via biology research or, for theorists, by working in laboratories where they can apply familiar paradigms to biological problems).

All of these approaches represent relatively inexpensive ways of expanding and energizing the Physical Biology community while at the same time providing valuable experiences for the individuals involved.

6. Interaction Elements. Critical scientific advances can emerge both from specifically programmed events and from casual conversations and unscripted interactions. Specific features of the daVinci Center will foster both types of contacts. (A) On an ongoing basis, the daVinci Center requires a common social interaction facility. This facility must include (a) a suitable social interaction space with suitable furnishings; (b) food; (c) a computer for immediate on-line access of scientific literature; and (d) a medium-size seminar room (capacity 50 people). More formal seminar space, i.e. a ~125 person lecture hall, should be available elsewhere in the involved Departments as needed. (B) Programmed events to be supported by the daVinci Center include (i) Friday afternoon pizza and beer; (ii) daVinci Group monthly lunch; (iii) the EPB annual symposium, described above.

II. INITIATIVE ORGANIZATION AND TIMING

Organizational Structure. The daVinci Center will function via three levels of organization.

Co-Organizers. Primary organizational responsibility will be taken by Professor Mara Prentiss (Physics) and Professor Nancy Kleckner (MCB) who will serve as Co-Organizers of The daVinci Center. Professor Kleckner, along with Professor John Hutchinson (DEAS), also co-directs the track for PhD training in Engineering and Physical Biology, thus permitting easy coordination and integration of EPB with other daVinci Center activities.

Advisory Board. The Co-Organizers will be assisted by a small advisory board comprising senior faculty member(s) from all component Departments plus selected extra-University scientists. External scientists will be named later.

The daVinci Group. To the extent possible, daVinci Center decisions will be taken collectively by daVinci Group faculty, acting as a committee of the whole. This consensus approach has functioned very successfully thus far, leading to two daVinci Group retreats, initiation of the EPB Program and planning for regular daVinci Group activities (e.g. monthly lunch) in the 2005-2006 academic year. The collaborative spirit of this Group, along with its intellectual resources (above), are the fundamental features which ensure the long-term success of the daVinci Center effort.

Administrative Aspects. Administration of daVinci Center activities will likely require three full time administrative staff. These staff will be in charge of the EPB graduate program, the International Scholar Center, faculty search and recruitment efforts, Center activities such as seminars, etc. Funds will also be required for daVinci Center recruitment and "advertising" activities.

Staging: The daVinci Center should be in full bloom by the end of ~7 years. We envision the following progression:

The first five years. During the first five years, the Harvard University daVinci Center will create a "buzz" that will attract world-wide attention and interest in Harvard as an exciting place to be. This effect will be achieved by progress in each of the proposed areas of effort.

- The EPB PhD traack is already underway, but with a great deal of work ahead. Assuming that necessary funding can be obtained, the Program should be stable by the end of its third year.

- The first two major new priorities will be (a) identification and recruitment of new faculty and (b) establishment of the International Scholar Center. These efforts will begin as soon as necessary funds are available. The first set of faculty appointments should be decided within three years of that point. The International Scholar Center should be up and running within the first year or so.

- Initiatives for undergraduates can be put in place once EPB is well underway, probably in the 2007-2008 or 2008-2009 academic year.

- Allowing for some temporal "slippage", all of these elements should be stably established in a functional form within the first five years.

Within this time frame, success will be measured by (i) ability of EPB to attract outstanding graduate students; (ii) ability of the daVinci Center to recruit exciting new faculty; (iii) emerging popularity and prominence of the International Scholar Center; and (iv) coalescence of new and existing faculty around program interaction elements into a stable, interactive community.

The second five years. By the end of ten years, the daVinci Center should be a stable, established entity with a world wide reputation. Phase 2 (years 6-10) will draw on the foundation laid in the first five years to strengthen and expand each of the starting elements. The EPB track for PhD training may (or may not) be expanded. The International Scholar Center should continue to fluorish and might add new elements such as an annual meeting. Faculty hiring will continue, initially

at a slow pace and then at an increased pace towards the end of this period. Undergraduate program elements can be expanded to include more formal efforts as warrented and as faculty teaching responsibilities permit.

III. RATIONALE

Physical Biology is a "hot" emerging area in which Harvard is not currently represented. Emergence of the discipline of Physical Biology is widely recognized as a trend throughout the world. It is often asssumed that investment of basic science in this area will eventually produce the next big wave at the life sciences/physical sciences interface. The intellectual mission of daVinci Center is to invest the power of basic science in creating something that will come to fruition 25 years from now. At this stage, the basic science of physics and engineering are being brought to bear on the life sciences in entirely new ways. It is not clear exactly what will emerge, but it will almost inevitably be something radically new. An apt analogy is provided by events of the past 50 years. Concomitant with, and immediately following, the elucidation of the structure of DNA in 1953, collaborations between basic scientists in the physics and biology communities as well as "conversions" of physicists into biologists, led to the molecular biology revolution.

Evidence for emergence of Physical Biology is present at every level of scientific endeavor. Some of the most important efforts are taking place abroad. The Institute Curie is one prominent center of activity, led by physicist Jacques Prost. Another emerging center is the Max Planck Institute in Dresden, led by Jonathan Howard. In this country, major new efforts in this area have recently come to fruition at a number of first rate institutions including Princeton (as one aspect of the Lewis-Sigler Institute for Integrative Genomics, led by David Botstein); Stanford University (within BioX and the James A Clark Center; e.g. Steve Block and Steve Quake); the University of California at Berkeley (Carlos Bustamante and Nicholas Cozzarelli), the Lawrence Berkeley National Laboratory (led by Steve Chu); Caltech (as part of the Annenberg Center for Information Sciences and Technology); and Rockefeller University (e.g. Marcelo Magnasco and Albert Liebchaber). Discussions about such programs are actively underway in many other US institutions, including MIT. Other indications of the emergence of Physical Biology include the recent initiation of a journal of this name, diverse efforts to develop novel curricula in this area in many institutions (e.g. by Philip Nelson, U. of Pennsylvania) and a recent

HHMI/NIBIB initiative to foster PhD programs in this, as well as other, aspects of the life sciences/physical sciences interface.

Bad News and Good News. It is clear that Harvard University (a) is currently not significantly represented in this important emerging area and (b) is seriously "underachieving" in this area as compared to its most important "competitor" institutions. This is the bad news. The good news is that the daVinci Center, if properly constituted and funded, has the intellectual underpinnings, the faculty "capital" and "star power", and the organizational structure required to catapult the University into a prominent role as a world-wide leader in this area.

Keys to Success: Intellectual Imperative, Faculty, Vision and Resource Utilization. The daVinci Center will be successful for the following reasons:

Intellectual Imperative. The current state of the Physical Biology community is similar to that of a super-saturated salt solution in a glass beaker, which only awaits a small local scratch in the glass to precipitate into a crystalline assembly. There is tremendous interest in Physical Biology, at the undergraduate and graduate levels as well as at the level of establish scientists, throughout the FAS community and throughout the world. Interest among younger scientists is particularly significant because it is an accurate predictor of future scientific directions. (For example, Harvard University had an Special Concentrations in neurosciences, followed by the Mind, Brain, Behavior initiative, long before it had a significant presence in this area at the faculty level). At Harvard, interest at the faculty level is apparent from the success of the daVinci Group and its activities (above) and from the fact that three different Departments, representing both the Life Sciences (MCB) and the Physical Sciences (Physics and DEAS) expressed enthusiasm for participation in the new track for PhD training (EPB). Interest among younger scientists is apparent to all involved from teaching and research contacts with faculty. All of this potential only awaits a nucleating event to coalesce into a dynamic new community. Establishment of the daVinci Center will be that, catalyzing the assembly and integrating this potential into an exciting new gem in the Harvard crown.

Faculty. The basic science faculty of FAS, as collected at the daVinci Group, are a very distinguished group of scientists whose combination of interests and expertise are unique in the world. This group has the potential to define the

intellectual scope of the field of Physical Biology and to attract the best and brightest younger scientists and students to this vision. One of the most exciting aspects of the proposed daVinci Center is that intermingling among this unique constellation of scientists, along with their ability to attract other top scientists from around the world, is going to produce something fabulous and uniquely "Harvard" in its deep reliance on basic science and its special combination of imaginative thinking with high technology. Clearly, daVinci Group faculty can have dramatically greater impact, for science and for the University in the context of the daVinci Center than as a simple collection of individuals. All of this underutilized potential is currently poised, waiting for support of an appropriate intellectual and organizational framework within which it can express itself. The daVinci Center initiative will provide that framework.

Vision. The daVinci Center is organized around an intellectual vision which is unique as compared to emerging life sciences/physical sciences initiatives at other institutions. Only at Harvard will there be such a strong emphasis on the basic "laws of nature", under the guardianship of our Department of Physics. Only at Harvard will a premier Engineering school be integrated so completely with the life sciences to address fundamental problems. And only at Harvard, which was a world pioneer in development of biochemistry and molecular biology as they emerged from chemistry and physics ~25-50 years ago, will those same traditions be reborn in a new form to provide analogous contributions 25-50 years from now.

The daVinci Center is also organized around a unique vision of how best to nucleate especially creative approaches to this area, with its focus on creating a new type of scientist and new experimental tools. Most importantly, the goal is to create a new generation of scientists who can function simultaneously in both biology/life sciences and physical sciences/engineering and to emphasize imagination, creativity and collaboration in every aspect and at every level. Each key element of the daVinci Center initiative is specifically designed to further these goals, in such a way that every important component of the emerging University community, from undergraduates through senior scholars, is recruited into the effort. Moreover, these approaches are taken in an international context, with the long term view that Harvard University should be the world leader in this area.

Resource Utilization. The daVinci Center approach is a very effective use of University resources: existing areas of strength will coalesce around an exciting new interdisciplinary area. Critical mass in a new area will be achieved by leveraging

existing resources, thus nucleating a very special new entity for Harvard's future, without the necessity of hiring a huge number of additional faculty. Put another way: Harvard University can have a high impact, via a new, important and challenging problem, by a vehicle that optimizes the utilization of existing resources.

The daVinci Center for Physical Biology will complete Harvard's approaches to the Life Sciences/Physical Sciences Interface. Development of scientific endeavors at the Life Sciences/Physical Sciences Interface is an important priority at the University. Thus far, two areas have emerged as intellectually and sociologically coherent entities: Bioengineering and Systems Biology. The daVinci Center initiative unites essentially all of the remaining elements in the University into the distinct and highly complementary third entity of Physical Biology. Taken together, these three areas provide Harvard with a diverse, and distinctive, face to the world.

Bioengineering is centered in the DEAS, which has a long and illustrious tradition in this area. In this area, scientists with an engineering background focus on biological problems that are of specific medical interest, e.g. tissue engineering, bone development and functioning of the vascular/circulartory system. This is a paradigmatic, and well-established, approach in which Harvard is already a world leader.

Systems Biology is the newest mature wave at the life sciences/physical sciences interface. It has recently been added to the Harvard portfolio via components at both the Medical School and Cambridge. The primary focus of this area, as described by its leader Marc Kirschner, is to "explain how higher level properties of complex systems materialize from the interactions among their parts" (http://www.gsas.harvard.edu/programs/degree/sysbio.html). Kirschner further notes that this field is built on molecular biology, that it comprises "the study of the behavior of complex biological organization and processes in terms of the molecular constituents and, importantly, that " it is not a branch of physics" (M.W.K. 2005, *Cell*121: 503-504). Science in this area revels in the overwhelming abundance of molecular information and details, seeking on the one hand to develop various data sets and, on the other hand, to distill this data into orderly patterns and networks, with the assumption that the whole will be greater than the sum of its parts. At Harvard, the heart of this community are cell biologists, biochemists and computational scientists.

Physical Biology, as manifested by daVinci Center activities, has an entirely different intellectual focus from either Bioengineering or Systems Biology. The goal here is nothing less than developing an entirely new conceptual approach to living systems in which life processes at the cellular and molecular levels are understood as manifestations of the basic principles of physics and engineering. Put another way, physical biology seeks to use the principles of physics and engineering to understand how living systems work. For example: it is a fundamental physical fact that small objects such as cells or molecules, in aquaeous solutions and at physiological temperatures, exist in a chaotic environment characterized by high thermal energy noise and low Reynolds number. A key question for physical biology is how biological processes overcome these intrinsic challenges (H.C. Berg, Professor of Molecular and Cellular Biology and Professor of Physics, *Random Walks in Biology*, Princeton University Press, 1993.) This approach is essentially orthogonal to the Systems Biology approach. Moreover, the intellectual core of Physical Biology lies in the "physical" while that of Systems Biology lies in the "biology". In essence, Physical Biology and Systems Biology look at the complexities of biological processes through different lenses.

Physical Biology is also at a much different stagefrom either Bioengineering or Systems Biology. These latter two disciplines are reaping the benefits of nucleating science that took place at Harvard and elsewhere 25-50 years ago. In sharp contrast, Physical Biology as a general discipline and, even more particularly the daVinci Center formulation of that discipline, are just at the stage of conception.

Correspondingly, Physical Biology involves an almost entirely different set of faculty from either of the other two areas. In accord with its focus on "laws of nature", the daVinci Center initiative involves the coalescence of the basic science faculty of FAS: the 24 daVinci Center faculty, senior and junior, represent Physics, DEAS, MCB and OEB. Among these 24, none is also participating in Bioengineering and only three are associated with either the Department of Systems Biology and/or its PhD program.

Finally, and most importantly, via the daVinci Center initiative, the University can re-invest and re-energize its commitment to promoting basic science. Our expectation is that this commitment will make Harvard University the place that generates the next new wave at the life sciences/physical sciences interface as seen some 25 years hence.

In addition to the three major interface areas discussed above, several smaller strands of activity complete the University's connections at the life sciences/physical sciences interface. (i) Biomechanics, currently represented by an NSF IGERT grant to fund PhD students, operates out of FAS/OEB and addresses mechanical aspects of biology at the larger scales of whole organisms (e.g. how humans and horses run). (ii) Biophysics is a PhD program funded by an NIH Training Grant. This program is run out of the Harvard Medical School and operates with the goal of taking talented undergraduates with a physical background and turning them into biologists. This program draws relatively little on FAS physics and engineering faculty; rather, its primary areas of strength are in structural biology and genomics. (iii) Important links between physicists and neuroscientists are developing through the Center for Brain Science.

Risk Factors. There are essentially no risk factors in the daVinci Center endeavor. The real risk is that Harvard will <u>not</u> pursue move as aggressively as it can in supporting Physical Biology and the daVinci Center. We are currently in a "double or nothing" situation. If Harvard does engage in this effort, it can become a world leader in an entirely new area of science, Physical Biology. If Harvard does not engage in this effort, it will be wasting the intellectual capital of its faculty in this area; it will miss a golden opportunity to be a world leader in an exciting new area; and it will fall (even farther) behind other institutions who are making strides in this area. In fact, we have already paid the price for having failed to act earlier in this direction. In at least four cases, efforts by individual groups of faculty to recruit dynamic young faculty whose research would match the mission of the daVinci Center have failed due to the combination of (a) lack of a coordinated effort of individuals in different Departments and (b) lack of an intellectually-coherent entity to which these individuals, if they came, could feel connected. Worse still, we are at risk of losing existing faculty who are committed to the area of Physical Biology but cannot function optimally in the current environment due to the lack of a coherent supporting entity.

IV. MEASURES OF SUCCESS

The real success of the daVinci Center will be measured only in the longer term, in the seminal contributions of its members and its alumni to scientific progress that we

cannot even presently imagine. Looking back at this effort 25 years from now, scientists will say that Harvard University was a place of special intellectual ferment and activity in the area of Physical Biology. In the more immediate term, we can expect the five- and ten-year progression described above.

V. INITIATIVE LEADERSHIP

The idea of this initiative has been widely discussed over the past year by the daVinci Group at its two retreats, in conversations amongst individual members and in conversations with Doug Melton, Chairman of the Life Sciences Resources Council; and Venky Narayanamurti, Dean of the Division of Engineering and Life Sciences and Dean of Physical Sciences. An important component of the initiative, a new track for PhD training in Engineering and Physical Biology, has just begun.

This white paper was prepared by the two senior faculty members of FAS who will serve as Co-Directors of the daVinci Center: Mara Prentiss (Department of Physics) and Nancy Kleckner (Department of Molecular and Cellular Biology) in consultation with John Hutchinson (DEAS, Co-Director of EPB). The final formulation of the initiative, as presented here, (will have been) endorsed by all members of the daVinci Group, Doug Melton and Dean Venky.

daVinci Center Faculty

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Nancy Kleckner Herchel Smith Professor of Molecular Biology (**MCB**)

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