Congratulations to Toshiyuki Miyata, PhD

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It is with great joy that I learned at the 30th Congress of the International Society of Thrombosis and Haemostasis (ISTH) in London, that Toshiyuki Miyata was presented the Esteemed Career Award for his outstanding scientific contributions to the field of thrombosis and hemostasis. Every year the ISTH honours five internationally recognized and distinguished scientists who made important discoveries advancing the knowledge on the pathophysiology of thrombotic or bleeding disorders and/or contributing to better diagnosis and treatment of these diseases.

I have known Toshi Miyata since 1989 when I first studied his excellent poster on the structural defect of coagulation factor XII Washington, D.C. at the ISTH Congress in Tokyo. This was the first dysfunctional factor XII (FXII) molecule from a cross reacting material-positive FXII deficient subject whose defect was elucidated by amino acid sequencing of tryptic peptides and the full paper, reporting the Cys571Ser variant (updated terminology as of 2022 Cys590Ser) was prominently published in the same year1). I was personally very much interested because we just had started studying similar dysfunctional FXII molecules, denoted FXII Bern2) and FXII Locarno3) but it took us quite some time to unravel the structural defect of the latter4). Understandably, I admired this young Japanese researcher at the Tokyo congress for his achievement together with his senior coauthors including Sadaaki Iwanaga, Hidehiko Saito and others.

In a surprising parallelism to my own primary scientific focus, Toshi Miyata, over the ensuing years moved his main scientific interest to the metalloprotease ADAMTS13, the Von Willebrand factor-cleaving protease, whose se-
vere deficiency is associated with the rare but potentially fatal disease thrombotic thrombocytopenic purpura (TTP).

Together with Professor Yoshihiro Fujimura and his team from Nara Medical University Toshiyuki Miyata and his group at the National Cardiovascular Center in Suita reported several pathogenic mutations of the ADAMTS13 gene in Japanese patients with the very rare hereditary form of TTP\(^5,6\). In addition they found a common polymorphism among the Japanese population.

An enormous highlight in the field of TTP was the invention and set-up of a rapid assay of ADAMTS13 activity using FRETS-VWF73, a first fluorogenic substrate for the VWF-cleaving protease\(^7\). This method revolutionized the laboratory diagnosis of TTP because many laboratories could now measure ADAMTS13 activity within 1–2 hours whereas before 2005 the assay of ADAMTS13 activity was reserved to some rare research laboratories worldwide and with some of the methods used it took up to several days to obtain a result. This new fluorescence resonance energy transfer system-based assay was—and still is—of utmost relevance for the diagnosis and management of hereditary and the more common autoimmune TTP when it became clear that a severe hereditary or acquired deficiency of ADAMTS13 activity was the diagnostic hallmark of both hereditary and acute acquired TTP.

Toshi Miyata’s team generated ADAMTS13 knock-out mice and nicely demonstrated that completely ADAMTS13 deficient mice were viable and did not show thrombocytopenia, hemolysis or microvascular thrombosis\(^8\) in contrast to a substantial number of humans with complete ADAMTS13 deficiency (so-called Upshaw-Schulman syndrome) who often have a disease-onset with intravascular hemolysis and thrombocytopenia in the neonatal period\(^9\). Nevertheless, ADAMTS13 \(--/--\) mice showed unusually large VWF multimers in plasma and were prothrombotic in several stimulated thrombosis models\(^9\).

In 2007 Toshi Miyata and Yoshi Fujimura generously invited me as a visiting professor to Japan and they showed me their laboratories and institutes and presented their exciting ongoing research activities and data. I was very warmly received in Japan and since this time there is a continuing friendship with Yoshihiro Fujimura, Masanori Matsumoto, Koichi Kokame, Toshiyuki Miyata and their teams.

Two years later, I met Toshi at the ISTH Congress in Boston in 2009. I remember him—during a break between scientific sessions—sitting in the recreational area at a table, smiling, with his laptop on. When I passed by and greeted him with joy, he showed me, very proud of his most recent achievement, an animated model of the crystal structure of the DTCS region of human ADAMTS13 (they had also included the M domain by analogy with other ADAMTS proteases). This allowed to gain insight into the ADAMTS13-VWF molecular interactions. The full paper was published in the same year in PNAS\(^10\).

Toshiyuki Miyata has contributed many more scientific papers, also on additional topics like thrombophilic markers. I am very thankful for a longstanding friendship with this excellent scientist and very sympathetic person.

**References**

4) Kremer Hovinga J et al.: Coagulation factor XII Locarno: The functional defect is caused by the amino acid substitution Arg 353 \(\rightarrow\) Pro leading to loss of a kallikrein cleavage site.

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