

Biomedical Research Advisory Group: Critical Areas of Research

Chemical Biology/Pharmacology/Therapeutics White Paper

Executive Summary

The related areas of chemical biology, pharmacology, and therapeutics afford enormous opportunities for innovation in education, research, and treatment of disease. There are major strengths in these areas at Harvard on which to build, particularly in basic biology and clinical research, and pockets of strength in therapeutically relevant chemistry and certain technology platforms, but there are also gaps in other research areas and technologies. Harvard should take a leadership position by building organizational structures that address the multidisciplinary nature of this field and the need for collaborations both within Harvard and with companies.

Scope:

This document covers three related areas:

- **Chemical biology:** application of chemistry to biological problems, recruitment of chemists to the biomedical enterprise
- **Pharmacology:** identifying/understanding therapeutically relevant biomolecules and pathways, and understanding/predicting how they respond to perturbation by drugs (see below for definition). How do existing drugs work, and how can they be improved? How can we develop new selective drugs? How do organisms process drugs and how does this affect the drug response? How does drug resistance arise, and how can it be avoided? How do genetic differences among individuals affect their response to drugs (pharmacodynamics) and their processing of drugs (pharmacokinetics)?
- **Therapeutics:** Use of drugs to treat or prevent disease. This includes small molecules, but also proteins, nucleic acids, other macromolecules and perhaps nanoparticles, also research on drug delivery. This document does not explicitly consider medical devices, vaccines (see appendix 2 for a proposal regarding a vaccine center), or cellular or gene therapies, but points raised here are relevant to these modalities.)

Scientific and Educational Opportunities

The confluence of genomic information, broad understanding of how biological systems function, and advances in tools to manipulate biological processes (including chemical biology and RNA interference) have set the stage for bold new approaches to target discovery, target validation and therapeutic design. At the same time, the pharmaceutical industry is experiencing great stress. It is not clear that the current “big pharma” model will be able to deal with the challenges presented by molecular understanding of disease, where patients are increasingly divided into smaller groups that need individualized therapies. This confluence of events represents both an opportunity and an obligation. Academics must step up to the challenge of therapeutic discovery. Academia’s role in creating a new science of therapeutic discovery will come both in advancing the basic science on which this new approach is built and in integrating the different forms of knowledge about a pathway to provide a potential route to intervention. Just a few of the specific areas that demand academic attention include, but are not limited to the following:

(1) A way to link our increasing biochemical understanding of the roots of disease to physiology. This implies that we should understand how genetic changes alter the risk of contracting a disease in biochemical detail, how the changes in biochemical interactions induced by a therapeutic generate changes in the behavior of individual cells, and how that alters the behavior of the organism as a whole. There is considerable scope for novel potential targets to be identified based on these considerations. At the same time, there is much to be learned about differences among cell types and among animal models. We should be able to trace physiological differences to biochemical and genomic differences. As well as improving the predictability of drug development, such an understanding will eventually make possible a truly personalized approach to medicine.

(2) Novel approaches to therapy. Increasingly, we will have detailed information on individual patients or cancers that could in principle provide a road-map to the interventions that would be most effective in treating their disease. For multifactorial disease, such road-maps will often prescribe combinations of two or more treatments. Currently, there is no route to converting this information into actual therapies. Progress will require the understanding of physiology at a

biochemical systems level described above, together with novel approaches to evaluating the efficacy of therapies, including combinations, in animal models and in human populations.

(3) New therapies for infectious diseases. Existing antibiotics are losing their effectiveness. There is a need both for antibiotics that address new targets, and for a better understanding of how antibiotic resistance arises and how it can be suppressed.

An effort in therapeutic discovery would also provide major opportunities for training of undergraduates, postdoctoral fellows, graduate students, medical students, and even students in schools such as law and business. In particular, the opportunity to integrate clinical understanding of a disease with molecular mechanism in a research project opens up the possibility of a new and very exciting approach to graduate education. For all these reasons, we see this area as an extremely important priority for HMS and Harvard as a whole.

Harvard's current strengths and challenges

Harvard has a significant base from which to draw in building a community to address these challenges, but we believe that many of the people leading and performing this research will need to be new hires. To be successful, we will need to build a new discipline that integrates human genetics with drug discovery efforts, and traces the effects of mutations and interventions all the way from the biochemical level to the organismal level; no single group currently attempts this. There are pockets of expertise in many important areas, however, including:

Strengths

Harvard's Cambridge Campus: Strong synthetic and analytic chemistry and molecular/cellular biology in Cambridge, but little interaction with HMS. The CCB Department has an appropriate focus on doing exciting chemistry rather than solving biological problems; however, a few CCB faculty are genuinely interested in drug development. A few MCB faculty have also shown an interest in translating their research into new therapies. Some faculty in HLS and HBS have relevant interests, too.

HMS Chemical Biology: A small but strong group of chemists at HMS, with particularly strong affinity for real biomedical problems. This group has extremely limited access to graduate students, and less than ideal access to analytical instruments and hood space. This group has so far relied on two senior leaders (Walsh and Clardy).

HMS Pharmacology: BCMP has a small group of senior faculty in pharmacology, but most recent hires have not been targeted in this area. Two successful community-building efforts have been the Pharmacological Sciences training grant, led by Don Coen, and a group effort to write a leading textbook of pharmacology, led by David Golan.

HMS Structural Biology: Structural information is critical for drug discovery. HMS has a small but very strong group, mainly in BCMP, led by Harrison (X-ray, EM) and Wagner (NMR). Most of the current structural biologists are interested in pharmacology. Harrison in particular is attempting to drive structural biology towards a much broader and dynamic understanding of protein behavior, which will be crucial for modern drug discovery efforts. There is a need for more junior faculty in this area.

HMS Biology/Medicine: A large, strong, and diverse faculty at HMS and the affiliated hospitals have identified or have the potential of identifying new targets (including pathways) for drug discovery, but have limited ability and, in some cases, impetus to translate these findings to create new therapeutics. Many of these scientists are enthusiastic about attempting to translate their discoveries to therapeutics, but naive about the methodology and resource requirements. There is outstanding clinical research at the hospitals who conduct both sponsored and investigator-initiated clinical trials of therapeutics, but have little ability to feedback the results

into new drug discovery. Competition among institutions impacts patient accrual and other facets of clinical investigation.

Broad Institute: The Broad has made a large investment in platform technology and cores for drug discovery. This resource is unavailable to most HMS groups, but is offering important help to some groups. Strengths at the Broad include the interface with human genetics and their recruitment of industry-trained experts. There is less effort to trace biochemical events to physiological and pathological consequences.

ICCB-L and DRSC: The Institute of Chemistry and Cell Biology-Longwood (ICCB-L) and Drosophila RNAi Screening Center (DRSC) are separate but linked screening efforts that together constitute a small but well run chemical and RNAi screening and automation center, accessible to all HMS faculty. ICCB-L also incorporates the New England Regional Center of Excellence in Biodefense and Emerging Infectious Disease (NERCE-BEID) screening core. Properly resourced and administered, ICCB-L could become even more important in enabling drug discovery and technology education at HMS.

Other platforms: There are several other valuable centers such as the Harvard Institute for Proteomics and the Harvard Neurodiscovery Center.

Clinical and Translational Science Center (CTSC): We are optimistic that the newly-formed CTSC will provide an important level of integration between therapeutic discovery efforts in all of the HMS institutions and innovative translational and clinical efforts in the affiliated academic health centers.

Challenges: What is missing?

The challenges can be divided into three classes: intellectual areas that are missing or need expanding; platforms that are missing or unavailable; and organizational challenges. The most important challenge is the lack of a central organizing principle for recruitments relevant to therapeutics and the lack of investment in the substantial resources required for therapeutic discovery and development. This is particularly acute for recruitment of chemists to HMS, but it applies to young scientists with translational interests in the basic science departments as well.

Intellectual areas for expansion include (but are not limited to): chemical biology; efforts in novel therapeutic modalities; pharmacogenomics; and a dedicated effort in drug delivery technology, which is closely linked to the therapeutic potential of RNAi and other macromolecule and nanoparticle drugs. In addition, we would need to bring together chemists, biochemists and biologists with clinicians and physician-scientists who understand disease processes.

Platform areas to add or expand include (but are not limited to): expanded screening facilities with broad access for all investigators; adding chemical libraries including one with all FDA-approved drugs and as many other characterized molecules as possible; a compound synthesis and analytical chemistry core; help for biologists to plan chemical synthesis projects (in a few cases leading to full-scale medicinal chemistry efforts); facilities for studying potential therapeutics in animal models; and better databases to share information across labs. Currently we have little to no capability to assess the pharmacokinetics or on- or off-target adverse effects of a potential therapeutic in an animal, and performing an experiment in which we know the concentration of the drug in the bloodstream and target tissue is more or less impossible. Expanding and enhancing these efforts is central to the report of the Tools and Technologies small molecule/therapeutics subgroup; we strongly endorse those proposals. (Also, see appendix 3 for a proposal for an institute for co-clinical animal pharmacogenomics that could dovetail with

these efforts, and see appendix 4 that summarizes issues regarding the relevance of animal models and related approaches to therapeutics that were raised by the Steering Committee.)

Organizational challenges include: (1) a multi-institutional environment that makes collaboration on projects that have significant potential value difficult (and collaboration using animals and humans extremely slow); (2) little first-hand expertise in real-world drug development efforts and little advice or help for faculty interested in taking steps to evaluate a therapeutic idea, e.g., advice on outsourcing medicinal chemistry or animal studies; lack of encouragement or help to start companies, which can be an important translational route (as well as opening the door to possible SBIR funding).

This team felt that the focus of this analysis should be the needs and opportunities in intellectual areas related to therapeutic discovery. We stress, however, that new and improved technology platforms, as well as funding, advice/mentoring/quality control (e.g. an advisory council), and innovative partnerships with industry, are absolutely required to allow existing and new faculty to take their research in the direction of novel therapeutics. The platform technology issues are dealt with to a large extent in the report of the Tools and Technologies small molecule and therapeutics subgroup, though that committee may have under-emphasized the importance of drug types other than small molecules, e.g., RNAi, etc. HMS has to aim at the drugs of the future, and lead the pharmaceutical industry, not follow it.

Organizational models

We next considered what organizational structure would be best suited to build a culture of therapeutic discovery, to help recruit new kinds of scientists to HMS, and to bring together existing groups that could synergize (e.g., CCB/Cambridge with Pharmacology/HMS). The key factors we identified as important were (1) the ability to create a new organizational culture that includes clinicians and translational scientists; (2) the ability to attract and nurture young investigators from different fields; and (3) resources to create new platforms to enable therapeutic discovery. We also felt that strong, capable leadership would be crucial.

Increased investment in existing units

Pros: An existing department such as BCMP could provide a home for a larger program in this area, including technology platforms such as compound libraries, screening, medicinal chemistry, and small-animal pharmacology. Science often flourishes when faculty engaged in diverse research areas interact.

Cons: Starting with an existing Department provides little opportunity for developing a new culture and connections with others. BCMP is already a large and rather diverse department that could become too large and too diverse with an expansion into a new area.

New non-departmental entity, such as a Center or Institute at HMS

Pros: Could provide a focal point and space for scientists and trainees (undergraduate, graduate, medical, postdoctoral) in diverse departments to come together around this area and create synergies. Could co-recruit relevant faculty with Departments. Could serve as a home for technology platforms such as compound libraries, screening, medicinal chemistry, and small animal pharmacology, and for educational initiatives.

Cons: Institutes usually don't have appointment power; thus, could be at a severe disadvantage relative to a Department in recruiting junior faculty, and in recruiting new senior leadership. Would not bring together different Harvard schools.

A new Quad-based department at HMS

Pros: In addition to the centralization advantages of an Institute: would be a bolder move and larger commitment than the choices above, providing appointment power and a home to this area. Would have major advantages in developing a new organizational culture. Would have significant advantages in recruiting and mentoring young faculty (especially important for chemistry faculty in an unusual environment, i.e. a medical school). Would offer enhanced possibilities for recruiting new senior leadership and supporting trainees. Could provide resources for joint appointments in departments and serve as a home for educational initiatives. Could be organizationally centralized but physically disperse (e.g., faculty interested in microbial disease could be located next to the Microbiology department, and/or part of the Department could be on the Quad and part in Allston).

Cons: Requires substantial resources. Might create fewer synergies among the departments or other Harvard hospitals and schools than an Institute or a cross-School department or committee. Could be perceived as an unduly applied focus for a "basic science" department. Could weaken other departments by recruiting their faculty (which could be mitigated by some remaining in their original locations).

A new University Department (or Committee)

Pros: In addition to the advantages of an HMS Department: could engage different Harvard schools (FAS, Business, Law, Public Health, etc.) and their students. If part or all of the new organization were to be located in Allston, this would allow interested Cambridge faculty to move to Allston and join the new community without losing the ability to teach undergraduates. In principle, could bring together faculty interested in therapeutic approaches from many different areas. A Committee would also have appointment powers, but faculty would be located in pre-existing Departments, thus providing some of the advantages of an HMS-based Institute mentioned above.

Cons: At present, relatively few FAS faculty are deeply interested in therapeutics, so that the FAS element of the new entity might lack critical mass; as noted above, this might be less of a problem if part of the new entity were to be located at Allston. Locating the whole Department at Allston would be unattractive, however, as it would reduce interactions with the Quad and hospitals. A split model would be most attractive in principle, but might pose major administrative challenges.

Conclusions

Although the issue clearly requires further study, the team overall favored either a new HMS department (or an HMS entity akin to a University Committee) or a University department or Committee. Such structures should provide homes for diverse scientists ranging from chemists to clinicians who are intellectual leaders in this field. The structure should promote new technology and initiatives in teaching and training, and should make technologies and educational opportunities broadly available. It would need to have close ties to many HMS units, especially those concerned with understanding and treating disease processes and identifying novel therapeutic targets. In either case, a split model, with part of the organization at the new Allston campus and part at Longwood could be beneficial. Such an arrangement would pose organizational challenges (similar to those faced by SCRB) but would have advantages from the point of view of education. The team favored a "big tent" approach in which many researchers and institutions could participate. A key issue is how best to involve and align the efforts of the various institutions including HMS, the hospitals, the Broad Institute, and the Cambridge schools as a core part of a new program in therapeutic discovery. We recommend

that this question should be discussed with these institutions as one of the next steps in the planning.

Appendix 1: Members of the Chemical Biology/Pharmacology/Therapeutics Team

Don Coen (BCMP, HMS), Team Leader

Bill Chin (Eli Lilly)

David Golan (BCMP and BWH, HMS)

Nathanael Gray (BCMP and DFCI, HMS)

Phil Kantoff (DFCI, HMS)

Dan Kahne (CCB, FAS; and BCMP, HMS)

Tim Mitchison (Systems Biol., HMS)

Bruce Spiegelman (Cell Biol. and DFCI, HMS)

Becky Ward (Systems Biol., HMS)

The team included a diverse group of scientists from various Harvard departments and institutions and included members with expertise in chemical biology, pharmacology, and therapeutics and with experience in both academic and company settings. The team met on Feb. 5, 2008 with all present except Bill Chin, who participated by telephone, and Phil Kantoff, who communicated his thoughts to Don Coen. Following that discussion, this white paper was written by Don Coen and Becky Ward with emailed input from all members of the team, and subsequently from members of the BRAG-CAR subcommittee. Additional revisions, including Appendix 4, were added by Don Coen and Becky Ward following the March 21, 2008 meeting of the Steering Committee at which this white paper was discussed.

Appendix 2. Draft Proposal for a Harvard Vaccine Institute (David Knipe, Ray Dolin, Laura Weisel)

INTRODUCTION

Vaccines are among the most effective public health interventions for disease control and are perhaps humankind's best or only defense against many global health care crises. Nonetheless, despite increasing medical knowledge and maturing technologies applicable to vaccines, the development and deployment of vaccines has slowed in recent years. In some cases, this has resulted from the formidable scientific challenges to vaccine development posed by diseases such as AIDS, tuberculosis, or malaria. In others, logistic and economic barriers obstruct the utilization of vaccines in areas where they might be needed the most. The establishment of the Harvard Vaccine Institute presents an opportunity to apply the considerable intellectual resources of the faculties of Harvard University to the problem of vaccine development and utilization in a coordinated and concerted manner.

With respect to the basic sciences of microbiology and immunology, and the clinical studies of vaccines, Harvard University and its affiliated institutions have enormous strength. For example, there is considerable expertise among the faculty of the University in the study of microbes and their genetics and pathogenesis, the host immune responses to these pathogens, design and preclinical testing of vaccine candidates, and clinical testing of vaccines. However, these efforts have been conducted largely in parallel in numerous laboratories around the university with limited collaboration. Furthermore, many vaccine candidates have languished because the only development route for these vaccines was licensing to for-profit organizations where development was not always the highest priority. In particular, vaccines for developing countries or for diseases with a limited market have not been pursued by corporations.

The establishment of the Harvard Vaccine Institute is aimed to address these issues by providing support for the development and clinical trials of vaccines that have not been fully utilized. These would include vaccine candidates that have not been tested adequately because of a lack of an available infrastructure for development or because of a lack of support from biotech and pharmaceutical companies.

This proposal describes the establishment of a basic and clinical science core as an initial step in the creation of a Harvard Vaccine Institute to be based in the faculties of the Schools of Medicine, Public Health, and Arts and Sciences. It provides for the recruitment of a Director of the institute, along with two junior scientists who would not only develop a specific program in vaccine related research, but would also provide leadership and coordination for vaccine research efforts of other investigators throughout Harvard. The Institute would also provide infrastructure to address regulations and logistic issues in development of vaccine candidates, including the generation of candidate vaccines for clinical testing on a limited scale. The Vaccine Institute will also have the capability to conduct Phase I and II clinical trials of promising vaccine candidates at Harvard. In subsequent stages of development, the Harvard Vaccine Institute will begin to address the economic, legal, and social aspects of vaccine development through

collaborative efforts with faculties throughout the University, particularly the Schools of Business, Law and Government.

MISSION

The mission of the Harvard Vaccine Institute will be to:

- Promote vaccine research, development and clinical evaluation at Harvard University and affiliated institutions, especially for neglected diseases and diseases in the developing world.
- Promote communication and collaboration among HMS basic and clinical scientists who work on vaccines.
- Stimulate educational opportunities in vaccine related fields at Harvard and affiliated institutions.

DESCRIPTION OF ORGANIZATION

HVI will be comprised of faculty at Harvard University and affiliated institutions who are interested in vaccine research and/or education. It will be led by a faculty member who will serve as director of the HVI, and be appointed by the Dean of Harvard Medical School. An Executive Committee consisting of faculty from various parts of the University involved in vaccine related activities will advise the Director. An initial role of the Executive Committee will be to prioritize the activities of the HVI, and subcommittees will be formulated to implement individual activities.

Members of the Executive Committee: To be named.

DIRECTOR OF HVI

The Director of the HVI will be a leading scientist with a successful program in vaccine related research that focuses on a major disease, for which vaccine development is needed. This Director's interests should be sufficiently broad to support vaccine development in other fields and to interact with multi-disciplinary research programs. The Director's research program will have dedicated laboratory and administrative space and resources for recruitment of additional investigators as needed for his program.

ACTIVITIES

The HVI will promote development of vaccines throughout the establishment of supporting resources, core facilities, and educational opportunities to facilitate basic and clinic research in vaccines and related fields. The following are planned:

1. Initiatives for education and training in vaccine related fields and for increased communication among faculty working in these areas. Examples of these are:

- Courses and lectures for graduate students, medical students and trainees
- Regular seminars focused on vaccine related topics
- Annual Harvard-wide scientific forum on vaccine development

2. Establishment of infrastructure to address logistic and regulatory requirements for development of vaccine candidates. Areas to be addressed are:

- Intellectual property issues
- Regulatory requirements
- GMP production lots

3. Assistance with conduct of pre-clinical studies of candidate vaccines.

- Laboratory (in vitro) studies
- Experimental animal models, including primates

4. Conduct of phase I and II clinical trials.

- Protocol design, IRB submission of studies
- Infrastructure for conduct of trials
 - recruitment of subjects
 - study monitors
 - volunteer facility for studies
- Laboratory assessment of immune responses as needed

5. Assistance with applications for and acquisition of funding from governmental and private sources for support of vaccine related activities.

Appendix 3. Proposal for an Institute for Co-Clinical Animal Pharmacogenomics (Pier Paolo Pandolif and Lew Cantley)

The core intellectual foundation of this proposal rests on a very simple and yet very novel idea not yet developed and implemented in any other center in the world which we term for brevity “the co-clinical project”.

The “Co-Clinical Project” idea stems from the realization of the tremendous power of preclinical testing of new drugs, novel drug combinations and novel therapeutic modalities in animal models that faithfully mimic human diseases. With recent advances in understanding the genetic basis for diseases such as cancers, diabetes and neurological disorders it has become possible to develop animal models that replicate the human defects. These animal models hold much promise in pre-clinical testing of drugs that directly target the defective genetic pathway known to be involved in the disease of interest.

While on the one hand this approach has already proven to be tremendously effective in a relatively small subset of diseases (mostly cancers) where the genetic defects are well-understood and where ‘druggable’ targets have been identified, there are operational barriers to making this approach a paradigm for formal clinical trials: i) pharmaceutical companies are reluctant to delay phase I & II clinical trials pending the outcome of pre-clinical trials in animal models where the study could take two or three years for conclusive results, ii) the concept that the results of these animal models will be predictive of human response to drugs is still novel and not broadly accepted by pharmaceutical companies, iii) the animal models are often generated in academic laboratories and the barriers for MTAs for animal transfers from academia to industry or for drug transfers from industry to academia are high (sometimes insurmountable) and, even if successful, can require years.

These operational barriers deny both academic scientists and pharmaceutical companies the opportunity to utilize information obtained from drug studies in animal models to design phase III human clinical trials that could predict which patients are likely to respond to which drugs based on the genetic basis of the disease.

We propose to formulate an infrastructure at Harvard Medical School and the associated hospitals, called the “Co-Clinical Project”, that could dramatically reduce these barriers and thereby encourage basic scientists and clinicians to collaborate to design well-conceived clinical trials that are more likely to stratify patients and accelerate drug approval.

In a nut-shell what we propose with the “Co-Clinical Project” is that each clinical trial (in cancer and other diseases) at HMS should be run “in parallel” with co-clinical trials in appropriate, faithful and genetically relevant mouse models (where available), and that the clinical, biological and pharmacological information (i.e. somatic mutational background, germline SNP variations, responsiveness to specific regimens; imaging, microarray and proteomics profiles) should be accrued, analyzed in parallel and integrated in order to facilitate the identification of biomarkers that predict response to specific treatments. These studies will ultimately lead to patient stratification criteria based on molecular and genetics information.

As an example, if during human phase I & II trials of novel drug X for treating human breast cancer, a mouse breast cancer model driven by mutations in gene A responds to the drug but a mouse breast cancer model driven by mutations in gene B fails to respond, this would prompt the investigators to design phase III clinical trials in which patients are stratified based on mutations in gene A versus gene B. This approach has indeed had a dramatic impact on the way by which treatment of APL has evolved during the last 10 years towards the cure, with the caveat that in

the case of APL the paradigm was still to complete the mouse studies first rather than conduct parallel trials, thereby slowing down the rate of progress.

For the “Co-Clinical Project” to succeed we need to create an engine at HMS that will render this simple and yet very ambitious idea a concrete reality. This ultimately lead us to formulate a proposal for the development of a “Institute for Co-Clinical Animal Pharmacogenomics” (ICAP) at HMS.

The idea of a new Institute in the Longwood/Boston area in turn stems from the realization that many components towards the realization of the project are already in place. Small and large animal imaging platforms and appropriately designed animal facilities exist in NRB, WA, HIM and CLS and the various hospitals, and animal models of human diseases are being developed by numerous investigators at HMS and the hospitals at an impressive rate. As indicated above, the major barrier that discourages academic scientists from conducting these animal studies is access to drugs. While individual scientists and subdivisions of hospitals have made grass roots attempts to gain access to investigational drugs (with some success), what is needed is a central pharmacy for animal studies.

We propose that the logical structure for organizing this pharmacy is via the ICCB. The ICCB has experience in generating and maintaining large libraries of drugs and drug-like compounds for experimental purposes and has an interest in expanding these libraries to include all approved drugs and ultimately to include subsets of patented drugs as they enter clinical trials. Professor Tim Mitchison is currently exploring mechanisms for obtaining these approved and investigational drugs in quantities that would be sufficient for cell-based screens and has estimates of costs that are not exorbitant (probably less than \$2 million). Expanding this to quantities that would be necessary for animal studies would cost considerably more, but would not be a linear increase. In any event, the users would be expected to pay for the cost of maintaining the pharmacy.

Here we will briefly and schematically outline some of the features and interactive potentials of the ICAP at HMS.

The focus and the scope: the ICAP should serve the HMS community and the Harvard teaching hospitals at large. As an example, we have outlined ICAP features from an oncological perspective since the applications are so immediate in this disease, but the intent is for the institute to serve the entire biomedical community. In fact, the Institute could be articulated in Programs/Centers or subcommittees that serve other critical areas of biomedical research and therapy: metabolic, neurological, cardiovascular and auto-immune diseases (Figure 1).

The location: While much of the ICAP can function in a virtual mode by coordinating existing facilities such as the ICCB, the CTSA, animal imaging facilities, mouse genome manipulation cores, mouse and human pathology cores to facilitate this mission, it is critical to have a central physical location for the ICAP that maximizes interactions with HMS and the associated hospitals. We propose that the ICAP be physically centered in Longwood with dry and wet labs in the HIM and NRB buildings, preferentially close to the CTSA (Figure 2). Animals could be generated with the desired genetic backgrounds and in sufficient quantities for the proposed studies in NRB, HIM, CLS and other animal facilities. In anticipation of larger demands on animal space and imaging we have also had discussions about utilizing the Jackson Labs as a partner in this endeavor (another possibility is U. Mass, Boston where there is interest in developing cancer-related research with translational potential).

The interactions: For its mandate the ICAP at HMS will have a strong and obvious interactive nature and scope (Figure 3). We have already established potential interactions with

local Institutions, national and international organizations (e.g. the MMHCC/NCI; the Jackson laboratories; Pharmaceutical companies; the Chinese government to name a few).

The administrative structure: We envision a structure, closely linked to the structure of the CTSA, in which leaders for individual disease programs facilitate collaborations between clinicians and basic scientists to design the animal model co-clinical trials (Figures 4 and 5). In the area of cancer, the Program Directors will almost certainly be the Directors of the disease-based programs of the DF/HCC that are already in place. These leaders will be expected to have knowledge not only of the molecular events (genetic and non-genetic) that cause the disease but also of the animal models that have been generated at HMS-associated institutions that recapitulate the human disease. These Program Directors already have a leadership role in deciding which clinical trials should be approved (across hospital boundaries – though this could work better). In many cases, these Program Directors are also directors of SPORE grants from the NCI. Their role would be to inform the basic scientists, who have generated the animal models, of the opportunity to collaborate in the co-clinical trials. The expectation is that comparable leaders will be identified in other diseases, such as neurological, metabolic, autoimmune and cardiovascular diseases. Ideally a co-director would exist in each disease to increase the possibility of having strong representation from both the clinical and basic science side. For political reasons, it would be wise to have a committee for each disease that has representation from all the hospitals and HMS institutions involved in research in the disease. The role of the Director and Co-Director of the ICAP is to supervise the structure, communicate its value and its opportunity to basic scientists and clinicians at all the associated institutions, identify and eliminate barriers to the success of the institute, insure that the Program Directors are engaged, and identify resources (grants, industrial collaborations and philanthropy) to support the institute.

Challenges:

- The biggest challenge is to obtain the quantities of approved and investigational drugs needed for the co-clinical trials. Initially pharmaceutical companies will be reluctant to provide these drugs for free and will resist blanket MTAs across institutions. For this reason we should circumvent the companies to obtain the compounds. We need to be sure that as non-profit institutions, we do not have legal concerns in using these investigational drugs in non-human trials (the NIH may help here). If it becomes clear that we will do this independent of pharmaceutical companies they may decide that it is better for them to participate and obtain pre-publication information than to stand on the sidelines. Thus, in the long run we could receive pharmaceutical support.
- The animal co-clinical trials are expensive, involving not only the cost of the drugs but also the mouse costs and the imaging costs. However, these costs are trivial compared to human clinical trials. These types of translational studies are attractive to the NIH and many investigators already have resources from SPORE grants, P01 grants and R01 grants that could be used for these purposes. The ICAP would be unlikely to have the resources to pay for these trials (though philanthropic support might make this possible in the future – see below) so individual investigators would have to pay for the various resources on their own.
- Since the ICAP crosses institutions, it could be perceived as being biased for or against a particular institution. It is critical that decisions about Cores and Disease Program Leaders involve representation from all the institutions and be viewed as based on the quality of the

science. The success of the DF/HCC indicates that this can work (and even be improved upon).

Opportunities:

- Since we are unaware of any other institution that is attempting to coordinate animal model co-clinical trials with human trials, we would be setting a standard for other institutions and the world. This approach requires breaking down barriers that prevent academic scientists from doing translational research and it should be extremely attractive to philanthropists.
- The ICAP will bring HMS scientists, hospital-based scientists and clinicians closer together and create excitement about converting basic science discoveries (e.g. identification of disease genes) into drug trials in appropriate animal models that ultimately influence the design of human clinical trials - all in record time.
- The availability of the Pharmacy will allow us to utilize combinations of drugs from different companies in the mouse models. Most MTAs from pharmaceuticals explicitly preclude these studies. More importantly, the Pharmacy will allow us to compare drugs against each other in a common disease model to predict which is most likely to work in a given genetic background. These comparisons are always excluded in MTAs. The outcome of such studies will influence which investigator-initiated clinical trials will be encouraged by the Disease Program Directors.

Appendix 4: Discussion of issues raised by the Steering Committee, March 21, 2008

The Steering Committee discussion of this white paper centered around two interrelated issues: 1) Why is the traditional pharmaceutical company approach failing? and 2) what can we do better?

One source of failure has been a lack of clinically validated drug targets. Although for any given disease, there may be several gene products that could potentially serve as targets for therapeutic intervention, often these targets haven't been clearly connected to the disease prior to the drugs that target them entering clinical trials. Research to identify and validate drug targets is already a strength at Harvard. There is a need to exploit this strength for development of better therapeutics.

The roles of animal models, particularly to validate drug targets and therapies, are highly relevant to these issues. In some cases, there are animal models for disease, but they are not necessarily predictive (some would say "never predictive") of human disease, or whether a drug will be successful in treating that disease, or whether a drug will exhibit adverse effects in humans.

Nevertheless, historically, there are many cases of animal models that have been invaluable in validating therapeutic approaches. For example, there have been successes with animal models of certain cancers, and much exciting progress has been made in this area as knowledge of the genetic changes that result in cancer has grown. There are also good reasons to believe that mice can mimic important aspects of the effects of drugs on human physiology. For example, for scores of the best selling drugs, when the genes that these drugs target are genetically altered in mice, the mutations mimic the effects of the drugs. Additionally, when clinical trials fail (too often after FDA approval), it is common that animal model studies had already offered clues as to why these failures would occur. Thus, clear-sighted analysis of animal studies, un-freighted by drug companies' investments in their outcomes, can provide valuable insights, not only in terms of mechanism but, at least in some cases, in terms of clinical outcomes.

Nevertheless, there are many cases where animal models have been misleading. Taking the example mentioned above of animal models of cancers, monotherapy with anti-angiogenic factors have had much more success in mice than in people. Such cases often illustrate the importance of being mindful of how key biological features of mice (e.g. short timespan of tumor establishment) differ from those of people. For some diseases, although animal models show many of the important clinical signs of the disease, the underlying cause is not representative. A classic example of this is the ob/ob mouse model for obesity, which is due to leptin deficiency. Leptin deficiency only rarely causes obesity in the human population. Yet, one drug company bet fairly heavily that the discovery of the gene defect in ob/ob mice would lead to successful therapies for obesity in the broad human population (although even at the time, this bet was seen by many biologists to be naive). For other diseases, particularly psychiatric disorders, there are few animal models, never mind ones that are predictive of the effects of therapy.

Thus, deriving animal models that can more faithfully mimic human disease and be predictive of therapeutic outcome (including adverse events) is an important goal. This effort will be clearly be a challenge, especially when multiple genetic and other factors are involved in disease causation. Indeed, some consider real humanization to be impossible, and that may be true for at least some disorders. Additionally, there will be financial challenges, given the expense of housing and care of animals. Many, however, think this effort to be highly worthwhile, likely to achieve more than minimal success, and certain to attract drug company funding. There is real potential for development of public-private partnerships.

Another area where new science can make contributions to therapeutics is in engineering of organ systems to study efficacy and toxicities. Stem cell science and organ engineering could play major roles in this field. Clinical research will clearly continue to be crucial for progress. As one Steering Committee member said, "The model organism of this century is the human".

Looking back at various failures in the pharmaceutical industry, with the benefit of 20:20 hindsight, many can be attributed to incomplete understanding of biology. Perhaps some of the failures have resulted from the risk-taking nature of companies, seeking to be first-to-market with innovative therapies in the absence of thorough biological investigations. Perhaps others can be attributed to a willingness to ignore biological data due to emotional or financial investment. Although there is no lack of emotional investment (and sometimes financial investment) in hypotheses by academic researchers, Harvard may be better positioned than a company to take a leadership role in the biology of therapeutics. One way in which it can leverage its strength in biology will entail integrating findings from cell culture, animal models, studies of human disease mechanisms, human genetics, including quantitative trait locus analysis, and other clinical research. Computation may be limiting. Therefore, the recommendations of the Tools & Technologies committee to invest heavily in computation (both in terms of innovative approaches and computing power), as well as the various platform areas directly related to therapeutics, are very important. Data sharing among institutions, including companies, may be especially valuable. Finally, organizational structures and leadership that promote productive interactions among the various investigators will be crucial. The challenge for our school is how to do it.