

Title: Pharmacogenetic Prediction of Hydroxyurea Response in Sickle Cell Disease

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Synopsis:

From the NY-CT CTSA regional consortium ("NYCON"), we aim to create a five site NYCON Pediatric Hemoglobinopathy Research Consortium to conduct four inter-related clinical/translational studies of Hydroxyurea (HU) use in sickle cell disease (SCD). Participation of CHRCO in one of the studies transforms us to "NYCON Plus 1" - six CTSA's. Collectively, these studies focus on identifying novel indications for HU, pharmaco-genomic prediction of response, risks of and barriers to its use. The sole FDA-approved pharmacologic treatment for SCD, HU increases levels of fetal hemoglobin (HbF), which actively inhibits the polymerization of sickle hemoglobin. Despite its unique and frequently dramatic impact, a 2008 NHLBI consensus statement affirmed the under-utilization of HU in treating SCD.

Each of the four proposed studies is currently underway at a single institution. These studies will be efficiently expanded with one year of funding through a federated model, whereby each PI will open their respective study to multi-site enrollment. Common patient eligibility, existing clinical data, research personnel and facilities link these four studies. A common database and DNA repository will be created, with utilization of existing protocols and procedures, informed consent, assent and other requisite study documents. Clinical data for these studies are already routinely collected as part of standardized health maintenance assessments of children with Sickle cell disease at our centers, thus minimizing incremental research costs. Each of our medical centers care for between 40-425 children with SCD. The variety of genotypes, ages and variability of manifestations of SCD limit the ability to enroll sufficient patients to study one or more pharmacologic targets and markers for HU. Collectively, we have more than 1000 patients to recruit into studies, as well as our collective NYCON CTSA capacity for clinical and translational research and training opportunities.

Aim 1: Develop an enduring infrastructure across the participating CTSA sites to support studies of Hydroxyurea (HU) use in children with Sickle Hemoglobinopathies:

- A) Standardized study design and recruitment protocols
- B) Shared consent and assent forms and other Human subject/IRB documents
- C) Common biomarkers and study database
- D) Shared DNA repository
- E) Contractual agreements for study personnel and for subject recruitment
- F) Participation of trainees and junior faculty in the execution and analysis of these studies

Aim 2: Enhance four existing SCD (HbSS or HbS-B0 thalassemia) pharmacology and/or natural history studies through expanding recruitment to all five of our CTSA sites:

- A) Columbia (PI Green): Genetic markers of response to HU
- B) Einstein (PI Driscoll): HU as a risk factor for avascular necrosis of the hip
- C) Yale (PI Pashankar) : Novel markers of and treatment for pulmonary HTN
- D) Einstein (PI Oyeku): Parental and Provider surveys of barriers to HU use