

Stem Cell Markers Research Literatures

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

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Key words: stem cell; life; research; literature

Introduction

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

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

Alexander, J. W. and M. Kroposki "Using a management perspective to define and measure changes in nursing technology." *J Adv Nurs*. 2001 Sep;35(5):776-83.

AIMS: The aims of this paper are to discuss the uses of the concept of technology from the medical science and the management perspectives; to propose a clear definition of nursing technology; and to present a study applying the use of the concept of nursing technology on nursing units. **BACKGROUND:** Nurse managers must use management terms correctly and the term technology may be misleading for some. A review of the nursing literature shows varied uses of the concept of technology. Thus a discussion of the dimensions, attributes, consequences, and definitions of nursing technology from the management perspective are

given. **DESIGN:** A longitudinal study to measure the dimensions of nursing technology on nursing units 10 years apart. **RESULTS:** The findings suggest that the dimensions of nursing technology change over time and support the need for nurse managers to periodically assess nursing technology before making management changes at the level of the nursing unit. **CONCLUSIONS:** This study helps health care providers understand the unique role of nurses as healthcare professionals by identifying and measuring nursing technology on the nursing unit.

Aligholi, H., S. M. Rezayat, et al. "Preparing neural stem/progenitor cells in PuraMatrix hydrogel for transplantation after brain injury in rats: A comparative methodological study." *Brain Res*. 2016 Mar 30. pii: S0006-8993(16)30182-2. doi: [10.1016/j.brainres.2016.03.043](https://doi.org/10.1016/j.brainres.2016.03.043).

Cultivation of neural stem/progenitor cells (NS/PCs) in PuraMatrix (PM) hydrogel is an option for stem cell transplantation. The efficacy of a novel method for placing adult rat NS/PCs in PM (injection method) was compared to encapsulation and surface plating approaches. In addition, the efficacy of injection method for transplantation of autologous NS/PCs was studied in a rat model of brain injury. NS/PCs were obtained from the subventricular zone (SVZ) and cultivated without (control) or with scaffold (three-dimensional cultures; 3D). The effect of different approaches on survival, proliferation, and differentiation of NS/PCs were investigated. In vivo study, brain injury was induced 45 days after NS/PCs

were harvested from the SVZ and phosphate buffered saline, PM, NS/PCs, or PM + NS/PCs were injected into the brain lesion. There was an increase in cell viability and proliferation after injection and surface plating of NS/PCs compared to encapsulation and neural differentiation markers were expressed seven days after culturing the cells. Using injection method, transplantation of NS/PCs cultured in PM resulted in significant reduction of lesion volume, improvement of neurological deficits, and enhancement of surviving cells. In addition, the transplanted cells could differentiate in to neurons, astrocytes, or oligodendrocytes. Our results indicate that injection and surface plating methods enhanced cell survival and proliferation of NS/PCs and suggest injection method as a promising approach for transplantation of NS/PCs in brain injury.

Ambele, M. A., C. Dessels, et al. "Genome-wide analysis of gene expression during adipogenesis in human adipose-derived stromal cells reveals novel patterns of gene expression during adipocyte differentiation." *Stem Cell Res.* 2016 Apr 19;16(3):725-734. doi: 10.1016/j.scr.2016.04.011.

We have undertaken an in-depth transcriptome analysis of adipogenesis in human adipose-derived stromal cells (ASCs) induced to differentiate into adipocytes in vitro. Gene expression was assessed on days 1, 7, 14 and 21 post-induction and genes differentially expressed numbered 128, 218, 253 and 240 respectively. Up-regulated genes were associated with blood vessel development, leukocyte migration, as well as tumor growth, invasion and metastasis. They also shared common pathways with certain obesity-related pathophysiological conditions. Down-regulated genes were enriched for immune response processes. KLF15, LMO3, FOXO1 and ZBTB16 transcription factors were up-regulated throughout the differentiation process. CEBPA, PPARG, ZNF117, MLXIPL, MMP3 and RORB were up-regulated only on days 14 and 21, which coincide with the maturation of adipocytes and could possibly serve as candidates for controlling fat accumulation and the size of mature adipocytes. In summary, we have identified genes that were up-regulated only on days 1 and 7 or days 14 and 21 that could serve as potential early and late-stage differentiation markers.

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.

Boozarpour, S., M. M. Matin, et al. "Glial cell derived neurotrophic factor induces spermatogonial stem cell marker genes in chicken mesenchymal stem cells." *Tissue Cell.* 2016 Mar 15. pii: S0040-8166(15)30005-7. doi: 10.1016/j.tice.2016.03.003.

Mesenchymal stem cells (MSCs) are known with the potential of multi-lineage differentiation. Advances in differentiation technology have also resulted in the conversion of MSCs to other kinds of stem cells. MSCs are considered as a suitable source of cells for biotechnology purposes because they are abundant, easily accessible and well characterized cells. Nowadays small molecules are introduced as novel and efficient factors to differentiate stem cells. In this work, we examined the potential of glial cell derived neurotrophic factor (GDNF) for differentiating chicken MSCs toward spermatogonial stem cells. MSCs were isolated and characterized from chicken and cultured under treatment with all-trans retinoic acid (RA) or glial cell derived neurotrophic factor. Expression analysis of specific genes after 7days of RA treatment, as examined by RT-PCR, proved positive for some germ cell markers such as CVH, STRA8, PLZF and some genes involved in spermatogonial stem cell maintenance like BCL6b and c-KIT. On the other hand, GDNF could additionally induce expression of POU5F1, and NANOG as well as other genes which were induced

after RA treatment. These data illustrated that GDNF is relatively more effective in diverting chicken MSCs towards Spermatogonial stem cell -like cells in chickens and suggests GDNF as a new agent to obtain transgenic poultry, nevertheless, exploitability of these cells should be verified by more experiments.

Charvet, H. J., H. Orbay, et al. "In Vitro Effects of Adipose-Derived Stem Cells on Breast Cancer Cells Harvested From the Same Patient." Ann Plast Surg. 2016 May;76 Suppl 3:S241-5. doi: [10.1097/SAP.0000000000000802](https://doi.org/10.1097/SAP.0000000000000802).

INTRODUCTION: Fat grafting for breast cancer (BrCa) reconstruction and breast augmentation has become increasingly more popular. A major area of debate and controversy is the effect of adipose-derived stem cells (ASCs) on remnant or undetected BrCa cells. We investigate the in vitro response of BrCa to ASCs in a coculture model with regards to cell migration. **METHODS:** The study was approved by the institutional review board. BrCa and adipose tissue specimens either from subcutaneous breast tissue or abdominal lipoaspirate were obtained from the same patient. BrCa cells and ASCs were harvested with either explant culture and/or enzymatic digestion. Tissues were grown in cell culture flasks until adequate cell libraries were established. Adipose-derived stem cells from adipose specimens were characterized with flow cytometry. Immunofluorescence (IF) staining of the initial cell population harvested from the BrCa specimens confirmed the presence of CD24, an epithelial marker of BrCa. A homogenous CD 24+/CD 90- BrCa cell population was obtained with flowcytometric cell sorting. The in vitro migration of BrCa cells was examined in coculture with and without ASCs. **RESULTS:** Adipose-derived stem cells harvested from the adipose specimens were positive for mesenchymal stem cell markers CD 105, CD 90, CD 73, and CD 44 and negative for lymphocyte cell marker CD 34 and leukocyte marker CD 45. The percentage of the CD 24+/CD 90- BrCa cells in the initial cell population harvested from BrCa specimens was 0.61%. The BrCa cells morphologically had large nuclei and small cytoplasm in clusters under the light microscope, suggesting a cancer cell phenotype. CD 24 expression on the surface of BrCa cells was confirmed with IF staining. The number of BrCa cells migrated in ASCs coculture was approximately 10 times higher than the number of BrCa cells migrated in BrCa cell only cultures. **CONCLUSIONS:** Adipose-derived stem cells significantly increase the migration capacity of BrCa cells in vitro in cocultures. This should be taken into consideration when performing fat grafting to the breast especially in

patients with a history of BrCa or strong family history of BrCa.

Condie, B. G. "The untapped potential of the GENSAT mice a valuable resource for developmental biology." Genesis. 2016 Apr 13. doi: [10.1002/dvg.22942](https://doi.org/10.1002/dvg.22942).

GENSAT (Gene Expression Nervous System Atlas) transgenic mice express EGFP, tdTomato or Cre recombinase in a wide range of cell types. The mice and the BAC transgenes are available from repositories (MMRRC or CHORI), thereby making these resources readily available to the research community. This resource of 1386 transgenic lines was developed and validated for neuroscience research. However, GENSAT mice have many potential applications in other contexts including studies of development outside of the CNS. The cell type specific expression of fluorescent proteins in these mice has been used to identify cells in living embryos, living embryo explants and in stem or progenitor cell populations in postnatal tissues. The large number of fluorescent protein driver lines generated by GENSAT greatly expands the range of cell type markers that can be used for live cell sorting. In addition, the GENSAT project has generated 278 new Cre driver lines. This review provides an overview of the GENSAT lines and information for identifying lines that may be useful for a particular application. I also provide a review of the few published cases in which GENSAT mice have been used for studies of embryonic development or analysis of stem/progenitor cells in non-neural tissues. This article is protected by copyright. All rights reserved.

Echizen, K., O. Hirose, et al. "Inflammation in gastric cancer: Interplay of the COX-2/prostaglandin E2 and Toll-like receptor/MyD88 pathways." Cancer Sci. 2016 Apr;107(4):391-7. doi: [10.1111/cas.12901](https://doi.org/10.1111/cas.12901). Epub 2016 Mar 18.

Cyclooxygenase-2 (COX-2) and its downstream product prostaglandin E2 (PGE2) play a key role in generation of the inflammatory microenvironment in tumor tissues. Gastric cancer is closely associated with *Helicobacter pylori* infection, which stimulates innate immune responses through Toll-like receptors (TLRs), inducing COX-2/PGE2 pathway through nuclear factor-kappaB activation. A pathway analysis of human gastric cancer shows that both the COX-2 pathway and Wnt/beta-catenin signaling are significantly activated in tubular-type gastric cancer, and basal levels of these pathways are also increased in other types of gastric cancer. Expression of interleukin-11, chemokine (C-X-C motif) ligand 1 (CXCL1), CXCL2, and CXCL5, which play tumor-promoting roles through a variety of

mechanisms, is induced in a COX-2/PGE2 pathway-dependent manner in both human and mouse gastric tumors. Moreover, the COX-2/PGE2 pathway plays an important role in the maintenance of stemness with expression of stem cell markers, including CD44, Prom1, and Sox9, which are induced in both gastritis and gastric tumors through a COX-2/PGE2 -dependent mechanism. In contrast, disruption of Myd88 results in suppression of the inflammatory microenvironment in gastric tumors even when the COX-2/PGE2 pathway is activated, indicating that the interplay of the COX-2/PGE2 and TLR/MyD88 pathways is needed for inflammatory response in tumor tissues. Furthermore, TLR2/MyD88 signaling plays a role in maintenance of stemness in normal stem cells as well as gastric tumor cells. Accordingly, these results suggest that targeting the COX-2/PGE2 pathway together with TLR/MyD88 signaling, which would suppress the inflammatory microenvironment and maintenance of stemness, could be an effective preventive or therapeutic strategy for gastric cancer.

Eitoku, M., N. Suganuma, et al. "Comparison of two types of non-adherent plate for neuronal differentiation of mouse embryonic stem cells." Cytotechnology. 2016 Apr 8.

In vitro differentiation systems of mouse embryonic stem cells (ESCs) are widely used as tools for studies of cell differentiation, organogenesis, and regenerative medicine. We have studied the regulation of neuron-specific imprinting genes, Ube3a and its antisense transcripts (Ube3a ATS), using in vitro neuronal differentiation of F1 hybrid ESCs. Each different non-adherent plate used for embryoid body (EB) formation during differentiation is associated with different costs; notably, plates coated with 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer are more expensive than untreated polystyrene plates. Here, we assessed whether the polymer-coated plates gave better results than the untreated plates. The first stage of differentiation was performed in the MPC polymer-coated or untreated plates. The formed EBs were then passaged onto laminin-coated plates for further differentiation into neurons. Neither the neuron-specific imprinting status of Ube3a nor the expression levels of the neuron-specific markers Ube3a ATS and Mtap2 differed between neurons prepared on untreated plates and those prepared on MPC polymer-coated plates. These results suggest that the two non-adherent plates displayed almost the same characteristics for inducing neuronal differentiation of mouse ESCs and EB formation. Our study proved that untreated polystyrene plates are a cost-effective choice for EB formation in in vitro differentiation systems of mouse ESCs.

Fliefel, R., C. Popov, et al. "Mesenchymal stem cell proliferation and mineralization but not osteogenic differentiation are strongly affected by extracellular pH." J Craniomaxillofac Surg. 2016 Mar 19. pii: S1010-5182(16)00081-0. doi: 10.1016/j.jcms.2016.03.003.

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.

Grau, J. J., R. Mesia, et al. "Enrichment of Cells with Cancer Stem Cell-Like Markers in Relapses of Chemoresistant Patients with Locally Advanced Head and Neck Squamous Cell Carcinoma." Oncology. 2016 Apr 15.

BACKGROUND: Patients with head and neck squamous cell carcinoma (HNSCC) present different responses to chemotherapy and radiotherapy. One explanation may be the differences in the individual rates of stem cell-like cells. METHODS: We included patients with HNSCC and tumor progression or relapse. Tumor samples were obtained before and after primary chemotherapy, and immunohistochemical analyses were performed for CD44, HLA class I (HLA-I), pancytokeratin, and phosphorylated epidermal growth factor receptor (p-EGFR). Differences in expression between the first and second specimens were assessed. RESULTS:

Expression between the first and second specimens varied as follows: CD44 increased by 14.67% (95% confidence interval, CI: 6.94 to 22.40; $p < 0.01$); HLA-I decreased by 16.72% (95% CI: -23.87 to -9.47; $p < 0.01$); pancytokeratin decreased by 24.91% (95% CI: -32.8 to -17.7; $p < 0.01$), and p-EFGR expression decreased by 12.30% (95% CI: -20.61 to -3.98; $p < 0.005$). CONCLUSIONS: Among patients with HNSCC, there is an enrichment of cells with stem-like markers in relapsed tumors when compared with the primary tumor. This finding should be considered when developing treatment strategies.

Greenwood-Goodwin, M., J. Yang, et al. "A novel lineage restricted, pericyte-like cell line isolated from human embryonic stem cells." *Sci Rep.* 2016 Apr 25;6:24403. doi: 10.1038/srep24403.

Pericytes (PCs) are endothelium-associated cells that play an important role in normal vascular function and maintenance. We developed a method comparable to GMP quality protocols for deriving self-renewing perivascular progenitors from the human embryonic stem cell (hESC), line ESI-017. We identified a highly scalable, perivascular progenitor cell line that we termed PC-A, which expressed surface markers common to mesenchymal stromal cells. PC-A cells were not osteogenic or adipogenic under standard differentiation conditions and showed minimal angiogenic support function in vitro. PC-A cells were capable of further differentiation to perivascular progenitors with limited differentiation capacity, having osteogenic potential (PC-O) or angiogenic support function (PC-M), while lacking adipogenic potential. Importantly, PC-M cells expressed surface markers associated with pericytes. Moreover, PC-M cells had pericyte-like functionality being capable of co-localizing with human umbilical vein endothelial cells (HUVECs) and enhancing tube stability up to 6 days in vitro. We have thus identified a self-renewing perivascular progenitor cell line that lacks osteogenic, adipogenic and angiogenic potential but is capable of differentiation toward progenitor cell lines with either osteogenic potential or pericyte-like angiogenic function. The hESC-derived perivascular progenitors described here have potential applications in vascular research, drug development and cell therapy.

Guneta, V., N. S. Tan, et al. "Comparative Study of Adipose-Derived Stem Cells From Abdomen and Breast." *Ann Plast Surg.* 2016 May;76(5):569-75. doi: 10.1097/SAP.0000000000000797.

BACKGROUND: Abdominal tissue enriched with adipose-derived stem cells (ASCs) is often used in cell-assisted lipotransfer procedures for breast reconstruction. However, as the tissue

microenvironment and stem cell niche play important roles in defining the characteristics of the resident cells, it is hypothesized that the stem cell population present in the donor abdominal tissue has dissimilar properties as compared with the cells in the recipient breast tissue, which may ultimately affect the long-term success of the graft. METHODS: Adipose-derived stem cells were isolated from breast and abdominal fat tissues and characterized for mesenchymal-specific cell surface markers, and their population doubling, colony-forming capabilities, and proliferative properties were compared. The multilineage potential of both cell populations was also investigated. RESULTS: Adipose-derived stem cells from both tissue sites were found to possess similar marker expression and multilineage differentiation potential. However, breast fat-derived ASCs were observed to have a higher self-renewal capability and an unstable population doubling as compared with abdominal fat-derived ASCs. Gene expression studies revealed that the breast fat-derived ASCs were predisposed to the osteogenic lineage and the abdominal fat-derived ASCs to the adipogenic lineage. CONCLUSIONS: Cells derived from both fat tissues possess different characteristics in terms of their growth kinetics and predisposition to the osteolinesages and adipolinesages. In particular, ASCs from the abdominal tissue appear to contribute to adipose tissue turnover, whereas ASCs from breast tissue, if used for cell-assisted fat grafting, may potentially be responsible for complications in fat grafting, such as oil cysts, calcifications, fat necrosis, and tumors.

Haahr, M. K., C. H. Jensen, et al. "Safety and Potential Effect of a Single Intracavernous Injection of Autologous Adipose-Derived Regenerative Cells in Patients with Erectile Dysfunction Following Radical Prostatectomy: An Open-Label Phase I Clinical Trial." *EBioMedicine.* 2016 Jan 19;5:204-10. doi: 10.1016/j.ebiom.2016.01.024. eCollection 2016 Mar.

BACKGROUND: Prostate cancer is the most common cancer in men, and radical prostatectomy (RP) often results in erectile dysfunction (ED) and a substantially reduced quality of life. The efficacy of current interventions, principal treatment with PDE-5 inhibitors, is not satisfactory and this condition presents an unmet medical need. Preclinical studies using adipose-derived stem cells to treat ED have shown promising results. Herein, we report the results of a human phase 1 trial with autologous adipose-derived regenerative cells (ADRCs) freshly isolated after a liposuction. METHODS: Seventeen men suffering from post RP ED, with no recovery using conventional therapy, were enrolled in a prospective phase 1 open-label and single-arm study. All subjects

had RP performed 5-18 months before enrolment, and were followed for 6 months after intracavernosal transplantation. ADRCs were analyzed for the presence of stem cell surface markers, viability and ability to differentiate. Primary endpoint was the safety and tolerance of the cell therapy while the secondary outcome was improvement of erectile function. Any adverse events were reported and erectile function was assessed by IIEF-5 scores. The study is registered with ClinicalTrials.gov, NCT02240823. FINDINGS: Intracavernous injection of ADRCs was well-tolerated and only minor events related to the liposuction and cell injections were reported at the one-month evaluation, but none at later time points. Overall during the study period, 8 of 17 men recovered their erectile function and were able to accomplish sexual intercourse. Post-hoc stratification according to urinary continence status was performed. Accordingly, for continent men (median IIEF inclusion = 7 (95% CI 5-12), 8 out of 11 men recovered erectile function (IIEF6months = 17 (6-23)), corresponding to a mean difference of 0.57 (0.38-0.85; $p = 0.0069$), versus inclusion. In contrast, incontinent men did not regain erectile function (median IIEF1/3/6 months = 5 (95% CI 5-6); mean difference 1 (95% CI 0.85-1.18), $p > 0.9999$). INTERPRETATION: In this phase I trial a single intracavernosal injection of freshly isolated autologous ADRCs was a safe procedure. A potential efficacy is suggested by a significant improvement in IIEF-5 scores and erectile function. We suggest that ADRCs represent a promising interventional therapy of ED following prostatectomy. FUNDING: Danish Medical Research Council, Odense University Hospital and the Danish Cancer Society.

Heidari, F., A. Yari, et al. "Bulge Hair Follicle Stem Cells Accelerate Cutaneous Wound Healing in Rats." *Wounds*. 2016 Apr;28(4):132-41.

OBJECTIVE: Skin wound healing is a serious clinical problem especially after surgery and severe injury of the skin. Cell therapy is an innovative technique that can be applied to wound healing. One appropriate source of stem cells for therapeutic use is stem cells from the adult bulge of hair follicles. This study examined the effects of adult bulge hair follicle stem cells (HFSC) in wound healing. MATERIALS AND METHODS: Hair follicle stem cells were obtained from rat vibrissa and labeled with DiI (Invitrogen, Carlsbad, CA), then special markers were detected using flow cytometry. A full-thickness excisional wound model was created and DiI-labeled HFSC were injected around the wound bed. Wound healing was recorded with digital photographs. Animals were sacrificed at 3, 7, or 14 days after surgery, and were used for the following histological analyses. RESULTS: Flow cytometry analysis showed

that HFSC were CD34 positive and nestin positive, but K15 negative. Morphological analysis of HFSC-treated wounds exhibited accelerated wound closure. Histological analysis of hematoxylin and eosin stained and Masson's trichrome-stained photomicrographs showed significantly more re-epithelialization and dermal structural regeneration in HF-SC-treated wounds than in the control group. Immunohistochemical analysis of CD31 protein-positive cells showed angiogenesis was also more significant in HFSC-treated wounds than in the control group. CONCLUSION: Hair follicle stem cells accelerate skin wound healing. Isolating HFSC from a small skin biopsy could repair less-extensive full-thickness skin wounds by autologous stem cells and overcome major challenges regarding the use of stem cells in clinical application, while avoiding immune rejection and ethical concerns.

Iskender, B., K. Izgi, et al. "Novel anti-cancer agent myrtucommulone-A and thymoquinone abrogate epithelial-mesenchymal transition in cancer cells mainly through the inhibition of PI3K/AKT signalling axis." *Mol Cell Biochem*. 2016 Mar 31.

Epithelial-mesenchymal transition (EMT) plays a prominent role in cancer progression and metastasis. Inhibition of EMT-associated regulators may hold a huge promise for cancer therapy. Although TGF-beta signalling has a pivotal role in the induction of EMT, alterations during the EMT process are usually initiated and controlled by the cross-talk of multiple signalling pathways, and in most cases this is context-dependent. In the present study, we aimed at identifying the molecular mechanisms during the inhibition of EMT by novel anti-cancer agent myrtucommulone-A (MC-A) and thymoquinone (TQ). We used epithelial cancer cells to study the effects of MC-A and TQ on EMT. We first showed the functional inhibition of EMT by MC-A or TQ using migration assays and confirmed the EMT inhibition by analysing the expression of EMT markers with RT-PCR, immunocytochemistry and Western blotting. We evaluated the changes in intracellular dynamics by Western blotting and compared the effects of MC-A and TQ with the effects of selective inhibitors of PI3K (LY294002), ERK 1/2 (U0126) and TGF-betaR (SB431542). We demonstrate that both MC-A and TQ treatment negatively regulate the EMT process through modulation of signalling pathways in cancer cells. MC-A and TQ treatment inhibited phosphorylation of multiple proteins in a context-dependent manner. Novel anti-cancer agent MC-A and TQ regulate distinct signalling pathways for the repression of EMT which emphasises the significance of combinational therapies in cancer treatment. MC-A and TQ could be considered as candidate molecules

for combinational therapies with their ability to interfere signalling pathways regulating cancer cell behaviour.

Kroon, J., S. Kooijman, et al. "Improving Taxane-Based Chemotherapy in Castration-Resistant Prostate Cancer." *Trends Pharmacol Sci.* 2016 Apr 7. pii: S0165-6147(16)00057-2. doi: [10.1016/j.tips.2016.03.003](https://doi.org/10.1016/j.tips.2016.03.003).

Currently, the clinical utility of taxane-based drug formulations in castration-resistant prostate cancer (CRPC) is severely limited by acquired chemotherapy resistance, dose-limiting toxicities, and nonresponders. Therefore, approaches to improve taxane-based chemotherapy are desperately required. In this review, we highlight the strategies that aim to overcome these limitations, such as bypassing therapy resistance, targeted drug delivery, and adequate prediction of therapy response. The involvement of the apoptotic pathway, ABC transporters, the glucocorticoid receptor (GR) axis, androgen receptor (AR) splicing, epithelial plasticity, and cancer stem cells in mediating taxane-resistance are outlined. Furthermore, passive and active targeted nanomedicinal drug delivery strategies and the use of circulating tumor cells in predicting docetaxel responses are discussed. Finally, recent advances towards clinical translation of these approaches in CRPC are reviewed.

Leppa, C. J. "Measuring nursing work in long-term care. The reliability and validity of the Leatt Measure of Nursing Technology." *J Gerontol Nurs.* 1999 Oct;25(10):40-5.

A projected 400% increase in the number of people age 85 and older by the year 2010, with one fourth of them needing nursing home care, forces attention on long-term care. This study establishes the validity and reliability of the Leatt Measure of Nursing Technology (LMNT) as a measure of the nature of nursing work in long-term care settings. The LMNT subscales measure the amount of uncertainty, instability, and variability of work which includes, but is not limited to, the technical equipment used. The LMNT was administered to licensed nursing staff in nine long-term care facilities in the Seattle area to evaluate its use in this environment. The nursing homes represented both for-profit and not-for-profit, and large (more than 250 beds) and small (70 beds) facilities. A total of 113 usable questionnaires were returned (45% response rate). Cronbach's alpha for subscales were .71 for Uncertainty, .66 for Instability, and .56 for Variability, with .77 for the total scale. Construct validity was evaluated by factor analysis, which confirmed the original factor structure. Content validity was evaluated using focus group discussions

with key informants at each facility. A comparative analysis was used to determine major and minor themes in each of the instrument subscale topic areas. Qualitative analysis, combined with reliability and item level analyses, resulted in suggested minor changes in the instrument to make it more usable in long-term care settings. While some revisions are suggested, a concerted effort must be made to preserve the ability to compare findings with those obtained using the LMNT in acute care settings by retaining the general structures and factors of the measure.

Mansson-Broberg, A., S. Rodin, et al. "Wnt/beta-Catenin Stimulation and Laminins Support Cardiovascular Cell Progenitor Expansion from Human Fetal Cardiac Mesenchymal Stromal Cells." *Stem Cell Reports.* 2016 Apr 12;6(4):607-17. doi: [10.1016/j.stemcr.2016.02.014](https://doi.org/10.1016/j.stemcr.2016.02.014). Epub 2016 Mar 24.

The intrinsic regenerative capacity of human fetal cardiac mesenchymal stromal cells (MSCs) has not been fully characterized. Here we demonstrate that we can expand cells with characteristics of cardiovascular progenitor cells from the MSC population of human fetal hearts. Cells cultured on cardiac muscle laminin (LN)-based substrata in combination with stimulation of the canonical Wnt/beta-catenin pathway showed increased gene expression of ISL1, OCT4, KDR, and NKX2.5. The majority of cells stained positive for PDGFR-alpha, ISL1, and NKX2.5, and subpopulations also expressed the progenitor markers TBX18, KDR, c-KIT, and SSEA-1. Upon culture of the cardiac MSCs in differentiation media and on relevant LNs, portions of the cells differentiated into spontaneously beating cardiomyocytes, and endothelial and smooth muscle-like cells. Our protocol for large-scale culture of human fetal cardiac MSCs enables future exploration of the regenerative functions of these cells in the context of myocardial injury in vitro and in vivo.

Mariotto, A., O. Pavlova, et al. "HOPX: The Unusual Homeodomain-Containing Protein." *J Invest Dermatol.* 2016 May;136(5):905-11. doi: [10.1016/j.jid.2016.01.032](https://doi.org/10.1016/j.jid.2016.01.032). Epub 2016 Mar 23.

The homeodomain-only protein homeobox (HOPX) is the smallest known member of the homeodomain-containing protein family, atypically unable to bind DNA. HOPX is widely expressed in diverse tissues, where it is critically involved in the regulation of proliferation and differentiation. In human skin, HOPX controls epidermal formation through the regulation of late differentiation markers, and HOPX expression correlates with the level of differentiation in cutaneous pathologies. In mouse skin, Hopx was additionally identified as a lineage

tracing marker of quiescent hair follicle stem cells. This review discusses current knowledge of HOPX structure and function in normal and pathological conditions.

Narayan, V., O. Gunnarsson, et al. "Risk-Stratified Initial Salvage Therapy for Relapsed or Refractory Metastatic Germ Cell Tumors." *Clin Genitourin Cancer*. 2016 Mar 24. pii: S1558-7673(16)30069-6. doi: [10.1016/j.clgc.2016.03.015](https://doi.org/10.1016/j.clgc.2016.03.015).

BACKGROUND: Salvage treatment with either conventional-dose chemotherapy (CDCT) or high-dose chemotherapy with autologous stem cell transplantation (HDCT) offers curative potential for patients with relapsed or refractory germ cell tumor (GCT). However, the optimal initial salvage strategy remains controversial, and the criteria for appropriate patient selection are not clear. **METHODS:** This was a retrospective analysis of the clinical outcomes for GCT patients receiving initial salvage therapy using a risk-stratified treatment approach. In general, patients with favorable-risk disease received CDCT with 4 cycles of paclitaxel, ifosfamide, and cisplatin, while patients with unfavorable-risk disease received HDCT per institutional protocol. The prognostic validity of the International Germ Cell Cancer Collaborative Group (IGCCCG) and the International Prognostic Factors Study Group (IPFSG) risk groups were evaluated in this context. **RESULTS:** Thirty-seven patients received initial salvage therapy. Twenty-four patients (65%) achieved a favorable response (including complete response to chemotherapy alone, complete response after post-chemotherapy surgical resection, or partial response with negative tumor markers). The favorable response rates for the CDCT and HDCT treatment groups were 69% and 62%, respectively. After a median follow-up of 31 months, the median survival for CDCT-treated patients has not been reached, and the median survival for the HDCT-treated group was 24 months. Both the International Germ Cell Cancer Collaborative Group and the International Prognostic Factors Study Group risk groups were significantly associated with progression-free survival (log-rank $P = .009$ and $P = .039$, respectively). **CONCLUSIONS:** Patients with favorable prognostic features may achieve durable remissions without requiring high-dose salvage chemotherapy. However, the criteria for optimal patient selection remain unclear, and these findings further support the need for a definitive randomized trial.

Pham, K., D. Delitto, et al. "Isolation of Pancreatic Cancer Cells from a Patient-Derived Xenograft Model Allows for Practical Expansion and Preserved Heterogeneity in Culture." *Am J Pathol*. 2016 Apr 18.

pii: S0002-9440(16)30022-0. doi: [10.1016/j.ajpath.2016.02.009](https://doi.org/10.1016/j.ajpath.2016.02.009).

Commercially available, highly passaged pancreatic cancer (PC) cell lines are of limited translational value. Attempts to overcome this limitation have primarily consisted of cancer cell isolation and culture directly from human PC specimens. However, these techniques are associated with exceedingly low success rates. Here, we demonstrate a highly reproducible culture of primary PC cell lines (PPCLs) from patient-derived xenografts, which preserve, in part, the intratumoral heterogeneity known to exist in PC. PPCL expansion from patient-derived xenografts was successful in 100% of attempts (5 of 5). Phenotypic analysis was evaluated with flow cytometry, immunofluorescence microscopy, and short tandem repeat profiling. Importantly, tumorigenicity of PPCLs expanded from patient-derived xenografts was assessed by subcutaneous injection into nonobese diabetic.Cg-PrkdcscidIl2rgtm1Wjl/SzJ mice. Morphologically, subcutaneous injection of all PPCLs into mice yielded tumors with similar characteristics to the parent xenograft. PPCLs uniformly expressed class I human leukocyte antigen, epithelial cell adhesion molecule, and cytokeratin-19. Heterogeneity within each PPCL persisted in culture for the frequency of cells expressing the cancer stem cell markers CD44, CD133, and c-Met and the immunologic markers human leukocyte antigen class II and programmed death ligand 1. This work therefore presents a reliable method for the rapid expansion of primary human PC cells and, thereby, provides a platform for translational investigation and, importantly, potential personalized therapeutic approaches.

Pinto, F., N. Pertega-Gomes, et al. "Brachyury as a potential modulator of androgen receptor activity and a key player in therapy resistance in prostate cancer." *Oncotarget*. 2016 Mar 31. doi: [10.18632/oncotarget.8499](https://doi.org/10.18632/oncotarget.8499).

Prostate cancer (PCa) is the most commonly diagnosed neoplasm and the second leading cause of cancer-related deaths in men. Acquisition of resistance to conventional therapy is a major problem for PCa patient management. Several mechanisms have been described to promote therapy resistance in PCa, such as androgen receptor (AR) activation, epithelial-to-mesenchymal transition (EMT), acquisition of stem cell properties and neuroendocrine transdifferentiation (NETd). Recently, we identified Brachyury as a new biomarker of PCa aggressiveness and poor prognosis. In the present study we aimed to assess the role of Brachyury in PCa therapy resistance. We showed that Brachyury overexpression in prostate cancer cells lines increased resistance to docetaxel and cabazitaxel

drugs, whereas Brachyury abrogation induced decrease in therapy resistance. Through ChiP-qPCR assays we further demonstrated that Brachyury is a direct regulator of AR expression as well as of the biomarker AMACR and the mesenchymal markers Snail and Fibronectin. Furthermore, in vitro Brachyury was also able to increase EMT and stem properties. By in silico analysis, clinically human Brachyury-positive PCa samples were associated with biomarkers of PCa aggressiveness and therapy resistance, including PTEN loss, and expression of NETD markers, ERG and Bcl-2. Taken together, our results indicate that Brachyury contributes to tumor chemotherapy resistance, constituting an attractive target for advanced PCa patients.

Sadeghian-Nodoushan, F., R. Aflatoonian, et al. "Pluripotency and differentiation of cells from human testicular sperm extraction: An investigation of cell stemness." *Mol Reprod Dev.* 2016 Apr;83(4):312-23. doi: 10.1002/mrd.22620. Epub 2016 Feb 22.

Human male germ-line stem cells (hmGSCs) and human testis-derived embryonic stem cell-like (htESC-like) cells are claimed to be in vitro pluripotent counterparts of spermatogonial stem cells (SSCs), but the origin and pluripotency of human testis-derived cell cultures are still under debate. The aim of this study was to generate putative pluripotent stem cells in vitro from human testicular sperm-extracted (TESE) samples of infertile men, and to assess their pluripotency and capacity to differentiate. TESE samples were minced, enzymatically disaggregated and dispersed into single-cell or cluster suspensions, and then cultured. Initially, cell clusters resembled those described for hmGSCs and htESC-like cells, and were positive for markers such as OCT4/POU5F1, NANOG, and TRA-2-54. Prolonged propagation of cell clusters expressing pluripotency markers did not thrive; instead, the cells that emerged possessed characteristics of mesenchymal stromal cells (MSCs) such as STRO-1, CD105/EGLN1, CD13/ANPEP, SOX9, vimentin, and fibronectin. KIT, SOX2, and CD44 were not expressed by these MSCs. The multipotential differentiation capacity of these cells was confirmed using Oil Red-O and Alizarin Red staining after induction with specific culture conditions. It is therefore concluded that pluripotent stem cells could not be derived using the conditions previously reported to be successful for TESE samples. *Mol. Reprod. Dev.* 83: 312-323, 2016. (c) 2016 Wiley Periodicals, Inc.

Sahu, S. K., A. Fritz, et al. "TOX3 plays a role in neuronal progenitor proliferation." *Biochim Biophys Acta.* 2016 Apr 11. pii: S1874-9399(16)30065-7. doi: 10.1016/j.bbagr.2016.04.005.

The human genomic locus for the transcription factor TOX3 has been implicated in susceptibility to restless legs syndrome and breast cancer in genome-wide association studies, but the physiological role of TOX3 remains largely unknown. We found Tox3 to be predominantly expressed in the developing mouse brain with a peak at embryonic day E14 where it co-localizes with the neural stem and progenitor markers Nestin and Sox2 in radial glia of the ventricular zone and intermediate progenitors of the subventricular zone. Tox3 is also expressed in neural progenitor cells obtained from the ganglionic eminence of E15 mice that express Nestin, and it specifically binds the Nestin promoter in chromatin immunoprecipitation assays. In line with this, over-expression of Tox3 increased Nestin promoter activity, which was cooperatively enhanced by treatment with the stem cell self-renewal promoting Notch ligand Jagged and repressed by pharmacological inhibition of Notch signaling. Knockdown of Tox3 in the subventricular zone of E12.5 mouse embryos by in utero electroporation of Tox3 shRNA revealed a reduced Nestin expression and decreased proliferation at E14 and a reduced migration to the cortical plate in E16 embryos in electroporated cells. Together, these results argue for a role of Tox3 in the development of the nervous system.

Sa-Ngiamsuntorn, K., A. Wongkajornsilp, et al. "A robust model of natural hepatitis C infection using hepatocyte-like cells derived from human induced pluripotent stem cells as a long-term host." *Virol J.* 2016 Apr 5;13(1):59. doi: 10.1186/s12985-016-0519-1.

BACKGROUND: Hepatitis C virus (HCV) could induce chronic liver diseases and hepatocellular carcinoma in human. The use of primary human hepatocyte as a viral host is restrained with the scarcity of tissue supply. A culture model restricted to HCV genotype 2a (JFH-1) has been established using Huh7-derived hepatocyte. Other genotypes including the wild-type virus could not propagate in Huh7, Huh7.5 and Huh7.5.1 cells. **METHODS:** Functional hepatocyte-like cells (HLCs) were developed from normal human iPS cells as a host for HCV infection. Mature HLCs were identified for selective hepatocyte markers, CYP450s, HCV associated receptors and HCV essential host factors. HLCs were either transfected with JFH-1 HCV RNA or infected with HCV particles derived from patient serum. The enhancing effect of alpha-tocopherol and the inhibitory effects of INF-alpha, ribavirin and sofosbuvir to HCV infection were studied. The HCV viral load and HCV RNA were assayed for the infection efficiency. **RESULTS:** The fully-developed

HLCs expressed phase I, II, and III drug-metabolizing enzymes, HCV associated receptors (claudin-1, occludin, CD81, ApoE, ApoB, LDL-R) and HCV essential host factors (miR-122 and SEC14L2) comparable to the primary human hepatocyte. SEC14L2, an alpha-tocopherol transfer protein, was expressed in HLCs, but not in Huh7 cell, had been implicated in effective HCVser infection. The HLCs permitted not only the replication of HCV RNA, but also the production of HCV particles (HCVcc) released to the culture media. HLCs drove higher propagation of HCVcc derived from JFH-1 than did the classical host Huh7 cells. HLCs infected with either JFH-1 or wild-type HCV expressed HCV core antigen, NS5A, NS5B, NS3 and HCV negative-stand RNA. HLCs allowed entire HCV life cycle derived from either JFH-1, HCVcc or wild-type HCV (genotype 1a, 1b, 3a, 3b, 6f and 6n). Further increasing the HCVser infection in HLCs was achieved by incubating cell with alpha-tocopherol. The supernatant from infected HLCs could infect both naive HLC and Huh7 cell. Treating infected HLC with INF-alpha and ribavirin decreased HCV RNA in both the cellular fraction and the culture medium. The HLCs reacted to HCVcc or wild-type HCV infection by upregulating TNF-alpha, IL-28B and IL-29. CONCLUSIONS: This robust cell culture model for serum-derived HCV using HLCs as host cells provides a remarkable system for investigating HCV life cycle, HCV-associated hepatocellular carcinoma development and the screening for new anti HCV drugs.

Sato, K., K. Suda, et al. "Clinical, Pathological, and Molecular Features of Lung Adenocarcinomas with AXL Expression." *PLoS One*. 2016 Apr 21;11(4):e0154186. doi: [10.1371/journal.pone.0154186](https://doi.org/10.1371/journal.pone.0154186). eCollection 2016.

The receptor tyrosine kinase AXL is a member of the Tyro3-Axl-Mer receptor tyrosine kinase subfamily. AXL affects several cellular functions, including growth and migration. AXL aberration is reportedly a marker for poor prognosis and treatment resistance in various cancers. In this study, we analyzed clinical, pathological, and molecular features of AXL expression in lung adenocarcinomas (LADs). We examined 161 LAD specimens from patients who underwent pulmonary resections. When AXL protein expression was quantified (0, 1+, 2+, 3+) according to immunohistochemical staining intensity, results were 0: 35%; 1+: 20%; 2+: 37%; and 3+: 7% for the 161 samples. AXL expression status did not correlate with clinical features, including smoking status and pathological stage. However, patients whose specimens showed strong AXL expression (3+) had

markedly poorer prognoses than other groups ($P = 0.0033$). Strong AXL expression was also significantly associated with downregulation of E-cadherin ($P = 0.025$) and CD44 ($P = 0.0010$). In addition, 9 of 12 specimens with strong AXL expression had driver gene mutations (6 with EGFR, 2 with KRAS, 1 with ALK). In conclusion, we found that strong AXL expression in surgically resected LADs was a predictor of poor prognosis. LADs with strong AXL expression were characterized by mesenchymal status, higher expression of stem-cell-like markers, and frequent driver gene mutations.

Seow, H. F., W. K. Yip, et al. "Advances in targeted and immunobased therapies for colorectal cancer in the genomic era." *Onco Targets Ther*. 2016 Mar 31;9:1899-920. doi: [10.2147/OTT.S95101](https://doi.org/10.2147/OTT.S95101). eCollection 2016.

Targeted therapies require information on specific defective signaling pathways or mutations. Advances in genomic technologies and cell biology have led to identification of new therapeutic targets associated with signal-transduction pathways. Survival times of patients with colorectal cancer (CRC) can be extended with combinations of conventional cytotoxic agents and targeted therapies. Targeting EGFR- and VEGFR-signaling systems has been the major focus for treatment of metastatic CRC. However, there are still limitations in their clinical application, and new and better drug combinations are needed. This review provides information on EGFR and VEGF inhibitors, new therapeutic agents in the pipeline targeting EGFR and VEGFR pathways, and those targeting other signal-transduction pathways, such as MET, IGF1R, MEK, PI3K, Wnt, Notch, Hedgehog, and death-receptor signaling pathways for treatment of metastatic CRC. Additionally, multitargeted approaches in combination therapies targeting negative-feedback loops, compensatory networks, and cross talk between pathways are highlighted. Then, immunobased strategies to enhance antitumor immunity using specific monoclonal antibodies, such as the immune-checkpoint inhibitors anti-CTLA4 and anti-PD1, as well as the challenges that need to be overcome for increased efficacy of targeted therapies, including drug resistance, predictive markers of response, tumor subtypes, and cancer stem cells, are covered. The review concludes with a brief insight into the applications of next-generation sequencing, expression profiling for tumor subtyping, and the exciting progress made in in silico predictive analysis in the development of a prescription strategy for cancer therapy.

Shah, S. M., N. Saini, et al. "Testicular cell-conditioned medium supports embryonic stem cell

differentiation toward germ lineage and to spermatocyte- and oocyte-like cells." *Theriogenology*. 2016 Mar 8. pii: S0093-691X(16)00097-2. doi: 10.1016/j.theriogenology.2016.02.025.

Testicular cells are believed to secrete various growth factors that activate signaling pathways finally leading to gametogenesis. In vitro gametogenesis is an obscure but paramountly important task primarily because of paucity of the precursor cells and first trimester gonadal tissues. To overcome these limitations for development of in vitro gametes, the present study was designed to induce differentiation of buffalo embryonic stem (ES) cells into germ lineage cells on stimulation by testicular cell-conditioned medium (TCM), on the basis of the assumption that ES cells have the intrinsic property to differentiate into any cell type and TCM would provide the necessary growth factors for differentiation toward germ cell lineage. For this purpose, buffalo ES cells were differentiated as embryoid bodies (EB) in floating cultures and as monolayer adherent cultures in different doses (10%, 20%, and 40%) of TCM for different culture intervals (4, 8, and 14 days), to identify the optimum dose-and-time period. We observed that 40% TCM dose induces highest expression of primordial germ cell-specific (DAZL, VASA, and PLZF), meiotic (SYCP3, MLH1, TNP1/2, and PRM2), spermatocyte-specific (BOULE and TEKT1), and oocyte-specific genes (GDF9 and ZP2/3) for a culture period of 14 days under both floating and adherent differentiation. Immunocytochemical analysis of EBs and adherent cultures revealed presence of primordial germ cell markers (c-KIT, DAZL, and VASA), meiotic markers (SYCP3, MLH1 and PROTAMINE1), spermatocyte markers (ACROSIN and HAPRIN), and oocyte markers (GDF9 and ZP4), indicating progression into post-meiotic gametogenesis. The detection of germ cell-specific proteins in Day 14 EBs like VASA, GDF9, and ZP4 by Western blotting further confirmed germ lineage differentiation. The significantly lower ($P < 0.05$) concentration of 5-methyl-2-deoxycytidine in optimally differentiated EBs is suggestive of the process of methylation erasure. Oocyte-like structures obtained in monolayer differentiation had a big nucleus and a surrounding ZP4 coat, the unique attributes of a female gamete. These oocyte-like structures, in extended cultures, showed embryonic development and progressed through two-cell, four-cell, eight-cell, morula, and blastocyst-like structures, indicative of their developmental competence. This, as per our knowledge, is first such study in higher mammals, especially farm animals, and assumes significance for its potential use in transgenic animal production, elite animal conservation and propagation, augmentation of reproductive performance in poor

breeding buffalo species, and as a model for understanding human germ cell formation.

Sharrow, A. C., B. Perkins, et al. "Characterization of aldehyde dehydrogenase 1 high ovarian cancer cells: Towards targeted stem cell therapy." *Gynecol Oncol*. 2016 Mar 24. pii: S0090-8258(16)30077-4. doi: 10.1016/j.ygyno.2016.03.022.

OBJECTIVE: The cancer stem cell (CSC) paradigm hypothesizes that successful clinical eradication of CSCs may lead to durable remission for patients with ovarian cancer. Despite mounting evidence in support of ovarian CSCs, their phenotype and clinical relevance remain unclear. We and others have found high aldehyde dehydrogenase 1 (ALDH^{high}) expression in a variety of normal and malignant stem cells, and sought to better characterize ALDH^{high} cells in ovarian cancer. **METHODS:** We compared ALDH^{high} to ALDH^{low} cells in two ovarian cancer models representing distinct subtypes: FNAR-C1 cells, derived from a spontaneous rat endometrioid carcinoma, and the human SKOV3 cell line (described as both serous and clear cell subtypes). We assessed these populations for stem cell features then analyzed expression by microarray and qPCR. **RESULTS:** ALDH^{high} cells displayed CSC properties, including: smaller size, quiescence, regenerating the phenotypic diversity of the cell lines in vitro, lack of contact inhibition, nonadherent growth, multi-drug resistance, and in vivo tumorigenicity. Microarray and qPCR analysis of the expression of markers reported by others to enrich for ovarian CSCs revealed that ALDH^{high} cells of both models showed downregulation of CD24, but inconsistent expression of CD44, KIT and CD133. However, the following druggable targets were consistently expressed in the ALDH^{high} cells from both models: mTOR signaling, her-2/neu, CD47 and FGF18/FGFR3. **CONCLUSIONS:** Based on functional characterization, ALDH^{high} ovarian cancer cells represent an ovarian CSC population. Differential gene expression identified druggable targets that have the potential for therapeutic efficacy against ovarian CSCs from multiple subtypes.

Sonomoto, K., K. Yamaoka, et al. "Spontaneous Differentiation of Human Mesenchymal Stem Cells on Poly-Lactic-Co-Glycolic Acid Nano-Fiber Scaffold." *PLoS One*. 2016 Apr 7;11(4):e0153231. doi: 10.1371/journal.pone.0153231. eCollection 2016.

INTRODUCTION: Mesenchymal stem cells (MSCs) have immunosuppressive activity and can differentiate into bone and cartilage; and thus seem ideal for treatment of rheumatoid arthritis (RA). Here, we investigated the osteogenesis and chondrogenesis potentials of MSCs seeded onto nano-fiber scaffolds

(NFs) in vitro and possible use for the repair of RA-affected joints. **METHODS:** MSCs derived from healthy donors and patients with RA or osteoarthritis (OA) were seeded on poly-lactic-glycolic acid (PLGA) electrospun NFs and cultured in vitro. **RESULTS:** Healthy donor-derived MSCs seeded onto NFs stained positive with von Kossa at Day 14 post-stimulation for osteoblast differentiation. Similarly, MSCs stained positive with Safranin O at Day 14 post-stimulation for chondrocyte differentiation. Surprisingly, even cultured without any stimulation, MSCs expressed RUNX2 and SOX9 (master regulators of bone and cartilage differentiation) at Day 7. Moreover, MSCs stained positive for osteocalcin, a bone marker, and simultaneously also with Safranin O at Day 14. On Day 28, the cell morphology changed from a spindle-like to an osteocyte-like appearance with processes, along with the expression of dentin matrix protein-1 (DMP-1) and matrix extracellular phosphoglycoprotein (MEPE), suggesting possible differentiation of MSCs into osteocytes. Calcification was observed on Day 56. Expression of osteoblast and chondrocyte differentiation markers was also noted in MSCs derived from RA or OA patients seeded on NFs. Lactic acid present in NFs potentially induced MSC differentiation into osteoblasts. **CONCLUSIONS:** Our PLGA scaffold NFs induced MSC differentiation into bone and cartilage. NFs induction process resembled the procedure of endochondral ossification. This finding indicates that the combination of MSCs and NFs is a promising therapeutic technique for the repair of RA or OA joints affected by bone and cartilage destruction.

Srankova, J., G. Doka, et al. "Daunorubicin Down-Regulates the Expression of Stem Cell Markers and Factors Involved in Stem Cell Migration and Homing in Rat Heart in Subchronic but not Acute Cardiomyopathy." *Basic Clin Pharmacol Toxicol.* 2016 Apr 19. doi: 10.1111/bcpt.12606.

We tested the hypothesis that daunorubicin (DAU) cardiotoxicity alters expression of cytokines involved in stem cell migration and homing. Male Wistar rats were treated with daunorubicin to induce acute DAU cardiomyopathy (6x3 mg/kg, i.p., every 48 hr, DAU-A) or subchronic DAU cardiomyopathy (15 mg/kg, i.v., DAU-C). The left ventricle was catheterized. The animals were killed 48 hr (DAU-A) and 8 weeks (DAU-C) after the last dose of DAU. Expression of foetal genes (Nppa, Nppb), isomyosins (Myh6, Myh7), sources of oxidative stress (Abcb8, gp91phox), cytokines (Sdf-1, Cxcr4, Scf, Vegf, Hgf, Igf-1), markers of cardiac progenitor (c-kit, Atxn-1), endothelial progenitor (CD34, CD133) and mesenchymal (CD44, CD105) stem cells were determined by qRT-PCR in left ventricular tissue.

Reduced body weight, decreased left ventricular weight and function, elevated Nppa, Nppb, Myh7 were observed in both models. Myh6 decreased only in DAU-C, which had a 35% mortality. Up-regulated gp91phox and down-regulated Abcb8 in DAU were present only in DAU-C where we observed markedly decreased expressions of Scf and Vegf as well as expressions of stem cell markers. Down-regulation of cytokines and stem cell markers may reflect impaired chemotaxis, migration and homing of stem cells and tissue repair in the heart in subchronic but not acute model of DAU cardiomyopathy. This article is protected by copyright. All rights reserved.

Takahara, S., T. Niikura, et al. "Human pseudoarthrosis tissue contains cells with osteogenic potential." *Injury.* 2016 Mar 15. pii: S0020-1383(16)30021-3. doi: 10.1016/j.injury.2016.02.022.

INTRODUCTION: Nonunion is a challenging problem that may occur after certain bone fractures. The treatment of nonunion is closely related to its type. To develop an effective treatment strategy for each type of nonunion, biological analysis of nonunion tissue is essential. Pseudoarthrosis is a distinct pathologic entity of nonunion. To understand the pathology of pseudoarthrosis, we investigated the cellular properties of pseudoarthrosis tissue-derived cells (PCs) in vitro. **PATIENTS AND METHODS:** PCs were isolated from four patients with pseudoarthrosis and cultured. Cells were evaluated for cell-surface protein expression by using flow cytometry. Osteogenic differentiation capacity was assessed by using Alizarin Red S staining, alkaline phosphatase (ALP) activity assay, and reverse transcription polymerase chain reaction (RT-PCR) after osteogenic induction. Chondrogenic differentiation capacity was assessed via Safranin O staining and RT-PCR after chondrogenic induction. **RESULTS:** PCs were consistently positive for the mesenchymal stem cell-related markers CD29, CD44, CD105, and CD166, but were negative for the haematopoietic-lineage markers CD31, CD34, CD45, and CD133. Alizarin Red S staining revealed that PCs formed a mineralised matrix that was rich in calcium deposits after osteogenic induction. ALP activity under osteogenic conditions was significantly higher than that under control conditions. Gene expression of ALP, Runx2, osterix, osteocalcin, and bone sialoprotein was observed in PCs cultured under osteogenic conditions. Induced pellets were negatively stained by Safranin O staining. Gene expression of aggrecan, collagen II, collagen X, SOX5, and SOX9 was not observed. **CONCLUSION:** We have shown for the first time the properties of cells in patients with pseudoarthrosis. Our results indicated that osteogenic cells existed in the pseudoarthrosis tissue. This study

might provide insights into understanding the pathology of pseudoarthrosis and improving the treatment for pseudoarthrosis.

Tateno, H., S. Saito, et al. "alpha2-6sialylation is a marker of the differentiation potential of human mesenchymal stem cells." *Glycobiology*. 2016 Apr 2. pii: cww039.

Human somatic stem cells such as human mesenchymal stem cells (hMSCs) are considered attractive cell sources for stem cell-based therapy. However, quality control issues have been raised concerning their safety and efficacy. Here we used lectin microarray technology to identify cell surface glycans as markers of the differentiation potential of stem cells. We found that alpha2-6Sia-specific lectins show stronger binding to early passage adipose-derived hMSCs (with differentiation ability) than late passage cells (without the ability to differentiate). Flow cytometry analysis using alpha2-6Sia-specific lectins supported the results obtained by lectin microarray. Similar results were obtained for bone marrow-derived hMSCs and cartilage tissue-derived chondrocytes. Little or no binding of alpha2-6Sia-specific lectins was observed for human dermal fibroblasts, which are unable to differentiate, suggesting that the binding of alpha2-6Sia-specific lectins is associated with the differentiation ability of cells, but not to their capacity to proliferate. Quantitative analysis of the linkage mode of Sia using anion-exchange chromatography showed that the percentage of alpha2-6Sia linkage type was higher in early passage adipose-derived hMSCs than late passage cells. Integrin alpha5 was found to be a carrier protein of alpha2-6Sia. Sialidase treatment significantly reduced the differentiation efficiency of bone marrow-derived hMSCs. Based on these findings, we propose that alpha2-6sialylation is a marker of differentiation potential in stem cells such as adipose-derived hMSCs, bone marrow-derived hMSCs, and cartilage tissue-derived chondrocytes.

Thayer, P. S., S. S. Verbridge, et al. "Fiber/collagen composites for ligament tissue engineering: influence of elastic moduli of sparse aligned fibers on mesenchymal stem cells." *J Biomed Mater Res A*. 2016 Apr 1. doi: 10.1002/jbm.a.35716.

Electrospun microfibers are attractive for the engineering of oriented tissues because they present instructive topographic and mechanical cues to cells. However, high-density microfiber networks are too cell-impermeable for most tissue applications. Alternatively, the distribution of sparse microfibers within a three-dimensional hydrogel could present instructive cues to guide cell organization while not inhibiting cell behavior. In this study, thin (

approximately 5 fibers thick) layers of aligned microfibers (0.7 μm) were embedded within collagen hydrogels containing mesenchymal stem cells (MSCs), cultured for up to 14 days, and assayed for expression of ligament markers and imaged for cell organization. These microfibers were generated through the electrospinning of polycaprolactone (PCL), poly(ester-urethane) (PEUR), or a 75/25 PEUR/PCL blend to produce microfiber networks with elastic moduli of 31, 15, and 5.6 MPa, respectively. MSCs in composites containing 5.6 MPa fibers exhibited increased expression of the ligament marker scleraxis and the contractile phenotype marker alpha-smooth muscle actin versus the stiffer fiber composites. Additionally, cells within the 5.6 MPa microfiber composites were more oriented compared to cells within the 15 and 31 MPa microfiber composites. Together, these data indicate that the mechanical properties of microfiber/collagen composites can be tuned for the engineering of ligament and other target tissues. (c) 2016 Wiley Periodicals, Inc. *J Biomed Mater Res Part A*, 2016.

Trosan, P., E. Javorkova, et al. "The Supportive Role of Insulin-like Growth Factor-I in the Differentiation of Murine Mesenchymal Stem Cells into Corneal-like Cells." *Stem Cells Dev*. 2016 Apr 6.

This study was focused on characterizing the differentiation of bone marrow-derived mesenchymal stem cells (MSCs) into corneal-like cells. Mouse MSCs were isolated from the bone marrow, grown in cell culture for 3 weeks and purified using a magnetic activated cell sorter. Purified MSCs were cultured with an extract prepared from excised corneas and in the presence or absence of insulin-like growth factor-I (IGF-I). Analysis by qPCR showed that the expression of corneal specific markers, such as cytokeratin 12 (K12), keratocan and lumican, were already induced after a 3-day cultivation and gradually increased during the 10-day incubation of MSCs with the extract. The presence of IGF-I significantly increased differentiation. Immunofluorescence analysis of differentiated MSCs showed positive results for the K12 protein. The morphology of the differentiated cells and the expression of cell surface markers CD45, CD11b, CD73, CD44 and CD105 were comparable in the control and differentiated MSCs. Proliferative activity was even higher in differentiated cells than in untreated MSCs. Both untreated and differentiated MSCs inhibited the production of interleukin-2 and interferon-gamma in spleen cells stimulated with Concanavalin A. The results thus show that MSCs cultured in the presence of corneal extract and IGF-I efficiently differentiate into corneal-like cells. The differentiated cells possess characteristics of corneal

epithelial cells and keratocytes, while at the same time maintaining MSCs properties.

Yabe, S., A. P. Alexenko, et al. "Comparison of syncytiotrophoblast generated from human embryonic stem cells and from term placentas." *Proc Natl Acad Sci U S A*. 2016 Apr 5. pii: 201601630.

Human embryonic stem cells (ESCs) readily commit to the trophoblast lineage after exposure to bone morphogenetic protein-4 (BMP-4) and two small compounds, an activin A signaling inhibitor and a FGF2 signaling inhibitor (BMP4/A83-01/PD173074; BAP treatment). During differentiation, areas emerge within the colonies with the biochemical and morphological features of syncytiotrophoblast (STB). Relatively pure fractions of mononucleated cytotrophoblast (CTB) and larger syncytial sheets displaying the expected markers of STB can be obtained by differential filtration of dispersed colonies through nylon strainers. RNA-seq analysis of these fractions has allowed them to be compared with cytotrophoblasts isolated from term placentas before and after such cells had formed syncytia. Although it is clear from extensive gene marker analysis that both ESC- and placenta-derived syncytial cells are trophoblast, each with the potential to transport a wide range of solutes and synthesize placental hormones, their transcriptome profiles are sufficiently dissimilar to suggest that the two cell types have distinct pedigrees and represent functionally different kinds of STB. We propose that the STB generated from human ESCs represents the primitive syncytium encountered in early pregnancy soon after the human trophoblast invades into the uterine wall.

Yahoo, N., B. Pournasr, et al. "Forced expression of Hnflb/Foxa3 promotes hepatic fate of embryonic stem cells." *Biochem Biophys Res Commun*. 2016 Apr 20. pii: S0006-291X(16)30607-6. doi: 10.1016/j.bbrc.2016.04.102.

Embryonic stem (ES) cell-derived hepatocytes have the potential to be used for basic research, regenerative medicine, and drug discovery. Recent reports demonstrated that in addition to conventional differentiation inducers such as chemical compounds and cytokines, overexpression of lineage-specific transcription factors could induce ES cells to differentiate to a hepatic fate. Here, we hypothesized that lentivirus-mediated inducible expression of hepatic lineage transcription factors could enhance mouse ES cells to hepatocyte-like cells. We screened the effects of candidate transcription factors Hnflb, Hnfla, Hnf4a, Foxa1, Foxa3 and Hex, and determined that the combination of Hnflb/Foxa3 promoted expression of several hepatic lineage-specific markers and proteins, in addition to glycogen storage, ICG

uptake, and secretion of albumin and urea. The differentiated cells were engraftable and expressed albumin when transplanted into a carbon tetrachloride-injured mouse model. These results demonstrated the crucial role of Hnflb and Foxa3 in hepatogenesis in vitro and provided a valuable tool for the efficient differentiation of HLCs from ES cells.

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