Review Article

iMedPub Journals
www.imedpub.com

Journal of Stem Cell Biology and Transplantation
ISSN 2575-7725

2019
Vol.3 No.1:4

DOI: 10.21767/2575-7725.100025

Stem Cell Regenerative Medicine (SCRM)-A New Hope in Orthopedics-Review Article

Atul Dwivedi[1], Shweta Shukla Dwivedi[*2], Muhammad Raheel Tariq[3], Muhammad Shoaib[3], Dorina Lauritano[4]

1 Department of clinical & Basic Sciences, Research Scientist & Core Member of Research Society of Hubei Polytechnic University, Assistant Professor & Assistant Director, Medical college of Hubei Polytechnic University (HBPU), Huangshi, Hubei PR China
2 Consultant Dental Surgeon, Jabalpur, Madhya Pradesh, India
3 Department of Internal Medicine, PG Resident, North Sichuan Medical College, Nanchong, China
4 Department of Medicine & Surgery, Assistant Professor, University of Milan-Bicocca, Italy

Abstract

Stem cell regenerative medicine is the fastest growing branch of clinical medicine and it has a tremendous role in Orthopedics. All orthopedic surgeries need implants of metal in the form of screws unipolar, bipolar implants, cages, artificial cervical disc, plates etc. After getting these metallic implants, our Bony tissues tend to face Heterotopic ossification and other complications. Problem with hardware implant is that, they can't work exactly as like our own organs & system, for instance hip arthroplasty can't be a substitute for original hip joint & ultimately patients may get decreased or limited mobility in joints & even implant failure might occur. Second problem is that even after successful surgical procedures we need a long time rehabilitation time to mobilise as a normal person. This is why we need regenerative medicine in the field of orthopedics, under which we can regenerate the damaged bone tissue, cartilage, tendon etc.in order to sustain the normal & efficient function of musculoskeletal system. The presented review aims to discuss all the potential benefits of SCRM in Orthopedics.

Keywords: Stem cell therapy; Stem cell therapy in orthopedics; bone marrow stem cells

Received: April 18, 2019; **Accepted:** May 09, 2019; **Published:** May 17, 2019

***Corresponding author:** Shweta Shukla Dwivedi

shweta0761@gmail.com

Consultant Dental Surgeon, Jabalpur, Madhya Pradesh, India.

Tel: 7982907863

Citation: Dwivedi A, Dwivedi SS, MR Tariq, Muhammad S, Lauritano D (2019) Stem Cell Regenerative Medicine (SCRM)-A New Hope in Orthopedics-Review Article. J Stem Cell Biol Transplant Vol.3 No.1:4

Abbreviations

BMSCs: Bone Marrow Derived Mesenchymal Stem Cells; MSC: Mesenchymal Stem Cells; OA: Osteoarthritis; PRP: Platelet Rich Plasma; MRI: Magnetic Resonance Imaging; ACL: Anterior Cruciate Ligament; HA: Hydrxyapatite; BMAC: Bone Marrow Aspirates Stem Cell Concentrate

Introduction

Stem cell regenerative medicine is the fastest emerging branch of medicine - Leland Kaiser introduced the term "Regenerative Medicine" in 1992. He already predicted that a new branch of medicine will develop that attempt to change the course of chronic disease & in many cases it will regenerate the exhausted and failing organ systems [1]. Since then, Scientists around the world are making efforts to develop reverse time therapy to regenerate damaged tissues & organs [2].

No doubt, scientists have great hopes from regenerative medicine towards orthopedics. They want to develop an alternative regenerative therapy for non-Union, Malunion, large bond defect, or atrophic tendon rupture etc. These are all indications where we are using conventional surgical procedures with implants [3,4]. Problem with hardware implant is that, they can't work exactly as like our own organs and systems, for instance hip arthroplasty can't be a substitute for original hip joint and ultimately patients may get decreased or limited mobility in joints

and even implant failure might occur. A Second problem is that even after successful surgical procedures we need a long time rehabilitation time to mobilise as a normal person. This is why we need regenerative medicine in the field of orthopedics, under which we can regenerate the damaged bone tissue, cartilage, tendon etc.in order to sustain the normal & efficient function of musculoskeletal system. Stem cell regenerative medicine is a unique method for treating patients with wide spectrum of diseases & injuries.

The presented review will concentrate on advancement of stem cell regenerative medicine (SCRM) towards orthopedics. Large bone defects & Non Union Cases present a huge therapeutic challenge to the surgeon & these complications put extra financial burden on health care system & society, it is the reason for significant morbidity [5].

SCRM is a combination of neoosteogenesis & neovascularization, by which we can restore the tissue deficit. This optimal approach includes the knowledge of biomaterial scaffold, cell biology technique, growth factor required for stem cell growth & optimum mechanical environment [5].

Material & Methods

We performed our online search using key word, stem cell therapy in orthopedics, mesenchymal stem cells, avascular necrosis, osteochondral defects, malunion in bones, spinal cord injury, cartilage regeneration, on pubmed, Springer, Google scholar. Full length articles were downloaded directly from pubmed research gate, Google scholar, Springer & other online research portals. After reviewing more than 160 articles, we extracted the clinical data from them to include in our study, which are found relevant and appropriate.

Table: 1 Application of stem cells in variety of Musculoskeletal Disorders.

Author	Diagnosis	Application / number of patients	Outcome
Connolly et al.	Atrophic pseudoarthrosis	Percutaneous autologous bone marrow injection/20	Healing capacity comparable to autologous cancellous bone grafting
Garg et al.	Non Union in long bones	Percutaneous autologous bone marrow injection/20	17 out of 20 cases shows Union in 5 months
Goel et al.	Tibial non-union	Percutaneous autologous bone marrow injection/20	15 out of 20 cases showed bone Union
Gangji et al.	Osteonecrosis femoral head	Autologous bone marrow concentrate injected13/18 hips	Pain significantly improved, function also improved significantly
Hernigou et al.	Osteonecrosis of femoral head	Autologous bone marrow concentrate injected342(534 hips)	Successful outcome depends on high amount of progenitor cells.
Salama & weissman	Different sort of bone defects	Xenografts with bone marrow aspirate/28	Most satisfactory results
Marcacci et al.	Large bone diaphysis defect	Autologous MSCs were expanded in vitro& grown with hydroxyapatite scaffolds/4	Follow up till 7 years after surgery, no secondary fractures, and good implant integrations.
Hendrich et al.	Bone healing anomalies	Bone marrow concentrate/101	Autogenous bone marrow concentrate applied safely.
Giannini et al.	Osteochondral talus defect	Autologous bone marrow aspirate with arthroscopic assisted injection/48	Improvement in functional efficiency.
Dallari et al.	High tibial osteotomy	Lyophilised bone chips including platelets-enriched plasma with bone marrow aspirate/33	Study shows Enhanced healing
Kitoh et al.	Femoral & tibial lengthenings	In vitro Expanded MSCs applied with PRP/28 (51 osteotomies)	bone healing Not enhanced by MSC/ PRP
Wong KL et al.	Knee OA	Cultured autologous BMSCs with hyaluronic acid / 56 knees in 56 patients	Cell recipient group showed remarkable clinical & MRI scores than control group. Intraarticular injection of cultured MSCs can effectively improve short term clinical and MRI outcomes in all recipients.
Vangsness et al.	KneeOA	Allogenic BMSCs applied with partial meniscectomy with additional partial meniscectomy/55	Evidence of Meniscus regeneration and knee pain improved following allogenic human mesenchymal stem cell treatment.
Wright et al.	Simple bone cyst	Autologous bone marrow aspirate in the form of intra lesional injection/77	Inferior results compared to methyl prednisolone Injection.

Park et al.	Simple bone cysts	Implantation of autologous bone marrow aspirate implanted in the combination with non-vital allogenic bone graft or injected with bone powder/20 (23cysts)	Bone marrow - bone powder injection is effective alternative to open treatment.
Wakitani et al.	Osteochondral defects in patellofemoral joint	Culture expanded autologousBMSCs with additional collagen gel& autologous periosteum or synovium/3 Pts	After 1 year of transplantation, defect completely covered.
Nejadnik et al.	Osteochondral defects	Culture - expanded autologous BMSCs/ knee with additional periosteal flap/ (72 Pts)	Study shows No difference between autologous chondrocyte implantation & BMSC
De Windt et al.	Cartilage defect	Allogenic MSCs mixed with 10% or 20% recycled autologous chondrocytes with additional fibrin glue/ 9	At 12 month follow up all patients shows Significant improvement in clinical outcome, histological analysis indicated hyaline like regeneration with high concentration of proteoglycan & type II Collagen.
Gobbi et al.	Osteochondral defect in knee	BMAC with additional collagen I /II matrix /15	Final follow up with significant improvement. MRI showed coverage of the lesion with hyaline like tissue in all patients
Clarke AW et al.	Patellar tendinopathy	Cultured stem cells got from skin fibroblasts & modulated to grow collagen producing cells/ 46 Pts, 60 patellar tendons	Improvement in function and pain
Kim SJ et al.	Improper fracture healing rate / safety	Cultured cells differentiated in to osteoblasts injected with fibrin/ 64 Pts	Fracture healing enhanced safely.
Sen RK et al.	Avascular necrosis of head of femur	Uncultured mononuclear cell instillation obtained from bone marrow instilled following core decompression.40 Pts /51 hips	Clinical scores & radiological outcomes become better.
Gangji V et al.	Avascular necrosis of head of femur	Uncultured cell instillation obtained from bone marrow & implanted with core decompression /19 Pts/ 24 hips	Improvement in pain & progression to collapse.
Dai G et al.	Complete and chronic cervix a spinal cord injury.	Cultured cells transplanted to region surrounding injury 20 cases, 20 control, altogether 40 Pts.	Neurological function improved at 6 months in 10/20 Pts in treatment group
Haleem et al.	Cartilage defects of femoral condyles	Culture expanded autologous BMSCs , platelet rich fibrin glue & periosteal flap/ ACL reconstruction & microfracture in 1 patient / total 5 Pts	12 months after transplantation, defect completely filled with complete surface congruity in 3 patients, congruity incomplete in 2 patients.
Buda et al.	Osteochondral lesion of knee	Uncultured bone marrow derived stem cells with hyaluronic acid membrane scaffold with platelet rich fibrin./20 pts	No significant improvement as compared to autologous chondrocytes implantation
Cristante AF et al.	Chronic spinal cord injury	Uncultured mononuclear cell concentrate obtained from peripheral blood and reinjected by arteriography /39 pts	26/39(66.7%) Pts showed recovery of somatosensory evoked potentials
Jäger M et al.	Bone defects because of trauma or Tumor.	Uncultured mononuclear cells obtained from bone marrow aspiration with collagen sponge scaffold/10	Healing of all bones defects

Results

Results are mentioned in the Table 1 on the basis of data extracted from different studies [6-33].

Discussion

SCRM is a fast growing & promising method for a wide variety of Orthopedic diseases and traumatic injuries. In several countries, scientific research about SCRM is promoted by providing more & more funds that's the reason, because of which many quality publications are coming in to light & moreover we are expecting further advanced innovations in the field of SCRM. Human and animals are commonly affected by orthopedic injuries in bone, muscle, tendons, cartilage and so on. Though natural healing power of bone is enough for normal healing process, massive trauma, and aggressive bone tumours can hamper regeneration power of osteogenic stem cells [34].

Mesenchymal cells (MSCs) have got the ability to develop in to any sort of mesodermal tissue, so that they could be directed to form precursor cells to develop in to several tissues like tendon, ligament, bone, cartilage, muscle. Stem cell regeneration therapy can be used in several conditions [35]. Neen reported that unselected stem cells used with hydroxyapatite (HA) scaffolds had homologous healing rates as autologous grafting & it also prevent donor site morbidity [36]. Bone Marrow aspirates containing stem cells in a ratio of 1:10000 to 1:1,000,000 of nucleated cells have been successfully used to enhance the healing in non-Union cases [37].

Animal experiments have shown increased proteoglycan content and maintenance of Disc height with percutaneous stem cell injection [38]. Clinical trials are running to explore these results in humans with positive interim results [39]. Effect of MSCs is positive in case of animal studies via intrathecal and local administration; however clinical studies response is mixed [40]. Tamaki reported that muscle derived MSCs involved in regeneration of a crushed peripheral nerve has been done successfully [41].

Mostly data is based on animal studies showing use of MSCs suitable scaffolds in cartilage healing. Only a few human case studies have been done and shows improved functional outcome after autologous MSCs implantation techniques [22]. Adams reported that stem cells used to treat rat with Achilles' tendon tear treated with stem cell containing sutures have higher failure strength and better histological characteristics [42]. Unselected MSCs were used for ultrasound guided injections in a case series for chronic patellar tendinopathy with good clinical outcomes [43]. Horwitz reported that systemic infusion of allogenic MSCs in six children with osteogenesis imperfecti showed improvement in bone mass & bone growth acceleration [44]. Though the studies showed promise, clear demonstration that the cells involved to the benefits seen in the recipient is still in paucity so these studies are still controversial regarding use of MSCs for osteogenesis imperfecti treatment [45]. Plank showed in a study on pig that MSCs with scaffolds used in physeal defects differentiated in to chondrocytes to give rise to hyaline cartilage & prevents bony bridge formation. Currently there is no clinical study available to support this study [46].

Another animal study presented by Guan used MSCs modified to express certain surface which enabled them to migrate to the periosteum leading increased bone mass. These methods can be used in the treatment of generalised bone diseases such as osteoporosis [47]. In sum, Table 1 Shows most of the studies are favour of SCRM, and in maximum number of studies showing positive results in osteonecrosis, osteoarthritis, spinal cord injury, fracture healing, patellar tendinopathy, cartilage defect, osteochondral defect, bone cyst, osteochondral talus defect, and non-Union cases. On the other hand in few studies SCRM results are comparable to conventional treatment and Buda [31] study (2010) stem cell therapy shows No Significant improvement as compared autologous chondrocyte implantation. Above studies also prove the safety of Stem cell regenerative medicine.

The presented review and analysis obviously has its own limitations because we choose limited number of studies. Core weakness of this study is lack of powerful data and heterogeneity of data to reveal the outcome of SCRM in different orthopedic procedure, so we could not compare all outcomes together. Some unidentifiable and hidden factors might be the limitations of our study. Other important studies about SCRM may be missed because of language barrier.

Conclusion

From the above study, it is quite clear that we need more clinical trials to overcome the contradiction between success and failure of SCRM, so that SCRM can be used safely and effectively in orthopedics & other branches of medicine. Last but not the least, because maximum number of clinical trials and animal experimental studies demonstrated the effectiveness of SCRM that's why we strongly suggest that SCRM has got a great potential in Orthopedics.

References

1 Kaiser LR (1992) The future of multi hospital systems. Top Health Care Financ 18: 32-45.

2 Ehnert S, Glanemann M, Schmitt A, Vogt S, Shanny N, et al. (2009) The possible use of stem cells in regenerative medicine: dream of reality? Langenbecks Arch Surg 394: 985-997.

3 Forriol F, Longo UG, Concejo C, Ripalda P, Maffulli N, et al (2009) Platelet rich plasma, rhOP-1 (rhBMP-7) and frozen rib allograft for the reconstruction of bony mandibular defects in sheep. A pilot experiment study. Injury 40: S44-49.

4 Maffulli N, Longo UG, Denaro V (2010) Novel approaches for the management of tendinopathy. J Bone Joint Surg Am 92: 2604-2613.

5 Fayaz HC, Giannoudis PV, Vrahas, Smith RM, Moran R, et al. (2011) The role of stem cells in fracture healing & non Union. Int Orthop 35: 1587-1597.

6 Connolly JF, Guse JR, Tiedman J, Dehne R (1991) Autologous marrow injection as a substitute for operative grafting of tibial non unions. Clin Orthop Relat Res 266: 259-270.

7 Garg NK, Gaur S, Sharma S (1993) Percutaneous autogenous bone marrow grafting in 20 cases of Ununited fracture. Acta Orthop Scand 64: 671-672.

8 Goel A, Sangwan SS, Siwach RC, Ali AM (2005) Percutaneous bone marrow grafting for the treatment of tibial non Union. Injury 36:203-206.

9 Gangji V, Hauzeur JP, Matos C, De Maertelaer V, Toungouz M, et al. (2004) Treatment of osteonecrosis of femoral head with implantation of autologous bone marrow cells. A pilot study. J Bone Joint Surg Am 86: 1153-1160.

10 Hernigou P, Poignard A, Zilber S, Rouard H (2009) Cell therapy of hip osteonecrosis with autologous bone marrow grafting. Indian J Orthop 43: 40-45.

11 Salama R, Weissman SL (1978) The clinical use of combine xenografts of bone and autologous red marrow.A preliminary report. J Bone Joint Surg Br 60: 111-115.

12 Marcacci M, Kon E, Moukhachev V, Lavroukov A, Kutepov S, et al. (2007) Stem cells associated with macro porous bioceramics for long bone repair :6-To 7-year outcome of a pilot clinical study. Tissue Eng 13: 947-955.

13 Hendrich C, Franz E, Waertel G, Krebs R, Jäger M (2009) Safety of autologous bone marrow aspiration concentrate transplantation: initial experience in 101 patients. Orthop Rev 1: e32.

14 Giannini S, Buda R, Vannini F, Cavallo M, Grigolo B (2009) One- step bone marrow - derived cell transplantation in talar osteochondral lesions. Clinical Orthopedics and related research 467: 3307-3320.

15 Dallari D, Savarino L, Stagni C , Cenni E, Cenacchi A, et al. (2007) Enhanced tibial osteotomy healing with use of bone grafts supplemented with platelet gel or platelet gel & bone marrow stromal cells. J Bone Joint Surg Am 89: 2413-2420.

16 Kitoh H, Kitakoji T, Tsuchiya H, Kitoh M, Ishiguro N (2007) Distraction osteogenesis of the lower extremity in patients with achondroplasia/hypochondroplasia treated with transplantation of culture-expanded bind marrow cells and platelet-rich plasma. J Pediatr Orthop 27: 629-634.

17 Wong KL, Lee KB, Tai BC, Law P, Lee EH, et al. (2013) Injectable cultured bone marrow derived mesenchymal stem cells in varus knees with cartilage defects undergoing high tibial osteotomy: a prospective , Randomized controlled clinical trial with years follow up. Arthroscopy 29: 2020-2028.

18 Vangsness CT, Farr J, Boyd J, Dellaero DT, Mills CR, et al. (2014) Adult human mesenchymal stem cells delivered via intraarticular injection to the knee following partial medial meniscectomy: a Randomized , double-blind , controlled study. J Bone Joint Surg Am 96: 90-98.

19 Wright JG, Yandow S, Donaldson S, Marley L (2008) A Randomized clinical trial comparing intralesional bone marrow and steroid injections for simple bone cysts. J Bone Joint Surg Am 90: 722-730.

20 Park IH, Micic ID, Jeon IH (2008) A study of 23 unicameral bone cysts of the calcaneus: open chip allogenic bone graft versus Percutaneous injection of bone powder with autogenous bone marrow. Foot Ankle Int 29: 164-170.

21 Wakitani S, Nawata M, Tensho K, Okabe T, Machida H, et al. (2007) Repair of articular cartilage defects in the patellofemoral joint with autologous bone marrow mesenchymal cell transplantation: three case reports involving nine defects in five knees. J tissue Eng Regen Med 1: 74-79

22 Nejadnik H, Hui JH,Feng Choong EP, Tai BC, LeeE H, (2010) Autologous bone marrow-derived mesenchymal stem cells versus autologous chondrocyte implantation : An observational cohort study. Am J Sports Med 38: 1110-1116.

23 De Windt TS, Vonk LA, Slaper-Cortenbach IC, van den Broek MP, Nizak R , et al. (2016) Allogeneic mesenchymal stem cells stimulate cartilage regeneration and are safe for single stage cartilage repair in humans upon mixture with recycled autologous chondrons. Stem Cells 35: 256-264.

24 Gobbi A, Karnatzikos G, Scotti C, Mahajan V, Mazzucco L, et al. (2011) One step cartilage repair with bone marrow aspirate concentrated cells and collagen matrix in full-thickness knee cartilage lesions results at 2- year follow up. Cartilage 2: 286-299.

25 Clarke AW, Aylas F, Morris T, Robertson CJ, Bell J, et al. (2011) Skin derived tenocyte like cells for the treatment of patellar tendinopathy. Am J Sports Med 39: 614-623.

26 Kim SJ, Shin YW, Yang KH, Kim SB, Yoo MJ, et al. (2009) A multicenter, Randomized , clinical study to compare the effect and safety of autologous cultured osteoblast(ossron) injection to treat fractures. BMC Musculoskelet Disord 12: 10-20.

27 Sen RK, Tripathy SK, Aggarwal S, Marwaha N, Sharma RR et al. (2012) Early results of core decompression and autologous

bone marrow mononuclear cells instillation in femoral head osteonecrosis: a randomised control study. J Arthroplasty 27: 679-86.

28 Gangji V, De Maertelaer V, Hauzeur JP (2011) Autologous bone marrow cell implantation in the treatment of non - traumatic osteonecrosis of the femoral head: Five year follow up of a prospective controlled study. Bone 49: 1005-1009

29 Dai G, Liu X, Zhang Z, Yang Z, Dai Y, et al. (2013) Transplantation of autologous bone marrow mesenchymal stem cells in the treatment of complete and chronic cervical spinal cord injury. Brain Res 1533: 73-79.

30 HaleemAM, El Singergy AA, Sabry D, Atta HM, Rashed LA, et al. (2010) The clinical use of human culture- expanded autologous bone marrow mesenchymal stem cells transplanted on platelet - rich glue in the treatment of articular cartilage defects: a pilot study and preliminary results. Cartilage 1: 253-261.

31 Buda R, Vannini F, Cavallo M, Grigolo B, Cenacchi A, et al. (2010) Osteochondral lesion of the knee: a new one - step repair technique with bone - marrow-derived cells. J Bone Joint Surg Am 92: 2-11.

32 Cristante AF, Baros Filho TE, Tatsui N , Mendrone A, Caldas JG, et al. (2009) Stem cells in the treatment of chronic spinal cord injury: evaluation of somatosensitive evoked potentials in 39 patients. Spinal cord 47: 733-8.

33 Jäger M, Jelinek EM, Wess KM, Scharfstädt A, Jacobson M, (2009) Bone marrow concentrate: a novel strategy for bone defect treatment. Curr Stem Cell Res Ther 4: 34-43.

34 Csaki C, Matis U, Mobasheri A, Ye H, Shakibaei M (2007) Chondrogenesis, osteogenesis and adipogenesis of canine mesenchymal stem cells: a biochemical, morphological and ultrastructural study. Histochem Cell Biol 128: 507-520.

35 Manihar HH, Tawari AA, Suk M, Horwitz DS, et al. (2015) The current role of stem cells in Orthopedic surgery. Malays Orthop J 9: 1-7.

36 Neen D, Noyes D, Shaw M, Gwilym S, Fairlie N, et al. (2006) Healos and bone marrow aspirate used for lumbar spine fusion: a case controlled study comparing Healos with autograft. Spine 31: E636-40.

37 Hernigou P, Poingnard A, Manicom O, Mathieu G, Rouard H (2005) The use of percutaneous autologous bone marrow transplantation in nonunion and a vascular necrosis of bone. J Bone Joint Surg Br 87: 896-902.

38 Miyamoto T, Muneta T, Tabuchi T, Matsumoto K, Saito H et al. (2010) Intradiscal transplantation of synovial mesenchymal stem cells prevents intervertebral disc degeneration through suppression of matrix metalloproteinase - related genes in nucleus pulposus cells in rabbits. Arthritis Res Ther 12: R206.

39 Dowdell J, Erwin M, Choma T, Vaccaro A, Iatridis J, at al. (2017) Intervertebral Disk Degeneration and Repair. 80: S46–S54.

40 Park JH, Kim DY, Sung IY, Choi GH, Jeon MH, et al. (2012) Long term results of spinal cord injury therapy using mesenchymal stem cells derived from bone marrow in humans. Neurosurgery 70: 1238-1247.

41 Tamaki T, Hirata M, Seoda S, Nakajima N, Saito K, et al. (2014) Preferential and comprehensive reconstitution of severely damaged sciatic nerve using murine skeletal muscle- derived multi potent stem cells. PLoS One 9: e91257.

42 Adams SB, Thrope MA, Parks BG, Aghazarian G, Allen E, et al. (2014) Stem cell-bearing suture improve Achilles' tendon healing in a rat model. Foot Ankle Int 35: 293-299.

43 pascaul-GarridoC , Rolon A, MakinoA, (2012) Treatment of chronic patellar tendinopathy with autologous bone marrow stem cells: a 5-year follow up. Stem cell Int 2012: 953510.

44 Horwitz EM, Prockop DJ, Gordon PL, Koo WW, Fitzpatrick LA, et al. (2001) Clinical responses to bone marrow transplantation in children with severe osteogenesis Imperfecta. Blood 97: 1227-1237.

45 Christopher Niyibizi, Feng Li, (2009) potential implications of cell therapy for Osteogenesis Imperfecta. Int J Clin Rheumatology. 1: 57-66.

46 Planka L, Srnec R, Rauser P, Stary D, Filova E, et al. (2012) Nanotechnology and mesenchymal stem cells with chondrocytes in prevention of partial growth plate arrest in pigs. Biomes Pap Med Fac Univ Palacky Olomouc Czeck Repub 156: 128-34.

47 Guan M, Yao W, Liu R, Lam KS, Nolta J, et al. (2012) Directing mesenchymal stem cells to bone to augment bone formation and increase bone mass. Nat Med 18: 456-62.