Stem Cell Research Literatures

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Abstract: Stem cells are derived from embryonic and non-embryonic tissues. Most stem cell studies are for animal stem cells and plants have also stem cell. Stem cells were discovered in 1981 from early mouse embryos. Stem cells have the potential to develop into all different cell types in the living body. Stem cell is a body repair system. When a stem cell divides it can be still a stem cell or become adult cell, such as a brain cell. Stem cells are unspecialized cells and can renew themselves by cell division, and stem cells can also differentiate to adult cells with special functions. Stem cells replace the old cells and repair the damaged tissues. Embryonic stem cells can become all cell types of the body because they are pluripotent. Adult stem cells are thought to be limited to differentiating into different cell types of their tissue of origin. This article introduces recent research reports as references in the related studies.
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Key words: stem cell; life; research; literature

Introduction

The stem cell is the origin of an organism's life that has the potential to develop into many different types of cells in life bodies. In many tissues stem cells serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a red blood cell or a brain cell. This article introduces recent research reports as references in the related studies.

The following introduces recent reports as references in the related studies.

Abe, K., et al. (2012). "Stem cell therapy for cerebral ischemia: from basic science to clinical applications." J Cereb Blood Flow Metab **32**(7): 1317-1331.

Recent stem cell technology provides a strong therapeutic potential not only for acute ischemic stroke but also for chronic progressive neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis with neuroregenerative neural cell replenishment and replacement. In addition to resident neural stem cell activation in the brain by neurotrophic factors, bone marrow stem cells (BMSCs) can be mobilized by granulocyte-colony stimulating factor for homing into the brain for both neurorepair and neuroregeneration in acute stroke and neurodegenerative diseases in both basic science and clinical settings. Exogenous stem cell transplantation is also emerging into a clinical scene from bench side experiments. Early clinical trials of intravenous transplantation of autologous BMSCs are showing safe and effective results in stroke patients. Further basic sciences of stem cell therapy on a neurovascular unit and neuroregeneration, and further clinical advancements on scaffold technology for supporting stem cells and stem cell tracking technology such as magnetic resonance imaging, single photon emission tomography or optical imaging with near-infrared could allow stem cell therapy to be applied in daily clinical applications in the near future.

Anzai, H., et al. (2001). "Stem cell factor and interleukin-3 induce stepwise generation of erythroid precursor cells from a basic fibroblast growth factor-dependent hematopoietic stem cell line, A-6." Biochem Biophys Res Commun **282**(4): 940-946.

A multipotent immature myeloid cell population was produced from a basic fibroblast growth factor (bFGF)-dependent hematopoietic stem cell line, A-6, when cultured with stem cell factor (SCF) replacing bFGF. Those cells were positive for stem cell markers, c-kit and CD34, and a myeloid cell marker, F4/80. Some cell fractions were also positive for Mac-1, a macrophage marker or Gr-1, a granulocytic maker, but negative for an erythroid marker TER119. They also showed the expression of mRNA for the myeloid-specific PU.1 but did not that for the erythroid-specific GATA-1. Among various cytokines, interleukin-3 (IL-3) induced erythroid precursor cells that expressed the erythroid-specific GATA-1 and beta-major globin. The quantitative analysis showed that erythroid precursor cells were newly produced from the immature myeloid cells by cultivation with IL-3. SCF and IL-3 induced stepwise

generation of erythroid precursor cells from an A-6 hematopoietic stem cell line.

Anzai, H., et al. (1999). "Self-renewal and differentiation of a basic fibroblast growth factor-dependent multipotent hematopoietic cell line derived from embryonic stem cells." Dev Growth Differ **41**(1): 51-58.

Despite the accumulation of informat on on the origin of hematopoietic stem cells, it is still unclear how these cells are generated in ontogeny. Isolation of cell lines equivalent to early embryonic hematopoietic progenitor cells can be helpful. A multipotent hematopoietic progenitor cell line, A-6, was isolated from H-1 embryonic stem (ES) cells. The self-renewal of A-6 cells was supported by basic-fibroblast growth factor (b-FGF) and their differentiation into definitive erythroid cells, granulocytes and macrophages was induced after co-culture with ST-2 stromal cells. A-6 cells were positive for the surface markers of hematopoietic stem cell, c-kit, CD31, CD34, Flt3/Flk2, PgP-1, and HSA, but were negative for that of the differentiated cells. Reverse transcription-polymerase chain reaction analysis showed that A-6 cells produced mRNA from SCL/tal-1 and GATA-2 genes. Among various cytokines examined, on y stem cell factor (SCF) and Flt3/Flk2 ligand (FL) supported the proliferation of A-6 cells instead of b-FGF. The FL, as well as b-FGF, supported the self-renewal of A-6 cells, whereas SCF induced differentiation into myeloid cells. A-6 cells will be useful for the characterization of hematopoietic progenitor cells derived from ES cells and provide a model system to realize the control mechanisms between self-renewal and different ation of hematopoietic stem cells.

Bahadorani, M., et al. (2015). "Glial cell line-derived neurotrophic factor in combination with insulin-like growth factor 1 and basic fibroblast growth factor promote in vitro culture of goat spermatogonial stem cells." Growth Factors **33**(3): 181-191.

Growth factors are increasingly considered as important regulators of spermatogonial stem cells (SSCs). This study investigated the effects of various growth factors (GDNF, IGF1, bFGF, EGF and GFRalpha-1) on purification and colonization of undifferentiated goat SSCs under in vitro and in vivo conditions. Irrespective of the culture condition used, the first signs of developing colonies were observed from day 4 of culture onwards. The number of colonies developed in GDNF + IGF1 + bFGF culture condition was significantly higher than the other groups ($p < 0.05$). In contrast, the size of colonies developed in GDNF + EGF + LIF culture condition was significantly higher than the other groups ($p < 0.05$). Immunocytochemical stationing for specific biomarkers of somatic cells (vimentin, alpha-inhibin and alpha-SMA) and spermatogonial cells (PLZF, THY 1, VASA, alpha-1 integrin, bet-1 integrin and DBA) revealed that both cell types existed in developing colonies, irrespective of the culture condition used. Even though, the relative abundance of VASA, FGFR3, OCT4, PLZF, BCL6B and THY1 transcription factors in GDNF + IGF1 + bFGF treatment group was significantly higher than the other groups ($p < 0.05$). Additionally, goat SSCs developed in the latter culture condition could colonize within the seminiferous tubules of the germ-cell depleted recipient mice following xenotransplantation. Obtained results demonstrated that combination of GDNF with IGF1 and bFGF promote in vitro culture of goat SSCs while precludes uncontrolled proliferation of somatic cells.

Banovic, M., et al. (2015). "[The Stem-Cell Application in Ischemic Heart Disease: Basic Principles, Specifics and Practical Experience from Clinical Studies]." Srp Arh Celok Lek **143**(7-8): 487-493.

Longer life duration, different clinical presentations of coronary disease, as well as high incidence of comorbidity in patients with ischemic heart disease have led to an increase in the incidence of ischemic heart failure. Despite numerous and new treatment methods that act on different pathophysiological mechanisms that cause heart failure, and whose aim is to slowdown or stop the progression of this devastating disease, morbidity and mortality in these patients remain high. These facts have firstly led to the introduction of the experimental, and then clinical studies with the application of stem cells in patients with ischemic heart disease. Previous studies have shown that the application of stem cells is a feasible and safe method in patients with acute coronary syndrome, as well as in patients with chronic ischemic cardiomyopathy, but the efficacy of these methods in both of the abovementioned clinical syndromes has yet to be established.This review paper outlines the basic principles of treatment of ischemic heart disease with stem cells, as well as the experience and knowledge gained in previous clinical studies.

Besser, D. (2012). "Stem cell biology--from basic research to regenerative medicine." J Mol Med (Berl) **90**(7): 731-733.

Betts, D. H., et al. (2010). "Stem cell roles in reproduction: what is the basic science?" Mol Hum Reprod **16**(11): 791-792.

Borowski, M., et al. (2008). Basic pluripotent stem cell culture protocols. StemBook. J. Laning. Cambridge (MA).

Stem cell research is a rapidly expanding field with the potential to develop therapeutic agents to treat diseases as well as study disease development from early stages. The culture of human pluripotent stem cells shares many of the same protocols as standard mammalian cell culture. However, the successful culture and maintenance of human pluripotent stem cells (hPSCs) in an undifferentiated state requires additional considerations to ensure that cells maintain their key characteristics of self-renewal and pluripotency. There are several basic techniques needed for the culturing of mammalian cells, including thawing frozen stocks, plating cells in culture vessels, changing media, passaging and cryopreservation. The protocols in this document represent a subset of the standard operating procedures used to maintain and culture stem cells at the Massachusetts Human Stem Cell Bank, and have been thoroughly testing and verified.

Brandl, B., et al. (2015). "Stem cell reprogramming: basic implications and future perspective for movement disorders." Mov Disord **30**(3): 301-312.

The introduction of stem cell-associated molecular factors into human patient-derived cells allows for their reprogramming in the laboratory environment. As a result, human induced pluripotent stem cells (hiPSC) can now be reprogrammed epigenetically without disruption of their overall genomic integrity. For patients with neurodegenerative diseases characterized by progressive loss of functional neurons, the ability to reprogram any individual's cells and drive their differentiation toward susceptible neuronal subtypes holds great promise. Apart from applications in regenerative medicine and cell replacement-based therapy, hiPSCs are increasingly used in preclinical research for establishing disease models and screening for drug toxicities. The rapid developments in this field prompted us to review recent progress toward the applications of stem cell technologies for movement disorders. We introduce reprogramming strategies and explain the critical steps in the differentiation of hiPSCs to clinical relevant subtypes of cells in the context of movement disorders. We summarize and discuss recent discoveries in this field, which, based on the rapidly expanding basic science literature as well as upcoming trends in personalized medicine, will strongly influence the future therapeutic options available to practitioners working with patients suffering from such disorders.

Bruedigam, C., et al. (2011). "Basic techniques in human mesenchymal stem cell cultures: differentiation into osteogenic and adipogenic lineages, genetic perturbations, and phenotypic analyses." Curr Protoc Stem Cell Biol **Chapter 1**: Unit1H 3.

This unit describes basic techniques in human mesenchymal stem cell (hMSC) cultures. It includes protocols for the differentiation of hMSCs into osteogenic and adipogenic lineages, genetic perturbations, and phenotypic analyses. hMSCs can be differentiated with dexamethasone and beta-glycerophosphate into mineralizing osteoblasts within 2 to 3 weeks, or with dexamethasone, indomethacin, and 3-isobutyl-1-methylxanthine into lipid vesicle-containing adipocytes within 1 to 2 weeks. Phenotypic changes during those highly dynamic differentiation processes can be detected by biochemical and histological assays and gene expression analyses of differentiation markers. In addition, this unit describes an electroporation method that allows the transient genetic perturbation of hMSCs.

Cai, Y. and J. Wu (2001). "[A study on effect of basic fibroblast growth factor on human limbal stem cell proliferation cultured in low calcium medium]." Zhonghua Yan Ke Za Zhi **37**(4): 259-262.

OBJECTIVE: To study how to obtain relatively pure stem cells and the effects of bFGF on the human limbal stem cell proliferation in order to set up the foundation of cultured limbal stem cells for treatment of ocular surface and tear diseases. METHODS: Limbal button inoculation was used in low calcium culture. Monoclonal antibody AE5 was used to identify the stem cells. To examine the effects of bFGF (1 - 100 ng/ml) on stem cell proliferation, the technique of digital camera and computer image analysis system were used. RESULTS: Cultured cells were mostly corneal stem cells. This was the first time to combine the method of obtaining basal cell layer and culture with low calcium medium, which could harvest relatively pure and undifferentiated stem cells in localization and nature. The basic FGF (1 - 100 ng/ml) promoted cultured stem cells to proliferate significantly ($P < 0.001$). CONCLUSIONS: Limbal stem culture provides resources of stem cells. It is very useful in treatment of ocular surface and tear diseases. The basic FGF plays an important role in proliferation of stem cells in graft. Computer image analysis system is an

effective and simple way for evaluating the proliferation of a primary culture.

Chen, Q., et al. (2011). "The basic helix-loop-helix transcription factor MYC2 directly represses PLETHORA expression during jasmonate-mediated modulation of the root stem cell niche in Arabidopsis." Plant Cell **23**(9): 3335-3352.

The root stem cell niche, which in the Arabidopsis thaliana root meristem is an area of four mitotically inactive quiescent cells (QCs) and the surrounding mitotically active stem cells, is critical for root development and growth. We report here that during jasmonate-induced inhibition of primary root growth, jasmonate reduces root meristem activity and leads to irregular QC division and columella stem cell differentiation. Consistently, jasmonate reduces the expression levels of the AP2-domain transcription factors PLETHORA1 (PLT1) and PLT2, which form a developmentally instructive protein gradient and mediate auxin-induced regulation of stem cell niche maintenance. Not surprisingly, the effects of jasmonate on root stem cell niche maintenance and PLT expression require the functioning of MYC2/JASMONATE INSENSITIVE1, a basic helix-loop-helix transcription factor that involves versatile aspects of jasmonate-regulated gene expression. Gel shift and chromatin immunoprecipitation experiments reveal that MYC2 directly binds the promoters of PLT1 and PLT2 and represses their expression. We propose that MYC2-mediated repression of PLT expression integrates jasmonate action into the auxin pathway in regulating root meristem activity and stem cell niche maintenance. This study illustrates a molecular framework for jasmonate-induced inhibition of root growth through interaction with the growth regulator auxin.

Chung, E. (2015). "Stem-cell-based therapy in the field of urology: a review of stem cell basic science, clinical applications and future directions in the treatment of various sexual and urinary conditions." Expert Opin Biol Ther **15**(11): 1623-1632.

INTRODUCTION: Stem cell (SC) research plays a key role in the increasingly promising area of regenerative medicine, with the potential to treat, prevent and cure disease. The following article provides an overview of the basic science and brief summary of major preclinical animal studies and clinical studies pertaining to SC-based research in the field of urology. AREAS COVERED: A literature review was conducted based on MEDLINE/PubMed searches for English articles using a combination of the following keywords: SC, SC-based therapy (SCT), urology, erectile dysfunction, Peyronie's disease (PD), bladder dysfunction, urinary incontinence, regeneration technology, tissue engineering, prostate disease and urinary bladder. EXPERT OPINION: While current evidence is accruing to suggest that SCT showed great promise in animal studies such as in erectile dysfunction, PD and urothelial tissue engineering, and is likely to be effective and has minimal adverse effects as observed in stress urinary incontinence and bladder dysfunction, there are still significant challenges to overcome before wide spread human application. Important issues, such as reliable outcomes, safety risks with genomic or epigenetic changes in the longer term, as well as potential immune reactions and infection risks, need to be identified in more stringent clinical trials.

Civin, C. I., et al. (1990). "Positive stem cell selection--basic science." Prog Clin Biol Res **333**: 387-401; discussion 402.

Immunologic strategies for removal of malignant cells from autologous marrow grafts by "negative selection" (i.e., "purging") requiring multiple specific monoclonal antibodies for each tumor type. "Positive selection" of marrow stem cells for grafting is a possible alternative strategy, using a monoclonal antibody which selectively recognizes lymphohematopoietic stem cells. The human hematopoietic progenitor cell antigen, CD34, is an integral cell membrane glycoprotein of approximately 115 kD, which has been molecularly cloned and sequenced. Although its function has not been determined, the glycoprotein has been characterized biochemically, including preliminary epitope mapping. Collective results from several laboratories indicate that CD34 monoclonal antibodies (My10, BI-3C5, 12.8, etc.) have the appropriate specificity to warrant testing their utility in positive selection for autologous bone marrow transplantation. First, precursors for all human hematopoietic lineages assayed (including most CFU-GM, BFU-E, CFU-MEG, CFU-EO, CFU-MIX or CFU-GEMM, pre-CFU, CFUBLAST, and terminal transferase+ B [and probably T] lymphoid precursors) are CD34+. Second, only 1.5% (mean) of low density human marrow mononuclear cells express CD34; mature human blood and marrow cells are CD34-. Endothelial cells are the only fixed tissue cells which express CD34. Third, the expression of CD34 in malignancies appears to parallel normal cellular expression: of hematopoietic malignancies, some acute leukemias and chronic myelogenous leukemia blasts are CD34+, but chronic lymphois leukemias, lymphomas, myelomas and non-hematopoietic malignancies are uniformly CD34-.

Fourth, it appears feasible to isolate CD34+ cells from clinical marrow harvest samples in large scale, using either columns or immunomagnetic microspheres. Fifth, recent studies in very small numbers of non-human primates and human patients suggest that isolated CD34+ cells include the true hematopoietic stem cell, since transplantation of CD34+ cells, into myeloblated recipients results in at least short-term hematopoietic engraftment. It is anticipated that transplantation of CD34+ marrow cells may have broad applicability in clinical bone marrow transplantation.

Curtis, D. J., et al. (2012). "Concise review: Blood relatives: formation and regulation of hematopoietic stem cells by the basic helix-loop-helix transcription factors stem cell leukemia and lymphoblastic leukemia-derived sequence 1." Stem Cells **30**(6): 1053-1058.

The basic helix-loop-helix (bHLH) proteins are a large family of transcription factors that regulate the formation and fate of tissue stem cells. In hematopoiesis, the two major bHLH factors are stem cell leukemia (SCL) and lymphoblastic leukemia-derived sequence 1 (LYL1), both identified more than 20 years ago in chromosomal translocations occurring in T-cell acute lymphoblastic leukemia. SCL was termed the master regulator of hematopoiesis following the observation that SCL knockout mice die from complete lack of blood formation. However, once established, SCL is no longer required for maintenance of hematopoiesis. Pull-down experiments together with add-back experiments in SCL-null embryonic stem cells and generation of mice carrying a germline DNA binding mutation of SCL demonstrates that most of SCL function is mediated through the formation of a large DNA binding multiprotein complex with both repressor and activator potential. Recent genome-wide binding studies in a hematopoietic stem progenitor cell line suggest that SCL and LYL1 preferentially bind target DNA sequences as components of a heptad of transcription factors. LYL1, a paralog of SCL has been the forgotten sibling until recent mouse studies demonstrated that LYL1 replaced the function of SCL in adult hematopoiesis. Why LYL1 can replace the function of SCL for the maintenance but not formation of hematopoiesis remains a fundamental question. This review will compare and contrast the roles of these two transcription factors in hematopoiesis focusing on recent functional and genome-wide binding studies.

Dai, K., et al. (2015). "[PDGFRalpha Participates in Basic Fibroblast Growth Factor-mediated Recovery of Human Bone Marrow Mesenchymal Stem Cell Proliferation and Osteogenic Differentiation after Irradiation]." Zhongguo Shi Yan Xue Ye Xue Za Zhi **23**(6): 1709-1715.

OBJECTIVE: To explore the effects of basic fibroblast growth factor (bFGF) on human bone marrow mesenchymal stem cell (hBMMSC) damaged by irradiation and its underlying mechanisms. METHODS: hBMMSC was irradiated with 0, 6, 12 Gy X ray, then flow cytometry, cell counting kit-8 (CCK-8), Western blot and alizarin red staining were used to detect the effects of X ray on apoptosis, proliferation and osteogenic differentiation of hBMMSC; 0, 1, 5, 10, 20 ng/ml bFGF was added to hBMMSC irradiated with X ray for selecting the suitable bFGF reaction concentration; then the Western blot was used to detect the expression of PDGFRalpha so as to evaluate whether the expression of PDGFRalpha participated in bFGF-mediated recovery of hBMMSC proliferation and osteogenic differentiation after irradiation. RESULTS: The proliferation and osteogenic differentiation of hBMMSC decreased remarkably after irradiation. bFGF promoted the recovery of proliferation and osteogenic differentiation of irradiated hBMMSC compared with untreated irradiated hBMMSC ($P < 0.05$); 5 ng/ml bFGF was identified as the optimal concentration. A significant difference in the number of apoptotic cells could be detected only between the 0 Gy group and 12 Gy group at the 24 h time point, while no differences were detected at later time points. Irradiated hBMMSC showed remarkable decrease of PDGFRalpha expression, while the PDGFRalpha expression increased after bFGF was added. CONCLUSION: Irradiation dose not show significant effect on apoptosis of hBMMSC, but the bFGF displays a effect on repairing the irradiation damage of hBMMSC and promotes the recovery of hBMMSC proliferation and osteogenic differentiation. The damage of hBMMSC proliferation and osteogenic differentiation associates with downregulation of PDGFRalpha expression induced by irrediation. PDGFRalpha involves in repairing effect of bFGF on irradiation damage of hBMMSC.

Denker, H. W. (2016). "Self-Organization of Stem Cell Colonies and of Early Mammalian Embryos: Recent Experiments Shed New Light on the Role of Autonomy vs. External Instructions in Basic Body Plan Development." Cells **5**(4).

"Organoids", i.e., complex structures that can develop when pluripotent or multipotent stem

cells are maintained in three-dimensional cultures, have become a new area of interest in stem cell research. Hopes have grown that when focussing experimentally on the mechanisms behind this type of in vitro morphogenesis, research aiming at tissue and organ replacements can be boosted. Processes leading to the formation of organoids in vitro are now often addressed as self-organization, a term referring to the formation of complex tissue architecture in groups of cells without depending on specific instruction provided by other cells or tissues. The present article focuses on recent reports using the term self-organization in the context of studies on embryogenesis, specifically addressing pattern formation processes in human blastocysts attaching in vitro, or in colonies of pluripotent stem cells ("gastruloids"). These morphogenetic processes are of particular interest because, during development in vivo, they lead to basic body plan formation and individuation. Since improved methodologies like those employed by the cited authors became available, early embryonic pattern formation/self-organization appears to evolve now as a research topic of its own. This review discusses concepts concerning the involved mechanisms, focussing on autonomy of basic body plan development vs. dependence on external signals, as possibly provided by implantation in the uterus, and it addresses biological differences between an early mammalian embryo, e.g., a morula, and a cluster of pluripotent stem cells. It is concluded that, apart from being of considerable biological interest, the described type of research needs to be contemplated carefully with regard to ethical implications when performed with human cells.

Dodson, M. V., et al. (2010). "Skeletal muscle stem cells from animals I. Basic cell biology." Int J Biol Sci **6**(5): 465-474.

Skeletal muscle stem cells from food-producing animals are of interest to agricultural life scientists seeking to develop a better understanding of the molecular regulation of lean tissue (skeletal muscle protein hypertrophy) and intramuscular fat (marbling) development. Enhanced understanding of muscle stem cell biology and function is essential for developing technologies and strategies to augment the metabolic efficiency and muscle hypertrophy of growing animals potentially leading to greater efficiency and reduced environmental impacts of animal production, while concomitantly improving product uniformity and consumer acceptance and enjoyment of muscle foods.

Elad, S., et al. (2015). "Basic oral care for hematology-oncology patients and hematopoietic stem cell transplantation recipients: a position paper from the joint task force of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) and the European Society for Blood and Marrow Transplantation (EBMT)." Support Care Cancer **23**(1): 223-236.

PURPOSE: Hematology-oncology patients undergoing chemotherapy and hematopoietic stem cell transplantation (HSCT) recipients are at risk for oral complications which may cause significant morbidity and a potential risk of mortality. This emphasizes the importance of basic oral care prior to, during and following chemotherapy/HSCT. While scientific evidence is available to support some of the clinical practices used to manage the oral complications, expert opinion is needed to shape the current optimal protocols. METHODS: This position paper was developed by members of the Oral Care Study Group, Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) and the European Society for Blood and Marrow Transplantation (EBMT) in attempt to provide guidance to the health care providers managing these patient populations. RESULTS: The protocol on basic oral care outlined in this position paper is presented based on the following principles: prevention of infections, pain control, maintaining oral function, the interplay with managing oral complications of cancer treatment and improving quality of life. CONCLUSION: Using these fundamental elements, we developed a protocol to assist the health care provider and present a practical approach for basic oral care. Research is warranted to provide robust scientific evidence and to enhance this clinical protocol.

Fan, F., et al. (2016). "Infusion of basic fibroblast growth factor ameliorates acute graft versus host disease in mice after haploidentical hematopoietic stem cell transplantation." Immunol Lett **170**: 1-6.

The aim of this study was to investigate the effect of basic fibroblast growth factor (bFGF) on acute graft versus host disease (aGVHD) in mice after haploidentical hematopoietic stem cell transplantation (haplo-HSCT). Haplo-HSCT mice model was established followed by dividing into three groups with 12 mice in each group, group 1 with infusion of 100g/kg bFGF, group 2 with infusion of 20 g/kg bFGF and control group without infusion. Clinical manifestation and survival time of mice after haplo-HSCT were monitored. On day 14 post transplantation, mice were sacrificed for pathology analysis of liver and the changes of mesenchymal stem cells (MSC). Compared to haplo-

HSCT group, clinical manifestations of aGVHD in bFGF infusion group were significantly ameliorated. Furthermore, bFGF infusion also significantly prolonged the survival time of mice after transplantation (P<0.05) as demonstrated by Kaplan-Meier survival analysis with more infusion of bFGF, the longer survival of mice. Pathology analysis showed the severity of aGVHD in bFGF infusion group (1 and 2) was less severe than haplo-HSCT group with higher proliferation of bone marrow MSC in group 1. In conclusion, these studies demonstrated that infusion of bFGF ameliorated aGVHD in mice after haplo-HSCT.

Fiorio Pla, A., et al. (2005). "Canonical transient receptor potential 1 plays a role in basic fibroblast growth factor (bFGF)/FGF receptor-1-induced Ca2+ entry and embryonic rat neural stem cell proliferation." J Neurosci **25**(10): 2687-2701.

Basic fibroblast growth factor (bFGF) and its major receptor FGF receptor-1 (FGFR-1) play an important role in the development of the cortex. The mechanisms underlying the mitogenic role of bFGF/FGFR-1 signaling have not been elucidated. Intracellular Ca2+ concentrations ([Ca2+]i) in proliferating cortical neuroepithelial cells are markedly dependent on Ca2+ entry (Maric et al., 2000a). The absence of voltage-dependent Ca2+ entry channels, which emerge later, indicates that other membrane mechanisms regulate [Ca2+]i during proliferation. Canonical transient receptor potential (TRPC) family channels are candidates because they are voltage independent and are expressed during CNS development (Strubing et al., 2003). Here, we investigated the involvement of TRPC1 in bFGF-mediated Ca2+ entry and proliferation of embryonic rat neural stem cells (NSCs). Both TRPC1 and FGFR-1 are expressed in the embryonic rat telencephalon and coimmunoprecipitate. Quantitative fluorescence-activated cell sorting analyses of phenotyped telencephalic dissociates show that approximately 80% of NSCs are TRPC1+, proliferating, and express FGFR-1. Like NSCs profiled ex vivo, NSC-derived progeny proliferating in vitro coexpress TRPC1 and FGFR1. Antisense knock-down of TRPC1 significantly decreases bFGF-mediated proliferation of NSC progeny, reduces the Ca2+ entry component of the Cai2+ response to bFGF without affecting Ca2+ release from intracellular stores or 1-oleoyl-2-acetyl-sn-glycerol-induced Ca2+ entry, and significantly blocks an inward cation current evoked by bFGF in proliferating NSCs. Both Ca2+ influx evoked by bFGF and NSC proliferation are attenuated by Gd3+ and SKF96365 two antagonists of agonist-stimulated Ca2+ entry. Together, these results show that TRPC1 contributes to bFGF/FGFR-1-induced Ca2+ influx, which is involved in self-renewal of embryonic rat NSCs.

Furuta, G. T., et al. (1998). "Stem cell factor influences mast cell mediator release in response to eosinophil-derived granule major basic protein." Blood **92**(3): 1055-1061.

Stem cell factor (SCF) is an important mast cell growth, differentiation, and survival factor. We investigated whether SCF influenced the response of mouse mast cells to an IgE-independent stimulus, eosinophil-derived granule major basic protein (MBP). Mouse bone marrow cultured mast cells (BMCMC) were derived in either concanavalin-stimulated mouse spleen conditioned medium (CM) or SCF. The cloned growth, factor-independent mast cell line Cl.MC/C57.1 was also studied. BMCMC in SCF exhibited cytochemical staining properties, protease and histamine content, and increased serotonin uptake consistent with more mature differentiated mast cells as compared with BMCMC in CM or Cl.MC/ C57.1 cells. BMCMC in SCF released serotonin, 14C-labeled arachidonic acid metabolites and tumor necrosis factor-alpha (TNF-alpha) on stimulation with MBP, while no response was seen from either BMCMC in CM or Cl.MC/C57.1 cells. All three mast cell populations released mediators on stimulation with the cationic MBP analog, poly-L-arginine, indicating that the cationic charge did not explain the selective response of BMCMC in SCF to eosinophil-derived granule MBP. These findings show that SCF significantly influences mast cell differentiation and the responsiveness of mast cells to eosinophil-derived granule MBP.

Gabrilove, J. L., et al. (1994). "Stem cell factor and basic fibroblast growth factor are synergistic in augmenting committed myeloid progenitor cell growth." Blood **83**(4): 907-910.

Stem cell factor (SCF) and basic fibroblast growth factor (bFGF) are hematopoietic cytokines produced by bone marrow stromal cells. It is known that, although SCF and bFGF have limited clonogenic activity on their own, they can augment colony-stimulating factor (CSF)-mediated progenitor cell growth. Because these factors are both sequestered by stromal cells, we examined their interaction on progenitor cell growth in conjunction with granulocyte-macrophage-CSF (GM-CSF). In this study, we show that clonogenic growth derived from low-density bone marrow cells stimulated by GM-CSF is significantly augmented (P < .001) in the

presence of maximal (100 ng/mL) concentrations of SCF in combination with 100 ng/mL of bFGF. When CD34+ cells are used, the synergistic effect of bFGF and SCF for GM-CSF-mediated progenitor cell growth is further increased, resulting in as much as a sevenfold increase in detectable colony-forming units granulocyte-macrophage ($P < .001$). These data suggest that the synergistic activity of bFGF and SCF is mediated directly on hematopoietic precursors. These observations suggest that bFGF and SCF, concentrated locally on stromal cell surfaces, might interact in concert with other hematopoietic cytokines to regulate stem cell proliferation and differentiation in hematopoietic niches in the bone marrow.

Giacomelli, E., et al. (2022). "Human stem cell models of neurodegeneration: From basic science of amyotrophic lateral sclerosis to clinical translation." Cell Stem Cell **29**(1): 11-35.

Neurodegenerative diseases are characterized by progressive cell loss leading to disruption of the structure and function of the central nervous system. Amyotrophic lateral sclerosis (ALS) was among the first of these disorders modeled in patient-specific iPSCs, and recent findings have translated into some of the earliest iPSC-inspired clinical trials. Focusing on ALS as an example, we evaluate the status of modeling neurodegenerative diseases using iPSCs, including methods for deriving and using disease-relevant neuronal and glial lineages. We further highlight the remaining challenges in exploiting the full potential of iPSC technology for understanding and potentially treating neurodegenerative diseases such as ALS.

Gorgens, A. and P. A. Horn (2015). "From Basic Biology to Engineering and Clinical Translation of Stem Cells: Meeting Report on the 8th International Meeting of the Stem Cell Network North Rhine Westphalia." Cell Reprogram **17**(6): 415-418.

Griffith, L. M., et al. (2006). "Target populations in allogeneic hematopoietic cell transplantation for autoimmune diseases--a workshop accompanying: cellular therapy for treatment of autoimmune diseases, basic science and clinical studies, including new developments in hematopoietic and mesenchymal stem cell therapy." Biol Blood Marrow Transplant **12**(6): 688-690.

Gugjoo, M. B., et al. (2019). "Mesenchymal stem cell: Basic research and potential applications in cattle and buffalo." J Cell Physiol **234**(6): 8618-8635.

Characteristic features like self-renewal, multilineage differentiation potential, and immune-modulatory/anti-inflammatory properties, besides the ability to mobilize and home distant tissues make stem cells (SCs) a lifeline for an individual. Stem cells (SCs) if could be harvested and expanded without any abnormal change may be utilized as an all-in-one solution to numerous clinical ailments. However, slender understanding of their basic physiological properties, including expression potential, behavioral alternations during culture, and the effect of niche/microenvironment has currently restricted the clinical application of SCs. Among various types of SCs, mesenchymal stem cells (MSCs) are extensively studied due to their easy availability, straightforward harvesting, and culturing procedures, besides, their less likelihood to produce teratogens. Large ruminant MSCs have been harvested from various adult tissues and fetal membranes and are well characterized under in vitro conditions but unlike human or other domestic animals in vivo studies on cattle/buffalo MSCs have mostly been aimed at improving the animals' production potential. In this document, we focused on the status and potential application of MSCs in cattle and buffalo.

Gugjoo, M. B., et al. (2019). "Mesenchymal stem cell basic research and applications in dog medicine." J Cell Physiol **234**(10): 16779-16811.

The stem cells, owing to their special characteristics like self-renewal, multiplication, homing, immunomodulation, anti-inflammatory, and dedifferentiation are considered to carry an "all-in-one-solution" for diverse clinical problems. However, the limited understanding of cellular physiology currently limits their definitive therapeutic use. Among various stem cell types, currently mesenchymal stem cells are extensively studied for dog clinical applications owing to their readily available sources, easy harvesting, and ability to differentiate both into mesodermal, as well as extramesodermal tissues. The isolated, culture expanded, and characterized cells have been applied both at preclinical as well as clinical settings in dogs with variable but mostly positive results. The results, though positive, are currently inconclusive and demands further intensive research on the properties and their dependence on the applications. Further, numerous clinical conditions of dog resemble to that of human counterparts and thus, if proved rewarding in the former may act as basis of therapy for the latter. The current review throws some light on dog mesenchymal stem cell properties and their potential therapeutic applications.

Gupta, S., et al. (2023). "Retinal Pigment Epithelium Cell Development: Extrapolating Basic Biology to Stem Cell Research." Biomedicines **11**(2).

The retinal pigment epithelium (RPE) forms an important cellular monolayer, which contributes to the normal physiology of the eye. Damage to the RPE leads to the development of degenerative diseases, such as age-related macular degeneration (AMD). Apart from acting as a physical barrier between the retina and choroidal blood vessels, the RPE is crucial in maintaining photoreceptor (PR) and visual functions. Current clinical intervention to treat early stages of AMD includes stem cell-derived RPE transplantation, which is still in its early stages of evolution. Therefore, it becomes essential to derive RPEs which are functional and exhibit features as observed in native human RPE cells. The conventional strategy is to use the knowledge obtained from developmental studies using various animal models and stem cell-based exploratory studies to understand RPE biogenies and developmental trajectory. This article emphasises such studies and aims to present a comprehensive understanding of the basic biology, including the genetics and molecular pathways of RPE development. It encompasses basic developmental biology and stem cell-based developmental studies to uncover RPE differentiation. Knowledge of the in utero developmental cues provides an inclusive methodology required for deriving RPEs using stem cells.

Haastert-Talini, K. and C. Grothe (2014). "Comment to the paper: Acceleration of peripheral nerve regeneration using nerve conduits in combination with induced pluripotent stem cell technology and a basic fibroblast growth factor drug delivery system by M. Ikeda, T. Uemura, K. Takamatsu, M. Okada, K. Kazuki, Y. Tabata, Y. Ikada, H. Nakamura, J Biomed Mater Res A. 2013 Jun 3 doi: 10.1002/jbm.a.34816." J Biomed Mater Res A **102**(4): 1219-1220.

Haley, E. M., et al. (2017). "Acidic pH with coordinated reduction of basic fibroblast growth factor maintains the glioblastoma stem cell-like phenotype in vitro." J Biosci Bioeng **123**(5): 634-641.

Glioblastoma stem cells (GSCs) are a unique subpopulation of cells within glioblastoma multiforme (GBM) brain tumors that possess the ability to self-renew and differentiate into bulk tumor cells. GSCs are resistant to currently available treatments and are the likely culprit behind tumor relapse in GBM patients. However, GSCs are currently inaccessible to the larger scientific community because obtaining a sufficient number of GSCs remains technically challenging and cost-prohibitive. Thus, the objective of this study was to develop a more efficient GSC culture strategy that results in a higher cell yield of GSCs at a lower cost. We observed that the basic fibroblast growth factor (bFGF) is indispensable in allowing GSCs to retain an optimal stem cell-like phenotype in vitro, but little change was seen in their stemness when grown with lower concentrations of bFGF than the established protocol. Interestingly, a dynamic fluctuation of GSC protein marker expression was observed that corresponded to the changes in the bFGF concentration during the culture period. This suggested that bFGF alone did not control stem cell-like phenotype; rather, it was linked to the fluctuations of both bFGF and media pH. We demonstrated that a high level of stem cell-like phenotype could be retained even when lowering bFGF to 8 ng/mL when the media pH was simultaneously lowered to 6.8. These results provide the proof-of-concept that GSC expansion costs could be lowered to a more economical level and warrant the use of pH- and bFGF-controlled bioprocessing methodologies to more optimally expand GSCs in the future.

Han, U., et al. (2017). "Efficient Encapsulation and Sustained Release of Basic Fibroblast Growth Factor in Nanofilm: Extension of the Feeding Cycle of Human Induced Pluripotent Stem Cell Culture." ACS Appl Mater Interfaces **9**(30): 25087-25097.

Basic fibroblast growth factor (bFGF) has an established pivotal function in biomedical engineering, especially for the human pluripotent stem cells (iPSCs). However, the limitation of bFGF is the ease of denaturation under normal physiological conditions, inducing loss of its activity. In this study, we designed multi-trilayered nanofilm composed of a repeating polycation/polyanion/bFGF structure, which has high loading efficiency and short buildup time. We also investigated that the loading and release of bFGF from the nanofilm with two parameters (counter-polyanion and film architectures). Then, we prepared the optimized nanofilm which maintains a sustained bFGF level in physiological condition to apply the nanofilm to human iPSCs culture. The amount of bFGF release from 12 trilayer nanofilm was 36.4 ng/cm(2), and activity of bFGF encapsulated into the nanofilm was maintained (60%) until 72 h during incubation at 37 degrees C. As a result, the iPSCs grown in the presence of the nanofilm with tridaily replacement of growth medium maintained undifferentiated morphology and expression levels of pluripotency marker proteins.

Harrell, C. R., et al. (2020). "Therapeutic Use of Mesenchymal Stem Cell-Derived Exosomes: From Basic Science to Clinics." Pharmaceutics **12**(5).

Mesenchymal stem cells (MSC) are, due to their immunosuppressive and regenerative properties, used as new therapeutic agents in cell-based therapy of inflammatory and degenerative diseases. A large number of experimental and clinical studies revealed that most of MSC-mediated beneficial effects were attributed to the effects of MSC-sourced exosomes (MSC-Exos). MSC-Exos are nano-sized extracellular vesicles that contain MSC-derived bioactive molecules (messenger RNA (mRNA), microRNAs (miRNAs)), enzymes, cytokines, chemokines, and growth factors) that modulate phenotype, function and homing of immune cells, and regulate survival and proliferation of parenchymal cells. In this review article, we emphasized current knowledge about molecular and cellular mechanisms that were responsible for MSC-Exos-based beneficial effects in experimental models and clinical trials. Additionally, we elaborated on the challenges of conventional MSC-Exos administration and proposed the use of new bioengineering and cellular modification techniques which could enhance therapeutic effects of MSC-Exos in alleviation of inflammatory and degenerative diseases.

Hartl, M., et al. (2010). "Stem cell-specific activation of an ancestral myc protooncogene with conserved basic functions in the early metazoan Hydra." Proc Natl Acad Sci U S A **107**(9): 4051-4056.

The c-myc protooncogene encodes a transcription factor (Myc) with oncogenic potential. Myc and its dimerization partner Max are bHLH-Zip DNA binding proteins controlling fundamental cellular processes. Deregulation of c-myc leads to tumorigenesis and is a hallmark of many human cancers. We have identified and extensively characterized ancestral forms of myc and max genes from the early diploblastic cnidarian Hydra, the most primitive metazoan organism employed so far for the structural, functional, and evolutionary analysis of these genes. Hydra myc is specifically activated in all stem cells and nematoblast nests which represent the rapidly proliferating cell types of the interstitial stem cell system and in proliferating gland cells. In terminally differentiated nerve cells, nematocytes, or epithelial cells, myc expression is not detectable by in situ hybridization. Hydra max exhibits a similar expression pattern in interstitial cell clusters. The ancestral Hydra Myc and Max proteins display the principal design of their vertebrate derivatives, with the highest degree of sequence identities confined to the bHLH-Zip domains. Furthermore, the 314-amino acid Hydra Myc protein contains basic forms of the essential Myc boxes I through III. A recombinant Hydra Myc/Max complex binds to the consensus DNA sequence CACGTG with high affinity. Hybrid proteins composed of segments from the retroviral v-Myc oncoprotein and the Hydra Myc protein display oncogenic potential in cell transformation assays. Our results suggest that the principal functions of the Myc master regulator arose very early in metazoan evolution, allowing their dissection in a simple model organism showing regenerative ability but no senescence.

Hayata, Y., et al. (2021). "Feeder-Free Human Induced Pluripotent Stem Cell Culture Using a DNA Aptamer-Based Mimic of Basic Fibroblast Growth Factor." Methods Mol Biol **2312**: 301-305.

Cell culture media are often supplemented with recombinant growth factors and cytokines to reproduce biological conditions in vitro. Basic fibroblast growth factor (bFGF) has been widely used to support the pluripotency and self-renewal activity of human induced pluripotent stem cells (hiPSCs). We had previously developed a synthetic surrogate for bFGF on the basis of a DNA aptamer that binds to one of the FGF receptors. Since DNA aptamers have advantages over recombinant proteins in terms of thermal stability and production cost, replacing recombinant growth factors in cell culture media with DNA aptamers would be of great interest. Herein, we describe our protocol for feeder-free hiPSC culture using a DNA aptamer-based mimic of bFGF.

Hebert, T. L., et al. (2009). "Culture effects of epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF) on cryopreserved human adipose-derived stromal/stem cell proliferation and adipogenesis." J Tissue Eng Regen Med **3**(7): 553-561.

Previous studies have demonstrated that EGF and bFGF maintain the stem cell properties of proliferating human adipose-derived stromal/stem cells (hASCs) in vitro. While the expansion and cryogenic preservation of isolated hASCs are routine, these manipulations can impact their proliferative and differentiation potential. This study examined cryogenically preserved hASCs (n = 4 donors), with respect to these functions, after culture with basic fibroblast growth factor (bFGF) and epidermal growth factor (EGF) at varying concentrations (0-10 ng/ml). Relative to the control, cells supplemented with EGF and bFGF significantly increased proliferation by up to three-fold over 7-8 days. Furthermore, cryopreserved hASCs expanded in the

presence of EGF and bFGF displayed increased oil red O staining following adipogenic induction. This was accompanied by significantly increased levels of several adipogenesis-related mRNAs: aP2, C/EBPalpha, lipoprotein lipase (LPL), PPARgamma and PPARgamma co-activator-1 (PGC1). Adipocytes derived from EGF- and bFGF-cultured hASCs exhibited more robust functionality based on insulin-stimulated glucose uptake and atrial natriuretic peptide (ANP)-stimulated lipolysis. These findings indicate that bFGF and EGF can be used as culture supplements to optimize the proliferative capacity of cryopreserved human ASCs and their adipogenic differentiation potential.

Hescheler, J. and C. Hauskeller (2008). "[From basic research to the clinic. Obstacles and options for stem cell therapies]." Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz **51**(9): 1014-1020.

Translation from the laboratory to the clinic is one of the key problems of stem cell research. One reason for this is that stem cell science is ethically charged and therefore its successful therapeutic application would support its social legitimacy and further funding. We discuss translation both theoretically and with reference to an example, namely efforts regarding the creation of cardiomyocytes from embryonic stem cell lines with the aim to regenerate a patient's myocardium post trauma. Using this case we explain the facts that need to be established scientifically and the subsequent steps that need to be taken in order to develop and implement clinical application. We also discuss aspects of current scientific development related to the moral charge of the research, in particular emerging methods aimed at the derivation of pluripotent cells, such as the hybridization of human DNA and animal egg cells, or the genetic modification of adult somatic cell nuclei in culture to induce pluripotency.

Hirobe, T., et al. (2010). "Life cycle of human melanocytes is regulated by endothelin-1 and stem cell factor in synergy with cyclic AMP and basic fibroblast growth factor." J Dermatol Sci **57**(2): 123-131.

BACKGROUND: Although the function of human melanocytes is well characterized at cellular and molecular levels, the mechanism of the regulation of the life cycle (proliferation, differentiation, and cell death) of human melanocytes is not fully understood. OBJECTIVE: This study aims to clarify what factors are involved in regulating the life cycle of human melanocytes using serum-free culture system. METHODS: Human epidermal melanocytes were cultured in a serum-free growth medium supplemented with several kinds of growth factors, cytokines, and hormones and the effects of these factors on the life cycle of melanocytes were investigated in detail. RESULTS: Of the factors tested, endothelin-1 (ET-1) stimulated the proliferation of melanoblasts and melanocytes in the presence of cyclic AMP (cAMP)-elevating factor such as dibutyryl cAMP (DBcAMP) and of basic fibroblast growth factor (bFGF). ET-1 also stimulated the proliferation and differentiation of human melanocytes in the presence of DBcAMP. Moreover, stem cell factor (SCF) stimulated the proliferation of melanoblasts and melanocytes synergistically with ET-1. The removal of ET-1 and SCF from the culture medium greatly inhibited the proliferation of melanocytes followed by apoptotic cell death. CONCLUSION: These results suggest that the life cycle of human melanocytes is regulated by ET-1 and SCF in synergy with cAMP and bFGF.

Hu, Y., et al. (2016). "Effects of nerve growth factor and basic fibroblast growth factor dual gene modification on rat bone marrow mesenchymal stem cell differentiation into neuron-like cells in vitro." Mol Med Rep **13**(1): 49-58.

Recent studies regarding regenerative medicine have focused on bone marrow mesenchymal stem cells (BMSCs), which have the potential to undergo neural differentiation, and may be transfected with specific genes. BMSCs can differentiate into neuron-like cells in certain neurotropic circumstances in vitro. Basic fibroblast growth factor (bFGF) and nerve growth factor (NGF) are often used to induce neural differentiation in BMSCs in vitro. However, previous studies regarding their combined actions are insufficient. The present study is the first, to the best of our knowledge, to thoroughly assess the enhancement of neural differentiation of BMSCs following transfection with bFGF and NGF. Sprague-Dawley (SD) rat BMSCs were separated through whole bone marrow adherence, and were then passaged to the third generation. The cells were subsequently divided into five groups: The control group, which consisted of untransfected BMSCs; the plv-blank-transfected BMSCs group; the plv-bFGF-transfected BMSCs group; the plv-NGF-transfected BMSCs group; and the plv-NGF-bFGF co-transfected BMSCs group. Cell neural differentiation was characterized in terms of stem cell molecular expression, and the neuronal morphology and expression of neural-like molecules was detected in each of the groups. A total of 72 h post-transfection, the expression levels of

neuron-specific enolase, glial fibrillary acidic protein, and nestin protein, were higher in the co-transfected group, as compared with the other groups, the expression levels of beta-tubulin III were also increased in the co-transfected cells, thus suggesting the maturation of differentiated neuron-like cells. Furthermore, higher neuronal proliferation was observed in the co-transfected group, as compared with the other groups at passages 2, 4, 6 and 8. Western blotting demonstrated that the transfected groups exhibited a simultaneous increase in phosphorylation of the AKT and extracellular signal-regulated kinases (ERK) signaling pathway. These results suggested that manipulation of the ERK and AKT signaling pathway may be associated with the differentiation of transfected BMSCs.

Huang, W., et al. (2012). "Effects of leukemia inhibitory factor and basic fibroblast growth factor on free radicals and endogenous stem cell proliferation in a mouse model of cerebral infarction." Neural Regen Res **7**(19): 1469-1474.

The present study established a mouse model of cerebral infarction by middle cerebral artery occlusion, and monitored the effect of 25 mug/kg leukemia inhibitory factor and (or) basic fibroblast growth factor administration 2 hours after model establishment. Results showed that following administration, the number of endogenous neural stem cells in the infarct area significantly increased, malondialdehyde content in brain tissue homogenates significantly decreased, nitric oxide content, glutathione peroxidase and superoxide dismutase activity significantly elevated, and mouse motor function significantly improved as confirmed by the rotarod and bar grab tests. In particular, the effect of leukemia inhibitory factor in combination with basic fibroblast growth factor was the most significant. Results indicate that leukemia inhibitory factor and basic fibroblast growth factor can improve the microenvironment after cerebral infarction by altering free radical levels, improving the quantity of endogenous neural stem cells, and promoting neurological function of mice with cerebral infarction.

Ikeda, M., et al. (2014). "Acceleration of peripheral nerve regeneration using nerve conduits in combination with induced pluripotent stem cell technology and a basic fibroblast growth factor drug delivery system." J Biomed Mater Res A **102**(5): 1370-1378.

Various modifications including addition of Schwann cells or incorporation of growth factors with bioabsorbable nerve conduits have been explored as options for peripheral nerve repair. However, no reports of nerve conduits containing both supportive cells and growth factors have been published as a regenerative therapy for peripheral nerves. In the present study, sciatic nerve gaps in mice were reconstructed in the following groups: nerve conduit alone (control group), nerve conduit coated with induced pluripotent stem cell (iPSc)-derived neurospheres (iPSc group), nerve conduit coated with iPSc-derived neurospheres and basic fibroblast growth factor (bFGF)-incorporated gelatin microspheres (iPSc + bFGF group), and autograft. The fastest functional recovery and the greatest axon regeneration occurred in the autograft group, followed in order by the iPSc + bFGF group, iPSc group, and control group until 12 weeks after reconstruction. Thus, peripheral nerve regeneration using nerve conduits and functional recovery in mice was accelerated by a combination of iPSc-derived neurospheres and a bFGF drug delivery system. The combination of all three fundamental methodologies, iPSc technology for supportive cells, bioabsorbable nerve conduits for scaffolds, and a bFGF drug delivery system for growth factors, was essential for peripheral nerve regenerative therapy.

Imsoonthornruksa, S., et al. (2015). "Expression and Purification of Recombinant Human Basic Fibroblast Growth Factor Fusion Proteins and Their Uses in Human Stem Cell Culture." J Mol Microbiol Biotechnol **25**(6): 372-380.

To reduce the cost of cytokines and growth factors in stem cell research, a simple method for the production of soluble and biological active human basic fibroblast growth factor (hbFGF) fusion protein in Escherichia coli was established. Under optimal conditions, approximately 60-80 mg of >95% pure hbFGF fusion proteins (Trx-6xHis-hbFGF and 6xHis-hbFGF) were obtained from 1 liter of culture broth. The purified hbFGF proteins, both with and without the fusion tags, were biologically active, which was confirmed by their ability to stimulate proliferation of NIH3T3 cells. The fusion proteins also have the ability to support several culture passages of undifferentiated human embryonic stem cells and induce pluripotent stem cells. This paper describes a low-cost and uncomplicated method for the production and purification of biologically active hbFGF fusion proteins.

Isenmann, S., et al. (2009). "TWIST family of basic helix-loop-helix transcription factors mediate human mesenchymal stem cell growth and commitment." Stem Cells **27**(10): 2457-2468.

The TWIST family of basic helix-loop-helix transcription factors, Twist-1 and Dermo-1 are

known mediators of mesodermal tissue development and contribute to correct patterning of the skeleton. In this study, we demonstrate that freshly purified human bone marrow-derived mesenchymal stromal/stem cells (MSC) express high levels of Twist-1 and Dermo-1 which are downregulated following ex vivo expansion. Enforced expression of Twist-1 or Dermo-1 in human MSC cultures increased expression of the MSC marker, STRO-1, and the early osteogenic transcription factors, Runx2 and Msx2. Conversely, overexpression of Twist-1 and Dermo-1 was associated with a decrease in the gene expression of osteoblast-associated markers, bone morphogenic protein-2, bone sialoprotein, osteopontin, alkaline phosphatase and osteocalcin. High expressing Twist-1 or Dermo-1 MSC lines exhibited an enhanced proliferative potential of approximately 2.5-fold compared with control MSC populations that were associated with elevated levels of Id-1 and Id-2 gene expression. Functional studies demonstrated that high expressing Twist-1 and Dermo-1 MSC displayed a decreased capacity for osteo/chondrogenic differentiation and an enhanced capacity to undergo adipogenesis. These findings implicate the TWIST gene family members as potential mediators of MSC self-renewal and lineage commitment in postnatal skeletal tissues by exerting their effects on genes involved in the early stages of bone development.

Itoh, T., et al. (2005). "Effect of basic fibroblast growth factor on cultured rat neural stem cell in three-dimensional collagen gel." Neurol Res **27**(4): 429-432.

OBJECTIVES: The effect of growth factors on the three-dimensional culture of neural stem cells has not been reported. We studied the effect of basic fibroblast growth factor (bFGF) on cultured rat neural stem cells in a three-dimensional culture. METHODS: We cultured rat neural stem cells in collagen gel matrix for three-dimensional culture and examined the effect of bFGF under such culture conditions. RESULTS: After 4 days culture, the cell density in the bFGF treatment group was 12 times that of the non-treatment group, reaching a significantly high value. In the bFGF treatment group, microtubule associate protein (MAP)-2-positive cell aggregation occurred, although in the bFGF non-treatment group there was no MAP-2-positive cell aggregation and few of the cells were sparsely distributed. Also, in the bFGF treatment group, MAP-2-positive cell aggregation had a luminal structure similar to neural rosettes. There was elongation of MAP-2-positive neurites from the cell aggregation to the circumference in the bFGF treatment group. DISCUSSION: bFGF is known to induce the proliferation, but not the differentiation of neural stem cells in two-dimensional cultures. However, in the three-dimensional culture, bFGF induced both the proliferation and differentiation of neural stem cells. The three-dimensional culture is, therefore, considered a useful method for predicting the response of neural stem cells to cytokines or biologically active substances in vivo.

Jagiello, J., et al. (2019). "Impact of Graphene-Based Surfaces on the Basic Biological Properties of Human Umbilical Cord Mesenchymal Stem Cells: Implications for Ex Vivo Cell Expansion Aimed at Tissue Repair." Int J Mol Sci **20**(18).

The potential therapeutic applications of mesenchymal stem/stromal cells (MSCs) and biomaterials have attracted a great amount of interest in the field of biomedical engineering. MSCs are multipotent adult stem cells characterized as cells with specific features, e.g., high differentiation potential, low immunogenicity, immunomodulatory properties, and efficient in vitro expansion ability. Human umbilical cord Wharton's jelly-derived MSCs (hUC-MSCs) are a new, important cell type that may be used for therapeutic purposes, i.e., for autologous and allogeneic transplantations. To improve the therapeutic efficiency of hUC-MSCs, novel biomaterials have been considered for use as scaffolds dedicated to the propagation and differentiation of these cells. Nowadays, some of the most promising materials for tissue engineering include graphene and its derivatives such as graphene oxide (GO) and reduced graphene oxide (rGO). Due to their physicochemical properties, they can be easily modified with biomolecules, which enable their interaction with different types of cells, including MSCs. In this study, we demonstrate the impact of graphene-based substrates (GO, rGO) on the biological properties of hUC-MSCs. The size of the GO flakes and the reduction level of GO have been considered as important factors determining the most favorable surface for hUC-MSCs growth. The obtained results revealed that GO and rGO are suitable scaffolds for hUC-MSCs. hUC-MSCs cultured on: (i) a thin layer of GO and (ii) an rGO surface with a low reduction level demonstrated a viability and proliferation rate comparable to those estimated under standard culture conditions. Interestingly, cell culture on a highly reduced GO substrate resulted in a decreased hUC-MSCs proliferation rate and induced cell apoptosis. Moreover, our analysis demonstrated that hUC-MSCs cultured on all the tested GO and rGO scaffolds showed no alterations of their typical

mesenchymal phenotype, regardless of the reduction level and size of the GO flakes. Thus, GO scaffolds and rGO scaffolds with a low reduction level exhibit potential applicability as novel, safe, and biocompatible materials for utilization in regenerative medicine.

Kang, H. B., et al. (2005). "Basic fibroblast growth factor activates ERK and induces c-fos in human embryonic stem cell line MizhES1." Stem Cells Dev **14**(4): 395-401.

Human embryonic stem (hES) cells can be maintained in a proliferative undifferentiated state in vitro by growing them on feeder layers of mouse embryonic fibroblast (MEF) cells along with basic fibroblast growth factor (bFGF/FGF-2). To understand the molecular mechanisms involved in the requirement of bFGF in human ES cells, we investigated expression of FGF receptors and intracellular signaling events in response to bFGF in human ES cell line MizhES1. On the basis of the results of RT-PCR, clear expression of FGF receptors FGFR1, FGR2, and FGFR3 was noticed. Because MAPK, PI3K, and PKC pathways are well-known pathways triggered by bFGF in other cells, these pathways were investigated after stimulation with bFGF. bFGF did not induce activation of PI3K or PKC, but induced activation of ERK (extracellular signal-regulated kinase). To monitor the consequences of ERK activation, we examined expression of the immediate early gene c-fos, one downstream target of the MEK1/ERK pathway. mRNA and protein levels of the c-fos gene were increased by bFGF. Induction of c-Fos was dependent on MEKl. Therefore, it is likely that bFGF contributes to maintenance of human ES cells, at least in part, through the MEK1/ERK pathway.

Kashyap, R. (2015). "SHED - Basic Structure for Stem Cell Research." J Clin Diagn Res **9**(3): ZE07-09.

The discovery that stem cells from dental pulp are capable of differentiating into endothelial cells raised the exciting possibility that these cells can be a single source of odontoblasts and vascular networks in dental tissue engineering. These so-called mesenchymal stem cell populations have been identified from human exfoliated deciduous teeth because of their ability to generate clonogenic adherent colonies when grown and expanded. In addition to these stem cells, other population of stem cells can be from adult human dental pulp and periodontal ligament. The identification and isolation of these stem cells in adult dental pulp was first reported by Gronthos and co-workers in 2000.These dental pulp stem cells have clonogenic abilities, rapid proliferative rates and the capacity to form mineralized tissues both in vitro and in vivo. The stem cells from human exfoliated deciduous teeth are distinct from dental pulp stem cells by virtue of their proliferation rate, increased cell population doublings and osteoinductive capacity in vivo. It is further demonstrated that human exfoliated deciduous teeth stem cells may not be a single-cell type, may well be a heterogenous population of cells from the pulp.

Katakura, M., et al. (2009). "Docosahexaenoic acid promotes neuronal differentiation by regulating basic helix-loop-helix transcription factors and cell cycle in neural stem cells." Neuroscience **160**(3): 651-660.

Recent studies have suggested that docosahexaenoic acid (DHA) enhances neuronal differentiation of neural stem cells (NSCs) isolated from rat embryonic day 14.5. However the underlying mechanism remains largely unknown. One hypothesis supported by DHA controls the expression level of basic helix-loop-helix (bHLH) transcription factors, such as hairy and enhancer of split 1 (Hes1), Mash1, neurogenin1, and NeuroD; another is that previous studies in retinal progenitor cells DHA affects the cell cycle. In this study, we show that treatment with DHA under differentiation conditions without basic fibroblast growth factor, (1) increases Tuj-1 and MAP2 positive cells in NSCs, (2) that the expression level of Hes1 mRNA and protein decreased significantly from day 1 to day 4, on the other hand, the NeuroD mRNA expression level increased from day 1 to day 4 after treatment with DHA and (3) decreased the percentage of S-phase cells, which correlated with prolonged expression of cyclin-dependent kinase inhibitor p27(kip1), suggesting that DHA enhances neuronal differentiation of NSCs, in part, by controlling the bHLH transcription factors and promoting cell cycle exit. We therefore speculate that DHA is one of the essential key molecules for neuronal differentiation of NSCs.

Kelsey, P. J., et al. (2016). "Haematopoietic stem cell transplantation in autoimmune diseases: From basic science to clinical practice." Curr Res Transl Med **64**(2): 71-82.

Based on animal studies and serendipitous clinical cases, haematopoietic stem cell transplantation (HSCT) has been used since 1995 as a specific treatment for patients with severe treatment-resistant autoimmune disease (ADs). Despite other clinical developments for autoimmune diseases, including biological therapies, there has been an ongoing requirement for HSCT in some diseases and several thousand procedures have been registered in

databases for a wide variety of diseases, predominantly for treatment with autologous HSCT. Currently, the main indications are multiple sclerosis, systemic sclerosis and Crohn's disease, which are supported by large series and randomised controlled trials (RCTs), whereas retrospective registry analyses support benefit in a range of rarer indications. Research into mechanisms of action has provided insight into how tolerance may be achieved with an intensive one-off treatment. In addition to the profound anti-inflammatory and immunosuppressive effects provided by the cytotoxic regimen, long-term responses in some diseases may be explained by 'resetting' the immune system through thymic reprocessing and generation of increased T-regulatory cell activity. This review aims to summarise the gradual evolution of HSCT in severe autoimmune diseases over the last 20 years, focussing on the recent publication of clinical and scientific studies, as well as evidence-based guidelines and recommendations.

Kim, S., et al. (2023). "Thermostable Human Basic Fibroblast Growth Factor (TS-bFGF) Engineered with a Disulfide Bond Demonstrates Superior Culture Outcomes in Human Pluripotent Stem Cell." Biology (Basel) **12**(6).

Human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) can differentiate into various tissues and are an essential source of various disease models and therapeutics. Various growth factors are required in order to culture pluripotent stem cells, among which basic fibroblast growth factor (bFGF) is essential for maintaining stem cell ability. However, bFGF has a short half-life (8 h) under normal mammalian cell culture conditions, and its activity decreases after 72 h, posing a serious problem in the production of high-quality stem cells. Here, we evaluated the various functions of pluripotent stem cells (PSCs) by utilizing an engineered thermostable bFGF (TS-bFGF) that is thermally stable and maintains activity longer under mammalian culture conditions. PSCs cultured with TS-bFGF showed better proliferation, stemness, morphology, and differentiation than cells cultured with wild-type bFGF. In light of the importance of stem cells in a wide range of applications in the medical and biotechnology fields, we anticipate that TS-bFGF, as a thermostable and long-acting bFGF, can play a key role in securing high-quality stem cells through various sets of stem cell culture processes.

Kono, K., et al. (2013). "Exposure to transforming growth factor-beta1 after basic fibroblast growth factor promotes the fibroblastic differentiation of human periodontal ligament stem/progenitor cell lines." Cell Tissue Res **352**(2): 249-263.

Basic fibroblast growth factor (bFGF) is a cytokine that promotes the regeneration of the periodontium, the specialized tissues supporting the teeth. bFGF, does not, however, induce the synthesis of smooth muscle actin alpha 2 (ACTA2), type I collagen (COL1), or COL3, which are principal molecules in periodontal ligament (PDL) tissue, a component of the periodontium. We have suggested the feasibility of using transforming growth factor-beta1 (TGFbeta1) to induce fibroblastic differentiation of PDL stem/progenitor cells (PDLSCs). Here, we investigated the effect of the subsequent application of TGFbeta1 after bFGF (bFGF/TGFbeta1) on the differentiation of PDLSCs into fibroblastic cells. We first confirmed the expression of bFGF and TGFbeta1 in rat PDL tissue and primary human PDL cells. Receptors for both bFGF and TGFbeta1 were expressed in the human PDLSC lines 1-11 and 1-17. Exposure to bFGF for 2 days promoted vascular endothelial growth factor gene and protein expression in both cell lines and down-regulated the expression of ACTA2, COL1, and COL3 mRNA in both cell lines and the gene fibrillin 1 (FBN1) in cell line 1-11 alone. Furthermore, bFGF stimulated cell proliferation of these cell lines and significantly increased the number of cells in phase G2/M in the cell lines. Exposure to TGFbeta1 for 2 days induced gene expression of ACTA2 and COL1 in both cell lines and FBN1 in cell line 1-11 alone. BFGF/TGFbeta1 treatment significantly up-regulated ACTA2, COL1, and FBN1 expression as compared with the group treated with bFGF alone or the untreated control. This method might thus be useful for accelerating the generation and regeneration of functional periodontium.

Kreja, L., et al. (1993). "The effect of recombinant human stem cell factor and basic fibroblast growth factor on the in vitro radiosensitivity of CD34+ hematopoietic progenitors from human umbilical cord blood." Exp Hematol **21**(11): 1436-1441.

Human umbilical cord blood (CB) cells selected by immunomagnetic beads for expression of the CD34 antigen were irradiated with increasing doses of x-rays (72 cGy/min). Clonogenic survival of the hematopoietic progenitors, including mixed colony-forming cells (Mix-CFC), erythroid burst-forming units (BFU-E), and granulocyte-macrophage colony-forming cells (GM-CFC), was determined in methylcellulose cultures containing placenta conditioned medium (PCM) and erythropoietin (Epo). Exponential survival curves were fitted to the data of

all the colonies, resulting in D0 = 95 cGy for Mix-CFC, 136 cGy for BFU-E, and 136 cGy for GM-CFC. Additionally, the radiosensitivity of CD34+ cells was studied employing cultures containing either recombinant human stem cell factor (rhSCF) or basic fibroblast growth factor (b-FGF) in combination with PCM and Epo. It was found that the colony-forming efficiency (CFE) of non-irradiated CD34+ cells of 5.5% (range 1.4 to 14.4%) did not increase after the addition of SCF or b-FGF to the culture. The radiation response characteristics showed, however, that in the presence of SCF, the D0 value and the extrapolation number n increased significantly. This suggests the stimulation of what operationally is termed "recovery from potentially lethal damage." In contrast, no response modifying effect could be seen for b-FGF.

Lakshman, N., et al. (2021). "Niche-dependent inhibition of neural stem cell proliferation and oligodendrogenesis is mediated by the presence of myelin basic protein." Stem Cells **39**(6): 776-786.

Neural stem and progenitor cells (collectively termed neural precursor cells [NPCs]) are found along the ventricular neuraxis extending from the spinal cord to the forebrain in regionally distinct niches comprised of different cell types, architecture, and cell-cell interactions. An understanding of the factors that regulate NPC behavior is critical for developing therapeutics to repair the injured central nervous system. Herein, we demonstrate that myelin basic protein (MBP), the major cytoplasmic protein constituent of the myelin sheath in oligodendrocytes, can regulate NPC behavior. Under physiological conditions, NPCs are not in contact with intracellular MBP; however, upon injury, MBP is released into the neural parenchyma. We reveal that MBP presented in a spinal cord niche is inhibitory to NPC proliferation. This inhibitory effect is regionally distinct as spinal cord NPCs, but not forebrain-derived NPCs, are inhibited by MBP. We performed coculture and conditioned media experiments that reveal the stem cell niche is a key regulator of MBP's inhibitory actions on NPCs. The inhibition is mediated by a heat-labile protein released by spinal cord niche cells, but not forebrain niche cells. However, forebrain NPCs are also inhibited by the spinal cord derived factor as revealed following in vivo infusion of the spinal cord niche-derived conditioned media. Moreover, we show that MBP inhibits oligodendrogenesis from NPCs. Together, these findings highlight the role of MBP and the regionally distinct microenvironment in regulating NPC behavior which has important implications for stem cell-based regenerative strategies.

Lee, S. K., et al. (2009). "Differential expression of cell surface proteins in human bone marrow mesenchymal stem cells cultured with or without basic fibroblast growth factor containing medium." Proteomics **9**(18): 4389-4405.

Mesenchymal stem cells (MSCs) are multipotent cells, which have the capability to differentiate into various mesenchymal tissues such as bone, cartilage, fat, tendon, muscle, and marrow stroma. However, they lose the capability of multi-lineage differentiation after several passages. It is known that basic fibroblast growth factor (bFGF) increases growth rate, differentiation potential, and morphological changes of MSCs in vitro. In this report, we have used 2-DE coupled to MS to identify differentially expressed proteins at the cell membrane level in MSCs growing in bFGF containing medium. The cell surface proteins isolated by the biotin-avidin affinity column were separated by 2-DE in triplicate experiments. A total of 15 differentially expressed proteins were identified by quadrupole-time of flight tandem MS. Nine of the proteins were upregulated and six proteins were downregulated in the MSCs cultured with bFGF containing medium. The expression level of three actin-related proteins, F-actin-capping protein subunit alpha-1, actin-related protein 2/3 complex subunit 2, and myosin regulatory light chain 2, was confirmed by Western blot analysis. The results indicate that the expression levels of F-actin-capping protein subunit alpha-1, actin-related protein 2/3 complex subunit 2, and myosin regulatory light chain 2 are important in bFGF-induced morphological change of MSCs.

Lennartsson, J. and L. Ronnstrand (2012). "Stem cell factor receptor/c-Kit: from basic science to clinical implications." Physiol Rev **92**(4): 1619-1649.

Stem cell factor (SCF) is a dimeric molecule that exerts its biological functions by binding to and activating the receptor tyrosine kinase c-Kit. Activation of c-Kit leads to its autophosphorylation and initiation of signal transduction. Signaling proteins are recruited to activated c-Kit by certain interaction domains (e.g., SH2 and PTB) that specifically bind to phosphorylated tyrosine residues in the intracellular region of c-Kit. Activation of c-Kit signaling has been found to mediate cell survival, migration, and proliferation depending on the cell type. Signaling from c-Kit is crucial for normal hematopoiesis, pigmentation, fertility, gut movement, and some aspects of the nervous system. Deregulated c-Kit kinase activity has been found in a number of

pathological conditions, including cancer and allergy. The observation that gain-of-function mutations in c-Kit can promote tumor formation and progression has stimulated the development of therapeutics agents targeting this receptor, e.g., the clinically used inhibitor imatinib mesylate. Also other clinically used multiselective kinase inhibitors, for instance, sorafenib and sunitinib, have c-Kit included in their range of targets. Furthermore, loss-of-function mutations in c-Kit have been observed and shown to give rise to a condition called piebaldism. This review provides a summary of our current knowledge regarding structural and functional aspects of c-Kit signaling both under normal and pathological conditions, as well as advances in the development of low-molecular-weight molecules inhibiting c-Kit function.

Levenstein, M. E., et al. (2008). "Secreted proteoglycans directly mediate human embryonic stem cell-basic fibroblast growth factor 2 interactions critical for proliferation." Stem Cells **26**(12): 3099-3107.

Human embryonic stem (ES) cells can be maintained in an undifferentiated state if the culture medium is first conditioned on a layer of mouse embryonic fibroblast (MEF) feeder cells. Here we show that human ES cell proliferation is coordinated by MEF-secreted heparan sulfate proteoglycans (HSPG) in conditioned medium (CM). These HSPG and other heparinoids can stabilize basic fibroblast growth factor (FGF2) in unconditioned medium at levels comparable to those observed in CM. They also directly mediate binding of FGF2 to the human ES cell surface, and their removal from CM impairs proliferation. Finally, we have developed a purification scheme for MEF-secreted HSPG in CM. Using column chromatography, immunoblotting, and mass spectrometry-based proteomic analysis, we have identified multiple HSPG species in CM. The results demonstrate that HSPG are key signaling cofactors in CM-based human ES cell culture.

Levenstein, M. E., et al. (2006). "Basic fibroblast growth factor support of human embryonic stem cell self-renewal." Stem Cells **24**(3): 568-574.

Human embryonic stem (ES) cells have most commonly been cultured in the presence of basic fibroblast growth factor (FGF2) either on fibroblast feeder layers or in fibroblast-conditioned medium. It has recently been reported that elevated concentrations of FGF2 permit the culture of human ES cells in the absence of fibroblasts or fibroblast-conditioned medium. Herein we compare the ability of unconditioned medium (UM) supplemented with 4, 24, 40, 80, 100, and 250 ng/ml FGF2 to sustain low-density human ES cell cultures through multiple passages. In these stringent culture conditions, 4, 24, and 40 ng/ml FGF2 failed to sustain human ES cells through three passages, but 100 ng/ml sustained human ES cells with an effectiveness comparable to conditioned medium (CM). Two human ES cell lines (H1 and H9) were maintained for up to 164 population doublings (7 and 4 months) in UM supplemented with 100 ng/ml FGF2. After prolonged culture, the cells formed teratomas when injected into severe combined immunodeficient beige mice and expressed markers characteristic of undifferentiated human ES cells. We also demonstrate that FGF2 is degraded more rapidly in UM than in CM, partly explaining the need for higher concentrations of FGF2 in UM. These results further facilitate the large-scale, routine culture of human ES cells and suggest that fibroblasts and fibro-blast-conditioned medium sustain human ES cells in part by stabilizing FGF signaling above a critical threshold.

Li, C., et al. (2017). "Suppression of Basic Fibroblast Growth Factor Expression by Antisense Oligonucleotides Inhibits Neural Stem Cell Proliferation and Differentiation in Rat models With Focal Cerebral Infarction." J Cell Biochem **118**(11): 3875-3882.

This study is designed to investigate the role of basic fibroblast growth factor (bFGF) antisense oligonucleotide (ASODN) on the proliferation and differentiation of neural stem cells (NSCs) in rat models with focal cerebral infarction (CI). Seventy-five Sprague-Dawlay (SD) rats were randomly divided into the control, sham, middle cerebral artery occlusion (MCAO), MCAO + nonsense oligonucleotide (NODN), and MCAO + ASODN groups. Proliferation and differentiation of NSCs were detected by bromodeoxyuridine (BrdU) and immunofluorescence staining, respectively. ELISA was performed to detect the expressions of endogenous factors that include insulin-like growth factor 1 (IGF-1), glial cell line derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), transforming growth factor-alpha1 (TGF-alpha1), bFGF, and nerve growth factor (NGF). Results show significant neurological deficits and focal CI in the MCAO and MCAO + NODN groups. An obvious increase of NSC proliferation, reactive proliferation of astrocytes in CI areas, differentiation of newly proliferated NSCs into mature neuronal cells, and expressions of endogenous growth factors exhibited in the MCAO, MCAO + NODN and MCAO + ASODN groups. Compared to the MCAO and MACO + NODN groups, the MCAO + ASODN

group showed a significant decrease NSC proliferation and differentiation in CI areas as well as decrease expressions of endogenous growth factors. These findings may offer insight to help us understand more as to how bFGF ASODN can effectively suppress the proliferation and differentiation of NSCs. These findings are expected to help contribute to research for new targets in the treatment of focal CI. J. Cell. Biochem. 118: 3875-3882, 2017. (c) 2017 Wiley Periodicals, Inc.

Li, R., et al. (2018). "Stem cell therapy for treating osteonecrosis of the femoral head: From clinical applications to related basic research." Stem Cell Res Ther **9**(1): 291.

Osteonecrosis of the femoral head (ONFH) is a refractory disease that is associated with collapse of the femoral head, with a risk of hip arthroplasty in younger populations. Thus, there has been an increased focus on early interventions for ONFH that aim to preserve the native articulation. Stem cell therapy is a promising treatment, and an increasing number of recent studies have focused on this topic. Many clinical studies have reported positive outcomes of stem cell therapy for the treatment of ONFH. To improve the therapeutic effects of this approach, many related basic research studies have also been performed. However, some issues must be further explored, such as the appropriate patient selection procedure, the optimal stem cell selection protocol, the ideal injection number, and the safety of stem cell therapy. The purpose of this review is to summarize the available clinical studies and basic research related to stem cell therapy for ONFH.

Ligler, A. (2001). "Egregious error or admirable advance: the memorandum of understanding that enables federally funded basic human embryonic stem cell research." Duke Law Technol Rev: E1.

Lim, J. M., et al. (2015). "Laboratory control and basic culture protocols for stem cell self-renewal." Methods Mol Biol **1212**: 1-20.

In this report, we introduce a standard protocol for stem cell self-renewal in vitro. Both fundamental and major procedures of stem cell manipulation, which are required for somatic cell coculture and self-renewal, are briefly described since they are important for stabilization and data normalization. In this chapter, information on the basic preparation of stem cell culture such as labware washing, equipment sanitization, microbe control, and mycoplasmosis prevention is provided. In addition, protocols for cell retrieval and preservation, proliferation assays, and basic manipulation techniques for the coculture of stem cells with somatic cells are described.

Liu, D. D., et al. (2006). "Stem cell therapy in stroke: strategies in basic study and clinical application." Acta Neurochir Suppl **99**: 137-139.

Stem cell therapies are an important strategy for the treatment of stroke. Bone marrow-derived stem cells (BMSCs) may promote structural and functional repair in several organs via stem cell plasticity. The tissue damage could stimulate the stem cells migration, and they track into the site of damage and then undergo differentiation. The plasticity functions of BMSCs in an injuries tissue are dependent on the specific signals present in the local environment of the damaged tissue. Recent studies have also identified the specific molecular signals, such as SDF-1/CXCR4, required for the interaction of BMSCs and damaged host tissues. This review summarizes the current understanding of how BMSCs reach and function in cerebral ischemic tissues.

Liu, H., et al. (2014). "Basic fibroblast growth factor promotes stem Leydig cell development and inhibits LH-stimulated androgen production by regulating microRNA expression." J Steroid Biochem Mol Biol **144 Pt B**: 483-491.

Leydig cells are the primary source of testosterone in the testes, and their steroidogenic function is strictly controlled by the hypothalamus-pituitary-gonad axis. Emerging evidence has indicated that fibroblast growth factors play a role in regulating stem Leydig cell development and steroidogenesis, but little is known about the regulatory mechanism. Using a seminiferous tubule culture system, we demonstrated that basic fibroblast growth factor (bFGF) can promote stem Leydig cell proliferation and commitment toward differentiation in testosterone-producing Leydig cells. However, these promoting effects decreased with an increase in the bFGF dose. Previous studies have reported that bFGF inhibits luteinizing hormone (LH)-stimulated androgen production by downregulating the mRNA expression of steroidogenic genes in immature Leydig cells. However, the expression levels of 677 microRNAs did not change significantly during the LH-mediated process of testosterone synthesis. Five microRNAs (miR-29a, -29c, -142-3p, -451 and -335) were identified, and their expression in immature Leydig cells was regulated simultaneously by bFGF and LH. These results suggested that the inhibition of LH-stimulated androgen production may be modulated by a change in bFGF-mediated microRNA expression, which further impacts the signaling

pathway of testosterone biosynthesis and steroidogenic gene expression.

Logue, M. and B. N. Savani (2013). "Understanding basic steps to hematopoietic stem cell transplantation evaluation." Am J Blood Res **3**(2): 102-106.

We are celebrating one millionth transplant in year 2013! With continued improvement in hematopoietic cell transplantation (HCT) outcome, the indications for HCT continue to grow. Furthermore the sources of stem cells and the number of suitable matches are expanding. At the same time, modified transplantation regimens have facilitated safer procedures despite increase in patient's age and comorbidies. In the current era, any patient indicated for HCT has a stem cell source and therefore steps to HCT and coordinated pre-transplant care is an integral part of management to improve transplant outcome. This review discusses our approach to the transplant evaluation process and this article will serve as a valuable tool for primary care physicians and referring hematologists/oncologists.

Lowenthal, J. and S. Gerecht (2016). "Stem cell-derived vasculature: A potent and multidimensional technology for basic research, disease modeling, and tissue engineering." Biochem Biophys Res Commun **473**(3): 733-742.

Proper blood vessel networks are necessary for constructing and re-constructing tissues, promoting wound healing, and delivering metabolic necessities throughout the body. Conversely, an understanding of vascular dysfunction has provided insight into the pathogenesis and progression of diseases both common and rare. Recent advances in stem cell-based regenerative medicine - including advances in stem cell technologies and related progress in bioscaffold design and complex tissue engineering - have allowed rapid advances in the field of vascular biology, leading in turn to more advanced modeling of vascular pathophysiology and improved engineering of vascularized tissue constructs. In this review we examine recent advances in the field of stem cell-derived vasculature, providing an overview of stem cell technologies as a source for vascular cell types and then focusing on their use in three primary areas: studies of vascular development and angiogenesis, improved disease modeling, and the engineering of vascularized constructs for tissue-level modeling and cell-based therapies.

Lu, J., et al. (2023). "Basic Fibroblast Growth Factor Promotes Mesenchymal Stem Cell Migration by Regulating Glycolysis-Dependent beta-Catenin Signaling." Stem Cells **41**(6): 628-642.

Migration of mesenchymal stem cells (MSCs) to the site of injury is crucial in transplantation therapy. Studies have shown that cell migration is regulated by the cellular microenvironment and accompanied by changes in cellular metabolism. However, limited information is available about the relationship between MSC migration and cellular metabolism. Here, we show that basic fibroblast growth factor (bFGF) promotes the migration of MSCs with high levels of glycolysis and high expression of hexokinase 2 (HK2), a rate-limiting enzyme in glycolysis. The enhancement of glycolysis via the activation of HK2 expression promoted the migration of MSCs, whereas the inhibition of glycolysis, but not of oxidative phosphorylation, inhibited the bFGF-induced migration of these cells. Furthermore, bFGF enhanced glycolysis by increasing HK2 expression, which consequently promoted beta-catenin accumulation, and the inhibition of glycolysis inhibited the bFGF-induced accumulation of beta-catenin. When the accumulation of glycolytic intermediates was altered, phosphoenolpyruvate was found to be directly involved in the regulation of beta-catenin expression and activation, suggesting that bFGF regulates beta-catenin signaling through glycolytic intermediates. Moreover, transplantation with HK2-overexpressing MSCs significantly improved the effect of cell therapy on skull injury in rats. In conclusion, we propose a novel glycolysis-dependent beta-catenin signaling regulatory mechanism and provide an experimental and theoretical basis for the clinical application of MSCs.

Lubowitz, J. H. (2015). "Editorial Commentary: Stem Cell Research in Arthroscopy Is Scant and Requires Basic Science Review." Arthroscopy **31**(9): 1844-1845.

Stem cell research in Arthroscopy is rare, but review of journals beyond orthopaedics yields many interesting highlights. The key points are that sources of stem cells vary with regard to cellular yield, but manipulation to improve the yield is severely limited by the United States Food and Drug Administration.

Lukaszewicz, A., et al. (2002). "Contrasting effects of basic fibroblast growth factor and neurotrophin 3 on cell cycle kinetics of mouse cortical stem cells." J Neurosci **22**(15): 6610-6622.

Basic fibroblast growth factor (bFGF) exerts a mitogenic effect on cortical neuroblasts, whereas neurotrophin 3 (NT3) promotes differentiation in

these cells. Here we provide evidence that both the mitogenic effect of bFGF and the differentiation-promoting effect of NT3 are linked with modifications of cell cycle kinetics in mouse cortical precursor cells. We adapted an in vitro assay, which makes it possible to evaluate (1) the speed of progression of the cortical precursors through the cell cycle, (2) the duration of individual phases of the cell cycle, (3) the proportion of proliferative versus differentiative divisions, and (4) the influence on neuroglial differentiation. Contrary to what has been claimed previously, bFGF promotes proliferation via a change in cell cycle kinetics by simultaneously decreasing G1 duration and increasing the proportion of proliferative divisions. In contrast, NT3 lengthens G1 and promotes differentiative divisions. We investigated the molecular foundations of these effects and show that bFGF downregulates p27(kip1) and upregulates cyclin D2 expression. This contrasts with NT3, which upregulates p27(kip1) and downregulates cyclin D2 expression. Neither bFGF nor NT3 influences the proportion of glia or neurons in short to medium term cultures. The data point to links between the length of the G1 phase and the type of division of cortical precursors: differentiative divisions are correlated with long G1 durations, whereas proliferative divisions correlate with short G1 durations. The present results suggest that concerted mechanisms control the progressive increase in the cell cycle duration and proportion of differentiative divisions that is observed as corticogenesis proceeds.

Maric, D., et al. (2003). "Prospective cell sorting of embryonic rat neural stem cells and neuronal and glial progenitors reveals selective effects of basic fibroblast growth factor and epidermal growth factor on self-renewal and differentiation." J Neurosci **23**(1): 240-251.

We directly isolated neural stem cells and lineage-restricted neuronal and glial progenitors from the embryonic rat telencephalon using a novel strategy of surface labeling and fluorescence-activated cell sorting. Neural stem cells, which did not express surface epitopes characteristic of differentiation or apoptosis, were sorted by negative selection. These cells predominantly expressed fibroblast growth factor receptor type 1 (FGFR-1), and a minority exhibited basic fibroblast growth factor (bFGF), whereas few expressed epidermal growth factor receptor (EGFR) or EGF. Clonal analyses revealed that these cells primarily self-renewed without differentiating in bFGF-containing medium, whereas few survived or expanded in EGF-containing medium. Culturing of neural stem cells in bFGF- and EGF-containing medium permitted both self-renewal and differentiation into neuronal, astroglial, and oligodendroglial phenotypes. In contrast, lineage-restricted progenitors were directly sorted by positive selection using a combination of surface epitopes identifying neuronal or glial phenotypes or both. These cells were also primarily FGFR-1(+), with few EGFR(+), and most expanded and progressed along their expected lineages in bFGF-containing medium but not in EGF-containing medium. Ca(2+) imaging of self-renewing neural stem cells cultured in bFGF-containing medium revealed that bFGF, but not EGF, induced cytosolic Ca(2+) (Ca(2+)c) responses in these cells, whereas in bFGF- and EGF-containing medium, both bFGF and EGF evoked Ca(2+)c signals only in differentiating progeny of these cells. The results demonstrate that bFGF, but not EGF, sustains a calcium-dependent self-renewal of neural stem cells and early expansion of lineage-restricted progenitors, whereas together the two growth factors permit the initial commitment of neural stem cells into neuronal and glial phenotypes.

Masuzawa, Y. and M. Kitazawa (2021). "Synthetic polymers as xeno-free materials for stabilizing basic fibroblast growth factor in human mesenchymal stem cell cultures." Biochem Biophys Rep **25**: 100929.

Series of sulfonated polymers were evaluated as additives in cell culture media. Some of the compounds, such as sulfated polyvinyl alcohol (PVA), prevented denaturation and loss of basic fibroblast growth factor during cell culture and enhanced human mesenchymal stem cell proliferation. These compounds are xeno-free alternatives of heparin, an animal-derived sulfated saccharide, often used as an additive. To the best our knowledge, this study is the first to show that chemically defined synthetic chemicals, such as sulfated polyvinyl alcohol, can be used for this purpose.

Masuzawa, Y. and M. Kitazawa (2022). "Xeno-Free Materials for Stabilizing Basic Fibroblast Growth Factor and Enhancing Cell Proliferation in Human Pluripotent Stem Cell Cultures." Materials (Basel) **15**(10).

Induced pluripotent stem cells (iPSCs) are widely considered important for developing novel regenerative therapies. A major challenge to the growth and proliferation of iPSCs is the maintenance of their undifferentiated status in xeno- and feeder-free conditions. Basic fibroblast growth factor (bFGF) is known to contribute to the expansion of stem cells; however, bFGF is notoriously heat-labile and easily denatured. Here, we investigate the effects of a series

of synthetic sulfated/sulfonated polymers and saccharides on the growth of iPSCs. We observed that these materials effectively prevented the reduction of bFGF levels in iPSC culture media during storage at 37 degrees C. Some of the tested materials also suppressed heat-induced decline in medium performance and maintained cell proliferation. Our results suggest that these sulfated materials can be used to improve the expansion culture of undifferentiated iPSCs and show the potential of cost effective, chemically defined materials for improvement of medium performance while culturing iPSCs.

Mayani, H. (2003). "A glance into somatic stem cell biology: basic principles, new concepts, and clinical relevance." Arch Med Res **34**(1): 3-15.

Somatic stem cells are undifferentiated cells with a high capacity for self-renewal that can give rise to one or more specialized cell types with specific functions in the body. Profound characterization of these cells has been difficult due to the fact that their frequency in different tissues of the body is extremely low; furthermore, their identification is not based on their morphology but on immunophenotypic and functional assays. Nevertheless, significant advances in the study of these cells at both cellular and molecular levels have been achieved during the last decade. The majority of what we know concerning somatic stem cell biology has come from work on hematopoietic stem cells. More recently, however, there has been a great amount of information on neural and epithelial stem cells. The importance of stem cell research has gone beyond basic biology and is currently contributing to the development of new medical approaches for treatment of hematologic, neurologic, autoimmune, and metabolic disorders (cellular therapy).

Mercier, F. and G. I. Hatton (2001). "Connexin 26 and basic fibroblast growth factor are expressed primarily in the subpial and subependymal layers in adult brain parenchyma: roles in stem cell proliferation and morphological plasticity?" J Comp Neurol **431**(1): 88-104.

The gap junction protein connexin 26 (Cx26) has been detected previously in the parenchyma of the developing brain and in the developing and adult meninges, but there is no clear evidence for the presence of this connexin in adult brain parenchyma. Confocal mapping of Cx26 through serial sections of the meningeal-intact rat brain with four antibodies revealed an intense Cx26 immunoreactivity in both parenchyma and extraparenchyma. In the extraparenchyma, a continuum of Cx26-immunoreactive puncta was observed throughout the three meningeal layers, the perineurium of cranial nerves, and meningeal projections into the brain, including sheaths of blood vessels and stroma of the choroid plexus. In the parenchyma, Cx26-immunoreactive puncta were located primarily in subependymal, subpial, and perivascular zones and were associated primarily with glial fibrillary acidic protein-positive (GFAP+) astrocytes, the nuclei of which are strongly immunoreactive for basic fibroblast growth factor (bFGF). Although it was found to a lesser extent than in astrocytes, bFGF immunoreactivity also was intense in the nuclei of meningeal fibroblasts. In addition, we have found a close correlation between the distribution of Cx26 and vimentin immunoreactivities in the meninges and their projections into the brain. We previously showed vimentin and S100beta immunoreactivities through a network of meningeal fibroblasts in the three layers of meninges, perivascular cells, and ependymocytes and in a population of astrocytes. The related topography of this network with GFAP+ astrocytes has also been demonstrated. Considering that connexin immunoreactivity may reflect the presence of functional gap junctions, the present results are consistent with our hypothesis that all of these various cell types may communicate in a cooperative network.

Minguell, J. J., et al. (2013). "Mesenchymal stem cells and the treatment of conditions and diseases: the less glittering side of a conspicuous stem cell for basic research." Stem Cells Dev **22**(2): 193-203.

Not too long ago, several motivated and forward-looking articles were published describing the cellular and molecular properties of mesenchymal stem cells (MSCs), specially highlighting their potential for self-renewal, commitment, differentiation, and maturation into specific mesoderm-derived lineages. A very influential publication of that period entitled "Mesenchymal stem cells: No longer second class marrow citizens" [1] raised the point of view that "...challenges to harness MSC cell therapy to treat diseases ... need to wait for the full comprehension that marrow is a rich source of mesenchyme-derived cells whose potential is still far from fully appreciated." Whether or not the prophecy of Gerson was fulfilled, in the last 8 years it has become evident that infusing MSCs into patients suffering a variety of disorders represents a viable option for medical treatment. Accordingly, a vast number of articles have explored the privileged cellular and molecular features of MSCs prepared from sources other than the canonical, represented by the bone marrow. This review will provide more

information neither related to the biological attractiveness of MSCs nor to the success after their clinical use. Rather, we would like to underscore several "critical and tangential" issues, not always discussed in biomedical publications, but relevant to the clinical utilization of bone-marrow-derived MSCs.

Miyasaka, N. and I. Matsuoka (2000). "Identification of basic fibroblast growth factor-responsive genes by mRNA-differential display in an immortalized neural stem cell line." Biol Pharm Bull **23**(3): 349-351.

Basic fibroblast growth factor (bFGF) has been shown to stimulate proliferation and differentiation of neural stem cells through regulation of gene expressions. To clarify the roles of bFGF during early neurogenesis, we performed a series of differential display with mRNAs from an immortalized neural stem cell line treated with bFGF for different periods. We isolated ten independent cDNAs whose mRNA levels were regulated by bFGF. Some of these cDNA were identical to known genes, including calmodulin and thrombospondin 1, while others were unknown genes. One of these unknown genes up-regulated by bFGF (clone 2C) was specifically expressed in the brain among various rat tissues. It is expected that further analysis of clone 2C will reveal important roles of bFGF in the regulation of brain development.

Morito, A., et al. (2009). "Effects of basic fibroblast growth factor on the development of the stem cell properties of human dental pulp cells." Arch Histol Cytol **72**(1): 51-64.

We isolated adherent fibroblastic cells after collagenase and dispase treatment of human dental pulp. When human dental pulp cells (hDPCs) were cultured in the presence of basic fibroblast growth factor (bFGF), the ratio of hDPCs in the S-phase was significantly higher in comparison with incubation without bFGF. The ratio of hDPCs expressing STRO-1 as a marker of stem cell populations increased approximately eightfold in the presence of bFGF as opposed to that in the absence of bFGF. We demonstrated the characterization and distinctiveness of the hDPCs and showed that, when cultured with the medium containing serum and bFGF, they were highly proliferative and capable of differentiating in vitro into osteoblasts, chondrocytes, and adipocytes. Furthermore, the in vitro differentiation was confirmed at both the protein and gene expression levels. Transplantation of hDPCs -- expanded ex vivo in the presence of bFGF into immunocompromised mice -- revealed the formation of bone, cartilage, and adipose tissue. The donor hDPC-derived cells were labeled in the bone tissues located near the PLGA in the subcutaneous tissues of recipient mice using a human-specific Alu probe. When cultured with a serum-free medium containing bFGF, the hDPCs strongly expressed STRO-1 immunoreactive products and sustained self-renewal, and thus were almost identical in differentiation potential and proliferation activity to hDPCs cultured with the medium containing serum and bFGF. The present results suggest that the hDPCs cultured in the presence of bFGF irrespective of the presence or absence of the bovine serum are rich in mesenchymal stem cells or progenitor cells and useful for cell-based therapies to treat dental diseases.

Nagasu, M., et al. (1990). "[The basic study of autologous peripheral stem cell transplantation--useful application of KLI and G-CSF]." Rinsho Ketsueki **31**(6): 837-841.

There has been increasing interest in autologous peripheral stem cell transplantation (APSCT) in the treatment of malignant disease because it is a convenient method and may have a lower risk of tumor cell contamination than autologous bone marrow transplantation (ABMT). Recently, it is reported that the number of peripheral blood stem cells increase during recovery phase of hemopoiesis after chemotherapy, and further increase is reported on the case of treatment with G-CSF. But influences of G-CSF to the residual malignant cells is still unknown. In this report, we have used clonal cell culture and kappa-lambda imaging (KLI) analysis to trace the level of CFU-GM, BFU-E, and malignant B-cell population (mBp) in peripheral blood before and after treatment with rhG-CSF. The peak level of CFU-GM in peripheral blood was a 2-fold increased when rhG-CSF was administered, and this peak appeared 5-7 days earlier than that in the case without rhG-CSF. MBp was detected in bone marrow, however, no mBp was detected before and after treatment with rhG-CSF in peripheral blood. These findings suggest that APSCT is acceptable for this patient in case of minimal bone marrow involvement. And KLI analysis might be an effective method for detecting residual malignant cells in bone marrow and peripheral blood.

Novitzky, N., et al. (2001). "Basic fibroblast growth factor corrects proliferative derangement of bone marrow stroma and CD34(+) population following allogeneic stem cell transplantation." Exp Hematol **29**(12): 1432-1438.

OBJECTIVE: Following stem cell transplantation (SCT), the integrity of the hematopoietic microenvironment is important for the recovery of bone marrow. We studied the effects of

basic fibroblast growth factor (bFGF) on the proliferation of clonogenic progenitors and bone marrow stroma from patients receiving cytokine-mobilized allogeneic stem cell transplants (SCT). MATERIALS AND METHODS: Patient bone marrow mononuclear cells were studied at a minimum of 6 months after transplantation. Control and patient samples were divided into two fractions, one to establish the adherent stroma layers (SL) and the other to select for the progenitor population. SL from normal subjects or from patients were supplemented with 0 (control), 2, or 20 ng/mL bFGF in combination with heparan sulfate, and the resulting area of the dish covered by stroma was quantitated in each group. At 3 weeks of culture, a monocellular suspension was prepared by exposing SL to 0.1% trypsin. Cells then were cultured in the colony-forming unit fibroblast (CFU-F) assay, which was supplemented with 0 (control), 2, or 20 ng/mL bFGF. With the second fraction, CD34(+) cells were selected with paramagnetic beads, and 1 x 10(4) cells were incubated in cross-culture studies on preformed SL from patient or control origin (with or without the addition of bFGF). SL adherent CD34(+) cells were covered with agar and cultured for 6 days. Aggregates of >20 cells were scored as blastic colonies (CFU-bl). RESULTS: At 3 weeks of culture, the median surface area of dishes covered by monoloayers from 13 patients was 40% (range 10-50% vs normal 55%, range 30-60%; p = 0.00006) and improved significantly, matching control values, in dishes supplemented with bFGF. Addition of bFGF to stroma monolayers had no effect on the number of CFU-F in both patient and control samples. Selected CD34(+) cells from patients receiving transplants and cultured on normal stroma gave significantly fewer CFU-bl than control samples (median 36, range 3-121 vs 147, range 10-184; p = 0.006), but colony numbers corrected following exposure to bFGF. Normal CD34(+) cells proliferated poorly on stroma from patients (median CFU-bl 37.5, range 6-84; p = 0.02), but also expanded significantly following bFGF supplementation (104, range 6-117; p = 0.001). CONCLUSIONS: Following SCT, poor SL and CD34(+) proliferation can be corrected by addition of bFGF.

O'Hearn, D. J., et al. (1999). "Pulmonary infiltrates after cytokine therapy for stem cell transplantation. Massive deposition of eosinophil major basic protein detected by immunohistochemistry." Am J Respir Crit Care Med **160**(4): 1361-1365.

Interleukin-2 (IL-2), a product of activated T-cells, is now being used in a number of protocols for cancer immunotherapy. In one stem cell transplantation protocol for breast cancer, IL-2 is used together with interferon-gamma (IFN-gamma) and cyclosporine to stimulate a graft-versus-tumor response and improve the likelihood of a prolonged remission. We present the case of a patient who developed peripheral eosinophilia, perihilar infiltrates, and hypoxemia after autologous stem cell transplantation and the use of recombinant IL-2 and IFN-gamma. Histologic analysis of transbronchial lung biopsies demonstrated a few eosinophils within the bronchial submucosa. Immunostaining using antibodies directed against eosinophil major basic protein (MBP), however, revealed massive extracellular deposition of this toxic granule protein throughout the lung parenchyma. IL-2 therapy is well known to induce a peripheral eosinophilia and to be associated with the capillary leak syndrome characterized by weight gain, edema, and oliguria. The findings noted in this case report suggest that the eosinophil activation that accompanies immunologic therapy with IL-2 can result in direct toxicity to the lung and a localized vascular leak syndrome. This syndrome should be considered in the differential diagnosis of pulmonary infiltrates that occur acutely after bone marrow transplantation with cytokine augmentation.

Okamura, G., et al. (2020). "Promoting Effect of Basic Fibroblast Growth Factor in Synovial Mesenchymal Stem Cell-Based Cartilage Regeneration." Int J Mol Sci **22**(1).

Synovial mesenchymal stem cell (SMSC) is the promising cell source of cartilage regeneration but has several issues to overcome such as limited cell proliferation and heterogeneity of cartilage regeneration ability. Previous reports demonstrated that basic fibroblast growth factor (bFGF) can promote proliferation and cartilage differentiation potential of MSCs in vitro, although no reports show its beneficial effect in vivo. The purpose of this study is to investigate the promoting effect of bFGF on cartilage regeneration using human SMSC in vivo. SMSCs were cultured with or without bFGF in a growth medium, and 2 x 10(5) cells were aggregated to form a synovial pellet. Synovial pellets were implanted into osteochondral defects induced in the femoral trochlea of severe combined immunodeficient mice, and histological evaluation was performed after eight weeks. The presence of implanted SMSCs was confirmed by the observation of human vimentin immunostaining-positive cells. Interestingly, broad lacunae structures and cartilage substrate stained by Safranin-O were observed only in the bFGF (+) group. The bFGF (+) group had significantly higher O'Driscoll scores in the cartilage

repair than the bFGF (-) group. The addition of bFGF to SMSC growth culture may be a useful treatment option to promote cartilage regeneration in vivo.

Olive, V. and F. Cuzin (2005). "The spermatogonial stem cell: from basic knowledge to transgenic technology." Int J Biochem Cell Biol **37**(2): 246-250.

Differentiation of germ cells in the testis originates from a constantly renewed small pool of stem cells. They give rise to the first differentiated spermatogenic cells (spermatogonia). These committed cells will then follow a strictly defined succession of steps, starting with six synchronized mitotic cycles before reaching the first meiotic stages. Following a first identification of the spermatogonial stem cells on morphological and cytological criteria, a functional assay was devised, based on their ability to repopulate the testis of a sterile recipient. Purification and characterization of the stem fraction is in progress. Fundamental knowledge of the biology of the germ line and preclinical studies in several important fields will benefit of these advances, while gene transfer prior to reimplantation opens a new approach in transgenic technology.

Onuma, Y., et al. (2015). "A stable chimeric fibroblast growth factor (FGF) can successfully replace basic FGF in human pluripotent stem cell culture." PLoS One **10**(4): e0118931.

Fibroblast growth factors (FGFs) are essential for maintaining self-renewal in human embryonic stem cells and induced pluripotent stem cells. Recombinant basic FGF (bFGF or FGF2) is conventionally used to culture pluripotent stem cells; however, because of the instability of bFGF, repeated addition of fresh bFGF into the culture medium is required in order to maintain its concentration. In this study, we demonstrate that a heat-stable chimeric variant of FGF, termed FGFC, can be successfully used for maintaining human pluripotent stem cells. FGFC is a chimeric protein composed of human FGF1 and FGF2 domains that exhibits higher thermal stability and protease resistance than do both FGF1 and FGF2. Both human embryonic stem cells and induced pluripotent stem cells were maintained in ordinary culture medium containing FGFC instead of FGF2. Comparison of cells grown in FGFC with those grown in conventional FGF2 media showed no significant differences in terms of the expression of pluripotency markers, global gene expression, karyotype, or differentiation potential in the three germ lineages. We therefore propose that FGFC may be an effective alternative to FGF2, for maintenance of human pluripotent stem cells.

Otsu, M., et al. (2014). "Pluripotent stem cell-derived neural stem cells: From basic research to applications." World J Stem Cells **6**(5): 651-657.

Basic research on pluripotent stem cells is designed to enhance understanding of embryogenesis, whereas applied research is designed to develop novel therapies and prevent diseases. Attainment of these goals has been enhanced by the establishment of embryonic stem cell lines, the technological development of genomic reprogramming to generate induced-pluripotent stem cells, and improvements in vitro techniques to manipulate stem cells. This review summarizes the techniques required to generate neural cells from pluripotent stem cells. In particular, this review describes current research applications of a simple neural differentiation method, the neural stem sphere method, which we developed.

Ouyang, H., et al. (2016). "Ocular Stem Cell Research from Basic Science to Clinical Application: A Report from Zhongshan Ophthalmic Center Ocular Stem Cell Symposium." Int J Mol Sci **17**(3): 415.

Stem cells hold promise for treating a wide variety of diseases, including degenerative disorders of the eye. The eye is an ideal organ for stem cell therapy because of its relative immunological privilege, surgical accessibility, and its being a self-contained system. The eye also has many potential target diseases amenable to stem cell-based treatment, such as corneal limbal stem cell deficiency, glaucoma, age-related macular degeneration (AMD), and retinitis pigmentosa (RP). Among them, AMD and glaucoma are the two most common diseases, affecting over 200 million people worldwide. Recent results on the clinical trial of retinal pigment epithelial (RPE) cells from human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) in treating dry AMD and Stargardt's disease in the US, Japan, England, and China have generated great excitement and hope. This marks the beginning of the ocular stem cell therapy era. The recent Zhongshan Ophthalmic Center Ocular Stem Cell Symposium discussed the potential applications of various stem cell types in stem cell-based therapies, drug discoveries and tissue engineering for treating ocular diseases.

Park, Y., et al. (2010). "Undifferentiated propagation of the human embryonic stem cell lines, H1 and HSF6, on human placenta-derived feeder cells without basic fibroblast growth factor supplementation." Stem Cells Dev **19**(11): 1713-1722.

In order for human embryonic stem cells (hESCs) to be cultured on mouse embryonic fibroblast (MEFs) feeder cells, continuous basic

fibroblast growth factor (bFGF) supplementation is required. However, the role of bFGF in a culture system using human-derived feeder cells has not been evaluated until now. In this study, we propagated the widely used hESC lines, H1 and HSF6, on human placenta-derived feeder cells (HPCs) without exogenous bFGF supplementation, and were able to propagate hESCs on HPC feeders up to 50 passages. The absence of bFGF in culture media did not interrupt the undifferentiated propagation and the expression of pluripotent stem cell markers ALP, SSEA-4, TRA-60, Oct-4, Nanog, and Rex-1, as well as the formation of embryoid bodies (EBs) and their differentiation potential. In contrast, hESCs cocultured with MEF feeders could not propagate and form EBs without exogenous bFGF supplementation. Expression of bFGF and the activation of the ERK1/2-c-Fos/c-Jun pathway, which is known as the signaling pathway of bFGF, were identifiable not only in hESCs cultured in bFGF-containing media regardless of feeder cell type, but also in hESCs cocultured with HPC feeder cells in media without bFGF. These findings may support the hypothesis that HPC feeder cells enhance endogenous bFGF production and activation of the ERK1/2-c-Fos/c-Jun pathway, which suggests that HPCs have an additional advantage in their hESC propagation compared with MEF.

Patil, S. and T. Schwarer (2009). "Natural killer cells--new understanding of basic biology may lead to more effective allogeneic haematopoietic stem cell transplantation." Intern Med J **39**(10): 639-647.

The natural killer (NK) cells are part of the innate immune system and are responsible for initial defences in the surveillance against malignant cells and virally infected cells. In addition to direct cytotoxicity, cytokines produced by NK cells amplify the immune response and help control the neoplasm/pathogen. Several activating and inhibitory receptors responsible for NK cell activation are recently characterized and play a crucial role in tumour eradication. These include, but are not limited to, the killer immunoglobulin-like receptors, C-type lectin receptors and natural cytotoxicity receptors. The downstream signalling of some of these receptors is also characterized. The net balance in the sum of the signals generated by ligation of activating and inhibitory receptors determines the final outcome, cytotoxicity versus tolerance. NK cell-based immunotherapy can be successfully exploited in the haematopoietic stem cell transplantation for the treatment of haematological malignancies and has a potential to separate the beneficial graft versus leukaemia effect from, often dangerous, graft versus host disease. This article reviews the NK receptors important in NK-mediated cytotoxicity in allogeneic haematopoietic stem cell transplantation.

Pavarajarn, W., et al. (2020). "Human Caesarean scar-derived feeder cells: a novel feeder cell type for culturing human pluripotent stem cells without exogenous basic fibroblast growth factor supplementation." Reprod Fertil Dev **32**(9): 822-834.

In a feeder-dependent culture system of human pluripotent stem cells (hPSCs), coculture with mouse embryonic fibroblasts may limit the clinical use of hPSCs. The aim of this study was to determine the feasibility of using human Caesarean scar fibroblasts (HSFs) as feeder cells for the culture of hPSCs. HSFs were isolated and characterised and cocultured with hPSCs, and the pluripotency, differentiation ability and karyotypic stability of hPSCs were determined. Inactivated HSFs expressed genes (including inhibin subunit beta A (INHBA), bone morphogenetic protein 4 (BMP4), fibroblast growth factor 2 (FGF2), transforming growth factor-beta1 (TGFB1), collagen alpha-1(I) (COL1A1) and fibronectin-1 (FN1) that have been implicated in the maintenance of hPSC pluripotency. When HSFs were used as feeder cells, the pluripotency and karyotypic stability of hPSC lines did not change after prolonged coculture. Interestingly, exogenous FGF2 could be omitted from the culture medium when HSFs were used as feeder cells for hESCs but not hiPSCs. hESCs cocultured with HSF feeder cells in medium without FGF2 supplementation maintained their pluripotency (as confirmed by the expression of pluripotency markers and genes), differentiated invitro into embryonic germ layers and maintained their normal karyotype. The present study demonstrates that HSFs are a novel feeder cell type for culturing hPSCs and that supplementation of exogenous FGF2 is not necessary for the Chula2.hES line.

Piliponsky, A. M., et al. (2003). "Non-IgE-dependent activation of human lung- and cord blood-derived mast cells is induced by eosinophil major basic protein and modulated by the membrane form of stem cell factor." Blood **101**(5): 1898-1904.

The allergic reaction begins with the antigen-induced aggregation of occupied high-affinity IgE receptors expressed on mast cell surface, their activation, and the release of proinflammatory mediators that cause the "early phase" of this process. In addition, mast cell activation induces the onset of a "late phase" reaction characterized by the tissue infiltration of inflammatory cells, mainly eosinophils. We have hypothesized that during the late phase mast

cells interact with and are activated by eosinophils. Here we report that highly purified human lung mast cells became responsive to eosinophil major basic protein (MBP) when in coculture with human lung fibroblasts. In addition, cord blood-derived mast cells maintained in coculture with 3T3 fibroblasts released more histamine and prostaglandin D(2) (PGD(2)) compared with cells maintained in suspension. The fibroblast-derived membrane form of stem cell factor (SCF) was found to be involved in the mast cell increased responsiveness to MBP. In fact, cord blood-derived mast cells cocultured with 3T3 in the presence of antisense for SCF or cocultured with fibroblasts that do not express the membrane form of SCF were inhibited in their histamine-releasing activity toward MBP. In addition, this form of SCF induced the expression of a pertussis toxin-sensitive G(i) protein, G(i3) that interacts with MBP to trigger mast cell non-IgE-dependent activation in a manner similar to other cationic compounds such as compound 48/80. Mast cell responsiveness to eosinophil mediators is a potentially novel evidence for an alternative pathway of allergen-independent activation able to contribute to the perpetuation of allergy.

Porse, B. T., et al. (2010). "[Basic stem cell biology and cancer]." Ugeskr Laeger **172**(38): 2600-2603.

The finding that tumours, like normal tissues, are endowed with varying degrees of cellular heterogeneity has far-reaching consequences for our understanding of cancer. The cancer stem cell and clonal evolution models have both been proposed to explain tumour-associated cellular heterogeneity. Here, we briefly review these two non-exclusive models with special emphasis on how they aid our understanding of cancer and their implications for therapeutic strategies. Finally, we discuss the close association between basic stem cell biology and cancer, focusing on the role of self-renewal.

Qin, H. and A. Zhao (2020). "Mesenchymal stem cell therapy for acute respiratory distress syndrome: from basic to clinics." Protein Cell **11**(10): 707-722.

The 2019 novel coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has occurred in China and around the world. SARS-CoV-2-infected patients with severe pneumonia rapidly develop acute respiratory distress syndrome (ARDS) and die of multiple organ failure. Despite advances in supportive care approaches, ARDS is still associated with high mortality and morbidity. Mesenchymal stem cell (MSC)-based therapy may be an potential alternative strategy for treating ARDS by targeting the various pathophysiological events of ARDS. By releasing a variety of paracrine factors and extracellular vesicles, MSC can exert anti-inflammatory, anti-apoptotic, anti-microbial, and pro-angiogenic effects, promote bacterial and alveolar fluid clearance, disrupt the pulmonary endothelial and epithelial cell damage, eventually avoiding the lung and distal organ injuries to rescue patients with ARDS. An increasing number of experimental animal studies and early clinical studies verify the safety and efficacy of MSC therapy in ARDS. Since low cell engraftment and survival in lung limit MSC therapeutic potentials, several strategies have been developed to enhance their engraftment in the lung and their intrinsic, therapeutic properties. Here, we provide a comprehensive review of the mechanisms and optimization of MSC therapy in ARDS and highlighted the potentials and possible barriers of MSC therapy for COVID-19 patients with ARDS.

Qu, Z., et al. (1998). "Synthesis of basic fibroblast growth factor by murine mast cells. Regulation by transforming growth factor beta, tumor necrosis factor alpha, and stem cell factor." Int Arch Allergy Immunol **115**(1): 47-54.

BACKGROUND: Mast cells (MC) are involved in a wide spectrum of disorders characterized by neovascularization and fibroproliferation. We and others recently reported that human MC are a source of basic fibroblast growth factor (b FGF-2), a potent angiogenic and mitogenic polypeptide, in several disease conditions, such as chronic inflammation, hemangioma, and benign cutaneous mastocytosis. These findings suggest that FGF-2 may be an important mediator of cell proliferation and angiogenesis associated with MC. Since MC are heterogeneous across species, it is unknown whether FGF-2 expression is a feature common to all MC, or whether FGF-2 expression by MC can be regulated. We therefore examined FGF-2 expression by MC in mouse tissue and MC lines. METHODS: Immunostaining, RT-PCR, ELISA, immunoblot and Northern blot analyses were employed to study four murine MC lines for FGF-2 expression and its regulation by transforming growth factor-beta (TGF-beta), stem cell factor (SCF), and tumor necrosis factor-alpha (TNF-alpha). RESULTS: Mouse tissue MC and three of four murine MC lines (CFTL-12, CFTL-15, ABFTL-3) express FGF-2 as judged by immunostaining, ELISA, Western blot and Northern blot analyses, and reverse transcription-polymerase chain reaction. While TNF-alpha appeared to downregulate FGF-2 mRNA levels, treatment with SCF or TGF-beta resulted in an increase in the expression of FGF-2 at mRNA level

which can be attenuated by TNF-alpha. However, the concurrent increase in FGF-2 protein was negligible, possibly due to immaturity of these cell lines. CONCLUSION: Expression of FGF-2 may be a ubiquitous feature of MC in other species in addition to humans, and can be selectively regulated by SCF, TGF-beta and TNF-alpha.

Radtke, S. and P. A. Horn (2013). "Pluripotent and somatic stem cells: from basic science to utilization in disease modeling and therapeutic application. Meeting report on the 7th International Meeting of the Stem Cell Network North Rhine Westphalia." Cell Reprogram **15**(5): 394-396.

Ramasamy, R., et al. (2012). "Basic fibroblast growth factor modulates cell cycle of human umbilical cord-derived mesenchymal stem cells." Cell Prolif **45**(2): 132-139.

BACKGROUND: Mesenchymal stem cells (MSC) have great potential in regenerative medicine, immunotherapy and gene therapy due to their unique properties of self-renewal, high plasticity, immune modulation and ease for genetic modification. However, production of MSC at sufficient clinical scale remains an issue as in vitro generation of MSC inadequately fulfils the demand with respect to patients. OBJECTIVES: This study has aimed to establish optimum conditions to generate and characterize MSC from human umbilical cord (UC-MSC). MATERIALS AND METHODS: To optimize MSC population growth, basic fibroblast growth factor (bFGF) was utilized in culture media. Effects of bFGF on expansion kinetics, cell cycle, survival of UC-MSC, cytokine secretion, expression of early stem-cell markers and immunomodulation were investigated. RESULTS: bFGF supplementation profoundly enhanced UC-MSC proliferation by reducing population doubling time without altering immunophenotype and immunomodulatory function of UC-MSC. However, cell cycle studies revealed that bFGF drove the cells into the cell cycle, as a higher proportion of cells resided in S phase and progressed into M phase. Consistent with this, bFGF was shown to promote expression of cyclin D proteins and their relevant kinases to drive UC-MSC to transverse cell cycle check points, thus, committing the cells to DNA synthesis. Furthermore, supplementation with bFGF changed the cytokine profiles of the cells and reduced their apoptotic level. CONCLUSION: Our study showed that bFGF supplementation of UC-MSC culture enhanced the cells' growth kinetics without compromising their nature.

Reimers, D., et al. (2001). "Developmental expression of fibroblast growth factor (FGF) receptors in neural stem cell progeny. Modulation of neuronal and glial lineages by basic FGF treatment." Neurol Res **23**(6): 612-621.

Neural stem cells (NSCs) are self-renewable, multipotential cells capable of differentiating into the three major neural cell types, but the mechanisms which regulate their development are not fully understood. Both basic fibroblast growth factor (bFGF) and epidermal growth factor (EGF) promote the proliferation of NSCs. However, studies on the role of FGFs in the differentiation of EGF-expanded NSCs are still incomplete. We have studied the expression of distinct FGF receptors (FGFRs) in the progeny of EGF-expanded NSCs isolated from E15 rat striatum. In situ hybridization analysis and immunocytochemistry showed a developmentally related expression pattern and a cell lineage-specific distribution of these receptors. FGFR1 and FGFR2 were identified in many early precursors and in the oligodendrocyte lineage. The latter receptor was also present in a subpopulation of astrocytes. FGFR3 was detected in a restricted population of early precursors, in oligodendroglial progenitors, and in neurons and protoplasmic astrocytes of late-term cultures. Basic FGF treatment of the progeny of NSCs increased the proliferative rate of precursors and the number of oligodendrocytes generated, whereas the number of differentiating neurons was significantly reduced. Together these data provide evidence that FGFs modulate the development of EGF-expanded NSCs, and that this is at least partly determined by a cell lineage-specific expression of multiple FGFRs.

Reis-Filho, J. S. and F. C. Schmitt (2002). "Taking advantage of basic research: p63 is a reliable myoepithelial and stem cell marker." Adv Anat Pathol **9**(5): 280-289.

p63 is a recently characterized p53-homolog that is consistently expressed by basal/somatic stem cells of stratified epithelia, myoepithelial cells of the breast and salivary glands, and proliferative compartment of gastric mucosa. p63 is located on the long arm of chromosome 3 (3q27) and it encodes six isoforms, three transactivating (TA) and three DeltaN-isoforms. While the first three isoforms may act as tumor suppressor genes, the DeltaN-isoforms may inhibit the p53/TA-p63-driven cell cycle arrest and apoptosis. Recently, the putative applications of p63 in the identification of myoepithelial cells of the breast and basal cells of the prostate acini have been evaluated; however, no critical systematic analysis of its role in surgical pathology practice have hitherto been reported. We review the putative roles of p63 in

surgical pathology practice and provide guidelines for future directions on p63 translational research.

Ren, M., et al. (2014). "[Effect of basic fibroblast growth factor on endogenous neural stem cell in rat cerebral cortex with global cerebral ischemia-reperfusion]." Sheng Wu Yi Xue Gong Cheng Xue Za Zhi **31**(4): 846-849.

The present paper is aimedto investigate the effect of basic fibroblast growth factor (bFGF) on proliferation, migration and differentiation of endogenous neural stem cell in rat cerebral cortex with global brain ischemia-reperfusion. A global brain ischemia-reperfusion model was established. Immunohistochemistry was used to observe the pathological changes and the expression of BrdU and Nestin in cerebral cortex. RT-PCR was used to measure the NSE mRNA in brain tissue. The results of measurements indicated that in sham operation group, there was no positive cell in cerebral cortex, and the content of NSE mRNA did not change. In the operation group, the expression of BrdU and Nestin increased significantly at the end of the 3rd day, and peaked on the 7th day. NSE mRNA expression did not significantly increase. In bFGF group, compared with sham operation group and model group, the number of BrdU-positive and Nestin-positive cells increased significantly at each time point (P<0. 05), and peaked at the end of the 11th day, and the content of NSE mRNA increased significantly (P<0. 05). This research demonstrated that the proliferation of endogenous neural stem cells in situ could be induced by global cerebral ischemia and reperfu- sion, and could be promoted and extended by bFGF. In additiion, bFGF might promote endogenous neural stem cells differentiated into neurons.

Rolf, H. J., et al. (2012). "Intercellular transport of Oct4 in mammalian cells: a basic principle to expand a stem cell niche?" PLoS One **7**(2): e32287.

BACKGROUND: The octamer-binding transcription factor 4 (Oct4) was originally described as a marker of embryonic stem cells. Recently, the role of Oct4 as a key regulator in pluripotency was shown by its ability to reprogram somatic cells in vitro, either alone or in concert with other factors. While artificial induction of pluripotency using transcription factors is possible in mammalian cell culture, it remains unknown whether a potential natural transfer mechanism might be of functional relevance in vivo. The stem cell based regeneration of deer antlers is a unique model for rapid and complete tissue regeneration in mammals and therefore most suitable to study such mechanisms. Here, the transfer of pluripotency factors from resident stem cell niche cells to differentiated cells could recruit more stem cells and start rapid tissue regeneration. METHODOLOGY/PRINCIPAL FINDINGS: We report on the ability of STRO-1(+) deer antlerogenic mesenchymal stem cells (DaMSCs) to transport Oct4 via direct cell-to-cell connections. Upon cultivation in stem cell expansion medium, we observed nuclear Oct4 expression in nearly all cells. A number of these cells exhibit Oct4 expression not only in the nucleus, but also with perinuclear localisation and within far-ranging intercellular connections. Furthermore, many cells showed intercellular connections containing both F-actin and alpha-tubulin and through which transport could be observed. To proof that intercellular Oct4-transfer has functional consequences in recipient cells we used a co-culture approach with STRO-1(+) DaMSCs and a murine embryonic fibroblast indicator cell line (Oct4-GFP MEF). In this cell line a reporter gene (GFP) under the control of an Oct4 responsive element is only expressed in the presence of Oct4. GFP expression in Oct4-GFP cells started after 24 hours of co-culture providing evidence of Oct4 transfer from STRO-1(+) DaMSCs to Oct4-GFP MEF target cells. CONCLUSIONS: Our findings indicate a possible mechanism for the expansion of a resident stem cell niche by induction of pluripotency in surrounding non-niche cells via transfer of transcription factors through intercellular connections. This provides a new approach to explain the rapid annual antler regrowth.

Rose, L. C., et al. (2013). "Effect of basic fibroblast growth factor in mouse embryonic stem cell culture and osteogenic differentiation." J Tissue Eng Regen Med **7**(5): 371-382.

Embryonic stem cells are actively explored as a cell source in tissue engineering and regenerative medicine involving bone repair. Basic fibroblast growth factor (bFGF) has been a valuable growth factor to support the culture of human stem cells as well as their osteogenic differentiation, but the influence of bFGF on mouse embryonic stem (mES) cells is not known. Towards this goal, D3 cells were treated with bFGF during maintenance conditions and during spontaneous and osteogenic differentiation. In feeder-free monolayers, up to 40 ng/ml of exogenous bFGF did not support self-renewal of mES without LIF during cell expansion. During spontaneous differentiation in high-density cultures, bFGF stimulated cell proliferation under certain conditions but did not influence differentiation, as judged by stage-specific embryonic antigen-1 expression. The addition of bFGF reduced the alkaline phosphatase (ALP) activity associated

with osteoblast activity during differentiation induced by osteogenic supplements, although the extent of mineralization was unaffected by bFGF. The bFGF increased the mesenchymal stem cell marker Sca-1 in an mES cell population and led to an enhanced increase in osteocalcin and runx2 expression in combination with BMP-2. These results suggest that bFGF could be utilized to expand the cell population in high-density cultures in addition to enriching the BMP-2 responsiveness of mES cells.

Russell, J. P., et al. (2018). "Basic Research Advances on Pituitary Stem Cell Function and Regulation." Neuroendocrinology **107**(2): 196-203.

As a central regulator of major physiological processes, the pituitary gland is a highly dynamic organ, capable of responding to hormonal demand and hypothalamic influence, through adapting secretion as well as remodelling cell numbers among its seven populations of differentiated cells. Stem cells of the pituitary have been shown to actively generate new cells during postnatal development but remain mostly quiescent during adulthood, where they persist as a long-lived population. Despite a significant body of research characterising attributes of anterior pituitary stem cells, the regulation of this population is poorly understood. A better grasp on the signalling mechanisms influencing stem proliferation and cell fate decisions can impact on our future treatments of pituitary gland disorders such as organ failure and pituitary tumours, which can disrupt endocrine homeostasis with life-long consequences. This minireview addresses the current methodologies aiming to understand better the attributes of pituitary stem cells and the normal regulation of this population in the organ, and discusses putative future avenues to manipulate pituitary stem cells during disease states or regenerative medicine approaches.

Santamaria, X., et al. (2018). "Uterine stem cells: from basic research to advanced cell therapies." Hum Reprod Update **24**(6): 673-693.

BACKGROUND: Stem cell research in the endometrium and myometrium from animal models and humans has led to the identification of endometrial/myometrial stem cells and their niches. This basic knowledge is beginning to be translated to clinical use for incurable uterine pathologies. Additionally, the implication of bone marrow-derived stem cells (BMDSCs) in uterine physiology has opened the field for the exploration of an exogenous and autologous source of stem cells. OBJECTIVE AND RATIONALE: In this review, we outline the progress of endometrial and myometrial stem/progenitor cells in both human and mouse models from their characterization to their clinical application, indicating roles in Asherman syndrome, atrophic endometrium and tissue engineering, among others. SEARCH METHODS: A comprehensive search of PubMed and Google Scholar up to December 2017 was conducted to identify peer-reviewed literature related to the contribution of bone marrow, endometrial and myometrial stem cells to potential physiological regeneration as well as their implications in pathologies of the human uterus. OUTCOMES: The discovery and main characteristics of stem cells in the murine and human endometrium and myometrium are presented together with the relevance of their niches and cross-regulation. The current state of advanced stem cell therapy using BMDSCs in the treatment of Asherman syndrome and atrophic endometrium is analyzed. In the myometrium, the understanding of genetic and epigenetic defects that result in the development of tumor-initiating cells in the myometrial stem niche and thus contribute to the growth of uterine leiomyoma is also presented. Finally, recent advances in tissue engineering based on the creation of novel three-dimensional scaffolds or decellularisation open up new perspectives for the field of uterine transplantation. WIDER IMPLICATIONS: More than a decade after their discovery, the knowledge of uterine stem cells and their niches is crystalising into novel therapeutic approaches aiming to treat with cells those conditions that cannot be cured with drugs, particularly the currently incurable uterine pathologies. Additional work and improvements are needed, but the basis has been formed for this therapeutic application of uterine cells.

Sayadi, L., et al. (2013). "Views of patients undergo hematopoietic stem cell transplantation on their basic needs." Int J Hematol Oncol Stem Cell Res **7**(2): 23-29.

BACKGROUND: Today, hematopoietic stem cells transplantation (HSCT) has been accepted as a therapeutic approach and is widely applied in many patients with disorders of hematopoietic systems or patients with malignancies. Concomitant use of this therapeutic approach with long term chemotherapeutic procedures and hospitalization requires special care. This study was conducted to examine basic needs of patients after HSCT. METHODS: In this study, 171 hospitalized patients were selected after transplantation, using convenience sampling method. They completed a questionnaire formulated on the basis of Yura and Walsh Theory of Basic Needs. RESULTS: Most of the needs reported in the areas of vital functions,

functional health status, and reaction to functional health status were chills (76.8%), insomnia (68.5%), and dissatisfaction with changes of lifestyle/habits (53.6%), respectively. Furthermore, 94.1% of the patients were aware of their disease. CONCLUSION: This study identified a broad spectrum of the needs in HSCT patients. Given the importance of determining needs to reach thorough nursing care, paying attention to the provided list can facilitate the achievement of the goals of the care program for these patients.

Shi, C. M. (2022). "[To strengthen the basic and translational research of mesenchymal stem cell-based therapy for refractory wounds]." Zhonghua Shao Shang Za Zhi **38**(11): 999-1003.

In recent years, the application of cell-based therapy in the field of refractory wound repair has shown broad prospects, among which the mesenchymal stem cell is the most concerned and widely studied cell type. Despite the rapid development of clinical translational research, the therapeutic effect of cell-based therapy is not consistent, and most clinical trials have not achieved the desired results. Further studies have found that heterogeneity is an important issue that restricts the further development of cell-based therapy and urgently needs to be studied. Based on the research progress of mesenchymal stem cells, in the review, we discuss the current status and challenges of cell-based therapy strategies for refractory wounds.

Shihabuddin, L. S., et al. (1999). "Stem cell technology for basic science and clinical applications." Arch Neurol **56**(1): 29-32.

Simeonova, K. and G. Milanova (2011). "Stem cell: from basic theoretical assumptions and mathematical concepts to the computational models." BMC Proc **5 Suppl 8**(Suppl 8): P108.

Siniscalco, D., et al. (2012). "Novel insights in basic and applied stem cell therapy." J Cell Physiol **227**(5): 2283-2286.

The achievement of novel findings in stem cell research were the subject of the meeting organized by Stem Cell Research Italy (SCR Italy) and by the International Society for Cellular Therapy-Europe (ISCT). Stem cell therapy represents great promise for the future of molecular and regenerative medicine. The use of several types of stem cells is a real opportunity to provide a valid approach to curing several untreatable human diseases. Before it is suitable for clinical applications, stem cell biology needs to be investigated further and in greater detail. Basic stem cell research could provide exact knowledge regarding stem cell action mechanisms, and pre-clinical research on stem cells on an in vivo model of disease provides scientific evidence for future human applications. Applied stem cell research is a promising new approach to handling several diseases. Along with tissue engineering, it offers a new and promising discipline that can help to manage human pathologies through stem cell therapy. All of these themes were discussed in this meeting, covering stem cell subtypes with their newest basic and applied research.

Siniscalco, D., et al. (2012). "State-of-the-art on basic and applied stem cell therapy; Stem Cell Research Italy-International Society for Cellular Therapy Europe, Joint Meeting, Montesilvano (PE)-Italy, June 10-12, 2011." Stem Cells Dev **21**(5): 668-669.

Over 160 stem cell-based therapeutic products are undergoing development for the treatment of several diseases, ranging from cardiac and artery diseases to immune and neurodegenerative pathologies, including diabetes, spinal cord injury. Therefore, stem cell therapy plays a key role for developing new cell-based drugs for the future molecular and regenerative medicine. The second meeting organized by Stem Cell Research Italy (SCR Italy) and by the International Society for Cellular Therapy-Europe (ISCT) in Montesilvano/Citta S. Angelo (Pescara)-Italy, on June 10th-12th, 2011, focused on the state-of-the-art of stem cell therapy and associated novel findings on stem cell research (www.stemcellitaly.org).

Spencer, H. L., et al. (2015). "A journey from basic stem cell discovery to clinical application: the case of adventitial progenitor cells." Regen Med **10**(1): 39-47.

Ischemia is a leading cause of death in the western world. Regenerative medicine aims to improve healing of ischemic injury by complementing pharmacologic/interventional treatments. Navigating regenerative therapies from 'bench-to-bedside' is a multistep time-consuming process, balancing cell expansion, purity, safety and efficacy while complying with regulatory guidelines. Studies started in academic laboratories unused to long-term planning often fail because of poor strategy design, lack of contingency plans or funding. We provide a strategic insight into our translation of saphenous vein-derived adventitial progenitor cells into a clinical grade product to treat angina. We discuss discovery phases, introduction of standard operating procedures and upgrade to clinical standards. We also examine contractual aspects of

transferring to GMP-accredited facilities for clinical production and unexpected hurdles.

Stem Cell Therapies as an Emerging Paradigm in Stroke, P. (2009). "Stem Cell Therapies as an Emerging Paradigm in Stroke (STEPS): bridging basic and clinical science for cellular and neurogenic factor therapy in treating stroke." Stroke **40**(2): 510-515.

Investigators developing cellular therapy for stroke face many challenges. Preclinical models used for cellular therapy studies should be relevant to human stroke and predictive of benefit despite differences in stroke size, cerebrovascular anatomy, immune status, and neurological responses. Translating preclinical testing to human trials is compounded by consideration of delivery method and translation of dosing with cell survival. Many issues must be approached in designing clinical trials of cellular therapy for stroke, including appropriate outcome measures, controlling for confounding factors such as rehabilitation therapy, and possible surrogate outcomes using imaging such as MRI and newer imaging techniques. It is also important to establish standardized clinical protocols and clinical database registries in advance of early proof-of-concept studies. Investigators must adopt a standardized nomenclature and characterization schema for cell products to accurately define potency and determine clinical outcome from early proof-of-concept studies. The Stem Cell Therapies as an Emerging Paradigm in Stroke (STEPS) meeting was organized to bring together clinical and basic researchers with industry and regulatory representatives to assess the critical issues in the field and to create a framework to guide future investigations.

Stover, A. E., et al. (2016). "Culturing Human Pluripotent and Neural Stem Cells in an Enclosed Cell Culture System for Basic and Preclinical Research." J Vis Exp(112).

This paper describes how to use a custom manufactured, commercially available enclosed cell culture system for basic and preclinical research. Biosafety cabinets (BSCs) and incubators have long been the standard for culturing and expanding cell lines for basic and preclinical research. However, as the focus of many stem cell laboratories shifts from basic research to clinical translation, additional requirements are needed of the cell culturing system. All processes must be well documented and have exceptional requirements for sterility and reproducibility. In traditional incubators, gas concentrations and temperatures widely fluctuate anytime the cells are removed for feeding, passaging, or other manipulations. Such interruptions contribute to an environment that is not the standard for cGMP and GLP guidelines. These interruptions must be minimized especially when cells are utilized for therapeutic purposes. The motivation to move from the standard BSC and incubator system to a closed system is that such interruptions can be made negligible. Closed systems provide a work space to feed and manipulate cell cultures and maintain them in a controlled environment where temperature and gas concentrations are consistent. This way, pluripotent and multipotent stem cells can be maintained at optimum health from the moment of their derivation all the way to their eventual use in therapy.

Stramandinoli-Zanicotti, R. T., et al. (2014). "Brazilian minipig as a large-animal model for basic research and stem cell-based tissue engineering. Characterization and in vitro differentiation of bone marrow-derived mesenchymal stem cells." J Appl Oral Sci **22**(3): 218-227.

Stem cell-based regenerative medicine is one of the most intensively researched medical issues. Pre-clinical studies in a large-animal model, especially in swine or miniature pigs, are highly relevant to human applications. Mesenchymal stem cells (MSCs) have been isolated and expanded from different sources. OBJECTIVE: This study aimed at isolating and characterizing, for the first time, bone marrow-derived MSCs (BM-MSCs) from a Brazilian minipig (BR1). Also, this aimed to validate a new large-animal model for stem cell-based tissue engineering. MATERIAL AND METHODS: Bone marrow (BM) was aspirated from the posterior iliac crest of twelve adult male BR1 under general anesthesia. MSCs were selected by plastic-adherence as originally described by Friedenstein. Cell morphology, surface marker expression, and cellular differentiation were examined. The immunophenotypic profile was determined by flow cytometry. The differentiation potential was assessed by cytological staining and by RT-PCR. RESULTS: MSCs were present in all minipig BM samples. These cells showed fibroblastic morphology and were positive for the surface markers CD90 (88.6%), CD29 (89.8%), CD44 (86.9%) and negative for CD34 (1.61%), CD45 (1.83%), CD14 (1.77%) and MHC-II (2.69%). MSCs were differentiated into adipocytes, osteoblasts, and chondroblasts as demonstrated by the presence of lipidic-rich vacuoles, the mineralized extracellular matrix, and the great presence of glycosaminoglycans, respectively. The higher gene expression of adipocyte fatty-acid

binding protein (AP2), alkaline phosphatase (ALP) and collagen type 2 (COLII) also confirmed the trilineage differentiation (p<0.001, p<0.001, p=0.031; respectively). CONCLUSIONS: The isolation, cultivation, and differentiation of BM-MSCs from BR1 makes this animal eligible as a useful large-animal model for stem cell-based studies in Brazil.

Su, X., et al. (2012). "[Effects of basic fibroblast growth factor on bone marrow mesenchymal stem cell differentiation into temporomandibular joint disc cells]." Sheng Wu Yi Xue Gong Cheng Xue Za Zhi **29**(4): 732-736.

The present paper is aimed to observe the effects of basic fibroblast growth factor (bFGF) on bone marrow mesenchymal stem cell (BMSCs) differentiation. The bFGF was used to stimulate BMSCs and histology, immunohistochemistry and enzyme linked immunosorbent assay (ELISA) were used to examine the extracellular matrix produced by induced BMSCs, evaluated the feasibility of BMSCs being the seeding cells of temporomandibular joint (TMJ) disc tissue engineering. The results showed that having been induced with bFGF, the BMSCs could differentiate into fibroblast-like cells, which could synthesize GAG and collagen type I matrix. So it is feasible for BMSCs as seeding cells for engineered TMJ disc.

Takagi, G., et al. (2011). "Controlled-release basic fibroblast growth factor for peripheral artery disease: comparison with autologous bone marrow-derived stem cell transfer." Tissue Eng Part A **17**(21-22): 2787-2794.

OBJECTIVE: We examined the safety and efficacy of controlled-release basic fibroblast growth factor (b-FGF) for peripheral artery disease (PAD), compared with autologous bone marrow mononuclear cell implantation (BMCI). BACKGROUND: We recently developed a b-FGF-incorporated biodegradable hydrogel that enables slow-releasing drug delivery system. METHODS: PAD patients were divided into a b-FGF group (n=10) and BMCI group (n=15). Injection of gelatin hydrogel containing 600 mug b-FGF or BMCI (0.4-5.1x10(10) cell) was performed. Visual analog pain scale (VAS), (99m)technetium-tetrofosmin (Tc-TF) scintigraphy, transcutaneous oxygen tension (TcPO(2)), and ankle-brachial index (ABI) were evaluated before and 4 weeks after each treatment, and 2-year prognosis was determined. RESULTS: VAS (b-FGF 67+/-15 to 4+/-5, p<0.01, BMCI 67+/-42 to 5+/-9 mm, p<0.01) and TcPO(2) (b-FGF 16+/-14 to 47+/-17, p<0.01, BMCI 13+/-13 to 37+/-21 mmHg, p<0.01) were significantly improved in both groups. Tc-TF and ABI were not changed. Prognosis was similar between the groups (b-FGF 91%, BMCI 80%, NS). CONCLUSION: Controlled-release b-FGF is as safe as BMCI, and its efficacy appears to be comparable. Thus, this therapy may be an alternative to BMCI.

Tamura, Y. and K. Fukuda (2008). "[Review of basic studies about the cardiac stem cell and regenerative medicine]." Nihon Rinsho **66**(5): 908-914.

The availability of enough cardiomyocytes to transplant as a cardiac tissue is able to read the achievement of regenerative cardiac medicine. Tissue derived stem cells, embryonic stem (ES) cells and induced pluripotent stem (iPS) cells are all potential cell sources. Several types of cardiac tissue stem cells have already been reported, and we describe about the characteristics and multipotency of these tissue stem cells with an accurate comparison. ES cells and iPS cells are highly proliferative and suitable for mass production, and efficient protocols for selective cardiomyocyte induction using ES cells and iPS cells are also significant. On the other hand, these cells still have several issues about purification and safety as well as ethical problems.

Tang, P. H. (2003). "Current basic research of hematopoietic stem cells in China and comments on stem cell plasticity." Zhongguo Shi Yan Xue Ye Xue Za Zhi **11**(1): 1-6.

The basic studies selected were mainly published since 1998 and related to stem cell biology and engineering and particularly the efforts for developing new sources of hematopoietic stem/progenitor cells ex vivo. Hematopoietic cells and lymphocytes can be developed by induced differentiation in a appropriate way of culture, originating in the embryo- or adult-derived stem cells or tissue-committed stem cells which still exist in the tissue of adults. The most primitive multipotential embryonic stem cell from embryo or adult tissue has the plasticity to differentiate into every kind of progenies, the committed tissue-specific stem cell, by different proper ways of induction in vitro. The committed tissue-specific stem cell, however, can only be induced to differentiate along the line of its committed origin of tissue. No studies in China strongly confirmed yet the existence of "transdifferentiation" among the tissue- or organ-specific stem cells.

Tang, W. P., et al. (2015). "Basic fibroblast growth factor-treated adipose tissue-derived mesenchymal stem cell infusion to ameliorate liver cirrhosis via

paracrine hepatocyte growth factor." J Gastroenterol Hepatol **30**(6): 1065-1074.

BACKGROUND AND AIM: Recent studies show that adipose tissue-derived mesenchymal stem cells have potential clinical applications. However, the mechanism has not been fully elucidated yet. Here, we investigated the effect of basic fibroblast growth factor-treated adipose tissue-derived mesenchymal stem cells infusion on a liver fibrosis rat model and elucidated the underlying mechanism. METHODS: Adipose tissue-derived mesenchymal stem cells were infused into carbon tetrachloride-induced hepatic fibrosis rats through caudal vein. Liver functions and pathological changes were assessed. A co-culture model was used to clarify the potential mechanism. RESULTS: Basic fibroblast growth factor treatment markedly improved the proliferation, differentiation, and hepatocyte growth factor expression ability of adipose tissue-derived mesenchymal stem cells. Although adipose tissue-derived mesenchymal stem cells infusion alone slightly ameliorated liver functions and suppressed fibrosis progression, basic fibroblast growth factor-treatment significantly enhanced the therapeutic effect in association with elevated hepatocyte growth factor expression. Moreover, double immunofluorescence staining confirmed that the infused cells located in fibrosis area. Furthermore, co-culture with adipose tissue-derived mesenchymal stem cell led to induction of hepatic stellate cell apoptosis and enhanced hepatocyte proliferation. However, these effects were significantly weakened by knockdown of hepatocyte growth factor. Mechanism investigation revealed that co-culture with adipose tissue-derived mesenchymal stem cells activated c-jun N-terminal kinase-p53 signaling in hepatic stellate cell and promoted apoptosis. CONCLUSIONS: Basic fibroblast growth factor treatment enhanced the therapeutic effect of adipose tissue-derived mesenchymal stem cells, and secretion of hepatocyte growth factor from adipose tissue-derived mesenchymal stem cells plays a critical role in amelioration of liver injury and regression of fibrosis.

Teshima, T. (2009). "[Basic and clinical research to improve the outcome of hematopoietic stem cell transplantation]." Rinsho Ketsueki **50**(8): 617-621.

Volz, A. C., et al. (2016). "Adipose-derived stem cell differentiation as a basic tool for vascularized adipose tissue engineering." Differentiation **92**(1-2): 52-64.

The development of in vitro adipose tissue constructs is highly desired to cope with the increased demand for substitutes to replace damaged soft tissue after high graded burns, deformities or tumor removal. To achieve clinically relevant dimensions, vascularization of soft tissue constructs becomes inevitable but still poses a challenge. Adipose-derived stem cells (ASCs) represent a promising cell source for the setup of vascularized fatty tissue constructs as they can be differentiated into adipocytes and endothelial cells in vitro and are thereby available in sufficiently high cell numbers. This review summarizes the currently known characteristics of ASCs and achievements in adipogenic and endothelial differentiation in vitro. Further, the interdependency of adipogenesis and angiogenesis based on the crosstalk of endothelial cells, stem cells and adipocytes is addressed at the molecular level. Finally, achievements and limitations of current co-culture conditions for the construction of vascularized adipose tissue are evaluated.

Wang, B., et al. (2016). "Injection of basic fibroblast growth factor together with adipose-derived stem cell transplantation: improved cardiac remodeling and function in myocardial infarction." Clin Exp Med **16**(4): 539-550.

Recent findings suggest that cell and gene transplantation in the infarcted myocardium may improve heart function. The aim of the study was to investigate the mechanism involved in improving heart function following the co-injection of adipose-derived stem cells (ADSCs) and basic fibroblast growth factor (bFGF) in a rat model of myocardial infarction. In this study, ADSCs were isolated from subcutaneous adipose tissues. The ADSCs were induced to differentiate into adipocytes, osteoblasts and cardiac myocytes in vitro. bFGF was co-injected with the ADSCs into the left ventricular wall in a rat myocardial infarction model. The structural and functional outcomes resulting from this transplantation were determined through detailed histological analysis and echocardiography. The graft size was significantly larger in the bFGF + ADSC group than in the PBS + ADSC group and PBS + bFGF group 4 weeks after injection ($p < 0.05$). The ADSCs were able to differentiate into cardiomyocytes, endothelial cells and vascular smooth muscle cells in vivo. There was a significant improvement in arteriole density within the infarcted area in the bFGF + ADSC group compared with the PBS + ADSC group and the PBS + bFGF group 4 weeks after transplantation ($p < 0.05$). The results of Western blot analysis showed that all of the treatments significantly reduced MMP2 and MMP9 protein levels compared with the PBS control group ($p < 0.05$) and that the levels of these proteins

displayed the largest decrease in the bFGF + ADSC group ($p < 0.05$). In addition, the results of a quantitative analysis revealed that the proportion of fibrotic areas was significantly lower in the PBS + ADSC and bFGF + ADSC groups compared with the PBS-only group and PBS + bFGF group ($p < 0.05$). The combined application of bFGF and ADSC transplantation may significantly increase the number of arterioles, reduce the infarcted size, attenuate ventricular remodeling and improve cardiac function. This ADSC + bFGF treatment strategy (or a variation thereof) may prove to be broadly applicable to other candidate cell preparations used in regenerative medicine.

Wang, C., et al. (2017). "Basic fibroblast growth factor is critical to reprogramming buffalo (Bubalus bubalis) primordial germ cells into embryonic germ stem cell-like cells." Theriogenology **91**: 112-120.

Primordial germ cells (PGCs) are destined to form gametes in vivo, and they can be reprogrammed into pluripotent embryonic germ (EG) cells in vitro. Buffalo PGC have been reported to be reprogrammed into EG-like cells, but the identities of the major signaling pathways and culture media involved in this derivation remain unclear. Here, the effects of basic fibroblast growth factor (bFGF) and downstream signaling pathways on the reprogramming of buffalo PGCs into EG-like cells were investigated. Results showed bFGF to be critical to buffalo PGCs to dedifferentiate into EG-like cells (20 ng/mL is optimal) with many characteristics of pluripotent stem cells, including alkaline phosphatase (AP) activity, expression of pluripotency marker genes such as OCT4, NANOG, SOX2, SSEA-1, CDH1, and TRA-1-81, and the capacity to differentiate into all three embryonic germ layers. After chemically inhibiting pathways or components downstream of bFGF, data showed that inhibition of the PI3K/AKT pathway led to significantly lower EG cell derivation, while inhibition of P53 activity resulted in an efficiency of EG cell derivation comparable to that in the presence of bFGF. These results suggest that the role of bFGF in PGC-derived EG-like cell generation is mainly due to the activation of the PI3K/AKT/P53 pathway, in particular, the inhibition of P53 function.

Wang, R., et al. (2018). "The differential effect of basic fibroblast growth factor and stromal cell-derived factor-1 pretreatment on bone morrow mesenchymal stem cells osteogenic differentiation potency." Mol Med Rep **17**(3): 3715-3721.

In situ tissue engineering has become a novel strategy to repair periodontal/bone tissue defects. The choice of cytokines that promote the recruitment and proliferation, and potentiate and maintain the osteogenic differentiation ability of mesenchymal stem cells (MSCs) is the key point in this technique. Stromal cell-derived factor-1 (SDF-1) and basic fibroblast growth factor (bFGF) have the ability to promote the recruitment, and proliferation of MSCs; however, the differential effect of SDF-1 and bFGF pretreatment on MSC osteogenic differentiation potency remains to be explored. The present study comparatively observed osteogenic differentiation of bone morrow MSCs (BMMSCs) pretreated by bFGF or SDF-1 in vitro. The gene and protein expression levels of alkaline phosphatase (ALP), runt related transcription factor 2 (Runx-2) and bone sialoprotein (BSP) were detected using reverse transcription-quantitative polymerase chain reaction and western blotting. The results showed that the expression of ALP mRNA on day 3, and BSP and Runx-2 mRNA on day 7 in the bFGF pretreatment group was significantly higher than those in SDF-1 pretreatment group. Expression levels of Runx-2 mRNA, and ALP and Runx-2 protein on day 3 in the SDF-1 pretreatment group were higher than those in the bFGF pretreatment group. However, there was no significant difference in osteogenic differentiation ability on day 14 and 28 between the bFGF- or SDF-1-pretreatment groups and the control. In conclusion, bFGF and SDF-1 pretreatment inhibits osteogenic differentiation of BMMSCs at the early stage, promotes it in the medium phase, and maintains it in the later stage during osteogenic induction, particularly at the mRNA level. Out of the two cytokines, bFGF appeared to have a greater effect on osteogenic differentiation.

Wang, S. J., et al. (2019). "The Characteristics of Human Resources and Related Research Activities among Basic Stem Cell Research Groups in China." Iran J Public Health **48**(1): 112-119.

BACKGROUND: This study aimed to evaluate the characteristics of faculty and research activities of basic stem cell research groups in China. METHODS: A questionnaire was administered to persons who knew the information among 46 basic stem cell research groups in China. Multiple linear regression models and repeated-measures analyses of variance were used. Repeated-measures analyses of variance were used. RESULTS: Of the 46 groups, 39.1% did not have any faculty recruited from abroad from 2009 to 2013, 37.0% did not have any faculty with junior-level title, 34.8% had </=25.0% faculty with either M.D. or Ph.D. degree. Papers published in SCI journals per faculty and having faculty recruited from abroad were positively associated with research funding per faculty. The groups with faculty recruited

from abroad had significantly higher research funding per faculty over time compared with the group without faculty recruited from abroad. Repeated-measures analyses of variance showed the group with faculty recruited from abroad had significantly higher research funding per faculty over time compared with the group without faculty recruited from abroad. CONCLUSION: To increase the development of basic stem cell research, some characteristics of human resources should be improved, and the groups should recruit more faculty with overseas experience.

Wang, W. F. and X. T. Pei (2004). "[Stem cell(non-embryonic)--from basic to clinic]." Zhonghua Yi Xue Za Zhi **84**(16): 1327-1328.

Wang, Y., et al. (2012). "Efficient derivation of human embryonic stem cell lines from discarded embryos through increases in the concentration of basic fibroblast growth factor." Hum Cell **25**(1): 16-23.

We describe the derivation and characterization of three novel human embryonic stem (hES) cell lines (YT1, YT2, YT3). One hES line (YT1) was obtained from six discarded blastocysts in a culture medium supplemented with 12 ng/ml basic fibroblast growth factor (bFGF), and two lines (YT2,YT3)were obtained from three discarded blastocysts in the same medium but supplemented with 16 ng/ml bFGF. These cell lines were derived by partial or whole embryo culture followed by further expansion after manual dissection of the passaged cells. These cells were passaged continuously for more than 6 or 8 months and possessed all of the typical features of pluripotent hES cell lines, such as typical morphological characteristics and the expression of hES-specific markers (TRA-1-60, TRA-1-81, SSEA-4, SSEA-3, alkaline phosphatase, Oct4, Nanog) and pluripotency-related genes (Oct4, Nanog, TDGF1, Sox2, EBAF, Thy-1, FGF4, Rex1). The lines maintained normal karyotypes after long-term cultivation. The karyotype of YT1 and YT3 was 46,XX, and that of YT2 was 46, XY. Pluripotency was confirmed by in vitro and in vivo differentiation, and genetic identity was demonstrated by DNA fingerprinting.Our results indicate that higher concentrations of bFGF at the early culture stage support efficient the hES cell derivation.

Wertheim, J. A. and J. R. Leventhal (2015). "Clinical implications of basic science discoveries: induced pluripotent stem cell therapy in transplantation--a potential role for immunologic tolerance." Am J Transplant **15**(4): 887-890.

Induced pluripotent stem cells (iPSCs) hold the potential for future development of genetically identical tissues from almost any mature cell lineage. For clinical applications in cell therapy and transplantation, it may provide a means to one-day restore dysfunctional or damaged tissue without the need for immunosuppression. A recent study by de Almeida et al published in the journal Nature Communications indicates that iPSCs may indeed elicit an immune response that evolves as cells differentiate toward maturity to induce a state of tolerance within a recipient animal. If these early findings hold true, it suggests a possible explanation for self-recognition of mature cells derived from iPSCs for use in future therapeutic interventions in transplantation such as cellular therapy or tissue engineering.

Xi, Y. and P. Tan (1999). "[Development of basic research and clinical study of umbilical blood hematopoietic stem cell transplantation]." Zhonghua Xue Ye Xue Za Zhi **20**(8): 397-398.

Xu, C., et al. (2005). "Basic fibroblast growth factor supports undifferentiated human embryonic stem cell growth without conditioned medium." Stem Cells **23**(3): 315-323.

Previous studies have shown that prolonged propagation of undifferentiated human embryonic stem cells (hESCs) requires conditioned medium from mouse embryonic feeders (MEF-CM) as well as matrix components. Because hESCs express growth factor receptors, including those for basic fibroblast growth factor (bFGF), stem cell factor (SCF), and fetal liver tyrosine kinase-3 ligand (Flt3L), we evaluated these and other growth factors for their ability to maintain undifferentiated hESCs in the absence of conditioned medium. We found cultures maintained in bFGF alone or in combination with other factors showed characteristics similar to MEF-CM control cultures, including morphology, surface marker and transcription factor expression, telomerase activity, differentiation, and karyotypic stability. In contrast, cells in media containing Flt-3L, thrombopoietin, and SCF, individually or in combination, showed almost complete differentiation after 6 weeks in culture. These data demonstrate that hESCs can be maintained in nonconditioned medium using growth factors.

Xu, W., et al. (2017). "Myelin Basic Protein Regulates Primitive and Definitive Neural Stem Cell

Proliferation from the Adult Spinal Cord." Stem Cells **35**(2): 485-496.

The adult mammalian forebrain comprises two distinct populations of neural stem cells (NSCs): rare, Oct4 positive, primitive NSCs (pNSCs) and definitive NSC (dNSC) which are more abundant and express GFAP. The pNSCs are upstream of the dNSCs in the neural stem cell lineage. Herein we show that pNSC and dNSC populations can also be isolated from the developing and adult spinal cord. Spinal cord derived pNSCs are similarly rare, Oct4 expressing cells that are responsive to leukemia inhibitory factor and dNSCs are 4-5X more abundant and express GFAP. We demonstrate that myelin basic protein (MBP) is inhibitory to both pNSC and dNSC derived colony formation. Similar to what is seen in the adult forebrain following injury, spinal cord injury results in a significant increase in the size of the dNSC and pNSC pools. Hence, both primitive and definitive neural stem cells can be isolated from along the embryonic and adult neuraxis in vivo and their behavior is regulated by MBP and injury. Stem Cells 2017;35:485-496.

Yamaguchi, S., et al. (2022). "Stem Cell Therapy for Acute/Subacute Ischemic Stroke with a Focus on Intraarterial Stem Cell Transplantation: From Basic Research to Clinical Trials." Bioengineering (Basel) **10**(1).

Stem cell therapy for ischemic stroke holds great promise for the treatment of neurological impairment and has moved from the laboratory into early clinical trials. The mechanism of action of stem cell therapy includes the bystander effect and cell replacement. The bystander effect plays an important role in the acute to subacute phase, and cell replacement plays an important role in the subacute to chronic phase. Intraarterial (IA) transplantation is less invasive than intraparenchymal transplantation and can provide more cells in the affected brain region than intravenous transplantation. However, transplanted cell migration was reported to be insufficient, and few transplanted cells were retained in the brain for an extended period. Therefore, the bystander effect was considered the main mechanism of action of IA stem cell transplantation. In most clinical trials, IA transplantation was performed during the acute and subacute phases. Although clinical trials of IA transplantation demonstrated safety, they did not demonstrate satisfactory efficacy in improving patient outcomes. To increase efficacy, increased migration of transplanted cells and production of long surviving and effective stem cells would be crucial. Given the lack of knowledge on this subject, we review and summarize the mechanisms of action of transplanted stem cells and recent advancements in preclinical and clinical studies to provide information and guidance for further advancement of acute/subacute phase IA stem cell transplantation therapy for ischemic stroke.

Yamamoto, N., et al. (2010). "Basic study of retinal stem/progenitor cell separation from mouse iris tissue." Med Mol Morphol **43**(3): 139-144.

We described the possibility of retinal regeneration using a novel and efficient technique for culturing and separating retinal stem/progenitor cells from iris tissue. Immunohistochemical staining of adult agouti mouse iris tissue revealed the presence of nestin/low-affinity neurotrophin receptor p75 (p75(NTR))-positive cells on the endothelium camerae anterioris side. Cultured mouse iris-derived cells contained little or no melanin and were found to be positive for nestin. Most nestin-positive cells were analyzed for the coexpression of p75(NTR) as a cell membrane protein. When the p75(NTR) was used as a marker to sort the cells, we obtained a dense population of nestin-positive cells. Furthermore, the nestin/p75(NTR)-positive cells were able to differentiate into neural retina cells. Thus, this culture and separation technique is useful for obtaining retinal stem/progenitor cells from adult mouse iris tissue and for the efficient production of neural retina cells.

Yi, S., et al. (2017). "Tcf12, A Member of Basic Helix-Loop-Helix Transcription Factors, Mediates Bone Marrow Mesenchymal Stem Cell Osteogenic Differentiation In Vitro and In Vivo." Stem Cells **35**(2): 386-397.

Several basic Helix-Loop-Helix transcription factors have recently been identified to regulate mesenchymal stem cell (MSC) differentiation. In the present study, Tcf12 was investigated for its involvement in the osteoblastic cell commitment of MSCs. Tcf12 was found highly expressed in undifferentiated MSCs whereas its expression decreased following osteogenic culture differentiation. Interestingly, Tcf12 endogenous silencing using shRNA lentivirus significantly promoted the differentiation ability of MSCs evaluated by alkaline phosphatase staining, alizarin red staining and expression of osteoblast-specific markers by real-time PCR. Conversely, overexpression of Tcf12 in MSCs suppressed osteoblast differentiation. It was further found that silencing of Tcf12 activated bone morphogenetic protein (BMP) signaling and extracellular signal-regulated kinase (Erk)1/2 signaling pathway activity and upregulated the expression of phospho-SMAD1

and phospho-Erk1/2. A BMP inhibitor (LDN-193189) and Erk1/2 signaling pathway inhibitor (U0126) reduced these findings in the Tcf12 silencing group. Following these in vitro results, a poly-L-lactic acid/Hydroxyappatite scaffold carrying Tcf12 silencing lentivirus was utilized to investigate the repair of bone defects in vivo. The use of Tcf12 silencing lentivirus significantly promoted new bone formation in 3-mm mouse calvarial defects as assessed by micro-CT and histological examination whereas overexpression of Tcf12 inhibited new bone formation. Collectively, these data indicate that Tcf12 is a transcription factor highly expressed in the nuclei of stem cells and its downregulation plays an essential role in osteoblast differentiation partially via BMP and Erk1/2 signaling pathways. Stem Cells 2017;35:386-397.

Zellner, J., et al. (2019). "Mesenchymal Stem Cell Based Regenerative Treatment of the Knee: From Basic Science to Clinics." Stem Cells Int **2019**: 7608718.

Zhang, X. and Y. Wu (2022). "Acupoint Massage plus Recombinant Bovine Basic Fibroblast Growth Factor Ophthalmic Gel and Limbal Stem Cell Transplantation on Visual Quality, Corneal Refraction, and Aesthetic Outcome in Patients with Pterygium." Evid Based Complement Alternat Med **2022**: 7103496.

OBJECTIVE: To investigate the clinical study of acupoint massage combined with recombinant bovine basic fibroblast growth factor (rbFGF) ophthalmic gel combined with limbal stem cell transplantation on visual quality, corneal refraction, and aesthetic outcome in patients with pterygium. METHODS: Sixty patients with pterygium treated in People's Hospital of Lujiang County from March 2018 to May 2021 were randomized into the control group and the research group by the random number table method, with 30 cases in each group. The control group received rbFGF plus limbal stem cell transplantation. The research group was treated with acupoint massage additionally. RESULTS: The total clinical effective rate in the study group was higher than that in the control group ($P < 0.05$); after treatment, the modulation transfer function (MTF) cutoff and Strehl ratio (SR) levels in the study group were significantly higher than those in the control group, and the tear film-related objective scatter index (TF-OSI) was significantly lower than that in the control group ($P < 0.05$); corneal horizontal curvature and corneal vertical curvature in the study group after treatment were significantly higher than those in the control group, and corneal astigmatism degree (CAD) levels were significantly lower than those in the control group ($P < 0.05$); the levels of the break-up time (BUT) and Schirmer test (SIT) in the study group were significantly higher after treatment, compared with the control group ($P < 0.05$); and the incidence of adverse manifestations in the study group was significantly lower than that in the control group ($P < 0.05$). CONCLUSION: Acupoint massage combined with rbFGF ophthalmic gel combined with limbal stem cell transplantation is effective in clinical treatment of pterygium.

Zhang, Y. H., et al. (2011). "Exogenous basic fibroblast growth factor promotes cardiac stem cell-mediated myocardial regeneration after miniswine acute myocardial infarction." Coron Artery Dis **22**(4): 279-285.

OBJECTIVE: To investigate the effects of exogenous basic fibroblast growth factor (bFGF) on myocardial regeneration after acute myocardial infarction (AMI). METHODS: AMI models were established by ligating the mid-third of left anterior descending artery, thereafter, miniswines were randomly divided into control (none treatment, $n = 6$) and bFGF groups ($n = 6$). For the bFGF group, bFGF (100 mug) was injected with a sterile microinjection at five sites within the ischemic region. 5-Bromo-2-deoxyuridine (250 mg) was administrated intravenously twice a week after the operation, to label cells undergoing DNA replication. The expression of stromal cell-derived factor-1alpha (SDF-1alpha) and CXC chemokine receptor 4 (CXCR4), cardiac stem cell-mediated myocardial regeneration, myocardial apoptosis, histological and immunohistochemical analyses, and cardiac function were evaluated at different time points. RESULTS: Four weeks after bFGF therapy, it showed an increased vessel density and myocardial perfusion ($P < 0.001$), upregulative expression of SDF-1alpha and CXCR4 ($P < 0.001$), increased c-kit and 5-bromo-2-deoxyuridine-positive cells ($P < 0.001$), enhanced myocardial viability ($P < 0.001$), and improved left ventricular ejection fraction ($P = 0.007$), compared with the control. CONCLUSION: Exogenous bFGF was shown to have increased angiogenesis and myocardial perfusion, promoted myocardial regeneration by activating the SDF-1alpha/CXCR4 axis, and thereby improved the cardiac function, which may provide a new therapeutic strategy for AMI.

Zhu, H., et al. (2014). "Basic fibroblast growth factor is a key factor that induces bone marrow

mesenchymal stem cells towards cells with Schwann cell phenotype." Neurosci Lett **559**: 82-87.

Bone marrow mesenchymal stem cells (MSCs) can be differentiate towards a Schwann cells (SCs) lineage when exposed to pre-inducing reagents beta-mercaptoethanol (BME) and retinoic acid (RA), followed by inducing factors: forskolin (FSK), basic fibroblast growth factor (bFGF), platelet derived growth factor (PDGF), and heregulin (HRG). However, the underlying mechanisms remain unclear. Here, we investigated the individual effects of these inducing factors on the differentiation of MSCs towards SC phenotype in rats. We show that the omission of either HRG or PDGF from the induction medium is not sufficient to change the SC-like phenotype or the expression level of the SC marker, S100beta. However, the omission of bFGF from the induction medium effectively blocked neural induction of the MSCs. Moreover, only bFGF was found to inhibit MSC proliferation during differentiation. To clarify the mechanism responsible for the effect of bFGF, we also investigated the activation of the extracellular signal-regulated kinase (ERK) pathway in the induced cells. Our results suggest that morphological changes in MSCs induced by bFGF depend on the activation of ERK, and bFGF may be an indispensable factor that induces MSCs to differentiate into cells with SCs phenotype.

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References

1. Baidu. http://www.baidu.com. 2024.
2. Google. http://www.google.com. 2024.
3. Ma H, Chen G. Stem cell. The Journal of American Science 2005;1(2):90-92.
4. Ma H, Cherng S. Eternal Life and Stem Cell. Nature and Science. 2007;5(1):81-96.
5. Ma H, Cherng S. Nature of Life. Life Science Journal 2005;2(1):7-15.
6. Ma H, Yang Y. Turritopsis nutricula. Nature and Science 2010;8(2):15-20. http://www.sciencepub.net/nature/ns0802/03_1279_hongbao_turritopsis_ns0802_15_20.pdf.
7. Ma H. The Nature of Time and Space. Nature and science 2003;1(1):1-11. Nature and science 2007;5(1):81-96.
8. National Center for Biotechnology Information, U.S. National Library of Medicine. http://www.ncbi.nlm.nih.gov/pubmed. 2024.
9. Wikipedia. The free encyclopedia. http://en.wikipedia.org. 2024.
10. Marsland Press. http://www.sciencepub.net. 2024.

7/25/2024