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 glucocorticoids, TNF inhibitors, or antagonists to CD26 ~~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~~ treating a disease 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~~ II 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~~lipodystrophy, 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~~in a subject wherein the subject has germinal centers within their lymphoid tissue; wherein the ~~therapeutic agent~~medicament is to be administered to said subject prior to or ~~in conjunction~~together with exogenously administered~~said~~ stem cells, wherein the medicament inhibits binding of stem cells to germinal centers within lymphoid tissue and wherein the ~~therapeutic agent~~medicament 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. Use of glucocorticoids, TNF inhibitors, or antagonists to CD26 in the manufacture of a medicament for treating a disease selected from the group consisting of: osteopetrosis, limbal stem cell deficiency, acute myocardial infarction, coronary artery disease, peripheral vascular disease, heart failure, type II diabetes mellitus, stroke, spinal cord injury, chronic wound healing, burns, fracture healing, cartilage degeneration, connective tissue diseases, osteoarthritis, renal failure, Parkinson's Disease, liver cirrhosis, dilated cardiomyopathy, retinitis pigmentosa, mastocytosis, epilepsy, myasthenia gravis, osteonecrosis, liver failure, PMD disease, lipodystrophy, demyelinating diseases, cartilage defects, retinal disease, Alzheimer's Disease, traumatic brain injury, hyperglycemia, macular degeneration, and muscle degeneration, in a subject wherein the subject has germinal centers within their lymphoid tissue;

wherein the medicament is to be administered to said subject prior to or together with exogenously administered stem cells, wherein the medicament inhibits binding of the stem cells to germinal centers within lymphoid tissue and wherein the medicament 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 or 2, 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.

4. The use of any one of claims 1 to 3, wherein the glucocorticoid is dexamethasone.

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.

Abstract

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

The present invention relates to compositions and methods of inhibiting stem cell binding to organs and tissues, including the blocking of stem cell binding to germinal centers present in lymph tissue. Disclosed are compositions and methods for regenerating germinal centers in lymphatic tissue. Included in the compositions are adjuvants, agonists to CD40, CD28 and the IL-21 receptor, and antagonist to CD20.

[Figure 1]

Abstract

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

The present invention relates to compositions and methods of inhibiting stem cell binding to organs and tissues, including the blocking of stem cell binding to germinal centers present in lymph tissue. Disclosed are compositions and methods for regenerating germinal centers in lymphatic tissue. Included in the compositions are adjuvants, agonists to CD40, CD28 and the IL-21 receptor, and antagonist to CD20.

[Figure 1]