DIFFERENT THERAPEUTIC INTERVENTIONS AND MECHANISMS OF ACTION OF ANTISICKLING AGENTS CURRENTLY IN USE IN SICKLE CELL DISEASE MANAGEMENT

* Ngozi Awa Imaga, Oluwole Taiwo

Department of Biochemistry, Faculty of Basic Medical Sciences, College of Medicine, University of Lagos, Lagos, Nigeria
*Correspondence to noaimaga@gmail.com

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ABSTRACT

Sickle cell disease is a genetic disorder caused by sickle haemoglobin. In many forms of the disease, the red blood cells can change shape upon deoxygenation due to abnormal sickle haemoglobin polymerisation. The haemoglobin proteins stick to each other, causing the cell to have a rigid surface and sickle shape and in the process damaging the red blood cell membrane, causing the cells to become stuck in blood vessels. This deprives the downstream tissues of oxygen and causes ischaemia and infarction (which may cause organ damage), such as stroke. Incidences of the disease are found most commonly in people of African descent and less commonly in people of Mediterranean, Latino, East Indian, and Arab descent (in that order). In African countries such as Nigeria, Gabon, Ghana, and the Republic of Congo, the prevalence of the sickle cell trait is between 20% and 30%, with the disease affecting 2–3% of the population. Herbal formulations prepared from plants are known as phytomedicines and are effective in keeping the patient out of a crisis state and enabling them to live stable lives in society, even though the faulty S gene is not eradicated but instead managed. This review highlights some of the therapeutic options in use in the management of sickle cell disease with a view to inspiring future research on this subject.

Keywords: Sickle cell, therapeutic options, fetal haemoglobin (HbF).

OCCURRENCE AND PREVALENCE OF SICKLE CELL DISEASE

Sickle cell anaemia is a genetically inherited disease in which the 'SS' homozygous individual possesses an abnormal β-globin gene (Figure 1). A single base substitution in the gene encoding the human β-globin subunit results in replacement of β6 glutamic acid by valine, leading to the various clinical manifestations of sickle cell disease (SCD). This substitution causes a drastic reduction in the solubility of sickle cell haemoglobin (HbS) when deoxygenated. Under these conditions, the HbS molecules polymerise to form a long crystalline intracellular mass of fibres that are responsible for the deformation of the biconcave disc shaped erythrocyte into a sickle shape.

Of all the genetic disorders, SCD is the most prevalent. Incidences of the disease are found most commonly in people of African descent and less commonly in people of Mediterranean, Latino, East Indian, and Arab descent (in that order). In African countries such as Nigeria, Gabon, Ghana, and the Republic of Congo, the prevalence of the sickle cell trait is between 20% and 30%, with the disease affecting 2–3% of the population.1

AVAILABILITY OF TREATMENT/FIRST-LINE HEALTHCARE MANAGEMENT

First-line clinical management of sickle cell anaemia includes the use of folic and amino acid supplementation (as nutritional supplements), antibiotic/penicillin prophylaxis (to prevent...
infection), and anti-malarial prophylaxis (to prevent malaria attack) in varying doses in childhood, adulthood, and pregnancy. The abnormal ‘S’ gene is not eradicated in treatment, rather the condition is managed and synthesis of red blood cells induced to stabilise the patient’s Hb level. Also, transfusion therapy after screening with transcranial Doppler and vaccinations are used to manage patients.

The cost of available therapeutic options is high and not within easy reach in rural communities. Examples are blood transfusions and bone marrow transplantation. Treatments such as penicillin prophylaxis and vaccinations are very cost-effective in comparison to transfusion and hydroxyurea.

In 1984, bone marrow transplantation in a child with SCD produced the first reported cure of the disease. The transplantation was done to treat acute leukaemia, and the child’s sickle cell condition was cured as a side-event. The procedure nonetheless set the precedent for later transplantation efforts directed specifically at SCD.²

The most popular approach to prevent or reverse sickling in vitro and in vivo is to employ compounds or techniques that directly affect the Hb molecule. This could be achieved through an increase in the cell volume of erythrocytes and thus a reduction in the intracellular Hb concentration below its minimum gelling concentration. This causes a delay time prior to the polymerisation of deoxygenated HbS molecules.

Another approach to affecting the Hb molecule is inducing a high concentration of fetal Hb (HbF) in sickle cell patients, which will delay/prevent HbS polymerisation. HbF differs functionally from normal adult Hb (HbA) because it has a higher affinity for oxygen. This HbF feature facilitates the binding of oxygen to Hb, giving the fetus easier access to oxygen from the mother’s blood stream.

**INDUCTION OF FETAL HAEMOGLOBIN**

Three types of Hb are synthesised in humans, starting from the embryonic stage (embryonic Hb, produced before birth), fetal stage (HbF, during fetal life), and from after birth (adult Hb, HbA).³ Generally, HbF usually disappears from the red blood cells of an infant soon after birth, giving way to the expression of the HbA variant of Hb. A genetic mutation at point 6 of the Beta chain of HbA gives rise to the expression of HbS, an abnormal variant.³ HbF, however, has been found to have a higher affinity for oxygen than all other variants of Hb.⁴ In adults, very small quantities of HbF (<2%) have been detected in the blood.⁵

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**Figure 1: Sickle cell disorder inheritance pattern.**

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Researchers found that SCD patients in Saudi Arabia and India that had high levels of HbF, even as adults, had milder anemic episodes. This was due to them having inherited a genetic determinant for high HbF. Increasing/sustaining intracellular HBF has thus been the target of therapy aimed at an anti-sickling effect.

In the past three decades, different drugs have been produced which aimed to induce production of HbF, albeit via different mechanisms of action. Hydroxycarbamide/hydroxyurea, butyrate, 5-azacytidine, and erythropoietin are some of the drugs approved for SCD management. These drugs, together with decitabine (an analogue of 5-azacytidine) have been shown to induce HbF in vivo in animal models and sickle cell patients. Hydroxyurea was found to have the ability to increase Hb concentration and HbF values and consequently decrease the rate of pain and acute chest syndrome. Other beneficial findings associated with usage of hydroxyurea include protection against recurrent stroke and improvement in proteinuria levels. A low-dose usage of decitabine tested in a small group of SCD patients promoted a marked increase in HbF concentration and a decrease in absolute neutrophil counts. Short chain fatty acid butyrates affect chromatin structure and promote transcription rates of HbF genes. In vitro and in vivo administration of recombinant erythropoietin have been shown to increase HbF concentration when used alone and in combination with hydroxyurea.

**HERBAL FORMULATIONS AND PHYTOMEDICINES**

Medicinal plants (also known as phytomedicines) are parts of a plant or the whole plant that possess healing properties. Folk medicine reportedly uses Carica papaya L. (Caricaceae) and Parquetina nigrescens L. (Asclepiadaceae) as a herbal remedy for the management of sickle cell anemia.

Research into the anti-sickling properties of medicinal plants has been rewarding. This alternative therapy using phytomedicines is used in folk medicine to reduce crisis manifestations in SCD individuals. Jobelyn® (Sorghum bicolor), Ciklavit® (Cajanus cajan), Dioscovite, and Carica papaya leaf extract are among the herbal remedies used in some African countries for the management of this disease. In vitro administration of Ciklavit showed a reversal of sickling effect when analysed. Ciklavit was reported to be more potent than hydroxybenzoic acid in laboratory experiments, which revealed that the anti-sickling effect of Ciklavit may not be through nitric oxide generation or arginase inhibition, but through the induction of HbF production. The extract of the seeds of Cajanus cajan (a major constituent of Ciklavit) has also been found to possess anti-sickling activity. Phytochemicals responsible for this effect were found to be free amino acids, phenolic compounds (p-hydroxybenzoic acid), tannins, globulins, and saponins. Ciklavit was reported in laboratory experiments to have an anti-sickling effect through the induction of HbF production.

Anti-sickling and membrane stabilising effects of Carica papaya leaf extracts were investigated and reports indicate that the pre-treatment of sickle cell suspensions with the extract inhibited the formation of sickled cells under severe hypoxic conditions. Zanthoxylum zanthoxyloides (otherwise called Fagara, orin-ata) roots have also been analysed for antiprotease and membrane stabilising activity.
Niprisan® (Nix-0699) is a herbal formulation comprising extracts of Piper guineense, Pterocarpus osun, Eugenia caryophyllum, and Sorghum bicolor. The herbal formulation reduced pain during crisis in paediatric and adult sickle cell patients. In vivo studies of Niprisan in transgenic mice showed an increase in hydrated cell volume, thus a reduction in intracellular HbS concentration and an increase in the delay time to polymerisation.6–12

Ajawaron herbal formulation (also known as Ajawaron HF) has, as its main constituent, Cissus populnea. It showed high anti-sickling activity in comparison with some controls (p-hydrobenzoic acid and n-saline). Its major phytoconstituents were found to be anthraquinone derivatives, steroidal glycosides, and cardiac glycosides.13

Earlier reports of the anti-sickling constituents of Cajanus cajan suggested cajaminose,14 phenylalanine, and hydroxybenzoic acid were responsible.15 Phytochemical studies on the aqueous extract confirmed the presence of phenylalanine and several other amino acids and phenolic compounds and tannins. The anti-sickling properties of amino acids in in vitro studies have been recognised much earlier. Of all the amino acids reported, L-phenylalanine, which was found to have anti-gelling effects, was shown to be most active.16

**AMINO ACID SUPPLEMENTATION**

In our daily diets, there are food substances that are rich in antioxidants and other nutritional components that help boost the immune system. Sickle cell anaemia is a genetic disease and so dietary supplements cannot stop the manifestation of the disorder, but a well-nourished and supplemented sickle cell individual can be spared the severity of the disease and go about life without the crisis episodes inherent in the disorder.

There are several compounds, such as amino acids, which prevent sickling by affecting the erythrocyte membrane, causing an increase in the cell volume of the erythrocyte and thus reducing the intracellular Hb concentration below its minimum gelling concentration. Anti-sickling properties of amino acids have been recognised much earlier; of all the amino acids reported, phenylalanine was shown to be the most active. L-phenylalanine benzyl ester (Phe-Bz), an aromatic compound, was found to be an effective anti-sickling agent at a low concentration and is therefore a potential therapeutic agent for the treatment of SCD.

**ANTIOXIDANT THERAPY**

A potential nutritional approach for the molecular disease found that from both in vitro and pilot clinical trials, a ‘cocktail’ of aged garlic extract, vitamin C, and vitamin E proved beneficial to patients. Ascorbic acid is important because significant oxidative stress occurs in the disease and its role as an antioxidant is very beneficial. Multivitamin supplements and a proper dietary, calorie, and protein intake are other ways to boost the immune system and extend the life span of the sickle cell individual. A scope of work on anti-sickling agents with the focus on nutrition found that the concentrations of ascorbic acid and alphatocopherol were significantly depressed, while that of retinol was slightly reduced in subjects tested. The depletion in the levels of the antioxidant vitamins A, C, and E may account for some of the observed manifestations of sickle cell anaemia, such as increased susceptibility to infection and haemolysis. Vitamin B12 levels have been observed to be diminished in patients with severe SCD. Patients with low vitamin B12 achieved a significant symptomatic improvement when treated with vitamin B12, 1 mg intramuscularly weekly for 12 weeks. It was concluded that many patients with severe SCD may suffer from unrecognised vitamin B12 deficiency.6

Antioxidants (scavengers of free radicals) are believed to be major components of these anti-sickling agents that add to their potential. Thus, it is believed that the higher the antioxidant property of an anti-sickling agent, the higher its potential anti-sickling effect, as this enables it to reduce oxidative stress that contributes to the sickle cell crisis. Antioxidants are found mostly in fruits (antioxidant vitamins) and vegetables. Diets rich in vitamins A, C, and E, and selenium and zinc will go a long way towards fortifying the SCD individual and preventing crisis. Research on antioxidant status and susceptibility of sickled erythrocytes to oxidative and osmotic stress has been reported using a range of diluted saline phosphate buffer in a typical osmotic fragility test to determine osmotic stress/membrane integrity and a peroxyl radical generator to induce haemolysis with oxygenated and deoxygenated red blood cells for oxidative stress analysis. It was discovered that although there are differences in antioxidant status between sickled and normal cells; these differences did not appear to be responsible for the observed difference in susceptibility to oxidative or osmotic stress-induced haemolysis.17
GENE THERAPY

Developing therapies based on the genetic manipulation of haematopoietic stem cells has long been proposed as a potential cure for sickle cell anaemia. The hallmark of a successful gene therapy includes safe and efficient gene transfer and a highly regulated and stable gene expression. A recent report on successful gene therapy in France has been widely acknowledged as a leap into the desired future of a cure for SCD. Researchers are reporting early success using gene therapy to treat, or even potentially cure, sickle cell anaemia. The findings come from just one patient, a teenage boy in France. The boy, now 15 years old, was treated at Necker Children’s Hospital, Paris, France, in October 2014. Researchers gave him a gene, taken up by his blood stem cells, to help prevent the sickling, but >15 months after receiving the treatment, he remained free of symptoms and his usual medications. Now, about half of his red blood cells have normal Hb; he has not needed a transfusion since 3 months after his treatment and is off all medicines.

Much more research is required before gene therapy can become an option for sickle cell anaemia. It is not clear how long the benefits will last, the authors of the study said. Furthermore, the approach obviously has to be tested in more patients. A stem cell transplant from a blood-matched sibling is a potential cure, but fewer than one in five people have a donor like that. Pain crises are treated with blood transfusions and drugs, but they are a temporary fix. Gene therapy offers hope of a lasting one. Herein lies the future of permanent therapy for SCD.

REFERENCES

HAEMOPHILIA patients have experienced a decrease of 87% in the incidence of bleeding episodes after subcutaneous treatment with the novel reagent, emicizumab, once a week. This result follows the HAVEN 1 study, a multicentre Phase III investigation into the treatment of haemophilia A patients with inhibitors, using this novel monoclonal antibody.

As a result of excessive bleeding, patients with haemophilia A require intravenous prophylactic treatment with a clotting factor multiple times a week. This often leads to the production of antibodies in the patient, named inhibitors, which target and destroy the administered clotting factor, therefore making treatment extremely challenging. An international team, led by Prof Guy Young, Children’s Hospital Los Angeles, Los Angeles, California, USA, studied 109 males ≥12 years of age, all with haemophilia A and inhibitors. “While the standard medications allow us to ‘bypass’ the need for Factor VIII, they do not do the job as efficiently or as well for these patients. Bleeding is harder to stop, and episodes last longer and do more damage to the patients,” Prof Young explained.

Once treated with emicizumab prophylaxis, patients experienced 87% fewer bleeds compared to individuals who were treated with on-demand bypassing agents and 79% fewer bleeds compared to prophylactic bypassing agents. In addition, no anti-drug antibodies were observed. Prof Alan S. Wayne, Children’s Center for Cancer and Blood Diseases, Children’s Hospital Los Angeles, expressed his excitement for this study: “This new therapy is dramatically more effective at preventing bleeding. Additionally, in comparison to bypassing agents, emicizumab is easier to administer, requires less frequent dosing, and based on this study, appears to have an improved safety profile.”

“ This is the most significant advancement I have seen during my 20 years working in the field of haemophilia. ”

At this time, this treatment is only available for patients participating in the clinical trial; however, it is currently under evaluation by the US Food and Drug Administration (FDA). In addition, studies investigating emicizumab treatment for haemophilia A patients without inhibitors are underway. Commenting on the results, Prof Young remarked: “This is the most significant advancement I have seen during my 20 years working in the field of haemophilia.” He added: “We have had families flying from all over the country to get access to this medication.”
Reversal of Immunotherapy Resistance in Blood Cancer Patients

The team highlighted that some lymphoma cells can develop resistance to this therapy by manipulating the Fc-gamma receptors on the surface of the macrophages, hence preventing their ability to engulf and destroy the cancer cells. By experimenting with immune stimulating drugs in combination with monoclonal antibodies, it was discovered that reagents named STING agonists were able to reverse the lymphoma resistance mechanism when administered alongside the immunotherapy. This combination therapy stimulated the macrophages once more and enabled them to eliminate the lymphoma cells; the finding was consistent in both mice and human cells when performed in the laboratory.

When asked to comment on the results, Prof Peter Johnson, Chief Clinician at Cancer Research UK, explained: “This exciting research suggests that using drugs to reprogramme the cells around a cancer may make antibody treatments much more effective in the future, and we should be able to start testing this in the clinic very soon.” The discovery of a successful combination treatment that can overcome resistance to monoclonal antibodies may therefore greatly benefit a number of lymphoma patients. With regard to the future of this finding, Dr Beers commented: “The next stage will be to modify STING agonists in the laboratory to make them as effective as possible at stimulating the immune system in lymphoma patients.”

BREAKTHROUGH research has identified the mechanism behind the resistance some lymphoma patients experience when treated with monoclonal antibodies, and has enabled the discovery of a novel reagent to reverse the resistance. Although this common type of immunotherapy has been successful in improving the prognosis of many blood cancer patients, not all cases respond to the treatment and have subsequently relapsed, for example in patients treated with the monoclonal antibody rituximab. This research, funded by the charities Bloodwise and Cancer Research UK, is therefore a promising development in improving lymphoma patient survival rates.

The researchers, led by Dr Stephen Beers and Prof Mark Cragg, Faculty of Medicine, University of Southampton, Southampton, UK, studied the mechanism of resistance of rituximab, which, when successful, stimulates macrophages, leading to the destruction of the lymphoma cells.

“The next stage will be to modify STING agonists in the laboratory to make them as effective as possible at stimulating the immune system in lymphoma patients.”
Cellular Mechanism of Immune Escape in Leukaemia

A PROTEIN that is solely released by cancer cells has been identified, paving the way for novel therapeutic biomarkers and targets for difficult-to-treat leukaemia cases. As a cancer that affects >250,000 people every year across the world, a better understanding of the cellular mechanism of acute myeloid leukaemia (AML), in particular, is vital for the detection and treatment of many blood cancer patients.

Although current treatment strategies are invasive and aggressive, they often do not result in patient remission due to the misunderstanding of how cancerous cells can escape the immune response. A team based at the Medway School of Pharmacy, University of Kent, Kent, UK, investigated the mechanism behind the inactivation of the body’s natural immune cells in AML patients, including the cytotoxic T lymphocytes and natural killer cells which usually perform immune surveillance.

Led by Dr Vadim Sumbayev, Dr Bernhard Gibbs, and Prof Yuri Ushkaryov, Medway School of Pharmacy, University of Kent, the team discovered that the malignant cells expressed a receptor named latrophilin 1 which was not present on healthy blood cells. On stimulation, this cancerspecific receptor stimulated the release of galectin-9 in leukaemia cells, which prevented destruction by the patient’s immune system. The release of this protein may therefore be the reason for the inactivation of the body’s immune system which commonly allows rapid progression of AML in many patients.

From these results, the researchers have gained a better understanding of the potential mechanism by which malignant cells escape the immune response. This discovery may lead to the development of novel biomarkers for AML diagnosis, as well as proposing a possible new target for AML therapeutics in the future. Referring to the clinical relevance of discovering this novel mechanism, Dr Sumbayev said: “Targeting this pathway will crucially enhance patients’ own immune defences, helping them to eliminate leukaemia cells.” He also suggested that the mechanism may not be limited to blood cancers and that this discovery could potentially benefit the treatment of other cancer types.

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Fluorine-labelled Ligand Detects Sites of Thrombus Formation

A NOVEL fluorine-labelled ligand for positron emission tomography (PET) has successfully detected small venous and arterial clots. Since current imaging techniques rely on structural characteristics like vascular flow impairment, this technique may be used to successfully detect critical molecular components which are major causes of mortality, such as blood clots in the veins and arteries commonly leading to strokes and embolisms.

“A single imaging modality that could visualise thrombi from various sources in different anatomic regions would be very valuable.”

“Currently available diagnostic techniques of thrombus [blood clot] imaging rely on different modalities depending on the vascular territory,” explained Dr Andrew Stephens, Piramal Imaging GmbH, Berlin, Germany. He continued: “A single imaging modality that could visualise thrombi from various sources in different anatomic regions would be very valuable.” During the preclinical study, the team of German researchers from Piramal Imaging GmbH developed a novel small fluorine-18 labelled tracer (18F-GP1) for PET imaging that bound to the GPⅡb/Ⅲa receptors with high affinity. By targeting these key receptors involved in platelet clumping, the researchers were able to use 18F-GP1 to show a strong accumulation of platelets at the site of a thrombus. In addition, PET imaging using a Cynomolgus monkey model detected small venous arterial clots, endothelial damage, and emboli in the brain when the novel tracer was used. The ligand was also not affected by common anticoagulants used in the clinic, such as aspirin and heparin.

Commenting on the results, Dr Stephens explained: “Although the current studies are preliminary, 18F-GP1 may provide not only more accurate anatomic localisation, but also information of the risk of the clot growth or embolisation.” In order to determine the techniques’ exact clinical relevance, a first-in-human study of 18F-GP1 is ongoing. Since the risk of life-threatening bleeding from anticoagulant treatment is high, the researchers expressed the importance of balancing the risk of bleeding against the risk of clotting in patients, and expressed their hope that 18F-GP1 may, in the future, assist with this important decision.

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11th Annual Sickle Cell Disease and Thalassaemia (ASCAT) Conference 2017
11th–13th October 2017
London, UK

Well established as one of Europe’s premier haematology events, this conference sheds light once again onto the fascinating topics of sickle cell disease and thalassaemia. This year’s theme is ‘Patient choice in a changing landscape of treatment and cure for sickle cell and thalassaemia’; a topic which well represents the rapid developments in the field in recent years. Featuring case scenarios, expert talks, and sessions on genetics and genomics, this innovative conference is not to be missed.

The 79th Annual Meeting of the Japanese Society of Hematology (JSH)
20th–22nd October 2017
Tokyo, Japan

Held in Tokyo, Japan, this historic event will focus on ‘innovation and creation’ within the field of haematology, particularly highlighting the importance of training future generations of haematology specialists. Exhibiting a range of symposia on a variety of subjects, there will be no shortage of cutting-edge research on show from the world’s leading haematology experts. With an emphasis on international collaboration, this conference will offer a magnificent platform for haematology discussion.

LIIX National Congress of the Spanish Society of Hematology and Hemotherapy (SEHH) and the XXXIII National Congress of the Hemotherapy and Spanish Society of Thrombosis and Haemostasis (SETH)
26th–28th October 2017
Málaga, Spain

The theme of collaboration is strong this year, with two Spanish societies combining to create an incredible opportunity for haematologists. The event features a wide range of speakers on a variety of topics, such as the management of myeloma and advances in haemotherapy and transfusion medicine, there will undoubtedly be something for everyone. Situated on the beautiful Costa del Sol, this conference is sure to be an enlightening and enjoyable experience.

59th American Society of Hematology (ASH) Annual Meeting and Exposition
9th–12th December 2017
Atlanta, Georgia, USA

With thousands of scientific abstracts on show and estimated to attract >25,000 haematology professionals, the scale of this exceptional event, held in Atlanta, Georgia, USA, is unquestionable. With the latest research on show and limitless opportunities to network with pioneers in the field of haematology, this event is well worth a trip ‘across the pond’. There will also be numerous opportunities for networking and forging new relationships with like-minded professionals.
12th Dutch Hematology Congress (DHC) 2018
24th–26th January 2018
Arnhem, Netherlands

This event stresses its accessibility to anyone with an interest in haematology, aiming to provide an educational bonanza for specialists of all disciplines. Oral presentations, meet-the-expert sessions, and abstracts presenting the latest research will all feature heavily in this event, so anyone with an interest in the latest developments in haematology is heartily encouraged to attend. Delegates will be attending against the backdrop of the historical and picturesque city of Arnhem, Netherlands.

European School of Haematology (ESH) 4th International Conference on Hematologic Malignancies at Older Age: Biology and Therapy
9th–11th March 2018
Mandelieu, France

A slightly more specialist event, this conference represents an excellent opportunity to delve into one of the core aspects of haematology practice. With an increasingly aged population worldwide, the focus of this conference is becoming more and more poignant. Particular attention will be given to promising treatments and drugs, chiefly those with limited or no myelosuppression, for the elderly, as well as conditions, such as anaemia, which are especially prevalent in this demographic.

12th World Hematologists Congress
15th–16th March 2018
London, UK

Featuring lectures, keynote presentations, workshops, and exhibitions, this event is set to be a hotbed for educational debate in 2018. Like so many events in the ever-changing discipline of haematology, the focus of this congress will be on new developments, following the theme: ‘Defining a New Outlook and Forefront Research in Hematology’. Situated in the heart of London, this event will be of interest to anyone involved in the field, covering areas such as blood disorders and immunohaematology.

23rd Congress of the European Hematology Association (EHA) 2018
14th–17th July 2018
Stockholm, Sweden

Following an incredibly successful 2017 congress in Madrid, Spain, this mammoth event moves north to the Swedish capital, Stockholm. The event will showcase the very latest cutting-edge research and provide an abundance of opportunities for discussion with the world’s leading haematological minds. With an enormous and varied programme, the largest haematology event in Europe is an absolute must-see for any medical professional.
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