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Control of globin gene switching and the search for foetal globin activating compounds

F. GROSVELD

MGC Department of Cell Biology, Erasmus University Rotterdam, PO Box 1738, 3000 DR, Rotterdam, The Netherlands

A construct containing the human γ-globin gene driving a luciferase reporter gene, was coupled to hypersensitive site 2 (HS2) of the human β-globin locus control region (LCR) and introduced into K562 (γ globin expressing) cells. These cells were screened by our industrial collaborator OSI (USA) for the upregulating of luciferase activity with a chemical library in a robotic assay. To date almost 200,000 compounds have been screened and this has yielded 8 lead compounds. Meanwhile a yeast artificial chromosome (YAC) containing the complete human β-globin locus has been retrofitted by homologous recombination in yeast to introduce a luciferase reporter gene into the γ-globin genes. This modified YAC has been transfected into K562 cells and MEL cells. The latter will provide a new and better system for compound screening as this cell expresses the β-globin gene, but not the silenced γ-globin genes and thus will provide a better assay for γ-globin reactivation. These data will be discussed in the context of our studies on the mechanism of globin gene switching and other possible approaches to the reactivation of γ-globin genes.