

Blood disorders stepping into the limelight

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What should we do when the promising treatment options for patients provided by hematology research cost more than the current treatments, when funding for hematology research is limited, and when the increasing cost of health care is such a major concern in many European Member states? This is the question that, under the guidance of the European Hematology Association (EHA), the hematology community in Europe has been addressing. The result is a consensus document: the European Hematology Research Roadmap. More than 300 leading European hematology experts have contributed to this important document, as well as patient organizations, national hematology societies, clinical trial groups, and many others. Typical of such a consensus document is that it needs to 'come alive' and this editorial is the first step towards that. However, more needs to be done.

- Politicians need to be made aware of the economic burden of hematologic diseases and of the huge number of patients involved. But these diseases do not only involve patients but also have an impact on society as a whole, and politicians need to be made aware of the importance of reducing this.

- Research funders need to pay more attention to creating better funding opportunities for hematology research.

- The European hematology research community needs to overcome the problem of fragmentation by bringing together basic researchers, clinical trial networks and patient advocates in comprehensive study groups.

The European Hematology Research Roadmap is instrumental to this and the EHA needs to play a co-ordinating role in achieving these goals.

These are contradictory times for patients with blood disorders and hematology researchers. On the one hand, patients and those involved in delivering healthcare are being told repeatedly that the continuing effects of the world economic crisis means that health budgets and resources must continue to be constrained at a time when demand for healthcare is increasing. In the words of Dr. Vytenis P Andriukaitis, European Commissioner for Health, "*health systems across the European Union (EU) face similar challenges, including: pressure on resources; an ageing population; increasing expectations and possibilities for treatment; and workforce shortages*", which are heightening "*the eternal problem of how to do 'more with less'*".¹ More recent research in blood disorders including blood cancers, coagulation and platelet disorders, and common diseases such as anemia, has resulted in breakthrough discoveries, new diagnostic methods and better treatments at a breathtaking pace. But research has to be carried out in a conservative funding environment.

Announcing the details of a €16 billion investment in research and innovation for 2016-17 under the Horizon 2020 program (the EU's research and innovation funding scheme),

Carlos Moedas, European Commissioner for Research, Science and Innovation said: "*Research and innovation are the engines of Europe's progress and vital to addressing today's new pressing challenges like (...) healthy societies. Over the next two years, €16 billion from Horizon 2020 will support Europe's top scientific efforts, making the difference to citizens' lives.*"² There is substantial evidence to show that there is a pressing medical need for more hematology research. As stated in the EHA Roadmap Consensus Document,³ an estimated 80 million people are currently affected with blood disorders in the EU. Various types of anemia affect more than 50 million children and adults in the World Health Organization's European region.⁴ Blood cancers, some of which mainly affect young people, contribute strongly to premature cancer-related mortality and lost productivity in Europe.⁵ Among cancers, blood cancers (leukemias, Hodgkin and non-Hodgkin lymphomas, and multiple myeloma) together rank third after lung cancer and colorectal cancer in terms of age-adjusted mortality in the European Economic Area.⁶

Inherited blood diseases, such as thalassemia, sickle cell disease, and glucose-6-phosphate dehydrogenase deficiency, also affect millions of people, and cause substantial morbidity and mortality. Rare forms of congenital blood disorders cause an immense burden on those affected. Many infectious diseases affect various types of blood or blood-forming cells, causing widespread diseases such as malaria and HIV/AIDS. Blood disorders also have immense economic consequences. In parallel with its Roadmap project, the EHA commissioned a study by the University of Oxford, UK, into the societal burden and cost of blood disorders in Europe (*EHA, 2015, unpublished data*). This study showed that the combined societal cost of hematologic diseases for the EU, Norway, Iceland, and Switzerland is estimated at €23 billion per year.

And yet, unfortunately, on a European level, current public spending on hematology research does not match this vast medical need. Of the €6.1 billion that the EU allocated to health research under its 7th Framework Programme (2007-2013), only 2.2% (€137 million) was granted to hematology research. This amounts to less than 0.1% of the societal cost of blood disorders in Europe over that same period. The current program (Horizon 2020) has been spared major budget cuts, but raising the relative level of funding for hematology research remains a work in progress. Governments, politicians and other policy-makers are responsible for making well-informed decisions on regulation and funding priorities for health research and medicinal product development. At the same time, the research community has a responsibility to provide policy-makers with the kind of information and evidence that they need to make those informed decisions.

Research in hematology has fundamentally improved our biological understanding of disease and has led to innovative

Table 1. Overarching topics and unmet needs in hematology.

1. Developing novel targeted therapies based on genomic profiling and chemical biology
2. Unleashing the power of cellular immunotherapy
3. Eradicating minimal residual disease in hematologic malignancies
4. Creating smarter combination treatments
5. Developing better tolerated treatments for blood disorders with a special emphasis on elderly patients
6. Using gene therapy to tackle blood disorders
7. Maximizing the clinical application of hematopoietic stem cells for transfusion, immunomodulation, and repair.

discoveries being made. Many of these discoveries are potent examples of how carefully designed basic research can lead to new approaches that block or interact with key pathways in diseased cells, resulting in very impressive anti-tumor effects. European hematologists have pioneered important inventions and played leading roles in developing curative approaches for patients with malignant diseases, such as lymphomas and leukemias.^{7,8}

It is within this context that, in 2014, the EHA, Europe's largest non-profit membership organization in hematology, decided to launch the Roadmap project. In addition to the general goal of raising public awareness of blood disorders and highlighting major achievements in their diagnosis and treatment, the specific goals of the EHA Roadmap include:

1) better informing European policy-makers and other stakeholders on the urgent needs and priorities of patients with blood disorders and of the hematology field for the next 5-10 years, thus helping them to make better-informed decisions on hematology research;

2) improving research funding opportunities for hematology;

3) helping the European hematology research community to reduce fragmentation by bringing together basic researchers, clinical trial networks and patient advocates in comprehensive study groups;

4) promoting a European consensus on medical and research priorities, thus promoting excellence and collaboration between academia and other researchers into blood disorders, such as the pharmaceutical industry.

The Roadmap Task Force included EHA board members and other top experts from all fields of hematology. Hundreds of hematologists, clinical trial groups, national hematology societies, patients' representatives and others were invited to provide input and advice. Draft texts and figures were discussed, developed, and reviewed, and the final draft was sent for consultation to stakeholders such as national hematology societies, patient organizations, hematology trial groups and other European organizations in, for example, overlapping disease areas. In all, some 300 hematologists contributed to the drafting of the document and the various stages of review, and its subtitle, "a consensus document", reflects this process.

The final product, the EHA Roadmap, distinguishes nine 'sections' in hematology: normal hematopoiesis, malignant lymphoid and myeloid diseases, anemias and related diseases, platelet disorders, blood coagulation and hemostatic disorders, transfusion medicine, infections in hematology,

and hematopoietic stem cell transplantation. These sections span 60 smaller study groups. The EHA Roadmap identifies the greatest unmet needs in hematology research and clinical science, and describes: 1) state-of-the-art hematologic research; 2) the research that needs to be carried out most urgently; and 3) the impact this research is anticipated to have. Some overarching topics and unmet needs can be recognized in nearly all of the nine EHA Roadmap sections (Table 1).

Chronic myeloid leukemia (CML) is a good example of successful hematology research that has led to a drastic improvement in treatment options and significantly increased survival rates. CML was almost always fatal until 15 years ago, but the excellent results of BCR-ABL1 tyrosine kinase inhibitor treatment are raising the expectation that a considerable proportion of patients will achieve treatment-free remission. Prevalence of patients with CML treated with kinase inhibitors is expected to increase by about 10% per year, so CML is a challenge for healthcare systems worldwide. With average treatment costs in Europe of between €40,000 and €70,000 per patient per year, the challenge now is how to maximize patient benefit with an affordable allocation of resources. The main objective is to integrate the leading European national trial groups in CML to form a co-operative network for advancements in CML-related research and healthcare. In-depth molecular and cellular characterization of CML patients will facilitate personalized medicine with regard to diagnosis, prognostication, and therapeutic decisions. Overall, a rational advanced treatment design will have a major impact on lowering the disease burden, reducing the rate of complications, and prospectively will result in higher remission rates, longer survival and a higher proportion of patients for whom treatment can be permanently discontinued as an indicator of cure. The cost of novel technologies and treatments might be balanced by their more specific application, having a favorable impact on patients' quality of life and lessening the burden for caregivers. This will translate into a more general positive impact on society by reducing the burden on available resources and improving individual work capabilities.

Classical Hodgkin lymphoma (HL) has become a highly curable malignancy and is considered one of the major success stories in hematology. More than 90% of patients with both localized and advanced-stage disease are alive five years after diagnosis. The progression-free survival ranges from 70% to 93%. As HL is one of the most common

malignancies in young adults, most patients will have a very long survival, which translates into substantial treatment and societal costs. During follow up, however, a significant proportion of patients experience serious long-term toxicities, such as secondary cancers, cardiovascular diseases, and infertility. Most of these late toxicities have been related to treatment. European clinical trials in HL have made an important contribution to reducing both radiation dose and field size, as well as the number of chemotherapy cycles. Since most HL patients will ultimately be cured from their disease and experience long-term survival, research should focus on better identifying patients who can be cured with less aggressive treatments. As discussed in the Roadmap document, research should also aim at further refining the use of new drugs and possible associations with the currently available treatment modalities as part of an individualized therapy strategy, thus meeting the urgent need of avoiding unnecessary toxicities for the vast majority of patients.

The EHA Roadmap also points the way towards repeating the success of research into CML and HL with diseases that currently suffer from low survival rates, such as acute myeloid leukemia (AML), where new technologies and additional funding are needed.

Overall, the EHA Roadmap highlights major past achievements in diagnosing and treating blood disorders, identifies unmet clinical and scientific needs in those same areas, and points to the anticipated benefits for patients of the proposed research areas. The authors trust that this will help decision-makers to focus their attention on how to

provide better funding for more targeted European hematology research.

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