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, 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, 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, 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, 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. 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, 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 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 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

case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

Other features and advantages of the disclosure will be apparent from the following detailed description, and from the claims.

DESCRIPTION OF DRAWINGS

Figure 1A is a schematic of a method for making an RPE monolayer with apical fibrin and loading it into a surgical implantation device. Figure 1B is a schematic of a method for making an RPE monolayer with basal fibrin and loading it into a surgical implantation device.

Figure 2A is a schematic of a method for implanting an RPE monolayer with apical fibrin into an eye to treat macular degeneration. Figure 2B is a schematic of a method for implanting an RPE monolayer with basal fibrin into an eye to treat macular degeneration.

Figure 3 is a schematic of a fibrinolysis process.

Figure 4A is a photograph of a sprayer system for forming thin layer fibrin gels. Figure 4B is an enlarged photograph of the nozzle of the sprayer system.

Figure 5 is a photograph of a fibrin gel according to some embodiments. The dimensions are 1.5 mm (W) x 5 mm (D) x 200 μm (H).

Figure 6 is a photograph of apical fibrin attached to an RPE monolayer.

Figure 7 is a photograph of live/dead staining of an RPE monolayer attached to apical fibrin. Attached cells are alive 2 hours later.

Figure 8 is a photograph of an RPE monolayer attached to apical fibrin. The image shows a continuous monolayer attached to fibrin.

Figure 9 is a photograph of ZO-1, a cell-cell tight junction protein, staining (red) and a DAPI (blue) staining of cell nuclei.

Figure 10 contains photographs showing biomaterial degradation of fibrin following treatment with tissue plasminogen activator (tPA) for two hours. The range of time of fibrin degradation can be from one hour to 72 hours.

Figure 11 contains graphs plotting the kinetics of degradation when varying fibrinogen concentrations. Plasminogen and tPA concentrations were fixed. Degradation