



**2016**

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RE: Request for Information: The Need for and Support of Research Resources for the Biomedical Research Community (NOT-GM-16-103)

Submitted electronically to: [nigmsresource@mail.nih.gov](mailto:nigmsresource@mail.nih.gov)

Dear Dr. Sheeley,

The American Society of Hematology (ASH) appreciates the opportunity to respond to the Request for Information (RFI) on the Need for and Support of Research Resources for the Biomedical Research Community (NOT-GM-16-103), issued April 4, 2016 by the National Institute of General Medical Sciences (NIGMS).

ASH represents over 16,000 clinicians and scientists worldwide, who are committed to the study of blood and blood-related diseases. These disorders encompass malignant hematologic disorders, such as leukemia, lymphoma, and multiple myeloma, as well as non-malignant conditions, such as sickle cell anemia, thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. ASH membership is comprised of basic, translational, and clinical scientists, as well as physicians, who are working in diverse settings, including universities, hospitals, and private practices. In the last few decades, hematologists have pioneered the use of gene therapy, recombinant protein expression, immunotherapy, and genome sequencing, and have applied these techniques to define novel treatments that have had a dramatic impact on patient survival.

Hematologists are at the forefront of biomedical discovery, and they have pioneered treatments like kinase inhibitors that have also proven to be beneficial for many patients who have other types of diseases. ASH commends the NIGMS for its interest in supporting development of technology, and for identifying areas of unmet need, as well as providing research resources that will benefit the biomedical community. ASH believes that development of technology with access to research resources is crucial for the safe and effective translation and use of evolving novel technologies in a clinical setting.

Technologies based on programmable nucleases, such as CRISPR/Cas9 and TALEN, as well as related emerging systems are currently the most widely used genome editing approaches. These forms of technology have shown great promise in proof-of-principle preclinical studies, and have attracted great interest as potential therapeutic approaches, particularly for the correction of inherited monogenic hematologic diseases, such as hemophilia, beta-thalassemia, chronic granulomatous disease, and sickle cell disease. While genome-editing technology represents a highly promising area for future therapies for treating hematologic disorders, the following critical aspects must be addressed in order to realize the full potential of genome editing and its effective translation into clinical use:

- Understanding the biology of genome editing and determining the different types of disorders that are amenable to genome editing correction;
- Optimizing the accuracy, safety, and efficiency of targeting vectors to minimize undesired off-target mutations and chromosomal rearrangements;
- Identifying strategies to reduce any toxicities of gene modification;
- Optimizing protocols for *ex vivo* propagation, and pairing such protocols with rigorous methods to monitor genetic alterations in modified and expanded cells to determine the functional/safety consequences of these alterations; and
- Developing a repository of high-throughput data generated by this technology.

The establishment of a funding mechanism to address the aforementioned challenges will undoubtedly help to foster gene correction strategies in monogenic inherited hematologic disorders. ASH believes that the advancement of this technology will build the foundation for translation of genome editing to treat a wide range of blood disorders and autoimmune conditions.

Advances in the field of epigenetics, and the understanding of various epigenetic mechanisms has provided a new ensemble of therapeutic targets for treating malignant and non-malignant hematologic disorders. Since coding DNA sequences only accounts for part of the complex regulation of gene function, epigenetic profiling of normal and malignant cells is critical for the identification of potential predictive epigenetic targets that could be identified by various forms of precision cancer immunotherapy. Potential epigenetic targets include proteins that control histone methylation and acetylation, as well as proteins that read histone marks and that orchestrate changes in gene expression which is associated with malignancy, and DNA methyltransferases. These approaches are already showing promise in treating a number of malignant and non-malignant hematologic disorders. However, the full potential of epigenetic targets and therapies relies on the development and application of technologies that decipher protein function at the whole genome level, and this requires sophisticated analytical approaches to contend with exceptionally large datasets. Fostering additional research in this area, and ensuring that new investigators in the hematology community gain highly advanced computational and biostatistical expertise will be crucial in laying the groundwork for precision medicine approaches. It will also provide insight into potentially critical determinants of responsiveness to therapeutic regimens for treating hematologic and other diseases.

In various blood disorders, including hematologic malignancies, there are both inherited and somatic genetic alterations that contribute to predisposition, transformation, disease progression, responsiveness to therapy, and treatment complications. The presence of such genetic alterations underscores the need for the identification of natural sequence variation, and the integration of this information into clinical trials. Developing proper infrastructure, harmonizing genetic result reporting, and ensuring that adequate resources are available (*e.g.*, procurement of suitable tumor/non-tumor material for sequencing), as well as additional pharmacodynamic and correlative biology studies in

hematologic diseases will foster the appropriate application of sequencing technology, both in the clinical and drug development setting.

The reprogramming of adult stem cells has resulted in the generation of induced pluripotent stem cells (iPSCs) that can develop in any tissue throughout the body. These iPSCs ultimately may be used to treat a variety of hematologic and other diseases. The iPSC technology has also enabled the generation of patient-specific or disease-specific stem cells that can serve as targets for both drug development and drug screening in patients with rare hematologic disorders. Looking forward, the major scientific hurdle has been the limited ability to create clinically meaningful functional blood products, including transplantable hematopoietic stem cells from differentiating iPSCs. Ultimately, the production of clinically functional blood products, *i.e.*, red blood cells derived from autologous iPSCs could replace allogeneic products in highly immunized patients, and the generation of megakaryocytes for patient-specific platelet production from iPSCs could drive significant progress in this area. In addition, while iPSC technology shows great promise, safety issues, such as insertional mutagenesis and tumor formation, represent a major concern in the development of iPSC-derived regenerative therapies. In order to overcome these safety concerns, resources are needed to further long-term preclinical *in vivo* studies before the clinical application of this technology.

As the body of evidence continues to grow on the potential applications for hematopoietic transplantation and other forms of immunotherapy, next-generation research must focus on addressing the possible curative effects that adoptive cellular immunotherapies can have for treating blood diseases. Although studies have demonstrated the significant potential applications of these therapies for the effective treatment of benign and malignant hematologic diseases, multiple challenges still need to be overcome to ensure the optimal use of this therapy. These include:

- Standardization of methods used in developing cellular products;
- Evaluation of optimal immune cell types to use in this therapy;
- Understanding the mechanisms mediating treatment-related toxicities, including graft vs. host disease, in order to enhance overall efficacy; and
- Optimizing delivery methods for the treatment of non-bone marrow based malignant disease.

Furthermore, as these forms of therapy are used increasingly for treating non-hematological based malignancies, there is an increasing need to better understand the mechanisms mediating local immunosuppression in the tumor microenvironment and in tumor intrinsic and extrinsic processes that limit the effectiveness of adoptive cell therapy. Additional infrastructure within health-care systems, and dedicated resources are needed to support interdisciplinary research that is aimed at optimizing the curative outcomes of transplantation and immunotherapy.

ASH would like to thank the NIGMS for the opportunity to comment on this important subject. As the research community continues to look to emerging technologies in areas of genetics, epigenetics, gene therapies, immunotherapy, stem cell, and regenerative medicine, dedicated resources for research and training from funding agencies, such as the NIGMS will be crucial for the acceleration of progress in these areas, while also ensuring the safe and effective translation of such technologies into the clinical setting.

*American Society of Hematology's Response to NIGMS on its RFI on Supporting Research Resources for the Biomedical Community.*

ASH looks forward to working with NIGMS on this important scientific priority, to provide further information, and to be a resource for the Institute. Please contact the ASH Scientific Affairs Specialist, Alice Kuaban, MS, at [akuaban@hematology.org](mailto:akuaban@hematology.org) for any additional information.

Sincerely,

A handwritten signature in black ink that reads "Charles S. Abrams". The signature is written in a cursive style with a large, prominent initial "C".

Charles S. Abrams, MD  
President