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A call to action in hematologic disorders: A report from the ASH scientific workshop on hematology and aging

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Abstract

The American Society of Hematology (ASH) has recently promoted efforts to advance the intersection of hematology and aging by sponsoring an annual Scientific Friday Workshop on Hematology and Aging [1]. Hematologic disorders, both malignant and benign, are highly prevalent among older adults [2–4]. Despite the disproportionate burden of hematologic disease among older adults [2–5], research studying the implications of age across the translational spectrum remains limited older adults understudied [6–8]. The lack of pre-clinical aging models, dearth of translational efforts across diseases, and under-enrollment of older adults in clinical trials result in substantial gaps in knowledge. Understanding the interface of human aging and hematologic disorders in a growing population of older adults is warranted. Here we outline the progress to date spearheaded by the ASH community dedicated to hematology and aging.

Research Gaps

Key research gaps limit evidence required to make rapid advances for older adults, including: 1) a need for age-specific pre-clinical models; 2) study of multi-morbidity; 3) adequate numbers of older adults enrolled in all phases of clinical trial development; 4) consistent inter-disciplinary research and practices; and 5) consensus on geriatric assessments, frailty metrics, and screening tools. Responding to these unmet needs, ASH

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held the inaugural Friday Scientific Workshop of Hematology and Aging at its annual meeting in 2014 and has since hosted the workshop annually, to highlight novel research focused on the biology of aging. The goal of the Workshop is to forge an intersection between novel insights in aging biology and the study of hematologic disorders. The pathogenesis of aging and hematologic disease have overlapping mechanisms, and creating collaborative scientific advances in this field is warranted. In line with the ASH agenda to prioritize research endeavors across the hematology continuum, this intersection of hematology and aging capitalizes on established strategies to gain momentum and increase the body of knowledge in field. [9]

Workshop Objectives and Structure

The Workshop was designed to cultivate interest, collaboration, and networking among scientists in gerontology and their counterparts in hematology, to address high-priority gaps and create a research agenda to meet the needs of aging adults with hematologic disorders. Its main objectives are to: 1) provide a forum within ASH for presentation of novel research related to the biology of aging and hematologic disorders, 2) identify research agenda priorities, and 3) propagate opportunities for collaboration while emphasizing bidirectional translation between pre-clinical and clinical models of aging. Speakers have included national and international leaders, as well as emerging investigators. Speakers have also represented key stakeholders, including the National Institute of Aging (NIA), National Cancer Institute (NCI), Food and Drug Administration (FDA), National Heart, Lung and Blood Institute (NHLBI), and the Cancer and Aging Research Group (CARG). The Workshop has focused on emerging basic science topics, translational science, and the clinical interface in both malignant and benign hematologic disorders. Following each themed session, a moderated discussion identified gaps in the field and research priorities, with audience engagement. The workshop has been well attended (>200 participants yearly) and feedback has been overwhelmingly positive and representative of a diverse audience.

Workshop Research Themes

The Workshop is organized to highlight recent advances in the study of aging and hematology from disease pathogenesis to treatment and survivorship. Each year the Workshop is composed of themed sessions (Table 1) broadly divided into understanding hematopoietic stem cells in aging, cellular senescence, aging and immunology, frailty, thrombosis and aging, and disease-specific clinical and biologic correlates.

One notable example is the recent discovery of clonal hematopoiesis in aging adults. Clonal hematopoiesis, the detection of clonal expanded hematopoietic stem and progenitor cells without a clinically apparent malignancy, occurs in 10–20% of older adults; ongoing work is focused on investigating driver genes and mutations [10] and persistence after therapy [11]. Applying the hallmarks of aging [12] in the pre-clinical context is an active area of investigation and highlighted at this session. Investigators have also presented their work on exploring the hematopoietic stem cell and role of the bone marrow microenvironment [13], epigenetic regulation [14], cellular senescence [15] and impact of these processes in the leukemic transformation. Others have presented overviews on the role of chronic

physiologic stress on hematopoietic stem cells resulting in direct DNA damage, stem cell exhaustion, and development of bone marrow failure syndromes [16,17]. We expect that future conferences will continue to explore pre-clinical malignant pathogenesis as well as benign hematologic disorders and thrombosis as high priority research items.

A second objective of the Workshop is to integrate basic and clinical science. Concepts such as physiologic aging, accelerated aging, and frailty are emerging as themes across hematologic disorders [18]. The Workshop aims to enhance attendees' understanding of pathophysiology, therapeutic risks and benefits, treatment allocation, and health outcomes among older individuals. Older adults with hematologic malignancies present unique treatment challenges. However, important considerations among older patients, such as treatment tolerance and physiologic reserve, cross many different disease- and treatment-specific challenges. This insight is particularly relevant given the growing numbers of older adults who may require hematopoietic stem cell transplants or other emerging therapeutic modalities, such as checkpoint inhibitors or CART therapy.

Many Workshop topics consider physiologic age rather than chronologic age, recognizing heterogeneity in the aging process. Moreover, the importance of studying long-term effects of those therapies in survivors [19] is increasingly being recognized. Equally important is understanding how treatment modalities accelerate aging, or conversely, how senolytic agents affect aging and/or cancer development.

Another area explored in the Workshop is that of benign hematologic disorders, which affect a disproportionate number of older adults [4]. Each year 164 million older adults worldwide are diagnosed with anemia [20] where half of aging adults have unexplained anemia [21,22]. Furthermore, age is the strongest risk factor for venous thromboembolism (VTE), which occurs in 1% of adults >65 years of age per year [23]. The relationship between aging and VTE has been described as one of the "least understood scientific interfaces." [24] At age 80, the likelihood of VTE is 1000-fold higher than those aged 45 and younger [25,26]. Use of antithrombotic agents and risk of bleeding with age are critical areas of investigation [27]. The ASH Hematology and Aging Workshop seeks to explore these critical areas of investigation in older adults with benign hematologic disorders and help promote scientific progress.

Call to Action

ASH support of the Scientific Workshop on Hematology and Aging and recent endeavors to establish guidelines for older adults with acute myelogenous leukemia [28] are examples of progress towards practice-changing strategies for older adults. Gaps in the evidence base related to under-enrollment of older adults in clinical trials [7], lack of dedicated aging adult studies, and limited study of pre-clinical models of aging can be remedied through novel scientific collaborations, education, and support through agencies such as ASH. The emerging field of geroscience affords an opportunity to translate the study of aging biology into clinical interventions [29]. Logistical challenges inherent in uniting multidisciplinary teams of scientists can be overcome with strategic efforts. We propose several such efforts below as a call to action:

- Embed geroscience in the curriculum of hematologic disorders, to better understand the similarities and differences of pre-clinical models (e.g. animal models, ex vivo techniques) that mimic the complexity of aging. This is relevant to the study of normal aging, accelerating aging, and in the context of pathologic states. Investigators should lobby funders to solicit such proposals and reward team science that promotes aging and hematologic disorders.
- Promote funding resources and public forums where researchers in aging, clinical research, and health outcomes can work collaboratively to interact and advance the field of aging in hematologic disorders.
- Create a policy whereby older adults are a target population in clinical trials across key stakeholders. Frameworks can be created to help academic institutions identify and address factors in clinical trial criteria that make it more difficult for aging adults to participate in research. Larger policy and regulatory changes will also be needed. Frailty assessments should be embedded in clinical trials to assess toxicity and benefit in the context of physiologic age, independent of chronologic age.
- Support cross-disciplinary research among disciplines that interface with aging and hematology population; examples could include palliative care, geriatrics, physical medicine and rehabilitation, dietetics, neurology, pharmacology, survivorship, and integrative oncology.
- Create an agency of change to shift our culture towards research of aging adults. Our current practice and research patterns have omitted the population most at risk: older adults. We strive for change to improve our own practice paradigms of treating older adults and to be transformative where we can advance the agenda. Working towards broader activities, including guideline development and research sessions targeted for older adults is imperative.
- Invest in people with education and training. By investing in geriatric research, we can prevent morbidity and mortality in the largest-growing demographic of people. We must continue to foster the academic development and education of early-career faculty, trainees, advanced care practitioners, and nurses in the emerging field of geriatric hematology.
- Enhance dissemination of new knowledge related to geriatrics and hematology. Every adult hematologist is a geriatric hematologist by nature, since hematologic diseases predominantly affect older adults. New knowledge gained regarding best practices of hemato-logic disorders is relevant to the entire hematology community.

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References

- [1]. <http://www.hematology.org/Annual-Meeting/Program/Friday-Scientific-Workshops.aspx>. [ASoHAAMFSWRf].
- [2]. Howlader NNA. In: Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA, editors. SEER Cancer Statistics Review, 1975–2014. Bethesda, MD: National Cancer Institute; 1 2018 [https://seer.cancer.gov/archive/csr/1975_2014/], based on November 2016 SEER data submission, posted to the SEER web site].
- [3]. McLean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anaemia, WHO vitamin and mineral nutrition information system, 1993–2005. Public Health Nutr 2009;12:444–54. [PubMed: 18498676]
- [4]. Smith BD, Smith GL, Hurria A, Hortobagyi GN, Buchholz TA. Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol 2009;27:2758–65. [PubMed: 19403886]
- [5]. Bron D, Ades L, Fulop T, Goede V, Stauder R. Elderly task force in hematology ES. Aging and blood disorders: new perspectives, new challenges. Haematologica 2015;100:415–7. [PubMed: 25828087]
- [6]. Kanapuru Bindu, Singh Harpreet, Myers Adrian, Beaver Julia A, Kwitkowski Virginia Elaine, Farrell Ann T, et al. Enrollment of Older Adults in Clinical Trials Evaluating Patients with Hematologic Malignancies – the Food and Drug Administration (FDA). ASH; 2017 [Abstract 861].
- [7]. Cherubini A, Pierri F, Gasperini B, et al. Are ongoing trials on hematologic malignancies still excluding older subjects? Haematologica 2013;98:997–1000. [PubMed: 23813644]
- [8]. Hamaker ME, Stauder R, van Munster BC. Exclusion of older patients from ongoing clinical trials for hematological malignancies: an evaluation of the National Institutes of Health Clinical Trial Registry. Oncologist 2014;19:1069–75. [PubMed: 25170014]
- [9]. <http://www.hematology.org/Research/Recommendations/Agenda.aspx>. [ASoHAafhrRf].
- [10]. Genovese G, Kahler AK, Handsaker RE, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med 2014;371:2477–87. [PubMed: 25426838]
- [11]. Wong TN, Miller CA, Klcio JM, et al. Rapid expansion of preexisting nonleukemic hematopoietic clones frequently follows induction therapy for de novo AML. Blood 2016;127(7):893. [PubMed: 26631115]
- [12]. Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell 2013;153:1194–217. [PubMed: 23746838]
- [13]. Schepers K, Pietras EM, Reynaud D, et al. Myeloproliferative neoplasia remodels the endosteal bone marrow niche into a self-reinforcing leukemic niche. Cell Stem Cell 2013;13:285–99. [PubMed: 23850243]
- [14]. Beerman I, Rossi DJ. Epigenetic control of stem cell potential during homeostasis, aging, and disease. Cell Stem Cell 2015;16:613–25. [PubMed: 26046761]
- [15]. Chang J, Wang Y, Shao L, et al. Clearance of senescent cells by ABT263 rejuvenates aged hematopoietic stem cells in mice. Nat Med 2016;22:78–83. [PubMed: 26657143]
- [16]. Walter D, Lier A, Geiselhart A, et al. Exit from dormancy provokes DNA-damage-induced attrition in haematopoietic stem cells. Nature 2015;520:549–52. [PubMed: 25707806]
- [17]. Kaschutnig P, Bogeska R, Walter D, Lier A, Huntscha S, Milsom MD. The Fanconi anemia pathway is required for efficient repair of stress-induced DNA damage in haematopoietic stem cells. Cell Cycle 2015;14:2734–42. [PubMed: 26178207]
- [18]. Abel GA, Klepin HD. Frailty and the management of hematologic malignancies. Blood 2018;131:515–24. [PubMed: 29141942]
- [19]. Arora M, Sun CL, Ness KK, et al. Physiologic frailty in nonelderly hematopoietic cell transplantation patients: results from the bone marrow transplant survivor study. JAMA Oncol 2016;2:1277–86. [PubMed: 27254472]

- [20]. McLean E, Cogswell M, Egli I, Woldyla D, de Benoist B. Worldwide prevalence of anaemia, WHO vitamin and mineral nutrition information system, 1993–2005. *Public Health Nutr* 2009;12:444–54. [PubMed: 18498676]
- [21]. Artz AS, Thirman MJ. Unexplained Anemia predominates despite an intensive evaluation in a racially diverse cohort of older adults from a referral Anemia clinic. *J Gerontol A Biol* 2011;66:925–32.
- [22]. Stauder R, Valent P, Theurl I. Anemia at older age: etiologies, clinical implications, and management. *Blood* 2018;131:505–14. [PubMed: 29141943]
- [23]. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost* 2007;5:692–9. [PubMed: 17367492]
- [24]. Silverstein RL, Bauer KA, Cushman M, Esmon CT, Ershler WB, Tracy RP. Venous thrombosis in the elderly: more questions than answers. *Blood* 2007;110:3097–101. [PubMed: 17684155]
- [25]. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O’Fallon WM, Melton LJ 3rd Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998;158:585–93. [PubMed: 9521222]
- [26]. Engbers MJ, Vlieg AV, Rosendaal FR. Venous thrombosis in the elderly: incidence, risk factors and risk groups. *J Thromb Haemost* 2010;8:2105–12. [PubMed: 20629943]
- [27]. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016;149:315–52. [PubMed: 26867832]
- [28]. <http://www.hematology.org/Clinicians/Guidelines-Quality/Guidelines.aspx>. [ASoHACPGf].
- [29]. Sierra F The emergence of geroscience as an interdisciplinary approach to the enhancement of health span and life span. *Cold Spring Harb Perspect Med* 2016;6: a025163. [PubMed: 26931460]

Table 1

Scientific workshop: Hematology and aging research agenda.

Topic	Presentations	Gaps in research
Hematopoietic stem cell biology	<ul style="list-style-type: none">• Aging and hematopoiesis (2014–2016)	<ul style="list-style-type: none">• HSC aging and disease pathogenesis
	<ul style="list-style-type: none">• Demethylation to reverse age-related stem cell senescence (2015)	<ul style="list-style-type: none">• Translation from animal models to human disease pathogenesis
	<ul style="list-style-type: none">• Erythroid progenitor cell differentiation in normal elderly and in unexplained anemia (2015)	<ul style="list-style-type: none">• Etiology of CHIP
	<ul style="list-style-type: none">• Clonal hematopoiesis of indeterminate potential (CHIP) (2016)	<ul style="list-style-type: none">• HSC exhaustion and disease pathogenesis
	<ul style="list-style-type: none">• Hematopoietic stem cell (HSC) aging (2014, 2016)	<ul style="list-style-type: none">• Role of bone marrow microenvironment aging in disease pathogenesis
	<ul style="list-style-type: none">• Physiologic stress and hematopoietic stem cell exhaustion (2016)	
	<ul style="list-style-type: none">• Aging vascular endothelium modulates HSC activity (2017)	
	<ul style="list-style-type: none">• Molecular mechanisms that contribute to HSC aging (2017)	
	<ul style="list-style-type: none">• Defects in aging marrow macrophages regulate HSC (2017)	
Cellular Senescence	<ul style="list-style-type: none">• Immunosenescence and aging (2015, 2016)	<ul style="list-style-type: none">• Connecting and identifying cellular senescence, exhaustion and immunosenescence
	<ul style="list-style-type: none">• Cellular senescence and biomarkers of aging (2015)	
	<ul style="list-style-type: none">• Telomere dysfunction and senescence in marrow failure syndromes (2015)	
Aging and Immunology	<ul style="list-style-type: none">• Immune reconstitution with aging (2016)	<ul style="list-style-type: none">• Tolerance and immunotherapeutic response of in aging adults
	<ul style="list-style-type: none">• Safety of immune based therapies in elderly (2016)	
	<ul style="list-style-type: none">• Transplant as a model for accelerated T-cell aging (2017)	
	<ul style="list-style-type: none">• Immunotherapy in older adults with hematologic malignancies (2017)	
Thrombosis and Aging	<ul style="list-style-type: none">• Platelet reprogramming and thrombosis in aging (2017)	<ul style="list-style-type: none">• Aging and VTE risk
	<ul style="list-style-type: none">• In vitro and in vivo models to dissect the pathophysiology of thrombosis in aging (2017)	<ul style="list-style-type: none">• Anemia and aging pathophysiology
	<ul style="list-style-type: none">• The megakaryocyte-platelet axis and pro-thrombotic functional responses in a murine model of aging (2017)	
Frailty	<ul style="list-style-type: none">• Therapy related MDS/AML a model disease of aging (2014)	<ul style="list-style-type: none">• Physiologic drivers of aging
	<ul style="list-style-type: none">• Comorbidity and risk of GVHD post-BMT (2014)	<ul style="list-style-type: none">• Phenotypic characterization of the heterogeneity of aging
	<ul style="list-style-type: none">• Markers of frailty in stem cell transplantation (2015)	<ul style="list-style-type: none">• Quantifying patient fitness and resilience
	<ul style="list-style-type: none">• Geriatric assessment to predict toxicities and survival in multiple myeloma (2015)	<ul style="list-style-type: none">• Balancing toxicity with tolerance
	<ul style="list-style-type: none">• Markers of frailty and survival in MDS (2015)	<ul style="list-style-type: none">• Clinical trial development for older adults
	<ul style="list-style-type: none">• Physiologic frailty among bone marrow transplant survivors (2016)	<ul style="list-style-type: none">• Interventions to mitigate frailty

Topic	Presentations	Gaps in research
	<ul style="list-style-type: none"> Geriatric Assessment among older adults with lymphoma (2017) Brief comprehensive Geriatric Assessment in older patients with hematologic malignancies: The GAH scale (2017) Frailty phenotype in childhood cancer: a model of treatment induced accelerated aging (2016) 	<ul style="list-style-type: none"> Biologic mechanisms of treatment-induced accelerated aging
Disease-specific clinical and biologic correlates	<ul style="list-style-type: none"> Aging bone marrow microenvironment and myeloma (2014) Treatment prediction models and tumor biology in AML (2014) Biology of Aging and CLL (2014) BTK inhibitors in older adults with CLL (2015) MGUS in Older Adults (2015) Inherited BMT syndromes in older adults (2015) Nutritional impairment in hematologic malignancies (2015) Haploidentical transplantation in older adults (2014) Cytokine signatures in AML (2016) Comorbidity, age, and outcomes in CLL (2016) Creation of a non-human primate model for hematopoietic aging and for CHIP (2017) • Age-related BACH2 expression down-regulation and decreased apoptosis in major lymphocyte subsets in healthy donors and CLL (2017) 	<ul style="list-style-type: none"> Therapeutic modalities in older adults (transplant, CAR-T) Disease-specific frailty Biologic correlates of aging Efficacy of therapies at extremes of age or in setting of comorbidities Age-specific toxicity profiles Precision medicine to adopt treatment based on individual physiologic age

Abbreviations: Hematopoietic stem cell (HSC); clonal hematopoiesis of indeterminate potential (CHIP); venous thromboembolism (VTE); myelodysplastic syndrome (MDS); acute myeloid leukemia (AML); graft vs host disease (GVHD); bone marrow transplant (BMT); Geriatric Assessment in Hematology (GAH); chronic lymphocytic leukemia (CLL); Bruton's tyrosine kinase (BTK); monoclonal gammopathy of undetermined significance (MGUS); chimeric antigen receptor-t (CAR-T);

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