less aggressive and better therapeutic options for the treatment of dry eye disease are needed and are described in this application.

SUMMARY

[0003a] In one aspect, provided herein is a use of a therapeutic composition in the manufacture of a medicament for treating a dry eye disease, wherein the therapeutic composition is obtained by:

differentiating an *ex-vivo* culturing of a population of induced pluripotent stem cells (iPSCs) into mature megakaryocyte-like cells (MLCs);

lysing the mature MLCs to produce lysates;

processing the lysates to form the therapeutic composition, wherein the therapeutic composition comprises factors of one or more of: epidermal growth factor (EGF)>10% higher or interleukin (IL)-10>10% higher as compared to plasma rich in growth factors (PRGF), and EGF>10% higher, IL-10>10% higher as compared to crude lysates; and

wherein an effective amount of the therapeutic composition is to be administered to a subject suffering from the dry eye disease, thereby treating the dry eye disease.

[0003b] In another aspect, provided herein is a use of a therapeutic composition in the manufacture of a medicament for treating a dry eye disease, wherein an effective amount of the therapeutic composition is to be administered to a subject suffering from the dry eye disease, wherein the therapeutic composition comprises lysates of megakaryocyte-like cells (MLCs), wherein, after processing, the lysates comprise factors of one or more of: epidermal growth factor (EGF)>10% higher or interleukin (IL)-10>10% higher as compared to plasma rich in growth factors (PRGF), and EGF>10% higher, IL-10>10% higher as compared to crude lysates.

[0003c] In another aspect, provided herein is a method for producing a therapeutic composition comprising an effective amount of processed lysates of MLCs, the method comprising:

an *ex-vivo* culturing of a population of iPSCs for a duration to differentiate the iPSCs to mature MLCs;

concentrating the MLCs;

lysing the MLCs; and

processing the lysed MLCs to form the therapeutic composition;

wherein, after processing, the therapeutic composition comprises factors of one or more of: epidermal growth factor (EGF)>10% higher or interleukin (IL)-10>10% higher as compared to plasma rich in growth factors (PRGF), and EGF>10% higher, IL-10>10% higher as compared to crude lysates.

[0003d] In yet another aspect, provided herein is a therapeutic composition for treating a dry eye disease in a subject, the therapeutic composition comprising an effective amount of an MLC lysate, wherein the MLC lysate comprise factors of one or more of: epidermal growth factor (EGF)>50% higher or interleukin (IL)-10>50% higher as compared to plasma rich in growth factors (PRGF), and EGF>50% higher, IL-10>50% higher as compared to crude lysates.

[0004] Provided herein are methods of treating, repairing or ameliorating dry eye disease in a subject in need of such treatment. In some embodiments, the methods comprise administering to the subject an effective amount of a composition comprising a megakaryocyte derivative, wherein an administration route is ophthalmic or intraglandular, wherein the megakaryocyte derivative includes megakaryocyte-like cell (MLC) lysates, platelet-like cells (PLC), or combinations thereof.

[0005] Provided herein are methods of treating, repairing or ameliorating a condition in a subject in need of such treatment comprising administering to the subject more than one dose of an effective amount of a composition comprising a megakaryocyte derivative, wherein the condition is selected from dry eye disease, ocular surface disease, osteoarthritis, and wound healing, and wherein the megakaryocyte derivative includes MLC lysates, PLCs, exosomes, megakaryocytes, or combinations thereof, and wherein the megakaryocyte derivative comprises one or more biomarkers selected from fibroblast growth factor-2 (FGF-2); hepatocyte growth factor (HGF); insulin-like growth factor 1 (IGF-1), regulated upon activation, normal T cell expressed and secreted (RANTES); nerve growth factor (NGF); vascular endothelial growth factor (VEGF-A); vascular endothelial growth factor (VEGF-C); epidermal growth factor (EGF); transforming growth factor-β1 (TGF-β1); transforming growth factor-β2 (TGF-β2); platelet-derived growth factor-AA (PDGF-AA); platelet-derived growth factor-BB (PDGF-BB); platelet-derived growth factor-AA/BB (PDGF-AA/BB); interleukin 2 (IL-2); interleukin 4 (IL-4); interleukin 12p40 (IL-12p40); interleukin 12p70 (IL-12p70); tissue inhibitors of metalloproteinases-1 (TIMP-1); tissue inhibitors of metalloproteinases-2 (TIMP-2); and tissue inhibitors of metalloproteinases-3 (TIMP-3).

[0006] Provided herein are method for producing megakaryocyte derivatives, the methods comprise: an *ex*-vivo culturing of a population of progenitor cells for a duration to differentiate the progenitor cells to mature megakaryocytes; isolating a population of MLCs, PLCs or derivatives thereof by separating from the megakaryocytes; concentrating the MLCs, PLCs or derivatives thereof; optionally lysing the MLCs, PLCs or derivatives thereof; and optionally

(OA). Figures 13B-13G illustrate efficacy results of megakaryocyte derivatives, MLC lysate and PLC, on dynamic weight bearing test (Figure 13B), electronic von frey filament analysis (Figure 13C), histology of MMT joint (Figure 13D), substantial cartilage degeneration width (Figure 13E), synovitis score (Figure 13F), and medial tibial osteophyte measurement results (Figure 13G).

[0065] Figures 14A-14B illustrate the effect of PLCs on HUVEC migration in scratch assays. Figure 14A illustrates results of the time course data (120 hours) of the resulting cell index, and Figure 14B illustrates AUC data normalized to the vehicle.

[0066] Figure 15A shows a schematic design of a study for evaluation *in vivo* effects of megakaryocyte derivatives, MLC lysate and PLC, treatment in a db/db diabetic mouse model of wound healing. Figures 15B-15F illustrate efficacy results of PLC and MLC lysate, including wound closure kinetics (Figure 15B), histology results of diabetic mouse wounds (Figure 15C), histological analysis of wounds for the quantification of wound closure (Figure 15D), granulation tissue area (Figure 15E) and epidermis tissue area (Figure 15F), endomucin-based histological visualization of vasculature (Figure 15G), and quantification of the endomucin fluorescent signal (Figure 15H).

[0067] Figure 16 illustrates a schematic of the differentiation process.

[0068] Figure 17A illustrates a schematic of the PLC production process. Figure 17B illustrates an exemplary microfluidic bioreactor (BioR) device for processing the MLCs.

[0069] While the above-identified drawings set forth presently disclosed embodiments, other embodiments are also contemplated, as noted in the discussion. This disclosure presents illustrative embodiments by way of representation and not limitation. Numerous other modifications and embodiments can be devised by those skilled in the art which fall within the scope and spirit of the principles of the presently disclosed embodiments.

DETAILED DESCRIPTION

[0070] Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art to which this disclosure belongs. The following references provide one of skill with a general definition of many of the terms used in this disclosure: Singleton et al., Dictionary of Microbiology and Molecular Biology (2nd ed. 1994); The Cambridge Dictionary of Science and Technology (Walker ed., 1988); The