EXECUTIVE SUMMARY

Technology may be the single most important driver of discovery in biomedical science. We distinguish three levels of research technology: (1) innovation, (2) development of applications (especially through collaboration), and (3) service and training. HMS has had substantial efforts at all three levels, but there has been no systematic school-wide approach to identifying and filling technology needs, and — partly as a result — we have underinvested in a number of key technology areas, especially at the level of innovation. This underinvestment has had serious and in some cases crippling effects on our ability to achieve and maintain a leadership position in specific areas of biomedical research. There are also organizational barriers that inhibit development and dissemination of cutting-edge technology: lack of information and coordination of service facilities, difficulty in sharing data sets across institutions, high costs of animal care, lack of collaboration among institutions in veterinary oversight and regulation, lack of uniform IRB procedures and standards, and a lack of attention to the career paths of technology innovators and core directors. To address these problems, we make the following recommendations.

Science. *Innovation and development:* To ensure that HMS achieve and maintain world leadership in critical areas of biomedical technology, we recommend substantial investment in therapeutics, imaging, and computational methods, with emphasis on recruiting new faculty with programs in technology innovation and development. HMS should also take full advantage of the opportunities offered by the ongoing collaborative planning effort with SEAS in bioengineering, and it should dedicate resources of its own to new programs in that area, to synergize with university-wide efforts. *Service and training:* Many of our service-oriented facilities were world-class when they were introduced but have not kept up with the times. In many cases instrumentation needs updating, and computational technology and support offerings have not increased in line with recent advances and increased demand. Immediate attention should also be given to creating a new service center aimed at supplying very high-throughput DNA sequencing, in response to the technological breakthroughs of the past year. New core services to support a range of animal experiments, especially translational studies, must also be developed.

Organization. To realize the scientific leadership goals just outlined, we recommend a new HMS-wide initiative to support the development and dissemination of novel tools and technologies, with the missions of strengthening technology recruitments across the community and of coordinating core facilities. Specifically, we recommend: (1) that the Dean convene a standing advisory group with responsibility for developing strategy in this area and set aside significant resources to support technology innovation appointments jointly with quad and hospital departments; (2) that this group, with suitable support from the Dean's office, should take on the mission of collecting and disseminating information about existing core facilities throughout the community, coordinating their activities, and supporting them in fund-raising; and (3) that a School-wide group should be convened to develop detailed proposals for new core services relevant to animal work, such as physiology laboratories and small animal imaging services, in close coordination with the related efforts in the Harvard Clinical and Translational Sciences Center (CTSC). We should also aim to create a partnership between faculty and IT professionals in the administration of research IT and better coordination between the IT infrastructure of the HMS Quad and the affiliated institutions.

Lowering barriers. The HMS community comprises a diverse set of institutions. The diversity contributes great intellectual strength but creates potentially disabling barriers. An immediate HMS-wide effort to reduce costs and barriers to technology sharing and co-development is critical. This issue is particularly evident and especially pressing in animal-based research. A plan to create uniform standards and unrestricted access to animal models, ancillary animal care services, and clinical-pathology services and to achieve uniform IRB and IUCAC approvals across institutions will be vital for the future of translational research.

Career tracks and appointments. Leadership in technology will require a focused effort to recruit and retain outstanding personnel at all levels. HMS should lead in this effort, not wait for university-wide adjustments.

The incentives for technology faculty and staff must be reconsidered from the ground up. A new career track for staff specialists is urgently required, with a status commensurate with their impact on the institution as a whole. We must ask ourselves what is necessary to recruit and retain outstanding scientists who relish the challenges of developing cutting-edge platform technology and training others to use the platform to its full effect, remembering always that such scientists are exceptionally valued and sought-after by industry. On the faculty level, the effect of the new promotion criteria on the promotion of technology innovators should be examined in detail; if necessary the criteria should be adjusted further to ensure that technology innovation is appropriately encouraged and rewarded.

I. OBJECTIVES AND CHALLENGES

The next decade is critical to the development of a cohesive community of scholars at Harvard Medical School. Our goal should be for HMS and its affiliated institutions to act as a single group of closely interacting laboratories, in which the environment is driven by the science and by the investigators who perform it. Tools, technologies and facilities are at the core of this development, and it is essential to foster activity at all three levels: (1) innovation, (2) development and collaboration, and (3) service and training. Technology innovation, and the subsequent phase of broad application by the research community, is increasingly key both to discovery science and to translation. The ability to recruit, retain, and encourage innovators in tools and technology is crucial not only for the development of new technology, but also for the outstanding service and training required to enable the broad application of technology.

We have identified major technology areas that are critical to the success of HMS as a whole and in which we believe investment to be inadequate. These are (1) therapeutic discovery, ranging from small molecules to RNAi, proteins, gene therapy and stem cells; (2) imaging, from the cellular level to the organismal level; (3) computational biology, especially for innovation in genomics, structural biology, and imaging, but also for enabling novel applications; and (4) bioengineering. Bioengineering is the subject of an ongoing planning effort that is a collaboration between HMS and SEAS, and it will not be treated in detail here. We recommend that a significant number of faculty appointments should be made in each of these areas.

We have also identified structural and cultural problems common to all areas of tools and technology. (1) There is no central mandate to collaborate in the development and application of tools and technologies, particularly across component institutions, and the current reward system even discourages both collaboration and methods development. Moreover, the frequent practice of recruiting technology innovators with the charge of establishing and overseeing a core facility creates confusion about their status and role and adds substantial distractions to their research focus. (2) Institutional support is required to make frontier technologies affordable, and support offered by a single institution is generally restricted to the members of that institution, leading to built-in restrictions that prevent sharing. (3) Regulatory barriers between components of the HMS community, the multiplicity and heterogeneity of regulatory committees, and financial barriers between institutions all discourage effective scientific interaction across an otherwise remarkable community. (4) There is no career track for those who foster, develop and design technology, or for the support staff who enable its broad application.

To meet these challenges, we believe that HMS, as the only source of common mission, must bring together the many disparate institutions to form a unified research and technology development community. The geographical dispersion of faculty and facilities, the differences in culture at each center, and the divergent history and evolution of the various institutions has created local and often isolated imperatives. Time is critical. As each of the HMS affiliates continues to address the issues of biomedical research and technology on its own, absence of central leadership will result inevitably in further particularization. This may be the last chance we have to reverse the trend toward fragmentation. The enthusiastic participation in the work of this task force has demonstrated that there is real determination, at least on the part of many investigators, to reverse this fragmenting trend and great eagerness to work together across institutions.

II. PRINCIPAL RECOMMENDATIONS

A. Make substantial new investments in technology areas essential for maintaining world leadership in biomedical research at HMS

1. Therapeutic discovery

HMS should position itself to lead in the technologies needed to discover bioactive molecules for research and potential therapy. HMS has long been a leader in enabling the earliest stage of small-molecule drug discovery, and has recently expanded existing screening facilities to enable very early phases of therapeutic RNAi discovery. Virtually no support is available for the later stages of therapeutic discovery, however, including small-molecule lead optimization (medicinal chemistry), formulation and delivery technologies, and therapeutic metabolism and safety studies. This is a major weakness that should be urgently addressed.

(a) To enable therapeutic discovery projects to be continued beyond the screening phase, we recommend that a number of faculty appointments be made in areas such as synthetic chemistry, small molecule metabolism and RNAi therapeutic technologies, distributed over several institutions. These faculty would then collaboratively oversee several new Cores for compound synthesis, analytical chemistry, and pharmacology (pharmacokinetics, etc.). An inter-institutional Center for Therapeutic Discovery is a possible structure for this effort.

(b) The existing screening and robotics Cores, ICCB-L and DSRC, should be integrated and strengthened, with increased investment in several new libraries including a comprehensive collection of known bioactive small molecules, cDNA/ORF expression libraries and possibly antibody libraries. The existing investment in ICCB-L and DSRC should be leveraged by expanding resources at HMS in the areas of microscopy and image analysis, mass spectrometry, statistical analysis of large data sets, bioinformatics and IT support.

(c) A stem-cell culture core facility should be created to provide support for basic and therapeutic studies of stem cells. Related to this, increased flow cytometry and sorting resources are needed.

(d) The existing infrastructure for high-throughput DNA sequencing should be expanded. This is rapidly becoming a critical need throughout HMS. The capacity and accessibility of these technologies at the Broad Institute will not be adequate for the coming wide demand.

(e) Other new resources that should be considered for development at HMS include those for monoclonal antibody production, and for analysis of biomolecules other than nucleic acids and proteins (e.g. metabolites, lipids, and carbohydrates).

2. Imaging, structural biology and biophysics

The committee concluded that the opportunities and potential applications of various optical imaging modalities, from advanced live-cell and tissue imaging to non-invasive methods of all kinds, as well as structural biology and single-molecule biophysics, are *so extensive and so enabling of other advances that we believe HMS must invest substantially more effort in these areas.* There are two areas in which we recommend that HMS should give especially high priority to recruitment of technology innovators:

(a) New imaging modalities in high resolution optical microscopy, including “superresolution” techniques. There are only a handful of outstanding leaders, but the group believes that HMS should recruit one of them. Collaboration with SEAS on such a recruitment might be appropriate.

(b) Development of imaging probes, including both genetically encoded fluorophores and MRI chemistry.

In addition, there are many possible improvements at the levels of development/dissemination and service/training, detailed below.

3. Computational biology

The committee recognized a number of areas, ranging from image analysis to metabolomics, in which computational research and computational technology development (hardware and software) should be strengthened. Computational biology is not a "one size fits all" territory. Specific fields in which computational approaches will have a critical role include: genomics, proteomics and metabolomics; imaging; systems biology and modeling; computational chemistry; and macromolecular modeling. We recommend that the new Standing Committee review these areas through a small subcommittee, preferably involving outside advisors. Computational methods are among the fastest-moving areas of scientific innovation and discovery today, and this is a particularly striking example of an area in which Harvard as a whole has under-invested. Some of the needs in this area should also be considered in collaboration with the ongoing effort in planning for bioengineering.

4. Bioengineering.

We endorse the effort to plan an expansive new vision in bioengineering, in collaboration with SEAS. It must be understood that such effort should have direct contact and broad-based interactions with HMS and its affiliated institutions. It will not be in the medical school's best interest for such an effort to be located solely in Allston or Cambridge without bidirectional dialogue and contributions that include HMS and its affiliates. It is further important to integrate discussions surrounding Bioengineering within the HMS Strategic Plan irrespective of more global interactions. Discussions supplementary to the ongoing Harvard University committee work should begin, to determine how medical school-based initiatives can fill immediate HMS and affiliate needs and take best advantage of emerging opportunities. We suggest a series of RFAs for seed grants to produce ideas and programs in this arena. These efforts could be coordinated through an Office for Tools, Technologies, and Facilities, as described in the next section.

B. Strengthen technology recruitments across the community and coordinate and enhance core facilities through a school-wide initiative in tools and technologies.

1. Establish a Standing HMS Committee on Technology Innovation.

The role of this committee would be to make HMS a major locus of technology innovation. We propose that the committee have the mandate and resources to support appointments, in collaboration with an appropriate department, either in the quad or in one of the affiliated institutions. The appropriate departmental partner will not always be obvious in advance, since exceptional technology candidates might not have made a commitment to working in a particular biological area, and working with one department at the beginning of a search might reduce our ability to recruit the best person. We therefore suggest that the Committee be able to propose to the Dean that a search be initiated in a specific area that has been identified as having high priority, with space and startup guaranteed by Dean's funds, leaving the partner department to be determined as the search proceeds. The Committee should also be able to work closely with any department (pre-clinical or clinical, quad or hospital based) that wished to initiate such a search using one of its regular slots.

We propose that committee membership should include a representative from each major affiliate and should include heads of technology centers as well as senior and junior faculty. The committee should also provide oversight for the coordination of technology platforms and core facilities.

2. Establish an Office of Tools, Technologies, and Facilities (OTTF).

The role of this office will be to collect and provide information about technology platforms and core facilities across the entire HMS community and to provide a mechanism for sharing across these facilities (for example, sharing of protocols, coordination of maintenance and technical support, exchange of time on specialized instruments, coordination of training efforts, etc.). The Office will also provide a mechanism for an HMS-wide

discussion of what new facilities are needed and will bring together faculty across many institutions to write equipment grants, coordinate Letters of Support, etc.

C. Reduce animal costs and lower barriers to animal transfer across institutions

1. Reduce animal costs.
Major areas of research are inhibited by the high cost of animal care at HMS. For example HMS mice (according to a 2005 survey) are among the most expensive in the country: mouse costs are in the top 5% nationwide. This situation hinders recruitment and makes retention of faculty with relevant interests far more difficult. Cost precludes large scale mouse genetics and mutagenesis programs. HMS must analyze the cost structure and work to reduce per diem charges. It is possible that wasteful duplication of oversight mechanisms is part of the problem.

2. Address regulatory barriers, in collaboration with the CTSC.
Collaboration on animal or human studies across institutions is enormously inhibited by regulatory structures. The need to re-derive mouse strains in order to transfer mice from one facility to the next, and the need to make several different applications for IRB approval to collaborate on a clinical study are two of the most egregious examples. We urge that the Dean work actively with relevant hospital authorities, to mandate resolving the various problems of barriers to collaboration. We recognize that these are not simple problems, but they are sufficiently important to justify major effort.

D. Create career tracks for technology specialists, both at the faculty level and at the staff level.

1. Urgent reconsideration of the career structure for staff technology specialists.
Staff specialists are treated as dispensable by our system, despite the fact that their impact on our research community is enormous. For example, they are currently not offered Harvard support to obtain visas or green cards. Industry offers far more in the areas of compensation, respect and security than does academia. These issues put Harvard at a grave disadvantage in recruiting and retaining personnel who would offer superior support and training.

Creating and maintaining cutting-edge platform technologies is an extremely complex task, requiring a level of scientific ability and commitment equivalent to that required of tenure-track faculty and an often very rare set of specific skills. In industry, and now at the Broad Institute, platform scientists have career tracks that are functionally equivalent to discovery scientists. Our structures for recruiting, supporting and rewarding platform scientists, programmers and other technology specialists fail to recognize the recent profound changes in the needs of biomedical research, which now depends so crucially on access to key technologies. We recommend an urgent and extensive search for solutions in this area.

2. Consideration of promotion criteria to encourage and reward technology innovation.
The new promotion criteria have gone some way towards offering increased flexibility to allow the promotion of faculty whose main interests are in technology. We believe additional effort will be necessary to ensure that technology contributions of all kinds are recognized appropriately, and we propose that a dedicated group should analyze this issue in detail. By creating recognized career tracks for platform scientists, as described in the previous paragraph, we can also dissociate management of facilities from faculty research, thereby strengthening our capacity to recruit and reward innovators.

III. SUBGROUP REPORTS

A. Process

The Tools and Technology Task Force (for membership, see Appendix), representing a broad range of technology expertise and the entire spectrum of HMS affiliated institutions, met for initial plenary discussion that acknowledged a set of major challenges. We then agreed to divide into five subgroups, to consider the directions and requirements of specific scientific areas, over the next 10-15 years. The five areas represented were:

1. Small molecules and therapeutics;
2. Genomics and proteomics;
3. Imaging at all levels (molecules to organisms);
4. Animal and human studies; and
5. Data management and analytics.

Two large areas missing from this list are Stem Cell Biology and Bioengineering. The former is briefly considered in section A (therapeutics) and is the focus of a new University-wide Department of Stem Cells and Regenerative Biology (SCRB). While the latter is also being considered at the university level, it is essential to involve Bioengineering within the HMS Strategic plan. Resource issues such as the sharing of tissue and cell technology and of nanotechnology and microfabrication will need to be incorporated into any effort that considers tools and technologies and are included in the discussion below. At the same time many of the global issues related to innovation, development of applications, service and training, and career development have aspects unique to HMS and its affiliates that must be addressed locally.

Each of the five subgroups generated its own report, included in summary form here and in complete form as Appendices. Many of the issues raised by these groups cut across fields and institutions. In discussions that followed completion of the subgroup reports, we considered how to organize addressing the various challenges. We concluded with the recommendations that HMS should make several key faculty recruitments in technology areas; that a Standing Committee on Technology Innovation should be created to support HMS in identifying important technology directions and relevant faculty; and an Office of Tools, Technology, and Facilities to help organize core facilities and reduce barriers to sharing. Summaries of the individual subteam reports follow.

B. Research and technology areas

1. Small molecules and therapeutics

a. Overview.

For most of the past half-century, therapy-directed research has been seen as external to the mission of academic institutions. As technology becomes more accessible and dispersed and as the understanding of biological systems becomes increasingly important for drug discovery, academic research can have substantial impact on the design of next-generation therapies. *HMS should position itself to lead in the technologies needed to discover bioactive molecules for research and potential therapy*.

We considered resources that would be needed at HMS to enable the discovery and development of bioactive small molecules, biologics (e.g., peptides, proteins, siRNA, recombinant antibodies, gene therapy methods, etc.), and specialized cell lines (or purified primary and stem cells). The earliest stage of small-molecule drug discovery is supported at HMS through several high-throughput screening centers. HMS is currently an academic leader in this area, and that leadership should continue and be reinforced. Support for discovery of biological therapeutics at HMS is weaker and should be strengthened. Virtually no support is available for the later stages of the drug discovery process, including small-molecule lead optimization (medicinal chemistry), drug formulation, and drug metabolism and safety studies.

For the most part the focus of HMS labs will be on using bioactive molecules as research tools and taking the first steps to evaluate their potential as therapeutics, rather than on drug development *per se*. Thus, we propose that the most broadly useful support services should be developed on campus (e.g., an analytical chemistry core), while other services should be accessed through outsourcing. In some cases, it might be beneficial to develop some resources on campus while also providing logistical support for those who prefer to outsource.

b. Improving existing HMS resources
There are a number of successful resources in this area that are in high demand and for which concentrated support could produce significant and immediate benefit. The ICCB-Longwood Screening Facility (ICCB-L) and the Drosophila RNAi Screening Center (DRSC) and resources dedicated to flow cytometry and cell sorting fall into this category.

(i) ICCB-L and DRSC. HMS took an early position at the leading edge of high throughput screening (HTS) technologies, but our leadership has eroded in recent years. This erosion should be reversed by continuing and expanding school and departmental support for ICCB-L and DRSC. First-rate facilities such as these cannot be supported on federal grants alone even if supplemented by affordable user fees.

Recommended improvements include:

(a') Physical integration of ICCB-L and DRSC, retaining the existing programmatic distinction.

(b') Expansion of ICCB-L to allow screening of full-length, sequence-verified cDNA/ORF expression libraries and possibly of antibody libraries; initiation of a collaborative effort with other screening facilities (e.g. the Broad) to collect a library as many as possible existing small molecules for which some pharmacological information is available, and make it broadly available to HMS faculty.

(c') Access to resources for medicinal chemistry, including an analytical chemistry core (see below and Appendix C of the subgroup report).

(d') Access to significant additional resources in the areas of microscopy and image analysis, mass spectrometry, statistical analysis of large data sets, bioinformatics and IT, to enable the screening centers to be used to full advantage.

(ii) Flow cytometry and cell sorting. Increased capacity for these methods is needed and should be provided at reasonable cost. FACS facilities should be distributed among departments and institutions to ensure easy access for multiple investigators, but there should some mechanism for coordination among facilities, for exchange of protocols, overflow usage, etc.

c. Developing new programs and resources
We have identified three areas in which new cores or centers are needed.

(i) We propose an inter-institutional Center for Therapeutic Discovery that would include a number of faculty appointments (distributed across several institutions) in areas such as synthetic chemistry, therapeutic RNAi technology, etc. The faculty recruited would then jointly oversee cores for compound synthesis, analytical chemistry, and pharmacology (pharmacokinetics, etc.). This will allow therapeutic discovery projects to be taken forward several more steps than is currently practical.

(ii) We propose a Stem-cell Culture Core Facility, to provide support for basic and therapeutic studies of stem cells. Current capacity in the laboratories of Doug Melton (FAS) and George Daley (TCH) will not be adequate

for the growing interest we anticipate. One centralized facility, with partial support from user fees and located at LMA or in Allston, can probably serve the needs of the entire community.

(iii) An Animal Specimen Core should be created, which would include the following functions, currently lacking at HMS: (a') CBC, plasma, serum, and urine measurements on all animals used at HMS (mouse, rat, frog, dog, pig, sheep, etc.); (b') mouse, rat, and beagle-dog toxicology studies

d. Lowering barriers:

Standard MTA documents have been developed to enable rapid and straightforward transfer of reagents between HMS institutions. Their use should be instituted immediately. We further suggest that the Harvard Office of Technology Development should provide expanded advice and assistance to investigators in outsourcing aspects of therapeutic development.

2. Genomics and proteomics

a. Overview

There was a wide range of opinion within this subgroup regarding the current state of genomics and proteomics research at HMS, and especially on how the development of HMS resources should be affected by the resources available at the Broad Institute. While the Broad is generally viewed as an effective organization at the cutting edge of genomics research, some felt that its resources were not sufficiently widely available, either for reasons of lack of transparency or lack of capacity. This view complicated the discussion of whether new resources were needed in several areas. In this area generally, transparency (of costs, project management, prioritization, etc) is essential. It may also be necessary to increase the "genomic literacy" of the HMS community in order to make substantial improvements in the usefulness of existing cores. The key to progress in this area was felt to be *a change in attitude towards technology-focused faculty, and towards expert staff who manage technology platforms.*

b. Improving existing HMS resources

Genomics and proteomics are areas in which innovation, at HMS or elsewhere, creates wide and very rapid demand for core facilities. Existing resources provide value, but demand exceeds infrastructure and capacity. The HMS biopolymers core facility, housed in the Department of Genetics, would be one natural home for new genomic technologies that have reached the "service" stage. Historically this facility has been very slow to implement new technologies, however, because it is required to be financially self-sustaining. Thus, new technologies cannot be implemented until there is clear demand. The same restriction impedes updating of the various mass spectrometry facilities. A new financial model for many of these facilities, including subsidies, would increase the rate at which new technologies could be implemented.

c. Developing new programs and resources

(i) There has been an explosion, during the past 6-12 months, in the next generation of DNA sequencing technologies. These advances have the potential to transform many areas of biological research. Demand in the HMS community is already beyond capacity. We therefore recommend immediate investment in infrastructure for high-throughput DNA sequencing. One model for "service" to the HMS community would be to expand sequencing capacity at the Broad Institute, which is a scaleable operation. What is not scaleable, however, is expert consulting in study design, interpretation, and computational data analysis. For this model to succeed one would therefore require investment in sequencing instrumentation and personnel at the Broad and separate investment in experts and interface personnel at HMS (including the hospitals). A second model would be to build a complete, Broad-run outpost in the Longwood area, although the benefits of such a model (for the production sequencing component) are not obvious. A third model would be to create a fully independent HMS facility, with extensive consultation from the Broad. Each of these models would require, before implementation, deep consideration of their impact on both Broad and HMS organization.

(ii) The subgroup believes that a large factor in the poor record of technology innovation at HMS is the difficulty of achieving tenure on the basis of primarily technological contributions. It recommended that immediate steps be taken to recruit and retain young technology innovators in genomics and proteomics. Success would open up the possibility of developing new service cores overseen by the technology innovators, provided that we also improve the career tracks for staff scientists. The HMS culture must adapt to the idea of having non-tenured colleagues who are nonetheless crucial and respected members of the community. These issues are not specific to genomics, but they have been made particularly evident by the success of the Broad Institute in using staff scientists to drive the development of cutting-edge technology platforms.

3. Imaging

a. Overview

The technologies covered by this group included structural biology, light microscopy, non-invasive imaging of organs and organisms, and probe design. In structural biology, HMS has world leaders in x-ray crystallography, nuclear magnetic resonance spectroscopy, and molecular electron microscopy, and it is beginning to build strength in single-molecule biophysics. A number of groups have been active in developing innovative technology. In optical microscopy, there is less cutting-edge development of instrumentation or software at HMS, although the community includes a number of laboratories that lead the way in application of new technologies to cell biological and neurobiological problems. There is a leading group in optical coherence tomography at MGH, and there are several laboratories designing novel, non-linear microscopes with special capabilities. The functional MRI group at MGH is a world leader in that field, including pioneering work in probe design; intravital microscopy techniques pioneered at CBRI/IDI and on the quad are similarly innovative. The opportunities and potential applications of various optical imaging modalities, from advanced live-cell and tissue imaging to non-invasive methods of all kinds, are so extensive and so enabling of other advances that *we believe HMS must invest substantially more effort in these areas, as well as in structural biology and single-molecule biophysics*.

The subgroup considered the Center for Photomedicine at MGH and the HMS Center for Molecular and Cellular Dynamics (CMCD) as case examples of success in combining technological innovation with development and dissemination. The structural biology community has assembled around common activities and infrastructure, such as the SBGrid software repository and use of the Northeast Collaborative Access Team synchrotron radiation beamlines at Argonne. The light microscopy community has lacked comparable coherence. Cross-Department cooperation has been largely limited to two service and training facilities (the Nikon Imaging Center, and the imaging facility in the NeuroDiscovery Center), both of which are extremely successful but which focus on maintaining essentially turnkey instrumentation rather than working at the rapidly advancing cutting edge. Similarly, the various outstanding imaging Centers at MGH and BIDMC appear not yet to have found ways to build a community and to make the whole greater than the sum of its parts.

b. Improving existing HMS resources:

(i) We should coordinate and reinforce expertise in implementation or development of novel hardware and software in high-resolution light microscopy. A number of leading groups have acquired or built advanced instrumentation and devised new applications. It was in the original plan for the CMCD that live-cell imaging and innovative optical microscopy would be part of its mission. Limited resources have not yet allowed full extension of its activities in these areas, but some steps have already been taken. We recommend expansion of CMCD activities to cover this scientific territory or creation of a related entity to do so in close coordination with CMCD.

(ii) We should similarly coordinate and reinforce expertise in development of methods for imaging of tissues and organisms. In this case the optimal model for coordination is not obvious and requires more discussion.

(iii) We should support and expand, as needed, the HMS quadrangle EM facility, the Nikon Imaging Center, and the Imaging Facility of the NeuroDiscovery Center. These core facilities serve critical needs, both for research and for training. The proposed OTTF should have the responsibility to ensure that these cores, and others like them in the affiliated institutions, continue to thrive. Both the NIC and the NeuroDiscovery Imaging Center have the potential to catalyze co-development projects with companies, if appropriately supported. Expansion of one or both of these facilities to better serve the needs of the Hospitals should be considered.

(iv) Nanofabrication will be of increasing importance for application of new imaging methods, especially in medium- to high-throughput assays. Systems Biology has recently begun to set up a microfabrication facility, partly supported by the Taplin Foundation, that is intended to serve the Quad. The OTTF should ensure that this core is funded and supported appropriately, and expanded (or supplemented by additional facilities) as the need increases.

c. Developing new programs and resources
There are two areas in which the subgroup believes that HMS should make major commitments to recruitment of technology innovators.

(i) New imaging modalities in high resolution optical microscopy, including "superresolution" techniques. There are only a handful of outstanding leaders, but the group believes that HMS should recruit one of them. This appointment would be most appropriately made on the Quad. Collaboration with SEAS on such a recruitment might also be appropriate.

(ii) Development of imaging probes. Many recent advances in imaging actually reflect advances in chemistry, relying either on biochemical insight (genetically encoded fluorophores or reporters of biochemical signaling) or on synthetic chemistry (synthetic fluorophores, PET ligands, MRI contrast agents and reporter). These are areas in which HMS should develop leadership by making several targeted recruitments of investigators with varied expertise in different locations (development of genetically encoded fluorophores might be more suitable for Quad departments, MRI chemistry for hospital departments).

d. Lowering barriers
Development and application of non-invasive imaging techniques requires use of animals, and the issues of animal transfer addressed in Section IIID, below, are critical. As these imaging techniques advance, ease of archiving, accessing and transferring very large data sets will become equally critical, and we recommend an effort to gain consensus among the leading imaging centers on data format and data sharing. Cross platform data transfer is hindered by proprietary formats generated by instrumentation from different vendors, and work on these issues will require substantial effort.

4. Molecular, animal, and human physiology

a. Overview
An overriding issue in considering the state of research with animal or human subjects is the regulatory environment. The subgroup was unanimously of the view that the animal care facilities supporting the HMS community should be made more research-friendly and less expensive. Effective regulatory oversight is critical when appropriate but crippling when reflexive. *A new strategy must be developed to address regulatory, legal, and media concerns, and this must be done in concert with the PIs who use these facilities.*

A shift to a more "PI-centered" philosophy will improve retention and recruitment efforts and allow for more direct collaboration between quadrangle and hospital-based investigators. Examples of current issues that hamper translational investigation include differences in conflict-of-interest policies at the hospitals and at HMS, lack of a central IRB, and lack of common web-based platforms to promote investigator communication. All of these will also be important for success of the CTSA program. Similar regulatory issues, such as

differences in veterinary programs and policies across institutions, present severe obstacles to basic science research.

Subcommittee members offered a range of opinions with regard to general support. The issue of when a given technology can be a service or when it requires collaboration is critical. Centralized HMS cores should only be formed if they are more efficient and less expensive than commercial or local resources. However, institutional agreements and licenses with unaffiliated organizations carry the weight and negotiating power that individuals could never harness.

b. Improving existing HMS resources

(i) Animal facilities

The largest core facility at HMS maintains animals, both large and small, for research. Tools for manipulating the mouse (and now the rat) genome have dramatically enhanced the utility of these species, and we anticipate that gains in genomics technologies (human and rodent) will further enhance the value of these animals for modeling human disease and for studying mammalian physiology. The Center for Animal Resources and Comparative Medicine (ARCM) facilities maintain approximately 500,000 mice. They cost $44M annually, compensated by federal and private funds. In addition to the ARCM, HMS supports the Institutional Animal Care and Use Committee (ACUC), which mediates regulatory oversight.

The key issues that need attention are cost and regulation.

(a') Cost. HMS mice (according to a 2005 survey) are among the most expensive in the country. The per diem of $1.18 per cage, increasing at about 10% for the past three years, ranks among the top 5% of mouse costs nationwide, hindering recruitment and retention and precluding large scale mouse genetics and mutagenesis programs. HMS must analyze the cost structure and work to reduce the per diem. It is possible that wasteful duplication of oversight mechanisms is part of the problem.

(b') Regulatory concerns. HMS animal care is overseen by more than nine external regulatory bodies, including the Office of Laboratory Animal Welfare (OLAW), United States Department of Agriculture (USDA), the Human Society, the Association of Assessment and Accreditation of Laboratory Animal Care (AAALAC), and the City of Cambridge. The HMS IACUC, in an attempt to reduce effort, tends to lump all facilities and all species together, to accommodate all of these regulatory agencies for all investigators and all institutions and all species. This deluge of regulation often severely hampers innovative research. One alternative institutional structure that would benefit researchers using mice and rats would be to have separate IACUC sub-committees and administrative personnel for rodents and larger animals.

(c') Veterinary oversight. Transfer of mice between HMS laboratories is dramatically inhibited by various measures to prevent infection. Different veterinary programs oversee the animals at different institutions in the HMS area. Transfer of animals between an institution with ARCM veterinary oversight (HMS, HSPH, BWH) and one with independent oversight (TCH, DFCI, BIDMC, MGH, Joslin) requires quarantine and/or rederivation (delaying collaborative studies and resulting in substantial costs). More transparent and research-friendly regulations for mouse husbandry, while still providing adequate protections against pathogens, appear feasible. Efforts to break the bottleneck are needed. There is at present no oversight or evaluation of regulatory (e.g., IACUC) or veterinary policies. We recommend that a faculty supervisory committee, composed of knowledgeable users, should evaluate such policies and report to the Dean on a regular basis.

(ii) Development and dissemination of technologies.

(a') Inventory. The subgroup members concur that HMS needs to inventory its existing small animal imaging and physiology resources and to make available on the web those resources that accept animals from any HMS institution. An electronic database of core labs and investigator expertise in specific areas should be developed, similar to the CONNECTS database proposed in the CTSA grant.

(b') Advice/guidance on use of technologies. A suitably constituted Office of Tools, Technologies, and Facilities could assist researchers in choice of the proper technology for their experiments. This function would require dedicated personnel (including technicians and technology specialists) to help document and disseminate key technologies, as well as a dynamic HMS committee of technology leaders who would serve as "go-to" people to help HMS researchers match their needs to a technology. The subgroup cautioned that such an Office should aim to efficiently provide researchers with services that they need, and at all costs avoid becoming a costly, ineffective layer of administration.

c. Developing new programs and resources:
(i) Animal physiology.
Quantification of small animal physiology is of paramount importance for understanding disease mechanisms and for assessing new therapeutic interventions. The subgroup believes that HMS has insufficient resources for small animal imaging and physiology to meet the high demand. Unmet needs include widely accessible metabolic/functional imaging and physiological testing. In creating new programs, attention must be paid to whether a given technology can be a service core or whether it requires expert collaboration.

(a') Animal physiological testing. Obtaining baseline physiological characterization of important rodent models should not require finding collaborators. Other areas need more careful consideration: metabolic characterization (glucose/insulin tolerance, euglycemic clamp, PET/CT, mouse MRI, cardiovascular function, including ECG and Echo, neurological function and learning, including EEG, exercise physiology, and GI and renal physiology. HMS might also consider the model of the "mouse hospital", e.g. the Institut Clinique de la Souris in Illkirch/Strasbourg (associated with IGBMC).

(b') Small animal imaging. HMS has several world-renowned laboratories in this field, but few provide custom contrast agent chemistry as a service. A suitable facility or center would require expert organic chemists, physiologists, and imaging scientists and would permit virtually any disease state to be monitored non-invasively and longitudinally in small animal model systems.

(c') Other core services. Cores in the following areas should be considered: animal blood lab, histopathology and toxicology. The Longwood Small Animal Imaging Facility could serve as a model for establishing additional resources.

(ii) Human physiology. Individual institutions have facilities for PET/CT (although mostly for clinical work rather than clinical research), but metabolic assessment though high-level NMR is a cutting edge of human metabolic research not represented here. Recruitment of investigators will require both large upfront equipment costs and on-going operational support costs.

(iii) A centralized "investigational pharmacy" to support clinical research. Investigators at individual institutions face challenges in determining how and where to obtain synthesis of investigational compounds (radioactive tracers for human studies, phamacological agents, etc.). Hospital pharmacies have limited and varied capacity and expertise concerning investigational drugs. An HMS-wide facility might have merit (see also discussion in the Therapeutics subcommittee, above).

d. Lowering barriers.
Uniform veterinary practices and requirements, lowered mouse costs, and uniform IRB requirements (or ideally, a single, HMS-wide IRB) are of particular urgency.

5. Informatics and data management

a. Overview.

Computational methods and informatics underlie all of contemporary scientific research. The subgroup focused primarily on informatics and information technology – in themselves large and heterogeneous territories. There is a very wide range of expertise among research groups in the HMS community – from those making novel contributions in algorithms, programs, use of distributed computing, and so forth, to those dependent on collaboration and consultation. The subgroup identified four recurring themes that affect research groups at almost all levels of sophistication, extending in some cases well beyond informatics and IT. These four themes are: (a) communication across the community about expertise and technology "assets"; (b) recruitment and retention of leader-innovators and of expert support staff; (c) limited number of expert support staff and lack of capacity to provide support for new projects; (d) capacity of existing IT facilities. It is important to recognize that there are no "one-size-fits-all" solutions to these problems and that a range of organizational structures should be possible, extending from relative autonomy for suitably qualified segments of the community to efficiently centralized facilities for others. In making decisions about platforms and resources, one member of the subgroup emphasized the need for transparency: the programmatic goals for allocations must be explicit (e.g., "computing infrastructure for Department X", rather than "data storage" or "high-performance computing" more generally). The Task Force as a whole has noted that expert faculty input will be essential for wise IT decisions. How best to insure faculty oversight of IT operations should be a charge to the Standing Faculty Committee on Tools and Technology.

b. Improving existing HMS resources.

(i) Lack of communication about tools and technology already present in the community was a common theme in all the subgroup discussions. In the realm of research and teaching covered by the CTSC, the group emphasized the role of the CONNECTS system, and it proposed that CONNECTS functionality could be extended beyond the CTSC. There is a need for suitable mechanisms to enable researchers to connect rapidly with others in their field (e.g., those with statistical and analytical expertise) and for a library documenting data sets that have been cleaned, transformed, and analyzed by HMS researchers. Communication technology, including instant messaging and teleconferencing capabilities, should be made much more widely available. Effective IT support will also be necessary to realize proposals such as more uniform IACUC and animal ordering (see recommendations under Animal and Human Physiology). (b) All institutions in the HMS community must recognize that there are substantial market disparities dictating higher salaries for competent computational support staff, particularly at the level of experts with higher degrees who expect to collaborate with faculty. The salaries of some of the technologists and information scientists will often need to be higher than those of the junior and mid-level faculty they serve.

c. Developing new programs and resources

(i) Frontier computational research. There are many areas (e.g., image analysis) in which frontier computational research at HMS must be strengthened. We define "computational biology" to include innovation in methods, approaches, and algorithms. New methods are usually implemented as computer programs, but the initial programs are often ad hoc and not useful outside the laboratory in which they are written. At a second stage, computational biologists who have pioneered a useful new method often collaborate with experimental biological scientists to develop more broadly applicable programs that other, suitably sophisticated users can run and (sometimes) adapt. At the third level, computing groups within institutes or laboratories adopt publicly available programs, advise and assist their colleagues in using them, and participate to one degree or another in the on-going research. These stages correspond to the categories of innovation, development, and service that we have defined for describing tools and technologies. Essential for all these efforts is routine information technology (IT): maintaining networks and servers and similar activities.

Innovative computational biology includes research that interprets independently gathered data (e.g., in modeling genome evolution or signal transduction or in studying protein folding) as well as research that

connects intimately with ways of gathering or analyzing the data (e.g., in assembling genomes or image analysis). Excellence in the entire range will be critical in the coming years.

Without the innovative cutting edge, an institution risks falling behind in application and service, not just because the new approaches are happening elsewhere, but because the lively expertise to direct truly effective service operations is lacking. The only area in which HMS is currently recruiting effectively at the frontiers of computational methods is systems biology, an important but restricted sector. Other areas in which we are doing well at the intermediate, developmental level, in many cases through external collaborations with innovators, include genomics, imaging, and structural biology. In each of these fields, computational methods and effective processing of massive data sets have historically determined the rate of discovery, hand-in-hand with new experimental methods, and it is likely that computational approaches will have an even more important role in the next decades. We recommend that HMS recruit exciting talent in these areas of computational biology, probably within existing departments and institutions. Innovative approaches to epidemiology and to the statistical analysis of clinical data also deserve attention.

A note on routine IT: in many cases, this activity is usefully centralized. Information technology infrastructure such as high performance computing, storage as a utility, and high-speed networks have proven to be successful centralized services supporting the research community and should be expanded proportionate to demand. But laboratories with unusual computational needs, for example those innovating or adopting novel computational methods, may often be best served by managing their own IT, in order to be able to reconfigure rapidly and flexibly, to choose specialized platforms, and the like. For these reasons it will be important not to be dogmatic about centralization for its own sake, and to give individual entities the opportunity to manage even their own routine systems where appropriate. The Standing Committee on Technology Innovation should work with Central IT to identify areas where flexibility is appropriate, and areas where increased support for IT functions is needed.

(ii) The subgroup discussion emphasized the need for a more appropriate promotions process for individuals with an engineering or technology development emphasis. Although the new promotions criteria have ample capacity to allow the promotion of such individuals, the crucial issues will of course concern who will serve on promotions committees, which journals and modes of publications will be admitted, and who will be asked for letters of support. The subgroup recommends that more explicit guidelines be added to ensure that an appropriate variety of contributions be properly evaluated.

(iii) The subgroup pointed out that HMS has a relatively small overall community of informatics experts. In planning resources for departments and centers, attention should be given to slots for such individuals. The Task Force notes that at the Broad Institute, informatics staff report directly to the faculty of the research program with which they work, not to a separate informatics group. This model can be contrasted with one in which a separate informatics group provides distributed services. The Broad model may have substantial advantages, especially for training of younger investigators.

d. Lowering barriers

Connections to and collaborations with SEAS should be explored more fully.

Members of the Tools and Technologies Advisory Group

Team Leads:

Steve Harrison
Elazer Edelman

Team Members:

Sangeeta Bhatia
George Church
David Corey
Steve Elledge
John Frangioni
Todd Golub
Robert Gould
Steve Gygi
John Halamka
Ronald Kahn
Zak Kohane
Cynthia Morton
James O'Malley
John Parrish
Paul Ridker
Bruce Rosen
Bernardo Sabatini
Brian Seed
Jonathan Seidman
Caroline Shamu
Arlene Sharpe
Joy Sircar
Judith Jebanathirajah Steen
Ralph Weissleder
Alan Zaslavsky

Subgroup Rapporteurs:

Todd Golub: Genomics and proteomics
Zak Kohane: Data management and analytics
Bernardo Sabatini: Imaging at all levels, molecules to organisms
Caroline Shamu: Small molecules and therapeutics
Arlene Sharpe: Animal and human studies

Staff Leaders:

Judy Glaven
Becky Ward