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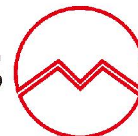

Stem Cell and Quantum Research Literatures

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

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Key words: stem cell; life; research; literature

Introduction

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

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

Askenasy, N. (2006). "From the atom to the cell: Is the cat alive? Quantum mechanics and stem cell plasticity as deja vu." Stem Cells Dev **15**(4): 488-491.

The concepts submitted by quantum mechanics fascinated the scientific community during the first half of the 20(th) century. The second half was dominated by biology, culminating in the sequencing of the human genome and the study of stem cells. Although the anticipated revolution of cellular therapies in medicine is in its infancy, the conceptual debate over stem cell plasticity shares similarities with evolution of the quantum theory. Are there notions and modes of thinking that stem cell biologists should adopt from the evolution in the interpretation of the laws of physics?

Biava, P. M., et al. (2017). "Stem Cell Differentiation Stage Factors and Their Role in Triggering Symmetry Breaking Processes during Cancer Development: A Quantum Field Theory Model for Reprogramming Cancer Cells to Healthy Phenotypes." Curr Med Chem.

A long history of research has pursued the use of embryonic factors isolated during cell differentiation processes for the express purpose of transforming cancer cells back to healthy phenotypes. Recent results have clarified that the substances present at different stages of cell differentiation-which we call stem cell differentiation stage factors (SCDSFs)-are proteins with low molecular weight and nucleic acids that regulate genomic expression. The present review summarizes how these substances, taken at different stages of cellular maturation, are able to retard proliferation of many human tumor cell lines and thereby reprogram cancer cells to healthy phenotypes. The model presented here is a quantum field theory (QFT) model in which SCDSFs are able to trigger symmetry breaking processes during cancer development. These symmetry breaking processes, which lie at the root of many phenomena in elementary particle physics and condensed matter physics, govern the phase transitions of totipotent cells to higher degrees of diversity and order, resulting in cell differentiation. In cancers, which share many genomic and metabolic similarities with embryonic stem cells, stimulated re-differentiation often signifies the phenotypic reversion back to health and non-

proliferation. In addition to acting on key components of the cellular cycle, SCDSFs are able to reprogram cancer cells by delicately influencing the cancer microenvironment, modulating the electrochemistry and thus the collective electrodynamic behaviors between dipole networks in biomacromolecules and the interstitial water field. Coherent effects in biological water, which are derived from a dissipative QFT framework, may offer new diagnostic and therapeutic targets at a systemic level, before tumor instantiation occurs in specific tissues or organs. Thus, by including the environment as an essential component of our model, we may push the prevailing paradigm of mutation-driven oncogenesis toward a closer description of reality.

Bignone, P. A., et al. (2016). "Selection of Phage Display Peptides Targeting Human Pluripotent Stem Cell-Derived Progenitor Cell Lines." Methods Mol Biol **1357**: 269-283.

The ability of human pluripotent stem cells (hPS) to both self-renew and differentiate into virtually any cell type makes them a promising source of cells for cell-based regenerative therapies. However, stem cell identity, purity, and scalability remain formidable challenges that need to be overcome for translation of pluripotent stem cell research into clinical applications. Directed differentiation from hPS cells is inefficient and residual contamination with pluripotent cells that have the potential to form tumors remains problematic. The derivation of scalable (self-renewing) embryonic progenitor stem cell lines offers a solution because they are well defined and clonally pure. Clonally pure progenitor stem cell lines also provide a means for identifying cell surface targeting reagents that are useful for identification, tracking, and repeated derivation of the corresponding progenitor stem cell types from additional hPS cell sources. Such stem cell targeting reagents can then be applied to the manufacture of genetically diverse banks of human embryonic progenitor cell lines for drug screening, disease modeling, and cell therapy. Here we present methods to identify human embryonic progenitor stem cell targeting peptides by selection of phage display libraries on clonal embryonic progenitor cell lines and demonstrate their use for targeting quantum dots (Qdots) for stem cell labeling.

Busca, A., et al. (2010). "Iron overload in patients receiving allogeneic hematopoietic stem cell transplantation: quantification of iron burden by a superconducting quantum interference device (SQUID) and therapeutic effectiveness of phlebotomy." Biol Blood Marrow Transplant **16**(1): 115-122.

Iron overload (IO) is a known adverse prognostic factor in patients who undergo allogeneic hematopoietic stem cell transplantation (HSCT) for thalassemia and appears to play a similar role in patients with other hematologic disorders. The estimation of IO is based primarily on serum ferritin level; however, many confounding factors can result in ferritin overestimation, especially in HSCT recipients. The aim of the present study was to quantify IO after HSCT using a superconducting quantum interference device (SQUID), and to evaluate the impact of IO on hepatic function and infections. In addition, the feasibility of iron depletion was investigated. A total of 102 consecutive allogeneic HSCT recipients admitted to our outpatient department between December 2005, and December 2007, were analyzed. Primary diagnosis included acute leukemia/myelodysplastic syndrome in 61% of cases. Assessment of IO after HSCT included serum ferritin; in those with hyperferritinemia (ferritin>1000 ng/mL), liver iron concentration (LIC) was evaluated by SQUID magnetic susceptometry. Iron removal therapy was offered to patients with moderate IO (LIC 1000-2000 microg Fe/g wet weight [ww]) or severe IO (LIC >2,000 microg Fe/g ww). Fifty-seven patients had a ferritin level <1000 ng/mL: the median time between HSCT and assessment of ferritin level was 1006 days (range, 93-5239 days), significantly different from the median time of 183 days (range, 78-2957 days) in the 45 patients with a ferritin level >1000 ng/mL. Out of 42 patients evaluated by SQUID, 29 had moderate to severe IO (median LIC value, 1493 microg Fe/g ww [range, 1030-3253]). In a multivariate analysis, a significant correlation was found between a ferritin level >1000 ng/mL and the presence of at least one abnormal liver function test (LFT) ORo=6.8; 95% CI=2.2-20.6). In addition, the rate of proven/probable invasive fungal disease was significantly higher in the patients with hyperferritinemia (13% vs 0%; P=.006).

Chen, C., et al. (2014). "[Enrichment and functional characterization of cancer stem cells from squamous cell carcinoma of head and neck by suspension culture]." Zhonghua Zhong Liu Za Zhi **36**(1): 17-22.

OBJECTIVE: Initiation, growth, recurrence, and metastasis of head and neck squamous cell carcinoma (HNSCC) have been related to the cancer stem cells (CSC) that can be identified by their aldehyde-dehydrogenase-isoform-1 (ALDH-1) activity. In this study, we try to prove that suspension culture can enrich ALDH-1 high expression cells within HNSCC cell lines and the enriched cells possess cancer stem cell properties. METHODS: Cells from five HNSCC cell lines were cultured in ultra-low attachment plates in serum-free Quantum 263 medium supplemented with 10 ng/ml EGF and 10 ng/ml bFGF, and ALDH-1

expression level was evaluated by ALDEFLUOR assay. ALDH-1 high expression cells were separated by FACS sorting, and their phenotypical and functional properties were characterized. RESULTS: Spheroids can be formed from all five HNSCC cell lines (UD-SCC1, UT-SCC22, UM-SCC11B, UT-SCC9 and UT-SCC24A) under anchorage independent culture condition. The proportion of ALDH1 high expression cells were highly increased in speroids derived cells (SDCs) compared with their monolayers (P < 0.05). The clones formed by ALDH1 high expression cells on average contained 197 (197 +/- 47) cells compared with 33 (33 +/- 16) cells in clones generated from ALDH1 low expression cells (P < 0.01). Single ALDH1 high expression cell could significantly better regenerate a spheroid (UT-SCC9: 17.1%, UD-SCC1:19.3%), whereas under the same conditions single ALDH1 low expression cells regenerated only in one case a spheroid (P < 0.01). SDCs from all five tested cell lines also showed a significantly increased invasion capacity (P < 0.05). We also found that the mRNA levels of Oct-4, Sox2, and Nanog were all significantly increased in the SDC. The reactive oxygen species (ROS) levels in SDCs from UD-SCC1 and UT-SCC24A were significantly increased compared with their monolayer counterpart [(26.3 +/- 4.9)% vs (8.6 +/- 1.7)% and (72.1 +/- 6.1)% vs (23.7 +/- 7.5)%, P < 0.05)]. CONCLUSION: Cancer stem cells can be enriched by suspension culture, which may be of importance in investigation of their contribution to therapy resistance, tumor recurrence and metastasis.

Chen, D., et al. (2017). "Bright Polymer Dots Tracking Stem Cell Engraftment and Migration to Injured Mouse Liver." Theranostics **7**(7): 1820-1834.

Stem cell therapy holds promise for treatment of intractable diseases and injured organs. For clinical translation, it is pivotal to understand the homing, engraftment, and differentiation processes of stem cells in a living body. Here we report near-infrared (NIR) fluorescent semiconductor polymer dots (Pdots) for bright labeling and tracking of human mesenchymal stem cells (MSCs). The Pdots exhibit narrow-band emission at 775 nm with a quantum yield of 22%, among the highest value for various NIR probes. The Pdots together with a cell penetrating peptide are able to track stem cells over two weeks without disturbing their multipotent properties, as confirmed by the analyses on cell proliferation, differentiation, stem-cell markers, and immunophenotyping. The in vivo cell tracking was demonstrated in a liver-resection mouse model, which indicated that the Pdot-labeled MSCs after tail-vein transplantation were initially trapped in lung, gradually migrated to the injured liver, and then proliferated into cell clusters. Liver-function analysis and histological examination revealed that the inflammation induced by liver resection was apparently decreased after stem cell transplantation. With the bright labeling, superior biocompatibility, and long-term tracking performance, the Pdot probes are promising for stem cell research and regenerative medicine.

Cheng, F., et al. (2009). "Quantum-dot-based technology for sensitive and stable detection of prostate stem cell antigen expression in human transitional cell carcinoma." Int J Biol Markers **24**(4): 271-276.

Quantum dots (QDs) as a biological labeling material for medical applications need to be evaluated for the sensitivity and stability of their fluorescence. Comparison of QD-based immunolabeling and commonly used immunohistochemical staining in detecting the expression of prostate stem cell antigen (PSCA) in bladder tumor tissues revealed that the two methods had similar sensitivity in the differential display of PSCA expression correlated with tumor stage and grade (kappa=0.92, p<0.001). In addition, the intensity of QD fluorescence remained stable for at least 10 days after conjugation to the PSCA protein and nearly 96% of the positive expression in samples lasted for one month.

Costa, C. R. M., et al. (2017). "Labeling of adipose-derived stem cells with quantum dots provides stable and long-term fluorescent signal for ex vivo cell tracking." In Vitro Cell Dev Biol Anim **53**(4): 363-370.

Stem cells derived from adipose tissue (ADSC) have been used in cell therapy as an alternative to treat chronic and degenerative diseases. Using biomedical and image trials to track the cells when infused in the target tissue is essential to control cell migration and adhesion. The objective of the present study was to label and assess the adhesion of goat adipose tissue-derived stem cells (g-ADSC) after cell infusion in animal models by tracking luminescent intracytoplasmatic nanocrystals. The cells were labeled by using Qdots. The g-ADSCs infused with nanocrystal were prepared either fresh or fixed and further visualized under a fluorescence microscope. The labeled cells were infused in the goat mammary glands and mouse testicles and kidneys via tail vein injection. Thirty days after cell infusion, biopsy was carried out for analyses. The g-ADSC cultures were presented with high cellularity and fibroblast morphology, even after infusion of the nanocrystals. It was possible, by processing in paraffin and under fluorescence microscopy, demonstrating the success of the labeling in the long term. Freezing mammary gland biopsies in liquid NO2 did not alter the quality of labeling with Qdots. Therefore, g-ADSCs can be

labeled with intracytoplasmatic nanocrystals (Qdots) enabling their in vitro and ex vivo tracking.

Csaszar, E., et al. (2014). "Real-time monitoring and control of soluble signaling factors enables enhanced progenitor cell outputs from human cord blood stem cell cultures." Biotechnol Bioeng **111**(6): 1258-1264.

Monitoring and control of primary cell cultures is challenging as they are heterogenous and dynamically complex systems. Feedback signaling proteins produced from off-target cell populations can accumulate, inhibiting the production of the desired cell populations. Although culture strategies have been developed to reduce feedback inhibition, they are typically optimized for a narrow range of process parameters and do not allow for a dynamically regulated response. Here we describe the development of a microbead-based process control system for the monitoring and control of endogenously produced signaling factors. This system uses quantum dot barcoded microbeads to assay endogenously produced signaling proteins in the culture media, allowing for the dynamic manipulation of protein concentrations. This monitoring system was incorporated into a fed-batch bioreactor to regulate the accumulation of TGF-beta1 in an umbilical cord blood cell expansion system. By maintaining the concentration of TGF-beta1 below an upper threshold throughout the culture, we demonstrate enhanced ex vivo expansion of hematopoietic progenitor cells at higher input cell densities and over longer culture periods. This study demonstrates the potential of a fully automated and integrated real-time control strategy in stem cell culture systems, and provides a powerful strategy to achieve highly regulated and intensified in vitro cell manufacturing systems.

Darkazalli, A. and C. W. Levenson (2012). "Tracking stem cell migration and survival in brain injury: current approaches and future prospects." Histol Histopathol **27**(10): 1255-1261.

In recent years, stem cell-mediated therapies have gained considerable ground as potential treatments for a wide variety of brain pathologies including traumatic brain injury, stroke and neurodegenerative diseases. Despite extensive preclinical studies, many of these therapies have not been fully translated into viable clinical approaches. This is partly due to our inability to reliably track and monitor transplanted stem cells longitudinally over long periods of time in vivo. In this review, we discuss the predominant histological cell tracing methodologies, such as immunohistochemistry, and fluorescent cellular dyes and proteins, and compare them to emerging cellular imaging technologies. We show that advances in magnetic resonance imaging (MRI) have resulted in opportunities to use this technology to further our understanding of stem cell characteristics and behaviors in vivo. While MRI may not completely replace conventional cell tracking methods in pre-clinical, mechanistic work, it is clear that it has the potential to function as a powerful diagnostic tool for tracking stem cell migration and survival as well as for evaluating the efficacy of stem cell-mediated therapies.

Das, B., et al. (2012). "Cyclic RGD peptide conjugated trypsin etched gold quantum clusters: novel biolabeling agents for stem cell imaging." J Stem Cells **7**(3): 189-199.

Quantum clusters are sub-nano sized materials mostly synthesized from noble metals with luminescence property and high quantum yield. They are important to biomedical scientists because of their excellent optical properties. Here we represent a tool for cell imaging purpose using protein stabilized gold quantum clusters. Intestinal protease Trypsin was used to develop clusters. They were conjugated to cyclic RGD peptides by EDAC coupling. Cell imaging property was checked by transfecting the RGD-conjugated quantum clusters to bone marrow stem cells. For characterization of RGD-conjugated quantum clusters UV-Vis, Fluorescence and FTIR spectroscopy was performed. DLS and Zeta potential measurement also have been done. To check the bio compatibility of the quantum clusters MTT assay, AFM and blood cell adhesion study were performed. The samples are found out to be good for cell imaging as well as bio compatible and hemo-compatible.

Dupont, K. M., et al. (2010). "Human stem cell delivery for treatment of large segmental bone defects." Proc Natl Acad Sci U S A **107**(8): 3305-3310.

Local or systemic stem cell delivery has the potential to promote repair of a variety of damaged or degenerated tissues. Although various stem cell sources have been investigated for bone repair, few comparative reports exist, and cellular distribution and viability postimplantation remain key issues. In this study, we quantified the ability of tissue-engineered constructs containing either human fetal or adult stem cells to enhance functional repair of nude rat critically sized femoral defects. After 12 weeks, defects treated with cell-seeded polymer scaffolds had significantly higher bone ingrowth and torsional strength compared to those receiving acellular scaffolds, although there were no significant differences between the cell sources. Next, stem cells were labeled with fluorescent quantum dots (QDs) in an attempt to noninvasively track their distribution after delivery on scaffolds. Clear fluorescence was observed at implantation sites

throughout the study; however, beginning 7-10 days after surgery, signals were also observed at contralateral sites treated with acellular QD-free scaffolds. Although immunostaining for human nuclei revealed retention of some cells at the implantation site, no human cells were detected in the control limb defects. Additional histological analysis of implantation and control defect tissues revealed macrophages containing endocytosed QDs. Furthermore, QD-labeling appeared to diminish transplanted cell function resulting in reduced healing responses. In summary, augmentation of polymeric scaffolds with stem cells derived from fetal and adult tissues significantly enhanced healing of large segmental bone defects; however, QD labeling of stem cells eliminated the observed therapeutic effect and failed to conclusively track stem cell location long-term in vivo.

Geng, H., et al. (2018). "Achieving stem cell imaging and osteogenic differentiation by using nitrogen doped graphene quantum dots." J Mater Sci Mater Med **29**(6): 85.

Nitrogen doped graphene quantum dots (N-GQDs) were synthesized to explore and extend their potential applications in biomedical field. The hemocompatibility and cytotoxity of the obtained N-GQDs were primarily assessed at concentrations ranging from 10 to 100 mug/ml. From the results, it was found that the proliferation of rat Bone Mesenchymal Stem Cells (rBMSCs) was depressed to a certain extent after incubating with the high concentration (100 mug/ml) of N-GQDs. The nanoscale size and superior dispersibility endow N-GQDs with good cell permeability. Meanwhile, owing to their intrinsic photoluminescence characteristic, the N-GQDs can be used to label cells with high uniformity and light stability in absence of chemical dyes. More importantly, the up-regulated expression of alkaline phosphate (ALP), extracellular matrix, osteopontin (OPN) and osteocalcin (OCN) in rBMSCs cultured with N-GQDs, indicating N-GQDs have the abilities to promote rBMSCs osteogenic differentiation. This work would help give a new insight into the advantages of N-GQDs and pave the way for application of N-GQDs in regenerative medicine fields.

Gu, H., et al. (2015). "A Stem Cell-Derived Platform for Studying Single Synaptic Vesicles in Dopaminergic Synapses." Stem Cells Transl Med **4**(8): 887-893.

The exocytotic release of dopamine is one of the most characteristic but also one of the least appreciated processes in dopaminergic neurotransmission. Fluorescence imaging has yielded rich information about the properties of synaptic vesicles and the release of neurotransmitters in excitatory and inhibitory neurons. In contrast, imaging-based studies for in-depth understanding of synaptic vesicle behavior in dopamine neurons are lagging largely because of a lack of suitable preparations. Midbrain culture has been one of the most valuable preparations for the subcellular investigation of dopaminergic transmission; however, the paucity and fragility of cultured dopaminergic neurons limits their use for live cell imaging. Recent developments in stem cell technology have led to the successful production of dopamine neurons from embryonic or induced pluripotent stem cells. Although the dopaminergic identity of these stem cell-derived neurons has been characterized in different ways, vesicle-mediated dopamine release from their axonal terminals has been barely assessed. We report a more efficient procedure to reliably generate dopamine neurons from embryonic stem cells, and it yields more dopamine neurons with more dopaminergic axon projections than midbrain culture does. Using a collection of functional measurements, we show that stem cell-derived dopamine neurons are indistinguishable from those in midbrain culture. Taking advantage of this new preparation, we simultaneously tracked the turnover of hundreds of synaptic vesicles individually using pH-sensitive quantum dots. By doing so, we revealed distinct fusion kinetics of the dopamine-secreting vesicles, which is consistent within both preparations.

Hansen, K. J., et al. (2016). "Functional Effects of Delivering Human Mesenchymal Stem Cell-Seeded Biological Sutures to an Infarcted Heart." Biores Open Access **5**(1): 249-260.

Stem cell therapy has the potential to improve cardiac function after myocardial infarction (MI); however, existing methods to deliver cells to the myocardium, including intramyocardial injection, suffer from low engraftment rates. In this study, we used a rat model of acute MI to assess the effects of human mesenchymal stem cell (hMSC)-seeded fibrin biological sutures on cardiac function at 1 week after implant. Biological sutures were seeded with quantum dot (Qdot)-loaded hMSCs for 24 h before implantation. At 1 week postinfarct, the heart was imaged to assess mechanical function in the infarct region. Regional parameters assessed were regional stroke work (RSW) and systolic area of contraction (SAC) and global parameters derived from the pressure waveform. MI (n = 6) significantly decreased RSW (0.026 +/- 0.011) and SAC (0.022 +/- 0.015) when compared with sham operation (RSW: 0.141 +/- 0.009; SAC: 0.166 +/- 0.005, n = 6) ($p < 0.05$). The delivery of unseeded biological sutures to the infarcted hearts did not change regional mechanical function compared with

the infarcted hearts (RSW: 0.032 +/- 0.004, SAC: 0.037 +/- 0.008, n = 6). The delivery of hMSC-seeded sutures exerted a trend toward increase of regional mechanical function compared with the infarcted heart (RSW: 0.057 +/- 0.011; SAC: 0.051 +/- 0.014, n = 6). Global function showed no significant differences between any group (p > 0.05); however, there was a trend toward improved function with the addition of either unseeded or seeded biological suture. Histology demonstrated that Qdot-loaded hMSCs remained present in the infarcted myocardium after 1 week. Analysis of serial sections of Masson's trichrome staining revealed that the greatest infarct size was in the infarct group (7.0% +/- 2.2%), where unseeded (3.8% +/- 0.6%) and hMSC-seeded (3.7% +/- 0.8%) suture groups maintained similar infarct sizes. Furthermore, the remaining suture area was significantly decreased in the unseeded group compared with that in the hMSC-seeded group (p < 0.05). This study demonstrated that hMSC-seeded biological sutures are a method to deliver cells to the infarcted myocardium and have treatment potential.

Jacobi, N. and L. Herich (2016). "Measurement of liver iron concentration by superconducting quantum interference device biomagnetic liver susceptometry validates serum ferritin as prognostic parameter for allogeneic stem cell transplantation." Eur J Haematol **97**(4): 336-341.

INTRODUCTION: There are conflicting data regarding the role of serum ferritin (SF) as surrogate parameter for iron overload as an independent prognostic factor for outcome after allogeneic stem cell transplantation (SCT). Superconducting quantum interference device (SQUID) biomagnetic liver susceptometry, a noninvasive measurement of iron overload, allows measurement of the interference of an exteriorly applied small but highly constant magnetic field by the paramagnetic liver storage iron. By measuring the true iron load of patients through SQUID, we wanted to assess the effect of iron overload on patients undergoing SCT. METHODS: We conducted a single-center retrospective analysis (1994-2010), comparing the effect of SF and liver iron content measured by SQUID shortly before transplantation on overall survival (OS), event-free survival (EFS), and transplant-related mortality (TRM) in 142 patients (median age 54.5 yr, range 5.6-75 yr) undergoing SCT (80% reduced intensity regimen). Patients were subdivided into five groups: myelodysplastic syndrome, de novo acute myeloid leukemia (AML), secondary AML, primary myelofibrosis, and others. RESULTS: Correlation between SF and SQUID was significant (r = 0.6; P < 0.001; log function). The chance of infection was increased 2.4-fold (95% CI 1.22-4.71) when SQUID values ranged >/=1000 mug Fe/g liver (P = 0.012). We found similar results for SF >1000 ng/mL (P = 0.003). A significant association between SQUID and fungal infection was also seen (P = 0.004). For patients with SQUID >/=1000, the risk of proven fungal infection was increased 3.08-fold (95% CI 1.43-6.63). A similar association between SF >1000 and fungal infection was shown (P = 0.01). In univariate analysis, age was a prognostic factor for TRM (P = 0.034, HR 1.04, CI 1.00-1.08). SF >/=1000 was associated with OS (P = 0.033, HR 2.09, CI 1.06-4.11) and EFS (P = 0.016, HR 2.15, 95% CI 1.15-4.10). In multivariate analysis on EFS, only age and SF >1000 remained as independent factors (HR 1.027, P = 0.040, 95% CI 1.001-1.054 and HR 2.058, P = 0.034, 95% CI 1.056-4.008, respectively). The multivariate analysis on TRM left age and SQUID values >/=1000 in the final model (HR 1.045, P = 0.041, 95% CI 1.002-1.090 and HR 2.110, P = 0.103, 95% CI 0.859-5.183, respectively). CONCLUSION: Our data confirmed that SF >/=1000 increases the risk of infection, moreover fungal infection in transplant recipients. As SQUID values correlate well with SF, we could show that SF is indeed a good surrogate parameter for iron overload when measured shortly before SCT. Prospective trials are needed to investigate the effect of iron chelation before or during SCT on transplant outcome.

Ju, H., et al. (2017). "Impact of Environmental Pollutant Cadmium on the Establishment of a Cancer Stem Cell Population in Breast and Hepatic Cancer." ACS Omega **2**(2): 563-572.

Cadmium, a heavy metal pollutant, causes cancer. The existence of cancer stem cells (CSCs) in tumors is widely considered to be the reason for the recurrence and treatment failure of cancer. Increasing evidence has confirmed that under certain conditions non-CSCs could be converted into CSCs. The impact of cadmium on the development of CSC lineage in the bulk tumor cell population is not yet studied. The aim of this study was to evaluate the effect of cadmium on the conversion of non-CSCs to CSCs and the identification of CSCs based on the concurrent monitoring of multiple CSC markers. High-content monitoring of molecular markers was performed using quantum dot (QD) nanoprobes and an acousto-optical tunable filter (AOTF)-based imaging device. Cadmium treatment significantly increased the CSC population in MCF-7 and HepG2 cell lines. The cadmium-induced CSCs were identified by a concurrent analysis of stem-cell markers, namely, CD44, CD24, CD133, and ALDH1. Moreover, increased m-RNA expression of CD44, ALDH1, and CD133 and protein expression of p-Ras, p-Raf-1, p-MEK-1, and p-ERK-1 were observed in the cadmium-treated MCF-7 and HepG2 cells. This study

demonstrates that cadmium induces the gene expression of CSC markers in the breast and liver cancer cell lineage and promotes the conversion of non-CSCs to CSCs.

Kanda, J., et al. (2011). "Iron overload and allogeneic hematopoietic stem-cell transplantation." Expert Rev Hematol **4**(1): 71-80.

Iron overload is frequently observed in patients with hematologic diseases before and after allogeneic stem-cell transplantation because they usually receive multiple red blood cell transfusions. Elevated pretransplant serum ferritin levels, which are widely used as indicators of body iron status, are significantly associated with a lower overall survival rate and a higher incidence of treatment-related complications; for example, infections and hepatic veno-occlusive disease. As serum ferritin levels are affected, not only by iron loading but also by inflammation, imaging techniques to quantify tissue iron levels have been developed, for example, quantitative MRI using the transverse magnetic relaxation rate, and superconducting quantum interference devices. Iron chelators, such as deferasirox, a new oral iron-chelating agent, reduce iron load in transfusion-dependent patients. Iron-chelating therapy before and/or after transplantation is a promising strategy to improve the clinical outcomes of transplant patients with iron overload. However, further research is needed to prove the direct relationship between iron overload and adverse outcomes, as well as to determine the effects of treatment for iron overload on outcomes of allogeneic stem-cell transplantation.

Kang, E. S., et al. (2018). "Two-dimensional material-based bionano platforms to control mesenchymal stem cell differentiation." Biomater Res **22**: 10.

Background: In the past decade, stem cells, with their ability to differentiate into various types of cells, have been proven to be resourceful in regenerative medicine and tissue engineering. Despite the ability to repair damaged parts of organs and tissues, the use of stem cells still entails several limitations, such as low differentiation efficiency and difficulties in guiding differentiation. To address these limitations, nanotechnology approaches have been recently implemented in stem cell research. It has been discovered that stem cells, in combination with carbon-based functional materials, show enhanced regenerative performances in varying biophysical conditions. In particular, several studies have reported solutions to the conventional quandaries in biomedical engineering, using synergetic effects of nanohybrid materials, as well as further development of technologies to recover from diverse health conditions such as bone fracture and strokes. Main text: In this review, we discuss several prior studies regarding the application of various nanomaterials in controlling the behavior of stem cells. We focus on the potential of different types of nanomaterials, such as two-dimensional materials, gold nanoparticles, and three-dimensional nanohybrid composites, to control the differentiation of human mesenchymal stem cells (hMSCs). These materials have been found to affect stem cell functions via the adsorption of growth/differentiation factors on the surfaces of nanomaterials and the activation of signaling pathways that are mostly related to cell adhesion and differentiation (e.g., FAK, Smad, Erk, and Wnt). Conclusion: Controlling stem cell differentiation using biophysical factors, especially the use of nanohybrid materials to functionalize underlying substrates wherein the cells attach and grow, is a promising strategy to achieve cells of interest in a highly efficient manner. We hope that this review will facilitate the use of other types of newly discovered and/or synthesized nanomaterials (e.g., metal transition dichalcogenides, non-toxic quantum dots, and metal oxide frameworks) for stem cell-based regenerative therapies.

Ki, J., et al. (2017). "High-content cell death imaging using quantum dot-based TIRF microscopy for the determination of anticancer activity against breast cancer stem cell." J Biophotonics **10**(1): 118-127.

We report a two color monitoring of drug-induced cell deaths using total internal reflection fluorescence (TIRF) as a novel method to determine anticancer activity. Instead of cancer cells, breast cancer stem cells (CSCs) were directly tested in the present assay to determine the effective concentration (EC50) values of camptothecin and cisplatin. Phosphatidylserine and HMGB1 protein were concurrently detected to observe apoptotic and necrotic cell death induced by anticancer drugs using quantum dot (Qdot)-antibody conjugates. Only 50-to-100 breast CSCs were consumed at each cell chamber due to the high sensitivity of Qdot-based TIRF. The high sensitivity of Qdot-based TIRF, that enables the consumption of a small number of cells, is advantageous for cost-effective large-scale drug screening. In addition, unlike MTT assay, this approach can provide a more uniform range of EC50 values because the average values of single breast CSCs fluorescence intensities are observed to acquire EC50 values as a function of dose. This research successfully demonstrated the possibility that Qdot-based TIRF can be widely used as an improved alternative to MTT assay for the determination of anticancer drug efficacies.

Kim, T. H., et al. (2014). "Electrically controlled delivery of cargo into single human neural stem cell." ACS Appl Mater Interfaces **6**(23): 20709-20716.

Nanoprobe-based techniques have emerged as an efficient tool for the manipulation and analysis of single cells. Here, we report a powerful whole-electrical single-cell manipulation tool that enables rapid and controllable delivery of cargo into single neural stem cells with precision monitoring of the cell penetration process using a conductive nanoprobe. The highly electrically sensitive nanoprobes that were fabricated and the indium tin oxide electrode-integrated cell chip were found to be very effective for monitoring the cell penetration process via current changes that appear as spike-like negative currents. Moreover, the assembly of cargoes onto the nanoprobes was controllable and could reach its maximum load in a very short period of time (<10 min) based on the same electrical system that was used for monitoring cell penetration and without the need for any complex chemical linkers or mediators. Even more remarkably, the cargo assembled on the surface of the nanoprobe was successfully released in a very short period of time (<10 s), regardless of the surrounding intracellular or extracellular environments. The monitoring of cell penetration, assembly of quantum dots (QDs), and release of QDs into the intracellular environment were all accomplished using our whole-electrical system that combined a conductive nanoprobe with cell chip technology. This is a novel technology, which can eliminate complex and time-consuming steps owing to chemical modifications, as well as reduce the time needed for the delivery of cargo into the cell cytosol/nucleus during cell penetration, which is very important for reducing cell damage.

Laver, C. R., et al. (2015). "Bimodal in vivo imaging provides early assessment of stem-cell-based photoreceptor engraftment." Eye (Lond) **29**(5): 681-690.

PURPOSE: Subretinal transplantation of stem-cell-derived photoreceptor precursor cells (PPCs) is a promising and innovative approach to treating a range of blinding diseases. However, common barriers to efficient preclinical transplantation comes in the form of suboptimal graft architecture, limited graft survival, and immune-rejection, each of which cannot be assessed using conventional in vivo imaging (i.e., rodent ophthalmoscopy). With the majority of PPCs reported to die within the first few weeks after transplantation, understanding the mechanisms of graft failure, and ultimately devising preventative methods, currently relies on lengthy end point histology. To address these limitations, we hypothesized that combining two imaging modalities, optical coherence tomography (OCT) and fluorescence confocal scanning laser ophthalmoscopy (fcSLO), could provide a more rapid and comprehensive view of PPC engraftment. METHODS: Human ESC-derived PPCs were transplanted into 15 retinal dystrophic rats that underwent bimodal imaging at 0, 8, and 15 days posttransplant. RESULTS: Bimodal imaging provided serial detection of graft: placement, architecture, and survival; each undetectable under ophthalmoscopy. Bimodal imaging determined graft placement to be either: subretinal (n=7), choroidal (n=4), or vitreal (n=4) indicating neural retinal perforation. Graft architecture was highly variable at the time of transplantation, with notable redistribution over time, while complete, or near complete, graft loss was observed in the majority of recipients after day 8. Of particular importance was detection of vitreal aggregates overlying the graft-possibly an indicator of host-site inflammation and rejection. CONCLUSION: Early real-time feedback of engraftment has the potential to greatly increase efficiency of preclinical trials in cell-based retinal therapeutics.

Lei, Y., et al. (2009). "Applications of fluorescent quantum dots to stem cell tracing in vivo." J Nanosci Nanotechnol **9**(10): 5726-5730.

Fluorescent quantum dots have great potential to act as labels in biological research, especially cellular tracking in vivo. Here, small thiol molecules-capped CdSe/ZnS quantum dots attached to Tat peptide were used for label agents, and introduced into living stem cells. The stem cells labeled with quantum dots were intravenously injected into the tail veins of NOD/SCID beta2M null mice, and whose tissue sections of major organs of null mice were examined with fluorescence microscope to assess the distribution of transplanted stem cells. Stem cells with internalized quantum dots offer a promising approach in stem cell transplantation, which will hold a significant impact on stem cell based therapy for several disorders.

Lei, Y., et al. (2008). "Applications of mesenchymal stem cells labeled with Tat peptide conjugated quantum dots to cell tracking in mouse body." Bioconjug Chem **19**(2): 421-427.

Fluorescent quantum dots have great potential in cellular labeling and tracking. Here, PEG encapsulated CdSe/ZnS quantum dots have been conjugated with Tat peptide, and introduced into living mesenchymal stem cells. The Tat peptide conjugated quantum dots in mesenchymal stem cells were assessed by fluorescent microscopy, laser confocal microscope and. flow cytometry. The result shows that Tat peptide conjugated quantum dots could enter mesenchymal stem cells efficiently. The Tat-quantum dots labeled

stem cells were further injected into the tail veins of NOD/SCID beta2 M null mice, and the tissue distribution of these labeled cells in nude mice were examined with fluorescence microscope. The result shows that characteristic fluorescence of quantum dots was observed primarily in the liver, the lung and the spleen, with little or no quantum dots accumulation in the brain, the heart, or the kidney.

Lei, Y., et al. (2012). "Labeling of hematopoietic stem cells by Tat peptide conjugated quantum dots for cell tracking in mouse body." J Nanosci Nanotechnol **12**(9): 6880-6886.

Fluorescent quantum dots have great potential to act as labeling tools in biological research, especially cellular tracking and imaging. Tat peptide conjugated quantum dots were introduced into living human hematopoietic stem cells (HSCs). The internalized quantum dots were assessed by laser confocal microscope and flow cytometer. The quantum dots labeled HSCs were injected intravenously into the tail veins of NOD/SCID beta2M null mice. The tissue collections in the major organs were examined with fluorescence microscope to assess the distribution of transplanted stem cells. HSCs with internalized quantum dots offer a promising approach for stem cell transplantation, which will hold a significant impact on stem cell based therapy for several disorders, especially to cure leukemia in current China.

Li, S. C., et al. (2010). "A biological global positioning system: considerations for tracking stem cell behaviors in the whole body." Stem Cell Rev **6**(2): 317-333.

Many recent research studies have proposed stem cell therapy as a treatment for cancer, spinal cord injuries, brain damage, cardiovascular disease, and other conditions. Some of these experimental therapies have been tested in small animals and, in rare cases, in humans. Medical researchers anticipate extensive clinical applications of stem cell therapy in the future. The lack of basic knowledge concerning basic stem cell biology-survival, migration, differentiation, integration in a real time manner when transplanted into damaged CNS remains an absolute bottleneck for attempt to design stem cell therapies for CNS diseases. A major challenge to the development of clinical applied stem cell therapy in medical practice remains the lack of efficient stem cell tracking methods. As a result, the fate of the vast majority of stem cells transplanted in the human central nervous system (CNS), particularly in the detrimental effects, remains unknown. The paucity of knowledge concerning basic stem cell biology--survival, migration, differentiation, integration in real-time when transplanted into damaged CNS remains a bottleneck in the attempt to design stem cell therapies for CNS diseases. Even though excellent histological techniques remain as the gold standard, no good in vivo techniques are currently available to assess the transplanted graft for migration, differentiation, or survival. To address these issues, herein we propose strategies to investigate the lineage fate determination of derived human embryonic stem cells (hESC) transplanted in vivo into the CNS. Here, we describe a comprehensive biological Global Positioning System (bGPS) to track transplanted stem cells. But, first, we review, four currently used standard methods for tracking stem cells in vivo: magnetic resonance imaging (MRI), bioluminescence imaging (BLI), positron emission tomography (PET) imaging and fluorescence imaging (FLI) with quantum dots. We summarize these modalities and propose criteria that can be employed to rank the practical usefulness for specific applications. Based on the results of this review, we argue that additional qualities are still needed to advance these modalities toward clinical applications. We then discuss an ideal procedure for labeling and tracking stem cells in vivo, finally, we present a novel imaging system based on our experiments.

Ma, K., et al. (2011). "Effects of nanofiber/stem cell composite on wound healing in acute full-thickness skin wounds." Tissue Eng Part A **17**(9-10): 1413-1424.

Acute full-thickness skin wounds (FTSW) caused by extensive burns or high-energy trauma are not adequately addressed by current clinical treatments. This study hypothesized that biomimetic nanofiber scaffolds (NFSs) functionalized with rich attachment of bone-marrow-derived mesenchymal stem cells (BM-MSCs) can promote wound healing in acute FTSW. Results in a rat model showed that both NFS and BM-MSCs contributed to the wound healing. Wounds in NFS group with a higher density of BM-MSCs achieved complete closure 8 days earlier than the control group. Implanted BM-MSCs were found to promote epithelial edge ingrowth and collagen synthesis. The colocation of BM-MSCs (tagged with quantum-dots) with the expression of keratin 10 and filaggrin indicated the participation of BM-MSCs in epidermal differentiation at early and intermediate stages under the local wounding environment. Overall, this study suggests a great potential of using NFS/BM-MSC composites for the treatment of acute FTSW.

Mangoni, M., et al. (2012). "Stem cell tracking: toward clinical application in oncology?" Tumori **98**(5): 535-542.

Noninvasive cellular imaging allows the tracking of grafted cells as well as the monitoring of their migration, suggesting potential applications to track

both cancer and therapeutic stem cells. Cell tracking can be performed by two approaches: direct labeling (cells are labeled with tags) and indirect labeling (cells are transfected with a reporter gene and visualized after administration of a reporter probe). Techniques for in vivo detection of grafted cells include optic imaging, nuclear medicine imaging, magnetic resonance imaging, microCT imaging and ultrasound imaging. The ideal imaging modality would bring together high sensitivity, high resolution and low toxicity. All of the available imaging methods are based on different principles, have different properties and different limitations, so several of them can be considered complementary. Transfer of these preclinical cellular imaging modalities to stem cells has already been reported, and transfer to clinical practice within the next years can be reasonably considered.

Miyazaki, Y., et al. (2013). "Adipose Tissue-Derived Stem Cell Imaging Using Cadmium-Free Quantum Dots." Cell Med **6**(1-2): 91-97.

Quantum dots (QDs) have received much attention for biomolecule and cell imaging applications because of their superior optical properties such as high quantum efficiency, size-tunable emission, and resistance to photobleaching process. However, QDs that are commercially available contain cadmium (Cd), a highly toxic element. Thus, the development of Cd-free and less toxic QDs is strongly desired. In this study, we developed Cd-free QDs (ZnS-coated ZnS-AgInS2 solid solution nanoparticles with a sulfo group: ZnS-ZAIS-SO3H) and investigated the ability of this material to label stem cells. ZnS-ZAIS-SO3H could be transduced into mouse adipose tissue-derived stem cells (mASCs) using octaarginine peptides (R8), known as cell-penetrating peptides. The optimal ratio of ZnS-ZAIS-SO3H:R8 was found to be 1:100 for labeling mASCs. More than 80% of mASCs labeled with 500 nM ZnS-ZAIS-SO3H were found to be alive, and the proliferation rates of labeled mASCs were maintained at the same rate as that of nonlabeled mASCs. In addition, no abnormalities in the morphology of mASCs labeled with ZnS-ZAIS-SO3H could be observed. These data suggest that ZnS-ZAIS-SO3H may be effective for the labeling of mASCs.

Ogihara, Y., et al. (2017). "Transduction Function of a Magnetic Nanoparticle TMADM for Stem-Cell Imaging with Quantum Dots." Anal Sci **33**(2): 143-146.

We investigated the transduction function of a cationic dextran hydroxypropyltrimethyl ammonium chloride-coated magnetic iron oxide nanoparticle (TMADM-03) for transducing quantum dots (QDs) into adipose tissue-derived stem cells (ASCs). As a result, the fluorescence intensity of ASCs labeled with QDs using TMADM-03 was much higher than that of QDs only labeling. These data suggest that TMADM-03 can be useful as a transduction agent for QDs in stem-cell imaging.

Onoshima, D., et al. (2015). "Multifunctional quantum dots-based cancer diagnostics and stem cell therapeutics for regenerative medicine." Adv Drug Deliv Rev **95**: 2-14.

A field of recent diagnostics and therapeutics has been advanced with quantum dots (QDs). QDs have developed into new formats of biomolecular sensing to push the limits of detection in biology and medicine. QDs can be also utilized as bio-probes or labels for biological imaging of living cells and tissues. More recently, QDs has been demonstrated to construct a multifunctional nanoplatform, where the QDs serve not only as an imaging agent, but also a nanoscaffold for diagnostic and therapeutic modalities. This review highlights the promising applications of multi-functionalized QDs as advanced nanosensors for diagnosing cancer and as innovative fluorescence probes for in vitro or in vivo stem cell imaging in regenerative medicine.

Patel, S. and K. B. Lee (2015). "Probing stem cell behavior using nanoparticle-based approaches." Wiley Interdiscip Rev Nanomed Nanobiotechnol **7**(6): 759-778.

Stem cells hold significant clinical potential to treat numerous debilitating diseases and injures that currently have no treatment plan. While several advances have been made in developing stem cell platforms and methods to induce their differentiation, there are two critical aspects need to be addressed: (1) efficient delivery of nucleic acids and small molecules for stem cell differentiation, and (2) effective, noninvasive, and real-time tracking of transplanted stem cells. To address this, there has been a trend of utilizing various types of nanoparticles to not only deliver biomolecules to targeted site but also track the location of transplanted stem cells in real time. Over the past decade, various types of nanoparticles, including magnetic nanoparticles, silica nanoparticles, quantum dots, and gold nanoparticles, have been developed to serve as vehicles for targeted biomolecule delivery. In addition of being biocompatible without causing adverse side effect to stem cells, these nanoparticles have unique chemical and physical properties that allow tracking and imaging in real time using different imaging instruments that are commonly found in hospitals. A summary of the landmark and progressive

demonstrations that utilize nanoparticles for stem cell application is described.

Quesenberry, P. J., et al. (2012). "A new stem cell biology: the continuum and microvesicles." Trans Am Clin Climatol Assoc **123**: 152-166; discussion 166.

The hierarchical models of stem cell biology have been based on work first demonstrating pluripotental spleen-colony-forming units, then showing progenitors with many differentiation fates assayed in in vitro culture; there followed the definition and separation of "stem cells" using monoclonal antibodies to surface epitopes and fluorescent-activated cell characterization and sorting (FACS). These studies led to an elegant model of stem cell biology in which primitive dormant G0 stem cells with tremendous proliferative and differentiative potential gave rise to progressively more restricted and differentiated classes of stem/progenitor cells, and finally differentiated marrow hematopoietic cells. The holy grail of hematopoietic stem cell biology became the purification of the stem cell and the clonal definition of this cell. Most recently, the long-term repopulating hematopoietic stem cell (LT-HSC) has been believed to be a lineage negative sca-1+C-kit+ Flk3- and CD150+ cell. However, a series of studies over the past 10 years has indicated that murine marrow stem cells continuously change phenotype with cell cycle passage. We present here studies using tritiated thymidine suicide and pyronin-Hoechst FACS separations indicating that the murine hematopoietic stem cell is a cycling cell. This would indicate that the hematopoietic stem cell must be continuously changing in phenotype and, thus, could not be purified. The extant data indicate that murine marrow stem cells are continually transiting cell cycle and that the purification has discarded these cycling cells. Further in vivo BrdU studies indicate that the "quiescent" LT-HSC in G0 rapidly transits cycle. Further complexity of the marrow stem cell system is indicated by studies on cell-derived microvesicles showing that they enter marrow cells and transcriptionally alter their cell fate and phenotype. Thus, the stem cell model is a model of continuing changing potential tied to cell cycle and microvesicle exposure. The challenge of the future is to define the stem cell population, not purify the stem cell. We are at the beginning of elucidation of quantum stemomics.

Roberts, I., et al. (2012). "Scale-up of human embryonic stem cell culture using a hollow fibre bioreactor." Biotechnol Lett **34**(12): 2307-2315.

The commercialisation of human embryonic stem cell derived cell therapies for large patient populations is reliant on both minimising expensive and variable manual-handling methods whilst realising economies of scale. The Quantum Cell Expansion System, a hollow fibre bioreactor (Terumo BCT), was used in a pilot study to expand 60 million human embryonic stem cells to 708 million cells. Further improvements can be expected with optimisation of media flow rates throughout the run to better control the cellular microenvironment. High levels of pluripotency marker expression were maintained on the bioreactor, with 97.7 % of cells expressing SSEA-4 when harvested.

Ruan, Y., et al. (2012). "Detection of prostate stem cell antigen expression in human prostate cancer using quantum-dot-based technology." Sensors (Basel) **12**(5): 5461-5470.

Quantum dots (QDs) are a new class of fluorescent labeling for biological and biomedical applications. In this study, we detected prostate stem cell antigen (PSCA) expression correlated with tumor grade and stage in human prostate cancer by QDs-based immunolabeling and conventional immunohistochemistry (IHC), and evaluated the sensitivity and stability of QDs-based immunolabeling in comparison with IHC. Our data revealed that increasing levels of PSCA expression accompanied advanced tumor grade (QDs labeling, $r = 0.732$, $p < 0.001$; IHC, $r = 0.683$, $p < 0.001$) and stage (QDs labeling, $r = 0.514$, $p = 0.001$; IHC, $r = 0.432$, $p = 0.005$), and the similar tendency was detected by the two methods. In addition, by comparison between the two methods, QDs labeling was consistent with IHC in detecting the expression of PSCA in human prostate tissue correlated with different pathological types ($K = 0.845$, $p < 0.001$). During the observation time, QDs exhibited superior stability. The intensity of QDs fluorescence remained stable for two weeks ($p = 0.083$) after conjugation to the PSCA protein, and nearly 93% of positive expression with their fluorescence still could be seen after four weeks.

Shim, Y. and J. M. Song (2015). "Quantum dot nanoprobe-based high-content monitoring of notch pathway inhibition of breast cancer stem cell by capsaicin." Mol Cell Probes **29**(6): 376-381.

Breast cancer is the major cause of cancer death for women worldwide. Breast cancer patients are treated with chemotherapy and radiotherapy. Although chemotherapy and radiotherapy are applied, some cancer cells still survive. These cells, called cancer stem cell (CSC), exhibit special capabilities, such as drug and radio resistance. The remaining CSC can trigger cancer recurrence. Thus, it is critical to find an effective way to target CSC. Capsaicin has been reported to affect anticancer activity in many cancers. It also has been shown that capsaicin induces apoptosis in the MCF-7 breast cancer cell line. In this study, we demonstrate that capsaicin causes dose-

dependent growth disruption in breast CSC and inhibits translocation of notch intracellular membrane domain (NICD) into the nucleus. MCF-7 cells were treated with capsaicin at various concentrations (5 muM, 10 muM, and 20 muM) for 24 h. After capsaicin treatment, it was found that the number of breast CSC (%) decreased as the treatment concentration of capsaicin increased. This result was also confirmed with FACS. NICD translocation to the nucleus and apoptotic cell death of breast CSC were concurrently observed at the single breast CSC level using highly sensitive quantum dot (Qdot)-antibody nanoprobes. The control breast CSCs without the capsaicin treatment were able to translocate NICD into the nucleus. On the other hand, translocation of NICD into the nucleus was not observed in capsaicin-treated cells. In addition, apoptotic cell death was caused when the breast CSC were treated with capsaicin at more than 10 muM. Although many studies have shown that capsaicin produces anticancer activity in cancer cell lines, the present result is the first report to demonstrate that capsaicin is capable of causing breast CSC apoptotic cell death via inhibiting its notch signaling pathway.

Shin, W. J., et al. (2017). "Cell Surface Nano-modulation for Non-invasive in vivo Near-IR Stem Cell Monitoring." ChemMedChem **12**(1): 28-32.

A stem cell tracking system is in high demand for the determination of cell destinations and for the validation of cell therapeutic efficacy in regenerative transplantation. To date, near-infrared (NIR) imaging technology has received considerable attention in cell behavior monitoring, owing to its patient compatibility, easy accessibility and cost effectiveness. Conventionally, in vivo cell tracking has been visualized by direct in-cell staining with NIR, where it may be achieved by complicated genetic engineering. Such genetic amendment techniques have suffered from serious challenges, which can destroy a cell's metabolism and can accidentally incur unexpected carcinoma. Herein we demonstrate a novel cell nano-modulation method for noninvasive stem cell monitoring. It is simply achieved by conjugating stem cells with lipid-supported, NIR-tagged, polymeric nanoparticles. These engineered cells, which are designated as NIR-labeled light-emitting stem cells (LESCs), maintain their biochemical functionality (i.e., differentiation, quantum efficacy, etc.) even after conjugation. LESCs were used for in situ stem cell monitoring at inoculation sites. It is speculated that the LESC technique could provide a new preparative methodology for in vivo cell tracking in advanced diagnostic medicine, where cell behavior is a critical issue.

Solanki, A., et al. (2008). "Nanotechnology for regenerative medicine: nanomaterials for stem cell imaging." Nanomedicine (Lond) **3**(4): 567-578.

Although stem cells hold great potential for the treatment of many injuries and degenerative diseases, several obstacles must be overcome before their therapeutic application can be realized. These include the development of advanced techniques to understand and control functions of microenvironmental signals and novel methods to track and guide transplanted stem cells. The application of nanotechnology to stem cell biology would be able to address those challenges. This review details the current challenges in regenerative medicine, the current applications of nanoparticles in stem cell biology and further potential of nanotechnology approaches towards regenerative medicine, focusing mainly on magnetic nanoparticle- and quantum dot-based applications in stem cell research.

Tirughana, R., et al. (2018). "GMP Production and Scale-Up of Adherent Neural Stem Cells with a Quantum Cell Expansion System." Mol Ther Methods Clin Dev **10**: 48-56.

Cell-based therapies hold great promise for a myriad of clinical applications. However, as these therapies move from phase I to phase II and III trials, there is a need to improve scale-up of adherent cells for the production of larger good manufacturing practice (GMP) cell banks. As we advanced our neural stem cell (NSC)-mediated gene therapy trials for glioma to include dose escalation and multiple treatment cycles, GMP production using cell factories (CellStacks) generated insufficient neural stem cell (NSC) yields. To increase yield, we developed an expansion method using the hollow fiber quantum cell expansion (QCE) system. Seeding of 5.2 x 10(7) NSCs in a single unit yielded up to 3 x 10(9) cells within 10 days. These QCE NSCs showed genetic and functional stability equivalent to those expanded by conventional flask-based methods. We then expanded the NSCs in 7 units simultaneously to generate a pooled GMP-grade NSC clinical lot of more than 1.5 x 10(10) cells in only 9 days versus 8 x 10(9) over 6 weeks in CellStacks. We also adenovirally transduced our NSCs within the QCE. We found the QCE system enabled rapid cell expansion and increased yield while maintaining cell properties and reducing process time, labor, and costs with improved efficiency and reproducibility.

Vanikar, A. V., et al. (2016). "Stem cell therapy emerging as the key player in treating type 1 diabetes mellitus." Cytotherapy **18**(9): 1077-1086.

Type 1 diabetes mellitus (T1DM) is an autoimmune disease causing progressive destruction of

pancreatic beta cells, ultimately resulting in loss of insulin secretion producing hyperglycemia usually affecting children. Replacement of damaged beta cells by cell therapy can treat it. Currently available strategies are insulin replacement and islet/pancreas transplantation. Unfortunately these offer rescue for variable duration due to development of autoantibodies. For pancreas/islet transplantation a deceased donor is required and various shortfalls of treatment include quantum, cumbersome technique, immune rejection and limited availability of donors. Stem cell therapy with assistance of cellular reprogramming and beta-cell regeneration can open up new therapeutic modalities. The present review describes the history and current knowledge of T1DM, evolution of cell therapies and different cellular therapies to cure this condition.

Wang, L., et al. (2017). "Fluorescent Poly (glycerol-co-sebacate) Acrylate Nanoparticles for Stem Cell Labeling and Longitudinal Tracking." ACS Appl Mater Interfaces **9**(11): 9528-9538.

The stable presence of fluorophores within the biocompatible and biodegradable elastomer poly (glycerol-co-sebacate) acrylate (PGSA) is critical for monitoring the transplantation, performance, and degradation of the polymers in vivo. However, current methods such as physically entrapping the fluorophores in the polymer matrix or providing a fluorescent coating suffer from rapid leakage of fluorophores. Covalent conjugation of fluorophores with the polymers and the subsequent core-cross-linking are proposed here to address this challenge. Taking rhodamine as the model dye and PGSA nanoparticles (NPs) as the model platform, we successfully showed that the synthesized rhodamine-conjugated PGSA (PGSAR) NPs only released less than 30% rhodamine at day 28, whereas complete release of dye occurred for rhodamine-encapsulated PGSA (PGSA-p-R) NPs at day 7 and 57.49% rhodamine was released out for the un-cross-linked PGSAR NPs at day 28. More excitingly, PGSAR NPs showed a strong quantum yield enhancement (26.24-fold) of the fluorophores, which was due to the hydrophobic environment within PGSAR NPs and the restricted rotation of (6-diethylamino-3H-xanthen-3-ylidene) diethyl group in rhodamine after the conjugation and core-cross-linking. The stable presence of dye in the NPs and enhanced fluorescence allowed a longitudinal tracking of stem cells both in vitro and in vivo for at least 28 days.

Wang, Y., et al. (2013). "Commercial nanoparticles for stem cell labeling and tracking." Theranostics **3**(8): 544-560.

Stem cell therapy provides promising solutions for diseases and injuries that conventional medicines and therapies cannot effectively treat. To achieve its full therapeutic potentials, the homing process, survival, differentiation, and engraftment of stem cells post transplantation must be clearly understood. To address this need, non-invasive imaging technologies based on nanoparticles (NPs) have been developed to track transplanted stem cells. Here we summarize existing commercial NPs which can act as contrast agents of three commonly used imaging modalities, including fluorescence imaging, magnetic resonance imaging and photoacoustic imaging, for stem cell labeling and tracking. Specifically, we go through their technologies, industry distributors, applications and existing concerns in stem cell research. Finally, we provide an industry perspective on the potential challenges and future for the development of new NP products.

Yiu, H. H., et al. (2010). "Preparation and characterization of iron oxide-silica composite particles using mesoporous SBA-15 silica as template and their internalization into mesenchymal stem cell and human bone cell lines." IEEE Trans Nanobioscience **9**(3): 165-170.

A new procedure for preparing iron oxide-silica nanocomposite particles using SBA-15 mesoporous silica as a template is described. These composite materials retained the 2-D hexagonal structure of the SBA-15 template. Transmission electron micrograms of the particles depicted the formation of iron oxide nanocrystals inside the mesochannels of SBA-15 silica framework. Powder x-ray diffraction showed that the iron oxide core of the composite particles consists of a mixture of maghemite (gamma-Fe (2)O (3)) and heamatite (alpha-Fe (2)O (3)), which is the predominant component. Superconducting quantum interference device (SQUID) magnetometry studies showed that these iron oxide-silica composite materials exhibit superparamagnetic properties. On increasing the iron oxide content, the composite particles exhibited a stronger response to magnetic fields but a less homogeneous core, with some large iron oxide particles which were thought to be formed outside the mesochannels of the SBA-15 template. Internalization of these particles into human cell lines (mesenchymal stem cells and human bone cells), which indicates their potential in medicine and biotechnology, is also discussed.

Yoo, M., et al. (2014). "Analysis of human embryonic stem cells with regulatable expression of the cell adhesion molecule l1 in regeneration after spinal cord injury." J Neurotrauma **31**(6): 553-564.

Cell replacement therapy is one potential avenue for central nervous system (CNS) repair. However, transplanted stem cells may not contribute to long-term recovery of the damaged CNS unless they are engineered for functional advantage. To fine tune regenerative capabilities, we developed a human neural cell line expressing L1, a regeneration-conducive adhesion molecule, under the control of a doxycycline regulatable Tet-off promoter. Controlled expression of L1 is desired because overexpression after regenerative events may lead to adverse consequences. The regulated system was tested in several cell lines, where doxycycline completely eliminated green fluorescent protein or L1 expression by 3-5 days in vitro. Increased colony formation as well as decreased proliferation were observed in H9NSCs without doxycycline (hL1-on). To test the role of L1 in vivo after acute compression spinal cord injury of immunosuppressed mice, quantum dot labeled hL1-on or hL1-off cells were injected at three sites: lesion; proximal; and caudal. Mice transplanted with hL1-on cells showed a better Basso Mouse Scale score, when compared to those with hL1-off cells. As compared to the hL1-off versus hL1-on cell transplanted mice 6 weeks post-transplantation, expression levels of L1, migration of transplanted cells, and immunoreactivity for tyrosine hydroxylase were higher, whereas expression of chondroitin sulfate proteoglycans was lower. Results indicate that L1 expression is regulatable in human stem cells by doxycycline in a nonviral engineering approach. Regulatable expression in a prospective nonleaky Tet-off system could hold promise for therapy, based on the multifunctional roles of L1, including neuronal migration and survival, neuritogenesis, myelination, and synaptic plasticity.

Yukawa, H., et al. (2013). "Induced Pluripotent Stem Cell Labeling Using Quantum Dots." Cell Med **6**(1-2): 83-90.

Induced pluripotent stem (iPS) cells have received remarkable attention as the cell sources for clinical applications of regenerative medicine including stem cell therapy. Additionally, labeling technology is in high demand for tracing transplanted cells used in stem cell therapy. In this study, we used quantum dots (QDs), which have distinct fluorescence abilities in comparison with traditional probes, as the labeling materials and investigated whether iPS cells could be labeled with QDs with no cytotoxicity. iPS cells could not be labeled with QDs alone but required the use of cell-penetrating peptides such as octaarginine (R8). No significant cytotoxicity to iPS cells was confirmed by up to 8 nM QDs, and the iPS cells labeled with QDs maintained their undifferentiated state and pluripotency. These data suggest that QDs can be used for fluorescence labeling of iPS cells.

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