Scope of thesis

Haemoglobin is the carrier of oxygen in the bloodstream. It is a tetrameric protein composed of two α-globin chains and two β-globin chains. These chains are encoded by the α- and β-globin gene loci. The globin loci are located on separate chromosomes and are composed of several developmentally regulated genes and regulatory elements located both upstream of the gene loci and around the individual genes. The α-cluster is composed of αMRE5'ζ-α_1-α_2-3' and the β-cluster consists of LCR 5'-ε-^{G}γ-^{A}γ-δ-β-3'.

Lesions in the globin clusters give rise to blood disorders known as haemoglobinopathies, such as α- and β- thalassemias, Hereditary Persistence of Foetal Haemoglobin (HPFH) and sickle cell anaemia. The study of the molecular basis of these disorders led to the identification of many regulatory elements of the globin loci, including the locus control region (LCR). The β-globin locus is one of the best-studied multi gene loci and has been extensively used as a model system for the study of gene regulation.

The aims of this thesis are to study the mechanism of transcriptional activation of the globin loci, the role of the hypersensitive sites in LCR function and the further characterisation of putative γ-globin regulatory elements.

Chapter 1, the introduction, will give a broad outline of chromatin structure and transcription, as well as detailed background on haemoglobin and the regulation of globin gene loci. Chapter 2 concentrates on fundamental aspects of the transcriptional activation process of the mouse globin gene loci, with the aim of to serve as a model system for understanding transcriptional activation in general. Chapter 3 describes the development of novel methodology that employs homologous recombination in *E. coli* in order to manipulate the entire 180 kb human β-globin locus, for example, through the introduction of specific mutations and/or deletions. Chapter 4 describes the analysis of transgenic mice with targeted deletions in the human β-globin locus which remove two elements, located 3' to the ^{A}γ-globin gene, and which have been implicated in the developmental regulation of the γ-globin gene. Chapter 5 describes an application of this technique in deleting two hypersensitive sites from the human β-globin locus LCR, with the aim of to study LCR function in chromatin organisation and gene activation. Chapter 6 is the general discussion.