Abstract

Genetics is the study of genes and traits we inherit from parents from one generation to another. Sickle cell disease (SCD) is the most inherited genetic disorder in the world. In Ghana, the Ashanti call it Ahotutuo, the Dagomba Damahiri Doro, the Fante Enwewe or Kwaha and the Wala Guri guri he. These tribal names describe the unrelenting pain ancestral Ghanaians associated with SCD long before genes and their role in human disease were defined. In the past 100 years, scientific understanding of SCD has come largely from studies conducted in the Western world. However, there is an emerging recognition that the development of a transformative gene-based cure for SCD may hinge on understanding the unrivalled human genetic diversity in Africa. My work straddles both worlds thus offering a unique perspective in this inaugural lecture on the evolution of scientific inquiry in SCD over the past thirty years, and my role in this journey.

In the 1990s, a major research area in SCD focused on defining DNA sequences responsible for persistent production of foetal haemoglobin (HbF). This topic is still important today as HbF is the most effective clinical modifier of SCD to date. My work in this area as part of a doctoral thesis in London, England centred on genetic variation at the globin gene locus on chromosome 11. I defined the restriction fragment length polymorphism haplotypes among SCD patients in London for the first time; identified DNA sequences in the HbF gene that influence its production; developed a novel mass spectral method for quantification of the two types of HbF and demonstrated that sequence variation at hypersensitivity-2 site of the globin locus control region influences enhancer activity. A rare plenary presentation as a final year PhD student in Malta in 1999 brought global attention to my work as I proposed the term functional haplotypes to describe patterns of DNA sequence variation within cis-active elements that influence HbF level.

In 2000, at the turn of the century, my postdoctoral studies in Mobile, Alabama, in the United States of America (USA) focused on trans-acting factors. Here, we defined for the first time an antagonism between transcription factors GATA-1 and Stat-3 beta on the HbF gene promoter and identified activating transcription factor 2 and cyclic AMP response element binding protein as mediators of HbF induction by histone deacetylase inhibitors. During this time several drugs including activators of nuclear factor erythroid factor 2 (Nrf2) that were being developed for other diseases were also studied intensely for repurposing in SCD. My body of work in this area spanning over 10 years helped to define the role and mechanism of Nrf2 in many aspects of SCD, including age-related disease progression and

cardiovascular dysfunction. The most significant finding showed that pharmacological augmentation of Nrf2 to slowdown age-related decline in the activity of haem oxygnase-1 (HO-1) improved survival of transgenic SCD mice in an experimental model of acute chest syndrome (ACS). My Nrf2 work became a magnet for globe-trotting as I travelled the world with stops in Brazil, Guyana, India, and many cities across Europe and USA to discuss the importance of this pathway in SCD. This work led to collaboration with industry to develop a truncated recombinant HO-1 biologic that remains a viable drug candidate to mitigate acute complications of SCD. My Nrf2 work also opened a new avenue of research in genomics that ultimately afforded me a soft landing in relocating my research to Africa.

In 2010, I had joined my work to the most controversial topic in SCD at the time, the importance of haemolysis in the disease process, particularly pulmonary hypertension, which was hotly contested. While nearly all the attention was on cell-free haemoglobin the proximate by-product of haemolysis, I focused my work on extracellular haem, a second line by-product of haemolysis and its role in ACS, which is a leading cause of death in SCD particularly among pregnant women. Studying patients and transgenic mice with SCD in Atlanta, Georgia, USA, my laboratory made the seminal discovery that excess extracellular haem triggers ACS in SCD, and we defined the TLR4/MyD88 signalling pathway as the mediator. This work provided for the first time, a mechanistic basis for how haemolysis can cause acute tissue injury in SCD, and identified many drug targets including hemopexin, currently in a phase-1 clinical trial. Other studies in my laboratory showed that extracellular haem contributes also to the development of acute kidney injury in SCD, and others implicated the same in yet more SCD-related complications collectively opening new avenues of research and attracting new researchers into the field.

In 2015, after two decades of working largely with animal models in the West, I decided to return home to focus my research on patients. To facilitate this, I designed the Sickle Cell Disease Genomics of Africa (SickleGenAfrica) network, a multi-national project that has become the largest SCD cohort study in the world with enrolment of over 7,000 patients in Ghana, Nigeria, and Tanzania. SickleGenAfrica has become the multifaceted seed I envisioned to catalyse transformative change in genetics and SCD in Africa. Thus far, it has spun; a) a genetics public

health education and awareness campaign in Ghana through the Ghanaian Genome (GhGenome) project, b) training of a new cadre of health professionals in Ghana and the sub-region in genetics including a first-of-its-kind MSc Genetic Counselling programme in the region, c) capacity

building in genetic health through establishment of the West African Genetic Medicine Centre (WAGMC). Finally, in collaboration with industry partners, we have designed the first study in Ghana to assess the feasibility of in vivo gene therapy to cure the disease our ancestors called Ahotutuo, Damahiri Doro, Enwewe and Guri guri he. Thus, my scientific journey with Enwewe continues here at home, to be supported in the years ahead by locally trained mentees, who are poised to take this journey into a brighter future.