

## **Sickle Pain – Understanding the Problem and Developing Solutions**

August 19<sup>th</sup> 2015, 8 AM to 12:00 noon.

### **Introduction: Kalpna Gupta, PhD**

#### **Panel A: Advanced imaging approaches to understand sickle pain**

*A molecular imaging approach to study descending pain pathway in chronic pain.* Raj Badgaiyan, MD. University of Minnesota, Minneapolis, MN.

*Altered Brain Network connectivity and association with frequent hospitalization for pain in patients with Sickle Cell Disease.* Deepika Darbari, MD. Children's National Health System, Washington DC.

*EEG Informed fMRI Analysis of Sickle Cell Disease Patients during Resting State.* Michelle Case, University of Minnesota, Minneapolis, MN.

**Discussion: Panel A (9 min)**

#### **Panel B: Understanding pain in sickle patients**

*Many Faces of Pain in Sickle Cell Disease.* Abdullah Kutlar, MD. GRU Sickle Cell Center, Augusta, GA.

*Novel Mechanisms of Pain in Patients with Sickle Cell Disease.* Amanda Brandow, DO, MS. Medical College of Wisconsin, WI.

**Discussion: Panel B (6 min)**

**Break (15 Min)**

#### **Panel C: Novel mechanisms underlying sickle pain**

*Peripheral Mechanisms Underlying Pain in Sickle Cell Disease.* Cheryl Stucky, Ph.D. Medical College of Wisconsin, WI

*Phosphorylation Mechanisms Underlying Pain in Sickle Cell Disease.* Z. Jim Wang, Ph.D. University of Illinois, Chicago

**Discussion: Panel C (6 min)**

#### **Panel D: Therapeutic strategies to treat sickle pain**

*Therapeutic Potential of Targeting the Nociceptin Opioid Receptor for Treating Pain in Sickle Cell Disease: Potent Analgesia without Opioid Liabilities.* Nurulain Zaveri, Ph.D., Astraea Therapeutics, LLC, Mountain View, CA.

*Integrative and Alternative approaches to treat sickle pain.* Kalpna Gupta, Ph.D. University of Minnesota, Minneapolis, MN.

*Targeting Pain and Inflammation in SCD Leg Ulcers.* Caterina P Minniti, MD, Albert Einstein College of Medicine, Bronx, NY.

**Discussion: Panel D (9 min)**

## A molecular imaging approach to study descending pain pathway in chronic pain

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Rajendra Badgaiyan, MD

Professor of Psychiatry

Director, Laboratory of Advanced Radiochemistry

Director, Laboratory of Molecular and Functional Imaging

Neuromodulation Scholar

University of Minnesota, Minneapolis, MN 55455

Dr Badgaiyan received training in psychiatrist and cognitive neuroscience. His research is focused on the study of neural and neurochemical mechanisms that control the human brain functions. He developed the single scan dynamic molecular imaging technique to detect, map, and measure neurotransmitters released acutely in the human brain during task performance. Using this technique he studies dopaminergic control of human cognition and behavior. He is also interested in learning the nature of dysregulated dopamine neurotransmission in different psychiatric and neuropsychiatric conditions. In recent years Dr. Badgaiyan has developed interest in the study of pain perception. He is particularly interested in the brain mechanisms that modify pain perception at cortical and subcortical levels. His research is funded by NIMH, NINDS, VA, and various foundations.

## Altered brain network connectivity and association with frequent hospitalization for pain in patients with sickle cell disease

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Deepika Darbari, MBBS, MS

Attending Physician

Division of Hematology

Children's National Medical Center

Assistant Professor of Pediatrics

The George Washington University

Washington, DC

Deepika Darbari, MBBS, MS is a board certified Pediatric Hematologist-Oncologist at the Children's National Medical Center and the George Washington University in Washington DC. At the Children's National Medical Center, her team provides care to one of the largest populations of children and adolescents with sickle cell disease in the United States. She received fellowship training in Pediatric Hematology-Oncology at the National Institutes of Health and Johns Hopkins University. Dr. Darbari studies complications of sickle cell disease. She conducts clinical and translational studies directed to better understanding of pain and its management in sickle cell disease. She has published many research articles and reviews on the subject. She is currently studying pain sensitization using functional magnetic resonance imaging in individuals with sickle cell disease. Dr. Darbari will present her findings showing that some individuals with high pain burden may have altered brain network connectivity, suggesting that central mechanisms may play a role in SCD pain.

# EEG informed fMRI Analysis of Sickle Cell Disease Patients during Resting State

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Michelle Case  
Research Assistant  
University of Minnesota  
Minneapolis, MN

Michelle Case is a research assistant at the University of Minnesota and is currently working in Dr. Bin He's Biomedical Functional Imaging and Neuroengineering Laboratory. Ms. Case received her BS degree in Electrical Engineering with an emphasis in Biomedical Engineering from Northern Illinois University in 2013 and is currently pursuing a Ph. D. in Biomedical Engineering. Her research interests include functional neuroimaging with an interest in multimodal imaging using EEG and fMRI to image pain in chronic pain patients to study biomarkers and to develop quantification methods for chronic and acute pain. She was awarded an NSF Integrative Graduate Education and Research Traineeship (IGERT) in 2013. Ms. Case is currently a member of IEEE, the Society of Women Engineers (SWE), and the Society for Neuroscience (SfN)

## Many Faces of Pain in Sickle Cell Disease

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Abdullah Kutlar

Professor of Medicine

Georgia Regents University Sickle Cell Center

Augusta, GA

As an adult hematologist, I have focused on clinical and laboratory aspects of hemoglobinopathies, specifically sickle cell disease (SCD). I have been the Director of the GRU Sickle Cell Center since 1994, and in this capacity have participated in many NIH and industry sponsored research trials. My laboratory continues to serve as the reference laboratory for the State's newborn screening program for hemoglobinopathies in GA and as a central lab for NIH/NHLBI sponsored trials in SCD. In addition, I have participated in a large number of clinical trials on novel therapies for SCD and am the PI of two investigator initiated studies. I have focused on the genetic modifiers for various phenotypes of SCD, and on clinical trials with novel Hb F inducing agents. Throughout my career, I have had the opportunity to train many pre-doctoral and post-doctoral students in both basic and clinical research.

# Novel Mechanisms of Pain in Patients with Sickle Cell Disease

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Amanda Brandow, DO, MS

Associate Professor of Pediatrics

Section of Hematology/Oncology

Medical College of Wisconsin

Milwaukee, WI

Dr. Brandow is an associate professor of pediatrics at the Medical College of Wisconsin/The Children's Hospital of Wisconsin in the section of hematology/oncology/bone marrow transplantation. Dr. Brandow's research is focused on understanding the pathophysiology of pain in children and adults with sickle cell disease. Specifically, she is investigating the underlying neurobiology of pain with a focus on pain sensitivity and whether peripheral and/or central sensitization contributes to the pain. Her past research found patients with sickle cell disease have increased thermal pain sensitivity compared to race-matched controls supporting evidence for a neuropathic component to sickle cell disease pain. Her current research is focused on determining reasons for this increased sensitivity. Dr. Brandow is a current recipient of both an NIH K23 Mentored Patient-Oriented Research Career Development Award from the NHLBI and an American Society of Hematology Scholar Award that support her research.

# Peripheral Mechanisms Underlying Pain in Sickle Cell Disease

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Cheryl L. Stucky, Ph.D

Professor

Dept. Cell Biology, Neurobiology and Anatomy

Director, Neuroscience Doctoral Program

Medical College of Wisconsin

Milwaukee, WI

I have studied somatosensory and pain research for the past 25 years. I graduated with a PhD in Neuroscience from the University of Minnesota under the guidance of Ginger Seybold. I then move to Germany for postdoctoral research where I learned the “skin-nerve” recording preparation as a postdoctoral fellow with Martin Koltzenburg in Würzburg, Germany, I then added further depth to my electrophysiological expertise by learning patch clamp recordings of sensory neurons as a postdoctoral fellow with Gary Lewin in Berlin, Germany. During my postdoctoral research, I investigated the roles of NGF, BDNF, NT-4, and the neurotrophin receptors p75 and GFR $\alpha$ 2 on the development and function of cutaneous sensory neurons. Since establishing my independent laboratory in 1999 at the Medical College of Wisconsin, I have utilize skin-nerve recordings, patch clamp recordings, calcium imaging and behavioral analyses to analyze the functional roles of Transient Receptor Potential ion channels in preclinical animal models of acute and chronic pain including inflammation, nerve injury, and sickle cell disease. My lab has also investigated the roles of TRP channels, sodium and potassium channels and Piezo channels in basic sensory transduction of mechanical, cold and heat stimuli. I’m Principal Investigator on two current NIH R01 grants that are funded by NINDS, and collaborate often with various pharmaceutical companies. I have a keen interest in the molecular mechanisms that underlie somatosensory mechanotransduction in the normal, healthy state and in conditions of tissue injury or disease.

# Phosphorylation Mechanisms Underlying Pain in Sickle Cell Disease

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Z. Jim Wang, PHD

Professor of Pharmacology

Department of Biopharmaceutical Sciences

University of Illinois, Chicago

Dr. Wang is a tenured professor at the University of Illinois Medical Center at Chicago. Dr. Wang's research is focused on pain and addiction, by employing the power of molecular genetics, epigenetics, and molecular/cellular/systems pharmacology in the studies.

# Therapeutic Potential of Targeting the Nociceptin Opioid Receptor for Treating Pain in Sickle Cell Disease: Potent Analgesia without Opioid Liabilities

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Nurulain Zaveri, Ph.D

President and Chief Scientific Officer

Astraea Therapeutics, LLC

Mountain View, CA.

Dr. Zaveri is the Founder, President and Chief Scientific Officer of Astraea Therapeutics, a preclinical discovery company she founded in 2008, whose mission is medication development for under-served diseases of the central nervous system (such as substance abuse and addiction, chronic pain and Parkinson's disease). A PhD medicinal chemist by training, Dr. Zaveri is a recognized expert in the field of GPCR-targeted– and ion channel–targeted drug discovery of CNS medications. Pioneering discoveries from her laboratory have contributed to the understanding of the pharmacology of drug addiction and pain, and are being advanced into medication development. Dr. Zaveri has been a leader in the discovery and rational design of nociceptin opioid receptor ligands, and compounds developed in her laboratory are under development for substance abuse treatment and chronic pain, including pain in sickle cell disease. Dr. Zaveri's discovery of the first truly selective and high affinity compounds targeted to the alpha3 □eta4 nicotinic recep garnered tremendous interest in the nicotine research arena and are being developed as smoking cessation medications. Before her entrepreneurial venture at Astraea Therapeutics, Dr. Zaveri was Principal Investigator and Director of the Drug Discovery Program at a nonprofit research institute for 16 years. Dr. Zaveri has a proven track record of driving drug discovery from 'target validation to IND', leading cross-functional teams through to translational development. Dr. Zaveri was elected as a Fellow of the American Association of Pharmaceutical Scientists (AAPS) to recognize the significant impact of her research to the Pharmaceutical Sciences and medication development. Dr. Zaveri also serves on several NIH grant review committees.

## Integrative and Alternative Approaches to Treat Sickle Pain

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Kalpna Gupta, PhD

Professor of Medicine

Vascular Biology Center

Division of Hematology, Oncology and Transplantation

Department of Medicine

Co-leader, Tumor Microenvironment Program

Masonic Cancer Center

Co-leader, Molecular and Cellular Engineering Program

Institute for Engineering in Medicine

University of Minnesota, Minneapolis, MN 55455

The Gupta laboratory studies pain in sickle cell disease (SCD) – a major issue affecting patients' daily lives and happiness. We seek to develop therapies by understanding pain in SCD from the molecular level onwards. These insights help us treat both pain and the underlying disease process causing pain in the first place. Our laboratory has identified several new targets at the intersection of the sickle disease process and pain, including cannabinoid receptors, mast cells, and the nociceptin receptor. We are also testing integrative approaches including diet modification, acupuncture and perception modulation to relieve pain. Ultimately, we hope to harness mechanistic insights to treat the root causes of pain in SCD.

Dr Gupta's research on sickle pain is funded by NHLBI and she is also a recipient of the Excellence in Hemaoglobinopathies Research Award from NHLBI to examine the potential of cannabinoids to treat pain and develop methods to quantify pain objectively.

## Targeting Pain and Inflammation in SCD Leg Ulcers

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Caterina P. Minniti, MD  
Professor of Medicine  
Einstein College of Medicine Division of Hematology-Oncology  
Department of Medicine  
Director, Sickle Cell Center  
Montefiore Medical Center  
Bronx, New York 10467

The focus of my career in benign hematology is to understand the basis of phenotypic variations in sickle cell disease with the ultimate goal of preventing end organ damage in patients with sickle cell disease. Risk stratification and identification of clinical and laboratory based markers of disease severity are and will be even more important as we approach the era when transplantation and gene therapy may be available to an increased number of individuals with sickle cell disease. My expertise is in designing and conducting clinical trials and translational research, bed to bench and back. The study of leg ulcer is a model to look at progressive endothelial dysfunction, and vasculopathy with resultant exacerbation of pain and pain induced neurogenic inflammation. I seek to develop therapies by understanding the progression of vasculopathy and end organ damage in SCD from the molecular level onwards. Treatment of ulcer related pain will improve the quality of life of patients that suffer from this debilitating complication. These insights will help treat both the ulcer itself and prevent the occurrence of other, more life threatening forms of vasculopathy, such as pulmonary hypertension and renal disease. Ultimately, I strive to harness mechanistic insights to treat the root causes of end organ damage in SCD, before it becomes irreversible.