is known as senescence, and may limit the lifetime of propagation of cells from an initial sample of a primary cell of interest.

Moreover, connective tissues such as bone, cartilage, skin, nerve, lung, muscle, and many others contain cells that secrete and organize extracellular matrix (ECM) proteins to create scaffolds to allow cells to migrate, proliferate, and organize to form tissues. The interplay between the organization of composition and structure of ECM is well documented. However, approaches for developing interfaces between such different cell types for therapeutic purposes or for analysis is currently lacking.

Therefore, there remains a need in the art for flexible platforms for methods of growing one more cells of interest, such as the growth of interfaces between different cell types of interest.

SUMMARY

One or more examples of the disclosure may address one or more of the aforementioned problems. Certain examples according to the disclosure provide a method of growing tissue cells *ex vivo*, in which the method may comprise the following: (i) interlocking together a plurality of interlocking porous hydrogel blocks (IPHB) including a first IPHB and a second IPHB, wherein each of the plurality of IPHBs include a respective three-dimensional (3D) macrostructure defined by a respective continuous polymeric matrix material and a respective network of microporous channels and/or chambers extending throughout the respective continuous polymeric matrix material, and wherein the respective 3D macrostructures each comprise a respective top surface, a respective bottom surface, and a respective thickness defined by at least one respective side edge extending from the respective top surface to the respective bottom surface, and wherein the respective 3D macrostructure structures each include at least one respective interlocking-male component and at least one respective interlocking-female component; (ii) seeding the first IPHB with a first cell type of interest; (iii) seeding the second IPHB with a second cell type of interest, wherein the first cell type of interest is different than the second cell type of interest; (iv) feeding the first cell type of interest with a first culture media, and allowing the first cell type of interest to propagate throughout a first network of microporous channels and/or chambers towards the second IPHB; (v) feeding the second cell type of interest with a second culture media, and allowing the second cell type of interest to propagate throughout a second network of microporous channels and/or chambers towards the first IPHB; and (vi) forming a first interface between the first cell type and the second cell type. In accordance with certain

THAT WHICH IS CLAIMED:

1. A method of growing of tissue *ex vivo* cells, comprising:

(i) interlocking together a plurality of interlocking porous hydrogel blocks (IPHB) including a first IPHB and a second IPHB, wherein each of the plurality of IPHBs include a respective three-dimensional (3D) macrostructure defined by a respective continuous polymeric matrix material and a respective network of microporous channels and/or chambers extending throughout the respective continuous polymeric matrix material, and wherein the respective 3D macrostructures each comprise a respective top surface, a respective bottom surface, and a respective thickness defined by at least one respective side edge extending from the respective top surface to the respective bottom surface, and wherein the respective 3D macrostructure structures each include at least one respective interlocking-male component and at least one respective interlocking-female component;

(ii) seeding the first IPHB with a first cell type of interest;

(iii) seeding the second IPHB with a second cell type of interest, wherein the first cell type of interest is different than the second cell type of interest;

(iv) feeding the first cell type of interest with a first culture media, and allowing the first cell type of interest to propagate throughout a first network of microporous channels and/or chambers towards the second IPHB;

(v) feeding the second cell type of interest with a second culture media, and allowing the second cell type of interest to propagate throughout a second network of microporous channels and/or chambers towards the first IPHB; and

(vi) forming a first interface between the first cell type and the second cell type.

2. The method of claim 1, wherein the first network of microporous channels and/or chambers has a first structure and the second network of microporous channels and/or chambers, wherein the first structure is different than the second structure.

3. The method according to any one of claims 1-2, wherein the first network of microporous channels and/or chambers, the second network of microporous channels and/or chambers, or both have (i) an average diameter comprising from 100 to 800 microns, such as at least about any of the following: 100, 120, 150, 180, 200, 220, and 250 microns, and/or at most about any of the following: 800, 780, 750, 720, 700, 680, 650, 620, 600, 580, 550, 520, 500, 480, 450, 420, 400, 380, 350, 320, 300, 280, and 250 microns; (ii) independently from each other comprises at least about 40% by volume of the respective 3D macrostructure, such as from at least about any of the following: 40, 50, 60, and 70% by volume of the respective 3D macrostructure, and/or at most about any of the following: 90, 85, 80, 75, and 70% by volume of the respective 3D macrostructure; or (iii) both (i) and (ii).

4. The method according to any one of claims 1-3, wherein a first continuous polymeric matrix material of the first IPHB and/or the second continuous polymeric matrix material comprises a non-degradable hydrogel material or a selectably degradable hydrogel material.

5. The method according to claim 4, wherein the first continuous polymeric matrix material of the first IPHB, the second continuous polymeric matrix material of the second IPHB, or both comprise a non-degradable hydrogel material comprising one or more synthetic polymers, such as synthetic polymers derived from petroleum.

6. The method according to claim 4, wherein the first continuous polymeric matrix material of the first IPHB, the second continuous polymeric matrix material of the second IPHB, or both comprise a selectably degradable hydrogel material comprising one or more degradable polymers, such as one or more biopolymers derived from a living organism.

7. The method of claim 6, wherein the one or more biopolymers comprises collagen, gelatin, laminin, alginate, glycosaminoglycans, oligonucleotides (e.g., DNA, RNA),

carbohydrates, lipids, cellulose, alginate, and proteins that can be gently and degraded, such as with the use of protein specific enzymes, ionic solvents, neutral detergents, weak acids, and peroxides to disrupt the biopolymer chains.

8. The method according to any one of claims 6-7, wherein the selectably degradable hydrogel material further comprises a synthetic polymer, such as a polyester, a polyanhydride, a polycarbonate, a polyurethane, a polyphosphate or combinations thereof.

9. The method according to any one of claims 1-8, further comprising interlocking a third IPHB directly to the second IPHB, and seeding the third IPHB with a third cell type of interest, wherein the third cell type of interest is different that the first cell type of interest and the second cell type of interest, and further comprising a step of feeding the third cell type of interest with a third culture media, and allowing the third cell type of interest to propagate throughout a third network of microporous channels and/or chambers towards the second IPHB; and forming a second interface between the first cell type and the second cell type.

10. The method according to any one of claims 1-9, further comprising a step of harvesting at least a portion of first cells from the first cell type of interest located throughout the first network of microporous channels and/or chambers of the first IPHB.

11. The method of claim 10, wherein the first continuous polymeric matrix material of the first IPHB comprise a non-degradable hydrogel material, and the step of harvesting comprises forming artificial tissue samples by cutting the first IPHB into a plurality of sections exposing at least a portion of the cells of the first cell type of interest at a surface of the artificial tissue sample.

12. The method of claim 11, further comprises freezing the first IPHB before or after forming artificial tissue samples.

13. The method according to any one of claims 11-12, wherein the second continuous polymeric matrix material of the second IPHB comprise a non-degradable hydrogel material, and the step of harvesting comprises harvesting (i) at least a portion of first cells from the first cell type of interest located throughout the first network of microporous channels and/or chambers of the first IPHB, (ii) at least a portion of second cells from the second cell type of interest located throughout the second network of microporous channels and/or chambers of the second IPHB, and (iii) at least a portion of first interfacing cells forming the first interface by forming multi-cell containing artificial tissue samples by cutting the interlocked first IPHB and second IPHB into a plurality of sections exposing the cells of (i)-(iii) at a surface of each multi-cell containing artificial tissue sample.

14. The method of claim 13, further comprises freezing the interlocked first IPHB and second IPHB before or after forming each multi-cell containing artificial tissue sample.

15. The method of claim 13, wherein the third continuous polymeric matrix material of the third IPHB comprise a non-degradable hydrogel material, and the step of harvesting comprises additionally harvesting (iv) at least a portion of third cells from the third cell type of interest located throughout the third network of microporous channels and/or chambers of the third IPHB, and (v) at least a portion of second interfacing cells forming the second interface by forming multi-cell containing artificial tissue samples by cutting the interlocked first IPHB, second IPHB, and third IPHB into a plurality of sections exposing the cells of (i)-(v) at the surface of each multi-cell containing artificial tissue sample.

16. The method of claim 15, further comprises freezing the interlocked first IPHB, second IPHB, and third IPHB before or after forming each multi-cell containing artificial tissue sample.

17. The method of claim 10, wherein the step of harvesting at least a portion of first cells from the first cell type of interest located throughout the first network of microporous channels and/or chambers of the first IPHB comprises (i) flushing them out of the first IPHB with a fluid medium, or (ii) degrading the 3D macrostructure of the first IPHB.

18. The method according to any one of claims 1-17, wherein (i) the first cell type of interest produces or secretes a first therapeutic of interest, such as a first biologic; (ii) the second cell type of interest produces or secretes a second therapeutic of interest, such as a second biologic; (iii) wherein the third cell type of interest produces or secretes a third therapeutic of interest, such as a third biologic; or (iv) any combination of claims (i), (ii), and (iii).

19. The method according to any one of claims 1-18, further comprising positioning or interlocking a first acellular substrate directly adjacent the first IPHB or directly between the first IPHB and the second IPHB, wherein the first acellular substrate comprises an acellular 3D macrostructure defined by a continuous matrix of extracellular matrix (ECM) material associated with a first cell type of interest and network of microporous channels and/or chambers extending throughout the continuous matrix of ECM material associated with a first cell type of interest, and wherein the acellular 3D macrostructure comprises a top surface, a bottom surface, and a thickness defined by at least one side edge extending from the top surface to the bottom surface.

20. The method of claim 19, wherein the first acellular substrate further comprises at least one interlocking-male component and at least one interlocking-female component, and wherein the method further comprises seeding the first acellular substrate with a fourth cell type of interest, wherein the fourth cell type of interest is different than the first cell type of interest and the second cell type of interest.

21. The method of claim 20, further comprising feeding the fourth cell type of interest with a fourth culture media, and allowing the fourth cell type of interest to propagate throughout the network of microporous channels and/or chambers extending throughout the continuous matrix of ECM material towards the first IPHB, and forming a third interface between the first cell type of interest and the fourth cell type of interest.

22. The method according to any one of claims 19-21, further comprising a step of harvesting at least a portion of fourth cells from the fourth cell type of interest located throughout the network of microporous channels and/or chambers extending throughout the continuous matrix of ECM material, wherein the step of harvesting comprises forming artificial tissue samples by cutting the first acellular substrate into a plurality of sections exposing at least a portion of the fourth cells of the fourth cell type of interest at a surface of the artificial tissue sample.

23. The method of claim 22, wherein the step of harvesting comprises harvesting (i) at least a portion of first cells from the first cell type of interest located throughout the first network of microporous channels and/or chambers of the first IPHB, (ii) at least a portion of fourth cells from the fourth cell type of interest located throughout network of microporous channels and/or chambers extending throughout the continuous matrix of ECM material of the first acellular substrate, and (iii) at least a portion of third interfacing cells forming the third interface by forming multi-cell containing artificial tissue samples by cutting the interlocked or adjacent first IPHB and first acellular substrate into a plurality of sections exposing the cells of (i)-(iii) at a surface of each multi-cell containing artificial tissue sample.