APSTH
Asian-Pacific Society on Thrombosis and Hemostasis
www.apsth.org
January 2014 Volume 4 No. 1

Inside

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Message from the Chairman

Lai Heng Lee

Dear Members of APSTH,

It is my privilege to address you in this newsletter once again.

The council met in Amsterdam on 1st July 2013 when we welcomed several new members to the council, namely Dr. Raymond Wong from Hong Kong, Dr. Soo-Mee Bang from Korea, Dr. Ming Hou from China, Dr. Lugyanti Sukrisman from Indonesia, Dr. Claire McLintock from New Zealand, Dr. Ponlapat Rojnuckarin, and Dr. Yingyong Chinthammitr from Thailand. We also welcomed Dr. Satoshi Fujii as the new Secretary General of APSTH as Dr. Yukio Ozaki relinquished this position to assume the new position as Treasurer of APSTH. Notably, the Executive Committee for the council, comprising of Dr. Lee Lai Heng, Dr. Yukio Ozaki, Dr. Pantep Angchaisuksiri, Dr. Doyuen Oh, Dr. Christopher Ward, Dr. Ming Hou, and Dr. Satoshi Fujii, was formed with unanimous support from the council.

The executive committee very quickly took on their first task as they work with Prof. Tri and his team on the scientific programme of the next APCTH to be held in Hanoi from 10th to 11th October 2014. We look forward to an informative and interactive programme with ample opportunities for networking and future collaborations within the Asia Pacific region. We congratulate Dr. Nguyen Anh Tri and Dr. Nguyen Trieu Van on their successful application for an ISTH funded education course which is a full day educational programme planned on 9th October 2014. This precedes the APCTH and is opened to all attendees of the APCTH, thus offering them extra educational benefits in addition to the rich scientific programme of the main conference. Do look out for the announcements on registrations and abstract submission for this APCTH cum ISTH-sponsored educational forum.

We also congratulate Dr. Maria Teresa Abola, our council member from the Philippines, on obtaining an educational grant from the ISTH for the first standalone ISTH Educational Forum on Thrombosis and Haemostasis in the Asia Pacific Region. It was held from 8th to 9th November 2013, in the National Philippine Heart in Manila. Dr. Abola and her colleagues, Dr. Patricio Palmes. Dr Enrico Tuy, Dr. Angelina Mirasol, and Dr. Maribeth Delos Santos, from the Philippine Society of Hematology and Blood Transfusion and the Philippine Society of Vascular Medicine, developed an excellent 2-day programme of didactic lectures and interactive discussions. International invited speakers from the Asia Pacific region were Professor Yukio Ozaki from Japan, Professor Lee Lai Heng from Singapore, Professor Chris Ward from Australia, and Dr Claire McLintock from New Zealand. We were both enriched and humbled by the knowledge, dedication, enthusiasm and challenges of our colleagues in the Philippines. This educational forum proved to be an excellent platform to introduce our colleagues to the APSTH and we welcome our new members from the Philippines who joined the APSTH after attending this forum. It was only as we head home that the enormous scale of the destructive effect of super-typhoon Yolanda became evident and our heartfelt condolences and best wishes go to those who are affected.

In our last newsletter, we celebrated the learning experiences of our young investigators from the APSTH who received travel awards to attend the APSTH-JSTH joint symposium. We are delighted that Dr. Toshiyuki Miyata, President of

the 36th JSTH annual meeting (May 29-31, 2014, Osaka), has kindly agreed to have the APSTH/JSTH joint symposium for the 9th consecutive year. We strongly urge our young investigators from the APSTH to compete for these travel grants and to showcase their work.

As 2013 draws to a close, I am humbled as I reflect on what APSTH has achieved, as well as encouraged by the friendship, support and camaraderie so evident in my fellow colleagues. As we work together, I am confident that the APSTH will be the platform to raise the levels of science and clinical practice in Thrombosis and Haemostasis in Asia-Pacific region. Best wishes for a very happy and blessed New Year.

From the Editor

Dear Colleagues,

Happy New Year! Welcome to both a new year and a new issue of our newsletter. In the articles, we are looking back on some highlights of 2013 as well as looking forward to another busy year ahead. Our coverage of recent events starts with articles from the Symposium on Thrombosis and Haemostasis in the Asian-Pacific during the XXIV Congress of the ISTH in Amsterdam in July, 2013. Our first article is from Chang Gung University, Taiwan. Wei-Lien Tseng tells us about Reelin as a novel regulator of haemostasis. In 2010, he demonstrated for the first time that Reelin is present in the human platelets and megakaryocyte-like leukemic cells. Since then, he continued his previous study by using Reelin-deficient mice as a model system. Next, Shinji Kunishima of the Nagoya Medical Center, Nagoya, Japan explains how ACTN1 mutations cause congenital macrothrombocytopenia. The team has been working on congenital platelet disorders. They are very much interested in the development of a diagnostic algorithm for congenital macrothrombocytopenia. Our next article is titled, “Identification of soluble epoxide hydrolase as a novel target of the stroke drug candidate SMTP-7, a thrombolytic with anti-inflammatory properties”. The author, Eriko Suzuki, Tokyo University of Agriculture and Technology, writes that their laboratory has been searching for small-molecule natural products that enhance the fibrinolysis system. They initially aimed at identifying a candidate small molecule that could contribute to the treatment of thrombotic and embolic complications.

Turning to our Research News section, Japan’s Registry of Congenital Thombotic Microangiopathies (TMA) is covered, courtesy of Prof. Yoshihiro Fujimura of Nara Medical University, Nara, Japan. He and his team have been functioning as a TMA referral center in Japan since 1998, and were able to establish a large TMA cohort. Next, we learn about the ISTH Sponsored Education Program last October in Suzhou, China. It focused on the basic and clinical research progress of thrombosis and hemostasis, especially new progress of diagnosis and treatment of hemorrhagic disease. This report came from Dr. Kesheng Dai of The First Affiliated Hospital of Soochow University, Suzhou. The newsletter continues with a summary of the ISTH Educational Forum on Thrombosis and Haemostasis hosted by the Philippine Society of Vascular Medicine and Philippine Society of Hematology and Blood Transfusion in Manila in November, 2013. Dr. Maria Teresa Abola of the Philippine Heart Center, Manila, writes that as with most fields in medicine, there has been rapid progress and development in the areas of thrombosis and haemostasis. In helping meet the ever-growing need to bridge the gap between current available knowledge and best local practice, the first ever Educational Course on Thrombosis and Haemostasis in Southeast Asia was held in one of Asia’s first cardiac institutions, the Philippine Heart Center. This course was a highly educational and fruitful activity.

Looking ahead to 2014 conferences, Prof. Nguyen Anh Tri, President of the 8th APSTH Congress 2014 and Director of the National Institute of Hematology and Blood Transfusion, Vietnam, gives us an advance look at that congress. Another upcoming conference we preview is the ISTH’s Second Advanced Training Course on Thrombosis and Haemostasis, March 13-16, 2014 in Cascais, Portugal.

***Pantep Angchaisuksiri**, Editor*
Officer of Public Relations and Communications APSTH

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Presentations from Symposium on Thrombosis and Haemostasis in the Asian-Pacific during the XXIV Congress of the ISTH in Amsterdam on July 3, 2013

Reelin is a novel regulator of haemostasis

Wei-Lien Tseng
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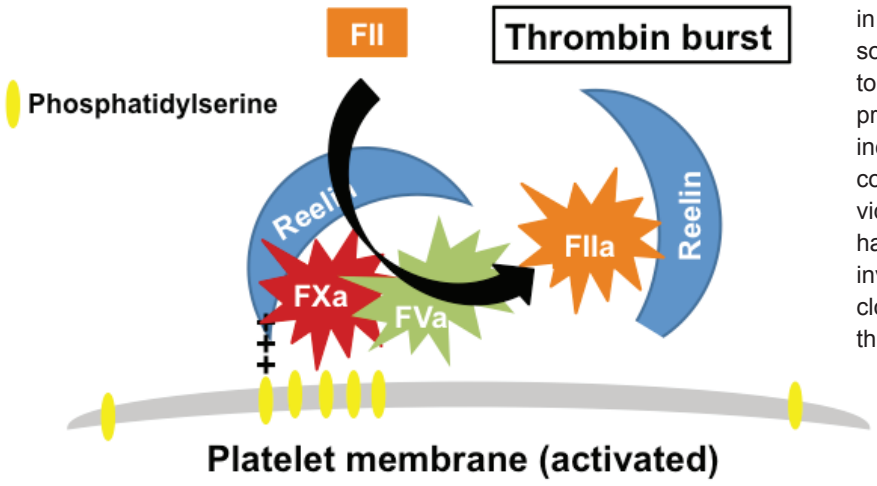
It is a great honor to present our study about Reelin function in haemostasis in the Congress of the International Society on Hemostasis and Thrombosis (ISTH) 2013. Reelin is a secreted glycoprotein originally identified as an essential protein for brain development. Besides appearance in the central nervous system, Reelin is also presented in plasma and the somatic tissues such as liver and lymphatic cells. In 2010, we demonstrated for the first time that Reelin is present in the human platelets and megakaryocyte-like leukemic cells. Reelin-binding assays revealed that extracellular Reelin can interact with platelets through the receptor belonging to the low density lipoprotein receptor gene family. Reelin-to-platelet interactions enhance platelet spreading on fibrinogen concomitant with the augmentation of lamellipodia formation and F-actin bundling.

We further demonstrated that Reelin is cleaved by thrombin and factor Xa. These findings were presented in the Congress of ISTH 2011. I have continued my previous study by using Reelin-deficient mice as a model system. The reeler mice displayed a normal platelet count, a prolonged tail-bleeding time with unstable plug and an increase in prothrombin time (PT) and activated partial thromboplastin time (aPTT). The delay of PT and aPTT in reeler mice is associated with a decrease in the change of light scatter, implicating a defect for the formation of fibrin clot in the absence of Reelin. In support of this notion, scanning electronic microscopy analysis of the blood clot obtained from the PT and aPTT assays of reeler mice revealed a loosen fibrin with thinner fibrin strands when compared to that of the wild-type mice. Thrombin generation assay was performed that revealed a decrease in endogenous thrombin potential and start tail time, but with a normal lag time of thrombin generation for the reeler mice. On the other hand, the decrease of dH in the reeler mice prompted us to investigate whether Reelin is associated with coagulation activation. Initiating platelet aggregation by re-calcification of citrated mouse plasma revealed Reelin deficiency resulted in delayed platelet aggregation and altered pattern of prothrombin activation. Furthermore, in vitro binding assay confirmed the association of Reelin with thrombin, factor Xa and phosphatidyleserine, thereby providing experimental evidence for the incorporation of Reelin in prothrombinase complex. Accordingly, these findings provide a novel insight of Reelin function in haemostasis and implicate that Reelin is involved in thrombin generation and fibrin clot formation and is likely a component of the coagulation cascade.



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ACTN1 mutations cause congenital macrothrombocytopenia

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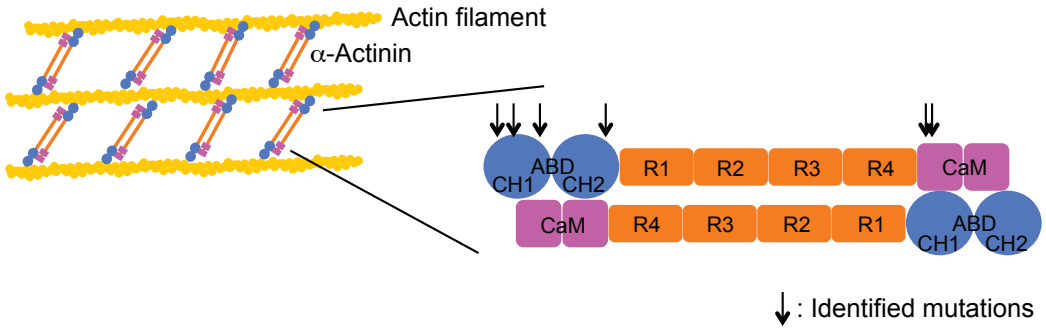
Congenital platelet disorders include quantitative (thrombocytopenia) and/or qualitative platelet defects. Once considered rare, these disorders are now being encountered in routine clinical examinations. We have been working on congenital platelet disorders. Especially, we are very much interested in the development of a diagnostic algorithm for congenital macrothrombocytopenia. We have characterized the genetic and molecular abnormalities of more than 40 cases with Bernard-Soulier syndrome. We identified the gene, MYH9, for May-Hegglin anomaly, established a novel diagnostic test, proposed a novel disease entity MYH9 disorders, and elucidated the molecular pathology. We reported new genes for congenital macrothrombocytopenia, TUBB1 and ITGA2B/ITGB3. At present, a definite diagnosis is possible in about half of the patients with congenital macrothrombocytopenia. In other words, the remaining half of the patients is not yet definitely diagnosed.

To identify novel causative genes for congenital macrothrombocytopenia, we performed whole-exome sequencing using next-generation sequencing platforms. Whole exome sequencing of 6 families, in which a dominant mode of transmission had been suspected, but mutations in other relevant genes had been excluded, revealed 3,601 novel nucleotide variants that had not been registered in either in-house SNP database or dbSNP131, of which 360 variants co-segregated with macrothrombocytopenia in corresponding families. Among these, 6 genes were mutated in more than one family and further considering the length of the coding sequences, only ACTN1 was thought to be significantly mutated in our cohort. Furthermore, only ACTN1 is expressed in platelets. Sanger sequencing in additional 7 dominant families revealed additional three variants. No ACTN1 variants were detected among the 39 sporadic cases with unknown inheritance or 120 control individuals except for one variant, which was found in a control individual who had a normal platelet count and size. Combined, ACTN1 variants were found in six out of 13 families with dominant inheritance.



ACTN1 encodes for actin bundling α-actinin-1

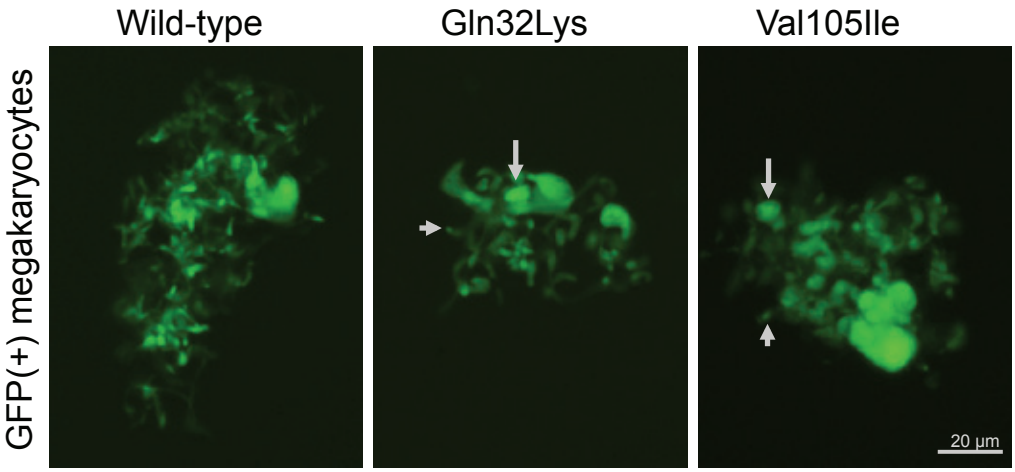
ACTN1 codes for α-actinin-1. Among the four known isoforms of α-actinin, α-actinin-1 is mainly expressed in platelets and megakaryocytes. The α-actinins exist as anti-parallel dimers with an N terminal actin-binding domain. α-Actinin bundles actin filaments and participate in the cytoskeletal organization. All identified mutations were located within the functional actin binding domain and calmodulin-like domain. Thus, ACTN1 mutations may exert a dominant-negative effect, by affecting actinin dimerization or actin crosslinking, and cause disorganization of actin-based cytoskeleton in megakaryocytes.

To analyze functional consequences of ACTN1 mutations, we first evaluated the effects of ACTN1 mutations on the organization of actin filaments by expressing identified ACTN1 mutations in Chinese hamster ovary cells. Wild-type transfected cells showed well-organized, fine actin filament networks, where α-actinin-1 co-localized onto the fine actin filaments. In contrast, all mutations, except for one found in a control individual, caused varying degrees of disorganization of the actin filaments, in which α-actinin-1 co-localized with less fine, shortened actin filaments.

We next investigated whether ACTN1 mutations also cause disorganization of the actin cytoskeleton in megakaryocytes and affect proplatelet formation by retroviral transduction of ACTN1 into mouse fetal liver cells. During the four-day culture period, the proportion of proplatelet formation-positive megakaryocytes was not different among wild-type and mutant-transduced megakaryocytes, suggesting that

ACTN1 mutations do not accelerate or inhibit the rate of proplatelet formation. The number of proplatelet tips per megakaryocyte tended to be decreased, and the diameter of the proplatelet tips increased in both of the mutant transduced megakaryocytes. These results are consistent with the moderate thrombocytopenia and increased platelet size accompanied by anisocytosis in the patients, demonstrating that abnormal α-actinin-1 affects proplatelet formation.

During the recent nine years, we have analyzed 178 patients suspected with congenital macrothrobocytopenia. Most common were MYH9 disorders and Bernard-Soulier syndrome. In our cohort, ACNT1 mutations account for 4% of the cases, representing the fourth most common cause in Japanese patients.



Abnormal proplatelet formation in mutant ACTN1-transduced megakaryocytes

Identification of soluble epoxide hydrolase as a novel target of the stroke drug candidate SMTP-7, a thrombolytic with anti-inflammatory properties

Eriko Suzuki
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Our laboratory has been searching for small-molecule natural products that enhance the fibrinolysis system. We initially aimed at identifying a candidate small molecule that could contribute to the treatment of thrombotic and embolic complications. As a result, we have identified several types of compounds, including modulators of zymogen activations. Among them, a family of small molecule compounds designated SMTPs, which are produced by the fungus *Stachybotris microspora*, have distinguished biological and pharmacological properties. SMTP-7, one of the most potent SMTP congeners, enhances plasminogen activation by modulating plasminogen conformation (Fig. 1). SMTP-7 promotes plasmin formation and clot clearance in vivo and it is effective in treating thrombotic and embolic strokes in experimental models in rodents and a nonhuman primate. Unexpectedly, SMTP-7 reduces hemorrhagic transformation and has an extended therapeutic time window as compared with t-PA. The distinct effects of SMTP-7 are partly explained by suppression of inflammatory responses following thrombolytic reperfusion. Experiments with animal inflammatory disease models (ulcerative colitis, Crohn's disease, and Guillain-Barré syndrome models) suggest that the anti-inflammatory action of SMTP-7 is independent of thrombolytic activity, as a thrombolytically inactive congener, SMTP-44D, exhibits anti-inflammatory action in those models.

We searched for a novel target protein using an SMTP-conjugated affinity matrix, which was synthesized by coupling SMTP-50, a congener with a primary amino group on the side chain, with gel beads. Mouse liver homogenates were subjected to affinity chromatography on this matrix, and specifically bound proteins were analyzed by peptide mass fingerprint. As a result, 4 major bound proteins were assigned to full length or fragments of soluble epoxide hydrolase (sEH), a hybrid enzyme with epoxide hydrolase activity in the C-terminal domain and lipid phosphatase activity in the N-terminal domain (Fig. 2). The sEH hydrolase converts epoxy fatty acids, such as epoxyeicosatrienoic acids (EETs), which are endogenous anti-inflammatory lipid me-

diators, to less-active diol forms, such as dihydroeicosatrienoic acids (DHETs). The sEH phosphatase is implicated in lipid metabolism and hydrolysis of lysophospatidic acid, whereas its precise biological role is still unclear. SMTP-7 and SMTP-44D inhibited both hydrolase and phosphatase activities of sEH. The simplest congener SMTP-0, which consists of only the core structure common with all the SMTP congeners, also effectively inhibited sEH hydrolase and phosphatase activities. Using SMTP-0, we identified that the inhibition of hydrolase by SMTP-0 was competitive with respect to 14,15-EET, and the inhibition of phosphatase is uncompetitive with respect to the synthetic substrate Attophos. The inhibition of phosphatase was unchanged in the presence of a potent competitive inhibitor of hydrolase, 12-(3-adamantan-1-yl-ureido)-dodecanoic acid. Thus, SMTP-0 may bind to two distinct sites in sEH: one is the active site in the hydrolase domain, and the other is an allosteric site that affects the phosphatase domain. Inhibition of sEH hydrolase was also observed in cells in culture. The conversion of 14,15-EET to 14,15-DHET in HepG2 cells was inhibited by SMTP-7, SMTP-44D, and SMTP-0. To confirm sEH inhibition in vivo, we traced the fate of intravenously injected EET in the liver. Treatment of wild-type mice with SMTP-7 significantly reduced the 14, 15-DHET level, while no significant reduction was observed in sEH KO mice (Suzuki et al., in preparation).

Our present study provides evidence that SMTP-7 targets sEH for anti-inflammatory action. The inhibition of sEH and the profibrinolytic action due to plasminogen modulator activity may synergistically contribute to treatment of ischemic stroke. SMTP-7 is thus a promising alternative therapy for ischemic stroke.

Fig. 1

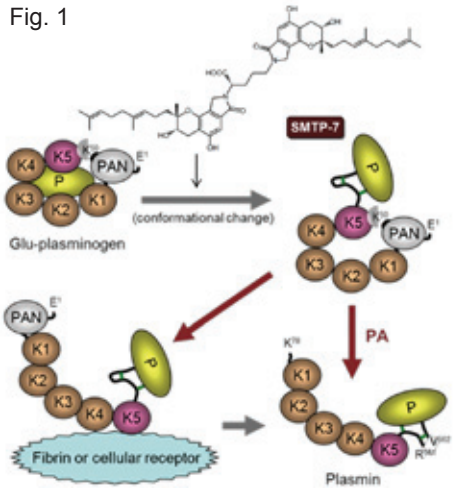
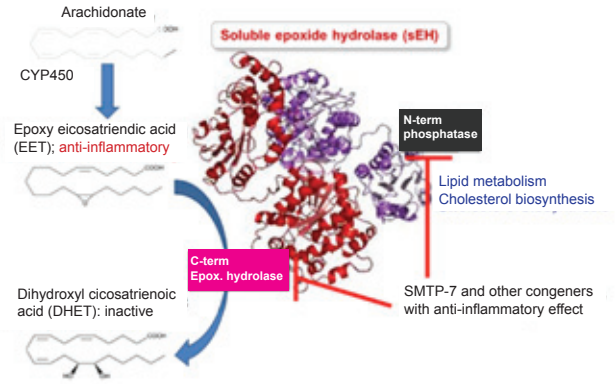


Fig. 2



Research News

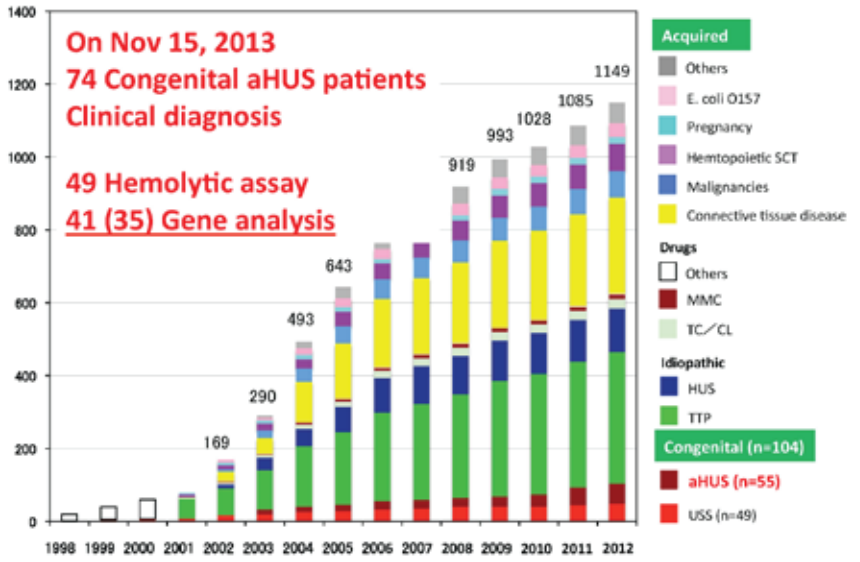
Registry of Congenital Thombotic Microangiopathies in Japan

Yoshihiro Fujimura, M.D.
Department of Blood Transfusion Medicine, Nara Medical University, Nara, Japan

Thrombotic microangiopathies (TMAs) are pathological conditions characterized by microangiopathic hemolytic anemia, thrombocytopenia, and organ failure (renal dysfunction) due to platelet thrombi (Moake J. N Engl J Med 2002; 347: 589-600). Two typical phenotypes of TMAs are life-threatening generalized diseases of thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), both of which are either caused by congenital form or acquired form. Now it is well established that most of the TTP patients have severely decreased activity of von Willebrand factor-cleaving protease (less than 10% of the normal), termed ADAMTS13 (a disintegrin-like and metalloproteinase with thrombopspondin type 1 motifs 13), due to its gene mutations or acquired autoantibodies to this enzyme (Scully M, et al. Br J Haematol 2012; 158: 323-335). In contrast, a major population of HUS patients develops in association with hemorrhagic enterocolitis by Shigatoxin-producing E. coli infection. But, a minor population of HUS patients, referred as atypical (a) HUS, in which the kidney is the primary target, develops their clinical sings usually without diarrhea and/or concern of Shigatoxin. In fact, aHUS occurs in both inherited and acquired forms, with both a high mortality and substantial risk of end-stage renal disease. Most patients with aHUS show chronic, uncontrolled

activation of the alternative complement pathway, which is related to a genetic deficiency in one or more soluble and/or membrane-bound complement regulatory proteins. Thus, a diagnostic guideline of aHUS in the United States or Japan basically consists of the exclusion for Shigatoxin-HUS and ADAMTS13 activity-deficient TTP from all TMAs. But a diagnostic guideline of the United Kingdom slightly differs, in which TMA patients related to infection (HIV, Streptococcus pneumonia), transplantation (bone marrow, liver, lung, cardiac but not de-novo renal), cobalamin deficiency, SLE, APL Ab syndrome, and scleroderma are excluded from aHUS (aHUS Rare Disease Group [RGD] http://rarerenal.org).

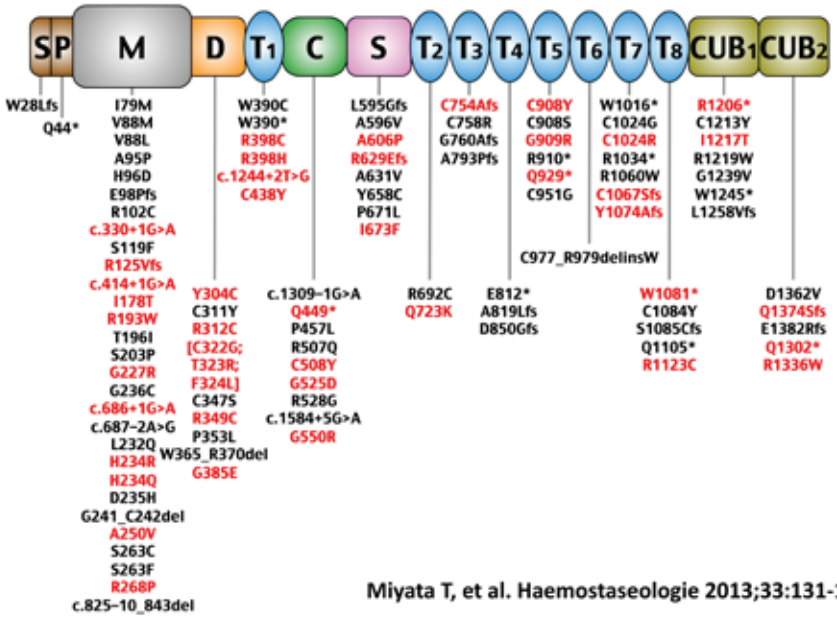
Fig. 1. Cumulative Number of TMA Patients in NMU Registry



Fujimura Y, et al. Rinsyo Ketsueki (in press, 2014)

Since 1998, my laboratory of Nara Medical University has been functioning as a TMA referral center in Japan through analyzing ADAMTS13. As a consequence, we were able to establish a large TMA cohort consisted of 1149 patients until the end of 2012 (Fig.1) (Fujimura et al, Rinsyo Ketsueki in press). Categorization of these TMA patients was performed based on a previous publication (Fujimura Y, Matsumoto M. Intern Med 2010; 49: 7-15).

Fig. 2. *ADAMTS13* gene mutations in Upshaw-Schulman syndrome



Miyata T, et al. Haemostaseologie 2013;33:131-137

Congenital TTP, termed Upshaw-Schulman syndrome (USS), is an autosomal recessive disorder caused by the genetic abnormalities of ADAMTS13. To date, approximately 150 USS-patients having 132 different ADAMTS13 gene mutations have been reported worldwide, in which 49 patients having 51 gene mutations were found in Japan (Fig. 2) (Miyata T, et al. Haemostaserologie 2013; 33: 131-137). Interestingly, the gene mutations found in Japanese patients were completely different from those in patients of Western countries. But, some ADAMTS13 gene mutations in Japanese patients were also reported in Korean or Chinese USS patients. Thus, it is likely that Asian and Caucasian patients have different routes of ADAMTS13 gene mutations, related to the founder effect. In Japan, we further disclosed the geographical features of 4 common ADAMTS13 gene mutations: p.R193W (whole area), p.Q449X (Tohoku district), p.C908Y (mainland), and pC754Afs (Kyushu district) (Fujimura J, et al. J Thromb Haemost 2011; 9: 283-301).

Congenital aHUS is basically an autosomal dominant disorder due to the gene mutations of complement factor H (CFH), complement factor I (CFI), membrane cofactor protein (MCP, or CD46), thrombomodulin (THBD), complement component 3 (C3), and complement factor B (CFB). The CFH autoantibodies with or without gene mutations of CFH related proteins (CFHR1-3) have also been reported to be the cause (Table 1) (Kavanagh D, Goodship T. Am Soc Hematol Educ Program 2011; 15-20). Further, most recently, mutations in the gene encoding diacylglycerol kinase epsilon (DGKE) have been reported as a novel cause of congenital aHUS (Lemaire M, et al. Nat Genet 2013; 45: 531-536 and Ozaltin F, et al. J Am Soc Nephrol 2013; 24: 377-384).

Table 1. Comparison of *aHUS* gene mutations between Western countries and Japan

Gene	Protein affected	Frequency (%)		
		Western countries	Japan (n= 41 ※)	
CFH	Factor H	20-30 %	7.3 % (3/41)	CFH: R1215Q (n=3)
CFHR1/3	CFHR1/3	6 %	4.9 % (2/41)	
MCP	MCP	10-15 %	12.2 % (5*/41)	
CFI	Factor I	4-10 %	0 % (0/41)	
CFB	Factor B	1-2 %	4.9 % (2/41)	
C3	C3	5-10 %	41.0 % (17/41)	C3: I1157T (n=15)
THBD	Thrombomodulin	5 %	4.9 % (2**/41)	
No identified mutation	*	30-50%	31.7 % (13/41) 3 patients had the anti-CFH autoantibody	

※ 35 patients were analyzed in National Cerebral and Cardiovascular Center.
(*1 patient carried the mutation in C3 and MCP. **1patient carried the mutation in CFH and THBD, 1 patient did in C3 and THBD)

Yoshida Y, et al. The 55th ASH meeting abs. 2318, 2013

In Japan, we made a diagnosis on 74 patients with congenital aHUS according to the Japanese guideline (Kagami S, et al. Nihon Jinzo Gakkai Shi 2013; 55: 91-93). Among them, 49 patients were evaluated by the inhibitory antibody-based hemolytic assay using sheep red cells, to whom 41 received the gene analysis (Yoshida Y, et al. The 55th ASH meeting abs. 2318, 2013). Consequently, patients carrying CFH gene mutations (p.R1215Q) or having anti-CFH antibodies with or without CFHR1-3 gene mutations showed the enhanced hemolytic reaction. The results of frequency in gene mutations were the following: CFH (3/41, 7.3%), CFH1/3 (2/41, 4.9%), MCP (5/41, 12.2%), CFI (0/41, 0%), CFB (2/41, 4.9%), C3 (17/41, 41.0%, 41.6%), THBD (2/41, 4.9%), and no mutations found (13/41, 31.7%) (Yoshida Y, et al. unpublished). Thus, different from the reports from Western countries, the frequency of CFH gene mutation in Japanese patients with congenital aHUS was less (20-30% vs 7.3%), but much more in C3 (5-10% vs 41.0%). Interestingly, 3 unrelated aHUS patients with CFH gene mutation in Japan had the same missense mutation of p.R1215Q, and 15 out of 17 aHUS patients with C3 gene mutation had the same missense mutation of p.C1157T, which was preferentially found in Kinki district (central area of Japan mainland). However, both missense mutations have been previously reported in Western countries. Thus, the geographical features of aHUS gene mutations are totally different from those of ADAMTS13 gene mutations in USS patients. Thus, in future it is interesting to elucidate whether or not the gene mutations related to aHUS phenotype may play a role for aggravating factors to severe renal involvements in Japanese USS patients.

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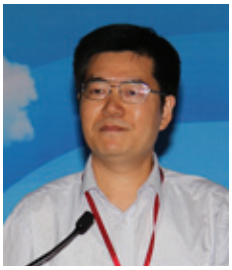
ISTH Sponsored Education Programs on Thrombosis and Hemostasis in Asia



Basic and Clinical Research Progress of Hemorrhagic Disease
Suzhou Conventional Center, Suzhou, China. October 11, 2013

Kesheng Dai, M.D. Ph.D.
Jiangsu Institute of Hematology
The First Affiliated Hospital of Soochow University
Suzhou, China

The Scientific Committee on Thrombosis and Hemostasis of the Chinese Society of Hematology, Jiangsu Institute of Hematology, and the First Affiliated Hospital of Soochow University hosted the "ISTH Sponsored Education Program on Thrombosis and Hemostasis" on October 11, 2013 at the Suzhou Conventional Center, Suzhou, China. Concurrent sessions of 14th National Congress on Thrombosis and Hemostasis &12th National Congress on Atherosclerosis Disease, China Engineering Science and Technology Forum, and Suzhou Summit on Hematology 2013 were held in the following two days. A total of almost 700 participants attended this activity. Most of the attendees were Chinese medicine specialists, hematologists, cardiologists, vascular specialists, and medical students. There were 9 resource speakers, including 6 international and 3 local, who delivered fantastic speeches and shared their experiences on thrombosis and hemostasis with the broad audience.

The ISTH Sponsored Education Program focused on basic and clinical research progress of thrombosis and hemostasis, especially new progress of diagnosis and treatment of hemorrhagic disease. The program started with the opening remarks of Dr. Changgeng Ruan, the overall organizing chairman, and director of Jiangsu Institute of Hematology and the Key Laboratory of Thrombosis and Hemostasis, Ministry of Health, China. He thanked the ISTH for giving this opportunity and felt honored to host the first ever ISTH educational course conducted in China. Then he welcomed the participants and guests, especially the foreign speakers to this important activity.

Opening remarks by Prof. Changgeng Ruan

The first plenary session (with Dr. Yu Hu as chairman and Dr. Xiaodong Xi as co-chairman) was about the educational course's theme on theories and mechanisms on hemorrhagic and cardiovascular diseases delivered by Dr. Hugo ten Cate, Dr. Yi Wu, and Dr. Jeroen C.J. Eikenboom. Dr. Hugo ten Cate, from cardiovascular institute of Dutch Maastricht University, gave a speech on the yin and yang of coagulation proteases in cardiovascular disease and illustrated the vascular aging and the formation process of atherosclerosis in the formation of thrombin and its physiological significance. Dr. Jeroen C.J. Eikenboom, from Leiden University medical center, put forward the new type of von willebrand factor pathophysiological mechanisms from different angles. A lively open forum and tea break followed with an active participation of the attendees.

In the second session (conducted by Dr. Yiqiang Wang and Dr. Hu Hu), Dr. Rodger P. McEver, Dr. Lijun Xia, and Dr. Heyu Ni tackled the course's topic on the significant roles of platelets during inflammation and hemostasis. Dr. Rodger P. McEver, and Dr. Lijun Xia, both from Oklahoma Medical Research Foundation, showed the inflammation and thrombosis caused by abnormal selectin signal transduction around the white blood cells, platelets, and blood vessels. Dr. Heyu Ni, from University of Toronto, introduced the versatile platelets and revealed the important role in the process of atherosclerotic thrombosis. At the end of the session, both speakers and audiences had an enjoyable and productive lunch.

In the third session (handled by Dr. Renchi Yang and Dr. Junlin Liu), Dr. Xiaoping Du, Dr. Li Zhu, and Dr. Kesheng Dai talked about the remarkable progress on platelets. Dr. Xiaoping Du, from University of Illinois, discussed integrin two-way signal transduction and the new concept of anti-thrombotic therapy. Dr. Li Zhu, from Cyrus Tang Hematology Center of Soochow University, discussed the relationship between inherent immune, platelet receptor shedding and cardiovascular disease which provided new ideas for the research on vascular biology. Dr. Kesheng Dai, from Jiangsu Institute of Hematology, and the Key Laboratory of Thrombosis and Hemostasis, Ministry of Health, China, revealed the interaction of GPIb-IX with VWF incurs platelet activation, apoptosis, and GPIbα ectodomain shedding which enriched the research on diagnosis and treatment of platelet related disease. Then there was an open discussion by the audience.

The last session was “Meet the Experts”, in which the panel was composed of Dr. Hugo ten Cate, Dr. Jeroen C.J. Eikenboom, and Dr. Rodger P. McEver. Various questions on basical and clinical researches of thrombosis and hemostasis from participants were raised to the panel. They comprehensively discussed and offered their opinions and comments. After that, a welcome dinner for the speakers was held at the hotel where the members of the organizing committee had the chance to meet them up close.

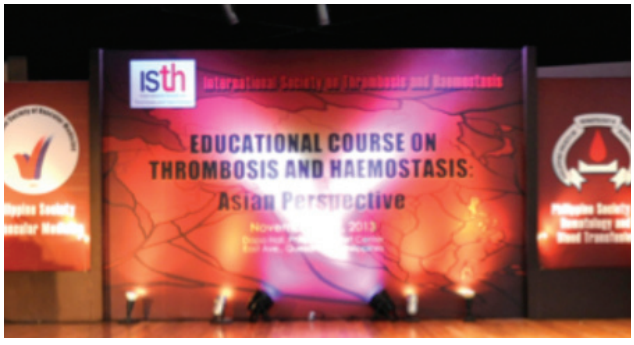
The speakers and the Thrombosis and Hemostasis Committee members of the Chinese Society of Hematology

The program provided a valuable opportunity for Chinese specialists in the fields of thrombosis and hemostasis to participate in, as well as exchange knowledge and experience with their colleagues, specialists all over the world. The event gave them great opportunities to learn about the latest research progress, strengthen the cooperation between domestic and foreign medical institutions, promote the development of basic theoretical and clinical research in the field of thrombosis and vascular biology.

ISTH Educational Forum on Thrombosis and Haemostasis hosted by the Philippine Society of Vascular Medicine and Philippine Society of Hematology and Blood Transfusion in Manila. November 8-9, 2013

Maria Teresa Abola, M.D. and Fred Fuentes, M.D.
Philippine Heart Center, Manila, the Philippines

As with most fields in medicine, there has been rapid progress and development in the areas of thrombosis and haemostasis. Better understanding of the science behind the various disorders that affect these two critical biologic processes have led to the development of a host of new drugs and medical procedures. Spanning several related disciplines and covering a multitude of diseases, thrombosis and haemostasis is undoubtedly wide in scope. In helping meet the ever-growing need to bridge the gap between current available knowledge and best local practice, the first ever Educational Course on Thrombosis and Haemostasis



in Southeast Asia was held in one of Asia's first cardiac institutions, the Philippine Heart Center in the Philippines, November 8-9, 2013. With the Philippine Heart Association's past president, Dr. Maria Teresa B. Abola as convenor, the activity was borne out of a joint collaboration between the venerable International Society on Thrombosis and Haemostasis (ISTH), the Philippine Society of Vascular Medicine (PSVM), and the Philippine Society of Haematology and Blood Transfusion (PSHBT). It was a hugely successful and productive two-day educational course, attended by more than three hundred medical and allied health professionals as they eagerly listened to, and participated in, the exchange of ideas with international experts, focusing particularly on the unique Asian perspective of thrombosis and haemostasis. The activity included several challenging panel case discussions that demand multidisciplinary approach, plenary sessions, and open forums.

Members of the Organizing Committee: Dr. Gerry Castillo, Dr. Joel Paz, Dr. Angie Mirasol, Dr. Tes Abola, Dr. Patricio Palmes, Dr. Maribeth de los Santos, Dr. Maribel Gonzales

Graced by four foreign experts, the plenary sessions aptly began with a concise overview of the Asian perspective of thrombosis and haemostasis by Professor Lee Lai Heng of Singapore General Hospital and current chairman of the Asia Pacific Society of Thrombosis and Haemostasis. Prof. Lee effectively pointed out several key differences in the incidence of some of the clotting and bleeding disorders between the Asian and Western populations, and subsequently offered customized ways of dealing with the rather unique Asian sociocultural setup. Professor Chris Ward of Royal North Shore Hospital and the University of Sydney brought the audience and delegates back to the basics as he meticulously discussed the pathophysiology and complications of dysregulation in the coagulation pathway, and the phenomenon of heparin-induced thrombocytopenia. His vast knowledge of the biomolecular underpinnings of the coagulation pathway provided the backbone of discussion when several audience members shared some of the more serious problems they encounter in clinical practice. Professor Yukio Ozaki of the University of Yamanashi, current vice-chairman of the Committee on Education and Outreach of the ISTH and, secretary general of the Asian-Pacific Society of Thrombosis and Haemostasis gave a sterling inspirational talk and a comprehensive lecture on thrombocytosis. On day two of the course, Professor Claire Mclintock, Lead Clinician for Obstetric Team at National Women's Health in New Zealand, shared her extensive experience on postpartum haemorrhage and pregnancy-related problems involving thrombosis and haemostasis in two interesting case presentations. She also gave an excellent impromptu lecture on "Anticoagulation in Pregnant Women with Mechanical Heart Valves" upon special request from the organizers. Aside from this line-up of excellent foreign speakers, several esteemed local speakers shared their experience and expertise as well, from the interrelated fields of cardiovascular medicine, haematology, obstetrics and gynaecology, paediatrics, pathology and even infectious disease.

Foreign experts: Prof. Lee Lai Heng, Prof. Chris Ward, Prof. Claire McClintock, Prof. Yukio Ozaki

Our young researchers also had the opportunity to have interacted with our experts during the moderated poster sessions held on both days. Three young investigators were given an award for having presented the most outstanding papers.

We can certainly look forward to another highly educational and fruitful activity as international societies collaborate and convene once again for the next ISTH Congress in Toronto, 2015. The organizers are extremely grateful to the ISTH for allowing this great forum to be held in Manila for our local medical practitioners who we are most certain benefited from this excellent learning activity.

Update on the 8th Congress of the Asian - Pacific Society of Thrombosis and Hemostasis. Hanoi, Vietnam. October 9th - 11th, 2014

Prof. Nguyen Anh Tri, M.D., Ph.D.
President – 8th APSTH Congress 2014
Director – National Institute of Hematology and Blood Transfusion, Vietnam

The first APSTH Congress was successfully organized in Taipei, Taiwan during July 1st-3rd, 2000. Since then, it has been organized biennially in the countries within Asia Pacific region. With seven successful past congresses, this congress is an event for senior experts in the region and all over the world in thrombosis and hemostasis to get together and share experiences.

The 8th APSTH Congress will be organized in Hanoi, Vietnam from October 9th-11th, 2014. Hanoi is center of politics, culture, economics, and tourism of Vietnam. In 2000, it has been recognized as "City for Peace" by UNESCO. Smart Travel Asia's 2013 Best in Travel Poll showed Hanoi ranked fifth among top 10 Holiday Destinations in Asia. With ancient charm, elegant appearance and beauty of a thousand year old city, Hanoi is one of the most important destinations of Vietnam to not only local Vietnamese people, but also international guests. With its highly developed social and economic systems, modern tourism facilities, efficient traffic management, and a secure environment, Hanoi has been host of many regional conferences and international conferences, such as APEC Summit in 2006, The 9th ASEM Foreign Ministers Meeting in 2009, The 16th ASEAN Summit in 2010, The 4th ASEM Labor and Employment Ministers' Conference in 2012, The 63rd session of the WHO Regional Committee for the Western Pacific in 2012, and others.

The program of the 2014 APSTH Congress has been developed by Vietnamese Organizing Committee based on counsel of the APSTH Council. The congress will be held in conjunction with the National Scientific Conference on Hematology and Blood Transfusion (during October 7th-8th, 2014).

The 8th APSTH Congress will include the following highlights:

• The Education Day (October 9th, 2014) will be made up of 7 lectures of the senior experts of the region on thrombosis and hemostasis. Opening ceremony of the congress will be in the evening of October 9th, 2014.

• On October 10th-11th, 2014, a useful and interesting workshop will be organized with 2 plenary and 30 symposia sessions. Besides, many scientific reports will be presented as oral presentations and poster presentations.

• The two plenary sessions last from 10:30 to 12:00 on October 10th-11th, 2014 at the main hall with topics "Woman and Coagulation Disorders" and "Bleeding disorders 'Hemophilia – von-Willebrand disease'". The plenary sessions are composed of three lectures presented by international experts.

• Beside plenary sessions, three symposia sessions are organized parallel at other three halls with various topics on thrombosis and hemostasis in other fields such as burn, cardiology, emergency resuscitation, surgery, and trauma.

Organized in conjunction with Vietnam National Scientific Conference on Hematology and Blood Transfusion, the congress will attract international and local experts from various medical fields. Welcoming about 200 international and 500 local attendances, the 8th APSTH Congress 2014 is pleased to be meeting in Vietnam. Please plan to attend the APSTH Congress 2014 in Hanoi, Vietnam! We are looking forward to welcoming you to Hanoi with Vietnamese hospitality and warmness.

Upcoming Meetings:

1. **The Second Advanced Training Course in Thrombosis and Haemostasis**
   13-16 March 2014 – Cascais, Portugal
   www.isth.org/page/EduPortugalCourse
   (For more details, see poster on the next page of this newsletter and article at the bottom of this page)

2. **Platelets 2014: 8th International Symposium**
   3-6 April 2014 – Ma'ale Hachamisha, Israel
   www.platelets2014.org

3. **18th International Vascular Biology Meeting (IVBM 2014)**
   14-17 April 2014 – Kyoto, Japan
   www2.convention.co.jp/ivbm2014/index.html

4. **7th International Conference on Thrombosis and Haemostasis Issues in Cancer**
   9-11 May 2014 – Bergamo, Italy
   www.icthic.com

5. **World Federation of Hemophilia (WFH) 2014 World Congress**
   11-15 May 2014 – Melbourne, Australia
   www.wfh.org/congress

6. **23rd Biannual International Congress on Thrombosis**
   14-17 May 2014 – Valencia, Spain
   www.thrombosis2014.org

7. **7th Symposium on Hemostasis: Old System, New Players, New Directions**
   15-17 May 2014 – Chapel Hill, North Carolina, USA
   www.med.unc.edu/hemonc/TF2014

8. **19th Congress of the European Hematology Society**
   12-15 June 2014 – Milan, Italy
   www.ehaweb.org

9. **60th Annual Meeting of the Scientific Standardization Committee of the ISTH**
   23-26 June 2014 – Milwaukee, WI, USA
   www.ssc2014.org

The International Society on Thrombosis and Haemostasis (ISTH) Hosts its Second Advanced Training Course on Thrombosis and Haemostasis on March 13-16, 2014

The ISTH is hosting its Second Advanced Training Course on Thrombosis and Haemostasis on March 13-16, 2014, at the Hotel Quinta da Marinha in Cascais, Portugal. As part of the Society's mission, the course will provide the latest training in the understanding and treatment of thrombosis and bleeding disorders to meet the needs of hematologists and related specialists from around the world. Space is limited to only 200 participants; early registration is recommended to ensure availability.

The meeting will provide three full days of intense examination on the subjects of blood coagulation and bleeding disorders, platelets and venous thrombosis. Leading scientists with vast experience in education will deliver focused lectures followed by ample time for discussion and close interaction with the participants. Meet the Expert sessions will be devoted to discussion groups with the course's speakers and interactive sessions with exercises relating to the analysis of the topics discussed during the day or on clinical case studies will be part of the program.

The Second Advance Training Course is a follow-up to the successful inaugural course organized in 2011 which was attended by 200 professionals. Course speakers include nine international and regional experts in the field of thrombosis and haemostasis. A complete list of faculty including biographical information is available on the course website: https://www.isth.org/page/EduPortugalCourse

Register Now—Space is Limited!

Second Advanced Training Course in Thrombosis and Haemostasis

March 13 - 16, 2014

Cascais, Portugal

https://www.isth.org/page/EduPortugalCourse/

FACULTY

Björn Dahlbäck *Sweden*
Sabine Eichinger *Austria*
Christian Gachet *France*
Andreas Greinacher *Germany*
Philip de Groot *The Netherlands*
David Lillicrap *Canada*
Bernd Pötzsch *Germany*
Sam Schulman *Canada*
Ted Warkentin *Canada*

Endorsed and accredited by

EUROPEAN HEMATOLOGY ASSOCIATION

ISth
International Society on Thrombosis and Haemostasis
www.isth.org

Plan to Attend

The course will provide three full days of intense examination on the subjectsof blood coagulation and bleeding disorders, platelets and venous thrombosis. Leading scientists with vast experience in education will deliver focused lectures followed by ample time for discussion and close interaction with the participants.

PROGRAM HIGHLIGHTS

BLOOD COAGULATION AND BLEEDING DISORDERS

- Current concepts of the coagulation system
- Challenges in the diagnosis and management of hemophilias
- Diagnosis and management of von Willebrand disease
- Control of coagulation
- Hemostasis in patients with impaired liver function
- How to approach a patient with bleeding

VENOUS THROMBOSIS

- Venous thrombosis: manifestations, diagnosis and therapy
- Anti-phospholipid syndrome
- Women's issues and thrombosis
- Novel antithrombotic drugs
- How to approach a patient with venous thrombosis
- Perioperative management in patients with risk for thrombosis

PLATELETS AND PLATELET DISORDERS

- Platelet function
- Heparin-induced thrombocytopenia
- Diagnosis and management of immune thrombocytopenias
- Diagnosis and treatment of inherited platelet disorders
- Diagnosis and treatment of acquired platelet disorders
- Disseminated intravascular coagulation

The formal program is available online at ***https://www.isth.org/page/EduPortugalCourse.***

Questions?

Call +1 919 929 8309 *or* email: headquarters@isth.org


The 18th International
Vascular Biology Meeting
In conjunction with
The 22nd Annual Meeting of
The Japanese Vascular Biology and Medicine Organization
The 12th Korea-Japan Joint Symposium on Vascular Biology
The 3rd Asia-Pacific Vascular Biology Meeting
The 2nd Neuro-Vascular Wiring Symposium (MEXT)
The 1st International Symposium on Tumor Microenvironment Network (MEXT)
April 14–17, 2014 Kyoto, Japan
Memorial Lecturers
Kari Alitalo (Finland) Napoleone Ferrara (USA)
Donald McDonald (USA)
Plenary Lecturers
Ralf Adams (Germany)
Peter Carmeliet (Belgium)
Elisabetta Dejana (Italy)
Göran Hansson (Sweden)
Daniel Rifkin (USA)
Toshio Suda (Japan)
Christer Betsholtz (Sweden)
Alan Daugherty (USA)
Linda Demer (USA)
Gou Young Koh (Korea)
Michael Simons (USA)
Brant Weinstein (USA)
Chairs
Issei Komuro Kohei Miyazono
Ryuichi Morishita Yasufumi Sato
Abstract Deadline: October 15, 2013
Early-registration Deadline: January 15, 2014
IVBM 2014
The 18th International Vascular Biology Meeting
http://www2.convention.co.jp/ivbm2014/
Venue: Miyakomesse, Kyoto
Conference Aid Office: c/o Japan Convention Services, Inc.
Tel: +81-3-3508-1214 E-mail: ivbm2014@convention.co.jp


Bangkok 2014
AFH
ASEAN Federation of Hematology Congress
THE THAI SOCIETY OF HEMATOLOGY
The 3rd ASEAN Federation of Hematology Congress
(AFH 2014)
October 23-25, 2014
Centara Grand & Bangkok Convention Centre
at CentralWorld
Bangkok, Thailand
www.afh2014.org