Scope and outline of the thesis

The aim of this thesis was to gain a detailed understanding of transcriptional regulation in the context of the living cell. The β-globin locus was used as a model system to study the question: how distal *cis*-regulatory DNA elements communicate to activate tissue- and developmental stage-specific gene expression. This question was addressed through two different approaches. The first approach was based on the observation that globin gene transcription alternates between embryonic, fetal and adult genes in a flip-flop mechanism [111] and the assumption that direct contacts between the Locus Control Region (LCR) and gene promoters is required for transcription (looping model). To monitor these putative interactions in the living cell we distinctly tagged the human β-globin locus on both the LCR and the β-globin gene. This work is still in progress (chapter 2). In a second approach, we adopted Chromosome Conformation Capture (3C) technology [229] to measure the spatial conformation of the β-globin loci in man and mouse *in vivo* (see chapters 3 and 4). This demonstrated that spatial interactions between the LCR, actively transcribed genes and distal DNase I hypersensitive regions occur *in vivo*. Furthermore, the data support the existence of an erythroid cell-specific nuclear compartment dedicated to the transcription of the globin genes by RNA polymerase (RNAP) II, called the active chromatin hub (ACH). The ACH model provides a mechanistic framework that may improve knowledge of transcription in the 3-dimensional space of the nucleus and will be extensively discussed in the general discussion (chapter 5). The thesis starts with an introduction (chapter 1), discussing the key players involved in transcription, the nuclear architecture in relation to transcription, and β-globin gene transcription.