**Sickle cell disease has emerged as a public health concern. Some drugs may conflict with curative therapies, yet they may be useful as a bridge to HSCT and gene therapy**

Abstract

Sickle cell disease has resurfaced as a health-care priority in high-income nations and low-income countries (LMICs). Transplantation results with haploidentical haematopoietic stem cell transplantation (HSCT) are improving, increasing the likelihood of a curative treatment for the majority of patients. The indications for HSCT and for disease-modifying drugs, for example, must be determined. There are still a few things to think about, including biomarkers for systemic vasculopathy. Some medications may compete with curative treatments, but they might potentially be an important bridge treatment to HSCT. One of the most difficult hurdles yet ahead is reaching out to general practitioners and haematologists to bridge the awareness gap about curative alternatives such as matched sibling donor HSCT so that patients and their families may be identified early.

## Introduction

Sickle cell disease is one of the most frequent and life-threatening non-communicable illnesses in the world, and it is recognized by the WHO and the UN as a worldwide problem and a serious public health concern. Sickle cell disease is a progressive debilitating disease, and despite significant improvements in preventive and therapeutic modalities that result in excellent survival in patients younger than 18 years, the morbidity and mortality of adults has not improved significantly in recent decades, with a continued reduced life expectancy in adulthood and an unacceptable quality of life despite current standards. The illness has progressed from a mostly vaso-occlusive manifestation to a systemic vasculopathy in high-income nations. Long-term cohort studies of adults with haemoglobin SS are scarce and have significant limitations, but they consistently indicate a shorter lifespan across populations and health-care systems. The median age of death is expected to be between 42 and 67 years old. Organ dysfunction indices have been linked to an elevated risk of death in a number of studies. 1, 2 Elevated tricuspid regurgitation velocity, pulmonary hypertension3, and a decreased glomerular filtration rate are among the dysfunctions. 3 Cardiovascular, cardiopulmonary, and renal complications are the leading causes of death in adults with sickle cell disease in the United States, and rising cerebrovascular illness is a major source of morbidity and mortality limitations.4

With cure rates of up to 90%5, improved health-related quality of life6, and potential cost-effectiveness7, haematopoietic stem cell transplantation (HSCT) is widely regarded as an acceptable therapeutic option for individuals with sickle cell disease.The current agreement on matched sibling donor HSCT indications is still restrictive 8 and is limited by less than 20% donor availability.9 For families that have a kid with sickle cell disease, directed cord blood banking might be a valuable stem cell resource. 10 alternative therapeutic treatments, such as a matched unrelated donor, haploidentical HSCT, or gene editing and treatment, have been developed for patients who do not have a matched sibling donor.

Similarly, various novel medicines with potential activity against sickle cell disease-related problems have become accessible following decades of standstill in traditional therapy approaches. This exciting expansion of the sickle cell disease treatment landscape creates a new level of complexity in decision-making and raises major concerns about extended indications for curative methods.

The most pressing topic is how to address the difficulties of the continent with the highest prevalence of sickle cell illness, Africa, which has an estimated 6 million sickle cell sufferers. 11

## Drugs that treat or prevent diseases

Reduced frequency and severity of acute vaso-occlusive crises, avoidance of chronic sequelae, better quality of life, and increased life expectancy are all goals of sickle cell disease treatment. Until 2017, hydroxycarbamide (commonly known as hydroxyurea) and continuous blood transfusions were the only two disease-modifying treatments available to patients and physicians. In the last 25 years, hydroxycarbamide has been studied extensively in both high- and low-income nations, with a positive effectiveness and safety profile.

In a randomized controlled study, Steinberg and colleagues12 looked at the dangers and benefits of long-term hydroxycarbamide usage and found that those who were exposed to hydroxycarbamide for a long time had a lower death rate. The European Sickle Cell Disease Cohort–Hydroxyurea study (NCT02516579) and the Long-Term Effects of Hydroxyurea Therapy in Children with Sickle Cell Disease research are two further studies now active (NCT00305175). These prospective trials will give a more thorough and systematic examination of long-term effectiveness and safety. Inadequate clinical response in some patients, poor treatment uptake in the real-world setting, residual concerns about toxicity, and insufficient data on its efficacy in preventing long-term chronic complications of sickle cell disease, such as renal impairment, pulmonary hypertension, and cerebral ischaemic damage, are all issues with hydroxycarbamide use. Men's fertility is still an issue, and French research found that 6 months of hydroxycarbamide medication resulted in a significant fall in sperm count in men. It's unclear how much of the hydroxycarbamide-induced spermatogenesis is reversible, or what the risk of infertility is for prepubertal boys taking the drug. 13

When hydroxycarbamide fails, regular transfusion has a well-established role in primary and secondary stroke prevention 14, and is increasingly being used to manage other severe complications of the condition.Older children and adults are treated at certain specialty centers with 3–8 weekly automatic exchange blood transfusions. This approach allows for a consistent reduction in red blood cell concentrations with haemoglobin S below 30%, an increase in haematocrit, and the management of transfusion-related iron excess. The treatment, however, is time-consuming, necessitates adequate vascular access, and requires huge amounts of donor blood. Chronic blood transfusions, even when optimized, reduce transcranial doppler velocities and help prevent stroke, but they do not always result in normal velocities or protect against the progression of cerebral vasculopathy and silent infarcts, especially in patients with a history of overt stroke, according to evidence. 15 and 16

Based on published phase 2 and 3 trials 17 that demonstrated small reductions in vaso-occlusive crises, the US Food and Drug Administration (FDA) approved glutamine (Endari, Emmaus Medical, Torrence, CA, USA) for the prevention of vaso-occlusive crises in 2017.However, the Committee for Medicinal Products for Human Use of the European Medicines Agency issued a negative judgment, hence glutamine is rarely used in Europe. Now that glutamine is on the market in the United States, post-marketing proof of effectiveness in US patients should help to clarify glutamine's role in the therapeutic landscape.

Voxelotor (Oxbryta, Global Blood Therapeutics, South San Francisco, CA, USA) binds to the N-terminal valine of the -globin chain in a Schiff-base linkage, preventing the physiological changeover from the relaxed, completely oxygenated state to the tense, totally deoxygenated state. The sickling process is inhibited by voxelotor because polymerization of haemoglobin S is only feasible in tense conditions. Voxelotor has shown a statistically significant improvement in haemoglobin concentrations, a decrease in major haemolytic indicators, and an acceptable safety profile in phase 2 and 3 trials. 18 and 19 These findings led to the expedited approval of voxelotor in the United States for the treatment of sickle cell disease, with continuous approval pending confirmation trials. The therapeutic advantages of the treatment of chronic illness symptoms have yet to be demonstrated in the published trials, which only report up to 6 months of medication. Furthermore, the phase 3 research did not employ acute vaso-occlusive crisis as a key endpoint, and published findings did not indicate a statistically significant difference in the rate of vaso-occlusive crisis between the medicine and the placebo. Longer-term follow-up of the trial cohorts will be required to determine if the observed trend of decreased incidence of vaso-occlusive crises is stable. In conclusion, it is uncertain whether increasing haemoglobin concentration and decreasing intracellular sickling at the price of decreased oxygen supply by drug-modified haemoglobin would result in long-term therapeutic benefit.

Crizanlizumab (Adakveo, Novartis, Basel, Switzerland) is a humanized monoclonal antibody that binds to P-selectin and disrupts the interaction between P-selectin and P-selectin glycoprotein ligand 1. In sickle cell disease, P-selectin is expressed on endothelial cells and activated platelets, and it mediates erythrocyte–endothelial, leucocyte–endothelial, and leucocyte–platelet interactions. It also contributes to poor microvascular flow and vaso-occlusion. In the phase 2 research, the risk of vaso-occlusive crises was decreased by 45 percent in the higher dose crizanlizumab (5 mg/kg) group compared to the placebo group, with a low number of side events. 20 Crizanlizumab was given fast approval by the FDA in November 2019 to help patients aged 16 and above have fewer vaso-occlusive crises. This approval will also be reliant on the drug's efficacy in the treatment of sickle cell disease's vaso-occlusive consequences.

Single agents or a combination of drugs targeting complementary pathophysiological mechanisms of red blood cell damage, vaso-occlusion, and vascular damage in sickle cell disease may be possible using FDA-approved new treatments and others in the development pipeline, offering hope for effective long-term control of the disease using single agents or a combination of drugs targeting complementary pathophysiological mechanisms of red blood cell damage, vaso-occlusion, and vascular damage in sickle cell disease.

Many people believe that HSCT has a higher death rate than supportive treatment. Unfortunately, there are no prospective comparisons between patients treated with HSCT and those treated with supportive therapy, and, hence, only indirect comparisons with historical controls are feasible. 21 Beyond overt stroke, Walters and colleagues22 identified a number of indications for HSCT in children, including aberrant transcranial doppler, acute chest syndrome, recurrent vaso-occlusive crises, and others, notably those that occur after hydroxycarbamide treatment. 23 Galadanci and colleagues [24] found that neurological problems, aside from overt stroke, occur more frequently than predicted in sickle cell disease children under the age of five. As a result, matched sibling donor HSCT in children with sickle cell disease, which has a 95 percent overall survival rate and a 93 percent event-free survival rate, is a curative therapy with a role even in young patients. 24, 25, and 26. Adults treated with non-myeloablative regimens showed promising outcomes, with an 87 percent event-free survival rate, a 13 percent rejection risk, maintenance of fertility, and no graft-versus-host disease (GVHD), but a significant proportion of mixed chimerism. 27 Adults with mixed chimerism have yet to be shown to be sufficiently protected from pulmonary hypertension or renal problems. Nonetheless, donor chimerism (minimum of 20–25 percent) has been demonstrated to be adequate for reversing the sickle phenotype and resolving sickle-related symptoms [28], even though the frequency of chimerism appears to be important in terms of donor and sickle-related haemolysis. 30, 29 The age of the patient, serotherapy, and the frequency of chimerism must all be considered when deciding between myeloablative and non-myeloablative conditioning regimens. When a matched sibling donor is available, HSCT at a young age is a crucial option to examine because of the outstanding overall survival and event-free survival results, as well as the growing evidence that irreparable damage to essential organs begins in infancy. 31, 24 However, the fact that chronic GVHD is the main factor determining normalisation of quality of life after transplantation in haemoglobinopathies and that chronic GVHD is the main factor determining normalisation of quality of life after transplantation in matched sibling donor HSCT31 must be taken into account. 32

Although data on health-care use for sickle-cell disease patients who have had HSCT is limited, a US trial has shown that HSCT is both helpful and cost-effective in children. Patients with sickle cell disease had lower post-transplant expenditures as compared to pre-transplant expenditures and the cost of care for patients who did not get transplantation. Outpatient visits following allogeneic HSCT were significantly less expensive than outpatient visits prior to allogeneic HSCT (US $30,000 vs 78180 per month; p = 0 0 0 0 0 0044).The median cost of hospital visits after HSCT was comparable to the cost of inpatient visits before HSCT ($0 vs 73000 per month; p = 0 079). Adults with typical chronic sickle cell-related multiorgan illnesses should see similar findings in a comparable study. 7

HSCT from an unrelated donor that was matched

Unfortunately, the majority of patients lack an HLA-identical sibling donor. There are numerous options for these individuals, including matched unrelated donor HSCT. In the last decade, researchers have looked at the function of matched unrelated donor HSCT, but high rates of graft failure, delayed immune reconstitution, regimen-related toxicities, and persistent GVHD have limited its use. 33 Screening criteria for sickle cell disease after HSCT have been established, allowing for better long-term health-care monitoring, early detection and treatment of problems, and assurance of wellness following matched unrelated donor HSCT. 34 Furthermore, the chances of obtaining an ideal unrelated HLA identical donor (with a full 8/8 match at the allele level) vary by racial and ethnic group, with patients of African origin having the lowest chance (16%). 9

The European Society for Blood and Marrow Transplantation's Paediatric Diseases Working Party and the Inborn Errors Working Party retrospectively analyzed matched unrelated donor HSCT in 70 individuals with sickle cell disease.

35 Graft failure occurred in 11 (16%) of the patients (six primary and five secondary). The 3-year cumulative incidence of acute GVHD grade 2–4 was 24%, while the cumulative incidence of chronic GVHD was 24%. Overall survival was 86.3% after three years, while GVHD-free and relapse-free survival was 62.6%.

HLA compatibility was found to be a significant risk factor for overall survival, as well as GVHD-free and relapse-free survival. Patients treated with fludarabine, thiotepa, and treosulfan had better 3-year overall survival, GVHD-free survival, and relapse-free survival than those treated with other regimens.

These findings support those of Eapen and colleagues25, who found that patients who got HSCT with a graft from an 8/8 HLA matched unrelated donor had better outcomes than those who got a transplant from a mismatched unrelated donor. In the study by Eapen and colleagues, patients who underwent HSCT when they were less than 12 years old had better event-free survival than older patients. Although there was a trend for better survival in the younger age group (16 years) in this study's European cohort, the results were not substantially different, perhaps due to the limited number of adult patients included (114 children vs 30 adults).

HSCT from a haploidentical donor

Because of the scarcity of related HLA matched donors, only around 1–2% of the entire population of children with sickle cell disease qualify for HSCT.

36 Even when socioeconomic and educational variables are taken into account, the shortage of donor availability has been recognized as the greatest obstacle to HSCT. 37

The development of both in-vivo and ex-vivo T-cell depletion techniques has aided the rise of haploidentical donor HSCT as a viable option with a large donor pool. The use of cyclophosphamide after transplantation enables the long-term engraftment of MHC-incompatible cells. 38 In sickle cell disease, a decreased intensity regimen for haploidentical donor HSCT39 was shown to be safe and feasible, although it had a high risk of graft failure (43 percent ).

A multi-institutional learning collaborative evaluated the inclusion of pre-transplantation conditioning and endogenous haematopoiesis inhibition using hypertransfusion, as well as the inclusion of thiotepa in the conditioning regimen, with the primary goal of lowering the graft failure rate.

40 When thiotepa was administered to 15 sickle cell disease patients, the results were similar to matched sibling HSCT, but there was an increase in mortality owing to macrophage activation when the preconditioning regimen was added. 41 After a median follow-up of 13 months, disease-free survival was 93 percent and overall survival was 100 percent. Grade 3–4 acute GVHD accounted for 13% (two of 15 cases), with one case of mild chronic GVHD accounting for 7%. (one of 15). 40 Following the normalization of haematopoiesis, there is also evidence of some functional improvement in cerebrovascular illness. 42 This strategy is now being explored in a phase 2 multicenter, single arm experiment (NCT03263559).

Increased total body irradiation to 400 centigray was used by the Johns Hopkins group43 to reduce graft failure, which significantly reduced graft failure (one [6% ] of 17 patients, of whom 12 [71 percent ] had sickle cell disease), while maintaining the safety of the post-transplantation cyclophosphamide approach. The rates of GVHD were identical to those seen in the research conducted by the Vanderbilt Institute for Global Health. 43

Escalating doses of post-transplantation cyclophosphamide (0–100 mg/kg total daily doses) in combination with alemtuzumab and total body irradiation of 400 centigray improved donor engraftment, with 10 (83%) of 12 patients engraftment with the 100 mg/kg dose compared to one (33%) of three in the cohort that did not receive post-transplantation cyclophosphamide. Although there was no clinically significant difference in GVHD across groups, this outcome came at the cost of substantial graft failure, with just half of the patients in the highest post-transplantation cyclophosphamide dosage group (six of 12) maintaining engraftment. 44

Ex-vivo T-cell depletion is an alternate treatment option. T-cell receptor (TCR) and CD19 cells are selectively reduced from HSCT grafts such that the resultant cell grafts contain a range of blood cells with various immunological features. The rapid engraftment kinetics observed in patients receiving CD3-depleted and CD19-depleted grafts compared to only CD34-enriched grafts, including CD34-negative haematopoietic stem cells with a high repopulating capacity, have already demonstrated the significant effect of graft composition and conditioning regimen on engraftment. Engraftment was quick in all patients who received TCR-depleted and CD19-depleted transplants. When compared to individuals who had CD3 and CD19 deletion, immune recovery was much enhanced, and TCR cells predominated at day 100. 45 Because of the low prevalence of GVHD, these qualities appear to be a benefit for haploidentical HSCT in non-malignant haematological diseases. In sickle cell disease, the feasibility of this method was demonstrated. 46 With a 25-month follow-up, 15 (75%) of 20 patients were transplanted with CD3-depleted and CD19-depleted grafts, whereas five (25%) were implanted with TCR-depleted and CD19-depleted grafts. Overall survival was 90% after conditioning with an anti-T-lymphocyte immune globulin (Grafalon, Neovii, Rapperswil, Switzerland) in combination with fludarabine, thiotepa, and treosulfan. One patient died of CMV pneumonitis, while the other died of macrophage activation syndrome. No patients experienced grade 3–4 acute GVHD, and four patients (20%) had mild or severe chronic GVHD47, which was cured 18 months following HSCT. In a future European Society for Blood and Marrow Transplantation experiment, the TCR-depleted and CD19-depleted technique will be compared to matched sibling donor HSCT (NCT04201210).

Cairo and colleagues48 used a different method in children with sickle cell disease, utilizing a CD34-enriched graft with a T-cell add-back after myeloimmunoablative conditioning. Erythroid donor chimerism (CD71) was 96 percent after 12 months. The prevalence of acute GVHD in grades 2–4 was 62%, while chronic GVHD was 67%. A 90 percent chance of surviving an event-free year was calculated.

How does HSCT from a matched unrelated or haploidentical donor compare to HSCT from a matched sibling donor?

The decision to proceed with alternative HSCT is the outcome of a lengthy decision-making process that weighs the risks and benefits of alternative HSCT against standard therapy. This treatment decision problem affects not just transplant doctors, but also patients, carers, haematologists, and paediatricians. Given the non-malignant nature of the condition, the possibility of persistent GVHD and graft failure must be considered. As a result, the standard donor algorithm for malignant illnesses (matched sibling donor > matched unrelated donor > mismatched unrelated donor > alternative donors) 49 has to be carefully examined, especially in adult patients with sickle cell disease.

The overall survival of patients transplanted with a graft from a 10/10 HLA matched unrelated donor and those treated with a fludarabine, thiotepa, and treosulfan conditioning regimen is comparable to that of patients transplanted with HLA-identical sibling grafts in certain studies.

5, 19, and 20 As a result, for individuals with sickle cell disease who do not have an HLA-identical sibling donor, matched unrelated donor HSCT is a viable choice. When matched unrelated donors are available, complete HLA-matched grafts (HLA-A, HLA-B, HLA-C, HLA-DRB1 and HLA-DQB1) and grafts without antigens for detectable antibodies in the patient are advised. A treosulfan–thiotepa–fludarabine-based conditioning regimen may be advised when available, 47, but other medication combinations must be investigated in larger cohorts of sickle cell disease patients before the best conditioning regimen for those individuals can be determined. Matching unrelated donor HSCT was shown to be less successful and safe than matching sibling donor HSCT in a large registry-based study. These findings differ from those of children with acute leukemia. 50 Chronic GVHD appeared to be much more common with matched unrelated donor HSCT (21 percent at 12 years and 23 percent at 15 years) than with matched sibling donor HSCT (21 percent at 12 years and 23 percent at 15 years) (9 percent at 13 years). 31, 25 Brazauskas and colleagues51 created a risk score that takes into account the patient's age and donor preference to predict event-free survival following HSCT in sickle cell disease patients. Furthermore, in order to justify HSCT and its possible long-term repercussions, disease-related problems, organ damage, and quality of life in elderly patients must be carefully examined. 52

Even in adolescents and young adults, there is accumulating evidence that, in addition to quick donor availability, which allows HSCT to take place before any potentially permanent end-organ damage or disease-related death, problems such as acute and chronic GVHD are rare. The significant graft failure rates seen in the early experiments were reduced by tweaking the conditioning regimens. However, concerns such as viral reactivation47, macrophage activation syndrome, and post-transplant microangiopathy53 must be treated with caution. To examine the effectiveness, safety, acceptability, and health economics of the different transplant alternatives, a prospective open-label worldwide trial comparing matched sibling donor HSCT with T-cell depleted haploidentical HSCT would be required, and such research is now ongoing (NCT04201210).

Gene therapy and gene editing are two other curative approaches.

Several gene editing and gene therapy techniques are being tested in clinical trials with the development of alternate donor HSCT methods. The use of a lentiviral vector with a modified -globin or -globin gene that integrates into the genome of collected autologous haematopoietic stem cells is one method. After myeloablation, modified stem cells are re-infused. Following encouraging early findings in a person, the HGB-206 study (NCT02140554) is looking at the safety and effectiveness of a modified -globin construct (haemoglobin AThr87Gln; LentiGlobin, bluebird bio, Cambridge, MA, USA). 54 The experiment is expected to enroll 50 patients, with the most recent data coming out in June 2020, with 25 patients treated with LentiGlobin and a median follow-up of 121 months. Engraftment of neutrophils took 19 days, while platelet engraftment (> 50 000 cells per L) took 28 days. Within 90 days of therapy, all patients had ceased receiving red blood cell transfusions. The median proportion of haemoglobin S in the blood was less than or equal to 60% in 15 patients with more than 6 months of follow-up, while haemoglobin AThr87Gln was higher than or equal to 40% of total haemoglobin. The median total haemoglobin concentration was 11 g/dL or greater. By 6 months, almost 70% of red blood cells had haemoglobin AThr87Gln, and 90% or more had it by 18 months. After therapy, no sickle cell problems such as acute chest syndromes or vaso-occlusive crises were detected. 55

BCL11A, which produces a protein that inhibits the -globin component of fetal haemoglobin, is the target of gene editing efforts employing clustered regularly interspaced short palindromic repeats (CRISPR) technology. The CRISPR–Cas9 repair method includes inserting or deleting DNA inside the non-coding BCL11A erythroid lineage-specific enhancer on chromosome 2, resulting in BCL11A downregulation in erythroid precursors with no effect on other haematopoietic lineages. This non-coding mutation is likely to reactivate the -globin gene and increase the amount of fetal haemoglobin protein in the red blood cells. The goal is to mimic the natural expression of elevated fetal haemoglobin concentrations throughout adulthood, 56, as observed in the disease known as hereditary persistence of fetal haemoglobin. Patients with coexisting thalassaemia or sickle cell disease who have inherited persistence of fetal haemoglobin have minimal or no symptoms. 57 The first CRISPR-mediated clinical trial in sickle cell disease patients (NCT04201210) is an open-label, worldwide and multisite, single-dose phase 1 and 2 research that has reported early findings in a 33-year-old female patient with severe sickle cell illness. 58 Adverse effects were typically consistent with myeloablation and autologous HSCT, and the gene-edited cells were not assumed to be the cause. The patient exhibited a near-normal haemoglobin A concentration of 118 g/dL 9 months following HSCT, with a 461% fetal haemoglobin expression. After HSCT, the patient had fetal haemoglobin expressed in 99.7% of red blood cells (F cells), was transfusion-independent, and had no vaso-occlusive crises. At 6 months following HSCT, bone marrow CD34 cells showed durable editing of BCL11A, with allelic editing of 814 percent.58 This long-term engraftment of altered haematopoietic stem cells suggests long-term therapeutic effectiveness, but additional patients need to be followed up on to validate this preliminary conclusion.

If the early results of these gene addition and gene editing approaches are confirmed in large prospective trials with longer follow-up and a benign adverse event profile, another curative option will be available in high-income countries. However, because the estimated costs of these curative approaches exceed alternative donor HSCT by about 6:1, they will not be a viable option. I Patients with advanced-stage illness, particularly CNS illness, will escape the problems of allogeneic HSCT, as well as the morbidity and mortality of graft rejection, GVHD, and delayed immune reconstitution, as gene addition and gene editing methods become more widely available.

Curative techniques in low- and middle-income nations are a problem.

The majority of people with sickle cell disease live in Africa and other malaria-endemic countries such as the Indian subcontinent and the Middle East. In low- and middle-income countries (LMICs) with historically big population influxes from Africa, such as Brazil and the Caribbean Islands, sickle cell disease is a severe health burden. It is clear that executing any therapeutic method in these nations and locations will be difficult. HSCT units are either not available in most LMICs where sickle cell disease is prevalent, or if they are, they cannot meet demand60, or the cost is prohibitively expensive for the majority of the population.

There is little information on the typical life expectancy and health-related quality of life of sickle cell disease patients in Africa, with a typical life expectancy of 33 years in Tanzania, compared to 58 years in high-income nations like the United Kingdom and the United States.

62 Children under the age of five are estimated to have a survival rate of less than 10% in areas with limited diagnostic and health-care facilities, 63, though subsequent data suggests that survival may have improved to 61, 64 with general improvements in public and child health.

In Sub-Saharan Africa, hydroxycarbamide has been shown to be effective for children with sickle cell disease, and escalation to a maximum tolerable dose is possible.

66, 67, 65, 66, 65, 65, 65, 65, 65. African countries have identified and are working to overcome challenges to implementing effective therapies such as newborn screening, invasive pneumococcal disease prevention (penicillin chemoprophylaxis and immunization), and hydroxycarbamide therapy.

In most LMICs, the aim is to deliver interventions at various levels of care, ranging from simple measures at basic and secondary health facilities to more complex treatments at higher levels of care. Countries are aiming to increase the referral system and the capability of tertiary-level health facilities to provide specialized services for interventions that need specialized health services, such as exchange blood transfusion, femoral head replacement, and skin transplants for chronic leg ulcers.

It is believed that with this approach of graded comprehensive treatment and the use of hydroxycarbamide, sickle cell disease life expectancy in Africa will improve.

65 However, enormous challenges remain, such as in health-care provider training and deployment, improving knowledge and removing stigma in patient groups and communities, ensuring adequate supply and access to medicines (such as hydroxycarbamide) and diagnostic tests to monitor therapy, and identifying complications.

The US National Institutes of Health supports a number of projects in Africa to battle sickle-cell disease, ranging from genetic and fundamental science research to clinical trials on disease-modifying therapies. Furthermore, research on neonatal screening and the use of point-of-care testing to enhance diagnosis is continuing. Giving a few patients the option of HSCT does not preclude providing full treatment to the others.It is critical that the two alternatives be considered as a continuum of treatment, with the majority of patients receiving comprehensive therapy and individuals with the necessary criteria having the choice of transplantation. Patients will seek professional health treatments and curative therapies outside of Africa if their nations do not supply them, at a considerably higher cost and with no post-transplantation care when they return home. Individuals seeking HSCT are increasingly leaving their native nations in Africa in search of treatment. This tendency is accompanied by greater costs and problems, and it continues to drain Africa's financial and human resources. There is little data on the outcomes of African children with sickle cell disease who received a successful HSCT overseas and then returned to their native country. Due to the lack of evidence, developing adequate recommendations on HSCT indications in this scenario is problematic. As has been demonstrated with specialised services such as dialysis, cardiovascular surgery, and oncology, developing HSCT capacity in LMICs has the potential to have a ripple impact by strengthening health systems and promoting higher professional motivation and retention.

Over 600 HSCTs for a variety of conditions were performed in several newly established HSCT services in LMICs across Southeast Asia from 2009 to 201969, and data on over 600 HSCTs for a variety of conditions in several newly established HSCT services in LMICs across Southeast Asia from 2009 to 2019 suggests that the following factors may emerge a trend.

Increasing support for HSCT programs

Blood transfusion services should be included in the early phases of the development of HSCT programs. There are other issues to consider when it comes to blood transfusion, such as the high incidence of sickle cell illness, which will result in a larger proportion of people with sickle cell trait and transfusion-transmitted illnesses, such as malaria, among blood donors.

Patients are chosen at random.

The initial success of HSCT centers is critical to their long-term viability. Ample time for patient and family preparation, as well as a relatively straightforward low-risk transplantation technique that begins with matched sibling donor HSCT and progresses to more sophisticated procedures, are all factors that contribute to successful outcomes following HSCT. The community's participation is critical. Offering free or discounted HLA typing is one way to involve the community (high-resolution, when appropriate, particularly in communities with high consanguinity rates or close ethnicity 70. The capability for HLA typing will be developed as a result of this community participation, and the first group of matched sibling donors will be identified.

Putting in place health data management systems

Establishing health information management systems is critical for documenting and tracking progress and clinical results, as well as monitoring and evaluating the program. The benefits of an online password-protected specialized information technology platform for enhancing access to and the safety of bone marrow transplantation have been demonstrated in research conducted in India. 71 In all phases of the program (planning, training, and execution), this initiative relied on a mix of onsite and online interactions. Transplantation centers in low- and middle-income countries (LMICs) are urged to communicate their HSCT experiences and outcomes, as well as to participate in international registries, HSCT reporting, quality assurance, and certification programs. The inclusion of a comprehensive health information management system will enable the attainment of these goals in all of these operations.

Putting money into a multifunctional team

Well-trained and devoted HSCT nurses, who are capable of identifying and avoiding issues before they occur, can avoid and rapidly treat a wide range of possible issues. Specialist doctors can be on-site or give support through online chats to help with medical decisions.

Putting in place evidence-based requirements

The European Society for Blood and Marrow Transplantation (ESBMT) has developed worldwide criteria that LMICs can use when establishing HSCT centers. These guidelines do not require the installation of complicated and costly equipment that has yet to have a significant impact on the outcomes of low-risk HSCT patients, such as positive pressure and high-efficiency centralised air filtration systems. 72 Furthermore, sophisticated infrastructure systems may be difficult to maintain and repair in LMIC environments, posing a threat to the long-term viability of HSCT centers. Specialist services are needed, not necessarily inside the hospital, but within an acceptable time frame, with a standard operating process for patient transfer in place.

LMICs should attempt to deliver HSCT at a reasonable cost to make this intervention accessible by launching safe and cost-effective HSCT programs. According to estimates, matched sibling donor HSCT for sickle cell disease might cost up to $15 000, including all medical costs. The costs of the Indian cooperation, which featured a collaboration between the Sankalp India Foundation and Cure2Children, were estimated to be as low as $12 000. It is accepted that African nations may not be able to provide HSCT at the same low cost as India, owing to India's availability of high-quality, low-priced pharmaceuticals, medical supplies, and laboratory services. Nonetheless, the cost of HSCT in Africa should not be significantly higher than in India. Medical tourism will be avoided if costs are kept low, and HSCT in patients' native countries (e.g., Africa) will make HSCT programs more viable and accessible.

The need for HSCT for sickle cell disease in LMICs is rising, and it will be critical to work together to examine variables and learn from experiences from both high-income nations and other LMICs in order to build a safe, cost-effective HSCT for sickle cell disease.

## Conclusion

Sickle cell disease has resurfaced as a health-care priority in high-income nations and low-income countries (LMICs) after a lengthy period of relative neglect. Transplantation results with alternative donors, especially haploidentical HSCT, are improving, increasing the likelihood of curative treatment for the majority of patients in high-income nations. There are still a few things to think about. To prevent any sickle-related problems, the indications for HSCT and for disease-modifying drugs, for example, must be determined. Furthermore, the list of sickle cell-related issues must be updated so that clinicians can pursue curative therapy regardless of donor type.Furthermore, it is uncertain if disease-modifying medications are a viable choice in LMICs, where a steady supply of medicines is not assured, or whether a one-time curative therapy, such as HSCT, is a preferable option. Another crucial aspect is the discovery of biomarkers for systemic vasculopathy that will serve as accurate outcome indicators for any treatment treatment, predicting long-term success and identifying individuals at higher risk of end-organ damage.

Because of the unexpected pharmacokinetics and the associated prevalence of sinusoidal obstruction syndrome, HSCT before the age of two years can be dangerous, regardless of donor availability. After the age of two, matched sibling donor HSCT can be safely administered with great results. If a donor is available, matched unrelated donor HSCT might be explored as early as the age of 2 years. After the age of 13, matched unrelated donor HSCT should be carefully scrutinized since outcome characteristics may begin to worsen. With future prospective studies (e.g., NCT04201210), haploidentical HSCT may become the standard of treatment for newborns and adolescents who do not have a matched sibling donor. Because fertility preservation is possible and they are able to give informed permission, adolescents and young adults with mild and non-irreversible problems represent a fascinating patient population. Furthermore, systemic vasculopathies linked with transplantation, such as GVHD, sinusoidal obstructive syndrome, and neurotoxicity, as well as delayed immunological reconstitution, are uncommon at that age. Because the risk of these vasculopathies rises dramatically in adulthood, 73 autologous HSCT using gene-edited stem cells may become the preferred option in patients over the age of 40.Although long-term efficacy and safety data from larger patient cohorts are needed to determine whether specific approaches or a combination of different curative therapies are required, gene addition and gene editing strategies are showing promising results as potential curative options for sickle cell disease and have demonstrated proof of principle.In patients older than 35–40 years, for example, treatment-related toxicities such as chronic GVHD, graft rejection, delayed immune reconstitution, and other transplant-related adverse effects are likely to outweigh the benefits of allogeneic HSCT, and patients older than 35–40 years may become a focus for gene editing and gene therapy trials. Furthermore, a number of disease-modifying medicines have been developed that might be utilized in conjunction with hydroxycarbamide. These medications may compete with curative treatments, but they might potentially be an important bridge treatment to HSCT.

One of the most difficult hurdles yet ahead is reaching out to general practitioners and haematologists to bridge the awareness gap about curative alternatives, such as matched sibling donor HSCT, so that patients and their families may be HLA typed to identify prospective donors and referred early.

References

1

MR DeBaun, DL Ghafuri, M Rodeghier, et al.

Decreased median survival of adults with sickle cell disease after adjusting for left truncation bias: a pooled analysis

Blood, 133 (2019), pp. 615-617

2

OS Platt, DJ Brambilla, WF Rosse, et al.

Mortality in sickle cell disease. Life expectancy and risk factors for early death

N Engl J Med, 330 (1994), pp. 1639-1644

3

DS Darbari, Z Wang, M Kwak, et al.

Severe painful vaso-occlusive crises and mortality in a contemporary adult sickle cell anemia cohort study

PLoS One, 8 (2013), Article e79923

4

MR DeBaun, FJ Kirkham

Central nervous system complications and management in sickle cell disease

Blood, 127 (2016), pp. 829-838

5

F Bernaudin, G Socie, M Kuentz, et al.

Long-term results of related myeloablative stem-cell transplantation to cure sickle cell disease

Blood, 110 (2007), pp. 2749-2756

6

G La Nasa, G Caocci, F Efficace, et al.

Long-term health-related quality of life evaluated more than 20 years after hematopoietic stem cell transplantation for thalassemia

Blood, 122 (2013), pp. 2262-2270

7

SD Arnold, Z Jin, S Sands, M Bhatia, AL Kung, P Satwani

Allogeneic hematopoietic cell transplantation for children with sickle cell disease is beneficial and cost-effective: a single-center analysis

Biol Blood Marrow Transplant, 21 (2015), pp. 1258-1265

8

AA Kassim, D Sharma

Hematopoietic stem cell transplantation for sickle cell disease: the changing landscape

Hematol Oncol Stem Cell Ther, 10 (2017), pp. 259-266

9

L Gragert, M Eapen, E Williams, et al.

HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry

N Engl J Med, 371 (2014), pp. 339-348

10

H Rafii, F Bernaudin, H Rouard, et al.

Family cord blood banking for sickle cell disease: a twenty-year experience in two dedicated public cord blood banks

Haematologica, 102 (2017), pp. 976-983

11

DJ Weatherall

The inherited diseases of hemoglobin are an emerging global health burden

Blood, 115 (2010), pp. 4331-4336

12

MH Steinberg, WF McCarthy, O Castro, et al.

The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: a 17·5 year follow-up

Am J Hematol, 85 (2010), pp. 403-408

13

I Berthaut, D Bachir, S Kotti, et al.

Adverse effect of hydroxyurea on spermatogenesis in patients with sickle cell anemia after 6 months of treatment

Blood, 130 (2017), pp. 2354-2356

14

M Adams, C Hanssens, T Lazarus

Battling HIV on many fronts

N Engl J Med, 338 (1998), p. 198

15

V Brousse, L Hertz-Pannier, Y Consigny, et al.

Does regular blood transfusion prevent progression of cerebrovascular lesions in children with sickle cell disease?

Ann Hematol, 88 (2009), pp. 785-788

16

ML Hulbert, RC McKinstry, JL Lacey, et al.

Silent cerebral infarcts occur despite regular blood transfusion therapy after first strokes in children with sickle cell disease

Blood, 117 (2011), pp. 772-779

17

Y Niihara, ST Miller, J Kanter, et al.

A phase 3 trial of l-glutamine in sickle cell disease

N Engl J Med, 379 (2018), pp. 226-235

18

E Vichinsky, CC Hoppe, KI Ataga, et al.

A phase 3 randomized trial of voxelotor in sickle cell disease

N Engl J Med, 381 (2019), pp. 509-519

19

J Howard, CJ Hemmaway, P Telfer, et al.

A phase 1/2 ascending dose study and open-label extension study of voxelotor in patients with sickle cell disease

Blood, 133 (2019), pp. 1865-1875

20

KI Ataga, A Kutlar, J Kanter, et al.

Crizanlizumab for the prevention of pain crises in sickle cell disease

N Engl J Med, 376 (2017), pp. 429-439

21

MC Walters, LM De Castro, KM Sullivan, et al.

Indications and results of HLA-identical sibling hematopoietic cell transplantation for sickle cell disease

Biol Blood Marrow Transplant, 22 (2016), pp. 207-211

22

MC Walters, M Patience, W Leisenring, et al.

Bone marrow transplantation for sickle cell disease

N Engl J Med, 335 (1996), pp. 369-376

23

MM Hsieh, CD Fitzhugh, JF Tisdale

Allogeneic hematopoietic stem cell transplantation for sickle cell disease: the time is now

Blood, 118 (2011), pp. 1197-1207

24

AA Galadanci, MR DeBaun, NA Galadanci

Neurologic complications in children under five years with sickle cell disease

Neurosci Lett, 706 (2019), pp. 201-206

25

M Eapen, R Brazauskas, MC Walters, et al.

Effect of donor type and conditioning regimen intensity on allogeneic transplantation outcomes in patients with sickle cell disease: a retrospective multicentre, cohort study

Lancet Haematol, 6 (2019), pp. e585-e596

26

E Gluckman, B Cappelli, F Bernaudin, et al.

Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation

Blood, 129 (2017), pp. 1548-1556

27

MM Hsieh, CD Fitzhugh, RP Weitzel, et al.

Nonmyeloablative HLA-matched sibling allogeneic hematopoietic stem cell transplantation for severe sickle cell phenotype

JAMA, 312 (2014), pp. 48-56

28

CD Fitzhugh, S Cordes, T Taylor, et al.

At least 20% donor myeloid chimerism is necessary to reverse the sickle phenotype after allogeneic HSCT

Blood, 130 (2017), pp. 1946-1948

29

A Magnani, C Pondarré, N Bouazza, et al.

Extensive multilineage analysis in patients with mixed chimerism after allogeneic transplantation for sickle cell disease: insight into hematopoiesis and engraftment thresholds for gene therapy

Haematologica, 105 (2020), pp. 1240-1247

30

F Bernaudin, JH Dalle, D Bories, et al.

Long-term event-free survival, chimerism and fertility outcomes in 234 patients with sickle-cell anemia younger than 30 years after myeloablative conditioning and matched-sibling transplantation in France

Haematologica, 105 (2020), pp. 91-101

31

B Cappelli, F Volt, K Tozatto-Maio, et al.

Risk factors and outcomes according to age at transplantation with an HLA-identical sibling for sickle cell disease

Haematologica, 104 (2019), pp. e543-e546

32

G Caocci, F Efficace, F Ciotti, et al.

Prospective assessment of health-related quality of life in pediatric patients with beta-thalassemia following hematopoietic stem cell transplantation

Biol Blood Marrow Transplant, 17 (2011), pp. 861-866

33

S Shenoy, M Eapen, JA Panepinto, et al.

A trial of unrelated donor marrow transplantation for children with severe sickle cell disease

Blood, 128 (2016), pp. 2561-2567

34

S Shenoy, J Gaziev, E Angelucci, et al.

Late effects screening guidelines after hematopoietic cell transplantation (HCT) for hemoglobinopathy: consensus statement from the second pediatric blood and marrow transplant consortium international conference on late effects after pediatric HCT

Biol Blood Marrow Transplant, 24 (2018), pp. 1313-1321

35

E Gluckman, B Cappelli, GM Scigliuolo, J De la Fuente, S Corbacioglu

Alternative donor hematopoietic stem cell transplantation for sickle cell disease in Europe

Hematol Oncol Stem Cell Ther (2020)

published online March 16, 2020.

https://doi-org.ezproxy.its.uu.se/10.1016/j.hemonc.2019.12.011

36

WC Mentzer, S Heller, PR Pearle, E Hackney, E Vichinsky

Availability of related donors for bone marrow transplantation in sickle cell anemia

Am J Pediatr Hematol Oncol, 16 (1994), pp. 27-29

37

MC Walters, M Patience, W Leisenring, et al.

Barriers to bone marrow transplantation for sickle cell anemia

Biol Blood Marrow Transplant, 2 (1996), pp. 100-104

38

L Luznik, S Jalla, LW Engstrom, R Iannone, EJ Fuchs

Durable engraftment of major histocompatibility complex-incompatible cells after nonmyeloablative conditioning with fludarabine, low-dose total body irradiation, and posttransplantation cyclophosphamide

Blood, 98 (2001), pp. 3456-3464

39

J Bolaños-Meade, EJ Fuchs, L Luznik, et al.

HLA-haploidentical bone marrow transplantation with posttransplant cyclophosphamide expands the donor pool for patients with sickle cell disease

Blood, 120 (2012), pp. 4285-4291

40

J de la Fuente, N Dhedin, T Koyama, et al.

Haploidentical bone marrow transplantation with post-transplantation cyclophosphamide plus thiotepa improves donor engraftment in patients with sickle cell anemia: results of an international learning collaborative

Biol Blood Marrow Transplant, 25 (2019), pp. 1197-1209

41

N Dhedin, J Fuente, F Bernaudin, et al.

Haploidentical bone marrow transplant with post-transplant cytoxan plus thiotepa improves donor engraftment in patients with sickle cell anemia: results of an international multicenter learning collaborative

Blood, 128 (2016), Article 1233

(abstr).

42

KV Prussien, DA Patel, K Wilkerson, et al.

Improvement in processing speed following haploidentical bone marrow transplant with posttransplant cytoxan in children and adolescents with sickle cell disease

Pediatr Blood Cancer, 67 (2020), Article e28001-e

43

J Bolaños-Meade, KR Cooke, CJ Gamper, et al.

Effect of increased dose of total body irradiation on graft failure associated with HLA-haploidentical transplantation in patients with severe haemoglobinopathies: a prospective clinical trial

Lancet Haematol, 6 (2019), pp. e183-e193

44

CD Fitzhugh, MM Hsieh, T Taylor, et al.

Cyclophosphamide improves engraftment in patients with SCD and severe organ damage who undergo haploidentical PBSCT

Blood Adv, 1 (2017), pp. 652-661

45

M Bonneville

Selection of intraepithelial gammadelta cells: the Holy GrIEL at last?

Nat Immunol, 7 (2006), pp. 791-792

46

J Foell, B Pfirstinger, K Rehe, D Wolff, E Holler, S Corbacioglu

Haploidentical stem cell transplantation with CD3+-/CD19+- depleted peripheral stem cells for patients with advanced stage sickle cell disease and no alternative donor: results of a pilot study

Bone Marrow Transplant, 52 (2017), pp. 938-940

47

J Foell, JH Schulte, B Pfirstinger, et al.

Haploidentical CD3 or α/β T-cell depleted HSCT in advanced stage sickle cell disease

Bone Marrow Transplant, 54 (2019), pp. 1859-1867

48

MS Cairo, JA Talano, TB Moore, et al.

Familial haploidentical stem cell transplant in children and adolescents with high-risk sickle cell disease: a phase 2 clinical trial

JAMA Pediatr, 174 (2019), pp. 195-197

49

F Ayuk, A Balduzzi

Donor selection for adults and pediatrics

In: Carreras E, Dufour C, Mohty M, Kröger N, eds. The EBMT handbook: hematopoietic stem cell transplantation and cellular therapies

https://link-springer-com.ezproxy.its.uu.se/content/pdf/10.1007%2F978-3-030-02278-5_12.pdf, Accessed 16th Sep 2020

50

A Balduzzi, JH Dalle, J Wachowiak, et al.

Transplantation in children and adolescents with acute lymphoblastic leukemia from a matched donor versus an HLA-Identical sibling: is the outcome comparable? Results from the International BFM ALL SCT 2007 Study

Biol Blood Marrow Transplant, 25 (2019), pp. 2197-2210

51

R Brazauskas, GM Scigliuolo, HL Wang, et al.

Risk score to predict event-free survival after hematopoietic cell transplant for sickle cell disease

Blood, 136 (2020), pp. 623-626

52

A Lawitschka, C Peters

Long-term effects of myeloablative allogeneic hematopoietic stem cell transplantation in pediatric patients with acute lymphoblastic leukemia

Curr Oncol Rep, 20 (2018), p. 74

53

JOJ Davies, AC Hart, J De La Fuente, BJ Bain

Macrophage activation syndrome and post-transplant microangiopathy following haploidentical bone marrow transplantation for sickle cell anemia

Am J Hematol, 93 (2018), pp. 588-589

54

JA Ribeil, S Hacein-Bey-Abina, E Payen, et al.

Gene therapy in a patient with sickle cell disease

N Engl J Med, 376 (2017), pp. 848-855

55

J Kanter, AK Tisdale, MY Mapara, et al.

Outcomes in patients treated with Lentiglobin for sickle cell disease (SCD) gene therapy: updated results from the phase 1/2 HGB-206 Group C Study

HemaSphere, 4 (2020), p. 102

(abstr).

56

GP Tamagnini, P Gonçalves, ML Ribeiro, et al.

Beta-thalassemia mutations in the Portuguese; high frequencies of two alleles in restricted populations

Hemoglobin, 17 (1993), pp. 31-40

57

N Murray, BE Serjeant, GR Serjeant

Sickle cell-hereditary persistence of fetal haemoglobin and its differentiation from other sickle cell syndromes

Br J Haematol, 69 (1988), pp. 89-92

58

S Corbacioglu, MD Cappelllini, J Chapin, et al.

Initial safety and efficacy results with a single dose of autologous CRISPR-Cas9 modified CD34+ hematopoietic stem and progenitor cells in transfusion-dependent β-thalassemia and sickle cell disease

HemaSphere, 4 (2020), p. 101

(asbtr).

59

B Modell, M Darlison

Global epidemiology of haemoglobin disorders and derived service indicators

Bull World Health Organ, 86 (2008), pp. 480-487

60
A Gratwohl, H Baldomero, M Aljurf, et al.
Hematopoietic stem cell transplantation: a global perspective
JAMA, 303 (2010), pp. 1617-1624

61
J Makani, SE Cox, D Soka, et al.
Mortality in sickle cell anemia in Africa: a prospective cohort study in Tanzania
PLoS One, 6 (2011), Article e14699

62
K Gardner, A Douiri, E Drasar, et al.
Survival in adults with sickle cell disease in a high-income setting
Blood, 128 (2016), pp. 1436-1438

63
GR Serjeant
Mortality from sickle cell disease in Africa
BMJ, 330 (2005), pp. 432-433

64
SD Grosse, I Odame, HK Atrash, DD Amendah, FB Piel, TN Williams
Sickle cell disease in Africa: a neglected cause of early childhood mortality
Am J Prev Med, 41 (suppl 4) (2011), pp. S398-S405

65
L Tshilolo, G Tomlinson, TN Williams, et al.
Hydroxyurea for children with sickle cell anemia in Sub-Saharan Africa
N Engl J Med, 380 (2019), pp. 121-131

66
L Luzzatto, J Makani
Hydroxyurea–an essential medicine for sickle cell disease in Africa

N Engl J Med, 380 (2019), pp. 187-189

67

CC John, RO Opoka, TS Latham, et al.

Hydroxyurea dose escalation for sickle cell anemia in Sub-Saharan Africa

N Engl J Med, 382 (2020), pp. 2524-2533

68

F Tluway, J Makani

Sickle cell disease in Africa: an overview of the integrated approach to health, research, education and advocacy in Tanzania, 2004–2016

Br J Haematol, 177 (2017), pp. 919-929

69

LB Faulkner, C Uderzo, G Masera

International cooperation for the cure and prevention of severe hemoglobinopathies

J Pediatr Hematol Oncol, 35 (2013), pp. 419-423

70

RK Agarwal, A Kumari, A Sedai, L Parmar, R Dhanya, L Faulkner

The case for high resolution extended 6-loci HLA typing for identifying related donors in the Indian subcontinent

Biol Blood Marrow Transplant, 23 (2017), pp. 1592-1596

71

RK Agarwal, A Sedai, S Dhimal, et al.

A prospective international cooperative information technology platform built using open-source tools for improving the access to and safety of bone marrow transplantation in low- and middle-income countries

J Am Med Inform Assoc, 21 (2014), pp. 1125-1128

72

R Kumar, R Naithani, P Mishra, et al.

Allogeneic hematopoietic SCT performed in non-HEPA filter rooms: initial experience from a single center in India

Bone Marrow Transplant, 43 (2009), pp. 115-119

73

AB Payne, JM Mehal, C Chapman, et al.

Mortality trends and causes of death in persons with sickle cell disease in the United States, 1979–2014

Blood, 130 (suppl 1) (2017), p. 865 (abstr).


74. Moataz Dowaidar, Hani Nasser Abdelhamid, Ülo Langel. Improvement of transfection with PepFects using organic and inorganic materials. 2021.
75. Tomas Venit, Moataz Dowaidar , Maxime Gestin , Syed Raza Mahmood, Ülo Langel , Piergiorgio Percipalle. Transcriptional profiling reveals ribosome biogenesis, microtubule dynamics and expression of specific LncRNAs to be part of a common response to cell penetrating peptides. Biomolecules, 10(11), pp. 1-21, 1567, 2020, https://doi.org/10.3390/biom10111567.
76. HN Abdelhamid, Moataz Dowaidar, Ü Langel. Carbonized chitosan encapsulated hierarchical porous zeolitic imidazolate frameworks nanoparticles for gene delivery. Microporous and Mesoporous Materials, 110200, 2020, https://doi.org/10.1016/j.micromeso.2020.110200.
77. HN Abdelhamid, Moataz Dowaidar, M Hällbrink, Ü Langel. Gene Delivery Using Cell Penetrating Peptides-Zeolitic Imidazolate Frameworks. Microporous and Mesoporous Materials, 2020, 110173, ISSN 1387-1811, DOI:10.1016/j.micromeso.2020.110173.
78. HN Abdelhamid, Moataz Dowaidar, M Hällbrink, Ü Langel. Cell Penetrating PeptidesHierarchical Porous Zeolitic Imidazolate Frameworks Nanoparticles: An Efficient Gene Delivery Platform. Available at SSRN 3435895, 2019.
79. Moataz Dowaidar. (2018). Chimeric gene delivery vectors : Design, synthesis, and mechanisms from transcriptomics analysis [Department of Biochemistry and Biophysics, Stockholm University]. https://www.diva-portal.org/smash/record.jsf?pid=diva2:1242000
80. Moataz Dowaidar, Hani Nasser Abdelhamid, Mattias Hällbrink, Ülo Langel, Xiaodong Zou: Chitosan enhances gene delivery of oligonucleotide complexes with magnetic nanoparticles–cell-penetrating peptide. Journal of Biomaterials Applications 09/2018; 33(3):392-401., DOI:10.1177/0885328218796623
81. Moataz Dowaidar, Maxime Gestin, Carmine Pasquale Cerrato, Mohammed Hakim Jafferali, Helerin Margus, Paula Ann Kivistik, Kariem Ezzat, Einar Hallberg, Margus Pooga, Mattias Hällbrink, Ülo Langel: Role of autophagy in cell-penetrating peptide transfection model. Scientific Reports 10/2017; 7(1)., DOI:10.1038/s41598-017-12747-z

82. Moataz Dowaidar, Hani Nasser Abdelhamid, Mattias Hällbrink, Krista Freimann, Kaido Kurrikoff, Xiaodong Zou, Ülo Langel: Magnetic Nanoparticle Assisted Self-assembly of Cell Penetrating Peptides-Oligonucleotides Complexes for Gene Delivery. Scientific Reports 08/2017; 7(1)., DOI:10.1038/s41598-017-09803-z
83. Moataz Dowaidar, Hani Nasser Abdelhamid, Mattias Hällbrink, Xiaodong Zou, Ülo Langel: Graphene oxide nanosheets in complex with cell penetrating peptides for oligonucleotides delivery. Biochimica et Biophysica Acta (BBA) - General Subjects 07/2017; 1861(9)., DOI:10.1016/j.bbagen.2017.07.002
84. Moataz Dowaidar, Jakob Regberg, Dimitar A. Dobchev, Tõnis Lehto, Mattias Hällbrink, Mati Karelson, Ülo Langel: Refinement of a Quantitative Structure–Activity Relationship Model for Prediction of Cell-Penetrating Peptide Based Transfection Systems. International Journal of Peptide Research and Therapeutics 07/2016; 23(1)., DOI:10.1007/s10989-016-9542-8
85. Maxime Gestin, Moataz Dowaidar, Ülo Langel: Uptake Mechanism of Cell-Penetrating Peptides. Peptides and Peptide-based Biomaterials and their Biomedical Applications, 10/2017: pages 255-264; ISBN: 978-3-319-66094-3, DOI:10.1007/978-3-319-66095-0_11
86. Ahmed A.A. Ali, Nahla M. Wassim, Moataz M. Dowaidar, Ahmed E. Yaseen: Genetic polymorphism of CYP2D6 gene among Egyptian hypertensive cases. The Journal of Basic & Applied Zoology, 08/2013; 66(4)., 228-233. DOI:10.1016/j.jobaz.2012.12.002
87. Ahmed A.A. Ali, Nahla M. Wassim, Moataz Dowaidar, Ahmed E. Yaseen: Association of eNOS (E298D) and CYP2J2 (-50 G/T) gene polymorphisms with hypertension among Egyptian cases. The Journal of Basic & Applied Zoology, 08/2013; 66(4)., 234-241. DOI:10.1016/j.jobaz.2012.12.001
88. Almeman Ahmad, Khalaf Hassan, Rasool Semaab, Moataz Dowaidar, Al Orainy Mohammad: The impact of CYP2C19 polymorphism on platelet reactivity for guiding clopidogrel treatment and cost analysis. Journal of the Saudi Heart Association 04/2013; 25(2):107., DOI:10.1016/j.jsha.2013.03.005
89. Abdullah Algasham, Hisham Ismail, Moataz Dowaidar, Ahmad A Settin: Methylenetetrahydrofolate Reductase (MTHFR) and Angiotensin Converting Enzyme (ACE) Gene Polymorphisms among Saudi Population from Qassim Region. 01/2013; 5(2 Suppl 1):3-4. PMC3533339
90. Abdullah Alghasham, Ahmad A Settin, Ahmad Ali, Moataz Dowaidar, Hisham Ismail: Association of MTHFR C677T and A1298C gene polymorphisms with hypertension. 12/2012; 6(1):3-11., DOI:10.12816/0005968
91. Ahmad Ali, Abdullah Alghasham, Hisham Ismail, Moataz Dowaidar, Ahmad Settin: ACE I/D and eNOS E298D gene polymorphisms in Saudi subjects with hypertension. Journal of Renin-AngiotensinAldosterone System 10/2012; 14(4)., DOI:10.1177/1470320312459976
92. Abdullah Alghasham, Ahmad Ali, Hisham Ismail, Moataz Dowaidar, Ahmad A Settin: CYP2J2-50 G/T and ADRB2 G46A gene polymorphisms in saudi subjects with hypertension. Genetic Testing and Molecular Biomarkers 06/2012; 16(9):1027-31., DOI:10.1089/gtmb.2012.0006

93. Ahmad A Settin, Abdullah Alghasham, Ahmad Ali, Moataz Dowaidar, Hisham Ismail: Frequency of thrombophilic genetic polymorphisms among Saudi subjects compared with other populations. Hematology (Amsterdam, Netherlands) 05/2012; 17(3):176-82., DOI:10.1179/102453312X13376952196575
94. HA Ismail, AA Alghasham, MM Dowaidar, AA Settin: Polymorophisms in MTHF and ace genes and the association with hypertension among Saudi population from Qassim region. 06/2011; 29(1)., DOI:10.4314/ejbmb.v29i1.67382
95. Badr Aljarallah, Ahmed Ali, Moataz Dowaidar, Ahmad Settin: Prevalence of α-1-Antitrypsin Gene Mutations in Saudi Arabia. Saudi Journal of Gastroenterology 03/2011; 17(4):256-60., DOI:10.4103/1319-3767.82580
96. Moataz Dowaidar, Ahmad Settin: Risk of Myocardial Infarction Related to Factor V Leiden Mutation: A Meta-Analysis. Genetic Testing and Molecular Biomarkers 08/2010; 14(4):493-8., DOI:10.1089/gtmb.2010.0017
97. Ahmad A Settin, Abdullah Algasham, Moataz Dowaidar, Hisham Ismail: Methylene Tetrahydrofolate Reductase and Angiotensin Converting Enzyme Gene Polymorphisms Related toOverweight/Obesity among Saudi Subjects from Qassim Region. Disease markers 11/2009; 27(2):97-102., DOI:10.3233/DMA-2009-0660
98. Ahmad Settin, Hala Almarsafawy, Ahmad Alhussieny, Moataz Dowaidar: Dysmorphic Features, Consanguinity and Cytogenetic Pattern of Congenital Heart Diseases: a pilot study from Mansoura Locality, Egypt. 07/2008; 2(2):101-11. PMC3068729
99. Ahmad Settin, Moataz Dowaidar, Rizk El-Baz, Ayman Abd-Al-Samad, Ibrahim El-Sayed, Mahmoud Nasr: Frequency of factor V Leiden mutation in Egyptian cases with myocardial infarction. Hematology (Amsterdam, Netherlands) 07/2008; 13(3):170-4., DOI:10.1179/102453308X316158
100. Ahmad Settin, Ibrahem S Abu-Saif, Rizk El-Baz, Moataz Dowaidar, Rabab Abu-Al Kasim, Shaimaa Shabana: Diagnosis of Sex Chromosome Disorders and Prenatal Diagnosis of Down Syndrome using Interphase Fluorescent In-Situ Hyperidization Technique. 07/2007; 1(2):203-9. PMID: 21475429 PMC: PMC3068641
101. Moataz Dowaidar. 2021. “Metabolic Syndrome_ the Presence of Inflammatory Mechanisms in Abdominal Obesity Is Undeniable, Gene Therapy Using Nanoparticles and Adenoviruses Technologies Is Promising.” OSF Preprints. April 5. doi:10.31219/osf.io/2j5xt.
102. Moataz Dowaidar. 2021. “Nanomedicine Has Elegantly Attempted to Cure Multiple Gene Polymorphisms and Mutations in Cardiovascular Diseases Using Gene Therapy Techniques.” OSF Preprints. April 5. doi:10.31219/osf.io/d3x8g.
103. Moataz Dowaidar. 2021. “Exosomes Can Make the Use of Circulating Mirna as a Biomarker More Feasible. The Aim of Gene Therapy Should Be to Learn Everything There Is to Know About Mirna Activity.” OSF Preprints. April 6. doi:10.31219/osf.io/edkua.
104. Moataz Dowaidar. 2021. “Key Genetic Factors in the Metabolic Syndrome Predisposition Which May Be a Therapeutic Options by Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/f38sk.

105. Moataz Dowaidar. 2021. “Anti-sense Pathways Have Been Generated Using Sirna. The Liver and Other Often Used Organs Will Now Be Targeted.” OSF Preprints. April 11. doi:10.31219/osf.io/m6xvp.
106. Moataz Dowaidar. 2021. “Discoveries in Gene-environment Interactions That Influence CVD, Lipid Traits, Obesity, Diabetes, and Hypertension Appear to Be Able to Influence Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/cr5af.
107. Moataz Dowaidar. 2021. “Genome Editing's Potential Target Diseases in the Cardiovascular Field.” OSF Preprints. April 11. doi:10.31219/osf.io/gc23p.
108. Moataz Dowaidar. 2021. “The Cardiometabolic-based Chronic Disease Model Lays the Foundations for Accurate, Evidence-based Preventive Targeting and Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/up9z4.
109. Moataz Dowaidar. 2021. “Researchers Would Be Able to Develop a Detailed Picture of Chromatin in Disease, Which Would Be Useful for Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/m9z48.
110. Moataz Dowaidar. 2021. “Mirna Can Be a Part of Both the Onset and Cure of Coronary Heart Disease.” OSF Preprints. April 11. doi:10.31219/osf.io/teqh8.
111. Moataz Dowaidar. 2021. “Crispr/cris Systems Are Highly Effective and Useful for Genomic Manipulation. Despite This, Cardiac Treatment Remains Difficult Due to Existing Genome Editing and Delivery Processes.” OSF Preprints. April 11. doi:10.31219/osf.io/3nwzd.
112. Moataz Dowaidar. 2021. “Metabolic Syndrome_ the Presence of Inflammatory Mechanisms in Abdominal Obesity Is Undeniable, Gene Therapy Using Nanoparticles and Adenoviruses Technologies Is Promising.” OSF Preprints. April 5. doi:10.31219/osf.io/2j5xt.
113. Moataz Dowaidar. 2021. “Nanomedicine Has Elegantly Attempted to Cure Multiple Gene Polymorphisms and Mutations in Cardiovascular Diseases Using Gene Therapy Techniques.” OSF Preprints. April 5. doi:10.31219/osf.io/d3x8g.
114. Moataz Dowaidar. 2021. “Exosomes Can Make the Use of Circulating Mirna as a Biomarker More Feasible. The Aim of Gene Therapy Should Be to Learn Everything There Is to Know About Mirna Activity.” OSF Preprints. April 6. doi:10.31219/osf.io/edkua.
115. Moataz Dowaidar. 2021. “Key Genetic Factors in the Metabolic Syndrome Predisposition Which May Be a Therapeutic Options by Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/f38sk.
116. Moataz Dowaidar. 2021. “Anti-sense Pathways Have Been Generated Using Sirna. The Liver and Other Often Used Organs Will Now Be Targeted.” OSF Preprints. April 11. doi:10.31219/osf.io/m6xvp.
117. Moataz Dowaidar. 2021. “Discoveries in Gene-environment Interactions That Influence CVD, Lipid Traits, Obesity, Diabetes, and Hypertension Appear to Be Able to Influence Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/cr5af.
118. Moataz Dowaidar. 2021. “Genome Editing's Potential Target Diseases in the Cardiovascular Field.” OSF Preprints. April 11. doi:10.31219/osf.io/gc23p.

119. Moataz Dowaidar. 2021. “The Cardiometabolic-based Chronic Disease Model Lays the Foundations for Accurate, Evidence-based Preventive Targeting and Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/up9z4.
120. Moataz Dowaidar. 2021. “Researchers Would Be Able to Develop a Detailed Picture of Chromatin in Disease, Which Would Be Useful for Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/m9z48.
121. Moataz Dowaidar. 2021. “Mirna Can Be a Part of Both the Onset and Cure of Coronary Heart Disease.” OSF Preprints. April 11. doi:10.31219/osf.io/teqh8.
122. Moataz Dowaidar. 2021. “Crispr/cris Systems Are Highly Effective and Useful for Genomic Manipulation. Despite This, Cardiac Treatment Remains Difficult Due to Existing Genome Editing and Delivery Processes.” OSF Preprints. April 11. doi:10.31219/osf.io/3nwzd.
123. Moataz Dowaidar, Hani Nasser Abdelhamid, Ülo Langel. Improvement of transfection with PepFects using organic and inorganic materials. 2021.
124. Tomas Venit, Moataz Dowaidar , Maxime Gestin , Syed Raza Mahmood, Ülo Langel , Piergiorgio Percipalle. Transcriptional profiling reveals ribosome biogenesis, microtubule dynamics and expression of specific LncRNAs to be part of a common response to cell penetrating peptides. Biomolecules, 10(11), pp. 1-21, 1567, 2020, https://doi.org/10.3390/biom10111567.
125. HN Abdelhamid, Moataz Dowaidar, Ü Langel. Carbonized chitosan encapsulated hierarchical porous zeolitic imidazolate frameworks nanoparticles for gene delivery. Microporous and Mesoporous Materials, 110200, 2020, https://doi.org/10.1016/j.micromeso.2020.110200.
126. HN Abdelhamid, Moataz Dowaidar, M Hällbrink, Ü Langel. Gene Delivery Using Cell Penetrating Peptides-Zeolitic Imidazolate Frameworks. Microporous and Mesoporous Materials, 2020, 110173, ISSN 1387-1811, DOI:10.1016/j.micromeso.2020.110173.
127. HN Abdelhamid, Moataz Dowaidar, M Hällbrink, Ü Langel. Cell Penetrating PeptidesHierarchical Porous Zeolitic Imidazolate Frameworks Nanoparticles: An Efficient Gene Delivery Platform. Available at SSRN 3435895, 2019.
128. Moataz Dowaidar. (2018). Chimeric gene delivery vectors : Design, synthesis, and mechanisms from transcriptomics analysis [Department of Biochemistry and Biophysics, Stockholm University]. https://www.diva-portal.org/smash/record.jsf?pid=diva2:1242000
129. Moataz Dowaidar, Hani Nasser Abdelhamid, Mattias Hällbrink, Ülo Langel, Xiaodong Zou: Chitosan enhances gene delivery of oligonucleotide complexes with magnetic nanoparticles–cell-penetrating peptide. Journal of Biomaterials Applications 09/2018; 33(3):392-401., DOI:10.1177/0885328218796623
130. Moataz Dowaidar, Maxime Gestin, Carmine Pasquale Cerrato, Mohammed Hakim Jafferali, Helerin Margus, Paula Ann Kivistik, Kariem Ezzat, Einar Hallberg, Margus Pooga, Mattias Hällbrink, Ülo Langel: Role of autophagy in cell-penetrating peptide transfection model. Scientific Reports 10/2017; 7(1)., DOI:10.1038/s41598-017-12747-z

131. Moataz Dowaidar, Hani Nasser Abdelhamid, Mattias Hällbrink, Krista Freimann, Kaido Kurrikoff, Xiaodong Zou, Ülo Langel: Magnetic Nanoparticle Assisted Self-assembly of Cell Penetrating Peptides-Oligonucleotides Complexes for Gene Delivery. Scientific Reports 08/2017; 7(1)., DOI:10.1038/s41598-017-09803-z
132. Moataz Dowaidar, Hani Nasser Abdelhamid, Mattias Hällbrink, Xiaodong Zou, Ülo Langel: Graphene oxide nanosheets in complex with cell penetrating peptides for oligonucleotides delivery. Biochimica et Biophysica Acta (BBA) - General Subjects 07/2017; 1861(9)., DOI:10.1016/j.bbagen.2017.07.002
133. Moataz Dowaidar, Jakob Regberg, Dimitar A. Dobchev, Tõnis Lehto, Mattias Hällbrink, Mati Karelson, Ülo Langel: Refinement of a Quantitative Structure–Activity Relationship Model for Prediction of Cell-Penetrating Peptide Based Transfection Systems. International Journal of Peptide Research and Therapeutics 07/2016; 23(1)., DOI:10.1007/s10989-016-9542-8
134. Maxime Gestin, Moataz Dowaidar, Ülo Langel: Uptake Mechanism of Cell-Penetrating Peptides. Peptides and Peptide-based Biomaterials and their Biomedical Applications, 10/2017: pages 255-264; ISBN: 978-3-319-66094-3, DOI:10.1007/978-3-319-66095-0_11
135. Ahmed A.A. Ali, Nahla M. Wassim, Moataz M. Dowaidar, Ahmed E. Yaseen: Genetic polymorphism of CYP2D6 gene among Egyptian hypertensive cases. The Journal of Basic & Applied Zoology, 08/2013; 66(4)., 228-233. DOI:10.1016/j.jobaz.2012.12.002
136. Ahmed A.A. Ali, Nahla M. Wassim, Moataz Dowaidar, Ahmed E. Yaseen: Association of eNOS (E298D) and CYP2J2 (-50 G/T) gene polymorphisms with hypertension among Egyptian cases. The Journal of Basic & Applied Zoology, 08/2013; 66(4)., 234-241. DOI:10.1016/j.jobaz.2012.12.001
137. Almeman Ahmad, Khalaf Hassan, Rasool Semaab, Moataz Dowaidar, Al Orainy Mohammad: The impact of CYP2C19 polymorphism on platelet reactivity for guiding clopidogrel treatment and cost analysis. Journal of the Saudi Heart Association 04/2013; 25(2):107., DOI:10.1016/j.jsha.2013.03.005
138. Abdullah Algasham, Hisham Ismail, Moataz Dowaidar, Ahmad A Settin: Methylenetetrahydrofolate Reductase (MTHFR) and Angiotensin Converting Enzyme (ACE) Gene Polymorphisms among Saudi Population from Qassim Region. 01/2013; 5(2 Suppl 1):3-4. PMC3533339
139. Abdullah Alghasham, Ahmad A Settin, Ahmad Ali, Moataz Dowaidar, Hisham Ismail: Association of MTHFR C677T and A1298C gene polymorphisms with hypertension. 12/2012; 6(1):3-11., DOI:10.12816/0005968
140. Ahmad Ali, Abdullah Alghasham, Hisham Ismail, Moataz Dowaidar, Ahmad Settin: ACE I/D and eNOS E298D gene polymorphisms in Saudi subjects with hypertension. Journal of Renin-AngiotensinAldosterone System 10/2012; 14(4)., DOI:10.1177/1470320312459976
141. Abdullah Alghasham, Ahmad Ali, Hisham Ismail, Moataz Dowaidar, Ahmad A Settin: CYP2J2-50 G/T and ADRB2 G46A gene polymorphisms in saudi subjects with hypertension. Genetic Testing and Molecular Biomarkers 06/2012; 16(9):1027-31., DOI:10.1089/gtmb.2012.0006

142. Ahmad A Settin, Abdullah Alghasham, Ahmad Ali, Moataz Dowaidar, Hisham Ismail: Frequency of thrombophilic genetic polymorphisms among Saudi subjects compared with other populations. Hematology (Amsterdam, Netherlands) 05/2012; 17(3):176-82., DOI:10.1179/102453312X13376952196575
143. HA Ismail, AA Alghasham, MM Dowaidar, AA Settin: Polymorophisms in MTHF and ace genes and the association with hypertension among Saudi population from Qassim region. 06/2011; 29(1)., DOI:10.4314/ejbmb.v29i1.67382
144. Badr Aljarallah, Ahmed Ali, Moataz Dowaidar, Ahmad Settin: Prevalence of α-1-Antitrypsin Gene Mutations in Saudi Arabia. Saudi Journal of Gastroenterology 03/2011; 17(4):256-60., DOI:10.4103/1319-3767.82580
145. Moataz Dowaidar, Ahmad Settin: Risk of Myocardial Infarction Related to Factor V Leiden Mutation: A Meta-Analysis. Genetic Testing and Molecular Biomarkers 08/2010; 14(4):493-8., DOI:10.1089/gtmb.2010.0017
146. Ahmad A Settin, Abdullah Algasham, Moataz Dowaidar, Hisham Ismail: Methylene Tetrahydrofolate Reductase and Angiotensin Converting Enzyme Gene Polymorphisms Related toOverweight/Obesity among Saudi Subjects from Qassim Region. Disease markers 11/2009; 27(2):97-102., DOI:10.3233/DMA-2009-0660
147. Ahmad Settin, Hala Almarsafawy, Ahmad Alhussieny, Moataz Dowaidar: Dysmorphic Features, Consanguinity and Cytogenetic Pattern of Congenital Heart Diseases: a pilot study from Mansoura Locality, Egypt. 07/2008; 2(2):101-11. PMC3068729
148. Ahmad Settin, Moataz Dowaidar, Rizk El-Baz, Ayman Abd-Al-Samad, Ibrahim El-Sayed, Mahmoud Nasr: Frequency of factor V Leiden mutation in Egyptian cases with myocardial infarction. Hematology (Amsterdam, Netherlands) 07/2008; 13(3):170-4., DOI:10.1179/102453308X316158
149. Ahmad Settin, Ibrahem S Abu-Saif, Rizk El-Baz, Moataz Dowaidar, Rabab Abu-Al Kasim, Shaimaa Shabana: Diagnosis of Sex Chromosome Disorders and Prenatal Diagnosis of Down Syndrome using Interphase Fluorescent In-Situ Hyperidization Technique. 07/2007; 1(2):203-9. PMID: 21475429 PMC: PMC3068641
150. Moataz Dowaidar. 2021. “Metabolic Syndrome_ the Presence of Inflammatory Mechanisms in Abdominal Obesity Is Undeniable, Gene Therapy Using Nanoparticles and Adenoviruses Technologies Is Promising.” OSF Preprints. April 5. doi:10.31219/osf.io/2j5xt.
151. Moataz Dowaidar. 2021. “Nanomedicine Has Elegantly Attempted to Cure Multiple Gene Polymorphisms and Mutations in Cardiovascular Diseases Using Gene Therapy Techniques.” OSF Preprints. April 5. doi:10.31219/osf.io/d3x8g.
152. Moataz Dowaidar. 2021. “Exosomes Can Make the Use of Circulating Mirna as a Biomarker More Feasible. The Aim of Gene Therapy Should Be to Learn Everything There Is to Know About Mirna Activity.” OSF Preprints. April 6. doi:10.31219/osf.io/edkua.
153. Moataz Dowaidar. 2021. “Key Genetic Factors in the Metabolic Syndrome Predisposition Which May Be a Therapeutic Options by Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/f38sk.

154. Moataz Dowaidar. 2021. “Anti-sense Pathways Have Been Generated Using Sirna. The Liver and Other Often Used Organs Will Now Be Targeted.” OSF Preprints. April 11. doi:10.31219/osf.io/m6xvp.
155. Moataz Dowaidar. 2021. “Discoveries in Gene-environment Interactions That Influence CVD, Lipid Traits, Obesity, Diabetes, and Hypertension Appear to Be Able to Influence Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/cr5af.
156. Moataz Dowaidar. 2021. “Genome Editing's Potential Target Diseases in the Cardiovascular Field.” OSF Preprints. April 11. doi:10.31219/osf.io/gc23p.
157. Moataz Dowaidar. 2021. “The Cardiometabolic-based Chronic Disease Model Lays the Foundations for Accurate, Evidence-based Preventive Targeting and Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/up9z4.
158. Moataz Dowaidar. 2021. “Researchers Would Be Able to Develop a Detailed Picture of Chromatin in Disease, Which Would Be Useful for Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/m9z48.
159. Moataz Dowaidar. 2021. “Mirna Can Be a Part of Both the Onset and Cure of Coronary Heart Disease.” OSF Preprints. April 11. doi:10.31219/osf.io/teqh8.
160. Moataz Dowaidar. 2021. “Crispr/cris Systems Are Highly Effective and Useful for Genomic Manipulation. Despite This, Cardiac Treatment Remains Difficult Due to Existing Genome Editing and Delivery Processes.” OSF Preprints. April 11. doi:10.31219/osf.io/3nwzd.
161. Moataz Dowaidar. 2021. “Metabolic Syndrome_ the Presence of Inflammatory Mechanisms in Abdominal Obesity Is Undeniable, Gene Therapy Using Nanoparticles and Adenoviruses Technologies Is Promising.” OSF Preprints. April 5. doi:10.31219/osf.io/2j5xt.
162. Moataz Dowaidar. 2021. “Nanomedicine Has Elegantly Attempted to Cure Multiple Gene Polymorphisms and Mutations in Cardiovascular Diseases Using Gene Therapy Techniques.” OSF Preprints. April 5. doi:10.31219/osf.io/d3x8g.
163. Moataz Dowaidar. 2021. “Exosomes Can Make the Use of Circulating Mirna as a Biomarker More Feasible. The Aim of Gene Therapy Should Be to Learn Everything There Is to Know About Mirna Activity.” OSF Preprints. April 6. doi:10.31219/osf.io/edkua.
164. Moataz Dowaidar. 2021. “Key Genetic Factors in the Metabolic Syndrome Predisposition Which May Be a Therapeutic Options by Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/f38sk.
165. Moataz Dowaidar. 2021. “Anti-sense Pathways Have Been Generated Using Sirna. The Liver and Other Often Used Organs Will Now Be Targeted.” OSF Preprints. April 11. doi:10.31219/osf.io/m6xvp.
166. Moataz Dowaidar. 2021. “Discoveries in Gene-environment Interactions That Influence CVD, Lipid Traits, Obesity, Diabetes, and Hypertension Appear to Be Able to Influence Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/cr5af.
167. Moataz Dowaidar. 2021. “Genome Editing's Potential Target Diseases in the Cardiovascular Field.” OSF Preprints. April 11. doi:10.31219/osf.io/gc23p.

168. Moataz Dowaidar. 2021. “The Cardiometabolic-based Chronic Disease Model Lays the Foundations for Accurate, Evidence-based Preventive Targeting and Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/up9z4.
169. Moataz Dowaidar. 2021. “Researchers Would Be Able to Develop a Detailed Picture of Chromatin in Disease, Which Would Be Useful for Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/m9z48.
170. Moataz Dowaidar. 2021. “Mirna Can Be a Part of Both the Onset and Cure of Coronary Heart Disease.” OSF Preprints. April 11. doi:10.31219/osf.io/teqh8.
171. Moataz Dowaidar. 2021. “Crispr/cris Systems Are Highly Effective and Useful for Genomic Manipulation. Despite This, Cardiac Treatment Remains Difficult Due to Existing Genome Editing and Delivery Processes.” OSF Preprints. April 11. doi:10.31219/osf.io/3nwzd.
172. Moataz Dowaidar, Hani Nasser Abdelhamid, Ülo Langel. Improvement of transfection with PepFects using organic and inorganic materials. 2021.
173. Tomas Venit, Moataz Dowaidar , Maxime Gestin , Syed Raza Mahmood, Ülo Langel , Piergiorgio Percipalle. Transcriptional profiling reveals ribosome biogenesis, microtubule dynamics and expression of specific LncRNAs to be part of a common response to cell penetrating peptides. Biomolecules, 10(11), pp. 1-21, 1567, 2020, https://doi.org/10.3390/biom10111567.
174. HN Abdelhamid, Moataz Dowaidar, Ü Langel. Carbonized chitosan encapsulated hierarchical porous zeolitic imidazolate frameworks nanoparticles for gene delivery. Microporous and Mesoporous Materials, 110200, 2020, https://doi.org/10.1016/j.micromeso.2020.110200.
175. HN Abdelhamid, Moataz Dowaidar, M Hällbrink, Ü Langel. Gene Delivery Using Cell Penetrating Peptides-Zeolitic Imidazolate Frameworks. Microporous and Mesoporous Materials, 2020, 110173, ISSN 1387-1811, DOI:10.1016/j.micromeso.2020.110173.
176. HN Abdelhamid, Moataz Dowaidar, M Hällbrink, Ü Langel. Cell Penetrating PeptidesHierarchical Porous Zeolitic Imidazolate Frameworks Nanoparticles: An Efficient Gene Delivery Platform. Available at SSRN 3435895, 2019.
177. Moataz Dowaidar. (2018). Chimeric gene delivery vectors : Design, synthesis, and mechanisms from transcriptomics analysis [Department of Biochemistry and Biophysics, Stockholm University]. https://www.diva-portal.org/smash/record.jsf?pid=diva2:1242000
178. Moataz Dowaidar, Hani Nasser Abdelhamid, Mattias Hällbrink, Ülo Langel, Xiaodong Zou: Chitosan enhances gene delivery of oligonucleotide complexes with magnetic nanoparticles–cell-penetrating peptide. Journal of Biomaterials Applications 09/2018; 33(3):392-401., DOI:10.1177/0885328218796623
179. Moataz Dowaidar, Maxime Gestin, Carmine Pasquale Cerrato, Mohammed Hakim Jafferali, Helerin Margus, Paula Ann Kivistik, Kariem Ezzat, Einar Hallberg, Margus Pooga, Mattias Hällbrink, Ülo Langel: Role of autophagy in cell-penetrating peptide transfection model. Scientific Reports 10/2017; 7(1)., DOI:10.1038/s41598-017-12747-z

180. Moataz Dowaidar, Hani Nasser Abdelhamid, Mattias Hällbrink, Krista Freimann, Kaido Kurrikoff, Xiaodong Zou, Ülo Langel: Magnetic Nanoparticle Assisted Self-assembly of Cell Penetrating Peptides-Oligonucleotides Complexes for Gene Delivery. Scientific Reports 08/2017; 7(1)., DOI:10.1038/s41598-017-09803-z
181. Moataz Dowaidar, Hani Nasser Abdelhamid, Mattias Hällbrink, Xiaodong Zou, Ülo Langel: Graphene oxide nanosheets in complex with cell penetrating peptides for oligonucleotides delivery. Biochimica et Biophysica Acta (BBA) - General Subjects 07/2017; 1861(9)., DOI:10.1016/j.bbagen.2017.07.002
182. Moataz Dowaidar, Jakob Regberg, Dimitar A. Dobchev, Tõnis Lehto, Mattias Hällbrink, Mati Karelson, Ülo Langel: Refinement of a Quantitative Structure–Activity Relationship Model for Prediction of Cell-Penetrating Peptide Based Transfection Systems. International Journal of Peptide Research and Therapeutics 07/2016; 23(1)., DOI:10.1007/s10989-016-9542-8
183. Maxime Gestin, Moataz Dowaidar, Ülo Langel: Uptake Mechanism of Cell-Penetrating Peptides. Peptides and Peptide-based Biomaterials and their Biomedical Applications, 10/2017: pages 255-264; ISBN: 978-3-319-66094-3, DOI:10.1007/978-3-319-66095-0_11
184. Ahmed A.A. Ali, Nahla M. Wassim, Moataz M. Dowaidar, Ahmed E. Yaseen: Genetic polymorphism of CYP2D6 gene among Egyptian hypertensive cases. The Journal of Basic & Applied Zoology, 08/2013; 66(4)., 228-233. DOI:10.1016/j.jobaz.2012.12.002
185. Ahmed A.A. Ali, Nahla M. Wassim, Moataz Dowaidar, Ahmed E. Yaseen: Association of eNOS (E298D) and CYP2J2 (-50 G/T) gene polymorphisms with hypertension among Egyptian cases. The Journal of Basic & Applied Zoology, 08/2013; 66(4)., 234-241. DOI:10.1016/j.jobaz.2012.12.001
186. Almeman Ahmad, Khalaf Hassan, Rasool Semaab, Moataz Dowaidar, Al Orainy Mohammad: The impact of CYP2C19 polymorphism on platelet reactivity for guiding clopidogrel treatment and cost analysis. Journal of the Saudi Heart Association 04/2013; 25(2):107., DOI:10.1016/j.jsha.2013.03.005
187. Abdullah Algasham, Hisham Ismail, Moataz Dowaidar, Ahmad A Settin: Methylenetetrahydrofolate Reductase (MTHFR) and Angiotensin Converting Enzyme (ACE) Gene Polymorphisms among Saudi Population from Qassim Region. 01/2013; 5(2 Suppl 1):3-4. PMC3533339
188. Abdullah Alghasham, Ahmad A Settin, Ahmad Ali, Moataz Dowaidar, Hisham Ismail: Association of MTHFR C677T and A1298C gene polymorphisms with hypertension. 12/2012; 6(1):3-11., DOI:10.12816/0005968
189. Ahmad Ali, Abdullah Alghasham, Hisham Ismail, Moataz Dowaidar, Ahmad Settin: ACE I/D and eNOS E298D gene polymorphisms in Saudi subjects with hypertension. Journal of Renin-AngiotensinAldosterone System 10/2012; 14(4)., DOI:10.1177/1470320312459976
190. Abdullah Alghasham, Ahmad Ali, Hisham Ismail, Moataz Dowaidar, Ahmad A Settin: CYP2J2-50 G/T and ADRB2 G46A gene polymorphisms in saudi subjects with hypertension. Genetic Testing and Molecular Biomarkers 06/2012; 16(9):1027-31., DOI:10.1089/gtmb.2012.0006

191. Ahmad A Settin, Abdullah Alghasham, Ahmad Ali, Moataz Dowaidar, Hisham Ismail: Frequency of thrombophilic genetic polymorphisms among Saudi subjects compared with other populations. Hematology (Amsterdam, Netherlands) 05/2012; 17(3):176-82., DOI:10.1179/102453312X13376952196575
192. HA Ismail, AA Alghasham, MM Dowaidar, AA Settin: Polymorophisms in MTHF and ace genes and the association with hypertension among Saudi population from Qassim region. 06/2011; 29(1)., DOI:10.4314/ejbmb.v29i1.67382
193. Badr Aljarallah, Ahmed Ali, Moataz Dowaidar, Ahmad Settin: Prevalence of α-1-Antitrypsin Gene Mutations in Saudi Arabia. Saudi Journal of Gastroenterology 03/2011; 17(4):256-60., DOI:10.4103/1319-3767.82580
194. Moataz Dowaidar, Ahmad Settin: Risk of Myocardial Infarction Related to Factor V Leiden Mutation: A Meta-Analysis. Genetic Testing and Molecular Biomarkers 08/2010; 14(4):493-8., DOI:10.1089/gtmb.2010.0017
195. Ahmad A Settin, Abdullah Algasham, Moataz Dowaidar, Hisham Ismail: Methylene Tetrahydrofolate Reductase and Angiotensin Converting Enzyme Gene Polymorphisms Related toOverweight/Obesity among Saudi Subjects from Qassim Region. Disease markers 11/2009; 27(2):97-102., DOI:10.3233/DMA-2009-0660
196. Ahmad Settin, Hala Almarsafawy, Ahmad Alhussieny, Moataz Dowaidar: Dysmorphic Features, Consanguinity and Cytogenetic Pattern of Congenital Heart Diseases: a pilot study from Mansoura Locality, Egypt. 07/2008; 2(2):101-11. PMC3068729
197. Ahmad Settin, Moataz Dowaidar, Rizk El-Baz, Ayman Abd-Al-Samad, Ibrahim El-Sayed, Mahmoud Nasr: Frequency of factor V Leiden mutation in Egyptian cases with myocardial infarction. Hematology (Amsterdam, Netherlands) 07/2008; 13(3):170-4., DOI:10.1179/102453308X316158
198. Ahmad Settin, Ibrahem S Abu-Saif, Rizk El-Baz, Moataz Dowaidar, Rabab Abu-Al Kasim, Shaimaa Shabana: Diagnosis of Sex Chromosome Disorders and Prenatal Diagnosis of Down Syndrome using Interphase Fluorescent In-Situ Hyperidization Technique. 07/2007; 1(2):203-9. PMID: 21475429 PMC: PMC3068641
199. Moataz Dowaidar. 2021. “Metabolic Syndrome_ the Presence of Inflammatory Mechanisms in Abdominal Obesity Is Undeniable, Gene Therapy Using Nanoparticles and Adenoviruses Technologies Is Promising.” OSF Preprints. April 5. doi:10.31219/osf.io/2j5xt.
200. Moataz Dowaidar. 2021. “Nanomedicine Has Elegantly Attempted to Cure Multiple Gene Polymorphisms and Mutations in Cardiovascular Diseases Using Gene Therapy Techniques.” OSF Preprints. April 5. doi:10.31219/osf.io/d3x8g.
201. Moataz Dowaidar. 2021. “Exosomes Can Make the Use of Circulating Mirna as a Biomarker More Feasible. The Aim of Gene Therapy Should Be to Learn Everything There Is to Know About Mirna Activity.” OSF Preprints. April 6. doi:10.31219/osf.io/edkua.
202. Moataz Dowaidar. 2021. “Key Genetic Factors in the Metabolic Syndrome Predisposition Which May Be a Therapeutic Options by Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/f38sk.

203. Moataz Dowaidar. 2021. “Anti-sense Pathways Have Been Generated Using Sirna. The Liver and Other Often Used Organs Will Now Be Targeted.” OSF Preprints. April 11. doi:10.31219/osf.io/m6xvp.
204. Moataz Dowaidar. 2021. “Discoveries in Gene-environment Interactions That Influence CVD, Lipid Traits, Obesity, Diabetes, and Hypertension Appear to Be Able to Influence Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/cr5af.
205. Moataz Dowaidar. 2021. “Genome Editing's Potential Target Diseases in the Cardiovascular Field.” OSF Preprints. April 11. doi:10.31219/osf.io/gc23p.
206. Moataz Dowaidar. 2021. “The Cardiometabolic-based Chronic Disease Model Lays the Foundations for Accurate, Evidence-based Preventive Targeting and Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/up9z4.
207. Moataz Dowaidar. 2021. “Researchers Would Be Able to Develop a Detailed Picture of Chromatin in Disease, Which Would Be Useful for Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/m9z48.
208. Moataz Dowaidar. 2021. “Mirna Can Be a Part of Both the Onset and Cure of Coronary Heart Disease.” OSF Preprints. April 11. doi:10.31219/osf.io/teqh8.
209. Moataz Dowaidar. 2021. “Crispr/cris Systems Are Highly Effective and Useful for Genomic Manipulation. Despite This, Cardiac Treatment Remains Difficult Due to Existing Genome Editing and Delivery Processes.” OSF Preprints. April 11. doi:10.31219/osf.io/3nwzd.
210. Moataz Dowaidar. 2021. “Metabolic Syndrome_ the Presence of Inflammatory Mechanisms in Abdominal Obesity Is Undeniable, Gene Therapy Using Nanoparticles and Adenoviruses Technologies Is Promising.” OSF Preprints. April 5. doi:10.31219/osf.io/2j5xt.
211. Moataz Dowaidar. 2021. “Nanomedicine Has Elegantly Attempted to Cure Multiple Gene Polymorphisms and Mutations in Cardiovascular Diseases Using Gene Therapy Techniques.” OSF Preprints. April 5. doi:10.31219/osf.io/d3x8g.
212. Moataz Dowaidar. 2021. “Exosomes Can Make the Use of Circulating Mirna as a Biomarker More Feasible. The Aim of Gene Therapy Should Be to Learn Everything There Is to Know About Mirna Activity.” OSF Preprints. April 6. doi:10.31219/osf.io/edkua.
213. Moataz Dowaidar. 2021. “Key Genetic Factors in the Metabolic Syndrome Predisposition Which May Be a Therapeutic Options by Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/f38sk.
214. Moataz Dowaidar. 2021. “Anti-sense Pathways Have Been Generated Using Sirna. The Liver and Other Often Used Organs Will Now Be Targeted.” OSF Preprints. April 11. doi:10.31219/osf.io/m6xvp.
215. Moataz Dowaidar. 2021. “Discoveries in Gene-environment Interactions That Influence CVD, Lipid Traits, Obesity, Diabetes, and Hypertension Appear to Be Able to Influence Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/cr5af.
216. Moataz Dowaidar. 2021. “Genome Editing's Potential Target Diseases in the Cardiovascular Field.” OSF Preprints. April 11. doi:10.31219/osf.io/gc23p.

217. Moataz Dowaidar. 2021. “The Cardiometabolic-based Chronic Disease Model Lays the Foundations for Accurate, Evidence-based Preventive Targeting and Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/up9z4.
218. Moataz Dowaidar. 2021. “Researchers Would Be Able to Develop a Detailed Picture of Chromatin in Disease, Which Would Be Useful for Gene Therapy.” OSF Preprints. April 11. doi:10.31219/osf.io/m9z48.
219. Moataz Dowaidar. 2021. “Mirna Can Be a Part of Both the Onset and Cure of Coronary Heart Disease.” OSF Preprints. April 11. doi:10.31219/osf.io/teqh8.
220. Moataz Dowaidar. 2021. “Crispr/cris Systems Are Highly Effective and Useful for Genomic Manipulation. Despite This, Cardiac Treatment Remains Difficult Due to Existing Genome Editing and Delivery Processes.” OSF Preprints. April 11. doi:10.31219/osf.io/3nwzd.