Sickle cell disease (SCD) is a genetic disorder affecting the haemoglobin genes of red blood cells, a mutation which changes a single amino acid within the haemoglobin protein (the oxygen carrier of the blood) and is responsible for the formation of rigid sickle-shaped red blood cells. These block the fine capillaries of the vascular system leading to acute and chronic episodes of tissue ischemia (oxygen deprivation) and a sustained organ-damaging inflammatory response. The disease is particularly prevalent in developing countries where malaria is endemic, because the heterozygous condition (the largely innocuous state where an individual has both a normal and a mutated version of the gene) confers partial protection from early death from the infection. This in turn confers a survival advantage to the heterozygotes who breed homozygotes (those who inherit two mutated genes and therefore have SCD).

UNDERSTANDING THE DISEASE AND THE CHALLENGES
This produces the first of many challenges. When considering potential treatment options, the ideal therapy would be simple and inexpensive as well as being robust enough to cope with the environment and economic conditions in tropical regions. Another challenge, however, is one of scale; red blood cells account for seventy percent of total cells in an adult, and there may be more than a kilogram of haemoglobin contained within them. As Prof Nathan, former President of the Dana-Farber Institute, makes clear, “Any attempt to apply a drug to haemoglobin must reckon with that awesome fact, treating that quantity of material is no mean feat.”

THE PROBLEM WITH SHAPE-SHIFTING
The transition to the low oxygen conformation of molecules occurs and the haemoglobin molecule of the protein. If left long enough (dubbed the delay time), polymerisation of all other mutated molecules. This causes distortion of red cell membranes and forces open pores within them which disrupt the electrolyte balance. Prof Nathan notes that, “The loss of electrolyte forces causes polymerisation, so increased levels of foetal haemoglobin can reduce this damage-causing aspect of SCD. Prof Nathan and colleagues introduced hydroxyurea, first to animal models and then to patients, to successfully increase foetal haemoglobin levels of these due to other conditions are more likely to suffer SCD crises. Conversely, drugs which can maintain high oxygen conformation may limit the extent of crises. Again, Prof Nathan sees potential, but the same issues arise: “Drugs that bind to haemoglobin may maintain the molecule in the high oxygen affinity state. But such molecules might be expected to be of limited value because very large amounts of drug would be required to deal with [the quantity of] haemoglobin. Such large doses over a protracted period might cause toxicity.” Despite this, one such drug is currently undergoing field tests.

LIMITED TREATMENT OPTIONS
The only treatment currently approved for prevention or reduction of SCD symptoms is related to mitigating the polymerisation of haemoglobin. Because mixtures of the constituent haemoglobin proteins within a red cell form hybrids under normal physiological conditions, the presence of certain variants can create hybrids which do not provide a pocket for the abnormal bulge and so inhibit polymerisation. Foetal blood is unaffected by the mutation of SCD because it contains a form of haemoglobin protein which is coded by another gene upstream of the affected SCD gene. The advantage of foetal haemoglobin is its increased affinity for oxygen enabling it to extract it from the mother’s blood. It remains in the high oxygen conformation and also does not contain the pocket required for polymerisation, so increased levels of foetal haemoglobin can reduce this damage-causing aspect of SCD. Prof Nathan and colleagues introduced hydroxyurea, first to animal models and then to patients, to successfully increase foetal haemoglobin levels.
That made me wonder about the use of such analogues in sickle cell anaemia.
Dana-Farber also remains true to its founder, Sidney Farber, MD, and his vision of a cancer centre that is just as dedicated to discoveries in cancer research as it is to delivering expert, compassionate care. Through strategic investment in research, they support scientific leaders and young investigators, develop new therapies, and ensure a spirit of collaboration and innovation. In the complex fight against cancer, Dana-Farber researchers are advancing the field on every front. They are probing the molecular changes that cause tumours, testing new drug therapies, addressing the needs of cancer survivors, and improving the delivery of care. In 2016, 500 faculty members worked on National Institutes of Health-Sponsored Research and conducted 921 clinical trials. Dana-Farber is a founding member of the Center for AIDS Research at Harvard Medical School.

Since 1948, the Jimmy Fund has raised millions of dollars through thousands of community efforts to advance Dana-Farber’s lifesaving mission. Dana-Farber cares for adults and children challenged with cancer, blood disorders, and related diseases. Their world-renowned specialists provide comprehensive and personalised care for each patient and support for their families. Their specialised treatment centres are staffed by teams of experts who work closely together to offer patients the latest therapies and strategies, including access to innovative clinical trials. In 2016, 4,826 employees delivered 157,533 infusion treatments via 321,900 patient appointments. Dana-Farber is the only hospital ranked in the top four nationally by US News and World Report in both adult and paediatric cancer care.