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ASH SICKLE CELL DISEASE RESEARCH PRIORITIES

– 2024 UPDATE –

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Introduction

Sickle cell disease (SCD) is the most common inherited red blood cell disorder in the United States, affecting approximately 100,000 Americans.[1] SCD refers to blood disorders where sickle hemoglobin HbS is the predominant hemoglobin within erythrocytes. The most prevalent SCD genotype is homozygous hemoglobin SS (HbSS), along with the compound heterozygous conditions hemoglobin $S\beta^0$-thalassemia ($HbS\beta^0$-thalassemia), hemoglobin $S\beta^+$-thalassemia ($HbS\beta^+$-thalassemia), and hemoglobin SC disease (HbSC). HbSS and $HbS\beta^0$-thalassemia are clinically very similar and therefore are commonly referred to as sickle cell anemia. In contrast, HbAS (sickle cell trait, a carrier state) is not a form of SCD.

Although the molecular basis of SCD was established in 1949 by Linus Pauling,[2] it has been challenging to translate this knowledge into the development of novel targeted therapies. In the early 1960s, SCD was described as a disorder of childhood because the average survival was 19 years of age; however, with early diagnosis by newborn screening, education, penicillin prophylaxis, and comprehensive medical care, most individuals living with SCD are expected to live into adulthood. This progress has created other pressing issues to address such as the burden of lifelong pain, end-organ injury, continued shortened overall survival, and cost of care.

New approaches in managing SCD have improved diagnosis and supportive care over the last few decades, but many individuals with SCD still have severe complications to overcome. The future of care for individuals with SCD will be dependent on advanced and highly targeted approaches to research, discovery, and implementation of proven and new interventions.

To ensure that individuals with SCD receive state-of-the-art care, the American Society of Hematology (ASH) developed the following list of the top research topics to address over the course of the next five years. This comprehensive document includes remaining unaddressed questions and specific research priorities aimed at accelerating progress in basic, translational, and clinical research to ultimately improve outcomes for individuals living with SCD worldwide. The research topics explored below are not presented in rank order.

ASH encourages the SCD stakeholder community to use multi-disciplinary approaches to support these research priority areas. Given the broad benefits derived from additional research, stakeholder organizations should coordinate their funding opportunities to produce the greatest impact. A multi-agency approach would deliver advances faster, more efficiently, and more economically, to people suffering from this debilitating disease in the United States and worldwide.

References

1. Kavanagh, P, Fasipe, TA, Wun, T Sickle Cell Disease: A Review. JAMA. 2020; Jul 5;328(1):57-68. doi: 10.1001/jama.2022.10233.
2. Pauling L, Itano HA, Singer SJ, Wells IC. Sickle cell anemia a molecular disease. Science 1949; Nov 25;110(2865): 543-8, doi:10.1126/science.110.2865.543.

Research Priorities by Topic

I. Assessment, Prevention and Treatment of End-Organ Dysfunction

Background

SCD is highly variable clinically, with some individuals experiencing a mild course and extended survival and others experiencing frequent and severe complications along with markedly shortened survival. Over the past three decades, using genetic approaches researchers have learned about the effects of other disease modifiers (e.g., gene polymorphisms, hemoglobin F levels, concomitant alpha thalassemia, co-morbidities, and environmental factors) and mutations in the hemoglobin (HBB) gene on disease severity.[1]

Identification of various predictors of disease severity is currently inadequate but is vital for the optimal prevention and management of SCD complications. For example, several urine and plasma biomarkers as well as genetic polymorphisms recently discovered influence specific clinical outcomes, including stroke, sickle cell nephropathy, acute chest syndrome, pulmonary hypertension, and survival.[2-4]

There is a need to fill knowledge gaps in the natural history of end-organ dysfunction in SCD and identification of risk factors in childhood/early adulthood to support development of targeted therapies to alter disease trajectory.[5] The development of multidisciplinary research teams is invaluable to achieve the goals of improved assessment, prevention, and treatment of end-organ dysfunction in people with SCD.

Unanswered Questions

1. Can specific biomarkers and/or genetic polymorphisms identify individuals at elevated risk for clinical events, such as recurrent vaso-occlusive episodes, nephropathy, cardiac disease, thromboembolism, and pulmonary hypertension?
2. Can specific biomarkers and/or genetic polymorphisms identify "responders" vs. "non-responders" to hydroxyurea and new pharmacologic therapies?
3. Can we more precisely define genotype-phenotype relationships?
4. What is the role of environmental factors and comorbidities in disease progression?
5. What do genetic polymorphisms and biological markers tell us about pathophysiologic mechanisms to identify new targets for treatment development?
6. How should whole person/integrated approaches to risk be incorporated?
7. What are the effects of therapies including medications and therapies with curative intent on organ dysfunction?

Research Priorities

1. Studies of biomarkers and/or genetic polymorphisms as a means of identifying individuals at elevated risk for acute clinical events and progressive organ dysfunction, such as acute chest syndrome, stroke, vaso-occlusive episodes, nephropathy, cardiac

disease, thromboembolism, and pulmonary hypertension. This should include biomarkers (clinical, laboratory, socioenvironmental, technological) throughout the lifespan and suitable for use in a variety of resource settings.

2. Studies of biomarkers and genetic polymorphisms and their relationships to pathophysiologic mechanisms, including new *in vitro* systems (e.g., patient derived induced pluripotent stem cells to create model systems of the vasculature, for cell adhesion, advanced imaging techniques) and animal models (e.g., organ pathophysiology studies in transgenic sickle mouse models) of disease mechanisms.
3. Studies of biomarkers, genetic markers, or epigenetic alterations in the context of clinical drug trials, to determine whether response (or lack thereof) may be predictable, allowing for personalized therapeutic decisions (e.g., Omics technologies on drug responders vs non responders; measurements using *in vitro* (red blood cell health, cell adhesion) and *in vivo* (blood flow, MRI, NIRS imaging) methods.
4. Development of integrated risk scores that incorporate medical history, social determinants of health, genetics and/or clinical, laboratory, socioenvironmental, and technological biomarkers to predict acute clinical events, progressive organ dysfunction and mortality.
5. Improved access to real-world longitudinal data coupled with biomarkers. This can be done through expansion of existing longitudinal studies to include biological specimens and real-world data in a variety of resources settings, including countries with fewer health care resources.
6. Improved functional assessments to correlate with progressive and/or irreversible organ dysfunction, limitations on daily living, and mortality in individuals with SCD. These assessments should go beyond the 6-minute walk test and patient-reported outcomes and include correlation with biomarkers such as biological age by methylation status.
7. In depth studies of adolescents and young adults including clinical phenotyping, biomarkers, and patient-reported outcomes; prospective collection of outcomes to address the contribution of social determinants of health to the pathophysiology of SCD and organ dysfunction.
8. Inclusion of long-term follow-up of organ function in clinical trials of new therapies for sickle cell disease.

References

1. Piel FB, Tewari S, Brousse V, et al. Associations between environmental factors and hospital admissions for sickle cell disease. Haematologica 2017;102(4):666-675. DOI: 10.3324/haematol.2016.154245.
2. Kirkham JK, Estepp JH, Weiss MJ, Rashkin SR. Genetic Variation and Sickle Cell Disease Severity: A Systematic Review and Meta-Analysis. JAMA Netw Open 2023;6(10):e2337484. (In eng). DOI: 10.1001/jamanetworkopen.2023.37484.

3. Rees DC, Brousse VAM, Brewin JN. Determinants of severity in sickle cell disease. Blood Rev 2022;56:100983. DOI: 10.1016/j.blre.2022.100983.
4. Delgadinho M, Veiga L, Ginete C, et al. Differential expression of adhesion molecules in sickle cell anemia and gut microbiome effect. Ann Hematol 2024;103(2):409-419. DOI: 10.1007/s00277-023-05589-5.
5. Liem RI, Lanzkron S, T DC, et al. American Society of Hematology 2019 guidelines for sickle cell disease: cardiopulmonary and kidney disease. Blood Adv 2019;3(23):3867-3897. DOI: 10.1182/bloodadvances.2019000916.

II. Enhance Pain Treatment and Research

Background

Pain is the most common clinical manifestation of SCD. Individuals with SCD experience severe acute and chronic pain that collectively has a profound impact on health-related quality of life. Pain treatment accounts for over 90% of emergency department visits and hospitalizations for individuals with SCD and more frequent hospital visits predict early death.[1] Importantly, pain is a multi-dimensional unpleasant sensory and emotional experience, thus the assessment and management of pain should be addressed using a Whole Person Health[2] approach.

The prevalence of SCD pain is underestimated by examining healthcare facility utilization alone, as individuals frequently manage pain at home, and adults often experience pain that is not defined as acute sickle cell pain. While acute care visits for pain are concentrated among people 18-30 years old; with increasing age most patients experience progressively more frequent pain. One quarter to one half of adults with SCD live with chronic pain.[3] Opioids remain the mainstay of acute SCD pain therapy but often do not provide effective analgesia. Rapid individualized opioid analgesia improves outcomes and reduces the probability of hospital admission; however, subsets of individuals do not experience positive outcomes and have a high frequency of hospital visits or protracted acute sickle cell pain with minimal opioid response.

Outside the hospital, many individuals with SCD use opioids for short-term management of pain exacerbations; a minority are on long-term opioid therapy, and relatively few take high daily doses.[4] Still, adverse opioid effects and fear of addiction pose a major challenge in opioid prescribing, and little consensus exists on the overall strategy for opioid therapy for chronic SCD pain. Dosing parameters vary widely due to a lack of evidence on expected benefits and risks, as do strategies to address the issue of terminating unsuccessful opioid therapy. Both clinicians and individuals with SCD labor under a cloud of disproportionate suspicion for addiction, “drug-seeking behavior,” and similar concerns; some of which may be related to racial biases. Many individuals with SCD use cannabinoids that are widely marketed to reduce suffering, with little evidence to support perceived benefits nor to quantify adverse effects - especially on developing brains of adolescents. Other pharmacotherapies for chronic non-cancer pain are recommended in expert consensus guidelines, though they generally have modest individual

effects and minimal clinical or preclinical evidence in SCD. Nonpharmacologic therapies, including cognitive behavior therapy, are also widely recommended despite poor access and a modest evidence base in SCD. Some of these problems stem from the minimal research focused on outpatient treatment of pain in adults with SCD, for whom chronic pain is more prevalent.

The scope of SCD pain is far reaching for individuals, interfering with their health-related quality of life, education, and employment. The biology of SCD pain is not well understood and is driven by multiple factors beyond the hematologic abnormalities underlying SCD. Further, SCD pain biology may vary within an individual over time and between individuals. This lack of biological understanding is a barrier to novel targeted pain treatments. The complex nature of pain biology in humans has resulted in very limited translation of pain therapeutics from animal models to humans. This is possibly due to limitations in translatable animal models and/or lack or reproducible results between laboratories; however, the availability of humanized sickle cell mouse models offers a major advantage for translational studies, since the characteristic sickle cell pain features occur in these models and pain develops naturally from the underlying SCD.[5] Progress in the understanding of SCD pain biology has been made, but remaining knowledge gaps hinder the development of novel and effective pain therapies. Thus, further research is needed to expand the understanding of SCD pain biology and identify novel mechanism-based targets for pain treatments.

Acute pain may be driven by multiple factors beyond sickling and vaso-occlusion. We propose that the routine use of the term “vaso-occlusive crisis(es) (VOCs)” in the setting of pain be replaced with “acute sickle cell pain (ASCP),” since additional etiologies beyond vaso-occlusion likely cause acute pain in SCD. We believe utilizing a more general term that does not imply a single mechanism supports the goal of both investigating and therapeutically targeting additional mechanisms of pain.

Unanswered Questions

1. What is the natural history, including risk and protective factors, for the development of different pain phenotypes over the lifespan of an individual with SCD?
2. What existing therapies, and in what order, are most effective for prevention and treatment of acute and chronic SCD pain?
3. Does earlier and/or more aggressive disease-modifying therapy delay/prevent/reduce acute and chronic pain?
4. Will bone marrow transplantation or gene therapy reverse chronic pain in patients with SCD, and over what time course?
5. What are the underlying mechanisms for acute and chronic SCD pain, how do these mechanisms account for the interindividual pain variability, different phenotypes (e.g.,

neuropathic, nociceptive) and sources (e.g., central and peripheral nervous system, bone, muscle, visceral) of pain?

6. Can we identify novel, modifiable, etiologic targets that can be therapeutically leveraged?
7. What pain biomarkers, associated with complications of SCD (e.g., inflammation, neural injury, vascular injury) can be developed? Ideal biomarkers could predict or evaluate the risk of pain, predict pain phenotypes and trajectory, and demonstrate response to therapy.
8. What integrative health interventions for SCD pain should be studied and what are the biological targets for such interventions? What is the most optimal way to investigate a Whole Person Health (i.e., biological, behavioral, social, and environmental areas)[6] approach to SCD pain?

Research Priorities

1. Determine the natural history and modifiable risk factors (e.g., social, environment, psychological, biological) for the development of varied SCD pain phenotypes that include acute and chronic pain. Examine the effect of social determinants of health, gender, and organ damage on the transition from acute to chronic pain.
2. Investigate the use of existing pharmacological (e.g., opioids, nonsteroidal anti-inflammatory drugs, serotonin and norepinephrine reuptake inhibitors, gabapentinoids, ketamine, cannabinoids) and non-pharmacologic therapies (e.g., behavioral health interventions, integrative approaches, physical therapy) for the treatment of acute and chronic pain and understand how to optimize the use of these for individualized pain treatment. Determine which treatment has the best evidence for efficacy and effectiveness, whether there are genetic factors that influence response to analgesics (e.g., opioids), and ensure risks, benefits, and long-term effects are clearly understood.
3. Assess the impact of pharmacologic (e.g., hydroxyurea, glutamine, voxelotor, crizanlizumab, etc.), curative and potentially curative therapies (i.e., bone marrow transplantation, gene therapy), and integrative approaches on the development of chronic pain.
4. Identify systematic challenges in the healthcare system that create barriers to receiving optimal pain treatment and develop strategies to address these barriers.
5. Understand the genetic underpinnings and molecular mechanisms that evoke acute and chronic pain. This should include investigating how abnormalities in the peripheral and central nervous system drive SCD pain, and whether pain mechanisms change over the lifespan, differ based on sex, and account for interindividual variability and SCD pain phenotypes.

6. Discover translatable targets to prevent and/or treat acute and chronic SCD pain using pharmacologic, integrative, and technology enhanced approaches. When appropriate, leverage FDA-approved drugs, interventions, or devices that can be repurposed for SCD pain treatment.
7. Develop pain biomarkers (e.g., circulating constituents, physiological neurovascular determinants, wearable devices with remote access, neuroimaging, quantitative sensory testing) that can be used in conjunction with patient-reported pain assessments. These composite biomarkers should be integrated into pre-clinical studies and clinical trials to validate their applicability for the assessment and treatment of acute and chronic pain and could ultimately be used to direct personalized pain treatment.
   (**Important note:** Pain biomarkers are NOT meant to replace patients' report which is the gold standard for pain assessment. Any such biomarker should be interpreted in the context of the patient report of pain, be used according to their specific purpose, and be tested for their predictive power to understand the patients' pain experience.)
8. Develop mechanism-based approaches to use the Whole Person Health care model to reduce pain and advance overall well-being.

References

1. Platt OS, Thorington BD, Brambilla DJ, Milner PF, Rosse WF, Vichinsky E, Kinney TR. Pain in sickle cell disease. Rates and risk factors. N Engl J Med 1991;Jul 4;325(1):11-6. doi: 10.1056/NEJM199107043250103.
2. NCCIH (nih.gov). *Whole Person Health: What You Need To Know* | https://www.nccih.nih.gov/health/whole-person-health-what-you-need-to-know
3. Smith WR, Penberthy LT, Bovbjerg VE, McClish DK, Roberts JD, Dahman B, Aisiku IP, Levenson JL, Roseff SD. Daily assessment of pain in adults with sickle cell disease. Ann Intern Med 2008;Jan 15;148(2):94-101. doi: 10.7326/0003-4819-148-2-200801150-00004.
4. Han J, Zhou J, Saraf S, Gordeuk VR, Calip GS. Characterization of opioid use in sickle cell disease. Pharmacoepidemiol Drug Saf 2018;May;27(5):479-486. doi: 10.1002/pds.4291. Epub 2017 Aug 16.
5. Brandow AM, Zappia KJ, Stucky CL. Sickle cell disease: a natural model of acute and chronic pain. Pain 2017; Apr;158 Suppl 1(Suppl 1):S79-S84. doi: 10.1097/j.pain.0000000000000824.
6. NCCIH (nih.gov) *Complementary, Alternative, or Integrative Health: What's In a Name?* https://www.nccih.nih.gov/health/complementary-alternative-or-integrative-health-whats-in-a-name

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III. Optimize the Use of Hydroxyurea, Blood Transfusions, and Currently Approved Pharmacologic Therapies

Background

Hydroxyurea and simple/exchange red blood cell transfusions are the most widely used disease-modifying therapies for SCD, but their effectiveness is currently limited by system, provider and individual barriers to utilization or dosing, toxicity or potential toxicity, suboptimal response, or contraindications for certain subgroups of individuals living with SCD.

Evidence-based guidelines are now available for the initiation and use of hydroxyurea, transfusions, and iron chelation therapy to manage transfusion-acquired hemosiderosis.[1] Additionally, the FDA approved two new drugs for the treatment of SCD including L-glutamine and crizanlizumab to reduce the onset and/or intensity of vaso-occlusive pain episodes. The third newly FDA-approved medication, voxelotor, is a novel agent with the ability to block hemoglobin S polymerization and improve total hemoglobin levels. These additional medications provide opportunities to develop rational approaches for combination therapy with hydroxyurea or the use of these agents alone.

In addition to these recently approved drugs, several new medications are currently in the development and testing pipeline that are likely to be approved in the coming years. The future of disease modifying therapy for SCD is likely to be combination therapy, but there are many unanswered questions as to how to best combine or utilize this growing number of medications to reduce the morbidity and mortality associated with SCD, as well as improve function and quality of life.[2]

Despite this, there remains considerable variation in utilization of these therapies such that many individuals with SCD remain sub-optimally treated or not treated with disease modifying therapies at all. Limits in medication adherence is another important concern that impedes the full benefits of existing treatments. Emphasis should be placed on standardizing the use of and access to these therapies to provide disease modification for as many individuals with SCD as possible, on improving adherence[3-5] to these evidence-based therapies, clarifying susceptibilities to toxicities based on individual, sub-group and population characteristics, and on determining whether these therapies can prevent or even reverse SCD-related organ dysfunction.

While continued efforts are needed to address the underlying pathophysiology of SCD, there is also a great need for additional research to develop and study the impact of additional therapies on co-morbidities such as kidney disease, acute chest syndrome, lung disease, and pulmonary hypertension, among others. There are certain subgroups of individuals with SCD, including those with less common genotypes (HbSC, HbSβ^+-thalassemia) and pregnant persons with SCD, for whom additional research is needed to generate evidence-based guidelines on the best pharmacologic management specific to these subpopulations. In addition, other potentially organ-sparing medications, used alone or in combination with SCD-specific therapies, used by other specialties (e.g., cardiology, pulmonary, renal, brain, etc.) could be considered for reducing the SCD-associated health burdens. Future therapeutic trials should also include the range of SCD genotypes and individuals with unique considerations such as safe pregnancy and lactation.

Additional major issues include access to medications in high income and low-middle income countries, assessing and addressing the values, priorities, and perceptions of disease treatment in diverse global populations and sub-groups (e.g., children, pregnancy, lactation).

Unanswered Questions

1. How should we effectively combine existing disease modifying therapies for SCD? Which patients? Which symptoms? At what age(s)?
2. How do we improve dosing and adherence to prescribed therapeutic interventions such as transfusions/chelation, hydroxyurea, and recently developed FDA-approved therapies?
3. How do we determine the safety, dosing, and benefits of hydroxyurea for individuals with genotypes other than HbSS/HbSβ^0-thalassemia, especially HbSC?
4. How do existing therapies impact SCD-related co-morbidities that include, but are not limited to, kidney disease, obstructive lung disease, cardiac fibrosis, and pulmonary hypertension?
5. What are the most effective chelation practices for SCD (especially compared to thalassemia)? How to choose single or multi-agent chelators to maximize feasibility and effectiveness, while minimizing toxicities?
6. What considerations are needed in low-resource settings such as access, feasibility, safety monitoring, toxicity, role, and cost-analysis of chelation, and approaches to disease modifying therapy, including hydroxyurea, the more novel pharmacologic agents, and transfusions?
7. What considerations are needed for safe and effective disease modifying therapy during pregnancy/lactation in both high and low-resource settings?
8. Why might providers not offer all treatment options to a patient with SCD?
9. How do SCD co-morbidities affect the efficacy and safety of existing disease modifying therapies? How to develop protocols for modifying approaches to dosing and monitoring of these agents in the setting of chronic organ damage or other co-morbidities?

Research Priorities

1. Longitudinal studies, including the use of real-world data, to determine the long-term effects of transfusions, hydroxyurea, and the newer disease modifying therapies, including gene therapy or hematopoietic stem cell transplant on preservation or restoration of organ function. Consider the establishment of long-term registries, especially for the newer medications, across lifespan and global settings.
2. Clinical trials to modify disease altering co-morbidities, such as kidney disease, obstructive lung disease, pulmonary hypertension, and cardiovascular injuries (e.g., cardiac and brain).
3. Consideration and investigation of the effect of existing co-morbidities on the potential use, efficacy, or safety of existing therapies to clearly understand the indications and approaches to differences in the appropriate dosing, safety, and efficacy across the lifespan.
4. Research on the effect and role of disease modifying therapies on reproductive health concerns and outcomes, and how to minimize the risks, for individuals with SCD including pregnancy, lactation, menstruation, and fertility for men and women.

5. Include assessment of patient-reported outcomes as a clinical endpoint for all studies investigating the effects of disease modifying therapies.
6. Pharmacogenomic studies investigating inter-patient variability in response or toxicity for existing disease modifying therapies to identify which individuals are more or less likely to benefit from specific medications and experience potential toxicity.
7. Define additional biomarkers (e.g., blood, metabolite, imaging) for detecting, longitudinal tracking and predicting utility (i.e., responsiveness), and impact of these disease modifying agents on long-term health and quality of life.
8. Design and execute prospective clinical trials to determine the efficacy of hydroxyurea in individuals with HbSC and other less common SCD genotypes. Considerations should include investigation of predictors of response, preliminary research utilizing existing real-world or registry data, research focused on the suboptimal medication adherence to hydroxyurea and other disease modifying pharmacologic therapies, and exploration of specific markers or definitions of treatment futility.
9. As part of improving global access to disease modifying therapies, assess the cost-effectiveness and the potential for local or regional manufacturing of high-quality disease-modifying therapies beyond hydroxyurea across high and low-middle income countries.
10. Research focused on short and long-term effects of blood transfusions on organs, with a focus on challenges that limit the safety or efficacy of transfusions, including mechanisms behind hyperhemolytic transfusion reactions and focused research to reduce the risk of alloimmunization and iron overload.
11. Research focused on novel approaches to identifying and addressing barriers to medication adherence as well as monitoring medication adherence, including development and evaluation of digital health tools and community-based interventions.

References

1. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, Jordan L, Lanzkron SM, Lottenberg R, Savage WJ, Tanabe PJ, Ware RE, Murad MH, Goldsmith JC, Ortiz E, Fulwood R, Horton A, John-Sowah J. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA. 2014;Sep 10;312(10):1033-48. doi: 10.1001/jama.2014.10517.
2. Lugthart S, Ginete C, Kuona P, Brito M, Inusa BP. An update review of new therapies in sickle cell disease: the prospects for drug combinations. Expert Opinion on Pharmacotherapy. 2024;Jan 22;25(2):157-70. doi: 10.1080/14656566.2024.2317336.
3. Newman TV, Yang J, Suh K, Jonassaint CR, Kane-Gill SL, Novelli EM. Use of Disease-Modifying Treatments in Patients With Sickle Cell Disease. JAMA Netw Open. 2023;Nov 1;6(11):e2344546. doi: 10.1001/jamanetworkopen.2023.44546.
4. Walsh KE, Cutrona SL, Kavanagh PL, Crosby LE, Malone C, Lobner K, Bundy DG. Medication adherence among pediatric patients with sickle cell disease: a systematic review. Pediatrics. 2014;Dec 1;134(6):1175-83. doi: 10.1542/peds.2014-0177.
5. Adams-Graves P, Bronte-Jordan L. Recent treatment guidelines for managing adult patients with sickle cell disease: challenges in access to care, social issues, and adherence. Expert review of hematology. 2016;Jun 2;9(6):541-52. doi: 10.1080/17474086.2016.1180242.

IV. Develop Novel Drug Therapies

Background

Hydroxyurea (HU), the first US Food and Drug Administration (FDA)-approved drug for the treatment of SCD, remains the standard of care for adults and children. Its benefits include fetal hemoglobin (HbF) induction, increase in total hemoglobin, and decreased inflammation, vaso-occlusive events, and hemolysis.[1] HU therapy, however, is myelosuppressive, requires frequent monitoring, and is not adequate for all patients. After decades of research, three additional agents: L-glutamine, crizanlizumab, and voxelotor, were US FDA-approved for SCD; yet these agents have limited efficacy.[2-4] There remains a dearth of specific treatment options for SCD compared to less common genetic diseases such as cystic fibrosis and hemophilia, with 8 and 21 US FDA-approved drugs, respectively.[5] Thus, we need significant research efforts focused on developing safe, effective, and affordable drug options for SCD. Whether the currently approved drugs produce additive or synergistic treatment benefits for SCD remains a knowledge gap since formal studies to define effective combination drug regimens with low toxicity are lacking.[6] Laboratory-based cellular systems such as human organoids, non-murine animal models, and computer-assisted design techniques (artificial intelligence) offer the means to evaluate combination therapies and inform innovative human clinical trial designs.

The root cause of SCD is deoxygenated hemoglobin S polymerization. Therefore, the development of affordable, effective oral small inhibitors for worldwide access should be a significant research goal. The most effective strategy to date for blocking hemoglobin S polymerization is increasing fetal hemoglobin levels; however, the challenge remains how to do so in a potent, safe, and selective manner and developing drugs targeting the erythroid lineage. Other recent approaches to inhibit hemoglobin S polymerization include increasing hemoglobin oxygen affinity and altering red cell ATP levels through pyruvate kinase activation. Downstream-specific cellular targets to alleviate the clinical severity and complications of SCD include decreasing oxidative stress and inflammation, reversing endothelial dysfunction, and decreasing heme levels produced by chronic hemolysis.[6,7] Targeting these mechanisms may significantly improve blood flow, endothelial function, and overall vascular health, thus reducing vaso-occlusion, pain, and organ damage. Methods to study globin gene regulation and erythropoiesis in SCD to identify druggable targets include *in vitro* cultures of immortalized cell lines, primary erythroid cells, and novel humanized systems, such as induced pluripotent stem cells, which are amenable to genetic and chemical screens and detailed mechanistic exploration. Drug discovery approaches for downstream targets include high-throughput screening, *in silico* structure-based drug design, and virtual screening. Animal models such as transgenic humanized mice and large animals are powerful adjuncts.

Another critical area to address in SCD is developing personalized medicine approaches for predicting individualized responses to drugs. Correlation of defined clinical endpoints and associated laboratory measurements with each patient's genomic, transcriptomic, proteomic, and metabolomic profiles is a step toward this goal. A final challenge is the progression of promising drug candidates to clinical trials and eventual regulatory approval. Employing adaptive and novel trial designs, such as those with control groups generated by artificial

intelligence from extensive electronic medical records, digital twin design, and surrogate endpoints will accelerate drug development. Engaging with regulatory agencies early in the drug development phase will ensure alignment with country-specific requirements and desirable outcome measures relevant to SCD.

Other critical adjuncts to ensure the success of clinical trials must include robust, cohesive, and well-supported prospective longitudinal SCD registries and sample biorepositories that integrate with historical and ongoing efforts including patients and healthy controls across healthcare systems. The support of these registries can lead to a clear understanding of the overall impact for current therapeutics and emerging new therapies for SCD. The absence of such registries has left us without a clear understanding of the global impact of HU. Hence, we should not repeat this mistake for emerging new therapies for SCD, especially those generating mixed hematopoietic chimerism, with uncertain short-term and long-term clinical outcomes.

Unanswered Questions

1. What strategies will help develop novel therapies for inhibiting the root cause of SCD (i.e., sickle hemoglobin polymerization)?
2. What are the most promising targets for new drug development in SCD, and how can they be targeted and assessed?
3. What are the rational approaches to developing safe and effective combination drug therapy?
4. What are the genetic and biochemical biomarkers that predict individualized responses to drugs, including novel therapies for pain and other complications?
5. What are novel disease-modifying therapies for patients with specific types of end-organ damage associated with poor survival?
6. How do we develop sustainable and robust clinical trial designs, and SCD patient registries and biorepositories to evaluate the efficacy of new agents?

Research Priorities

1. Develop novel approaches to inhibit sickle hemoglobin polymerization while simultaneously exploring strategies to mitigate adverse effects of emerging therapies; with a focus on targeting fetal hemoglobin modifiers to the erythroid lineage enhancing treatment efficacy and safety for SCD.
2. Expand studies in animal models and novel cell-based *in vitro* systems to assess the mechanism of action and efficacy of druggable targets.
3. Develop therapeutics that address downstream organ-specific damage observed in SCD.
4. Develop combination and long-acting formulations as a new therapeutic group of drugs for SCD.
5. Consider repurposing FDA-approved drugs and new therapeutics for SCD complications such as stroke, renal, and cardiovascular disease.
6. Develop novel approaches, such as artificial intelligence or drug modeling, for defining additive or synergistic drug combinations.

7. Develop innovative and creative research trial designs that include subjects with all SCD genotypes (HbSS, HbSβ^0-Thalassemia, HbSC, HbSβ^+-Thalassemia, etc.) and study endpoints to determine treatment safety and efficacy while measuring and prioritizing key biochemical, clinical, and patient-reported outcomes.
8. Establish long-term follow up of all individuals with SCD, including those treated with novel drugs, cellular, and gene therapies and track the correlation between the percentages of corrected cells (chimerism), durable efficacy, side effects, toxicity, and safety of transformative therapies. Using comprehensive robust prospective longitudinal registries for SCD clinical trials addressing current gaps will align with recognized practices for other inherited diseases.

References

1. McGann PT, Ware RE. Hydroxyurea therapy for sickle cell anemia. Expert Opin Drug Saf, 2015;14:1749-58. doi: 10.1517/14740338.2015.1088827.
2. Niihara Y, et al. A Phase 3 Trial of l- Glutamine in Sickle Cell Disease, A phase 3 Trial of l-glutamine in sickle cell disease, N Engl J Med. 2018;379(3), 226–235. doi: 10.1056/ NEJMoa1715971.
3. Ataga KI, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease, N Engl J Med. 2017;376(5), 429–439. doi: 10.1056/NEJMoa1611770.
4. Vichinsky E et al. A phase 3 randomized trial of voxelotor in sickle cell disease, N. Engl. J. Med. 2019;381(6), 509–519. doi: 10.1056/NEJMoa1903212,381(6).
5. CenterWatch A WCG Company. FDA Approved Drugs. https://www.centerwatch.com/directories/1067-fda-approved-drugs/topic/175
6. Pace BS, Starlard-Davenport A, Kutlar A. Sickle cell disease: progress towards combination drug therapy Br J Haematol. 2021; July;194(2):240-251. doi: 10.1111/bjh.17312. 194:240-251.
7. Steinberg MH, Gladwin MT. "Severity" in adult sickle cell disease. Am J Hematol. 2023;98:1508-1511. doi: 10.1002/ajh.27024.

V. Strengthen Curative Therapies

Background

The exciting expansion in the therapeutic landscape for SCD raises important questions in relation to the further development of curative approaches for the disease. Curative therapies can currently be divided into two categories: allogeneic hematopoietic stem cell transplant (allo-HSCT) and autologous hematopoietic stem cell therapies. While the potential to modify long-term hematopoietic stem cells safely and successfully *in situ* (aka "*in vivo*" therapies) is being actively pursued, we believe success in this area goes beyond a five-year horizon. Thus, we focused on the improvement of hematopoietic stem-based therapies to cure SCD.

Ever since a report of successful allogeneic stem cell transplantation in 1984, there has been steady improvement in both the utilization and safety of allo-HSCT.[1, 2] There is broad consensus that individuals with SCD who have an human leukocyte antigen (HLA) matched sibling donor (MSD) should consider undergoing MSD allo-HSCT due to positive outcomes; 90-95% long-term cure rates.[3] MSD allo-HSCT has been used to cure SCD globally, and the cost has been reduced to $10-20,000 USD in India, thus making it financially and geographically accessible to a broader range of individuals (including those from Africa who travel to India to receive the therapy). The cost of $10,000 USD amortized over a 70-year lifespan equates to $0.40/day.[4] Only a fraction of

individuals (15-20%) with SCD[5], however, have a MSD. While HLA haplo-identical HSCT has been identified as a potential solution to the problem of donor availability; until recently, results have been mixed. The development of post-transplant cyclophosphamide, alpha-beta T-cell depletion, and refined conditioning regimens have also made HLA haploidentical HSCT a suitable approach to curative therapy for SCD.[6,7]

In parallel with allo-HSCT, genetically engineered autologous HSCTs to potentially cure SCD ("gene therapy") has also been developed. Genetic engineering is accomplished through lentiviral delivery of an anti-sickling beta-globin-like transgene, or through gene editing. The approvals of exagamaglogene autotemcel (a CRISPR-Cas9 gene editing/HbF induction based drug) and lovotibeglogene autotemcel (a lentiviral anti-sickling based drug) in December 2023 highlights the exciting progress being made.[8] The high cost, however, and the challenging commercial expansion of these therapies has raised significant concerns about whether autologous based approaches will be widely accessible in the US and globally.[9] In addition, there are a variety of other gene therapy/gene editing approaches in pre-clinical and clinical development that have different mechanisms of action and may provide future alternatives. [10]

There remain, however, several unanswered questions and research priorities to make curative therapies safer, more effective, and more accessible.

Unanswered Questions

1. The clinical end point assessed most often is frequency of vaso-occlusive events, but the impact of allogeneic and autologous HSCT therapies on other organs affected by SCD is incompletely defined, especially in the long-term.
2. Polyclonal engraftment is considered a protective outcome against myelodysplasia syndrome/leukemia following curative therapy, but what differences in polyclonality are achieved by the different approaches?
3. High dose chemotherapy conditioning is applied commonly in both allogeneic and autologous therapies. Can conditioning regimens be made safer (and thereby more accessible) through non-chemotherapy with non-genotoxic agents (e.g., antibodies, conjugated antibodies, bispecific or CAR-T therapies)?
4. For autologous therapies, an important barrier is the ability to mobilize and collect $CD34^+$ HSPCs safely and effectively. The patient experience would be significantly improved if the number of mobilization/pheresis cycles could be reduced (ideally to one). Can new drugs and regimens provide a solution to this problem?
5. In allogeneic setting sickle-related inflammation may impact risks of both engraftment and graft-versus host disease. In autologous therapies, inflammation affects the efficacy of mobilization/pheresis and the quality of the harvested and engineered CD34+ hematopoietic stem progenitor cells. How do we minimize the negative effect of inflammation on curative therapy outcomes?
6. Can curative therapy technology and safety be improved and cost reduced for broader delivery to more medical centers globally?

Research Priorities

1. Support development of improved HLA haplo-identical transplant regimens.
2. Continue to support a diversity of approaches in autologous potentially curative therapies, including studies of long-term safety and efficacy, cost, and accessibility.
3. Adapt curative therapies for RBC alloimmunized patients or for patients lacking a safe, accessible blood supply.
4. Develop measures and strategies to measure and increase polyclonal engraftment.
5. Develop reduced conditioning or non-chemotherapy conditioning regimens for allogeneic and autologous therapies.
6. Develop improved mobilization and pheresis regimens.
7. Elucidate the pathophysiology of inflammation and develop anti-inflammation therapies to improve safety and efficacy in curative therapies.
8. Identify biomarkers to guide providers and assist individuals with SCD in making informed decisions about the best curative therapy option (personalized medicine), and support studies comparing curative therapies with disease modifying therapies including evaluation of quality of life and impacts on daily life.
9. Standardize assessment of psychosocial readiness before curative therapy - to be conducted in all prospective participants.

References

1. de la Fuente J, Gluckman E, Makani J, et al. The role of haematopoietic stem cell transplantation for sickle cell disease in the era of targeted disease-modifying therapies and gene editing. *Lancet Haematol*. 2020;7(12):e902-e911. doi:10.1016/S2352-3026(20)30283-0
2. Krishnamurti L, Hematopoietic cell transplantation for sickle cell disease, Front Pediatr, 2021;8
3. Kanter J, Liem RI, Bernaudin F, et al. American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation. *Blood Adv*. 2021; 5(18):3668-3689. doi:10.1182/bloodadvances.2021004394C https://doi.org/10.1038/s41409-020-0983-5
4. (FaulknerL and Al. Setting up and sustaining blood and marrow transplant services for children in middle income economies BMT 2021,56,536-543
5. Gluckman E, Cappelli B, Bernaudin F, et al. Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. *Blood*. 2017;129(11):1548-1556. doi:10.1182/blood-2016-10-745711PMID: 32202248; https://doi.org/10.1182/blood.2023023301
6. Gluckman E and Al. Alternative donor hematopoietic stem cell transplantation for sickle cell disease in Europe. Hematol Oncol Stem Cell Ther. 2020,13(4),181-188
7. Kassim AA, de la Fuente J, Nur E, Wilkerson KL, Alahmari AD, Seber A, Bonfim C, Simões BP, Alzahrani M, Eckrich MJ, Horn B, Hanna R, Dhedin N, Rangarajan HG, Gouveia RV, Almohareb F, Aljurf M, Essa M, Alahmari B, Gatwood K, Connelly JA, Dovern E, Rodeghier M, DeBaun MR. An international learning collaborative phase 2 trial for haploidentical bone marrow transplant in sickle cell disease. Blood. 2024 Jun 20;143(25):2654-2665.
8. Sickle Cell Disease Association of America. *SCDAA Statement About Gene Therapy Approval.* https://www.sicklecelldisease.org/2023/12/08/scdaa-statement-about-gene-therapy-approval/
9. Sharma A, John TD. Dismantling cost and infrastructure barriers to equitable access to gene therapies for sickle cell disease. *Lancet Haematol*. 2024;11(8):e556-e559. doi:10.1016/S2352-3026(24)
10. Park SH, Bao G CRISPR/Cas9 gene editing for curing sickle cell disease Transf Apher Sci 2021,60:103060

VI. Impact of the Dissemination and Implementation of Evidence Based Guidelines for SCD

Background

Major randomized controlled trials and high-quality observational studies in SCD have significantly impacted morbidity. Patients and providers in low- and middle-income settings, where the greatest burden of SCD exists, are challenged to access and implement evidence-based care. New therapies including gene therapy have emerged that offer more options. Still, evidence of inadequate uptake of efficacious treatment modalities in the standard care setting of higher income countries is apparent as exemplified by the underuse of disease modifying therapies in adults with SCD.

There is a lack of systematic procedures for clinical trials outcomes and guidelines dissemination to patients and providers that impact their implementation. Variability of resources and care delivery models present critical barriers to individuals with SCD, providers, and healthcare systems, limiting implementation of evidence-based guidelines.

Finally, evidence-based guidelines have been developed for SCD; however, these guidelines need to be widely and equitably implemented to improve quality of care, health-related quality of life, and outcomes for individuals with SCD. Thus, there is a collective need to optimize the use of proven therapies and implement evidence-based guidelines using an active approach that is based on the principles of dissemination and implementation research.

In the next five years, we anticipate that the following areas will need to be addressed:

- Collaborative approaches for disseminating guidelines will need to be established.
- Studies to identify strategies to assist staff at medical centers and providers to adapt and implement evidenced based guidelines/practices based on relevant contextual factors, including culture.
- Financial alignment – cost effectiveness studies, cost avoidance, and work addressing payors will need to occur.
- Key partnerships outside of the medical setting need to be encouraged to test new and innovative approaches with schools, community-based organizations, community health workers, and more patient-centered care.
- Although ASH currently has five guidelines developed for the clinical management of SCD, there are many areas that could use stronger guidelines. Those areas include but are not limited to guidelines for chronic pain, gene therapy, and treatment for leg ulcers. Multidisciplinary collaboration with other sub-specialties may be necessary to tackle topics such as mental health and women's health.

Unanswered Questions

1. How do we optimally implement published evidence-based guidelines for SCD?
2. What are appropriate quality indicators for medical care delivered outside of a comprehensive SCD center?

3. Are outcomes – clinical trial measures that determine efficacy and effectiveness – implementable outside of academic medical centers?
4. What patient-centered healthcare delivery models and implementation strategies are effective in providing evidence-based SCD-related interventions?
5. What are optimal approaches for providing timely acute and chronic pain management in all care delivery settings?

Research Priorities

1. Evaluate the implementation of quality care/evidence-based guidelines including the need to define metrics for quality of dissemination AND quality of implementation. Develop strategies to evaluate the uptake of established guidelines by academic SCD centers and community physicians to determine challenges faced during implementation, fidelity of use, and adherence rates [1,2]
2. Identify barriers to receiving recommended SCD-specific treatment of evidence-based screening and treatment guidelines in variable resource settings external to academic (or traditional large) medical centers using a multi-stakeholder approach. Consider qualitative and quantitative evaluation of facilitators or techniques using determinant implementation science frameworks that assesses contextual factors including equity which can be leveraged for success.
3. Test interventions to overcome barriers to receiving recommended SCD-specific treatment evidence-based screening and treatment guidelines in variable resource settings. Identify practices (facilitators) that support implementation (possibly through multidisciplinary input) and test strategies to implement interventions. Include mobile health strategies and telemedicine when applicable.
4. Test dissemination and implementation strategies that support adaptation and implementation within multidisciplinary care across specialties and settings, including the emergency department, where gaps remain.
5. Develop guidelines for acute and chronic pain, leg ulcers, and gene therapy, which are high priority. Identify existing evidence-based guidelines in related fields that applied to individuals with SCD such as women's health (including pregnancy/reproductive health), infertility, and psychosocial and mental health. If no evidence exists, then randomized controlled trials should be pursued.

References

1. Oyeku, SO, Faro, EZ. Rigorous and practical quality indicators in sickle cell disease care. Hematology Am Soc Hematol Educ Program 2017 (1): 418–422. https://doi.org/10.1182/asheducation-2017.1.418.
2. Proctor, E Silmere H, Raghavan R, Hovmand P, Aarons G, Bunger A, Griffey R, Hensley M. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. Adm Policy Ment Health. 2011; Mar;38(2):65-76. doi: 10.1007/s10488-010-0319-7.

VII. Expansion of Sickle Cell Trait Research

Background

While approximately 100,000 individuals live with SCD in the United States, 2.5 million to 3 million individuals carry sickle cell trait (SCT). Carrier rates are estimated at one in twelve African Americans and 0.01% to 0.07% of the remaining population—primarily those of Arab, Southeast Asian, Hispanic, or Mediterranean descent. Worldwide, SCT affects an estimated 300 million individuals, with a prevalence ranging from 2% to 30% in more than 40 countries.[1] The Sickle Cell Anemia Control Act passed in 1972 by Congress paved the way to establish newborn screening (NBS) in the United States. It wasn't until research findings in 1995 demonstrating the effectiveness of oral penicillin prophylaxis in reducing pneumococcal sepsis in young children[2] with SCD, however, did all US states, Puerto Rico, and US Virgin Islands mandate universal NBS for all babies; and standardized protocols for reporting results for SCD and SCT positive babies were established by each state. While it is standard of care to refer all infants with SCD to a hematologist, often time parents with infants positive for SCT do not receive this information. Moreover, since SCT is a carrier state, evaluation by a specialist is not recommended. NBS identifies about 50 infants with SCT for each baby diagnosed with SCD. Individuals with SCT will benefit from genetic counseling to understand the implications of transmission to their children.

Sickle cell trait is generally an asymptomatic carrier state, and most carriers never have manifestations or clinical symptoms; however, numerous studies have reported potential clinical manifestations.[3-6] There has been substantial research to expand the understanding of SCT as a risk factor for chronic kidney disease and venous thromboembolism. Now, the field must move toward understanding genetic mechanisms, the role of the environment, and modifying factors in SCT that require additional intentional research studies. More rigorous epidemiologic, genetic, and clinical research studies are needed in areas such as venous thromboembolism, chronic kidney disease, and renal medullary carcinoma risk related to SCT status.

To understand the genetic history of SCT and SCD, researchers used whole genome sequencing to identify a single origin of the sickle mutation. This mutation originated in the Sahara during the Holo Wet Phase roughly 7,300 years ago.[7] Chromosomal recombination subsequently yielded five common haplotypes - Arabian/Indian, Benin, Cameroon, Central African Republic/Bantu, and Senegal .[7,8] This is clinically important because these haplotypes contribute to phenotypic variability in SCD. For example, the Senegal and Arabian/Indian haplotypes are associated with higher fetal hemoglobin levels and tend to have milder clinical disease.[9] Although prior studies have focused specifically on SCD, similar genomic differences may also modify phenotype in individuals with SCT.

To enhance research knowledge related to SCT, we need prospective natural history studies that follow these individuals from birth through adulthood to determine the risk for clinical

complications for this group. This approach will also provide better phenotype data and sample collection to conduct genomic, transcriptomic, proteomic and metabolomics studies in this population. In addition, more research is required to understand the contribution of exercise physiology to the risk of adverse clinical outcomes and to provide sound evidence-based clinical guidance for these individuals. Novel clinical research is needed to understand maternal and fetal pregnancy risk. Finally, rigorous and replicable research on SCT, including its pathology and genetic risk factors, is required.

Unanswered Questions

1. What is appropriate medical education for individuals with SCT, primary care providers, and hematologists?
2. How can we improve the communication of newborn screening results that their baby has SCT to parents?
3. What research is needed to understand and address misinformation and communication regarding the absolute risks of SCT?
4. What are the best practices for reproductive counseling for individuals with SCT?
5. What environmental factors, or combination of factors, modify the risk of rhabdomyolysis and exercise-related injury in individuals with SCT? What is the degree of rigorous exercise that results in exercise-related injury?
6. Can we predict who is most at risk for clinical outcomes where SCT is a known risk factor, such as venous thromboembolism and chronic kidney disease?
7. How do genetic variants/genotypes modify the risk of complications (i.e., alpha-thalassemia, glucose-6-phosphate dehydrogenase, pyruvate kinase deficiency)?
8. Can we quantify the degree of risk for rarer clinical outcomes, such as renal medullary carcinoma, and determine key modifying factors that increase this risk?

Research Priorities

1. Establish effective protocols for communication of newborn screening results to the parents of babies identified with SCT and offer genetic counseling.
2. Conduct community-based participatory research around misinformation, perceptions of risks/stigma, and best practices for patient-centered messaging about reproductive and genetic counseling.
3. Establish a large natural history study in SCT that will provide better precision on estimates and collect targeted data. Conduct prospective cohort studies of individuals with SCT and other medical complications to determine the occurrence rates.
4. Perform in-depth laboratory and clinical studies to determine modifying factors of clinical complications, both short-term and long-term, and understand mechanisms of risk.

5. Conduct population-based studies of SCT using existing databases and biorepository samples, including studies on participants of diverse genetic ancestry, ethnic groups, and environmental backgrounds.
6. Conduct prospective studies to understand exertion-associated risk, including identifying exertion-associated genetic risks. Conduct cohort studies of athletes with exertion-related symptoms and develop evidence-based interventions.
7. Assess universal precaution protocols that impact exertion-associated risk.
8. Study pregnancy-related complications for individuals with SCT.

References

1. Grant AM, Parker CS, Jordan LB, et al. Public health implications of sickle cell trait: a report of the CDC meeting. Am J Prev Med 2011;41:435. doi: 10.1016/j.amepre.2011.09.012.
2. M H Gaston, J I Verter, G Woods, C Pegelow, J Kelleher, G Presbury, H Zarkowsky, E Vichinsky, R Iyer, J S Lobel et al. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. N Engl J Med 1986 Jun 19;314(25):1593-9. PMID: 3086721 doi: 10.1056/NEJM198606193142501
3. Naik RP, Smith-Whitley K, Hassell KL, et al. Clinical Outcomes Associated With Sickle Cell Trait: A Systematic Review. Ann Intern Med 2018;169:619-27. doi: 10.7326/M18-1161.
4. Austin H, Key NS, Benson JM, et al. Sickle cell trait and the risk of venous thromboembolism among blacks. Blood 2007;110:908-12. doi: 10.1182/blood-2006-11-057604.
5. Naik RP, Haywood C, Jr. Sickle cell trait diagnosis: clinical and social implications. Hematology Am Soc Hematol Educ Program 2015;2015:160-7. doi: 10.1182/asheducation-2015.1.160
6. CDC. What is Sickle Cell Trait? https://www.cdc.gov/sickle-cell/sickle-cell-trait/
7. Shriner D, Rotimi CN. Whole-Genome-Sequence-Based Haplotypes Reveal Single Origin of the Sickle Allele during the Holocene Wet Phase. Am J Hum Genet. 2018 Apr 5;102(4):547-556.
8. Okpala, Iheanyi (2008). Practical Management of Haemoglobinopathies. John Wiley & Sons. p. 21. ISBN 978-1-4051-4020-1. Retrieved 2 June 2016.
9. Green NS, Fabry ME, Kaptue-Noche L, Nagel RL (Oct 1993). Senegal haplotype is associated with higher HbF than Benin and Cameroon haplotypes in African children with sickle cell anemia. Am. J. Hematol. 44 (2): 145–6. doi:10.1002/ajh.2830440214. ISSN 0361-8609. PMID 7505527. S2CID 27341091.

Advancing Fundamental Knowledge to Enable Improved Approaches to SCD

Introduction

Mechanistic studies have been critical to dissecting the pathophysiology of SCD by defining its molecular basis, mechanisms of deoxyhemoglobin S polymerization, and sickle hemoglobin inhibition by fetal hemoglobin (HbF). Subsequent, critical laboratory studies defined the role of chronic hemolysis and increased endothelial cell activation in mediating blockage of blood flow and resulting ischemia-reperfusion injury, free-heme oxidative damage, platelet and coagulation activation, and inflammation.[1,2] These fundamental and cellular discoveries have led to the development and regulatory approval of the HbF inducer hydroxyurea,[3] the sickle hemoglobin polymerization inhibitor voxeletor,[4] and the anti-adhesion drug crizanlizumab.[5] Recent research efforts focus on novel agents such as pyruvate kinase activators are a novel class of drugs that target red cell metabolism by reducing the buildup of 2,3-diphosphoglycerate and increasing production of adenosine triphosphate, which reduces HbS polymerization. Parallel drug development efforts and the hope for gene therapy led to the discovery of both a successful lentivirus-based vector that safely delivers a modified β^{A}-globin gene ($\beta^{A\text{-}T87Q}$) and the achievement of CRISPR-Cas9 technology to reactivate HbF production. This research led to the historic US-Food and Drug Administration approval of two gene therapies for SCD and β-thalassemia in December 2023.[6,7] However, basic research to resolve complex pathologic networks in SCD provide opportunities for precise and novel drug targeting, and the design of combination drug regimens. A few areas of high priority for consideration over the next five years include globin gene regulation, genomics, mechanisms of pain control and safe transfusion therapy are discussed herein as examples of how fundamental research efforts continue to change the landscape for SCD treatment.

Regulation of Globin Gene Expression

Hemoglobin switching refers to dynamic globin gene expression throughout an individual's lifespan. Comprehension of this process promises new therapeutic opportunities for SCD based on HbF reactivation after infancy. Enormous essential research progress over the past two decades, following human and experimental genetics, has revealed a network of DNA-binding transcription factors, chromatin complexes, and master developmental regulators that together orchestrate hemoglobin switching.[8] The recognition of BCL11A as a crucial repressor of fetal γ-globin transcription has enabled the development of the first FDA-approved gene editing therapy, exa-cel, which targets critical sequences in *BCL11A* to induce HbF. [9-11] Top priorities for ongoing research include a complete understanding of the mechanisms involved in hemoglobin switching with the goal of novel therapeutics development, including improved small molecule,

gene, and cell-based therapies to interfere with γ-globin gene silencing without causing undesirable effects on erythropoiesis, hematopoiesis, or other biological functions. Advances in chemical biology, gene editing, and artificial intelligence may catalyze the next generation of treatments to deliver outstanding outcomes and reach patients broadly.

Genomic Medicine

The tremendous genomic understanding of SCD is the foundation for applying new genetic engineering technologies to develop diverse curative approaches to the disease. These new technologies include the discovery and development of novel classes of site-specific nucleases, homology-directed repair-based genome editing improvements, and the development of base editing and prime editing.[12] Also included is the discovery of new genetic engineering platforms, such as site-specific recombinases and transposases, and the applications of these approaches to new biological techniques, such as epitope engineering/stem cell shielding.[13,14] These new technologies provide a ripe environment to develop curative strategies that are safer and more effective than allogeneic hematopoietic stem cell transplantation, the current gold standard for the cure of SCD. The research priority to move the field forward in the next five years is to make the overall patient experience safer and more accessible by

1) finding improved methods of mobilizing and purifying hematopoietic stem cells[15]
2) developing cheaper and more reproducible automated and closed system manufacturing utilizing different genome editing technologies
3) developing conditioning regimens for autologous transplantation[16] that could generally be performed in an outpatient setting with minimal risk of organ damage with the preservation of fertility
4) developing *in vivo* gene therapy approaches

The iterative development to make curative therapies more accessible will involve a bench-to-bedside and back-again process in which laboratory scientists, clinical researchers, federal regulators, process engineers, reagent suppliers, patients, and their advocates work collaboratively to identify and solve the real-world problems that are currently barriers to the use of genomic medicines to cure individuals with SCD.

Pain Mechanisms

Pain is a significant comorbidity of SCD that leads to hospitalization, impaired quality of life, and reduced survival. However, gaps persist in understanding mechanisms that lead to acute and chronic pain, deep tissue/bone pain, top-down inhibitory pain pathways, and perception-based mechanisms, the impact of cannabinoids and opioids on sickle cell pathobiology, and evolution of molecular, cellular, and neural networks throughout the lifespan.[17] It is imperative to ask how we can more robustly predict, prevent, and treat SCD pain. The unique pathobiology

underlying SCD pain must be characterized by basic researchers in conjunction with the associated peripherally and centrally mediated nociceptive systems.[18] A significant gap exists in understanding neuromodulation and brain circuits involved in pain processing. How different genotypes modulate pain propensity, severity, and phenotype is critical to developing personalized interventions. Expertise from multiple fields, including other pain conditions, organ systems, Omics, technology development, neuroscience, nutrition, psychology, integrative medicine, pediatrics, and geriatrics, is required to understand pain phenotypes in SCD and develop the next generation of therapies. Some progress has been made in identifying treatable targets for chronic pain, which require clinical translation.[19] To date, one study demonstrated that involvement of the autonomic nervous system and vasoconstriction as contributors to inciting acute pain with physiological markers to predict the onset of acute pain.[20] Technology-enhanced approaches to quantify pain with a quantitative electroencephalogram, transcranial-focused ultrasound, and wearable devices with remote access must be advanced to clinical applications.[21,22] Data analytics and computational modeling efforts are challenged by small sample sizes and a need for clinically annotated biorepositories already identified as a research priority in this document.

Transfusion Medicine

Red blood cell (RBC) transfusions remain the cornerstone treatment for SCD, decreasing the anemia, the percentage of sickle RBCs, and blood viscosity. The beneficial effects of transfusions include overt stroke and silent infarct prevention. A comprehensive mechanistic understanding of how transfusions influence key pathways in SCD will optimize transfusion management and reveal new targets for drug development. Important mechanistic examples include how transfusions improve bone marrow niche cells[23,24] and the pulmonary microvasculature in acute chest syndrome. However, the complications of transfusions in SCD, such as alloimmunization with potential delays in transfusion support, life-threatening hemolytic transfusion reactions, and hyperhemolysis, need further investigation.[25] Areas of high research priority include elucidating SCD-specific mechanisms of humoral response to transfusions,[26] the role of specific innate and adaptive immune subsets in the induction and clinical severity of allo- and autoantibodies, and developing novel experimental models to study hyperhemolysis. Basic researchers should further explore the intrinsic characteristics of sickle RBCs and reticulocytes in auto- and alloimmunization. Also critical to progress is the use of Omics[27] with subsequent validation using *in vitro* and *in vivo* experimental platforms to define immune signatures and predict the differential response to inflammatory microenvironments,[28] which individuals with SCD are at the highest risk of alloimmunization and likely to develop severe hemolytic transfusion reactions. Developing biobanks with well-annotated biospecimens

tested against panels incorporating antigens more common in African Americans is central for these studies. Preventive safety systems to minimize alloimmunization should include high throughput genotypic matching tools that more accurately match donors to recipients and reduce the cost of care while improving clinical outcomes.[29] There is also an unmet need for new therapeutics to minimize transfusion complications. Strategies include novel immunomodulatory drugs targeting the humoral response, inhibition of innate immune inflammation (e.g., with anti-IL-1β), and drugs that reduce intravascular hemolysis.[30]

References

1. Hebbel RP, Osarogiagbon R, Kaul D. The endothelia biology of sickle cell disease: inflammation and a chronic vasculopathy. Microcirculation. 2004 Mar;11(2):129-51.
2. Belcher JD, Beckman JD, Balla G, Balla J, Vercellotti G. Heme degradation and vascular injury. Antioxid Redox Signal. 2010 Feb;12(2):233-48. doi: 10.1089/ars.2009.2822.
3. Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, McMahon RP, Bonds DR. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Engl J Med. 1995 May 18;332(20):1317-22. doi: 10.1056/NEJM199505183322001.
4. Vichinsky E, Hoppe CC, Ataga KI, Ware RE, Nduba V, El-Beshlawy A, Hassab H, Achebe MM, Alkindi S, Brown RC, Diuguid DL, Telfer P, Tsitsikas DA, Elghandour A, Gordeuk VR, Kanter J, Abboud MR, Lehrer-Graiwer J, Tonda M, Intondi A, Tong B, Howard J; HOPE Trial Investigators. A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. N Engl J Med. 2019 Aug 8;381(6):509-519. doi: 10.1056/NEJMoa1903212.
5. Ataga KI, Kutlar A, Kanter J, Liles D, Cancado R, Friedrisch J, Guthrie TH, Knight-Madden J, Alvarez OA, Gordeuk VR, Gualandro S, Colella MP, Smith WR, Rollins SA, Stocker JW, Rother RP. Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. N Engl J Med. 2017 Feb 2;376(5):429-439. doi: 10.1056/NEJMoa1611770.
6. Kanter J, Walters MC, Krishnamurti L, Mapara MY, Kwiatkowski JL, Rifkin-Zenenberg S, Aygun B, Kasow KA, Pierciey FJ Jr, Bonner M, Miller A, Zhang X, Lynch J, Kim D, Ribeil JA, Asmal M, Goyal S, Thompson AA, Tisdale JF. Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease. N Engl J Med. 2022 Feb 17;386(7):617-628. doi: 10.1056/NEJMoa2117175.
7. Frangoul H, Altshuler D, Cappellini MD, Chen YS, Domm J, Eustace BK, Foell J, de la Fuente J, Grupp S, Handgretinger R, Ho TW, Kattamis A, Kernytsky A, Lekstrom-Himes J, Li AM, Locatelli F, Mapara MY, de Montalembert M, Rondelli D, Sharma A, Sheth S, Soni S, Steinberg MH, Wall D, Yen A, Corbacioglu S. CRISPR-Cas9 Gene Editing for Sikcle Cell Disease and beta-Thalassemia. N Engl J Med. 2021 Jan 21;384(3):252-260. doi: 10.1056/NEJMoa2031054.
8. Khandros, E. & Blobel, G. A. Elevating fetal hemoglobin: recently discovered regulators and mechanisms. Blood 144, 845–852 (2024).
9. Menzel, S. et al. A QTL influencing F cell production maps to a gene encoding a zinc-finger protein on chromosome 2p15. Nat. Genet. 39, 1197–1199 (2007).
10. Xu, J. et al. Correction of sickle cell disease in adult mice by interference with fetal hemoglobin silencing. Science 334, 993–996 (2011).
11. Frangoul, H. et al. Exagamglogene Autotemcel for Severe Sickle Cell Disease. N. Engl. J. Med. (2024) doi:10.1056/NEJMoa2309676.
12. Bak RO, Gomez-Ospina N, Porteus MH. Gene Editing on Center Stage. Trends Genet. 2018 34:600-611. doi: 10.1016/j.tig.2018.05.004.
13. Marone R. Landmann E, Devaux A. et al. Epitope-engineered human hematopoietic stem cells are shielded from CD123-targeted immunotherapy. J Exp Med 2023 220(12):e20231235. doi: 10.1084/jem.20231235.
14. Park SH, Lee CM, Dever DP, Davis TH, Camarena J, Srifa W, Zhang Y, Paikari A, Chang AK, Porteus MH, Sheehan VA, Bao G. Highly efficient editing of the beta-globin gene in patient-derived hematopoietic stem and progenitor cells to treat sickle cell disease. Nucleic Acids Res. 2019 47:7955-7972. doi: 10.1093/nar/gkz475.
15. Ruminski PG, Rettig MP, DiPersio JF. Development of VLA4 and CXCR4 Antagonists for the Mobilization of Hematopoietic Stem and Progenitor Cells. Biomolecules. 2024 Aug 14;14(8):1003. doi: 10.3390/biom14081003.
16. Canarutto D, Omer Javed A, Pedrazzani G, Ferrari S, Naldini L.Mobilization-based engraftment of haematopoietic stem cells: a new perspective for chemotherapy-free gene therapy and transplantation. Br Med Bull. 2023 Sep 12;147(1):108-120. doi: 10.1093/bmb/ldad017.

17. Unmet Need: Mechanistic and Translational Studies of Sickle Cell Disease Pain as a Whole-Person Health Challenge. Belfer I, Chen W, Weber W, Edwards E, Langevin HM. J Pain. 2024 Jun 13:104603. doi: 10.1016/j.jpain.2024.104603.
18. Belfer I, Chen W, Weber W, Edwards, E, Langevin H. Unmet Need: Mechanistic and Translational Studies of Sickle Cell Disease Pain as a Whole-Person Health Challenge. J Pain 2024 Jun 13:104603. doi: 19.1016/j.jpain.2024.104603.
19. Sagi V, Mittal A, Tran H and Gupta K. Pain in sickle cell disease: current and potential translational therapies. Translational Res Mar 9:S1931-5244(21)00057-8. doi: 10.1016/j.trsl.2021.03.007.
20. Nocturnal peripheral vasoconstriction predicts the frequency of severe acute pain episodes in children with sickle cell disease. Chalacheva P, Ji Y, Rosen CL, DeBaun MR, Khoo MCK, Coates TD. Am J Hematol. 2021 Jan;96(1):60-68. doi: 10.1002/ajh.26014.
21. Increased theta band EEG power in sickle cell disease patients. Case M, Shirinpour S, Zhang H, Datta YH, Nelson SC, Sadak KT, Gupta K, He B. J Pain Res. 2017 Dec 27;11:67-76. doi: 10.2147/JPR.S145581.
22. Low-intensity transcranial focused ultrasound suppresses pain by modulating pain processing brain circuits. Kim MG, Yu K, Yeh CY, Fouda R, Argueta DA, Kiven SB, Ni Y, Niu X, Chen Q, Kim K, Gupta K, He B. Blood. 2024 Jul 8:blood.2023023718. doi: 10.1182/blood.2023023718.
23. Park SY, Matte A, Jung Y, et al. Pathologic angiogenesis in the bone marrow of humanized sickle cell mice is reversed by blood transfusion. Blood. 2020;135(23):2071-2084.
24. Tang A, Strat AN, Rahman M, et al. Murine bone marrow mesenchymal stromal cells have reduced hematopoietic maintenance ability in sickle cell disease. Blood. 2021;138(24):2570-2582.
25. Arthur CM, Stowell SR. The Development and Consequences of Red Blood Cell Alloimmunization. Annu Rev Pathol. 2023;18:537-564.
26. Pal M, Bao W, Wang R, et al. Hemolysis inhibits humoral B-cell responses and modulates alloimmunization risk in patients with sickle cell disease. Blood. 2021;137(2):269-280.
27. D'Alessandro A, Nouraie SM, Zhang Y, et al. *In vivo* evaluation of the effect of sickle cell hemoglobin S, C and therapeutic transfusion on erythrocyte metabolism and cardiorenal dysfunction. Am J Hematol. 2023;98(7):1017-1028.
28. Godefroy E, Liu Y, Shi P, et al. Altered heme-mediated modulation of dendritic cell function in sickle cell alloimmunization. Haematologica. 2016;101(9):1028-1038.
29. Gleadall NS, Veldhuisen B, Gollub J, et al. Development and validation of a universal blood donor genotyping platform: a multinational prospective study. Blood Adv. 2020;4(15):3495-3506.
30. Pinto VM, Mazzi F, De Franceschi L. Novel Therapeutic Approaches in Thalassemias, Sickle Cell Disease, and Other Red Cell Disorders. Blood. 2024.

Cross-Cutting Topics

Throughout the exploration of the varied scientific topics presented in this ASH Sickle Cell Disease Research Priorities document, several consistent themes emerged. These themes have been designated “cross-cutting topics’ as the belief is that developments in these areas would improve research across all topics explored. These cross-cutting topics below are not listed in any order of priority.

Artificial Intelligence, Data Science, and Bioinformatic Approaches

There is a recognized need to leverage the latest data science tools and approaches to address many of the research priorities. Several groups discussed harnessing information from big data and using artificial intelligence and machine learning for data analyses. Examples included using these approaches to:

- Refine drug target detection and animal model testing using bedside-to-bench reverse translational research approaches.
- Understand the epidemiology, risk factors and outcomes of SCD complications.

- Develop surrogate and/or composite endpoints to determine the efficacy of interventions in clinical trials.

Biomarkers and Individualized Medicine

Biomarkers and the concept of individualized medicine is called out within individual topic areas where additional details are outlined; but it is worth noting that many groups expressed a need to develop specific biomarkers and/or understand the impact of genetic polymorphisms that could identify individuals at elevated/high risk for clinical events. Genetic and biochemical biomarkers are needed to effectively predict individual drug responses (or lack thereof) and for standard, curative, transformative and/or new therapeutics/therapies. Finally, a particular emphasis was placed on the need for pain biomarkers, and it was clearly stated that such biomarkers should not replace patient reporting of pain, which is the gold standard for pain assessment. Pain biomarkers should be interpreted in the context of the patient report of pain, be used only to their specific purpose, and tested for their predictive power to understand the patients' pain experience. Overall, biomarkers could guide providers and assist individuals with SCD in making informed decisions about the best therapy options for them (individualized medicine).

Impact on Fertility/Pregnancy/Reproductive Health

Increased research around fertility, pregnancy, and overall reproductive health in individuals with SCD was also identified as an area of need. It was noted that guidelines in the topic areas of women's health, infertility, and pregnancy are weak or lacking. The group focused on pain research stated that it was a priority to determine the mechanisms by which women with SCD have pain during menses, pregnancy, and childbirth. Another priority focused on disease modifying therapies and understanding the impact these therapies have on reproductive health, pregnancy, lactation, menstruation and fertility for men and women. The group focused on SCT research recommended increased community-based participatory research around misinformation, perceptions of risks/stigma, and best practices for messaging about reproductive and genetic counseling for individuals with SCT.

Social Determinants of Health

Several questions regarding the impact of social determinants of health (SDOH) on SCD-related outcomes were put forth including:

- Can we develop integrated risk scores that incorporate medical history, SDOH, genetics and/or clinical, laboratory, socioenvironmental, and technological biomarkers to predict acute clinical events, progressive organ dysfunction and mortality?

- Can we conduct prospective studies with adolescents and young adults to address the contribution of SDOH to the pathophysiology of SCD, organ dysfunction, pain, and other clinical outcomes?
- What is the contribution of nutrition and SDOH in promoting pain? What is the most optimal way to investigate a whole person health approach (i.e., biological, behavioral, social, and environmental areas) to SCD pain and overall care?

A Global Lens Perspective

ASH believes prioritizing research in regions around the world with large populations affected by SCD is needed. Given the overwhelming burden of SCD in low- and middle-income countries, these academic institutions should be included in efficacy trials. Collaborations with global partners and research networks in countries with high SCD prevalence, such as Sub-Saharan Africa and India, will increase access to large patient groups and decrease the time required for clinical trial completion. Increased research is needed in low-resource settings to determine how to utilize and ensure access to disease modifying therapies for SCD populations living in these regions. These studies should prioritize short- and long-term safety and should include pediatric and adult populations. Additionally, novel drugs should be available and affordable to all individuals with SCD worldwide, so researchers should consider how new therapies can truly be studied and be accessible in low resource settings. This should include removing barriers and increasing facilitation to equitable access across locations and populations in implementation studies. Furthermore, work should be done to identify barriers to receiving recommended SCD-specific evidence-based screening, and treatment guidelines in settings external to academic (or traditional large) medical centers using a multi-stakeholder approach. Success in implementation of qualitative and quantitative assessment of facilitators or techniques should be leveraged globally.

Conclusion: A Strategic Path Forward

To achieve the basic and translational research priorities presented in the updated ASH Sickle Cell Disease Research Priorities – 2024 Update document; clinical collaborations and initiatives are fundamental to achieving transformative treatment options for individuals with SCD. It is imperative to build a robust, interdisciplinary SCD health delivery network to develop treatment standards, implement new therapies, and communicate feedback about clinical knowledge to basic and translational research investigators. Leaders in the field should make every effort to cultivate ideas from different perspectives and expand diversity and inclusion of underrepresented SCD investigators contributing to the field. Individuals living with SCD are widely distributed across the United States, with relatively few well-resourced medical centers to deliver healthcare, which has been a barrier to implementation of new therapies. More extensive clinical networks will facilitate collaboration across medical centers and disciplines,

including connecting researchers and clinicians to support investigation of novel mechanisms, treatments, and clinical outcomes. User-friendly electronic data platforms for dissemination of knowledge among SCD investigators, clinicians and individuals living with SCD will speed the process. In addition, long-term follow up is needed of all individuals with SCD to evaluate the natural history and long-term efficacy and safety of transformative therapies. There remains a critical need for robust prospective longitudinal registries for SCD clinical trials, which align with recognized practices for other inherited diseases.

Related Efforts to Support SCD Research

The ASH Center for Sickle Cell Disease Initiatives houses programs that advance research, create SCD resources, and advocate for legislation. In addition, its global coalitions help researchers connect across institutions, countries, and career stages.

The ASH Research Collaborative® (ASH RC)

Dedicated to advancing hematology through research and enhanced care delivery. ASH RC focuses on driving progress in hematology by curating health data, generating real-world evidence, and accelerating clinical research to improve outcomes for individuals with hematologic diseases. At its core are Research Networks composed of clinicians, care team members, and clinical investigators with a deep culture of cooperative research. The SCD Research Network is dedicated to advancing SCD therapeutics and accelerating the generation of high-quality evidence that improves our understanding of the disease and advances SCD care. One of the Network's cornerstone programs is the Data Hub which collects and aggregates longitudinal real-world data for consecutive patients to generate high-quality evidence and advance SCD research. Researchers have access to this crucial data resource to accelerate research and development, support regulatory decision-making, and identify opportunities for quality improvement. Foundational to the ASH RC's research efforts is the active involvement of the SCD Community, those living with SCD, their caregivers and families in the research process, ensuring research aligns with their needs and perspective.

Consortium on Newborn Screening in Africa (CONSA)

The goals and objectives of CONSA are to:

1. Evaluate the effectiveness of early identification and clinical interventions for newborns with SCD.
2. Create sustainable networks for newborn screening and clinical interventions.
3. Foster collaboration between African hematologists and public health services to develop an organized network of researchers.
4. Increase hematology capacity throughout sub-Saharan Africa.

Clinical networks have been approved to launch participating sites in Ghana, Kenya, Liberia, Nigeria, Uganda, Tanzania, and Zambia. CONSA also incorporates both laboratory-based and point of care testing, family education and engagement, health provider awareness, and enhanced supply chain management.

Sickle Cell Disease Coalition

Focuses on coordinating efforts to produce the greatest impact for individuals with SCD. Members, who represent public health, research, scientific associations, community-based organizations, federal agencies, and industry, collaborate to spread awareness, and improve health outcomes and quality of life for individuals with SCD.

Other ASH Resources

ASH Agenda for Hematology Research

ASH's Agenda for Hematology Research serves as a roadmap to prioritize research within the hematology field. Within the Research Agenda, key emerging and transformative areas of research are identified that will launch the field into the next generation of therapies for hematologic conditions. The agenda is updated periodically and is designed to be a living document. ASH encourages everyone in the hematology community to embrace the ASH Agenda for Hematology Research as a resource and consider citing it in publications, grant applications or other efforts. These recommendations for dedicated resources will help equip researchers to make practice-changing discoveries.

Hematology-Focused Fellowship Training Program Consortium (HFFTP)

Addresses the shortage of hematologists caring for individuals with SCD. The HFFTP is an exclusive pathway that offers physicians the opportunity to pair comprehensive classical hematology training with career-enhancing education in transfusion medicine, sickle cell disease, and hemostasis/thrombosis, among other topics. The HFFTP program supports twelve new hematology-focused fellowship tracks created within existing hematology-oncology programs across twelve different institutions across the United States. These new Hematology Tracks will train fifteen new hematology-focused fellows per year, producing seventy-five new academic hematologists by 2030.

ASH SCD Away Elective

Allows select fellowship programs to serve as host institutions for an away elective rotation in areas with higher patients with SCD populations. The ASH SCD Away Elective Rotation gives fellows the opportunity to gain practical experience in treating individuals living with sickle cell disease. This rotation is specifically focused on SCD care for adults and is designed to be an immersive experience in both outpatient and inpatient SCD care. The host institution embeds the rotating fellow into their existing SCD program and fosters engagement with physicians, advanced practice providers (APPs), social workers/care coordinators, mental health providers, and individuals living with SCD.

ASH SCD Centers Workshop

Provides educational and training opportunities to healthcare teams from institutions with nascent adult sickle cell treatment programs who are seeking to develop comprehensive adult care programs. In total, there are sixty participating hospital systems across twenty-seven states/provinces in the United States and Canada. The workshop program walks participants through the components and services of a comprehensive SCD care center, the development of a business plan for this center, advocacy for that plan, its implementation, and the assessment and improvement of a center. Along with providing education and training opportunities, a primary component of the ASH SCD Centers Workshop program is to foster a supportive community of healthcare providers and staff. This goal is achieved by connecting nascent clinic

teams with experienced faculty mentors and colleagues, both in-person during the live workshop and through regular virtual formats.

ASH Advocacy for Sickle Cell Disease

ASH continues to advocate for issues impacting hematology research and practice, including research and public health funding, access to quality care for individuals with SCD, physician payment and coverage for hematologists, and policy issues related to SCD. During 2022, ASH continued to advocate for federal support of biomedical research and public health funding for the National Institutes of Health, the Centers for Disease Control and Prevention, and the Health Resources and Services Administration. ASH submitted a statement to the Senate Appropriations Subcommittee on Labor, Health, and Human Services, supporting $49 billion for NIH in FY 2023, $10 million for the CDC Sickle Cell Data Collection Program and continued support for the sickle cell demonstration projects coordinated by the Health Resources and Services Administration.

The Sickle Cell Disease Comprehensive Care Act (H.R. 6216/S.3389), sponsored by ASH, directs CMS to create a demonstration program in up to ten states to improve access to comprehensive, high quality, outpatient care for individuals enrolled in Medicaid with SCD. The bill is currently under consideration.

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- Dr. Victor Gordeuk, University of Illinois – Chicago
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- Dr. Jeffrey Lebensburger, University of Alabama – Birmingham
- Dr. Robert Liem, Northwestern University

Enhance Pain Treatment and Research

- Dr. Amanda Brandow (Co-Chair, Lead), Medical College of Wisconsin
- Dr. C. Patrick Carroll, Johns Hopkins University
- Dr. Deepika Darbari, Children's National Hospital, George Washington University
- Dr. Kalpna Gupta, University of California – Irvine
- Dr. Nirmish Shah, Duke University
- Dr. Cheryl Stucky, Medical College of Wisconsin

Optimize the Use of Hydroxyurea, Blood Transfusions, and Currently Approved Pharmacologic Therapies

- Dr. Patrick McGann (Lead), Brown University
- Dr. Charles Abrams, University of Pennsylvania
- Dr. Susan Creary, The Ohio State University
- Dr. Payal Desai, Wake Forest University
- Dr. Nancy Green, Columbia University
- Dr. Alexis Thompson, University of Pennsylvania

Develop Novel Drug Therapies

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- Dr. Claudia R. Morris, Emory University School of Medicine
- Dr. Jane Little, University of North Carolina – Chapel Hill
- Dr. Stefano Rivella, University of Pennsylvania
- Dr. Angela Rivers, University of California – San Francisco
- Dr. Yogen Saunthararajah, Case Western Reserve University
- Dr. Russell Ware, University of Cincinnati
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Impact of the Dissemination and Implementation of Evidence Based Guidelines for SCD

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- Dr. Marsha Treadwell, University of California – San Francisco
- Dr. Wanda Whitten-Shurney, Wayne State University

Advancing Fundamental Knowledge to Enable Improved Approaches to Sickle Cell Disease

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