Submission by The American Association of Immunologists (AAI) to the National Institute of Allergy and Infectious Diseases (NIAID) Request for Information (RFI): Inviting Comments and Suggestions on NIAID’s Strategic Plan

May 24, 2024

Introduction

The American Association of Immunologists (AAI) is one of the world’s largest organizations of immunologists and scientists in related disciplines. Our mission is to improve global health and well-being by advancing immunology and elevating public understanding about the immune system. AAI members, many of whom are funded by the National Institutes of Health (NIH), are responsible for some of the most significant biomedical discoveries of the past century. Members represent different sectors (academia, government, industry, non-profit) and conduct research that contributes to development of life-saving cancer immunotherapies, monoclonal antibodies, transplant technologies, biomarkers in autoimmune diseases, vaccines, and more. AAI supports scientists across the field of immunology through knowledge dissemination, community building, advocacy, and public outreach.

Many AAI members rely on funding from the National Institute of Allergy and Infectious Diseases (NIAID) for both research and/or training and, therefore, are keenly interested in the strategic direction of NIAID. AAI appreciates the opportunity to submit comments in response to NOT-AI-24-032 (Request for Information, RFI: Inviting Comments and Suggestions on NIAID’s Strategic Plan) and commends NIAID for clearly outlining ongoing and future research priorities. Below, AAI provides general feedback and specific comments on each research priority.

General feedback:

Several NIAID research priorities focus on the application of knowledge to develop and test prevention, diagnostic, and treatment strategies for infectious and immune-mediated diseases. AAI shares an interest in advancing applied research in each of these areas. AAI would like to emphasize, however, the absolute necessity and importance of continuing to fund a robust portfolio of foundational and discovery-based research. As the primary defense against extrinsic and intrinsic threats to the human body, the immune system intersects with every organ system and plays a role in nearly all diseases. Therefore, supporting collaborative research on fundamental immunological processes is essential to ensuring steady and transformative progress in foundational, translational, and clinical immunology. Similarly, promoting collaborations not only across the NIH Institutes and Centers (ICs) but also across U.S. scientific funding agencies is crucial to furthering our understanding of the role of the immune system in health and disease more broadly. In addition, AAI encourages NIAID to support innovative and bold research ideas that promote discoveries that could be the basis for future novel therapies and potential cures.

While not stated as a research priority, NIAID should play a role in advancing research on how the immune system responds to cancer, including cancers with infectious etiologies, and applying this knowledge to developing preventative measures, diagnostic tools, and treatments for cancer. This is especially important given the global incidence of cancer is projected to increase 77% by 2050 and occurrence of “early-onset” cancers (e.g., colorectal cancer) continues to increase. Studying the role of the immune system in eliminating tumors could offer valuable insight for other conditions, such as rare...
diseases involving the immune system. Furthermore, there has been recent application of immunotherapy strategies (most commonly used to combat cancer) to autoimmune diseases with some early and exciting success. This further highlights the cross-disciplinary nature of the study of the immune system and the importance of effective collaboration among NIH ICs.

AAI appreciates that NIAID includes “workforce training” as a topic of interest. AAI recommends that NIAID more strongly emphasize the importance of biomedical research workforce development in its strategic plan. Advancing foundational, translational, and clinical immunological research requires a robust workforce, including trainees and postdoctoral scholars, within all sectors (including academia, government, industry, and non-profit organizations). Attracting and retaining early-career talent is vital to maintaining a strong pipeline. Strengthening NIAID’s training portfolio, in particular by increasing support for F and K awards and diversity supplements, may help achieve this. AAI is pleased that fiscal year (FY) 2024 paylines for F31 and F32 training grants are the highest they have been in years, reflecting NIAID’s commitment to fostering the next generation of biomedical researchers. However, NIAID T32 paylines remain stagnant. Because of the level of administrative burden and complexity of trainee grant applications, AAI encourages NIAID to thoughtfully assess its portfolio to ensure it is optimizing support for trainees and not overburdening PIs who are already facing steep challenges due to the current funding environment.

AAI urges NIAID to substantially invest in supporting postdoctoral scholars on their path to independence. In 2023, NIAID had the lowest success rate of all NIH ICs for K99/R00 awards at just 13.4%. As these awards serve as an important bridge for postdoctoral researchers who strive to successfully obtain independent positions, AAI appreciates that NIAID recently increased support for the salary, research, and length of award for the K99/R00, but would like to emphasize the importance of increasing the success rate of these awards to retaining talent in academia.

Given the emphasis placed on the application of knowledge to disease interventions and translational immunology in NIAID’s research priorities, AAI urges NIAID to consider the differences in key questions and experimental design between foundational and translational research and to encourage training to reflect these differences and distinct needs.

Specific comments:

Priority 1: Advance foundational research on the immune system, host-pathogen interactions, and pathogen biology.

AAI particularly appreciates the emphasis on expanding foundational knowledge of immunology. Strategies for funding foundational research should be developed bearing in mind the transdisciplinary nature of the immune system and how it is involved in many aspects of human biology, in both homeostatic and disease states. To this end, AAI strongly encourages collaboration between NIAID and other NIH ICs that study diseases and conditions with immune-related components.

NIAID supports foundational immunological research in large part through the R01 funding mechanism. AAI notes that the NIAID R01 payline for established investigators has either been flat or decreased every year since 2019, even as the NIH budget steadily increased (until the recently enacted FY 2024 appropriations law, which cut the NIH budget and provides flat funding for NIAID). AAI suggests that NIAID consider a broad evaluation of its research portfolio to determine whether there are opportunities to scale back some of the larger NIAID programs to allow additional funding for investigator-initiated foundational research.
Consistent with NIH Director Monica Bertagnolli’s acceptance of the Advisory Committee to the NIH Director (ACD) recommendations to catalyze the development and use of novel alternative methods (NAMs), this NIAID research priority includes development of non-animal alternative models. The use of innovative technologies like microphysiological systems (MPS) can increase the ability to study primary human tissue in physiologically relevant contexts, which would be especially beneficial when studying complex immune tissues and/or tissue-specific immunity. Such alternative methods hold great promise for complementing the use of animal models. Still, scientific progress often requires the study of whole-body processes. Until NAMs have advanced to the point of successful utilization for all relevant research areas, AAI urges NIAID to support the responsible use of animals in research and enhance the development of more predictive animal models to advance knowledge within its mission space.

**Priority 2: Apply foundational knowledge of the complex interactions between microbes and the immune system to develop and test medical countermeasures against known infectious diseases (non-HIV/AIDS).**

Antimicrobial resistance (AMR) is an enormous threat to human health globally. The importance of understanding and combatting AMR, as well as developing countermeasures like new antibiotics and novel therapeutics (including immunotherapies) cannot be overstated. AAI is pleased to see this as a priority of NIAID. Understanding what contributes to AMR, for example antibiotic use in food animals and climate change, will help combat current and future mechanisms of antimicrobial resistance.

While research priority 1 includes expanding knowledge of tissue-specific immunity, AAI wishes to highlight the importance of studying the microbiota and its relationship with the immune system at steady state and during disease and is uncertain whether NIAID intends this to be a focus of priority 2, given the use of the word “microbe” rather than “pathogen.” AAI urges clearer and consistent messaging of research priorities.

**Priority 3: Apply knowledge of HIV/AIDS to reduce HIV incidence through the development of safe and effective prevention, treatment, and cure strategies.**

AAI commends NIAID for the enormous progress made in the prevention and treatment of HIV/AIDS and recognizes that there is more to be done. As the only research priority dedicated to a single disease, it is clear that NIAID intends to continue allocating significant resources to HIV/AIDS research. While HIV/AIDS is still a major health concern in the U.S., and even more so globally, long-term investment in research has led to effective prevention and treatment options. Given this excellent progress against HIV/AIDS, AAI urges NIAID to expand the scope of research to more substantially encompass comorbidities associated with the disease, including coinfection, autoimmunity, and cancer, as well as other relevant research like immune system development and thymus biology. Directing additional resources to understanding the fundamental biology of the immune system and other diseases and conditions that affect those living with HIV/AIDS will lead to treatments and cures not only for those with HIV/AIDS but for many other patient populations.

In addition, AAI urges NIAID to continue addressing disparities in HIV/AIDS research. Socioeconomic, cultural, and structural factors lead to the disproportionate rate of disease in certain communities, in particular men who have sex with men, racial and ethnic minorities, transgender individuals, and those who live in low resource settings. These factors include lack of access to education, healthcare, and prevention services. Research funding and priorities, as well as clinical trial design, sample collection, and data analysis, should align with the needs of these communities and aim to address these gaps.

**Priority 4: Apply knowledge of basic immunology to develop and enhance intervention strategies for asthma, allergic and immune-mediated diseases, and transplantation.**
While AAI appreciates that the category of “immune-mediated diseases” covers a broad range of conditions, AAI recommends that NIAID specifically mention autoimmunity/autoimmune diseases and chronic inflammatory diseases in its stated research priorities, especially given the fact that autoimmune diseases are the fifth leading cause of death in women younger than 65. In addition, AAI suggests adding “inborn errors of immunity” to this priority. NIAID may also consider prioritizing research aimed at understanding the common underlying mechanisms of autoimmunity and chronic inflammatory diseases and applying that knowledge to prevention and treatment. For all listed conditions in priority 4, AAI believes NIAID should include advancing the foundational knowledge of disease, rather than just the application of knowledge to develop and enhance intervention strategies.

In addition, AAI encourages NIH to increase research on alterations in the immune response in individuals with Down syndrome, including interferonopathies, autoimmune diseases, increased susceptibility to infections, and impaired responses to some vaccines, among other challenges. Further understanding the immune disease spectrum in Down syndrome is of the utmost importance to advancing the well-being of this vulnerable population and can also provide invaluable insight for other populations. To that end, AAI also encourages appropriate inclusivity in research and clinical trial design.

AAI supports NIAID’s emphasis on applying cutting-edge technologies and engineering approaches like cell-based therapies for cancer to diseases affecting or affected by the immune system, including asthma and allergy. As an example, a recent NIAID-sponsored phase III clinical trial showed that treatment with a monoclonal antibody reduces severe food allergy reactions and led to U.S. Food and Drug Administration approval for use in adults and children over one year old. Innovation in prevention and treatment is vital to enhancing the lives of those suffering from asthma, allergy, autoimmunity, and other immune-mediated diseases.

Priority 5: Support innovative research efforts to prepare for and respond to nationally or internationally significant biological incidents affecting public health.

Preparing for acute biological threats, including viral pandemics, emerging infectious diseases, and bioterrorism, is crucial. In addition to the research areas outlined in priority 5, AAI suggests that NIAID consider emphasizing development of innovative platforms that can be adapted and used for future unknown threats, including the use of artificial intelligence and machine learning strategies, for example to identify novel drug and vaccine targets. AAI supports the ongoing effort by NIAID to identify “prototype pathogens” that are most likely to cause the next pandemic and proactively develop vaccines, therapeutics, and monoclonal antibodies for use against such threats.

Investment in COVID-19 research should also remain a priority for NIAID even as emergency funding provided by Congress is no longer available. In particular, NIAID should further invest in better understanding and treating long COVID and in developing transmission-blocking vaccines, including mucosal vaccines, and other prophylactics. As of March 2024, four years after the onset of the COVID-19 pandemic, 17 million people in the U.S. report that they are suffering from long COVID, exemplifying the significant gaps in knowledge related to post-acute infection syndromes. AAI urges NIAID to devote the necessary resources to foundational knowledge of post-acute infection syndromes, including gaining a better understanding of the underlying mechanisms of long COVID, identifying who is most susceptible, and developing effective prevention and treatment options.

Furthermore, there are other “biological incidents” currently affecting public health with relevance to the immune system that NIAID may consider including under this priority. Examples include the worsening obesity epidemic having wide ranging effects on the microbiome and immune system; climate change

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affecting immune cells and patterns of vector-borne infectious diseases; and sustained pollution playing a significant role in exacerbation of allergy and asthma.

2 Ledford, H. 2024. Why are so many young people getting cancer? What the data say. Nature. https://doi.org/10.1038/d41586-024-00720-6
4 https://www.niaid.nih.gov/grants-contracts/niad-paylines