Review Article

Journal of Genetic Engineering and Biotechnology Research

Stem Cell and Markers

Subramanyam Gangapatnam[1]* and Suneetha Subramanyam[2]

[1]*Director & Cardiologist, Narayana Medical College & Hospital, Nellore- 524003, AP, India*

[2]*Professor of Obstetrics & Gynaecology & Medical Superintendent, Narayana Medical College & Hospital, Nellore- 524003, AP, India*

***Corresponding author**

Subramanyam Gangapatnam, Director & Cardiologist, Narayana Medical College & Hospital, Nellore- 524003, AP, India, E-Mail: Director.nmch@gmail.com

Submitted: 31 Jan 2019; **Accepted**: 07 Feb 2019; **Published**: 14 Feb 2019

Abstract

Stem cells have the ability to go through various cell divisions and also maintain undifferentiated state. Stem cells are Embryonic (Pluripotent) and adult stem cells. Pluripotent stem cells give rise to all tissues such as ectoderm, mesoderm and endoderm. Embryonic stem cells isolated from inner cell mass of embryo blastocyst. Adult stem cells are also undifferentiated cells present in adult organisms and repair the tissue when damaged occurs but number in less. Adult stem cells are present in bone marrow, adipose tissue, blood and juvenile state umbilical cord and tissue of specific origin like liver, heart, intestine and neural tissue. Embryonic stem cells from blastocyst have the ethical problems and tumorogenecity. These can be identified by flow cytometry. There are wide range of stem cell markers which are useful in identifying them. Most of the pluripotent cell markers are common with tumor cell markers which throws a challenge for certainty.

Keywords: Adult Stem Cells. Embryonic Stem Cells, Flow Cytometry, Totipotent Cells, Progenitor Cells

Introduction

Stem cells are undifferentiated cells have capacity to replicate as same cells that are undifferentiated and to differentiate to an unlimited extent. Stem cells are totipotent, pluri potent, multi potent, oligopotent or unipotent. Totipotent cells give rise to all the cells in the body including placenta and are from 4 cell or Morula stage of embryo. Pluripotent stem cell forms all the cells (Ectoderm, mesoderm and endoderm cells) in the body but not placenta and originates from blastocyst. Adult stem cells may be multipotent, oligopotent or unipotent. Unipotent means cell give one type of cell only like muscle stem cell giving myocyte. Oligopotent cells will differentiate to a limited number like one or two differentiated cells like progenitor cells as seen by endothelial progenitor cells to smooth cells and endothelial cells, lymphoid and myeloid progenitor cells into other cells in the same entity. Progenitor cells will differ from adult stem cells, as they cannot replicate as the same progenitor cells even though they can become final differentiated cells. This is the intermediate stage between stem cell and fully differentiated state.

Multi Potent Stem Cells

They are unspecialized cell and forming similar cells (Self-renewal) and to differentiated cells with specialized function. These cells can develop into more than one cell type but are limited than plurepotent cells. Adult stem cells are considered as multipotent. Haemopoitic stem cells Mesenchymal stem cells are multi potent. Mesenchymal stem cells can differentiate into chondrocyes, osteocytes, and adipocytes.Haemopoitic stem cells are multipotent and differentiate into both lymphoid and myeloid series apart from their self-renewal nature. Myeloid cells include monocytes, macrophages, basophiles, eosinophils, erythrocytes, dendritic cells and megakaryocytic or platelets. Lymphoid cells include T ells, B cells and natural killer cells.

Adipose Derived Stem Cell Markers (Ads)

ADS markers are CD_{44}, ICAM /CD54 CD34 and integrin family members. Anti body applications, immune histo chemistry, immonuo cytochemistry, flow cytometry and Elisa are the important investigations to identify the various markers. Intestinal cell markers LVIGI, Bmil, tart, Hopx and LVIGI, $Lgrs^{+}$ and gremlin [1-3].

Plasticity and Tran Differentiation

Plasticity is the potentiality of the cell to have the different cell characteristics. For example, bone marrow stem cells after transplantation will function like liver or cardiac cell.

Transdifferention (TD) is also known as lineage reprogramming. It is a process in which one mature somatic cell transform into another mature somatic cell without undergoing pluri potent or progenitor state [4]. It is a type of metaphase the first example of functional trans differention and has been shown by Ferber, et al., by inducing a shift in the developmental fate of cells in liver and convert them into pancreatic beta cells [5]. Hepatocytes are obtained by liver biopsy from diabetic patient, cultured and expanded in Vivo transduced with a PDXI virus which trans differentiated into functional insulin producing beta cells and transplanted back to patient [6-8].

S.No	Embryonic stem cell (pluri potent)	Adult stem cell
1.	Can become all cell	Limit to different cell type of their tissue of origin
2.	Grown easily reactively in culture	Grown not easily

Progenitor cell can divide only limited number of times where as the stem cell can replicate indefinitely, the term progenitor cell and stem cell are equated [9,10]. Progenitor cells cannot replicate and give same progenitor cells and give only specialized cells to a limited extent.

	Stem cell	Progenitor cells
Self renewal in vitro	Unlimited	Limited
Potentiality	Multipotent	Unipotent, oligopotent
Maintenance of self renewal	Yes	No
Population	Reaches maximum number of cells before differentiated	Does not reach maximum population

Cytokines and growth factors trigger the progenitor cells, mobilize towards the damaged tissue, and differentiate into target cell. It leads to recovery of tissue. Endothelial progenitor cells, pancreatic progenitor cells, bone marrow stromal cells are used for the reparative process.

Embryonic Stem Cells (Esc) Induced Pluri Potent Cells (Ipc)

ESC and IPC are similar genetically, surface markers, transcription factors. But premature senescence of differentiated cells is seen with IPC. There is considerable variability in the efficiency of generating differenced lineages and lower efficiency seen with IPCS [11].

Allogenic Stem Cells/ Autologus Stem Cells

Autologous stem cells were initially preferred because they are instanteously available and non-immunogenic. Allogenic stem cells have the problem of immune genicity. So immunuo pheno typing of stem cells is an important aspect before giving the treatment. Major high compatibility complex (MHC) class 1 and 11 molecules (HLA I, II) are recognized. Antibody mediated rejection occur in allografts. 1gG antibodies directed to HLA class1 are seen. MHC class1 antigen HLA-A,-B,-C) and MHC class II (HLA-DR,-DQ, DP in humans) also seen [12]. There are three types of HSCT haemopoitic stem cell therapy, syngenic, autologus and allogenicc transplantation.

Syngenic Transplants

Transplantation occurring between two identical twins.

Autologus Transplants

It is taken directly from the patient and giving it to him and rejection will not occur.

Allogenic Transplants

Donor haemopoitic cells graft rejection may occur so it is essential to satisfy the compatibility of HLA, but mesenchymal stem transplantation is not common [13].

Prochymal Stem Cell Theraphy

Prochymal stem cell therapy was approved in Canada in 2012 for the management of acute graft vs host disease in children who are unresponsive to steroids [13]. It is an allogenic stem cell therapy of mesenchymal stem cells from bone marrow.

Stem Cell Sectretome

Stem cell secretome or stromal cell secretome is utilized for their inner cell communication, development of homeostasis and regeneration. Stem cell secretome consists of extracellular vesicles, exosomes, micro vesicles, peptides and cytokins. Secrotome mediate the effects of degenerative, autoimmunue and inflammatory diseases [14]. Preliminary results of phase 3 trial for GVHD were released in september 2009 [15].

Ips Cells

Takhasi and yamanka showed enforced expression of key transcription factors Oct4, sox2, Klf4 and CMYC by reprogramme mouse somatic cell such as mouse fibroblasts to pluri potency state, later yamanka demonstrated from human fibroblasts [16]. IPS cells share many key properties with ESCS including morphology, pluri potency, self renewal and similar gene expression profile.

During expantion and prolonged passage, hESc and IPS cells acquire trisony 12 and 20q 11.21 genetic amplification [17-19]. Reprogrammed cells pose a great risk of genome mutation and genome instability [20]. Epigenetic memory persists in IPS cells and has been attributed to the incomplete removal of somatic cell specific DNA methylation. DNA methylation represses the genetic transcription.

IPCS induced teratoma were more aggressive with shorter latency than ESCS [21]. This may be considered as a major obstacle for clinical use.

Harvad and john Hopkins University have shown that certain epigenic changes in IPC which can differentiate from ESC differential methylation of tissues distinguishes human induced pluri potent stem cells and fibroblasts. Erin podolak 2009 biotechniques international journal of life sciences methods. CD34 is a phosphoglycoprotein identified on haemopoitic stem and progenitor cells strong evidence demonstrates Cd34 is expressed in multipotent mesenchymal cells, muscle satellite cells, corneal keratocytes, intestinal cells, epithelial progenitor and vascular endothelial progenitors even though it is predominantly regarded as a marker of haemopoietic stem cells (HSC). So CD34 can be regarded as a general marker of progenitor cells [22].

Different CD_{34}^{+} cell types

CD34+ cell type	Associated markers	Differentiation potential	Properties
HSC and progenitors	HLA-DR, CD38	Hematopoietic cells	Large nucleus, little cytoplasm, high proliferative capacity
MSC	Stro-1, CD73, CD90, CD105, CD146, CD29, CD44, CD271	Adipogenic, osteogenic, chondrogenic, myogenic, angiogenic	High cfu colonies fibrobastic cells
Muscle Cells	CD56, Myf5, Desmin, M-cadherin, CD90, CD106, Flk-1, VEGFR, MyoD, CD146	Myogenic, adipogenic, osteogenic, chondrogenic	The $CD56^{+}CD34^{+}$ population may represent a more primitive or pluripotent stem cell. In vivo, CD34+ cells are located near the basal lamina
Keratocytes	CD34, CD133, L-selectin, keratocan, ALDH	Fibroblastic, myofibroblastic, adipogenic, osteogenic, chondrogenic	Dendritic morphology. In vitro population acquires an MSC phenotype
Endothelial cells	CD146, VE-cadherin, CD133, CD117, CD14, CD31	Angiogenesis	Quiescent in vivo/low proliferation activity

CD34 also present in epithelial progenitor intestinal and fibrocytes. CD34cells majority in bone marrow are progenitor cells [23].

Progenitor Cell Markers

Progenitor cells are satellite cells, radial glial cells, bone marrow stromal cells, periosteal progenitor, pancreatic progenitor, EPC, and blast cells. Both haemopoitic and endothelial progenitor cells expressCD^{34}, FLK-1 FLT-1, TLE2, and VE-cadherin.Endothelial progenitor cells have CD_{45}, CD_{133}, CD_{117} (C-KIT) in addition. Hepatic progenitor markers CD133 cludin-7, cadherin 22, mucin-1, ros-1 gabrl [24].

Human and mouse ESC marker panel is designed with 5 antibodies to Oct4, Nanog, SOX2, SSEA4 and TRA1-60 by abcan in USA.

Mesenchymal Stem Cell Markers

Mesenchymal stem cells are multipotent. MSC are also known as marrow stromal cells. They are derived from non haemopoitic bone marrow and also from skin, fat, periosteem. MSC can be induced to differentiate into osteoblasts, myocyte, adipocyte, beta pancreatic islet cells and neuron cells. MSC are non immunogenic and they are used as prochyl cells for allogenic transplantation. Mesenchymal stem cell markers are CD_{44}, CD_{73} and CD_{90}/ thy-1 negative markers are CD_{19} and CD_{45}.

Neural stem cells can differentiate into neurons, astrocytes and oligo dendrocytes. Neural stem cells give rise to glial progenitor and neuron progenitor cells. Glial progenitors give rise to astrocytes and oligo dendrocytes. Neuron progenitor cells give risk to neurons.

Neural Stem Cell Markers

SOX_2 , $ABCG_2$, $CXCR_4$, BMI-1, Musashi-1 GFAP, survivin, SOX1, SHH and NTF-3

Neural Progenitor Cell Markers

Cendi, MELK, MAP_2 , SIOOB, NESTIN, BETAIII TUBULIN, FABP7 VIMENTIN, PAX6

Neuron Markers are

Alpha synuclein, double cortin, GAP43, PSD95, stathmin, synapsin1, synaptophysin.

Stem cell signaling pathways (SSPS) maintain the stem cells and can pass to differentiation. Various proteins are involved the process. They are wnt proteins, pten, stat3. Signalling pathways of stem cells are notch signaling, hedgehog signaling, wnt signaling and **BMP/ Activ/nodel signaling**.

Progenitor Cells

Progenitor cell can divide only a limited number times. The potentiality olipotent and unipotent they are in the center between pluri potent and fully differentiated cell progenitor cells cannot maintain self-renewal and population does not reach maximum. Tissue damage and stress results in Progenitor cell activation by the cytokines and growth factors, repair the damage, and lost tissue. However, they are not sufficient if extensive damage occurs. Satellite cells in muscle stromal cells in bone marrow, endothelial progenitor cells in vessels, and blast cells in the haemopitic system are important progenitor cells.

Adult stem cells also behave like progenitor cells as both of them are present in the body. Adult stem cells are usually unipotent where as progenitor may be uni or oligopotent but now it has been shown that adult stem cells by reprogramming and altering the genes can be converted to embryonic stem cells which are pluri potent. Oligo potent cells can differentiate into only a few cells such as lymphoid or myclid stem cells [25]. Unipotent stem cell produces only one cell type. They are different from other progenitor cells because they have the property of self renewal even though their capacity is to differentiate into one cell. Hepatoblast will differentiate to Hepatocyte. Markers of Embryonic, Multipotent, unipotent and progenitor cells. SSEA1, SSEA4, TRA 1-60, TRa1-81, AP, FZD-1-TDGF, are the established markers for embryonic stem cells. SSEA is a stage specific embryonic antigen [26,27]. Other cell markers vary depending on their site of origin.

Transcription Factors

Reprogramming of fibroblast into IPS cells were developed by the over expression of self of genes Oct4 CMYC, SOC@ and KIF4 [28,29].

SOX1, SOX3 SOX15, SOX18 can generate IPS cells and they have down regulation CD13 a fibroblast marker, up regulation of SSEA4 and TRA 1-60 .endogenous expression of nanog gene similar expression like pluri potent cells are also seen for TRA1-81, TRA2-49/6E, genome wide H3 K4 me3 and H3K 27 me 3. In mouse

IPCS express genes like undifferentiated stem cells oct ¾, SOX2, Nanog, GDF3 Rex1, FGF4, ESG1, DPPA2, DPPA4, and hTERT.

Ectoderm markers are OTX2, chordin P63/ TP73L, FGF8, Pax2, Foxj3, Pax6, GBX2, SOX1, nestin, beta tubulin and Noggin. Endoderm markers are cripto, BMP4/wnt3 to sustain nodal signaling from implantation throughout gastruation [30]. Other markers are enzymes alkaline phosphatase, telomerase and small molecules like lectins, peptides and quantum dots.

Multipotent Stem Cells

Haemopoitic stem cells will give rise to differentiated cells of myeloid, lymphoid series, enthrocytes and platelets. HSC has long time self renewl unlike progenitor cells. Haemopoitic stem cell markers are CD48, CD150, CD244, CD_{34}, SCA1+, Cd135, CD150 [31-34]

Lymohid lineage markers are Ckit Sca1, LIN- and $1L7R^{+}$ (labome 2015 labone the world of laboratories 2015) Cancer stem cell markers are CD44, CD133, CD24, CD90, Cd271, CD49F, CD13,CXCR4, CD44. And cd 44 is the prominent marker [35-43].

Cardiac Stem Cell Markers (csc)

Cardiac stem cell markers have self-renewal and differentiate into cardiomyocytes vascular smooth muscle cells and endothelial cells. FLK1+,cd 31.VE Cadherin are the haemangioblast markers. FLK1 is a receptor for VEGF. NKX2.5 is expressed in cardiomyocyte [44]. Osteoprogenitor markers are TGF beta, BMP-2 and bFGF, gremin [45,46].

Osteocyte markers are TGF beta, Rankl and MSCF [47].

Mesenchymal stem cell markers are CD_{10}, CD_{13}, CD_{73}, CD_{105}, CD_{271}, CD_{349}, CD_{90}, CD_{146} [48].

Adipose derived stem cell markers are CD_{44}, ICAMI, and CD_{54} (13)

References

1. Haegebarth A, Clevers H (2009) Wnt signaling, lgr5, and stem cells in the intestine and skin. Am J Pathol 174: 715-721.
2. Munoz J, Stange D, Schepers A, van de Wetering M, Koo BK, et al. (2012) The Lgr5 intestinal stem cell signature: robust expression of proposed quiescent '+4' cell markers. EMBO J 31: 3079-3091.
3. Worthley D, Churchill M, Compton J, Tailor Y, Rao M, et al. (2015) Gremlin 1 identifies a skeletal stem cell with bone, cartilage, and reticular stromal potential. Cell 160: 269-284.
4. Orkin SH, Zon LI (2008) Hematopoiesis: An Evolving Paradigm for Stem Cell Biology. Cell 132: 631-644.
5. Ferber S, Halkin A, Cohen H, Ber I, Einav Y, et al. (2000) Pancreatic and duodenal homeobox gene 1 induces expression of insulin genes in liver and ameliorates streptozotocin-induced hyperglycemia. Nature medicine 6: 568.
6. Aguayo-Mazzucato C, Bonner-Weir S (2010) Stem cell therapy for type 1 diabetes mellitus. Nature Reviews Endocrinology 6: 139.
7. Brignier AC, Gewirtz AM (2010) Embryonic and adult stem cell therapy. J Allerg Clin Immun 125: S336-S344.
8. Sapir T, Shternhall K, Meivar-Levy I, Tamar Blumenfeld, Hamutal Cohen, et al. (2005) Cell-replacement therapy for diabetes: Generating functional insulin-producing tissue from adult human liver cells. Proc Natl Acad Sci 102: 7964-7969.
9. Seaberg RM, Van Der Kooy D (2003) Stem and progenitor cells: The premature desertion of rigorous definitions. Trends in Neuroscience 26: 125-131.
10. Dorland WA (2011) Dorland's Illustrated Medical Dictionary 32: Dorland's Illustrated Medical Dictionary. Elsevier Health Sciences.
11. Puri MC, Nagy A (2012) Concise review: embryonic stem cells versus induced pluripotent stem cells: the game is on. Stem Cell 30: 10-14.
12. Charron D (2013) Allogenicity & immunogenicity in regenerative stem cell therapy. Indian j med res 138: 749.
13. Petra R (2012) Prochymal—first stem cell drug approved. Bexhill-on-Sea (UK), Medical News Today, May 22. www.medicalnewstoday.com/articles/245704.php.
14. Teixeira FG, Carvalho MM, Sousa N, Salgado AJ (2013) Mesenchymal stem cells secretome: a new paradigm for central nervous system regeneration?. Cell Mol Life Sciences 70: 3871-3882.
15. Osiris Therapeutics Announces Preliminary Results for Prochymal Phase III GVHD Trials. http://investor.osiris.com/releasedetail.cfm?releaseID=407404.
16. Takahashi K, Yamanaka S (2006) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126: 663-676.
17. Lefort N, Feyeux M, Bas C, Féraud O, Bennaceur-Griscelli A, et al. (2008) Human embryonic stem cells reveal recurrent genomic instability at 20q11.21. Nat Biotechnol 26: 1364-1366.
18. Spits C, Mateizel I, Geens M, Mertzanidou A, Staessen C, et al. (2008) Recurrent chromosomal abnormalities in human embryonic stem cells. Nat Biotechnol 26: 1361-1363.
19. Mayshar Y, Ben-David U, Lavon N, Biancotti JC, Yakir B, et al. (2010) Identification and classification of chromosomal aberrations in human induced pluripotent stem cells. Cell Stem Cell 7: 521-531.
20. Ramos-Mejia V, Munoz-Lopez M, Garcia-Perez JL, Menendez P (2010) iPSC lines that do not silence the expression of the ectopic reprogramming factors may display enhanced propensity to genomic instability. Cell Res 20: 1092-1095.
21. Gutierrez-Aranda I, Ramos-Mejia V, Bueno C, Martin Munoz-Lopez, Pedro J Real, et al. (2010) Human induced pluripotent stem cells develop teratoma more efficiently and faster than human embryonic stem cells regardless the site of injection. Stem Cells 28: 1568-1570.
22. Sidney LE, Branch MJ, Dunphy SE, Dua HS, Hopkinson A (2014) Concise review: evidence for CD34 as a common marker for diverse progenitors. Stem cells 32: 1380-1389.
23. Majeti R, Park CY, Weissman IL (2007) Identification of a hierarchy of multipotent hematopoietic progenitors in human cord blood. Cell Stem Cell 1: 635-645.
24. Mladen 1 yochev, petar N.grozdanon, brigadjoseph, sanjeev gupta, mariana D. Dabeva (2007) Novel hepatic progenitor cell surface markers in the adult rat liver. Hepatology 45: 139-149.
25. Ruiz JC, Sherwood S, Clark J (2008) inventors; Vesta Therapeutics Inc, assignee. Matrix and method for isolation of hepatic progenitor cells. United States patent application US 11/768,452.
26. Kooner KS, Joseph A, Shar A, Francisco A Marquardt, Mohannad AlBdoor, et al. (2011) Dallas Glaucoma Registry: Preliminary Results. J Clinic Experiment Ophthalmol 2: 164.
27. Yu L, Ma J, Ma R, Yongping Zhang, Xiaoyu Zhang, et al. (2011)

Repair of Excitotoxic Neuronal Damage Mediated by Neural Stem Cell Lysates in Adult Mice. J Cell Sci Ther 2: 109.
28. Lambert APF, Moura D, Zandonai AF, Mariana Assis Lemos, Jeremiah Lubianca, et al. (2011) The Role of DNA Damage and Repair Proteins in Adipose-Derived Adult Stem Cell Differentiation in Neural- Like Cells. J Tissue Sci Eng 2: 109.
29. Newman JP, Yi TX, Chan JKY, Berwini Endaya, Paula Lam (2011) Migration of Human Fetal Bone Marrow-derived Mesenchymal Stem Cells: Possible Involvement of GPCR and MMPs. J Stem Cell Res Ther S2: 007.
30. Shevinsky L, Knowles B, Damjanov I, Solter D (1982) Monoclonal antibody to murine embryos defines a stage-specific embryonic antigen expressed on mouse embryos and human teratocarcinoma cells. Cell 30: 697-705.
31. Henderson J, Draper J, Baillie H, Fishel S, Thomson JA, et al. (2002) Preimplantation human embryos and embryonic stem cells show comparable expression of stage-specific embryonic antigens. Stem Cells 20: 329-337.
32. Nakagawa M, Koyanagi M, Tanabe K, Takahashi K, Ichisaka T, et al. (2008) Generation of induced pluripotent stem cells without Myc from mouse and human fibroblasts. Nat Biotechnol 26: 101-106.
33. Wernig M, Meissner A, Cassady J, Jaenisch R (2008) c-Myc is dispensable for direct reprogramming of mouse fibroblasts. Cell Stem Cell 2: 10-12.
34. Ben-Haim N, Lu C, Guzman-Ayala M, Pescatore L, Mesnard D, et al. (2006) The nodal precursor acting via activin receptors induces mesoderm by maintaining a source of its convertases and BMP4. Dev Cell 11: 313-323.
35. Chan K, Espinosa I, Chao M, Wong D, Ailles L, et al. (2009) Identification, molecular characterization, clinical prognosis, and therapeutic targeting of human bladder tumor-initiating cells. Proc Natl Acad Sci USA 106: 14016-14021.
36. Akashi K, Traver D, Miyamoto T, Weissman IL (2000) A clonogenic common myeloid progenitor that gives rise to all myeloid lineages. Nature 404: 193-197.
37. Al-Hajj M, Wicha M, Benito-Hernandez A, Morrison SJ, Clarke MF (2003) Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci USA 100: 3983-3988.
38. Li C, Heidt D, Dalerba P, Burant CF, Zhang L, et al. (2007) Identification of pancreatic cancer stem cells. Cancer Res 67: 1030-1037.
39. Takaishi S, Okumura T, Tu S, Wang SS, Shibata W, et al. (2009) Identification of gastric cancer stem cells using the cell surface marker CD44. Stem Cells 27: 1006-1020.
40. Hurt E, Kawasaki B, Klarmann G, S B Thomas, W L Farrar, et al. (2008) CD44+ CD24(-) prostate cells are early cancer progenitor/stem cells that provide a model for patients with poor prognosis. Br J Cancer 98: 756-765.
41. Prince M, Sivanandan R, Kaczorowski A, Wolf GT, Kaplan MJ, et al. (2007) Identification of a subpopulation of cells with cancer stem cell properties in head and neck squamous cell carcinoma. Proc Natl Acad Sci USA 104: 973-978.
42. Dalerba P, Dylla S, Park I, Liu R, Wang X, et al. (2007) Phenotypic characterization of human colorectal cancer stem cells. Proc Natl Acad Sci USA 104: 10158-10163.
43. Zhang S, Balch C, Chan M, Lai HC, Matei D, et al. (2008) Identification and characterization of ovarian cancer-initiating cells from primary human tumors. Cancer Res 68: 4311-4320
44. .Iida M, Heike T, Yoshimoto M, Baba S, Doi H, et al. (2005) Identification of cardiac stem cells with FLK1, CD31, and VE-cadherin expression during embryonic stem cell differentiation. FASEB J 19: 371-378.
45. Long M, Robinson J, Ashcraft E, K G Mann (1995) Regulation of human bone marrow-derived osteoprogenitor cells by osteogenic growth factors. J Clin Invest 95: 881-887.
46. 46. Worthley D, Churchill M, Compton J, Yagnesh Tailor, Meenakshi Rao, et al. (2015) Gremlin 1 identifies a skeletal stem cell with bone, cartilage, and reticular stromal potential. Cell 160: 269-284.
47. Kulkarni R, Bakker A, Everts V, Klein-Nulend J (2010) Inhibition of osteoclastogenesis by mechanically loaded osteocytes: involvement of MEPE. Calcif Tissue Int 87: 461-468.
48. Buhring H, Battula V, Treml S, Schewe B, Kanz L, et al. (2007) Novel markers for the prospective isolation of human MSC. Ann N Y Acad Sci 1106: 262.