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RE: ASH Recommendations to the National Cancer Institute on the National Cancer Moonshot Initiative

Submitted electronically to: https://cancerresearchideas.cancer.gov/

The American Society of Hematology (ASH) appreciates the opportunity to submit recommendations to the National Cancer Institute (NCI) on National Cancer Moonshot Initiative. The Society's recommendations were developed based on the ASH Agenda for Hematology Research and ASH's Recommendations to the Moonshot Initiative, have been written in the format requested by the NCI and submitted through the NCI platform.

I. Precision, Prevention, and Early Detection

Improve early hematologic cancer detection and prevention: Understanding an inherited predisposition to hematologic malignancies, and how a pre-cancerous condition becomes cancer will allow for early intervention and cancer prevention.

a) What is the research problem? Hematologic diseases provide a unique model for studying pre-cancerous disorders. Specifically, they provide researchers with the opportunity to utilize non-invasive techniques that allow for the monitoring of circulating blood cells, DNA, RNA, and other biologic material to help identify or determine the disease state. There is a need for continuous research focused on the identification of genetic or epigenetic changes, as well as on biomarkers that could have an impact on disease risk and progression.

b) What is your proposed solution?

ii. Develop funding opportunities for research aimed at understanding the role of inherited predisposition to specific blood cancers and pre-cancerous hematologic conditions such as:

- Bone Marrow Failure Syndromes (i.e. Fanconi Anemia & Dyskeratosis Congenita);
- Monoclonal gammopathy of undetermined significance;
- Monoclonal B-cell lymphocytosis;
- Clonal Hematopoiesis of Indeterminate Potential; and
- Myeloproliferative neoplasms

ii. Develop funding opportunities for investigators to use platforms, such as the Genomic Data Commons (GDC) to sequence samples from patients with hematologic pre-cancer and cancer conditions, especially for rare subtypes. Comprehensive standardized sequencing and data analysis of hematological cancers can inform research on the pathology of all cancers.

iii. Develop funding opportunities for basic research, longitudinal genomic natural history studies, and preventive clinical trials to study hematologic models of the progression from normal blood production to hematologic cancers, in collaboration with other institutes and centers (e.g., NHLBI, NIDDK).

c) How will your solution make a difference? Investing in these research areas will facilitate disease detection, monitoring, development of important tools for diagnosis, and possible prevention of hematologic malignancies and other cancers.

II. Expanding Clinical Trials

Improve access to clinical trials of novel targeted therapies for hematologic cancers: Genomic profiling of DNA and RNA has provided valuable new insights into the genetic basis of hematologic cancers. Translating this knowledge into meaningful results for patients with hematologic diseases will require improved patient access to clinical trials for these rare diseases.

a) What is the research problem? There are several challenges involved in improving patient access to clinical trials, especially trials of novel targeted therapies for rare hematologic malignancies:

i. Lack of a comprehensive understanding of the natural history of rare cancers to inform trial design;
ii. Lack of alternatives to randomized controlled clinical trials;
iii. Limited access to resources (including funding) required to develop clinical trials for hematologic malignancies;
iv. Lack of validated genomic biomarkers to predict response;
v. Difficulties in the recruitment and retention of patients with rare hematologic malignancies.

b) What is your proposed solution?

i. Develop funding opportunities aimed at discovery and validation of genetic/genomic biomarkers of response to targeted therapies for hematologic malignancies;
ii. Expand existing precision medicine clinical trials of novel targeted therapies (e.g., NCI-MATCH) to include hematologic cancers; and
iii. Develop and fund nation-wide multicenter umbrella clinical trials of targeted therapies for treating hematologic cancers using the existing NCI infrastructure to ensure consistent sample collection, data storage, annotation, and sharing.

c) How will your solution make a difference? Efforts to improve access to clinical trials of novel targeted therapies for treating hematologic malignancies will have a tremendous impact on the development of potentially life-saving treatments for all cancer patients.

III. Cancer Immunology and Prevention

Support the development of immune-based therapies for hematologic cancers: Novel immunologic approaches, such as hematopoietic stem cell transplant, CAR T-cell therapy, and checkpoint blockade strategies show great curative potential in their application and treatment of malignant hematologic diseases.

a) What is the research problem? Although studies have demonstrated the significant potential applications of immunotherapies for the treatment of hematologic malignancies, several challenges still need to be overcome to ensure the optimal use of these therapies:

i. Identifying optimal molecular targets and biomarkers of response;
ii. Standardization of methods used in developing cellular products;
iii. Identifying appropriate tumor-specific antigens in hematologic malignancies that can be targeted by CAR T-cell therapy; and
iv. Understanding toxicities associated with these therapies.

b) What is your proposed solution?

i. Support collaborative research opportunities aimed at improving the efficacy and reducing the toxicity of immunotherapies for hematologic cancers:
   - Identify optimal molecular targets for existing curative therapies (e.g., allogeneic hematopoietic stem cell transplant);
   - Identify biomarkers that predict response to immunotherapies;
   - Understand the mechanisms mediating treatment-related toxicities, including graft vs. host disease, in order to enhance overall efficacy;
   - Understand mechanisms mediating local immunosuppression in the tumor microenvironment, as well as understand tumor intrinsic/extrinsic processes that limit the effectiveness of these therapies;
   - Standardize methods used in developing cellular products;
   - Evaluate optimal immune cell types to use in these therapies; and
   - Optimize delivery methods for the treatment of non-bone marrow based malignant disease.

ii. Support efforts aimed at the development of vaccination strategies that will confer long-term memory immune protection against the development or recurrence of hematologic malignancies.
iii. Develop funding opportunities aimed at identifying tumor or tissue-specific antigens in hematologic malignancies that can be targeted by immunologic approaches, such as CAR T-cell therapy.
iv. Support clinical trials for immunotherapies in rare cancers, including hematologic cancers.

c) How will your solution make a difference? Successes in the treatment of blood cancers with immunotherapy have provided a proof of principle for using this type of treatment in a wide array of cancers. Addressing these challenges will expand the utility of novel immunologic approaches, and support their implementation far beyond hematologic diseases.

IV. Enhanced Data Sharing

Enhance sharing of clinical and genetic/genomic hematological cancer data: A robust data sharing infrastructure for basic scientists, clinical researchers, and clinicians will enable more efficient interpretation and integration of genomic information into clinical care.

a) What is the research problem? Hematologic malignancies, such as lymphomas, leukemias, and myelodysplastic and myeloproliferative neoplasms are rare and heterogeneous. Pooling genomic and clinical patient data over time would be an invaluable resource for caregivers, patients, researchers, and others in delivering the promise of targeted therapy.

b) What is your proposed solution?

i. Improve access to cancer data available through the NCI and the NIH as a whole;
ii. Support additional sequencing efforts for rare cancers, including hematologic malignancies;
iii. Support collaboration among multiple stakeholders that are willing to support data generation and sharing (e.g., philanthropy, foundations, academia, industry, medical associations, etc.);
iv. Provide administrative supplements to offset the costs of collecting, analyzing, and storing clinically and genomically profiled data from patients with hematologic malignancies;
v. Support efforts aimed at designing proper infrastructure to host sequencing data to enable efficient interpretation and integration of genomic information into clinical care; and
vi. Support training/education opportunities as well as tools needed by hematologists and oncologists to enhance their ability to interpret genomic/genetic data and apply it to clinical care.

c) How will your solution make a difference? Easily available accurate genomic data linked to clinical features are essential to advance curative strategies and the delivery of personalized medicine to all cancer patients.

V. Pediatric Cancers

Advance research for pediatric hematologic cancers: Hematologic malignancies, such as leukemia are one of the leading causes of cancer-related deaths in children. Basic, translational, and clinical research efforts addressing early diagnosis, treatment, and prevention will be vital to improving survival rates in children fighting cancer.

a) What is the research problem? Although survival rates have improved greatly for childhood cancers, like acute lymphoblastic leukemia, there is still a great need for new therapeutic approaches, such as immunotherapy to help treat high-risk leukemias, as well as relapse. In addition, the effective use of genomic approaches will provide new insights into childhood hematologic cancers. Some of the challenges in pediatric hematologic cancers include:

i. Limited access to novel therapies for the pediatric population;
ii. High toxicity levels due to the types of therapies designed for pediatric hematologic malignancies; and
iii. Absence of robust clinical trials for pediatric hematologic malignancies.

b) What is your proposed solution?

i. Develop funding opportunities for basic and translational research that is aimed at the discovery of new therapeutic targets in pediatric hematologic cancers;
ii. Support research focused on identifying determinants of toxicity in children;
iii. Develop funding opportunities to support precision medicine trials in children with hematologic cancers and/or expanding the pediatric NCI-MATCH trial to include this population; and
iv. Provide support for clinical trials testing novel therapies in children with hematologic malignancies.

c) How will your solution make a difference? Advancing basic, translational, and clinical research in pediatric hematologic cancers will enhance the effectiveness of existing treatments, as well as foster the development of novel therapies that will improve long-term survival and the quality of life of children with cancer.

VI. Tumor Evolution and Progression

Advance research on hematologic tumor development and progression: Germline and somatic genetic mutations play a key role in cancer predisposition, transformation, progression, responsiveness to therapy, and treatment complications. As genomic profiling is driving significant research progress across all cancer research, it is essential to adopt this technology in drug discovery efforts and build the infrastructure to integrate genomic medicine into the clinic.

a) What is the research problem? While sequencing studies have generated important information for various hematologic malignancies, there are still several challenges that need to be overcome in order to translate genetic data into the clinical setting:

i. Determining functional consequences of mutations to aid drug design;
ii. Developing cell lines and animal models of complex genomic and epigenomic alterations seen in human tumors; and
iii. Improving understanding of epi-transcriptome in normal and malignant hematopoiesis.

b) What is your proposed solution?

i. Support research of the functional consequences of mutations in disease subclones and the therapeutic targeting of complex cancer cell populations with evolving resistance mechanisms;
ii. Develop funding opportunities aimed at the generation of new cell lines and animal models that recapitulate the many genomic alterations found in human tumors and that are amenable to high throughput sequencing efforts, and making these tools available to the community; and
iii. Support research to advance the understanding of modifications that occur at the epi-transcriptome level in normal and malignant hematopoietic processes for potential treatment opportunities.

c) How will your solution make a difference? Supporting efforts that facilitate the integration of genomic and epigenomic profiling into drug discovery efforts by using genomic methods to sequence and analyze disease subtypes will allow for more rapid development of novel targeted cancer therapies.

ASH looks forward to working with the NCI on these important priority areas, 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 for any additional information.

Sincerely,

Charles S. Abrams, MD
President