Received: 3 June 2022 | Accepted: 11 June 2022

DOI: 10.1111/jth.15786

jth

COMMENTARY

A new harmony for hemorrhagic disorders: The Dutch SYMPHONY consortium

Benjamin J. Samelson-Jones[1,2,3]

[1]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[2]The Raymond G. Perelman Center for Cellular and Molecular Therapeutics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

[3]Division of Hematology, Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Correspondence
Benjamin J. Samelson-Jones, The Children's Hospital of Philadelphia, 3501 Civic Center Blvd, 5028 Colket Translational Research Center, Philadelphia, PA 19104, USA.
Email: samelsonjonesb@chop.edu

Improving the understanding of the hemostatic system and the clinical care of people with inherited bleeding disorders have been reinforcing harmonies of modern hematology.[1,2] The deciphering of the coagulation cascade and platelet signaling was facilitated by patients with inherited bleeding disorders found to be missing essential components in these biological pathways. In turn, the medical management of these patients was transformed by molecularly defining their disorder, which has often, though with a number of notable exceptions, led to disease-specific replacement therapies with better and safer hemostatic efficacy. These complementing endeavors will be further synchronized within SYMPHONY, a new Dutch research consortium described in detail in this issue by Cnossen et al. and outlined on their website.[3,4] This enviable scientific program builds on the strong track records of clinical and basic-science hemostatic research in the Netherlands. SYMPHONY aims to ultimately enhance the clinical care of people with hemorrhagic disorders by better describing their bleeding diathesis to account for interindividual variation in bleeding behavior and response to therapy. Their interdisciplinary, patient-focused, research framework will likely serve as a model both for hemostasis groups at other locales as well as groups focused on other rare genetic diseases.

Their ambitious agenda directly attacks many of the unmet needs of patients with bleeding disorders (in the Netherlands) and the unanswered questions of hemostasis; and by tackling both in a united research effort, they aim to accelerate progress on both fronts. They concentrate on three interlocking themes: (1) optimization of diagnostic assays, (2) personalization of optimal clinical care, and (3) unraveling the biological basis of hemostasis. Theme 1 focuses on the development and improved clinical use of advanced diagnostic assays, intersecting with research from theme 3 to generate better *in vitro* models that recapitulate *in vivo* hemostasis and thrombopoiesis. An expanded armamentarium of diagnostic assays will also help to address the large proportion of patients with a mild bleeding phenotype currently only classified as bleeding of undefined cause (BUC)[5,6] and potentially characterize rare severe disorders that reveal new aspects of hemostasis.[7] Theme 2 focuses on improving the delivery of clinical care for bleeding disorders. Here, projects are aimed at developing and implementing cutting-edge pharmacokinetic-based dosing, determining the value and cost effectiveness of new therapies in a rapidly evolving treatment landscape,[7,8] and ensuring patients' perspectives are forefront when considering emerging ethical dilemmas of these new innovations. To facilitate these aims, they also intend to develop a patient-managed nationwide digital personal health record. This is a bold endeavor that if successful will likely produce data for many years to come. Its development within the nationwide multidisciplinary SYMPHONY consortium should ease the accessibility of these data for future research. Theme 3 focuses on elucidating the basic biology hemostasis by applying state-of-the-art techniques to plasma and cell samples from both bleeding disorder patients and appropriate controls; proposed projects utilize nano-liquid chromatography mass spectrometry for a proteomics study and induced pluripotent stems cells and endothelial colony forming cells to develop new cellular models of bleeding disorders. Here again the close interplay between the clinical care and basic research within the consortium should help expediate these projects especially in the acquisition of patient samples.

Several attributes of the SYMPHONY consortium framework should be emphasized. First, the scope of their ambition results in potentially multiple points of synergy; by uniting scientists and

Manuscript handled by: Riitta Lassila Final decision: Riitta Lassila, 13 June 2022

clinicians across the 25 listed disciplines, they will invariably bring new perspectives and personnel to the basic and clinical problems of inherited bleeding disorders. This broad spectrum of expertise was possible, in part, because of the inclusion of a range of different types on institutions including medical facilities comprising both adult and pediatric hospitals, universities, and industry partners of variable size. The consortium is also comprehensive, including every hemophilia treatment center in the Netherlands. Furthermore, the framework encompassing both basic science and clinical care should help rapidly and efficiently implement research results into clinical care. Last, its governance structure is patient forward with a large and diverse patient panel participating in the management of the entire consortium.

One unaddressed underlying assumption is whether personalized treatments should always be the goal. The early clinical use of emicizumab simplified prophylaxis for severe hemophilia A, with the same mg/kg/week dose prescribed for patients with and without inhibitors and without consideration of pharmacokinetics, which have only moderate interindividual variability.[10] Emicizumab allowed for a more one-size-fits-all approach to prophylaxis in hemophilia A compared to the recommended tailoring of factor VIII concentrate administration.[11,12] This streamlined dosing likely contributed to the reduced estimated cost of prophylaxis when patients switched to emicizumab in the United States.[13] However, with accumulating clinical experience, the question has recently been raised if there is a role for personalizing emicizumab dosing.[12] Indeed, a recent abstract reported marked clinical benefit of low-dose emicizumab (<25% recommended dose) in a resource-scarce setting.[14] This early example of customizing emicizumab dosing to available resources likely anticipates future efforts to tailor the dosing of emicizumab and other non-factor therapies based on a variety of considerations. The SYMPHONY consortium's inclusion of value-based and cost-effectiveness assessments will address this question of the benefits (and costs) of personalized treatment, though as the case study of emicizumab suggests, the answer may not be static.

It is an exciting time in hemostasis research and clinical care. New therapies and new insights into hemostasis have rapidly changed the management of hemophilia and to a lesser extent, other inherited bleeding disorders.[7,8] The SYMPHONY consortium is a big research effort with ambitious goals that will hopefully further this trajectory. This effort is very much welcomed, because despite the many achievements in the field, a functional cure that results in normal hemostasis and comparable health equity to those without bleeding disorders remains an aspirational goal for all bleeding disorders.[15] Ideally, it will inspire additional large research efforts in hemostasis in other countries or perhaps even across countries. Though SYMPHONY is aimed to enhancing the care of Dutch patients with bleeding disorders, the lack of care for most worldwide patients should not be ignored.[16] I hope that its successes will be applicable globally.

CONFLICTS OF INTEREST

The author has no conflicts of interest to declare.

ORCID

Benjamin J. Samelson-Jones https://orcid.org/0000-0001-6772-4140

REFERENCES

1. Coller BS. Historical perspective and future directions in platelet research. *J Thromb Haemost*. 2011;9(Suppl 1):374-395.
2. Saito H, Matsushita T, Kojima T. Historical perspective and future direction of coagulation research. *J Thromb Haemost*. 2011;9(Suppl 1):352-363.
3. Symphony. Accessed June 06, 2022. https://symphonyconsortium.nl/team/
4. Cnossen MH, van Moort I, Reitsma SH, et al. SYMPHONY consortium. SYMPHONY consortium: Orchestrating personalized treatment for patients with bleeding disorders. *J Thromb Haemost*. 2022. Epub ahead of print. https://doi.org/10.1111/jth.15778
5. Mezzano D, Quiroga T. Diagnostic challenges of inherited mild bleeding disorders: a bait for poorly explored clinical and basic research. *J Thromb Haemost*. 2019;17(2):257-270.
6. Rodeghiero F, Pabinger I, Ragni M, et al. Fundamentals for a systematic approach to mild and moderate inherited bleeding disorders: an EHA consensus report. *Hemasphere*. 2019;3(4):e286.
7. Zimowski KL, Petrillo T, Ho MD, et al. F5-Atlanta: a novel mutation in F5 associated with enhanced East Texas splicing and FV-short production. *J Thromb Haemost*. 2021;19(7):1653-1665.
8. Callaghan MU, Sidonio R, Pipe SW. Novel therapeutics for hemophilia and other bleeding disorders. *Blood*. 2018;132(1):23-30.
9. Muczynski V, Christophe OD, Denis CV, Lenting PJ. Emerging Therapeutic Strategies in the Treatment of Hemophilia A. *Semin Thromb Hemost*. 2017;43(6):581-590.
10. Donners A, Rademaker CMA, Bevers LAH, et al. Pharmacokinetics and associated efficacy of emicizumab in humans: a systematic review. *Clin Pharmacokinet*. 2021;60(11):1395-1406.
11. Srivastava A, Santagostino E, Dougall A, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2020;26(Suppl 6):1-158.
12. Mahlangu J, Iorio A, Kenet G. Emicizumab state-of-the-art update. *Haemophilia*. 2022;28(Suppl 4):103-110.
13. Samelson-Jones BJ, Guelcher C, Kuhn J, et al. Real-world cost estimates of initiating emicizumab in US patients with haemophilia A. *Haemophilia*. 2021;27(4):591-598.
14. Chuansumrit A, Sirachainan N, Jaovisidha S, et al. Effectiveness of monthly low-dose emicizumab prophylaxis without 4-week loading doses among patients with hemophilia a with and without inhibitor: a case series report. *Blood*. 2021;138:2116.
15. Skinner MW, Nugent D, Wilton P, et al. Achieving the unimaginable: health equity in haemophilia. *Haemophilia*. 2020;26(1):17-24.
16. Skinner MW. WFH: closing the global gap--achieving optimal care. *Haemophilia*. 2012;18(Suppl 4):1-12.