March 18, 2008 **DRAFT REPORT**

IMMUNOLOGY AND INFLAMMATION AT HARVARD

1. Executive Summary

Harvard already has a very strong program in Immunology/Inflammation, structured as the Committee on Immunology, and many opportunities to substantially enhance its excellence and impact continue to present themselves. However, the program does face a number of challenges. To address these issues, we propose leveraging the existing organization of the Committee on Immunology, but augmenting its "presence" at Harvard and its contributions both internally and externally by: a) reinforcing its structure through granting direct representation on the critical decision-making bodies, and providing the means to influence future hires and promotions; and b) enriching its programs with financial support for existing activities, funding for an innovative set of seed grants, development of a series of discipline-tailored technology platforms; and financial and logistic support for new intra-program and campus-wide consortia. Simply stated**, *our vision is that the Immunology/Inflammation program at Harvard be the best in the world, and also that it serve as a nidus for translational advances, a valuable resource for the research efforts of the broader -- non-immunological -- community, and an educational driver at the undergraduate, graduate and post-graduate levels.***

2. Definitions and Scope

Immunology is the branch of the Biomedical Sciences that focuses on the structure, function, development and evolution of the immune system. Minimalistically defined, the immune system is the collection of molecules, cells, tissues and organs responsible for defending the body against external or internal attack by microbes or tumors. Innate immunity, mediated via germline-encoded receptors, refers to the first-line, essentially hard-wired, response of a battery of cells that includes macrophages, dendritic cells, Natural Killer (NK) cells, neutrophils and mast cells. Adaptive immunity represents a more directed and sophisticated response, mobilizing T and B lymphocytes, which display a variable, somatically generated repertoire of antigen-specific receptors. ***Inflammation*** is the body's stereotyped reply to various forms of injury or irritation, a protective attempt to both remove the stimulant and initiate the healing process. As such, it encompasses innate and adaptive immunity, as well as a diversity of molecular and cellular responses by the afflicted tissues.

The fields of Immunology and Inflammation are truly interdisciplinary, encompassing a vast range of perspectives, approaches and tools. Genetics, molecular biology, structural biology, cell biology, animal physiology and developmental biology are foundations of this intertwined pair of domains. Experimental tools include classical methods invented to address a particular issue in the field and subsequently exported to the broad community of Biomedical Science investigators (such as monoclonal antibodies, radioimmunoassay, immunoprecipitation, ELISA and flow cytometry), as well as the full palette of rapidly evolving modern technologies (e.g. imaging, mouse-germline manipulation, the various "omics", bioinformatics, high-throughput platforms, etc). Because of its focus on a complex, interactive, dynamic and evolving system, Immunology may be considered both a precursor to and a paradigmatic substrate for systems biology. Because all tissues are subject to injury or irritation, Inflammation is a domain that touches virtually the entire body, as we are appreciating more and more. Not surprisingly, then, investigators from these overlapping domains have often been the discoverers of basic biological mechanisms or been pioneers in the development or application of emerging technologies.

Immunology and Inflammation are also critically important, far-ranging medical domains. In the normal state, immune and inflammatory responses control bacterial, viral and parasitic infections, contain tumors, and limit the effects of injury and irritation of a multitude of origins. When these processes go awry -- because the response is too weak, too strong or misplaced – the result may be immunodeficiency, autoimmunity, allergy or cancer. Lastly, the systemic nature, mobility and/or specificity of immunity and inflammation have been harnessed to therapeutic ends in a number of contexts, e.g. via monoclonal-antibody, cytokine or cell-based therapies. Translation in this arena often goes in both directions: bench to bedside and back to the bench.

3. History and Current Status

The Graduate Program in Immunology is HMS's oldest Ph.D. program. Dr Baruj Benacerraf, who won a Nobel Prize in 1980 for discovering the immune response (IR) genes, became chair of the Quad-based Pathology Department in 1970. At that time, he conceived of a separate graduate program for the immunological sciences, rather than submerging this discipline within his own department. Recognizing the relevance of Immunology to the clinical world, he envisaged a Committee on Immunology, in which hospital-based faculty would be on an equal footing with members of the Pathology Department engaged primarily in basic research. This vision has held to this day, permitting investigation and teaching of the fields of Immunology and Inflammation to flourish. Since its inception, the Committee on Immunology has belonged to all of the Harvard-affiliated institutions, and investigators from all of them have been active and equal partners in its endeavors.

The first phase of the graduate program began in 1974 when Harvard University granted the Division of Medical Sciences at HMS the authority to award a Ph.D. in Immunology. Dr Benacerraf was a key figure in these early days, both in establishing the graduate program and in recruiting a group of top immunologists into the Pathology department and to the Farber, of which he became President. Dr. Albert Coons, who pioneered the use of immunofluorescence as a Professor of Bacteriology and Immunology, was the first Chair of the Committee on Immunology and Director of the Immunology Graduate Program. Dr. Martin Dorf took over these roles in 1986, and managed sustained and substantial growth through 1997. The current phase of the Immunology/Inflammation Program began in 1997. All relevant and interested faculty members submitted an application to the newly structured Committee on Immunology, led by an eight-member professorial-level Executive Committee for Immunology (ECI) with a rotating Chair distinct from the Director of the Immunology Graduate Program (Dr Hidde Ploegh). In 2006, Dr Michael Carroll became the graduate program's director, a position he holds today.

The Committee on Immunology currently has almost 90 faculty members, distributed throughout the Harvard constellation, including on the HMS quad, within all of the major hospitals and most of the specialty hospitals, at the FAS, and at the Broad Institute. About 20% (19/88) of our faculty members are women, of whom 11 are full professors, a number unrivaled in the top counterpart programs at Stanford, UCSF, Yale and Washington University. The Immunology Graduate Program hosts about 60 students drawn from all over the US and several foreign countries, approximately 10 in each class. There are also innumerable postdoctoral fellows.

4. Strengths

A major strength of Harvard's program in Immunology/Inflammation is its outstanding faculty. Almost ninety-strong, our faculty members consistently populate the speaking programs of the premier conferences relevant to the discipline; lead university, business and government forums that deliberate on the fields' state and direction, and receive the fields' most prestigious prizes. More than a quarter (12/46) of the US-based members of the Immunology section of the National Academy of Sciences are members of our program's faculty. Another strength has been the leadership and integration provided by the Committee on Immunology, making us one of the most collaborative, cross-institutional endeavors at Harvard, this being achieved so far with only minimal financial support from HMS. The benefits of this collaborative outlook are many, a few examples being: the new Jeffrey Modell Immunology Center to house our graduate program and facilitate our teaching and research activities; the Immune Circuits Consortium, which, under the auspices of the Broad Institute, promotes shRNA screens relevant to Immunology/Inflammation; ImmGen, a world-wide Harvard-piloted genomics consortium focused on the "immunological genome;" and a new initiative, driven by the Executive Committee for Immunology, to promote awareness of and to optimize purchasing and distribution of shared research tools and materials. Lastly, an undeniable strength is our program's context within the Harvard community. Most of our members enjoy a richness of collaborations with non-immunologists within their home institutions, as well as spread throughout the constellation of departments and hospitals. Particularly appreciated

are the exceptional opportunities provided by the Broad Institute, the Harvard Stem Cell Institute, the Dana Farber/Harvard Cancer Center and the various clinical departments. As concerns the last point, we eagerly await the new CTSC structure to integrate and enrich our already extensive clinical research projects.

5. Challenges

Despite the many strengths of the Committee on Immunology in its current form, the various discussion groups identified a number of weaknesses and potential threats. Chief amongst these were:

a. An inadequate "presence" at HMS – no "seat at the table", insufficient integration, little financial support. The Committee on Immunology does not have the statute of an HMS department, and its leader, the Chair of the ECI, does not have the status of a pre-clinical chair. Some of the consequences are that we have no direct voice in the major decision-making bodies at Harvard, other members of the Harvard community are fairly ignorant of our activities, and we have received only minimal financial support from HMS.

b. A "top-heavy" faculty with deficiencies in some key areas. Of the 90 or so faculty members in the Committee on Immunology, only 13 are Assistant Professors. It is obviously important to assure the future vigor of our program by recruiting and retaining top entry-level investigators. Optimally, these – in addition to new senior scientists – will be researchers in one of the areas generally considered to be under-represented within the Committee on Immunology – for example, innate immunity, structural immunology, signaling, immunoparasitology, imaging and systems immunology.

c. A disproportionately small graduate student body. On average, 8-10 new graduate students join the Immunology Graduate Program every year, of which 1-3 are typically from the Harvard MD/PhD pool. About 1/3 of our faculty members also have exposure to students in the context of the BBS Graduate Program. This is a woefully small cohort of graduate students, especially considering that we have to turn away many very good applicants to the Graduate Program, including a number that are under-represented minority applicants.

d. Little support for teaching. Teaching of Immunology/Inflammation takes place at all levels through HU and HMS. There are currently two full undergraduate courses (and a great demand for more), as well as four semester and many quarter courses at the graduate level. Immunology is taught to medical students as part of IMP (Immunology, Microbiology and Pathology), and as a full course within the HST program. While the course directors are often quadrangle faculty or are otherwise compensated, little or no compensation is provided for the vast majority of faculty who perform most of the Immunology teaching, as they are hospital-based.

e. Suboptimum integration/provision of technological resources. The Harvard research community has an impressive wealth of technological assets, but access to these valuable resources by members of the Immunology/Inflammation program is often less than optimal, due either to a lack of information or to an insufficient level of priority. Even within the program itself, better organization of and knowledge about common resources and tools would almost certainly reap benefits in greater efficiency, lower prices and more informed choices.

f. Poor support for translational immunology. On the one hand, Immunology and Inflammation are critically important and broad-ranging medical fields, and many of our faculty members are housed at Harvard's affiliated hospitals, often having significant clinical expertise and responsibilities. On the other hand, our basic researchers have been leaders in the dissection of fundamental immunological mechanisms and their subversion in disease states, yielding new strategies and tools for clinical diagnosis and intervention. Unfortunately, there is currently an inadequate infrastructure in place to foster translation back-and-forth between the clinic and the laboratory – indispensable help with items such as regulatory processes, patient recruitment, sample procurement and archiving, maintenance/exploitation of databases, and optimum access to new technologies. While HMS is in the process of coordinating its translational efforts under the CTSC umbrella, it is not clear how our model of cross-institutional, discipline-focused research will be integrated into this context

6. Opportunities

Several factors converge to make this an ideal time to enrich the Immunology/Inflammation program.

First, recent technological advances have rendered solvable a number of previously intractable issues: e.g. new genetic tools permit the definition of loci controlling complex traits such as susceptibility to infection, autoimmune diseases and asthma; emerging chemical biology and high-throughput screening platforms speed the identification of novel agonistic and antagonistic immunomodulators; genomic, proteomic and bioinformatic methods provide a more global, integrative, view of the immune system operating in normal and diverse pathological states, likely to result in more accurate mathematical models.

Secondly, we are becoming increasingly cognizant of the fact that inflammation subtends a number of pathological conditions affecting a broad range of organ systems: metabolic diseases like obesity and type-2 diabetes; neurodegenerative disorders, notably Alzheimer's disease; cardiovascular diseases, notably atherosclerosis; ocular pathologies, including macular degeneration and glaucoma; psychiatric abnormalities, for example schizophrenia, and a number of cancers.

Thirdly, the increasing promotion of translational research by the NIH and other grant agencies falls on fertile ground – Immunology and Inflammation have always had close ties to clinical practice, both because of the great variety and relative accessibility of biological material related to immunological diseases and because many diagnostic and therapeutic strategies are rooted in immunological processes (for example, biologic disease modulators such as antibodies).

Fourthly, there is an increasing recognition that global health challenges are solvable and that Harvard should be at the forefront of tackling them – old scourges like malaria and tuberculosis, newer ones such as HIV and SARS, particularly frightening ones like Ebola Virus. Immunology and Microbiology must orchestrate their forces in tandem to tackle these challenges.

In brief, the fields of Immunology and Inflammation have become substantially more important in the domain of Medicine over the past few decades. Their traditional implication in infectious diseases and vaccine development has taken on present-day urgency. They have taken stage center in medical therapeutics, with dramatic new treatments for a range of inflammatory and autoimmune disorders, including anti-cytokine therapy for rheumatoid arthritis, inflammatory bowel disease and psoriasis, and new biological therapies for allergic diseases. And the ultimate success of transplantation of a variety of organs now largely rests on the ability to control immunological rejection.

7. Organizational Models

The various discussion groups addressed the optimal future structure for the Immunology/Inflammation program at Harvard, weighing four potential organizational models:

a. Increased investment in existing units (no change in structure)
b. A new non-departmental entity, such as a Center or Institute
c. A new quad-based department at HMS
d. A new University department or "committee" (as defined by HUSEC)

It may be worth mentioning that an *ad hoc* committee charged with reviewing the state of Immunology at HMS also formally addressed this issue in 1997.

The broad consensus is (and was in 1997) that a combination of options "a" and "d" would best serve our needs: retain the Committee on Immunology in its current form, but enhance its effectiveness through two structural improvements and by the set of new programs recommended below. As concerns the Committee's structure: First, our impact in the Harvard community and our potential for continued growth and excellence need to be strengthened by attributing to the elected Chair of the Executive Committee for Immunology a formal appointment from the Dean of HMS, accompanied by a seat on any governing council of pre-clinical department chairs. Second, in order to optimize the composition of the Immunology/Inflammation faculty -- in particular to fill perceived "holes" in subject matter or demographics, and to foster complementarity over competitiveness – the ECI should have the means to exert an influence on new hires and advancements. This influence need not represent true appointment power. Rather, we envisage, under the direction of the ECI: providing leadership in identifying and conveying key areas for recruitment and, potentially, desirable and amenable recruits; furnishing complementary financial support for critical recruitments and promotions;

coordinating and supporting recruitment efforts at the different institutions; facilitating the transition of new recruits; and chaperoning promotions.

The options of a new Center or Institute ("b") or a new quad-based department ("c") did not elicit much support in these discussions because they do not adequately leverage the existing strength of the Committee on Immunology, poorly accommodate its institutional and geographic diversity, and have the potential of constraining its multi-disciplinary nature, encompassing strengths in both basic and clinical research, and stretching into many non-immunological research and clinical fields.

8. Recommendation

To address the opportunities and challenges discussed above, in addition to the structural ameliorations just rationalized, the discussion groups came up with the following list of recommendations. **(The parenthesized numbers refer to the particular challenge or opportunity each recommendation addresses).**

a. Support the existing activities of the Immunology Program. The following activities represent the core of our educational program, but are not adequately financed under our current structure. Indeed, this year we were forced to ask for contributions from the hospitals to keep some of these endeavors running. We suggest that, going forward, HMS fund, and in certain cases augment, the following foundation activities **(5a, 5c, 5d):**

- Administrative coordination and assistance
- The weekly Immunology/Inflammation seminar series (HMS's most highly attended)
- Our yearly retreat
- Our teaching efforts at all levels – undergraduate at HU, graduate and medical at HMS.
- The summer undergraduate program
- A larger graduate student body
- Our shared resources initiative

b. Institute an innovative set of seed grants. Especially at this time of painful funding constraints, seed grants offer a powerful means of both nudging research along desired axes and supporting the independent research efforts of the junior faculty. Recent experience (e.g. from the Broad Institute and the Harvard Stem Cell Institute) argues that seed grants may be one of the strongest "glues" we have at our disposal. The basic idea is to provide limited funding for 1-2 years to generate preliminary data in support of eventual R01 and P01 (or equivalent) applications. The discussion groups were particularly enthusiastic about the following types of seed grant:

- Junior faculty consortia – groups of 3-5 Assistant Professors will be funded to address a particular theme with closely integrated projects **(5b).**
- Basic/clinical investigator twinning – to support new projects in translational immunology **(5f).**
- Immunologist/non-Immunologist matching. The goal here is to "export" our expertise to the broader Harvard community, as well as to facilitate the use of the immune and hematopoietic systems as experimental systems to understand basic cellular processes. One stimulus, for example, is the increasing awareness that inflammation underlies pathological processes associated with a number of organ systems. (e.g. obesity and type-2 diabetes, neurodegenerative and psychiatric disorders, cardiovascular disease, etc). Another example is the comparatively advanced state of haematopoietic stem cell identification, isolation and transfer, which may offer valuable lessons in other stem-cell contexts. Finally, the wealth of information available on immune/haematopoietic cell differentiation could be used very profitably by other disciplines to extend our overall understanding of the transcriptional and epigenetic mechanisms in play during the specification of cell lineages **(6).**
- Solicited tools/resources. Examples would be a mouse line or monoclonal antibody critical to the research efforts of a number of members of the Committee on Immunology. Funding would be provided to an investigator with the requisite expertise to generate such a resource, which would be made immediately available to all HMS investigators **(5e).**

c. Development of Immunology/Inflammation-tailored technological platforms. Our intention is not to simply duplicate technologies available elsewhere at HMS. Rather, we have two complementary goals: to optimize the availability of resources of particular utility in Immunology research, and to leverage our community's expertise with certain resources to facilitate their use by the broader community of non-Immunologists. The best example is probably flow cytometry, the invention, amelioration and application of which have been primarily the purview of Immunologists. We are proposing that the Committee on Immunology be drivers of this technology at Harvard, assuring that it is broadly available and remains at the cutting edge. A central facility would house certain "high-end" equipment or activities, e.g. high-throughput cytofluorimetric analysis or large-particle sorters. In addition, a network of dispersed sites would be organized and financially supported, to capitalize on particular areas of expertise at the different institutions' or departments' flow cytometry cores, and to provide a mechanism for centralizing and collating knowledge and protocols. A liaison with the new Bioengineering initiative might prove very fruitful. Other technological platforms that lend themselves to this approach are monoclonal antibody production and certain aspects of imaging **(5e).**

d. Support for new consortia. The discussion groups expressed significant interest in facilitating two types of research consortia under the auspices of the Committee on Immunology. The first is akin to the existing Immune Circuits consortium on immunologically relevant shRNA screens, run in collaboration with the Broad Institute. While this has been a popular and quite successful endeavor, many investigators feel that it would be even more valuable were funds available for some basic technical and organizational support, which might also have permitted expansion to a wider range of projects. It is easy to envisage analogous consortia for small-molecule screens and high-throughput cellular imaging, for example **(5e).**

The second type of consortium that elicited substantial enthusiasm was Harvard-wide focus groups on confined topics in Immunology/Inflammation that are synergistic conglomerations of both Immunologists and non-Immunologists. Interest in such endeavors results from mounting awareness that perspectives, experimental approaches and tools emanating from the domains of Immunology and Inflammation are fundamental to the study of pathologies afflicting many – perhaps all – other organ systems. The vision is that a member (or members) of the Committee on Immunology would act to crystallize a focus group on a particular topic – say, for example, "Inflammatory Aspects of Atherosclerosis". The consortium's activities might include discussion groups, a retreat, pilot studies and/or data and resource exchanges. It is envisaged that the Committee on Immunology would facilitate such a consortium with administrative and some financial support **(6).**

Appendix 1

This draft report reflects discussions amongst the members of the Executive Committee for Immunology and additional senior and junior faculty members, namely Drs:

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