specific genome remodeling processes such as Immunoglobulin (Ig) somatic hypermutation (SHM), and class switch recombination (CSR), allowing the expansion and selection of B cells with high affinity for the antigen and their further differentiation into memory B cells and plasma cells [1].

1. Two mechanisms of genetic lesion in B-NHL. The pathogenesis of B-NHL is associated with errors in genetic functions specific to GC B cells: (i) chromosomal translocations that lead to deregulated expression of oncogenes (BCL2, BCL6, c-MYC) and are thought to derive from DNA breaks associated with the Ig remodeling mechanisms (VDJ recombination, SHM, and CSR); and (ii) aberrant somatic hypermutation (ASHM), which is active in the majority of diffuse large B cell lymphomas (DLBCL) causes mutations in the 5′ region of multiple oncogenes and is due to the misfiring of SHM on non-physiologic targets. The role of CSR and SHM in lymphomagenesis was demonstrated in mice by crossing three oncogene-driven mouse models of B-NHL with mice lacking activation-induced cytidine deaminase (AID), the enzyme required for both processes. The results showed that AID deficiency prevents the development of GC-derived B-NHL, indicating that AID is required for GC-derived lymphomagenesis [2].

2. BCL6, the master regulator of GC development. The unique biology of GC and its implications in the pathogenesis of GC-derived B-NHL is explained in part by the function of the BCL6 gene, which encodes a transcriptional repressor necessary for GC formation and which is also a common pathogenetic target of both translocations and SHM. Recent results [3–4] have shown that in the first phase of GC development (centroblasts), BCL6 is involved in the repression of a number of biological functions including: (a) the response to DNA damage: (b) cell cycle arrest; (c) T-cell- and cytokine-mediated activation; (d) antiapoptotic pathways; (e) genomic instability and replication stress; (f) plasmacell differentiation. In a second phase of GC development, BCL6 is downregulated, thus allowing GC centrocytes to reestablish the above functions, including the ability to arrest proliferation and differentiate into plasmacells.

3. Genetic lesions deregulate the BCL6 program in B-NHL. The elucidation of the multiple BCL6 functions has allowed the development of a unifying model for the pathogenesis of major B-NHL types. In fact, the different NHL-associated chromosomal translocations as well as other B-NHL-associated genetic lesions appear to disrupt pathway that are regulated by or regulate BCL6: (1) chromosomal translocations involving the c-MYC gene prevent its downregulation by BCL6 in BL, and a fraction of DLBCL; (2) chromosomal translocations involving the BCL2 gene prevent downregulation by BCL2 in FL, and a fraction of DLBCL; (3) the pathway leading to BCL6 downregulation and BLIMP1 activation is disrupted by chromosomal translocations and mutations affecting BCL6 or by inactivation of BLIMP1 in non-overlapping cases of DLBCL [1]; both these lesions are often associated with genetic lesions leading to the constitutive activation of the NF-kB transcription complex in the majority of DLBCL, thus providing an anti-apoptotic stimulus in this disease [5]. The discovery of these genetic lesions and their conceptual organization in defined biological pathways has important implications for the definition of additional B-NHL subtypes and their specific therapeutic targeting.

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Leukaemias

7
Is molecular biology something more than occupational therapy for basic scientists?

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Our understanding of the molecular pathology of many haematological neoplasms has grown considerably over the last few decades, and years. Whilst such a gain of information is undeniably fascinating, the clinical relevance of molecular data needs to be reviewed critically.

Diagnosis of leukaemias and lymphomas still rests on morphology, topped up with immunological markers (used either in flow cytometry, or as histological markers). However, the advent of molecular markers has enabled us to pinpoint particular leukaemias or lymphomas as “entities” that were previously not recognised as such. NPM+ acute myeloblastic leukaemias are a point in case. NPM+ AML occurs more often in women than men, has high platelet counts at diagnosis, high remission rates and a reasonably good prognosis even without allogeneic stem cell transplantation.

Many molecular markers are prognostic, indicating either a good natural history of the disease (for example, CLL with del13q detected by FISH), or a bad one (for example, NOTCH1 mutations in adult T-cell ALL). In many instances, however, clinical risk scores are still more important than the molecular factors. For example, commonly used risk scores used in B-cell lymphoma (IPI and FLIPI) are based on simple clinical and routine lab criteria, and do not incorporate any molecular data.

A common misconception has it, that prognostic markers guide treatment choice, where intuitively patients with a “terrible” prognosis are offered more aggressive therapy than those with a better outlook. However, a predictive marker should help to identify patients who will respond well to a given therapy, and sort out patients with an *a priori* low chance of benefiting from a specific compound or treatment modality. Some practical examples show the way to go. The BCR-ABL + leukaemias will respond to blockade of this fusion molecule, and AML with duplications of the FLT3 gene may possibly respond to FLT3 inhibitors, regardless of whether they imply a good or a bad prognosis. In many neoplasms, however, there are still no specific drugs targeting given molecular abnormalities. For example, there is no compound in clinical use for the specific therapy of NMPmut AML. Likewise, the practical clinical relevance of molecular profiles of leukaemias or lymphomas worked out by microarrays still

needs to be defined, and this technology is still not fully incorporated into the routine work-up of our patients.
In summary, molecular analyses have become technically feasible in virtually all patients with haematological neoplasms. They may help to define "molecular entities" as a starting point to find new more specific therapies. They often provide prognostic information which although easily publishable, has limited practical importance as such (a personal statement that will predictably yield some controversy from the audience). Predictive markers useful to select individualised treatment are welcome, but still not applicable in the majority of cases seen in our clinics. To refer to the title, molecular biologists are encouraged to continue to improve our understanding of the "gene pathology" of these cancers, but should seek links with clinicians, who in turn need to speak their language for an improved mutual understanding.

8
Acute myeloid leukemia

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The treatment of acute myeloid leukemia (AML) in spite of a steady progress is still associated with considerable failure rates. This applies to patients with AML of any age. The majority of patients with AML are 60 years of age or older, in whom treatment disease outcome has remained most unsatisfactory. When treated with chemotherapy, this age group has an estimated survival of approximately 10–20% at 5 years. There has been an intense interest in the introduction of new modalities and exploring new ways of using conventional approaches. In this respect particularly the use of high-dose daunorubicin chemotherapy in patients with AML has raised recent interest.
From a biologic and clinical viewpoint acute myeloid leukemia is an extraordinarily heterogeneous disease. The molecular heterogeneity of the leukemia is the key determinant of treatment failure. Today, cytogenetics are commonly used in clinical practice for the assessment of individual prognosis. The recently postulated monosomal karyotype appears to provide better predictability of adverse outcome than the classical complex karyotype. Modern high-throughput approaches provide powerful tools for the discovery genetic biomarkers and the evaluation of their clinical relevance. Numerous, widely diverse genetic abnormalities (gene mutations, expression abnormalities) have been discovered. Examples of clinically relevant gene aberrations involve CEBP-alpha, RAS, nucleophosmin-1, FLT-3, WT1, EVI-1, MN-1, ERG, TET-2, IDH1 but there are many more to come.
The remarkable genomic heterogeneity is a reflection of the underlying somatic genetic abnormalities in transformed hematopoietic stem cells that as successive events over years accumulate in the neoplastic clone of a patient's leukemia during the evolution of the disease. As these genetic changes perturb diverse cellular pathways and functions, they often confer a profound impact upon the clinical phenotype of the disease at presentation and treatment response. Knowledge about the somatic mutations and genetic alterations driving these phenotypic variations in the leukemia will establish novel defined diagnostic subtypes of AML with diverse prognosis (diagnosis). The identification of biomarkers with prognostic significance using genome-wide approaches and large numbers of well defined cohorts will construct an informative background for risk adapted treatment decisions according disease risk (prognosis and treatment choice). For instance, allogeneic hematopoietic stem cell transplantation (alloSCT) furnishes the most effective antileukemic postremission modality available today but the advantage in terms of antileukemic activity has to be cautiously balanced against the increased risk of death and morbidity that is typically connected with alloSCT. The increasing insight into the remarkably diverse genetics of AML provides a backgound for a decision algorithm of alloSCT in AML according the estimated individual relapse risks of patients with AML. Finally, these insights will most likely furnish leads to potential therapeutic targets for drug development (treatment). Thus therapeutic and diagnostic developments emerging at the interface of laboratory and clinical research create a perspective of personalized therapeutics in AML.

9
Chronic lymphocytic leukaemia

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Rapid progress has been achieved recently in the management of chronic lymphocytic leukemia (CLL). New insights into the molecular pathology of CLL have generated a plethora of biological markers that predict the prognosis and influence therapeutic decisions. Moreover, fludarabine, bendamustine, and two monoclonal antibodies, alemtuzumab and rituximab, have been approved by European and/or American regulatory agencies. Additional monoclonal antibodies targeting CD20, CD23, CD37, CD38 or CD40, as well as drugs designed to interfere with proteins regulating the cell cycle, the apoptotic machinery, or the leukemic microenvironment (e.g. flavopiridol, oblimersen, ABT-263, or lenalidomide) are currently tested in clinical trials. An increased experience with reduced-intensity allogeneic progenitor cell transplantation allows offering this option to physically fit patients. In my presentation, I will review and summarize the current use of these different modalities in CLL therapy.

10
Myeloproliferative neoplasms Ph- negative

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Polycythemia Vera (PV), Essential Thrombocythemia (ET) and Primary Myelofibrosis (PMF) are included in the group of classical Ph-negative Myeloproliferative Neoplasms (MPNs) Understanding of the pathophysiology of these disorders dramatically improved following the description, in the last five years, of recurrent molecular abnormalities represented by: (1) the V617F mutation in *JAK2* exon 14, that is the most frequent and involves >95% of PV and ~60–70% of ET patients; (2) a number of molecular alterations located in *JAK2* exon 12, that have been described in 50–80% of the *JAK2*-wild type PV patients; (3) mutations in *MPL*, mostly represented by the W515L or W515K allele, that are presented by ~7% of ET patients; (4) mutations of the TET2 (ten-eleven translocation (2) gene reported in 20% of MDS and MPN/MDS and 8–15% of MPNs. Genotyping for such molecular abnormalities has already become a standard tool in the diagnostic work-up of patients suspected to have a MPN and constitutes a major criterion for diagnosis, according to the new WHO classification of myeloid neoplasms. As a consequence of an early diagnosis, it is very likely that the frequency and clinical presentation of these disorders will change in the next future. Currently, there is no therapy able to eradicate the molecular hallmark leading to these malignant diseases. Thus, therapy is aimed at preventing the major clinical relevant complications such as thrombosis in PV and ET and to alleviate anemia and splenomegaly in PMF.
Polycythemia Vera and Essential Thrombocythemia Major causes of morbidity and mortality in polycythemia vera (PV) and essential thrombocythemia (ET) are represented by