Key Note Address: Conference Day 1

Sickle Cell Anaemia: Kal, Aaj aur Kal

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Sickle Cell Anaemia, a monogenic disease with a single point mutation in β-globin gene is highly prevalent in several states in the country making India the 2nd most affected country in the world. The estimated gene frequency is 10% (1% homozygotes and 9% carriers). Further, the disease is also known to occur with beta Thalassemia better known as Sickle beta Thalassemia. Despite such a high prevalence and absence of curative treatment, there has been no systematic study to investigate its burden, managing clinical course, its treatment and prevention of the disease transmission to the next generation. Most of the studies are hospital based and focused on a small number of samples with targeted objectives. Under the CSIR – Sickle Cell Anaemia Mission launched in 2017, we undertook comprehensive research on early diagnostic methods, severity of clinical course and complications, response to hydroxyurea treatment and prevention of disease burden in the next generation through prenatal diagnosis and genetic counseling. We have undertaken a combination of simple screening approaches at every level in the society and generated a large cohort of thousands of patients. We have also used high throughput molecular biology approaches to identify proteo-genomic markers to predict disease severity and response to hydroxyurea treatment. This talk will summarize the observations made under CSIR – Sickle Cell Anaemia Mission and how it is likely to contribute to National Sickle Cell Anaemia Elimination Mission by 2047, as announced by the Prime Minister of India.

International Speaker's Address on SCD:

Day 1 Conference (Online, Live from Seattle, USA)

Paradigm Shift in Designing SCD Therapeutics: Balancing Between the Proper Brain Tissue Oxygenation and Attenuation of Vaso Occlusion During Therapy of SCD is an Essential Aspect of Designing New Therapeutics

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Polymerization of deoxy sickle cell hemoglobin (HbS) *in vivo* is the primary molecular aspect initiating the pathophysiology of sickle disease (SCD) Accordingly, the design of polymerization inhibitors that increase solubility of deoxy HbS, particularly the delay time of polymerization has been focus of the therapeutic approaches of SCD studies and *in vivo* therapeutic benefits are assessed by establishing the number and duration of sickle crisis. Early on considerable attention has been given to make sure that the oxygen affinity of *in vivo* modified HbS is not increased, as such an effect is expected to increase the severity of anemia and hence increase the *in vivo* propensity to polymerize. SCD is now recognized as a comorbidity disease and accordingly, many therapies are being developed, antioxidant and/or anti-inflammatory therapies, that mitigate the severity of the disease. Therapeutic benefits are generally reflected by attenuation of steady state vaso-occlusion. Increasing the oxygen affinity of HbS by *in vivo* modification by chemical approaches by Vaxelotor (Oxbryta) has been a novel strategy developed by GBT. Our studies with antioxidant therapeutics using pyridoxamine and quercetin, as well supra plasma expander with and without oxygen carrying capacity have demonstrated that improved perfusion seen as a consequence of attenuation of steady state vaso-occlusion as seen in transgenic mice need to be balanced with the potential reduction with the reduction in cerebral blood flow (CBF) to ensure oxygen debt is not created in the brain as a consequence of therapeutic approach. The level of anemia (hematocrit) in sickle cell patients can dictate the development of oxygen debt in brain tissue.

The design Polyethylene Glycol Conjugated high oxygen affinity hemoglobins (PEG Hb's) as a new class of oxygen therapeutics in our group at Einstein has exposed that Extension Arm Facilitated Hexa PEGylation of Hb and Alb endows a novel supra plasma expander property to these proteins. The high oxygen affinity of EAF PEG Hb was chosen for targeted oxygen delivery to tissues with oxygen debt during anemia. The of concept of increasing the oxygen affinity of HbS in red blood cell (RBC) is counterintuitive to treat sickle anemia patients as a therapy and enhance the anemia effect by reducing the oxygen delivered to already oxygen starved tissues, i.e amplify the disease severity. The net result should be the amplification of the ischemia reperfusion injuries. On the other hand, the oxygen therapeutics like EAF PEG Hb with high oxygen affinity and Supra plasma expansion activity when placed in plasma of sickle cell patients, can increase the oxygen extraction from RBC thereby reducing the ischemia reperfusion injury in such patients. The therapeutic benefit should be distinct compared to that seen with increasing

the oxygen affinity of HbS in RBC *in vivo* as the deoxygenated HbS will be reoxygenated in the lungs, i.e. deoxygenation influence is transient.

In brief, different isomers of PEGylated Alb and Hb, i.e., Supra Plasma Expanders without oxygen extraction activity have been designed, developed using protein engineering with a series of technologies using protein purification process development, followed by biophysical characterization for biopharma product development in the lab. Resulting purified products were tested on sickle cell disease transgenic mouse models with and without severe anemia using intravital microscopy and fMRI. Various parameters were tested, and few are discussed here indicating efficacy of the tested product as preclinical trials, e.g., leukocyte adhesion and cerebral blood flow as *ex vivo* experiment in the post capillary venules using intravital microscopy and tissue oxygenation in the brain tissues of SCD mice by fMRI.

Our results comparing the therapeutic efficacy of PEG-5K conjugated to albumin (EAF P5K6 Alb), EAF P5K6Alb Tempol Adduct, and EAF P3K6-Hb as well as small molecular weight antioxidant molecules using transgenic sickle mice NY1DD, S+S Antilles and Berk have supported the development of novel concepts in terms of designing therapeutics for SCD and the potential application of antioxidant therapies to improve the quality of sickle trait like patients and/or less severity disease patients with higher hematocrit compared to homozygous patients with severe SCD pathogenesis.

EAF P3K6 Hb, a high oxygen affinity supra plasma expander that increased the extraction of oxygen from RBC at low oxygen tension regions *in vivo* is expected to prove a novel therapeutic for homozygous patients in crisis in hospital setting as this therapeutic will also improve/normalize cerebral blood flow (CBF) as well as per fMRI studies on SCD mice without inducing an oxygen debt in the brain.

Key words: Plasma Expander, SCD therapy, SCD transgenic mouse, CBF, Intravital Microscopy, Protein purification process development

Conference Day 1: Session I: Theme: SCD status in India (Invited Guest Speaker)

I.SCD status of Gujarat and Western India
Title: Sickle cell anemia: Experience of Gujarat model

Dr. Yazdi Italia,

Ex. Hon. Director, Go-NGO Sickle Cell Anemia Control Program, Govt. of Garat.

Gujarat is the first state in India to incorporate Sickle Cell Anemia Control Program (SCACP) in the government health services under the Commissionerate of Health and Family Planning, Ministry of Health.

During 1952 to 1978, i.e., when Lehman reported the first incidence of Sickle gene amongst tribals of Nilgiri Hills in Tamil Nadu and Dr. Italia reported first case of Sickle Cell Disease in Gujarat in 1978, many research articles were published in scientific journals about the incidence of Sickle gene in India by mostly Ph.D. students for their thesis or by MD students for their dissertations. Research papers were published but the real subjects, the tribals in villages, were not informed or counselled or treated for their existing disease. The fruits of research have not reached the common tribal people.

Since 1978, in south Gujarat, Dr. Italia started advocacy for awareness of this disease amongst medicos as well as amongst tribal people and also the policy makers. Since he found the first case, he followed up and counselled the patient, his family and his community, followed by the entire tribal belt of south Gujarat. Dr. Italia strongly believed that all activities for Sickle Cell Anemia should be carried out free of cost by the government as the tribal people will never go to lab on their own money and will be misdiagnosed and mistreated.

In 2006, He was successful in his advocacy to Modi Government of Gujarat state, which resulted in the statewide program and Valsad Raktdan Kendra, an NGO initiated by Dr. Italia, has successfully designed the modern Sickle Cell Anemia Control Program of Gujarat state, which was awarded Prime Minister's Award by Hon. PM. Shri Manmohan Singh. Ongoing program of the Gujarat state and its pros and cons will be discussed in the presentation.

Conference Day 1: Session I: Theme: SCD status in India (Invited Guest Speaker)

Theme: SCD status of Maharashtra and Central India

Screening of Target Population Towards Sickle Cell Disease Control - Central India Experience

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Background- Hemoglobin Disorders are inherited genetic abnormalities in the structure, function and quantity of one or more of the Globin chains. The £ Thalassemia, B Thalassemia and Sickle Cell Disease (SCD) are the most common abnormalities. Structural variants of Hemoglobin, compound heterozygous states and rare Hb Syndromes constitute the rest of the Hb disorders, and therefore population screening programs must be aware that some of these clinically relevant cases may be encountered during screening of the susceptible group which will need clinical attention.

Objective-Diagnosis of Hb disorders requires knowledge of the genetics of the disorders, the precise diagnostic tests that are required, when to request the more specialized and costly tests and how to interpret the test results. Identification of the subgroup of people who have the disease or the potential to pass it on to their offspring. Advise to form support groups

Methods -Sickle Cell Association Nagpur is a Non-Governmental Organization (NGO) working for Control of Sickle Cell Disease in Central India. The target population for screening from newborn & neonatal units, and antenatal clinics was investigated after obtaining the proper consent from Government, Private Medical colleges, Muncipal Hospitals, Public Health department urban & rural medical set ups. Marriageable youth were targeted from schools and colleges after getting permission from the respective schools and universities. Solubility test for screening and Agar Gel Electrophoresis & High-Performance Liquid Chromatography, were used for confirmation of the diagnosis. Family screening of Index cases was offered. Patients were referred for clinical assessment & treatment, premarital, prenatal & parental counseling was offered.

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Results - Experience of 4464NewBorns, 54571Marriageable youth & 3430 Pregnant Mothers screened, problems encountered & lessons learnt will be discussed. Solubility appears cost effective screening test. HPLC of Index cases & cascade screening of relatives is cost effective.

Conclusion-Genetic screening policies have often been determined by technical capability, advocacy & medical opinion rather than crash & rigorous evidence-based review process. Decision making should take into account principles of ethics and opportunity costs. Those tested are protected against stigmatization & discrimination. Address economic, ethical, educational, evidentiary, issues that arise in the screening programs and screening tests used.

Keywords- Screening, Target population, Index case, Cascade Screening, Sickle Cell Association Nagpur (SCAN)

Conference Day 1: Session I: Theme: SCD status in India (Invited Guest Speaker)

Theme: SCD status of Karnataka and South India
Title: Screening and management of Sickle Cell Disease -Lessons from ICMR NTF SCD multicentric study

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Globally, sickle cell disease (SCD) is one of the most serious public health problems. There is a disproportionately high burden of SCD in socioeconomically disadvantaged tribal communities in India. The Indian Council of Medical Research (ICMR) conducted a study to develop an effective intervention model for SCD patients in tribal areas through government health care systems. The intervention includes raising awareness and preparing communities for accessing the government health care system for SCD care, as well as strengthening primary health care systems, including training health care providers in screening and managing SCD. A quasi-experimental design was used with pre-intervention and post-intervention comparisons of outcome variables within and between the interventional groups. The study was conducted in six districts endemic to SCD, spread across different geographical zones of India, including Karnataka. In each district, we selected four primary health care (PHC) areas primarily inhabited by tribal groups. Of these four PHC areas, two were randomly chosen to implement the intervention, and the remaining two were control areas. The study was implemented in three phases: formative, intervention and evaluation. An intervention model applicable to the primary care level in terms of its suitability, replicability, and sustainability for the tribal population was developed and tested. The findings of this multicentric study, with a specific focus on Karnataka findings, will be detailed. The lessons from the task force that can be a guiding force towards fruitful implementation of National SCD mission shall be discussed.

Conference Day 1: Session I: Theme: SCD status in India (Invited Guest Speaker)

Sickle Cell Disorders in the State of Odisha: Past, Present and Future

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The occurrence of Sickle Cell Disorder (SCD) in Odisha state has been known from the scientific report of Dunlop and Majumder (1952). They had encountered two cases of SCD cases those were originated from Sambalpur and Ganjam districts of Odisha while screening the tea garden labourers in Assam. Subsequently, Praharaj et al (1967) have reported sickle cell disorder among the Agharia caste group of Western Odisha.

However, the new dawn on sickle cell research in Odisha was due to the collaborative work between Prof. Kar of V.S.S. Medical College and Hospital Burla, and Prof. Serjeant of MRC, Laboratory Jamaica, Prof. Weatherall of Oxford University. The first comparative study between Odisha and Jamaica SCD patients highlighted several peculiar clinical characteristics among them (Kar et al 1986). The unique independent Asian β^s Globin gene haplotype among the SCD cases of Odisha and Maharashtra states was also reported (Kulozik et al 1986). The genetic link between Asian haplotype and higher level of foetal haemoglobin in Indian patients was established by them (Kulozik et al 1987). The widespread distribution of sickle cell gene among the different population groups and districts was reported by Kar et al in 1987. The molecular interaction of Alpha Thalassaemia for mild clinical expression of SCD patients of Indian patients was established by Kulozik et al 1988. Occurrence of Sickle Cell - β^+ Thalassaemia in Odisha state was reported by Kulozik et al in 1991.

Due to the establishment of Sickle Cell Research Unit at VSS Medical College Hospital, Burla by Regional Medical Research Centre (ICMR), Bhubaneswar in the year 1987 had helped to undertook several studies on the distribution, haematological and clinical aspects of the SCD cases on Odisha and adjoining states elaborately and enriched the scientific knowledge on Indian SCD cases. Besides the scientific studies the centre had counselled thousand of Sickle Cell Trait or carriers and SCD cases for their future marriage and health management. The ICMR-RMRC, Bhubaneswar has been conducting several research studies and mass awareness camps and workshops on SCD since 1991.

State Government in collaboration with National Health Mission initiated the Odisha Sickle Cell Project in 2010 and subsequently established the Sickle Cell Institute at VIMSAR, Burla in 2015 for conducting long term studies on SCD. The institute has enrolled around 30000 SCD cases and reported several new sickle cell double heterozygous cases till now. The government is also collaborating with CMC, Vellore and CSCR since 2017 for control and prevention of Thalassaemia and Sickle Cell Disease in Odisha. From 1st July 2023 the state government has started the National Sickle Cell Mission Project of Government of India in 20 highly venerable districts of the state with an aim to eliminate the disease by 2047.

Key Words: Sickle Cell Disorders, Odisha sickle cell project, Asian β^s globin haplotype.

Conference Day 1: Session II: Theme: SCD and RGD Epidemiology and Diagnostics (Invited Guest Speaker)

Advance diagnostic approaches for inherited haemolytic anaemia in the genetic era

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Abstract

Inherited hemolytic anaemias (IHAs) are rare genetic disorders caused by the early destruction of RBC due to intrinsic defects. Common symptoms of CHA include relatively harmless to chronic hemolytic anaemia, exchange transfusion during early infancy, recurrent blood transfusion, neonatal jaundice, indirect hyperbilirubinemia, reticulocytosis, hepatosplenomegaly, cholelithiasis. The RBC abnormalities are classified into three major disorders membranopathies, hemoglobinopathies, and enzymopathies. Traditional diagnosis of IHA has been performed via a step-wise process combining clinical and laboratory findings. Various infrequent forms also exist. The conventional methodology is limited in providing a diagnosis to the severe transfusion-dependent cases and hence the new molecular approach is required. Recent advances in molecular technologies, including next-generation sequencing, inspire us to apply these technologies as a first-line approach for the identification of potential mutations and to determine novel causative genes in patients with IHAs. Thus, we have used targeted NGS technology as an advanced diagnostic approach for the diagnosis of unexplained hemolytic anaemia, which helps us to provide insight into genotype-phenotype correlation and management of the disease.

We have provided molecular diagnoses to 119 unexplained hemolytic anaemia patients referred to our laboratory from all around the country in the last three years. Among which 112 have been diagnosed. We have offered prenatal diagnosis to 9 severely affected families and counseled them. In our study, we have incorporated both the DNA Sanger sequencing and NGS approach for molecular diagnosis of the patient making it cost-effective, quick and easier. A total of 54 cases of RBC enzyme defect, 27 cases of RBC membrane protein defect, 9 cases of RBC hemoglobinopathy, which was missed by a conventional method, and 22 cases of rare aetiology comprising of CDA. CSA, DBA, Iron overload and others. With the advent of NGS, the identification of rare and lesser-studied causes has become convenient and approachable.

Conference Day 1: Session II: Theme: SCD and RGD Epidemiology and Diagnostics (Invited Guest Speaker)

Is Screening enough to eliminate Sickle Cell Anemia by 2047?

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National Sickle Cell Anaemia Elimination Mission was declared by PM Narendra Modi as mission of Sickle cell disease elimination till 2047.
Objectives are set as provision of affordable and accessible care to all sickle cell disease patients, ensure quality care and reduce prevalence of sickle cell disease. Strategies are planned to achieve objectives. Various actions are planned under primary prevention. Under this action plan, at health care facility level counsellors are supposed to provide counselling services to all individuals diagnosed positive with sickle cell anaemia. Effective counselling at the significant level is utmost important to prevent new cases.

In our one-year experience, in bimonthly camp we found that numbers will increase in absence of pre-marital, pre-conceptional and ante-natal counselling. People are getting screened, but they must be informed about the significance of testing. Carrier status should be explained in detail. Screening people and distributing red cards to sufferers will not help to prevent new cases in the absence of effective counselling.

Even after extensive screening we can come across the mother in prenatal period who need timely prenatal investigation to diagnose foetal sickle cell status. Rural patients who could reach tertiary care and advanced technology is near to impossible at present. To provide timely, affordable, and accessible prenatal diagnostic facility action plan should be effectively implemented.

Education and awareness make a good impact in each field. Here applies the same. Educated carriers and sufferer from marriageable age group are informing and getting their partners screened before marriage. Awareness is increasing with education and proper counselling.

Keywords: Premarital counselling, Preconceptional counselling, Antenatal screening and counselling, Prenatal investigation.

Conference Day 1: Session II:

Theme: SCD and RGD Epidemiology and Diagnostics (Invited Guest Speaker)

Sickle Cell Disease nationwide testing of 7,00,00,000: What are the challenges and solutions for developing India specific program

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Abstract:

Prime Minister Shree Narendra Modiji launched “National Sickle Cell Elimination Mission 2047, as first Amrit Kaal Mission in July 2023 with biggest funding of all time for SCD testing only i.e. Rs. 700 crores. Aim of this program is to confirm status of Sickle Cell Carriers and follow these cases for pre marriage counselling to avoid marriages between two sickle cell carriers. This is a very challenging marathon with reference to time and space. Four main pillars of any diagnosis program, man, machine, reagent, technology should be perfect, cost effective, best quality, and reach to every village in 3 years, e.g. skilled labour from testing to follow-up, genetic counselling and pre marriage counselling at every village level. This time bound program is not impossible but challenging with reference to not only diagnostics, but different types of pathogenesis and their treatment at the bedside. At present we know that approximately 15 to 20 lakh homozygous SCD patients are in India as per various literature on paper. But even if a fraction of them come together in next 3 years, scientific and medical community needs to be geared up to answer those challenges. And this is the right time, i.e. beginning of the SCD elimination mission.

Implementing a national sickle cell elimination program in India, with 70 million tests at a cost of Rs. 100 per test, presents a substantial financial challenge, and that’s practical challenges from tenders, to quality with need of 100% accuracy to final beneficiary, because genetic disorder results are not like COVID19 antigen tests. Its permanent, its in DNA the sickle cell carriers and patients. However, the disparity between manufacturing costs and the final price is often attributed to various factors like distribution, administrative overheads, and corruption is as usual, as highlighted in the famous remark by then PM Rajiv Gandhi, "paisa ghista hai." To tackle this issue, the government can take several measures. Firstly, it should promote transparency in procurement and distribution processes, minimizing opportunities for corruption. Secondly, investing in local manufacturing facilities can help lower production costs. Thirdly, streamlining administrative procedures and eliminating unnecessary intermediaries can reduce overheads. Fourthly, digital technology can be leveraged for efficient tracking and monitoring, ensuring that resources reach the intended beneficiaries. Moreover, public awareness campaigns should emphasize the importance of efficient resource allocation. By addressing these challenges, the government can maximize the impact of the sickle cell elimination program, making it more accessible and affordable for the millions it aims to benefit. To enhance India's sickle cell elimination program, this can be optional if current process is derailed. A village-based Direct Benefit Transfer (DBT) model can be implemented. This involves identifying beneficiaries in tribal communities, using existing Jan Dhan accounts, and directly transferring testing funds after testing and reporting to dashboard. Monitoring and awareness campaigns are vital for accountability and community empowerment, ensuring efficient resource allocation. Based on COVID19 and SCD experience in real world practical aspects, this presentation will address challenges and possible solutions and discussion on difference of infectious diseases and genetic disorders based on future impact of field level data and confirmatory test reports to final beneficiary. In this presentation various aspects of challenges and possible solutions are discussed.

Conference Day 1: Session III

Rare Genetic Disorders: Pathogenesis, Treatment and Management

(Invited Guest Speaker)

Tackling Beta-Thalassemia Menace by Prevention, Prenatal Diagnosis, Postnatal Care and Cure

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Unlike sickle cell anemia, beta thalassemia is a more complex genetic disease caused by over two hundred mutations in beta globin gene, that results in the reduction in beta globin gene synthesis. As beta globin is made less also in the RBC of thalassemia asymptomatic carriers, there is excess free alpha protein. Detection of free alpha protein can detect thal-carrier and preventing thal-carrier carrier marriage can prevent thalassemia birth in the country. However, in the event of carrier marriage there is 25 % risk of birth of thal child, which can be prevented by prenatal diagnosis and medical termination of pregnancy. Under the unfortunate circumstances if a thal child is born, very frequent blood transfusion would be needed to survive. Frequency of transfusion, can be reduced by protein and omega-3 fatty acid supplementation to prolong life and premature death. The best course to give relief to the family would be to treat the child by bone marrow transplantation. Although, there are several relief options are in practice after birth, the best easy way is to avoid carrier-carrier marriage altogether to vison thal free India.

Conference Day 1: Session III

Rare Genetic Disorders: Pathogenesis, Treatment and Management

(Invited Guest Speaker)

Haemophilia diagnosis , management and newer trends

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Haemophilia is a rare genetic disorder which predominantly affects males. There are 3 types of haemophilia, A due to factor VIII, B due to F IX & C due to F XI deficiency. Approximately 1 in 5,000 males is born with Hemophilia A, and 1 in 30,000 males is born with Hemophilia B. Hemophilia affects people of all races and ethnic origins globally.Haemophilia A & B are X-linked recessive disorders & C is autosomal dominant. Rarely females may also be affected. People affected may be categorized into mild, moderate or severe depending on their factor level being >5, >1-5 or <1 % respectively. Presentation is with spontaneous bleed into muscles, joints or other vital structures in severe cases within the first year. The primary treatment of haemophilia is with deficient factor replacement along with other supportive measures like PRICE therapy. The major complication of factor replacement is the development of inhibitors. There are several factor which predispose to inhibitor development. In presence of inhibitors, the mainstay of treatment are bypassing agents- FEIBA, activated Prothrombin complex concentrates & recombinant f VIIa. Among the newer therapies we also have non-factor agents like Emicizumab, Fitusiran & Concizumab. Haemophilia as a disease is difficult to live by & needs a mutidisciplinary approach as well as social support.

Conference Day 1: Session III

Rare Genetic Disorders: Pathogenesis, Treatment and Management

(Invited Guest Speaker)

Chemical corrections of G6PDd to cut the Gordian Knot of malaria elimination

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A major roadblock towards malaria elimination is development of antimalarial drugs resistance, that heavily require new drugs with validated targets. To achieve malaria elimination, drug discovery for the next generation needs to focus on blocking disease transmission and on targeting the liver-stage forms of the malaria parasite, which remain dormant in the liver as hypnozoites for many months or years. Currently, primaquine is the only treatment targeting the liver stage of vivax malaria but it cannot be used in individuals with glucose-6-phosphate dehydrogenase deficiency, a common genetic abnormality in malaria endemic areas. Severe hemolysis may result in population of G6PDd individuals following primaquine treatment. The chemical correction for hemolytic anemia in G6PD-deficient patients can be an innovative way to tackle this problem. A supportive treatment can be developed to avoid the complications by therapeutically correcting the deficiency. We have repurposed a clinically approved drug to correct the G6PD-deficiency and propose its use as a framework for the path to breakthrough treatments that could be taking us a step closer to the vision of malaria elimination.

Conference Day 2: Session IV

Sickle Cell Disease Pathogenesis and Therapeutics

(Invited Guest Speaker)

Models of Care for Indian Sickle Cell Disease

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Abstract

The occurrence of sickle cell disease in India presents a fascinating challenge because it has occurred against a different genetic background characterized by consistently high frequencies of fetal haemoglobin (HbF) and varying frequencies of deletional alpha thalassaemia. Both features are important because they inhibit polymerization of sickle haemoglobin molecules and so change expression of the disease. Many other differences occur in diet and lifestyle which may also influence the disease. The result is that the world may learn much about the pathophysiology of the disease by careful clinical and haematological comparisons with the disease elsewhere but of more immediate relevance is the need to develop models of care appropriate to Indian conditions and Indian sickle cell disease. This is a challenge gradually being met by the many Indian colleagues working in sickle cell disease, advances which will be important for Indian patients but also contribute to the understanding of the disease worldwide.

Conference Day 2: Session IV

Sickle Cell Disease Pathogenesis and Therapeutics

(Invited Guest Speaker)

Role of genetic modifiers associated with raised HbF in clinical presentation of Sickle cell Anemia

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Abstract :
Background: Sickle cell anemia though a monogenic disorder, show phenotypic variability. Hence, understanding the genetics underlying the heritable sub-phenotypes of hemoglobinopathies, specific to each population, would be prognostically useful and could inform personalized therapeutics.
Objective : This study aimed to evaluate the role of genetic modifiers leading to higher HbF production with cumulative impact of the modifiers on disease severity.

Material and methods: 100 Sickle Cell Anemia patients and 50 healthy controls were recruited. Primary screening followed with molecular analysis for confirming the β-hemoglobinopathy was done by using CRDB and ARMS was performed. Co-existing α-thalassemia and the polymorphisms located in 3 genetic loci linked to HbF regulation were screened by Gap PCR and DNA sequencing respectively.
Results: The most remarkable result was the association of SNPs with clinically relevant phenotypic groups. The γ-globin gene promoter polymorphisms [− 158 C→T, + 25 G→A],BCL11A rs1427407 G→T, − 3 bp HBS1L-MYB rs66650371 and rs9399137 T→C polymorphisms were correlated with higher HbF, in group that has lower disease severity score (P< 0.00001), milder clinical presentation, and a significant delay in the age of the first transfusion.
Conclusion: Our study emphasizes the complex genetic interactions underlying the disease phenotype that may be a prognostic marker for predicting the clinical severity and assist in disease management.

Key words: Sickle cell anemia, BCL11A, HBS1L-MYB, HbF levels.

Conference Day 2: Session IV

Sickle Cell Disease Pathogenesis and Therapeutics (Invited Guest Speaker)

Sickle Cell Disease and Human parvovirus B19 journey: From first reporting in India to BSL2+ Lab facility development for future B19 R&D, therapeutics, and preventive vaccine development

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Ever since the discovery of human parvovirus B19 in 1975 and its role in sickle cell disease (SCD) recognized by developed countries, due to one or the other reasons, this was not a priority area for developed nations since half of the (SCD) patients are living in India (1.5 to 2.0 million) and remaining in African countries, although significant population are in USA too (0.1 million). With SCD research background from ICMRs' primitive tribe SCD multicentric project in India in 1999 and first ever efforts were done during 2003 to 2005 for research on Human parvovirus B19 with specific interest on its epidemiology and pathogenesis in homozygous SCD (Lingojwar DP et. al., 2004). With this background experience in SCD and B19 virus research, now we are committed to develop BSL2+ lab for RG2 level virus followed by SCD epidemiology, and pathogenesis with reference to Human parvovirus B19. An ambitious endeavour was undertaken to equip the research with state-of-the-art facilities, a cutting-edge laboratory was meticulously designed to cater to all aspects of human parvovirus research and development, under Biosafety Level II+ (BSL2+) lab at Shradhasai Lifesciences Pvt. Ltd. Pune in collaboration with ADEETECHGENE Biotech Pvt. Ltd (ADEETECH®). Spread across 4000 sq. ft. and core virology BS2+ lab of 1500 sq ft, it has all the facilities from initial sampling to DNA isolation, virus sample storage, virus cultivation, rDNA technology, genomics and proteomic facilities, cell and tissue culture etc.

The vaccine's potential impact is profound. It could save countless lives, especially in India and developing nations where human parvovirus B19 often goes unnoticed. This promise is supported by both medical and commercial considerations. Medically, the vaccine targets a sizable population, particularly homozygous (SCD) patients, including those from all 17 Indian states. By averting severe complications and fatalities linked to parvovirus B19, the vaccine addresses a vulnerable group. Commercially, success seems viable due to the high prevalence of SCD cases in India and other developing countries, generating significant market demand. In conclusion, fusion of existing scientific expertise and experience of handling B19 virus as pioneer in this field i.e. expertise of SCD and B19 virus together along with RG2 BSL2+ facility, currently available advanced science of vaccine development, an huge SCD population in paediatric age group which will get recorded due to national sickle cell anemia elimination mission 2047, and commercial viability due to nationwide coverage in 200 plus districts, forms a compelling case for further research, development, and eventual deployment of the vaccine, promising to save lives and alleviate the burden of this often overlooked disease.

Key words: Human parvovirus B19, Transient Aplastic Crisis, VLP based B19 vaccine, Sickle Cell Disease, SCD Pathogenesis

Conference Day 2: Session IV

Sickle Cell Disease Pathogenesis and Therapeutics (Invited Guest Speaker)

Drug Development For Management Of Sickle Cell Anaemia And Roadmap Towards Commercialization

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Sickle Cell Disease is a genetic disorder affecting around 20 million people world-wide and truly a global challenge. The conventional therapeutic management majorly involves the use of drugs hydroxyurea, which has side effects. Treatments like Bone marrow transplantation and Gene therapy require highly sophisticated infrastructure and appropriate donors, besides the high cost. Hence, there is a need to find an ideal therapy for Sickle Cell disease which is potent and safe with no side effects.

In the present invention, a novel herbal drug 'Haemadhaar' is developed from unique medicinal plant extracts like *Punica granatum* (Pomegranates peel), *Rubia cordifolia* (Indian madderstem) and *Aegle marmelos* (Indian bael leaf). The formulation shows better antisickling properties such as haemoglobin Hb S polymerization inhibition, increases oxygen affinity and membrane stability of Sickle Cell RBCs as compared to standard drug hydroxyurea. Besides, the drug formulation is very cost effective, safe and has no side effects. Overall, herbal formulation has individual and synergistic pharmacological potential of bioactive compounds for overall management of cascades of pathophysiological conditions, thus preventing multiple organs impact in Sickle Cell Disease. The patent (Patent no. 202021023652) has been filed for this novel formulation and has achieved FDA/AYUSH approval for commercialization.

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Conference Day 2: Session V

SCD and RGD: New Born Prevention and New Technology to Cure

(Invited Guest Speaker)

Prevention of Sickle Cell Anemia and Thalassemia in present revolutionary advanced science and technology

Dr. Yazdi Italia
Ex. Hon. Director, Go-NGO Sickle Cell Anemia Control Program, Govt. of Gujarat.

To take care of patients of Sickle Cell Anemia and Thalassemia Major is our **Responsibility** and to prevent birth of Sickle Cell Disease and Thalassemia Major is our **Duty.**

It is time for India, as our Hon. PM Shri Narendra Modi says “Tribal populations in India share a disproportionate burden of sickle cell disease. We will usher in a social revolution against this disease and bring in the most advanced science and technology to tackle it.”

So, we must work with all resources to improve the life of people living with this genetic burden. Side by side we must think about the short-term goal and the long-term goal in reducing the burden of these genetic diseases, **as both are preventable.**

First time in India, at Valsad district, Gujarat, 100% voluntary and ethically counselled program with support of CSR funding from BAYER Vapi Pvt. Ltd., for screening of all antenatal cases in government, private and trust hospitals in urban as well as rural areas, will be carried out for haemoglobinopathies by HPLC technique. Those ANC cases found to have abnormal genes, their husbands will be counselled and tested to detect high risk couples.

With the goal of prevention of double heterozygous or homozygous child birth further counselling will be carried out and only with the ethical consent of the couple, PND will be advised with the option of opting out at any time.

This presentation will discuss about Go-NGO partnership program for prevention of Sickle Cell Disease and Thalassemia Major to be carried out by Valsad Raktdan Kendra and Government Health Department, Jilla Panchayat, Valsad.

Conference Day 2: Session V

SCD and RGD: New Born Prevention and New Technology to Cure

(Invited Guest Speaker)

Sickle Cell New Born Screening program India

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Sickle cell disease (SCD) is a major public health problem in India with the highest prevalence amongst the tribal and some non-tribal ethnic groups. The clinical manifestations are extremely variable ranging from a severe to mild or asymptomatic condition. Early diagnosis and providing care is critical in SCD because of the possibility of lethal complications in early infancy in pre-symptomatic children. Children with SCD have an increased susceptibility to bacteremia due to Streptococcus pneumoniae which can occur as early as 4 months of age and carries a case fatality rate as high as 30 percent. The primary purpose of neonatal screening is to identify infants with sickle cell disease, for whom early diagnosis, parental education, prophylactic penicillin and comprehensive medical care markedly reduce morbidity and mortality.

Approaches and Technologies for Newborn Screening for Sickle Cell Disease : Universal screening includes all consecutives newborm screened and Target screening includes Selective group screened (tribal babies or babies of sickle cell traits). Blood sample for newborn screening is taken by Heel prick and cord blood sample. Technologies for newborn screening includes Iso electric focusing, HPLC analysis – NBS HPLC machine for dried blood spots and Variant II HPLC machine for cord blood samples, Capillary electrophoresis, Point of care testing.

Confirmation of Diagnosis by using a second method at or after 9 months of age, DNA analysis in ambiguous / difficult cases.

Since 2010, neonatal screening programs for SCD have been initiated in a few states of India. At present there is no national neonatal screening programme in India and children get identified only when they become symptomatic. There is therefore an urgent need to diagnose babies with sickle cell disease at birth so that complications can be ameliorated by early intervention and prophylactic penicillin and anti-pneumococcal vaccination can be started within the first few months. At the same time parents can be taught to detect acute splenic sequestration and be given counselling for prevention of the birth of further children with sickle cell disease in the family by prenatal diagnosis.

The Lancet Haematology Commissions July 2023 recommends that all globally newborn babies are offered Sickle Cell neonatal screening by 2025, to inform parental reproductive choices and allow all infants to receive clinical care from an early age.

Conference Day 2: Session V

SCD and RGD: New Born Prevention and New Technology to Cure

(Invited Guest Speaker)

Genetic counselling – vital intervention towards sickle cell eradication by 2047 in India

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Sickle cell disease (SCD) is an inherited hemoglobin disorder. SCD is the second-most common disease in India after Africa, with a prevalence of 4.3%. Genetic counselling (GC) is the most cost-effective intervention for reducing the burden of SCD. Although GC is well-established in reducing the prevalence of SCD births, it has not yet been integrated into Indian national policy, and most Indians approaching marriageable age and childbirth are not able to access it. The perception and efficacy of GC have also not been examined yet among young adults, especially in Indian tribal communities. These communities require careful consideration of their socioeconomic, cultural, and ethical values when providing counselling. An effective GC requires community engagement with local tribes and healthcare infrastructure on multiple levels. The session highlights the essentials of GC in the prevention and management of SCD among tribal communities based on personal counselling experience in South India.

Conference Day 2: Session V

SCD and RGD: New Born Prevention and New Technology to Cure

(Invited Guest Speaker)

Discovering newer drugs for Sickle cell disease: National efforts and CSIR's contributions

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CSIR has initiated a mission project in 2017 on Sickle Cell Anemia and National Chemical Laboratory, a key member of the team of 7 CSIR Labs, is leading the drug discovery component. During the same time a new sHb modulating drug, GBT440 (now approved by FDA), with promising anti-sickling activity was reported. NCL has been working on similar grounds, using structure-based knowledge and we have developed molecules that block the polymerization of sHb and hence the subsequent sickling of red blood cells. Unusual adhesion of RBCs, leading to Vaso-occlusion is another manifestation of SCA. In another effort we have identified molecules, which show promising anti-RBC adhesion activity. In this talk I will present our approaches in developing small molecule inhibitors towards the discovery of anti-sickling drugs.

Participant's Presentation: PP1

Prenatal Diagnosis of Sickle cell Disease in India: impact on prevention programme

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Objectives: Sickle cell disease (SCD) is the common haemoglobinopathy in India with a carrier frequency varying from 0 to 40%.It is prevalent in the scheduled caste and tribal populations in India. The clinical presentation of sickle cell disease is extremely variable. Prenatal diagnosis (PND) remains an important option for couples at risk of having a child with sickle cell disorder. During the last 15 years, a total of 1041 cases were referred to us from various parts of the country for prenatal diagnosis of SCA (915 families),HbS-β thalassemia (127 families) and HbS-D diseases (6 families).

Materials and Methods: Identification of carriers and couples at risk of sickle cell disorder by antenatal screening using HPLC. The fetal diagnosis was done in the first trimester (CVS) at10-12 weeks gestation and in the second trimester (Amniocentesis) at 16 to 17 weeks or (Cordocentesis) at 18 to 22 weeks of gestation. Characterization of mutation using Covalent Reverse Dot Blot Hybridization, ARMS, Restriction enzyme assay (Dde1) and DNA sequencing. For maternal contamination, VNTR analysis was done in CVS and Amniotic fluid sample, Kleihauer Betke staining in the fetal blood sample.

Results: 23.7%of fetuses were affected (sickle cell anemia-217,sickle thalassemia-31, Hb S-D diseases -2). Among 127 HbS-β thalassemia group, IVS 1-5 (G→C) and Codon 15(G→A) mutations were seen.
A significant increase in the number of couples at risk referred for prenatal diagnosis was seen over the years. Despite genetic counselling, our study showed that 3 (0.28%) continued pregnancy even after the fetus was homozygous. The most possible complication of the prenatal procedure is miscarriage however in our case we did not observe such a condition.

Conclusion: With the successful implementation of awareness programs as well as screening and genetic counselling in antenatal clinics, there are a significant number of couples opting for prenatal diagnosis despite the fact that it is impossible to predict the severity of the diseases and many individuals may have a milder clinical presentation. An increase in the number of couples in the first trimester shows greater awareness in the communities. Our experience has shown that around 30% of couples come for prenatal diagnosis prospectively and the majority of them opt for termination of pregnancy when the fetus is affected.

Key words: SCD , Prenatal diagnosis, CRDB, ARMS, VNTR

Participant's Presentation: PP2

Management of sickle cell: Beyond Acute chest

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Sickle cell disease (SCD) is a genetic disorder affecting haemoglobin, and it causes red blood cells to become sickle shaped. These deformed sickled red cells cause vaso-occlusive symptoms limiting blood flow to tissues and organs, leading to a variety of complications, including acute chest syndrome (ACS). ACS is a life-threatening condition that can cause lung injury, breathing difficulty, and low oxygen levels. Apart from ACS, these patients can also have other issues, including Pain crisis, aplastic crisis, sequestration, priapism, stroke, chronic organ damage etc. It should be kept in mind that presentation is variable amongst patients, especially the difference between African and Indian Sickle patients. The severity of SCD and the risk of complications vary from person to person. There is limited cure for SCD like Stem cell transplant and the upcoming gene therapy, but there are treatments that can alleviate the suffering like Transfusions, Medications (Hydroxyurea, Crizanlizumab), Pain management, Preventive measures, such as vaccination against infections. Now a days with better understanding, better facilities and vaccination, people are living longer and we a seeing many adults with sickle. We need a multidisciplinary approach for managing these adults with sickle cell with a haematologist playing central role.

Participant's Presentation: PP3

CRISPR/Cas9 engineered *ex vivo* sickle cell disease model system and its therapeutic application in malaria

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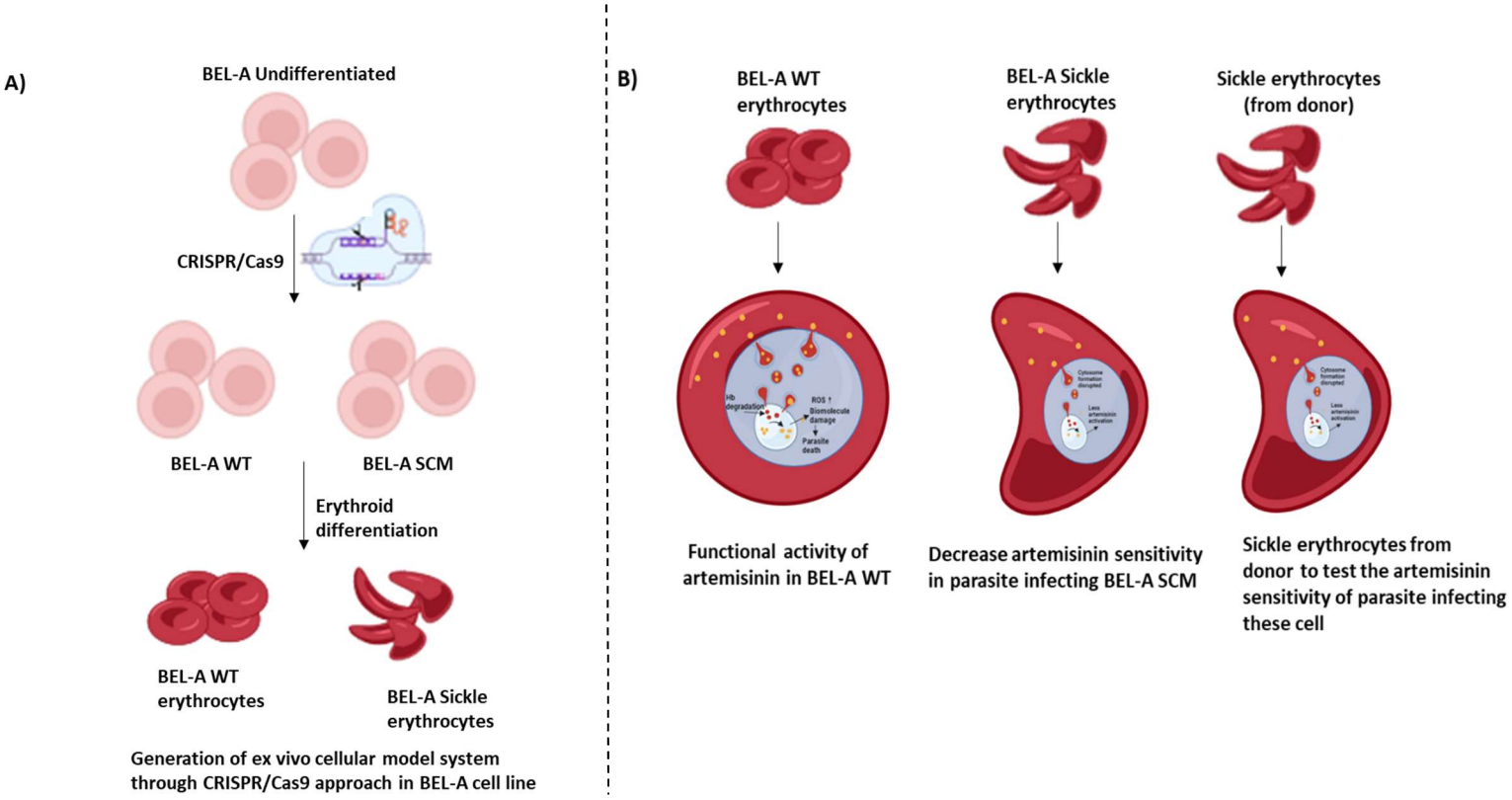
Sickle cell disease (SCD) is the most prevalent severe hemoglobinopathy in the world and an inherited, monogenic condition. To study underlying disease mechanism for novel therapeutic strategy there is an urgent need for the development of pathophysiologically relevant *ex vivo* cellular systems. As, this trait has been shown to provide some degree of protection against serious life-threatening falciparum malaria, this cell-based system can further be used to understand malaria pathogenesis to develop novel antimalarials. In this study, we report the CRISPR-mediated generation of erythroid progenitor lines for BEL-A sickle cell mutation (BEL-A SCM). Erythroid cells differentiated from BEL-A SCM, sustainably generate reticulocytes and mimic characteristic pathological conditions such as sickling phenotype under hypoxic conditions. Although this trait may provide some protection from serious, life-threatening falciparum malaria, partial Artemisinin combination therapy (ACT) failure has been reported in sickle cell malaria patients. To study the underlying mechanism behind it, we first tested the artemisinin sensitivity in BEL-A SCM, cells were infected with both artemisinin sensitive (3D7) and resistant strain (R539T) of *Plasmodium falciparum* respectively. In both plasmodium strains tested, the IC_{50} values were markedly higher than their respective IC_{50} values in BEL-A WT RBCs. Further, artemisinin sensitivity of parasite was also monitored in sickle cell erythrocytes derived from donor patient. Result obtained show similar artemisinin activity profile as that of BEL-A SCM, suggesting it can be used as a powerful in vitro SCD model system for malaria disease modelling. As higher doses of artemisinin required to halt the parasite growth in sickle erythrocytes. An additional in vitro RSA was conducted to monitor the survival rate of the parasites after artemisinin treatment, result showed 70-80% more survivors in RBCs of SCD phenotype than AA phenotype. Moreover, to understand the mechanism of artemisinin resistant, formation of the cytostome (a specialised parasite feeding apparatus used to endocytose host cell haemoglobin) was monitored in BEL-A SCM and BEL-A WT RBCs infected with malaria parasite, which showed less cytosome formation in BEL-A SCM derived sickle erythrocyte. Based on our findings, artemisinin resistance may be a result of decreased artemisinin activation caused by a decrease in haemoglobin uptake and consequently reduced haem production. The present study demonstrated for the first time the sustainable *ex vivo* cellular systems generated through CRISPR/Cas9 modification in BEL-A cell line that faithfully recapitulate the healthy and SCD phenotype. Further development of this cell-based system enabled the identification of potential host-mediated mechanisms that may cause artemisinin resistance in malaria parasites infecting sickle erythrocytes, opening up the possibility of testing new molecular targets to circumvent the emergence of resistant parasites.

KEY WORDS - Sickle cell disease, CRISPR/Cas9, BEL-A cell line, Artemisinin resistance, Cytosome

Graphical Abstract



A) Generation of *ex vivo* disease model for sickle cell disease through CRISPR/Cas9 approach.

B) *Ex vivo* cellular model system for sickle cell disease is used to study the molecular pathogenesis of malaria parasite. In this study we evaluated the possible host-mediated mechanism for the development of artemisinin resistant parasite in sickle erythrocytes, which showed decreased artemisinin activation caused by the decrease in haemoglobin uptake and consequently reduced haem-production.

Participant's Presentation: PP4

Amyloids in Sickle Cell Disease: New Therapeutic Possibilities for the Disease Management

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Sickle Cell Disease (SCD) is an autosomal recessive genetic disorder marked by defective hemoglobin, leading to distortion, or sickling of red blood cells, leading to reduction in oxygen binding capacity and obstruction of the blood vessel and capillaries. Several downstream but inter-related path-physiological processes contribute to the manifestation of SCD, which is characterised by chronic inflammation, hypercoagulability, ischaemic injury, functional nitric oxide deficiency, endothelial, platelet and leucocyte activation, and oxidative stress. Chronic and persistent inflammation results in up-regulation of an acute phase protein, commonly referred as Serum Amyloid A (SAA), which results in widespread end-organ damage due to chronic vaso-occlusive episodes and reduced life expectancy. SAA is an amyloid precursor protein produced in liver and overexpressed up to 1000-fold during inflammatory response. At higher concentrations, these proteins self-assemble into an ordered protein aggregates rich in cross-beta sheet structures known as amyloids. A recent study confirmed the presence of non-branching amyloid-like protein fibrils in renal biopsy of a young African American SCD patient, consistent with AA amyloidosis histopathology. This case report adds a new dimension of SCD mediated renal AA amyloidosis in sickle cell disease. The talk will highlight the molecular mechanism of SCD-mediated inflammation and its relationship with AA amyloidosis and delineate the emerging pathophysiological conditions and new therapeutic strategies in SCD.

Participant's Presentation: PP5

Fatal interaction between dengue and sickle cell disease: A hypothesis validation for disease control

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Dengue, a mosquito borne disease, is endemic in more than hundred countries all over the world including India. World Health Organization (WHO) in 2019, designated dengue as one of the top ten health threats in the world. In India dengue affects almost all of its states wherein the infection is more prevalent in urban areas; however, it has been reported to spread to peri-urban and rural areas. A less sever dengue infection with mild symptoms is self limiting however more sever forms *viz.* dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), require hospitalization and may turn fatal. Like dengue fever, sickle cell disease is also a major public health concern over the globe including India where the prevalence of sickle gene in tribal populations varies from 1-40 % affecting approximately 4 million people. Previous case studies have demonstrated that DHF and DSS in sickle cell disease (SCD) patients have turned out fatal in almost all cases, indicating a fatal interaction between the two disease conditions with vascular endothelial damage being the central and common manifestation. Endothelial dysfunction and damage in SCD likely to augment the sever form of DHF/DSS. In dengue infection, the secretary form of the non-structural protein -1 (NS-1) has been shown to cause the vascular leakage symptoms. To manage dengue fever complications in SCD background may therefore require a two-way approach – one that manages DHF and another that may address SCD. DHF may be prevented by NS-1 based vaccines or drug molecules, whereas targeting mutant haemoglobin S multimers in sickle RBCs could offer far reaching effects for DHF as well as SCD. Drug molecules, with hydrophobic, however, soluble surface may prove vital in disrupting the otherwise dynamic equilibrium between mutant haemoglobin S (HbS) monomers and fibers. To test the hypothesis three dipeptides, QLK, RVN and VRG were chosen as test agents to bind on the HbS surface with exposed β-globin 6Val residue, to assess the shielding capacity of such molecules *in silico*.

Key Words: dengue hemorrhagic fever (DHF), sickle cell disease (SCD), haemoglobin S, non-structural protein -1 (NS-1)

Participant's Presentation: PP6

Sphingosine kinase-1 as an important host erythrocytic factor for the management of malaria in sickle cell disease.

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KEY WORDS- Sickle cell disease, Sphingosine 1-phosphate, Artemisinin resistance, Sphingosine Kinase-1.

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Inherited hemoglobinopathies encompass the most commonly occurring dreadful disorders of the red blood cells. Sickle cell disease (SCD) is one such abnormality whereby a faulty protein, called 'hemoglobin S' is produced as a result of a mutation in the β-globin chain of hemoglobin molecule. SCD is truly a great issue for the public health programmes running across the globe. The obvious impression of Sickle cell crisis has been reported from malaria endemic regions where it has been shown to affect an individual's response and survivability towards parasite infection. This cross talk between SCD and malaria infection is supported by evidences which suggest that individuals heterozygous for the sickle gene (Hb genotype AS) are relatively protected against death due to malaria. On the other hand, homozygous (Hb SS) individuals are at increased risk of dying from malaria. Furthermore, such patients also present episodes of decreased Artemisinin (ART) efficacy as correlated with a delay in parasite clearance from the blood. Though the studies showing mutation in parasite cellular genes in response to ART have been exhaustive, no coherent picture of the involvement of host erythrocytic factors in regulating parasite's artemisinin sensitivity or resistance has been defined. In one of the related studies, it was reported that artemisinin treatment resulted in the inhibition of malaria parasite growth by inducing the generation of ceramide. This effect of ceramide was then shown to be antagonised by host lipid mediator, sphingosine 1-phosphate (S1P). Additionally, We, through our studies, have already established parasite co-dependency on the endogenous S1P pool of host erythrocytes, and have provided molecular insights into the cellular processes regulated by S1P in the parasite. Sickle erythrocytes have been reported to have a dramatic enrichment of S1P which promotes the sickling and disease progression in the patient. Additionally, treatment of SCD mice with PF-543, a known specific clinical inhibitor of Sphingosine kinase-1 (SphK-1), has shown to induce a significant 'antisickling' effect. Thus, we hypothesize that the elevated levels the host S1P might be responsible for artemisinin resistance phenotype in malaria infected SCD patients. To test this hypothesis, we have initially treated the normal erythrocytes infected with laboratory strain of *Plasmodium falciparum* 3D7, using S1P and ART in combination. As expected, both the molecules imparted an antagonistic effect on the parasite growth. Since elevated S1P is providing survival benefits to the parasite, we used PF543 together with ART to treat the parasites and

could show their synergism in inhibiting parasite growth. Hence, we propose that this cross talk between S1P and ART might be one of the crucial key behind the generation of ART resistance in the SCD patients. Hence, using PF-543 alongside the existing antimalarials and antisickling drugs, can contribute greatly towards the therapeutics of malaria in SCD.

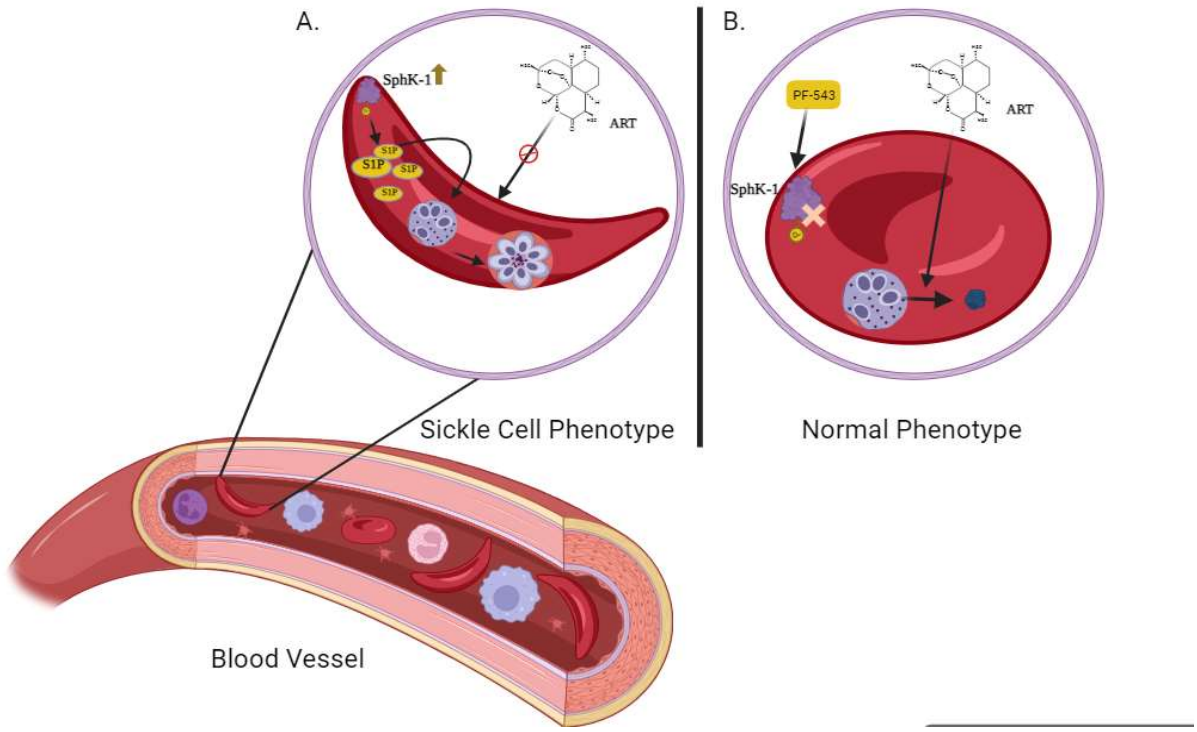

Figure 1. The combined effect of PF-543 and Artemisinin in the management of malaria in sickle cell disease. **A.** The elevated levels of sphingosine 1-phosphate in sickle shaped RBCs provide protection to the invading parasite against artemisinin. **B.** In the presence of PF-543, the SphK-1 activity is inhibited, making the malaria parasite more susceptible towards artemisinin treatment. Additionally, PF-543 also imparts an 'antisickling' effect to the erythrocytes.

Participant's Presentation: PP7

Documentation of Sickle cell disease for surveillance and patient management of Koraput, Odisha, India

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In Odisha, sickle cell disease (SCD) predominantly occurs in indigenous people, who are approximately 95 lakhs in thirteen tribal dominant districts comprising 22.84% of the state's total population and 0.79% of India's total population as per 2011 Census. Nonetheless, screening and diagnosis of SCD rarely occur in the tribal dominant districts. Such condition demands the development of a comprehensive SCD database model, which should encompass the establishment of the documentation. The present study focuses on the creation and execution of Odisha's SCD database of Koraput district of Odisha's predominantly tribal communities. The research emphasises the viability of establishing an SCD database by gathering systematic data on individuals with SCD in Koraput, Odisha. Such data is crucial for the purposes of program planning and management for future research on SCD in Odisha.

Participant's Presentation: PP8

Sickle Cell Disease and Amyloidosis: An *in-silico* Correlation Between Two Protein Structural Diseases

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Sickle Cell Disease (SCD), caused by the structural alteration in oxygen-carrying hemoglobin molecule, originating from hereditary genetic changes needs to be addressed from several perspectives of physiology. As a protein-related disease of connective tissue that reaches almost every part of the body, there are high chances of the interaction of this misstructured hemoglobin with other proteins due to the shortened life span (10-20 days) of sickled RBC. Very little but promising literature is available that tries to explore the interaction of released hemoglobin with other pathogenic proteins in human physiology. The brain being an organ with a high oxygen demand is prone to blood-borne diseases. SCD has been strongly associated with Parkinson's Disease, Alzheimer's Disease, and other cognitive impairments. Also, a correlation between SCD and renal amyloidosis has been noted in case reports which signifies some link between amyloid and SCD.

Our approach tries to find out the structural similarity based on polymerization and aggregation between Sickle hemoglobin (HbS) and amyloidogenic proteins and the ability of the deformed protein to interact or interfere with other amyloid-related proteins.

In this study, we first obtained protein sequences from the NCBI-NLM protein database. Thereafter, performed an *in-silico* test for the aggregation propensity of hemoglobin subunit chains α, β, γ1, γ2, and HbS sequence using Tango and amylpred aggregation tools. The amyloidogenic core sequences of pathogenic protein sequences were obtained from the literature. A comparison of the sequence of amyloidogenic proteins causing neurodegenerative disorders including Parkinson's Disease, Alzheimer's Disease, and others with that of the HbS sequence was executed by online available tools including Clustal ω. Structural interaction was performed using the Structure2Net online tool.

A high aggregation propensity in a few regions of hemoglobin subunits was reported according. Alignment comparison of satisfactory with alignment score between 14.99 to 77 for various combinations of proteins. Protein-protein interaction positively supports our hypothesis. The pathogenic amyloid protein and hemoglobin protein appear to interact in our *in-silico* studies. Further high-throughput computational and *in-vitro* studies are required to confirm the results.

Keywords: SCD, Amyloid, Hemoglobin, Neurodegenerative disorder

Participant's Presentation: PP9

Therapeutic and diagnostic interventions for dengue virus infection associated with sickle cell disease

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Sickle cell disease (SCD) is a hereditary hemoglobinopathy and the co-occurrence of severe dengue fever in individuals with SCD represents a complex medical challenge. The pathophysiological interactions between dengue virus (DENV) infection and SCD at cellular and molecular levels, develop severe forms of dengue fever, dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). This abstract provides an overview of managing individuals who experience DENV infection with SCD. In silico high throughput virtual screening (HTVS) and molecular dynamics (MD) simulation studies were performed to identify potential lead candidates from a PubChem database library, targeting the envelope protein of DENV-2. The results of HTVS have yielded a few protein-ligand complexes with significant binding scores using DENV-2 E protein. Furthermore, MD simulations have played a crucial role in characterizing the dynamic behaviour of the DENV-2 E protein in complex with lead candidates. SCD and DENV, share overlapping clinical manifestations, such as fever, fatigue, and pain. But the coexistence of these two illnesses is underreported. Therefore, there is an urgent requirement for improved diagnostic accuracy, customized management techniques, and raised awareness among healthcare professionals and the affected communities. Herein, we propose the development of a diagnostic kit aimed at assessing the genetic components from RBCs and viruses in a single patient sample, facilitating rapid and accurate co-diagnosis of SCD and dengue fever. Keywords: SCD, DENV, Virtual screening, MD simulations, Co-diagnosis

Participant's Presentation: PP10

G-Tri-BAL's Road Map for eradication of Sickle Cell Anemia in ASR District, Andhra Pradesh - A Management Model

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Center for Integrated Tribal Research and Development (G-Tri-BAL) a collaborative initiative of Tribal Cultural Research and Training Mission (TCR&TM), Tribal Welfare Department, Govt. of Andhra Pradesh and Gayatri Vidya Parishad College for Degree and PG Courses (A).

G-Tri-BAL proposes a road map for the eradication of sickle cell Disease, as a part of National Sickle Cell Anemia Elimination Mission by 2047, in one of the two tribal districts of AP namely ASR District, as a model center. This is in continuation of the present pilot project on identification and prevalence of SCD in Hukumpeta Mandal, ASR District.

Objectives: This Road Map has been prepared with two objectives

1. To control the severity of the disease in the people identified with it through regular monitoring and provision of access to timely healthcare and thereby improve their quality of life.
2. To prevent the spread of the disease by creating awareness among the vulnerable population and the extensive counselling to discourage consanguine marriages which are major cause for the spread of the disease.

As a part of this, G-Tri-BAL proposes to establish five Regional SCD Eradication Centers at Mandal headquarters and Local Administrative Control Centers for SCD Eradication (LACCSE) at each PHC.

The Regional SCD Eradication Center arrange Capacity building program for employees of PHCs, Teachers, ANMs, ASHA workers, LACCSE and local community on a regular basis to create social awareness about the consequences of SCD and need for its elimination through counselling and medical education.

G-Tri-BAL in collaboration with Gayatri Vidya Parishad Hospital attached to Gayatri Vidya Parishad Institute of Health Care and Medical Technology (Medical college) will undertake SCD screening in two stages. In stage I, LACCES contacts DEO, DM&HO, ICDS, CDPO, PHCs and other District Officials to mobilize the school students, Anganwadi children, pregnant women and lactating women to the SCD screening camp at school premises and the persons with SCD or Sickle cell trait or Thalassemia Traits will be identified. In Stage II, screening for the parents and siblings of the persons identified with SCD or Traits will be taken up.

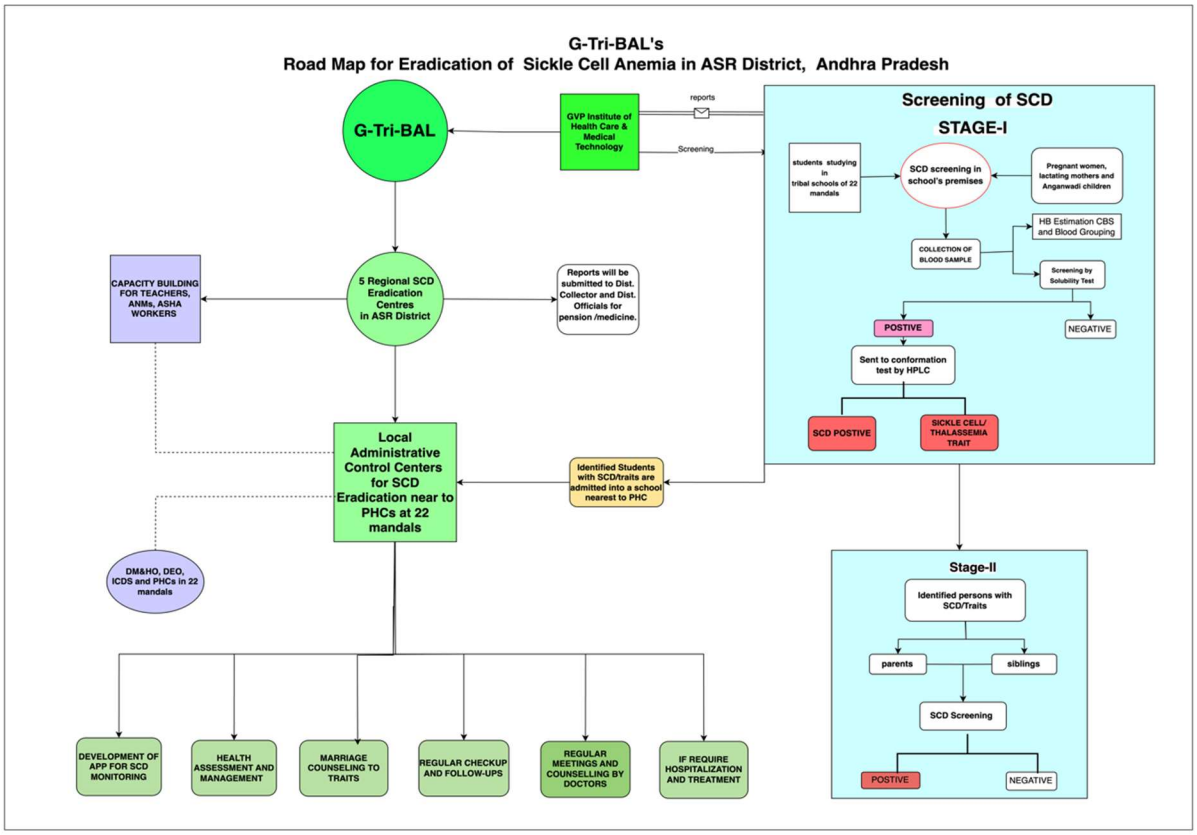
LACCSE works for bringing effective social and medical education, especially counselling the need to control the practice of consanguine marriages in the society, this is very essential to maintain a stable condition and also improve the quality of life of the effected persons. The persons identified with SCD or Traits, parents, village elders and social leaders are brought to a place nearest to LACCSE centers in each Mandal and offer counselling both group wise and one on one. The LACCSE Centers will monitor the health status of the patients. An android application

will be developed to distribute to the persons identified with SCD or Traits for assessing and monitoring the health condition.

Doctors from the GVP Hospital will monitor the health condition by regular meetings at Regional SCD Eradication Centers and LACCSE centers. In the case of persons who require treatment, they will be treated at local PHCs, District Hospital and if required at the GVP Hospital attached to the Medial college. This program will be continued for a minimum period of 5 years and will be extended depending on the financials to achieve the objective of eradication of SCD in ASR District, Andhra Pradesh at the earliest.

Key Words: ASR District, Sickle Cell Disease, Capacity building, consanguine marriages, LACCSE

Graphical Abstract:



Participant's Presentation: PP11

Birth weight of newborns with Normal, Sickle Cell Trait and Sickle Cell Disease genotypes in Kandhamal: a tribal dominated district of Odisha

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Birth weight of the newborn plays very significant role in assessing the future growth, development, and health status of the child. The normal birth weight of the newborn as per the World Health Organisation is 2.5 kg to 4 kg. The birth weight below 2.5 kg is termed as Low Birth weight. The frequency of low birth weight globally is about 15.5% and in India it is 26%. The abnormality in newborn weight is attributed to several factors such as maternal age, multiple births, pregnancy-induced hypertension, obstetric complications, chronic medical disorders, maternal health, and nutritional status etc. Besides the educational status of the spouse, lack of proper antenatal care (ANC), history of obstetric problems, maternal weight during pregnancy and gravidity are significantly correlated with low birth weight. The genetic disorder status of the babies may also be responsible for the abnormal birth weight.

Sickle cell disease is widespread among the population of the Odisha state including the scheduled tribes. The Kandhamal district is located centrally and dominated by the tribal population. Earlier studies have reported on prevalence of Sickle Cell disorders among the population of the district.

The birth weight of 7823 newborn babies of different geographical localities of the Kandhamal district (5 PHCs, 5 CHCs and one SDH) was taken randomly. Based on the HPLC haemoglobin variant analysis the subjects were identified as Normal (HbAA, n=6720, 3449 male + 3271 Female), Sickle Cell Trait (HbAS, n=980, 496 male + 484 Female) and Sickle Cell Disease (HbSS, n=123, 58 Male + 65 Female) neonates. The mean birth weight of newborn babies was found to be 2.7+0.4 kg (1.4-4.3 kg), 2.7+0.4 kg (1.3-4.0 kg) and 2.8+0.4 kg (1.8-3.9 kg) in Normal, Sickle Cell Trait and Sickle Cell Disease genotype respectively. There is no significant difference between the mean birth weights among the studied groups. There was more percentage of low-birth-weight babies (< 2.5 Kg) in Sickle Cell Trait (30.1%) group than Normal (27.1%), and Sickle Cell Disease (22.8%) genotype groups.

Key Words: Birth weight, Newborn babies, Sickle Cell Disorders, Odisha

Participant's Presentation: PP12

Differential Expression of Metabolites in Sickle Haemoglobin Containing Red Blood Cells

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Blood circulation involving red blood cells (RBCs) is a fundamental process of human physiology and glucose is the sole energy provider for the RBCs. A sizable population in India and Odisha, including the indigenous tribes are acutely affected by the Sickle Cell Disease (SCD) – an autosomal recessive disorder caused by inherited genetic process.

In patients affected with SCD, the life of RBC is reduced from the usual 120 days to around 20-30 days and studies including ours have already indicated abnormality in red blood cell glucoses metabolism. Thus, glucose levels in RBCs can be attributed to having direct effect on the energy metabolism of RBCs, which in turn may be responsible for reduction of the lifespan of red cells in sickle disease cases. This scientific study was undertaken to study and corelate the observable changes in the glucose level and other associated metabolites of Sickle RBCs in comparison to normal red blood cells.

Sickle RBCs from patients of Odisha were subjected to assay for glucose consumption and RBC hemolysate were subjected to mass spectrometry. The sickle RBCs hemolysate (SS samples) were analysed against the normal RBCs hemolysate (AA samples) using PCA (Principal Component Analysis) Plot. The functional significance of the individual metabolites was derived using KEGG pathway database.

The study revealed substantially higher consumption of glucose in the SS RBCs as compared to AA RBCs and the mass spectrometer data revealed that in SS RBCs 185 raw metabolites were upregulated & 1095 raw metabolites were down regulated, in comparison to AA RBCs. This indicative study which throws light on the differentiating metabolites in each case may probably holds the potential for identifying and characterized some fundamental key metabolites, the regulation of which may have sustained solution for addressing the life-span and overall health of RBCs and thus could provide a better life for the patients of Sickle Cell Disease.

Keywords: Glucose metabolism, Sickle Cell Disease, Red Blood Cells, Odisha.

Participant's Presentation: PP13

Sickle Cell Disease Management and Eradication- Empowering people Through Mobile App Innovation

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Sickle Cell Disease (SCD), a hereditary blood disorder characterized by abnormal hemoglobin resulting in rigid, crescent-shaped red blood cells, poses substantial challenges in management and eradication. Innovative solutions are imperative, and mobile applications (apps) have emerged as promising tools for enhancing SCD management and awareness. This paper presents a comprehensive overview of the pivotal role of mobile apps in both aspects.

Dedicated SCD management apps address crucial facets of the disease. These apps offer patients, caregivers, and healthcare providers accessible platforms to monitor symptoms, Educate people and parents, track medication adherence and schedule appointments. By providing personalized health plans and reminders, these apps empower patients and persons having traits to proactively engage in their disease management. Additionally, they facilitate efficient information exchange between patients and healthcare professionals, allowing for timely interventions and improved treatment outcomes.

Beyond individual care, mobile apps play a crucial role in raising awareness and educating the broader community about SCD. Interactive content, infographics, and educational modules within these apps disseminate accurate disease information, dispel misconceptions, and encourage early screening and diagnosis. These apps also serve as connective platforms for patients, families, and support groups, alleviating the isolation often associated with chronic conditions like SCD.

The collection of data through mobile apps supports efforts to eradicate SCD. Aggregating anonymized patient data equips researchers with insights into disease patterns, treatment efficacy, and emerging trends. This data informs the development of targeted interventions, shapes public health policies, and advances scientific knowledge in hematology.

In conclusion, mobile apps have evolved into versatile tools for SCD management and eradication. Their capacity to empower patients, enhance healthcare communication, drive awareness, and facilitate data-driven research renders them indispensable assets in combatting this challenging genetic disorder. As technology progresses, the potential for these apps to further revolutionize SCD care and contribute significantly to its ultimate eradication remains promising. Enhancing Disease Management:

The primary objective is to utilize mobile apps to provide a comprehensive and accessible platform for patients, persons having traits, caregivers, and healthcare providers to manage SCD more effectively. This includes monitoring symptoms, tracking medication adherence, and scheduling appointments, ultimately empowering patients to take proactive steps in their disease management.

Objectives:

1. Improving Communication and Timely Interventions:
The paper aims to highlight how mobile apps can facilitate improved communication between patients and healthcare professionals. This communication channel enables timely interventions, adjustments to treatment plans and overall better patient-provider interactions.

2. Disseminating Accurate Information and Raising Awareness:
The objective is to use mobile apps as tools for disseminating accurate information about SCD to a broader audience. This includes interactive content, infographics, and educational modules to debunk misconceptions, promote early screening and diagnosis, and raise awareness within the community.

3. Fostering Community and Support:
The paper emphasizes the importance of using mobile apps to create a sense of community among SCD patients, families, and support groups. This community-building objective aims to reduce the isolation often experienced by individuals with chronic conditions and facilitate emotional support and information sharing.

4. Contributing to Research and Data Collection:
One of the objectives is to showcase how mobile apps can contribute to research efforts by aggregating anonymized patient data. This data-driven approach aims to provide insights into disease patterns, treatment effectiveness, and emerging trends, ultimately guiding the development of targeted interventions and informing public health policies.

5. Potential for Disease Eradication:
The paper explores the potential of mobile apps to not only manage SCD but also contribute to efforts aimed at reducing its prevalence and eventual eradication. By leveraging technology and data, the objective is to demonstrate how these apps can play a significant role in advancing the fight against SCD.

Keywords: Sickle cell disease (SCD), Disease management, Eradication Innovative solutions, Mobile applications (apps), Personalized health plans, Technology evolution.

Participant's Presentation: PP14

Empowering Tribal Youths: ADEETECH® Single Blood Drop Technology Sickle Cell Hemoglobin Electrophoresis for Village-Level Confirmatory Testing

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Abstract:

This genetic disorder has existed in the Indian subcontinent for over 5,000 years. To gradually reduce the sickle cell gene frequency over the next 25 years, we must intervene in marriages between carriers. However, based on data from the Vidarbha region (1987 and 2005), where the carrier prevalence increased by approximately 3.43% in 18 years (one generation), it would take around two centuries to reduce the gene frequency from 40% to 0%. This estimation assumes strict avoidance of carrier-carrier marriages and perfect genetic counselling, without genetic engineering methods like gene therapy or CRISPR technology, which are costly and impractical for India's large SCD-affected population. Given the limited resources, the most viable option is a nationwide program focusing on genetic counselling for carrier couples and pre-marriage counselling for unmarried individuals, ideally with village-based testing centres for confirmatory diagnoses.. There is an urgent need of ADEETECH® Decentralization model of *Comprehensive Sickle Cell Control Program of the SCD affected community, by the SCD affected community and for SCD affected community*.

Conventional existing testing methods of Hb electrophoresis often involve intricate procedures and substantial blood quantities of minimum 2 ml intravenous sample and maximum loading/application of 10 hemolysate on one 14 cm long cellulose acetate strip, limiting their feasibility in resource-constrained settings. In this context, we have pioneered a simplified method of confirmatory testing of sickle cell anemia through the utilization of a modified single blood drop technology (Lingojwar DP, 2008).Both these limitations are satisfactorily solved using our method. Also our product and services will be used by trained technicians of ADEETECH® or trained by ADEETECH® which provides further uniformity of the final reporting. One of the key differentiators of this method lies in its utilization of only a single blood drop for testing, around 30 to 40 ul finger prick peripheral blood sampling as compared to 2 ml whole blood by established earlier Hb electrophoresis method, which significantly reducing the sample volume required. ADEETECH's method streamlines the entire procedure from sample collection to testing at school level and testing at site, obviating the need. Man Machine Technology and Reagents, four pillars of successful program, which is discussed in the presentation.

Keywords: sickle cell anemia, confirmatory testing, single blood drop technology, cellulose acetate membrane, resource-constrained settings.

Participant's Presentation: PP15

Green Synthesized Copper Nano-biosensors for Sickle Cell Disease

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Sickel cell anaemia is an autosomal recessive disorder with a point mutation in which the glutamic acid at the 6th position in the β-chain of haemoglobin is replaced with valine, giving rise to sickle-shaped RBCs. The defective shape and rigidity of RBCs result in blockage of blood vessels and ultimately death. Though people carrying sickle cells have acquired resistance against malaria and are living everyday life, the target sufferers are people with homozygous traits for sickle cell anaemia. The disease has been seen to affect people who have any ancestry from Africa, the Middle East, and India. 1,430,412,968 is the estimated population of India according to the UN. The Indian government had aimed to screen around 1 crore population by 2023 for SCD. However, the success rate remains only 1%, which hurts the ambitious goals of the government. The goal is to eradicate SCD from India by 2047 completely. Currently, Hydroxyurea, the first discovered treatment for SCD has been proven to be effective in relieving pain but people are still hoping for permanent, effective, and economical diagnosis and treatment strategies. Thus, based on some of the studies we aim to develop nano biosensors for rapid, cheap, and effective diagnosis of SCD using green synthesised copper nanoparticles.

Keywords: Green synthesis, copper nanoparticles, Biosensor, Sickel Cell Disease

Participant's Presentation: PP16

Yoga and sickle cell disease - A case study

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Sickle cell disease (SCD) is a hereditary disorder that arises from a specific point mutation resulting in the substitution of amino acid glutamine with valine at the sixth position in the β-globin chain of the haemoglobin molecule. Worlds 50% of Sickle cell population lives in India, with prevalence ranging from 1 to 40% with higher prevalence observed in lower socio-economic categories. Various studies looked at difference in distribution and found that it is around 73% in tribal people compared to other lower socio-economic categories. In India it is highly prevalent in central Indian tribal belt. Till today there is no cure and limited options of therapies for SCD. Stem cell therapy is one such treatment available, but it is unaffordable for most of the affected population. This paper presents a case study of a child from remote tribal area from central India diagnosed with SCD experiencing frequent episodes of splenic sequestration crisis resulting in repeated hospitalization. The child was one of the participants of a six-month yoga-based lifestyle intervention Pilot research program viz. " Integrated Sickle Cell Anaemia Research Program", aimed at managing SCD. After the passage of one month of yoga therapy, the participant attended a medical follow-up appointment during which a significant positive change was observed in haemotology and basic diagnostic parameters leading to stopping of all medications by the paediatric haematologist. Further, the participant did not require hospitalization throughout the duration of one year, encompassing a six-month yoga-based lifestyle intervention and six month follow up period. This is the first study assessing the effect of Yoga on SCD on molecular, biochemical, clinical parameters and quality of life.

Keywords: yoga therapy, sickle cell disease, severe anemia, sequestration crisis

Participant's Presentation: PP17

Molecular insights into the mechanism underlying fetal hemoglobin's inhibitory effect on sickle hemoglobin polymerization

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Sickle cell disease (SCD) is a genetic disorder caused by the polymerization of sickle hemoglobin (HbS) in its deoxy state that eventually precipitates inside red blood cells (RBCs) resulting in the sickling of RBCs. The polymerization of HbS is known to be inhibited by fetal hemoglobin (HbF) via an increase in molecular crowding. However, the molecular details of its role in inhibiting polymerization have not been thoroughly explored. In this study, we have analyzed a sample of a 2-year child, using high performance liquid chromatography (HPLC), comprising of 40.2% HbF and 51.1% HbS, whose father having β-thalassemia trait and the mother having sickle cell trait. The presence of HbS and HbF is further verified by electrospray ionization mass spectrometer (ESI-MS) platform. A meagre 2.2% sickling of the RBCs in a deoxy state was observed along with a 1651 second delay time for the polymerization of the HbS (*ex vivo*). The analysis of hemoglobin using a native mass spectrometry platform revealed the existence of $\alpha_2{}^G\gamma\beta^S$, a hybrid tetramer of HbF and HbS. Additionally, $\alpha_2{}^G\gamma\beta^S$ and $\alpha_2\beta^S{}_2$ were found to be almost equally populated (33%) among all observed tetrameric hemoglobin molecules. Furthermore, the difference in alignment score and Solvent Accessible Surface Area (SASA) was observed in the nearby region of the hydrophobic groove between deoxy HbF and deoxy HbS. Moreover, a difference in SASA of deoxy HbF and HbS was also observed in the residues involved in the axial and lateral contacts that help to stabilize the HbS polymers. These variations in the structure of HbF from HbS might play a key role in inhibiting the polymerization of HbS.

Keywords: Sickle cell disease, sickle hemoglobin, fetal hemoglobin, polymerization, Solvent Accessible Surface Area

Declaration of contribution:

N.Y. performed the experiment and analysed the data. A.K.M designed the study and helped in data analysis and interpretation.

Participant's Presentation: PP18

Comparison of Sickle Cell Disease gene frequency amongst tribal nontribal communities in malaria endemic Vs non malaria region in Eastern Maharashtra and Marathwada region

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Abstract

This study is based on current lab experiments from one location, with no or less malaria prevalence and its comparison with earlier two locations with malaria endemic background. This work is based on detailed analysis of the sickle cell gene frequency in both malarial and non-malarial regions of Maharashtra, India, specifically focusing on Vidarbha and Marathwada. The study investigates the prevalence of the sickle cell gene in different populations, compares the findings with previous studies, and explores the implications of the results. The sickle cell gene frequency in non-malarial regions of Marathwada was found to be extremely low, measuring 0.005. This finding aligns with the 1967 study by Negi et al., which was published in the first edition of the Genetic Atlas of India. It also corresponds to a subsequent study conducted in 1987 by Bankar and Kate from B J Medical College, Pune, India. These earlier studies provide the foundational groundwork for the present investigation. To delve deeper into the relationship between sickle cell gene frequency and malaria, the study examined two locations within Marathwada. The first location, Amdi village, adhered to the standard sample size of N=115, consistent with the previous reports from 1967 and 1987. Within this population, the sickle cell gene frequency was determined to be 0.08 for the tribal population and 0.12 for the non-tribal population. The second location, Visapur city in Chandrapur district of Vidarbha region, featured a larger sample size of N=628. In this expanded population, the sickle cell gene frequency measured 0.03 for the tribal population and 0.09 for the non-tribal population. The results indicate a comparatively lower sickle cell gene frequency in the tribal population compared to the non-tribal population across both the small and large sample size populations. This observation suggests the presence of potential differences in genetic susceptibility and evolutionary factors between these groups.

Interestingly, the sickle cell trait frequency was found to be lower in historically non-malarial regions such as Marathwada when compared to malarial endemic regions in Vidarbha. This finding implies that the presence of malaria, accompanied by selective pressures, likely influenced the frequency of the sickle cell gene. However, in the studied Marathwada region, which historically lacked significant malaria prevalence, no constant selective pressure was observed. Moreover, the identification of a single positive case in the Marathwada region, originating from Vidarbha, highlights the potential migration and interplay of populations within Maharashtra. In conclusion, this study provides a comprehensive analysis of the sickle cell gene frequency in Marathwada, Maharashtra, India, with a comparison to previous reports and an exploration of the impact of malaria. The findings indicate lower sickle cell gene frequencies in the tribal population compared to the non-tribal population and lower frequencies in historically non-malarial regions compared to malarial endemic regions. These findings enhance our understanding of genetic diversity and evolutionary forces within the studied region and emphasize the significance of historical and geographical factors in population studies.

Kew words: Malaria, SCD, Gene frequency, Selective pressure, Malaria Sickle Cell Hypothesis

Participant's Presentation: PP19

Use of medicinal plants to cure Sickle cell anemia disease: a review

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Sickle cell disease (SCD) presents a significant public health crisis in Sub-Saharan Africa. With over 30,000 annual births attributed to this hereditary disorder, it ranks as one of the most prevalent genetic conditions worldwide. Notably, SCD primarily affects individuals of African descent. Despite its impact, the output of scientific research related to SCD remains relatively limited and poorly understood.

Early in the 1910s, various treatments such as analgesics, antipyretics, intravenous fluids (hydrants), anti-dehydrants, oral antibiotics (penicillin), and the anticancer drug hydroxyurea (utilized to stimulate fetal haemoglobin production) were available to manage the painful crises associated with SCD. Among these treatments, hydroxyurea stands out as the first medicine proven to be both safe and effective in preventing painful sickle cell anaemia crises in adults. Nevertheless, the global treatment of sickle cell anaemia remains a significant challenge.

A potential avenue for addressing this challenge lies in the exploration of medicinal plants. Certain species of plants from various families contain active bio-components and chemical compounds that can be extracted for use in treating various diseases, including sickle cell anaemia. Traditional medicinal practices have brought the useful parts of these plants into the spotlight, with scientific studies shedding light on their rationale and effectiveness.

This article's primary objective is to focus on how traditional therapists have employed medicinal plants to treat patients with SCD and the underlying principles guiding this practice. By delving into the knowledge and wisdom passed down through generations, we can gain valuable insights into potential alternative treatments for sickle cell disease.

Key words: Sickle cell anaemia, medicinal plants, bioactive compounds

Participant's Presentation: PP20

DNA sequencing and online RFLP, a tool for restriction site analysis in SCD *Hinc Ⅱ* as one of the haplotype site

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Abstract

Sickle cell disease (SCD) is an inherited genetic blood disorder caused by a single nucleotide polymorphism (SNP) of (Adenine) A to Thymine (T) leading mutation from glutamic acid to valine at 6^{th} position in β-globin chain for both the alleles of hemoglobin protein, homozygous SCD. After 6 months of birth, fetal haemoglobin expression gradually decreases with increase in adult haemoglobin (HbA) expression, which is replaced by mutant sickle haemoglobin (HbS) in case of SCD. Its origin is dated back to nearly 5000 to 7000 years with reference to haplotyping. The recent genomics studies attract scientists due to genetic modifiers mutations present in β-globin cluster region span on 73308 bp (Ac.No. GenBank: U01317.1). Sickle cell haplotypes are the DNA markers present on the chromosome 11. Five such haplotypes associated with SCD are as follows; Bantu, Senegal, Benin, Cameroon and Indo-Arab with each differing in fetal haemoglobin levels and SCD pathogenesis. Established method for SCD haplotyping is PCR RFLP, in which "presence or absence of the restriction site determines the haplotype". Although this method is largely well established we need to rethink in the background of availability of Sanger's DNA sequencing technology and establishing Indian database of this sequences associated with Indo Arab haplotype and any possible mutations other that specific mutation which is already well established, to map the severity of the illness, and possible correlation with fetal haemoglobin present in the homozygous Indian SCD patient.

In this research, we focused on one of the upstream region's restriction sites, i.e. *HincII* site for haplotype analysis in the SCD DNA sample in the epsilon gene (HBE). We originally contributed for DNA sequencing data analysis of the SCD haplotyping PCR for *HincII* region using Sanger's DNA sequencing of the PCR product followed by sequence data analysis using NEB Cutter, we have given term to this method as "online RFLP" for the first time. The accession number for DNA sequence including *HincII* polymorphic site is (NCBI Database: OQ995303). There is no other mutation upstream or downstream of this SNP, other than the earlier reported Indo Arab mutation for *HincII* site. Reference SNP i.e., rs3834466. This methodology overcomes the limitations of the analyzing mutations in the restriction and recognition site by performing age old PCR followed by enzyme base RFLP method. Large population analysis would contribute in identifying the SNPs and indel site in the β-globin chain and its clinical significance. Other most significant outcome is analyzing mutation nearby this restriction site to keep watch on new variants of Indian Arab haplotype, since compared to reported genomics data from western world and India, there is a huge gap of such genomics studies. And due to presence of half of the global SCD population in India and there is a need to establish India specific genomics data of haplotype for pathogenesis studies by new and innovative ways of next generation molecular biology tools and technology.

Keywords: Sickle cell disease, haplotype, genetic modifiers, RFLP, β-globin gene

Participant's Presentation: PP21

ADEETECH® SickleThal5050: Point of care two-in-one kit for thalassemia and sickle cell anemia simultaneous testing in one sample

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Abstract:
This initiative focuses on enhancing the efficiency and cost-effectiveness of village-level or school screenings for hereditary blood disorders like sickle cell anemia and thalassemia. It introduces innovative modifications to existing screening tests: the Solubility Test for Sickle Cell Anemia (SCST) and NESTROFT for Thalassemia. These tests have traditionally relied on commercial kits with a minimum of 50 tests per pack, creating issues such as the need for a reducing agent and limited usability timeframe. The innovation involves converting these tests into single-tube, ready-to-use methods, eliminating wastage and streamlining the process for peripheral pathology laboratories. This advancement holds promise for improving healthcare efforts on a global scale.

In our novel Solubility50 and NESTROFT50 kits, we offer ready-to-use individual tests in packs of 50. This innovative packaging allows for extended storage in refrigeration, circumventing the time-sensitive nature of prepared solutions. The single-tube format not only zero reagent wastage but also enhances convenience for laboratory technicians and healthcare providers, since there is no measurement involve and only by adding single blood drop by finder prick method and after mixing observe the results, offering greater flexibility in testing single samples. Moreover, the elimination of bulk kit preparation ensures that no resources are squandered and that the tests remain efficient for extended periods. In the Solubility50 kit for sickle cell anemia screening, the challenge of the reducing agent is ingeniously addressed. By providing a single-tube solution, we eliminate the need for large-scale reducing agent preparation, promoting resource conservation without compromising accuracy. Similarly, the NESTROFT50 kit for thalassemia offers a practical solution for peripheral labs by providing a single-test-ready package, reducing logistical complexities, and enhancing usability.

This two in one kit Solubility50 and NESTORFT50 can be used for decision making next level test i.e. HPLC or Hb Electrophoresis. NESTROFT50 positive sample can be directly moved to HPLC and Solubility50 test can be tested either by Hb electrophoresis or HPLC depending on resources available. Hence its use in combination, i.e. same samples tested by both tests, can yield better decision-making options for confirmatory testing of sickle cell disease Vs thalassemia. Additionally, if the tested person is positive for sickle-thal, then, both the tests show positive results, in that case sample should be tested for HPLC for confirmatory sickle thal test with A2 and HbS band retention time. This innovation is not only technologically relevant but also socially impactful. By democratizing access to accurate screening tests, particularly in regions with limited healthcare infrastructure, our approach has the potential to accelerate early detection of these blood disorders. Early identification plays a pivotal role in optimizing treatment strategies and minimizing the burden on affected individuals and their families.
Our SickleThal5050 i.e. individually Solubility50 tests for sickle cell anemia screening and NESTROFT50 tests for thalassemia screening simplify sickle cell anemia and thalassemia primary screening program, offering efficient single-tube kits for peripheral labs, reducing waste, and improving global health access to diagnostics for developing countries.

Keywords: SickleThal, sickle cell anemia, thalassemia, Solubility Test, NESTROFT

Participant's Presentation: PP22

Ethnomedicinal use of Guduchi (Tinospora Cordifolia) Ghanvati and Kiratatikta (Swertia chirayata) Ghanvati in the management of Sickle Cell Anaemia

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Background: Sickle cell Anaemia (SCA) is one of the most common worldwide distributed mutant genetic disorders and is very common among many tribal and backward populations in central India and in western Odisha tribal areas with the prevalence varying from 8-40% and 10-17% respectively. SCA has been classified as a homozygous (HbSS) and heterozygous (HbAS) state. In Classical Ayurveda texts, word-to-word correlation with SCA is not found but clinical features of SCA correspond with Sannipataja sahaja pandu roga as described in Ayurveda texts.

Material and Methods: After CTRI registration 60 patients were randomly selected from hospital of Govt. Ayurvedic College, Bilaspur and Balangir. After assessing of subjective and objective parameters of Sickle cell Anaemia, patients were randomly selected in three groups (20 patients each). In Group – A, Guduchi Ghanvati was administrated, in Group - B Kiratatikta Ghanvati was administrated with the dose of 500 mg twice a day respectively, In Group - C both trial drugs were administrated with the same dose. The trial duration was 60 days. The total effect of the therapy was inferred in 15-day intervals and evaluated statistically by the student's pair t-test.

Observation and Result: The overall improvement assessed in both subjective and objective parameters in Group A was 42.45%, Group B was 44.92% and Group C was 62.23%. The statistical evaluation revealed that Group A and Group B trial medications were statistically significant ($p<0.05$). while Group C was Highly significant ($p<0.001$). No adverse effect was observed during and after the study period.

Conclusion: From this study, it can be concluded that Guduchi Ghanvati and Kiratatikta Ghanvati both are effective in SCA, but probably more improvement was revealed in their combined use in both parameters.

Key words: Sickle Cell Anaemia, Guduchi Ghanvati, Kiratatikta Ghanvati, Sannipataja sahaja pandu roga.
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Participant's Presentation: PP23

Initial Perceptions of the Sickle card system recently launched by the Indian government

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The Indian government has recently launched the 'National Sickle Cell Anaemia Elimination Mission (**NSCAEM 2047**)' with the aim to control Sickle cell disease, particularly among tribal populations. As a part of this mission, '**Sickle Cards'** with instructions not to marry a partner with sickle cell anemia were also distributed to the patients/carriers. The government's approach of issuing 'carrier cards' sends the wrong message that two carriers should not enter into a marriage as even if two carriers do marry, there is only a 25 percent chance of having an affected child. Denying the right to marriage based solely on carrier status creates a significant emotional burden & stigma for the entire community.

The tribal communities often view sickle cell status as a source of shame and social ostracism. The issuance of carrier cards further alienates the patients and some of them may choose to hide their cards or withhold information about their genetic condition. This can lead to difficulties in identifying carriers within the community and providing them with the necessary support and guidance. We have conducted an interview-based qualitative study that will document the recipient's perspective and opinions about the Sickle card system. We have interviewed consented SCD patients/carriers/community leaders/ASHA and health workers/medical officers to understand their expectations and fears attached to the Sickle card system. These initial perceptions and opinions across the various stakeholders would be reviewed and presented in our poster.

The issues surrounding the Sickle card system highlight the need for a more comprehensive and compassionate approach to genetic counselling and reproductive decision-making. Education and awareness campaigns are essential to dispel the myths and misconceptions surrounding sickle cell anemia. By disseminating accurate information, communities can be empowered to overcome the stigma associated with the disease and make informed decisions regarding marriage and reproductive choices, reducing the risk of passing on the condition to their children.

Participant's Presentation: PP24

DNA sequencing and online RFLP, a tool for restriction site analysis in SCD *XmnI* as one of the haplotype site

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Abstract:

Sickle cell disease (SCD) is an inherited genetic blood disorder caused by a single nucleotide polymorphism (SNP) of (Adenine) A to Thymine (T) leading mutation from glutamic acid to valine at 6th position in β-globin chain for both the alleles of hemoglobin protein, homozygous SCD. After 6 months of birth, fetal hemoglobin expression gradually decreases with an increase in adult hemoglobin (HbA) expression, which is replaced by mutant sickle hemoglobin (HbS) in case of SCD. Its origin is dated back to nearly 5000 to 7000 years with reference to haplotyping. The recent genomics studies attract scientists due to genetic modifiers mutations present in β-globin cluster region span on 73308 bp (Ac. No. GenBank: U01317.1). Sickle cell haplotypes are the DNA markers present on chromosome 11. Five such haplotypes associated with SCD are as follows; Bantu, Senegal, Benin, Cameroon and Indo-Arab with each differing in fetal hemoglobin levels and SCD pathogenesis. The established method for SCD haplotyping is PCR RFLP, in which "presence or absence of the restriction site determines the haplotype". Although this method is largely well established, we need to rethink in the background of availability of Sanger's DNA sequencing technology and establishing Indian database of this sequences associated with Indo Arab haplotype and any possible mutations other that specific mutation which is already well established, to map the severity of the illness, and possible correlation with fetal hemoglobin present in the homozygous Indian SCD patient.

In this research, we focused on one of the upstream region's restriction sites, i.e., *XmnI* site for haplotype analysis in the SCD DNA sample in the G-gamma gene. We originally contributed for DNA sequencing data analysis of the SCD haplotyping PCR for *XmnI* region using Sanger's DNA sequencing of the PCR product followed by sequence data analysis using NEB Cutter, we have given term to this method as "online RFLP" for the first time. There is no other mutation upstream or downstream of this SNP, other than the earlier reported Indo Arab mutation for *XmnI γG158* site. Reference SNP i.e., rs7842144. This methodology overcomes the limitations of the analyzing mutations in the restriction and recognition site by performing age old PCR followed by enzyme base RFLP method. Large population analysis would contribute in identifying the SNPs and indel site in the β-globin chain and its clinical significance. Other most significant outcome is analyzing mutation nearby this restriction site to keep watch on new variants of Indian Arab haplotype, since compared to reported genomics data from western world and India, there is a huge gap of such genomics studies. And due to presence of half of the global SCD population in India and there is a need to establish India specific genomics data of haplotype for pathogenesis studies by new and innovative ways of next generation molecular biology tools and technology.

Keywords: Sickle cell disease, haplotype, genetic modifiers, *XmnI* RFLP, β-globin gene

Participant's Presentation: PP25

Serum Bilirubin level in relation to foetal, total haemoglobin and reticulocyte count in Sickle cell disease patients of Odisha

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Sickle cell disorders are very common among the population of Odisha. About 12.5% of western Odisha population are reported to have sickle cell gene. Such cases were also reported from coastal eastern parts of the state recently. A good deal of reports regarding the occurrence, clinical and haematological aspects of sickle cell patients of the state have been available. But the relationship between serum Bilirubin levels with different haematological parameters of SCD patients of this region is largely unknown. As haemolysis and jaundice are the hall marks of the SCD patients of other parts of the globe, we have studied the level of serum bilirubin and its relationship with some haematological parameters in the SCD patients of Odisha state.

Data were collected randomly from 236 sickle patients (146 Males + 90 Females) of age groups (2-56 yrs) from all over Odisha after taking consent under the guidance of the health authorities. The data of some patients were obtained through verbal discussion and sharing of the primary investigations through electronic social media. The mean value of total serum bilirubin of the studied Sickle cell disease cases was 3.0mg/dl with a range of 0.6-27mg/dl and the mean direct bilirubin was 1.3mg/dl (0.3-17.4mg/dl). About eighty four percent (84%) of sickle cell disease cases showed a higher level of serum bilirubin i.e. > 1mg /dl. Only sixteen percent (16%) had normal serum bilirubin (<1mg/dl). Majority (32%) of SCD cases were in the range of 1-2mg/dl and about twenty seven (27%) percent cases were in the range of 2-3mg/dl serum bilirubin. A weak negative correlation (r = -0.04) was observed between total serum bilirubin value and total haemoglobin level. Similarly a negative correlation (r = -0.14) was also observed between total serum bilirubin and foetal haemoglobin level. However a positive (r = 0.18) correlation was found between serum Bilirubin value and reticulocyte count.

Sickle cell disease is haemolytic in nature. Due to the presence of sickle haemoglobin inside the red blood cells of the patients the red cell undergoes repeated sickle and de-sickle phases during oxygenated and deoxygenated stages and becomes abnormal. Such abnormal rigid sickle cells are rapidly destroyed and eliminated from the circulation. Haemolysis of RBCs is directly proportional to the elevated level of bilirubin in the blood, which consequently could express as haemolytic jaundice. The higher serum bilirubin in the studied sickle cell patients may be due to the hyper haemolysis of the sickle red blood cells. The lower mean total haemoglobin (8.5g/dl) and higher mean reticulocyte count (11.2%) in the studied cases also support the mechanism. The higher serum bilirubin was observed in patients having low foetal haemoglobin. The occurrence of haemolysis among SCD cases was not observed in all the patients as about 16% of SCD patients had normal serum bilirubin (1mg/dl). Similarly, more than 7% of SCD cases had normal total haemoglobin (11g/dl) also. Looking at the vast geographical and clinical diversity among the patients, such type of study with large number of patients from different parts of the country is highly desirable to explore the possible mechanism behind this.

Key words: Sickle cell disease, Serum Bilirubin, Foetal haemoglobin, Reticulocyte count.

Participant's Presentation: PP26

Young age parents carry forward HbS alleles more frequently than older age parent for their first progeny: An evidence based retrospective study from malaria endemic tribal Central India

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Abstract:

Introduction: Early age marriages are very common in the developing countries including India, specifically in tribal population. Malaria and sickle cell sickle cell disease (SCD) are most common in tribal populations of India, with varying prevalence amongst different ethnic groups. SCD affects mostly the socioeconomically deprived communities living in the three clusters of 10 neighboring states in India. Most of this endogamous population in India, including scheduled caste, scheduled tribe, and similar communities are confined to locations where SCD coexists with endemic malaria. The effect of child birth order in these communities on increasing SCD prevalence is not well understood. This the first of its kind retrospective observational in India based on assessment of order of child birth outcome in the family with sickle cell carrier status.
Methods: With the specific aim of analyzing gene frequency difference in first two births, 17 geographic locations were selected from Ballarpur tehsil, Chandrapur district, Central India, an area known for endemic malaria. From the initial confirmed diagnosis data (N=3408, HbAA 2829, Hb AS 526 and Hb SCD 53), families were selected where one parent was sickle cell trait and there was no record of miscarriages or abortions. Only the first and second-born children were analyzed. Pedigree analyses and gene frequency studies were performed.
Results: Fifty–one (51) families were selected, 24 with heterozygote father and 27 with heterozygote mother. Children had their hemoglobin electrophoresis performed after the age of 1 (average age 9.1, range 1.6 – 23 yrs). Gene frequency of HbS was 0.39 in the first pregnancy (40 children with sickle cell trait and 11 with AA, $p=4.9 \times 10^{-5}$) to 0.31 in the second birth (32 with AS and 19 with AA, p=ns). The age of the father and mother who gave birth to the AS child was nonsignificant younger than the age of the parents who gave birth to the AA child, whether it was the first or second birth. When the childbirths were analyzed according to sickle status of the parent, the first children born were more likely to be AS only in the case of mothers/fathers who were younger than average.
Conclusion: This retrospective evidenced based family studies observed more selection of HbS gene at first child birth as compared to second child birth, correlated with early reproductive age. Further research is needed in this area to explore with large dataset from SC and ST community.

Key words: Early marriages, SCD, Gene Frequency, Sickle Cell Anemia, Reproductive age

Participant's Presentation: PP27

Predicting the presence of Sickle Cell Disease, Sickle Cell Trait, and Thalassemia from CBC Histogram using Machine Learning Models

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Introduction: This study aimed to explore the potential of machine learning models in predicting the presence of sickle cell disease, sickle cell trait, and thalassemia based on complete blood count (CBC) histograms. These haematological disorders pose significant health challenges, and early and accurate diagnosis is crucial for effective management. This study leverages the power of machine learning to enhance diagnostic accuracy and facilitate timely interventions.
Methods: A dataset comprising CBC histograms from individuals with sickle cell disease, sickle cell trait, thalassemia, and those with normal profiles was collected. Machine learning models, including decision trees, random forests, support vector machines, and neural networks, were employed to develop predictive algorithms. The dataset was split into training and testing sets for model development and evaluation. Model performance was assessed using metrics such as accuracy, sensitivity, specificity, and area under the receiver operating characteristic curve (AUC-ROC).
Results: The machine learning models demonstrated promising predictive capabilities for distinguishing among sickle cell disease, sickle cell trait, thalassemia, and normal haematological profiles. The models exhibited reasonably good values of accuracy of 54%, sensitivity is 52%, specificity of 53.3%, Precision of 54.7% and AUC-ROC of 0.545, indicating their ability to discriminate between different conditions based on CBC histograms. Notably, certain models achieved exceptional performance, highlighting their potential clinical utility.
Discussion: The study findings underscore the potential of machine learning models in leveraging CBC histogram data to predict the presence of haematological disorders. These models offer a non-invasive and efficient approach to early diagnosis and screening, enabling timely interventions and improved patient outcomes. The predictive accuracy of the models suggests their potential integration into clinical practice to aid healthcare professionals in making informed diagnostic decisions.
Conclusion: Machine learning models utilizing CBC histograms present a promising avenue for accurate prediction of sickle cell disease, sickle cell trait, thalassemia, and normal profiles. These models offer a valuable tool for enhancing diagnostic capabilities and streamlining the diagnostic process. Incorporating machine learning into clinical practice holds the potential to revolutionize haematological disorder diagnosis, contributing to more effective patient care and management. Further research and validation are essential to establish the clinical applicability of these models in real-world settings.

Key Words: Sickle cell, Disease, Trait, Anaemia, Machine learning

Participant's Presentation: PP28

Development of Artificial Intelligence (AI) tools for the diagnosis and treatment of SCD and rare genetic disorders

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This study investigated the efficacy of artificial intelligence (AI) in SCD and rare genetic disorders. Numerous medical fields are increasingly relying on artificial intelligence (AI) for clinical practice and research. AI also plays a vital tool in the discovery and designing of medicine. The concept of artificial intelligence is demonstrating intelligence by machines. The term Artificial Intelligence is used when a machine shows cognitive behavior associated with humans, such as learning or problem-solving. Much pathology, including sickle cell disease (SCD), are being studied, diagnosed, and treated using artificial intelligence (AI). Using AI we can learn and predict novel properties like physicochemical and ADMET properties (absorption, distribution, metabolism, excretion, and toxicity properties) have lately appeared and bolster the strength of this technology in quantitative structure-property connections (QSPR) or quantitative structure-exertion connections (QSAR). Specifically, the evolution of artificial intelligence is primarily driven by deep neural networks (DNN) and recurrent neural networks (RNN). This study investigated the efficacy of AI in drug designing for preventing and treating Sickle cell disease (SCD). In de novo design, artificial intelligence drives the development of meaningful new molecules with desirable properties. The strength of artificial intelligence in this field can be seen in several examples. Shortly, we can anticipate seeing more computer-aided automated drug discovery combined with synthesis planning and ease of synthesis. Through advancements in diagnosing SCD and its complications, risk stratification, and individualized approaches, AI applications may improve SCD management in managing SCD patients. In conclusion, AI can be used as a smart and effective drug-designing tool against SCD and rare genetic disorders in the near future.

Keywords: Artificial Intelligence, SCD, ADMET, QSAR, QSPR, Drug Designing.

Participant's Presentation: PP29

DNA sequence analysis Sickle Cell Haplotype regions of high and low fetal hemoglobin SCD samples and correlation with oxidative stress

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Abstract:

The study investigates the HbS β-globin gene's diverse haplotypes, reflecting origins across Africa, the Middle East, and the Indian subcontinent. These haplotypes serve as genetic markers for Sickle Cell Disease (SCD) subjects, aiding in predicting disease severity. Varied HbF levels across haplotypes impact clinical and hematologic aspects of Sickle Cell Anemia (SCA). The research addresses genetic diversity determination within populations and gene flow tracking. The Palghar district in Maharashtra, with a significant tribal population, is studied for HbS β-haplotypes. Novelty lies in whole genome sequence analysis of HbS β-haplotypes in Palghar's SCD subjects, aiming to identify new SNPs influencing disease severity.

Sampling involves 250 Sickle cell subjects, with 49 HbSS homozygous individuals categorized into two groups based on HbF levels: Group 1: HbF < 5%Group 2: HbF > 20%. Six established RFLP sites define the β-haplotype, using PCR amplification and restriction digestion. An A or T nucleotide presence at the 6th codon of β-globin is confirmed through whole genome DNA sequence analysis. Haplotype analysis proceeds through steps: 1. Extracting FASTA sequences from forward and reverse chromatograms. 2. Data cleaning to remove certain sequences. 3. Identifying restriction sites using ReBase 4. Locating restriction sites on chromatograms. SNP analysis involves stages: 1. Obtaining FASTA sequence from chromatograms 2. Using NCBI Blast 2 to compare with the known 72kb region of beta globin cluster 3. Identifying new SNPs, if any. The study provides DNA sequence data generated by Sanger's DNA sequencing for SNP analysis of all six-restriction site of prominent haplotyping PCR products from tribal areas in Palghar, Maharashtra and based on two population types, i.e. fetal hemoglobin levels <5 and >20 gm% along with oxidative stress studies on few selected patients. Both the studies, molecular haplotyping and oxidative stress in SCD with reference to HbF are discussed in the presentation.

Key words: Sickle Cell Disease, Genetic Diversity studies, HbF levels, Oxidative stress, SCD Haplotype.

Participant's Presentation: PP30

Sickle Cell Disease and rare genetic disorders

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Abstract

Sickle cell anemia is one of a group of inherited disorders known as sickle cell disease. It affects the shape of red blood cells, which carry oxygen to all parts of the body. Sickle cell conditions are a classic example of balanced polymorphism. In humans, each gene contains two copies (alleles), one inherited from each parent. Mutations can affect one allele or both. In some genetic conditions, like SCD, these mutations can have a detrimental effect. When both copies of a gene are affected, this causes you to have a dangerous, often life-threatening condition. But if only one copy is affected, it sometimes can create a certain health benefit. This situation is called balanced polymorphism. When it comes to sickle cell conditions, one affected copy is responsible for SCT, which protects against malaria. If both copies are affected, this results in SCD, a dangerous blood disorder. Having different copies of the gene may give you a survival advantage in regions where malaria is common. This allows the affected gene to continue being more common in a community. Patients who are homozygous for the sickle gene and therefore suffer from sickle cell anaemia (SCA) are highly susceptible to the lethal effects of malaria. The simplest explanation of this fact is that malaria makes the anaemia of SCA more severe; in addition, in SCA there is often hyposplenism, which reduces clearance of parasites. From the point of view of public health it is important that in malaria-endemic countries patients with SCA, and particularly children, be protected from malaria by appropriate prophylaxis.