



American Society of Hematology Recommendations for the NIDDK's Strategic Plan

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is embarking on an Institute-wide [strategic planning process](#) aimed at developing a broad vision for accelerating research into the causes, prevention, and treatment of diseases and conditions within its mission. Below are ASH's recommendations in response to the NIDDK's request for input on this initiative.

I. Advancing understanding of biological pathways and environmental contributors to health and disease.

Understanding the fundamental molecular mechanisms impacting the onset and progression of hematologic diseases is vital for the identification of therapeutic targets and development of curative treatment. To ensure that such research questions are answered, NIDDK should prioritize the following topics in its strategic vision:

- **The use of “omics” in understanding health and disease** – Enhancing our grasp of several omics (i.e. genomics, epigenomics, transcriptomics, proteomics and metabolomics etc.) could further improve our knowledge of these pathways. This can be achieved by leveraging technologies such as next generation sequencing and single cell sequencing which could help shed light into why certain germline alleles have been linked to a subset of heritable hematologic diseases, elucidate the role somatic mutations may play in causing certain hematologic complications, and enhance the efficiency of mutation correction approaches like gene editing. In the case of sickle cell disease (SCD) and venous thromboembolism, for example, leveraging such genotyping tools could vastly enhance the identification of biomarkers predictive of disease risk, future complications, and response to different therapeutic modalities. Furthermore, omics research on sickle cell trait has the potential of addressing unanswered questions related to morbidity and mortality of this condition particularly as it relates to kidney outcomes. ASH has highlighted [unanswered questions and research](#) for sickle cell trait.
- **Epigenetic research in hematologic diseases** – Understanding epigenetic mechanisms can provide insight into the development and regulation of the normal hematopoietic system, since alterations to these mechanisms can contribute to hematologic diseases. Support for research focused on investigating the epigenetic control of genes involved in hematologic diseases like myelodysplastic syndrome, thalassemia, and SCD could further inform precision medicine and provide a plethora of new druggable targets.
- **The interplay between immunology, immunotherapies and non-malignant hematologic diseases** – Given the successful use of bispecific antibodies for the treatment of hemophilia¹ and the use of immune cells as a therapeutic option for the regulation of inflammation in diseases such as graft-versus-host-disease,² it is essential that studies aimed at enhancing our understanding of immunology as it correlates with disease onset and therapeutic modalities be supported. This research will improve our knowledge of the immune system, but more importantly, provide new perspectives on how to manipulate this system to develop and enhance existing immunotherapies geared towards non-malignant hematologic diseases.

- **Characterizing hematopoietic stem cell biology** – Basic hematopoietic stem cell (HSC) biology is another area of hematology that is not fully understood but plays a pivotal role in research and treatment of diseases. For example, strategies to improve the use of gene corrected HSCs to enhance the treatment of diseases such as SCD and congenital immunodeficiencies have not achieved widespread clinical translation. Efficiently characterizing the development and differentiation of HSCs could advance our knowledge of hematopoietic function, including how immune cells respond.
- **Identifying factors impacting maternal mortality during pregnancy** – Iron regulation during pregnancy is critical for maternal and fetal development with iron deficiency specifically being linked to increased risk of maternal mortality.³ Despite the risks associated with iron deficiency, mechanisms involved in iron homeostasis during pregnancy are not fully understood. Furthermore, treatment strategies for vascular dysfunction (e.g., placental dysfunction, and preeclampsia – leading contributors to maternal and fetal mortality⁴) have been limited due to lack of biomarkers identifying at-risk pregnancies. By supporting research aimed at understanding iron regulation, and the development of novel biomarkers especially as it correlates with racial disparities, NIDDK will be helping enhance researcher’s knowledge of iron deficiency anemia and development of possible therapeutic targets.
- **Assessing the correlation between infectious diseases and hematologic disorders** – In light of the COVID-19 pandemic, it is essential that research exploring the interplay between viral infections, immune function, and hematopoiesis be supported since such research could inform our understanding of how hematologic diseases impact COVID-19 pathophysiology/severity and vice versa. ASH commends the NIDDK for the recently released [funding opportunity](#) on this issue and encourages the institute to also prioritize research focused on the long-term implications of this infection.

As COVID-19 transitions to an endemic disease and the long-term impact of infection is better understood, it is essential to investigate how long-term hematologic complications and underlying hematologic dysfunction are altered as a result of infection. Furthermore, assessing the underlying biology of COVID-19 in the context of race in hematology patient populations could detect indicators that provide clarity on which subset of patients are likely to exhibit higher infection rates or worse outcomes.

II. Advancing progress in pivotal clinical studies and trials for prevention, treatment, and cures in diverse populations.

Innovative clinical trial design that includes the enrollment of a diverse patient population and facilitates efficient data sharing is critical for expediting new therapies for the treatment of hematologic diseases. To advance progress in this arena in the field of hematology, the NIDDK should:

- **Prioritize clinical trials that evaluate the effectiveness of existing antithrombotic agents in preventing venous thromboembolism (VTE) in high risk populations** – Anticoagulants such as oral anti-factor Xa and antithrombin

agents have been shown to have similar antithrombotic effects as other VTE therapeutics like warfarin or low-molecular-weight heparin. However, new trials are needed to determine if these agents are safe and effective for preventing initial onset and recurrence in populations such as children or patients with anti-phospholipid antibody syndrome or hereditary thrombophilias. While ASH acknowledges that VTE research might be a new area of focus for NIDDK, the Society believes that trials focused on exploring the safety and efficacy of these new anticoagulants or determining the most optimal therapy to be applied to high risk patient populations could inform evidence-based guidelines and, in turn, clinical practice.

- **Creating a clinical trial infrastructure to expeditiously, yet safely, advance therapeutic development and understanding of novel applications** – It is essential that an adequate clinical trial infrastructure is created to ensure that trials run and sponsored by large national organizations are open for accrual in areas in which diverse populations (racial, ethnic) reside. In addition, for novel applications like gene editing, as more is learned about the preclinical efficacy of this technology, it is critical that aspects such as toxicity testing, vector production, development and monitoring of gene editing clinical trials be supported in order to maximize the efficacy of this approach.
- **Collaborating with stakeholders who are actively pursuing clinical trial initiatives to advance the development of treatments for orphan hematologic diseases like sickle cell disease (SCD)** – Given the challenges involved in conducting clinical trials for SCD (e.g., shortage of primary investigators and trial sites, inadequate enrollment of participants, flawed study design, lack of a centralized data repository, etc.), ASH's Research Collaborative has created a [Clinical Trials Network](#) aimed at expediting the development of treatments for SCD. NIDDK could explore collaborating with ASH on this initiative to further advance the implementation of effective SCD trials.

III. Promoting participant engagement - including patients and other participants as true partners in research.

- **Create more opportunities for communities in rural areas (or areas without a large medical center) to have exposure and access to on-going clinical trials** – NIDDK should explore novel ways to engage patients in clinical trials, especially those who historically have had limited access to care. Novel approaches to informed consent acquisition and expanding trial sites without incurring protocol deviations should be implemented in future studies. Having a broad and diverse population in clinical trials will improve patient outcomes overall.
- **Develop a network of patient community members who can provide their views on future directions for research relevant to their disease** – Having a network of SCD community members from around the country that are willing to weigh-in on future directions for SCD research, cell-based therapy development, and implementation of guidelines can help inform requests for applications that NIDDK

may put out for this disease area. ASH is continuing to build such a community and welcomes the opportunity to work with NIDDK to advance this critical initiative.

IV. Advancing research training and career development to promote a talented, diverse biomedical research workforce.

ASH commends the NIDDK for establishing a “K-award” portfolio that continues to create a productive biomedical research workforce. Given that training the next generation of biomedical researchers and physicians in hematology is a top priority for ASH (evidenced through various [ASH awards](#)), the Society recommends that NIDDK continue to make this an important priority while also taking into consideration the following areas as it develops its strategic plan:

- **Develop programs that offer adequate mentorship support for investigators and physicians wishing to pursue a career in hematology.**
- **Provide training programs (with a mentorship component) for PhD students and post-doctoral fellows wishing to pursue hematology research.**
- **Include interventions that reduce the risk of bias in the grant review process.**

V. Promoting innovation, rigor and reproducibility in research, partnerships, communicating research results, and other critical efforts as part of efficient and effective stewardship of public resources.

ASH recommends that the NIDDK prioritize the following issues to help promote innovation and partnerships:

- **Ensure that NIDDK’s grant review committees continue to feature a diverse population of experts.**
- **Create incentives to enhance collaborative research.**

Sincerely,



Stephanie J. Lee, MD, MPH
President

References:

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4. Laurent L. Extracellular Vesicle microRNA: A Biomarker for Vascular Dysfunction in Pregnancy? (Annual Meeting abstract). *Blood* 2018; 132 (Supplement 1): SCI-27.