

WHAT IS CLAIMED IS:

1. A tissue replacement implant comprising photoreceptor precursor cells (PRP) and/or photoreceptor cells (PR) in combination with retinal pigment epithelium cells (RPE) on a biodegradable scaffold.
2. The tissue replacement implant of claim 1, wherein the implant is defined, xeno-free, and feeder-free.
3. The tissue replacement implant of claim 1 or 2, wherein the RPE are mature RPE expressing Bestrophin-1 (BEST1) and/or ZO-1.
4. The tissue replacement implant of any of claims 1-3, wherein the RPE are polarized.
5. The tissue replacement implant of any of claims 1-4, wherein the PR/PRP and RPE are in a bilayer.
6. The tissue replacement implant of claim 1-5, wherein bilayer PR/PRP are attached to RPE via cell-cell contact or attachment to a shared matrix.
7. The tissue replacement implant of any of claims 1-6, wherein the biodegradable scaffold comprises poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLLA), polycaprolactone (PCL), poly(glycerol sebacate) (PGS), polypyrrole (PPy), polyvinyl alcohol (PVA), gelatin, collagen, laminin, fibronectin, fibrin, hyaluronic acid, silk, chitosan, and/or polyhydroxyethylmethacrylate (PHEMA).
8. The tissue replacement implant of claim 1-7, wherein the biodegradable scaffold comprises PLGA.
9. The tissue replacement implant of claim 8, wherein the PLGA has a DL-lactide/glycolide ratio of about 1:1.

10. The tissue replacement implant of any of claims 8-9, wherein the PLGA has an average pore size of less than about 1 micron.
11. The tissue replacement implant of any of claims 8-10, wherein the PLGA has a fiber diameter of about 150 to about 650 nm.
12. The tissue replacement implant of any of claims 1-11, wherein the biodegradable scaffold is coated with an extracellular matrix (ECM) protein.
13. The tissue replacement implant of claim 12, wherein the ECM protein comprises vitronectin, laminin, collagen I, collagen IV, or fibronectin.
14. The tissue replacement implant of claim 13, wherein the ECM protein comprises vitronectin.
15. The tissue replacement implant of any of claims 1-14, wherein the biodegradable scaffold is about 20 to about 30 microns in thickness.
16. The tissue replacement implant of any claims 1-15, wherein the PR/PRP and RPE are present in a ratio of about 2:1 to about 30:1.
17. The tissue replacement implant of any claims 1-16, wherein PR/PRP and RPE are present in a ratio about 1:1 to about 5:1.
18. The tissue replacement implant of any of claims 1-17, wherein the RPE and/or the PR/PRP are derived from pluripotent stem cells (PSCs).
19. The tissue replacement implant of claim 18, wherein PSCs are induced pluripotent stem cells (iPSCs) or embryonic stem cells (ESCs).
20. The tissue replacement implant of claim 19, wherein the iPSCs are universal, HLA-matched, or hypo-immune iPSCs.

21. The tissue replacement implant of claim 19, wherein the iPSCs are human iPSCs (hiPSCs).
22. The tissue replacement implant of any of claims 1-21, wherein PR/PRP were not derived from organoids.
23. The tissue replacement implant of any of claims 1-21, wherein the RPE and/or the PR/PRP have been previously cryopreserved.
24. The tissue replacement implant of claim 23, wherein the cryopreserved RPE and/or PR/PRP have been thawed and cultured for at least one week.
25. The tissue replacement implant of claim 23, wherein the cryopreserved RPE and/or PR/PRP have been thawed and cultured for less than one week.
26. The tissue replacement implant of any of claims 1-24, wherein the RPE are present at a density of about 100,000 cells/cm² to about 1,000,000 cells/cm².
27. The tissue replacement implant of any of claims 1-26, wherein the RPE are present at a density of about 300,000 cells/cm² to about 800,000 cells/cm².
28. The tissue replacement implant of any of claims 1-27, wherein the PR/PRP are present at a density of about 100,000 cells/cm² to about 10,000,000 cells/cm².
29. The tissue replacement implant of any of claims 1-28, wherein the PR/PRP are present at a density of about 300,000 cells/cm² to about 5,000,000 cells/cm².
30. The tissue replacement implant of any of claims 1-29, wherein the PR/PRP are present at a density of about 4 million cells/cm².
31. The tissue replacement implant of any of claims 1-30, wherein the RPE and/or the PR/PRP are from same donor.

32. The tissue replacement implant of any of claims 1-31, wherein the PR/PRP are rod-predisposed.
33. The tissue replacement implant of any of claims 1-31, wherein the PR/PRP are cone-predisposed.
34. A pharmaceutical composition comprising the tissue replacement implant of any of claims 1-33.
35. The pharmaceutical composition of claim 34, further comprising sodium hyaluronate.
36. The pharmaceutical composition of claim 35, wherein the hyaluronate is present at a concentration of less than about 0.5%.
37. The pharmaceutical composition of any of claims 34-36, further comprising sodium bicarbonate, calcium chloride, potassium chloride, potassium phosphate monobasic, magnesium chloride, magnesium sulfate, sodium chloride, and/or sodium phosphate dibasic.
38. A method for producing the tissue replacement implant of any of claims 1-33 comprising:
 - (a) seeding RPE on a biodegradable scaffold;
 - (b) culturing the RPE on the biodegradable scaffold in a first tissue culture medium for a period of time sufficient to produce polarized RPE;
 - (c) seeding PR/PRP on the RPE to form a tissue replacement implant; and
 - (d) culturing the tissue replacement implant in a second tissue culture medium for a period of time sufficient to enable PR/PRP attachment to RPE.
39. The method of claim 38, wherein the scaffold is held in place by a plastic O-ring.

40. The method of claim 38 or 39, wherein the polarized RPE express Bestrophin1 (BEST1).
41. The method of any of claims 38-40, wherein the second tissue culture medium is essentially identical to the first tissue culture medium.
42. The method of any of claims 38-41, wherein the biodegradable scaffold comprises poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLLA), polycaprolactone (PCL), poly(glycerol sebacate (PGS), polypyrrole (PPy), polyvinyl alcohol (PVA), gelatin, collagen, laminin, fibronectin, fibrin, hyaluronic acid, silk, chitosan, or polyhydroxyethylmethacrylate (PHEMA).
43. The method of claim 42, wherein the biodegradable scaffold comprises PLGA.
44. The method of claim 43, wherein the PLGA has a DL-lactide/glycolide ratio of about 1:1.
45. The method of any of claims 42-44, wherein the PLGA has an average pore size of less than about 1 micron.
46. The method of any of claims 42-45, wherein the PLGA has a fiber diameter of about 150 to about 650 nm.
47. The method of any of claims 38-46, wherein the biodegradable scaffold is coated with an extra-cellular matrix (ECM) protein.
48. The method of claim 47, wherein the ECM protein comprises vitronectin, laminin, collagen I, collagen IV, or fibronectin.
49. The method of claim 47, wherein the ECM protein comprises vitronectin.
50. The method of claim 49, wherein the vitronectin is added to the surface at a concentration of greater than about 0.5 $\mu\text{g}/\text{cm}^2$.

51. The method of claim 49, wherein the vitronectin is added to the surface at a concentration of about 10 $\mu\text{g}/\text{cm}^2$.
52. The method of any of claims 38-51, wherein the RPE are seeded at a density of about 100,000 cells/ cm^2 to about 1,000,000 cells/ cm^2 .
53. The method of any of claims 38-52, wherein the RPE are seeded at a density of about 300,000 cells/ cm^2 to about 800,000 cells/ cm^2 .
54. The method of any of claims 38-53, wherein the PR/PRP are seeded at a concentration of about 100,000 cells/ cm^2 to about 10 million cells/ cm^2 .
55. The method of any of claims 38-54, wherein the PR/PRP are seeded at a concentration of about 3 million cells/ cm^2 to about 5 million cells/ cm^2 .
56. The method of any of claims 38-55, wherein the PR/PRP are seeded at a concentration of about 4 million cells/ cm^2 .
57. The method of any of claims 38-56, wherein the RPE and/or the PR/PRP have been previously cryopreserved.
58. The method of any of claims 38-57, wherein the biodegradable scaffold is placed in a multi-well support with a tissue culture insert.
59. The method of claim 58, wherein the first tissue culture medium is added to a lower compartment of the multi-well support with a tissue culture insert.
60. The method of any of claims 58-59, wherein the second tissue culture medium is added to an upper compartment of the multi-well support with a tissue culture insert.
61. The method of any of claims 38-60, wherein the first tissue culture medium comprises taurine and hydrocortisone.

62. The method of claim 61, wherein the first tissue culture media further comprises triiodothyronine.
63. The method of any of claims 38-62, wherein the first tissue culture medium is defined media or serum-free media.
64. The method of any of claims 38-63, wherein the first tissue culture medium comprises serum replacement.
65. The method of any of claims 38-64, wherein the first tissue culture medium further comprises prostaglandin E2 (PGE2).
66. The method of claim 65, wherein the PGE2 is at a concentration of 50 μ M to 100 μ M.
67. The method of any of claims 38-64, wherein the first tissue culture medium is RPE-MM media.
68. The method of any of claims 38-67, wherein the second tissue culture medium is essentially identical to the first tissue culture medium.
69. The method of any of claims 38-67, wherein the second tissue culture media is distinct from the first tissue culture medium.
70. The method of claim 69, wherein the second tissue culture medium is minimal medium (RMN).
71. The method of any of claims 58-70, wherein the first tissue culture medium is added to a lower compartment of the multi-well support and the second tissue culture medium is added to an upper compartment of the multi-well support.
72. The method of claim 71, wherein the pressure on the tissue culture insert from the medium in the lower compartment is higher than the pressure from the medium of the upper compartment.

73. The method of any of claims 38-70, wherein step (b) is for at least about 2 weeks.
74. The method of any of claims 38-73, wherein step (b) is for at least about 3 weeks.
75. The method of any of claims 38-74, wherein step (d) is for at least about 5 days.
76. The method of any of claims 38-75, wherein step (d) is for at least about 1 week.
77. The method of any of claims 38-74, wherein step (d) is for about 1 day.
78. The method of any of claims 38-76, wherein the PRP are rod-predisposed.
79. The method of any of claims 38-76, wherein the PRP are cone-predisposed.
80. The method of any of claims 38-79, wherein the first tissue culture medium and the second tissue culture medium are exchanged at least once every five days.
81. The method of any of claims 38-80, wherein the first tissue culture medium and the second tissue culture medium are exchanged at least once every three days.
82. The method of any of claims 38-81, wherein the first tissue culture medium and the second tissue culture medium are exchanged at least once every other day.
83. The method of any of claims 38-82, wherein the ratio of PR/PRP to RPE in the tissue replacement implant is about 2:1 to about 30:1.
84. The method of any of claims 38-83, wherein the ratio of PR/PRP to RPE in the tissue replacement implant is about 1:1 to about 5:1.
85. A tissue replacement implant of any of claims 1-32 produced according to the methods of any of claims 38-84.
86. A method for producing a PR/PRP-RPE bilayer comprising:
 - (a) seeding RPE in a tissue culture medium in an upper compartment of a multi-well support with a tissue culture insert;

- (b) seeding PR/PRP in a tissue culture medium in the upper compartment of said multi-well support, directly in contact with RPE, wherein medium pressure of the lower compartment is higher than medium pressure of the higher compartment; and
- (c) culturing for a period of time sufficient to produce the PR/PRP-RPE bilayer.

- 87. The method of claim 86, wherein the media in the lower and upper compartments of the multi-well support with a tissue culture insert are essentially identical.
- 88. The method of claim 86, wherein the media in the lower and upper compartments of the multi-well support with a tissue culture insert are distinct.
- 89. The method of any of claims 86-88, wherein the RPE are polarized RPE.
- 90. The method of claim 89, wherein the polarized RPE express BEST1.
- 91. The method of claim 86, wherein the RPE are seeded on a biodegradable scaffold.
- 92. The method of claim 91, wherein the biodegradable scaffold comprises poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLLA), polycaprolactone (PCL), poly(glycerol sebacate (PGS), polypyrrole (PPy), polyvinyl alcohol (PVA), gelatin, collagen, laminin, fibronectin, fibrin, hyaluronic acid, silk, chitosan, or polyhydroxyethylmethacrylate (PHEMA).
- 93. The method of claim 92, wherein the biodegradable scaffold comprises PLGA.
- 94. The method of claim 93, wherein the PLGA has a DL-lactide/glycolide ratio of about 1:1.
- 95. The method of any of claims 92-94, wherein the PLGA has an average pore size of less than about 1 micron.
- 96. The method of any of claims 92-95, wherein the PLGA has a fiber diameter of about 150 to about 650 nm.

97. The method of any of claims 91-96, wherein the biodegradable scaffold is coated with an extra-cellular matrix (ECM) protein.
98. The method of claim 97, wherein the ECM protein comprises vitronectin, laminin, collagen I, collagen IV, or fibronectin.
99. The method of claim 98, wherein the ECM protein comprises vitronectin.
100. The method of claim 99, wherein the vitronectin is added to the surface at a concentration of greater than about 0.5 $\mu\text{g}/\text{cm}^2$.
101. The method of claim 99, wherein the vitronectin is added to the surface at a concentration of about 10 $\mu\text{g}/\text{cm}^2$.
102. The method of any of claims 86-101, wherein the RPE are seeded at a density of about 100,000 cells/ cm^2 to about 1,000,000 cells/ cm^2 .
103. The method of any of claims 86-102, wherein the RPE are seeded at a density of about 300,000 cells/ cm^2 to about 800,000 cells/ cm^2 .
104. The method of any of claims 86-103, wherein the PR/PRP are seeded at a concentration of about 100,000 cells/ cm^2 to about 10 million cells/ cm^2 .
105. The method of any of claims 86-104, wherein the PR/PRP are seeded at a concentration of about 3 million cells/ cm^2 to about 5 million cells/ cm^2 .
106. The method of any of claims 86-105, wherein the PR/PRP are seeded at a concentration of about 4 million cells/ cm^2 .
107. The method of any of claims 86-106, wherein the RPE and/or the PR/PRP have been previously cryopreserved.
108. The method of any of claims 86-101, wherein the first tissue culture medium comprises taurine and hydrocortisone.

109. The method of claim 108, wherein the first tissue culture media further comprises triiodothyronine.
110. The method of any of claims 86-109, wherein the first tissue culture medium is defined media or serum-free media.
111. The method of any of claims 86-110, wherein the first tissue culture medium comprises serum replacement.
112. The method of any of claims 86-111, wherein the first tissue culture medium is RPE-MM media.
113. The method of any of claims 86-112, wherein the second tissue culture medium comprises taurine and hydrocortisone.
114. The method of claim 113, wherein the second tissue culture media further comprises triiodothyronine.
115. The method of any of claims 86-114, wherein the second tissue culture medium is defined media or serum-free media.
116. The method of any of claims 86-115, wherein the second tissue culture medium comprises serum replacement.
117. The method of any of claims 86-116, wherein the second tissue culture medium is RPE-MM media.
118. The method of any of claims 86-118, wherein the PR/PRP are rod-predisposed.
119. The method of any of claims 86-118, wherein the PR/PRP are cone-predisposed.
120. The method of any of claims 86-119, wherein the first tissue culture medium and the second tissue culture medium are exchanged at least once every five days.

121. The method of any of claims 86-120, wherein the first tissue culture medium and the second tissue culture medium are exchanged at least once every three days.
122. The method of any of claims 86-121, wherein the first tissue culture medium and the second tissue culture medium are exchanged at least once every other day.
123. The method of any of claims 86-122, wherein the ratio of PR/PRP to RPE in the tissue replacement implant is about 2:1 to about 30:1.
124. The method of any of claims 86-123, wherein the ratio of PR/PRP to RPE in the tissue replacement implant is about 1:1 to about 5:1.
125. A RPE-PR/PRP bilayer cell composition comprising a distinct bilayer of mature PRPs cultured on polarized RPE.
126. The composition of claim 125, wherein the polarized RPE are positive for Bestrophin and/or ZO-1.
127. The composition of claim 125 or 126, wherein the mature PR/PRP are positive for peripherin-2 and/or neural retina leucine zipper (NRL).
128. The composition of any of claims 125-127, wherein the wherein the ratio of PR/PRP to RPE in the distinct bilayer is 1:1 to 5:1.
129. A method of treating an ocular injury or disorder in a subject comprising transplanting an effective amount of a retinal epithelial cells (RPE) and PR/PRP (RPE-PR/PRP) bilayer composition to an eye of the subject.
130. The method of claim 129, wherein the ocular disorder is due to RPE dysfunction or photoreceptor dysfunction.
131. The method of claim 129, wherein the ocular disorder is age-related macular degeneration, retinitis pigmentosa, cone-rod dystrophies, or Leber congenital amaurosis.

132. The method of any of claims 129-131, wherein the RPE-PR/PRP bilayer composition is transplanted into the retina of the subject.
133. The method of any of claims 129-132, wherein the RPE-PR/PRP bilayer composition is transplanted on a scaffold.
134. The method of any of claims 129-133, wherein the RPE-PR/PRP bilayer composition comprises the tissue replacement implant of any of claims 1-33 or the pharmaceutical composition of any of claims 34-37.
135. The method of claim 134, wherein the tissue replacement implant is transplanted into the subretinal space.
136. The method of claim 134, wherein the tissue replacement implant is transplanted by using a subretinal injection tool.
137. The method of claim 129, wherein the RPE and/or PR/PRP are derived from human induced pluripotent stem cells (hiPSCs).
138. The method of claim 129, wherein the RPE and/or PR/PRP have been previously cryopreserved.
139. The method of claim 129, wherein the RPE are mature RPE.
140. The method of claim 139, wherein the mature RPE are positive for Bestrophin and/or ZO1.
141. The method of any of claims 129-140, wherein the RPE are on an extracellular matrix (ECM) protein-coated surface.
142. The method of claim 141, wherein the ECM protein is vitronectin, laminin, collagen I, collagen IV, or fibronectin.
143. The method of claim 141, wherein the ECM protein is vitronectin.
144. The method of any of claims 129-142, wherein the RPE are on a copolymer scaffold.

145. The method of claim 144, wherein the copolymer scaffold comprises poly(lactic-co-glycolic acid) (PLGA), polylactic acid (PLLA), polycaprolactone (PCL), poly(glycerol sebacate) (PGS), polypyrrole (PPy), polyvinyl alcohol (PVA), gelatin, collagen, laminin, fibronectin, fibrin, hyaluronic acid, silk, chitosan, or polyhydroxyethylmethacrylate (PHEMA).
146. The method of any of claims 129-145, wherein the PR/PRP were not derived from organoids.
147. The method of any of claims 129-146, wherein the RPE- PR/PRP bilayer is in media comprising taurine and hydrocortisone.
148. The method of claim 147, wherein the media further comprises triiodothyronine.
149. The method of claim 147 or 148, wherein the media is defined media or serum-free media.
150. The method of any of claims 147-149, wherein the media comprises serum replacement.
151. The method of claim 147, wherein the media is RPE-MM media.
152. The method of any of claims 129-151, wherein the PR/PRP are positive for peripherin-2 and/or neural retina leucine zipper (NRL).
153. The method of any of claims 129-152, wherein the ratio of PR/PRP to RPE in the distinct bilayer is 1:1 to 5:1.
154. Use of the tissue replacement implant of any of claims 1-33 as a model retina.
155. Use of the tissue replacement implant of any of claims 1-33 as a substrate grow growing tissue.