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Editorial

Mesenchymal Stem Cells: Novel Therapeutic Option Besides their Stem Cell Properties-Utilizing the Niche Effect

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Abstract

Mesenchymal StemCells (MSC's) are multipotent stem cells having diverse inflammatory, antimicrobial and regenerative therapeutic efficacy because of which there is effect on damaged tissues and inflammation.MSC's may be used for direct clinical effects but its manipulation of host response in different occasionsvia cell-cellactions including through production of bioactive secreted factors which include smallproteins, chemokines, cytokines & other cellular regulators. The following factors can induceangiogenesis by chemotactic and induction of cellular recruitment manner. This differential can also be bettered in vitro before in vivo administration potentiating the versatility of the MSC's => active communication between newly administered cells&host tissue.Various clinical trials are on and studiesconducted on MSC'sability for therapy in human disease.Still controversy existand deeper insight required to bring them into therapeutic arena.

Editorial

Introduction

Mesenchymal stem cells constitutive - hematopoietic stromal cells which have the differentiation capacity along with leading to regeneration of mesenchymal tissue like bone,cartilage, muscle,ligament,tendon and adipose tissue,along with lungs,pancreas,CNS,GIT and the circulatory system [1]. In bone marrow, they are rare and represent 1in 10,000 nucleated cells. They can enlarge multifold in culture while retain in their growthas well as multilineage potential.For identification of MSC's expression of certainmolecules including CD105(SH2),and CD73(SH3/4),absence of hematopoietic makers CD34, CD45 and CD14 is required.These properties make these cells ideal candidates for tissue engineering.On systemic administration MSC's can migrate to sites of important role in tissue specific homing of leukocytes and have been involved in trafficking of hematopoietic precursors into and through tissues.Functional expression of various chemokines receptors and adhesion molecules on human MSC's utilizing their chemokine-chemokine receptor interactionsmight be an important way of increasing their ability to correct inherited disorders of mesenchymal tissues or facilitate tissue repair in vivo [2]. Still there is controversy regarding their use in therapeutics and deeper understanding regarding their being important niche factors may help in developing them for till now unsuccessful use in therapeutic arena.

Wound Treatment by Stem Cells

For healing of wounds to occur there is interaction of mitosis, inflammation, synthesis, angiogenesis and remodeling of extracellular matrix [3]. Without treatment these wounds become chronic requiring further treatment [3]. Hence the pro and anti-

inflammatory responses besides angiogenesis [1] is offered by MSC's.Use of MSC's regarding wound treatment is both by direct as well as indirectdelivery to the wound site.For indirect methods MSC's are infused into the circulating system [4]. MSC's home at sites of injury giving a therapeutic benefit [4]. MSC' s reach the region of injury by trafficking to chemokine ligand 7(CCL7) [5,6]. On reaching the injury area MSC's leave the vasculature in the connective tissue stromal region [4]. MSC's respond to the specific tissue milieuand themselves add to the milieu by secreting biomolecules [7]. By this interaction occurring between the tissue and MSC's gives the efficacy,potency and total therapeutic effects of MSC's.I/v deliveryof MSC's means localization in the lungs.Based on this fact MSC's get used in treatment of lung diseases which are associated with marked inflammation like asthma and cystic fibrosis.Although initially MSC's are distributedin the lung they are hardly seen in lung after a week in most studies. This maybedue to the proposal that localization of MSC's to tissue sites of damage followed by migration to the destined tissue occurs.Indirect delivery cause the risk that the MSC's may go to the spleen,liver and lungand if destined site for effect is not in these areas there may be a marked reduction in therapeutic efficacy.New way of getting the therapeutic effect of MSC at their site of impact have become important research issue involving direct application of MSC's to the wound areas [4].The new methods include direct injection into the wound site as seen in new models of urinary incontinence,arthritic lesionsalong with different kind of neuronal diseases [7]. For use of this method MSC's need to be injected close to the wound siteor put directly onto site of injury [4]. Stoff et al showed that human MSC's n injected close to injury site in immunocompetent rabbits improved tissue functionand decreased the amount of scarring [8].They also found that no evidence of rejection of MSC's existed. Similarly, Falanga et al placed MSC's directly on the site of injury=>wound betterment [9]. Stoff et al demonstrated that using fibrin MSC's sprayed in wound =>healing much faster and a better histologyas compared to wound not treated with topical MSC's [4,9]. This creates path for studying immunomodulation action of MSC's in wound healing.Previous studieshave shown that MSC's can be activated by use of cytokines like granulocyte colony stimulating factor(GM-CSF),Tumor Necrosis Factor Alpha (TNF-α) or Interferon Gama(IFN-γ)to increase activity and therapeutic efficacy. Once MSC's are activated using IFN-γ, MSC's secrete soluble factors which enhance killer T cells and early stage dendritic cells [4,10], as shown in these studies.As per the disease or specific setup MSC's maybe made even more potent with the aspect of application.Moreover, soluble factors developed by MSC' s may also give new and innovative directions in cell therapy beyond treating wounds and in commercialization of studied products [4,11].

Orthopedic Use of Stem Cells

As shown earlier MSC's bear the capacity to move chemotactically to inflammation and infection sites in an organism's tissues [12].They secrete variety of cytokines, which exert anti-inflammatory mechanisms in the micro environment [12]. There is an active role of MSC's in causing tissue regenerationlike by giving them i/v they secrete soluble factors and regulate inflammatory response [12]. They also secrete factors which help in bone regeneration.For cartilage regeneration MSC's use is to repair damage. Shafiee et al in a rabbit modelshowed that full thickness cartilage defects showed improved healing as seen by macroscopicscore [13]. 6months following the study MSC's showed efficacy of chondrocyte transplantation along with tissue regeneration [13]. Overall clinical scores were markedly improved although no complete hyaline cartilage was found [14]. Scott et al used cellular allograft having MSC's for high risk foot and ankle reconstruction [14]. MSC's have come to be of use in vivo secondary to their osteogenic potential.Stem cells got grafted in hind foot and ankle surgery which improved healing and interval to partial weight bearing which suggests the use in foot and ankle surgery [14].

Biggest problems come in big bone defects due to infection, tumors, trauma, insufficient blood supply or due to post infection sequelae [15]. In these defects since blood supply is very limited they are difficult to treat by producing autologous bone grafts [15]. Also these bone graft cause a great level of morbidity in donors along with increased risk of disease transmission or rejection in recipients [15]. Granerro-Motto in a mouse models showed bone marrow MSC's showed movement toward the site of fracture to begin regeneration after systemic application of MSC's [16]. Bone marrow MSC'sincreased tissue healing in the site and actively aided to a marked fracture promoting the production of angiogenic paracrine factors [15,16]. Lin et al used luminescence and fluorescence tagged MSC's and demonstrated that by whatever means MSC's are given they localize to areas of injury including bone damage.With time the MSC's became less dense but had the ability to localize to bone injury followed by some regenerative capacity [17]. Still more work is needed in terms of bettering wound healing by developing new and innovative scaffolds and increasing the production of soluble mediators.

Hematological Pathology and Stem Cells

Hematological Stem cells (HSC's) get used for hematological pathologies,but for many side effectslike bleeding, Graft versus Host Disease(GvHD)and other ways of rejection [18]. MSC's can help in HSC engraftmentand prevent rejectionwith their properties of immune suppression.Besides that MSC's produce cytokineswhich aid hematopoiesis and can improve the efficiency of MSC's in bone marrow recovery after chemotherapy and/or irradiation [18]. After MSC/HSC infusion in a patient having severe idiopathic aplastic anemia, most of these problems got resolved, although still there was no recovery of hematopoietic tissue [18]. Thus, MSC had the capability to be used as safe addition for useas

a co-infusion cellular therapeutic with HSC's [18]. There was further proof of MSC use in hematopoietic pathologyin a phase 1 clinical trial. In the trial, hematopoietic recovery occurred for most patients with 50%of patients not developing GvHD [18,19]. The suggestions got from these studiesusing cultured expanded MSC's with the HSC's for transplantation could be an effective and safe process that could minimizethe side effectsto facilitate bone marrow recovery [19].

Neurological Diseases and Stem Cells

MSC's have the capacity to change in to neurons and astrocytes [20]. Because of these findings mouse models have been tested for MSC transplantation on mice with acid sphingomyelin, a neurodegenerative disease.MSC infusion caused a delay in the initiation of neurological abnormalities and increased overall survival in the mouse model [18]. On this basis to study the effectiveness of MSC transplantation in human beings having amyotrophic lateral sclerosis characterized by degeneration of motor neurons and muscle functionality a study was started [18].Taking bone marrow aspirates from every patient of the 7 patients MSC cultures were done over 3-4 weeks.On injecting MSC's into spinal cord of the patient Magnetic Resonance Imaging(MRI) was done at 3 and 6months [20].There was a pattern of increase in muscle strength slow though there is not enough data to conclude for how long the direct effect can be sustained. Various conditions like stroke, trauma or basic neurological conditions can produce situations mimickingthat caused by Central Nervous System (CNS) injury. Neural MSC's (NSC's) and MSC's are used for the purpose of regeneration in CNSto prepare new cells which replace that were lost [21,22]. Still this has not been totally successful because of oxidative stress and toxic byproducts which have a bearing on MSC transplantation [22,23]. Because of this there is slowing of tissue regeneration along with decreased longevity.Carbon nanotubes(CNT's)are being used to help MSC differentiation in the field of Nanomedicinein this arena.CNT/MSC composites were put to use for increasing neurite growth after CNS damage.Both In vivo as well as in-vitrosetting biocompatibilityof the CNT's with the MSC's and NSC's was shown [22]. This could direct neuron function and promotehealing of damaged neural tissue [21,22]. In Parkinson's disease MSC's have been shown to beuseful for inhibiting inflammatory cytokine production,a main factor which contributes to the disease.Another way of giving MSC's was from nose as shown by workers in Tubingen, Germany. In Parkinson's induced rat model intranasal bone marrow MSC's were given [20]. MSC's were detected in olfactory bulb,cortex,striatum,cerebellu m,brain stem and hippocampus up to 4-5 months after they were given in the rodents which gives data which suggests MSC's can multiply in vivo successfully. Intranasal administration increased tyrosine hydroxylaselevels in the lesioned ipsilateral striatum & substantia nigra while levels of toxin 6 hydroxy dopamine got reduced [23]. Reduction of TNF-α,IL2,6&12,&IFN-γ were seenin combination with cell therapy [23].The i/nasal method of administration could change the face of MSC administration [23].

In case of genetically inherited diseases bone marrow MSCs have been used as therapeutic for Hurler syndrome & metachromatic leukodystrophy. After bone marrow transplantation from these sibling donors 11 patients having metachromatic leukodystrophy were given bone marrowMSC'sfrom their sibling donorsby injection significant improvements occur in nerve conduction velocities in 4/11patients [23,24]. Still more studies are needed,before one can conclude success or failure ofmarrow MSC'S in situations of inherited diseases [24].

Diabetes &Stem Cells

In type 1 DM there is shortage of insulin producing cells in diabetic pancreas&with useof islet transplantationit has been tried-to reduce the need for insulin injections on a regular basis [25]. The problem is that pancreas &islet cells are scarce &are rejected by recipients after transplantation.Use of ESC's has ethical issues besides high rates of rejection after use [21].Thus, Autologous Stem Cells (ASC) became a good alternative because there is no risk of rejection&noethical stigma ofESC's.Most attainable sets of ASCs' in peripheral bloodwhich also contains the normal human insulin producing cells [24,25]. These cells can be isolated by ease fromautologous blood based on this phenotype [25], Zhao et al conductedexperiments where peripheral blood insulin containing cells could be isolated and preservedfor future insulin productionsince they have the ability to cling onto polystyrene petri-dishand they show transcription and insulin production at protein & mRNA level [25], reviewed In KKK [26]. This technology could allowpatients to generate their own insulin producing cells [25] & with this complication of rejection by immune system gets removedand decreases the time to transplant because of shortage of donors & has no ethical issues. Voltarelli et al did a clinical trial on newly diagnosed Type1DM patients who showed long periods of insulin independence in most participants after transplantation with MSC's [27]. Besides this MSC's can also be used in DM when defective wound healing &diabetic neuropathy [28] is there. Thus, MSC's may have marked effect in giving better care in DM.

Lung Diseases and Stem Cells

MSC's carry the capacityto affect damaged or inflamed lung areasby repairing the tissue or stimulating the host tissue to regenerate itself.In fibrotic lung disease, there is a possibility that MSC's may reverse ECM deposition and collagen synthesis.In case of Idiopathic Pulmonary Fibrosis(IPF),lung fibrosis=>scarring and terminal pulmonary insufficiency [28-30]. In a Bleomycin model which shows morphology same as IPF, bone marrow MSC administration following bleomycin treatment showed decrease in both

collagen deposition &in inflammation [29-31]. In another study, it was found that murine MSC's home to lung in response to injuryand become epithelium like in phenotype while decreasing lung tissue inflammation [29,31-33]. There is great morbidity and mortalityrate in Acute Lung Injury (ALI) [4,33]. Injury to alveolar epithelium, vascular endothelium and endotoxins are common effects.Treatment with MSC's decreased proinflammatory cytokines while the resolution response anti-inflammatory cytokine levels increased [31,34]. Also, mice receiving murine MSC's had decreased levels of alveolar capillary permeability, extravasation, edema and mortality [31]. MSC's in patients suffering from chronic obstructive pulmonary disease (COPD) characterized by severe lung and systemic inflammationin a placebo controlled study, MSC's got infused i/v [35].There was a marked decrease in Circulating Reactive Protein (CRP) with MSC treatment which created a basis for continuous clinical trials of MSC's for COPD [35], endotoxin induced lung injury[23,31,34].The use of MSC's in ALI,COPD &IPFcan be a therapeutic option as suggested by these studies.

Cystic Fibrosis (CF) and Stem Cells

Cystic Fibrosis CF occurs secondaryto mutations in Cystic Fibrosis Transmembrane Regulator(CFTR)gene. This mutation affects practically every organ in the body→main causes of morbidity &mortality is the inability to controlling infection and inflammation.

Bone Marrow MSC's have both anti-inflammatory and antimicrobial properties,studies were done to investigate properties of MSC's for use for therapeutic purpose in murine models of CF lung infection & inflammation [1,35,36]. In this model, CF mice lose considerable weight without resolution&often succumb to infection.Bone marrow MSC's used for treatment purposes in these model => weight changes same as control mice which improved gross lung pathology and decreased cellular recruitment into the lung.Bone marrow MSC's moved the pulmonary differential from mainly neutrophils to an equally distributed differential of both neutrophils & macrophages [36]. What is important is that even though inflammatory profile was decreased in severity there was no increase in bacterial as well.These studies have given the 1st series of preclinical data to support potential of using MSC as a newcell based treatment option in CF [35,37].

Allergy and Asthma & Stem Cells

Asthma ischaracterized by airway inflammation and reactivity which =>lung injury finally. MSC's are properties of anti-inflammatory as well as growth promoting mechanism which make them an attractive treatment approach for chronic asthma.Studies inWeiss laboratory demonstrated thatin ovalbumin asthma model given murine MSC'S has a marked decrease in airway hyper responsiveness and eosinophil levels in Broncho Alveolar Lavage (BAL) [33]. The direction of T-cell response shifting away from Helper Cells (Th2) cytokines is also influenced [33] MSC's administered to mice decreased epithelial hyperplasia, inflammation, ECM deposition as shown by separate studies found in these models despite human MSC' being used in mice [31,37].

Immunomodulatory properties of MSC's give new way of treating allergy.In Sun laboratorymice received allergic inflammation in their upper and lower airways. With the use of murine MSC'sthe mice showed inhibited nasal eosinophilia and lung pathology [38] With the pathology suppressed along with balancing of immune response inflammationwas markedly decreased in both upper and lower airways in the model after challenge with MSC's [38]. This may be relevant in hematopoietic stem cells source.Bone marrow stromal cells inhibit mast cell function though Cyclooxygenase (COX2)dependent mechanisms which suggest that there maybe potential applications of bone marrow MSC's towards the treatment of mast cell inflammatory diseases such as anaphylaxis [39] but the source of MSC's maybe important in these studies. These observations give credit to MSC use as an alternative cell source for the treatment of severe allergic diseases.

Cardiac Disease and MSC's

Williams&Hare reviewed the use of MSC's in cardiac diseases.Animal Models of myocardial infarction have shown the abilityof transplanted MSC's to engraft and differentiate into cardiomyocytes and vasculature cells,recruiting endogenous cardiac stem cells and secrete a wide type of paracrine factors.These properties can be utilizedfor both avoiding and revert remodeling in the damaged ischemic ventricle.In phase I clinical trials MSC therapy improved left ventricular function,induce reverse remodeling and decrease [40].

Further Sahara et al reviewed how these discoveries of MSC's in cardiac regenerative medicine can be used for programming and reprogramming a human heart cell.Progress in this field Has been affected by a lack of reproducible and convincing evidencewhich has given modest outcomes and is still far from clinical practiceand have discussed current controversies and for making cardiac regenerative medicineforward cellular and molecular programs are discussed [41].

References

1. Bonfield TL, Lennon D, Ghosh SK, Di Marino AM, Weinberg A, et al. (2013) Cell based therapies aides in infection and inflammation in the murine model of cystic fibrosis and lung disease. Stem Cell Discovery 3: 139-153.

2. Chamberlaine G, Fox J, Ashton B, Middleton J (2007) Concise Review: Mesenchymal Stem Cells: Their Phenotype, Differentiation Capacity, Immunological Features and Potential for Homing. Stem Cells 25: 2739-2749.

3. Caplan AI, Correa D (2011) The MSC: an injury drug store Cell Stem Cell 9: 11-15.

4. Sorrell MJ, Baber MA, Caplan AI (2009) Influence of adult mesenchymal stem cells on in-vitro vascular formation. Tissue Eng Part A 15: 1751-1761.

5. Da Silva Meirelles L, Fontes AM, Covas DT, Caplan AI (2009) Mechanism involved in the therapeutic properties of mesenchymal stem cells. Cytokine and Growth Factor Reviews 20: 419-427.

6. Ren G, Zhang L, Zhao X, Xu G, Zhang Y, et al. (2008) Mesenchymal stem cells: mediated immune suppression occurs via concerted action of chemokines and nitric oxide. Cell Stem Cell 2: 141-150.

7. Murphy BM (2013) Mesenchymal stem cells: environmentally responsive therapeutics for regenerative medicine. Experimental and Molecular Medicine 45: e54.

8. Stoff A, Moore ST, Numnum M, Siegal GP, Chow LT, et al. (2009) Promotion of incisional wound repair by human mesenchymal stem cell transplantation. Experimental Dermatol 18: 362-369.

9. Falonga V, Iwamoto S, Chatier M, Yufit T, Butmarc J, et al. (2007) Autologous bone marrow derived cultured mesenchymal stem cell derived in a fibrin spray accelerate healing in murine and human cutaneous wounds. Tissue Eng 13: 1299-1312.

10. Ghannam S, Boufl C, Djounaud F, Jorgensen C, Nels D (2010) Immunosuppression by mesenchymal stem cells: mechanisms and clinical applications. Stem Cell Res Ther 15: 2.

11. Dexter TM, Allen TD, Lajtha LG (1977) Conditions controlling the proliferation of hematopoietic stem cells in vitro. J of Cell Physiol 91: 335-344.

12. Shi C (2012). Recent progress towards understanding the physiological function of bone marrow mesenchymal stem cells. Immunology 136: 133-138.

13. Shafee A, Soleimani M, Chaneidhari GA, Sayedjafari E, Dodel M, et al. (2011) Electro span nanofiber based regeneration of cartilage enhanced by mesenchymal stem cells. J Biomed Mater Res A 99: 467-478.

14. Scott R, Hyer CF (2013) Role of cellular allograft containing mesenchymal stem cells in high risk foot and ankle reconstruction. J Foot Ankle Surg 52: 32-35.

15. Schmitt A, Van Griensven M, Imhoff AB, Buchmann S (2012) Application of stem cells in orthopedics. Stem Cell Int 2012: 394962.

16. Granero-Molto F, Weis JA, Miga MI, Landis B, Myers TJ, et al. (2009) Regenerative effect of transplanted mesenchymal stem cells in fracture healing. Stem Cells 27: 1887-1898.

17. Lin P, Caplan A, Kean TJ, Awadallah A, Dennis JE, et al. (2014) Serial transplantation and long term engraftment of intraarterially delivered clonally derived mesenchymal stem cells to injured bone marrow. Molecular Therapy 22: 160-168.

18. Giordano A, Galderisi U, Marino IR (2007) From the laboratory bench to the patient's bed side: an update on clinical trials with mesenchymal stem cells. J Cell Physiol 211: 27-35.

19. Lazarus HM, Haynesworth SE, Gerson SL, Rosenthal NS, Caplan AI (1995) Ex vivo expansion and subsequent infusion of human bone marrow derived stromal progenitor cells (mesenchymal progenitor cells): implications for therapeutic use. Bone Marrow Transplantation 16: 557-564.

20. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, et al. (2013) Multilineage potential of adult human mesenchymal stem cells. Science 284: 143-147.

21. Fabino A, Prato M, Ballerini L (2013) Carbon Nano tubes in neuro regeneration and repair. Advanced drug Delivery Reviews 65: 2034-2044.

22. Chao TI, Xiang S, Chen CS, Chin WC, Nelson AJ, et al. (2009) Carbon nanotubes promote neuronal differentiation from human embryonic stem cells. Biochemical Biophysical Research Communications 384: 426-430.

23. Danielyan.Inhaling stem cells for treating Parkinsons's. Cell Medicine. In Press.

24. Koc ON, Day J, Nieder M, Gerson SL, Lazaeus HM, Krivit W (2002) Allogenic mesenchymal stem cells infusion for treatment of Metachromatic Leuko Dystrophy (MLD) and Hurlers Syndrome (MPS-IH). Bone Marrow -Transplant 30: 215-222.

25. Zhao Y (2007) New hope for diabetics: adult blood stem cells can make insulin. Discovery Medicine 7: 63-67.

26. Kochar Kaur K, Allabbadia G, Singh M (2017) An Update on Etiopathogenesis and Management of Type 1 Diabetes Mellitus. Open Access Journal of Endocrinology 1: 1-23.

27. Voltarelli JC, Couri CE, Rodriques MC, Moraes DA, Pieroni F, et al. (2011) Stem cell therapies for type 1 diabetes mellitus. Indian Journal of Experimental Biology 49: 395-400.

28. Sukpat S &Patumraj S (2013) Vasculoprotective effects of combined endothelial progenitor cells and mesenchymal stem cells in diabetic wound care: their potential role in decreasing wound oxidative stress. BioMed Research International 2013: 459196.

29. Tzouvelekes A, Antoniadis A, Bourus D (2011) Stem Cell Therapy in pulmonary fibrosis. Current Opinion in Pulmonary Medicine 17: 368-373.

30. Toonkel RN, Hare JM, Mathay MA, Glassberg MK (2013) Mesenchymal stem cells and idiopathic pulmonary fibrosis.Potential for clinical testing. The American Respiratory and Critical Care Medicine 188: 133-140.

31. Nueringer IP & Randell SH (2006) Lung stem cell update: promise & controversy. Mondali Arch Chest Discovery 65: 47-51.

32. Weiss DJ, Casaburi R, Flannery M, Le-Roux -Williams M, Tashkin DP (2013) A placebo controlled randomized trial of Mesenchymal stem cells in COPD. Chest 143: 1590-1598.

33. Weiss DJ Oritz A, Panoskaltsis-Mortari, Prockop DJ (2008) Stem Cells and cell therapies in lung biology & lung diseases. Proceedings of The American Thoracic Society 5: 637-667.

34. Krasnodembskaya A, Song Y, Fang X, Gupta N, Serikov V, et al. (2010) Antibacterial effect of human Mesenchymal stem cells is mediated in part from secretion of the antibacterial peptide LL-37. Stem Cells 28: 2229-2238.

35. Bonfield TL, Nolan MT, Lennon DP, Caplan AI (2010) Defining human Mesenchymal stem cells efficacy in vivo. J of Inflammation 7: 51.

36. Bonfield TL, Caplan AI (2010) Adult Mesenchymal stem cells an innovative therapeutic for lung diseases. Discovery Medicine 4: 337-345.

37. Bonfield TL, Koloze MT, Lennon B, Zuchowski SE, Yang SE, et al. (2010) Human Mesenchymal stem cells suppress chronic airway inflammation in the murine ovalbumin asthma model. The American J of Physiology-Ling Cellular and Molecular Physiology 299: L760-L770.

38. Sun Y, Deng M, He J, Zeng QX, Wen W, et al. (2012) Human Pluripotent stem cell derived Mesenchymal stem cells prevent allergic airway inflammation in mice. Stem Cells 30: 2692-2699.

39. Brown JM, Nemeth K, Kushnir-Sukhov NM, Metcalfe DD, Mezay E (2011) Bone marrow stromal cells inhibit mast cells function via a COX 2 dependent mechanism. Clinical and Experimental Allergy 41: 526-534.

40. Williams AR, Hare JM (2011) Mesenchymal stem cells: Biology, Pathophysiology, Translational Findings & Therapeutic Implications for Cardiac Disease. Circ Res 109 :923-940.

41. Sahara M, Santoro F, Clien KR (2015) Programming and reprogramming a human heart Cell. The EMBO Journal 34: 710-738.