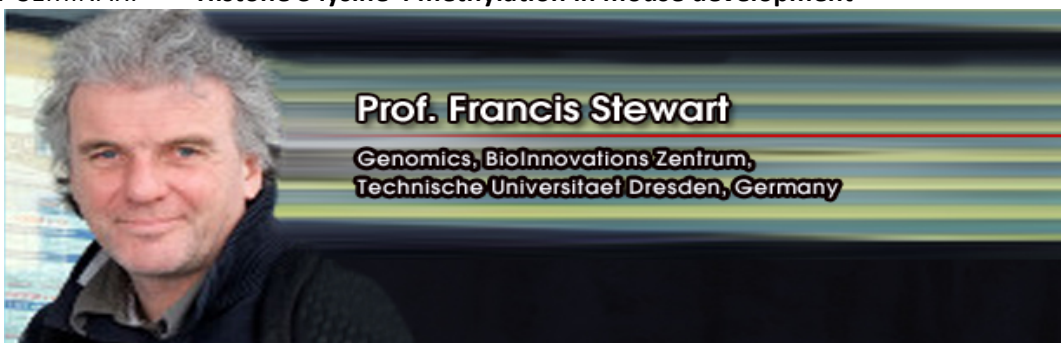
Institute of Molecular and Cell Biology
A*STAR

SEMINAR ANNOUNCEMENT

DATE: 10 February 2012, Friday
TIME / VENUE: 10:00AM @ Level 3, IMCB Seminar Room 3-46, Proteos Building, Biopolis
SPEAKER: Prof. Francis Stewart
TITLE OF SEMINAR: **Histone 3 lysine 4 methylation in mouse development**



The epigenome is reprogrammed during germ cell development and the early cleavage stages leading to the pluripotency of the epiblast, which equates with an uncommitted epigenetic state. For the regulation of gene expression, the primary epigenetic mechanism is based on a balance between activation by the Trithorax-Group and silencing by the Polycomb-Group. This opposition is reflected in part by opposing methylations at lysines 4 and 27 on the histone 3 tail of promoter nucleosomes. However these methylations can occur simultaneously to establish a bivalent promoter, which is silent but believed to be poised for a developmental decision. We are interested in understanding how the pluripotent epigenome is established. Our main focus is on the Trx-G and histone 3 lysine 4 trimethylation (H3K4me3), during mouse development. Mammals have at least six H3K4 methyltransferases related to yeast Set1 and fly Trithorax (Setd1a and b, Mll1/Kmt2a, Mll2/Kmt2b, Kmt2c and Kmt2d; ref 1). All six are found in Set1C-like complexes (2) and all six mRNAs appear to be expressed ubiquitously. We have knocked out all six to find that each appears to be uniquely required during mouse development in different ways however only one or two of them are implicated in the establishment of pluripotency. Kmt2b is required in at least two phases. During oogenesis and early development, when the epigenome is reprogrammed to establish pluripotency, Kmt2b is required for bulk H3K4me3 but not for bulk H3K4me1, indicating that mono- and tri-methylation are conveyed by different enzymes (3). However, Kmt2b is not required for bulk H3K4me3 in ES cells, later development or the adult (4), although it is apparently required for neurogenesis. In contrast, its sister gene, Mll1, is not required until the establishment of definitive haematopoiesis. By ChIP-seq and expression profiling after conditional mutagenesis, we have identified genes that are directly regulated by these factors. However these relationships appear to be at least partially cell-type specific. These data reveal not only unexpected specializations amongst H3K4 methyltransferases during mouse development but also role switching that suggests further layers of complexity in transcriptional regulation by epigenetic mechanisms.

1. Glaser S et al (2006) Multiple epigenetic maintenance factors implicated by the loss of Mll2 in mouse development. Development 133,1423 - 32.
2. Roguev A et al (2001) The S. cerevisiae Set1 complex includes an Ash2-like protein and methylates histone 3 lysine 4. EMBO J. 20, 7137-7148
3. Andreu-Vieyra CV et al (2010) Mll2 is required in oocytes for bulk H3K4 trimethylation and global transcriptional silencing. PLoS Biology, 17, 8(8).
4. Glaser S et al (2009) The H3K4 methyltransferase, Mll2, is only required briefly during development and spermatogenesis. Epigen. and Chromatin, 2:5.

Host: Prof. Stephen Cohen