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Message from the Chairman

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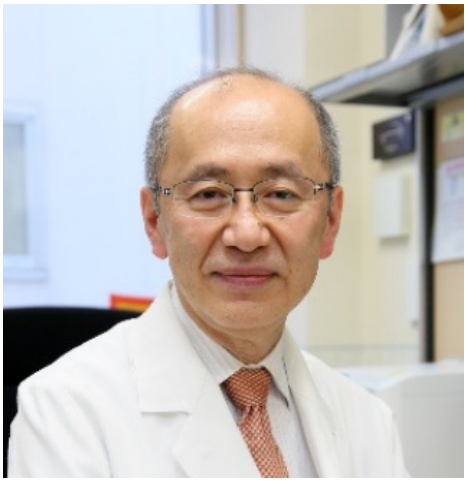

Satoshi Fujii

Greetings to everyone! I hope you have enjoyed summer (or winter) vacations, days at the beach or snowy mountains, and time to slow down with family and friends. Now you are FULL of energy!

The Asian-Pacific Society on Thrombosis and Hemostasis continues to establish itself as a key society in our region. Our newsletter reaches every member to increase the interactions among all members of the society. Under the leadership of our Officer of Public Relations and Communications, Ponlapat Rojnuckarin, we have informative and useful contributions from member countries. We would like to hear from many clinicians and scientists so that we can understand each other better. There are considerable technologies and expertise in the Asian-Pacific region and we have to ensure that this is shared by all members. Many members also engage in the World Thrombosis Day activities to encourage and educate patients to save their lives. Thus, I encourage you to write to us what you are working on and what needs you may have so that we can help each other better. Please feel free to email us through the “Contact” section at our website https://www.apsth.org/ or at apsth@comet.ocn.ne.jp with any feedback or questions on any APSTH initiative.

Early career professionals are the future of APSTH and it is important to provide as many opportunities as possible to them. In this newsletter you can find the highlights of APSTH-JSTH (Japanese Society on Thrombosis and Hemostasis) joint symposium 2023 held in June at Kitakyusyu, Japan organized by Professor Teruto Hashiguchi, who is the chairman of the JSTH international committee and APSTH treasurer. With the end of pandemic, participants were happy to come to Japan and enjoyed face-to-face exchange with Japanese researchers and clinicians. Our early career professionals are encouraged to join APSTH and become members. Joining the society is “free.” This has been made possible by the kind goodwill donations from regional and national societies among our membership countries. By receiving our newsletters they are informed of the clinical and science progress in the region. They also find the opportunities for their research, important events and conferences in the field of thrombosis and hemostasis.

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The field of thrombosis and hemostasis continues to develop. We have more and more diagnosis modalities and therapeutic measures. We now have a better understanding of what the coagulation factors and platelets do in inflammation process and immune reactions. We are also just moving beyond factor Xa inhibitors. Advances go at an unprecedented pace. We hope to communicate some of these advances at our upcoming scientific meeting in Malaysia. In fact, we are just weeks away from the APSTH2023 Congress in Malaysia from October 18 to October 21. Our colleague Prof. Dr. Narazah Mohd Yusoff serves as Chair of the Organizing Committee and has been working hard with many of our colleagues in Malaysia. They plan a wonderful scientific program. The APSTH Council is very much looking forward to meeting members, exhibitors and guests to attend this very important event. The organizing committee is in collaboration with the International Society on Thrombosis and Haemostasis (ISTH) to provide an exciting educational seminar for laboratory professionals and scientists as well. The local organization committee has offered travel support grant for young scientists and trainees from around the region. This award will contribute to inclusivity and widespread participation in the meeting.

I am also pleased to remind you that following this year's APSTH2023 congress in Malaysia, ISTH has set a major international congress, ISTH2024, in Bangkok, Thailand from June 22-June 26, 2024. ISTH 2024 Annual Congress Planning Committee includes many APSTH members. Chris Ward from Australia is the chair of ISTH2024, Ponlapat Rojnuckarin from Thailand is the clinical chair of ISTH2024, Midori Shima from Japan is the Educational Committee Member and Pantep Angchaisuksiri from Thailand is the president-elect of ISTH. Members attending APSTH2023 will have further information for this upcoming congress.

I am eagerly looking forward to the opportunity to meet many of you in Malaysia at the middle of October. I am certain you will be impressed by the excellent scientific program and the beauty of Kuching during the upcoming congress. At long last, we meet with colleagues and friends, and participate with a new joy and new enthusiasm.

See you soon,
Satoshi Fujii

From the Editor

Dear Colleagues and Friends

As COVID19 is transforming from pandemics to endemics, there are several previous and future exciting events on thrombosis and hemostasis in our Asia Pacific regions. Certainly, they become face-to-face activities to enhance more active networking and collaborations among members.

Firstly, we would like to promote the upcoming 12th APSTH 2023 meeting on 18-21 October 2023. This greatly important conference is organized every 2 years rotating among Asia-Pacific countries. It will be held in a beautiful city of Kuching, Malaysia, this year. The meeting gives wonderful opportunities for knowledge and scientific exchanges on thrombosis and hemostasis in our area. As usual, the international Society of Thrombosis and Haemostasis (ISTH) provides a strong support for the educational program. The congress conference, Professor Dr. Narazah Mohd Yusoff, kindly delivers the welcome remark in this issue. Hopefully, we will meet you all there.

There are reports from the APSTH-JSTH joint symposium that was on June 15-17, 2023 in conjunction with the 2023 JSTH congress. It was be held in Kitakyusyu, Japan. The meeting was really successful. The main purpose was achieved by cultivating and nourishing talented young investigators for our future.

The World Thrombosis Day (WTD) activities in this region have been very intense for the previous years. In 2022, many online, onsite and hybrid events were organized disseminating importance of disease awareness as well as thrombosis risk assessments through social media for both health workers and general public.

Dr Kazuya Sakai informs us regarding the research news on Thrombotic Microangiopathy (TMA). He has gathered a very large TMA registry in Asian patients and revealed the molecular mechanisms of autoimmune thrombotic thrombocytopenic purpura (iTTP).

Finally, we are thrilled to know that the next ISTH congress which is the world largest scientific events on thrombosis and hemostasis will take place in Bangkok, Thailand, during 22-26 June 2024. This is a superb chances for everybody from the Asia-Pacific region to attend this marvelous conference with affordable costs. We can assure you all that Bangkok is magnificent destination for people all over the world. Please make your plan early for this exciting forum. We are looking forward to welcoming you.

If you have any comments and/or suggestions on this bulletin, as well as any news or information you would like to spread among the Asia-Pacific Thrombosis and Hemostasis community, please do not hesitate to contact me via email.

Ponlapat Rojnuckarin, *Editor*
Officer of Public Relations and Communications

Message from APSTH2023 Organizing Committee

Dear Friends and Colleagues,

We eagerly anticipate and extend a warm invitation to all to participate in the distinguished 12th Congress of the Asian-Pacific Society of Thrombosis and Hemostasis (APSTH) - APSTH 2023, themed “Hemostasis and Thrombosis: Bench to Bedside.”

APSTH 2023 is a collaborative effort between the Asian-Pacific Society of Thrombosis and Hemostasis (APSTH), Members of the Malaysian Laboratory Hematology Society (MMLHS), Malaysian Society of Hematology (MSH) and the International Society on Thrombosis and Haemostasis (ISTH).

Aligned with the theme “Hemostasis and Thrombosis: Bench to Bedside,” the scientific program encompasses both clinical and laboratory aspects of thrombosis and hemostasis. Encompassing topics such as venous thromboembolism (VTE), challenges in inhibitor assays, laboratory diagnosis of antiphospholipid syndrome (APLS), women’s issues in thrombosis and hemostasis, and more, this program caters to clinicians, researchers, trainees, nurses, scientific officers, laboratory technologists, and medical students alike.

An array of educational workshops by ISTH will feature sessions on Hemophilia, Antiphospholipid Syndrome (APLS), and Viscoelastic testing.

This event stands as the paramount international gathering of the Asia-Pacific region in the domain of thrombosis and hemostasis. It serves as a vital platform for the exchange of academic accomplishments across nations and the cultivation of collaborative endeavours among researchers and clinicians from diverse countries, supported by ISTH.

As the organizing committee labours diligently in the background, I urge everyone to secure their spots well in advance for this unmissable opportunity. Beyond the enriching conference sessions and networking prospects, the event offers a chance for you and your family to revel in the captivating landscapes and attractions that the state of Sarawak has to offer.

Kuching, Sarawak—the largest state in Malaysia situated on Borneo Island—will host the event. This charming city is enveloped by breath-taking natural marvels, providing delegates with the chance to immerse themselves in a tapestry of cultures, adventures, nature, cuisine, and festivals unique to Sarawak.

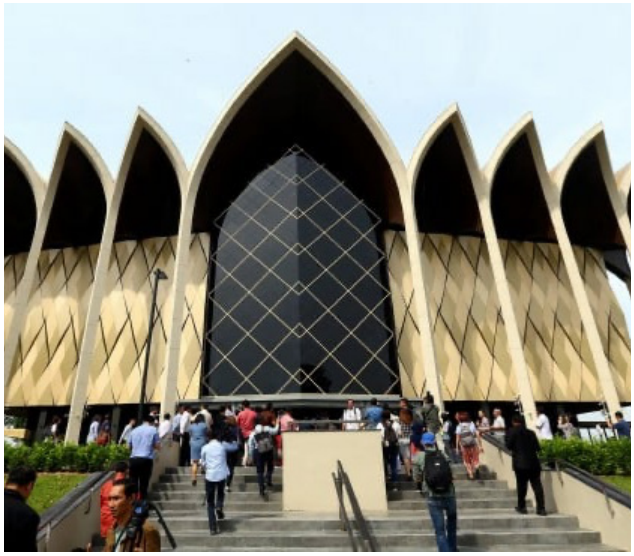
We encourage you not to forgo this momentous occasion. We eagerly anticipate the pleasure of your presence in Sarawak.

Warm regards,

P/S For more details of the congress,
please visit our website: www. apsth2023.com

Professor Dr Narazah Mohd Yusoff
MBBS (Malaya), DCP, M MED SC (LONDON), PhD (KOBE)
Chair, Local Organising Committee APSTH 2023
President, Members of the Malaysian Laboratory Hematology Society (MMLHS)

Dr Jameela Shatar
MD, MRCP, FRCPath
Scientific Program and Speaker Arrangement APSTH 2023
Member APSTH Council
Malaysian Society of Hematology (MSH)




12th Congress of the Asian-Pacific
Society of Thrombosis and Hemostasis
APSTH 2023
"Hemostasis and Thrombosis : Bench to Bedside"
18-21 October 2023
Borneo Convention Centre Kuching(BCCK)
Kuching, Sarawak, Malaysia
HIGHLIGHTED SESSION
• PRE-CONFERENCE WORKSHOPS (INCLUDING PRACTICAL SESSIONS)
• MEET THE EXPERTS
• CONCURRENT SESSIONS FOR CLINICAL, LABORATORY & NURSING
• POSTER PRESENTATION
• HEALTHCARE EXHIBITION
• DINNER & CULTURAL PERFORMANCE
PRE-CONFERENCE WORKSHOP
PRE-CONFERENCE WORKSHOP DAY 1
18 OCT 2023
BY INVITATION
Local Malaysian
PRE-CONFERENCE WORKSHOP DAY 2
19 OCT 2023
RM50
Local Malaysian
USD30
International
EARLY BIRD BEFORE 1 JULY 2023
CONFERENCE FEES
LOCAL
INTERNATIONAL
MSH/APSTH/ISTH/ MMLHS MEMBERS
RM750
(NR: RM950)
USD300
(NR: USD400)
NON-MEMBERS
RM850
(NR: RM1050)
USD400
(NR: USD500)
MEDICAL STUDENTS/ PARAMEDICS/SARAWAKIAN
RM500
(NR: RM700)
USD150
(NR: USD200)
Normal rate (NR) : after 1st July 2023
Main Organizer:
Official Website
www.apsth2023.com
SCAN ME

Report from Highlights of APSTH-JSTH joint symposium in Kitakyushu, Japan

The APSTH/JSTH joint symposium was held at the 45th Congress of the Japanese Society on Thrombosis and Hemostasis in Kitakyushu, Japan on June 15, 2023. The APSTH/JSTH joint symposium of the Japanese Society on Thrombosis and Hemostasis (JSTH) has been held since 2005, inviting young researchers from Asian countries each time to present their research. In 2023, three oral and one poster presentations were made. This symposium was started as an activity to foster researchers in the Asia-Pacific region, and past participants have been very happy to come to Japan and deepen exchanges with Japanese researchers. Once again, there were presentations of great depth and lively discussions. The three oral presentations are as follows.

We look forward to receiving many submissions for the next symposium.

Professor Dr Teruto Hashiguchi, MD, PhD
Chair, International Committee of JSTH

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Treatment related outcome from Patient Report Outcome (PRO) of children with severe and moderate hemophilia A in China: an analysis report of Registration data from Patient Organization

Dr. Di Ai

Tao Guan[1]#, Di Ai[2]#, Nan Zhao[1], Guoqing Liu[2], Wanru Yao[2], Zhenping Chen[3], Zhenping Li[2], Yaohan Zhou[2], Runhui Wu[2]

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# Tao Guan and Di Ai have contributed equally to this work and share first authorship

Hemophilia A (HA) is a rare inherited bleeding disorder caused by the deficiency of coagulation factor VIII (FVIII). Patients with moderate and severe HA are prone to spontaneous bleeding in muscles and joints, resulting in joint damage and disability and, consequently, poor quality of life (QoL).

In 2004, China created an "Hemophilia Home Care Center", a nationwide hemophilia Patient Organization. Over the years, a large number of patients and data have been collected through digital website (http://web.bjxueyou.cn). In this study, we analyzed the treatment-related data from "Hemophilia Home Care Center" website aiming to formulate a suitable strategy for HA treatment in China.

This cross-section PRO report collected PRO data of severe and moderate cHAs registered in the Hemophilia Home Care Center" database between January 2021 and November 2022. Data included records of bleeding, activities, and concentrates consumption. All patients had a confirmed diagnosis of moderate or severe hemophilia A (FVIII: C ≤ 5%) and were <18 years old.

Among 1038 analyzable cases, 9.6% of children with inhibitors had a higher rate of intracranial hemorrhage, dropout school rate, and higher FVIII consumption than children without inhibitors. Among 100 children with inhibitors, 36 patients were treated without immune tolerance induction (ITI), 14 patients with irregular treatment and 50 patients received ITI. Children with ITI had a lower ABR (2.4 (0,6.6) vs. 13.4 (9.5, 26.6), P<0.001) and AJBR (0 (0, 3.1) vs. 8.9 (1.6, 19.3), P<0.001) compared to those without ITI. Among 938 children without inhibitors, 28.5% received on-demand treatment and 71.5% received prophylaxis. Of 528 children with 1343.8 (1050.4, 2922.9) IU/kg/year median FVIII consumption, 43.0% received low-dose, 43.2% received intermediate-dose, and 13.8% received high-dose regimen; these children with prophylaxis had a lower ABR (3.1 (0, 10.7) vs. 12.8 (2.4, 45.5), P<0.001), AJBR (0.5 (0, 3.9) vs. 3.0 (0, 12.0), P<0.001) and disability rate (9.0% vs.18.5%, P=0.032) compared to children who received on-demand treatment.

The high rate of drop-out of school and disability still present a huge gap to meet the needs in China. It is necessary to improve the level of medical accessibility and medicine affordability and strengthen the patient/parent's education in China.

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Patient-specific platelet phenotypes distinguish ITP from isolated thrombocytopenia using multivariate analyses

Sidra A. Ali[1], Sarah M. Hicks[1], Lucy A. Coupland[1], Robert K. Andrews[1], Aaron Chuah[1], Thomas D. Andrews[1], Elizabeth E. Gardiner[1,2], and Philip Y. Choi[1,2,3]

[1] Division Genome Science and Cancer, The John Curtin School of Medical Research, The Australian National University, Canberra, Australia.
[2] The National Platelet Research and Referral Centre (NPRC), Canberra, Australia.
[3] Haematology Department, The Canberra Hospital, Canberra, Australia.

Dr. Sidra A. Ali

Primary immune thrombocytopenia (ITP) is a haematological autoimmune disorder characterised by bleeding and a low platelet count of less than 100 × 10^9/L. ITP is often diagnosed through exclusion, with platelet count as a pivotal diagnostic criterion. Nevertheless, the reliability of platelet counts in diagnosing ITP and predicting bleeding remains limited. Severe thrombocytopenia in ITP further complicates conventional platelet function assessment.

In light of these challenges, we used a novel avenue of investigation by utilising flow-cytometric analysis to evaluate platelet adheso-signalling receptor levels and functions. We hypothesised that this approach can potentially quantify platelet dysfunction in ITP or patients with thrombocytopenia due to other causes (non-ITP), that can help distinguish the two disorders. A comprehensive study of platelet surface proteins and functions was conducted on blood samples from 98 cases, with platelet disorders and historical bleeding events, juxtaposed with contemporaneous healthy controls. Several noteworthy observations emerged. Platelets from primary ITP cases exhibited heightened mean platelet volume. Surprisingly, key platelet adheso-signalling receptors like α2 and αIIb integrin subunits, GPIbα, GPVI, and sGPVI maintained normal levels in primary ITP. However, platelet degranulation markers P-selectin and TLT1 showed elevation in primary ITP compared to healthy or non-ITP samples. Elevated serum thrombopoietin (TPO) was also a distinguishing factor in primary ITP. Addressing the challenge of limited platelet counts, a tailored “standard curve” was generated for ROTEM analysis. When evaluating platelet contribution to clot size, a correlation emerged between ITP patient data and clinical bleeding. This encouraged us to perform a multivariate analysis to assess all platelet and plasma measurements and functional outcomes in unison.

Using PACMAP plots, primary ITP was clustered separately from healthy donors and non-ITP. Remarkably, even when excluding platelet count from analyses, this separation persisted, underscoring the distinctive attributes of ITP platelets. We then utilised machine learning-based approaches, constructed six models, and evaluated their performance in predicting ITP based on platelet function. The random forest model exhibited superior performance, boasting 94% sensitivity and 90% specificity in predicting ITP.

By harnessing advanced research tools, we were able to quantify platelet dysfunction in ITP. While no single measure could stand alone, a comprehensive analysis of multiplexed platelet data demonstrated the capability to distinguish primary ITP from other forms of thrombocytopenia. We are excited to share that ongoing studies targeting patients with low platelet counts are underway, promising further insights into this intriguing area of research to assist treatment and improve disease outcomes.

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Rhein Sensitizes Megakaryocytes to Thrombopoietin Receptor Agonists (TPO-RA) in Immune Thrombocytopenia

Lu sun, MD[1], Yu Hou, MD, PhD,[1,2] Ming Hou, MD, PhD[1]

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Dr. Lu sun

Primary immune thrombocytopenia (ITP) is an autoimmune hemorrhagic disease characterized by decreased platelet counts. Impaired megakaryocyte maturation and insufficient platelet formation play vital roles in its pathogenesis. Thrombopoietin receptor agonists (TPO-RA) are first choice for second-line therapy of ITP. However, clinical data have indicated that nearly half of ITP patients failed or relapsed after eltrombopag maintenance, and increasing drug dose cannot reverse therapeutic response. Our clinical evidence indicates that the combination of eltrombopag and diacerein can reverse the clinical dilemma of eltrombopag resistance. Diacerein is an anti-inflammatory drug in osteoarthritis, and its active metabolite is rhein. This study investigated the sensitizing effects of rhein on megakaryocyte maturation and platelet formation when added to TPO-RA in patients with ITP and in mice.

Twenty-eight eltrombopag-inefficient or relapsed ITP patients and 15 healthy volunteers were included. CD34+ cells from healthy umbilical cord blood mononuclear cells were sorted and cultured in SFEM medium containing TPO, IL-3, SCF and 10% serum from ITP patients or healthy donors. Different doses of rhein (0-100 μM) with or without eltrombopag were added on the fourth day, cultured cells were collected on the 14th day. Flow cytometry, RNA sequencing, proteomic sequencing and cytokine assay were performed. In addition, active ITP murine models were established to evaluate the therapeutic effects of TPO-RA plus rhein on megakaryocytes in vivo.

In vitro, eltrombopag plus rhein significantly increased CD41+, CD41+CD42+, CD41+CD61+ megakaryocyte proportion and promoted megakaryocyte polyploid maturation and platelet production than eltrombopag monotherapy. Since eltrombopag could not activate TPO receptor in mice, we chose romiplostim to complete vivo experiments. Romiplostim plus rhein significantly alleviated thrombocytopenia and stimulated megakaryocyte generation and polyploidization than romiplostim in active ITP mice. Further, RNA sequencing and proteomic analysis revealed that the combination of eltrombopag and rhein promoted megakaryocyte differentiation and platelet formation, decreased proinflammatory cytokines, up-regulated phosphorylated PI3K. Cytokine analysis showed that eltrombopag plus rhein significantly increased supernatant level of TGF-β, and reduced IFN-α, IFN-γ, IL-12p70, IL-17A and IL-18 than eltrombopag. Subsequently, we confirmed that the addition of rhein to TPO-RA significantly promoted megakaryocyte PI3K phosphorylation in vitro and in vivo. PI3K inhibition offset the enhanced effect of TPO-RA plus rhein over TPO-RA in megakaryocyte maturation and platelet formation. Finally, for patients who received eltrombopag plus diacerein, RNA-sequencing and cytokine analysis showed that this combination promoted megakaryocyte differentiation and platelet release, decreased proinflammatory cytokines and modulated PI3K signaling.

Compared with TPO-RA monotherapy, rhein combined with TPO-RA significantly promoted megakaryocyte polyploidization and platelet production by activating PI3K phosphorylation and decreasing proinflammatory cytokines. Furthermore, our preliminary data indicated that diacerein, the prodrug of rhein, in combination with eltrombopag, may be considered as a promising salvage therapy for eltrombopag-refractory ITP patients.

World Thrombosis Day Activities in Asia Pacific Region (2022)

In 2022 APSTH hosted virtual scientific conferences among member countries and open seminars for general citizen in Thailand, Japan and Singapore. Face-to-face meeting was made possible in 2022 due to end of COVID-19 pandemic.

On October 12, 2022 in Thailand for the hospital activity, approximately fifty general citizens attended the in-person public seminar (Figure 1, Figure 2, Figure 3). The participants in the public seminar understood that Thailand Society of Hematology shed an important spotlight on blood clots as an urgent need. The activity was recorded and available on Facebook with 420 views.
https://www.facebook.com/TSH.Public.Education/videos/636729897855612/

Figure 1 World Thrombosis Day activity at Srinagarind Hospital, Khon Kaen, Thailand

Figure 2 World Thrombosis Day activity at Srinagarind Hospital, Khon Kaen, Thailand

Figure 3 World Thrombosis Day activity at Srinagarind Hospital, Khon Kaen, Thailand

An educational webinar was held as World Thrombosis Day updates again. APSTH members were invited to World Thrombosis Day activities in Asia Pacific (VTE Burden of Disease and Prophylactic Considerations) on August 11, 2022 (Figure 4). This webinar had talks from expert speakers (Lai Heng Lee from Singapore, Pantep Angchaisuksiri from Thailand, Christopher Ward from Australia) as well as Q&A with expert panelists from Asia-Pacific region. The meeting moderator was Jameela Sathar from Malaysia. Approximately 190 people virtually participated in the educational webinar. The meeting was announced through thrombosis society in each country using posters, e-mails, and Facebook. APSTH homepage was also used. The healthcare professionals who participated in the educational seminar understood that there are important clinical issues for the management of venous thromboembolism (VTE) and the use of anticoagulants among doctors in Asia. In Asian inherited thrombophilia, coagulation is disturbed by the loss-of-function mutations of protein S and protein C (causing protein S and protein C deficiencies). In Asia the gain-of-function factor V Leiden and prothrombin G20210A mutations are almost absent. Cancer is the most important acquired risk factor for VTE in Asia. Most clinical trials for VTE treatment and prevention of VTE include small number of Asian patients. Individualized assessment of thrombotic and bleeding risks should be used for all Asian patients when deciding pharmacologic thromboprophylaxis. More research is needed to understand the factors contributing to VTE risks and anticoagulant-associated bleeding in Asian patients. These may differ from Western population. In Thailand Professor Ponlapat Rojnuckarin started a Facebook site for WTD program in native language so that Thailand citizen in general can easily understand the WTD missions and increase awareness about thrombosis.

Figure 4 WTD Educational Webinar

In Japan Japanese Society on Thrombosis and Hemostasis continued to focus on topics related to urgent needs for the thrombosis associated with viral infections. Four meetings were held. On February 14, 2022 zoom meeting was held with the topic of “Complications of COVID-19 and thrombotic complications with vaccination.” This scientific conference focused on the thrombotic complications on COVID-19 and vaccine related thrombosis (thrombosis with thrombocytopenia syndrome) (Figure 5). On May 17, 2022 WEBEX webinar was held with the topic of “Perspective of cancer-associated thrombosis.” One hundred and sixty healthcare professionals attended (Figure 6). On November 6, 2022 WTD public program and open lecture was held in-person in Tokyo with the topic of “COVID-19 and thrombosis: why thrombosis is associated with COVID-19?” Fifty-eight citizens attended (Figure 7, Figure 8). On December 4, 2022 WTD public program and open lecture was held in Osaka virtually with the topic of “Cancer and thrombosis: when you see thrombosis, think about cancer.” Forty citizens attended (Figure 9).

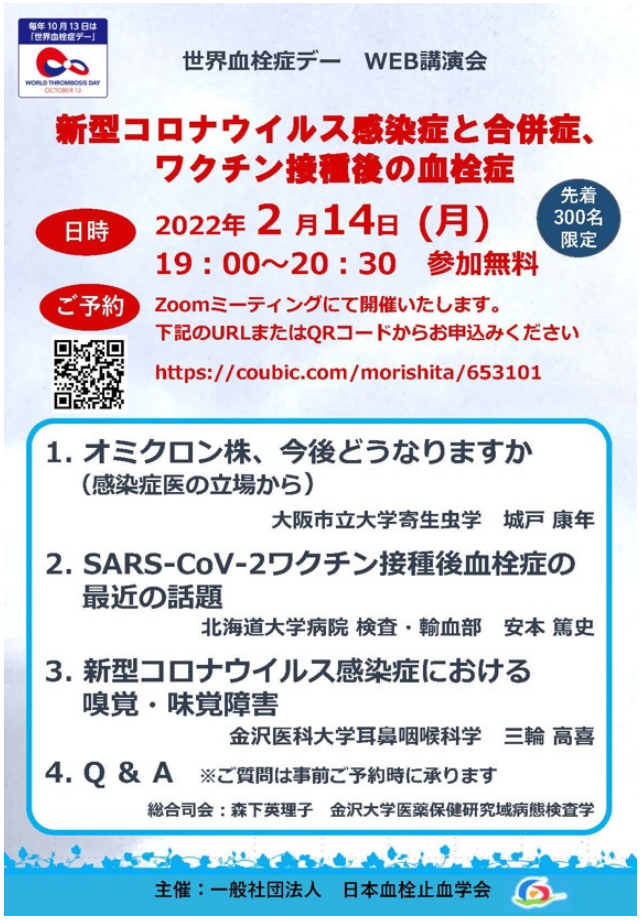


Figure 5 Webinar “Complications of COVID-19 and thrombotic complications with vaccination.”

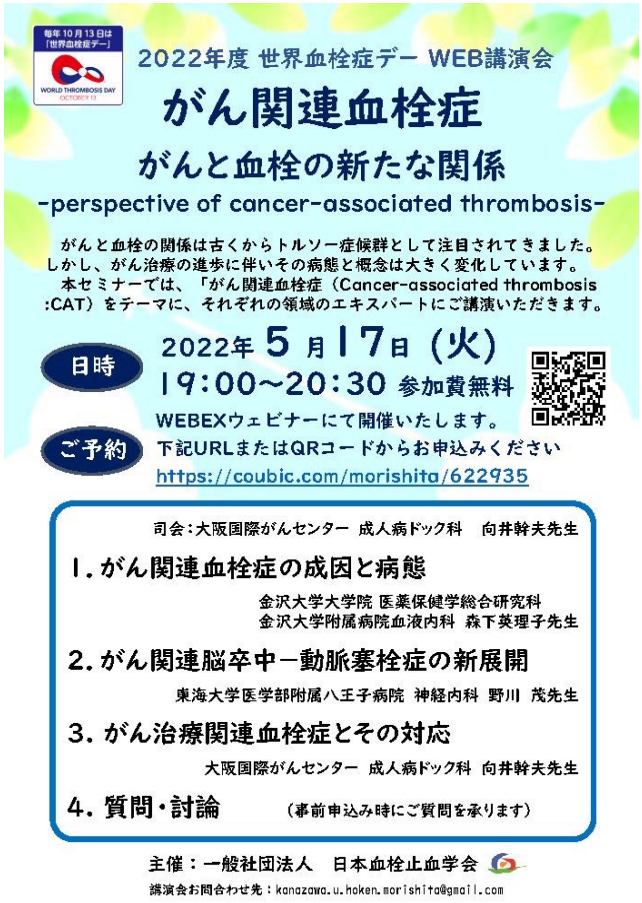


Figure 6 Webinar “Perspective of cancer-associated thrombosis”

Figure 7 On-site lecture in Tokyo "COVID-19 and thrombosis: why thrombosis is associated with COVID-19?"

Figure 8 On-site lecture in Tokyo, Japan "COVID-19 and thrombosis: why thrombosis is associated with COVID-19?"

Figure 9 In-person lecture in Osaka, Japan "Cancer and thrombosis: when you see thrombosis, think about cancer."

Figure 10 WTD educational symposium in Singapore

Singapore will be holding their annual WTD education symposium on October 5, 2023 (Figure 10). The topic is “Assess, Prevent & Treat Venous Thromboembolism.” This is part of the annual WTD education symposium.

APSTH member countries continue to raise awareness and promote WTD to family, friends and colleagues. APSTH will help our members keep safe and at the same time increase awareness. For scientific meetings for medical professionals virtual events will be carefully planned. And for seminars for citizen in general social media such as Facebook will be extensively utilized. And starting website in the native language in each country would be ideal. In APSTH2023 in Malaysia WTD activities are added to the scientific meeting to raise awareness and promote WTD among our friends and colleagues of APSTH.

Research News

“To unravel the pathophysiology of a rare thrombotic disorder, thrombotic thrombocytopenic purpura (TTP).”

Kazuya SAKAI, MD, PhD.
Senior lecturer
Department of Blood Transfusion Medicine, Nara Medical University, Japan

Thrombotic thrombocytopenic purpura is a rare thrombotic disorder, characterized by severe ADAMTS13 depletion due to autoantibodies production against ADAMTS13 (immune-mediated TTP: iTTP) and biallelic ADAMTS13 mutations (congenital TTP: cTTP). In absence of ADAMTS13, von Willebrand factor (VWF) multimer with higher binding capacity against platelet receptor GPIb can readily contribute to the formation of microvascular thrombi. In the end, ischemic organ damage, including myocadiac infarction and stroke, lead to fatal outcomes without appropriate interventions like plasma exchange combined with immunosuppressive treatments.

Since 1998, our institution in Japan has been actively involved in diagnosing TTP and other conditions falling under the category of thrombotic microangiopathy (TMA) as a national reference center. In-depth, citrated plasma from a suspicious patient with TTP is sent to our center, and ADAMTS13 act-ELISA measures ADAMTS13 activity and its inhibitor with a short turnaround time (1-2 days). We have previously developed the ELISA using a unique monoclonal antibody, N10, that captures the cleavage site of artificial recombinant protein, VWF73. (Kato S, et al. Transfusion. 2006.) FRETS-VWF73 and ADAMTS13act-ELISA are commonly used as a gold standard to measure ADAMTS13 activity levels globally. As of 2022, our center has successfully diagnosed more than 1,600 cases of TMA, and our database is regarded as one of the largest TMA cohorts in the world. (Figure 1).

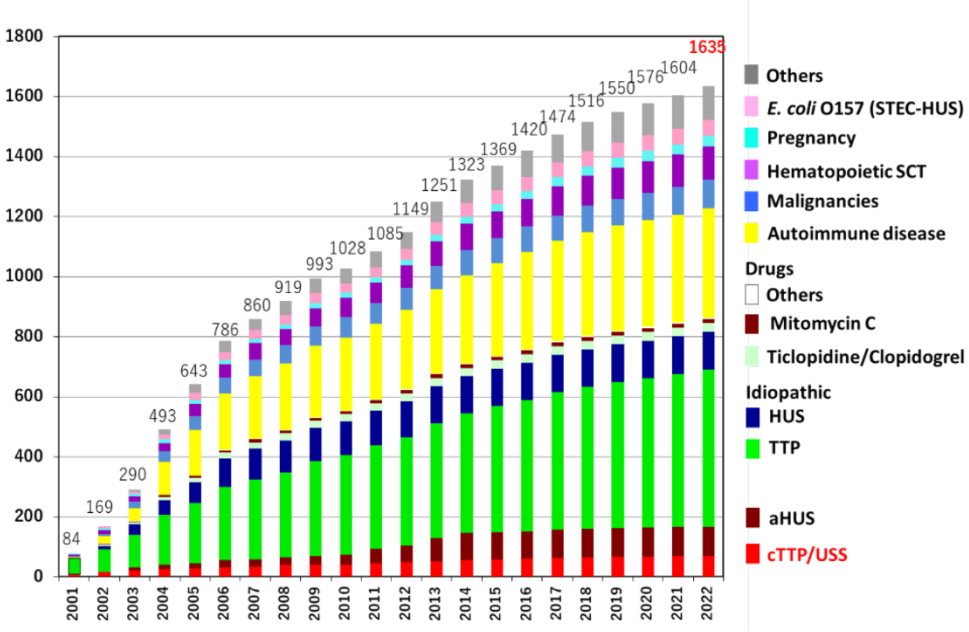
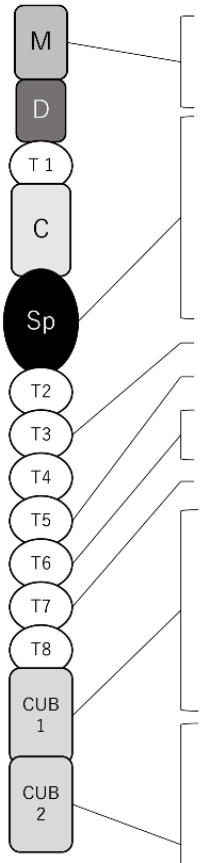


Figure 1
Japanese thrombotic microangiopathy registry 1998-2022

Over the previous years, our research efforts have been dedicated to unraveling the pathophysiology of iTTP in the Japanese population. It has not been well elucidated how ADAMTS13-derived peptides can be presented by antigen-presenting cells to auto-reactive helper T-cells among patients with iTTP. In the early 2010s, the European groups revealed that European patients with iTTP have DRB1”11’01 more frequently than those without, suggesting the DR-allele is a genetic risk for developing iTTP. Intriguingly, we recently reported DRB1*08:03 as the susceptible allele in Japanese patients with iTTP and the 2 risk alleles, DRB1*11 and DRB1*08:03, belong to distinct serotype groups and differ in their peptide-binding specificity. (Sakai K ,et al Blood. 2020.) For DRB1*11:01, potential T-cell epitopes in ADAMTS13 have been identified through peptide elution and mass spectrometry analyses [major histocompatibility complex (MHC)-peptidome. Among these peptides, 2 regions (1328–1336: FINVAPAHR and 1239–1253: GDMLLLWGRLTWRKM) were recognized by the T cells in patients with DRB1*11 in the acute phase. To determine allele-restricted T-cell epitopes in DRB1*08:03, a novel HLA expression assay, called MHC-density assay, was applied in 24 peptide candidates from whole domains of ADAMTS13, selected from previous studies and in silico MHC-peptide binding prediction model (NetMHCIIpan version 4.0). (Figure 2) Using flow cytometry, the MHC-density assay measures the fold increase in cell-surface MHCpeptide complex expression relative to the negative control peptides. The assay has been primarily developed to estimate MHC protein stability and is further optimized to estimate the strength of peptide presentation to MHC. To determine the peptide-mediated increase in cell surface MHC II, the ratio of MFI (MHC) to MFI (GFP) for each MHC II-peptide was normalized to that of the negative control peptide, g9. Some of the peptides that showed a high g9 ratio for DRB1*08:03 may be persistently presented by DRB1*08:03 and contribute to developing iTTP. In addition, the finding of overlapping six ADAMTS13-derived peptides that bind DRB1*08:03 and DRB1*11:01 suggest a common path that induces autoimmune reaction in iTTP. (Figure 3) Further studies are required to confirm the immunological roles of these peptides and unravel the immune reactions that cause the onset of iTTP.(Sakai K et al. J Thromb Haemost. 2023.)



Peptide ID	Peptide Residue Number	Amino Acid Sequence
p101	101-115	ERYVLTNLNIGAELL
p110	110-124	IGAELLRDPSLGAQF
p244	244-258	PSGHVMASDGAAPRA
p266	266-280	SRRQLLSLLSAGRAR
p569	569-583	EYVTFLTVTPNLTSV
p589	589-603	RPLFTHLAVRIGGRY
p598	598-612	RIGGRYVVAGKMSIS
p622	622-636	EDGRVEYRVALTEDR
p651	651-665	EDADIQVYRRYGEEY
p774	774-788	GSLLKTLPPARCRAG
p913	913-927	MELRFLCMDSALRVP
p970	970-984	VVRRILYCARAHGED
p986	986-1000	GEEILLDTQCQGLPR
p1034	1034-1048	RRSVACVQLDQGQDV
p1194	1194-1208	RQHLEPTGTIDMRGP
p1207	1207-1221	GPSQADCAVAIGRPL
p1239	1239-1253	GDMLLLWGRLTWRKM
p1258	1258-1272	LDMTFSSKTNTLVVR
p1266	1266-1280	TNTLVVRQRCGRRGG
p1279	1279-1293	GGGVLLRYGSQLAPE
p1324	1324-1338	GCRLFINVAPHARIA
p1327 (9mer)	1327-1335	GGGLFINVAPHAGGG
p1328 (9mer)	1328-1336	GGGFINVAPHARGGG
p1334	1334-1348	HARIAIHALATNMGA
p1355	1355-1369	ASYILIRDTHSLRTT
p1392	1392-1406	EGFLKAQASLRGQYW

Figure 2
Locations of the ADAMTS13 peptides used in the MHC-density assay. M, metalloprotease domain; D, disintegrin-like domain; T, thrombospondin type 1 repeat domain; C, cysteine-rich domain; Sp, spacer domain; CUB, complement C1r/C1s, sea urchin epidermal growth factor, and bone morphogenetic protein.

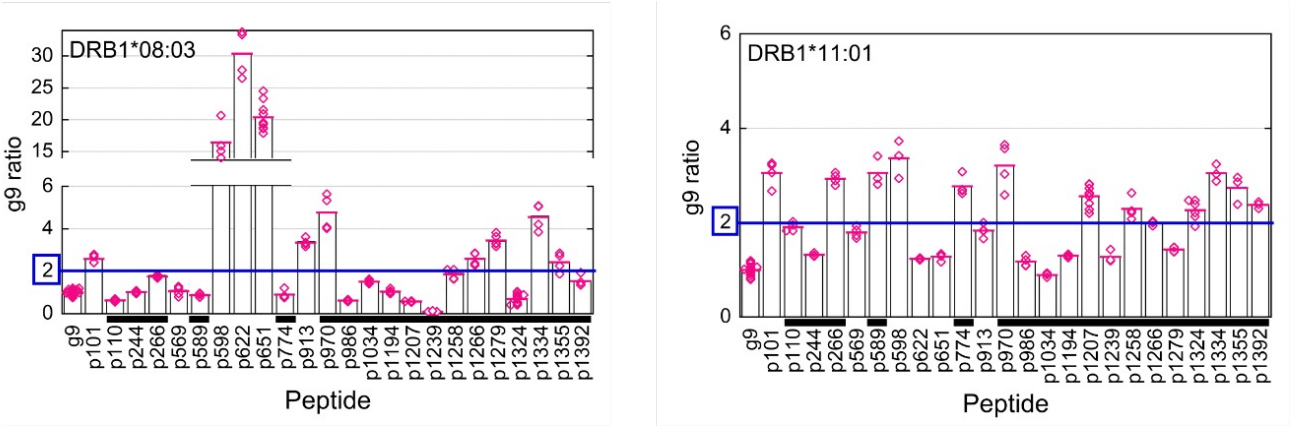


Figure 3
MHC-density assay of the ADAMTS13 peptides for DRB1*08:03 and DRB1*11:01. Dot plots showing the g9 ratio of ADAMTS13 peptides to DRB1*08:03 and DRB1*11:01 measured by the MHC-density assay.

Our research would continue to comprehend further the mechanisms behind self-antigen recognition, cell signaling to enrich ADAMTS13-specific B-cell and autoantibody production from plasma cells in patients with iTTP.

Upcoming Meetings:

1. **The 12th Congress of the Asian-Pacific Society of Thrombosis and Hemostasis.**
October 18-21, 2023
Kuching, Sarawak, Malaysia
https://www.apsth2023.com

2. **Highlights of ASH (HOA) in Asia-Pacific Region**
February 16-17, 2024
Sydney, Australia
https://www.hematology.org/meetings/highlights

3. **World Federation of Hemophilia (WFH) World Congress**
April 21-24, 2024
Madrid, Spain
https://wfh.org/congress/

4. **The 32nd International Society on Thrombosis and Haemostasis (ISTH)**
June 22-26 of 2024
Bangkok, Thailand
https://www.isth2024.org/