

BRIEF SUMMARY

[0005] In accordance with various embodiments of the present disclosure, cell culture apparatuses having one or more plates, which can be stacked, are described. The plates have a major surface defining a structured surface. The structured surface defines a plurality of wells in which cells can be cultured. The wells can have dimensions on the micrometer scale and can be configured to promote formation of spheroid cell clusters. The apparatuses described herein also have a plurality of spacers to maintain the space between stacked plates. In embodiments, such spacers include posts or spaced apart rails that extend from the major surface along the length of the plate. A plurality of flow channels are formed between adjacent plates and/or rails for perfusion of cell culture media. The structured surfaces can support very high cell density cell growth, which can be enhanced by spheroid formation. Spheroid formation should also enhance cell functional stability, as spheroids can maintain differentiated cell function indicative of a more in vivo like response relative to cells grown in a monolayer. In some embodiments, the wells in which cells are cultured are non-adherent to the cells, which can facilitate harvesting of the cells. In various embodiments described herein, the apparatuses are designed to allow for passive diffusion of metabolic gases, which can allow for lower media perfusion rates and thus subject the cultured cells to less shear.

[0005a] In an aspect, there is provided a cell culture apparatus comprising:

one or more plates having a first major surface and an opposing second major surface, wherein the first major surface comprises a plurality of microwells; and a plurality of spacers extending from the first major surface, wherein a plurality of cell culture media flow channels are defined between adjacent plates.

[0006] In various embodiments, this disclosure describes a cell culture apparatus. The cell culture apparatus includes one or more plates having a first major surface and an opposing second major surface. The first major surface comprises a structured surface defining a plurality of wells. Each well has an interior surface defining an upper aperture and a nadir, wherein the upper aperture of each well has a diametric dimension in a range from 200 micrometers to 500 micrometers, or a range from 100 micrometers to 2000 micrometers. The apparatus also includes a plurality of spaced apart rails (spacers) extending from the first

major surface along a length of the first major surface. A plurality of flow channels are defined between adjacent rails.

[0006a] In another aspect, there is provided a cell culture system comprising:

a cell culture apparatus as defined above; and

an oxygenator coupled to the inlet.

[0007] In some embodiments, provided herein are methods of producing protein (e.g., a therapeutic protein, such as a therapeutic antibody or antibody fragment), comprising: a) culturing cells expressing a protein in the wells of a cell culture apparatus as described herein; and b) isolating the protein from the cells.

[0007a] In another aspect, there is provided a method comprising:

introducing cells into the wells of a cell culture apparatus as defined above ; and perfusing a cell culture medium through the media flow channels of the cell culture apparatus at a first rate to culture the cells in the wells.

[0007b] A method of producing protein, comprising:

a) culturing cells expressing a protein in the wells of a cell culture apparatus as defined above; and

b) isolating said protein from said cells.