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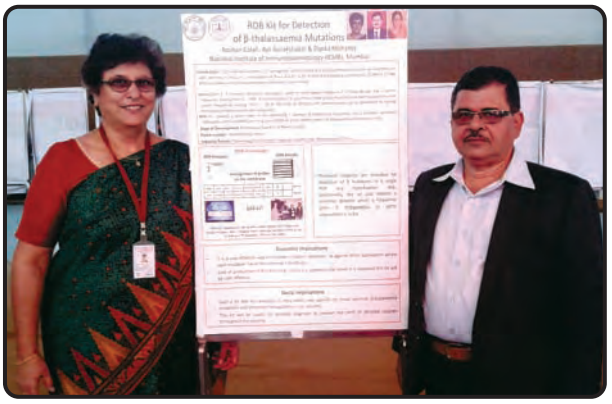

ICMR-NFI Exhibition on Innovations in Medical Science and Biotechnology Rashtrapati Bhavan, New Delhi

Foundation day celebration of the institute

Dr Anita Nadkarni, Scientist receiving BGRC Oration

Training Programme on Transfusion Medicine for North East region

The genetic basis of Hyperbilirubinemia

Ashish Chiddawar

Hyperbilirubinemia is an elevated level of the pigment bilirubin in the blood. A sufficient elevation of bilirubin produces jaundice. Some degree of hyperbilirubinemia is very common right after birth, especially in premature babies. It has been known for many years that mild to severe deficiency of bilirubin UDP-glucuronosyltransferase in the liver is the cause of two types of familial unconjugated hyperbilirubinemia, e.g Crigler-Najjar syndromes I and II, and Gilbert's syndrome.

Bilirubin:

Bilirubin is the breakdown product of the haem moiety of haemoglobin, other haemoproteins, such as cytochromes, catalase, peroxidase and tryptophan pyrrolase. In humans, 250–400 mg of bilirubin is produced daily, of which approximately 20% are from non haemoglobin sources [1]. Bilirubin is a water insoluble product with a molecular weight of 584 daltons and is the principle pigment of bile [2]. Bilirubin consists of an open chain of four pyrrole-like rings (tetrapyrrole). The sequence of the four methyl (M), two vinyl (V), one central methyne group and two propionic side chains was identical with that found in the proptoporphyrin IX α ring of haem after removal of carbon at the α methene bridge, and also designated bilirubin IX α [3] (Fig 1)

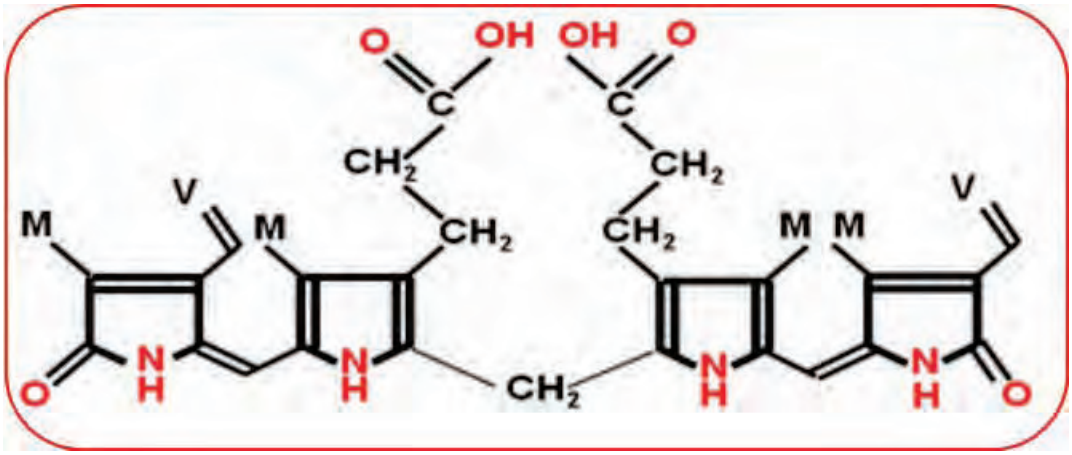

Fig.1 Bilirubin (Adapted from www.jacobimed.org)

Bilirubin has a linear structure, contains several polar groups, which suggest that it is highly polar and water soluble, however the intra molecular hydrogen bonds between the propionic and the carboxyl group and opposing pyrole lactum make the molecule to fold over itself which make it non polar and almost insoluble in water at physiologic pH [3]. As the bilirubin is insoluble in water, therefore it cannot be excreted from the body and is known as unconjugated bilirubin (Indirect bilirubin). Bilirubin first bind to serum albumin and then transfer to liver, where it is conjugated with glucoronic acid by the enzyme glucuronyltransferase, making it soluble in water and can be excreted via urine. This is known as conjugated bilirubin (Direct bilirubin).

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Bilirubin Metabolism:

Studies of bilirubin metabolism and related bile pigments are closely linked to studies of the red blood cell. Within the past decades, interest in bilirubin metabolism among hematologists has been increased due to the toxic effect of bilirubin when it is in excess. So, its chemistry, metabolism and disposal have been studied systematically as a model for hepatic disposal of biologically important organic anions of limited aqueous solubility [4].

Bilirubin Production

Bilirubin is the oxidative product of the protoporphyrin portion of the heme group of proteins. More than 80% of the bilirubin produced in the human body derives from heme catabolism liberated from senescent red cells (RBC). The remainder of heme derives from other hemoproteins such as myoglobin and cytochrome P-450. Heme is degraded to biliverdin, and the latter subsequently metabolized to bilirubin. These processes are catalyzed by the enzymes heme oxygenase and biliverdin reductase, respectively. For each molecule of bilirubin derived by this process, equimolar quantities of carbon monoxide are produced. The latter binds to hemoglobin to form carboxyhemoglobin (COHb) and is transported to the lungs and exhaled. Unconjugated, or indirect reacting bilirubin, enters the blood and is transported to the liver bound to albumin with the help of Organic anion transpoter protein 2 (OATP2). Under physiological conditions, sufficient serum albumin should be available to bind the amounts of bilirubin produced and free (unbound) bilirubin is unlikely to accumulate in the serum. The binding of bilirubin to albumin is a protective mechanism against bilirubin encephalopathy, as only free bilirubin is regarded as capable of crossing the blood-brain barrier and entering the basal ganglia of the brain [5].

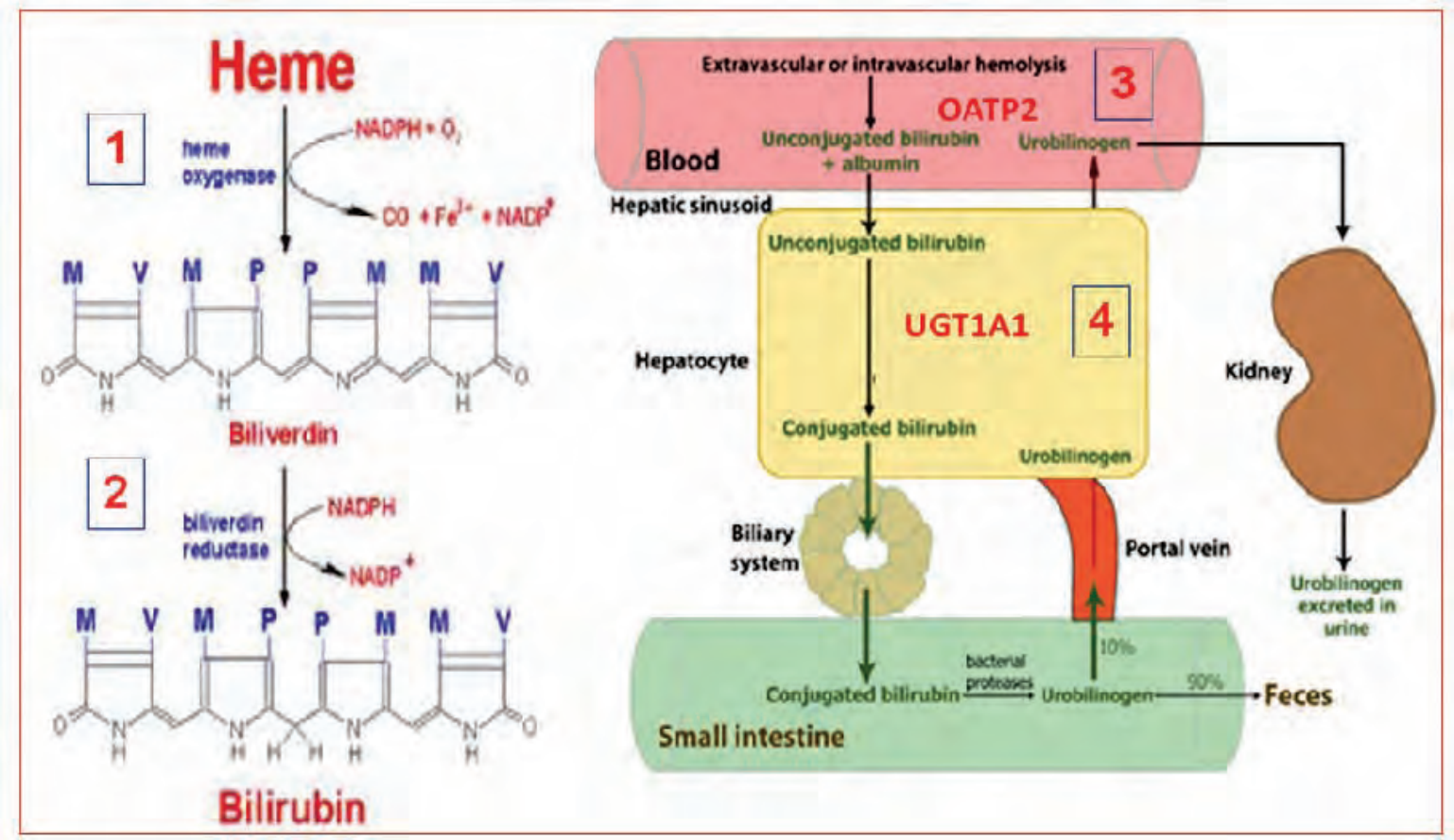

Fig.2 Bilirubin Metabolism pathway (http://www.eclinpath.com/chemistry/liver/cholestasis/bilirubin/bilirubin-metabolism/)

Hyperbilirubinemia occurs when bilirubin exceeds in the blood. This condition could be due to more bilirubin production than the normal liver can excrete, or may result from damaged liver that fails to excrete bilirubin produced in normal amounts. In the absence of hepatic damage, obstruction of the excretory ducts of liver will also cause hyperbilirubinemia. In all these situations, bilirubin accumulates in the blood, and when it reaches a certain concentration it diffuses in the tissues, which then become yellow and this condition known as jaundice or icterus [6].

Classification of hyperbilirubinemia:

Any classification of hyperbilirubinemia is difficult. However, Thompson et al [7] classified hyperbilirubinemia as conjugated or unconjugated hyperbilirubinemia depending on the type of bilirubin present in the serum. The first consideration is whether unconjugated or conjugated bilirubin predominates in the blood (Table 1), the latter being much the commoner cause of hyperbilirubinemia. Thus massive haemolysis will overload the normal capacity to excrete bilirubin and occasionally ineffective erythropoiesis may be a cause of hyperbilirubinemia. These are prehepatic causes of unconjugated hyperbilirubinemia. The second group, hepatic causes of unconjugated hyperbilirubinemia, includes impairment of uptake of bilirubin, as may occur in Gilbert's syndrome or after the administration of a few drugs such as flavaspidic acid. The conjugation of bilirubin may be inadequate in the Crigler-Najjar syndrome, Gilbert Syndrome, in normal neonates, and possibly in children born to the rare women who have high serum levels of 3α, 20β- pregnandiol or of the Lucey-Driscoll factor.

Table 1: Classification of hyperbilirubinemia (Adapted from Thompson et.al, 1970)

Predominant pigment in Blood	Anatomical	Physiology	Examples of Aetiology
Unconjugated	Prehepatic	Increased bilirubin production	Haemolysis Ineffective erythropoiesis ? Hepatic haem catabolism
	Hepatic	Hepatic uptake impaired	? Gilbert's syndrome Flavaspidic acid
		Glucuronyl-transferase activity	
		—low	Neonates Crigler-Najjar (Type I)
		—absent	" " (Type II)
		—inhibited	3,20—pregnanediol Lucey-Driscoll syndrome
Conjugated	Hepatic	Secretion of bilirubin impaired	Dubin–Johnson syndrome
		Intrahepatic cholestasis	Early primary biliary cirrhosis Intrahepatic atresia Drugs—for example: steroids chlorpromazine
		Hepatocellular damage	Drug or viral hepatitis Cirrhosis
	Posthepatic	Extrahepatic cholestasis	Gallstones or carcinoma

Hepatic causes of conjugated hyperbilirubinemia are the commonest group. In the rare Dubin-Johnson syndrome, there is an isolated abnormality of bilirubin secretion, while in intrahepatic cholestasis due to primary biliary cirrhosis in its early stages, intrahepatic biliary atresia, or steroid drugs secretion of all biliary constituents is held up. In drug or viral hepatitis and in cirrhosis there may be multiple defects, including haemolysis, impaired transport, and cholestasis due to widespread damage to the liver cells. Posthepatic or extrahepatic obstructive jaundice may be due to factors such as gallstones, carcinoma of the pancreas, etc [7].

Elevated unconjugated bilirubin could occur in the following disorders:

1. **Hemolytic Disorders:** Hemolytic disorders are important causes of unconjugated hyperbilirubinemia. Hemolytic disorders that cause excessive heme production may either be inherited or acquired. The inherited disorders include spherocytosis, sickle cell anemia and deficiency of red cell enzymes such as pyruvate kinase (PK) and glucose-6-phosphate dehydrogenase (G6PD). An acquired hemolytic disorder includes immune hemolysis, ineffective erythropoiesis and iron deficiency [8].

2. **Neonatal jaundice:** This transient condition is the most common cause of unconjugated hyperbilirubinemia. Neonatal jaundice results from hemolysis around the birth time and an immature hepatic system for the uptake and conjugation of bilirubin. It causes the increased amount of unconjugated bilirubin and is capable of penetrating the blood brain barrier. This can result in hyperbilirubinemic toxic encephalopathy, or kernicterus. The Phenobarbital and exposure to blue light is effective in this disorder [8].

3. **Crigler-Najjar syndrome type I (CN I):** CN I is congenital non-hemolytic jaundice with kernicterus. This disorder is characterized by serum bilirubin level of about 20 to 45 mg/dl. Bilirubin glucuronides are markedly reduced or absent from the nearly colorless bile and there is no detectable expression of UGT1A1 activity in hepatic tissue. Majority of the patients with CN I exhibit defects in one of the common exons 2 to 5 of the UGT1A1 gene. In smaller subset, the defect is limited largely to exon A1. Prior to availability of phototherapy, most patients with CN I died of bilirubin encephalopathy or kernicterus [8].

4. **Crigler-Najjar syndrome type II (CN II):** This is characterized with serum bilirubin level 10 to 25 mg/dl. Bile is deeply colored and bilirubin glucuronides are present. The level of UGT1A1 enzyme is reduced by > 30 % of the normal. In these patients, mutations always consist of a single amino acid transition that significantly reduces bilirubin-UGT activity. There are very few who survive up to early adult life without overt neurological damage [8].

5. **Gilbert's syndrome (GS):** Of the many causes of jaundice, GS is probably the most common and innocuous [9]. GS was first described in 1901 by Augustine Gilbert and Pierre Lereboullet [10]. Patients with Gilbert's syndrome have mild, chronic unconjugated hyperbilirubinemia in the absence of liver disease or overt hemolysis [10, 11]. In most patients, the hyperbilirubinaemia of GS manifests itself during adolescence or early adulthood. The total serum bilirubin concentration usually rises and fluctuates between 20 and 50 mmol/L. The lower amount of the enzyme is the result of mutation of the UGT1A1 gene [12]. Although the syndrome is genetic, many people do not have a clear family history and both autosomal dominant and recessive patterns of inheritance have been suggested [13]. On the basis of serum bilirubin levels, 3 to 10% of the general populations are estimated to have Gilbert's syndrome.

   Although instances of GS may be seen at any age, the disorder is more commonly noted in the young persons. Jaundice may be present from birth or may not be noted until adulthood [13]. Usually, male is more prone to GS than female and the male:female ratio was found to be 4:1[12]

   It is most important to consider GS as a condition with no clinical consequences for adults, other than the potential anxiety generated for the patient. There can be coincidental associations with other common conditions like fatty liver, gallstones, haemoglobinopathies and spherocytosis that can cause confusion, but these rarely if ever cause any clinical problem. In the neonate, GS, when in combination with additional icterogenic factors, may play a role in potentiating severe hyperbilirubinaemia. Such causes of jaundice in the newborn include glucose-6-phosphate dehydrogenase deficiency, direct Coomb's-negative, ABO blood group incompatibility and hereditary spherocytosis [14].

allele in the UGT1A1 promoter and the proportion of GS patients who are homozygous for the (TA)7TAA allele vary widely across populations [19]. Homozygosity for the (TA)7 allele occurs in 10–25% of the populations of Africa and the Indian subcontinent, with a variable frequency in Europe. It occurs at a much lower frequency in Southeast Asia, Melanesia, and the Pacific Islands, ranging from 0 to 5%. African populations show a much greater diversity of length alleles than other populations [20]. By contrast, the predominant variation in the coding region of this gene is a GA substitution at nucleotide (nt) 211 for Japanese and Taiwanese populations however, this variation has not been observed in Caucasians [21, 22]. The variation at the promoter area of the UGT1A1 gene is reportedly related to Gilbert's syndrome for Caucasians adults [23], whereas both variations in the promoter area, and within the coding region of this gene, are involved in Gilbert's syndrome for Asian adults [17]. Recent data also suggest that variants at -3279 T→ G and -3156 G→ A in UGT1A1 gene other than the classical dinucleotide insertion in its promoter, can also contribute to high bilirubin levels [24, 25]. Both UGT1A1-53 (TA)6/7 and -3156G → A have been found to be associated with hyperbilirubinemia and irinotecan toxicity [26].

2. OATP1B1:

OATP1B1 (previously known as OATP2, OATP-C and LST-1, SLCO1B1) is mainly expressed on the sinusoidal membrane of human hepatocytes. SLCO1B1 mRNA has been detected also in other tissues, including small intestinal epithelial cells. In vitro, OATP1B1 has been shown to transport both unconjugated and conjugated bilirubin to liver. Other endogenous OATP1B1 substrates include bile acids (cholate and taurocholate), conjugated steroids estrone-3-sulfate and dehydroepiandrosterone-3-sulfate), eicosanoids (leukotrienes C4 and E4, prostaglandin E2 and thromboxane B2) and thyroid hormones (thyroxine and triiodothyronine).

The OATP1B1 protein is present on 12p12 chromosome consisting of 14 exons from which 691 amino acids are encoded. In recent years, SLCO1B1 gene has also been reported to be responsible for the transportation of organic anions into hepatocytes and unconjugated bilirubin. Population-based studies have shown the association of variants in SLCO1B1 gene with serum bilirubin levels. The minor allele of SNP rs2306283: C→ T and rs4149056:T→ C in the SLCO1B1 gene increases the risk of unconjugated hyperbilirubinemia among Taiwanese adults [27]. Among the neonates, minor allele of rs2306283:C→T were at high risk to develop severe hyperbilirubinemia, whereas the minor allele of rs4149056:T→ C did not show any association with hyperbilirubinemia [28].

3. HMOX-1

Heme oxygenase, the rate-limiting enzyme in heme catabolism, catalyzes the stereospecific degradation of heme to biliverdin, with the concurrent release of iron and CO. In addition to its role in regulating cellular levels of heme, HMOX-1 is responsible for the recycling of iron from senescent red blood cells and extra hematopoietic cells, such as liver cells. Heme oxygenase, was first purified to homogeneity from rat liver and pig and bovine spleen and was shown to have a molecular weight of 32,000 Da. Human HMOX1 activity can be increased in vitro by either NADH or NADPH as reducing agents and its sensitivity to synthetic metalloporphyrins has been well studied [29]. Although the enzyme consists of three different isoforms viz. HMOX-1, HMOX-2 and the most recently discovered HMOX-3, however, HMOX1 is the only most well studied isoform. It was thought that HMOX-1 plays the predominant role in the degradation of heme to biliverdin. As expression of the HMOX-1 gene may be induced as a response to oxidative stress, this gene has also been termed a stress response gene.

Population-based studies have shown that carriers of short alleles (<25 GT) of the (GT)n repeat polymorphism in the HMOX1 promoter region is associated with higher bilirubin levels as compared

Diagnosis of Gilbert's Syndrome:

For the diagnosis of GS, following criteria to be followed:

1) Unconjugated hyperbilirubinemia.
2) No evidence of haemolysis (normal full blood count, reticulocyte count, blood film, Coombs'test, haptoglobin and lactate dehydrogenase levels);
3) Normal liver function test (hepatic enzymes, protein, except bilirubin).
4) An absence of other disease processes associated with unconjugated hyperbilirubinaemia.
5) No history of drugs.

If these criteria fulfills, then GS can be confirm by DNA study.

Molecular basis of Hyperbilirubinemia:

The molecular defects lie within the genes involved in bilirubin conjugation. Serum bilirubin is derived primarily from hemoglobin in aging red blood cells, which is broken down to heme and globin. Heme oxygenases (HMOX) convert heme to biliverdin, which is reduced by biliverdin reductase A (BLVRA) to bilirubin. Bilirubin is carried by albumin in the blood and is taken into the liver by the solute carrier organic anion transporter 2 (OATP2). Within hepatocytes, the solubility of bilirubin is increased by the addition of one or two molecules of glucuronic acid, a process that is catalyzed by uridine diphosphate glucuronosyltransferase 1 (UGT1A1). Bilirubin monoglucuronide and diglucuronide metabolites are then actively transported into the bile. Hence, the epistatic factors for unconjugated hyperbilirubinemia should in the least depend on the polymorphisms/mutations in these genes [15]. Although, studies have shown that the polymorphisms in the promoter and coding region of the UGT1A1 gene is associated with hyperbilirubinemia, however, it remains unclear what role the polymorphisms play in influencing serum total bilirubin (TBIL) levels and whether other polymorphisms involved in the bilirubin metabolism gene pathway are associated with TBIL levels.

1) **UGT1A1 gene:**

The UGT gene is a superfamily of genes. Their function is to encode a biochemical reaction leading to the conjugation of glucuronic acid to certain target substrates in order to facilitate their elimination from the body. Of major importance to the conjugation and elimination of bilirubin is the UGT1A1 gene, which has been mapped to chromosome 2q37. The UGT1A gene is 218 kb long and is composed of 527–530 amino-acid residues, for a molecular weight of 50–57 kDa [16]. The gene consists of 4 common exons (exons 2,3,4 and 5) and 13 variable exons, although only 9 (UGT1A1, UGT1A3-UGT1A10) of these code for functional proteins and 4 corresponds to pseudogenes [p] (UGT1A2p, UGT1A11p, UGT1A12p, UGT1A13p). Variable exons 1A2 to 1A13 do not participate in bilirubin metabolism. Genetic mutations associated with absent or decreased enzyme activity, that cause deficiencies of bilirubin conjugation, have been localized to these variable exon 1A1, its promoter, or the common exons 2 to 5 [5].

Variations in the promoter and coding region of the UGT1A1 gene have been previously reported to be associated with mild unconjugated hyperbilirubinemia (Gilbert's syndrome) amongst adults [17]. In most ethnic groups, hyperbilirubinemia arises from a polymorphism in the UGT1A1 promoter, which contains a TA repeat element, (TA)5-8TAA, involved in the modulation of UGT1A1 transcriptional activity. Wild-type activity is associated with the (TA)6TAA allele, but UGT1A1 expression decreases with increasing number of TA repeats. Thus, homozygosity for the TA-insertion alleles (TA)7/7TAA is required for Gilbert's syndrome, although not necessarily for manifestation of hyperbilirubinaemia (which also depends on bilirubin production and hepatic uptake). The uncommon (TA)5TAA variant, which has been reported in individuals of African origin, appears slightly increase in their expression [18].

The prevalence of GS, the frequency of the (TA)7TAA

with non carriers of this allele[15]. These repeats modulate the transcription of the HMOX-1 gene and the longer repeat sequences are known to reduce the transcription. A similar observation has been made among the neonates with prolonged unconjugated hyperbilirubinemia [30] and patient with marked hyperbilirubinemia during an acute episode of autoimmune hemolytic anemia [31]. In the previous case control studies, individuals with carriers of short (GT)n alleles had significantly higher serum bilirubin concentrations and were associated with a significant reduction in coronary artery disease (CAD) risk and incidence of ischemic heart disease [32,33]. On the other hand Lüblinghoff et al [34] did not find any association between HMOX-1 genotypes and bilirubin concentration among patients with CAD. This probably indicates that other genes involved in bilirubin metabolism pathway superpose the effect of different HMOX-1 genotypes.

4. Biliverdin reductase (BVR)

BVR drives, in a powerful redox cycle, the conversion of Biliverdin to Bilirubin. Thereby, it enables continuous protection of cells against oxidative stress. But this is not a sole function of BVR [35]. Studies in recent years have led to the identification of the human BVR along with its substrate and activity product as key players in the signal-transduction pathways, a regulator of gene expression, and a crucial component of cellular defense mechanisms and immune response. Perhaps the most unexpected and arguably important finding is the dual-specificity kinase character of BVR. Dual-specificity kinases control functions such as glucose metabolism, cell growth, and apoptosis, as well as development of human diseases such as cancer and diabetes [36]. Biliverdin reductase has two forms of different molecular weight: A and B (BVR IXα and BVR IXβ), each of them with two isoforms. BVRA reacts most effectively with biliverdin IX α, whereas BVRB does not reduce BV-IXα at all. BVRB has been reported to be predominant during fetal development, while BVRA dominates in adult life. Its genomic location is 7p13, encoded by a single copy gene consisting of 10 exons and 9 introns. The enzyme is composed of 296 amino acids which gives a mass of 33.5 kD [35].

BVRA reduces biliverdin to bilirubin, binds to HMOX1 protein, and regulates enzyme activities. Moreover, BVRA is a regulator for induction of HMOX1 expression by oxidative stress [37]. It is possible that single nucleotide polymorphisms (SNPs) within BVRA gene might affect TBIL levels. Although, the polymorphism in this gene is not extensively studied like UGT1A1 gene and SLCO1B1 gene, nevertheless, a recent study suggest that SNP rs699512:A→G was associated with TBIL levels and the allele frequency of rs699512 (A/G) was 0.23 in Caucasians, 0.08 in African Americans, 0.27 in Chinese, and 0.40 in Japanese. [15].

National

In India, Gilbert's syndrome is not very uncommon and about 2 to 5% of the general population have Gilbert's syndrome. Among the Gilbert's syndrome patients, 80% were found to be homozygous for the (TA)7 allele, which was several-fold higher than reports from other ethnic groups. A trinucleotide (CAT) insertion in the promoter region was also found in a subset (10%) of GS patients, but not among the normal controls. In-silico analysis showed marked changes in the DNA-folding of the promoter and functional analysis showed a 20-fold reduction in transcription efficiency of UGT1A1 gene resulting from this insertion [19]. A recent study among the healthy adults suggests that individuals who carried the -53(TA)7, -3279G and -3156A mutant alleles in homozygous or heterozygous states had significantly higher mean serum bilirubin levels [38]. Among the North Indian neonates, a higher proportion of babies with hyperbilirubinemia had a variation of the (TA)n promoter polymorphism compared with control group. The frequency of (TA)7 and (TA)8 alleles was also significantly higher in the hyperbilirubinemic neonates. A novel polymorphism (Ala72Pro) at nucleotide position 214 (214 G→ C) of exon 1 of UGT1A1 gene was also observed [39]. The allele frequency of variant (TA)7 among the neonatal hyperbilirubinemia cases was 48.7% and the mean unconjugated serum bilirubin level was

elevated among individuals with only one copy of this insertion, which was not significantly different from those with two copies [40]. Mutation (Gly71Arg) in the coding region was neither found in neonates with hyperbilirubinemia [37] nor did it have an impact on unconjugated bilirubin level in GS patients [19]. It was also observed that healthy adults who carry short (GT)n alleles of the HMOX-1 gene promoter are at a high risk of developing unconjugated hyperbilirubinemia [41].

Pharmacological implications of the Gilbert's syndrome mutation:

UGT1A1 is involved in the excretion of several endogenous and exogenous compounds, and reduced expression may cause increased susceptibility towards some drugs. Several investigators indeed have reported decreased glucuronidation and/or elimination of drugs like menthol, tolbutamine and rifamycin in Gilbert's syndrome patients. There are many xenobiotic substrates of UGT1A1 like octyl gallate, emodin and buprenorphine have the potential to cause jaundice by competitive inhibition of UGT1A1, especially GS patients whose hepatic activity is reduced to 35% of normal levels [42].

Although the data on the role of Gilbert's syndrome in the susceptibility towards drugs are limited, nevertheless, the available studies indicate that GS indeed may have implications in the clinic [43]. A very common drug use for Cancer treatment i.e Irinotecan or CPT-11, a semi-synthetic analogue of the cytotoxic alkaloid camptotecin (CPT), which is an inhibitor of topoisomerase I and seems promising in the treatment of metastatic colon cancer. In vivo, CPT-11 is biotransformed by carboxyl esterase into SN-38 which is a substrate for UGT1A1, and was found to be 100 to 1000-fold higher anti-tumour activity. The resulting SN38 glucuronide is inactive and is excreted into bile and urine. The major dose-limiting toxicity of CPT-11 is diarrhoea, possibly due to direct enteric injury caused by SN38, which accumulates in the intestine. Because in human there appeared to be an inverse relation between SN38 glucuronidation rate and toxicity, patients homozygous for the Gilbert's syndrome mutation are expected to be more susceptible to these adverse effects. Gilbert's syndrome patients treated with irinotecan indeed suffered from severe diarrhoea. In a retrospective study, a large number of cancer patients revealed that homozygosity for the UGT1A1*28 mutation indeed is a significant risk factor for CPT-11 related toxicity. Furthermore, mutations in the coding region that affect UGT1A1 activity also caused an increased susceptibility towards this drug [43]. Therefore, Gilbert's syndrome can also be described as a pharmacogenetic variation affecting glucuronidation and toxicity of the therapeutic drugs.

NIIH Experience:

Our experience on GS patients suggests that genetic polymorphisms of the UGT1A1 promoter, specifically the T-3279G phenobarbital responsive enhancer module and (TA)7 dinucleotide repeat as well as the intron and coding region variants of the OATP2, HMOX1 and BVRA genes [rs2306283(A→G), rs2071749 (A→G), rs1802846(T→C)] are significantly higher among the cases than the controls. Further, nearly 62% of the cases showed the presence of more than 4 variants as compared to 20% of the controls and the mean total serum bilirubin levels also increased according to the number of variants co-expressed. Exon-wise sequencing of the UGT1A1 gene revealed a variant at nt 6846 A→G in exon 2, with a predicted amino acid change of Ile→Val at codon 322 in heterozygous condition among the hyperbilirubinia cases. Therefore, polymorphisms in the bilirubin metabolism genes could be genetic risk factors for hyperbilirubinemia. Our data also suggests that (TA)7 dinucleotide repeat may serve as an important biomarkers for the diagnosis of Gilbert's syndrome.

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LIBRARY INFORMATION SCIENCE 2015

Vijay Padwal, ALIO

GENERAL INFORMATION

High spur of activities are continued during the first quarter under report, procuring, training and awareness programmes for library and information professionals. Digital Library Software Ver-4.0 from Focuz Infotech Pvt Ltd. Kochi, Kerala and Library Automation Software SLIM21 supported by Algorhythms Consultants Pvt. Ltd., Pune have been procured. Data entry and Data mining for both the softwares are under process. Online databases like J-Gate Plus i.e. JCCC@ICMR, NML-ERMED Medical e-journals consortia and the ICMR journal consortia for Lancet, Nature, Science and NEJM have been renewed for this year.

Techfocuz Digital Library 4.00

It facilitates multiple accessibility of CDs locally. It is an integrated system which deals with the CD & Image administration, local & global access by users. Multiple accessibility of CDs, centralized data ware housing, easy retrievals, administrator managed options are the important advantages of the system. Core application area are:

Network Storage Solutions

This will facilitate through Archive facility. The potential area of this facility is Backups for systems, Dataware housing, Centralised storage facility.

Digital Photo Library

This module has been incorporated with the following features

Add/Edit/Delete/reorder photos
Album Creation and its management
View-properties of Album, Photos
Add-comments
Slide Show

SLIM 21-Library Management Software 3.2

SLIM21 was installed and the data of previous Library Automation Software (GLAS) was converted to the SLIM21. Training and data conversation of software is in progress.

SLIM21 have the following features :

Cataloguing system
Circulation system
Acquistion system
Serial control system
Web-BasedOPAC
Current Awareness Service
Selective Dissemination of Information
Web proposal for new books
Inter library loan module
Usage statistics
Library Map

Publications

Annual report of the Institute for the year 2014-2015 compilation is in progress.

Some Recent Additions (Apr2014-Mar 2015):

Books	-	25
Journals (International)	-	26
(National)	-	08
E-Journals	-	15
CD-ROM/DVD	-	26

NIIH HAPPENINGS

Department of Hematogenetics

Dr Roshan Colah, Scientist G & Director-in-charge

1. Appointed Director-in-Charge of the Institute from 1st January 2015.
2. Attended the Stake Holders Consultation Meeting of the Tribal Health Research Forum(THRF) of ICMR and Ministry of Tribal Affairs (MOTA) at ICMR Headquarters on 7th January,2015.
3. Invited to give a talk on "Inherited Hemoglobin Disorders and their Prevention" at Patuck Technical Junior College, Mumbai on 22nd January 2015.
4. Organized the Pre-Conference Workshop of the Annual Conference of Indian Society of Human Genetics-2015 on "Screening and Molecular Diagnosis of Hemoglobinopathies" on 27th January 2015.
5. Visited Valsad Raktdan Kendre, Valsad and Seva Rural, Jagadhia for follow-up of babies under the THRF project on Newborn Screening for Sickle Cell Disorders from 2nd to 4th March 2015.
6. Participated in the ICMR-NFI Exhibition on Innovations in Medical Science and Biotechnology at Rashtrapati Bhavan, New Delhi to display our RDB kit for detection of beta Thalassemia mutations on 11th March 2015.
7. Organized a training programme for newly appointed staff under the THRF for diagnosis of G6PD deficiency and for prenatal diagnosis of hemoglobinopathies at 4 centres at Jabalpur, Belgaum, New Delhi and Port Blair under these two multicentre projects from 16th to 18th March 2015.
8. Attended the National Plasma Fractionation Centre Technical SAC meeting on 17th March, 2015 at Mumbai.
9. Invited to give a talk on "Prenatal diagnosis of sickle cell anemia" at the National Seminar on Sickle Cell Anemia-2015 at Pune on 26th March, 2015.
10. Invited to give a talk on "Hemoglobinopathies - A Genetic Prespective" at the CME on "Molecular Genetics for the Practicing Clinician" on 19th April 2015 held at Mumbai.
11. Invited to give a talk on "HPLC-Screening for Hemoglobinopathies" at the CME in Hematology at Nair Hospital, Mumbai on 25th April 2015.

Dr Malay Mukherjee, Scientist E

1. Organizing secretary for the International Symposium on "Genomics in Health and Diseases" and 40th Annual Conference of Indian Society of Human Genetics held at Mumbai from 28th to 30th January 2015.
2. Visited Bulsar Raktadan Kendra, Valsad and Seva Rural Hospital, Jagadiha, Baruch for follow up of babies in relation to New Born Screening programme among the tribal groups of South Gujarat from 2nd to 4th March 2015.
3. Attended 38th Annual Conference of Mumbai Hematology Group held at Mumbai from 14th to 15th March, 2015 and chaired a session entitled "Next Generation Sequencing".
4. Co-Organizer for the workshop for newly appointed technical staff under the THRF for diagnosis of G6PD deficiency and for prenatal diagnosis of hemoglobinopathies held at NIIH, Mumbai from 16th to 18th March 2015.
5. Visited Agartala Medical College, Tripura for setting up Molecular Biology laboratory under the DBT sponsored project on "Newborn screening for red cell enzymopathies and hemoglobinopathies" from 7th – 9th April 2015.
6. Invited to participate in the Workshop entitled "Sickle Cell Anemia and Water Bodies" organized by the Ministry of Tribal Affairs, Government of India, held at Gandhinagar, Gujarat on 11th April 2015 and delivered a lecture on "Hemoglobinopathies in India".
7. Attended "5th Hemoglobin Update Meets" held at Mumbai on 21st April 2015.

Dr Anita Nadkarni, Scientist E

1. Attended Indian Science congress (ISC) held at University of Mumbai from 3rd to 7th January 2015.

2. Participated as a faculty member and delivered a lecture on " Role of borderline HbA2 levels in carrier detection of β thalassemia trait" in the International Symposium on "Genomics in Health and Disease" and 40th Annual conference of Indian Society of Human Genetics held at Mumbai from 28th to 30th January 2015 by National Institute of Immunohaematology.

3. Received **BGRC Oration award** in the 38th Annual conference of Mumbai Hematology Group 2015. The title of the Oration lecture was "Is Hemoglobinopathy a monogenic disorder".

Following staff and students have attended and presented papers in the 40th Annual Conference of Indian Society of Human Genetics held at Mumbai from 28th to 30th January 2015:

1. **Ashish Chiddarwar, Technician C:** Presented a poster entitled "Genetic factors related to unconjugated hyperbilirubinemia amongst adults".

2. **Dr. Madhavi Sawant, PDF:** Presented a paper entitled "Effect of hydroxyurea on microRNA expression and its role in fetal hemoglobin induction in sickle cell anemia patients".

3. **Snehal Martin, JRF:** Presented a poster entitled "Association of Toll like receptor and CD14 genes polymorphisms with neonatal sepsis".

4. **Priya Hariharan, JRF:** Presented a poster entitled "Do some δ- globin gene variations result in substantial reduction of HbA2 levels?".

5. **Pallavi Mehta, Technician:** Presented a poster entitled "A rare interaction of homozygous β thalassemia with HbH Disease".

Following staff and students have attended and presented papers in the 38th Annual Conference of Mumbai Hematology Group held at Mumbai from 14th to 15th March 2015:

1. **Dr. Prabhakar Kedar, TO:** Presented a paper entitled "Novel mutation in PKLR gene associated with hemolytic anemia due to red cell pyruvate kinase (PK) deficiency: structural implications of amino acid substitutions in PK".

2. **Dr. Prashant Warang, TA:** Presented a paper entitled "Novel nine nucleotide deletion in the NADH-Cytochrome b5 reductase gene in a patient with hereditary methemoglobinema with severe mental retardation: Enzyme structure-function implication".

3. **Pratibha Sawant, TA:** Presented a poster entitled "Outcome of workshops for establishing screening and molecular diagnosis of hemoglobinopathies in medical colleges in India".

4. **Manju Gorivale, Technician A:** Awarded second prize (Dr. A.J. Desai and L.H. Hiranandani) for poster presentation entitled "Challenges in Prenatal Diagnosis of β Thalassemia: Couples with Normal HbA2 in One Partner".

5. **Dr. Madhavi Sawant, PDF:** Presented a paper entitled "Gene correction of sickle cell point mutation (β6: A→T) by use of single stranded DNA oligonucleotides (ssODNs)".

6. **Dr. Dipti Upadhye, SRF:** Awarded "Dr. H.M. Bhatia & Dr. L.D. Sanghvi award" for the best oral presentation entitled "Understanding the natural history of sickle cell disease and the role of ameliorating factors in disease severity".

7. **Stacy Colaso, SRF:** Presented a paper on "Genotypes of subjects with borderline HbA2 levals and their effects on β thalassemia carrier screening".

8. **Vrushali Pathak, SRF:** Presented a paper entitled "Can tyrosine kinase inhibitors serves as antimalarials? – An in-vitro study".

9. **Snehal Martin, JRF:** Presented a poster entitled "Is CD14 promoter region gene polymorphism associated with neonatal sepsis?".

10. **Priya Hariharan, JRF:** Presented a poster entitled "Do KLF-1 gene variations lead to borderline HbA2 level? A preliminary study".

Department of Transfusion Medicine

Dr Ajit Gorakshakar, Scientist F

1. Attended 102nd session of Indian Science Congress held at Mumbai from 3rd to 7th January 2015.
2. Attended Health and Hospital Expo in Vibrant Gujarat Global Trade Expo held at Gandhinagar from 8th to 12th January 2015 and demonstrated the Reverse Dot Blot kit at ICMR stall.
3. Chairman, Abstract Committee for the International Symposium on "Genomics in Health and Disease" and 49th Annual Conference of Indian Society of Human Genetics held at Mumbai from 28th to 30th January 2015.
4. Presented a paper entitled "ASGPR mediated uptake of pullulan anchored Doxorubicin nano particles with enhanced nuclear delivery" in the 14th International Symposium on Advances in Technology and Business Potential of New Drug Delivery Systems held at Mumbai from 23rd to 24th February 2015
5. Organized essay, drawing and elocution competitions in R.M.Bhatt High School, Mumbai on 27th February 2015 under "Swaccha Bharat Abhiyan".
6. Attended National Seminar on Sickle Cell Anemia held at Pune on 26th March 2015 and presented a poster entitled "Sickle Cell Disease in Madhya Pradesh".
7. Participated in "Medical Science and Biotechnology Innovation Exhibition" at Rashtrapati Bhawan , New Delhi on 11th March 2015 and displayed the RDB kit.

Dr Swati Kulkarni, Scientist C

1. Presented a paper entitled "Antigen negative red blood cell inventory of Indian blood donors" in the 38th Annual Conference of Mumbai Haematology Group held at Mumbai from 14th to 15th March 2015.
2. Presented a poster entitled "Role of Rituximab in Thalassemia Intermedia with alloimmunisation: A case series" in the 38th Annual conference of Mumbai Haematology Group held at Mumbai from 14th to 15th March 2015.

Following students have attended and presented papers in the 40th Annual Conference of Indian Society of Human Genetics held at Mumbai from 28th to 30th January 2015:

1. **G Vidhya, SRF:** Awarded third prize for the poster presentation entitled "Identification and characterization of D variants in apparently RhD negative individuals".
2. **Disha Parchure, SRF:** Presented a poster entitled "Determination of RhD zygosity based on most probable genotype and PCR-SSP".

Following students have attended and presented papers in the 38th Annual Conference of Mumbai Hematology Group held at Mumbai from 14th to 15th March 2015:

1. **Harita Gogri, SRF:** Presented a poster entitled "Molecular characterization of weaker variants of A and B".
2. **Disha Parchure, SRF:** Awarded 1st prize (Dr. A.J. Desai & L.H Hiranandani) for the poster presentation entitled "Noninvasive fetal RhD typing".
3. **Kanchan Mahadik:** Presented a poster entitled "Human genetic polymorphism and malaria; A study in tribal population of Maharashtra".

Department of Hemostasis

Dr Shreemati Shetty, Scientist E

1. Invited to deliver a talk on "Warfarin pharmacogenomic in Indian population" in the International Symposium on "Genomics in Health and Disease" & 40th Annual Conference of Indian Society of Human Genetics held at Mumbai from 28th to 30th January 2015.
2. Invited to deliver a talk on "Inhibitors in haemophilia: are there risk factors?" in the 20th National CME in Hematology and Hemato-

oncology, held at Bombay Hospital from 30th Jan to 1st February 2015.

3. Awarded "J.G. Parekh Oration award" for the work entitled "Prevalence, diagnosis and risk factors for inhibitor development in Indian haemophilia patients" in the 38th Annual Conference of Mumbai Hematology Group held at Mumbai from 14th to 15th March 2015.

4. Took part in the panel discussion on "Unusual bleeding disorders" in the 38th Annual Conference of Mumbai Hematology Group held at Mumbai from 14th to 15th March 2015.

5. Invited to give a lecture on "Platelet Function Studies" In the TNMC Haematology CME held at Nair hospital from 25th to 26th April 2015.

Following students have attended and presented papers in the 40th Annual Conference of Indian Society of Human Genetics held at Mumbai from 28th to 30th January 2015:

1. **T Gaikwad, SRF:** Presented a paper entitled "Study of various polymorphisms in Indian warfarin treated patients".

2. **R Patil, SRF:** Presented a paper entitled "Inherited and acquired thrombophilia in women with recurrent pregnancy loss".

3. **A Mukaddam, MSc Student:** Presented a paper entitled "Molecular basis of afibrinogenemia: application in prenatal diagnosis of affected families".

Following staff and students have attended and presented papers in the 38th Annual Conference of Mumbai Hematology Group held at Mumbai from 14th to 15th March 2015:

1. **Sharda Shanbhag, TA:** Presented a paper entitled "Genetic basis of factor XIII deficiency in India: application to carrier detection and prenatal diagnosis of the affected families".

2. **Nikesh Kawankar, TA:** Presented a paper entitled "Prenatal diagnosis in families with multiple genetic disorders".

3. **Patricia Pinto, SRF:** Presented a paper entitled "Antibody profile in severe haemophilia A patients with FVIII inhibitors".

5. **Rucha Patil, SRF:** Presented a poster entitled "A simple assay for detection of Microparticles".

6. **Anshul Jadli, SRF:** Presented a paper entitled "Biomarker prediction of preeclampsia".

7. **Darshana Mirgal, PhD Student:** Presented a poster entitled "Folate metabolism pathway gene polymorphisms among symptomatic and asymptomatic malaria from North east".

8. **Rutuja Deshpande, PhD Student:** Presented a poster entitled "A common antithrombin (AT) Pro305His mutation in Indian patients with thrombosis".

Department of Pediatric Immunology and leukocyte Biology

Dr. Manisha Madkaikar, Scientist F

1. Invited to conduct viva-voce for a PhD student on 16th January 2015 by Gujarat University at Ahmadabad.

2. Invited to deliver a lecture on "Molecular basis of Primary Immunodeficiency disorders" in the International Symposium on "Genomics in Health and Disease" & 40th Annual Conference of Indian Society of Human Genetics held at Mumbai from 28th to 30th January 2015.

3. Invited to deliver lectures in the workshop entitled "Primary immunodeficiency in pediatric practice" (PEDICON 2015) held at Sir Gangaram Hospital, New Delhi from:

   i. Clinical and laboratory approach to suspected immunodeficiency.

   ii. HLH: When to suspect?

4. Invited to deliver a lecture on "Autoimmunity in PID" in the '20thNational CME in Hematology' held at Bombay Hospital, Mumbai on 1st February 2015.

Following staff and students have attended and presented papers in the 3rd International Conference

on Primary Immunodeficiency held at Chennai, India from 21st to 23rd February 2015:

1. **Maya Gupta, TA:** Presented a poster entitled "Spectrum of Perforin gene mutation in Familial Hemophagocytic Lymphohistiocytosis (FHL) patients in India".

2. **Aparna Dalvi, Technician C:** Presented a poster entitled "Evaluating IL 12-23/IFNγ pathway in patients with suspected Mendelian susceptibility to mycobacterial diseases using flowcytometry based assays".

3. **Manasi Kulkarni, SRF:** Presented a paper entitled "strategy for molecular screening of Chronic Granulomatous Disease in India".

4. **Jahnavi Aluri, SRF:** Presented a poster entitled "Spectrum of severe combined immunodeficiency disorders seen in a tertiary referral center in India".

Aparna Dalvi, Technician C: Attended a workshop entitled "Basic flowcytometry and its application in multicolor flowcytometry" held at NIRRH, (ICMR), Mumbai from 9th to 10th April 2015.

Department of Cytogenetics

Dr V Babu Rao, Scientist E

1. Organizing Secretary for the "International Symposium on Genomics in Health and Disease & 40th Annual conference of Indian Society of Human Genetics" held at Mumbai from 28th to 30th January 2015.

2. Invited as an external expert in selection committee to select Research Assistant in ICMR project at Entero Virus Research Centre, Mumbai on 20th April 2015

3. Invited as a Chairman of the selection committee to select Technical Assistant (Flow Cytometry) at NIRRH, Mumbai on 24th April 2015.

Following staff and students have attended and presented papers in the 40th Annual Conference of Indian Society of Human Genetics held at Mumbai from 28th to 30th January 2015:

1. **Seema Korgaonkar, TO:** Presented a poster entitled "Study of chromosomal aberrations and molecular mutations in Myelodysplastic syndrome".

2. **Dolly Joshi, PDF:** Presented a poster entitled "DNA repair gene defects and its association with myelodysplastic syndrome".

3. **Avani Solanki, SRF:** Received 1st Prize for the poster presentation entitled "Molecular study of FANCA complementation group in Indian population".

4. **Purvi Mohanty, JRF:** Presented a poster entitled "DNA copy number changes in myelodysplastic syndromes".

Department of Clinical and Experimental Immunology

Dr Vandana Pradhan, Scientist B

1. Presented a paper entitled "Pathological Implications of Abzymes" in the 38th Annual conference of Mumbai Hematology Group held at Mumbai from 14th to 15th March 2015.

2. Attended a brain storming session on Lupus Research in India, sponsored by DBT at SGPGI, Lucknow from 27th to 29th April 2015.

Following staff and students have attended and presented papers in the 40th Annual Conference of Indian Society of Human Genetics held at Mumbai from 28th to 30th January 2015:

1. **Vinod Umare, PhD Student:** Presented a poster entitled "Association of pro-inflammatory cytokines (IL-6, TNF-α and IL-1β) polymorphism with disease susceptibility in Indian SLE patients".

Following staff and students have attended and presented papers in the 38th Annual Conference of Mumbai Hematology Group held at Mumbai from 14th to 15th March 2015:

1. **Prathamesh Surve Technician:** Presented a paper entitled "An Association between Mannose Binding Lectin (MBL 2) gene haplotypes with clinical manifestations in Western Indian Systemic Lupus Erythematosus (SLE) patients".

2. **Hemant Vira, PhD student:** Presented a paper entitled "Role of MMP7 in SLE pathogenesis: A preliminary study".

Marathi day celebration

Workshop on G6PD and Prenatal diagnosis of hemoglobinopathies

Dr S C Gupte, Director, Surat Raktadan kendra receiving Dr H M Bhatia Memorial Oration

BBOT training programme

MDACS training programme

Hindi Karyashala

Dr Nagesh Prabhu, Jt Secretary DHR addressing the staff

Dr V M Katoch, former Secretary, DHR and DG, ICMR addressing the staff and students

Innaguration of "International Symposium on Genomics in Health and Diseases" and ISHG 2015

Prof S E Antonarakis delivering Key Note Address in ISHG 2015

Farewell to Dr. K. Ghosh, Director

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