COMPOSITIONS AND METHODS TO INHIBIT STEM CELL AND PROGENITOR CELL BINDING TO LYMPHOID TISSUE AND FOR REGENERATING GERMINAL CENTERS IN LYMPHATIC TISSUES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to US Provisional Patent Application Serial No. 61/374,943 filed August 18, 2010; US Provisional Patent Application Serial No. 61/441,485 filed February 10, 2011; US Provisional Patent Application Serial No. 61,449,372 filed March 4, 2011 and US Provisional Patent Application Serial No. 61/524,102 filed August 17, 2011. All of the foregoing applications are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] Subject matter of the disclosure concerns methods and compositions to modulate stem cell binding to organs and tissues and for regenerating germinal centers in lymphatic tissues.

BACKGROUND OF THE INVENTION

[0003] Regenerative Medicine is the process of creating living, functional tissues to repair or replace tissue or organ function lost due to damage, or congenital defects. This field holds the promise of regenerating damaged tissues and organs in the body by stimulating previously irreparable organs to heal themselves.

[0004] One method used to regenerate tissue or organ function is the delivery of stem cells to the affected organ or tissue. However, stem cells are not well retained in the organ targeted for tissue regeneration even when the stem cells are directly injected into the tissue of the injured organ. Imaging studies in humans and animals have demonstrated that most of the delivered stem cells can be found within the spleen within an hour after stem cell injection. Animal studies have also demonstrated that surgical removal of the spleen prior to stem cell therapy after induced myocardial infarction improved functional recovery of the damaged hearts (Blood, Vol 84, No 5 : 1482-1491, 1994; NATURE 410 :701-705, 2001). Splenectomy has also been shown to improve engraftment in human patients after bone marrow transplantation (Stem Cells Dev 13(1):51-62, 2004; Transplant Proc. 28(2):736-7, 1996; Am J Hematol. 22(3):275-83, 1986). However, splenectomy is also associated with surgical mortality, sepsis, and lifelong thrombotic complications (Blood Rev. 14(3):121-129, 2000; Leukemia.15(3):465-467, 2001; Pediatr Transplant 13(2):171-176, 2009)

[0005] Thus, there is a need to develop methods and compositions that can be used to prevent localization of stem cells in the spleen and other lymphoid tissues without removal of the spleen.

SUMMARY

[0005a] In one aspect, there is provided the use of a immune modulator that inhibits binding of stem cells to germinal centers in the manufacture of a medicament for inhibiting binding of stem cells to germinal centers within lymphoid tissue in a subject suffering from a condition selected from the group consisting of: osteopetrosis, limbal

stem cell deficiency, acute myocardial infarction, coronary artery disease, peripheral vascular disease, heart failure, type I diabetes mellitus, type 2 diabetes mellitus, stroke, spinal cord injury, multiple sclerosis, systemic sclerosis, lupus erythematosus, chronic wound healing, burns, fracture healing, cartilage degeneration, connective tissue diseases osteoarthritis, rheumatoid arthritis, renal failure, Parkinson's Disease, myelomas, diabetic foot, liver and biliary cirrhosis, dilated cardiomyopathy, retinitis pigmentosa, Crohn's Disease, diabetic neuropathy, mastocytosis, epilepsy, myasthenia gravis, autoimmune diseases, granulomatous disease, osteonecrosis, liver failure, PMD disease, lypodystrophy, demyelinating diseases, cartilage defects, retinal disease, lupus nephritis, Alzheimer's Disease, traumatic brain injury, myositis, hyperglycemia, macular degeneration, ulcerative colitis, and muscle degeneration, wherein the subject has germinal centers within their lymphoid tissue;wherein the therapeutic agent is to be administered to said subject prior to or in conjunction with said stem cells, and wherein the therapeutic agent does not block the binding of the stem cells to a target organ or tissue; and wherein the stem cells are not derived from a human embryo greater than 14 days old.

~~WHAT IS CLAIMED IS:~~

1. A method to inhibit stem cells binding to lymphoid tissue comprising:

administering the stem cells in conjunction with a therapeutic agent that inhibits binding of the stem cells to said lymphoid tissue.

2. The method of claim 1 wherein the lymphoid tissue is comprised of spleen, Peyer's patches and lymph nodes.

3. The method of claim 1 wherein the therapeutic agent inhibits binding of the stem cells to germinal centers within the lymphoid tissue.

4. The method of claim 3 wherein the germinal centers are present in a lymph tissue selected from the group consisting of spleen, Peyer's patches and lymph node tissue.

5. The method of claim 3 wherein the germinal center is active.

6. The method of claim 1, wherein the therapeutic agent is selected from the group consisting of:

agents that interfere with the synthesis of purines, the anti-metabolites, radiation to the spleen, chemotherapeutic agents, immunosuppressants, glucocorticoids, anti-beta amyloid agents, anti-rhesus factor, anti-TNF agents, anti-eotaxins, anti-T cell receptor (TCR) agents, anti-interferons agents, anti-interferon alpha agents, anti-interferon beta agents, anti-interferon gamma agents, anti-TGF agents, anti-TGFalpha agents, anti-TGF beta agents, anti-Integrins agents, anti-alpha 4 agents, anti-Interleukin agents, anti-Interleukin 1 agents, anti-interleukin 2 agents, anti-Interleukin 4 agents, anti-interleukin 5 agents, anti-interleukin 6 agents, anti-Interleukin 12 agents, anti-Interleukin 13 agents, anti-Interleukin 23 agents, anti-IgE agents, anti-Vascular Adhesion Protein (VAP) agents, anti-B7 agents, anti-Vascular Endothelial Growth Factor (VEGF) agents, anti-BAFF (BLyS) agents, anti-CTLA4 agents, anti-complement agents, anti-CD2 agents, anti-CD3 agents, anti-CD4 agents, anti-CD5 agents, anti-CD20 agents, anti-CD23 agents, anti-CD25a agents, anti-CD40 agents, anti-CD154 (CD40L) agents, anti-CD62L agents, anti-CD80 agents, anti-CD147 agents, anti-LFA1 agents,

anti-(CD11a) agents, anti-CD18 agents, inhibitors of purine synthesis, inhibitors of pyrimidine synthesis, anti-proliferative agents, anti-metabolite agents, anti-folate agents, and anti-mTOR agents.

7. The method of claim 1 wherein the therapeutic agents are selected from the group consisting of: azathioprine, mycophenolic acid, leflunomide, teriflunomide, methotrexate, tacrolimus, ciclosporin, pimecrolimus, abetimus, gusperimus, thalidomide, lenalidomide, anakinra, sirolimus, deforolimus, everolimus, temsirolimus, zotarolimus, biolimus A9, eculizumab, infliximab, adalimumab, certolizumab pegol, afelimomab, golimumab, mepolizumab, omalizumab, nerelimomab, faralimomab, elsilimomab, lebrikizumab, ustekinumab, muromonab-CD3, otelixizumab, teplizumab, visilizumab, clenoliximab, keliximab, zanolimumab, efalizumab, erlizumab, afutuzumab, ocrelizumab, pascolizumab, lumiliximab, teneliximab, toralizumab, aselizumab, galiximab, gavilimomab, ruplizumab, belimumab, ipilimumab, tremelimumab, bertilimumab, lerdelimumab, metelimumab, natalizumab, tocilizumab, odulimomab, basiliximab, daclizumab, inolimomab, zolimomab aritox, atorolimumab, cedelizumab, dorlixizumab, fontolizumab, gantenerumab, gomiliximab, maslimomab, morolimumab, pexelizumab, reslizumab, rovelizumab, siplizumab, talizumab, telimomab aritox, vapaliximab, vepalimomab, abatacept, belatacept, etanercept, pegsunercept, aflibercept, alefacept, rilonacept, lymphotoxin alpha and beta inhibitors, dacetuzumab SGN-40, HCD-122.

8. The method of claim 1, wherein the binding of stem cells to the lymphoid tissue is inhibited by administering a therapeutic agent that down-regulates or blocks a CD45 antigen.

9. The method of claim 1 wherein the therapeutic agent is radiation.

10. The method of claim 1 wherein the stem cells are either exogenous or endogenous stem cells.

11. The method of claim 1 wherein the therapeutic agent is a chemotherapeutic agent.

12. The method of claim 1 wherein the stem cells are administered to treat a disease selected from the group consisting of: hematological malignancies, leukemias, lymphomas, cancers, osteopetrosis, aplastic anemia and cytopenias, sickle cell disease and thalassemia, limbal stem cell deficiency, breast cancer, acute myocardial infarction, coronary artery disease, peripheral vascular disease, heart failure, type I diabetes mellitus, type 2

diabetes mellitus, stroke, spinal cord injury, neuroblastoma, multiple sclerosis, systemic sclerosis, lupus erythematosus, chronic wound healing, burns, fracture healing, cartilage repair, CNS tumors, osteoarthritis, renal failure, Parkinson's Disease, myelomas, diabetic foot, liver and biliary cirrhosis, dilated cardiomyopathy, anemia, retinitis pigmentosa, Crohn's Disease, diabetic neuropathy, mastocytosis, ovarian cancer, epilepsy, myasthenia gravis, autoimmune diseases, granulomatous disease, osteonecrosis, liver failure, PMD disease, lypodystrophy, demyelinating diseases, cartilage defects, retinal disease, lupus nephritis, Alzheimer's Disease, traumatic brain injury, sarcoma, myositis, hyperglycemia, macular degeneration, ulcerative colitis, and muscle degeneration.

13. A method for inhibiting binding of stem cells to lymph tissues in an individual comprising inhibiting the formation of germinal centers present in lymph tissues or destroying or ablating germinal centers in lymph tissue.

14. The method of claim 13 wherein a therapeutic agent is administered to the individual that inhibits the formation of the germinal cells or promotes destruction or ablation of the germinal cells wherein the therapeutic agent is selected from the group consisting of agents that interfere with the synthesis of purines, anti-metabolites, radiation, immunosuppressants, glucocorticoids, anti-beta amyloid agents, anti-rhesus factor, anti-TNF agents, anti-eotaxins, anti-T cell receptor (TCR) agents, anti-interferons agents, anti-interferon alpha agents, anti-interferon beta agents, anti-interferon gamma agents, anti-TGF agents, anti-TGFalpha agents, anti-TGF beta agents, anti-Integrins agents, anti-alpha 4 agents, anti-Interleukin agents, anti-Interleukin 1 agents, anti-interleukin 2 agents, anti-Interleukin 4 agents, anti-interleukin 5 agents, anti-interleukin 6 agents, anti-Interleukin 12 agents, anti-Interleukin 13 agents, anti-Interleukin 23 agents, anti-IgE agents, anti-Vascular Adhesion Protein (VAP) agents, anti-B7 agents, anti-Vascular Endothelial Growth Factor (VEGF) agents, anti-BAFF (BLyS) agents, anti-CTLA4 agents, anti-complement agents, anti-CD2 agents, anti-CD3 agents, anti-CD4 agents, anti-CD5 agents, anti-CD20 agents, anti-CD23 agents, anti-CD25a agents, anti-CD40 agents, anti-CD154 (CD40L) agents, anti-CD62L agents, anti-CD80 agents, anti-CD147 agents, anti-LFA1 agents, anti-(CD11a) agents, anti-CD18 agents, inhibitors of purine synthesis, inhibitors of pyrimidine synthesis, anti-proliferative agents, anti-metabolite agents, anti-folate agents, and anti-mTOR agents.

15. The method of claim 13 wherein the therapeutic agent is a chemotherapeutic agent.

16. A method for regenerating germinal centers in lymphatic tissue, wherein said germinal centers have been damaged by a chemical agent, a biologic agent or by radiation comprising administering one or more agents that stimulates regeneration of the germinal centers.

WHAT IS CLAIMED IS:

1. Use of an immune modulator that inhibits binding of stem cells to germinal centers in the manufacture of a medicament for inhibiting binding of stem cells to germinal centers within lymphoid tissue in

a subject suffering from a condition selected from the group consisting of: osteopetrosis, limbal stem cell deficiency, acute myocardial infarction, coronary artery disease, peripheral vascular disease, heart failure, type I diabetes mellitus, type 2 diabetes mellitus, stroke, spinal cord injury, multiple sclerosis, systemic sclerosis, lupus erythematosus, chronic wound healing, burns, fracture healing, cartilage degeneration, connective tissue diseases osteoarthritis, rheumatoid arthritis, renal failure, Parkinson's Disease, myelomas, diabetic foot, liver and biliary cirrhosis, dilated cardiomyopathy, retinitis pigmentosa, Crohn's Disease, diabetic neuropathy, mastocytosis, epilepsy, myasthenia gravis, autoimmune diseases, granulomatous disease, osteonecrosis, liver failure, PMD disease, lypodystrophy, demyelinating diseases, cartilage defects, retinal disease, lupus nephritis, Alzheimer's Disease, traumatic brain injury, myositis, hyperglycemia, macular degeneration, ulcerative colitis, and muscle degeneration, wherein the subject has germinal centers within their lymphoid tissue;

wherein the therapeutic agent is to be administered to said subject prior to or in conjunction with said stem cells, and wherein the therapeutic agent does not block the binding of the stem cells to a target organ or tissue; and

wherein the stem cells are not derived from a human embryo greater than 14 days old.

2. The use of claim 1 wherein the lymphoid tissue is comprised of spleen, Peyer's patches and lymph nodes.

3. The use of claim 1 wherein the germinal centers are present in a lymph tissue selected from the group consisting of spleen, Peyer's patches and lymph node tissue.

4. The use of claim 1, wherein the immune modulator is selected from the group consisting of: glucocorticoids, anti-TNF agents, dexamethasone, and anti-CD26 agents.

5. The use of claim 1 wherein the immune modulators are selected from the group consisting of: methotrexate, tacrolimus, ciclosporin, thalidomide, infliximab, adalimumab, certolizumab, golimumab, omalizumab, lebrikizumab, ustekinumab, muromonab-CD3, teplizumab, visilizumab, efalizumab, afutuzumab, ocrelizumab, teneliximab, toralizumab, natalizumab, talizumab, abatacept, belatacept, etanercept, alefacept, rilonacept, dacetuzumab, HCD-12, and rituximab.

6. The use of claim 1, wherein the binding of stem cells to the germinal centers within the lymphoid tissue is to be inhibited by administering a immune modulator that down-regulates or blocks a CD45 antigen.

7. The use of claim 1 wherein the immune modulator is radiation.

8. The use of claim 1 wherein the stem cells are either exogenous or endogenous stem cells.

9. The use of any one of claims 1 to 8, wherein the stem cells are selected from the group consisting of: Mesenchymal, mesodermal, adipose, stromal vascular, induced pluripotent, embryonic, olfactory, epidermal, neural, limbal, skin, cardiac, skeletal, myoblasts, oval, liver, epithelial, intestinal, pancreatic, corneal, and keratinocyte.