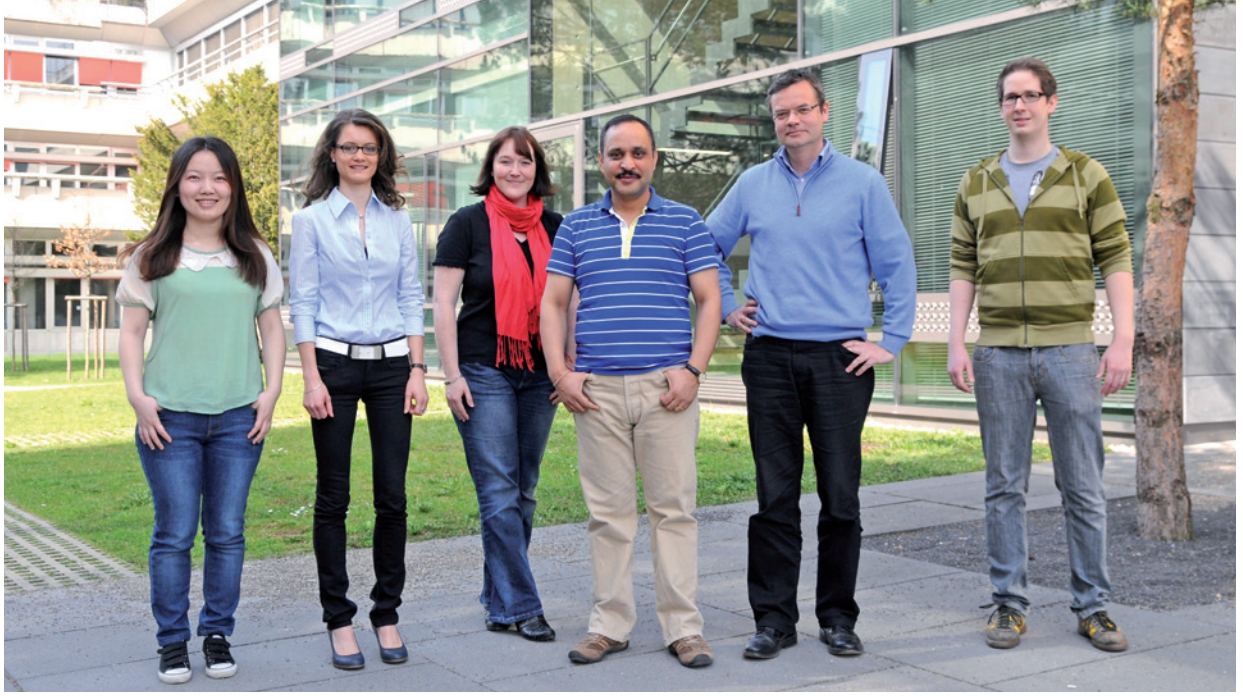


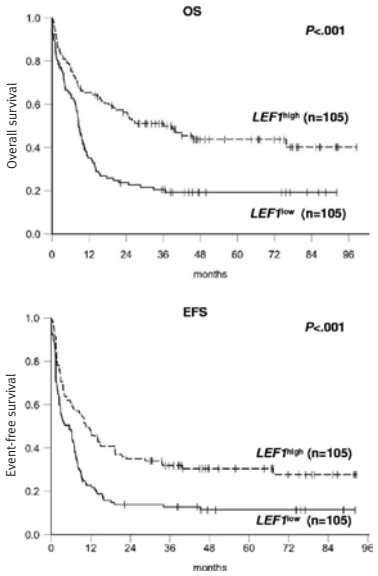
Institute of Experimental Cancer Research

Characterization of the Molecular Biology of Normal and Leukemic Hematopoiesis

Head: Christian Buske

The Team:
Head of Institute: C. Buske
Professor: V.P.S. Rawat
Group Leaders/Postdocs: A. Muranyi, A. Mulaw, N. Vegi, M. Feuring-Buske (Internal Medicine III), F. Kuchenbauer (Internal Medicine III)
PhD Students: S. Bamezai, D. Daria, K. Edmaier, S. Ihme, T. Mandal, K. Stahnke, J. Huang, F. Mohr, E. Gentner, L. Ferruzzi
Study Programme Experimental Medicine Students: A. Grunenberg, E. Panina, A. Bootz
Additional Members of Thesis Advisory Committees: S. Fulda (Frankfurt), H. Glimm (Heidelberg), H. Geiger (Ulm), S. Bohlander (Munich), H. Döhner (Ulm), A. Koul (Belgium)

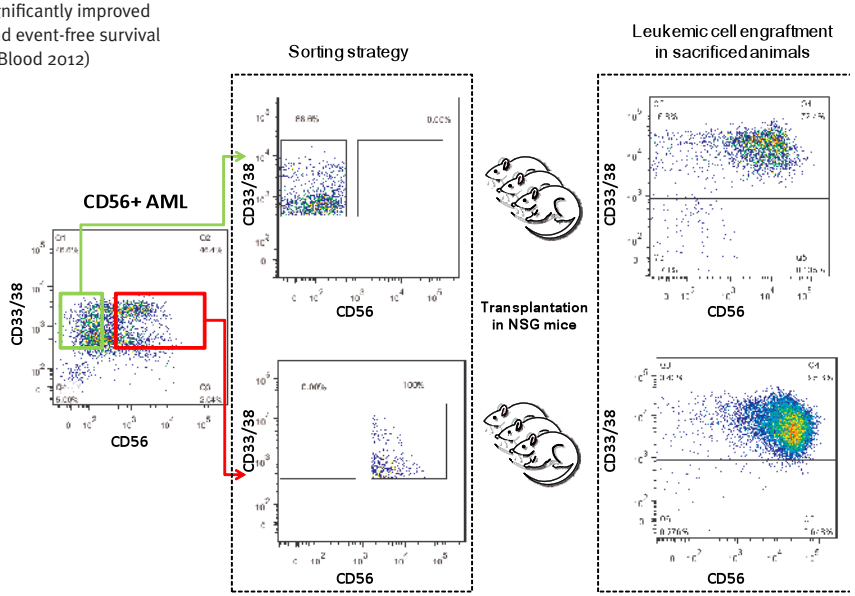
It is well accepted that leukemia originates from normal hematopoietic stem or progenitor cells which have acquired critical genetic alterations leading to uncontrolled self-renewal and impaired differentiation of the leukemic cells. The institute focuses on characterizing key molecular events which cause malignant transformation of normal hematopoietic stem cells into leukemic stem cells using a wide panel of different murine models that mimic human leukemias. Using murine bone marrow transplantation assays and retroviral gene transfer, we were able to identify several novel regulators of normal and leukemic stem cells, such as *VENTX* or *CDX2*. Furthermore, we could demonstrate that genetic alterations have to collaborate to induce acute myeloid leukemias (AML), such as the fusion gene *AML1-ETO* and the *FLT3* length mutation. In addition, we used murine leukemia models to profile leukemic stem cells and to identify differences between normal and leukemic stem cells, and could thus show that in acute myeloid leukemia characterized by



We identified LEF1 as a novel independent prognostic factor in human AML patients with normal karyotype. High expression of LEF1 is associated with a significantly improved overall survival (OS) and event-free survival (EFS). (Metzeler et al., Blood 2012)

the fusion gene CALM-AF10 the leukemic stem cell differs from its normal counterpart by the expression of the lymphoid-associated antigen B220. Currently, the group focuses on the relevance of lymphoid antigen expression in acute myeloid leukemias (J. Huang*, M. Feuring-Buske), the role of the LEF1 in human AML (K. Edmaier*, C. Buske), the identification of novel regulatory genes of leukemic stem cells (E. Gentner*, C. Buske), the function of the TET protein family in normal and malignant hematopoiesis (F. Mohr*, VPS Rawat), the role of non-coding RNAs in human leukemogenesis (S. Ihme, M. Mulaw), and the biology of NPM1 mutated leukemias (A. Muranyi, C. Buske). For this research program, the institute has access to state-of-the-art FACS technology as well as to next generation sequencing technology.

**Students of the International Graduate School*



Leukemic subfractions isolated from patients with acute myeloid leukemia (AML) harbor leukemic stem cells and engraft into NSG mice.

Ulm University
Institute of Experimental Cancer Research
Prof. Dr. Christian Buske
Albert-Einstein-Allee 11
89081 Ulm, Germany
Tel. +49 (0)731 500 65801
Fax +49 (0)731 500 65802
christian.buske@uni-ulm.de
www.uniklinik-ulm.de/tumorforschung

Selected Publications:

- *Metzeler KH, Heilmeier B, Edmaier KE, Rawat VP, Dufour A, Döhner K, Feuring-Buske M, Braess J, Spiekermann K, Büchner T, Sauerland MC, Döhner H, Hiddemann W, Bohlander SK, Schlenk RF, Bullinger L, Buske C (2012) High expression of lymphoid enhancer-binding factor-1 (LEF1) is a novel favorable prognostic factor in cytogenetically normal acute myeloid leukemia. Blood. 120(10):2118-26.*
- *Rawat VP, Humphries RK, Buske C (2012): Beyond Hox: the role of ParaHox genes in normal and malignant hematopoiesis. Blood. 120(3):519-27.*
- *Eppert K, Takenaka K, Lechman ER, Waldron L, Nilsson B, van Galen P, Metzeler KH, Poeppl A, Ling V, Beyene J, Canty AJ, Danska JS, Bohlander SK, Buske C, Minden MD, Golub TR, Jurisica I, Ebert BL, Dick JE (2011) Stem cell gene expression programs influence clinical outcome in human leukemia. Nat Med. 17(9):1086-93.*
- *Rawat VP*, Arseni N*, Ahmed F, Mulaw MA, Thoene S, Heilmeier B, Sadlon T, D' Andrea RJ, Hiddemann W, Bohlander SK, Buske C*, Feuring-Buske M* (2010): The vent-like homeobox gene VENTX promotes human myeloid differentiation and is highly expressed in acute myeloid leukemia. Proc Natl Acad Sci U S A. 107(39):16946-51. * both authors contributed equally*
- *Petropoulos K, Arseni N, Schessl C, Stadler CR, Rawat VP, Deshpande AJ, Heilmeier B, Hiddemann W, Quintanilla-Martinez L, Bohlander SK, Feuring-Buske M, Buske C (2008): A novel role for Lef-1, a central transcription mediator of Wnt signaling, in leukemogenesis. J Exp Med. 205:515-522.*
- *Deshpande AJ, Cusan M, Rawat VP, Reuter H, Krause A, Pott C, Quintanilla-Martinez L, Kakadia P, Kuchenbauer F, Ahmed F, Delabesse E, Hahn M, Lichter P, Kneba M, Hiddemann W, Macintyre E, Mecucci C, Ludwig WD, Humphries RK, Bohlander SK, Feuring-Buske M, Buske C (2006): Acute myeloid leukemia is propagated by a leukemic stem cell with lymphoid characteristics in a mouse model of CALM/AF10-positive leukemia. Cancer Cell. 10:363-374.*