Immunology research: challenges and opportunities in a time of budgetary constraint

Charles J Hackett, Daniel Rotrosen, Hugh Auchincloss & Anthony S Fauci

There have been enormous advances in the field of immunology over the past 3 decades, and those advances have had a positive effect on many subspecialties of medicine. Opportunities for even more notable advances remain. However, present and projected budget constraints for the National Institutes of Health have created formidable challenges. This commentary addresses the opportunities and challenges for the field of immunology during a period of restricted budgets.

Many of the world's major diseases—infection, cancer, autoimmunity and allergy—critically involve the immune system. Continued progress in understanding basic immune mechanisms is essential for developing new abilities to treat and prevent diseases that affect millions worldwide. Although federal support for biomedical research has increased considerably over the past decade, funding has remained flat over the past 3 years, leading to a decrease in 'purchasing power' in the face of a biomedical research inflation of approximately 3%. Those budgetary constraints arrive at a time of progress and excitement in the field of immunology. This commentary addresses certain select opportunities for immunology research, along with the challenges of implementing a robust immunology research agenda in an era of fiscal constraint.

The role of the NIH

Substantial but by no means the only support for immunology research comes from the National Institutes of Health (NIH). Most of the 27 NIH institutes and centers fund research and training grants on immunology, attesting to the fundamental importance of immunology to every main disease area. In the NIH, the National Institute of Allergy and Infectious Diseases (NIAID) oversees the largest portion of research on basic immunology and immune responses related to infectious and immune-mediated diseases. Over the past decade, the NIH overall budget has grown considerably, increasing from $11.9 billion in fiscal year (FY) 1996 to $28.5 billion in FY 2005. In the same interval, the NIAID budget has grown at an even faster pace, making NIAID the second largest NIH institute, with an overall budget of $4.4 billion.

At present, the NIAID appropriation falls into three approximately equal categories aligned with the institute's main mission areas: human immunodeficiency virus (HIV) and AIDS; biodefense; and immunology and infectious diseases, a category that includes research on basic immunology, immune-mediated diseases, microbiology, and infectious diseases not in the HIV-AIDS or biodefense categories. Although most immunology research has traditionally been supported by the appropriation for immunology and infectious diseases, the discipline of immunology has also received support from HIV-AIDS and biodefense appropriations (**Fig. 1**). In FY 2005, the latest year for which final figures are available, the NIAID allocated more than $940 million to immunology research. Given the importance of the science of immunology to biodefense, HIV-AIDS and other infectious diseases, the investment by NIAID in immunology research has the potential to grow considerably.

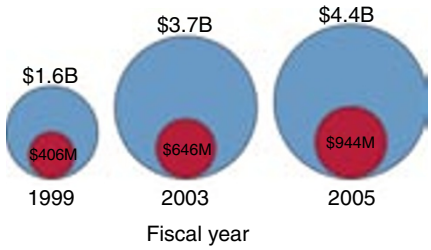

Figure 1 Spending on immunology has continued to grow considerably along with the overall budget of the NIAID. As the NIAID budget increased from $1.6 billion ($1.6B) in FY 1999 to $4.4B in FY 2005, the spending on immunology (red disc; M, million) also more than doubled.

Investigator-initiated research

Advances in fundamental immunology remind us that the most important breakthroughs in biomedical science generally have been achieved through the open-ended enquiry that is the hallmark of investigator-initiated research. Basic immunology research also provides the critical discoveries and mechanistic insights to underpin targeted programs that address a growing expectation on the part of the administration, Congress and the general

Charles J. Hackett, Daniel Rotrosen, Hugh Auchincloss and Anthony S. Fauci are with the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20892, USA.
e-mail: chackett@niaid.nih.gov

public for concrete health-related advances in the form of 'deliverables', or products that can be used to diagnose, prevent or treat disease. A more detailed breakdown of NIAID spending shows that growth in immunology research occurred in several funding categories, with the largest continuing to be investigator-initiated research, which includes grants such as the individual R01, the exploratory or developmental R21, small R03 and 1-year R56 bridge awards. Together these grants account for about 70% of all NIAID immunology research spending. Historically, solicited and unsolicited research programs typically have grown in line with the overall budgetary growth of the institute, with occasional deviations from that general trend to address the urgent needs of emerging research areas or the requirements for advanced development of medical countermeasures such as diagnostics, vaccines and therapeutics. For example, solicited research as a fraction of the NIAID immunology research portfolio grew from about 20% in FY 1999 to about 30% in FY 2005, due mainly to biodefense contracts.

Nonetheless, we remain steadfastly convinced that it is the ingenuity of individual scientists, expressed through investigator-initiated research, that will drive future discovery in immunology, as in most areas of biomedical science. That principle is broadly supported in the scientific community, as demonstrated by editorials and commentaries in the scientific press[1] and by the recommendations of many focus groups and expert panels convened by the NIAID (http://www.niaid.nih.gov/publications/). Such discussions, including our ongoing dialog with academic and industry scientists, professional societies and advocacy groups, emphasize the readiness of the scientific community to pursue the many emerging opportunities in immunology, a few examples of which are discussed below.

Select opportunities

The genetic control of immune responses demonstrates both complexity and flexibility. Of the 20,000–25,000 genes estimated to comprise the human genome[2], more than 4,000 are broadly associated with immune system function. Although there are many immune-related genes, they function with great efficiency. For example, frontline recognition of pathogens falls mainly to ten Toll-like receptors (TLRs) and several nucleotide-binding oligomerization domain proteins[3,4], whereas just two genetic loci, the immunoglobulin variable-diversity-joining-constant regions and the corresponding T cell receptor genes, rearrange to provide millions of distinct T cell and B cell specificities, enabling responses to almost any biological molecule[5]. Harnessing new knowledge about immune system function is leading to ever-increasing capabilities to prevent or treat immune-mediated and infectious diseases. However, even the considerable capacity of the immune system can be overwhelmed by organisms naturally adapted for virulence and immune evasion. For example, poxviruses, which include the smallpox agent *Variola major*, may devote as many as one half of their genes to virus-host interactions[6]. Understanding of the complexities of the scope of interactions between microbes and the immune system is just beginning.

Although innate immunity is the most ancient form of host defense, it is a key area of discovery in contemporary immunology. The first 'cluster of differentiation' molecule, CD1, was identified in 1979 (ref. 7); however, more than 15 years passed before its function as a lipid antigen-presenting molecule in both innate and adaptive immunity was established[8]. At present, the field of innate immunity is moving rapidly and is providing the molecular basis for addressing decades-old questions concerning host defense mechanisms. For example, although the function of type 1 interferon responses to viral infection has been appreciated since 1957 (ref. 9), understanding of the triggering of interferon synthesis was ill defined until studies showed it to be based, for many viruses, on cellular recognition of viral single-stranded or double-stranded RNA. The innate immune system casts a wide net for viral RNA, including the endosomal receptors TLR3 (which recognizes double-stranded RNA) and TLR7 and TLR8 (which recognize single-stranded RNA), as well as the cytosolic receptors RIG-I, specific for the uncapped 5′-triphosphate of viral RNA, and MDA-5, capable of recognizing the protein-associated RNA of picornaviruses[4,10–12]. Viral evasion of innate immune recognition and defense pathways can now be understood in greater depth, generating new questions related to viral pathogenesis as well as to host defense mechanisms. Studies of virus-host interactions are generating new findings that will enable the development of improved strategies for antiviral therapeutics and vaccines.

In addition, research on innate immunity has provided understanding and practical direction for the observation first made more than 70 years ago that most immunogens require adjuvants to induce robust adaptive immune responses[13,14]. With the knowledge that adjuvants target antigen-presenting cells, especially dendritic cells, by triggering activation through TLRs and other pattern-recognition receptors, molecular libraries are being screened for their ability to upregulate costimulatory molecules and antigen presentation mediated by major histocompatibility complex class II molecules. Based on those principles, a growing list of adjuvant candidates now promises to provide improved vaccine immunogenicity and reduced nonspecific reactivity while taking advantage of the ability of the innate immune system to channel adaptive immunity toward the type of antibody or cellular responses most appropriate for the control of a particular pathogen[15].

Immune tolerance holds the key to controlling unwanted immunological attacks on self and transplanted tissues. Alloreactive responses to transplanted tissues and organs have long been recognized as among the most powerful known in immunology, being at least 100-fold greater than those elicited by conventional antigens; such responses require potent, nonspecific immunosuppression to maintain organ allografts in clinical practice. In contrast, autoimmune diseases involve the loss of tolerance to self antigens. The identification of genes involved in the establishment and maintenance of central and peripheral tolerance provides a new level of understanding and, potentially, control of deleterious immune responses. For example, induction of central T cell tolerance is promoted by thymic expression of peripheral antigens related to the function of the gene encoding the transcription factor Aire[16]. In the peripheral tissues, active antigen-specific suppression mediated by a variety of T cells has been repeatedly and reliably observed over decades. The association of the gene encoding the transcription factor Foxp3 with immune disorders and the linking of that gene to regulatory T cells represent a substantial milestone, allowing new approaches to determine the origin and mode of action of a potentially important regulatory T cell population[17]. An emerging understanding of the genetic and cellular processes involved in central and peripheral tolerance should enable more robust and antigen-specific approaches to prevent organ transplant rejection and provide treatment strategies for autoimmunity.

Protecting mucosal tissues from infection and inflammation is one of the most important challenges to immunology research today. Vaccines against pathogens that enter or target the mucosa include those for poliomyelitis, influenza, rotavirus and genital papilloma virus, demonstrating the enormous benefits of protecting those complex tissues and using their potential as effective barriers against the entry of pathogenic microbes into the host. Among the mucosally spread diseases in urgent need of protective vaccines are HIV-AIDS and a potential pandemic influenza; however, many scientific hurdles still must be overcome in the

development of such vaccines. Immunity at mucosal surfaces must conform to a spectrum of demands, from maintaining strict sterility in the lungs and upper genital tract to achieving a dynamic coexistence with over 10^{14} bacteria in the intestines[18,19]. Because aberrant hyper-reactivity of the mucosal immune system to commensal organisms, foods or even pathogens can be lethal or very debilitating, the innate immune detection of microbes is highly adapted to the specific mucosal tissue. For example, recognition of bacterial lipopolysaccharide by TLR4 uses the coreceptors CD14 and MD-2 systemically but not in mucosal epithelial cells; such a restriction most likely prevents continuous triggering by minute amounts of lipopolysaccharide. Instead, data indicate that bacterial adhesion receptors may serve as obligate TLR4 coreceptors in the mucosa, triggering TLR activation only when there is a threat of colonization or invasion by pathogens[20]. Restriction of TLR expression to certain cells is an important strategy for protecting mucosal tissues. 'Preferential' expression of TLR5, specific for flagellin present in most motile bacteria, occurs on lamina propria cells of the mouse intestine, and those cells do not express TLR4 (ref. 21). An emerging paradigm in mucosal immunity is the requirement for bacterial stimulation to achieve normal immune system development. For example, intestinal immune homeostasis depends on TLR signaling; unexpectedly, in a study of intestinal colonization in mice, that requirement for microbial stimulation extended to normal T cell maturation by means of a bacterial sugar presented by major histocompatibility complex class II (refs. 22,23). Those and other studies present unexpected yet credible explanations regarding the requirements for the development of a competent mucosal immune system. Continued progress on a fundamental level should enable the rational development of distinct but conceptually linked capabilities, such as safe and effective mucosal adjuvants and immunotherapeutics for a wide range of mucosal diseases, including asthma and autoimmune diseases of the digestive tract.

Antibodies provide much of the protection afforded by the vaccines in the present arsenal; however, only recently has an in-depth understanding emerged of the molecular basis of B cell development, selection and effector function that may allow more strategic manipulation of the B cell compartment. Strides made over the past 5–10 years that may allow new strategies for B cell vaccination include an understanding of B cell receptor antigen recognition, receptor editing and growth factors involved in the chief transitions in B cell maturation before, during and after antigen selection. For example, the tumor necrosis factor–related cytokines BLyS (also called BAFF) and APRIL target three receptors on B cells: BR3, which responds to BLyS to support primary B cell survival and growth; BCMA, which promotes memory B cell development in response to APRIL; and TACI, which is important in B cell responses to bacterial capsular polysaccharides[24]. Additional developmental signals may also derive from the stimulation of innate immune receptors on human B cells[25]. Those findings raise the possibility that coadministration of critical cytokines or their triggers along with vaccine immunogens may constitute a new vaccine strategy to expand the capabilities of responding B cells beyond those now appreciated. The prospects for a new approach to B cell manipulation seem to be near; however, studies are needed to address whether new approaches might also bring new problems, such as induction of autoimmunity.

Research on HIV-AIDS, emerging infectious diseases, including influenza, and biodefense is a public health priority with substantial funding support by the US federal government. Notably, basic immunology research is central to future progress in those areas, including the development of effective therapeutics, diagnostics and vaccines. For example, at present the ability to induce broadly protective immune responses to HIV or to elicit heterotypic immunity to the ever-evolving influenza virus is lacking. Similarly, protective strategies cannot yet be defined that would thwart many potential agents of bioterrorism, especially those that could be genetically engineered to lack immunodominant epitopes or to incorporate immune-evasion molecules. Many immunologists have proposed research projects addressing the challenging questions posed in those priority areas, but even more could be done. We fully anticipate that such projects that are directed in part toward specific pathogens will advance fundamental knowledge on immune mechanisms that are considerably more 'generic' and broadly applicable.

During the period of doubling of the NIH budget from FY 1998 to FY 2003, the NIAID expanded its capacity for 'translational' and clinical research that included research on immune-mediated diseases. For example, the Non-Human Primate Tolerance Cooperative Research Study Group and several clinical research networks now support preclinical studies and clinical trials in asthma, allergic and autoimmune diseases and transplantation. Many of those programs benefit from the support and expertise of multiple NIH institutes, and are funded in part through special government appropriations of funds (http://www.niddk.nih.gov/fund/diabetesspecialfunds/about.htm) as well as by a variety of public-private partnerships. Each of those programs involves cross-disciplinary efforts, with a focus on the underlying basis of disease and mechanisms of therapeutic efficacy. They provide a framework for 'bench-to-bedside' and 'bedside-back-to-bench' research that is yielding new therapeutic and preventive approaches and fresh insights into basic processes. Although the challenges are considerable, scientific opportunities abound, including the potential for breakthroughs that could dramatically alter existing treatment paradigms. In this framework, it is important that NIAID resources continue to focus on underserved populations, such as inner-city children with asthma, and on new approaches that lack industry support or on partnerships with industry in which the commitment of NIH resources allows academic investigators to pose questions unlikely to be addressed by industry without NIH involvement.

The way forward

Although the generous support and resulting achievements of biomedical research in recent years argue convincingly for continued robust support, the sobering reality is that the NIH budget has been essentially flat for the past 3 years with little immediate prospect for improvement. Concomitantly, annual increases in the requested costs of R01 applications are anticipated (the long-term historical average has been about 5% annually), as is continued growth in the number of grant applications submitted to the NIAID. Adding to concerns in the scientific community is the fact that many US scientists have been fortunate to have worked most or all of their careers relatively unfettered by the fiscal constraints of previous eras. In the early 1980s, NIH inflation-adjusted spending power also decreased, but modest growth in the dollars appropriated to NIH bolstered morale (http://officeofbudget.od.nih.gov/UI/GDP_fromGenBudget.htm). Today, US researchers are well aware that national priorities, economic policies and demographic trends seem poised to stress federal discretionary spending programs, including those of the NIH, for an extended period[26,27]. An unintended and damaging consequence of that budget flattening is that new investigators have fewer opportunities to enter the research arena with independent funding and those who do may lack the resources to 'ride out' times of fiscal stress.

As enormous scientific opportunities still remain despite the fiscal constraints, it is important to map a way forward to optimally use the resources that are available until the period of

fiscal constraint is relieved. An important and difficult challenge will be to preserve as fully as possible a robust commitment to the fundamental, investigator-initiated research that lays the bedrock of the research enterprise while meeting expectations for more applied research, including the advanced development of vaccines, therapeutics and diagnostics. In FY 2005, the NIAID awarded 2,977 noncompetitive grant renewals and 1,164 competing research project grants. However, maintaining our commitment to investigator-initiated research will require the continuation of cost-cutting measures imposed in recent years and the adoption of some unfamiliar measures. Investigators should anticipate a continuation of the restriction on yearly inflationary increases on research project grants imposed by the NIH in FY 2006 and of the longstanding NIAID cap on budgetary increases for competing awards. Very likely, we may need to reduce the average dollar amount of new awards, as was done in the 1990s when the NIAID imposed across-the-board single- to double-digit cuts. Despite those and similar measures, many of the funding 'paylines' (the funding cutoff based on percentile ranking from peer review) of NIH institutes, including those of the NIAID, will decrease under the proposed NIH budget in FY 2007, and success rates (the proportion of grant applications that receive funding) throughout the NIH will drop from about 22% in FY 2005 to about 18–19% in FY 2006 and perhaps lower in FY 2007 to FY 2009.

Beyond those steps, additional measures may be needed. In FY 2006 (and in NIAID planning for FY 2007 through FY 2008), funding for solicited research programs has been reduced to sustain the NIAID 'payline' for investigator-initiated research. Some planned initiatives have been eliminated or postponed; others will proceed, but at lower funding levels. The NIAID and most other NIH institutes plan to fund first R01 grants of individual applicants at a more lenient 'payline' to provide new investigators a competitive edge as they enter the grant arena. Having taken those steps, our challenge will be to achieve our objectives in clinical research and critical product development, endeavors that rely heavily on solicited research programs.

A decade ago, the NIH was facing the prospect of an equally sobering budget. To ensure the best use of the available resources, the NIAID undertook a top-to-bottom review of its entire research portfolio. It was enlightening to find that there were many areas in which research might be carried out more efficiently, and it is likely that the same holds true today. Where possible, the NIAID is facilitating more collaboration among NIH institutes and other research sponsors, including industry, academic institutions and philanthropic organizations. Although a degree of redundancy and replication is beneficial to most scientific inquiry, unnecessary duplication must be recognized and eliminated. Throughout our clinical trial networks, the NIAID is striving to improve the standardization of assays, reagents and endpoints and to establish partnerships that will capitalize on economies of scale. Also, every effort must be made to streamline those aspects of clinical research that are especially time consuming and costly; for example, more can be done to accelerate protocol development and to evaluate the feasibility and reliability of projections for subject accrual and retention. When studies fall short of those targets, action must take place promptly to identify and address impediments. Those principles are already in place, but more can be done to implement them in practice. Addressing those and other issues make programmatic and fiscal sense, and doing so will be in keeping with an evolving paradigm for stewardship of NIH-sponsored research. In this context, the NIH director has established the Office of Portfolio Analysis and Strategic Initiatives to provide 'trans-NIH' programmatic and budgetary authorities. That office will be charged with the responsibility of developing and promoting cross-cutting strategic initiatives and of evaluating their achievements and the rationale for their continued support. Given the importance of immunology to nearly all biomedical disciplines and the range of immune-mediated diseases under the purview of many NIH institutes, we foresee many opportunities for the NIAID and the immunology research community to have critical involvement in those activities.

History has shown that support for biomedical research on the part of the US federal government has repeatedly rebounded from periodic times of fiscal constraint. Facing similarly sobering prospects for budgetary constraints on the NIH 10 years ago, one of us (A.S.F.) wrote that "…resources for biomedical research in general are unlikely to increase substantially in the foreseeable future, and in some areas will be constrained. Yet the opportunities for advances in knowledge and the practical application of these advances will surely increase. Hence, the dichotomy between aspirations and resources will probably widen."[28] Although there are no assurances as to when the rebound will occur, we are optimistic about the long-term prospects and the certainty that the discipline of immunology will remain essential to the research agendas of many NIH institutes and will continue to thrive.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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