Stem Cell Research Review

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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 literatures on stem cell researches.
[Smith MH. **Stem Cell Research Review.** *Stem Cell* 2014;5(1):77-91] (ISSN 1545-4570). http://www.sciencepub.net/stem. 7

Key words: stem cell; life; gene; DNA; protein; research

Introduction

Mouse embryonic stem cells were first discovered in 1981. Since then, they have been an invaluable tool of modern biology and medical research. They have provided models to study diseases, they have brought about the discovery of many genes associated with diseases and they have been used to cure certain human disorders in animal models. After 20 years of exciting research, the mouse embryonic stem cell has helped to establish the value of these cells in *regenerative medicine*, which is the creation of cells or organs to replace tissues lost to disease or injury. The discovery of *human* embryonic stem cells in 1998 triggered important ethical controversy and debate, yet scientists are convinced that they hold enormous potential for clinical applications. Many diseases plaguing the modern world may be improved, or even cured, with therapies using human stem cells. Whether human embryonic stem cells or adult stem cells are used in future therapies will depend on the type of disease or injury. There are specific advantages for each stem cell type. Thanks to the ease of growing them in the laboratory, human embryonic stem cells may one day become the source of artificial organs. Or scientists might one day be able to mobilize one's own adult stem cells to repair tissue damage caused by trauma, disease, and even aging. To reach such goals, both human embryonic and adult stem cells will have to be extensively studied. The complementary information acquired from studying both stem cell types is the key to unlocking their full potential.

A stem cell is the base building block of an entire family of cells that make up any organ. A common trait of stem cells is that they can maintain themselves indefinitely in a stem cell state, which is referred to as "self-renewal," while also producing — through division — more specialized cells. For example, the blood stem cell can produce all the cells in the blood, including the red blood cells, white blood cells and platelets.

Harnessing the power of human stem cells will revolutionize our health, our lives, and our society. In principle, any affliction involving the loss of cells, including many diseases, injuries and even aging, could be treated with stem cells. In the United States alone, more than 100 million people could benefit from therapies derived from stem cell research.

Adult stem cells are more specialized stem cells living in the majority of tissues and organs in our bodies and generate the mature cell types within that tissue or organ. In tissues where adult stem cells have been found, they are extremely rare and very difficult to isolate. Once isolated, adult stem cells grow poorly in culture, and it is difficult to obtain enough of these cells for use in clinical trials. In addition, access to the tissues harboring these cells is problematic since most human tissue is not easily available. Two readily available sources of human adult stem cells are the bone marrow and the umbilical cord blood. In both these tissues are blood stem cells, as well as other rare types of stem cells, which can produce bone, muscle, blood vessels, heart cells and possibly more.

The majority of stem cell clinical trials now underway use blood stem cells from the bone marrow or umbilical cord blood to treat blood disorders or diseases, such as leukemia, different types of anemia, systemic lupus, and certain other autoimmune diseases or deficiencies. A handful of clinical trials are evaluating the use of one's own bone marrow stem cells to repair heart tissue and to improve blood flow or to help to repair bone and cartilage. Other adult stem cells being explored for use in the clinic include stem cells in the eye and the skin. Adult stem cells are

also thought to play a role in tissue transplants that have been performed for several years. For example, insulin-producing cells for type I diabetes, fetal neurons for Parkinson's disease, and skin for bladder reconstruction have been transplanted successfully. It is possible that in cases where long-term regeneration has been achieved, stem cells contained in these tissues have contributed to regeneration. The widespread use of adult stem cell-derived therapies and treatments is complicated by several factors. First, available human tissue is scarce, with only 6000 donors/year for more than 100 million Americans that could benefit from cellular therapy. Second, immune rejection caused by not using one's own cells or tissue is a problem. On the other hand, using one's own cells or tissue may become a problem for older patients, as evidence has been accumulating that adult stem cells age during the life of the body and lose their potential. Thus, stem cells isolated from a young adult may have a greater potential to produce numerous daughter cells than the cells of an older person.

Human embryonic stem cells are like a blank slate and can produce all the cells of the body. They are obtained from the ICM (inner cell mass) of the blastocyst.The blastocyst is a very early stage of human development, which forms about 5 days after fertilization of an egg. It is approximately 1/10 the size of the head of a pin, almost invisible to the eye, and it has not yet implanted into the uterus.

Once the blastocyst has implanted and a normal pregnancy can be detected, it is too late to derive human embryonic stem cells from the embryo. At the blastocyst stage, organ formation has not started and more specialized cells are not yet present, not even the beginning of the nervous system. To obtain human embryonic stem cells, blastocysts created in culture for *in vitro fertilization* (IVF) treatment by combining sperm and egg in a dish, are used. If they are not implanted into the uterus, the blastocysts are either discarded or frozen for later fertility cycles. They can also be donated to other patients or to research. If not donated, they will stay in the freezer as long as the storage fees are paid, otherwise they will be discarded. Because the cells obtained from the blastocyst have not yet specialized, they are considered highly valuable. They can generate cells that go on to form all the body's tissues and organs.

While grown in a dish, human embryonic stem cells can maintain their *"stem-cellness"* and provide an unlimited supply of more stem cells, as well as specialized cells that can be used for experiments and for the development of therapies. Apart from their potential to treat or cure diseases, human embryonic stem cells also provide a model to study very early human development and some of the disorders that lead to birth defects and childhood cancers. Many of these disorders develop in early pregnancy and are impossible to study in humans. Also, human embryonic stem cells also can be used to examine the genes that are turned "on" or "off" as stem cells generate more specialized cell types, permitting a unique understanding of the genetics of human development. The specialized cells derived from human embryonic stem cells also can be used to study the effectiveness of potential new drugs to treat diseases. This provides a human cellular model and can reduce animal experimentation and drug development costs. Additionally, embryonic stem cells can be derived from human blastocysts with specific genetic abnormalities. These types of blastocysts are identified through genetic diagnosis during IVF treatment, to screen out genetically abnormal blastocysts, and are usually discarded. The stem cells from them can provide a unique resource to understand genetic diseases and to develop cures. Human embryonic stem cells also could be used to understand the origin or causes of various diseases such as Alzheimer's disease or Parkinson's disease, which are currently unknown. Stem cells derived through *nuclear transfer* (more info below) from patients with such afflictions would provide special tools to study these diseases and possibly develop drugs for treatments.

Embryonic stem cells have not yet been used in treating humans. But numerous animal studies have shown that many of the specialized cells derived from them can indeed integrate into damaged tissues and function properly. Thus, diseases such as myocardial infarction, severe immune deficiency, diabetes, Parkinson's disease, spinal cord injury, and demyelination have been successfully treated in animal models. But the pathway from animal models to the clinic is still complex and burdened with obstacles to be overcome. First, not all specialized cells derived from human embryonic stem cells have been shown to integrate into animal tissue and function properly. This can be due to the poor quality of the specialized cells derived in culture, or to a lack of adequate communication between the human cells and the animal environment in which they are placed. Then there is the problem of scaling up to yield enough of the specialized cells to treat a human, since this requires many more cells than to treat a tiny mouse. Such cells will have to be produced under specific conditions to ensure safety for use in patients. Most human embryonic stem cells are still grown on a layer of mouse feeder cells, a potential source of contamination. Last, there's the problem of immune rejection by the patient. While the drugs used in the organ transplantation field to suppress immune rejection have been improved over the years, rejection is still a major problem.

Literatures

Since the discovery of testicular carcinoma in situ (CIS) -- the precursor cell for the vast majority of germ cell tumours -- it has been proposed that CIS cells could be derived from transformed primordial germ cells or gonocytes. Here, we review recent discoveries not only substantiating that initial hypothesis but also indicating that CIS cells have a striking phenotypic similarity to embryonic stem cells (ESC). Many cancers have been proposed to originate from tissue-specific stem cells [so-called 'cancer stem cells' (CSC)] and we argue that CIS may be a very good example of a CSC, but with exceptional features due to the retention of embryonic pluripotency. In addition, considering the fact that pre-invasive CIS cells are transformed from early fetal cells, possibly due to environmentally induced alterations of the niche, we discuss potential risks linked to the uncontrolled therapeutic use of ESC [Almstrup, K., S. B. Sonne, et al. (2006). "From embryonic stem cells to testicular germ cell cancer-- should we be concerned?" Int J Androl **29**(1): 211-8].

Adoptive immunotherapy with antigen-specific cytotoxic T lymphocytes (CTLs) has proven effective in restoring cellular immunity to cytomegalovirus (CMV) and preventing viral reactivation after allogeneic stem cell transplantation (SCT). In an effort to develop a cost-effective, relatively rapid method of CMV CTL expansion, we investigated the use of a pool of overlapping CMV peptides. Because the possibility exists of vaccinating CMV-seronegative donors, and these individuals may have T cell responses predominantly against IE-1, commercially available peptide mixes for pp65 as well as IE-1 were used to stimulate CTLs from 10 seropositive donors. Of these 10 donors, 4 responded to pp65 only, 1 did not respond to either pp65 or IE-1, 4 responded to both pp65 and IE-1, and 1 responded to IE-1 only. These CMV- specific T cells included a mixture of CD4(+) and CD8(+) effectors, and specific cytotoxicity correlated with interferon-gamma production. The costs associated with a 28-day maintenance course of intravenous ganciclovir, cidofovir, foscarnet, and valganciclovir, as well as the preparation and shipping a single dose of CTLs, were determined. The price of generating CMV CTLs using this method was comparable to or less expensive than a 28-day maintenance course for these agents, not including the costs associated with drug administration, supportive care, and the treatment of drug-related complications. Considering the relative ease, low cost, and the fact that CTL administration can result in CMV-specific immune reconstitution, this option should be considered for patients with CMV reactivation or for prophylaxis in patients at high risk for infection [Bao, L., K. Dunham, et al. (2008). "Expansion of cytomegalovirus pp65 and IE-1 specific cytotoxic T lymphocytes for cytomegalovirus-specific immunotherapy following allogeneic stem cell transplantation." Biol Blood Marrow Transplant **14**(10): 1156-62].

Accessibility of human oocytes for research poses a serious ethical challenge to society. This fact categorically holds true when pursuing some of the most promising areas of research, such as somatic cell nuclear transfer and embryonic stem cell studies. One approach to overcoming this limitation is to use an oocyte from one species and a somatic cell from another. Recently, several attempts to capture the promises of this approach have met with varying success, ranging from establishing human embryonic stem cells to obtaining live offspring in animals. This review focuses on the challenges and opportunities presented by the formidable task of overcoming biological differences among species [Beyhan, Z., A. E. Iager, et al. (2007). "Interspecies nuclear transfer: implications for embryonic stem cell biology." Cell Stem Cell **1**(5): 502-12].

Stem cells provide fascinating prospects for biomedical applications by combining the ability to renew themselves and to differentiate into specialized cell types. Since the first isolation of embryonic stem (ES) cells about 30 years ago, there has been a series of groundbreaking discoveries that have the potential to revolutionize modern life science. For a long time, embryos or germ cell-derived cells were thought to be the only source of pluripotency--a dogma that has been challenged during the last decade. Several findings revealed that cell differentiation from (stem) cells to mature cells is not in fact an irreversible process. The molecular mechanism underlying cellular reprogramming is poorly understood thus far. Identifying how pluripotency maintenance takes place in ES cells can help us to understand how pluripotency induction is regulated. Here, we review recent advances in the field of stem cell regulation focusing on key transcription factors and their functional interplay with non-coding RNAs [Bosnali, M., B. Munst, et al. (2009). "Deciphering the stem cell machinery as a basis for understanding the molecular mechanism underlying reprogramming." Cell Mol Life Sci **66**(21): 3403-20].

The purpose of our study was to evaluate the incidence and clinical characteristics of febrile episodes during neutropenia following chemotherapy in children with cancer. A prospective, 3-year single-center observational study of periods of neutropenia was performed. Epidemiology and clinical diagnoses of febrile episodes occurring during the neutropenic periods were evaluated, taking into consideration different categories of anticancer treatment based on the type of tumor and phase of therapy. RESULTS: A

total of 703 febrile episodes were observed during 614 (34%) of 1792 neutropenic periods (34%), for a total of 28,001 days at risk, accounting for a rate of 0.76 episodes per 30 days at risk. The highest proportions of neutropenic periods with primary febrile episodes were observed after autologous hemopoietic stem cell transplantation (58%), aggressive treatment for acute leukemia or non-Hodgkin lymphoma (48%), and allogeneic hemopoietic stem cell transplantation (44%); the lowest proportion (9%) was observed during maintenance chemotherapy for acute leukemia (P<.001). The most frequent clinical diagnosis was fever of unknown origin (in 79% of cases), followed by bacteremia (10%); invasive mycosis was diagnosed in only 2% of cases. The overall incidence of febrile neutropenia and severe infectious complications in children with cancer is low, with differences according to the aggressiveness of chemotherapy. This fact must be considered when designing clinical trials on the management of infectious complications in children with cancer [Castagnola, E., V. Fontana, et al. (2007). "A prospective study on the epidemiology of febrile episodes during chemotherapy-induced neutropenia in children with cancer or after hemopoietic stem cell transplantation." Clin Infect Dis **45**(10): 1296-304].

In order to support drug research in the selection process for non-embryotoxic pharmaceutical compounds, a screening method for embryotoxicity is needed. The murine embryonic stem cell test (EST) is a validated in vitro test based on two permanent mouse cell lines and delivering results in 10-days. Implementation of this test within our laboratory, revealed variability in the differentiation potential of the embryonic stem cells and, as a consequence, a lot of assays needed to be rejected due the fact the acceptance criteria were not reached. In order to gain a better yield of contracting myocardial cells, we used (1) a stringent control of the cell growth during subcultivation and a standardised hanging drop culture method and (2) a non-enzymatic cell harvest instead of a trypsin/EDTA cell harvest. Implementing of these cell culture modifications resulted in a decreased variability in the size of embryonic bodies, an increase of the number of acceptable tests and a significant increase of the differentiation potential of embryonic cells into strong beating myocardium, which made scoring less time consuming. Testing of 6 reference compounds in the optimized EST showed that the cell culture modifications did not changed the in vitro classification [De Smedt, A., M. Steemans, et al. (2008). "Optimisation of the cell cultivation methods in the embryonic stem cell test results in an increased differentiation potential of the cells into strong beating myocard cells." Toxicol In Vitro **22**(7): 1789-96].

In vivo, stem cell factor (SCF) exists in both a bound and soluble isoform. It is believed that the bound form is more potent and fundamentally required for the maintenance of hematopoietic stem cells (HSCs). This theory is supported by the observation that steel-Dickie mice lacking the bound isoform of SCF are unable to maintain hematopoiesis and by the fact that bound SCF displayed on the surface of transgenic cells is better able to maintain c-kit activation than soluble SCF. Further work has shown that recombinant SCF molecules, which include a surface-binding domain, are more potent than their soluble equivalent. It is generally assumed that such an elegant approach is necessary to provide the correct molecular orientation and avoid the pitfalls of random cross-linking or the denaturation associated with the adsorption of proteins to surfaces. However, in this work we demonstrate that SCF physisorbed to tissue culture plastic (TCP) is not only bioactive, but more potent than the soluble equivalent. By contrast, cross-linking of SCF via free amines is shown to compromise its bioactivity. These observations demonstrate that simple surface modification solutions cannot be discounted and with the advent of low-cost pharmaceutical grade proteins, they should not be [Doran, M. R., B. D. Markway, et al. (2009). "Surface-bound stem cell factor and the promotion of hematopoietic cell expansion." Biomaterials **30**(25): 4047-52].

Neural stem cells (NSCs) are defined by their ability to self-renew while retaining differentiation potential toward the three main central nervous system (CNS) lineages: neurons, astrocytes, and oligodendrocytes. A less appreciated fact about isolated NSCs is their narrow repertoire for generating specific neuron types, which are generally limited to a few region-specific subtypes such as GABAergic and glutamatergic neurons. Recent studies in human embryonic stem cells have identified a novel neural stem cell stage at which cells exhibit plasticity toward generating a broad range of neuron types in response to appropriate developmental signals. Such rosette-stage NSCs (R-NSCs) are also distinct from other NSC populations by their specific cytoarchitecture, gene expression, and extrinsic growth requirements. Here, we discuss the properties of R-NSCs within the context of NSC biology and define some of the key questions for future investigation. R-NSCs may represent the first example of a NSC population capable of recreating the full cellular diversity of the developing CNS, with implications for both basic stem cell biology and translational applications in regenerative medicine and drug discovery [Elkabetz, Y. and L. Studer (2008). "Human ESC-derived neural rosettes and neural stem cell progression." Cold Spring Harb Symp Quant Biol **73**: 377-87].

While many regulatory mechanisms controlling the development and function of root and shoot apical meristems have been revealed, our knowledge of similar processes in lateral meristems, including the vascular cambium, is still limited. Our understanding of even the anatomy and development of lateral meristems (procambium or vascular cambium) is still relatively incomplete, let alone their genetic regulation. Research into this particular tissue type has been mostly hindered by a lack of suitable molecular markers, as well as the fact that thus far very few mutants affecting plant secondary development have been described. The development of suitable molecular markers is a high priority in order to help define the anatomy, especially the location and identity of cambial stem cells and the developmental phases and molecular regulatory mechanisms of the cambial zone. To date, most of the advances have been obtained by studying the role of the major plant hormones in vascular development. Thus far auxin, cytokinin, gibberellin and ethylene have been implicated in regulating the maintenance and activity of cambial stem cells; the most logical question in research would be how these hormones interact during the various phases of cambial development [Elo, A., J. Immanen, et al. (2009). "Stem cell function during plant vascular development." Semin Cell Dev Biol **20**(9): 1097-106.

In this study, we have observed dental pulp stem cells (SBP-DPSCs) performances on different scaffolds, such as PLGA 85:15, hydroxyapatite chips (HA) and titanium. Stem cells were challenged with each engineered surface, either in plane cultures or in a rotating apparatus, for a month. Gingival fibroblasts were used as controls. Results showed that stem cells exerted a different response, depending on the different type of textured surface: in fact, microconcavities significantly affected SBP-DPSC differentiation into osteoblasts, both temporally and quantitatively, with respect to the other textured surfaces. Actually, stem cells challenged with concave surfaces differentiated quicker and showed nuclear polarity, an index of secretion, cellular activity and matrix formation. Moreover, bone-specific proteins were significantly expressed and the obtained bone tissue was of significant thickness. Thus, cells cultured on the concave textured surface had better cell-scaffold interactions and were induced to secrete factors that, due to their autocrine effects, quickly lead to osteodifferentiation, bone tissue formation, and vascularization. The worst cell performance was obtained using convex surfaces, due to the scarce cell proliferation on to the scaffold and the poor matrix secretion. In conclusion, this study stresses that for a suitable and successful bone tissue reconstruction the surface texture is of paramount importance [Graziano, A., R. d'Aquino, et al. (2008). "Scaffold's surface geometry significantly affects human stem cell bone tissue engineering." J Cell Physiol **214**(1): 166-72].

The discovery of microRNAs (miRNAs - small non-coding RNAs of approximately 22 nt) heralded a new and exciting era in biology. During this period miRNAs have gone from ignominy due to their origin mainly in 'junk DNA' to notoriety where they can be at once characterized as being all powerful (a single miRNA can target and potentially silence several hundred genes) and yet marginal (a given gene can be targeted by several miRNAs such that a given miRNA typically exerts a modest repression) [1-4]. The emerging paradox is exemplified by miRNAs that are prominently expressed in embryonic stem (ES) cells. The collective importance of miRNAs is firmly established by the fact that Dicer-/- mouse embryos die on day 7.5 due to defects in differentiation [5]. However, oppositely correlated expression that is expected of conventional repressors is increasingly being defied in multiple systems in relation to miRNA-mRNA target pairs. This is most evident in ES cells where miR-290-295 and 302 clusters the most abundant ES cell miRNAs are found to be driven by pluripotency genes Oct4, Nanog and Sox2 and also target these genes in 'incoherent feed-forward loops' [7]. Here the miRNAs are co-expressed and positively correlated with these targets that they repress suggesting that one of their primary roles is to fine tune gene expression rather than act as ON/OFF switches. On the other hand, let-7 family members that are notably low in ES cells and rapidly induced upon differentiation exhibit more conventional anti-correlated expression patterns with their targets [7-8]. In an intricately designed auto-regulatory loop, LIN28, a key 'keeper' of the pluripotent state binds and represses the processing of let-7 (a key 'keeper' of the differentiated state) [9-11]. One of the let-7 family members, let-7g targets and represses LIN28 through four 3'-UTR binding sites [12]. We propose that LIN28/let-7 pair has the potential to act as a 'toggle switch' that balances the decision to maintain pluripotency vs. differentiation. We also propose that the c-Myc/E2F driven miR17-92 cluster that together controls the G1 to S transition is fundamental for ES self-renewal and cell proliferation [13-18]. In that context it is no surprise that LIN28 and c-Myc (and therefore let-7 and miR-17-92 by association) and more recently Oct4/Sox2 regulated miR-302 has been shown to be among a handful of factors shown to be necessary and sufficient to convert differentiated cells to induced pluripotent stem (iPS) cells [19-29]. It is also no surprise that activation of miR-17-92 (OncomiRs) and down-regulation of let-7 (tumor suppressors) is a recurring theme in relation to cancers from multiple systems

[30-48]. We speculate that the LIN28/let-7; c-MYC-E2F/miR-17-92 and Oct4/Sox2/miR-302-cyclin D1 networks are fundamental to properties of pluripotency and self-renewal associated with embryonic stem cells. We also speculate that ES cell miRNA-mRNA associations may also regulate tissue homeostasis and regeneration in the fully developed adult. Consequently, the appropriate regulation of LIN28/let-7; c-MYC-E2F/miR-17-92 and Oct4/Sox2/miR-302-cyclin D1 gene networks will be critical for the success of regenerative strategies that involve iPS cells. Any perturbation in key ES cell miRNA-mRNA networks during any of the above processes maybe a hallmark of (CSCs) [Gunaratne, P. H. (2009). "Embryonic stem cell microRNAs: defining factors in induced pluripotent (iPS) and cancer (CSC) stem cells?" Curr Stem Cell Res Ther **4**(3): 168-77].

Recent advances from our own group and others have defined a novel PML/PTEN/Akt/mTOR/FoxO signaling network, and highlighted its critical importance in oncogenesis as well as in the functional regulation of normal stem cell and cancer-initiating cell (CIC) biology. These findings are of great importance in cancer therapy in view of the fact that this network is amenable to pharmacological modulation at multiple levels. The integrated analysis of these data allows us to propose a new provocative working model whereby the aberrant superactivation of Akt/mTOR signaling elicits built-in cellular fail-safe mechanisms that could be effectively utilized for cancer treatment to extinguish the CICs pool. In this review, we will discuss these recent findings, this working model, and their therapeutic implications [Ito, K., R. Bernardi, et al. (2009). "A novel signaling network as a critical rheostat for the biology and maintenance of the normal stem cell and the cancer-initiating cell." Curr Opin Genet Dev **19**(1): 51-9].

Although O(2) concentrations are considerably lowered in vivo, depending on the tissue and cell population in question (some cells need almost anoxic environment for their maintenance) the cell and tissue cultures are usually performed at atmospheric O(2) concentration (20-21%). As an instructive example, the relationship between stem cells and micro-environmental/culture oxygenation has been recapitulated. The basic principle of stem cell biology, "the generation-age hypothesis," and hypoxic metabolic properties of stem cells are considered in the context of the oxygen-dependent evolution of life and its transposition to ontogenesis and development. A hypothesis relating the self-renewal with the anaerobic and hypoxic metabolic properties of stem cells and the actual O(2) availability is elaborated ("oxygen stem cell paradigm"). Many examples demonstrated that the cellular response is substantially different at atmospheric O(2) concentration when compared to lower O(2) concentrations which better approximate the physiologic situation. These lower O(2) concentrations, traditionally called "hypoxia" represent, in fact, an in situ normoxia, and should be used in experimentation to get an insight of the real cell/cytokine physiology. The revision of our knowledge on cell/cytokine physiology, which has been acquired ex vivo at non physiological atmospheric (20-21%) O(2) concentrations representing a hyperoxic state for most primate cells, has thus become imperious [Ivanovic, Z. (2009). "Hypoxia or in situ normoxia: The stem cell paradigm." J Cell Physiol **219**(2): 271-5].

Cancer stem cells have been isolated from many tumors. Several evidences prove that neuroblastoma contains its own stem cell-like cancer cells. We chose to analyze 20 neuroblastoma tumor samples in the expression of 13 genes involved in the regulation of stem cell properties to evaluate if their misregulation could have a clinical relevance. In several specimens we detected the expression of genes belonging to the OCT3/SOX2/NANOG/KLF4 core circuitry that acts at the highest level in regulating stem cell biology. This result is in agreement with studies showing the existence of malignant stem cells in neuroblastoma. We also observed differences in the expression of some stemness-related genes that may be useful for developing new prognostic analyses. In fact, preliminary data suggests that the presence/absence of UTF1 along with differences in BMI1 mRNA levels could distinguish low grade neuroblastomas from IV stage tumors [
Melone, M. A., M. Giuliano, et al. (2009). "Genes involved in regulation of stem cell properties: studies on their expression in a small cohort of neuroblastoma patients." Cancer Biol Ther **8**(13): 1300-6].

So far, the major safety issue raised by the use of stem cells for cardiac repair has been the occurrence of ventricular arrhythmias, particularly after skeletal myoblast transplantation. Although one cannot refute a potential intrinsic arrhythmogenicity of stem cells, primarily related to their common lack of electromechanical integration into the recipient myocardium, it is also important to recognize that patients eligible for cell replacement therapy are prone to develop arrhythmias because of their underlying ischemic heart disease. Another confounding factor is the method used for the intramyocardial delivery of the cells, which can cause enough inflammatory tissue damage to further increase ventricular irritability on top of an already high baseline level. Thus any strategy designed to minimize the risk of stem cell-associated ventricular arrhythmias should take into

account, besides the cell-specific ability to appropriately couple with host cardiomyocytes, the method of cell transfer and the nature of the myocardial environment targeted for cell engraftment. A more accurate characterization of the baseline risk of arrhythmias in these patients would thus be helpful for better assessing the respective contribution of the donor cells and the host myocardium to these complications. The risk-to-benefit ratio of stem cell therapy will finally have to be revisited in light of the fact that because this baseline risk is usually high, most of these patients will in any way be fitted with an implantable defibrillator [Menasche, P. (2009). "Stem cell therapy for heart failure: are arrhythmias a real safety concern?" Circulation **119**(20): 2735-40].

A paracrine regulation was recently proposed in human embryonic stem cells (hESCs) grown in mouse embryonic fibroblast (MEF)-conditioned media (MEF-CM), where hESCs spontaneously differentiate into autologous fibroblast-like cells to maintain culture homeostasis by producing TGF-beta and insulin-like growth factor-II (IGF-II) in response to basic fibroblast growth factor (bFGF). Although the importance of TGF-beta family members in the maintenance of pluripotency of hESCs is widely established, very little is known about the role of IGF-II. In order to ease hESC culture conditions and to reduce xenogenic components, we sought (i) to determine whether hESCs can be maintained stable and pluripotent using CM from human foreskin fibroblasts (HFFs) and human mesenchymal stem cells (hMSCs) rather than MEF-CM, and (ii) to analyze whether the cooperation of bFGF with TGF-beta and IGF-II to maintain hESCs in MEF-CM may be extrapolated to hESCs maintained in allogeneic mesenchymal stem cell (MSC)-CM and HFF-CM. We found that MSCs and HFFs express all FGF receptors (FGFR1-4) and specifically produce TGF-beta in response to bFGF. However, HFFs but not MSCs secrete IGF-II. Despite the absence of IGF-II in MSC-CM, hESC pluripotency and culture homeostasis were successfully maintained in MSC-CM for over 37 passages. Human ESCs derived on MSCs and hESCs maintained in MSC-CM retained hESC morphology, euploidy, expression of surface markers and transcription factors linked to pluripotency and displayed in vitro and in vivo multilineage developmental potential, suggesting that IGF-II may be dispensable for hESC pluripotency. In fact, IGF-II blocking had no effect on the homeostasis of hESC cultures maintained either on HFF-CM or on MSC-CM. These data indicate that hESCs are successfully maintained feeder-free with IGF-II-lacking MSC-CM, and that the previously proposed paracrine mechanism by which bFGF cooperates with TGF-beta and IGF-II in the maintenance of hESCs in MEF-CM may not be fully extrapolated to hESCs maintained in CM from human MSCs [Montes, R., G. Ligero, et al. (2009). "Feeder-free maintenance of hESCs in mesenchymal stem cell-conditioned media: distinct requirements for TGF-beta and IGF-II." Cell Res **19**(6): 698-709].

Advances in infertility treatment had the most extraordinary breakthrough with the birth of the first in vitro fertilization baby in 1978. Fourteen years later, intracytoplasmic sperm injection has been introduced for the treatment of male factor infertility. Intra cytoplasmic sperm injection in combination with testicular sperm extraction has allowed men with azoospermia to father children. In fact, as long as a fully developed spermatozoon is identified, it can be utilized or can even be duplicated to inseminate several oocytes while providing information on its genomic content. There are, however, men who are suffering from spermatogenic arrest, where no post-meiotic germ cells are retrieved, and therefore, unable to generate their own offspring. More recently, the successful isolation and cultivation of spermatogonial stem cells has allowed the exploration of their biological characteristics and their application in therapeutic approaches following transplantation or in vitro maturation. Finally, men diagnosed with germ cell aplasia can only be treated by donor or de novo generated gametes. In the past several years, we have attempted to manufacture gametes by inducing haploidization of somatic cells and more recently, generating sperm-like cells through embryonic stem cell differentiation [Neri, Q. V., T. Takeuchi, et al. (2009). "Treatment options for impaired spermatogenesis: germ cell transplantation and stem-cell based therapy." Minerva Ginecol **61**(4): 253-9].

Post-transplant lymphoproliferative disorder (PTLD) is one of the most important complications of solid organ transplantation or hematopoietic stem cell transplantation. Most PTLDs are associated with Epstein-Barr virus (EBV) infection. Although post-transplant Hodgkin lymphoma (HL) is included in PTLD, there have been no studies in the literature on adult cases of post-transplant HL after cord blood stem cell transplantation (CBSCT). Three years and eight months after CBSCT, the enlarged cervical lymph node was histologically diagnosed as EBV associated post-transplant HL, which showed immunophenotypes of classical HL and latency type II EBV infection. She underwent chemotherapy, and has survived 4 years and 6 months after CBSCT. Differential diagnosis of post-transplant HL with good prognosis and HL-like PTLD with aggressive behavior is important, and immunohistochemical methods were useful and essential for it. The source of EBV associated HL in this case will be discussed [Okuno, K., Y. Horie, et al. (2009). "Epstein-Barr virus associated post-transplant Hodgkin lymphoma in

an adult patient after cord blood stem cell transplantation for acute lymphoblastic leukemia." J Clin Exp Hematop **49**(1): 45-51].

CD34+ peripheral blood hematopoietic stem cells (HSC) are usually collected following mobilization therapy accomplished by using growth factors (GF) such as rHuG-CSF or rHuGM-CSF with or without chemotherapy. A target dose of yielded CD34+ is usually prescribed by the attending physician depending on different protocols, which may include single or double transplantation. HSC collection usually is performed when at least 20 CD34+ HSC/microL are detected by means of flow cytometry. A cumulative dose of at least 2 x 10(6)/Kg/bw CD34+ HSC has been considered as the threshold to allow a prompt and persistent hematopoietic recovery. Unfortunately, this goal is not achieved by the totality of patients undergoing mobilization regimen. In fact, 5-46% of patients who underwent mobilization therapy fail HSC collection due to very low peripheral blood HSC CD34+ count. Patients' characteristics, including age, sex, stage of the underlying disease (complete or partial remission), diagnosis, previously administered radio/chemotherapy regimens, time-lapse from last chemotherapy before mobilization and mobilization schedule (including dose of GF) were considered as possibly predictive of poor or failed mobilization. We performed a retrospective analysis in 2177 patients from three large Italian academic institutions to assess the incidence of poor mobilizers within our patients' series. Therefore, a patient who fails a first mobilization (and when an HLA-compatible related on unrelated donor is not available) could undergo a second attempt either with different mobilization schedule or by using different GF, such as stem cell factor, growth hormone (GH), or more recently newly introduced drugs such as AMD3100, alone or in combination with rHuG- or -rHuGM-CSF. Thus, we investigated the fate of those who failed a first mobilization and subsequently underwent a second attempt or alternative therapeutic approaches [Perseghin, P., E. Terruzzi, et al. (2009). "Management of poor peripheral blood stem cell mobilization: incidence, predictive factors, alternative strategies and outcome. A retrospective analysis on 2177 patients from three major Italian institutions." Transfus Apher Sci **41**(1): 33-7].

Mesenchymal stem cells (MSCs) have been isolated from a variety of human tissues, e.g., bone marrow, adipose tissue, dermis, hair follicles, heart, liver, spleen, dental pulp. Due to their immunomodulatory and regenerative potential MSCs have shown promising results in preclinical and clinical studies for a variety of conditions, such as graft versus host disease (GvHD), Crohn's disease, osteogenesis imperfecta, cartilage damage and myocardial infarction. MSC cultures are composed of heterogeneous cell populations. Complications in defining MSC arise from the fact that different laboratories have employed different tissue sources, extraction, and cultivation methods. Although cell-surface antigens of MSCs have been extensively explored, there is no conclusive evidence that unique stem cells markers are associated with these adult cells. Therefore the aim of this study was to examine expression of embryonic stem cell markers Oct4, Nanog, SOX2, alkaline phosphatase and SSEA-4 in adult mesenchymal stem cell populations derived from bone marrow, adipose tissue, dermis and heart. Furthermore, we tested whether human mesenchymal stem cells preserve tissue-specific differences under in vitro culture conditions. We found that bone marrow MSCs express embryonic stem cell markers Oct4, Nanog, alkaline phosphatase and SSEA-4, adipose tissue and dermis MSCs express Oct4, Nanog, SOX2, alkaline phosphatase and SSEA-4, whereas heart MSCs express Oct4, Nanog, SOX2 and SSEA-4. Our results also indicate that human adult mesenchymal stem cells preserve tissue-specific differences under in vitro culture conditions during early passages, as shown by distinct germ layer and embryonic stem cell marker expression patterns. Studies are now needed to determine the functional role of embryonic stem cell markers Oct4, Nanog and SOX2 in adult human MSCs [Riekstina, U., I. Cakstina, et al. (2009). "Embryonic stem cell marker expression pattern in human mesenchymal stem cells derived from bone marrow, adipose tissue, heart and dermis." Stem Cell Rev **5**(4): 378-86].

In order to monitor CsA serum levels after SCT, trough levels (C0) are widely used. The aim of this study was to estimate the population and individual PK parameters for patients receiving intravenous CsA after SCT. In 27 pediatric patients after SCT receiving CsA (3 mg/kg/day) every 12 h, a total of 289 CsA concentrations was obtained. To describe the PK parameters of CsA, a two-compartment model with first order elimination was used. Covariate analysis identified body weight, age, and the co-administration with itraconazole and tobramycine as factors influencing the Cl. The statistical comparison of AUC, trough level, and C2 indicates a correlation between AUC and C2, but no correlation between the AUC and C0, $r = 0.24$ ($p = 0.146$) vs. $r = 0.526$ ($p = 0.000692$), respectively. Our results underscore the fact that CsA trough levels do not reflect the drug exposure in patients receiving intravenous CsA after SCT. By contrast, CsA blood levels measured 2-6 h after CsA infusion showed a better correlation with the AUC. Our data provide new information to optimize the balancing act

between GvHD-prophylaxis, graft vs. leukemia effect, and CsA side-effects after SCT [Schrauder, A., S. Saleh, et al. (2009). "Pharmacokinetic monitoring of intravenous cyclosporine A in pediatric stem-cell transplant recipients. The trough level is not enough." Pediatr Transplant **13**(4): 444-50].

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is known to cause parkinsonism in humans and this fact is a major incentive for using this toxin as an animal model to study the pathogenesis of Parkinson's disease (PD). Although the monkey MPTP model remains the best, most studies have been performed in mice. The so-called acute and sub-acute regimens are commonly used. Both induce tissue striatal dopamine (DA) depletion and nigral neuron death. Tissue striatal DA depletion does not necessarily correlate with impairment of striatal dopaminergic functioning. In freely moving mice, systemic acute or sub-acute MPTP directly induces prolonged release of striatal DA. Such DA release may be considered the first step in MPTP-induced striatal DA depletion. Reportedly, neural stem cells improve symptoms in the MPTP model of PD by interacting with the MPTP-induced pathological nigrostriatal milieu [Serra, P. A., S. Pluchino, et al. (2008). "The MPTP mouse model: cues on DA release and neural stem cell restorative role." Parkinsonism Relat Disord **14 Suppl 2**: S189-93].

High-dose melphalan and autologous hematopoietic stem cell transplantation (HSCT) is a standard treatment for myeloma, but very little is known about the psychosocial or quality-of-life difficulties that these patients encounter during treatment. Data regarding older patients is particularly scarce. Using a prospective design, this investigation evaluated 94 patients at stem cell collection and again after high-dose therapy and transplantation. Outcomes included quality-of-life (FACT-BMT) and psychosocial adjustment (ie, Brief Symptom Inventory, Impact of Events Scale, and Satisfaction with Life Scale). Findings were compared with age- and sex-adjusted population norms and with transplantation patient norms. At stem cell collection, physical deficits were common, with most patients scoring 1 standard deviation below population norms for physical well-being (70.2%) and functional well-being (57.5%), and many reporting at least moderate fatigue (94.7%) and pain (39.4%). Clinically meaningful levels of anxiety (39.4%), depression (40.4%), and cancer-related distress (37.0%) were evident in a notable proportion of patients. After transplantation, there was a worsening of transplant-related concerns ($P < .05$), depression ($P < .05$), and life-satisfaction ($P < .001$); however, pain improved ($P < .01$), and social functioning was well preserved. Overall, the declines in functioning after transplantation were less pronounced than anticipated. Older patients were not more compromised than younger ones; in multivariate analyses, they reported better overall quality of life ($P < .01$) and less depression ($P < .05$) before transplantation. Our findings emphasize the importance of early screening and intervention [Sherman, A. C., S. Simonton, et al. (2009). "Changes in quality-of-life and psychosocial adjustment among multiple myeloma patients treated with high-dose melphalan and autologous stem cell transplantation." Biol Blood Marrow Transplant **15**(1): 12-20].

Given their self-renewing and pluripotent capabilities, human embryonic stem cells (hESCs) are well poised as a cellular source for tissue regeneration therapy. However, the host immune response against transplanted hESCs is not well characterized. In fact, controversy remains as to whether hESCs have immune-privileged properties. To address this issue, we used in vivo bioluminescent imaging to track the fate of transplanted hESCs stably transduced with a double-fusion reporter gene consisting of firefly luciferase and enhanced GFP. We show that survival after transplant is significantly limited in immunocompetent as opposed to immunodeficient mice. Repeated transplantation of hESCs into immunocompetent hosts results in accelerated hESC death, suggesting an adaptive donor-specific immune response. Our data demonstrate that transplanted hESCs trigger robust cellular and humoral immune responses, resulting in intragraft infiltration of inflammatory cells and subsequent hESC rejection. Moreover, we have found CD4(+) T cells to be an important modulator of hESC immune-mediated rejection. Finally, we show that immunosuppressive drug regimens can mitigate the anti-hESC immune response and that a regimen of combined tacrolimus and sirolimus therapies significantly prolongs survival of hESCs for up to 28 days. Taken together, these data suggest that hESCs are immunogenic, trigger both cellular and humoral-mediated pathways, and, as a result, are rapidly rejected in xenogeneic hosts. This process can be mitigated by a combined immunosuppressive regimen as assessed by molecular imaging approaches [Swijnenburg, R. J., S. Schrepfer, et al. (2008). "Immunosuppressive therapy mitigates immunological rejection of human embryonic stem cell xenografts." Proc Natl Acad Sci U S A **105**(35): 12991-6].

Immune-mediated cytopenias after allogeneic stem cell transplantation can be categorized as either alloimmune when host or donor immunity reacts against donor or host elements, respectively, or autoimmune when donor immunity reacts against donor hematopoietic tissue, owing to poorly

understood mechanisms that result in severe impairment of central and peripheral tolerance. Immune cytopenias are manifested as monolineage or more rarely as bilineage cytopenias, and are usually mediated through humoral immune mechanisms. On the contrary, immune-mediated pancytopenia is a rare event with only few cases reported in the literature. The exact pathogenesis of immune pancytopenia is not well known although it is possible that cellular immunity may play a significant role. The importance of these syndromes lies in the fact that they can cause severe morbidity and mortality. Differential diagnosis from other causes of post-transplant pancytopenia is of extreme value because these disorders can respond to various treatment modalities [Tsirigotis, P. D., I. B. Resnick, et al. (2009). "Post-hematopoietic stem cell transplantion immune-mediated cytopenias." Immunotherapy **1**(1): 39-47].

Stem cell transplantations from related or unrelated donors are used to cure leukaemia and other blood diseases. When a patient dies after an unsuccessful transplantation, interested unrelated donors are informed about the failure by their donor centre. Studies focussing on failed related donations show that donors undergo an intense grieving process. Questionnaires were sent to 395 unrelated donors who received the news of their recipients' deaths between November 2005 and August 2006. In addition, twelve in-depth interviews with selected donors were carried out. Unrelated donors were emotionally affected by the recipients' deaths, and it is appropriate to speak about a "Donor Grief" phenomenon, as the results of 325 returned questionnaires (return rate 82.3%) and in-depth interviews show. Donors demonstrated a range of feelings such as sadness, disappointment, grief, and helplessness. These feelings were often unexpectedly intense given the fact that the recipient was a stranger. Although the news caused grief, donors underlined that they nevertheless wanted to be informed. They preferred knowledge of the failure to uncertainty. The method of providing the information is only of secondary importance. Most donors favoured the way of communication they had experienced. This result indicates that both phone and letter communication can be justified. However, phone communication seems to be superior with respect to aspects of sensitivity. In spite of transplantation failure and the associated negative feelings, most donors were happy to have donated and would be willing to do so again. Our results underline the special responsibility of donor centres for informing and supporting unrelated volunteer donors in case their recipients have died [Wanner, M., S. Bochert, et al. (2009). "Losing the genetic twin: donor grief after unsuccessful unrelated stem cell transplantation." BMC Health Serv Res **9**: 2].

Previous studies described that neurons could be generated in vitro from human umbilical cord blood cells. However, there are few data concerning their origin. Notably, cells generating neurons are not well characterized. The present study deals with the origin of cord blood cells generating neurons and mechanisms allowing the neuronal differentiation. We studied neuronal markers of both total fractions of cord blood and stem/progenitor cord blood cells before and after selections and cultures. We also compared neuronal commitment of cord blood cells to that observed for the neuronal cell line SK-N-BE(2). Before cultures, neuronal markers are found within the total fraction of cord blood cells. In CD133+ stem/progenitor cell fraction only immature neuronal markers are detected. However, CD133+ cells are unable to give rise to neurons in cultures, whereas this is achieved when total fraction of cord blood cells is used. In fact, mature functional neurons can be generated from CD133+ cells only in cell-to-cell close contact with either CD133- fraction or a neurogenic epithelium. Furthermore, since CD133+ fraction is heterogenous, we used several selections to precisely identify the phenotype of cord blood-derived neuronal stem/progenitor cells. Results reveal that only CD34- cells from CD133+ fraction possess neuronal potential. These data show the phenotype of cord blood neuronal stem/progenitor cells and the crucial role of direct cell-to-cell contact to achieve their commitment. Identifying the neuron supporting factors may be beneficial to the use of cord blood neuronal stem/progenitor cells for regenerative medicine [Zangiacomi, V., N. Balon, et al. (2008). "Cord blood-derived neurons are originated from CD133+/CD34 stem/progenitor cells in a cell-to-cell contact dependent manner." Stem Cells Dev **17**(5): 1005-16.

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8/7/2010