CLAIMS

1. An *ex vivo* method for controlling transcription of a genetic sequence in a cell comprising

a) targeted insertion of a gene encoding a transcriptional regulator protein into a first genetic safe harbour site; and

b) targeted insertion of an inducible cassette into a second genetic safe harbour site, wherein said inducible cassette comprises said genetic sequence operably linked to an inducible promoter, and said promoter is regulated by the transcriptional regulator protein;

wherein said first and second genetic safe harbour sites are different, and

wherein the method does not comprise a process for modifying the germ line genetic identity of a human being.

2. An *ex vivo* method as claimed in claim 1, wherein the genetic sequence is a transgene or encodes a non-coding RNA.

3. An *ex vivo* method as claimed in claim 1 or claim 2, wherein the activity of said transcriptional regulator protein is controlled by an exogenously supplied substance.

4. An *ex vivo* method as claimed in any one of claims 1 to 3, wherein said transcriptional regulator protein is constitutively expressed.

5. An *ex vivo* method as claimed in any preceding claim, wherein said transcriptional regulator protein is selected from any one of: tetracycline - responsive transcriptional activator protein (rtTa), Tetracycline repressor (TetR), VgEcR synthetic receptor or a hybrid transcriptional regulator protein comprising a DNA binding domain from the yeast GAL4 protein, a truncated ligand binding domain from the human progesterone receptor and an activation domain from the human NF-κB.

6. An *ex vivo* method as claimed in claim 5, wherein the activity of rtTA is controlled by tetracycline or a derivative thereof, optionally doxycycline, and wherein the inducible promoter includes a Tet Responsive Element (TRE).

7. An *ex vivo* method as claimed in any preceding claim, wherein said first and second genomic safe harbour sites are selected from any two of the hROSA26 locus, the AAVS1 locus, the *CLYBL* gene or the *CCR5* gene.

8. An *ex vivo* method as claimed in any preceding claim, wherein additional genetic material is inserted at the first/and or second genomic safe harbour sites, optionally one or more of the following:

a) suicide gene;

b) selectable marker;

c) reporter gene; and/or

d) gene for a non-coding RNA.

9. An *ex vivo* method as claimed in any preceding claim, wherein said cell is selected from a pluripotent stem cell, a somatic stem cell or a mature cell.

10. An *ex vivo* method as claimed in any preceding claim, wherein said cell is a human, marsupial, non-human primate, camelid or livestock animal cell.

11. An *ex vivo* method as claimed in claim 1 or claim 2, wherein said method is for the programming of pluripotent stem cells into defined mature cells.

12. An *ex vivo* method as claimed in claim 1 or claim 2, wherein said cell is a pluripotent stem cell and said genetic sequence is a transgene for one or more master regulators, optionally a transcription factor, and optionally wherein the transcription of said genetic sequence results in the forward programming of the cell into a defined mature cell type.

13. An *ex vivo* method as claimed in claim 1, wherein said method is for the insertion of a genetic sequence for the purposes of gene therapy, optionally wherein the genetic sequence encodes a protein including a wild-type protein, a modified protein, an antigen, an enzyme, a selectable marker or a non-coding RNA molecule.

14. A cell made by the method of claim 1.

15. A cell with a modified genome that comprises an inserted gene encoding a transcriptional regulator protein into a first genetic safe harbour site; and an inserted inducible cassette comprising a genetic sequence operably linked to an inducible promoter into a second genetic safe harbour site, wherein said inducible promoter is regulated by the transcriptional regulator protein and said first and second sites are different.

16. A cell as claimed in claim 14 or claim 15, for use in therapy, or use of a cell as claimed in claim 14 or claim 15 for *in vitro* diagnostics or for tissue engineering.

17. An *ex vivo* method for the production of myocytes from pluripotent stem cells, comprising the steps of:

a) targeted insertion of a gene encoding a transcriptional regulator protein into a first genetic safe harbour site; and

b) targeted insertion of the *MYOD1* gene operably linked to an inducible promoter into a second genetic safe harbour site, wherein said inducible promoter is regulated by the transcriptional regulator protein; wherein said first and second genetic safe harbour sites are different,

and culturing said cells in the presence of retinoic acid,

wherein the method does not comprise a process for modifying the germ line genetic identity of a human being.

18. An *ex vivo* method for the production of oligodendrocytes from pluripotent stem cells, comprising the steps of:

a) targeted insertion of a gene encoding a transcriptional regulator protein into a first genetic safe harbour site; and

b) targeted insertion of the *SOX-10* gene operably linked to an inducible promoter into a second genetic safe harbour site, wherein said inducible promoter is regulated by the transcriptional regulator protein; wherein said first and second genetic safe harbour sites are different,

and culturing said cells in the presence of retinoic acid,

wherein the method does not comprise a process for modifying the germ line genetic identity of a human being.

19. An *ex vivo* method for reducing the transcription and/or translation of an endogenous gene in a cell, comprising the following steps:

a) targeted insertion of a gene encoding a transcriptional regulator protein into a first genetic safe harbour site; and

b) targeted insertion of an inducible cassette into a second genetic safe harbour site, wherein said inducible cassette comprises DNA encoding a non-coding RNA sequence operably linked to an inducible promoter and said promoter is regulated by the transcriptional regulator protein and wherein said non-coding RNA sequence suppresses the transcription or translation of an endogenous gene;

wherein said first and second genetic safe harbour sites are different, and

wherein the method does not comprise a process for modifying the germ line genetic identity of a human being.

20. An *ex vivo* method for knocking out an endogenous gene in a cell, comprising the following steps:

a) targeted insertion of a gene encoding a transcriptional regulator protein and a gene encoding Cas9 into a first genetic safe harbour site; and

b) targeted insertion of an inducible cassette into a second genetic safe harbour site, wherein said inducible cassette comprises a guide RNA operably linked to an inducible promoter and said promoter is regulated by the transcriptional regulator protein and wherein said gRNA sequence targets the endogenous gene;

wherein said first and second genetic safe harbour sites are different, and

wherein the method does not comprise a process for modifying the germ line genetic identity of a human being.