

CLAIMS

We claim:

1. A method of enhancing thymic regeneration, the method comprising administering an effective amount of a therapeutic composition comprising engineered non-thymic endothelial cells (ntECs) to a subject in need of thymic regeneration, wherein the engineered ntECs are either E4ORF1+ or BMP4+E4ORF1+, thereby enhancing thymic regeneration in the subject.
2. The method of claim 1, wherein the thymic regeneration comprises recovery of at least one cell type from among CD45- thymic stromal cells and CD45+ T cells.
3. The method of claim 1, wherein the thymic regeneration comprises recovery of both CD45- thymic stromal cells and CD45+ T cells.
4. The method of claim 2 or claim 3, wherein the CD45- thymic stromal cells are selected from the group consisting of thymic epithelial progenitors (TEPCs), cortical thymic epithelial cells (cTECs), and medullary thymic epithelial cells (mTECs).
5. The method of claim 2 or claim 3, wherein the CD45+ T cells are selected from the group consisting of CD3+ T cells, CD4+ T cells, CD8+ T cells, double-positive T cells (DP), double-negative T cells (DN), double-negative type 1 (DN1) T cells, double-negative type 2 (DN2) T cells, double-negative type 3 (DN3) T cells and double-negative type 4 (DN4) T cells.
6. The method of any of the preceding claims, wherein the ntECs are selected from the group consisting of: umbilical vein endothelial cells (UVECs), adipose endothelial cells, skin endothelial cells, lung endothelial cells, heart endothelial cells, kidney endothelial cells and bone marrow endothelial cells.
7. The method of any of the preceding claims, wherein the subject is a human.
8. The method of any of the preceding claims, wherein the ntECs are human umbilical vein endothelial cells (HUVECs).

9. The method of any of the preceding claims, wherein the ntECs are autologous to the subject.
10. The method any of claims 1-8, wherein the ntECs are allogeneic to the subject.
11. The method of any of the preceding claims, wherein the ntECs are MHC/HLA-matched to the subject.
12. The method of any of the preceding claims, wherein the subject has previously been treated with chemotherapy, radiation therapy, a pre-transplantation conditioning regimen, or a myeloablative conditioning regimen.
13. The method of any of the preceding claims, wherein the subject has an immunodeficiency.
14. The method of claim 13, wherein the subject has an HIV infection.
15. The method of any of the preceding claims, wherein the subject has an ageing-related deficiency in thymic tissue mass, thymic function, or T-cell production.
16. The method of any of the preceding claims, wherein the engineered ntECs are administered to the subject by IV infusion.
17. The method of any of the preceding claims, wherein the engineered ntECs are administered to the subject in multiple IV infusions over the course of several days or weeks.
18. The method of any of the preceding claims, further comprising administering to the subject a therapeutic composition comprising hematopoietic stem cells (HSCs).
19. The method of claim 18, wherein engineered ntECs and the HSCs are administered concurrently.
20. The method of claim 18, wherein engineered ntECs and the HSCs are administered to the subject in the same IV infusion.
21. The method of any of the preceding claims, further comprising an initial step of genetically modifying ntECs by transducing or transfecting the ntECs *ex vivo* with a

nucleic acid molecule encoding E4ORF1 and optionally a nucleic acid molecule encoding BMP4, prior to administering the ntECs to the subject.

22. The method of any of the preceding claims, further comprising an initial step of genetically modifying autologous ntECs from the subject by transducing or transfecting the ntECs *ex vivo* with a nucleic acid molecule encoding E4ORF1 and optionally a nucleic acid molecule encoding BMP4, prior to administering the autologous ntECs to the subject.
23. An isolated population of engineered BMP4+E4ORF1+ non-thymic endothelial cells (ntECs).
24. The population of engineered ntECs of claim 23, wherein the population is a substantially pure population.
25. The population of engineered ntECs of claim 23, wherein the ntECs comprise a recombinant nucleic acid molecule that comprises a nucleotide sequence that encodes BMP4.
26. The population of ntECs of claim 25, wherein the nucleotide sequence that encodes BMP4 is operatively linked to a heterologous promoter.
27. The population of ntECs of claim 25, wherein the ntECs comprise a recombinant nucleic acid molecule that comprises a nucleotide sequence that encodes E4ORF1.
28. The population of ntECs of claim 27, wherein the nucleotide sequence that encodes E4ORF1 is operatively linked to a heterologous promoter.
29. The population of ntECs of any of claims 25-28, wherein the recombinant nucleic acid molecule is an expression vector.
30. The population of ntECs of claim 29, wherein the expression vector is a viral vector.
31. The population of ntECs of claim 29, wherein the expression vector is a lentiviral vector.
32. The population of ntECs of claim 29, wherein the expression vector is a retroviral vector.

33. The population of ntECs of any of claims 23-32, wherein the ntECs are selected from the group consisting of: human umbilical vein endothelial cells (HUVECs), adipose endothelial cells, skin endothelial cells, lung endothelial cells, heart endothelial cells, kidney endothelial cells and bone marrow endothelial cells.
34. The population of ntECs of any of claims 23-32, wherein the ntECs are human umbilical vein endothelial cells (HUVECs).
35. A composition comprising a population of ntECs according to any of claims 23-34.
36. A therapeutic composition comprising a population of ntECs according to any of claims 23-34 and a solution suitable for administration to a subject.
37. A therapeutic composition comprising a population of ntECs according to any of claims 23-34 and a biocompatible matrix material.
38. A therapeutic composition according to claim 37, wherein the biocompatible matrix material is a liquid.
39. A therapeutic composition according to claim 37, wherein the biocompatible matrix material is a solid.