Institute of Medical Biology
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Seminar Announcement
- All Are Welcome -

Speaker: **Dr Heinrich Leonhardt**
Ludwig Maximilians University

Title : ***Role and Regulation of DNA Modifications in Development and Disease***

Date : **30 March 2012 (Friday)**

Time : **11.00am – 12.00pm**

Venue : **Breakthrough Theatrette, Matrix Level 4, Biopolis**

Host : **Dr Colin Stewart**
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Abstract:
DNA methylation plays a central role in the regulation of gene expression, chromatin condensation and genome stability. Downregulation of DNA methyltransferase1 (Dnmt1) causes hypomethylation and induces tumors (Gaudet et al., *Science*, 300, 489-492). Dnmt1 shows a complex and cell cycle dependent distribution, it associates with the replication machinery during S phase and with constitutive heterochromatin from late S till M phase (Easwaran et al., *EMBO Reports* 5, 1181-1186). Interestingly, Dnmt1 is also recruited to DNA repair site likely contributing to the restoration of epigenetic information (Mortusewicz et al., *PNAS*, 102, 8905-9). We are now analyzing the cell cycle specific dynamics of Dnmt1 and mutants thereof with photodynamic techniques in living cells (Schermelleh et al., *Nature Methods,* 2, 751-756). Recently, we could demonstrate that DNMT1 is also essential for proliferation and survival of human cancer cells (Spada et al., *J. Cell Biol.,* 176, 565-71). We have identified several interacting factors and functional domains and are now systematically mutagenizing them to study their function *in vivo.* Last not least, we are studying the expression of these epigenetic factors during normal and malignant hematopoiesis. Most recently, we started to investigate the newly discovered DNA modification.

Genomic 5-methylcytosine, a prominent epigenetic modification, can be further modified to 5-hydroxymethylcytosine (hmC) formylcytosine (fC) and carboxycytosine (caC) by Tet dioxygenases. We developed two methods based on purified enzymes for fast and accurate quantification and mapping of hmC in genomic DNA samples (Szwagierczak et al. *NAR* 38, e181 and 39, 5149-56). We determined hmC levels in various mouse tissues and differentiating embryonic stem cells and show a correlation with differential expression of tet genes. Recently, hemizygous deletions and mutations of TET2 were found in a wide range of myeloid malignancies. We used our enzymatic assay to measure hmC levels in genomic DNA in a series of sAML patients and found that TET2 and IDH2 mutations correlated with low hmC levels. Gene expression profiling revealed that patients with low hmC levels had a distinct gene expression profile (Konstandin et al., *Leukemia*, 25, 1649-52). These results suggest that changes of hmC affect epigenetic gene regulation and correlate with distinct changes in gene expression. We are currently investigating the regulation and biochemical properties of Tet enzymes and determine the effect of the new DNA modifications on chromatin structure and gene expression.

About the Speaker:
Heinrich Leonhardt studied Biochemistry at the Free University in Berlin and did a postdoctoral training at the Harvard Medical School in Boston. He established his own research group back in Germany at the Max Delbrück Centre for Molecular Medicine in Berlin. Since 2002 he is a professor of Molecular Human Biology at the Ludwig Maximilians University in Munich where he is studying the role and regulation of DNA methylation in development and disease. In addition, he has developed a number of new technologies to study structure and function in living cells. These include new antibody technologies for high content analyses and target validation as well as microscopy techniques.