Duke Clinical & Translational Science Institute

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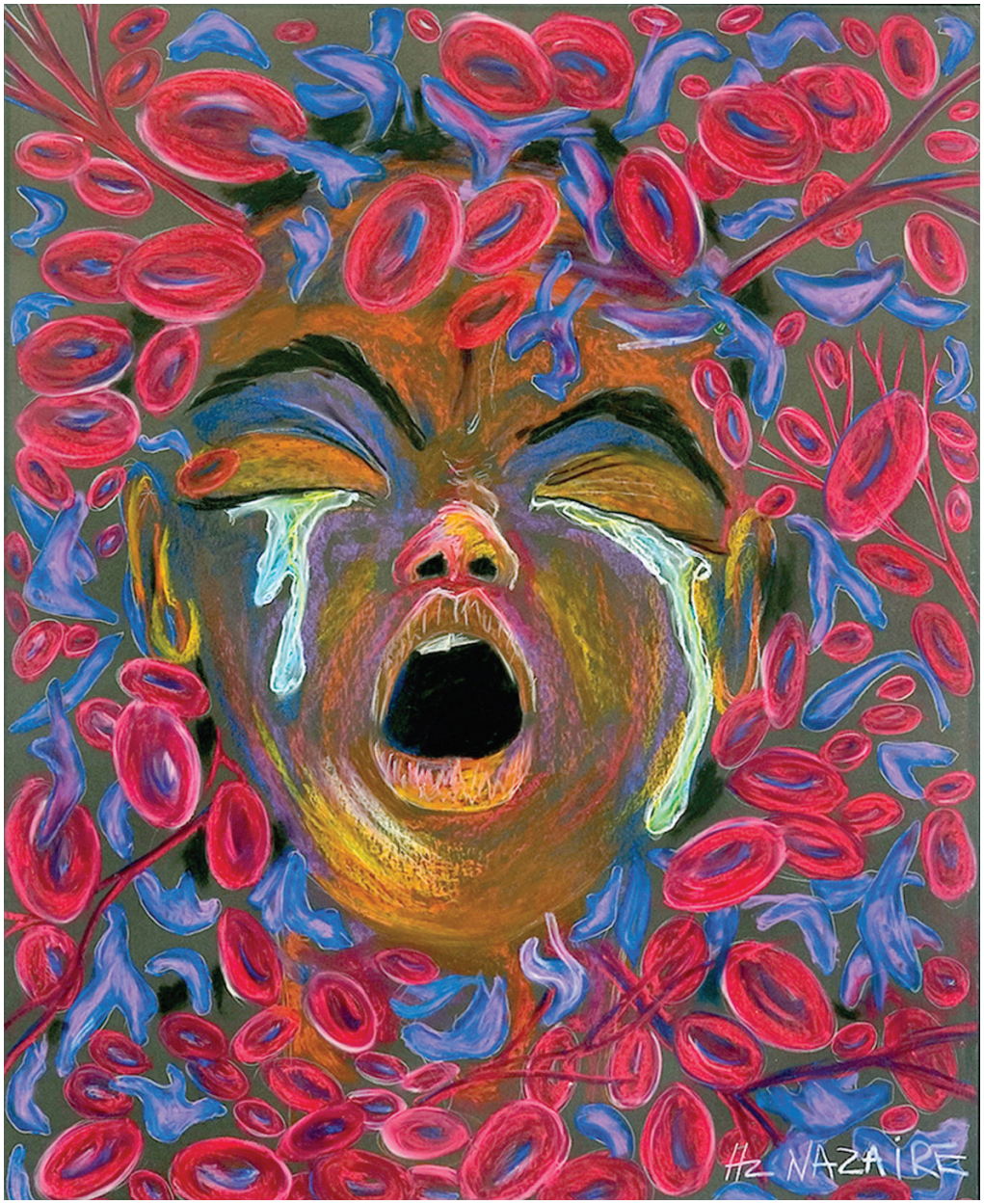
Biopsychosocial Determinants of Pain in Sickle Cell Disease

A Study of the Contributors to Severe Pain, Toward Better Management



"Ten Redefined" by Hertz Nazaire
See page 8 for more information.

A TRANSLATIONAL SCIENCE BENEFITS MODEL **CASE STUDY**

Project in a Nutshell

Many people with sickle cell disease frequently experience severe pain, and the contributing factors to that symptom have not been fully understood.

This study identified a biomarker that is significantly associated with pain in people with sickle cell disease, offering a new exploratory direction for research.

Significance of the Project

Sickle cell disease (SCD) is characterized by abnormally shaped red blood cells that can clump and stick to blood vessel walls, affecting the flow of oxygen throughout the body. In the United States, SCD disproportionality affects Black and African American individuals.

SCD is the most commonly inherited blood disorder in the US and affects 1 in 396 Black Americans. It is now understood that the pathophysiology of SCD is quite complex, including elements of inflammation and adhesion, all of which contribute to significant vascular and organ damage over time. While these disease processes cause significant medical complications, severe pain is among the most common and impactful symptoms experienced by individuals with SCD.

Other than opioids, there are few effective treatments to manage pain in this population. More than half (55%) of adults with SCD report pain on the majority of days in a 6-month period, with 29% reporting pain ≥95% of the days. However, there is a limited understanding of the mechanisms unique to the development of persistent SCD pain. Few studies have explored the relationships between inflammatory biomarkers (i.e., cytokines) and SCD pain.

A better understanding of the occurrence of severe pain, as well as biological contributors, can lead to improved assessment and management of pain in this population.

Summary of the Project

Principal Investigator Mitchell Knisely and other researchers led a study for people with SCD who were ≥15 years of age and lived in North Carolina.

The goals of this study were to:

1. examine different SCD-related pain phenotypes based on the occurrence of severe pain in the past 6-months, and
2. identify blood levels of inflammatory biomarkers connected with occurrence of severe SCD pain in people with SCD.

Blood samples were collected from people with SCD to generate biomarker data; the samples were also stored for future research.

74 individuals with SCD participated in the study, more than 65% of whom reported severe pain occurring sometimes or often.

Summary of Results

- When evaluating inflammatory plasma markers associated with the frequency of severe pain, the soluble endothelial leukocyte adhesion molecule 1 (sE-selectin) biomarker was significantly associated with the pain phenotype groups. Particularly, participants reporting severe pain occurring often or always had significantly higher plasma concentrations of sE-selectin compared to the other pain groups.
- sE-selectin is a glycoprotein commonly used as a marker of systemic endothelial dysfunction. The processes of endothelial activation and resultant dysfunction are particularly pertinent in SCD; these mechanisms contribute to the multifactorial pathology of SCD and can lead to long-term complications such as blood vessel and organ damage.

The study findings were published in June 2021, in a report titled *Severe Persistent Pain and Inflammatory Biomarkers in Sickle Cell Disease: An Exploratory Study*.

Impact of the Project

Community

This study reported the frequent occurrence of severe pain and provided preliminary evidence of the potential role of endothelial dysfunction in chronic severe pain in this population.

The study also identified potential biomarkers in the blood (i.e. sE-selectin) that may be associated with experiences of severe pain in patients with SCD. Identifying SCD-related biomarkers may help clinicians better understand which SCD patients are likely to experience extreme pain, and may help clinicians and patients better manage their pain.

If we can better understand and properly manage pain, we can improve quality of life and properly address health care needs.

Economic

The findings of this study have the potential to reduce lifetime costs associated with SCD. Pain is the number one reason people with SCD seek health care, if we have more effective treatments/management of pain, there is potential there will be decreased health care encounters and cost savings.

Health Equity & Disparities

Patients with SCD are often disenfranchised and underrepresented in clinical research. This pilot adds to the work aimed at improving outcomes in this population.

Health care professionals and medical institutions may stigmatize persons with SCD due to sociodemographic factors. Future research should create targeted interventions for providers to reduce the stigmatization of SCD patients, so that they receive equitable pain management and health care.

Comprehensive health care is essential to improving the well-being and quality of life of this underserved population.

About the Research Team

Mitchell Knisely, PhD, RN
Principal Investigator

- Assistant Professor, Duke University School of Nursing

Paula Tanabe, PhD

- Laurel Chadwick Distinguished Professor, Duke University Schools of Nursing and Medicine

Julia Walker, PhD

- Professor, Duke University School of Nursing and Duke Department of Medicine

Qing Yang, PhD

- Associate Research Professor and Biostatistician, Duke University School of Nursing

Nirmish Shah, MD

- Associate Professor, Duke University Department of Medicine, Department of Pediatrics, and School of Nursing

Sydney Sullivan, MPH

- Project Leader, Duke Clinical & Translational Science Institute

Challenges and Strategies

Challenge: Recruitment

There were various recruitment issues in this study. Patients with SCD often have challenges attending medical appointments, and this project required in-person participation in order to collect blood samples.

In order to increase participation and reduce no show rates, the team coordinated blood draws for clinical and research visits to avoid people coming in twice. The study worked with the outpatient lab to do this, but due to a challenge in the visualization of the order in the medical record (the research order would fall off the screen bin), these blood draws did not consistently happen. To address this problem, the study team improved its relationship with the outpatient lab by making them a partner and adjusted the way the lab orders were written.

Challenge: Consent

Although the study team was able to find participants through a pre-existing registry, the original consent participants signed didn't speak clearly to the duration of the specimen storage. Because of that, the team needed to develop an amendment.

The Duke University School of Nursing, where the research team was based.
Photo: Les Todd/Duke University

Strategy: Leveraging Existing Infrastructure

The team was able to leverage existing infrastructure using the already created registry from the Sickle Cell Disease Implementation Consortium at Duke. This allowed the study team to build directly on the preexisting registry by using it to find potential participants that had already consented into data collection.

Strategy: Building Trust

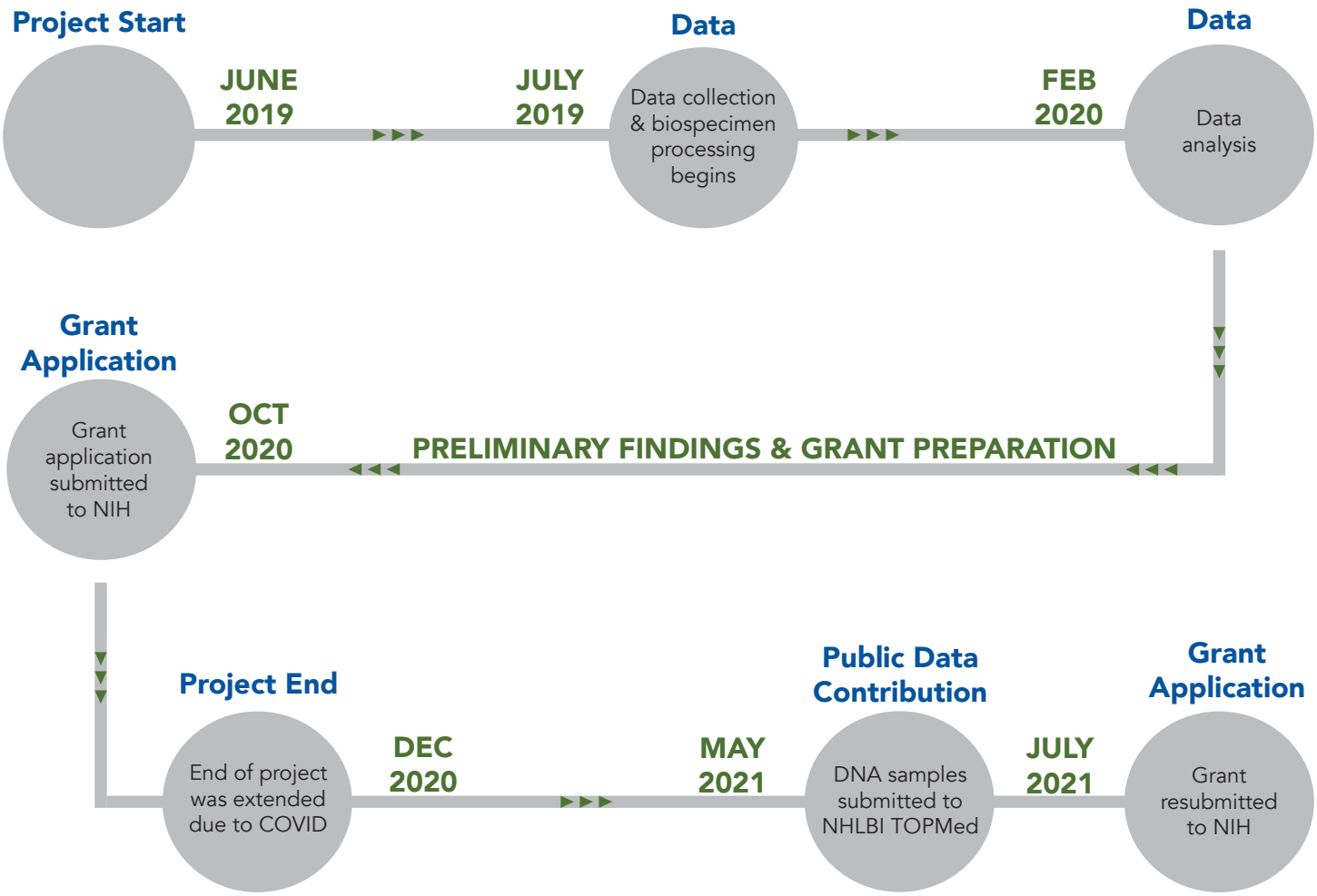
Staff members were able to establish personal connections with research participants. This facilitated gaining trust in the community which enhanced the team's ability to bring people in to participate in the research project.

The sickle cell patients wanted to participate in, and were engaged with, the research. They also had pre-established trust in providers, which enhanced their willingness to participate in the project.

Strategy: Collaboration

The team was able to leverage existing collaborations in order to identify potential biomarkers in the blood (i.e. sE-selectin) that may be associated with the experience of severe pain in patients with SCD.

Project Milestones to Date



Research Funding

Special Populations Pilot Grant — Duke Clinical & Translational Science Institute. More information about this funding program.

SCDIC Funding for Phenotypic Data Collection — National Center for Advancing Translational Sciences of the National Institutes of Health under award number UL1TR002553 and the National Heart, Lung, and Blood Institute under award number U01HL133964. More information about this funding program.

Translational Science Benefits Summary

ECONOMIC

Cost Savings:
Reduce lifetime costs associated with SCD. Pain is the number one reason people with SCD seek emergency department care and are admitted to the hospital, ultimately contributing to the significant healthcare costs for this population. If we have more effective treatments and management of pain, there is potential for decreased health care encounters and cost savings. *(Potential)*

Societal & Financial Cost of Illness:
Societal costs of SCD, such as lost work productivity, could be reduced with improved management of pain for this population. *(Potential)*

COMMUNITY

Public Health Practice:
This study reported the frequent occurrence of severe pain and provided preliminary evidence of the potential role of endothelial dysfunction in chronic severe pain in this population. *(Demonstrated)*

Health Care Delivery:
Identify potential biomarkers in the blood (i.e. sE-selectin) that may be associated with experiences of severe pain in patients with SCD. Identifying SCD-related biomarkers may help clinicians better understand which SCD patients are likely to experience extreme pain, and may help clinicians and patients better manage their pain. *(Demonstrated)*

Special Benefit: Biorepository

The pilot grant allowed for initiating the establishment of a biorepository from collected samples and linked to the Sickle Cell Disease Implementation Consortium (SCDIC) research registry. This creates an opportunity to answer pressing research questions in the future, and represents an exciting outcome that wasn't initially planned as part of this study. DNA samples from the specimens collected as part of this pilot study were submitted for inclusion in the NHLBI Trans-Omics For Precision Medicine (TOPMed) program.

Whole genome sequencing is being completed on these samples, and the genomic data generated will be available through the National Institutes of Health (NIH)'s publicly accessible databases.

This is particularly impactful because people with SCD are underrepresented in the TOPMed program, and the samples provided will help increase the power to advance and improve the scientific understanding of the biological processes that underlie this disease.

Learn more about the Sickle Cell Disease Implementation Consortium: https://scdic.rti.org/

Learn more about NHLBI TOPMed: https://topmed.nhlbi.nih.gov/

Institutional Resources Used

Group	Type of Service
Duke CTSA Integrating Special Populations Core	*Funding and project management*
Duke University School of Nursing Biomarker Lab	*Specimen processing & storage*
Duke Immune Profiling Core	*Generated inflammatory biomarker data from specimens*
Center for Nursing Research	*Grant administration*
Duke SCDIC Research Registry	*Participant phenotype data*

For More Information

About Dr. Mitchell Knisely: https://scholars.duke.edu/person/mitchell.knisely

About Duke Clinical & Translational Science Institute: Visit ctsi.duke.edu or email us at DukeCTSI@dm.duke.edu

Translational Science Benefits Model citation: *Institute of Clinical & Translational Sciences at Washington University in St. Louis. Translational Science Benefits Model website. https://translationalsciencebenefits.wustl.edu. Published February 1, 2019. Accessed December 20, 2020.*

About the cover art: Hertz Nazaire (1973-2021) was a Haitian-American artist whose work drew attention to the lived experience of Sickle Cell Disease. Of this piece, "Ten Redefined," Nazaire said: "I created it about what the pain of Sickle Cell Disease feels like for me. I wish to inspire empathy and compassion in others so that we may someday end the suffering of the Sickle Cell community worldwide." To learn more about Mr. Nazaire and his art, visit http://hertznazaire.com/.