Summary ~~of the Invention~~

In one aspect, there is provided the use of expanded multipotent cells that: are not embryonic stem cells, embryonic germ cells, or germ cells; can differentiate into at least one cell type of each of at least two of the endodermal, ectodermal, and mesodermal embryonic lineages; do not provoke a deleterious immune response in a subject and are effective to treat an immune dysfunction characterized by deleterious T-cell proliferation in the subject in the manufacture of a medicament for treating an immune dysfunction characterized by deleterious T-cell proliferation in the subject, wherein said cells are allogeneic to the subject, have telomerase activity, are positive for oct-3/4, and have undergone at least 10 to 40 cell doublings in culture prior to their administration to the subject.

In another aspect, there is provided the use of an effective amount of expanded human multipotent stem cells that: are not embryonic stem cells, embryonic germ cells, or germ cells; can differentiate into at least one cell type of all three of the endodermal, ectodermal, and mesodermal embryonic lineages; do not provoke a deleterious immune response in the subject; and are effective to treat graft versus host disease or host versus graft disease in a subject, in the manufacture of a medicament for treating the subject at risk for suffering from graft versus host or host versus graft disease, wherein said cells are allogeneic to the subject, have telomerase activity, are positive for oct-3/4, and have undergone at least 10 to 40 cell doublings in culture prior to their administration to the subject.

In some of its embodiments, therefore, the disclosure~~invention~~ provides cells that: (i) are not embryonic stem cells, not embryonic germ cells, and not germ cells; (ii) can differentiate into at least one cell type of each of at least two of the endodermal, ectodermal, and mesodermal embryonic lineages; (iii) do not provoke a deleterious immune response upon introduction to a non-syngeneic subject; and (iv) can modulate an immune response upon introduction into a subject. In certain embodiments in this regard, the disclosure~~invention~~ provides cells that, in addition to the foregoing, are immunosuppressive. Furthermore, various embodiments of the disclosure~~invention~~ provide cells in accordance with the foregoing that have immunomodulatory properties that are useful for treating, such as to preclude, prevent, ameliorate, lessen, decrease,

minimize, eliminate, and/or cure deleterious immune responses and/or processes in a host. In some embodiments of the disclosure~~invention~~ the cells are used in this regard alone or together with other therapeutic agents and modalities as primary therapeutic modalities. In some embodiments of the disclosure~~invention~~ the cells are used in an adjunctive therapeutic modality in which they may be used either as the sole therapeutic agent or together with other therapeutic agents. In some embodiments of the disclosure~~invention~~ the cells are used, alone or with other therapeutic agents or modalities, both in one or more primary therapeutic modalities and in one or move adjunctive therapeutic modalities.

Cells in accordance with the disclosure~~invention~~ are described in greater detail herein and generally are referred to herein as "multipotent adult progenitor cells" and by the acronyms "MAPC" (singular) and "MAPCs" (plural). It is to be appreciated that these cells are not ES, not EG, and not germ cells, and that they have the capacity to differentiate into cell types of at least two of the three primitive germ layer lineages (ectoderm, mesoderm, and endoderm), e.g., into cells of all three primitive lineages.

For instance, MAPCs can form the following cells and other cells of the lineages thereof: splanchnic mesodermal cells, muscle cells, bone cells, cartilage cells, endocrine cells, exocrine cells, endothelial cells, hair forming cells, teeth forming cells, visceral mesodermal cells, hematopoietic cells, stromal cells, marrow stromal cells, neuronal cells, neuroectodermal cells, epithelial cells, ocular cells, pancreatic cells, and hepatocyte-like cells, among many others. Among cells formed by MAPCs are osteoblasts, chondroblasts, adipocytes, skeletal muscle cells, skeletal myocytes, biliary

epithelial cells, pancreatic acinary cells, mesangial cells, smooth muscle cells, cardiac muscle cells, cardiomyocytes, osteocytes, vascular tube forming cells, oligodendrocytes, neurons, including serotonergic, GABAergic, dopaminergic neurons, glial cells, microglial cells, pancreatic epithelial cells, gut epithelial cells, liver epithelial cells, skin epithelial cells, kidney epithelial cells, renal epithelial cells, pancreatic islet cells, fibroblasts, hepatocytes, and other cells of the same lineages as the foregoing, among many others.

MAPCs have telomerase activity necessary for self-renewal and thought to be necessary for maintaining an undifferentiated state. Generally they also express oct-3/4. Oct-3/4 (oct-3A in humans) is otherwise specific to ES, EG, and germ cells. It is considered to be a marker of undifferentiated cells that have broad differentiation abilities. Oct-3/4 also is generally thought to have a role in maintaining a cell in an undifferentiated state. Oct-4 (oct-3 in humans) is a transcription factor expressed in the pregastrulation embryo, early cleavage stage embryo, cells of the inner cell mass of the blastocyst, and embryonic carcinoma ("EC") cells (Nichols, J. et al. (1998) Cell 95: 379-91), and is down-regulated when cells are induced to differentiate. The oct-4 gene (oct-3 in humans) is transcribed into at least two splice variants in humans, oct-3A and oct-3B. The oct-3B splice variant is found in many differentiated cells whereas the oct-3A splice variant (also previously designated oct-3/4) is reported to be specific for the undifferentiated embryonic stem cell. See Shimozaki et al. (2003) Development 130: 2505-12. Expression of oct-3/4 plays an important role in determining early steps in embryogenesis and differentiation. Oct-3/4, in combination with rox-1, causes transcriptional activation of the Zn-finger protein rex-1, which is also required for maintaining ES cells in an undifferentiated state (Rosfjord, E. and Rizzino, A. (1997) Biochem Biophys Res Commun 203: 1795-802; Ben-Shushan, E. et al. (1998) Mol Cell Biol 18: 1866-78).

MAPCs generally also express other markers thought to be specific to primitive stem cells. Among these are rex-1, rox-1, and sox-2. Rex-1 is controlled by oct-3/4, which activated downstream expression of rex-1. Rox-1 and sox-2 are expressed in non-ES cells.

Various embodiments of the disclosure~~invention~~ provide methods for using MAPCs for precluding, preventing, treating, ameliorating, lessening, decreasing, minimizing,

eliminating, and/or curing a disease and/or an adverse immune response and/or processes in a subject. Certain embodiments of the disclosure~~invention~~ provide methods for using the cells by themselves as a primary therapeutic modality. In some embodiments of the disclosure~~invention~~ the cells are used together with one or more other agents and/or therapeutic modalities as the primary therapeutic modality. In some embodiments of the disclosure~~invention~~ the cells are used as an adjunctive therapeutic modality, that is, as an adjunct to another, primary therapeutic modality. In some embodiments the cells are used as the sole active agent of an adjunctive therapeutic modality. In others the cells are used as an adjunctive therapeutic modality together with one or more other agents or therapeutic modalities. In some embodiments the cells are used both as primary and as adjunctive therapeutic agents and/or modalities. In both regards, the cells can be used alone in the primary and/or in the adjunctive modality. They also can be used together with other therapeutic agents or modalities, in the primary or in the adjunctive modality or both.

As discussed above, a primary treatment, such as a therapeutic agent, therapy, and/or therapeutic modality, targets (that is, is intended to act on) the primary dysfunction, such as a disease, that is to be treated. An adjunctive treatment, such as a therapy and/or a therapeutic modality, can be administered in combination with a primary treatment, such as a therapeutic agent, therapy, and/or therapeutic modality, to act on the primary dysfunction, such as a disease, and supplement the effect of the primary treatment, thereby increasing the overall efficacy of the treatment regimen. An adjunctive treatment, such as an agent, therapy, and/or therapeutic modality, also can be administered to act on complications and/or side effects of a primary dysfunction, such as a disease, and/or those caused by a treatment, such as a therapeutic agent, therapy, and/or therapeutic modality. In regard to any of these uses, one, two, three, or more primary treatments may be used together with one, two, three, or more adjunctive treatments.

In some embodiments MAPCs are administered to a subject prior to onset of a dysfunction, such as a disease, side effect, and/or deleterious immune response. In some embodiments the cells are administered while the dysfunction is developing. In some embodiments the cells are administered after the dysfunction has been established. Cells can be administered at any stage in the development, persistence, and/or propagation of the dysfunction or after it recedes.

As discussed above, embodiments of the disclosure~~invention~~ provide cells and methods for primary or adjunctive therapy. In certain embodiments of the disclosure~~invention~~, the cells are administered to an allogeneic subject. In some embodiments they are autologous to the subject. In some embodiments they are syngeneic to the subject. In some embodiments the cells are xenogeneic to a subject. Whether allogeneic, autologous, syngeneic, or xenogeneic, in various embodiments of the invention the MAPCs are weakly immunogenic or are non-immunogenic in the subject. In some embodiments the MAPCs have sufficiently low immunogenicity or are non-immunogenic and are sufficiently free of deleterious immune responses in general, that when administered to allogeneic subjects they can be used as "universal" donor cells without tissue typing and matching. In accordance with various embodiments of the invention the MAPCs can also be stored and maintained in cell banks, and thus can be kept available for use when needed.

In all of these regards and others, embodiments of the disclosure~~invention~~ provide MAPCs from mammals, including in one embodiment humans, and in other embodiments non-human primates, rats and mice, and dogs, pigs, goats, sheep, horses, and cows. MAPCs prepared from mammals as described above can be used in all of the methods and other embodiment~~aspect~~s of the disclosure~~invention~~ described herein.

MAPCs in accordance with various embodiments of the disclosure~~invention~~ can be isolated from a variety of compartments and tissues of such mammals, including but not limited to, bone marrow, blood, spleen, liver, muscle, brain, and others discussed below. MAPCs in some embodiments are cultured before use.

In some embodiments MAPCs are genetically engineered, such as to improve their immunomodulatory properties. In some embodiments genetically engineered MAPCs are produced by *in vitro* culture. In some embodiments genetically engineered MAPCs are produced from a transgenic organism.

In various embodiments the MAPCs are administered to a subject by any route for effective delivery of cell therapeutics. In some embodiments the cells are administered by injection, including local and/or systemic injection. In certain embodiments the cells are administered within and/or in proximity to the site of the dysfunction they are intended to treat. In some embodiments, the cells are administered by injection at a location not in proximity to the site of the dysfunction. In some

embodiments the cells are administered by systemic injection, such as intravenous injection.

In some embodiments, MAPCs are administered one time, two times, three times, or more than three times until a desired therapeutic effect is achieved or administration no longer appears to be likely to provide a benefit to the subject. In some embodiments MAPCs are administered continuously for a period of time, such as by intravenous drip. Administration of MAPCs may be for a short period of time, for days, for weeks, for months, for years, or for longer periods of time.

The following numbered paragraphs describe a few illustrative embodiments of the disclosure~~invention~~ that exemplify some of its aspects and features. They are not exhaustive in illustrating its many aspects and embodiments, and thus are not in any way limitative of the disclosure~~invention~~. Many other aspects, features, and embodiments of the disclosure~~invention~~ are described herein. Many other aspects and embodiments will be readily apparent to those skilled in the art upon reading the application and giving it due consideration in the full light of the prior art and knowledge in the field.

The numbered paragraphs below are self-referential. The phrase "according to any of the foregoing or the following" refers to all of the preceding and all of the following numbered paragraphs and their contents. All phrases of the form "according to #" are direct references to that numbered paragraph, e.g., "according to 46." means according to paragraph 46. in this collection of numbered paragraphs. All cross-references are combinatorial, except for redundancies and inconsistencies of scope. The cross-references are used explicitly to provide a concise description showing the inclusion of the various combinations of subject matter with one another.

1. A method of treating an immune dysfunction in a subject, comprising: administering to a subject likely to suffer, suffering, or who has suffered from an immune dysfunction, by an effective route and in an effective amount to treat the immune dysfunction, cells (MAPCs) that: are not embryonic stem cells, embryonic germ cells, or germ cells; can differentiate into at least one cell type of each of at least two of the endodermal, ectodermal, and mesodermal embryonic lineages; do not provoke a deleterious immune response in the subject; and are effective to treat the immune dysfunction.