Stem Cell and Regenerative Medicine Literatures

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Abstract: The definition of stem cell is "an unspecialized cell that gives rise to a specific specialized cell, such as a blood cell". Stem Cell is the original of life. All cells come from stem cells. Serving as a repair system for the living body, the stem cells can divide without limit to replenish other cells as long as the living body is still alive. When a stem cell divides, each new cell has the potential to either remain a stem cell situation or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, a bone cell, a nerve cell, or a brain cell. Stem cell research is a typical and important topic of life science. This material collects some literatures on stem cell and regenerative medicine.
[Smith MH. **Stem Cell and Regenerative Medicine Literatures.** *Stem Cell* 2013;4(1):53-64] (ISSN 1545-4570). http://www.sciencepub.net/stem. 4

Key words: stem cell; life; gene; DNA; protein; regenerative medicine

Literatures:

Abuljadayel, I. S. (2006). "Harnessing pluripotency from differentiated cells: a regenerative source for tissue-specific stem cell therapies." Curr Stem Cell Res Ther **1**(3): 325-31.

Processes involving conversion of mature adult cells into undifferentiated cells have tremendous therapeutic potential in treating a variety of malignant and non-malignant disorders, including degenerative diseases. This can be achieved in autologous or allogeneic settings, by replacing either defective cells or regenerating those that are in deficit through reprogramming more committed cells into stem cells. The concept behind reprogramming differentiated cells to a stem cell state is to enable the switching of development towards the required cell lineage that is capable of correcting the underlying cellular dysfunction. The techniques by which differentiated cells can reverse their development, become pluripotent stem cells and transdifferentiate to give rise to new tissue or an entire organism are currently under intense investigation. Examples of reprogramming differentiation in mature adult cells include nuclear reprogramming of more committed cells using the cytoplasm of empty oocytes obtained from a variety of animal species, or cell surface contact of differentiated cells through receptor ligand interaction. Such ligands include monoclonal antibodies, cytokines or synthetic chemical compounds. Despite controversies surrounding such techniques, the concept behind identification and design/screening of biological or pharmacological compounds to enable re-switching of cell fate in-vivo or ex-vivo is paramount for current drug therapies to be able to target more specifically cellular dysfunction at the tissue/organ level. Herein, this review discusses current research in cellular reprogramming and its potential application in regenerative medicine.

Alvarez, A., F. Unda, et al. (2009). "Stem cell and regenerative medicine." Curr Stem Cell Res Ther **4**(4): 287-97.

Stem cells have been identified and isolated in many adult tissues. They exhibit a great plasticity and the ability to give rise to differentiated cells of several lineages. The possibility of transplantation of these stem cells into an adult to develop, integrate and rebuild destroyed tissues or organs has encouraged the study of the mechanisms of the differentiation of stem cells. These cells are nowadays being called a panacea in numerous diseases and, although their functional role is not well known, they are present in several areas of the human therapy, increasing the clinical applications. They represent the future of the transplant in medicine, and open, moreover, new perspectives in the treatment of diseases, as it is the case of the regenerative medicine. Here we review the current literature examining several aspect of medical therapy such as the applicability of experimental models to clinical practice.

Audet, J. (2004). "Stem cell bioengineering for regenerative medicine." Expert Opin Biol Ther **4**(5): 631-44.

Stem cells can be used to treat a variety of diseases and several recent studies in animal models demonstrate the potential of bioengineering strategies targeting adult and embryonic stem cells. In order to obtain the desired cells for transplantation, stem cell bioengineering approaches entail the manipulation of environmental signals influencing cell survival, proliferation, self-renewal and differentiation. In that regard, multivariate analytical approaches have been

used with success to optimise different stem cell culture processes. The genetic or molecular enhancement of stem cells is also a powerful means to control their proliferation or differentiation or to correct genetic defects in recipients. In the future, systems-level approaches have the potential to revolutionise the field of stem cell bioengineering by improving our understanding of regulatory networks controlling cellular behaviour. This advance in basic biology will be instrumental for the implementation of many stem cell-based regenerative therapies at the clinical level, as treatment accessibility will depend on the development of robust technologies to produce sufficient cell numbers.

Blackmore, D. G., M. G. Golmohammadi, et al. (2009). "Exercise increases neural stem cell number in a growth hormone-dependent manner, augmenting the regenerative response in aged mice." Stem Cells **27**(8): 2044-52.

The exercise-induced enhancement of learning and memory, and its ability to slow age-related cognitive decline in humans led us to investigate whether running stimulates periventricular (PVR) neural stem cells (NSCs) in aging mice, thereby augmenting the regenerative capacity of the brain. To establish a benchmark of normal aging on endogenous NSCs, we harvested the PVR from serial vibratome sections through the lateral ventricles of juvenile (6-8 weeks), 6-, 12-, 18-, and 24-month-old mice, culturing the cells in the neural colony-forming cell assay. A significant decline in NSC frequency was apparent by 6 months (approximately 40%), ultimately resulting in a approximately 90% reduction by 24 months. Concurrent with this decline was a progressive loss in regenerative capacity, as reflected by an incomplete repopulation of neurosphere-forming cells following gamma cell irradiation-induced depletion of the PVR. However, voluntary exercise (i.e., 21 days of running) significantly increased NSC frequency in mice > or = 18 months of age, augmenting the regeneration of irradiation-ablated periventricular cells and restoring NSC numbers to youthful levels. Importantly, and consistent with the demonstrated ability of growth hormone (GH) to increase NSC proliferation, and the elevated secretion of GH during exercise, exercise failed to stimulate NSCs in GH receptor-null mice. These findings now provide a novel basis for understanding the ability of exercise to delay the onset and rate of decline in neurodegenerative conditions not typically associated with the hippocampus and suggest that the GH-dependent activation of endogenous NSCs may be effective in reversing or preventing age-related neurodegeneration in humans.

Bushell, W. C. (2005). "From molecular biology to anti-aging cognitive-behavioral practices: the pioneering research of Walter Pierpaoli on the pineal and bone marrow foreshadows the contemporary revolution in stem cell and regenerative biology." Ann N Y Acad Sci **1057**: 28-49.

Evidence is accruing that a cognitive-behavioral regimen integrating cognitive techniques (meditation-based anti-stress, anti-inflammatory techniques, others), dietary modification ("dietary restriction" or modified dietary restriction), and certain forms of aerobic exercise, may prolong the healthy life span in humans. Recent research has identified some of the likely molecular mediators of these potentially broad-ranging, health-enhancing and anti-aging effects; these include DHEA, interleukins -10 and -4 (IL-10, 1L-4), and especially melatonin. Relatedly, what some are calling a revolution in biology and medicine has been emerging from research on stem cells and regeneration processes more generally. Dogma regarding limitations on the regenerative capacities of adult vertebrates is being cautiously yet enthusiastically revised in the wake of rapidly accumulating discoveries of more types of adult stem cells in mammals, including humans. For example, a recent review by D. Krause of Yale concluded that "in the [adult] bone marrow, in addition to hematopoietic stem cells and supportive stromal cells, there are cells with the potential to differentiate into mature cells of the heart, liver, kidney, lungs, GI tract, skin, bone, muscle, cartilage, fat, endothelium and brain." In addition, very recent studies have shown that DHEA, ILs-10 and -4, and melatonin all possess potential regenerative, including stem cell-activating, properties. More than a quarter of a century ago, Walter Pierpaoli initiated a series of extraordinary studies that demonstrated in experimental animals the potential for dramatic regeneration associated with changes in the pineal gland and bone marrow. This appeared to be not only retardation of aging, but also its reversal. Furthermore, as Pierpaoli was attempting to understand both anti-aging regeneration and oncogenesis, he was focusing on both pro- and anti-mitotic mechanisms: recent research now suggests that there is a nonpathologic, "healthy" form of regeneration that is actually antagonistic to oncogenesis, and that melatonin may be important in this form of regeneration. This paper explores Pierpaoli's pioneering studies in light of recent developments in stem cell and regenerative biology, particularly as related to the regenerative potential associated with certain cognitive-behavioral practices, and includes evidence on this subject presented for the first time.

Carlson, M. E. and I. M. Conboy (2007). "Loss of stem cell regenerative capacity within aged niches." Aging Cell **6**(3): 371-82.

This work uncovers novel mechanisms of aging within stem cell niches that are evolutionarily conserved between mice and humans and affect both embryonic and adult stem cells. Specifically, we have examined the effects of aged muscle and systemic niches on key molecular identifiers of regenerative potential of human embryonic stem cells (hESCs) and post-natal muscle stem cells (satellite cells). Our results reveal that aged differentiated niches dominantly inhibit the expression of Oct4 in hESCs and Myf-5 in activated satellite cells, and reduce proliferation and myogenic differentiation of both embryonic and tissue-specific adult stem cells (ASCs). Therefore, despite their general neoorganogenesis potential, the ability of hESCs, and the more differentiated myogenic ASCs to contribute to tissue repair in the old will be greatly restricted due to the conserved inhibitory influence of aged differentiated niches. Significantly, this work establishes that hESC-derived factors enhance the regenerative potential of both young and, importantly, aged muscle stem cells in vitro and in vivo; thus, suggesting that the regenerative outcome of stem cell-based replacement therapies will be determined by a balance between negative influences of aged tissues on transplanted cells and positive effects of embryonic cells on the endogenous regenerative capacity. Comprehensively, this work points toward novel venues for in situ restoration of tissue repair in the old and identifies critical determinants of successful cell-replacement therapies for aged degenerating organs.

Dominici, M., R. Marino, et al. (2008). "Donor cell-derived osteopoiesis originates from a self-renewing stem cell with a limited regenerative contribution after transplantation." Blood **111**(8): 4386-91.

In principle, bone marrow transplantation should offer effective treatment for disorders originating from defects in mesenchymal stem cells. Results with the bone disease osteogenesis imperfecta support this hypothesis, although the rate of clinical improvement seen early after transplantation does not persist long term, raising questions as to the regenerative capacity of the donor-derived mesenchymal progenitors. We therefore studied the kinetics and histologic/anatomic pattern of osteopoietic engraftment after transplantation of GFP-expressing nonadherent marrow cells in mice. Serial tracking of donor-derived GFP(+) cells over 52 weeks showed abundant clusters of donor-derived osteoblasts/osteocytes in the epiphysis and metaphysis but not the diaphysis, a distribution that paralleled the sites of initial hematopoietic engraftment. Osteopoietic chimerism decreased from approximately 30% to 10% by 24 weeks after transplantation, declining to negligible levels thereafter. Secondary transplantation studies provided evidence for a self-renewing osteopoietic stem cell in the marrow graft. We conclude that a transplantable, primitive, self-renewing osteopoietic cell within the nonadherent marrow cell population engrafts in an endosteal niche, like hematopoietic stem cells, and regenerates a significant fraction of all bone cells. The lack of durable donor-derived osteopoiesis may reflect an intrinsic genetic program or exogenous environmental signaling that suppresses the differentiation capacity of the donor stem cells.

Faustman, D. L. (2005). "Regenerative medicine: Stem cell research turns to the spleen." Discov Med **5**(29): 447-9.

Extract: Though conventional medical wisdom has long considered the spleen a dispensable organ, it appears to be more than it seems. Newly identified stem cell populations have been found in the spleen of adult mice, challenging conventional wisdom and providing a potential source of stem cells for treating disease. These stem cells are relevant to future cellular therapies for diabetes and other diseases. At the interface of the circulatory and immune systems, the spleen normally has dual roles in maintenance and adaptation to stress or disease. The red pulp of the spleen holds macrophages (a type of white blood cell) that normally filter and remove cellular debris and bacteria from the circulation. The white pulp of the spleen -- its lymphoid compartment -- is crucial for immune surveillance and response. It creates antibodies against invading pathogens (infectious agents) and releases platelets and neutrophils (another type of white blood cell) in response to bleeding or infection. The spleen also has a lesser known but well-documented function. It has long been established that the spleen contains a reserve population of hematopoietic, or blood-forming, stem cells that is tapped when the bone marrow cannot fully meet the body's demand in times of stress and disease.

Franco, D., N. Moreno, et al. (2007). "Non-resident stem cell populations in regenerative cardiac medicine." Cell Mol Life Sci **64**(6): 683-91.

The adult heart displays a low proliferation capacity, compromising its function if exposed to distinct biological insults. Interestingly, the observation that an increasing number of cell types display an unpredicted cellular plasticity has opened new therapeutical avenues. In this review we will summarize the current knowledge of non-resident stem cells that can be putatively used for cardiac

regeneration. At present, bone marrow stem cells have been extensively studied as a cellular source to heal the heart; however, their myocardial contribution is highly limited. Experimental studies have demonstrated that skeletal myoblasts can engraft into the heart, although, unfortunately, they lead to myocardial uncoupling. Embryonic stem cells can spontaneously generate cardiomyocytes that exhibit a variety of electrophysiological phenotypes. Several constrains should nonetheless be overcome before entering the clinical arena, such as the ability to direct and control the generation of cardiomyocytes into a single myocardial lineage.

Illa-Bochaca, I. and L. M. Montuenga (2006). "The regenerative nidi of the locust midgut as a model to study epithelial cell differentiation from stem cells." J Exp Biol **209**(Pt 11): 2215-23.

A better knowledge of the regulatory mechanisms involved in stem cell proliferation and/or differentiation could reveal new methods for the treatment of some diseases. Most previous studies in the field of stem cell biology have been carried out on cultured isolated cells. In the case of adult tissue stem cells, mesenchymal bone marrow derived cells have been most widely studied, while the undifferentiated stem cells present in the epithelial tissues are less known. In order to advance further our understanding of epithelial tissue stem cells, new in vivo models are required. The present study focuses on the dynamics of a new and simple model of intestinal epithelial regeneration found in the midgut of the migratory locust, Locusta migratoria (Linnaeus 1758). The locust midgut consists of three cell types: columnar cells, endocrine cells and undifferentiated regenerative clustered cells. The undifferentiated epithelial midgut cells give rise to two other cell types and are located in a nest of regenerative cells known as regenerative niche. We have performed single and continuous bromodeoxyuridine (BrdU) administration experiments to study regeneration niches and their cellular dynamics. Immunocytochemistry and immunofluorescence techniques were used to detect the incorporation of BrdU into regenerative niches and the presence of FMRFamide-like immunoreactivity, as a marker for endocrine cell differentiation. Some isolated label retaining cells (LRC) were observed at the niche base 10-15 days after the final BrdU administration. We propose that these cells are the stem cells of this epithelial tissue. We also calculated the length of the cell cycle phases for a subpopulation of transit amplifying cells within the regenerative niche: G1, 2.5+/-0.5 h; S, 5.5+/-0.5 h; G2, 0.75+/-0.25 h; M, 2.5+/-0.5 h. These amplifying cells will give rise to the columnar epithelial non-endocrine lineage. The differentiation of an endocrine cell from a niche stem cell occurs less frequently and thus leads to a lower proportion of endocrine cells as compared with epithelial columnar digestive cells (up to three endocrine cells per niche). Endocrine cell commitment seems to occur very early in the differentiation process within the niche, as double-labelled BrdU and FMRF endocrine cells have never been found. The only exception is the endocrine cells located in the ampullar region of the midgut, some of which show double immunostaining after long-term chronic BrdU injection. In summary, we have characterized a new and simple animal model of epithelial stem cell regeneration that may be useful for understanding the complex biological process that drives tissue renewal from undifferentiated and uncommitted progenitor cells.

Jain, K. K. (2002). "Stem cell technologies in regenerative medicine." Expert Opin Biol Ther **2**(7): 771-3.

The IIR Life Sciences conference on stem cell technologies in regenerative medicine was held in London, UK on 11 - 12 July 2002. The conference covered not only technologies but also ethical/regulatory and financial aspects of embryonic stem (ES) cell therapy. An excellent introduction to embryonic stem cells was given by Prof. William Kridel (Ferghana Partners, London, UK). Details of basic technologies are not described as they are covered in a detailed report on cell therapy [1]. Due to limitation of space only a selected few of the seventeen presentations are reported here.

Jankowski, R. J. and J. Huard (2004). "Establishing reliable criteria for isolating myogenic cell fractions with stem cell properties and enhanced regenerative capacity." Blood Cells Mol Dis **32**(1): 24-33.

Despite a focused effort within the myogenic cell transplantation community, little progress has been made toward the reliable identification and isolation of progenitors that are capable of tolerating the initial posttransplantation environment and effectively regenerating clinically relevant quantities of muscle. The future success of myogenic-based treatment modalities requires an enhanced understanding of the highly heterogeneous nature of the myogenic progenitor cell pool, which has been previously documented by numerous researchers. Further, for translation of experimental animal results to clinical application, reliable in vitro selection criteria must be established and must be translatable across species. While research into the utility of surface markers is ongoing, as an alternative we have investigated in vitro cell behavioral characteristics under imposed conditions which challenge the propensity of myogenic progenitors to choose between

various cell fates (i.e., proliferation, quiescence, or differentiation). Previous observations in the mouse suggest an enhanced in vivo regenerative capacity of myogenic populations with respect to their in vitro ability to maintain a proliferative and undifferentiated state [J. Cell Sci. 115 (2002) 4361]. From these observations it is thus proposed that such behavior may represent an a priori indicator of regenerative capacity following transplantation. To challenge this proposition, a rat cell isolation and transplantation model was evaluated in an identical manner. In agreement with the results obtained from the mouse, a significant correlation between regenerative capacity and induction of differentiation was observed. These results contribute to the growing body of scientific evidence documenting the underlying behavioral differences that exist between various myogenic progenitors while also, importantly, providing evidence that such differences may significantly impact the functional capabilities of these cells posttransplantation. This information further implies that from a therapeutic standpoint isolation strategies aimed toward obtaining efficient myogenic progenitors should, in the absence of a reliable surface marker(s), focus on identifying populations displaying desirable in vitro behavior (i.e., high proliferative capacity and low induced differentiation). Incorporating such criteria into cell isolation and/or purification schemes may yield significant returns in the clinical myogenic transplantation setting.

Karlsson, C., K. Emanuelsson, et al. (2009). "Human embryonic stem cell-derived mesenchymal progenitors--potential in regenerative medicine." Stem Cell Res **3**(1): 39-50.

Tissue engineering and cell therapy require large-scale production of homogeneous populations of lineage-restricted progenitor cells that easily can be induced to differentiate into a specific tissue. We have developed straightforward protocols for the establishment of human embryonic stem (hES) cell-derived mesenchymal progenitor (hES-MP) cell lines. The reproducibility was proven by derivation of multiple hES-MP cell lines from 10 different hES cell lines. To illustrate clinical applicability, a xeno-free hES-MP cell line was also derived. None of the markers characteristic for undifferentiated hES cells were detected in the hES-MP cells. Instead, these cells were highly similar to mesenchymal stem cells with regard to morphology and expression of markers. The safety of hES-MP cells following transplantation was studied in severely combined immunodeficient (SCID) mice. The implanted hES-MP cells gave rise to homogeneous, well-differentiated tissues exclusively of mesenchymal origin and no teratoma formation was observed. These cells further have the potential to differentiate toward the osteogenic, adipogenic, and chondrogenic lineages in vitro. The possibility of easily and reproducibly generating highly expandable hES-MP cell lines from well-characterized hES cell lines with differentiation potential into several mesodermal tissues entails an enormous potential for the field of regenerative medicine.

Katoh, M. (2008). "WNT signaling in stem cell biology and regenerative medicine." Curr Drug Targets **9**(7): 565-70.

WNT family members are secreted-type glycoproteins to orchestrate embryogenesis, to maintain homeostasis, and to induce pathological conditions. FZD1, FZD2, FZD3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, FZD10, LRP5, LRP6, and ROR2 are transmembrane receptors transducing WNT signals based on ligand-dependent preferentiality for caveolin- or clathrin-mediated endocytosis. WNT signals are transduced to canonical pathway for cell fate determination, and to non-canonical pathways for regulation of planar cell polarity, cell adhesion, and motility. MYC, CCND1, AXIN2, FGF20, WISP1, JAG1, DKK1 and Glucagon are target genes of canonical WNT signaling cascade, while CD44, Vimentin and STX5 are target genes of non-canonical WNT signaling cascades. However, target genes of WNT signaling cascades are determined in a context-dependent manner due to expression profile of transcription factors and epigenetic status. WNT signaling cascades network with Notch, FGF, BMP and Hedgehog signaling cascades to regulate the balance of stem cells and progenitor cells. Here WNT signaling in embryonic stem cells, neural stem cells, mesenchymal stem cells, hematopoietic stem cells, and intestinal stem cells will be reviewed. WNT3, WNT5A and WNT10B are expressed in undifferentiated human embryonic stem cells, while WNT6, WNT8B and WNT10B in endoderm precursor cells. Wnt6 is expressed in intestinal crypt region for stem or progenitor cells. TNF/alpha-WNT10B signaling is a negative feedback loop to maintain homeostasis of adipose tissue and gastrointestinal mucosa with chronic inflammation. Recombinant WNT protein or WNT mimetic (circular peptide, small molecule compound, or RNA aptamer) in combination with Notch mimetic, FGF protein, and BMP protein opens a new window to tissue engineering for regenerative medicine.

Knoepfler, P. S. (2009). "Deconstructing stem cell tumorigenicity: a roadmap to safe regenerative medicine." Stem Cells **27**(5): 1050-6.

Many of the earliest stem cell studies were conducted on cells isolated from tumors rather than

from embryos. Of particular interest was research on embryonic carcinoma cells (EC), a type of stem cell derived from teratocarcinoma. The EC research laid the foundation for the later discovery of and subsequent work on embryonic stem cells (ESC). Both ESC isolated from the mouse (mESC) and then later from humans (hESC) shared not only pluripotency with their EC cousins, but also robust tumorigenicity as each readily form teratoma. Surprisingly, decades after the discovery of mESC, the question of what drives ESC to form tumors remains largely an open one. This gap in the field is particularly serious as stem cell tumorigenicity represents the key obstacle to the safe use of stem cell-based regenerative medicine therapies. Although some adult stem cell therapies appear to be safe, they have only a very narrow range of uses in human disease. Our understanding of the tumorigenicity of human induced pluripotent stem cells (IPSC), perhaps the most promising modality for future patient-specific regenerative medicine therapies, is rudimentary. However, IPSC are predicted to possess tumorigenic potential equal to or greater than that of ESC. Here, the links between pluripotency and tumorigenicity are explored. New methods for more accurately testing the tumorigenic potential of IPSC and of other stem cells applicable to regenerative medicine are proposed. Finally, the most promising emerging approaches for overcoming the challenges of stem cell tumorigenicity are highlighted.

Koch, T. G., L. C. Berg, et al. (2009). "Current and future regenerative medicine - principles, concepts, and therapeutic use of stem cell therapy and tissue engineering in equine medicine." Can Vet J **50**(2): 155-65.

This paper provides a bird's-eye perspective of the general principles of stem-cell therapy and tissue engineering; it relates comparative knowledge in this area to the current and future status of equine regenerative medicine.The understanding of equine stem cell biology, biofactors, and scaffolds, and their potential therapeutic use in horses are rudimentary at present. Mesenchymal stem cell isolation has been proclaimed from several equine tissues in the past few years. Based on the criteria of the International Society for Cellular Therapy, most of these cells are more correctly referred to as multipotent mesenchymal stromal cells, unless there is proof that they exhibit the fundamental in vivo characteristics of pluripotency and the ability to self-renew. That said, these cells from various tissues hold great promise for therapeutic use in horses. The 3 components of tissue engineering - cells, biological factors, and biomaterials - are increasingly being applied in equine medicine, fuelled by better scaffolds and increased understanding of individual biofactors and cell sources.The effectiveness of stem cell-based therapies and most tissue engineering concepts has not been demonstrated sufficiently in controlled clinical trials in equine patients to be regarded as evidence-based medicine. In the meantime, the medical mantra "do no harm" should prevail, and the application of stem cell-based therapies in the horse should be done critically and cautiously, and treatment outcomes (good and bad) should be recorded and reported.Stem cell and tissue engineering research in the horse has exciting comparative and equine specific perspectives that most likely will benefit the health of horses and humans. Controlled, well-designed studies are needed to move this new equine research field forward.

Kramer, J., F. Bohrnsen, et al. (2006). "Stem cell-derived chondrocytes for regenerative medicine." Transplant Proc **38**(3): 762-5.

The regenerative capacity of cartilage is limited. Transplantation methods used to treat cartilage lesions are based mainly on primary cultures of chondrocytes, which dedifferentiate during cultivation in vitro and lose their functional properties. Stem cells are considered as an alternative source to generate cells for two reasons: first, they can almost indefinitely divide in culture, and second, they are able to differentiate into various mature cell types. Herein, we asked the question whether chondrocytes could be differentiated from mouse embryonic stem (ES) cells to a state suitable for regenerative use. When cultivated as embryoid bodies (EBs), murine ES cells differentiate into mesenchymal progenitor cells, which progressively develop into mature, hypertrophic chondrocytes and transdifferentiate into calcifying cells recapitulating all of the cellular processes of chondrogenesis. Chondrocytes isolated from EBs exhibit a high regenerative capacity. They dedifferentiate initially in culture, but later reexpress stable characteristics of mature chondrocytes. However, in cultures of chondrocytes isolated from EBs, additional mesenchymal cell types can be observed. Mesenchymal stem (MS) cells from bone marrow have already been used in tissue engineering settings. We compared the chondrogenic differentiation of MS and ES cells.

Kume, S. (2005). "Stem-cell-based approaches for regenerative medicine." Dev Growth Differ **47**(6): 393-402.

Recent success in transplantation of islets raises the hopes of diabetic patients that replacement therapies may be a feasible treatment of their disease. Although several lines of evidence suggest that stem cells exist in the pancreas, it is still technically hard for us to isolate or maintain the stem cells in vitro. The establishment of human embryonic stem (ES) cells

has excited scientists regarding their potential medical use in tissue replacement therapy. When applied with appropriate signals, ES cells can be directed to differentiate into a specific cell lineage. Therefore, ES cells are no doubt an excellent source not only for regenerative medicine but also for studies of early events of pancreatic development, and to portray the pancreatic progenitor cells. Despite many attempts that have been tried, the efficiency of differentiation of ES cells into islets is still very low. This low efficiency reflects our lack of understanding of the intrinsic and extrinsic signals which regulate the developmental processes of the pancreas. In this review, I present a summary of recent works on ES cells, the identification of pancreatic progenitor cells from the adult pancreas, and refer to the possibilities of transdifferentiation from adult stem cells derived from other tissues.

Mimeault, M., R. Hauke, et al. (2007). "Stem cells: a revolution in therapeutics-recent advances in stem cell biology and their therapeutic applications in regenerative medicine and cancer therapies." Clin Pharmacol Ther **82**(3): 252-64.

Basic and clinical research accomplished during the last few years on embryonic, fetal, amniotic, umbilical cord blood, and adult stem cells has constituted a revolution in regenerative medicine and cancer therapies by providing the possibility of generating multiple therapeutically useful cell types. These new cells could be used for treating numerous genetic and degenerative disorders. Among them, age-related functional defects, hematopoietic and immune system disorders, heart failures, chronic liver injuries, diabetes, Parkinson's and Alzheimer's diseases, arthritis, and muscular, skin, lung, eye, and digestive disorders as well as aggressive and recurrent cancers could be successfully treated by stem cell-based therapies. This review focuses on the recent advancements in adult stem cell biology in normal and pathological conditions. We describe how these results have improved our understanding on critical and unique functions of these rare sub-populations of multipotent and undifferentiated cells with an unlimited self-renewal capacity and high plasticity. Finally, we discuss some major advances to translate the experimental models on ex vivo and in vivo expanded and/or differentiated stem cells into clinical applications for the development of novel cellular therapies aimed at repairing genetically altered or damaged tissues/organs in humans. A particular emphasis is made on the therapeutic potential of different tissue-resident adult stem cell types and their in vivo modulation for treating and curing specific pathological disorders.

Mironov, V., R. P. Visconti, et al. (2004). "What is regenerative medicine? Emergence of applied stem cell and developmental biology." Expert Opin Biol Ther **4**(6): 773-81.

Regenerative medicine is an emerging, but still poorly defined, field of biomedicine. The ongoing 'regenerative medicine revolution' is based on a series of new exciting breakthrough discoveries in the field of stem cell biology and developmental biology. The main problem of regenerative medicine is not so much stem cell differentiation, isolation and lineage diversity, although these are very important issues, but rather stem cell mobilisation, recruitment and integration into functional tissues. The key issue in enhancing tissue and organ regeneration is how to mobilise circulating stem and progenitor cells and how to provide an appropriate environment ('niche') for their tissue and organo-specific recruitment, 'homing' and complete functional integration. We need to know more about basic tissue biology, tissue regeneration and the cellular and molecular mechanisms of tissue turnover (both cellular and extracellular components) at different periods of human life and in different diseases. Systematic in silico, in vitro and in vivo research is a foundation for further progress in regenerative medicine. Regenerative medicine is a rapidly advancing field that opens new and exciting opportunities for completely revolutionary therapeutic modalities and technologies. Regenerative medicine is, at its essence, an emergence of applied stem cell and developmental biology.

Payne, N., C. Siatskas, et al. (2008). "The promise of stem cell and regenerative therapies for multiple sclerosis." J Autoimmun **31**(3): 288-94.

The regenerative capacity of the adult central nervous system (CNS) is severely limited and although partial regeneration can be observed in the CNS of multiple sclerosis (MS) patients, these attempts at repair have been universally unsuccessful in preventing the accumulation of irreversible neurological deficits. Novel therapies to treat MS must therefore take into account the need for both immunomodulation and neuroprotection and, as such, multifaceted treatment strategies are required. Two complimentary approaches that aim to regenerate an incapacitated CNS have recently emerged. Firstly, targeting degraded myelin growth inhibitory molecules released as a consequence of the inflammatory process provides a unique opportunity to manipulate the microenvironment of the degenerating CNS. Proof of concept studies have established that this therapeutic approach has tremendous potential in regenerating damaged axons as demonstrated in models of spinal cord injury (SCI)

and experimental autoimmune encephalomyelitis (EAE), an animal model for MS. In addition, stem cell based therapies offer a means of modulating inflammatory immune cells and promoting tissue repair as shown in a number of allogeneic transplant and autoimmune settings. This review attempts to summarise some of these approaches.

Perin, L., S. Giuliani, et al. (2008). "Stem cell and regenerative science applications in the development of bioengineering of renal tissue." Pediatr Res **63**(5): 467-71.

A rising number of patients with acute and chronic renal failure worldwide have created urgency for clinicians and investigators to search out alternative therapies other than chronic renal dialysis and/or organ transplantation. This review focuses on the recent achievements in this area, and discusses the various approaches in the development of bioengineering of renal tissue including recent discoveries in the field of regenerative medicine research and stem cells. A variety of stem cells, ranging from embryonic, bone marrow, endogenous, and amniotic fluid, have been investigated and may prove useful as novel alternatives for organ regeneration both in vitro and in vivo. Tissue engineering, developmental biology, and therapeutic cloning techniques have significantly contributed to our understanding of some of the molecular mechanisms involved in renal regeneration and have demonstrated that renal tissue can be generated de novo with similar physiologic functions as native tissue. Ultimately all of these emerging technologies may provide viable therapeutic options for regenerative medicine applications focused on the bioengineering of renal tissue for the future.

Plikus, M. V., R. B. Widelitz, et al. (2009). "Analyses of regenerative wave patterns in adult hair follicle populations reveal macro-environmental regulation of stem cell activity." Int J Dev Biol **53**(5-6): 857-68.

The control of hair growth in the adult mammalian coat is a fascinating topic which has just begun to be explored with molecular genetic tools. Complex hair cycle domains and regenerative hair waves are present in normal adult (> 2 month) mice, but more apparent in mutants with cyclic alopecia phenotypes. Each hair cycle domain consists of initiation site(s), a propagating wave and boundaries. By analyzing the dynamics of hair growth, time required for regeneration after plucking, in situ hybridization and reporter activity, we showed that there is oscillation of intra-follicular Wnt signaling which is synchronous with hair cycling, and there is oscillation of dermal bone morphogenetic protein (BMP) signaling which is asynchronous with hair cycling. The interactions of these two rhythms lead to the recognition of refractory and competent phases in the telogen, and autonomous and propagating phases in the anagen. Boundaries form when propagating anagen waves reach follicles which are in refractory telogen. Experiments showed that Krt14-Nog mice have shortened refractory telogen and simplified wave dynamics. Krt14-Nog skin grafts exhibit non-autonomous interactions with surrounding host skin. Implantation of BMP coated beads into competent telogen skin prevents hair wave propagation around the bead. Thus, we have developed a new molecular understanding of the classic early concepts of inhibitory "chalone", suggesting that stem cells within the hair follicle micro-environment, or other organs, are subject to a higher level of macro-environmental regulation. Such a novel understanding has important implications in the field of regenerative medicine. The unexpected links with Bmp2 expression in subcutaneous adipocytes has implications for systems biology and Evo-Devo.

Rubenstein, M., Y. Sai, et al. (2009). "Regenerative patterning in Swarm Robots: mutual benefits of research in robotics and stem cell biology." Int J Dev Biol **53**(5-6): 869-81.

This paper presents a novel perspective of Robotic Stem Cells (RSCs), defined as the basic non-biological elements with stem cell like properties that can self-reorganize to repair damage to their swarming organization. Self here means that the elements can autonomously decide and execute their actions without requiring any preset triggers, commands, or help from external sources. We develop this concept for two purposes. One is to develop a new theory for self-organization and self-assembly of multi-robots systems that can detect and recover from unforeseen errors or attacks. This self-healing and self-regeneration is used to minimize the compromise of overall function for the robot team. The other is to decipher the basic algorithms of regenerative behaviors in multi-cellular animal models, so that we can understand the fundamental principles used in the regeneration of biological systems. RSCs are envisioned to be basic building elements for future systems that are capable of self-organization, self-assembly, self-healing and self-regeneration. We first discuss the essential features of biological stem cells for such a purpose, and then propose the functional requirements of robotic stem cells with properties equivalent to gene controller, program selector and executor. We show that RSCs are a novel robotic model for scalable self-organization and self-healing in computer simulations and physical implementation. As our understanding of stem cells advances, we expect that future robots will be more versatile,

resilient and complex, and such new robotic systems may also demand and inspire new knowledge from stem cell biology and related fields, such as artificial intelligence and tissue engineering.

Sakurada, K., F. M. McDonald, et al. (2008). "Regenerative medicine and stem cell based drug discovery." Angew Chem Int Ed Engl **47**(31): 5718-38.

As William Shakespeare beautifully described, increasing age often causes loss of tissue and organ function. The increase in average life expectancy in many countries is generating an aging society and an increase in age-related health problems. Regenerative medicine is expected to be a powerful actor in this drama, and stem cell technology may hold the key to the development of innovative treatments for acute and chronic degenerative conditions. This Review surveys the present situation and some future prospects for regenerative medicine and stem cell based drug discovery.

Santillano, D. R., L. S. Kumar, et al. (2005). "Ethanol induces cell-cycle activity and reduces stem cell diversity to alter both regenerative capacity and differentiation potential of cerebral cortical neuroepithelial precursors." BMC Neurosci **6**: 59.

BACKGROUND: The fetal cortical neuroepithelium is a mosaic of distinct progenitor populations that elaborate diverse cellular fates. Ethanol induces apoptosis and interferes with the survival of differentiating neurons. However, we know little about ethanol's effects on neuronal progenitors. We therefore exposed neurosphere cultures from fetal rat cerebral cortex, to varying ethanol concentrations, to examine the impact of ethanol on stem cell fate. RESULTS: Ethanol promoted cell cycle progression, increased neurosphere number and increased diversity in neurosphere size, without inducing apoptosis. Unlike controls, dissociated cortical progenitors exposed to ethanol exhibited morphological evidence for asymmetric cell division, and cells derived from ethanol pre-treated neurospheres exhibited decreased proliferation capacity. Ethanol significantly reduced the numbers of cells expressing the stem cell markers CD117, CD133, Sca-1 and ABCG2, without decreasing nestin expression. Furthermore, ethanol-induced neurosphere proliferation was not accompanied by a commensurate increase in telomerase activity. Finally, cells derived from ethanol-pretreated neurospheres exhibited decreased differentiation in response to retinoic acid. CONCLUSION: The reduction in stem cell number along with a transient ethanol-driven increase in cell proliferation, suggests that ethanol promotes stem to blast cell maturation, ultimately depleting the reserve proliferation capacity of neuroepithelial cells. However, the lack of a concomitant change in telomerase activity suggests that neuroepithelial maturation is accompanied by an increased potential for genomic instability. Finally, the cellular phenotype that emerges from ethanol pre-treated, stem cell depleted neurospheres is refractory to additional differentiation stimuli, suggesting that ethanol exposure ablates or delays subsequent neuronal differentiation.

Satija, N. K., V. K. Singh, et al. (2009). "Mesenchymal stem cell-based therapy: a new paradigm in regenerative medicine." J Cell Mol Med **13**(11-12): 4385-402.

Mesenchymal stem cells (MSCs), adherent fibroblastoid cells, present in bone marrow and many other tissues can be easily isolated and expanded in vitro. They are capable of differentiating into different cell types such as osteoblasts, chondrocytes, adipocytes, cardiomyocytes, hepatocytes, endothelial cells and neuronal cells. Such immense plasticity coupled with their ability to modulate the activity of immune cells makes them attractive for stem cell-based therapy aimed at treating previously incurable disorders. Preclinical studies have reported successful use of MSCs for delivering therapeutic proteins and repairing defects in a variety of disease models. These studies highlighted the in vivo potential of MSCs and their ability to home to injury sites and modify the microenvironment by secreting paracrine factors to augment tissue repair. Their therapeutic applicability has been widened by genetic modification to enhance differentiation and tissue targeting, and use in tissue engineering. Clinical trials for diseases such as osteogenesis imperfecta, graft-versus-host disease and myocardial infarction have shown some promise, demonstrating the safe use of both allogeneic and autologous cells. However, lack of knowledge of MSC behaviour and responses in vitro and in vivo force the need for basic and animal studies before heading to the clinic. Contrasting reports on immunomodulatory functions and tumorigenicity along with issues such as mode of cell delivery, lack of specific marker, low survival and engraftment require urgent attention to harness the potential of MSC-based therapy in the near future.

Solanki, A., J. D. Kim, et al. (2008). "Nanotechnology for regenerative medicine: nanomaterials for stem cell imaging." Nanomedicine (Lond) **3**(4): 567-78.

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.

Strunk, D., E. Rohde, et al. (2005). "Phenotypic characterization and preclinical production of human lineage-negative cells for regenerative stem cell therapy." Transfusion **45**(3): 315-26.

BACKGROUND: Regenerative stem cell therapy (SCT) is currently being tested in clinical trials. The ideal type and source of cells have not yet been defined. Lineage (Lin) depletion is an experimental procedure capable of enriching all recently recognized SC types with regenerative potency. This study was performed to define a practicable monoclonal antibody (MoAb) cocktail for Lin depletion and to test whether clinical-scale Lin depletion is possible. STUDY DESIGN AND METHODS: MoAbs (CD2/14/15/19/41/56/glycophorin A) were selected to mark seven mature hematopoietic lineages. Lin7-negative (Lin7NEG) cells were analyzed in peripheral blood (PB, n = 9), mobilized PB (MPB, n = 5), umbilical cord blood (UCB, n = 5), and marrow aspirates (BM, n = 4) by flow cytometry. Preclinical Lin depletion was tested with leukapheresis products from PB following good manufacturing practice (GMP) principles. RESULTS: Lin7NEG cells comprised 0.23 +/- 0.04, 0.27 +/- 0.03, 0.53 +/- 0.07, and 0.49 +/- 0.03 percent of PB, MPB, UCB, and BM, respectively. Basophils, CD34+, and dendritic cells constituted the major Lin7NEG subpopulations (84 +/- 2, 90 +/- 3, 40 +/- 3, and 80 +/- 3% in PB, MPB, UCB, and BM, respectively). Minor populations included CD7- and CD45- cells. Preclinical CD2/14/15/19/56 (Lin5) depletion after automated red blood cell and platelet reduction resulted in up to a 16.7-fold enrichment of CD34+ and CD34-/Lin5NEG cells. CONCLUSIONS: A seven-MoAb cocktail is sufficient to label more than 99 percent of nucleated cells in PB, MPB, UCB, and BM. Preclinical Lin depletion can be performed under GMP conditions from PB apheresis procedures.

Sundelacruz, S. and D. L. Kaplan (2009). "Stem cell- and scaffold-based tissue engineering approaches to osteochondral regenerative medicine." Semin Cell Dev Biol **20**(6): 646-55.

In osteochondral tissue engineering, cell recruitment, proliferation, differentiation, and patterning are critical for forming biologically and structurally viable constructs for repair of damaged or diseased tissue. However, since constructs prepared ex vivo lack the multitude of cues present in the in vivo microenvironment, cells often need to be supplied with external biological and physical stimuli to coax them toward targeted tissue functions. To determine which stimuli to present to cells, bioengineering strategies can benefit significantly from endogenous examples of skeletogenesis. As an example of developmental skeletogenesis, the developing limb bud serves as an excellent model system in which to study how osteochondral structures form from undifferentiated precursor cells. Alongside skeletal formation during embryogenesis, bone also possesses innate regenerative capacity, displaying remarkable ability to heal after damage. Bone fracture healing shares many features with bone development, driving the hypothesis that the regenerative process generally recapitulates development. Similarities and differences between the two modes of bone formation may offer insight into the special requirements for healing damaged or diseased bone. Thus, endogenous fracture healing, as an example of regenerative skeletogenesis, may also inform bioengineering strategies. In this review, we summarize the key cellular events involving stem and progenitor cells in developmental and regenerative skeletogenesis, and discuss in parallel the corresponding cell- and scaffold-based strategies that tissue engineers employ to recapitulate these events in vitro.

Torella, D., G. M. Ellison, et al. (2005). "Cardiac stem and progenitor cell biology for regenerative medicine." Trends Cardiovasc Med **15**(6): 229-36.

Stem cell therapy is a new and promising treatment of heart disease. However, the race is still on to find the "best" cell to reconstitute the myocardium and improve function after myocardial damage. The recent discovery in the adult mammalian myocardium of a small cell population with the phenotype, behavior, and regenerative potential of cardiac stem and progenitor cells has proposed these cells as the most appropriate for cell therapy. The existence of these cells has provided an explanation for the hitherto unexplained existence of a subpopulation of immature cycling myocytes in the adult myocardium. These findings have placed the heart squarely among other organs with regenerative potential despite the fact that the working myocardium is mainly constituted of terminally differentiated cells. Although CSCs (cardiac cells proven to have stem

and/or progenitor characteristics) can be isolated and amplified in vitro or stimulated to differentiate in situ, it has become reasonable to exploit this endogenous regenerative potential to replace the lost muscle with autologous functional myocardium. Therefore, it is imperative to obtain a better understanding of the biology and regenerative potential of the endogenous CSCs. This will enable us to design better protocols for the regeneration of functional contractile mass after myocardial injury.

Yuasa, S. and K. Fukuda (2008). "Recent advances in cardiovascular regenerative medicine: the induced pluripotent stem cell era." Expert Rev Cardiovasc Ther **6**(6): 803-10.

Induced pluripotent stem (iPS) cells have recently been established by transfecting mouse and human fibroblasts with the transcription factors Oct3/4, Sox2, Klf4 and c-Myc, known to be expressed at high levels in embryonic stem (ES) cells. These cells have great potential in regenerative medicine as they have the capacity to differentiate into all three germ layer-derived cells and are syngeneic. The differentiation of ES cells into cardiomyocytes mimics the early processes involved in heart development. Recent studies describe the contribution of various growth factors and corresponding inhibitors to heart development during embryogenesis. Bone morphogenetic proteins, Wnt protein and Notch signals play critical roles in heart development in a context- and time-dependent manner. Consistent with ES cells, the exposure of iPS cells to such growth factors is hypothesized to augment differentiation into cardiomyocytes. The combination of iPS cells and appropriate developmental signal information has the potential for providing the foundations for future regenerative medicine.

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11/10/2012