culture supports and subsequently harvesting the expanded MSCs from the cell culture supports using enzymatic digestion and/or mechanical dissociation. However, such harvesting procedures have detrimental impacts on the MSCs, and the MSCs obtained as such generally require a recovery time from the harvesting procedure before resuming their full functional potential. Thus, it is an object of the present invention to provide alternative methods to produce implantable constructs, preferably those containing stem cells such as MSCs, for use in the therapeutic treatment of cartilage diseases and bone diseases.

SUMMARY

[0007] In one aspect, the present disclosure refers to a method of manufacturing an implantable construct comprising chondrogenically differentiated cells and one or more polycaprolactone (PCL) microcarriers, the method comprises: a) culturing mesenchymal stromal cells with one or more PCL microcarriers in a suspension culture in a mesenchymal stromal cells growth medium to allow the mesenchymal stromal cells to attach to the PCL microcarriers to form one or more mesenchymal stromal cells-PCL microcarrier complexes, wherein the suspension culture is agitated; b) harvesting the one or more mesenchymal stromal cells-PCL microcarrier complexes from the suspension culture in a) while the suspension culture is agitated; c) culturing the one or more mesenchymal stromal cells-PCL microcarrier complexes from b) under agitation-free and centrifugation-free conditions in the mesenchymal stromal cells growth medium; d) culturing the one or more mesenchymal stromal cells-PCL microcarrier complexes from c) under agitation-free and centrifugation-free conditions in a chondrogenic differentiation medium to enact differentiation of the mesenchymal stromal cells into chondrogenically differentiated cells, wherein b) is carried out during the early log phase of a), wherein the confluency of mesenchymal stromal cells on the microcarriers at the early log phase is at 20% to 30%.

[0008] In another example, the present disclosure refers to an implantable construct comprising chondrogenically differentiated cells and one or more PCL microcarriers, produced using the method as described above. In another example, there is provided an implantable construct comprising chondrogenically differentiated cells and one or more PCL microcarriers, wherein the number of chondrogenically differentiated cells per PCL microcarrier is 10 to 30.

[0009] In another example, the present disclosure refers to the use of the implantable construct as disclosed herein in the manufacture of a medicament for treating a disease or disorder associated with cartilage defect. In an example, there is provided a method of treating a disease or disorder associated with cartilage defect, the method comprises administering the implantable construct as described above in a patient suffering from the disease or disorder. In another example, the present disclosure refers to the use of the implantable construct as disclosed herein in the manufacture of a medicament for promoting cartilage tissue regeneration in a patient in need thereof.

CLAIMS

1. A method of manufacturing an implantable construct comprising chondrogenically differentiated cells and one or more polycaprolactone (PCL) microcarriers, the method comprises:

a) culturing mesenchymal stromal cells with one or more PCL microcarriers in a suspension culture in a mesenchymal stromal cells growth medium to allow the mesenchymal stromal cells to attach to the PCL microcarriers to form one or more mesenchymal stromal cells-PCL microcarrier complexes, wherein the suspension culture is agitated;

b) harvesting the one or more mesenchymal stromal cells-PCL microcarrier complexes from the suspension culture in a) while the suspension culture is agitated;

c) culturing the one or more mesenchymal stromal cells-PCL microcarrier complexes from b) under agitation-free and centrifugation-free conditions in the mesenchymal stromal cells growth medium;

d) culturing the one or more mesenchymal stromal cells-PCL microcarrier complexes from c) under agitation-free and centrifugation-free conditions in a chondrogenic differentiation medium to enact differentiation of the mesenchymal stromal cells into chondrogenically differentiated cells,

wherein b) is carried out during the early log phase of a),

wherein the confluency of mesenchymal stromal cells on the microcarriers at the early log phase is at 20% to 30%.

2. The method of claim 1, wherein the number of mesenchymal stromal cells to be cultured in a) is 3×10^4 to 7×10^4, or 4.5×10^4 to 5.5×10^4, or about 5×10^4 per construct of PCL microcarriers.

3. The method of claim 1, wherein the early log phase of a) is 2.5 to 3.5 days, or about 3 days from starting the culturing in a).

4. The method of any one of claims 1 to 3, wherein the confluency is about 21%.

5. The method of any one of claims 1 to 4, wherein c) and/or d) comprises culturing the one or more mesenchymal stromal cell-microcarrier complexes in an adherent culture on a support surface.

6. The method of claim 5, wherein the support surface is a low adhesion support surface.

7. The method of any one of claims 1 to 6, wherein c) comprises culturing the one or more mesenchymal stromal cell-microcarrier complexes for about 1 day, or 18 to 24 hours.

8. The method of any one of claims 1 to 7, wherein d) comprises culturing the one or more mesenchymal stromal cell-microcarrier complexes from c) for 14 days to 28 days, or for 21 days to 28 days, or for about 28 days.

9. The method of claim 1, comprising:

a) culturing about 5×10^4 mesenchymal stromal cells with one construct of PCL microcarriers in a suspension culture in a mesenchymal stromal cells growth medium for 2.5 to 3.5 days or until the confluency of the mesenchymal stromal cells is about 21%, to allow the mesenchymal stromal cells to attach to the PCL microcarriers to form mesenchymal stromal cells-PCL microcarrier complexes, wherein the suspension culture is agitated;

b) harvesting the mesenchymal stromal cells-PCL microcarrier complexes from the suspension culture in a) while the suspension culture is agitated;

c) culturing the mesenchymal stromal cells-PCL microcarrier complexes from b) under agitation-free and centrifugation-free conditions in the mesenchymal stromal cells growth medium for 0.5 to 1.5 days;

d) culturing the mesenchymal stromal cells-PCL microcarrier complexes from c) under agitation-free and centrifugation-free conditions in a chondrogenic differentiation medium for 14 days to 28 days to enact differentiation of the mesenchymal stromal cells into chondrogenically differentiated cells.