SUMMARY OF THE INVENTION

[0004a] In one aspect, provided herein is a composition for induced pluripotent stem cell (iPSC) production comprising: (i) a TGFβ family protein, (ii) a ROCK inhibitor, and (iii)a MEK inhibitor and a WNT activator, wherein the composition does not comprise a TGFβ inhibitor, wherein the composition is effective to improve iPSC pluripotency and genomic stability in a long-term iPSC maintenance.

[0004b] In another aspect, provided herein is a composition for induced pluripotent stem cell (iPSC) production comprising: (i) a ROCK inhibitor, a MEK inhibitor, and a WNT activator; (ii) an HDAC inhibitor; and (iii) a TGFβ inhibitor, wherein the composition is effective to improve reprogramming of a non-pluripotent cell to obtain iPSCs having established pluripotency and improved genomic stability, and optionally, wherein, addition of (i), (ii) or (iii) to the composition is stage-specific during reprogramming of the non-pluripotent cell for an increased reprogramming efficiency.

[0004c] In another aspect, provided herein is a method of producing induced pluripotent stem cell (iPSC), comprising a step of cryopreserving a population of iPSCs, wherein the iPSCs are in contact with the composition as described herein, and wherein pluripotency and genomic stability of the iPSCs are maintained during cryopreservation; and optionally, wherein the population of iPSCs comprising homogeneous iPSCs is expanded from a clonal iPSC single cell.

[0004d] In another aspect, provided herein is a method of producing induced pluripotent stem cell (iPSC), wherein the method comprises: (i) transferring to a non-pluripotent cell one or more reprogramming factors to initiate reprogramming of the cell; and (ii)contacting the cell after step (i) with the composition as described herein for a sufficient period, thereby generating at least one colony comprising iPSCs by reprogramming the non-pluripotent cell.

[0004e] In another aspect, provided herein is a method of producing induced pluripotent stem cell (iPSC), wherein the method comprises: (i) transferring to a non-pluripotent cell one or more reprogramming factors to initiate reprogramming of the cell; (ii) contacting the cell after step (i) with the composition as described herein for a sufficient period, thereby generating at least one colony comprising iPSCs, wherein pluripotency and genomic stability of the iPSCs are established; (iii) dissociating the iPSC colony of step (ii) to dissociated iPSCs, wherein the iPSCs are in contact with the composition of as described herein; (iv) sorting dissociated iPSCs to obtain one or more single cell iPSC clones, wherein the single cell iPSC clones are in contact with the composition as described herein; and optionally, (v) expanding the single cell iPSC clone to a population of clonal iPSCs, wherein the population of clonal iPSCs is in contact with the composition as described herein 8; and optionally (vi) cryopreserving the

population of clonal iPSCs, wherein the cryopreserved population is in contact with the composition as described herein; wherein pluripotency and genomic stability of the iPSCs are maintained during the step of dissociating, sorting, expanding, cryopreserving, or thawing.

[0004f] In another aspect, provided herein is a kit comprising the system as described herein.

[0005] In view of the foregoing, there is a substantial need in the art for an efficient production of a homogenous population of footprint-free iPSCs, preferably in a “naïve” or “grounded” state of pluripotency, and preferably in defined culture conditions. The “naïve” or “grounded” state of pluripotency imparts the iPSCs with qualities including, but not limited to, high clonality, sustainable self-renewal, minimal spontaneous differentiation and genomic abnormality, and high survivability as dissociated single cells. Methods and compositions, and particularly the novel culture media and plasmid vector systems, of embodiments according to the present disclosure address this need and provide other related advantages in the field of cellular reprogramming.

[0006] By using an efficient but transient and temporal expression system that minimizes the presence of exogenous genes for reduced probability of host genome integration, it is an object of the present disclosure to provide methods and compositions efficient in generating an iPSC without comprising exogenous DNA introduced to a non-pluripotent cell for induction of reprogramming. It is an object of the present disclosure to provide a combinational plasmid system to efficiently produce iPSCs with a “naïve” or “grounded” state of pluripotency and/or high clonality. iPSCs having ground state pluripotency enable long term survival and genetic stability of single cell dissociated iPSCs, and thus make it possible to generate clonal iPSC lines suitable for banking and manipulation such as single cell sorting and/or depletion, clonal iPSC targeted genomic editing, and directed redifferentiation of a homogenous population of iPSCs. Therefore, it is also an object of the present disclosure to provide methods and compositions to generate single cell derived iPSC clonal lines, or derivative cells therefrom, comprising one or several genetic modifications at selected sites, which include polynucleotides insertion, deletion, and substitution, and which modifications are retained and remain functional in subsequently derived cells after differentiation, dedifferentiation, reprogramming, expansion, passaging and/or transplantation.

[0007] One aspect of the present application provides a composition (e.g., FMM2) for induced pluripotent stem cell (iPSC) production, the composition comprising (i) a TGFβ family protein, (ii) a ROCK inhibitor, and (iii) a MEK inhibitor and a WNT activator, wherein the composition does not comprise a TGFβ inhibitor, wherein the composition is effective to improve iPSC pluripotency and genomic stability in a long-term iPSC maintenance. In some embodiments, the long-term iPSC maintenance comprises one or more of stages comprising: single cell dissociation of iPSC colonies, single cell sorting of dissociated iPSCs, iPSC single