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Treatments for Sickle Cell Disease: A Global Problem in Cell and Developmental Biology

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Sickle cell disease (SCD) is the world's most common genetic disorder, being most prevalent among populations in the regions where malaria has been endemic [1]. SCD is caused by a point mutation (A → T) in the sixth codon of the β-globin gene on chromosome 11, resulting in the substitution of the amino acid valine for glutamic acid in the expressed protein. The result is that the mutated hemoglobin S (HbS) polymerizes and precipitates within the red blood cells (RBCs) during deoxygenation or dehydration, altering the RBC's form from a flexible biconcave disc to a rigid elongated cell that is often in the shape of a crescent or sickle. Sickling results in a vascular train wreck, producing abnormally increased adhesion to other blood cells and to the vascular walls, hyper-coagulation, hemolysis, hypoxia, widespread inflammation, organ damage, and premature death. There are approximately 340,000 deaths per year attributed to the effects of SCD, most of the deaths being children under five years of age. Although the molecular basis of sickle cell has been understood for over sixty years [2,3], there is still no treatment that is highly effective and available to the millions of affected individuals worldwide.

In the early 1970's, a population in Saudi Arabia was discovered whose members are homozygous for the sickle mutation but exhibit few or no clinical symptoms of SCD [4]. Further studies showed that the absence of major disease was due to a second mutation that results in hereditary persistence of fetal hemoglobin (HPFH) [5]. The presence of 25-30% fetal Hb (HbF) in a SCD red cell prevents sickling, and high levels of HbF are known to be safe [6]. Therefore, if HbF could be induced to these high levels in the RBCs of adults with SCD, a phenotypic cure of this genetic disease could be realized. In 1976, the Hemoglobin Switching Program was initiated at the National Institutes of Health through a joint RFA (request for applications) by two institutes, NIDDK and NHLBI. Thus, the search was on for factors that could be used clinically to reverse the perinatal fetal-to-adult Hb switch, i.e., make adult erythroid cells express significant amounts of fetal Hb–a problem in cell and developmental biology.

It has been forty years since the beginning of the Hb Switching Program. What has been accomplished? There is good news and bad news. Certainly, much more is known about the molecular biology of globin genes and their expression, as well as about the population genetics of other genes that affect HbF expression [6]. And clinically, more about the "train wreck" that is the manifestation of SCD has been elucidated, such that we now have improved treatments for the effects of the disease. But the only FDA-approved drug targeted at stimulating HbF expression is hydroxyurea (HU); and HU is not a particularly effective HbF inducer, is not tolerated by all patients, and has the long-term potential of being carcinogenic. We have witnessed a non-linear progression over these forty years that has included sequencing the human globin gene cluster (before there was the Human Genome Project), an ongoing effort to identify and characterize regulatory proteins and RNAs that bind globin gene promoters and affect expression, construction of transgenic mouse models carrying human normal and/or sickle globin genes, and (beginning ca. 1989) methods of altering globin and other genes *ex vivo* and *in vivo* ('gene therapy'). In parallel, the study of stem cells, especially pluripotent hematopoietic stem cells, has progressed greatly, leading to improvements of bone marrow/stem cell transplants (currently, the only "cure" for SCD) as well as *in vitro* methods of maturing erythroid cell precursors that allows the study of the mechanisms of promising HbF-inducing agents. However, we still do not have a safe, effective, inexpensive, easy-to-deliver Hb switching agent that can be delivered to millions of sufferers.

Fairly early in the Hb Switching Program, the emphasis switched to the promise of gene therapy. In the early 1990's, both NIDDK and NHLBI initiated 'Gene Therapy Center grants'. Although the aim was to continue the search for gene regulatory factors and HbF-inducing agents while pursuing gene therapy, there was a significant shift in emphasis marked by the founding of the 'American Society for Gene Therapy' and a greater emphasis on gene therapy at the every-other-year 'Hemoglobin Switching Conferences'. Two and a half decades of research on vectors, targeting mechanisms, and enzyme effectors have produced impressive results, with more efficient and accurate methods of altering specific gene sequences (e.g., CRISPER-Cas9) [7]. These recent advances, combined with the increased knowledge and techniques of handling stem cells, have provided the tools for curing SCD by altering the genes of the patients own hematopoietic stem cells *ex vivo*, followed by transfusing the corrected cells back into the patient, affecting a cure without the risks associated with a bone marrow transplant from another individual. It appears that a safe and efficient gene therapy cure for SCD will soon be available, certainly a major accomplishment worthy of celebration.

However, gene therapy and stem cell/bone marrow transplants are sophisticated procedures. The personnel, the resources, and hospital time required are great, as are the costs. It is unlikely that more than a small fraction of the estimated 100,000 SCD sufferers in US can be cured by these means in the near future, much less the millions of sufferers worldwide, until a way is found to bring the costs down dramatically. Many in African countries and in India do not have access to medical facilities, making heath delivery of anything but simple medicines problematic. What is needed is a pill, a pill that can deliver daily doses of a safe compound that induces and maintains a high level of an effective inducer of HbF.

This is a scientific problem that is also a social problem. There has never been enough funding for sickle cell. In US, the original fifteen 'National Sickle Cell Centers' proposed by President Nixon were immediately cut to ten by Congress; and the funding for those ten centers was recently 'reallocated' by NHLBI with the social burden transferred in part to the 'Center for Disease Control'. In the US, SCD

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was labelled an "orphan disease,"the category established for diseases with less than 200,000 affected individuals. The 'Hemoglobin Switching Program' has not grown and prospered. Yet the economic burden has grown as medical care has become more expensive. The US spends over one billion dollars each year on largely palliative care that does little to alleviate the pain or alter the course of the disease. In the countries of Africa and in India, the economic burden of SCD is huge. On a smaller, individual scale, imagine the burden of a family of four, a husband and wife with two children, one with SCD. In countries without good medical care, one parent must stay home with the afflicted child. But with an inexpensive, effective, easily available pill that keeps that child healthy and in school, both parents become wage earners and the family economic situation improves immensely.

The goal of finding a safe, inexpensive, easy-to-deliver method of raising fetal hemoglobin levels in children and adults with SCD is still a worthy one - a goal that is in need of significant additional funding and the support of WHO and other agencies that operate on a global scale. There are a number of candidate drugs in the pipeline e.g. [8], and one or more of them may alleviate SCD, at least in part. But more possibilities are needed and the problem needs new eyes and minds, especially minds that understand animal development from a comparative, evolutionary point of view, i.e., how the globin gene system and developmental Hb switching came to be–a view which includes all vertebrates, including those animal models that have fallen from funding favor but still have somethings to tell us in our quest to solve this developmental mystery [9], how to reverse the perinatal developmental hemoglobin switch.

We need political and business leaders of vision to support scientists of vision, leaders that realize that science helps solve global problems and is a good investment in a healthful, productive future for all.

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