

Investigational curative gene therapy approaches to sickle cell disease

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Sickle cell disease (SCD) is an inherited blood condition resulting from abnormal hemoglobin production. It is one of the most common genetic diseases in the world. The clinical manifestations are variable and range from recurrent acute and debilitating painful crises to life-threatening pulmonary, cardiovascular, renal, and neurologic complications. The only curative treatment of SCD at this time is bone marrow transplantation (also called hematopoietic stem cell transplantation) using healthy blood stem cells from an unaffected brother or sister or from an unrelated donor if one can be identified who is a match in tissue typing. Unfortunately, only a minority of patients with sickle cell has such a donor available. The use of autologous hematopoietic stem cells and alternative types of genetic modifications is currently under study in clinical research trials for this disease. The approaches include the use of viral vectors to express globin genes that are modified to prevent sickle hemoglobin polymerization or to express interfering RNAs to “flip the switch” in adult red cells from adult β -sickle hemoglobin to fetal hemoglobin using a physiologic switch, and several gene editing approaches with the goal of inducing fetal hemoglobin or correcting/modifying the actual sickle mutation. In this audio review, we will discuss these different approaches and review the current progress of curative therapy for SCD using gene therapy.

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The complete text of this *Blood Advances* Talk is available as a data supplement.

DOI 10.1182/bloodadvances.2021005567

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Contribution: D.A.W. drafted the paper; E.E. provided editorial review.

Conflict-of-interest disclosure: D.A.W. received research funding from bluebird bio for research in hemoglobinopathies in the past. Boston Children's Hospital (BCH)

licensed certain intellectual property relevant to hemoglobinopathies to bluebird bio. The current license includes the potential for future royalty/milestone income. Bluebird has indicated it will not pursue this as a clinical program and BCH is negotiating return of the intellectual property. D.A.W. received payment in past through BCH institutional licensing agreement. Bluebird bio provided good manufacturing practice vector for sickle cell disease clinical trial. E.E. participated in consulting for bluebird bio.

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