SUMMARY

The structure and regulation of the human β-like globin gene cluster has been studied extensively. Genetic disorders connected with this gene cluster are responsible for human diseases associated with high levels of morbidity and mortality, such as β-thalassaemia and sickle cell anaemia. The work described in this thesis is concerned with a novel tissue-specific regulatory element. The human β-globin Dominant Control Region (DCR) confers integration-site independent, copy-number related, high-level expression to a linked β-globin gene in a tissue-specific manner in transgenic mice (see Chapter 2) and mouse erythroleukemia (MEL) cells (Chapter 3). The discovery of the human β-globin DCR sequences is an important step towards somatic gene therapy for thalassaemia and sickle-cell patients (Chapter 5).

The globin DCR as originally cloned in the "mini-locus" cosmid construct spans 33kb of DNA sequences. Deletion constructs were made to determine different functional areas within the DCR sequences (Chapter 3 and 4). It is now thought that the DCR functional elements are located within defined regions (as discussed in Chapter 5) characterized by the presence of strong DNase I hypersensitive sites (Chapters 2 and 3).

The human β-globin DCR can confer high level expression to other erythroid genes, namely the human α- and γ-globin genes (Chapter 5), and non-erythroid genes such as Thy-1 and tk-neo (Chapter 3).

The recent discovery of a region 3' flanking to the human T-cell specific CD2 gene with functional properties similar to those of the human β-globin DCR (discussed in Chapter 5) suggests that expression of other tissue-specific genes might also be regulated by DCR-like elements.