the RPE monolayer for improved RPE attachment. In some cases, modular tiling of multiple (e.g., two, three, four, or more) RPE monolayer/fibrin implants can provide large area coverage, and laser tacking can be used to enable precision of delivery location. In some cases, the fibrin scaffold can be degraded under controlled conditions during surgery using, for example via tPA.

In general, this document features a retinal implant comprising, or consisting essentially of, (a) a retinal pigment epithelium monolayer having an apical surface and a basal surface, and (b) a fibrin hydrogel layer attached to the apical and/or basal surface of the monolayer. In one ~~aspect~~example, the present disclosure refers to a retinal implant comprising (a) a retinal pigment epithelium monolayer having an apical surface and a basal surface, and (b) a fibrin hydrogel layer attached to said apical surface of said monolayer. The fibrin hydrogel layer can be from about 20 μm to about 400 μm thick. The implant can comprise plasminogen. The implant can comprise from about 0.1 U of plasminogen per mL to about 40 U of plasminogen per mL. In some cases, the implant can comprise from about 0.001 U of plasminogen per mL to about 40 U of plasminogen per mL. In some cases, the fibrin hydrogel layer can be obtained autologously.

In another example, this document features a method for making a retinal or sub-retinal implant. The method comprises, or consists essentially of, (a) obtaining a retinal pigment epithelium monolayer having an apical surface and a basal surface, and (b) depositing a coating of fibrinogen and thrombin onto the apical surface of the monolayer. In one ~~aspect~~example, the present disclosure refers to a method for making a retinal implant, wherein said method comprises: (a) obtaining a retinal pigment epithelium monolayer having an apical surface and a basal surface, and (b) depositing a coating of fibrinogen and thrombin onto said apical surface of said monolayer. The coating can be from about 20 μm to about 400 μm thick. The method coating can comprise from about 20 mg of fibrinogen per mL to about 80 mg of fibrinogen per mL. The method coating can comprise from about 2 U of thrombin per mL to about 1500 U of thrombin per mL. The method can comprise depositing plasminogen onto the apical surface of the monolayer. The method can comprise depositing plasminogen within the fibrin hydrogel onto the apical surface of the monolayer. The method coating can comprise from about 0.1 U of plasminogen per mL to about 40 U of plasminogen per mL. In some cases, the implant can comprise from about 0.001 U of plasminogen per mL to about 40 U of plasminogen per mL.

In another example, this document features a method for making a retinal or sub-retinal implant. The method comprises, or consists essentially of, culturing retinal epithelial cells on a fibrin basal support substrate in a medium comprising a protease inhibitor or an antifibrinolytic agent (e.g., a small molecule protease inhibitors). In one ~~aspect~~example, the present disclosure refers to a method for making a retinal implant, wherein said method comprises culturing retinal epithelial cells on a fibrin basal support substrate in a medium comprising a protease inhibitor or an anti-fibrinolytic agent. The

medium can comprise the protease inhibitor, and the protease inhibitor can be aprotinin. The medium can comprise from about 5 U of aprotinin per mL to about 500 U of aprotinin per mL. The medium further can comprise plasminogen. The medium can comprise from about 0.1 U of plasminogen per mL to about 40 U of plasminogen per mL (e.g., 0.1 U of plasminogen per mL to about 30 U of plasminogen per mL). In some cases, the implant can comprise from about 0.001 U of plasminogen per mL to about 40 U of plasminogen per mL. In some examples, plasminogen can be added to the medium just prior to transplantation. The fibrin basal support substrate can comprise endothelial cells. In some cases, the endothelial cells were obtained from a source selected from the group consisting of iPSC-derived endothelial cells, blood outgrowth endothelial cells (BOEC), endothelial colony-forming cells (ECFCs), endothelial progenitor cells (EPCs), and umbilical vein endothelial cells (UVEC). The fibrin basal support substrate can comprise sub-RPE tissue cell populations. The sub-RPE tissue cell populations can comprise melanocytes, pericytes, or fibroblasts. In some cases, the fibrin basal support substrate can be obtained autologously.

In another ~~aspect~~example, this disclosure features a retinal implant comprising (a) a retinal pigment epithelium monolayer having an apical surface and a basal surface, and (b) a fibrin hydrogel layer attached to said basal surface of said monolayer. In one aspect, the present disclosure refers to a retinal implant comprising (a) a retinal pigment epithelium monolayer having an apical surface and a basal surface and that is a flat, wrinkle-free monolayer, and (b) a fibrin hydrogel layer directly attached to said basal surface of said monolayer, wherein said apical surface is free of a fibrin hydrogel layer, wherein said retinal implant lacks patches of degraded fibrin hydrogel within said fibrin hydrogel layer, and wherein said fibrin hydrogel layer degrades when said retinal implant is implanted into an eye of a mammal. The fibrin hydrogel layer can be from about 20 μm to about 400 μm thick. The implant can comprise plasminogen. The implant can comprise from about 0.1 U of plasminogen per mL to about 40 U of plasminogen per mL or from about 0.001 U of plasminogen per mL to about 40 U of plasminogen per mL. The fibrin hydrogel layer can comprise a coating. The coating can comprise basement membrane proteins, matrigel, or geltrex. In some cases, the fibrin hydrogel monolayer can be obtained autologously.

In another example, this document features a method for making a retinal implant. The method comprises (a) obtaining a fibrin hydrogel layer, (b) coating a surface of the fibrin hydrogel layer with an agent, and (c) forming a retinal pigment epithelium monolayer having an apical surface and a basal surface on the coating, wherein the basal surface is closer to the fibrin hydrogel layer than the apical surface. In one ~~aspect~~example, the present disclosure refers to a method for making a retinal implant, wherein said method comprises: (a) obtaining a fibrin hydrogel layer, (b) coating a surface of said fibrin hydrogel layer with an agent, and (c) forming a retinal pigment epithelium monolayer having an apical surface and a basal surface on said coating, wherein said basal surface is closer to said fibrin hydrogel layer than said apical surface. The fibrin hydrogel layer can be from about 20 μm to about 400 μm thick. The fibrin hydrogel layer can comprise from about 20 mg of fibrinogen per mL to about 80 mg of fibrinogen per mL.

The fibrin hydrogel layer can comprise from about 2 U of thrombin per mL to about 1500 U of thrombin per mL. The fibrin hydrogel layer can comprise from about 0.1 U of plasminogen per mL to about 40 U of plasminogen per mL or from about 0.001 U of plasminogen per mL to about 40 U of plasminogen per mL. In some cases, the fibrin hydrogel monolayer can be obtained autologously.

In another example, this document features a method for making a retinal implant. The method comprises culturing retinal epithelial cells on a fibrin basal support substrate in a medium comprising a protease inhibitor or an anti-fibrinolytic agent. In one aspect, the present disclosure refers to a method for making a retinal implant, wherein said method comprises culturing retinal epithelial cells directly on a fibrin basal support substrate in a medium comprising a protease inhibitor or an anti-fibrinolytic agent to form a retinal pigment epithelium monolayer having an apical surface and a basal surface, wherein said basal surface is closer to said fibrin basal support substrate than said apical surface, wherein said apical surface is free of said fibrin basal support substrate, wherein said retinal implant lacks patches of degraded fibrin hydrogel within said fibrin hydrogel layer, wherein said fibrin hydrogel layer degrades when said retinal implant is implanted into an eye of a mammal, and wherein said retinal pigment epithelium monolayer is a flat, wrinkle-free monolayer. The medium can comprise the protease inhibitor, and the protease inhibitor can be aprotinin. The medium can comprise from about 5 U of aprotinin per mL to about 500 U of aprotinin per mL. The medium can comprise the anti-fibrinolytic agent, and the antifibrinolytic agent can be transexamic acid or aminocaproic acid. The medium can further comprise plasminogen. The medium can comprise from about 0.1 U of plasminogen per mL to about 40 U of plasminogen per mL or from about 0.001 U of plasminogen per mL to about 40 U of plasminogen per mL. The fibrin basal support substrate can comprise endothelial cells. The endothelial cells can be obtained from a source selected from the group consisting of iPSC-derived endothelial cells, blood outgrowth endothelial cells (BOEC), endothelial colony-forming cells (ECFCs), endothelial progenitor cells (EPCs), and umbilical vein endothelial cells (UVEC). The fibrin basal support substrate can comprise a coating. The coating can comprise basement membrane proteins, matrigel, or geltrex. The coating can be present prior to culturing the retinal epithelial cells on the fibrin basal support substrate. The fibrin basal support substrate can comprise sub-RPE tissue cell populations. The sub-RPE tissue cell populations can comprise melanocytes, pericytes, or fibroblasts. In some cases, the fibrin basal support substrate can be obtained autologously.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure pertains. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In

WHAT IS CLAIMED IS:

~~1. A retinal implant comprising (a) a retinal pigment epithelium monolayer having an apical surface and a basal surface, and (b) a fibrin hydrogel layer attached to said apical surface of said monolayer.~~

~~2. The implant of claim 1, wherein said fibrin hydrogel layer is from about 20 μm to about 400 μm thick.~~

~~3. The implant of any one of claims 1-2, wherein said implant comprises plasminogen.~~

~~4. The implant of any one of claims 1-2, wherein said implant comprises from about 0.1 U of plasminogen per mL to about 40 U of plasminogen per mL or from about 0.001 U of plasminogen per mL to about 40 U of plasminogen per mL.~~

~~5. A method for making a retinal implant, wherein said method comprises:~~

~~(a) obtaining a retinal pigment epithelium monolayer having an apical surface and a basal surface, and~~

~~(b) depositing a coating of fibrinogen and thrombin onto said apical surface of said monolayer.~~

~~6. The method of claim 5, wherein said coating is from about 20 μm to about 400 μm thick.~~

~~7. The method of any one of claims 5-6, wherein said coating comprises from about 20 mg of fibrinogen per mL to about 80 mg of fibrinogen per mL.~~

~~8. The method of any one of claims 5-7, wherein said coating comprises from about 2 U of thrombin per mL to about 1500 U of thrombin per mL.~~

~~9. The method of any one of claims 5-8, wherein said method comprises depositing plasminogen onto said apical surface of said monolayer.~~

~~10. The method of claim 9, wherein said coating comprises from about 0.1 U of plasminogen per mL to about 40 U of plasminogen per mL or from about 0.001 U of plasminogen per mL to about 40 U of plasminogen per mL.~~

~~11. A method for making a retinal implant, wherein said method comprises culturing retinal epithelial cells on a fibrin basal support substrate in a medium comprising a protease inhibitor or an anti-fibrinolytic agent.~~

~~12. The method of claim 11, wherein said medium comprises said protease inhibitor, and said protease inhibitor is aprotinin.~~

~~13. The method of claim 12, wherein said medium comprises from about 5 U of aprotinin per mL to about 500 U of aprotinin per mL.~~

~~14. The method of claim 11, wherein said medium comprises said anti-fibrinolytic agent, and said antifibrinolytic agent is transexamic acid or aminocaproic acid.~~

~~15. The method of claim 11, wherein said medium further comprises plasminogen.~~

~~16. The method of claim 15, wherein said medium comprises from about 0.1 U of plasminogen per mL to about 40 U of plasminogen per mL or from about 0.001 U of plasminogen per mL to about 40 U of plasminogen per mL.~~

~~17. The method of claim 11, wherein said fibrin basal support substrate comprises endothelial cells.~~

~~18. The method of claim 17, wherein said endothelial cells were obtained from a source selected from the group consisting of iPSC-derived endothelial cells, blood outgrowth endothelial cells (BOEC), endothelial colony-forming cells (ECFCs), endothelial progenitor cells (EPCs), and umbilical vein endothelial cells (UVEC).~~

1~~9~~. A retinal implant comprising (a) a retinal pigment epithelium monolayer having an apical surface and a basal surface and that is a flat, wrinkle-free monolayer, and (b) a fibrin hydrogel layer directly attached to said basal surface of said monolayer, wherein said apical surface is free of a fibrin hydrogel layer, wherein said retinal implant lacks patches of degraded fibrin hydrogel within said fibrin hydrogel layer, and wherein said fibrin hydrogel layer degrades when said retinal implant is implanted into an eye of a mammal.

2~~0~~. The implant of claim 1~~9~~, wherein said fibrin hydrogel layer is from ~~about~~ 20 µm to ~~about~~ 400 µm thick.

~~21~~3. The implant of ~~any one of claims 19-20~~claim 1, wherein said implant comprises plasminogen.

~~22~~4. The implant of ~~any one of claims 19-20~~claim 1, wherein said implant comprises from ~~about~~ 0.1 U of plasminogen per mL to ~~about~~ 40 U of plasminogen per mL or from ~~about~~ 0.001 U of plasminogen per mL to ~~about~~ 40 U of plasminogen per mL.

~~23. The implant of any one of claims 19-22, wherein said fibrin hydrogel layer comprises a coating.~~

~~24. The implant of claim 23, wherein said coating comprises basement membrane proteins, matrigel, or geltrex.~~

~~25. A method for making a retinal implant, wherein said method comprises:~~

~~(a) obtaining a fibrin hydrogel layer,~~

~~(b) coating a surface of said fibrin hydrogel layer with an agent, and~~

~~(c) forming a retinal pigment epithelium monolayer having an apical surface and a basal surface on said coating, wherein said basal surface is closer to said fibrin hydrogel layer than said apical surface.~~

~~26. The method of claim 25, wherein said fibrin hydrogel layer is from about 20 μm to about 400 μm thick.~~

~~27. The method of any one of claims 25-26, wherein said fibrin hydrogel layer comprises from about 20 mg of fibrinogen per mL to about 80 mg of fibrinogen per mL.~~

~~28. The method of any one of claims 25-27, wherein said fibrin hydrogel layer comprises from about 2 U of thrombin per mL to about 1500 U of thrombin per mL.~~

~~29. The method of any one of claims 25-28, wherein said fibrin hydrogel layer comprises from about 0.1 U of plasminogen per mL to about 40 U of plasminogen per mL or from about 0.001 U of plasminogen per mL to about 40 U of plasminogen per mL.~~

~~30~~5. A method for making a retinal implant, wherein said method comprises culturing retinal epithelial cells directly on a fibrin basal support substrate in a medium comprising a protease inhibitor or an anti-fibrinolytic agent to form a retinal pigment epithelium monolayer having an apical surface and a basal surface, wherein said basal surface is closer to said fibrin basal support substrate than said apical surface, wherein said apical surface is free of said fibrin basal support substrate, wherein said retinal implant lacks patches of degraded fibrin hydrogel within said fibrin hydrogel layer, wherein said fibrin hydrogel layer degrades when said retinal implant is implanted into an eye of a mammal, and wherein said retinal pigment epithelium monolayer is a flat, wrinkle-free monolayer.

~~31~~6. The method of claim ~~30~~5, wherein said medium comprises said protease inhibitor, and said protease inhibitor is aprotinin.

~~32~~7. The method of claim ~~31~~6, wherein said medium comprises from ~~about~~ 5 U of aprotinin per mL to ~~about~~ 500 U of aprotinin per mL.

~~33~~8. The method of claim ~~30~~5, wherein said medium comprises said anti-fibrinolytic agent, and said antifibrinolytic agent is transexamic acid or aminocaproic acid.

~~34~~9. The method of claim ~~30~~5, wherein said medium further comprises plasminogen.

~~35~~10. The method of claim ~~34~~9, wherein said medium comprises from ~~about~~ 0.1 U of plasminogen per mL to ~~about~~ 40 U of plasminogen per mL or from ~~about~~ 0.001 U of plasminogen per mL to ~~about~~ 40 U of plasminogen per mL.

~~36~~11. The method of claim ~~30~~5, wherein said method further comprises culturing endothelial cells on said fibrin basal support substrate ~~comprises endothelial cells~~.

~~37~~12. The method of claim ~~36~~11, wherein said endothelial cells were obtained from a source selected from the group consisting of iPSC-derived endothelial cells, blood outgrowth endothelial cells (BOEC), endothelial colony-forming cells (ECFCs), endothelial progenitor cells (EPCs), and umbilical vein endothelial cells (UVEC).

~~38. The method of any one of claims 30-37, wherein said fibrin basal support substrate comprises a coating.~~

~~39. The implant of claim 38, wherein said coating comprises basement membrane proteins, matrigel, or geltrex.~~

~~40. The implant of claim 38, wherein said coating was present prior to culturing said retinal epithelial cells on said fibrin basal support substrate.~~

~~41~~13. The method of claim ~~11 or 30~~5, wherein said ~~fibrin basal support substrate~~method further comprises culturing sub-RPE tissue cell populations on said fibrin basal support substrate.

~~42~~14. The method of claim ~~41~~13, wherein said sub-RPE tissue cell populations comprise melanocytes, pericytes, or fibroblasts.

15. The method of claim 5, wherein said fibrin basal support substrate is from 20 µm to 400 µm thick.

16. The method of claim 5, wherein said fibrin basal support substrate comprises from 20 mg of fibrinogen per mL to 80 mg of fibrinogen per mL.

17. The method of claim 5, wherein said fibrin basal support substrate comprises from 2 U of thrombin per mL to 1500 U of thrombin per mL.

18. The method of claim 5, wherein said fibrin basal support substrate comprises from 0.1 U of plasminogen per mL to 40 U of plasminogen per mL or from 0.001 U of plasminogen per mL to 40 U of plasminogen per mL.