Hyacinth Harding-Goldson, Marvin Reid & Richard Augier

Urinary Leukotriene E4 in Patients with Homozygous Sickle Cell Disease
Sickle cell disease predominantly affects populations in tropical and sub-tropical Africa and their descendants in the Americas and Europe but also occurs in populations from the Mediterranean, the Middle East, and India. Jamaica has a relatively high prevalence of sickle cell disease (SCD) which accounts for 1:150 births (approx 300/year). It is an inherited genetic variation in which there is production of abnormal haemoglobin S in red blood cells. The haemoglobin S molecule crystallises when exposed to low oxygen concentrations resulting in a conformational change in the shape of red blood cells from their normal biconcave, round shape to crescents called ‘sickling’. This results in increased fragility of the red blood cells, increased destruction and a shortened life span. The latter results in a low red blood cell count called anaemia. Sickling also causes blockage of small blood vessels with impaired blood supply. There is also inflammation of the blood vessels resulting from damage to their lining and activation of the body’s immunological/hormonal stress response. Blockage of blood vessels leads to tissues being starved of oxygen resulting in tissue death but more commonly in severe and debilitating pain.

Patients with sickle cell disease suffer from acute painful crises (APC). These involve the extremities, pelvis, abdomen, chest and back. Cysteinyl leukotrienes (CysLT) are inflammatory molecules produced from arachidonic acid through the 5-lipoxygenase pathway. There is evidence that CysLT-related vascular effects may be the cause of occlusion of blood vessels in SCD. Cysteinyl leukotriene E4 (LTE4) is a metabolic by-product which can be measured in the urine. Discovery of an association between urinary leukotriene E4 (uLTE4) levels and acute painful crisis would support the use of uLTE4 as a biomarker of disease severity (in terms of frequency of episodes of APC) and the use of leukotriene inhibitors as a possible therapy for APC.

Pain affects all persons with the disease. It can be acute, chronic or acute on a background of chronic pain and often is so severe as to have a destructive socio-economic impact on their lives. People who suffer from frequent painful episodes are often stigmatized because of often missing work or school and requiring strong pain-relieving drugs. Approximately 50 cases of acute painful crisis are managed monthly at the Sickle cell unit and another 30 cases are seen at the University Hospital of the West Indies Casualty Department, placing additional healthcare requirements on an already overburdened service.

Presently there is only one treatment that can reduce the frequency of acute painful crisis, and this drug cannot be used in all patients, so the search for other treatments continues.
A biomarker that could be used as an objective method of measuring the severity of disease and the level of pain would allow for more targeted care, and help to reverse common misperceptions. Such a tool would be extremely useful in improving the standard of care available to persons with sickle cell disease and by extension the quality and productivity of their lives. This project investigates the possibility that the inflammatory molecules Cysteinyl leukotrienes (CysLT) could be one such biomarker.

Cysteinyl leukotrienes have been implicated in the pathophysiology of asthma. They cause constriction of the pulmonary blood vessels, increase mucous secretion and pulmonary vascular permeability. The discovery of the association has resulted in the use of leukotriene inhibitors in management of asthmatic patients.

A demonstrated association between sickle-related painful episodes and uLTE4 will suggest a possible application of leukotriene inhibitors in SCD patients and allow for measurement of the relationship between dose and effect. This would allow for future investigations into the use of leukotriene inhibitors as therapy for sickle cell pain.

This experimental study investigates uLTE4 concentration in patients with homozygous sickle cell disease during periods when they have no pain and during painful episode. It comprises of three phases:

**Phase 1**

An experimental study comparing uLTE4 in patients with homozygous SCD during steady state with age and gender matched HbAA controls.

**Phase 2**

An experimental study comparing steady state levels of uLTE4 in two groups of patients with homozygous SCD. Group 1, those with a history of a “high frequency” of APCs (>5/year high) and group 2, those who have a “low frequency” (<2/year low) history. These two groups will be matched for age, gender and pulmonary function status.

**Phase 3**

A longitudinal study comparing uLTE4 levels during painful crisis and then in steady state in the same homozygous SCD subjects.

This project is a collaboration between the Section of Anaesthesia and Intensive Care in the Department of Surgery, Radiology, Anaesthesia & Intensive Care and the Sickle cell Unit of the Tropical Medicine Research Institute, UWI Mona. It grew out of a common interest in sickle cell pain, its causes and treatment. It also forms part of the ongoing effort by the Faculty of Medical Sciences UWI and the SCU/TMRI to improve the research capability of clinical faculty members through the provision of research fellowships. International dissemination of the results and future collaborations will accrue. The Funding for this project was obtained from the Mona New Initiative programme and the Caribbean Health Research Council.

**Dr Hyacinth Harding** is a Senior Lecturer & Head, Section Anaesthesia and Intensive Care Department of Surgery, Radiology, Anaesthesia and Intensive Care University of the West Indies, Mona.

**Dr Richard Augier** is a Consultant Anaesthetist Research Fellow and Associate Lecturer Department of Surgery, Radiology, Anaesthesia and Intensive Care University of the West Indies, Mona.
Collaborators:
Professor Marvin Reid, Director, Sickle Cell Unit, UWI, Mona.
Dr Susanna Bortolusso-Ali, Director Clinical Services, Sickle Cell Unit, UWI, Mona.
Dr Jennifer Knight-Madden, Sickle Cell Unit, UWI.