AMERICAN SOCIETY OF HEMATOLOGY
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December 28, 2016

Jue Chen, PhD
National Heart, Lung, and Blood Institute (NHLBI)
Building 31, Room 5A52
31 Center Drive
Bethesda, MD 20892

Re: Request for Information (RFI) for Scientific Opportunities and Needs for NHLBI Ancillary Studies (NOT-HL-16-451)

Dear Dr. Chen,

The American Society of Hematology (ASH) appreciates the opportunity to submit comments to the NHLBI in response to the Institute's RFI for Scientific Opportunities and Needs for NHLBI Ancillary Studies (NOT-HL-16-451).

ASH represents more than 17,000 clinicians and scientists worldwide, who are committed to the study and treatment of blood and blood-related diseases. These diseases encompass non-malignant conditions such as sickle cell disease (SCD), thalassemia, aplastic anemia, venous thromboembolism, hemophilia and malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma. Furthermore, hematologists have been pioneers in the fields of stem cell biology, regenerative medicine, bone marrow transplantation, transfusion medicine, gene therapy, and the development of many drugs for the prevention and treatment of heart attacks and strokes. ASH membership is comprised of basic scientists, physician scientists, and physicians who are working in diverse settings including universities, hospitals, and private practices.

Many ASH members are involved in clinical research, including through ancillary studies. ASH is pleased to provide the following suggestions in response to the topics outlined in the RFI as they relate to opportunities, needs and strategies for supporting ancillary studies in hematology research.

- **Scientific opportunities that can be realized or have been accomplished through conducting ancillary studies.**

  There are a number of important research questions an ancillary study funding mechanism could support, as these studies often elucidate fundamental biological processes that underlie diseases and investigate new concepts that have originated after a clinical trial has been initiated. The availability of unbiased broad scale sequencing and proteomic technologies provides additional opportunity for discovery in clinical trial specimens. For example, sequencing of samples from CALGB 10603/RATIFY study could provide insights into interactions between NPM1 and FLT3 mutations. Furthermore, ancillary studies aimed at identification and validation of biomarkers in cancer-associated thrombosis and myeloproliferative disorders would make

important contributions to the field of hematology. Ancillary studies often permit study sites to broaden the scope of their research by taking advantage of the "parent" trial's established infrastructure. They present the opportunity to enrich the primary trial by allowing a defined patient population to be characterized further, answering questions relative to new or unexpected clinical findings during the course of the trial, and developing new approaches to study the disease. For example, targeted mutational analysis (e.g., whole genome/exome sequencing, RNASeq) of patients with acute myeloid leukemia and diffuse large B-cell lymphoma provide valuable insights into clinical outcomes and phenotypic variability of the disease.[1,2]

- **Critical challenges that have hindered and will continue to hinder the development of a successful ancillary study proposal and strategies to overcome the critical challenges.**

  Ancillary research funding is vulnerable to a number of challenges related to the parent study. One obstacle that often arises in hematology-focused ancillary studies is the frequent need to use banked tissue specimens that were collected as part of the primary clinical trial. These are often difficult to access due to the reluctance from "owners" of the tissue bank who may want to use the specimens for their own studies. In the case of SCD, having access to biospecimen archives and databases would be invaluable to advancing the gaps in the knowledge for this devastating disease. To address this major barrier, ASH recommends that the NHLBI consider requiring the "parent" application to include a primary sample analysis plan as well as a secondary analysis plan for access to the repository samples by ancillary studies whose hypotheses could be tested with these specimens.

  HIPAA requirements, informed consent, protected health information, retroactive institutional review board approval, and potential issues with re-consenting patients for studies not authorized under the original protocol are all challenges that could hinder ancillary studies. Furthermore, there are additional barriers when investigators not originally authorized as part of the "parent" trial request access to important material and biospecimens, which would require additional informed consent for secondary research. Earlier this year, ASH submitted a response letter regarding the Federal Policy for the Protection of Human Subjects (Docket ID No: HHS-OPHS-2015-0008) recommending improved access to biospecimens for future research as long as participants are allowed to withdraw consent at any time. The Society strongly supports rigorous patient protection and urged the Administration to issue a template for a broad informed consent form that is clearer, shorter, and simpler than existing documents. ASH recommends that NHLBI

[1] *Lindsley RC, Mar BG, Mazzola E, Grauman PV, Shareef S, Allen SL, Pigneux A, Wetzler M, Stuart RK, Erba HP, Damon LE, Powell BL, Lindeman N, Steensma DP, Wadleigh M, DeAngelo DJ, Neuberg D, Stone RM, Ebert BL. Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. Blood 125: 1367 -76, 2015.*

[2] *Wilson WH, Jung SH, Pitcher BN, Hsi ED, Friedberg J, Cheson B, Bartlett NL, Smith S, Johnston NW, Kahl BS, Staudt LM, Blum K, Abramson J, Press OW, Fisher RI, Richards KL, Schoder H, Chang JE, Zelenetz AD, Leonard JP. MD19Phase III Randomized Study of R-CHOP Versus DA-EPOCH-R and Molecular Analysis of Untreated Diffuse Large B-Cell Lymphoma: CALGB/Alliance 50303. American Society of Hematology 58th Annual Meeting and Exposition, Abstract #469, 2016.*

consider strategies to address these barriers and to simplify the process for informed consent for multiple studies.

Need for more focused grant categories and review panels.

Typically the request for applications (RFAs) related to ancillary studies are quite broad and the correlative work is somewhat varied. The grant review committee members may not be as well versed in the content area, which may result in several disease areas being underrepresented. This is particularly important for rare diseases, such as the majority of hematologic disorders. Thus, ASH recommends having more focused categories for the grant opportunities and subsequently more focused review panels for ancillary grant applications. For example, the NHLBI could consider having separate review panels for the different categories within the Institute's portfolio. In the case of hematology, ASH recommends that NHLBI separate the grant categories and panels to represent the various types of hematologic conditions, as well as delineate between rare and more prevalent conditions. Additionally, clinical expertise is often underrepresented on most ancillary grant review panels with most members focusing on hypothesis-driven studies in pre-clinical settings. However, correlative studies are by their nature typically led in large part by clinical translational teams that focus on descriptions of the clinical events and not in the classical sense clearly hypothesis-driven. Therefore, ASH recommends that the NHLBI make a concerted effort to include clinical and translational experts in future ancillary review panels.

- **Strategies for increasing the number of successful ancillary study applications from junior investigators.**

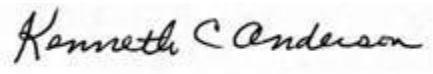
To overcome the barriers faced by junior investigators, ASH recommends that NHLBI issue targeted request for proposal (RFP) to support ancillary studies using the R03 and R21 funding mechanisms as well as T and K awards that could serve as bridge grants for future R01 grant applications. The Society would be pleased to support NHLBI's efforts to increase awareness of ancillary grants by sending targeted communications to ASH members. Furthermore, data generated from ancillary studies can be valuable in informing future R01 applications from young investigators, providing continuity or a renewal process of the existing funding mechanisms. These changes to the current ancillary study mechanisms could make this opportunity more attractive to young investigators, potentially increasing the number of applications and supporting the next generation of investigators.

Effective mentorship plays a pivotal role in the success of a junior hematology investigator who has acquired an ancillary grant. However, the challenges faced by junior investigators when identifying the right mentors could constitute an obstacle that would prevent them from submitting an ancillary study grant application. Such investigators might be more inclined to apply for ancillary grants if they had access to mentors who would offer guidance throughout the course of the project. Thus, ASH recommends that NHLBI explore efforts to facilitate relationships between young investigators and mentors, as a strategy to increase the number of successful ancillary applications from junior

investigators. The Society would welcome the opportunity to assist the NHLBI in facilitating this process.

In closing the Society would like to emphasize the importance of NHLBI continuing to invest in ancillary studies as there are no other sources of funding for correlative studies outside of federal investments. Thank you for your consideration of ASH's comments and recommendations. The Society looks forward to continuing to work with you as the Institute continues to explore opportunities and strategies to maximize scientific output of clinical research through support of ancillary studies, specifically those related to hematological diseases. Please contact ASH Senior Manager of Government Relations and Public Health, Stephanie Kaplan (*skaplan@hematology.org* or 202-776-0544), if the Society can provide additional information or assistance.

Sincerely,



Kenneth C. Anderson, MD
President