temperature is lowered, and the cells detach. Unlike enzymatic treatments, this method of detachment may reduce the risk of damage to the physiology of the cell. In *Cell Transplantation*, Vol. 19, pp. 1123-1132, 2010, the thermosensitive polymer, PNIPAAm, is conjugated onto microcarrier beads having a diameter of 170 to 380 microns.

SUMMARY

[0005a] In one aspect, the present disclosure refers to a macrocarrier for the propagation of biological cells, said macrocarrier comprising substrate particles that are coated with a thermoresponsive polymer that provides the macrocarrier with a cell-receiving surface and responding to a change in temperature to release cells from the macrocarrier, wherein: the cell-receiving surface is porous; each substrate particle has a spherical, ellipsoid, ovoid or ring shape; and at least 50% of the substrate particles have a particle size of at least 1 mm, wherein the particle size is the largest linear dimension across the substrate particle.

[0005b] In another aspect, the present disclosure refers to a system for the propagation of biological cells, said system comprising a bio-reactor and a microcarrier as disclosed herein.

[0005c] In another aspect, the present disclosure refers to a process for the propagation of biological cells, said process comprising: a. contacting biological cells with a macrocarrier as disclosed herein in a cell culturing medium; b. propagating the cells on the macrocarrier by subjecting the macrocarrier to a temperature at which the thermoresponsive polymer presents a cell-receiving surface; and c. altering the temperature of the macrocarrier to release any propagated cells from the macrocarrier.

BRIEF DESCRIPTION OF THE FIGURES

[0006] Aspects of the present disclosure are shown schematically, by way of example only, in the accompanying drawings, in which:

[0007] Figure 1 is a schematic diagram of thermo-responsive polymer grafting onto the surfaces of PCL and the temperature-dependent effect of cell attachment to and detachment from the grafted surface;

[0008] Figures 2a and 2b show FTIR and XPS spectra showing the conjugation of PNIPAAm-NH_2 to the surface of PCL beads;

[0009] Figure 3 shows cell proliferation on macrocarrier surfaces;

[0010] Figures 4a and 4b show cell detachment and cell viability data of cells detached from macrocarrier surfaces (i.e. trypsinization vs. reduced temperature comparison of cell detachment ratio and viability);

[0011] Figure 5 shows recovered cell proliferation comparisons between different cells detached by reduced temperature and trypsinization;

[0012] Figure 6 is a Western blot analysis of proteins collected from cells grown on tissue culture plates and thermoresponsive macrocarriers; the cells were detached by trypsin-EDTA and by reducing the temperature;

[0013] Figure 7 is a diagram containing a series of images that show the preparation of PCL pellets;

[0014] Figure 8 shows SEM images of PCL beads that were prepared according to the method described in Example 2 and SEM images of PCL beads that are commercially available;

[0015] Figure 9 shows an SEM image of PCL beads and a series of histograms showing the size distribution of the beads;

[0016] Figure 10 show FTIR and XPS spectra of PCL beads that were prepared according to the method described in Example 2 and PCL beads that are commercially available;

Claims

1. A macrocarrier for the propagation of biological cells, said macrocarrier comprising substrate particles that are coated with a thermoresponsive polymer that provides the macrocarrier with a cell-receiving surface and responding to a change in temperature to release cells from the macrocarrier, wherein:
the cell-receiving surface is porous;
each substrate particle has a spherical, ellipsoid, ovoid or ring shape; and
at least 50% of the substrate particles have a particle size of at least 1 mm, wherein the particle size is the largest linear dimension across the substrate particle.

2. A macrocarrier as claimed in claim 1, wherein at least 50% of the substrate particles have a particle size of 1 to 10 mm.

3. A macrocarrier as claimed in claim 2, wherein at least 50% of the substrate particles have a particle size of 2 to 6 mm.

4. A macrocarrier as claimed in any one of the preceding claims, wherein at least 70% of the substrate particles have a particle size of 1 to 10 mm.

5. A macrocarrier as claimed in claim 4, wherein at least 70% of the substrate particles have a particle size of 2 to 6 mm.

6. A macrocarrier as claimed in any one of the preceding claims, wherein at least 90% of the substrate particles have a particle size of 1 to 10 mm.

7. A macrocarrier as claimed in claim 6, wherein at least 90% of the substrate particles have a particle size of 2 to 6 mm.

8. A macrocarrier as claimed in any one of the preceding claims, wherein the substrate particles are partially coated with the thermoresponsive polymer.

9. A macrocarrier as claimed in any one of the preceding claims, wherein the substrate particle is formed of a biocompatible material, wherein the material is biocompatible according to ISO 10993 and optionally is selected from polysaccharide, protein, glass, polystyrene, polyester, polyolefin, silica, silicone, polyacrylamide and polyacrylate.

10. A macrocarrier as claimed in any one of the preceding claims, wherein the substrate particle comprises polycaprolactone.

11. A macrocarrier as claimed in any one of the preceding claims, wherein the thermo-responsive polymer provides the macrocarrier with a cell-receiving surface above a

threshold temperature and releases cells from the macrocarrier below the threshold temperature.

12. A macrocarrier as claimed in claim 11, wherein the threshold temperature is a temperature of 20 to 40 degrees C.

13. A macrocarrier as claimed in claim 1, wherein the thermoresponsive polymer is capable of transforming from a hydrophilic, cell-receiving state to a hydrophobic, cell-releasing state in response to a change in temperature.

14. A macrocarrier as claimed in any one of the preceding claims, wherein the thermoresponsive polymer comprises poly(N-isopropyl acrylamide) (PNIPAAm).

15. A macrocarrier as claimed in claim 11, wherein the substrate particles comprise polycaprolactone and wherein the poly(N-isopropyl acrylamide) (PNIPAAm) is coupled to the polycaprolactone via an amide linkage.

16. A macrocarrier as claimed in any one of the preceding claims, which further comprises biological cells attached to the thermoresponsive polymer.

17. A macrocarrier as claimed in claim 16, wherein the biological cells are selected from mesenchymal stem cells (“MSCs”), human dermal fibroblasts (“HDFs”), human umbilical vein endothelial cells (HUVEC) and neuroblastoma Sy5y cells.

18. A system for the propagation of biological cells, said system comprising a bio-reactor and a macrocarrier as claimed in any one of claims 1 to 17.

19. A process for the propagation of biological cells, said process comprising:
    a. contacting biological cells with a macrocarrier as claimed in any one of claims 1 to 17 in a cell culturing medium;
    b. propagating the cells on the macrocarrier by subjecting the macrocarrier to a temperature at which the thermoresponsive polymer presents a cell-receiving surface; and
    c. altering the temperature of the macrocarrier to release any propagated cells from the macrocarrier.

20. A process as claimed in claim 19, wherein the biological cells are contacted with the macrocarrier in a bioreactor.

21. A process as claimed in claim 19 or 20, wherein the macrocarrier is exposed to a first temperature of 20 to 40 degrees to propagate the cells, and wherein the temperature of the macrocarrier is reduced below the first temperature to release the propagated cells.