These data support previous observations that myosin-mediated contractile forces contribute to proper thrombus formation and may have important, clinically related implications for patients with MYH9-related platelet disorders suffering from altered hemostatic function.[12]

In conclusion, Lian *et al*. convincingly revealed a so far unknown role for arginylation, a lesser known post-translational modification, in platelet biology and demonstrate that there is a hierarchical network of post-translational modifications, with myosin ELC/MYL6 arginylation regulating the level of myosin RLC phosphorylation. Whether this is a general regulatory mechanism in cells remains to be determined. For example, the authors identified the arginylation of the cytoskeletal and scaffold protein filamin A in platelets. Filamin A plays a critical role in platelet morphology and signaling, as it cross-links actin filaments, tethers the von Willebrand factor receptor glycoprotein Ib-IX-V complex and integrins to the underlying actin cytoskeleton, and serves as a scaffold for signaling intermediates, e.g. the tyrosine kinase Syk[13] (reviewed by Falet *et al.*[14]). Filamin A arginylation occurs on three different sites, *i.e*. Pro2151, Phe2311 and Tyr2501, among which Pro2151 is particularly important, as it is located near Ser2152, a major phosphorylation site and a possible regulator of integrin binding. It will be interesting to investigate if and how ATE1-mediated arginylation influences the function of the more than 20 arginylated proteins, for example filamin A, in platelets. Thus, we are just at the beginning of understanding the importance of arginylation in platelet biology.

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References

1. Lian L, Suzuki A, Hayes V, Saha S, Han X, Xu T, et al. Loss of ATE1-mediated arginylation leads to impaired platelet myosin phosphorylation, clot retraction, and in vivo thrombosis formation. Haematologica. 2013;99(3):554-60.
2. Nieswandt B, Pleines I, Bender M. Platelet adhesion and activation mechanisms in arterial thrombosis and ischaemic stroke. J Thromb Haemost. 2011;9 (Suppl 1):92-104.
3. Zahedi R, Lewandrowski U, Wiesner J, Wortelkamp S, Moebius J, Schütz C, et al. Phosphoproteome of resting human platelets. J Proteome Res. 2008;7(2):526-34.
4. Saha S, Kashina A. Posttranslational arginylation as a global biological regulator. Dev Biol. 2011;358(1):1-8.
5. Soffer R. Enzymatic modification of proteins. 4. Arginylation of bovine thyroglobulin. J Biol Chem. 1971;246(5):1481-4.
6. Wang J, Han X, Saha S, Xu T, Rai R, Zhang F, et al. Arginyltransferase is an ATP-independent self-regulating enzyme that forms distinct functional complexes in vivo. Chem Biol. 2011;18(1):121-30.
7. Rai R, Kashina A. Identification of mammalian arginyltransferases that modify a specific subset of protein substrates. Proc Natl Acad Sci USA. 2005;102(29):10123-8.
8. Rai R, Wong C, Xu T, Leu N, Dong D, Guo C, et al. Arginyltransferase regulates alpha cardiac actin function, myofibril formation and contractility during heart development. Development. 2008;135(23):3881-9.
9. Kwon Y, Kashina A, Davydov I, Hu R-G, An J, Seo J, et al. An essential role of N-terminal arginylation in cardiovascular development. Science. 2002;297(5578):96-9.
10. Levayer R, Lecuit T. Biomechanical regulation of contractility: spatial control and dynamics. Trends Cell Biol. 2012;22(2):61-81.
11. Ono A, Westein E, Hsiao S, Nesbitt W, Hamilton J, Schoenwaelder S, Jackson S. Identification of a fibrin-independent platelet contractile mechanism regulating primary hemostasis and thrombus growth. Blood. 2008;112(1):90-9.
12. Balduini C, Pecci A, Savoia A. Recent advances in the understanding and management of MYH9-related inherited thrombocytopenias. Br J Haematol. 2011;154(2):161-74.
13. Falet H, Pollitt A, Begonja A, Weber S, Duerschmied D, Wagner D, et al. A novel interaction between FlnA and Syk regulates platelet itam-mediated receptor signaling and function. J Exp Med. 2010;207(9):1967-79.
14. Falet H. New insights into the versatile roles of platelet FlnA. Platelets. 2013;24(1):1-5.

Survey of professional competence in hematology in Europe

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Competence in hematology: a prerequisite for good patient care

The purpose of specialty training in medicine is to supply the population with a sufficient number of adequately educated medical specialists. The majority of hematologic disorders often require immediate attention, investigation and treatment. The diversity of hematologic diagnoses and specialized treatments set high demands on the competence of hematologists and access to specialist care. Moreover, the specialty of hematology is unique in its requirement to blend both clinical and laboratory skill sets. It is, therefore, a concern that the number of hematologic specialists, as well as their training, varies consider-

1B: BONE MARROW FAILURE

The trainee has received specialized training in:

a) Franconi's anemia

b) Acquired aplastic anemia

c) Paroxysmal nocturnal hemoglobinuria

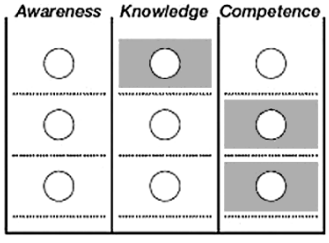


Figure 1. European Curriculum for Hematology version 1.0 showing options for self-assessed competence in bone marrow failure disorders.

ably between European countries, potentially leading to inequality in patient care. A previous, unpublished study revealed that the number of new hematologic specialists per million inhabitants per year varied from 0.2 to 3.5 and that the length of training in hematology ranged from 1-5 years.

As recently described in three editorials in this Journal, the European Hematology Association (EHA) has been the lead organization for two consecutive projects within the Leonardo da Vinci (LdV) Lifelong Learning Programme.[1-3] The first project ran from 2003 to 2006 and established hematology as a mono-specialty within the EU, performed the above-mentioned survey, and developed the first version of a European Hematology Curriculum, called the CV Passport. The CV Passport is a booklet (an online version of the CV Passport became available at ehaweb.org in 2012), developed through a bottom-up process involving senior and junior hematologists across Europe, describing the desired minimum competences of a recently trained specialist in hematology. Divided into sections, the CV Passport allows for mentors to sign off parts of their trainees' education. CV Passport in hand, the trainee can then take another part of her or his specialty training at another training school. Thus, the CV Passport is a tool to support mobility during hematology training be that in a national or international context. It has been translated and implemented in some countries, but its main effect has probably been to serve as a source of inspiration for national educational development.

With the creation of the CV Passport a first truly European curriculum for hematology training was born. Its creation involved nearly all national and international societies of hematology in Europe who reached a consensus on the scope and content of the medical specialty of hematology, and the minimum competence levels to which a specialist in hematology should be trained. The scope of the first version of the hematology curriculum encompassed five sections: clinical hematology, diagnosis, coagulation and hemostasis, transfusion medicine, and general skills. Each section had subsections, e.g. bone marrow failure, malignant hematology, and stem cell transplantation, and each subsection encompassed a varying number of specific items (Figure 1). The level of competence for each item was scored according to a 3-grade scale, with a recommended level given for each item. For the first time, it was possible to describe the European hematologist as a medical specialist who has been trained to achieve competences that are on or above recommended levels in all items of the hematology curriculum.

Linkers: a network of European hematologists

An important outcome of the first LdV project was the establishment of a group of national representatives, the so-called curriculum linkers. The linkers were appointed by the respective national societies (NS) for hematology and represented their country in the European educational projects. They were usually appointed for longer periods of time and independently of the rotation of the NS boards. The linkers were crucial collaborators in the second project: H-Net 2008-2011. They were responsible for the survey at the national level, the implementation of the different H-Net deliverables, and the endorsement process of the revised curriculum. After the termination of the H-Net project, the group of curriculum linkers was instituted into a regular structure of the EHA, hence also active outside the periods of the project.

H-Net survey of hematologic competence

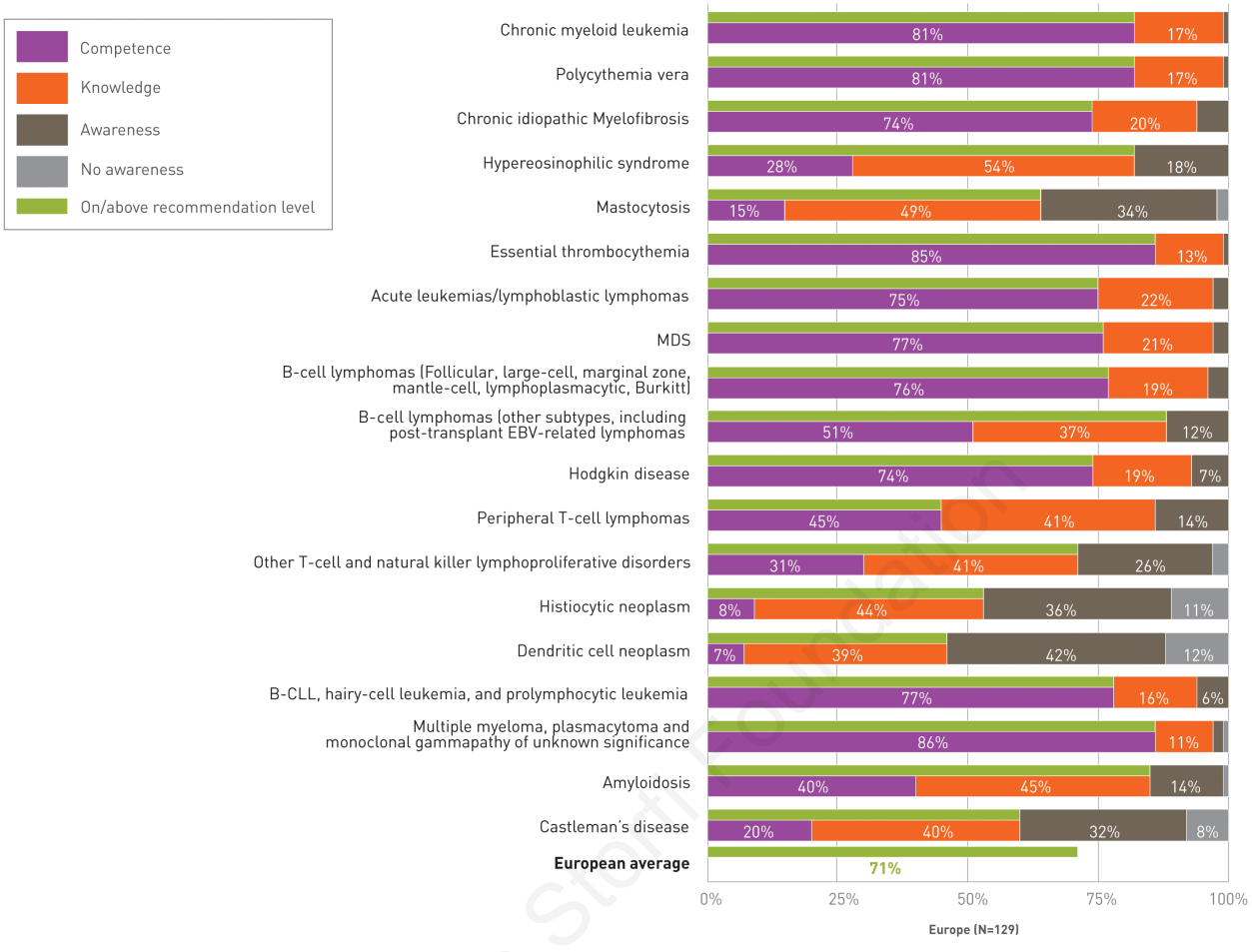
One of the main goals of the H-Net project was to develop a harmonized curriculum for European hematology based on the existing version. The H-Net pan-European survey was developed with two main objectives: 1) to get a first map of the competence levels to which hematologists are trained in the different countries in Europe; and 2) to identify structures and items in the curriculum with a potential for improvement. To this purpose, a questionnaire was developed that, apart from demographical, professional and selection questions, mirrored the European Hematology Curriculum. On each item of the curriculum, respondents were asked to self-assess their competence level on a 4-point scale.

Selection of respondents

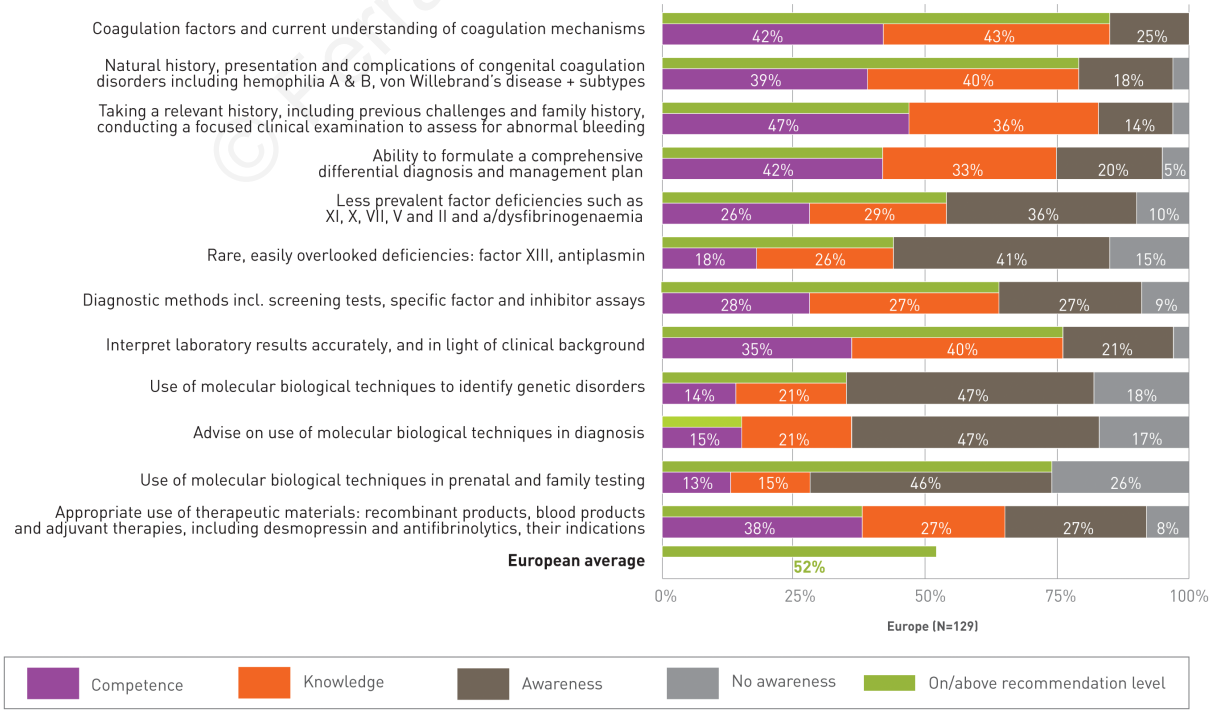
Ideally, the survey should have targeted a population of all hematologists who had just completed specialist training within the H-Net participating countries. However, to attain statistically more sophisticated results the population was extended to include all hematologists who had completed their training within three years (or five, in some small countries). As expected, a complete coverage of the target group was not achievable in the majority of countries, and different solutions adapted to national prerequisites were, therefore, adopted to canvass more respondents:

1) countries with obligatory national registers for trainees could access all hematologists in training;

1D: HEMATOLOGIC NEOPLASTIC DISORDERS



3C: CONGENITAL BLEEDING DISORDERS



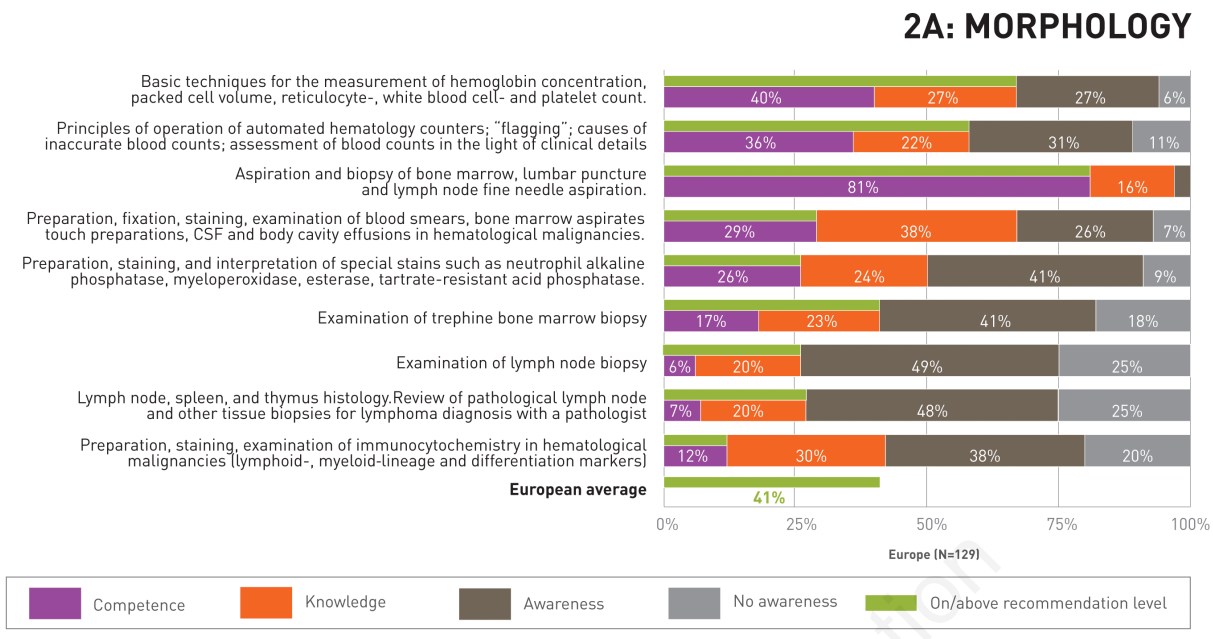


Figure 2. Results from the curriculum survey regarding hematologic neoplastic disorders. Green line shows the fraction of respondents who assess themselves at or above the recommended competence level.

2) countries with non-obligatory registries usually developed by the NS could target the majority of trainees;

3) countries with no formal or NS registries but where the linkers were able to address a number of hospitals by other routes of contact reached a more selected cohort;

4) countries where communication at the national level was impossible selected respondents from a particular hospital or region.

This latter strategy was mainly adopted by the large European countries. Selection also depended on the willingness of identified hematologists to fill-in the survey. In all, 245 individuals from 24 countries responded to the survey and self-assessed their competence according to the first version of the European hematology curriculum. As the different countries were compared mainly with the European mean and not with each other, the pattern of selection was deemed to be less important.

Self-assessment

In line with the bottom-up process, self-assessment in combination with anonymity was the basis for acquiring the individual responses. The national linkers had no access to the individual profiles of their countries, only to the national profile in comparison to the European mean. There was a fear that this would lead to an overestimation of competence by the respondent, but a subsequent inquiry actually showed the opposite; the young hematologists were in general very eager to display their competence gaps with the hope that this would lead to improved training programs. The present EHA Curriculum Committee has discussed how to proceed with the next survey and whether the competence profiles should be signed-off by a mentor. We have, however, come to the conclusion that self-assessment has worked so well and has so many advantages that it will be kept as the basis for subsequent investigations.

Main results: a map of European competence in hematology

The median response rate among those who were invited to take part was 41% (range in the countries that were studied 6-99%): 54% were male, 46% female and the median age was 37 years (range 28-58 years). Forty-three percent were specialists only in hematology, 47% had a specialty in both hematology and internal medicine, while 10% had other types of specialties. The median duration of specialty (hematology) training was 5.4 years (range 1.3-8.3 years). The survey results and their national consequences have been discussed in previous articles[1-3] and will not be reported in detail here. Overall, the self-assessed competence in malignant hematology was better than the competence in non-malignant hematology including coagulation (Figure 2). One can speculate whether this pattern is influenced by the higher availability of financed training opportunities within the malignant field, and several countries have taken these findings as an initiative to develop their training programs. The competence in diagnostic procedures was the section that scored lowest in most countries.

Preparing for a revised curriculum version 2.0

The survey also offered the respondents the possibility to identify structures and items in the curriculum which they considered ambiguous, irrelevant for their training, or difficult to understand. Some items were removed either because they were unclear or because they had become irrelevant with respect to training in hematology. We also received suggestions about competence items that were not part of routine hematology in 2004, but had become so since then. The revised curriculum, dubbed the European Hematology Curriculum and endorsed by 27 national societies, followed to a much greater extent the ICD10 and WHO 2008 classifications than the first ver-

sion. The levels of competence and their descriptions were revised to meet with the standard EU formulations. The diagnostic parts were modified, where relevant, to assess competence in interpretation of diagnostic tests rather than hands-on ability to perform them. With increasing demands for accreditation in particular within the laboratory specialties this is a logical development, but it remains to be seen if young hematologists would score better in the new version of the European Hematology Curriculum. The new CV Passport, revised according to the European Hematology Curriculum, is internet-based and includes tags to selected educational material for each section and individualized interactive features which makes it an ideal tool for self-assessment by hematologists in training.

It is difficult to underestimate the importance of the European Hematology Curriculum in the context of an integrated Europe. Now there is professional consensus where the scope, content and minimum competences of our medical specialty are concerned. Meanwhile, Europe is slashing its borders to allow for free movement of its citizens. This development may or may not deliver on its promise of professional mobility, employment opportunities and, finally, greater prosperity and equity for all. But it will definitively affect the geographical scope of training medical specialists. To have already come so far as to agree upon a European Hematology Curriculum is one thing. Another is to acquire knowledge about the educational realities that exist in the different countries in order to face the challenges that Europe is posing. To this end it is important to regularly perform the Competence Survey and to act upon its results.

Testing the relevance of the European Curriculum version 2.0: a prospective European survey

A prospective continuous survey would be the ideal next step in assessing the present and future impact of the European Curriculum on hematology training in Europe. If implemented as a self-assessment tool for hematology trainees at all stages of training, competence information could be gathered at any time from the beginning of training until up to two years following completion of training.

The competence data registered in this survey would, first and foremost, enable trainees to monitor their own progress and ensure they have covered all the diverse areas which hematology encompasses. The survey would also enable the generation of national or regional reports, providing important information regarding the patterns of hematology competence in various regions of Europe. This will enable national societies to monitor how learning objectives are met over time and change training programs in response to the shortfalls that may have been identified.

This prospective survey could be an important tool to ensure and increase the quality of professional competence in this specialty. It may provide trainees with a tool for professional excellence and mobility. In addition, national societies will be able to assess the efficacy of their training programs and adapt them if necessary, thereby promoting harmonization of hematology training in Europe.

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References

1. Ossenkoppele G, Evans-Jones G, Jaeger U, Hellström-Lindberg E; Curriculum Update Working Group. Towards a joint definition of European hematology. Haematologica. 2012;97(5):636-7.
2. Duyvené de Wit T, Hellström-Lindberg E, Jäger U, Evans-Jones G, Smand C. H-Net, the European Network for Harmonization of Training in Hematology, and its policy. Haematologica. 2012;97(12): 1776-8.
3. Strivens J, Hellström-Lindberg E, Bjerrum OW, Toh CH. A European strategy for targeted education in hematology. Haematologica. 2013;98(7):1000-2.

Treatment of autologous stem cell transplant-eligible multiple myeloma patients: ten questions and answers

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Autologous stem cell transplantation is currently considered the standard of care for multiple myeloma in young patients with adequate organ function, based on the results of trials conducted in the era prior to the advent of novel agents. While these trials demonstrated the superiority of high-dose therapy with stem cell support over conventional chemotherapy, relapse remained an issue for the majority of patients. With the introduction of the novel agents, a dramatic change in treatment strategies in the transplant setting has taken place. These agents are now incorporated prior to and following the transplant procedure, and have resulted in improvements in outcome. Importantly, improvements have also been seen in patients with high-risk cytogenet-