

The Team:

Head of Department: H. Döhner

Professors: K. Döhner, S. Stilgenbauer

Group Leaders: L. Bullinger, S. Fröhling, D. Mertens, C. Scholl

Postdocs: A. Dolnik, A. Philippen, N. Azoitei

PhD Students: D. Allegra, M. Dedic, K. Faber, B. Jebaraj, B. Koch, S. Lück, J. Mohr, A. Ruß

Study Programme Experimental Medicine Students:

K. Lang, R. Wiehe, S. Grasedieck

Additional Members of Thesis Advisory Committees:

J. Dürig (Essen), H.J. Fehling (Ulm), T. Fischer (Magdeburg), S. Fulda (Frankfurt), T. Kindler (Mainz), B. Schlegelberger (Hannover), T. Seufferlein (Halle), A. Silahtaroglu (Copenhagen, DK), K. Spiekermann (Munich), T. Wirth (Ulm)

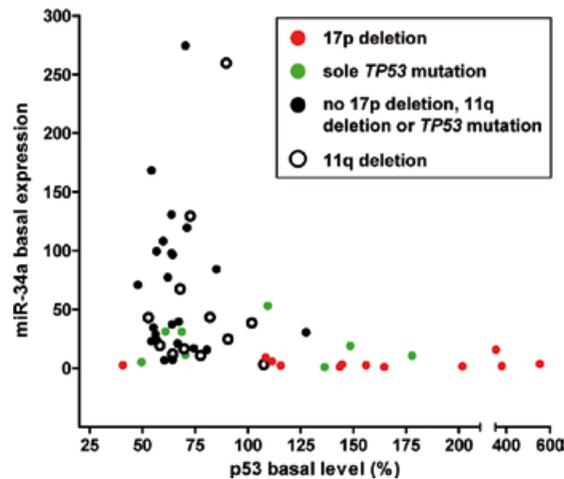
Department of Internal Medicine III

Identification and Characterization of Genetic Lesions and Development of Novel Therapies in Patients with Hematopoietic and Epithelial Malignancies

Head: Hartmut Döhner

The major research fields of the Department of Internal Medicine III are the pathomechanisms of acute and chronic leukemias, lymphoproliferative disorders, and epithelial malignancies. Students of the *International PhD Programme in Molecular Medicine* work in the areas of: (1) genetic and posttranscriptional mechanisms leading to autonomous cell growth and clinical disease progression in chronic lymphocytic leukemia (CLL); (2) genome and transcriptome-wide characterization of acute myeloid leukemia (AML); (3) comprehensive functional genetic and proteomic studies in AML and epithelial cancers.

CLL is the most common leukemia in the western world but the underlying pathomechanism remains unclear. Loss of genomic material from a critical region in chromosomal band 13q14.3 is detected in more than 50% of cases, thus making it the most common aberration in CLL. To date, no single tumor suppressor gene has been identified in this region but we have described an epigenetic regulatory mechanism in 13q14.3. In his PhD project, Danilo Allegra characterizes the non-coding RNA genes localized in this region. Billy Jebaraj is focusing on the pathogenetic link between telomere attrition and CLL. Additional genomic alterations, such as loss of chromosome 11q or 17p, are important prognostic factors, and Julia Mohr has identified and characterized the signaling pathways involved. The findings of these projects will be useful for elucidating the pathomechanism of CLL and for identifying novel therapeutic options for this incurable disease.



FACS-based quantification of TP53 protein and qPCR analysis of miR-34a in 55 CLL samples with different genomic aberrations show different patient subgroups (Mohr, Blood 2010).

In time, technological advances in genomics will provide the opportunity to capture the molecular variation of AML. By means of gene expression profiling (GEP), SNP microarray analysis and DNA methylation profiling, we are currently aiming to elucidate the biological basis of AML. In two newly identified core-binding factor leukemia subgroups, differentially regulated pathways, such as apoptotic signaling with the use of, for example, IAP (inhibitor of apoptosis protein) inhibitors, will be targeted (PhD project Sonja Lück). Similarly, by profiling microRNAs in a large cohort of AML cases and by integrating this data with corresponding GEP information, we found potential leukemia-relevant miR target genes of functional relevance (PhD project Annika Ruß).

Several projects in the department are centered on the identification of molecular abnormalities in hematopoietic and epithelial malignancies that are important for the initiation and/or maintenance of the transformed phenotype, with a particular focus on alterations that can be exploited to design better therapeutic strategies. Katrin Faber is using functional genomic screens and transcriptional profiling to search for genetic vulnerabilities in specific subtypes of AML. Britta Koch is applying various proteomic strategies to determine the mechanism underlying the selective requirement for the serine/threonine kinase STK33 in cancers driven by mutations in KRAS, the most frequently mutated human oncogene.

Ulm University
Department of Internal Medicine III
Prof. Dr. Hartmut Döhner
Albert-Einstein-Allee 23
89081 Ulm, Germany
Tel. +49 (0)731 500 45501
Fax +49 (0)731 500 45505
sekr-dir.innere3@uniklinik-ulm.de
www.uniklinik-ulm.de/onkologie

Selected Publications:

- Zenz T, Mertens D, Küppers R, Döhner H, Stilgenbauer S (2010) From pathogenesis to treatment of chronic lymphocytic leukaemia, *Nat Rev Cancer* 10, 37-50.
- Scholl C, Fröhling S, Dunn IF, Schinzel AC, Barbie DA, Kim SY, Silver SJ, Tamayo P, Wadlow RC, Ramaswamy S, Döhner K, Bullinger L, Sandy P, Böhm JS, Root DE, Jacks T, Hahn WC, Gilliland DG (2009) Synthetic lethal interaction between oncogenic KRAS dependency and STK33 suppression in human cancer cells, *Cell* 137, 821-34.
- Roos, G, Kröber A, Grabowski P, Kienle D, Bühler A, Döhner H, Rosenquist R, Stilgenbauer S (2008) Short telomeres are associated with genetic complexity, high-risk genomic aberrations, and short survival in chronic lymphocytic leukemia, *Blood* 111, 2246-52.