Advancing a Field by Building Consortia: The Example of the European LeukemiaNet

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Building consortia sounds straightforward and simple because the advantage of consortia for advancement, particularly of rare diseases, appears obvious: achieving goals faster by combining forces and resources. The insight of the individual scientist that cooperation is better than competition for one's personal career is not so obvious. If one wants to include younger colleagues competing for grants and promotions, it is essential that they realize that consortia not only advance the field but also their careers. A good starting experience for younger colleagues may be participation in clinical study groups of a defined scope. Consortia require interaction between individuals. Even if the reason for the interaction is clear, consortia need individuals (eg, in the case of leukemia, hematologists, medical oncologists, and scientists such as cytogeneticists, molecular biologists, or statisticians) who are motivated to interact.

The strongest motivation for cooperation is success. Consortia need to be structured for the greatest amount of success to the largest possible number of patients to have the optimum impact on the field. Working together successfully requires an atmosphere of cooperation and mutual trust. Regular meetings at little or no cost to the participants are essential to get to know and trust each other and achieve the best possible outcome.

This does not happen by chance at big international conferences such as the American Society of Hematology, European Hematology Association, American Association for Cancer Research, and American Society of Clinical Oncology but rather requires organization and structuring by an established authority or institution of excellence with personal contacts to leading hematologists and scientists. Networks of excellence such as the European LeukemiaNet (ELN) have been proven to serve this purpose well.

Founded in 2002, the ELN originates from a consortium dealing with 1 leukemia in the majority of European countries, the European Investigators on Chronic Myeloid Leukemia (EI-CML), and a consortium dealing with all leukemias in 1 country, the German Competence Network for Acute and Chronic Leukemias.[1] Its goal is to cure leukemia through cooperative research. To achieve this goal, the need to accelerate progress by combining resources (patients) was recognized, as well as the need for a "common language" for cooperation (ie, common definitions of diagnosis and outcomes and common standards and data sets [eg, for conducting clinical trials or monitoring treatment]).

For this purpose, leading European hematologists and scientists created the ELN and made use of a call of the European Union within the 6th Framework Program to compete for a network of excellence. The ELN ranked among the top 5% and was awarded funding from 2004 onward. For sustainability, an ELN foundation was established in 2009 and support was solicited from the European Science Foundation from 2010 through 2015. An initial report on the ELN was published in 2011.[2]

To actively include as many participants as possible, working groups (called work packages [WPs]) were established for each major leukemia and related syndrome (ie, CML, acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, myelodysplastic syndrome [MDS], and myeloproliferative neoplasms) for each interdisciplinary specialty required for the diagnosis and

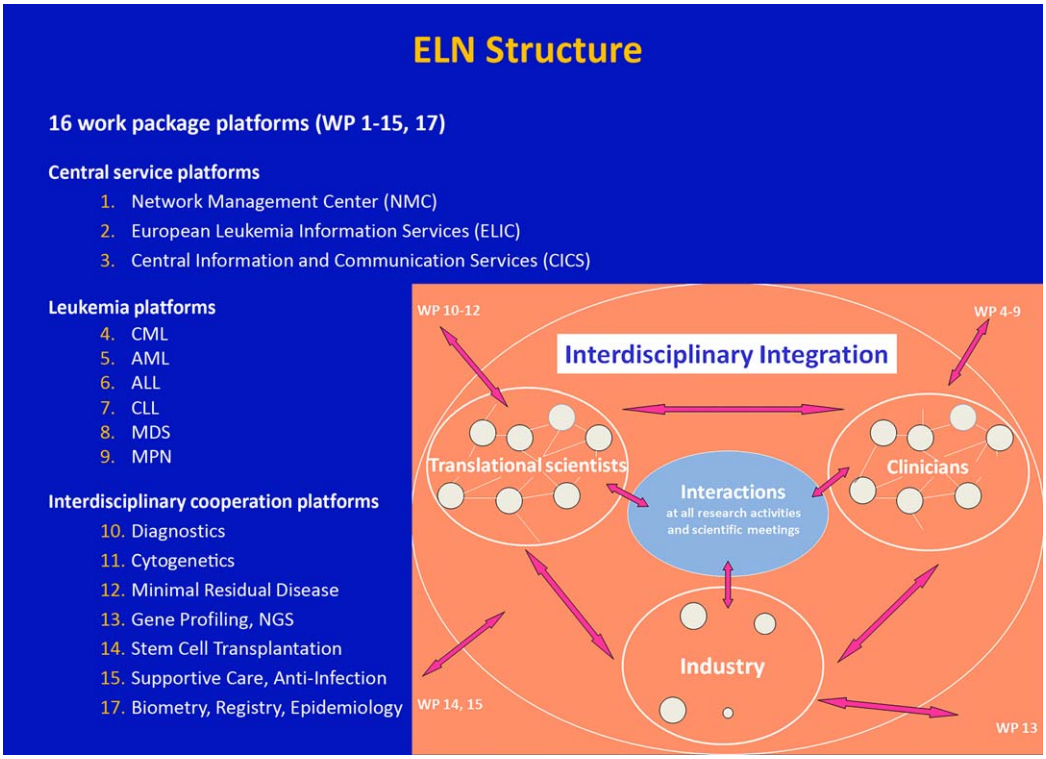

Figure 1. Overview of the European LeukemiaNet (ELN) networking structure. The left side shows a list of work packages (WPs) 1 to 15 and 17 (there is no WP 16). The pink insert indicates the cooperation between clinical groups, interdisciplinary basic science groups, and industry. The blue insert indicates the activities of central services (WP 1-3 and 17). In the case of industry, large spots indicate large companies and small spots indicate small companies. WP 1 lead participants: Hehlmann, Hochhaus, and Saussele; WP 2 lead participants: Hoelzer, Gökbuget, and Serve; WP 3 lead participant: Dugas; WP 4 lead participants: Baccarani, Guilhot, Hehlmann, Hochhaus, and Simonsson; WP 5 lead participants: Ossenkoppele, Bloomfield, Döhner, and Müller-Tidow; WP 6 lead participants: Hoelzer, Gökbuget, Dombret, Ribera, M. Sanz, Bassan, Willemze, and Foa; WP 7 lead participants: Ghia, Montserrat, and Hallek; WP 8 lead participants: de Witte, Fenaux, and Hellström-Lindberg; WP 9 lead participants: Barbui, Barosi, Pahl, and Kiladjian; WP 10 lead participants: Bené and Zini; WP 11 lead participants: Rieder, Haase, and C. Haferlach; WP 12 lead participants: Thiede, M.C. Müller, T. Haferlach, and Hernandez-Rivas; WP 13 lead participants: T. Haferlach and Martinelli; WP 14 lead participants: Niederwieser and Apperley; WP 15 lead participants: Ljungmann and Einsele; WP 17 lead participant: Hasford. ALL indicates acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms; NGS, next-generation sequencing.

management of all leukemias such as morphology, flow cytometry, cytogenetics, molecular monitoring, gene sequencing, etc, and for several central service areas such as transplantation, biometry of clinical trials, and leukemia information and network management centers.

All WPs are subnetworks of their own, comprising the leading national study groups of the respective leukemias or specialties. Clinical study groups and interdisciplinary partner groups include junior as well as senior investigators. Having a common goal and network structure favors personal input and leadership by excellence.

Each WP is chaired by one or more lead participants who oversee the cooperative research within the WP and participate in the ELN Steering Committee. The ELN itself is chaired by the network coordinator. It may have been helpful in forming the ELN that at the start the coordinator already was at an age and position that excluded competition for his own career. Figure 1 provides an overview of the ELN networking structure. Figure 2 provides a map of the 220 currently participating centers in 44 countries, 3 of which are in the United States.

Key elements of networking are management recommendations at the highest international level. The bases of the recommendations usually are comprehensive reviews of the literature and expert panels selected by the ELN for excellence. This is different from other organizations such as the National Comprehensive Cancer Network. In addition, the term "recommendation" is preferred over "guidelines" in the absence of sufficient randomized evidence. The panels include experts who also are from outside Europe to guarantee high-level expertise and international acceptance. With the increasing number of participants from the Americas and Asia, the ELN has evolved from a European to an international network. Some of the more recent ELN recommendations are listed in Table 1.[3-21]

Figure 2. Map of the 220 currently participating centers. Outside of the map, New York, Atlanta, and Columbus are located in the United States; Yekaterinburg and Novosibirsk are located in Russia; Bishkek is located in Kyrgyzstan; Tashkent is located in Uzbekistan; Yerevan is located in Armenia; Doha is located in Qatar; and Riyadh is located in Saudi Arabia.

Cooperation with industry was an integral part of networking from the very beginning of the ELN. Visible projects are public-private partnerships (eg, the European Treatment and Outcome Study [EUTOS] for CML[22] or the European MDS registry [EUMDS]). To advance research on a disease that requires products from pharmaceutical companies, it is important that industry is included. By taking the lead in research and clinical trials, the consortium is in a position to ensure that marketing interests do not become a dominant factor of common research.

A second key element of networking is regular meetings of all participants. To maintain independence with regard to management recommendations and research goals, the meetings are funded publicly or by donations with no service provided in return. Representatives of industry are invited as guests and equal partners (not as sponsors). There have been no commercial exhibitions or satellite symposia permitted at ELN symposia. Public funding has enabled all participants to contribute to ELN research projects free of personal financial considerations.

The greatest efforts in time and resources are directed toward the research projects of the respective WPs (with help from the ELN, some ELN members have even won projects funded by the European Union). Some work has been practice-changing, such as the standardization of *BCR-ABL* polymerase chain reaction through the definition of conversion factors for interlaboratory comparability (International Scale), or the minimal residual disease-guided treatment of acute lymphoblastic leukemia.

The greatest visibility of the ELN is achieved by its management recommendations and, since 2003, its annual symposia. These 2 activities by far require the largest percentage of the ELN budget, whereas research projects as such are, as a rule, not financed by the ELN directly but are supported by ELN infrastructure and the annual symposium.

The key limitation of the ELN is its budget. The free-for-all symposium for 400 to 500 attendants each year, including housing and travel, may not be sustainable in the long term. Smaller and less costly solutions currently are being considered. An ELN Foundation Circle has been established to provide financial infrastructure support through donations. A task force of ELN lead participants currently is working out new strategies to adapt the ELN for the future.

TABLE 1. Recommendations and Guidelines: 2013 to 2017

Area	Subject	Publication
AML	Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel	Döhner 2017[3]
CML	Management recommendations	Baccarani 2013[4]
	Laboratory recommendations for scoring deep molecular responses after treatment for CML	Cross 2015[5]
	ELN recommendations for the management and avoidance of adverse events of treatment of CML	Steegmann 2016[6]
MPN	Revised response criteria for myelofibrosis	Tefferi 2013[7]
	Revised response criteria for ET and PV	Barosi 2013[8]
	ELN-SIE recommendations for ruxolitinib in myelofibrosis	Marchetti 2017[9]
MDS	Diagnosis and treatment of primary MDS in adults: recommendations from the ELN	Malcovati 2013[10]
	Allogeneic hematopoietic SCT for MDS and CMML: recommendations from an international expert panel	de Witte 2017[11]
Morphology	Harmonemia: a universal strategy for flow cytometry immunophenotyping-a ELN WP 10 study	Lacombe 2016[12]
	Leukemia diagnosis: today and tomorrow	Bené 2015[13]
SCT	Prophylaxis and treatment of graft-versus-host disease	Ruutu 2014[14]
Supportive care	Targeted therapy against multiresistant bacteria in leukemic and hematopoietic SCT recipients: guidelines of ECIL-4	Averbuch 2013[15]
	ECIL-4 guidelines for diagnosis, prevention, and treatment of invasive fungal diseases in pediatric patients with cancer or allogeneic hematopoietic SCT	Groll 2014[16]
	Management of EBV infections and posttransplantation lymphoproliferative disorders in patients after allogeneic hematopoietic SCT: ECIL-6 guidelines	Styczynski 2016[17]
	ECIL guidelines for the diagnosis of Pneumocystis jirovecii pneumonia in patients with hematological malignancies and SCT recipients	Alanio 2016[18]
CLL	Immunoglobulin gene sequence analysis in CLL: updated ERIC recommendations	Rosenquist 2017[19]
	A complementary role of multiparameter flow cytometry and high-throughput sequencing for MRD detection in CLL: an ERIC study	Rawstron 2016[20]
	ERIC and EBMT: managing high-risk CLL during transition to a new treatment era: SCT or novel agents?	Dreger 2014[21]

Abbreviations: AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; EBMT, European Society for Blood and Marrow Transplantation; EBV, Epstein-Barr virus; ECIL, European Conference on Infections in Leukemia; ELN, European LeukemiaNet; ERIC, European Research Initiative on CLL; ET, essential thrombocythemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms; MRD, minimal residual disease; PV, polycythemia vera, SIE, Italian Society of Hematology; SCT, stem cell transplantation; WP, work packages.

Take-Away Points

- Building consortia represents an efficient and economical approach to advancing fields in urgent need of progress, such as currently incurable cancers.
- Participants of consortia have a competitive advantage over those not participating.
- The ELN has structured leukemia research internationally through the creation of standards, definitions, and high-level management recommendations and has contributed toward improved outcomes.
- Management recommendations providing definitions and standards have laid the groundwork for cooperative research by clinical study groups and interdisciplinary partner groups.
- The ELN provides an example of advancing a field with little budget and high impact.

ACKNOWLEDGMENTS

I thank Jean Khoury from Emory University for the suggestion to write this article and my networking partners (ELN lead participants) for reading the text and contributing toward Table 1.

FUNDING SUPPORT

Sixth Framework Program of the European Union, European Science Foundation, ELN Foundation.

CONFLICT OF INTEREST DISCLOSURES

The author made no disclosures.

REFERENCES

1. Hehlmann R, Berger U, Aul C, et al. The German competence network 'Acute and chronic leukemias.' *Leukemia.* 2004;18:665-669.

2. Hehlmann R, Grimwade D, Simonsson B, et al; European LeukemiaNet. The European LeukemiaNet: achievements and perspectives. *Haematologica.* 2011;96:156-162.
3. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood.* 2017;129:424-447.
4. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood.* 2013;122:872-884.
5. Cross NC, White HE, Colomer D, et al. Laboratory recommendations for scoring deep molecular responses following treatment for chronic myeloid leukemia. *Leukemia.* 2015;29:999-1003.
6. Steegmann JL, Baccarani M, Breccia M, et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. *Leukemia.* 2016;30:1648-1671.
7. Tefferi A, Cervantes F, Mesa R, et al. Revised response criteria for myelofibrosis: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report. *Blood.* 2013;122:1395-1398.
8. Barosi G, Mesa R, Finazzi G, et al. Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. *Blood.* 2013;121:4778-4781.
9. Marchetti M, Barosi G, Cervantes F, et al. Which patients with myelofibrosis should receive ruxolitinib therapy? ELN-SIE evidence-based recommendations. *Leukemia.* 2017;31:882-888.
10. Malcovati L, Hellstrom-Lindberg E, Bowen D, et al; European Leukemia Net. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. *Blood.* 2013;122:2943-2964.
11. de Witte T, Bowen D, Robin M, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. *Blood.* 2017;129:1753-1762.
12. Lacombe F, Bernal E, Bloxham D, et al. Harmonemia: a universal strategy for flow cytometry immunophenotyping-a European LeukemiaNet WP10 study. *Leukemia.* 2016;30:1769-1772.
13. Bené MC, Grimwade D, Haferlach C, Haferlach T, Zini G; European LeukemiaNet. Leukemia diagnosis: today and tomorrow. *Eur J Haematol.* 2015;95:365-373.
14. Ruutu T, Gratwohl A, de Witte T, et al. Prophylaxis and treatment of GVHD: EBMT-ELN working group recommendations for a standardized practice. *Bone Marrow Transplant.* 2014;49:168-173.
15. Averbuch D, Cordonnier C, Livermore DM, et al; ECIL4, a joint venture of EBMT, EORTC, ICHS, ESGICH/ESCMID and ELN. Targeted therapy against multi-resistant bacteria in leukemic and hematopoietic stem cell transplant recipients: guidelines of the 4th European Conference on Infections in Leukemia (ECIL-4, 2011). *Haematologica.* 2013;98:1836-1847.
16. Groll AH, Castagnola E, Cesaro S, et al; Fourth European Conference on Infections in Leukaemia; Infectious Diseases Working Party of the European Group for Blood Marrow Transplantation (EBMT-IDWP); Infectious Diseases Group of the European Organisation for Research and Treatment of Cancer (EORTC-IDG); International Immunocompromised Host Society (ICHS); European Leukaemia Net (ELN). Fourth European Conference on Infections in Leukaemia (ECIL-4): guidelines for diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or allogeneic haemopoietic stem-cell transplantation. *Lancet Oncol.* 2014;15:e327-e340.
17. Styczynski J, van der Velden W, Fox CP, et al; Sixth European Conference on Infections in Leukemia, a joint venture of the Infectious Diseases Working Party of the European Society of Blood and Marrow Transplantation (EBMT-IDWP), the Infectious Diseases Group of the European Organization for Research and Treatment of Cancer (EORTC-IDG), the International Immunocompromised Host Society (ICHS) and the European Leukemia Net (ELN). Management of Epstein-Barr Virus infections and post-transplant lymphoproliferative disorders in patients after allogeneic hematopoietic stem cell transplantation: Sixth European Conference on Infections in Leukemia (ECIL-6) guidelines. *Haematologica.* 2016;101:803-811.
18. Alanio A, Hauser PM, Lagrou K, et al; 5th European Conference on Infections in Leukemia (ECIL-5), a joint venture of The European Group for Blood and Marrow Transplantation (EBMT), The European Organization for Research and Treatment of Cancer (EORTC), the Immunocompromised Host Society (ICHS) and The European LeukemiaNet (ELN). ECIL guidelines for the diagnosis of Pneumocystis jirovecii pneumonia in patients with haematological malignancies and stem cell transplant recipients. *J Antimicrob Chemother.* 2016;71:2386-2396.
19. Rosenquist R, Ghia P, Hadzidimitriou A, et al. Immunoglobulin gene sequence analysis in chronic lymphocytic leukemia: updated ERIC recommendations. *Leukemia.* 2017;31:1477-1481.
20. Rawstron AC, Fazi C, Agathangelidis A, et al. A complementary role of multiparameter flow cytometry and high-throughput sequencing for minimal residual disease detection in chronic lymphocytic leukemia: an European Research Initiative on CLL study. *Leukemia.* 2016;30:929-936.
21. Dreger P, Schetelig J, Andersen N, et al; European Research Initiative on CLL (ERIC) and the European Society for Blood and Marrow Transplantation (EBMT). Managing high-risk CLL during transition to a new treatment era: stem cell transplantation or novel agents? *Blood.* 2014;124:3841-3849.
22. Hoffmann VS, Baccarani M, Hasford J, et al. Treatment and outcome of 2904 CML patients from the EUTOS population-based registry. *Leukemia.* 2017;31:593-601.

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