Advancing a field by building consortia: The example of the European LeukemiaNet.

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

The strongest motivation for cooperation is success. Consortia need to be structured for the most possible success to the largest possible number of people 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 for the participants are essential to get to know and trust each other and achieve the best possible outcome.
This does not happen per chance at big international conferences like ASH, EHA, AACR and ASCO but 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 proven to serve this purpose well.

ELN, founded in 2002, originates from a consortium dealing with one leukemia in most European countries, the European Investigators on Chronic Myeloid Leukemia (EI-CML), and a consortium dealing with all leukemias in one country, the German Competence Network for Acute and Chronic Leukemias (1). Its goal is to cure leukemia by cooperative research. To achieve this goal the need for accelerating progress by combining resources (patients) was recognized, but also the need for a 'common language' for cooperation, i.e. common definitions of diagnosis and outcome and common standards and data sets e.g. for conducting clinical trials or monitoring of treatment.

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

To actively include as many participants as possible, working groups (called work package or WP) were established for each major leukemia and related syndrome (i.e. chronic myeloid leukemia = CML, acute myeloid leukemia = AML, acute lymphoblastic leukemia = ALL, chronic lymphatic leukemia = CLL, myelodysplastic syndrome = MDS and myeloproliferative neoplasms = MPN), for each interdisciplinary specialty required for diagnosis and 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. Common goal and network structure favor 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 helped in forming the ELN that at the start the coordinator was already at an age and position excluding competition for his own career. Figure 1 provides an overview of the ELN networking structure, Figure 2 a map of the 220 currently participating centers in 44 countries, 3 of them in the USA.

Key elements of networking are management recommendations at the highest international level. Basis of the recommendations usually are comprehensive reviews of the literature and expert panels selected by ELN for excellence. This is different from other organizations e.g. NCCN. Also, the term recommendation is preferred over guidelines in the absence of sufficient randomized evidence. The panels include experts also from outside Europe to guarantee high level expertise and international acceptance. With the increasing number of participants from America and Asia, ELN has evolved from a European to an international network. Some of the more recent ELN recommendations are listed in Table 1.

Cooperation with industry was an integral part of networking from the very beginning of ELN. Visible projects are public-private partnerships, e.g. the European treatment and outcome study (EUTOS) for CML (3) or the European MDS registry (EU-MDS). It is important for advancing research on a disease that requires products from pharmaceutical companies that industry is included. By taking the lead in research and clinical trials, the consortium is in a position to make sure that marketing interests do not become a dominant factor of common research.

A second key element of networking are 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 in return. Representatives of industry are invited as guests and equal partners (not as sponsors). To date, there have been no commercial exhibitions or satellite symposia permitted at ELN symposia. Public funding enabled all participants to contribute to ELN research projects free of personal financial considerations.

The greatest efforts in time and resources go to research projects of the respective WPs (with help from 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 PCR by the definition of conversion factors for interlaboratory comparability (International Scale), or the MRD-guided treatment of ALL.
The greatest visibility of ELN is achieved by its management recommendations and its Annual Symposia since 2003. These two activities require by far the largest proportion of the ELN budget, whereas research projects as such are, as a rule, not financed by ELN directly, but supported by ELN infrastructure and the annual symposium.
The key limitation of ELN is the 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 are being considered. An ELN-Foundation Circle has been established to provide financial infrastructure support by donations. A task force of ELN lead participants is working out new strategies to adapt ELN for the future.

Take-away points:

- Building consortia represents an efficient and economical approach to advancing fields in urgent need of progress such as currently incurable cancers.
- Management recommendations providing definitions and standards laid the groundwork for cooperative research by clinical study groups and interdisciplinary partner groups.
- ELN provides an example for advancing a field with little budget and high impact.
- ELN has structured leukemia research internationally by the creation of standards, definitions and high-level management recommendations.

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Legends to Figures:

- Fig. 1: Overview of the European LeukemiaNet networking structure. On the left side, there is a list of Work Packages 1-15 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 (WP1-3 and 17). The sizes of the grey spots relate to the size of the groups. In the case of industry, large spots indicate large companies and small spots small ones.

  Lead participants of WP1 are Hehlmann, Hochhaus and Saussele; of WP2 Hoelzer, Gökbuget, Serve; of WP3 Dugas; of WP4 Baccarani, Guilhot, Hehlmann, Hochhaus, Simonsson; of WP5 Ossenkoppele, Bloomfield, Döhner, Müller-Tidow; of WP6 Hoelzer, Gökbuget, Dombret, Ribera, M. Sanz, Bassan, Willemze, Foa; of WP7 Ghia, Montserrat, Hallek; of WP8 de Witte, Fenaux, Hellström-Lindberg; of WP9 Barbui, Barosi, Pahl, Kiladjian; of WP10 Bené, Zini; of WP11 Rieder, Haase, C. Haferlach; of WP12 Thiede, M.C. Müller, T. Haferlach, Hernandez-Rivas; of WP13 T. Haferlach, Martinelli; of WP 14 Niederwieser, Apperley; of WP 15 Ljungmann, Einsele and of WP17 Hasford.

- Fig. 2: Map of the 220 currently participating centers outside of the map. New York, Atlanta and Columbus are in the United States, Yekaterinburg and Novosibirsk are in Russia, Bishkek is in Kirgistan, Tashkent in Usbekistan, Yerevan in Armenia, Doha in Katar and Ryadh in Saudi Arabia.

Table 1: Recommendations and Guidelines 2013-2017

Area	Ttile	Publication	
AML	Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel	(4)Döhner et al. Blood 2017	
CML	Management Recommendations	(5)Baccarani et al. Blood 2013	
	Laboratory recommendations for scoring deep molecular responses following treatment for chronic myeloid leukemia	(6)Cross et al. Leukemia 2015	
	European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia	(7)Steegmann et al. Leukemia 2016	
MPN	Revised response criteria for Myelofibrosis	(8)Tefferi A. Blood 2013	
	eria for ET and PV	(9)Barosi et al. Blood 2013	
	ELN-SIE recommendations on ruxolitinib in myelofibrosis	(10)Marchetti et al. Leukemia 2017	
MDS	Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet.	(11)Malcovati et al. Blood 2013	
	Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel	(12)de Witte et al. Blood 2017	
Morphology	Harmonemia: a universal strategy for flow cytometry immunophenotyping – A European LeukemiaNet WP10 study	(13)Lacombe et al. Leukemia 2016	
	Leukemia diagnosis: today and tomorrow	(14)Bené et al. Eur J Haematol. 2015	

SCT Supportive Care	Prophylaxis and treatment of graft versus-host disease 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) Fourth European Conference on Infections in Leukemia (ECIL-4): guidelines for diagnosis, prevention, and treatment of invasive fungal diseases in paediatric patients with cancer or allogeneic haemopietic stem-cell transplantation	(15)Ruutu et al. BMT 2013 (16)Averbuch et al. Haematologica 2013 (17)Groll et al. Lancet Oncol. 2014	
	Management of Eppstein-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	(18)Styczynski et al. Haematologica 2016	
	ECIL guidelines for the diagnosis of Pneumocystis jirovecii pneumonia in patients with haematological malignancies and stem cell transplant recipients	(19)Alanio et al. J Antimicrob Chemother. 2016	
CLL	Immunoglobulin gene sequence analysis in chronic lymphocytic leukemia: updated ERIC recommendations A complementary role of multiparameter flow-cytometry and high-throughput sequencing for minimal residual disease (MRD) detection in chronic lympocytic leukemia (CLL): An European research initiative on CLL (ERIC) study. 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?	(20)Rosenquist et al. Leukemia 2017 (21)Rawstron et al. Leukemia 2016 (22)Dreger et al. Blood 2014	

Abbreviations: ET= essential thrombocythemia, PV= polycythemia vera, SIE= Italian Society of Haematology, ECIL= European conference on infections in leukemia.

Fig. 1

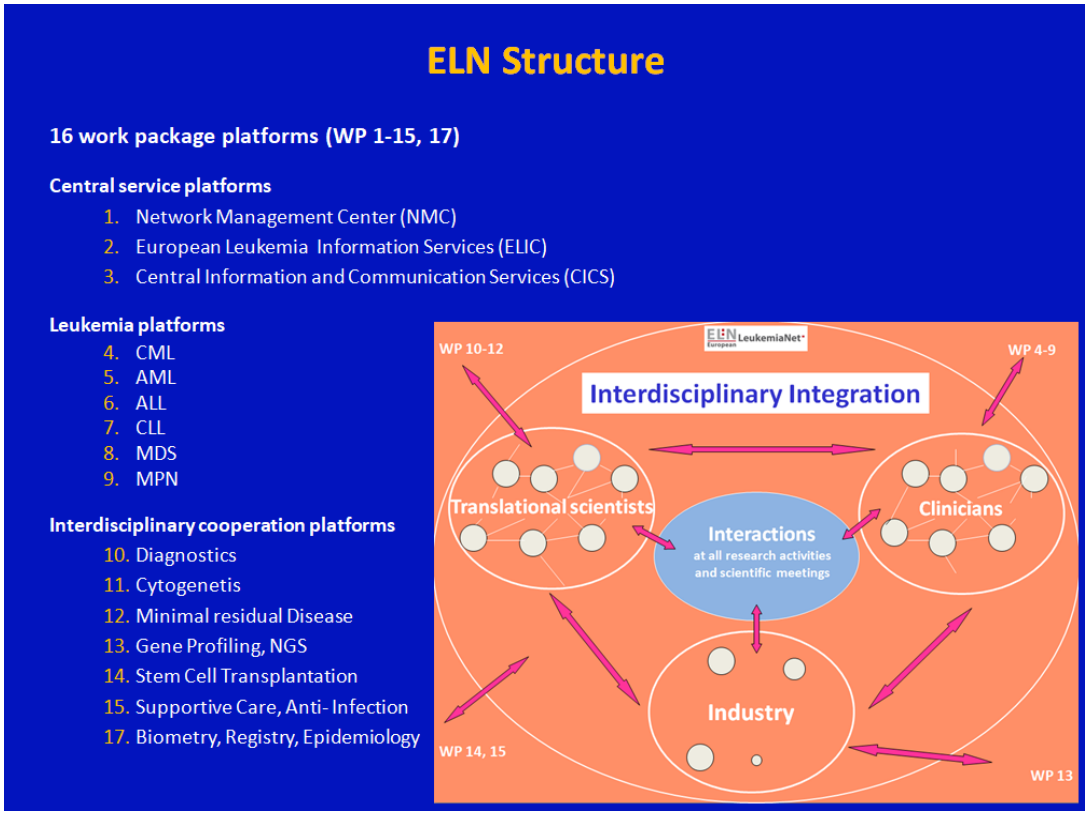
ELN Structure
16 work package platforms (WP 1-15, 17)
Central service platforms
1. Network Management Center (NMC)
2. European Leukemia Information Services (ELIC)
3. Central Information and Communication Services (CICS)
Leukemia platforms
4. CML
5. AML
6. ALL
7. CLL
8. MDS
9. MPN
Interdisciplinary cooperation platforms
10. Diagnostics
11. Cytogenetis
12. Minimal residual Disease
13. Gene Profiling, NGS
14. Stem Cell Transplantation
15. Supportive Care, Anti- Infection
17. Biometry, Registry, Epidemiology
WP 10-12
WP 4-9
Interdisciplinary Integration
Translational scientists
Clinicians
Interactions
at all research activities
and scientific meetings
Industry
WP 14, 15
WP 13

Fig. 2


ELN European LeukemiaNet
New centers in 2017
Yekaterinburg
Novosibirsk
New York
Columbus
Atlanta
Bishkek
Tashkent
Yerevan
Las Palmas
Doha
Riyadh
220 centers in 44 countries
123 national leukemia study groups
114 interdisciplinary partner groups
1000 physicians and scientists
Caring for ten thousands of patients

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