Stem Cell Differentiation Research Literatures

Ma Hongbao *, Margaret Young **, Zhu Yucui ***, Yang Yan *, Zhu Huaijie ****

* Brookdale University Hospital and Medical Center, Brooklyn, New York 11212, USA, ma8080@gmail.com; ** Cambridge, MA 02138, USA; *** Department of Dermatology, Columbia University Medical Center, 630 West, 168th Street, New York, New York 10032, USA; **** The 2nd Affiliated Hospital of Zhengzhou University, 2 Jingba Road, Zhengzhou, Henan, China, yz81@columbia.edu

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 stem cell differentiation related studies.

[Ma H, Young M, Zhu Y, Yang Y, Zhu H. **Stem Cell Differentiation Research Literatures.** Stem Cell. 2016;7(1):44-64] ISSN: 1945-4570 (print); ISSN: 1945-4732 (online). http://www.sciencepub.net/stem. 5. doi:10.7537/marsscj07011605.

Key words: stem cell; life; differentiation; 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.

Abboud, N., A. Fontbonne, et al. "Laminopathies disrupt epigenomic developmental programs and cell fate." J Tissue Eng Regen Med. 2016 Apr 21. doi: 10.1002/term.2163.

The generation of replacement inner ear hair cells (HCs) remains a challenge and stem cell therapy holds the potential for developing therapeutic solutions to hearing and balance disorders. Recent developments have made significant strides in producing mouse otic progenitors using cell culture techniques to initiate HC differentiation. However, no consensus has been reached as to efficiency and therefore current methods remain unsatisfactory. In order to address these issues, we compare the generation of otic and HC progenitors from embryonic stem (ES) cells in two cell culture systems: suspension vs. adherent conditions. In the present study, an ES cell line derived from an Atoh1-green fluorescent protein (GFP) transgenic mouse was used to track the generation of otic progenitors, initial HCs and to compare these two differentiation systems. We used a two-step short-term differentiation method involving an induction period of 5 days during which ES cells were cultured in the presence of Wnt/transforming growth factor TGF-beta inhibitors and insulin-like growth factor IGF-1 to suppress mesoderm and reinforce presumptive ectoderm and otic lineages. The generated embryoid bodies were then differentiated in medium containing basic fibroblast growth factor (bFGF) for an additional 5 days using either suspension or adherent culture methods. Upon completion of differentiation, quantitative polymerase chain reaction analysis and immunostaining monitored the expression of otic/HC progenitor lineage markers. The results indicate that cells differentiated in suspension cultures produced cells expressing otic progenitor/HC markers at a higher efficiency compared with the production of these cell types within adherent cultures. Furthermore, we demonstrated that a fraction of these cells can incorporate into ototoxin-injured mouse postnatal cochlea explants and express MYO7A after transplantation. Copyright (c) 2016 John Wiley & Sons, Ltd.

Abomaray, F. M., M. A. Al Jumah, et al. "Genetic Comparison of Stemness of Human Umbilical Cord and Dental Pulp." Stem Cells Int. 2016;2016:5184601. doi: 10.1155/2016/5184601. Epub 2016 Feb 10.

This study focuses on gene expression patterns and functions in human umbilical cord (UC) and dental pulp (DP) containing mesenchymal stem cells (MSCs). DP tissues were collected from 25 permanent premolars. UC tissue samples were obtained from three newborns. Comparative gene profiles were obtained using cDNA microarray analysis and the expression of tooth development-associated and MSC-related genes was assessed by the quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR). Genes related to cell proliferation, angiogenesis, and immune responses were expressed at higher levels in UC, whereas genes related to growth factor and receptor activity and signal transduction were more highly expressed in DP. Although UC and DP tissues exhibited similar expression of surface markers for MSCs, UC showed higher expression of CD29, CD34, CD44, CD73, CD105, CD146, and CD166. qRT-PCR analysis showed that CD146, CD166, and MYC were expressed 18.3, 8.24, and 1.63 times more highly in UC, whereas the expression of CD34 was 2.15 times higher in DP. Immunohistochemical staining revealed significant differences in the expression of genes (DSPP, DMP1, and CALB1) related to odontogenesis and angiogenesis in DP. DP and UC tissue showed similar gene expression, with the usual MSC markers, while they clearly diverged in their differentiation capacity.

Antonucci, I., M. Provenzano, et al. "Amniotic Fluid Stem Cells: A Novel Source for Modeling of Human Genetic Diseases." Int J Mol Sci. 2016 Apr 22;17(4). pii: E607.

In recent years, great interest has been devoted to the use of Induced Pluripotent Stem cells (iPS) for modeling of human genetic diseases, due to the possibility of reprogramming somatic cells of affected patients into pluripotent cells, enabling differentiation into several cell types, and allowing investigations into the molecular mechanisms of the disease. However, the protocol of iPS generation still suffers from technical limitations, showing low efficiency, being expensive and time consuming. Amniotic Fluid Stem cells (AFS) represent a potential alternative novel source of stem cells for modeling of human genetic diseases. In fact, by means of prenatal diagnosis, a number of fetuses affected by chromosomal or Mendelian diseases can be identified, and the amniotic fluid collected for genetic testing can be used, after diagnosis, for the isolation, culture and differentiation of AFS cells. This can provide a useful stem cell model for the investigation of the molecular basis of the diagnosed disease without the necessity of producing iPS, since AFS cells show some features of pluripotency and are able to differentiate in cells derived from all three germ layers "in vitro". In this article, we describe the potential benefits provided by using AFS cells in the modeling of human genetic diseases.

Baker, J. L., K. Dunn, et al. "Genome Editing of Human Pluripotent Stem Cells for Modeling Metabolic Disease." Genetics. 2016 Apr 13. pii: genetics.115.183889.

The pathophysiology of metabolic diseases such as coronary artery disease, diabetes and obesity is complex and multifactorial. Developing new strategies to prevent or treat these diseases requires in vitro models with which researchers can extensively study the molecular mechanisms that lead to disease. Human pluripotent stem cells (hPSCs) and their differentiated derivatives have the potential to provide an unlimited source of disease-relevant cell types and when combined with recent advances in genome editing, make the goal of generating functional metabolic disease models for the first time, consistently attainable. However, this approach still has certain limitations including lack of robust differentiation methods and potential off-target effects. This review describes the current progress in hPSC-based metabolic disease research using genome-editing technology.

Becker, M., T. Potapenko, et al. "Polycomb protein BMI1 regulates osteogenic differentiation of human adipose tissue-derived mesenchymal stem cells downstream of GSK3." Stem Cells Dev. 2016 Apr 21.

Polycomb proteins such as the B lymphoma Mo-MLV insertion region 1 homolog (BMI1) are essential chromatin factors for the self-renewal and differentiation of embryonic and adult stem cells. BMI1 also plays a critical role in osteogenesis as Bmi1 deficient mice display a skeletal phenotype caused by the exhaustion of the mesenchymal stem cell pool. Here, we have studied the role of BMI1 in the osteogenic differentiation of human adipose tissue-derived mesenchymal stem cells (hASCs). BMI1 protein but not RNA levels increase during in vitro osteogenic differentiation of hASCs. Overexpression of BMI1 leads to an osteogenic priming of hASCs under non-differentiating conditions and enhanced osteogenesis upon differentiation, along with increased BMP2 und WNT11 expression. Conversely, knockdown of BMI1 expression reduces osteogenic differentiation. Furthermore, our studies indicate that during osteogenic differentiation of hASCs, BMI1 is a downstream target of GSK3 signaling. BMI1, therefore, acts as a pro-osteogenic differentiation factor in hASCs and hence it is a promising target for active modulation of hASC-derived osteogenesis.

Beeravolu, N., I. Khan, et al. "Isolation and comparative analysis of potential stem/progenitor cells from different regions of human umbilical cord." Stem Cell Res. 2016 Apr 13;16(3):696-711. doi: 10.1016/j.scr.2016.04.010.

Human umbilical cord (hUC) blood and tissue are non-invasive sources of potential stem/progenitor cells with similar cell surface properties as bone marrow stromal cells (BMSCs). While they are limited in cord blood, they may be more abundant in hUC. However, the hUC is an anatomically complex organ and the potential of cells in various sites of the hUC has not been fully explored. We dissected the hUC into its discrete sites and isolated hUC cells from the cord placenta junction (CPJ), cord tissue (CT), and Wharton's jelly (WJ). Isolated cells displayed fibroblastoid morphology, and expressed CD29, CD44, CD73, CD90, and CD105, and showed evidence of differentiation into multiple lineages in vitro. They also expressed low levels of pluripotency genes, OCT4, NANOG, SOX2 and KLF4. Passaging markedly affected cell proliferation with concomitant decreases in the expression of pluripotency and other markers, and an increase in chondrogenic markers. Microarray analysis further revealed the differences in the gene expression of CPJ-, CT- and WJ-hUC cells. Five coding and five lncRNA genes were differentially expressed in low vs. high passage hUC cells. Only MAEL was expressed at high levels in both low and high passage CPJ-hUC cells. They displayed a greater proliferation limit and a higher degree of multi-lineage differentiation in vitro and warrant further investigation to determine their full differentiation capacity, and therapeutic and regenerative medicine potential.

Behrens, K., I. Triviai, et al. "Decoding the Epigenetic Heterogeneity of Human Pluripotent Stem Cells with Seamless Gene Editing." Blood. 2016 Apr 13. pii: blood-2015-09-668129.

Pluripotent stem cells exhibit cell cycle-regulated heterogeneity for trimethylation of histone-3 on lysine-4 (H3K4me3) on developmental gene promoters containing bivalent epigenetic domains. The heterogeneity of H3K4me3 can be attributed to Cyclin-dependent kinase-2 (CDK2) phosphorylation and activation of the histone methyltransferase, MLL2 (KMT2B), during late-G1. The deposition of H3K4me3 on developmental promoters in late-G1 establishes a permissive chromatin architecture that enables signaling cues to promote differentiation from the G1 phase. These data suggest that the inhibition of MLL2 phosphorylation and activation will prevent the initiation of differentiation. Here, we describe a method to seamlessly modify a putative CDK2 phosphorylation site on MLL2 to restrict its phosphorylation and activation. Specifically, by utilizing dimeric CRISPR RNA-guided nucleases, RFNs (commercially known as the NextGEN CRISPR), in combination with an excision-only piggyBac transposase, we demonstrate how to generate a point mutation of threonine-542, a predicted site to prevent MLL2 activation. This gene editing method enables the use of both positive and negative selection, and allows for subsequent removal of the donor cassette without leaving behind any unwanted DNA sequences or modifications. This seamless "donor-excision" approach provides clear advantages over using single stranded oligo-deoxynucleotides (ssODN) as donors to create point mutations, as the use of ssODN necessitate additional mutations in the donor PAM sequence, along with extensive cloning efforts. The method described here therefore provides the highest targeting efficiency with the lowest "off-target" mutation rates possible, while removing the labor-intensive efforts associated with screening thousands of clones. In sum, this chapter describes how seamless gene editing may be utilized to examine stem cell heterogeneity of epigenetic marks, but is also widely applicable for performing precise genetic manipulations in numerous other cell types.

Blair, H. C., E. Kalyvioti, et al. "High-efficiency cellular reprogramming with microfluidics." Lab Invest. 2016 Apr 18. doi: 10.1038/labinvest.2016.51.

We report that the efficiency of reprogramming human somatic cells to induced pluripotent stem cells (hiPSCs) can be dramatically improved in a microfluidic environment. Microliter-volume confinement resulted in a 50-fold increase in efficiency over traditional reprogramming by delivery of synthetic mRNAs encoding transcription factors. In these small volumes, extracellular components of the TGF-beta and other signaling pathways exhibited temporal regulation that appears critical to acquisition of pluripotency. The high quality and purity of the resulting hiPSCs (mu-hiPSCs) allowed direct differentiation into functional hepatocyte- and cardiomyocyte-like cells in the same platform without additional expansion.

Botezatu, L., L. C. Michel, et al. "Oncogenic roles and drug target of CXCR4/CXCL12 axis in lung cancer and cancer stem cell." Exp Hematol. 2016 Apr 11. pii: S0301-472X(16)30064-9. doi: 10.1016/j.exphem.2016.04.001.

Although the great progress has been made in diagnosis and therapeutic in lung cancer, it induces the most cancer death worldwide in both males and females. Chemokines, which have chemotactic abilities, contain up to 50 family members. By binding

to G protein-coupled receptors (GPCR), holding seven-transmembrane domain, they function in immune cell trafficking and regulation of cell proliferation, differentiation, activation, and migration, homing under both physiologic and pathologic conditions. The alpha-chemokine receptor CXCR4 for the alpha-chemokine stromal cell-derived-factor-1 (SDF-1) is most widely expressed by tumors. In addition to human tissues of the bone marrow, liver, adrenal glands, and brain, the CXC chemokine SDF-1 or CXCL12 is also highly expressed in lung cancer tissues and is associated with lung metastasis. Lung cancer cells have the capabilities to utilize and manipulate the CXCL12/CXCR system to benefit growth and distant spread. CXCL12/CXCR4 axis is a major culprit for lung cancer and has a crucial role in lung cancer initiation and progression by activating cancer stem cell. This review provides an evaluation of CXCL12/CXCR4 as the potential therapeutic target for lung cancers; it also focuses on the synergistic effects of inhibition of CXCL12/CXCR4 axis and immunotherapy as well as chemotherapy. Together, CXCL12/CXCR4 axis can be a potential therapeutic target for lung cancers and has additive effects with immunotherapy.

Cacci, E., R. Negri, et al. "Tumor Necrosis Factor-alpha Attenuates the Osteogenic Differentiation Capacity of Periodontal Ligament Stem Cells by Activating Protein Kinase Like Endoplasmic Reticulum Kinase Signaling." Curr Top Med Chem. 2016 Apr 14.

BACKGROUND: Human periodontal ligament stem cells (PDLSCs) display efficient osteogenic differentiation capacity, but fail to rescue the bone destruction associated with periodontitis. Endoplasmic reticulum (ER) stress and the unfolded protein response (UPR) have recently been linked to inflammation and osteogenic differentiation. Therefore, we investigated the role of the protein kinase RNA-like ER kinase (PERK) pathway in the impaired osteogenic differentiation ability of PDLSCs treated with tumor necrosis factor-alpha (TNF-alpha). METHODS: PDLSCs were isolated and stimulated with osteogenic media containing 1, 10, or 20 ng/ml TNF-alpha. The expression of runt-related transcription factor 2 (Runx2) and osteocalcin (OCN), mRNA expression and activity of alkaline phosphatase (ALP), and formation of mineralization nodules were assessed. Furthermore, the expression of PERK pathway-related factors, glucose regulated protein 78 (GRP78), PERK, activating transcription factor 4 (ATF4), and C/EBP homologous protein (CHOP), were also measured. Osteogenic differentiation and inhibition of the PERK pathway were also examined in cells pretreated with an inhibitor of ER stress, 4-phenylbutyric acid (4-PBA), followed by TNF-alpha stimulation. Finally, PERK siRNA was used to examine osteogenic differentiation attenuated by TNF-alpha. RESULTS: Higher concentrations of TNF-alpha (10 ng/ml and 20 ng/ml) impaired the osteogenic differentiation of PDLSCs, but activated the PERK pathway. Pretreatment of PDLSCs with lower concentrations of 4-PBA prevented the TNF-alpha-induced upregulation of GRP78, PERK, and ATF4, and recovered differentiation ability. Finally, PERK knockdown also restored osteogenic differentiation. CONCLUSION: TNF-alpha attenuates the osteogenic differentiation ability of PDLSCs through activation of the PERK pathway.

Canciani, E., C. Dellavia, et al. "Adipose derived stem cells for regenerative therapy in osteoarticular diseases." J Craniofac Surg. 2016 Apr 15.

In the recent years, adipose derived stem cells (ASCs) led to significant findings in the field of regenerative therapy. ASCs have various biological properties and capacity as differentiation in three lineages (chondrocytes, osteocytes and adipocytes) or immunomodulation by releasing paracrine factors. Osteoarthritis (OA) is the most frequent osteoarticular disease characterized by none curative treatment. We reviewed all current data on the proof of concept of ASCs in OA pathophysiology as well as an inventory of ASC promising cell therapy in OA.

Cangelosi, A. L. and O. H. Yilmaz "Quantitative Phosphoproteomic Study Reveals that PKA Regulates Neural Stem Cell Differentiation through Phosphorylation of Catenin beta-1 and Glycogen Synthase Kinase 3beta." Cell Cycle. 2016 Apr 20:0.

Protein phosphorylation is central to the understanding of multiple cellular signaling pathways responsible for regulating the self-renewal and differentiation of neural stem cells (NSCs). Here we performed a large-scale phosphoproteomic analysis of rat fetal NSCs (rfNSCs) utilizing strong cation exchange chromatography (SCX) prefractionation and citric acid-assisted two-step enrichment with TiO2 (CATSET) strategy followed by nanoLC-MS/MS analysis. Totally we identified 32,546 phosphosites on 5,091 phosphoproteins, among which 23,945 were class I phosphosites, and quantified 16,000 sites during NSC differentiation. More than 65% of class I phosphosites were novel when compared with PhosphoSitePlus database. Quantification results showed that the early and late stage of NSC differentiation differ greatly. We mapped 69 changed phosphosites on 20 proteins involved in Wnt signaling pathway, including S552 on catenin beta-1 (Ctnnb1) and S9 on glycogen synthase kinase 3beta (Gsk3beta).

Western blotting and real-time PCR results proved that Wnt signaling pathway plays critical roles in NSC fate determination. Furthermore, inhibition and activation of PKA dramatically affected the phosphorylation state of Ctnnb1 and Gsk3beta, which regulates the differentiation of NSCs. Our data provides a valuable resource for studying the self-renewal and differentiation of NSCs.

Cao, Y., Y. Fang, et al. "Indoleamine 2,3-dioxygenase and regulatory T cells in acute myeloid leukemia." Hematology. 2016 Apr 6:1-6.

BACKGROUND AND OBJECTIVES: The microenvironment of acute myeloid leukemia (AML) is suppressive for immune cells. Regulatory T cells (Tregs) have been recognized to play a role in helping leukemic cells to evade immunesurveillance. The mesenchymal stem cells (MSCs) are essential contributors in immunomodulation of the microenvironment as they can promote differentiation of Tregs via the indoleamine 2,3-dioxygenase (IDO) pathway. The aim of the present work was to evaluate the expression of IDO in bone marrow derived MSCs and to study its correlation to percentage of Tregs. METHODS: Thirty-seven adult bone marrow samples were cultured in appropriate culture medium to isolate MSCs. Successful harvest of MSCs was determined by plastic adherence, morphology, and positive expression of CD271 and CD105; negative expression of CD34 and CD45 using flowcytometry. MSCs were examined for IDO expression by immunocytochemistry using anti-IDO monoclonal antibody. CD4+ CD25+ cells (Tregs) were measured in bone marrow samples by flowcytometry. RESULTS: MSCs were successfully isolated from 20 of the 37 bone marrow samples cultured. MSCs showed higher expression of IDO and Tregs percentage was higher in AML patients compared to control subjects ($P = 0.002$ and $P < 0.001$, respectively). A positive correlation was found between IDO expression and Tregs percentage (P value = 0.012, r = 0.5). CONCLUSION: In this study, we revealed an association between high IDO expression in MSCs and elevated levels of Tregs which could have an important role in the pathogenesis of AML, providing immunosuppressive microenvironment.

Cullen, C. L. and K. M. Young "Fine processes of Nestin-GFP-positive radial glia-like stem cells in the adult dentate gyrus ensheathe local synapses and vasculature." Front Neural Circuits. 2016 Apr 5;10:26. doi: 10.3389/fncir.2016.00026. eCollection 2016.

Adult hippocampal neurogenesis relies on the activation of neural stem cells in the dentate gyrus, their division, and differentiation of their progeny into mature granule neurons. The complex morphology of radial glia-like (RGL) stem cells suggests that these cells establish numerous contacts with the cellular components of the neurogenic niche that may play a crucial role in the regulation of RGL stem cell activity. However, the morphology of RGL stem cells remains poorly described. Here, we used light microscopy and electron microscopy to examine Nestin-GFP transgenic mice and provide a detailed ultrastructural reconstruction analysis of Nestin-GFP-positive RGL cells of the dentate gyrus. We show that their primary processes follow a tortuous path from the subgranular zone through the granule cell layer and ensheathe local synapses and vasculature in the inner molecular layer. They share the ensheathing of synapses and vasculature with astrocytic processes and adhere to the adjacent processes of astrocytes. This extensive interaction of processes with their local environment could allow them to be uniquely receptive to signals from local neurons, glia, and vasculature, which may regulate their fate.

De Veirman, K., J. Wang, et al. "Induction of miR-146a by multiple myeloma cells in mesenchymal stromal cells stimulates their pro-tumoral activity." Cancer Lett. 2016 Apr 19. pii: S0304-3835(16)30259-2. doi: 10.1016/j.canlet.2016.04.024.

Mutual communication between multiple myeloma (MM) cells and mesenchymal stromal cells (MSC) plays a pivotal role in supporting MM progression. In MM, MSC exhibit a different genomic profile and dysregulated cytokine secretion compared to normal MSC, however the mechanisms involved in these changes are not fully understood. Here, we examined the miRNA changes in human MSC after culture with conditioned medium of MM cells and found 19 dysregulated miRNAs, including upregulated miR-146a. Moreover, exosomes derived from MM cells contained miR-146a and could be transferred into MSC. After overexpressing miR-146a in MSC, secretion of several cytokines and chemokines including CXCL1, IL6, IL-8, IP-10, MCP-1, and CCL-5 was elevated, resulting in the enhancement of MM cell viability and migration. DAPT, an inhibitor of the endogenous Notch pathway, was able to abrogate the miR-146a-induced increase of cytokines in MSC, suggesting the involvement of the Notch pathway. Taken together, our results demonstrate a positive feedback loop between MM cells and MSC: MM cells promote the increase of miR146a in MSC which leads to more cytokine secretion, which in turn favors MM cell growth and migration.

Deshpande, N. and A. Rangarajan "Human thrombopoiesis depends on PKCdelta/PKCepsilon functional couple." Indian J Surg Oncol. 2015 Dec;6(4):400-14. doi: 10.1007/s13193-015-0451-7. Epub 2015 Aug 19.

A deeper understanding of the molecular events driving megakaryocytopoiesis and thrombopoiesis is essential to regulate in vitro and in vivo platelet production for clinical applications. We previously documented the crucial role of PKCepsilon in the regulation of human and mouse megakaryocyte maturation and platelet release. However, since several data show that different PKC isoforms fulfill complementary functions, we targeted PKCepsilon and PKCdelta, which show functional and phenotypical reciprocity, at the same time to boost platelet production in vitro. Results show that PKCdelta, at the opposite of PKCepsilon, is persistently expressed during megakaryocytic differentiation, and a forced PKCdelta down-modulation impairs megakaryocyte maturation and platelet production. PKCdelta and PKCepsilon work as a functional couple with opposite roles on thrombopoiesis, and the modulation of their balance strongly impacts platelet production. Indeed, we show an imbalance of PKCdelta/PKCepsilon ratio both in primary myelofibrosis and essential thrombocytemia, featured by impaired megakaryocyte differentiation and increased platelet production, respectively. Finally, we demonstrate that concurrent molecular targeting of both PKCdelta and PKCepsilon represents a strategy for in vitro platelet factories.

Deshwar, A. R., S. C. Chng, et al. "Inhibitors of LSD1 as a potential therapy for acute myeloid leukemia." Elife. 2016 Apr 14;5. pii: e13758. doi: 10.7554/eLife.13758.

INTRODUCTION: Epigenetic dysregulation plays a critical role in the pathogenesis of acute myeloid leukemia (AML). Alterations in histone methylation lead to aberrant silencing of expression of multiple genes involved in tumor suppression and cell cycling, resulting in myeloid maturation arrest and proliferation of early myeloid progenitors. One promising approach targeting chromatin regulatory proteins is inhibition of lysine specific demethylase-1 (LSD1), an enzyme responsible for demethylation of histone H3 as well as other functions Areas covered: Available literature on LSD1 in normal and malignant hematopoiesis was identified in PubMed and reviewed. Areas addressed here include the biology of LSD1, pharmacologic inhibitors, and preclinical data supporting the rationale for LSD1 inhibition in AML therapy. Expert opinion: LSD1 inhibitors represent a promising novel epigenetic approach for AML therapy. Preclinical studies have revealed that pharmacologic LD1 inhibitors function primarily by altering stem cell programs and restoring myeloid differentiation to AML cells. These effects are markedly enhanced in combination with trans-retinoic acid or histone deacetylase inhibitors with little toxicity. Currently, multiple oral LSD1 inhibitors are undergoing phase 1 investigation in patients with AML. The results of these clinical trials are eagerly awaited.

Genbacev, O., N. Larocque, et al. "BMP2 induces chondrogenic differentiation, osteogenic differentiation and endochondral ossification in stem cells." Hum Reprod. 2016 Apr 15. pii: dew077.

Bone morphogenetic protein 2 (BMP2), a member of the transforming growth factor-beta (TGF-beta) super-family, is one of the main chondrogenic growth factors involved in cartilage regeneration. BMP2 is known to induce chondrogenic differentiation in various types of stem cells in vitro. However, BMP2 also induces osteogenic differentiation and endochondral ossification in mesenchymal stem cells (MSCs). Although information regarding BMP2-induced chondrogenic and osteogenic differentiation within the same system might be essential for cartilage tissue engineering, few studies concerning these issues have been conducted. In this study, BMP2 was identified as a regulator of chondrogenic differentiation, osteogenic differentiation and endochondral bone formation within the same system. BMP2 was used to regulate chondrogenic and osteogenic differentiation in stem cells within the same culture system in vitro and in vivo. Any changes in the differentiation markers were assessed. BMP2 was found to induce chondrogenesis and osteogenesis in vitro via the expression of Sox9, Runx2 and its downstream markers. According to the results of the subcutaneous stem cell implantation studies, BMP2 not only induced cartilage formation but also promoted endochondral ossification during ectopic bone/cartilage formation. In fetal limb cultures, BMP2 promoted chondrocyte hypertrophy and endochondral ossification. Our data reveal that BMP2 can spontaneously induce chondrogenic differentiation, osteogenic differentiation and endochondral bone formation within the same system. Thus, BMP2 can be used in cartilage tissue engineering to regulate cartilage formation but has to be properly regulated for cartilage tissue engineering in order to retain the cartilage phenotype.

Hofer, T., M. Barile, et al. "Stem-cell dynamics and lineage topology from in vivo fate mapping in the hematopoietic system." Curr Opin Biotechnol. 2016 Apr 20;39:150-156. doi: 10.1016/j.copbio.2016.04.001.

In recent years, sophisticated fate-mapping tools have been developed to study the behavior of stem cells in the intact organism. These experimental approaches are beginning to yield a quantitative picture of how cell numbers are regulated during steady state and in response to challenges. Focusing on hematopoiesis and immune responses, we discuss how novel mathematical approaches driven by these fate-mapping data have provided insights into the dynamics and topology of cellular differentiation pathways in vivo. The combination of experiment and theory has allowed to quantify the degree of self-renewal in stem and progenitor cells, shown how native hematopoiesis differs fundamentally from post-transplantation hematopoiesis, and uncovered that the diversification of T lymphocytes during immune responses resembles tissue renewal driven by stem cells.

Hosseinpur, Z., S. M. Hashemi, et al. "Induction of Human iPSC-Derived Cardiomyocyte Proliferation Revealed by Combinatorial Screening in High Density Microbioreactor Arrays." Immunopharmacol Immunotoxicol. 2016 Apr 21:1-7.

Inducing cardiomyocyte proliferation in post-mitotic adult heart tissue is attracting significant attention as a therapeutic strategy to regenerate the heart after injury. Model animal screens have identified several candidate signalling pathways, however, it remains unclear as to what extent these pathways can be exploited, either individually or in combination, in the human system. The advent of human cardiac cells from directed differentiation of human pluripotent stem cells (hPSCs) now provides the ability to interrogate human cardiac biology in vitro, but it remains difficult with existing culture formats to simply and rapidly elucidate signalling pathway penetrance and interplay. To facilitate high-throughput combinatorial screening of candidate biologicals or factors driving relevant molecular pathways, we developed a high-density microbioreactor array (HDMA) - a microfluidic cell culture array containing 8100 culture chambers. We used HDMAs to combinatorially screen Wnt, Hedgehog, IGF and FGF pathway agonists. The Wnt activator CHIR99021 was identified as the most potent molecular inducer of human cardiomyocyte proliferation, inducing cell cycle activity marked by Ki67, and an increase in cardiomyocyte numbers compared to controls. The combination of human cardiomyocytes with the HDMA provides a versatile and rapid tool for stratifying combinations of factors for heart regeneration.

Hosseinzadeh, S., M. Mahmoudifard, et al. "Mesenchymal stem cell proliferation and mineralization but not osteogenic differentiation are strongly affected by extracellular pH." Bioprocess Biosyst Eng. 2016 Apr 16.

Osteomyelitis is a serious complication in oral and maxillofacial surgery affecting bone healing. Bone remodeling is not only controlled by cellular components but also by ionic and molecular composition of the extracellular fluids in which calcium phosphate salts are precipitated in a pH dependent manner. OBJECTIVE: To determine the effect of pH on self-renewal, osteogenic differentiation and matrix mineralization of mesenchymal stem cells (MSCs). METHODS: We selected three different pH values; acidic (6.3, 6.7), physiological (7.0-8.0) and severe alkaline (8.5). MSCs were cultured at different pH ranges, cell viability measured by WST-1, apoptosis detected by JC-1, senescence was analyzed by beta-galactosidase whereas mineralization was detected by Alizarin Red and osteogenic differentiation analyzed by Real-time PCR. RESULTS: Self-renewal was affected by pH as well as matrix mineralization in which pH other than physiologic inhibited the deposition of extracellular matrix but did not affect MSCs differentiation as osteoblast markers were upregulated. The expression of osteocalcin and alkaline phosphatase activity was upregulated whereas osteopontin was downregulated under acidic pH. CONCLUSION: pH affected MSCs self-renewal and mineralization without influencing osteogenic differentiation. Thus, future therapies, based on shifting acid-base balance toward the alkaline direction might be beneficial for prevention or treatment of osteomyelitis.

Ikegame, M., Y. Tabuchi, et al. "Tensile stress stimulates the expression of osteogenic cytokines/growth factors and matricellular proteins in the mouse cranial suture at the site of osteoblast differentiation." Biomed Res. 2016;37(2):117-26. doi: 10.2220/biomedres.37.117.

Mechanical stress promotes osteoblast proliferation and differentiation from mesenchymal stem cells (MSCs). Although numerous growth factors and cytokines are known to regulate this process, information regarding the differentiation of mechanically stimulated osteoblasts from MSCs in in vivo microenvironment is limited. To determine the significant factors involved in this process, we performed a global analysis of differentially expressed genes, in response to tensile stress, in the mouse cranial suture wherein osteoblasts differentiate from MSCs. We found that the gene expression levels of several components involved in bone morphogenetic protein, Wnt, and epithelial growth factor signalings were elevated with tensile stress. Moreover gene expression of some extracellular matrices (ECMs),

such as cysteine rich protein 61 (Cyr61)/CCN1 and galectin-9, were upregulated. These ECMs have the ability to modulate the activities of cytokines and are known as matricellular proteins. Cyr61/CCN1 expression was prominently increased in the fibroblastic cells and preosteoblasts in the suture. Thus, for the first time we demonstrated the mechanical stimulation of Cyr61/CCN1 expression in osteogenic cells in an ex vivo system. These results suggest the importance of matricellular proteins along with the cytokine-mediated signaling for the mechanical regulation of MSC proliferation and differentiation into osteoblastic cell lineage in vivo.

Jang, J. Y., S. H. Park, et al. "Anterior pituitary influence on adipokine expression and secretion by porcine adipocytes." Macromol Biosci. 2016 Apr 14. doi: 10.1002/mabi.201600001.

Nutritional stressors may cause negative effects on animal health and growth and lead to significant economic impact. Adipose tissue is an endocrine organ producing, mediators and hormones, called adipokines. They play a dynamic role in body homeostasis and in the regulation of energy expenditure, interacting with feeding behavior, hormones and growth factors. This in vitro study aimed to investigate how nutritional conditions and growth hormone (GH) can influence nitric oxide (NO) production and the expression and secretion of three important adipokines, that is leptin, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), by swine adipocytes. In our experimental model, mesenchymal stem cells from omental adipose tissue were induced to adipogenic differentiation. After differentiation, adipocytes were incubated for 24 h (T0) with DMEM/Ham's F12 (group A) or DMEM/Ham's F12 salts (group B), a DMEM/Ham's F12 formulation deprived of nutritional components. Primary adipocyte cells were also co-cultured for 4 h (T+4) or 12 h (T+12) with or without anterior pituitary slices. To stimulate GH secretion by pituitary cells, growth hormone releasing hormone at 10-8 M was added at the start of the incubation times (4 or 12 h). At T0, T+4 and T+12, NO production, leptin, IL-6 and TNF-alpha expression and secretion were measured. NO increased ($P<0.05$) up to twofold in restricted culture conditions. Deprived medium and coincubation with anterior pituitary positively influenced leptin secretion and expression. TNF-alpha was expressed and secreted only in deprived culture condition groups (B, B1 and B2). Nutrients availability and pituitary co-culture did not affect IL-6 expression and secretion. Our study shows an endocrine function for porcine adipocytes. In our model, adipocytes readily responded to nutritional inputs by secretion of molecules affecting energy balance. This secretion capacity was modulated by GH. Improving our knowledge of the role of adipocyte in the endocrine system, may lead to a more complete understanding of regulating energy balance in swine.

Jones, J. R. and S. C. Zhang "Electro-Acupuncture Promotes Endogenous Multipotential Mesenchymal Stem Cell Mobilization into the Peripheral Blood." Curr Opin Biotechnol. 2016 Apr 12;40:133-138. doi: 10.1016/j.copbio.2016.03.010.

BACKGROUND/AIMS: Mobilization of endogenous stem cells is an appealing strategy for cell therapy However, there is little evidence for reproducible, effective methods of mesenchymal stem cell (MSC) mobilization. In the present study, we investigated the mobilizing effect of electro-acupuncture (EA) on endogenous MSCs. METHODS: Normal adult rats were randomly divided into six groups, namely, EA for 14 days (EA14d), sham EA14d, EA21d, sham EA21d and matched control groups. MSC mobilization efficiency was determined by colony-forming unit fibroblast (CFU-F) assays. Mobilized peripheral blood (PB)-derived MSCs were identified by immunophenotype and multi-lineage differentiation potential. RESULTS: CFU-F frequency was significantly increased in the PB of EA14d rats compared with the sham EA and control groups. Moreover, the number of CFU-Fs was increased further in the EA21d group. MSCs derived from EA-mobilized PB were positive for CD90 and CD44, but negative for CD45. Additionally, these cells could differentiate into adipocytes, osteoblasts, chondrocytes and neural-like cells in vitro. Finally, stromal cell-derived factor-1alpha (SDF-1alpha) was increased in the PB of rats subjected to EA, and the migration of MSCs was improved in response to SDF-1alpha. CONCLUSIONS: MSCs with multi-lineage differentiation potential can be mobilized by EA. Our data provide a promising strategy for MSC mobilization.

Krug, C., A. Beer, et al. "The effect of amniotic membrane extract on umbilical cord blood mesenchymal stem cell expansion: is there any need to save the amniotic membrane besides the umbilical cord blood?" Handchir Mikrochir Plast Chir. 2016 Apr;48(2):87-94. doi: 10.1055/s-0042-104655. Epub 2016 Apr 20.

OBJECTIVES: Umbilical cord blood is a good source of the mesenchymal stem cells that can be banked, expanded and used in regenerative medicine. The objective of this study was to test whether amniotic membrane extract, as a rich source of growth factors such as basic-fibroblast growth factor, can promote the proliferation potential of the

umbilical cord mesenchymal stem cells. MATERIALS AND METHODS: The study design was interventional. Umbilical cord mesenchymal stem cells were isolated from voluntary healthy infants from hospitals in Shiraz, Iran, cultured in the presence of basic-fibroblast growth factor and amniotic membrane extracts (from pooled - samples), and compared with control cultures. Proliferation assay was performed and duplication number and time were calculated. The expression of stem cell's specific markers and the differentiation capacity toward osteogenic and adipogenic lineages were evaluated. RESULTS: Amniotic membrane extract led to a significant increase in the proliferation rate and duplication number and a decrease in the duplication time without any change in the cell morphology. Both amniotic membrane extract and basic-fibroblast growth factor altered the expressing of CD44 and CD105 in cell population. Treating basic-fibroblast growth factor but not the amniotic membrane extract favored the differentiation potential of the stem cells toward osteogenic lineage. CONCLUSION: The amniotic membrane extract administration accelerated cell proliferation and modified the CD marker characteristics which may be due to the induction of differentiation toward a specific lineage. Amniotic membrane extract may enhance the proliferation rate and duplication number of the stem cell through changing the duplication time.

Kumar, A., R. B. Chalamalasetty, et al. "Functional interference in the bone marrow microenvironment by disseminated breast cancer cells." Mol Cell Biol. 2016 Apr 18. pii: MCB.01010-15.

Skeletal metastasis of breast cancer is associated with a poor prognosis and significant morbidity. Investigations in other solid tumors have revealed an impairment in hematopoietic function upon bone marrow invasion. However, the interaction between disseminated breast cancer cells and the bone marrow microenvironment which harbors them has not been addressed comprehensively. Employing advanced co-culture assays, proteomic studies, organotypic models as well as in vivo xenotransplant models, we define the consequences of this interaction on the stromal compartment of bone marrow, affected molecular pathways and subsequent effects on the hematopoietic stem and progenitor cells (HSPCs). The results showed a basic fibroblast growth factor (bFGF)-mediated, synergistic increase in proliferation of breast cancer cells and mesenchymal stromal cells (MSCs) in co-culture. The stromal induction was associated with elevated phosphoinositide-3 kinase (PI3K) signaling in the stroma, which coupled with elevated bFGF levels resulted in increased migration of breast cancer cells towards the MSCs. The perturbed cytokine profile in the stroma led to reduction in the osteogenic differentiation of MSCs via downregulation of platelet-derived growth factor-BB (PDGF-BB). Long term co-cultures of breast cancer cells, HSPCs, MSCs and the in vivo studies in NSG mice showed a reduced support for HSPCs in the altered niche. The resultant non-conducive phenotype of the niche for HSPC support emphasizes the importance of the affected molecular pathways in the stroma as clinical targets. These findings can be a platform for further development of therapeutic strategies aiming at the blockade of bone marrow support to disseminated breast cancer cells.

Makhoul, G., R. Jurakhan, et al. "The Potential and Limits of Hematopoietic Stem Cell Transplantation for the Treatment of Autosomal Dominant Hyper-IgE Syndrome." Life Sci. 2016 Apr 15. pii: S0024-3205(16)30229-6. doi: 10.1016/j.lfs.2016.04.009.

PURPOSE: Autosomal dominant hyper-IgE syndrome (AD-HIES) is included among primary immunodeficiencies, and results from heterozygous mutations in the signal transduction and activator of transcription 3 (STAT3) gene. AD-HIES leads to impaired Th17 cell differentiation and IL-17 production, and is associated with increased susceptibility to bacteria and fungi. It was reported that several patients with AD-HIES were treated with hematopoietic stem cell transplantation (HSCT). The efficacy of HSCT in treating AD-HIES is variable. This study aims to evaluate the long-term clinical and immunological efficacy of HSCT for AD-HIES. METHODS: We have followed for more than 8 years two patients with AD-HIES who were treated with HSCT. Their ability of IL-17 production was evaluated by flow cytometry. RESULTS: Both patients indicated the normal ability of IL-17 production and their serum IgE levels decreased after HSCT. On the other hand, they suffered from pulmonary complications of AD-HIES such as pneumatoceles and bronchiectasis even after HSCT; however, the frequency of infections was decreased. CONCLUSIONS: Although the dysfunction of STAT3 in non-hematological tissues such as the lungs could not be corrected by HSCT, AD-HIES patients with risk factors for pulmonary complications may benefit from immunological correction by HSCT before severe pulmonary complications occur. Future studies should investigate risk factors for pulmonary complications in AD-HIES patients.

Malara, A., C. Gruppi, et al. "Differentiation of mouse iPS cells is dependent on embryoid body size in microwell chip culture." Stem Cells. 2016 Apr 19. doi: 10.1002/stem.2381.

A microwell chip possessing microwells of several hundred micrometers is a promising platform for generating embryoid bodies (EBs) of stem cells. Here, we investigated the effects of initial EB size on the growth and differentiation of mouse iPS cells in microwell chip culture. We fabricated a chip that contained 195 microwells in a triangular arrangement at a diameter of 600 mum. To evaluate the effect of EB size, four similar conditions were designed with different seeding cell densities of 100, 500, 1000, and 2000 cells/EB. The cells in each microwell gradually aggregated and then spontaneously formed a single EB within 1 d of culture, and EB size increased with further cell proliferation. EB growth was regulated by the initial EB size, and the growth ability of smaller EBs was higher than that of larger EBs. Furthermore, stem cell differentiation also depended on the initial EB size, and the EBs at more than 500 cells/EB promoted hepatic and cardiac differentiations, but the EBs at 100 cells/EB preferred vascular differentiation. These results indicated that the initial EB size was one of the important factors controlling the proliferation and differentiation of stem cells in the microwell chip culture.

Mansour, I., R. A. Zayed, et al. "Simultaneous control of stemness and differentiation by the transcription factor Escargot in adult stem cells: how can we tease them apart?" Hematology. 2016 Mar 4:1-7.

The homeostatic turnover of adult organs and their regenerative capacity following injury depend on a careful balance between stem cell self-renewal (to maintain or enlarge the stem cell pool) and differentiation (to replace lost tissue). We have recently characterized the role of the Drosophila Snail family transcription factor escargot (esg) in testis cyst stem cells (CySCs) 1, 2 and intestinal stem cells (ISCs). 3, 4 Esg mutant CySCs are not maintained as stem cells, but they are capable of differentiating normally along the cyst cell lineage. In contrast, esg mutant CySCs that give rise to a closely related lineage, the apical hub cells, cannot maintain hub cell identity. Similarly, esg maintains stemness of ISCs while regulating the terminal differentiation of progenitor cells into absorptive enterocytes or secretory enteroendocrine cells. Therefore, our findings suggest that Esg may play a conserved and pivotal regulatory role in adult stem cells, controlling both their maintenance and terminal differentiation. Here we propose that this dual regulatory role is due to simultaneous control by Esg of overlapping genetic programs and discuss the exciting challenges and opportunities that lie ahead to explore the underlying mechanisms experimentally.

Manukjan, G., T. Ripperger, et al. "GABP is necessary for stem/progenitor cell maintenance and myeloid differentiation in human hematopoiesis and chronic myeloid leukemia." Stem Cell Res. 2016 Apr 12;16(3):677-681. doi: 10.1016/j.scr.2016.04.007.

Maintenance of hematopoietic stem cells and their potential to give rise to progenitors of differentiated lymphoid and myeloid cells are accomplished by a network of regulatory processes. As a part of this network, the heteromeric transcription factor GA-binding protein (GABP) plays a crucial role in self-renewal of murine hematopoietic and leukemic stem cells. Here, we report the consequences of functional impairment of GABP in human hematopoietic and in leukemic stem/progenitor cells. Ectopic overexpression of a dominant-negative acting GABP mutant led to impaired myeloid differentiation of CD34+ hematopoietic stem/progenitor cells obtained from healthy donors. Moreover, drastically reduced clonogenic capacity of leukemic stem/progenitor cells isolated from bone marrow aspirates of chronic myeloid leukemia (CML) patients underlines the importance of GABP on stem/progenitor cell maintenance and confirms the relevance of GABP for human myelopoiesis in healthy and diseased states.

Matsuno, K., S. I. Mae, et al. "Ultrastructural study of mouse adipose-derived stromal cells induced towards osteogenic direction." Differentiation. 2016 Apr 14. pii: S0301-4681(16)30023-8. doi: 10.1016/j.diff.2016.04.002.

We investigated the ultrastructural characteristics of mouse adipose-derived stem/stromal cells (ASCs) induced towards osteogenic lineage. ASCs were isolated from adipose tissue of FVB-Cg-Tg(GFPU)5Nagy/J mice and expanded in monolayer culture. Flow cytometry, histochemical staining, and electron microscopy techniques were used to characterize the ASCs with respect to their ability for osteogenic differentiation capacity. Immunophenotypically, ASCs were characterized by high expression of the CD44 and CD90 markers, while the relative content of cells expressing CD45, CD34 and CD117 markers was <2%. In assays of differentiation, the positive response to osteogenic differentiation factors was observed and characterized by deposition of calcium in the extracellular matrix and alkaline phosphatase production. Electron microscopy analysis revealed that undifferentiated ASCs had a rough endoplasmic reticulum with dilated cisterns and elongated mitochondria. At the end of the osteogenic differentiation, the ASCs transformed from their original fibroblast-like appearance to having a polygonal osteoblast-like morphology. Ultrastructurally, these cells were characterized by

large euchromatic nucleus and numerous cytoplasm containing elongated mitochondria, a very prominent rough endoplasmic reticulum, Golgi apparatus and intermediate filament bundles. Extracellular matrix vesicles of variable size similar to the calcification nodules were observed among collagen fibrils. Our data provide the ultrastructural basis for further studies on the cellular mechanisms involved in osteogenic differentiation of mouse adipose-derived stem/stromal cells. Microsc. Res. Tech., 2016. (c) 2016 Wiley Periodicals, Inc.

Mohammed, O. J., R. McAlpine, et al. "Assessment of developmental cardiotoxic effects of some commonly used phytochemicals in mouse embryonic D3 stem cell differentiation and chick embryonic cardiomyocyte micromass culture models." Reprod Toxicol. 2016 Apr 19. pii: S0890-6238(16)30061-2. doi: 10.1016/j.reprotox.2016.04.011.

Pregnant women often use herbal medicines to alleviate symptoms of pregnancy. The active phytochemicals eugenol (from holy basil) and alpha-bisabolol (from chamomile) are recommended to promote calmness and reduce stress. There is evidence that both eugenol and alpha-bisabolol possess pro-apoptotic and anti-proliferative effects and induce reactive oxygen species. The potential effect was examined by monitoring cardiomyocyte contractile activity (differentiation), cell activity, protein content and ROS production for mouse D3 embryonic stem cell and chick embryonic micromass culture. The results showed that eugenol (0.01-80muM) demonstrated effects on cell activity (both systems) and ROS production (stem cell system only), as well as decreasing the contractile activity and protein content at high concentrations in both systems. Additionally, alpha-bisabolol (0.01-80muM) at high concentrations decreased the contractile activity and cell activity and in the stem cell system induced ROS production and decreased protein content. The results suggest only low concentrations should be ingested in pregnancy..

Morris, S. L. and S. Huang "Targeting Enhancer of Zeste Homolog 2 as a promising strategy for cancer treatment." Genes Dis. 2016 Mar;3(1):41-47. Epub 2016 Jan 6.

Polycomb group proteins represent a global silencing system involved in development regulation. In specific, they regulate the transition from proliferation to differentiation, contributing to stem-cell maintenance and inhibiting an inappropriate activation of differentiation programs. Enhancer of Zeste Homolog 2 (EZH2) is the catalytic subunit of Polycomb repressive complex 2, which induces transcriptional inhibition through the tri-methylation of histone H3, an epigenetic change associated with gene silencing. EZH2 expression is high in precursor cells while its level decreases in differentiated cells. EZH2 is upregulated in various cancers with high levels associated with metastatic cancer and poor prognosis. Indeed, aberrant expression of EZH2 causes the inhibition of several tumor suppressors and differentiation genes, resulting in an uncontrolled proliferation and tumor formation. This editorial explores the role of Polycomb repressive complex 2 in cancer, focusing in particular on EZH2. The canonical function of EZH2 in gene silencing, the non-canonical activities as the methylation of other proteins and the role in gene transcriptional activation, were summarized.

Moss, J., E. Gebara, et al. "Erythroleukemia cells acquire an alternative mitophagy capability." Proc Natl Acad Sci U S A. 2016 Apr 18. pii: 201514652.

Leukemia cells are superior to hematopoietic cells with a normal differentiation potential in buffering cellular stresses, but the underlying mechanisms for this leukemic advantage are not fully understood. Using CRISPR/Cas9 deletion of the canonical autophagy-essential gene Atg7, we found that erythroleukemia K562 cells are armed with two sets of autophagic machinery. Alternative mitophagy is functional regardless of whether the canonical autophagic mechanism is intact or disrupted. Although canonical autophagy defects attenuated cell cycling, proliferation and differentiation potential, the leukemia cells retained their abilities for mitochondrial clearance and for maintaining low levels of reactive oxygen species (ROS) and apoptosis. Treatment with a specific inducer of mitophagy revealed that the canonical autophagy-defective erythroleukemia cells preserved a mitophagic response. Selective induction of mitophagy was associated with the upregulation and localization of RAB9A on the mitochondrial membrane in both wild-type and Atg7(-/-) leukemia cells. When the leukemia cells were treated with the alternative autophagy inhibitor brefeldin A or when the RAB9A was knocked down, this mitophagy was prohibited. This was accompanied by elevated ROS levels and apoptosis as well as reduced DNA damage repair.

Muzzarelli, R. A., M. E. Mehtedi, et al. "Physical properties imparted by genipin to chitosan for tissue regeneration with human stem cells." Int J Biol Macromol. 2016 Apr 19. pii: S0141-8130(16)30234-3. doi: 10.1016/j.ijbiomac.2016.03.075.

Genipin is a fully assessed non-cytotoxic crosslinking compound. The chitosan|genipin physical properties such as morphology, roughness, porosity,

hydrophilicity, zeta-potential, surface area and surface energy exert control over cell adhesion, migration, phenotype maintenance and intracellular signaling in vitro, and cell recruitment at the tissue-scaffold interface in vivo. For example a therapy using fucose|chitosan|genipin nanoparticles encapsulating amoxicillin, based on the recognition of fucose by H. pylori, leads to sharply improved clinical results. A bioactive scaffold sensitive to environmental stimuli provides an alternative approach for inducing adipose stem cell chondrogenesis: the expression of specific genes, the accumulation of cartilage-related macromolecules and the mechanical properties are comparable to the original cartilage-derived matrix (CDM), thus making the CDM|genipin a contraction-free biomaterial suitable for cartilage tissue engineering. For the regeneration of the cartilage, chitosan|genipin permits to modulate matrix synthesis and proliferation of chondrocytes by dynamic compression; chondrocytes cultured on the composite substrate produce much more collagen-II and sulfated GAG. The main advantages gained in the bone regeneration area with chitosan|genipin are: acceleration of mineral deposition; enhancement of adhesion, proliferation and differentiation of osteoblasts; promotion of the expression of osteogenic differentiation markers; greatly improved viability of human adipose stem cells.

Mykhaylichenko, V. Y., A. V. Kubyshkin, et al. "Experimental induction of reparative morphogenesis and adaptive reserves in the ischemic myocardium using multipotent mesenchymal bone marrow-derived stem cells." Pathophysiology. 2016 Apr 13. pii: S0928-4680(16)30008-6. doi: 10.1016/j.pathophys.2016.04.002.

INTRODUCTION: Current experimental research has proven the efficacy of transplantation bone marrow-derived mesenchymal stem cells (MSC) in the treatment of myocardial infarction (MI). The one of the main purposes of research was to evaluate the comparative data of the MSC transplantation with (5-azacytidine) and without commitment and to assess the post transplantation effects. METHODS: The efficiency of intravenous cardiomyoplasty by infusion of MSC was evaluated in female Wistar-Kyoto rats with myocardial infarction model using echocardiography, morphological study, morphometry, immunohistostaining, data from in situ hybridization, and by measurement of blood serum levels of nitric oxide, endothelin-1, vascular endothelial growth factor (VEGF), and fibroblast growth factor 2 (FGF2). RESULTS: The transplanted MSC were detected in all layers of the myocardium; MCS actively participate in the formation of blood vessels and connective tissue in the scar zone. There was no observable differentiation of male MSC into cardiomyocytes in female rats with MI.

Narakornsak, S., N. Poovachiranon, et al. "miR-128 regulates differentiation of hair follicle mesenchymal stem cells into smooth muscle cells by targeting SMAD2." Acta Histochem. 2016 Apr 14. pii: S0065-1281(16)30059-9. doi: 10.1016/j.acthis.2016.04.004.

Human hair follicle mesenchymal stem cells (hHFMSCs) are an important source of cardiovascular tissue engineering for their differentiation potential into smooth muscle cells (SMCs), yet the molecular pathways underlying such fate determination is unclear. MicroRNAs (miRNAs) are non-coding RNAs that play critical roles in cell differentiation. In present study, we found that miR-128 was remarkably decreased during the differentiation of hHFMSCs into SMCs induced by transforming growth factor-beta1 (TGF-beta1). Moreover, overexpression of miR-128 led to decreased expression of SMC cellular marker proteins, such as smooth muscle actin (SMA) and calponin, in TGF-beta1-induced SMC differentiation. Further, we identified that miR-128 targeted the 3'-UTR of SMAD2 transcript for translational inhibition of SMAD2 protein, and knockdown of SMAD2 abrogated the promotional effect of antagomir-128 (miR-128 neutralizer) on SMC differentiation. These results suggest that miR-128 regulates the differentiation of hHFMSCs into SMCs via targeting SMAD2, a main transcription regulator in TGF-beta signaling pathway involving SMC differentiation. The miR-128/SMAD2 axis could therefore be considered as a candidate target in tissue engineering and regenerative medicine for SMCs.

Nekrasov, E. D., V. A. Vigont, et al. "GFI1 as a therapeutic and prognostic marker for myelodysplastic syndrome (MDS)." Mol Neurodegener. 2016 Apr 14;11(1):27. doi: 10.1186/s13024-016-0092-5.

Inherited gene variants play an important role in malignant diseases. The transcriptional repressor Growth factor independence 1 (GFI1) regulates hematopoietic stem cell (HSC) self-renewal and differentiation. A single nucleotide polymorphism of GFI1 (rs34631763) generates a protein with an asparagine (N) instead of a serine (S) at position 36 (GFI136N) and has a prevalence of 3-5% among Caucasians. Since GFI1 regulates myeloid development, we examined the role of GFI136N on MDS disease course. To this end, we determined allele frequencies of GFI136N in four independent MDS cohorts from the Netherlands and Belgium, Germany, the ICGC consortium and the USA. The GFI136N allele frequency in the 723 MDS patients genotyped ranged between 9-12%. GFI136N was an independent adverse prognostic factor for overall

survival, AML-free survival and event-free survival in an univariate analysis. After adjusting for age, bone marrow blast percentage, IPSS score, mutational status and cytogenetic findings, GFI136N remained an independent adverse prognostic marker. With regard to therapy, whereas GFI136S homozygous patients showed sustained response to treatment with hypomethylating agents, GFI136N patients show poor sustained response to this therapy. Since allele status of GFI136N is readily determined using basic molecular techniques, we propose to include GFI136N status in future prospective studies for MDS patients to better predict prognosis and guide therapeutic decisions.

Niada, S., C. Giannasi, et al. "Redefining definitive endoderm subtypes by robust induction of human induced pluripotent stem cells." Differentiation. 2016 Apr 14. pii: S0301-4681(15)30104-3. doi: 10.1016/j.diff.2016.04.001.

Many reports have described methods that induce definitive endoderm (DE) cells from human pluripotent stem cells (hPSCs). However, it is unclear whether the differentiation propensity of these DE cells is uniform. This uncertainty is due to the different developmental stages that give rise to anterior and posterior DE from anterior primitive streak (APS). Therefore, these DE cell populations might be generated from the different stages of APS cells, which affect the DE cell differentiation potential. Here, we succeeded in selectively differentiating early and late APS cells from human induced pluripotent stem cells (hiPSCs) using different concentrations of CHIR99021, a small molecule Wnt/beta-catenin pathway activator. We also established novel differentiation systems from hiPSCs into three types of DE cells: anterior and posterior domains of anterior DE cells through early APS cells and posterior DE cells through late APS cells. These different DE cell populations could differentiate into distinct endodermal lineages in vitro, such as lung, liver or small intestine progenitors. These results indicate that different APS cells can produce distinct types of DE cells that have proper developmental potency and suggest a method to evaluate the quality of endodermal cell induction from hPSCs.

Nosrati, A., F. Naghshvar, et al. "MicroRNA-224 regulates self-renewal of mouse spermatogonial stem cells via targeting DMRT1." Gastroenterol Hepatol Bed Bench. 2016 Spring;9(2):132-9.

AIM: We aimed to study the expression of CD24 and CD133 in colorectal cancer and normal adjacent tissues to assess a relationship between these markers and clinic-pathological characteristics and patient's survival. BACKGROUND: Cancer stem cells are a group of tumor cells that have regeneration and multi-order differentiation capabilities. PATIENTS AND METHODS: Expression of CD24 and CD133 was studied in a paraffin block of colorectal cancer and normal tissues near tumors with the immuneohistochemical method in patients who were referred to Imam Khomeini Hospital in Sari. RESULTS: A total of 50 samples (25 males and 25 females) with a mean age of 67.57+/-13.9 years old with range 28-93 years, included 3 mucinous carcinoma and 47 adenocarcinoma. Expression of CD133 marker was negative in 29 cases and positive in 21 cases. Expression of CD24 in tissue near tumor cells was found in 30% of available samples. The relationship between expressing CD24 with treatment (surgery and chemotherapy) was significant and its relationship with patient's survival was insignificant statistically. However, there was a clear difference as mean survival age of patients based on CD24 expression was 26.64+/-18.15 for negative cases and 41.75+/-28.76 months for positive cases. CD24 and CD133 expressions and their co-expression with other clinic-pathological factors were not significant. CONCLUSION: During this study, the relationship between CD24 and treatment type was significant. To confirm this result, various studies with high sample numbers and other stem cell markers are recommended.

Panaccione, A., M. T. Chang, et al. "Upregulation of RNA Processing Factors in Poorly Differentiated Lung Cancer Cells." Clin Cancer Res. 2016 Apr 15;22(8):2083-95. doi: 10.1158/1078-0432.CCR-15-2208.

Intratumoral heterogeneity in non-small cell lung cancer (NSCLC) has been appreciated at the histological and cellular levels, but the association of less differentiated pathology with poor clinical outcome is not understood at the molecular level. Gene expression profiling of intact human tumors fails to reveal the molecular nature of functionally distinct epithelial cell subpopulations, in particular the tumor cells that fuel tumor growth, metastasis, and disease relapse. We generated primary serum-free cultures of NSCLC and then exposed them to conditions known to promote differentiation: the air-liquid interface (ALI) and serum. The transcriptional network of the primary cultures was associated with stem cells, indicating a poorly differentiated state, and worse overall survival of NSCLC patients. Strikingly, the overexpression of RNA splicing and processing factors was a prominent feature of the poorly differentiated cells and was also observed in clinical datasets. A genome-wide analysis of splice isoform expression revealed many alternative splicing events that were specific to the differentiation state of the

cells, including an unexpectedly high frequency of events on chromosome 19. The poorly differentiated cells exhibited alternative splicing in many genes associated with tumor progression, as exemplified by the preferential expression of the short isoform of telomeric repeat-binding factor 1 (TERF1), also known as Pin2. Our findings demonstrate the utility of the ALI method for probing the molecular mechanisms that underlie NSCLC pathogenesis and provide novel insight into posttranscriptional mechanisms in poorly differentiated lung cancer cells.

Papadopoulou, T., A. Kaymak, et al. "Synthesis of Eupalinilide E a Promoter of Human Hematopoietic Stem and Progenitor Cell Expansion." Cell Cycle. 2016 Apr 20:0.

Improving the ex vivo and in vivo production of hematopoietic stem and progenitor cells (HSPCs) has the potential to address the short supply of these cells that are used in the treatment of various blood diseases and disorders. Eupalinilide E promotes the expansion of human HSPCs and inhibits subsequent differentiation, leading to increased numbers of clinically useful cells. This natural product represents an important tool to uncover new methods to drive expansion, while inhibiting differentiation. However, in the process of examining these effects, which occurs through a novel mechanism, the natural product was consumed, which limited additional investigation. To provide renewed and improved access to eupalinilide E a laboratory synthesis has been developed and is reported herein. The synthetic route can access >400 mg in a single batch, employing reactions conducted on useful scales in a single vessel. Key transformations enabling the approach included a diastereoselective borylative enyne cyclization and late-stage double allylic C-H oxidation, as well as adapted Luche reduction and aluminum-mediated epoxidation reactions to maximize synthetic efficiency. Retesting synthetic eupalinilide E confirms the compound's ability to expand HSPCs and inhibit differentiation.

Passaro, D., C. T. Quang, et al. "Hematopoiesis and T-cell specification as a model developmental system." Immunol Rev. 2016 May;271(1):156-72. doi: 10.1111/imr.12402.

The pathway to generate T cells from hematopoietic stem cells guides progenitors through a succession of fate choices while balancing differentiation progression against proliferation, stage to stage. Many elements of the regulatory system that controls this process are known, but the requirement for multiple, functionally distinct transcription factors needs clarification in terms of gene network architecture. Here, we compare the features of the T-cell specification system with the rule sets underlying two other influential types of gene network models: first, the combinatorial, hierarchical regulatory systems that generate the orderly, synchronized increases in complexity in most invertebrate embryos; second, the dueling 'master regulator' systems that are commonly used to explain bistability in microbial systems and in many fate choices in terminal differentiation. The T-cell specification process shares certain features with each of these prevalent models but differs from both of them in central respects. The T-cell system is highly combinatorial but also highly dose-sensitive in its use of crucial regulatory factors. The roles of these factors are not always T-lineage-specific, but they balance and modulate each other's activities long before any mutually exclusive silencing occurs. T-cell specification may provide a new hybrid model for gene networks in vertebrate developmental systems.

Perovanovic, J., S. Dell'Orso, et al. "The minimum required level of donor chimerism in hereditary hemophagocytic lymphohistiocytosis." Sci Transl Med. 2016 Apr 20;8(335):335ra58. doi: 10.1126/scitranslmed.aad4991.

The nuclear envelope protein lamin A is encoded by thelamin A/C(LMNA) gene, which can contain missense mutations that cause Emery-Dreifuss muscular dystrophy (EDMD) (p.R453W). We fused mutated forms of the lamin A protein to bacterial DNA adenine methyltransferase (Dam) to define euchromatic-heterochromatin (epigenomic) transitions at the nuclear envelope during myogenesis (using DamID-seq). Lamin A missense mutations disrupted appropriate formation of lamin A-associated heterochromatin domains in an allele-specific manner-findings that were confirmed by chromatin immunoprecipitation-DNA sequencing (ChIP-seq) in murine H2K cells and DNA methylation studies in fibroblasts from muscular dystrophy patient who carried a distinctLMNAmutation (p.H222P). Observed perturbations of the epigenomic transitions included exit from pluripotency and cell cycle programs [euchromatin (open, transcribed) to heterochromatin (closed, silent)], as well as induction of myogenic loci (heterochromatin to euchromatin). In muscle biopsies from patients with either a gain- or change-of-functionLMNAgene mutation or a loss-of-function mutation in theemeringene, both of which cause EDMD, we observed inappropriate loss of heterochromatin formation at theSox2pluripotency locus, which was associated with persistent mRNA expression ofSox2 Overexpression ofSox2inhibited myogenic differentiation in human immortalized myoblasts. Our findings suggest that nuclear envelopathies are disorders of developmental

epigenetic programming that result from altered formation of lamina-associated domains.

Pers, Y. M. and C. Jorgensen "Aberrant Levels of Hematopoietic/Neuronal Growth and Differentiation Factors in Euthyroid Women at Risk for Autoimmune Thyroid Disease." Horm Mol Biol Clin Investig. 2016 Apr 19. pii: /j/hmbci.ahead-of-print/hmbci-2016-0010/hmbci-2016-0010.xml. doi: 10.1515/hmbci-2016-0010.

BACKGROUND: Subjects at risk for major mood disorders have a higher risk to develop autoimmune thyroid disease (AITD) and vice-versa, implying a shared pathogenesis. In mood disorder patients, an abnormal profile of hematopoietic/neuronal growth factors is observed, suggesting that growth/differentiation abnormalities of these cell lineages may predispose to mood disorders. The first objective of our study was to investigate whether an aberrant profile of these hematopoietic/neuronal growth factors is also detectable in subjects at risk for AITD. A second objective was to study the inter relationship of these factors with previously determined and published growth factors/cytokines in the same subjects. METHODS: We studied 64 TPO-Ab-negative females with at least 1 first- or second-degree relative with AITD, 32 of whom did and 32 who did not seroconvert to TPO-Ab positivity in 5-year follow-up. Subjects were compared with 32 healthy controls (HCs). We measured serum levels of brain-derived neurotrophic factor (BDNF), Stem Cell Factor (SCF), Insulin-like Growth Factor-Binding Protein 2 (IGFBP-2), Epidermal Growth Factor (EGF) and IL-7 at baseline. RESULTS: BDNF was significantly lower (8.2 vs 18.9 ng/ml, $P<0.001$), while EGF (506.9 vs 307.6 pg/ml, $P = 0.003$) and IGFBP-2 (388.3 vs 188.5 ng/ml, $P = 0.028$) were significantly higher in relatives than in HCs. Relatives who seroconverted in the next 5 years had significantly higher levels of SCF than non-seroconverters (26.5 vs 16.7 pg/ml, $P = 0.017$). In a cluster analysis with the previously published growth factors/cytokines SCF clustered together with IL-1beta, IL-6 and CCL-3, of which high levels also preceded seroconversion. CONCLUSION: Relatives of AITD patients show aberrant serum levels of 4 hematopoietic/neuronal growth factors similar to the aberrancies found in mood disorder patients, suggesting that shared growth and differentiation defects in both the hematopoietic and neuronal system may underlie thyroid autoimmunity and mood disorders. A distinct pattern of four inter correlating immune factors in the relatives preceded TPO-Ab seroconversion in the next 5 years.

Pfeiffer, E. R., R. Vega, et al. "Reduced Nrf2 expression mediates the decline in neural stem cell function during a critical middle-age period." J Pharmacol Toxicol Methods. 2016 Apr 16. pii: S1056-8719(16)30034-X. doi: 10.1016/j.vascn.2016.04.007.

Although it is known that the regenerative function of neural stem/progenitor cells (NSPCs) declines with age, causal mechanisms underlying this phenomenon are not understood. Here, we systematically analyze subventricular zone (SVZ) NSPCs, in various groups of rats across the aging spectrum, using in vitro and in vivo histological and behavioral techniques. These studies indicate that although NSPC function continuously declines with advancing age, there is a critical time period during middle age (13-15 months) when a striking reduction in NSPC survival and regeneration (proliferation and neuronal differentiation) occurs. The studies also indicate that this specific temporal pattern of NSPC deterioration is functionally relevant at a behavioral level and correlates with the decreasing expression of the redox-sensitive transcription factor, Nrf2, in the NSPCs. When Nrf2 expression was suppressed in 'young' NSPCs, using short interfering RNAs, the survival and regeneration of the NSPCs was significantly compromised and mirrored 'old' NSPCs. Conversely, Nrf2 overexpression in 'old' NSPCs rendered them similar to 'young' NSPCs, and they showed increased survival and regeneration. Furthermore, examination of newborn Nrf2 knockout (Nrf2 -/-) mice revealed a lower number of SVZ NSPCs in these animals, when compared to wild-type controls. In addition, the proliferative and neurogenic potential of the NSPCs was also compromised in the Nrf2-/- mice. These results identify a novel regulatory role for Nrf2 in NSPC function during aging and have important implications for developing NSPC-based strategies to support healthy aging and to treat age-related neurodegenerative disorders.

Pietras, E. M., C. Mirantes-Barbeito, et al. "Chronic interleukin-1 exposure drives haematopoietic stem cells towards precocious myeloid differentiation at the expense of self-renewal." Nat Cell Biol. 2016 Apr 25. doi: 10.1038/ncb3346.

Haematopoietic stem cells (HSCs) maintain lifelong blood production and increase blood cell numbers in response to chronic and acute injury. However, the mechanism(s) by which inflammatory insults are communicated to HSCs and their consequences for HSC activity remain largely unknown. Here, we demonstrate that interleukin-1 (IL-1), which functions as a key pro-inflammatory 'emergency' signal, directly accelerates cell division and myeloid differentiation of HSCs through precocious activation of a PU.1-dependent gene

program. Although this effect is essential for rapid myeloid recovery following acute injury to the bone marrow, chronic IL-1 exposure restricts HSC lineage output, severely erodes HSC self-renewal capacity, and primes IL-1-exposed HSCs to fail massive replicative challenges such as transplantation. Importantly, these damaging effects are transient and fully reversible on IL-1 withdrawal. Our results identify a critical regulatory circuit that tailors HSC responses to acute needs, and is likely to underlie deregulated blood homeostasis in chronic inflammation conditions.

Rauner, M., K. Franke, et al. "Tumorigenesis of nuclear transfer-derived embryonic stem cells is reduced through differentiation and enrichment following transplantation in the infarcted rat heart." J Bone Miner Res. 2016 Apr 15. doi: 10.1002/jbmr.2857.

The aim of the present study was to evaluate the tumorigenic potential of nuclear transfer-derived (nt) mouse embryonic stem cells (mESCs) transplanted into infarcted rat hearts. The ntmESCs were cultured using a bioreactor system to develop embryoid bodies, which were induced with 1% ascorbic acid to differentiate into cardiomyocytes. The ntmESCderived cardiomyocytes (ntmESCsCMs) were enriched using Percoll density gradient separation to generate ntmESCspercollenriched (PE)CMs. Ischemia was induced by ligating the left anterior descending coronary artery in female Sprague Dawley rats. Immunosuppressed rats (daily intraperitoneal injections of cyclosporine A and methylprednisolone) were randomly assigned to receive an injection containing 5x106 mESCs, ntmESCs, ntmESCCMs or ntmESCPECMs. Analysis performed 8 weeks following transplantation revealed teratoma formation in 80, 86.67 and 33.33% of the rats administered with the mESCs, ntmESCs and ntmESCCMs, respectively, indicating no significant difference between the mESCs and ntmESCs; but significance ($P<0.05$) between the ntmESCCMs and ntmESCs. The mean tumor volumes were 82.72+/-6.52, 83.17+/-3.58 and 50.40+/-5.98 mm3, respectively ($P>0.05$ mESCs, vs. ntmESCs; $P<0.05$ ntmESCCMs, vs. ntmESCs). By contrast, no teratoma formation was detected in the rats, which received ntmESCPECMs. Octamerbinding transcription factor4, a specific marker of undifferentiated mESCs, was detected using polymerase chain reaction in the rats, which received ntmESCs and ntmESCCMs, but not in rats administered with ntmESCPECMs. In conclusion, ntmESCs exhibited the same pluripotency as mESCs, and teratoma formation following ntmESC transplantation was reduced by cell differentiation and enrichment.

Rolland, M., X. Li, et al. "A 3D vascularized bone remodeling model combining osteoblasts and osteoclasts in a CaP nanoparticle-enriched matrix." PLoS Pathog. 2016 Apr 14;12(4):e1005547. doi: 10.1371/journal.ppat.1005547. eCollection 2016 Apr.

AIM: We aimed to establish a 3D vascularized in vitro bone remodeling model. MATERIALS & METHODS: Human umbilical endothelial cells (HUVECs), bone marrow mesenchymal stem cells (BMSCs), and osteoblast (OBs) and osteoclast (OCs) precursors were embedded in collagen/fibrin hydrogels enriched with calcium phosphate nanoparticles (CaPn). We assessed vasculogenesis in HUVEC-BMSC coculture, osteogenesis with OBs, osteoclastogenesis with OCs, and, ultimately, cell interplay in tetraculture. RESULTS: HUVECs developed a robust microvascular network and BMSCs differentiated into mural cells. Noteworthy, OB and OC differentiation was increased by their reciprocal coculture and by CaPn, and even more by the combination of the tetraculture and CaPn. CONCLUSION: We successfully developed a vascularized 3D bone remodeling model, whereby cells interacted and exerted their specific function.

Ryu, J. R., C. J. Hong, et al. "Comparison of TGF-beta1 and NO production by mesenchymal stem cells isolated from murine lung and adipose tissues." Mol Brain. 2016 Apr 21;9(1):43. doi: 10.1186/s13041-016-0224-4.

CONTEXT: Mesenchymal stem cells (MSCs) are cell sources for tissues regeneration. By secretion of soluble factors including transforming growth factor-beta (TGF-beta1) and nitric oxide (NO), MSCs are also able to regulate the immune system. MSCs have been disclosed in lung and adipose tissues with insufficient comparison between the tissues. OBJECTIVES: In this study, specific differentiation and the expression of surface antigens as well as TGF-beta1 and NO productive levels were compared in murine lung-derived MSCs (LMSCs) and adipose tissue-derived MSCs (ADMSCs). MATERIALS AND METHODS: MSCs were isolated from murine lung and adipose tissues and cultured. Both cell populations were characterized using multilineage potential and the expression of surface antigenic proteins, CD73, CD105, CD34, CD45, and CD11b. Finally, levels of TGF-beta1 and NO were evaluated and compared in ADMSCs and LMSCs. RESULTS: Expression of CD73 and CD105; lack of the expression of CD34, CD45, and CD11b markers; as well as adipocyte and osteocyte differentiations were detected in both adult stem cells. No significant difference was found in TGF-beta1 and NO production between two stem cell

populations. CONCLUSION: Our data showed that LMSCs and ADMSCs have comparable phenotype and TGF-beta1 and NO production.

Sadeghian-Nodoushan, F., R. Aflatoonian, et al. "Isolation and Differentiation of Adipose-Derived Stem Cells from Porcine Subcutaneous Adipose Tissues." Mol Reprod Dev. 2016 Apr;83(4):312-23. doi: 10.1002/mrd.22620. Epub 2016 Feb 22.

Obesity is an unconstrained worldwide epidemic. Unraveling molecular controls in adipose tissue development holds promise to treat obesity or diabetes. Although numerous immortalized adipogenic cell lines have been established, adipose-derived stem cells from the stromal vascular fraction of subcutaneous white adipose tissues provide a reliable cellular system ex vivo much closer to adipose development in vivo. Pig adipose-derived stem cells (pADSC) are isolated from 7- to 9-day old piglets. The dorsal white fat depot of porcine subcutaneous adipose tissues is sliced, minced and collagenase digested. These pADSC exhibit strong potential to differentiate into adipocytes. Moreover, the pADSC also possess multipotency, assessed by selective stem cell markers, to differentiate into various mesenchymal cell types including adipocytes, osteocytes, and chondrocytes. These pADSC can be used for clarification of molecular switches in regulating classical adipocyte differentiation or in direction to other mesenchymal cell types of mesodermal origin. Furthermore, extended lineages into cells of ectodermal and endodermal origin have recently been achieved. Therefore, pADSC derived in this protocol provide an abundant and assessable source of adult mesenchymal stem cells with full multipotency for studying adipose development and application to tissue engineering of regenerative medicine.

Sahu, S. K., A. Fritz, et al. "Manifestation of Huntington's disease pathology in human induced pluripotent stem cell-derived neurons." Biochim Biophys Acta. 2016 Apr 11. pii: S1874-9399(16)30065-7. doi: 10.1016/j.bbagrm.2016.04.005.

BACKGROUND: Huntington's disease (HD) is an incurable hereditary neurodegenerative disorder, which manifests itself as a loss of GABAergic medium spiny (GABA MS) neurons in the striatum and caused by an expansion of the CAG repeat in exon 1 of the huntingtin gene. There is no cure for HD, existing pharmaceutical can only relieve its symptoms. RESULTS: Here, induced pluripotent stem cells were established from patients with low CAG repeat expansion in the huntingtin gene, and were then efficiently differentiated into GABA MS-like neurons (GMSLNs) under defined culture conditions. The generated HD GMSLNs recapitulated disease pathology in vitro, as evidenced by mutant huntingtin protein aggregation, increased number of lysosomes/autophagosomes, nuclear indentations, and enhanced neuronal death during cell aging. Moreover, store-operated channel (SOC) currents were detected in the differentiated neurons, and enhanced calcium entry was reproducibly demonstrated in all HD GMSLNs genotypes. Additionally, the quinazoline derivative, EVP4593, reduced the number of lysosomes/autophagosomes and SOC currents in HD GMSLNs and exerted neuroprotective effects during cell aging. CONCLUSIONS: Our data is the first to demonstrate the direct link of nuclear morphology and SOC calcium deregulation to mutant huntingtin protein expression in iPSCs-derived neurons with disease-mimetic hallmarks, providing a valuable tool for identification of candidate anti-HD drugs. Our experiments demonstrated that EVP4593 may be a promising anti-HD drug.

Surrati, A., R. Linforth, et al. "Non-destructive characterisation of mesenchymal stem cell differentiation using LC-MS-based metabolite footprinting." Analyst. 2016 Apr 22.

Bone regeneration is a complex biological process where major cellular changes take place to support the osteogenic differentiation of mesenchymal bone progenitors. To characterise these biological changes and better understand the pathways regulating the formation of mature bone cells, the metabolic profile of mesenchymal stem cell (MSC) differentiation in vitro has been assessed non-invasively during osteogenic (OS) treatment using a footprinting technique. Liquid chromatography (LC)-mass spectrometry (MS)-based metabolite profiling of the culture medium was carried out in parallel to mineral deposition and alkaline phosphatase activity which are two hallmarks of osteogenesis in vitro. Metabolic profiles of spent culture media with a combination of univariate and multivariate analyses investigated concentration changes of extracellular metabolites and nutrients linked to the presence of MSCs in culture media. This non-invasive LC-MS-based analytical approach revealed significant metabolic changes between the media from control and OS-treated cells showing distinct effects of MSC differentiation on the environmental footprint of the cells in different conditions (control vs. OS treatment). A subset of compounds was directly linked to the osteogenic time-course of differentiation, and represent interesting metabolite candidates as non-invasive biomarkers for characterising the differentiation of MSCs in a culture medium.

Vagaska, B., S. E. New, et al. "Third generation poly(hydroxyacid) composite scaffolds for tissue engineering." Sci Rep. 2016 Apr 15;6:24251. doi: 10.1038/srep24251.

Bone tissue engineering based on scaffolds is quite a complex process as a whole gamut of criteria needs to be satisfied to promote cellular attachment, proliferation and differentiation: biocompatibility, right surface properties, adequate mechanical performance, controlled bioresorbability, osteoconductivity, angiogenic cues, and vascularization. Third generation scaffolds are more of composite types to maximize biological-mechanical-chemical properties. In the present review, our focus is on the performance of micro-organism-derived polyhydroxyalkanoates (PHAs)-polyhydroxybutyrate (PHB) and polyhydroxybutyrate-co-valerate (PHBV)-composite scaffolds with ceramics and natural polymers for tissue engineering applications with emphasis on bone tissue. We particularly emphasize on how material properties of the composites affect scaffold performance. PHA-based composites have demonstrated their biocompatibility with a range of tissues and their capacity to induce osteogenesis due to their piezoelectric properties. (c) 2016 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater, 2016.

Vasko, T., J. Frobel, et al. Control of adult neurogenesis by programmed cell death in the mammalian brain, J Hematol Oncol. 2016 Apr 21;9(1):43. doi: 10.1186/s13045-016-0273-2.

The presence of neural stem cells (NSCs) and the production of new neurons in the adult brain have received great attention from scientists and the public because of implications to brain plasticity and their potential use for treating currently incurable brain diseases. Adult neurogenesis is controlled at multiple levels, including proliferation, differentiation, migration, and programmed cell death (PCD). Among these, PCD is the last and most prominent process for regulating the final number of mature neurons integrated into neural circuits. PCD can be classified into apoptosis, necrosis, and autophagic cell death and emerging evidence suggests that all three may be important modes of cell death in neural stem/progenitor cells. However, the molecular mechanisms that regulate PCD and thereby impact the intricate balance between self-renewal, proliferation, and differentiation during adult neurogenesis are not well understood. In this comprehensive review, we focus on the extent, mechanism, and biological significance of PCD for the control of adult neurogenesis in the mammalian brain. The role of intrinsic and extrinsic factors in the regulation of PCD at the molecular and systems levels is also discussed. Adult neurogenesis is a dynamic process, and the signals for differentiation, proliferation, and death of neural progenitor/stem cells are closely interrelated. A better understanding of how adult neurogenesis is influenced by PCD will help lead to important insights relevant to brain health and diseases.

Vega, S. L., M. Kwon, et al. "Single Cell Imaging to Probe Mesenchymal Stem Cell N-Cadherin Mediated Signaling within Hydrogels." Ann Biomed Eng. 2016 Apr 22.

N-cadherin (Ncad) mediates cell-cell interactions, regulates beta-catenin (betacat) signaling, and promotes the chondrogenic differentiation of mesenchymal lineage cells. Here, we utilized confocal imaging to investigate the influence of Ncad interactions on single mesenchymal stem cell (MSC) behavior within 3-dimensional hydrogel environments under conditions that promote chondrogenic differentiation. Human MSCs were photoencapsulated in hyaluronic acid hydrogels functionalized with Ncad mimetic peptides and compared to cells in environments with control non-active peptides (Ctrl). Using single-cell imaging, we observed a significant increase in membrane betacat, nuclear betacat, and cell roundness after 3 days in Ncad hydrogels compared to Ctrl hydrogels. The extent of membrane and nuclear betacat localization and MSC roundness decreased to Ctrl hydrogel levels via pre-treatment with Ncad-specific antibodies prior to encapsulation in the Ncad hydrogels, confirming the activity of the peptide. Interestingly, there was a pronounced (>80%) increase in betacat nuclear localization in two-cell clusters within the Ctrl hydrogels, which was much greater than the increase (~30%) in betacat nuclear localization in two-cell clusters within the Ncad hydrogels. In summary, we utilized fluorescent imaging to demonstrate Ncad-mediated single cell responses to developmental cues within hydrogels towards chondrogenesis.

Vojdani, Z., A. Babaei, et al. "Laminin matrix promotes hepatogenic terminal differentiation of human bone marrow mesenchymal stem cells." Iran J Basic Med Sci. 2016 Jan;19(1):89-96.

OBJECTIVES: The application of stem cells holds great promises in cell transplants. Considering the lack of optimal in vitro model for hepatogenic differentiation, this study was designed to examine the effects of laminin matrix on the improvement of in vitro differentiation of human bone marrow mesenchymal stem cells (hBM-MSC) into the more functional hepatocyte-like cells. MATERIALS AND METHODS: Characterization of the hBM-MSCs was performed by immunophenotyping and their

differentiation into the mesenchymal-derived lineage. Then, cells were seeded on the laminin-coated or tissue culture polystyrene (TCPS). The differentiation was carried out during two steps. Afterward, the expression of hepatocyte markers such as AFP, ALB, CK-18, and CK-19 as well as the expression of C-MET, the secretion of urea, and the activity of CYP3A4 enzyme were determined. Moreover, the cytoplasmic glycogen storage was examined by periodic acid-Schiff (PAS) staining. RESULTS: The results demonstrated that the culture of hBM-MSC on laminin considerably improved hepatogenic differentiation compared to TCP group. A significant elevated level of urea biosynthesis and CYP3A4 enzyme activity was observed in the media of the laminin-coated differentiated cells ($P<0.05$). Furthermore higher expressions of both AFP and ALB were determined in cells differentiated on laminin matrix. Glycogen accumulation was not detected in the undifferentiated hBM-MSCs, however, both differentiated cells in laminin and TCPS groups demonstrated the intracellular glycogen accumulation on day 21 of hepatogenic differentiation. CONCLUSION: Taken together, these findings may indicate that laminin matrix can improve terminal differentiation of hepatocyte-like cells from hBM-MSCs. Thus, laminin might be considered as a suitable coating in hepatic tissue engineering designs.

Yamazaki, A., M. Yashiro, et al. "Isoproterenol directs hair follicle-associated pluripotent (HAP) stem cells to differentiate in vitro to cardiac muscle cells which can be induced to form beating heart-muscle tissue sheets." Cell Cycle. 2016 Mar 3;15(5):760-5. doi: 10.1080/15384101.2016.1146837.

Nestin-expressing hair-follicle-associated pluripotent (HAP) stem cells are located in the bulge area of the follicle. Previous studies have shown that HAP stem cells can differentiate to neurons, glia, keratinocytes, smooth muscle cells, and melanocytes in vitro. HAP stem cells effected nerve and spinal cord regeneration in mouse models. Recently, we demonstrated that HAP stem cells differentiated to beating cardiac muscle cells. The differentiation potential to cardiac muscle cells was greatest in the upper part of the follicle. The beat rate of the cardiac muscle cells was stimulated by isoproterenol. In the present study, we observed that isoproterenol directs HAP stem cells to differentiate to cardiac muscle cells in large numbers in culture compared to HAP stem cells not supplemented with isoproterenol. The addition of activin A, bone morphogenetic protein 4, and basic fibroblast growth factor, along with isoproternal, induced the cardiac muscle cells to form tissue sheets of beating heart muscle cells. These results demonstrate that HAP stem cells have great potential to form beating cardiac muscle cells in tissue sheets.

Yanagimachi, M., T. Ohya, et al. "The trans-spliced long noncoding RNA tsRMST impedes human ESC differentiation through WNT5A-mediated inhibition of the epithelial-to-mesenchymal transition." J Clin Immunol. 2016 Apr 18.

The trans-spliced non-coding RNA RMST (tsRMST) is an emerging regulatory lncRNA in the human pluripotency circuit. Previously, we found that tsRMST represses lineage-specific transcription factors through the PRC2 complex and NANOG in human pluripotent stem cells (hESCs). Here, we demonstrate that tsRMST also modulates non-canonical Wnt signaling to suppress the epithelial-to-mesenchymal transition (EMT) and in vitro differentiation of ESCs. Our results demonstrate that disruption of tsRMST expression in hESCs results in the up-regulation of WNT5A, EMT, and lineage-specific genes/markers. Furthermore, we found that the PKC inhibitors Go6983 and Go6976 inhibited the effects of WNT5A, indicating that WNT5A promotes the EMT and in vitro differentiation though conventional and novel PKC activation in hESCs. Finally, we showed that either antiserum neutralization of WNT5A or Go6983 treatment in tsRMST knockdown cells decreased the expression of mesenchymal and lineage-specific markers. Together, these findings indicate that tsRMST regulates Wnt and EMT signaling pathways in hESCs by repressing WNT5A, which is a potential EMT inducer for promoting in vitro differentiation of hESCs through PKC activation. Our findings provide further insights into the role of trans-spliced RNA and WNT5A in hESC differentiation, in which EMT plays an important role. This article is protected by copyright. All rights reserved.

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

References

1. Abboud, N., A. Fontbonne, et al. "Laminopathies disrupt epigenomic developmental programs and cell fate." J Tissue Eng Regen Med. 2016 Apr 21. doi: 10.1002/term.2163.
2. Abomaray, F. M., M. A. Al Jumah, et al. "Genetic Comparison of Stemness of Human Umbilical Cord and Dental Pulp." Stem Cells Int. 2016;2016:5184601. doi: 10.1155/2016/5184601. Epub 2016 Feb 10.
3. Antonucci, I., M. Provenzano, et al. "Amniotic Fluid Stem Cells: A Novel Source for Modeling of Human Genetic Diseases." Int J Mol Sci. 2016 Apr 22;17(4). pii: E607.
4. Baidu. http://www.baidu.com. 2016
5. Baker, J. L., K. Dunn, et al. "Genome Editing of Human Pluripotent Stem Cells for Modeling Metabolic Disease." Genetics. 2016 Apr 13. pii: genetics.115.183889.

6. Becker, M., T. Potapenko, et al. "Polycomb protein BMI1 regulates osteogenic differentiation of human adipose tissue-derived mesenchymal stem cells downstream of GSK3." Stem Cells Dev. 2016 Apr 21.
7. Beeravolu, N., I. Khan, et al. "Isolation and comparative analysis of potential stem/progenitor cells from different regions of human umbilical cord." Stem Cell Res. 2016 Apr 13;16(3):696-711. doi: 10.1016/j.scr.2016.04.010.
8. Behrens, K., I. Triviai, et al. "Decoding the Epigenetic Heterogeneity of Human Pluripotent Stem Cells with Seamless Gene Editing." Blood. 2016 Apr 13. pii: blood-2015-09-668129.
9. Blair, H. C., E. Kalyvioti, et al. "High-efficiency cellular reprogramming with microfluidics." Lab Invest. 2016 Apr 18. doi: 10.1038/labinvest.2016.51.
10. Botezatu, L., L. C. Michel, et al. "Oncogenic roles and drug target of CXCR4/CXCL12 axis in lung cancer and cancer stem cell." Exp Hematol. 2016 Apr 11. pii: S0301-472X(16)30064-9. doi: 10.1016/j.exphem.2016.04.001.
11. Cacci, E., R. Negri, et al. "Tumor Necrosis Factor-alpha Attenuates the Osteogenic Differentiation Capacity of Periodontal Ligament Stem Cells by Activating Protein Kinase Like Endoplasmic Reticulum Kinase Signaling." Curr Top Med Chem. 2016 Apr 14.
12. Canciani, E., C. Dellavia, et al. "Adipose derived stem cells for regenerative therapy in osteoarticular diseases." J Craniofac Surg. 2016 Apr 15.
13. Cangelosi, A. L. and O. H. Yilmaz "Quantitative Phosphoproteomic Study Reveals that PKA Regulates Neural Stem Cell Differentiation through Phosphorylation of Catenin beta-1 and Glycogen Synthase Kinase 3beta." Cell Cycle. 2016 Apr 20:0.
14. Cao, Y., Y. Fang, et al. "Indoleamine 2,3-dioxygenase and regulatory T cells in acute myeloid leukemia." Hematology. 2016 Apr 6:1-6.
15. Cullen, C. L. and K. M. Young "Fine processes of Nestin-GFP-positive radial glia-like stem cells in the adult dentate gyrus ensheathe local synapses and vasculature." Front Neural Circuits. 2016 Apr 5;10:26. doi: 10.3389/fncir.2016.00026. eCollection 2016.
16. De Veirman, K., J. Wang, et al. "Induction of miR-146a by multiple myeloma cells in mesenchymal stromal cells stimulates their pro-tumoral activity." Cancer Lett. 2016 Apr 19. pii: S0304-3835(16)30259-2. doi: 10.1016/j.canlet.2016.04.024.
17. Deshpande, N. and A. Rangarajan "Human thrombopoiesis depends on PKCdelta/PKCepsilon functional couple." Indian J Surg Oncol. 2015 Dec;6(4):400-14. doi: 10.1007/s13193-015-0451-7. Epub 2015 Aug 19.
18. Deshwar, A. R., S. C. Chng, et al. "Inhibitors of LSD1 as a potential therapy for acute myeloid leukemia." Elife. 2016 Apr 14;5. pii: e13758. doi: 10.7554/eLife.13758.
19. Genbacev, O., N. Larocque, et al. "BMP2 induces chondrogenic differentiation, osteogenic differentiation and endochondral ossification in stem cells." Hum Reprod. 2016 Apr 15. pii: dew077.
20. Google. http://www.google.com. 2016
21. Hofer, T., M. Barile, et al. "Stem-cell dynamics and lineage topology from in vivo fate mapping in the hematopoietic system." Curr Opin Biotechnol. 2016 Apr 20;39:150-156. doi: 10.1016/j.copbio.2016.04.001.
22. Hosseinpur, Z., S. M. Hashemi, et al. "Induction of Human iPSC-Derived Cardiomyocyte Proliferation Revealed by Combinatorial Screening in High Density Microbioreactor Arrays." Immunopharmacol Immunotoxicol. 2016 Apr 21:1-7.
23. Hosseinzadeh, S., M. Mahmoudifard, et al. "Mesenchymal stem cell proliferation and mineralization but not osteogenic differentiation are strongly affected by extracellular pH." Bioprocess Biosyst Eng. 2016 Apr 16.
24. Ikegame, M., Y. Tabuchi, et al. "Tensile stress stimulates the expression of osteogenic cytokines/growth factors and matricellular proteins in the mouse cranial suture at the site of osteoblast differentiation." Biomed Res. 2016;37(2):117-26. doi: 10.2220/biomedres.37.117.
25. Jang, J. Y., S. H. Park, et al. "Anterior pituitary influence on adipokine expression and secretion by porcine adipocytes." Macromol Biosci. 2016 Apr 14. doi: 10.1002/mabi.201600001.
26. Jones, J. R. and S. C. Zhang "Electro-Acupuncture Promotes Endogenous Multipotential Mesenchymal Stem Cell Mobilization into the Peripheral Blood." Curr Opin Biotechnol. 2016 Apr 12;40:133-138. doi: 10.1016/j.copbio.2016.03.010.
27. Krug, C., A. Beer, et al. "The effect of amniotic membrane extract on umbilical cord blood mesenchymal stem cell expansion: is there any need to save the amniotic membrane besides the umbilical cord blood?" Handchir Mikrochir Plast Chir. 2016 Apr;48(2):87-94. doi: 10.1055/s-0042-104655. Epub 2016 Apr 20.
28. Kumar, A., R. B. Chalamalasetty, et al. "Functional interference in the bone marrow microenvironment by disseminated breast cancer cells." Mol Cell Biol. 2016 Apr 18. pii: MCB.01010-15.
29. Ma H, Chen G. Stem cell. The Journal of American Science 2005;1(2):90-92.
30. Ma H, Cherng S. Eternal Life and Stem Cell. Nature and Science. 2007;5(1):81-96.
31. Ma H, Cherng S. Nature of Life. Life Science Journal 2005;2(1):7 - 15.
32. 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.
33. Ma H. The Nature of Time and Space. Nature and science 2003;1(1):1-11.Nature and science 2007;5(1):81-96.
34. Makhoul, G., R. Jurakhan, et al. "The Potential and Limits of Hematopoietic Stem Cell Transplantation for the Treatment of Autosomal Dominant Hyper-IgE Syndrome." Life Sci. 2016 Apr 15. pii: S0024-3205(16)30229-6. doi: 10.1016/j.lfs.2016.04.009.
35. Malara, A., C. Gruppi, et al. "Differentiation of mouse iPS cells is dependent on embryoid body size in microwell chip culture." Stem Cells. 2016 Apr 19. doi: 10.1002/stem.2381.
36. Mansour, I., R. A. Zayed, et al. "Simultaneous control of stemness and differentiation by the transcription factor Escargot in adult stem cells: how can we tease them apart?" Hematology. 2016 Mar 4:1-7.
37. Manukjan, G., T. Ripperger, et al. "GABP is necessary for stem/progenitor cell maintenance and myeloid differentiation in human hematopoiesis and chronic myeloid leukemia." Stem Cell Res. 2016 Apr 12;16(3):677-681. doi: 10.1016/j.scr.2016.04.007.
38. Matsuno, K., S. I. Mae, et al. "Ultrastructural study of mouse adipose-derived stromal cells induced towards osteogenic direction." Differentiation. 2016 Apr 14. pii: S0301-4681(16)30023-8. doi: 10.1016/j.diff.2016.04.002.
39. Mohammed, O. J., R. McAlpine, et al. "Assessment of developmental cardiotoxic effects of some commonly used phytochemicals in mouse embryonic D3 stem cell differentiation and chick embryonic cardiomyocyte micromass culture models." Reprod Toxicol. 2016 Apr 19. pii: S0890-6238(16)30061-2. doi: 10.1016/j.reprotox.2016.04.011.
40. Morris, S. L. and S. Huang "Targeting Enhancer of Zeste Homolog 2 as a promising strategy for cancer treatment." Genes Dis. 2016 Mar;3(1):41-47. Epub 2016 Jan 6.
41. Moss, J., E. Gebara, et al. "Erythroleukemia cells acquire an alternative mitophagy capability." Proc Natl Acad Sci U S A. 2016 Apr 18. pii: 201514652.

42. Muzzarelli, R. A., M. E. Mehtedi, et al. "Physical properties imparted by genipin to chitosan for tissue regeneration with human stem cells." Int J Biol Macromol. 2016 Apr 19. pii: S0141-8130(16)30234-3. doi: 10.1016/j.ijbiomac.2016.03.075.
43. Mykhaylichenko, V. Y., A. V. Kubyshkin, et al. "Experimental induction of reparative morphogenesis and adaptive reserves in the ischemic myocardium using multipotent mesenchymal bone marrow-derived stem cells." Pathophysiology. 2016 Apr 13. pii: S0928-4680(16)30008-6. doi: 10.1016/j.pathophys.2016.04.002.
44. Narakornsak, S., N. Poovachiranon, et al. "miR-128 regulates differentiation of hair follicle mesenchymal stem cells into smooth muscle cells by targeting SMAD2." Acta Histochem. 2016 Apr 14. pii: S0065-1281(16)30059-9. doi: 10.1016/j.acthis.2016.04.004.
45. National Center for Biotechnology Information, U.S. National Library of Medicine. http://www.ncbi.nlm.nih.gov/pubmed. 2015.
46. Nekrasov, E. D., V. A. Vigont, et al. "GFI1 as a therapeutic and prognostic marker for myelodysplastic syndrome (MDS)." Mol Neurodegener. 2016 Apr 14;11(1):27. doi: 10.1186/s13024-016-0092-5.
47. Niada, S., C. Giannasi, et al. "Redefining definitive endoderm subtypes by robust induction of human induced pluripotent stem cells." Differentiation. 2016 Apr 14. pii: S0301-4681(15)30104-3. doi: 10.1016/j.diff.2016.04.001.
48. Nosrati, A., F. Naghshvar, et al. "MicroRNA-224 regulates self-renewal of mouse spermatogonial stem cells via targeting DMRT1." Gastroenterol Hepatol Bed Bench. 2016 Spring;9(2):132-9.
49. Panaccione, A., M. T. Chang, et al. "Upregulation of RNA Processing Factors in Poorly Differentiated Lung Cancer Cells." Clin Cancer Res. 2016 Apr 15;22(8):2083-95. doi: 10.1158/1078-0432.CCR-15-2208.
50. Papadopoulou, T., A. Kaymak, et al. "Synthesis of Eupalinilide E a Promoter of Human Hematopoietic Stem and Progenitor Cell Expansion." Cell Cycle. 2016 Apr 20:0.
51. Passaro, D., C. T. Quang, et al. "Hematopoiesis and T-cell specification as a model developmental system." Immunol Rev. 2016 May;271(1):156-72. doi: 10.1111/imr.12402.
52. Perovanovic, J., S. Dell'Orso, et al. "The minimum required level of donor chimerism in hereditary hemophagocytic lymphohistiocytosis." Sci Transl Med. 2016 Apr 20;8(335):335ra58. doi: 10.1126/scitranslmed.aad4991.
53. Pers, Y. M. and C. Jorgensen "Aberrant Levels of Hematopoietic/Neuronal Growth and Differentiation Factors in Euthyroid Women at Risk for Autoimmune Thyroid Disease." Horm Mol Biol Clin Investig. 2016 Apr 19. pii: /j/hmbci.ahead-of-print/hmbci-2016-0010/hmbci-2016-0010.xml. doi: 10.1515/hmbci-2016-0010.
54. Pfeiffer, E. R., R. Vega, et al. "Reduced Nrf2 expression mediates the decline in neural stem cell function during a critical middle-age period." J Pharmacol Toxicol Methods. 2016 Apr 16. pii: S1056-8719(16)30034-X. doi: 10.1016/j.vascn.2016.04.007.
55. Pietras, E. M., C. Mirantes-Barbeito, et al. "Chronic interleukin-1 exposure drives haematopoietic stem cells towards precocious myeloid differentiation at the expense of self-renewal." Nat Cell Biol. 2016 Apr 25. doi: 10.1038/ncb3346.
56. Rauner, M., K. Franke, et al. "Tumorigenesis of nuclear transfer-derived embryonic stem cells is reduced through differentiation and enrichment following transplantation in the infarcted rat heart." J Bone Miner Res. 2016 Apr 15. doi: 10.1002/jbmr.2857.
57. Rolland, M., X. Li, et al. "A 3D vascularized bone remodeling model combining osteoblasts and osteoclasts in a CaP nanoparticle-enriched matrix." PLoS Pathog. 2016 Apr 14;12(4):e1005547. doi: 10.1371/journal.ppat.1005547. eCollection 2016 Apr.
58. Ryu, J. R., C. J. Hong, et al. "Comparison of TGF-beta1 and NO production by mesenchymal stem cells isolated from murine lung and adipose tissues." Mol Brain. 2016 Apr 21;9(1):43. doi: 10.1186/s13041-016-0224-4.
59. Sadeghian-Nodoushan, F., R. Aflatoonian, et al. "Isolation and Differentiation of Adipose-Derived Stem Cells from Porcine Subcutaneous Adipose Tissues." Mol Reprod Dev. 2016 Apr;83(4):312-23. doi: 10.1002/mrd.22620. Epub 2016 Feb 22.
60. Sahu, S. K., A. Fritz, et al. "Manifestation of Huntington's disease pathology in human induced pluripotent stem cell-derived neurons." Biochim Biophys Acta. 2016 Apr 11. pii: S1874-9399(16)30065-7. doi: 10.1016/j.bbagrm.2016.04.005.
61. Suchanek, J., T. Suchankova Kleplova, et al. "UCP2 regulates energy metabolism and differentiation potential of human pluripotent stem cells." Folia Biol (Praha). 2016;62(1):1-14.
62. Surrati, A., R. Linforth, et al. "Non-destructive characterisation of mesenchymal stem cell differentiation using LC-MS-based metabolite footprinting." Analyst. 2016 Apr 22.
63. Vagaska, B., S. E. New, et al. "Third generation poly(hydroxyacid) composite scaffolds for tissue engineering." Sci Rep. 2016 Apr 15;6:24251. doi: 10.1038/srep24251.
64. Vasko, T., J. Frobel, et al. Control of adult neurogenesis by programmed cell death in the mammalian brain, J Hematol Oncol. 2016 Apr 21;9(1):43. doi: 10.1186/s13045-016-0273-2.
65. Vega, S. L., M. Kwon, et al. "Single Cell Imaging to Probe Mesenchymal Stem Cell N-Cadherin Mediated Signaling within Hydrogels." Ann Biomed Eng. 2016 Apr 22.
66. Vojdani, Z., A. Babaei, et al. "Laminin matrix promotes hepatogenic terminal differentiation of human bone marrow mesenchymal stem cells." Iran J Basic Med Sci. 2016 Jan;19(1):89-96.
67. Wikipedia. The free encyclopedia. http://en.wikipedia.org. 2015.
68. Yamazaki, A., M. Yashiro, et al. "Isoproterenol directs hair follicle-associated pluripotent (HAP) stem cells to differentiate in vitro to cardiac muscle cells which can be induced to form beating heart-muscle tissue sheets." Cell Cycle. 2016 Mar 3;15(5):760-5. doi: 10.1080/15384101.2016.1146837.
69. Yanagimachi, M., T. Ohya, et al. "The trans-spliced long noncoding RNA tsRMST impedes human ESC differentiation through WNT5A-mediated inhibition of the epithelial-to-mesenchymal transition." J Clin Immunol. 2016 Apr 18.