

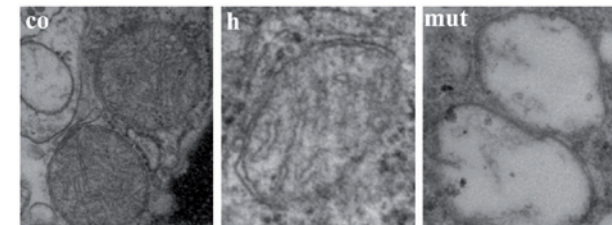
**The Team:****Head of Department:** K. Scharffetter-Kochanek**Professors:** H. Geiger, J.M. Weiss**Labmanager:** M. Wlaschek**Group Leaders/Postdocs:** A. Basu, A. Brown, M.C. Florian, M. Gatzka, S. Iben, D. Jiang, P. Maity, T. Peters, A. Sindrilaru, R. Tiwari, N. Treiber, S. Vander Beken**PhD Students:** R. Assfalg, J. de Vries, V. Farsam, F. Ferchiu, O.G. Gonzalez, A. Gregoryan, N. Guidi, S. Koch, S. Köllner, A. Kügler, P. Meyer, Y. Qi, Kamayani Singh, Karmveer Singh, B. Überle**Study Programme Experimental Medicine Student:** B. Meier**Additional Members of Thesis Advisory Committees:**

M. Berneburg (Tübingen), C. Buske (Ulm), D. Kletsas (Athens), C. Mauch (Cologne), C. Niessen (Cologne), R. Nischt (Cologne), K.L. Rudolph (Jena/Ulm), A. Wells (Pittsburgh), S. Wells (Cincinnati), T. Wirth (Ulm), L. Wiesmüller (Ulm), G. Van Zant (Lexington)

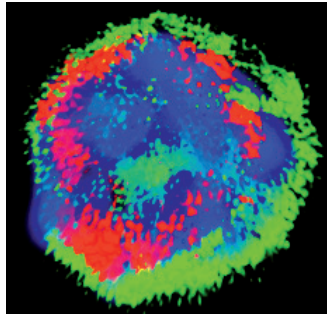
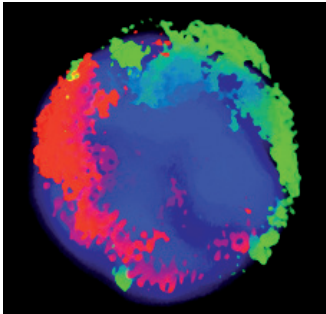
**Department of Dermatology and Allergic Diseases****Work Group:  
Aging: Mechanisms and Novel Preventive Strategies****Head:** Karin Scharffetter-Kochanek

Life expectancy has risen in developed societies and the mystery of aging has still not been resolved. The prevalence of infectious, autoimmune, endocrine and mental diseases and of connective tissue degeneration has sharply increased. We are testing the hypothesis whether oxidative stress and/or DNA damage pathways are of general relevance to the intrinsic and extrinsic aging of the connective tissue and life span. The connective tissue-specific SOD2 deficient mouse shows a complex aging phenotype. We are interested in the role of free radicals and its impact on signaling pathways involved in the organization of the extracellular matrix, organ maintenance, metabolic homeostasis and renewal capacities of stem cells (Karmveer Singh). The DNA damage response pathway (DDR) resulting in cellular senescence is addressed in dermal fibroblasts (Florentina Ferchiu). Stromal cells influence the tumorigenesis of skin tumors. The role of senescent fibroblasts in tumor progression is investigated on the cellular and organismic levels

(Vida Farsam). The complex cellular interactions in aging are addressed in a systems biology approach with specific focus on NFkB (Patrick Meyer). The nucleolus is studied as stress sensor of DDR and related signaling pathways (Robin Assfalg) that possibly also affect ribosomal biogenesis (Sylvia Koch). The regenerative and repair effect of mesenchymal stem cells (MSC) and their mediators is analyzed in acute wound healing in mice (Yu Qi). Molecular and cellular mechanisms of wound repair by MSC in mouse models of impaired regeneration are analyzed (Andrea Kügler).



Electron micrograph of Sod2-deficient fibroblast mitochondria (mut) reveals a severely disturbed structure with loss of cristae and degeneration of structure compared to Sod2 heterozygous (h) and Sod2-competent fibroblasts (co).



The distribution of tubulin (green) and acetylated histone 4 lysine 16 (red) in hematopoietic stem cells shows polarity in a young cell (now left) that is lost in an older cell (now right). The nucleus (blue) has been rendered slightly transparent to allow for visualization of the distribution of acetylated histone 4 lysine 16 within the nucleus. The image was acquired and analyzed by M.C. Florian. Based on an idea from M.C. Florian, H. Geiger, and A. Ronchi.

## Work Group: Hematopoiesis and Hematopoietic Stem Cells

Head: Hartmut Geiger

Hematopoiesis is the process by which mature blood cells are formed from hematopoietic stem cells (HSC). Research in our laboratory is centered on stem cell aging, leukemia and DNA damage responses. In mice and humans there is a successive decline in stem cell function from adulthood to old age. This decline has been associated with perturbed tissue homeostasis and impaired injury repair in aged individuals. HSCs from aged animals are impaired by their inability to self-renew, to contribute efficiently to hematopoiesis and to differentiate. Our hypothesis is that distinct molecular and cellular pathways contribute to stem cell aging. Our data supports the view that the elevated activity of small RhoGTPases found in hematopoietic cells in aged animals results in altered adhesion to stroma cells. We were able to demonstrate that aged stem cells are more active inside the bone marrow niche in vivo, which most likely results in less stable stem cell stroma interactions. Altered adhesion to the niche/stroma could be one underlying cause for phenotypes associated with aged HSCs. Altered DNA damage response pathways in aged HSCs might be critical for increased incidence of age-associated disease. We are developing molecular tools to determine DNA damage responses in HSCs (Bettina Überle). Aging in stem cells might contribute to an increase in leukemia with age. We are interested in determining whether the age of the stem cell niche/stroma influences leukemia development (Novella Guidi).

Ulm University  
Department of Dermatology and Allergic Diseases  
Prof. Dr. Karin Scharffetter-Kochanek  
Albert-Einstein-Allee 23  
89081 Ulm, Germany  
Tel. +49 (0)731 500 57501  
Fax: +49 (0)731 500 57502  
karin.scharffetter-kochanek@uniklinik-ulm.de  
www.uniklinik-ulm.de/struktur/kliniken/dermatologie-und-allergologie.html

### Selected Publications:

- Sindrilaru A, Peters T, Wieschalka S, Baican C, Baican A, Peter H, Hainzl H, Schatz S, Qi Y, Schlecht A, Weiss JM, Wlaschek M, Sunderkoetter C, Scharffetter-Kochanek K (2011): An unrestrained inflammatory M1 macrophage population induced by iron impairs wound healing in humans and mice, *J Clin Invest* 121, 985-997.
- Treiber N, Maity P, Singh K, Kohn M, Keist AF, Ferchiu F, Sante L, Frese S, Bloch W, Kochanek S, Sindrilaru A, Iben S, Högel J, Ohnmacht M, Claes LE, Ignatius A, Chung JH, Lee MJ, Kamenisch Y, Berneburg M, Nikolaus T, Braunstein K, Sperfeld AD, Ludolph AC, Briviba K, Wlaschek M, Scharffetter-Kochanek K (2011): Accelerated aging phenotype in mice with conditional deficiency for mitochondrial superoxide dismutase in the connective tissue, *Aging Cell* 10, 239-254.
- Singh K, Gatzka M, Peters T, Borkner L, Hainzl A, Wang H, Sindrilaru A, Scharffetter-Kochanek K (2013): Reduced CD18 levels drive Treg conversion into Th17 cells in the CD18<sup>hypo</sup> PL/J mouse model of psoriasis, *J Immunol* 190, 2544-53.
- Geiger H, Pawar SA, Kerschen EJ, Nattamai KJ, Hernandez I, Liang HP, Fernández JA, Cancelas JA, Ryan MA, Kustikova O, Schambach A, Fu Q, Wang J, Fink LM, Petersen KU, Zhou D, Griffin JH, Baum C, Weiler H, Hauer-Jensen M. (2012): Pharmacological targeting of the thrombomodulin-activated protein C pathway mitigates radiation toxicity, *Nature Med* 18, 1123-9.
- Florian MC, Dörr K, Niebel A, Daria D, Schrezenmeier H, Rojewski M, Filippi MD, Hasenberg A, Gunzer M, Scharffetter-Kochanek K, Zheng Y, Geiger H (2012): Cdc42 Activity Regulates Hematopoietic Stem Cell Aging and Rejuvenation, *Cell Stem Cell* 10, 520-530.
- Assfalg R, Lebedev A, Gonzalez OG, Schelling A, Koch S, Iben S. (2012): TFIIH is an elongation factor of RNA polymerase I, *Nucleic Acids Res* 40, 650-9.