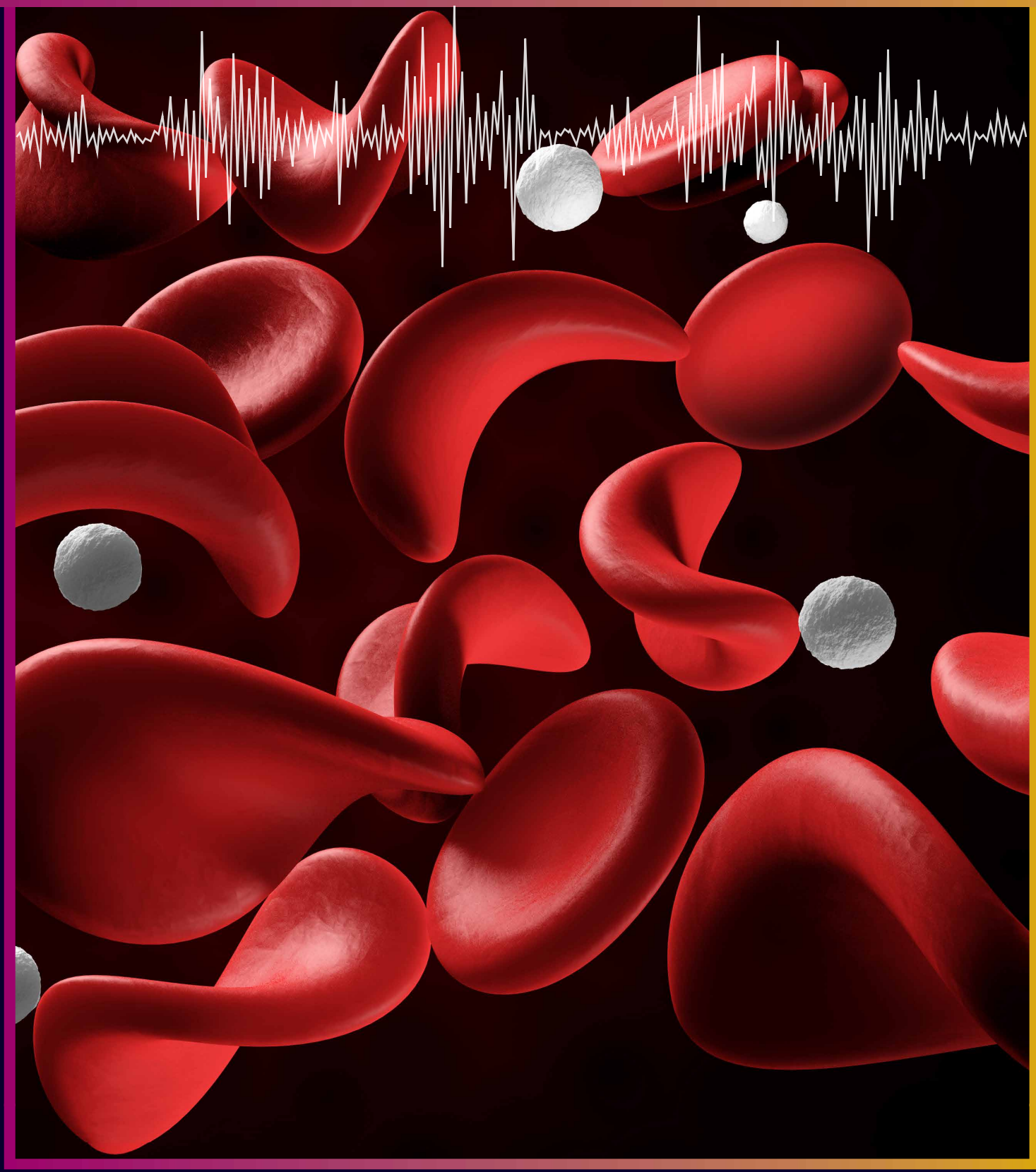
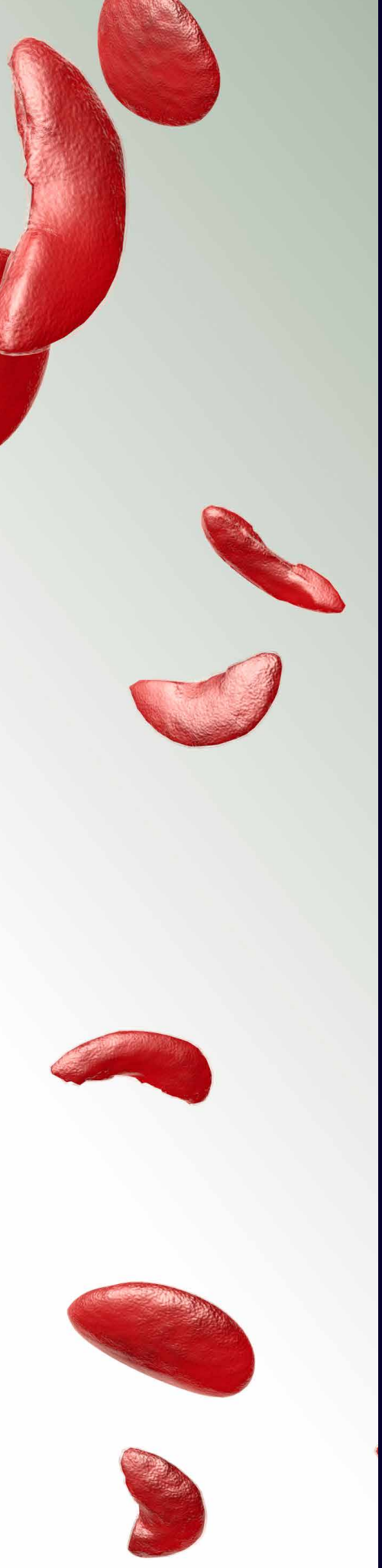
SCIPOD

# OPTIMISING THE PRENATAL TREATMENT OF INHERITED DISEASES

Dr Panicos Shangaris





# Optimising the Prenatal Treatment of Inherited Diseases

Sickle cell disease is an inherited disorder affecting the blood. Recently, promising new treatment strategies have emerged involving gene editing therapies and the administration of stem cells directly into the developing foetus in the womb. Along with his colleagues, Dr Panicos Shangaris at Kings College London, has conducted a comprehensive review of the available evidence to support this novel approach.

Sickle Cell Disease is a prevalent and severe hereditary condition arising from a genetic mutation, which may cause wide-ranging complications in the organs and tissues of the body. It is a life-long, debilitating condition which can prove fatal.

Haemoglobin is a protein component of red blood cells comprised of four subunits and is responsible for oxygen transportation. In Sickle Cell Disease, the mutated gene results in an abnormal haemoglobin structure which eventually causes red blood cells to irreversibly alter their shape from biconcave disks to curved, or sickle-shaped, cells causing blockages in vessels. This in turn modifies their normal function and negatively affects oxygen migration within the body.

Treatment for Sickle Cell Disease currently focuses on symptom management, and while some success has been attained using disease-modifying drugs, such therapeutic approaches are primarily aimed at delaying or preventing complications. Conversely, transplantation of stem cells, the only known cure for Sickle Cell Disease, seeks to substitute malfunctioning progenitor cells to alter the course of the disease. This may be used in conjunction with gene therapy, whereby the defective genetic material of the host is replaced by disease-free genetic material from a healthy donor.

Advances in prenatal screening mean that Sickle Cell Disease can be diagnosed in the developing foetus during high-risk pregnancies by obtaining a sample of the amniotic fluid which surrounds the foetus in the womb, or by taking a blood sample from the mother. Furthermore, it is now possible to administer stem cells directly to the foetus whilst in the uterus.

To further investigate this fascinating area of research, Dr Panicos Shangaris and colleagues at Kings College London recently conducted a review investigating current genetic editing techniques and stem cell transplantation options, the results of preliminary experimental procedures, and potential new approaches to optimising patient outcomes.

Gene therapy involves the transfer of healthy genetic material from a healthy donor into the cells of an affected host. Microscopic viral particles are used as a vessel to deliver a normal version of a gene, in this case, the gene encoding haemoglobin proteins, into the recipient. The donor genetic

material is inserted into the host genome and hence begins to produce normal haemoglobin proteins, thus preventing structural changes in the red blood cells and leading to the production of normally shaped, fully functional cells. Surprisingly, this occurs even if the recipient continues to produce the abnormal version of the protein.

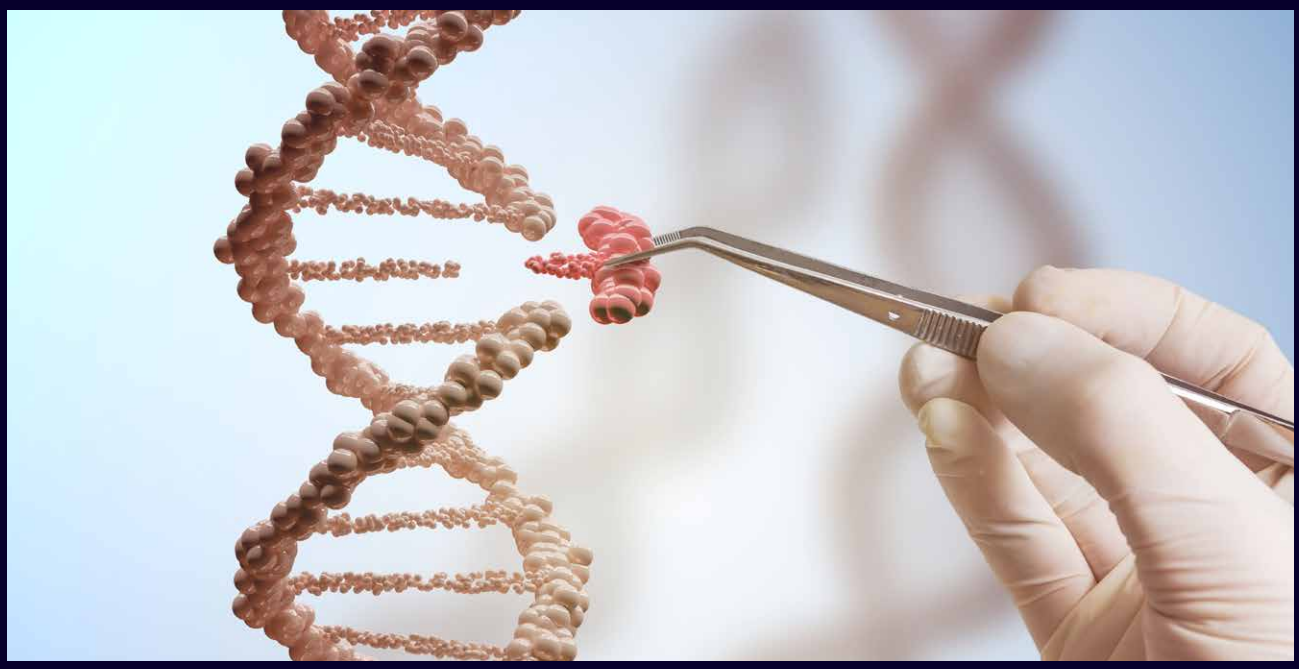
In their review, Dr Shangaris and his team explain that foetal haemoglobin has two gamma subunits which persist in the blood until around 6 months after birth, following which they are replaced by the beta subunits characteristic of adult haemoglobin. Both types also have two alpha subunits.

Gene editing involves the alteration of genetic material to induce a permanent modification, by intervening in the mechanistic processes. For example, upon completion of foetal development, production of the gamma subunit ceases. However, disruption of the gene which shuts off gamma subunit production prevents subsequent shape changes in the red blood cells of Sickle Cell Disease patients. This increases the output of functional haemoglobin units and healthy red blood cells.

Alternatively, the segment of the gene containing the mutated globin protein may be entirely removed using a genetic snipping method, and replaced with that of a healthy donor, again resulting in the production of normally shaped red blood cells and replacing the defective variant.

Gene therapy may be administered via *ex vivo* means, whereby cells are harvested from the patient, genetically modified in the laboratory, and reintroduced into the body. However, *ex vivo* methods usually involve destroying recipient bone marrow to minimise the possibility of rejection and may be limited by the availability of compatible donor material. Direct, in vivo gene transfer, is closer to ideal, whereby genetic material is infused directly into the patient or foetus, using viral vectors or nanoparticles.

The risk of failure associated with stem cell transplantation occurs because the recipient's immune system recognises the transplanted material as extrinsic and rejects the transplanted cells. However, Dr Shangaris and his colleagues describe how *in utero* transplantation can potentially overcome this by taking advantage



of the immaturity of the foetal immune system. This, together with the naturally increased migration of stem cells to tissue compartments in the developing foetus, results in a decreased likelihood of rejection and an immune tolerance specific to Sickle Cell Disease. Moreover, the need for immunosuppression prior to transplantation to mitigate rejection is unnecessary. Indeed, many advantages exist in the administration of stem cell transplants directly to the foetus, as opposed to postnatally, including the comparatively smaller size of the developing foetus, thus requiring fewer transplanted cells for a greater effect.

Once a foetus has been diagnosed with Sickle Cell Disease, *in utero* stem cell transplantation can be utilised to pre-empt the establishment of the modified gene by directly introducing healthy precursor cells. The immaturity of the foetal immune system is apparent until the end of the first trimester of pregnancy, after which differentiation into mature immune cells commences. Thus, there is a unique window of opportunity in which to infuse stem cells before migration to the bone marrow begins. This could potentially eliminate the need for life-long symptom management and drastically improve the lives of Sickle Cell Disease patients.

Despite encouraging outcomes using animal models, the achievement of therapeutic engraftment levels in humans remains elusive. Understanding the competitive nature of the foetal immune system may provide valuable insights into the underlying mechanisms of donor cell engraftment, which may aid in the development of clinical protocols. Certainly, Dr Shangaris and his team envisage the eventual implementation of *in utero* therapies into routine clinical practice, either via a single stem cell transplantation or in adjunct with a postnatal booster transplant, to support engraftment.

The refinement of procedural proficiency in this field will undoubtedly facilitate the evolution of this fascinating technique, and this compelling area of research holds much future promise. Capitalising on his lauded expertise, Dr Shangaris aims to establish a new collaborative research team to further explore the use of *in utero* stem cell transplantation and gene editing techniques for the treatment of hereditary diseases. This will inevitably promote understanding and accelerate the identification of optimal treatment modalities, ultimately improving outcomes and eliminating the need for life-long therapies.

This SciPod is a summary of the paper **'*In utero* Therapy for the Treatment of Sickle Cell Disease: Taking Advantage of the Fetal Immune System'**, from Frontiers in Cell and Developmental Biology. DOI: https://doi: 10.3389/fcell.2020.624477

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