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Hock Laboratory

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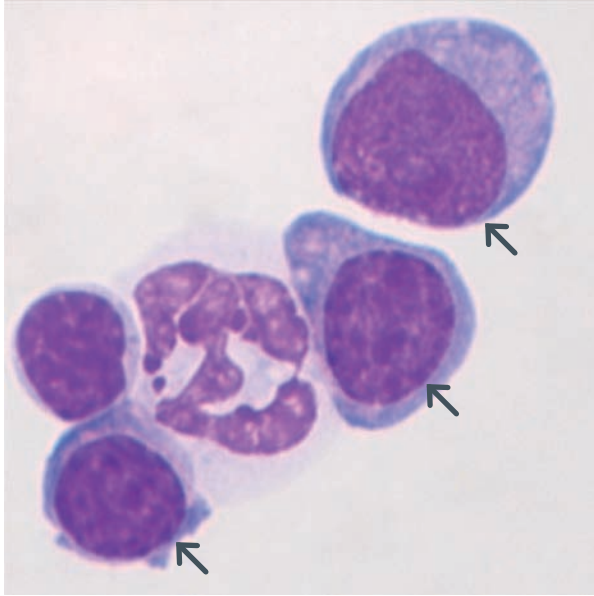
The Hock laboratory explores the molecular basis of blood cell formation and the pathogenesis of leukemia and lymphoma. Specifically, we study the transcription factors that regulate gene activity during normal blood cell development and how the transcriptional apparatus goes awry in cancer. For example, we have developed important insights into a network of transcription factors that help maintain blood stem cells in the bone marrow; this work could lead to new strategies for increasing the yield of stem cells for bone marrow transplantation. Another project in our laboratory focuses on deciphering the multistep process that leads to lymphoblastic leukemia of childhood, with the goal of identifying new drug targets for this devastating disease. Finally, we are interested in how DNA packaging affects the interaction between genes and transcription factors, especially with regard to oncogenes and tumor suppressor genes important in human cancer.

Our laboratory is interested in the molecular control of normal and malignant stem cells with an emphasis on the hematopoietic system. Blood cells need to be continuously replenished by a small population of hematopoietic stem cells (HSCs) that have the capacity to both self-renew and mature stepwise into all known blood lineages. HSCs are also the ancestors of leukemia and lymphoma cells. As HSCs mature, they undergo successive changes in gene expression. The transcriptional apparatus must ensure that genes specific to immature cells are repressed as differentiation proceeds, while genes that are necessary for mature cells become activated. This activating and inactivating of genes is achieved by cooperative action of a variety of lineage-specific and general transcription factors and the complex molecular machinery that regulates the accessibility of different regions of the genome in chromatin. We investigate how transcription factors establish differentiation-specific transcriptional programs and how such

programs can become derailed in cancer, leukemia and lymphoma.

Transcriptional control of normal and malignant hematopoietic stem cells in the adult bone marrow

Hematopoiesis in the bone marrow emanates from HSCs. We are studying the basic biology of HSCs. Specifically we explore how a network of transcription factors that includes *Tel-Etv6*, *Gfi1*, *Gfi1b* and *Gata2* maintains HSCs in the bone marrow (Hock et al. 2004, *Genes & Development*; Hock et al. 2004, *Nature*). The goal is to exploit the biology of transcriptional regulation of HSCs to maintain, expand, and possibly even generate HSCs *ex vivo* so that more patients will have the option of bone marrow transplantation. In a closely related effort, we are exploring the molecular programs of stem cells in leukemia and lymphoma to identify differences in their molecular regulation compared with normal HSCs. Such differences may allow us to specifically target tumor stem cells while sparing normal blood formation.



Dr. Hock's laboratory works on molecular mechanisms of normal differentiation and malignant transformation. The image shows normal blood cells and leukemic cells (arrows) from a novel experimental model generated in the lab.

Deciphering the molecular events leading to acute lymphoblastic leukemia of childhood

About one in 2000 children develops this catastrophic illness, most often with a t(12;21) translocation. Despite very aggressive treatments, not all children can be cured, and some suffer from long-term side effects of their therapy. Rational development of more specific, less toxic treatments requires a precise understanding of the molecular mechanisms that cause the disease. We have discovered that TEL-AML1, the first hit in childhood leukemia, generates a preleukemic, latent lesion in HSCs. We are now exploring how additional genetic hits cooperate to derail normal blood development and generate leukemia. Deciphering the multistep pathogenesis of this entity is likely to serve as a paradigm for the development of other malignant diseases.

Exploration of novel epigenetic regulators in stem cells

Our understanding of how specialized cells of the body establish their identity by

regulating access to genes continues to increase. For example, a large fraction of the genes active in brain cells are inactive in blood cells and, therefore, are stored in a very dense, inaccessible state. As most molecules involved in the regulation of gene accessibility have only recently been identified, studying their biology is likely to provide unique opportunities for the development of entirely novel therapies. We are investigating the utility of a group of proteins termed MBT-proteins, which is very important for condensing DNA and modifying histones. Evidence suggests that this protein family may play important roles in normal and malignant blood formation, but its precise functions remain poorly understood. Our laboratory has recently discovered an entirely novel, essential function of the family member L3mbtl2 in pluripotent stem cells.

Selected Publications:

Foudi A, Kramer DJ, Qin J, Ye D, Behlich AS, Mordecai S, Preffer FI, Amzallag A, Ramaswamy S, Hochedlinger K, Orkin SH and Hock H. Distinct, strict requirements for Gfi-1b in adult bone marrow red cell and platelet generation. *J Exp Med.* 2014; 211, 909-927.

Qin J, Whyte WA, Anderssen E, Apostolou E, Chen H, Akbarian S, Bronson RT, Hochedlinger K, Ramaswamy S, Young RA, and Hock H. The Polycomb Group Protein L3mbtl2 Assembles an Atypical PRC1-family Complex with Essential Roles in Pluripotent Stem Cells and Early Development. *Cell Stem Cell.* 2012; 11, 319-332, 2012.

Hock H. A complex Polycomb issue: the two faces of EZH2 in cancer. *Genes Dev.* 2012; 26, 751-755.

Qin J, Van Buren D, Huang HS, Zhong L, Mostoslavsky R, Akbarian S, Hock H. Chromatin protein L3MBTL1 is dispensable for development and tumor suppression in mice. *J Biol Chem.* 2010; Sep 3, 285(36):27767-75.

Schindler JW, Van Buren D, Foudi A, Krejci O, Qin J, Orkin SH, Hock H. TEL-AML1 corrupts hematopoietic stem cells to persist in the bone marrow and initiate leukemia. *Cell Stem Cell.* 2009; Jul 2, 5(1):43-53.

Eminli S, Foudi A, Stadtfeld M, Maherali N, Ahfeldt T, Mostoslavsky G, Hock H, Hochedlinger K. Differentiation stage determines potential of hematopoietic cells for reprogramming into induced pluripotent stem cells. *Nat Genet.* 2009; Sep, 41(9):968-76.