



TRANSFUSION TODAY

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Platelet & Granulocyte Immunobiology

A look inside the research and teamwork of two ISBT Working Parties

2010: an exceptional vintage for Platelet Immunobiology

ISBT Working Party on Granulocyte Immunobiology

Platelet Immunology Investigations in Allo immune thrombocytopenia

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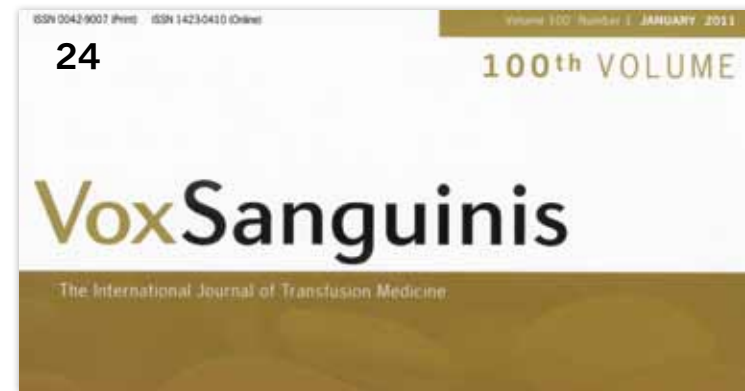
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Judith Chapman

Editorial

This focus section of this issue of Transfusion Today is principally on platelet immunobiology but also contains three focus articles on granulocyte immunobiology. The two ISBT Working Parties associated with these two areas of transfusion medicine have contributed much to the development of the specialities.

Cecile Kaplan, chairman of the ISBT platelet immunobiology Working Party organized a very successful European symposium on platelet and granulocyte immunobiology in Beaune, France in October 2010. The high quality of the scientific content led the delegates to discover new insights into these two distinctive areas of transfusion medicine. The symposium was so successful and interesting it seemed right to ask Cécile to provide a focus on platelet immunobiology for this issue. Whilst most of the sessions at the symposium were centred on platelets the last morning session was devoted to granulocytes.

The ISBT granulocyte Working Party met in Beaune to discuss its latest workshop and to elect Lin Fung as its new chairman. Lin has provided three articles for this issue: one on the work of the Working Party, one with information on a granulocyte master class at the regional congress in Taipei and one on the history and development of granulocyte immunobiology. We also pay tribute to our journal Vox Sanguinis celebrating its 100th volume.

Finally ISBT is pleased to announce that Roche and Haemonetics are the first members of the ISBT corporate members programme. Find out more in the next issue of Transfusion Today.

2010: An exceptional vintage for Platelet Immunology



E. Bouman (award winner), C. Kaplan, J. Chapman

This year two international meetings were focused on Platelet Immunology:

- The ISBT Working Party on Platelet Immunology and the International Platelet Immunology Workshop during the XXXIst International Congress of the ISBT in Berlin in June.
- The XIth European Symposium on platelet and Granulocyte Immunobiology in Beaune, France in October, 21-24.

The international workshops in Platelet immunology are dedicated to sharing knowledge, evaluating the different

technologies in use, establishing proficiency testing and developing standardization and are organized in the format of wet workshops. This 15th workshop was organized by Institute for Clinical Immunology and Transfusion Medicine, Justus Liebig University, Sentot Santoso (Chair) and Ulrich Sachs (Secretary), in co-operation with the Institute for Transfusion Medicine, University of Rostock (Volker Kiefel) with the help of Gregor Bein, and Hartmut Kroll (Dessau), Germany. The results will be published in Vox Sanguinis by the end of 2011. Meanwhile the results of the 14th ISBT-Platelet Immunology Workshop organized by Pr Wu from Nanning, China, have been recently published in Vox Sanguinis, 2010.99:375-381.



Cécile Kaplan (middle) and her work colleagues

The XIth European Symposium on Platelet and Granulocyte Immunobiology, under the aegis of the ISBT, took place in Burgundy. Despite the “French national sport” (strikes) the 20th anniversary of this symposium was celebrated by delegates coming from all over the world, showing its vitality and staying power. The attendees were granted with the latest news and development in the field. The thrilling figures in Beaune were:

- More than 300 registration
- Delegates from 33 countries, 5 continents
- 34 invited lectures
- 100 abstracts received for oral and poster presentation
- Industry exhibition
- Satellite symposia
- And of course a unique occasion to explore the charms and delights of the heart of France with wine and local specialities tasting event and the gala dinner in the Beaune Hospices, a jewel of gothic architecture.

For the first time the new biennial award to honour Alan Waters, a founding member of the Symposium, was granted to a young researcher, first author and presenter of the highest-scoring abstract. Due to the number and quality of submitted abstracts the scoring was a true challenge.

The 2010 recipient was E. Bouwmans from Cambridge University for her work on: “Development of novel reagents to study the presentation of HPA-1a peptide in the context of HLA-DRA/DRB* 30101 by maternal antigen presenting cells”. The keynote address of this Symposium honoured the memory of Diana Beardsley who was a strong leader in platelet studies. Sessions were dedicated to Platelet biology, Granulocyte biology and immune response and role in disease. In fact platelets are not the only key players in hemostasis but are

“ For the first time the new biennial award to honour Alan Waters, a founding member of the Symposium, was granted to a young researcher, first author and presenter of the highest-scoring abstract.”

also involved in vascular biology, tissue regeneration, tumor metastasis and inflammation, involving complex interaction with other cells. Concerning the main clinical disorders, autoimmune thrombocytopenia, alloimmune thrombocytopenia, Heparin-induced thrombocytopenia, highlights have focused on immunopathogenesis and therapy. Recent studies through development of animal models have been presented and the knowledge gained from these animal models is of interest for a better approach of the disease. Fruitful discussions took place during this meeting and collaborative projects may have emerged from these friendly dialogs.

In conclusion platelet immunology nowadays is not only focused on the identification of antibodies and antigens but is dedicated to a very stimulating challenge: understanding the role of platelets at the crossroad of hemostasis, inflammation, immune response. The next decade will probably give new insights in such domains. In the articles dedicated to platelet immunology my collaborators will give a few brief glimpses on current work developed in the laboratory.

Platelet Immunology Investigations in alloimmune thrombocytopenia: towards a standardization of the methods

Platelet immunology investigations are essential for the diagnosis and therapy of alloimmune disorders such as fetal/neonatal alloimmune thrombocytopenia (F/NAIT), platelet refractoriness, post-transfusion purpura.

The diagnosis of alloimmunization relies on (1) the detection of the antibodies, and (2) the identification of the offending antigen. Thus far, 27 human platelet antigens (HPA) have been described. Most of them are located on the platelet glycoprotein (GP) complex GPIIb/IIIa. In this issue, we report the most common methods in use in the laboratories, and give new insights on the future developments for a procedure standardization.

Serological investigations

In the seventies, the Platelet Immunofluorescence Test (PIFT) was the first method to detect platelet antibodies. To date, the MAIPA (Monoclonal Antibody-specific Immobilization of Platelet Antigens¹) is considered the gold standard reference method in platelet immunology. The MAIPA is an antigen-capture assay, based on the formation of trimolecular complexes by the binding of specific mouse monoclonal antibodies (MoAbs) and the human antibody targeting the platelet membrane molecule on which the respective epitopes are located (Figure 1).

This assay has been shown to be reproducible and it allows identification of a mixture of antibodies with a good sensitivity and specificity. False-negative results might be observed resulting from competition between the MoAbs and the human antibody.² The use of a panel of MoAbs directed against the same glycoprotein with distinct epitopes may solve this problem. Moreover it has been shown that the detection of low affinity/avidity antibodies as well as antibodies against labile platelet antigens may be somehow difficult (e.g. against HPA-3a/b²). This method requires a technical expertise, is time-consuming and not automatable. Consequently alternative methods have been developed (e.g. the MACE³ or the MPHA⁴), and commercial kits are now available.

Platelet typing

Phenotyping is the method of choice for the identification of the platelet antigens exposed at the cell surface, but it requires human reference sera containing anti-HPA antibodies, which restricts phenotyping to the most frequent antigens. Moreover it is not suitable for severe thrombocytopenic patients or recently transfused individuals. With the progress in molecular biology, genotyping is the routine method for most laboratories. Platelet genotyping is commonly performed by PCR-Sequence-specific primers (SSP), faster than the historical method of PCR-Restriction fragment length polymorphism (RFLP). The recent development of high-throughput technologies allows simultaneous genotyping of as many as 17 HPAs, but these expensive techniques are not affordable for all laboratories. However genotype is not phenotype. Discrepancies due to unknown mutations may alter the technique and may be responsible for false typing assignment with potential consequences on diagnosis and therapy^{5,6}. For that reason we recommend the use of both phenotyping and genotyping for at least the most frequently involved platelet antigens.

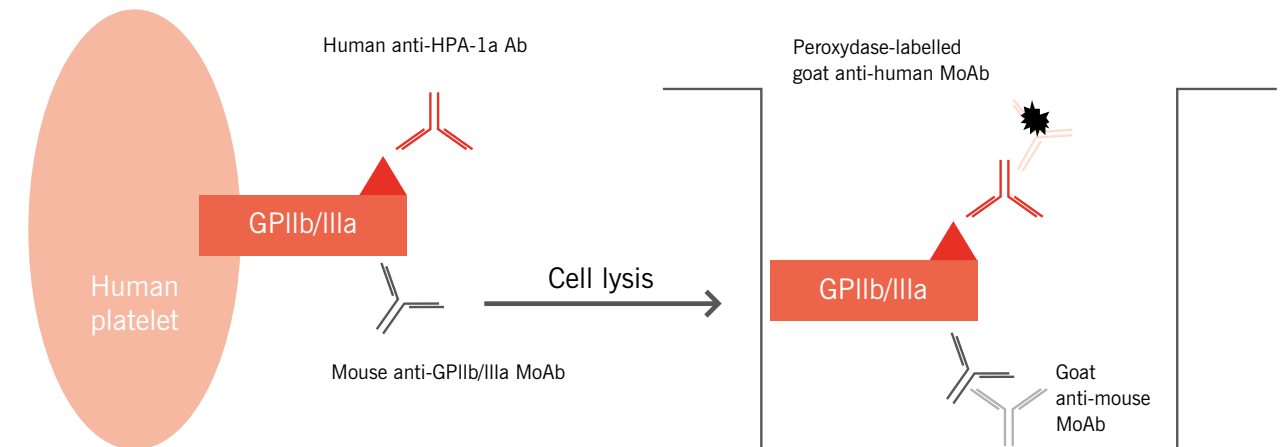


Figure 1: Detection of anti-HPA-1a antibodies with the MAIPA assay (from Metcalfe et al., Vox Sanguinis, 2004. Modified with permission).

Towards the standardization of the platelet immunological methods

Serology

The standardization of platelet serology testing is actually a challenge, many laboratories still using “in-house” ELISA methods. Reference sera are now available against HPA-1a, HPA-3a and HPA-5b (supplied by the National Institute for Biological Standards and Control, UK). These reagents are useful, assuring operator and test performance, thus ensuring the quality of biological diagnosis. Additionally, a reference serum with high anti HPA-1a antibody concentration is proposed for quantification. In a context of F/NAIT, we have shown that the maternal anti HPA-1a antibody concentration measured before 28 weeks of gestation and before treatment is predictive of the fetal status⁷. To overcome the problem of labile platelet antigens, recombinant cells expressing human GPs may be used as substitutes of platelets in the MAIPA⁸.

Platelet typing

Phenotyping is still rarely in use due to the scarcity of reagents, but recent developments of human monoclonal antibodies may counter this problem. For platelet genotyping, the problem of internal positive controls for rare antigens can be bypassed by Whole Genome Amplification (WGA). This method allows amplification of the full genome of an individual without PCR process. Its usefulness in platelet genotyping has already been proven⁹.

To conclude, the implementation of new technologies in platelet immunology will probably be beneficial for the standardization of the methods. The collaborative efforts shown by the worldwide participants and the exchange of experience of the ISBT platelet working party have been a major contribution to the development of platelet immunology.

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Alloimmune thrombocytopenia:

Non invasive fetal genotyping

Fetal/neonatal alloimmune thrombocytopenia (FNAIT) occurs at an estimated frequency of 1/800 to 1/1000 live births¹, and is the commonest cause of severe isolated thrombocytopenia in the fetus and newborn. FNAIT is due to Human Platelet Antigen (HPA) incompatibility between mother and fetus and results from maternal alloimmunization against fetal platelet antigens inherited from the father and different from those present in the mother.

The diagnosis is made either during the pregnancy or more usually at delivery. Due to the risk of recurrence in subsequent pregnancies, antenatal managements have been developed. Pregnant women with a past-history of confirmed fetal/neonatal alloimmune thrombocytopenia should be taken in charge in a referral center. Not all the fetuses will be at risk of alloimmune thrombocytopenia, but only those incompatible with their mother. It is therefore important to determine if the father is homozygous or heterozygous for the implicated antigen. In case of paternal heterozygosity, fetal genotyping should be performed. The fetal genotype should also be performed in case of uncertain paternity. Fetal genotyping is possible by using molecular techniques on either chorionic villi or amniocentesis, but with a risk of in utero termination and stimulation of maternal alloimmunization. Therefore non invasive procedures have to be considered. Lo et al. detected, in 1997, the presence of around 3-6% of cffDNA in maternal plasma and serum by screening for SRY sequences in samples obtained from mothers carrying male fetuses².

In clinical medicine, the detection of cffDNA in the maternal circulation is already used for fetal RhD blood typing³, and gender determination, but may have more applications for prenatal diagnosis of fetal disorders and pregnancy complications. Non invasive fetal HPA-1a genotyping has recently become available in laboratories, based on cell-free fetal DNA. Scheffer et al. are developing a non-invasive fetal HPA-1a genotyping assay based on the HPA-1b polymorphism with the use of a restriction enzyme that digests the maternal HPA-1b allele, preventing amplification of maternal DNA. In a first analysis on 35 samples from pregnant women, all the results were correct (HPA-1a positive fetus: n=29; HPA-1a negative fetus: n=6)⁴.

E. Muniz-Diaz's team is working on another approach to genotype cffDNA⁵. After automated DNA extraction from maternal plasma samples, the HPA-1a/1b polymorphism was analyzed by real-time PCR with allele-specific primers. Of 38 samples, 31 were from pregnant women carrying an

HPA-1a positive fetus. In all cases, the fetal HPA-1a genotype detected was concordant with the genotype at birth, with no unspecific amplification. They also used a fetal DNA marker independent of the fetus' gender: the RASSF1A gene which is hypermethylated in the placenta and hypomethylated in maternal blood cells⁶. Treatment of DNA with the methylation-sensitive restriction enzyme BstUI results in digestion of RASSF1A promoter sequences derived from maternal DNA, but not from placental, and therefore fetal DNA. The undigested sequences could then be detected by real-time PCR. Unfortunately, the RASSF1A promoter can also be hypermethylated in various diseases: described as a tumor suppressor gene, it is known to be silenced and frequently inactivated by promoter region hypermethylation in many adult and childhood cancers, including lung, breast, kidney, gastric, bladder, neuroblastoma, medulloblastoma and gliomas (for a review⁷). It is therefore important to have detailed medical history of the pregnant women before using this fetal marker.

In conclusion, non invasive fetal genotyping is of interest, and initial results are promising. However, larger studies are needed to conclude for reliability and efficiency, and a better fetal DNA marker is potentially required.

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3D protein structure modeling:

A tool to provide insight into the platelet alloimmune response

Fetal / Neonatal alloimmune thrombocytopenia (FNAIT) is a severe bleeding syndrome in which fetal / neonatal platelet destruction is mediated by maternal antibodies directed to specific antigens (or alloantigens) inherited from the father¹. These antigens depend on polymorphisms of genes coding for several membrane glycoproteins (GPIb-IX-V, GPIIb/IIIa, and GPIIa) or lipo-protein (CD109) receptors expressed at the platelet surface. These polymorphisms are classified in the Human Platelet Alloantigen, or HPA, nomenclature². α IIb β 3 (or GPIIb/IIIa) carries the majority of the HPA systems described to date (HPA-1, 3, 4, 6, 7, 8, 9, 10, 11, 14, 16, 17, 19, 20 and 21). This complex is highly immunogenic and is responsible for most FNAIT. α IIb β 3 belongs to the large family of the integrins that is composed of heterodimeric membrane receptors involved in cell-cell or cell-matrix interactions³. It mediates platelet aggregation as a receptor for fibrinogen, a major plasmatic adhesion molecule⁴. Resting platelets express on their surface about 50 000 copies of α IIb β 3 and 30 000 additional copies when activated.

Protein 3D structures (or structure models) help understand relationships between the protein dynamics and their biological functions. They provide new insight into atomic mechanisms of macromolecular recognition and conformational changes. Integrin structures are available from the Protein Data Bank (PDB). We have used a 3D structure of α IIb β 3 (PDB code 3FCS) to propose an explanation for the structure effect of the β 3 Lys253Met substitution identified in a Glanzmann patient, a mutation impairing α IIb β 3 expression⁵. Immune response relies on both immunogenicity and antigenicity. Antigenicity can depend on the 3D molecular

structure surrounding the polymorphic site. We have used a 3D structure of α IIb β 3 and modeling experiments to study the impact of HPA polymorphisms on the complex structure, and their role in antigenicity. Different HPA allelic forms of α IIb and β 3 were modeled from the structures 3FCS or 3IJE respectively and resulting structure characteristics of residue accessibility, mobility, and electrostatic change were analyzed.

Four polymorphisms of IIb identified in a context of FNAIT were studied, HPA-20w6, Cab27, Cab3 and Lec (table 1). The other α IIb polymorphisms described, HPA-3, -9 and Ak, could not be studied because they locate on an unresolved part of the α IIb crystal structure. As an example, figure 1 reports the 3D structures of the α IIb Cab2a- and Cab2a+ allelic forms. The corresponding computed electrostatic map has been projected on the molecular surface of each allelic form of α IIb. Red color corresponds to a negative charge whereas blue is positive

“ Protein 3D structures (or structure models) help understand relationships between the protein dynamics and their biological functions.”

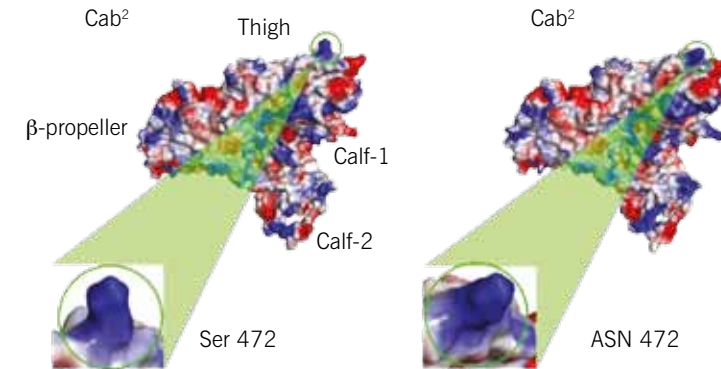


Figure 1: Modeling of the Cab2a+ and Cab2a- forms of the α IIb structure. The Ser472 (Cab2a-) and the Asn472 (Cab2+) α IIb forms were modeled from the PDB structure 3FCS. The computed electrostatic maps were projected on the molecular surfaces of each structure, blue, red and white colors respectively corresponding to positive, negative and neutral electrostatic charges. Detailed pictures present the structure features of the polymorphic site for each allele. It appears that the Ser472Asn substitution impairs neither the accessibility nor the electrostatic charge nor the mobility of the side chain (respectively assessed by computing the solvent surface accessible surface, the electrostatic charge and the B-factor).

and white neutral. The Ser472Asn substitution does not really affect either the local positive electrostatic charge or the residue mobility or its accessibility. Structure features of all α IIb polymorphisms studied (summarized in Table 1) suggest that alloantibody presence depends on residue accessibility (accessibility ranging between 50 and 90%) but not really on mobility or electrostatic characteristics.

3D structure of the 3 HPA polymorphisms 1a, 1b, 4a, 4b, 6a, 7a, 10a, 11a, 14a, 16a, 17a, 19a and 21a have also been studied. Figure 2 shows a model of the β 3 backbone structure (green ribbon) and the molecular surface (grey). HPA polymorphic amino acids are represented as magenta spheres. Analysis of the structure features of the β 3 HPA residues studied confirmed the observation made for the α IIb HPA polymorphisms. Alloantibodies rely on the residue presence at the surface of the structure (accessibility) but do not tightly depend on its mobility or its electrostatic charge (not shown).

Finally, a comparative study of a selection of published primary sequences of the β subunits of the integrins revealed that residues involved in β 3 HPA polymorphisms are not evolutionarily conserved. These results were also reported by Landau et al⁸ who used a similar approach. Mutations affecting evolutionarily conserved amino acids generally result in defective expression or function of α IIb β 3 that impair platelet aggregation (Glanzmann Thrombasthenia syndrome).⁸

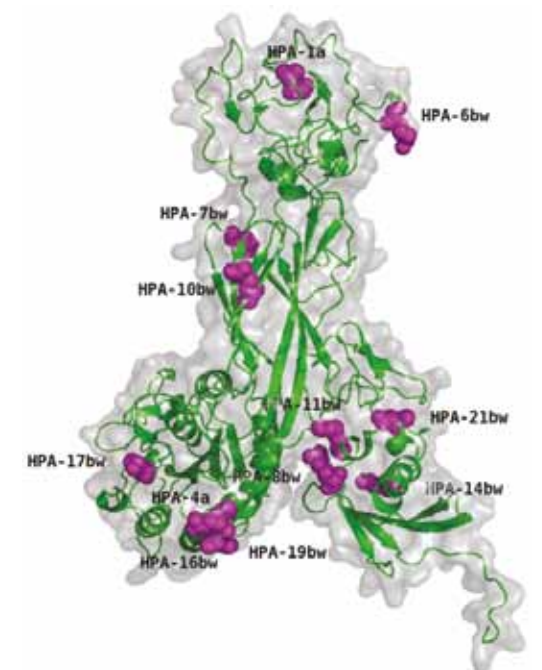


Figure 2: Location of the HPA polymorphisms of the β 3 structure. 3D model of the β 3 obtained from the PDB structure 3IJE. Shown are the peptidic backbone (green), the molecular surface (grey) and the atoms of the HPA polymorphic residues (magenta spheres). HPA codes are indicated. This representation was made by using PyMOL (<http://www.pymol.org>)

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Table 1: α Ib polymorphisms

Name	Polymorphism	AlloAb ^a	Accessibility	Mobility	Electr. Change ^c
Cab2 ⁷	Ser472Asn	Yes	60 %	Rigid	Not really
HPA-20w ⁶	Thr619Met	Yes	60 %	Flexible	Neg » Pos
Cab3 ^d	Glu667Lys	Yes	90 %	Flexible + + +	Neg » Pos
Lec ^d	Arg512Trp	suspected	50 %	Intermediate	Neut » Pos

a. AlloAb: alloantibody presence; c. Electr. Change: electrostatic change; d. polymorphisms not published

Conclusion:

Modeling of the different HPA forms of α Ib β 3 from 3D structure data and comparative analyses of the structure characteristics suggest that, as expected, antigenicity mainly depends on residue accessibility. The other structure features such as residue mobility and electrostatic do not appear critical for the presence of an alloantibody although they can modulate its binding affinity. These structure analyses are performed on static structures obtained directly from the Protein Data Bank, or after modeling of a specific allele. However, most molecular structures are highly dynamic, and static analyses can be insufficient to unveil subtle differences or peculiarities. To solve this problem, dynamic analysis can be used but such technique requires large computational resources and is time consuming. Dynamic analysis technique will be applied to study the HPA-1 system of β 3, the most frequent HPA system involved in FNAIT in Caucasian population in term of frequency and pathology severity.

“...residues involved in β 3 HPA polymorphisms are not evolutionarily conserved.”

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Future, Present and Past Frontiers of Neutrophil Immunobiology

Neutrophils have finally arrived in the collective consciousness of the international transfusion medicine community. Neutrophil serology has been largely unrecognised and certainly underappreciated, in spite of the pioneering work carried out at the Central Laboratories of the Netherlands Red Cross Blood Transfusion Service¹.

Neutrophils have finally arrived in the collective consciousness of the international transfusion medicine community. Neutrophil serology has been largely unrecognised and certainly underappreciated, in spite of the pioneering work carried out at the Central Laboratories of the Netherlands Red Cross Blood Transfusion Service¹. This work resulted in crucial technical breakthroughs which revolutionised the confident demonstration of neutrophil specific antibodies. Neutrophil immunology was no longer a craft, but a science.

Neutrophils are challenging cells to work with in vitro. Their in vivo half life of 6-12 hours and their fragile constitution demands the avoidance of membrane damage, unwanted clumping, apoptotic changes and low cell yield.

The need for diagnosis and treatment of immune neutropenias drove the development and refinement of the first neutrophil serological assays; the Granulocyte Agglutination Test (GAT) and Granulocyte Immunofluorescence Test (GIFT). The GIFT combined the use of freshly harvested neutrophils, paraformaldehyde fixation and labelling of bound antibodies with an F(ab')₂ fragment of antihuman globulin. Good practice in neutrophil serology is underpinned by established red cell serological practice which emphasises test sensitivity and specificity. Optimisation of incubation temperature and time, awareness of the behavioural characteristics of each antibody class, understanding the challenges of

“ Good practice in neutrophil serology is underpinned by established red cell serological practice which emphasises test sensitivity and specificity.

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“ Clarification of the nature of the human neutrophil specific alloantigens (HNA) and the need to better define antibody specificity lead to the design of more sophisticated serological tests.

antibody avidity, knowledge of the different characters and lineage representation of each antigen, the use of suitable serum to cell ratios and other similar technical pillars, combine to support good neutrophil serology practice. The ISBT Granulocyte Immunobiology Working Party now oversees the International Granulocyte Immunology Workshop (IGIW) whose aims include recognition of new neutrophil alloantigens, better definition of their antibodies and improved cooperation and education to cement a standardised and reliable approach to neutrophil immunology.

Clarification of the nature of the human neutrophil specific alloantigens (HNA) and the need to better define antibody specificity lead to the design of more sophisticated serological tests. The assay presently recognised in the IGIW for this purpose is the Monoclonal Antibody Immobilisation of Granulocyte Antigens (MAIGA or MAINA) test.

Now, the demand to mitigate the transfusion risk of TRALI is driving the development and evaluation of a range of test platforms potentially offering high through put screening of blood donor sera for the presence of clinically significant HLA and HNA antibodies. These three history-making technological shifts represent the natural iterative cycle of systems biology. The needs of biology and medicine push the creation of new technology, while this same new technology revolutionises biology and medicine. **It must be recognised**, however, that a commercial “pull” factor is also influencing this virtuous cycle. While great

potential exists, there are hazards to be avoided. Release of a high throughput commercial, screening system which does not ensure meaningful identification of donors at risk of triggering TRALI could not only jeopardise blood product banks, but could result in loss of confidence in neutrophil serology for the diagnosis and treatment of immune neutropenias.

The holy grail of mass serological screening must include test sensitivity and specificity, high throughput via automation and cost effectiveness. Presently, target antigen choice is amongst whole neutrophils (and other blood cells), transduced erythroleukaemia lines and recombinant peptide epitopes. Each has its serological costs and benefits. Robust evaluation to determine the sensitivity and specificity limits of each new platform compared with validated classical methods is needed, but developmental platforms remain challenged in these dimensions.

Because the focus of the new technologies is detecting antibodies that may trigger TRALI, TRALI implicated sera need to make up a substantial proportion of any validation materials. Comprehensive validation can be onerous for single laboratories and may be more effectively done in collaboration with established reference groups.

Neutrophil immunobiology as a discipline sits within the broader landscape of cell biology and innate immunity. These disciplines are informing research into the complex mechanism of TRALI. Proteomics and genomics have enabled better characterisation of the HNA. Neutrophil immunobiologists are accessing the most advanced technologies to answer new and old questions being posed by advances in transfusion medicine practice. As the future unfolds, they need to keep a firm grip on their own technological history to ensure better prevention, meaningful screening, diagnosis and helpful treatment of clinical conditions in which the neutrophil plays a pathogenetic role.



**Lin Fung, PhD, BAppSc(MLS),
GradDipMnmt,**
Principal Research Fellow,
Critical Care Research Group,
The Prince Charles Hospital &
University of Queensland
Chairperson of the ISBT
Working Party on Granulocyte
Immunobiology

The ISBT Working Party on Granulocyte Immunobiology

Our innate immune system is dependent on the function of neutrophils (PMNs) which migrate to sites of infection to phagocytose foreign microorganisms and interact with other key innate system cells. In spite of the immunological importance of PMNs, the field of granulocyte immunobiology is small, because these cells have a short life, making them difficult to work with. (Note: the term granulocyte is often interchangeable with neutrophil because (i) the majority of granulocytes are PMNs and (ii) because serological assays usually test all the granulocytes without removing the eosinophils or basophils.) Recently, the investigation of PMN reactive antibodies has become a "hot topic" because PMN reactive antibodies have been implicated in severe and fatal TRALI events^{1,2}.

Investigations of PMN reactive antibodies are one of the primary interests of the ISBT's Working Party on Granulocyte Immunobiology (WPGI). This group works to bring together ISBT members working on laboratory and clinical aspects of Granulocyte Immunobiology (refer to <http://www.isbtweb.org/working-parties/granulocyte-immunobiology/> for terms of reference etc) and seeks to promote international best practice in this specialised field. To do this, the Chair of the ISBT-WPGI is also the Chair of the International Granulocyte Immunobiology Workshop (IGIW) which conducts the annual Quality Assessment Exercises (QAE). Participation in the IGIW is limited only to reference laboratories for granulocyte immunobiology and there are currently 16 participants (13 in Europe, 2 in USA, 1 in Japan and 1 in Australia). The

expertise of the group is shared through publications such as the "Recommendations of the ISBT Working Party on Granulocyte Immunobiology for leukocyte antibody screening in the investigation and prevention of antibody-mediated transfusion-related acute lung injury" *Vox Sang* 2009;96:266-269. Therefore, the ISBT-WPGI is an ideal resource for laboratories interested in developing skills in granulocyte immunobiology and also for the evaluation of new HNA antibody platforms.

In 2011, both regional ISBT conferences (Lisbon, Portugal <http://www.isbtweb.org/lisbon/>; Taipei, Taiwan <http://www.isbtweb.org/taipei/>) will have sessions dedicated to TRALI investigation. ISBT members can access the substantial accumulated granulocyte immunobiology expertise within the ISBT-WPGI by contacting Dr Lin Fung (Chairperson) office@isbtweb.org.

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21st Regional
Congress
of the ISBT

June 18-22, 2011
Europe, Lisbon, Portugal

Final
Announcement

ISBT
LISBON
2011



**Yoke Lin FUNG, PhD,
BAppSc(MLS), GradDipMnmt**
Principal Research Fellow,
Critical Care Research Group,
The Prince Charles Hospital &
University of Queensland

Granulocyte Feast in Taipei

Want to learn more about granulocytes?
The XXIIInd Regional Congress of the ISBT,
Asia in Taipei is where you want to be.

The organisers have scheduled a “Master Class in Granulocytes” and a “TRALI State of the Art lecture” to tell you all you ever wanted to know about granulocytes.

The Master Class will start with Dr Lin Fung (Chair of the ISBT Working Party on Granulocyte Immunobiology) providing you with an introduction

This will be followed by a talk on a transfected cell line which expresses human neutrophil antigens (HNA) by one of its creators, Dr Fumiya Hirayama (Chief of Preparation Section and Research Section, Osaka Blood Center). These novel transfected cell lines are known as KY cells lines and express HNA-1a, -1b, -1c, -2a, -4a, -4b, -5a and -5b. Importantly, KY cell provide a potential unlimited source of HNA for mass screening of HNA antibodies.

“The organisers have scheduled a Master Class in Granulocytes and a TRALI State of the Art lecture to tell you all you ever wanted to know about granulocytes.”

Dr. Chen-Cheng Chu (Taiwan) will then go on to discuss the clinical scenarios of both auto and allo-immune neutropenias. Dr Chu and colleagues recently published data from 155 cases of neutropenia in children, and found that in Taiwan anti-HNA-1a is the most commonly detected antibody in autoimmune neutropenia and that it is associated with HLA-DQB1*0503 (Wang LY et al Transfusion 2009).

to neutrophil antigens and explaining why granulocytes and neutrophils are used interchangeably. She will provide details on the validated techniques for neutrophil investigations (GIFT and GAT) and discuss the difficulties, strengths and limitations of those techniques.

In addition to the Master Class, there will be a TRALI state of the art talk on “Animal models of TRALI” by Dr Lin Fung. Dr Fung has been actively involved with both mouse and sheep models of TRALI. She will share her experience as well as review antibody mediated TRALI in small animal models and non-immune TRALI in the rat and sheep model.



“ Don't forget to include Lisbon in your agenda!”

Silvano Wendel

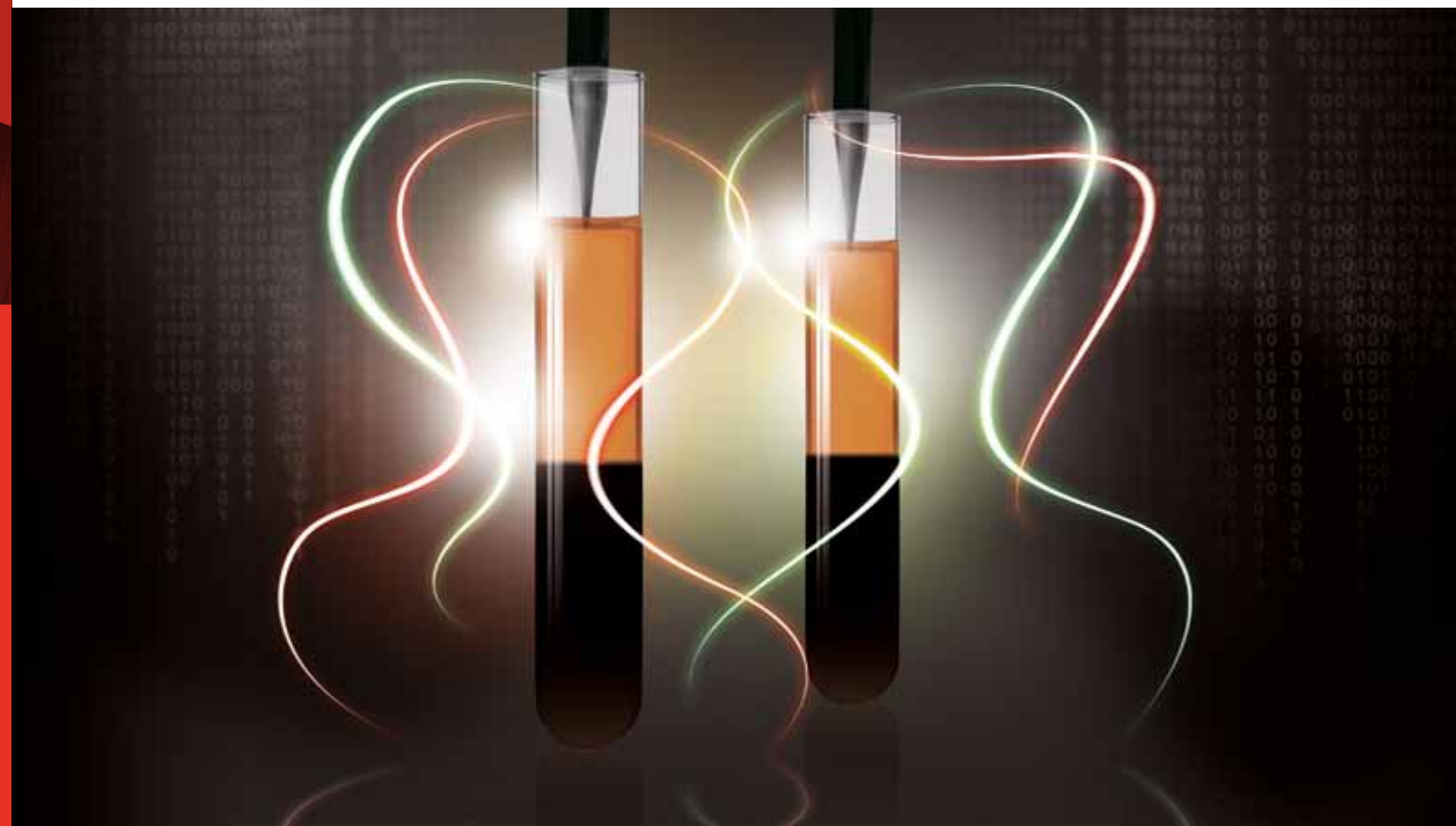
As you all might know, the recent Ausbio court case judged in favor of ISBT. The ISBT's aims include "modeling the highest standards of corporate governance". With the lessons learnt from the case we are now working to improve the current Statutes to render our Society more modern, plural and dynamic. It is time now to move forward and faster in order to promote development, harmonization and good understanding amongst the whole ISBT membership spread around 105 countries. Only by sharing knowledge, support and expertise can we achieve this task. And I certainly count with all ISBT members to continue this honorable mission; after all, global blood safety is our ultimate goal.

After the excellent meeting held last October in Beaune, France, a series of interesting articles organized by Cécile Kaplan (chair of the ISBT Working Party on Platelet Immunobiology) are published in this issue covering the most recent and important aspects related to this field. Starting with basic and general concepts, the reader will move to 3D protein structure modeling as an insight of platelet alloimmune response, and its main consequence on the development of clinical neonatal alloimmune thrombocytopenia. This severe disease is still under-recognized in many countries and certainly deserves more attention from medical authorities, as well as investigation and clinical laboratories to promptly standardize non-invasive methods to be made available as a general procedure worldwide. This will relieve the current burden on pregnant women and neonates. It is fortunate to have this important subject covered in Transfusion Today. Granulocytes also play a very important role in immunogenetics, and the subject is covered by members of the ISBT Working Party on Granulocyte Immunobiology, under

the new leadership of Lin Fung. The need for diagnosis and treatment of immune neutropenias, classification of human specific alloantigens (HNA), the need for standardization of new immunological methods apart from GAT (Granulocyte Agglutination Test) and GIFT (Granulocyte Immunofluorescence Test), and the ever increasing need to reduce the life-threatening TRALI cases are certainly a major contribution from this group. In addition, all members are encouraged to attend the forthcoming meetings in Lisbon and Taipei, where there will be special sessions dedicated to this field, which I think will be very enticing.

I would also like to recognize the splendid meeting organized in Cairo last December by Faten Mofteh and Kemel Boukef, during the VIII Arab Transfusion Medicine Course (ATMC8). I had the opportunity to witness the importance of this group and the experience gained by them has to be shared with other regions of the world. In addition, the recent 13th International Hemovigilance Seminar in Amsterdam provided to the attendees an excellent venue for exchanging the latest achievements in this important Transfusion Medicine area. Congratulations to Martin Schipperus, René R.P. de Vries and all the Organization Committee. Finally, I am proud to announce that over 800 abstracts from 66 countries were submitted to our Regional Congress in Lisbon. This is a positive proof that we are more united than ever. Don't forget to include Portugal in your agenda. You will enjoy this beautiful country.

Silvano Wendel
ISBT President



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Welcome to our new members

November 2010 - January 2011

Americas

- **MEXICO:** Jose Antonio Arroyo Perez, Maria Sagrario Romero Estrella
- **UNITED STATES OF AMERICA:** Logan Barnett, Rodeina Davis, Richard Forero, Mary Kowalski, William Reed, Susan Roseff

Western Pacific

- **AUSTRALIA:** Damien Heathcote, Ellen Maxwell, Catherine Willis
- **JAPAN:** Magumi Hayashi
- **KOREA, REPUBLIC OF:** Dong Hee Seo

Europe

- **IRELAND:** Barry Doyle
- **NETHERLANDS:** Henk Meekers

Eastern Mediterranean

- **IRAN:** Zeyd Merenkon
- **SAUDI ARABIA:** Osama El Fayoumi



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Geoff Daniels
Secretary-General ISBT

Happy Anniversary, Vox Sanguinis!

Vox Sanguinis, the International Journal of Transfusion Medicine, is the official journal of the ISBT. It is provided free-of-charge to all ISBT members and is also sold to many other individuals and libraries worldwide.



1955

1996

2011

This year sees the publication of the 100th volume of Vox Sanguinis, which is being celebrated by the publication of a special anniversary edition containing 16 invited reviews on a variety of topics related to transfusion medicine and science. In contrast to the usual red, the cover is mostly in gold because, since Vox publishes two volumes per year, 2011 also represents a golden anniversary.

The history of Vox Sanguinis, however, is not that straightforward. The predecessor of Vox Sanguinis, first published as a newsletter of the Netherlands Red Cross Blood Transfusion Service (CLB), was named Bulletin van het Centraal Laboratorium van de Bloedtransfusiedienst van het Nederlandse Rode Kruis and adopted the more catchy title of Vox Sanguinis (Voice of Blood) in 1953. In 1956 Karger of Basle took over publication and at the beginning of that year volume 1 of the relaunched Vox Sanguinis was published, the previous volumes becoming known as the 'Original Series'. In 2001, Blackwell Science (now Wiley-Blackwell) replaced Karger as publishers of the journal. The first and founding Editor of Vox Sanguinis was JJ van Loghem of Amsterdam; subsequent Editors-in-Chief have included LP Holländer (Basle), Paul Engelfriet (Amsterdam), Marcela Contreras (London), and, the current

Editor-in-Chief, Wolfgang Mayr from Vienna. A detailed history of Vox Sanguinis by Leikola and Van Aken is published in the anniversary edition (Vox Sang 2011;100:2-9) and has been a source for much of the information in this brief article.

In addition to original papers and reviews, Vox Sanguinis publishes regular International Forums, which are effectively printed discussions by experts in the field on various topical subjects, often involving some controversy. Vox Sanguinis also publishes reports arising from ISBT Working Parties and, as supplements, the abstracts from the ISBT International and Regional Congresses. Before 2006, Vox Sanguinis also published the proceedings of ISBT Congresses as plenary, but these are now published in the 'ISBT Science Series'.

Editorial policy of Vox Sanguinis is managed by the Editorial Board, which acts independently of the ISBT. The Editorial Board is chaired by the Editor-in Chief, and is composed mainly of the Section Editors. The journal is governed by a standing committee, which is chaired by the ISBT Secretary General and members of this committee are appointed by the ISBT Board of Directors. It is the

Vox Sanguinis Standing Committee that appoints the Editor-in Chief.

Vox Sanguinis always welcomes the submission of pertinent papers. Manuscripts should be submitted through the website (<http://mc.manuscriptcentral.com/vox>) to the Editor-in Chief, who distributes them to the appropriate Section Editors, experts in various aspects of transfusion medicine and science. If the Section Editor considers the paper to be suitable it will be sent out for peer review. Finally, if accepted, the paper will initially be published online and then in print.

Will Vox Sanguinis be around to celebrate its centenary? I would not expect journals to be published in print form in 2051, but I suspect that Vox will still be published in some format.

So, happy anniversary Vox Sanguinis, may you continue to be the voice of blood transfusion, cellular therapies, and other related topics for many years to come.

Geoff Daniels

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From ISBT Central Office



ISBT appoints Scientific Secretary

We are pleased to announce that Martin Olsson has been elected by the Board of Directors as ISBT's first Scientific Secretary.

The purpose of appointing a Scientific Secretary is to ensure that the scientific programme of ISBT international and regional congresses is of a consistently high standard, that new speakers and new topics are a feature of the scientific programme of international and regional congresses and that new ideas are captured in the scientific programme e.g. a new format if appropriate etc. The Scientific Secretary will appoint a scientific programme committee which will advise the Scientific Secretary on appropriate topics and speakers for ISBT regional and international congresses. The Scientific Secretary and programme committee will work in collaboration with the local organising committee. The Scientific Secretary will also use the ISBT Working Parties as a sounding board for suggestions for sessions and speakers in the scientific programme.

Martin writes: It is an honour and a privilege to be appointed as the first Scientific Secretary of the ISBT. Needless to say, I very much look forward to meet the challenge of keeping this 75-year old organization scientifically vital and fit for the future. When I started my carrier in the Blood Bank back in 1987, I was still in medical school. Before this, I had earned my living as a piano player at a ballet school, in parallel with my studies. My plan was to find a more medically relevant but still entertaining job for vacations, nights and weekends so that I could continue to earn and learn at the same time, even if I realized that the view would be very different. Little did I know then, that this new field would become the love of my life, at least in professional terms. Little did I understand that, internship and residency aside, I would never really want to move on because of what I felt for all the cool things that were going on in the wonderful world of transfusion medicine and transplantation immunology. I cannot make my mind up if I see myself more as a physician, a scientist or an administrator – maybe simply a phascilitator (read: facilitator)?! However, the great opportunity in this profession is that we don't have to make that choice. It is more a question of what your preferences are and what tasks lie ahead for the moment. Similarly, ISBT requires all those qualities to achieve its goals and its strategic vision – luckily, not necessarily rolled into one

single person but throughout the member- and leadership. In my professional life, I have goals similar to those of the ISBT: Promoting scientific excellence, collegial exchange and educational efforts within our field, both to push the frontiers of what is possible by research-driven development and to help those around the globe in need of basic learning, continued training and proper equipment. My experience from previous and current roles within the ISBT and other organizations should help me serve ISBT to achieve this.

Thus, I look forward to your support in taking ISBT into the future by achieving our common goals. Together we will continue to make ISBT reach out to the world and all the amazing people out there devoting their lives to the gift of blood. ISBT is built by us and works through its members. Our popular congresses constitute one of our most important tools. I will work very hard to make sure we keep on rejuvenating these mobile meeting places, as well as our other education platforms, by inviting the best speakers, sharing with us the most exciting and innovative science out there.

Looking forward to seeing you at high-quality conferences around the world in the future.

Martin L. Olsson, M.D., Ph.D.
Scientific Secretary of the ISBT

Professor and Senior Consultant in Transfusion Medicine
Dept. of Laboratory Medicine, Faculty of Medicine,
Lund University, Sweden.

Medical Director of the Nordic Reference Laboratory
for Genetic Blood Group Typing at the Department
of Clinical Immunology and Transfusion Medicine,
University and Regional Laboratories, Lund, Sweden



ATMC8 IN CAIRO

Blood component preparation and appropriate clinical use of blood. December 1-4, 2010

The 8th Arabic speaking transfusion medicine course (ISBT-ATMC8). Organised by ATMC Executive Board in collaboration with ISBT Academy took place in Cairo December 1-4, 2010.

The aim of the courses is to enhance the professional development of individual transfusion medicine specialists and scientists, to be able to influence the decisions of policy makers in the respective countries, to establish safer transfusion services and promote good transfusion practice across the region. The specific topic of the 2010 course was blood component preparation and appropriate clinical use of blood. By tradition and also this year, ISBT supported the meeting through participation of its Academy.

It is always a pleasure to participate in transfusion related events in Arab Countries. This is due to the kindness of the people, the focus of improvement in transfusion medicine, the scientific work which develops in the Arabic countries and the energy that the participants show in the very well organised meeting. There were 122 participants in the meeting from 18 countries in the Middle East and Pakistan. In addition, participants from 8 non-Arabic speaking countries 15 international and regional speakers were participated.

The program included 23 presentations, 6 activity reports, 2 workshops, 1 Interactive session, posters and two symposia organised by the industry. The importance and beauty of the meeting is related to the engaged discussions of local solutions to challenges in transfusion medicine and the ability of the countries with variable standard of transfusion medicine to share experiences and help each other.

One scientific presentation must be highlighted, namely the presentation of a relatively inexpensive and efficient system for SD virus inactivation of mini-pools of plasma and cryoprecipitate for production of safe plasma products. A small clinical trial of virus inactivated cryoprecipitate was presented. The results were promising both with regard to effect and lack of side effects.

ACTM8 is an example of a transfusion meeting in an area with common culture and strong driving forces in improving the standard of transfusion medicine by joint effort and willingness to share experience and solutions. The Arab Hemovigilance Network is established and reported in the meeting and a common assessment-system was discussed.

We are already looking forward to ACTM9.

EASTERN MEDITERRANEAN

British transfusion visitors in Smolensk

In Russia transfusion medicine is a separate physician profession (named "transfusiologiya"). Each hospital that wishes to transfuse blood must have a transfusionist in the staff. A surgeon or internist should have a special 504 hours post-graduated course to become a transfusionist.

Such a course took place in the Smolensk Medical Academy in the beginning of 2011. The Russian Transfusionist Association invited three well-known British colleagues to share their experience to help with improving the quality of education of Russian Transfusionists (see photo).

The most interesting part of the meeting was a question & answer session which developed into a double-side discussion. As opposed to the Russian transfusion system there is mandatory use of disposable sampling pouch and needle protector integrated with a blood bag system as

well as universal leukoreduction in the British blood service.

Visiting Smolensk Regional Blood Center British colleagues were surprised to see two working devices for plasma and platelets pathogen inactivation.

Two different approaches for multiple sclerosis treatment were also discussed: total plasma exchange in Britain and autologous stem cell transplantation in Russia.

This kind of meeting enriches blood transfusion knowledge and practice to improve blood recipient treatment.

Foreign colleagues are kindly invited to join blood transfusion seminars in Moscow in May (18-20) and in December (14-16) 2011.



Course participants and (left to right at first row) Natalya Mikhailova (Deputy Head of Smolensk Regional Blood Center), Martin Gorham (England), Jurai Petrik and Angus Douglas (both Scotland)

EASTERN EUROPE

The cord blood bank of “Mexican Institute of Social Security” a Mexican experience

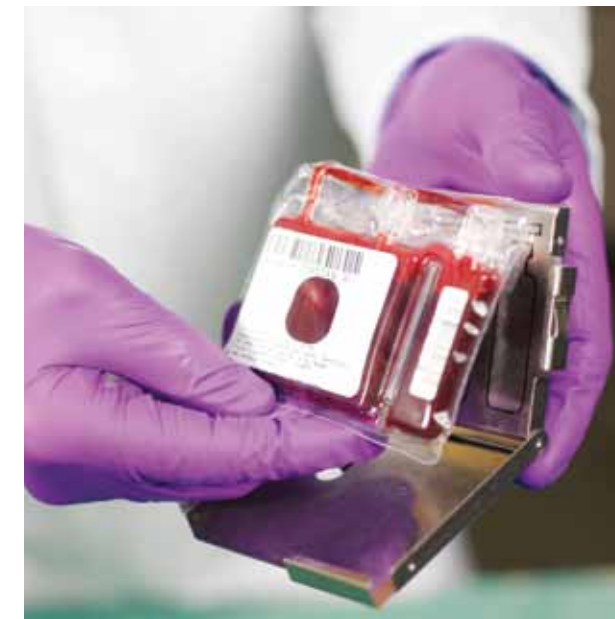
The cord blood bank of the “Mexican Institute of Social Security” (IMSS) has been operational since the year 2005 and obtained ISO-9001-2000 certification in January 2006 by the organization QMI SAI Global, in proving the quality of its operating processes based on Good Manufacturing Practices (GMP) and its Standard Operating Procedures (SOP) suggested by NetCord. In 2009 IMSS obtained re-certification regulated under ISO-9001-2008 and in 2009 was invited to participate in the World Marrow Donor Association (WMDA) Registry, given its relevance reached in only four years working.

In June, 2010 the WMDA published its Annual Report 2009, with statistical information of 132 Cord Blood Banking in the five continents. For the first time, the IMSS Cord Blood Bank appears in the Annual Report of WMDA, reaching the fifth position as the most productive Cord Blood Bank in respect to the consumption rate.

The experience in our public Cord Blood Bank, in 6 years of operation though limited, has showed interesting aspects. One of them consists in the high rate of consumption in units provided for transplantation. Until December 2010

it represented 9.57 % of its inventory, that is, from 689 units cryopreserved, 66 have been released for transplantation. This high rate of consumption has been possible because of the low genetic diversity in our donors and recipients in the center and south of our country, which has made possible to find a match unit in 70.2 % of cases. In the transplanted units, the degree of matching in respect to Human Leukocyte Antigen (HLA) was 6/6 in 2.6 % of the cases, 5/6 in 17.4% and 4/6 in 80% of cases. In an evaluation made from February 2005 to October 2009, the median values of total nucleated cells transfused to patients consisted of 6.71x10⁷ per kg and the median values of CD34+ cells was 4.8x10⁵ per kg. Engraftment was reported in 56% of cases. The myeloid engraftment was observed on average in 23 days, platelet (PLT) engraftment on average in 38 days. The event free survival according to disease was 41%, while the overall survival is 47%, with survival periods of 126 to 1654 days.

Until December 2010, 66 units have been used in 47 recipients for 54 transplants, 7 recipients were re-transplanted and 6 received a double-unit of cord blood, this happened in 7 transplantation centers of “Mexican Institute of Social Security”.



The two patients transplanted in June 2006 have almost 5 years with event free survival according to disease. The results of transplantation in our centers is published currently in the online version of Transfusion. We are working to reach an international certification that gives us the possibility to make available our cord blood units for the international community.

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“ ... the IMSS Cord Blood Bank appears in the Annual Report of WMDA, reaching the fifth position as the most productive Cord Blood Bank in respect to the consumption rate.

Launch of World Blood Donor Day 2011 in Argentina



voluntary donation. In recent years we have come far, but this does not change from day to day, it will be modified with education and work only. We have a plan, we know where we are going and on this basis we can move forward", Dr. Manzur said. On the other hand, Dr Pla Illa said he felt a great pleasure to share the announcement of Argentina as host of World Blood Donor after remembering that Barcelona hosted the event in 2010, which has seen a before and after in the field of Transfusion Medicine not only for Catalonia, but also to Spain.

Every year Argentine celebrates on November 9th its own National Blood Donor Day in order to commemorate the first time in the world a citrated blood transfusion was performed by Dr Luis Agote in 1914 without side effects for the patient.

The event in 2010 gave the opportunity for the official launch of Argentina 2011 as headquarters of World Blood Donor Day, which is celebrated every June 14th.

During the ceremony, some football teams were distinguished because of their work in promoting voluntary blood donation.

The meeting was attended by authorities of National Ministry of Health (Minister, Dr. Manzur, Assistant Secretary of Policy, Regulation and Supervision Dr. Leibovich and Dr. Maschio, Director of National Blood Plan), Niels Mikkelsen, Secretary General of FIODS, Dr. Ramon Pau Pla Illa, Director of the Blood Bank of Catalonia, the ISBT Regional Director Southern Americas among other officials representatives of Blood Programs from different Latin American countries, Provincial Blood Plans and over 200 representatives from voluntary blood donation associations nationwide.

"The mechanism of blood donation by replacement has to be gradually changing to the model of

Currently, 70% of Argentine's population donates blood for friends or relatives who need a blood transfusion. This model does not have optimal results and forced the health authorities to change to another one, based on altruistic and repeated blood donations. Argentina's application for hosting the World Blood Donor Day Blood was based on three pillars: ethics, government-society relationship and the regional approach because we not only offer the house, but we are working on behalf of Latin America, Leibovich noted in his speech.

As Latin Americans we are proud to celebrate the World Blood Donor Day 2011 in Buenos Aires, taking in consideration that Argentina is the first Latin American country which was chosen for hosting this event.

We invite to share this experience to people from our region and the rest of the world.

Contact us for be informed and plan your participation:

Website: www.msal.gov.ar
e-mail: plannacionaldesangre@msal.gov.ar
e-mail: plannacionaldesangre@gmail.com
Service Call Center, toll free: 0 800 222 1002

The Sixth Red Cross and Red Crescent Symposium on Blood Programs in the Asian Region: Securing Stable Supply of Safe Blood



The titled symposium was successfully held in Tokyo Japan during 24th -26th November, 2010 with more than 70 participants from 25 countries and regions.

International Federation of Red Cross and Red Crescent Societies advocates provision of safe blood and blood products based on the Voluntary Non Remunerated Blood Donation. Securing safe blood and preventing AIDS, hepatitis, and other transfusion-transmissible infections continue to be issues of common concern for blood programs in many Asian countries. The Federation also promotes further strengthening of cooperative ties within the region. To achieve this, the Japanese Red Cross Society (JRCS) and the Thai Red Cross Society (TRCS) organized symposia entitled "Securing Safe Blood" in 1995, 1998, 2001, 2004 and 2007. National Societies that participated in these last five symposia have persevered with their efforts to ensure the provision of safe blood in their national context.

In November 2010, three years since the last symposium, the JRCS and the TRCS hosted the Sixth Red Cross and Red Crescent Symposium on Blood Programs in the Asian Region: Securing Stable Supply of Safe Blood (I), in cooperation with the International Federation of Red Cross and Red Crescent Societies (IFRC) and the International Society of Blood Transfusion (ISBT). The symposium overviewed progress and changes in the blood program in each

country, while country representatives exchanged information on their blood programs and shared experiences in Donor Recruitment, Blood Component Therapy & TTI, Data Management for Donors and Patients, Blood Program Management including technical aspects of these topics.

In addition, the program included Tokyo bay dinner cruise on the second day which deepened the friendship among the participants. Also, after the closing ceremony, the participants had an opportunity to visit Tokyo Metropolitan Blood Center, the largest blood service facility in Japan. The organizers are sure that the symposium could contribute to the steady development and cooperation of blood programs in the Asian region.



2011

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Lyon, France
www.sfts.asso.fr
insc-sfts@europa-organisation.com

May 10 – 11

**The 2nd International
Congress on Transfusion
Medicine-Plasma Industry**
Tehran, Iran
www.ibto.ir
congress@ibto.ir

May 11 – 14

**14th TIF International
Conference for Patients
and Parents,**
Istanbul, Turkey
www.tif2011.org
info@imterium.com.tr

May 18 – 21

17th Annual ISCT Meeting
Rotterdam, Netherlands
www.celltherapysociety.org
isct@celltherapysociety.org

May 24 – 25

**IPFA/PEI 18th International
Workshop on Surveillance
and Screening of Blood
Borne Pathogens**
Dublin, Ireland
www.sanquin.nl/ipfa/
ipfa@sanquin.nl

June 18 - 22

21st Regional Congress of the ISBT, Europe
Lisbon, Portugal
www.isbtweb.org/lisbon
lisbon@isbtweb.org

November 20 - 23

22nd Regional Congress of the ISBT, Asia
Taipei, Taiwan
www.isbtweb.org/taipei
taipei@isbtweb.org



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