University of Birmingham

Professor Constanze Bonifer

Chair of Experimental Haematology

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About

Constanze is a Professor within the School of Cancer Sciences and has spent her career engaged in research in the field of gene regulation in the hematopoietic system.

Constanze has published more than 100 papers in the field of gene regulation and holds programme grants from the BBSRC and Leukaemia Lymphoma Research, several studentships as well as project grants from the MRC, CRUK, and the Kay Kendall Leukaemia fund.

Her group is particularly interested in how transcription factors program chromatin in development and has specialised in establishing sophisticated methods to study gene regulation in development and in leukaemia.

Qualifications

1995 Habilitation in Molecular Biology and Genetics, University of Freiburg, Germany

1985 PhD in Natural Sciences 1985, University of Heidelberg, Germany

Biography

Constanze Bonifer studied Biology at the University of Cologne, Germany and graduated 1980 with a first class degree in Biochemistry, Chemistry and Genetics. She then went on to do a PhD in Biochemistry and Molecular Biology, first at the University of Cologne, then at the Centre for Molecular Biology (ZMBH), University of Heidelberg.

This was followed by Postdoctoral training periods at the Karolinska Institute, Stockholm, and the National Institute for Medical Research in London where she started to work on gene regulation.

1990 she became Assistant Professor and independent group leader at University of Freiburg, Germany, where she worked on gene regulation in the hematopoietic system.

1997 she went back to the UK and became a group leader at the Molecular Medicine Unit, University of Leeds, where she started to work not only on basic mechanisms controlling blood cell development, but also on epigenetic mechanisms controlling leukemogenesis.

She became a Reader in 2000, a Professor in 2003 and in 2004 became a full Professor and Chair of Experimental Haematology. In 2006 she was appointed Head of Section of Expeirmental Haematology at the Leeds Institute of Molecular Medicine.

Since August 2011, Constanze is in Birmingham as Chair of Experimental Haematology at the Institute of Biomedical Research.

Teaching

Professor Bonifer has only recently moved to the University of Birmingham and has not yet taken up undergraduate teaching responsibilities. However, she teaches Master Classes for PhD students.

Postgraduate supervision

Constanze has currently two PhD students and is interested in supervising doctoral research in the following areas:

- Basic mechanisms controlling blood cell development
- Molecular mechanisms regulating aberrant gene regulation in leukaemia

For currently advertised studentships visit:

http://www.medicine.bham.ac.uk/pg/grad/Studentships_0910.shtml (http://www.medicine.bham.ac.uk/pg/grad/Studentships_0910.shtml)

Research

Our main research interest is to study the mechanism of cell fate decisions at the level of gene regulation. All blood cells arise from pluripotent stem cells of the bone marrow. We want to understand in mechanistic detail how different genetic programs are activated and silenced at specific stages of blood cell development and which factors are involved in this process. In addition, we study how this finely balanced process is subverted in leukaemic cells.

In our work, we address the question of how the regulators of transcription, the sequence-specific DNA binding proteins or transcription factors, interact with the chromatin template and change its structure. We know from genetic studies that chromatin modification complexes play essential roles in all phases of the development of multicellular organisms. We also know that transcription factors bring these epigenetic regulatory proteins to specific genes. Together, they are responsible for the

expression of different genes. Our research has shown that even the process of expressing one gene at the right time and in the right cell is a breathtakingly complex process that involves the coordinate action of hundreds of different molecules. We have also made progress in understanding how these intricately balanced processes are disturbed in leukaemia.

We have now taken these studies one step further. One of the great challenges for future biological and medical research will be to understand how all genes and all molecules in a cell work together to generate different cells that each express only one set of genes. This means that we will have to study all genes simultaneously. To this end, we employ genome-wide methods such as ChIP-sequencing and DNaseI-sequencing to generate such data. We also collaborate with computational biologists to reconstruct models of the molecular interactions driving blood cell development. However, we also study the global consequences of expression of aberrant transcription factors in form of nuclear oncogenes on how the epigenetic landscape is altered in leukaemic cells. The outcome of such studies will shed light on the complex deregulation processes that turn normal into leukaemic cells and will uncover novel therapeutic targets to combat a disease with a high death toll, in particular amongst the elderly. The results of our experiments are therefore not only important for our understanding of how blood cells form, but are extremely important for how we may diagnose and treat patients in the future.

Recent highlights of our work include the identification of chromatin priming mechanisms in early blood cell progenitor cells (Lichtinger et al., 2012), studies of epigenetic consequences of oncoprotein expression in acute myeloid leukaemia (Ptasinska et al., 2012) and recently the discovery that aberrantly activated repeat elements can drive the expression of oncogenes in lymphoma (Lamprecht et al., 2010; see podcast below).

Nature Medicine Podcast (May 2010)

Other activities

Constanze is a member of the the International Society of Experimental Haematology.

She reviews many grants for a variety of funding bodies and is Vice-Chair of BBSRC committee C.

She serves on the editorial board of Experimental Hematology and Stem Cell Research.

Publications

Selected peer reviewed publications in the last five years:

Sox4 is a key oncogenic target in C/EBPα mutant acute myeloid leukemia. Zhang H, Alberich-Jorda M, Amabile G, Yang H, Staber PB, Diruscio A, Welner RS, Ebralidze A, Zhang J, Levantini E, Lefebvre V, Valk PJ, Delwel R, Hoogenkamp M, Nerlov C, Cammenga J, Saez B, Scadden DT, **Bonifer C**, Ye M, Tenen DG (2013). Cancer Cell 24(5):575-88.

Piper, J., Elze, M., Cauchy, P., Cockerill, P.N*., **Bonifer, C***. and Ott, S*. (*corr. Authors) (2013). Wellington: A novel method for the accurate identification of digital genomic footprints from DNase-seq data. **Nucleic Acids Research**. 41(21):e201

Lineage-inappropriate PAX5 expression in t(8;21) acute myeloid leukemia requires signaling-mediated abrogation of polycomb repression. Ray D, Kwon SY, Tagoh H, Heidenreich O, Ptasinska A**, Bonifer C.** Blood. 2013 Aug 1;122(5):759-69.

Ladopoulos, V., Hofemeister, H., Hoogenkamp, M., Riggs, A.D. Stewart, A.F. and **Bonifer, C**. (2013) Mechanistic insights into the function of MLL2 in CpG island promoter regulation. Mol Cell Biol. 33(7):1383-139

Lichtinger, M., Ingram, R.M., Hannah, R., Clarke, D., Müller, D., Lie-A-Ling, M., Noailles, L., Zhang, P., Wu, M., Tenen, D.G., Assi, S., Westhead, D.R., Kouskoff, V., Lacaud, G., Göttgens, B., and **Bonifer, C.** (2012) RUNX1 reshapes the epigenetic landscape at the onset of haematopoietic development. EMBO J. 31, 4318 - 4133

Ptasinska, A.; Assi, S.A., James, S.R.,Williamson, D.,Hoogenkamp, M., Mengchu, W., Care, M., McNeill, H., Cullen, M., Tooze, R., Tenen, D.G., Cockerill, P.N. Westhead, D.R.,Heidenreich, O. and **Bonifer, C.** (2012). Reversible genome-wide epigenetic reprogramming by the leukemia-initiating fusion protein RUNX1/ETO. Leukemia 26:1829-41

Lamprecht, B., Walter, K., Kreher, S., Kumar, R., Hummel, M., Lenze, D., Köchert, K., Bouhlel, M.A., Richter, J., Soler, E., Stadhouders, R., Jöhrens, C., Wurster, K.D., Callen, C., Harte, M.F., Giefing, M., Barlow, R., Stein, H., Anagnostopoulos, I., Janz, M., Cockerill, P.N., Siebert, R., Dörken, B., **Bonifer, C.*,** and Mathas, S.* (2010). (*Joint corresponding authors). De–repression of an endogenous long terminal repeat activates the CSF1R proto–oncogene in human lymphoma. Nature Medicine. 16, 571 – 579

Hoogenkamp, H.; Lichtinger, M.; Krysinska, H.; Lancrin, C.; Clarke, D.; Williamson, A.; Mazzarella,L.; Ingram, R.; H. Jorgensen, A. Fisher, D,G. Tenen, Kouskoff, V.; G.Lacaud, and C.Bonifer (2009). Early chromatin unfolding by Runx1 - a molecular explanation for differential requirements during specification versus maintenance of the hematopoietic gene expression program. Blood 114; 299-309.

And many more since 1986