



International Society of Hematology
and the Interamerican Division

Newsletter ISH IAD

December 2008 - January 2009

XXXII World Congress of the International Society of Hematology

The Future of ISH

From remarks of president-elect, Dr. Saengsuree Jootar, at the opening of the Congress.

The 32nd World Congress of ISH in Bangkok, October 19-23, 2008, was a great success with more than 1,400 participants from 66 countries. The Thai Society of Hematology must be congratulated for its great effort.

To be appointed as the next ISH chair starting next year is a great challenge for me. Ours is the oldest hematology society with members from 99 countries around the world. I am very pleased to learn that ASH president, Professor Kaushansky has designated Dr. Rubin Mesa as council from USA and ASH representative in ISH with full support for his activities. This is very good news.

My mission is to initiate the Society's official journal, something we have struggled to achieve for several years. It would be a great benefit to the members around the world, especially those in the developing countries where resources are limited and where members have difficulty in publishing in journals with high impact factors. An official ISH journal would give them an alternative for presenting their work to the world. We don't expect that the impact factor of this journal will be great at the beginning; We may start online, and then work our way up until it is at the standard of other peer-reviewed journals.

Also, I believe we can recruit more members from those countries who have had no representation in ISH. The hematologists from Myanmar have already shown interest in joining, and I think this is a good sign. And there are many more countries we can encourage to join us. ISH can help countries with resource limitations to develop the skills, laboratory techniques, or training to allow our young colleagues help set up the units.

These goals need time and effort to develop, but I believe that together we can achieve them. We need all your support.

ISH for Developing Countries

From remarks of Dr. Guillermo Ruiz Arguelles, chairman of the board, at the opening of the Congress.

Dr. Ruiz Arguelles thanked the organizers for their efforts as well as for allowing the participation of members of the Society's three divisions in its academic program. His remarks focused on the importance of encouraging participation from developing countries. The American Society of Hematology and the European Hematology Association, which are growing exponentially but "have not focused enough on the practice of hematology in develop countries where more than two thirds of the inhabitants of the world reside. This is the scope and purpose of the International Society of Hematology: our sphere of influence is substantially larger... and the impact of our activities will benefit a far larger number of patients, as always, the most important actors in all our endeavors."

Dr. Ruiz went on to say that the organization of academic meetings in these countries could help counter the "Matthew effect," in which final credit for a discovery or new achievement tends to be ascribed to the most famous researcher associated with it. This hurts academicians in developing countries because of the great difficulty entailed in pursuing high-caliber research under non-optimal conditions. ISH meetings, he said, "should become a forum for scientific accomplishments conducted in developing countries."

ISH-IAD Joint Meeting April 29-May 2, 2009

Agrupación Mexicana para el Estudio de la Hematología / IAD
Morelia, Michoacán, Mexico
www.amehac.org

VIII Jornada Latinoamericana de Hematología, Inmunología y Medicina Transfusional Mayo 18 al 22, de 2009, La Habana
<http://www.hematologia2009.com>

ISH-EAD Meeting. Cairo, Egypt, October 10-13, 2009
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XXXIII ISH World Congress Israel, October 2010





International Society of Hematology Interamerican Division

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The International Society of Hematology is the first worldwide professional hematology society, founded in 1946 at a meeting that included Mexican and American hematologists, plus one Canadian and one British hematologist. For a decade the ISH was the only society in which the leading international hematologists participated, presenting the most important advances in the field. It now consists of three divisions: the Interamerican, the European & African, and the Asian Pacific, each with an executive secretary and a board with a periodically rotating president. The society holds a world congress every two years, and each division holds a divisional meeting every two years on the alternate year. Find more information on the International Society of Hematology on its new webpage: www.ishworld.org.

Membership Benefits:

Benefits include membership in the world's oldest hematology society, and participation in congresses on all the continents, which provides you the opportunity to learn about the health problems of the different regions of the world and to share information with the leaders in hematology from different countries. You have access to our webpage with information about our activities. A periodic newsletter with the latest developments from the latest hematology congresses is a new benefit. Our annual dues of \$20 a year are the lowest in the field.

Dr. Saengsuree Jootar, President-Elect of ISH

Dr. Saengsuree Jootar was elected president of the ISH Board, for a term to in October 2009. Dr. Jootar is professor of medicine at the Mahidol University in Bangkok, Thailand, and director of the bone marrow transplantation program of Ramthibodi Hospital. She is a former president of the Thai Society of Hematology. She served as congress president of the XXXII World Congress of the International Society of Hematology recently held in Bangkok. After graduating from Mahidol University she went to Saint Louis University in Missouri for training in Hematology. Subsequently, she was at Beth Israel Medical Center in New York and Vanderbilt University Hospital in Tennessee in the United States.

Dr. Jootar has been on the editorial board of the *Thai Journal of Hematology*. She has published more than 70 times, and is a leader in the field of bone marrow transplantation.

Dr. Ruben Mesa Appointed Editor of ISH Newsletter

Norman Maldonado MD, MACP
Secretary General, ISH Interamerican Division

Dr. Ruben Mesa, the recently appointed representative of ASH and the United States to the Executive Board of ISH, was appointed editor of our newsletter. He is associate professor and section head of the Mayo Clinic's Hematology Division in Rochester, Minnesota. He did his undergraduate studies at the University of Illinois in Urbana, graduating with two bachelors' degrees, one in nuclear engineering and another in physiology in 1991.

Graduating from Mayo Medical School, he completed an internal medicine residency there and a Hematology and Medical Oncology Fellowship in 2002. He is board certified in Internal Medicine, Hematology and Medical Oncology.

He is a very productive researcher and prolific writer. In 2005 he received the Mentor Award from Mayo and in 2007 the Educator of the Year award of the Internal Medicine Residency Program. He has published 106 scientific papers, and five book chapters mainly on myeloproliferative disorders. He is a reviewer for many journals and last year was named to the Blood editorial board. He is very active in the American Society of Hematology and during the past few years has delivered many presentations at its annual meetings and participated as a board member for the meetings' newsletters. He is the secretary of the International Working Group on Myelofibrosis.

Stem Cell Transplantation

Dr. Guillermo Ruiz-Arguelles

Several salient topics concerning the field of stem cell transplantation were addressed during the XXXII World Congress of the International Society of Hematology, mainly related to the use of reduced intensity conditioning regimens to conduct allogeneic stem cell grafting. Professor Shimon Slavin of Tel Aviv, Israel, one of the pioneers of non-ablative stem cell transplantation (NST) presented data on the use of this type of allografting in several hematological diseases. Considering the fact that early mortality is substantially decreased when using NST to graft allogeneic hematopoietic stem cells, and that this effect is somehow counteracted by the incidence of post-transplant relapse, which is apparently increased, the long-term results of NST are similar to those of conventional allografting. Since the anti-malignancy effect of NST relies mainly on the graft-versus malignancy effect, the results of NST are better in those malignancies sensitive to this effect and in cases with a low-tumor burden. Along this line, the results of NST

seen to be particularly good in patients with chronic myelogenous leukemia (CML) as shown by researchers from Israel, México and Latin America. Data about the costs and long-term results of the treatment of individuals with CML were also presented during a symposium of CML therapeutics: Obtaining long-term similar results with the use of tyrosine-kinase inhibitors (TKI) or stem cell allografting using NST, the costs of long-term use of TKI are substantially higher than those of NST. Data were shown about costs: With the cost of the 180-day treatment with TKI, an allograft can be afforded in circumstances where limited resources prevail. Accordingly, in México and probably in other developing countries, NST is currently preferred as a once-in-life procedure over the prolonged use of expensive drugs such as TKI. NST has also been used to allograft umbilical cord blood cells, thus offering this therapeutic opportunity to a larger number of aged individuals or those with comorbidities. Professor Nelson Chao from

Duke University, Durham, presented an update in cord blood allografting. He placed special emphasis on the two salient prognostic factors to successfully allograft both children and adults with placental blood: The degree of HLA match and the number of grafted cells, both the total number of nucleated cells and the number of CD34 (+) cells. It seems clear now that in patients with a full match (6/6), the number of CD34 cells needed to successfully engraft can be lower than in individuals with a partial match (5/6 or 4/6). The topic of stem cell grafting in the treatment of patients with multiple myeloma (MM) was also addressed by Professor Sundar Jagannath from New York. The effectiveness of new drugs in the treatment of patients with MM such as bortezomib, thalidomide and lenalidomide has resulted in the reappraisal of stem cell autografting after high-dose therapy, which currently continues to be the best treatment option for these patients. Data concerning the results of allografting in MM patients were also presented.

MDS at ISH

David P. Steensma, Mayo Clinic Rochester, Minnesota

The myelodysplastic syndromes (MDS) featured in several sessions at the ISH meeting in Bangkok, Thailand. In the prepared education sessions on the first day of the conference, Dr. John Bennett, chairman of the MDS Foundation, discussed the latest revision of the World Health Organization MDS classification and also reviewed newer therapies for MDS. Dr. Yataro Yoshida of Takeda General Hospital in Japan discussed the biology of MDS in the education session, including our evolving understanding of apoptosis regulation and its contribution to marrow failure

and disease progression. Dr. Yoshida also reviewed newer MDS clinical trial data and emerging drugs in a special symposium, "New Horizons in Hematological Malignancies," later in the meeting.

The Myeloid Scientific Session at the ISH meeting also featured several presentations on MDS. Dr. Barry Skikne of the University of Kansas in the United States described an ongoing multicenter study of oral azacitidine for MDS, in which azacitidine has shown bioavailability ranging between 6% and 15%. Pharmacodynamic studies are on-

going, and data on treatment responses are eagerly awaited. Continuing with the theme of hypomethylating agents, Dr. David Steensma of Mayo Clinic presented an ancillary study of a previously presented clinical trial of a five-day outpatient decitabine regimen; Dr. Steensma's laboratory was unable to confirm a correlation between *ATRX* gene expression and either karyotypic findings or decitabine clinical response. Finally, Dr. Guang-sheng He of China presented several laboratory studies on the role of the complex mTOR pathway in MDS.

Red Cell Disorders

Dr. Lucio Luzzatto, Istituto Toscano Tumori, Florence, Italy

The mammalian red cell has been studied for decades as a unique example of differentiation pushed to an extreme. Few other cells are willing to sacrifice the ability to divide, the ability to make protein and even the right to obtain energy through oxidative phosphorylation; and probably no other cell is able, in return for that sacrifice, to accumulate, to the tune of 34% of its wet weight, a single protein that will serve the oxygen requirements of the entire body. Thus, there is hardly anything left in a mature red cell than this very protein, hemoglobin; the enzymes required for a minimalist style of intermediary metabolism; and an envelope for all of the above. Therefore we have traditionally classified intrinsic red cell disorders as (i) hemoglobinopathies, (ii) enzyme disorders and (iii) membrane disorders. Of these three, item (i) always features prominently in haematology conferences; items (ii) and (iii) are often Cinderellas, but at the recent ISH meeting in Bangkok an educational session was devoted precisely to these two topics, and it was well attended.

Glucose 6-phosphate dehydrogenase (G6PD) deficiency and pyruvate kinase (PK) deficiency are the two most common red cell enzyme disorders. The former is X-linked, and characterized by the fact that in the steady state almost all G6PD deficient subjects (who are very numerous and prevalent in tropical and sub-tropical parts of the world on account of malaria selection) are clinically and haematologically normal. Only when they are exposed to oxidative stress through eating fava beans, or through infection or certain drugs, do they develop an acute haemolytic anemia which may be life-threatening especially in children. By contrast, PK deficiency is rare, but it causes chronic non-spherocytic haemolytic anemia. For both disorders we have known the molecular basis for some time, and for each over one-hundred different mutations are known; now the three-dimensional structure also has been solved, and this has helped to understand genotype-phenotype correlations.

Membrane abnormalities, such as those giving rise to hereditary spherocytosis and hereditary elliptocytosis, have long been identified; but they have yielded only recently to molecular analysis. We now know that they can arise through mutations in at least eight different genes (including those of α and β spectrins, of ankirin, of band 3 of the Rhesus protein), some of which encode integral membrane proteins, whereas some encode proteins of the cytoskeleton. Thus, we can visualize how individual molecular lesions may affect either horizontal or vertical membrane-cytoskeletal interactions; and here, too, we begin to outline genotype-phenotype correlations: although we do not yet fully understand how exactly specific morphological changes are produced.

In contrast to these rather exciting advances in the molecular pathogenesis of two entire groups of disorders, it is humbling to admit that rather little progress has been made in treatment: Indeed, for both groups, when the condition is severe, offering blood transfusion support or splenectomy is just about all we can do. In this respect, it is noteworthy that attempts at gene therapy in animal models of some of these disorders have been carried out; and one hopes that clinical developments in real patients will follow in due course.

ASH 2008 Update: Bulls Eye or Near Miss? JAK2 Inhibitors for MPNs

Dr. Ruben Mesa

The discovery of the JAK2-V617F mutation was met in 2005 with great fanfare for its association and pathogenetic role in the Philadelphia chromosome negative myeloproliferative neoplasms (MPNs). The explosion of research that followed (discovery of related mutations signaling through JAK-STAT pathway) led to the rapid development of specific and targeted inhibitors of JAK2. The initial trials

for these latter tyrosine kinase inhibitors were begun with soaring expectations, hoping to mirror some of the remitting efficacy of imatinib in chronic myeloid leukemia. These agents, and a range of pre-clinical models and clinical trial results, take center stage in multiple MPN sessions today and tomorrow.

The pipeline of JAK2 inhibitors in development is amazing for a group

of disorders, the MPNs, which have long suffered from a lack of targeted or particularly efficacious therapy especially for advancing disease (namely for myelofibrosis [MF] both primary and occurring after antecedent polycythemia vera [PV] or essential thrombocythemia [ET]). Several trials have and will be discussed both in the MPN oral and poster sessions that have primarily focused on MF

patients (based on the greatest initial clinical need). The most mature clinical experience for a JAK2 inhibitor is for INCB018424 shared by Srdan Verstovsek, MD, PhD, of M. D. Anderson Cancer Center regarding the results of the largest MF trial in history (>120 patients) where the agent leads to significant reduction in splenomegaly and dramatic improvement in constitutional symptoms. Although a well-tolerated drug, the suppression of the JAK-STAT pathway can lead to treatment related thrombocytopenia and anemia. Additional drugs being described during an oral session titled Myeloproliferative Disorders – Experimental Therapeutics are largely earlier in their clinical testing (TG101348, XL019, CEP-701, ITF2357) but preliminary results also report improvements in splenomegaly and symptoms in MF patients. No drug yet has reported a significant ability to improve cytopenias, fibrosis, or histologic changes associated with MF. “What separates MF from PV and ET

is not yet clear, but is probably not solely the currently identified JAK2 or MPL mutations” commented Animesh Pardhanani, MBBS, PhD, of the Mayo Clinic and lead investigator on the TG101348 trial. “This latter fact could explain why a JAK2 inhibitor could lead to only a partial response in MF patients, akin to the more limited ability of imatinib to achieve response in accelerated or blast phase CML.”

PV (with 99% of patients having a mutation somewhere in their JAK2) could well be the most straightforward target of JAK2 inhibition, and preliminary results of trials were unveiled with discussion of initial efficacy of XL019, CEP-701, and ITF2347. These are significant and will be compared and contrasted with increasing discussion of pegylated interferon — 2a in PV. “We have seen long lasting molecular remissions with this agent in PV” described French investigator Jean-Jacques Kiladjian, who will be updating ASH on the progress of the

PV, NORD trial during the oral session titled Myeloproliferative Disorders – Clinical Trials.

Although the pipeline of JAK2 inhibitors is strong, will any of the agents discussed or in development achieve remissions or alter the course of MF? Clearly they have provided a valuable and incremental benefit over existing options particularly for symptoms and quality of life. A study focusing on pomalidomide, a non JAK2 inhibitor IMiD, will be presented by Ayalew Tefferi, MD, of Mayo Clinic, tomorrow. It will demonstrate activity for anemia in MF in results of a large randomized international trial.

Perhaps MF will require multiple forms of simultaneous therapy given the disorder’s complex pathogenesis. Although a bulls-eye for the MPNs has not yet been achieved, the improved understanding, initial trial results, and breadth of potential future agents encourage patients and clinicians alike.

Dengue Hemorrhagic Fever

Dr. Norman Maldonado

Very appropriately for a tropical country such as Thailand, there was a session on tropical hematology during the recent ISH Congress. Dr. Suchitra Nimmennitya a former director of the Queen Sinkit National Institute of Child Health in Bangkok made a comprehensive presentation. She differentiated between dengue fever, a non-fatal disease, and dengue hemorrhagic fever, a life-threatening disease. In the latter there is an abnormal hemostasis and plasma leakage as a result of vascular permeability resulting in ascites, pleural effusion and hypovolemic shock complicated with a bleeding diathesis.

The pathogenesis involves humoral as well as cell-mediated immune responses to a second dengue infection of the four distinct dengue subtypes. There is immune complex formation, cytokines activation leading to vascular permeability, disseminated intravascular coagulation (DIC) and abnormal hemostasis. A rise in hematocrit on or about the 4th or 5th day and a drop in platelet counts signals a dangerous period of the disease. There is bone marrow suppression, atypical lymphocytosis, followed by leucopenia and subsequently anemia.

Metabolic acidosis and hypoproteinemia are present. There is a shortening of the platelet half-life to 16 hours followed by increase in FDP and D-dimers. A prolongation of the PTT is often seen, at times not correlated with the bleeding. Liver enzymes are elevated transiently.

Therapy includes hydration preferably with Ringers lactate. Fresh frozen plasma and cryoprecipitate can be used. They do not use corticosteroids, but if bleeding is severe are using rFV11 (Novo seven), 40-100 mcg/kg. Two doses at 20 to 120 minute intervals are used.

A hemophagocytosis syndrome has been observed in some patients.

The Educational Mission and Future Potential of the International Society of Hematology

Dr. Szu-Hee Lee, chairman, Science and Education Committee, Asia-Pacific Division and National Councillor (Australia).

The ISH (International Society of Hematology) is a global network of hematologists from almost every country in the world. It is structured as three divisions, the IAD (Inter-American Division), EAD (European and African Division) and APD (Asia-Pacific Division). A primary mission of the ISH is the dissemination of the latest advances in clinical and laboratory practice and research to hematologists worldwide. Towards this goal, each division of the ISH holds a World Congress every six years and a regional Congress every two to four years. Recent successful World Congresses of the ISH were held in Istanbul, Turkey, in 2005, Punta del Este, Uruguay, in 2007 and in Bangkok, Thailand, in 2008.

A popular feature of the ISH Congresses has been the Education Program in which invited experts to review a broad range of hematology topics in depth. Articles from ISH Education Programs have been distributed as Education Books or journal supplements and on the internet. The Education Programs of ISHAPD Congresses have been freely available on the internet since 1996 (www.ishapd.org).

A problem faced by the ISH has been a lack of effective communications with members in less-developed countries. Information technology can bridge this gap to some extent. In particular, the internet is an effective tool for communication and delivery of educational and scientific materials to ISH members. Other ways in which ISH members may benefit from internet technologies, such as an online journal, need to be explored. In future, eventual worldwide internet connectivity should significantly advance the ISH mission.

One of the aims of the ISH is the international standardization of hematology laboratory methods to achieve reliable and reproducible results. In 1964, the ICSH (International Council for Standardization in Hematology) was founded by the ISH for this purpose. Since its creation, the ICSH has published over 100 monographs on standardization, and is recognised by the World Health Organisation as a Non-Governmental Organisation. The ICSH became dormant after 2000 due to the retirement of its senior members, but was reconstituted in 2007 jointly by the ISH and the ISLH (International Society for Laboratory Hematology). The ISH World Congresses continue to serve as a platform for communication of the latest ICSH recommendations.

A recent innovation at the ISH World Congress in Uruguay 2007 was the introduction of a Young Investigator Award. It is hoped that the Award will stimulate young researchers to present their findings at future meetings of the ISH.

The ISH has supported hematology education, practice and research by conducting regional and World Congresses since 1946. These meetings provide a forum for hematologists worldwide to engage in discussions of the latest advances, and have the potential to unify an international network of hematologists with common interests in clinical, scientific and research activities.

XXX World Congress of the International Society of Hematology Closing Remarks of Dr. Guillermo Ruiz Arguelles

The sad moment has come to say farewell to this 32nd meeting of the International Society of Hematology. Bangkok, and all of Thailand, can be proud of the great success of this Congress. To all those who have contributed to this success—to the organizers, to the officials, to the volunteers and especially to the scientists from around the world—we say thank you. We are also grateful to the eminent leaders of this city, the Thai Society of Hematology and this country whose support has

made this Congress possible. Thanks to the excellent conditions provided by the organizers, you have truly been able to go beyond the boundaries of race, religion and color and allow us to gather in friendship and peace.

You will agree with me that over the past few days, we have participated in an extremely well-organized, informative and enjoyable conference. We have heard excellent speakers and surely made some progress toward the improvement of knowledge in hematology. As I said in

the opening ceremony, education means more than dishing out facts; it also involves skills, attitudes and personal contact with exchange of ideas. I truly believe that we have accomplished these goals.

I now ask all the attendants to take with you this profound lesson of harmony and understanding and to share this message of hope with the people of your country, now and in the future. All of us will bring home fond memories of this most informative and colorful event.