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Stem Cell

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Stem Cell Technology Research Literatures

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

Introduction

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

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

Acab, A. and A. R. Muotri (2015). "The Use of Induced Pluripotent Stem Cell Technology to Advance Autism Research and Treatment." Neurotherapeutics **12**(3): 534-545.

Autism spectrum disorders (ASDs) are a heterogeneous group of neurodevelopmental disorders sharing a core set of symptoms, including impaired social interaction, language deficits, and repetitive behaviors. While ASDs are highly heritable and demonstrate a clear genetic component, the cellular and molecular mechanisms driving ASD etiology remain undefined. The unavailability of live patient-specific neurons has contributed to the difficulty in studying ASD pathophysiology. The recent advent of induced pluripotent stem cells (iPSCs) has provided the ability to generate patient-specific human neurons from somatic cells. The iPSC field has quickly grown, as researchers have demonstrated the utility of this technology to model several diseases, especially neurologic disorders. Here, we review the current literature around using iPSCs to model ASDs, and discuss the notable findings, and the promise and limitations of this technology. The recent report of a nonsyndromic ASD iPSC model and several previous ASD models demonstrating similar results points to the ability of iPSC to reveal potential novel biomarkers and therapeutics.

Agrawal, S., et al. (2004). "Short tandem repeat technology has diverse applications: individual identification, phylogenetic reconstruction and chimerism based post haematopoietic stem cell transplantation graft monitoring." Indian J Med Sci **58**(7): 297-304.

BACKGROUND: Short Tandem Repeat (STR) loci are widely considered to be effective for variety of applications including forensic applications, phylogenetic reconstruction and chimerism based post Haematopoietic Stem Cell Transplantation (HSCT) graft monitoring. For each application, specific sets of STR loci are used. AIMS: In the present study, we have attempted to use same set of STR loci for varied purposes based on their efficacy and informativity. SETTINGS AND DESIGN: Population and patient based study. MATERIALS AND METHODS: We have analyzed 5 STR loci--vWA, Tho1, FES, F13 and TPOX in 1000 North Indians. All five markers were also analyzed for chimerism based graft monitoring after HSCT in 42 HLA matched pair of patient-donor to predict the outcome of transplantation. STATISTICAL ANALYSIS: The analysis was done for Hardy Weinberg equilibrium (HWE), Heterozygosity, Polymorphism information content

(PIC) and Power of Exclusion and Phylogenetic assessment. RESULTS AND CONCLUSIONS: High allelic variability in term of Heterozygosity (0.68-0.76), PIC (0.66-0.74) and high Power of exclusion (0.28-0.38) indicating high forensic utility. The ensuing PC plots finely resolved three basal clusters corresponding to three geo-ethnic groups of African, Orientals, and Caucasians. In post HSCT chimerism analysis, it was found that together these markers were informative in 38 pairs (98%) and were able to predict the chimerism status successfully. There is a possibility that these STR loci along with forensic and phylogenetic importance, can predict the outcome of HSCT successfully.

Airan, B., et al. (2007). "Application of stem cell technology for coronary artery disease at the All India Institute of Medical Sciences, New Delhi, India." Heart Surg Forum **10**(3): E231-234.

Stem cell technology is rapidly gaining popularity as a way to improve the prognosis of patients with coronary artery disease and heart failure. In this review, we systematically analyze the basis, methods, and results of stem cell technology for coronary artery disease at the All India Institute of Medical Sciences, New Delhi, India.

Akamatsu, W. (2012). "[Exploring the neural diseases using stem cell technology]." Rinsho Shinkeigaku **52**(11): 937-938.

The rapid and efficient induction of neural stem cells (NSCs) from pluripotent stem cells is required for the research of patient-specific iPS cells and regenerative medicine to induce their own neural cells. Here, we induced NSCs from human pluripotent stem cells within 2 weeks and these clonal NSCs were expanded efficiently by their self-renewal ability. Further, we directly induced NSCs from both mouse and human fibroblasts using four reprogramming factors (Oct4, Sox2, Klf4, and cMyc) without the clonal isolation of induced pluripotent stem cells (iPSCs). Since these NSCs rapidly developed into mature gliogenic neural stem cells, we were able to purify these rapidly differentiating NSCs without contamination of differentiation-resistant pluripotent cells. These methods will facilitate high throughput screening of phonotypes appeared in neural cells induced from the somatic cells derived from sporadic neurodegenerative diseases.

Anderson, R. H. and K. R. Francis (2018). "Modeling rare diseases with induced pluripotent stem cell technology." Mol Cell Probes **40**: 52-59.

Rare diseases, in totality, affect a significant proportion of the population and represent an unmet medical need facing the scientific community. However, the treatment of individuals affected by rare diseases is hampered by poorly understood mechanisms preventing the development of viable therapeutics. The discovery and application of cellular reprogramming to create novel induced pluripotent stem cell models of rare diseases has revolutionized the rare disease community. Through developmental and functional analysis of differentiated cell types, these stem cell models carrying patient-specific mutations have become an invaluable tool for rare disease research. In this review article, we discuss the reprogramming of samples from individuals affected with rare diseases to induced pluripotent stem cells, current and future applications for this technology, and how integration of genome editing to rare disease research will help to improve our understanding of disease pathogenesis and lead to patient therapies.

Armstrong, R. J., et al. (2001). "Neural stem cell technology as a novel treatment for Parkinson's disease." Methods Mol Med **62**: 289-307.

The transplantation of human fetal ventral mesencephalic (VM) tissue for patients with advanced Parkinson's disease (PD) has now proved to be of benefit in early clinical trials (1-3). This has been clearly seen in terms of improved motor function, which has been correlated with increased fluorodopa signal on positron emission tomographic scanning at the site of the implant and the presence of abundant tyrosine hydroxylase (TH)-positive neurons in those patients who have come to postmortem analysis (4,5). However, although the concept of restoration of function through neural transplantation is promising, there are major practical as well as ethical problems with the use of aborted human fetal tissue. In particular, aborted fetal tissue is not available in many countries, and even where it can be obtained, isolation of the VM from the large numbers of fetuses the procedure requires presents major logistical difficulties. For example, in PD the best results have been obtained using an average of six to eight fetuses per patient. Therefore, the search for alternative sources of tissue for transplantation is imperative if the procedure is to be widely adopted in the clinical domain. A number of possibilities are currently being explored experimentally (see Table 1), although all of them present difficulties that must be overcome before they can be adopted clinically (reviewed in ref. 6). Table 1 Alternatives to Primary Human Neuronal Cells for Transplantation in PD Dopamine-containing polymers that release dopamine slowly over months/years. Catecholamine-producing cells found naturally within the adult, which may thus be suitable for autotransplantation, e.g., adrenal medulla, carotid body, superior cervical ganglion. Catecholamine-producing cell lines that may be encapsulated to prevent rejection and spread of the tumour cells out into the host brain, e.g., PC12 cells. Cells transfected with tyrosine hydroxylase, which potentially allows for the possibility of autotransplantation, e.g., skin fibroblasts.

Xenografts of dopamine-rich tissue, e.g., embryonic porcine ventral mesencephalic tissue. Neural stem cells. Embryonic stem (ES) cells.

Asatrian, G., et al. (2015). "Stem cell technology for bone regeneration: current status and potential applications." Stem Cells Cloning **8**: 39-48.

Continued improvements in the understanding and application of mesenchymal stem cells (MSC) have revolutionized tissue engineering. This is particularly true within the field of skeletal regenerative medicine. However, much remains unknown regarding the native origins of MSC, the relative advantages of different MSC populations for bone regeneration, and even the biologic safety of such unpurified, grossly characterized cells. This review will first summarize the initial discovery of MSC, as well as the current and future applications of MSC in bone tissue engineering. Next, the relative advantages and disadvantages of MSC isolated from distinct tissue origins are debated, including the MSC from adipose, bone marrow, and dental pulp, among others. The perivascular origin of MSC is next discussed. Finally, we briefly comment on pluripotent stem cell populations and their possible application in bone tissue engineering. While continually expanding, the field of MSC-based bone tissue engineering and regeneration shows potential to become a clinical reality in the not-so-distant future.

Barquinero, J. (1998). "Stem cell gene therapy--second conference. Biology and technology. 31 May - 3 June 1998, Orcas Island, WA, USA." IDrugs **1**(3): 278-280.

This conference, which was organized by George Stamatoyanno-poulos (University of Washington, Seattle, WA, USA), comprised 44 oral and 55 poster presentations. It started immediately after the First Annual Meeting of the American Society of Gene Therapy in Seattle, and took place at the Rosario Resort, located in the beautiful and quiet Orcas Island, in the Pacific Northwest. Several issues including stem cell biology, viral vectors, gene transfer into hematopoietic stem cells (HSCs) and a variety of clinical trials were covered. There were about 150 attendees including students, postdoctoral fellows and prominent experts in different aspects of the field. Most of these were from academia including research institutes, universities and hospitals, with a very small proportion from industry. Some of the information had already been presented a few days before at the Seattle meeting.

Borgonovo, T., et al. (2014). "Genetic evaluation of mesenchymal stem cells by G-banded karyotyping in a Cell Technology Center." Rev Bras Hematol Hemoter **36**(3): 202-207.

OBJECTIVE: To present the initial results of first three years of implementation of a genetic evaluation test for bone marrow-derived mesenchymal stem cells in a Cell Technology Center. METHODS: A retrospective study was carried out of 21 candidates for cell therapy. After the isolation of bone marrow mononuclear cells by density gradient, mesenchymal stem cells were cultivated and expanded at least until the second passage. Cytogenetic analyses were performed before and after cell expansion (62 samples) using G-banded karyotyping. RESULTS: All the samples analyzed, before and after cell expansion, had normal karyotypes, showing no clonal chromosomal changes. Signs of chromosomal instability were observed in 11 out of 21 patients (52%). From a total of 910 analyzed metaphases, five chromatid gaps, six chromatid breaks and 14 tetraploid cells were detected giving as total of 25 metaphases with chromosome damage (2.75%). CONCLUSION: The absence of clonal chromosomal aberrations in our results for G-banded karyotyping shows the maintenance of chromosomal stability of bone marrow-derived mesenchymal stem cells until the second passage; however, signs of chromosomal instability such as chromatid gaps, chromosome breaks and tetraploidy indicate that the long-term cultivation of these cells can provide an intermediate step for tumorigenesis.

Bosman, A., et al. (2015). "Bioengineering and Stem Cell Technology in the Treatment of Congenital Heart Disease." J Clin Med **4**(4): 768-781.

Congenital heart disease places a significant burden on the individual, family and community despite significant advances in our understanding of aetiology and treatment. Early research in ischaemic heart disease has paved the way for stem cell technology and bioengineering, which promises to improve both structural and functional aspects of disease. Stem cell therapy has demonstrated significant improvements in cardiac function in adults with ischaemic heart disease. This finding, together with promising case studies in the paediatric setting, demonstrates the potential for this treatment in congenital heart disease. Furthermore, induced pluripotent stems cell technology, provides a unique opportunity to address aetiological, as well as therapeutic, aspects of disease.

Boucherie, C., et al. (2011). "Induced pluripotent stem cell technology for generating photoreceptors." Regen Med **6**(4): 469-479.

The discovery of methods to produce pluripotent stem cells from human skin cells and other adult tissues has created a new era in stem cell research. In this article, we discuss the generation and use of pluripotent stem cells for the study of retinal disorders and the development of cell-based therapies. We describe advances in protocols for differentiating pluripotent cells into photoreceptor precursors that might be suitable for transplantation and discuss the use of human induced pluripotent stem cell-derived

photoreceptors for disease modeling and drug screening.
Burgess, R. and R. P. Huang (2016). "Cancer Stem Cell Biomarker Discovery Using Antibody Array Technology." Adv Clin Chem **73**: 109-125.

Cancer is a complex disease involving hundreds of pathways and numerous levels of disease progression. In addition, there is a growing body of evidence that the origins and growth rates of specific types of cancer may involve "cancer stem cells," which are defined as "cells within a tumor that possess the capacity to self-renew and to cause the development of heterogeneous lineages of cancer cells that comprise the tumor.(1)" Many types of cancer are now thought to harbor cancer stem cells. These cells themselves are thought to be unique in comparison to other cells types present within the tumor and to exhibit characteristics that allow for the promotion of tumorigenesis and in some cases metastasis. In addition, it is speculated that each type of cancer stem cell exhibits a unique set of molecular and biochemical markers. These markers, alone or in combination, may act as a signature for defining not only the type of cancer but also the progressive state. These biomarkers may also double as signaling entities which act autonomously or upon neighboring cancer stem cells or other cells within the local microenvironment to promote tumorigenesis. This review describes the heterogeneic properties of cancer stem cells and outlines the identification and application of biomarkers and signaling molecules defining these cells as they relate to different forms of cancer. Other examples of biomarkers and signaling molecules expressed by neighboring cells in the local tumor microenvironment are also discussed. In addition, biochemical signatures for cancer stem cell autocrine/paracrine signaling, local site recruitment, tumorigenic potential, and conversion to a stem-like phenotype are described.

Cagnin, S., et al. (2012). "Overview of micro- and nano-technology tools for stem cell applications: micropatterned and microelectronic devices." Sensors (Basel) **12**(11): 15947-15982.

In the past few decades the scientific community has been recognizing the paramount role of the cell microenvironment in determining cell behavior. In parallel, the study of human stem cells for their potential therapeutic applications has been progressing constantly. The use of advanced technologies, enabling one to mimic the in vivo stem cell microenviroment and to study stem cell physiology and physio-pathology, in settings that better predict human cell biology, is becoming the object of much research effort. In this review we will detail the most relevant and recent advances in the field of biosensors and micro- and nano-technologies in general, highlighting advantages and disadvantages. Particular attention will be devoted to those applications employing stem cells as a sensing element.

Cai, C. Y., et al. (2020). "[Induced pluripotent stem cell technology and its application in disease research]." Yi Chuan **42**(11): 1042-1061.

Since Takahashi and Yamanaka reported the generation of induced pluripotent stem cells (iPSCs) in 2006, the field of pluripotent stem cells has entered an unprecedented state of development. It plays an important role in disease modeling, drug discovery and cell therapy, and promotes the development of cell biology and regenerative medicine. At present, iPSC technology has become an important tool for studying of pathological mechanisms. New drugs screened by iPSC technology are being developed, and the number of clinical trials using iPSC-derived cells is gradually increasing. The latest research progress of iPSCs, combined with gene editing technology and 3D organoid methodology, promotes the further applications of iPSCs in disease research. In this review, we introduce the innovation of reprogramming methods in recent years, analyze the advantages and disadvantages of four reprogramming methods: integrated virus vector system, integrated non-viral vector system, non-integrated virus vector system and non-integrated non virus vector system. At the same time, we summarize the latest research progress on iPSCs in disease modeling and clinical treatment strategies, so as to provide a reference for further in-depth research in various fields of iPSCs.

Camper, S. A., et al. (1995). "Implementing transgenic and embryonic stem cell technology to study gene expression, cell-cell interactions and gene function." Biol Reprod **52**(2): 246-257.

This review highlights the use of transgenic mice and gene targeting in the study of reproduction, pituitary gene expression, and cell lineage. Since 1980 numerous applications of transgenic animal technology have been reported. Altered phenotypes resulting from transgene expression demonstrated that introduced genes can exert profound effects on animal physiology. Transgenic mice have been important for the study of hormonal and developmental control of gene expression because gene expression in whole animals often requires more DNA sequence information than is necessary for expression in cell cultures. This point is illustrated by studies of pituitary glycoprotein hormone alpha- and beta-subunit gene expression (Kendall et al., Mol Endocrinol 1994; in press [1]. Transgenic mice have also been invaluable for producing animal models of cancer and other diseases and testing the efficacy of gene therapy. In addition, cell-cell interactions and cell lineage relationships have been explored by cell-specific expression of toxin genes in transgenic mice. Recent studies suggest that attenuated and inducible toxins hold promise for future transgene ablation

experiments. Since 1987, embryonic stem (ES) cell technology has been used to create numerous mouse strains with targeted gene alterations, contributing enormously to our understanding of the functional importance of individual genes. For example, the unexpected development of gonadal tumors in mice with a targeted disruption of the inhibin gene revealed a potential role for inhibin as a tumor suppressor (Matzuk et al., Nature 1992:360: 313-319 [2]. The transgenic and ES cell technologies will undoubtedly continue to expand our understanding and challenge our paradigms in reproductive biology.

Chan, W. C., et al. (1994). "Detection of tumor contamination of peripheral stem cells in patients with lymphoma using cell culture and polymerase chain reaction technology." J Hematother **3**(3): 175-184.

The important question of whether residual tumor in the bone marrow or peripheral blood stem cell graft contributes to relapse in autologous bone marrow transplantation in patients with non-Hodgkin's lymphoma can be addressed only if there is an accurate and sensitive measurement of tumor cell contamination of the graft. Assays utilizing DNA amplification based on the polymerase chain reaction (PCR) are highly sensitive. Tumor-specific primers and probes can be designed for the clonally rearranged Ig or T cell antigen receptor genes in the original tumors, and these can then be used to detect minimal residual disease in subsequent specimens. Specific translocations can also be exploited as tumor markers, and the t(14;18) translocation has been widely employed for detecting tumor cells in blood and bone marrow samples. Lymphoma cells have also been grown successfully in tissue culture, and the detection of tumor contamination of autologous grafts has been associated with a poorer prognosis in patients with intermediate- or high-grade lymphoma. It is of interest to compare the sensitivity of tumor detection and the predictive value for patient survival of the PCR-based and culture-based assays. The information obtained may help to determine whether minimal tumor contamination of an autologous graft is clinically significant and, if so, the assay(s) that should be employed.

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

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

Chiotaki, R., et al. (2016). "Stem cell technology in breast cancer: current status and potential applications." Stem Cells Cloning **9**: 17-29.

Breast cancer, the leading cause of cancer among females, is supported by the presence of a rare subset of undifferentiated cells within the tumor, identified as breast cancer stem cells (BCSCs). BCSCs underlie the mechanisms of tumor initiation and sustenance and are implicated in the dissemination of the primary tumor to metastatic sites, as they have been found circulating in the blood of breast cancer patients. The discovery of BCSCs has generated a great amount of interest among the scientific community toward their isolation, molecular characterization, and therapeutic targeting. In this review, after summarizing the literature on molecular characterization of BCSCs and methodologies used for their isolation, we will focus on recent data supporting their molecular and functional heterogeneity. Additionally, following a synopsis of the latest approaches for BCSC targeting, we will specifically emphasize on the therapeutic use of naive or engineered normal stem cells in the treatment of breast cancer and present contradictory findings challenging their safety.

Cobo, F. and A. Concha (2007). "Application of microarray technology for microbial diagnosis in stem cell cultures: a review." Cytotherapy **9**(1): 53-59.

Stem cell lines used for cell therapy and regenerative medicine programs could be contaminated by several types of microorganism, such as bacteria, fungi, yeasts, viruses and prion particles. The presence of these pathogens makes the stem cell cultures unsuitable for transplant in humans. At the moment, tests for detecting these kinds of pathogens are carried out by means of standardized diagnosis procedures, in order to avoid the possibility of transmitting infectious diseases to the recipients of stem cell products. Some of the methods that can be included in a microbiologic control program are culture-based methods for sterility assessment, molecular techniques (PCR, RT-PCR), Ag detection and electron microscopy. However, new technologies based on DNA microarrays and protein arrays could also be applied for microbial diagnosis in stem cell lines in order to improve the microorganism detection. In this review, we summarize the main features concerning microarray methodology, the advantages and disadvantages regarding microbial diagnosis for stem cell cultures and possible future application in stem cell research centers in the microbiology field.

Collin, J., et al. (2016). "Using Zinc Finger Nuclease Technology to Generate CRX-Reporter Human Embryonic Stem Cells as a Tool to Identify and Study the Emergence of Photoreceptors Precursors During Pluripotent Stem Cell Differentiation." Stem Cells **34**(2): 311-321.

The purpose of this study was to generate human embryonic stem cell (hESC) lines harboring the green fluorescent protein (GFP) reporter at the endogenous loci of the Cone-Rod Homeobox (CRX) gene, a key transcription factor in retinal development. Zinc finger nucleases (ZFNs) designed to cleave in the 3' UTR of CRX were transfected into hESCs along with a donor construct containing homology to the target region, eGFP reporter, and a puromycin selection cassette. Following selection, polymerase chain reaction (PCR) and sequencing analysis of antibiotic resistant clones indicated targeted integration of the reporter cassette at the 3' of the CRX gene, generating a CRX-GFP fusion. Further analysis of a clone exhibiting homozygote integration of the GFP reporter was conducted suggesting genomic stability was preserved and no other copies of the targeting cassette were inserted elsewhere within the genome. This clone was selected for differentiation towards the retinal lineage. Immunocytochemistry of sections obtained from embryoid bodies and quantitative reverse transcriptase PCR of GFP positive and negative subpopulations purified by fluorescence activated cell sorting during the differentiation indicated a significant correlation between GFP and endogenous CRX expression. Furthermore, GFP expression was found in photoreceptor precursors emerging during hESC differentiation, but not in the retinal pigmented epithelium, retinal ganglion cells, or neurons of the developing inner nuclear layer. Together our data demonstrate the successful application of ZFN technology to generate CRX-GFP labeled hESC lines, which can be used to study and isolate photoreceptor precursors during hESC differentiation.

Coombe, L., et al. (2018). "Current approaches in regenerative medicine for the treatment of diabetes: introducing CRISPR/CAS9 technology and the case for non-embryonic stem cell therapy." Am J Stem Cells **7**(5): 104-113.

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder in which the body destroys its pancreatic beta cells. Since these cells are responsible for insulin production, dysfunction or destruction of these cells necessitates blood glucose control through exogenous insulin shots. Curative treatment involves pancreas transplantation, but due to the incidence of transplant rejection and complications associated with immunosuppression, alternatives are being explored. Despite facing clinical challenges and issues with public perception, the field of regenerative stem cell therapy shows great promise for the treatment of diabetes. The idea of harnessing pluripotency to derive cells and tissues with characteristics of choice is astounding but feasible, and this review seeks to determine which method of stem cell derivation is preferable for diabetes treatment. In this report, we outline the methods for deriving human embryonic stem cells (hESCs), induced pluripotent stem cells (iPSCs), and adult stem cells or progenitor cells to generate functional islet cells and related tissues. We discuss the specific uses and advantages of each method, and we comment on the ethics and public perceptions surrounding these methods and how they may affect the future of stem cell research. For the reasons outlined in this paper, we believe that non-embryonic stem cell lines, including iPSCs, somatic cell nuclear transfer lines, and adult tissue derived stem cells, offer the highest therapeutic potential for treating diabetes.

Cortes, J. L., et al. (2008). "Whole-blastocyst culture followed by laser drilling technology enhances the efficiency of inner cell mass isolation and embryonic stem cell derivation from good- and poor-quality mouse embryos: new insights for derivation of human embryonic stem cell lines." Stem Cells Dev **17**(2): 255-267.

The optimization of human embryonic stem (hES) cell line derivation methods is challenging because many worldwide laboratories have neither access to spare human embryos nor ethical approval for using supernumerary human embryos for hES cell derivation purposes. Additionally, studies performed directly on human embryos imply a waste of precious human biological material. In this study, we developed a new strategy based on the combination of whole-blastocyst culture followed by laser drilling destruction of the trophoectoderm for improving the efficiency of inner cell mass (ICM) isolation and ES cell derivation using murine embryos. Embryos were divided into good- and poor-quality embryos. We demonstrate that the efficiency of both ICM isolation and ES cell derivation using this strategy is significantly superior to whole-blastocyst culture or laser drilling technology itself. Regardless of the ICM isolation method, the ES cell establishment depends on a feeder cell growth surface. Importantly, this combined methodology can be successfully applied to poor-quality blastocysts that otherwise would not be suitable for laser drilling itself nor immunosurgery in an attempt to derive ES cell lines due to the inability to distinguish the ICM. The ES cell lines derived by this combined method were characterized and shown to maintain a typical morphology, undifferentiated phenotype, and in vitro and in vivo three germ layer differentiation potential. Finally, all ES cell lines established using either technology acquired an aneuploid karyotype after

extended culture periods, suggesting that the method used for ES cell derivation does not seem to influence the karyotype of the ES cells after extended culture. This methodology may open up new avenues for further improvements for the derivation of hES cells, the majority of which are derived from frozen, poor-quality human embryos.

Coyle, R., et al. (2016). "Polymer microarray technology for stem cell engineering." Acta Biomater **34**: 60-72.

UNLABELLED: Stem cells hold remarkable promise for applications in tissue engineering and disease modeling. During the past decade, significant progress has been made in developing soluble factors (e.g., small molecules and growth factors) to direct stem cells into a desired phenotype. However, the current lack of suitable synthetic materials to regulate stem cell activity has limited the realization of the enormous potential of stem cells. This can be attributed to a large number of materials properties (e.g., chemical structures and physical properties of materials) that can affect stem cell fate. This makes it challenging to design biomaterials to direct stem cell behavior. To address this, polymer microarray technology has been developed to rapidly identify materials for a variety of stem cell applications. In this article, we summarize recent developments in polymer array technology and their applications in stem cell engineering. STATEMENT OF SIGNIFICANCE: Stem cells hold remarkable promise for applications in tissue engineering and disease modeling. In the last decade, significant progress has been made in developing chemically defined media to direct stem cells into a desired phenotype. However, the current lack of the suitable synthetic materials to regulate stem cell activities has been limiting the realization of the potential of stem cells. This can be attributed to the number of variables in material properties (e.g., chemical structures and physical properties) that can affect stem cells. Polymer microarray technology has shown to be a powerful tool to rapidly identify materials for a variety of stem cell applications. Here we summarize recent developments in polymer array technology and their applications in stem cell engineering.

Das, A. K. and R. Pal (2010). "Induced pluripotent stem cells (iPSCs): the emergence of a new champion in stem cell technology-driven biomedical applications." J Tissue Eng Regen Med **4**(6): 413-421.

Pluripotent stem cells possess the unique property of differentiating into all other cell types of the human body. Further, the discovery of induced pluripotent stem cells (iPSCs) in 2006 has opened up new avenues in clinical medicine. In simple language, iPSCs are nothing but somatic cells reprogrammed genetically to exhibit pluripotent characteristics. This process utilizes retroviruses/lentiviruses/adenovirus/plasmids to incorporate candidate genes into somatic cells isolated from any part of the human body. It is also possible to develop disease-specific iPSCs which are most likely to revolutionize research in respect to the pathophysiology of most debilitating diseases, as these can be mimicked ex vivo in the laboratory. These models can also be used to study the safety and efficacy of known drugs or potential drug candidates for a particular diseased condition, limiting the need for animal studies and considerably reducing the time and money required to develop new drugs. Recently, functional neurons, cardiomyocytes, pancreatic islet cells, hepatocytes and retinal cells have been derived from human iPSCs, thus re-confirming the pluripotency and differentiation capacity of these cells. These findings further open up the possibility of using iPSCs in cell replacement therapy for various degenerative disorders. In this review we highlight the development of iPSCs by different methods, their biological characteristics and their prospective applications in regenerative medicine and drug screening. We further discuss some practical limitations pertaining to this technology and how they can be averted for the betterment of human life.

De Rosa, A., et al. (2009). "A new method for cryopreserving adipose-derived stem cells: an attractive and suitable large-scale and long-term cell banking technology." Tissue Eng Part C Methods **15**(4): 659-667.

Recent studies have shown potential ways for improving stem cell cryopreservation. The major need for autologous stem cell use is a long-term storage: this arises from the humans' hope of future use of their own cells. Therefore, it is important to evaluate the cell potential of vitality and differentiation before and after cryopreservation. Although several studies have shown a long-term preservation of adipose tissue, a few of them focused their attention to stem cells. The aim of this study was to evaluate the fate of cryopreserved stem cells collected from adipose tissue and stored at low a temperature in liquid nitrogen through an optimal cryopreservation solution (using slowly cooling in 6% threalose, 4% dimethyl sulfoxide, and 10% fetal bovine serum) and to develop a novel approach to efficiently preserve adipose-derived stem cells (ASCs) for future clinical applications. Results showed that stem cells, after being thawed, are still capable of differentiation and express all surface antigens detected before storage, confirming the integrity of their biology. In particular, ASCs differentiated into adipocytes, showed diffuse positivity for PPARgamma and adiponectin, and were also able to differentiate into endothelial cells without addition of angiogenic factors. Therefore, ASCs can be long-term cryopreserved, and this, due to their great

numbers, is an attractive tool for clinical applications as well as of impact for the derived market.

Di Baldassarre, A., et al. (2018). "Human-Induced Pluripotent Stem Cell Technology and Cardiomyocyte Generation: Progress and Clinical Applications." Cells **7**(6).

Human-induced pluripotent stem cells (hiPSCs) are reprogrammed cells that have hallmarks similar to embryonic stem cells including the capacity of self-renewal and differentiation into cardiac myocytes. The improvements in reprogramming and differentiating methods achieved in the past 10 years widened the use of hiPSCs, especially in cardiac research. hiPSC-derived cardiac myocytes (CMs) recapitulate phenotypic differences caused by genetic variations, making them attractive human disease models and useful tools for drug discovery and toxicology testing. In addition, hiPSCs can be used as sources of cells for cardiac regeneration in animal models. Here, we review the advances in the genetic and epigenetic control of cardiomyogenesis that underlies the significant improvement of the induced reprogramming of somatic cells to CMs; the methods used to improve scalability of throughput assays for functional screening and drug testing in vitro; the phenotypic characteristics of hiPSCs-derived CMs and their ability to rescue injured CMs through paracrine effects; we also cover the novel approaches in tissue engineering for hiPSC-derived cardiac tissue generation, and finally, their immunological features and the potential use in biomedical applications.

Dirschinger, R. J., et al. (2012). "Recapitulating long-QT syndrome using induced pluripotent stem cell technology." Pediatr Cardiol **33**(6): 950-958.

The generation of patient-specific stem cells by reprogramming somatic cells to induced pluripotent stem cells (iPSC) provides the basis for a promising new type of in vitro disease models. Patient-specific iPSC derived from individuals with hereditary disorders can be differentiated into somatic cells in vitro, thus allowing the pathophysiology of the diseases to be studied on a cellular level. Different types of long-QT syndrome have been successfully modeled using this approach, demonstrating that the iPSC-derived patient-specific cardiomyocytes recapitulated key features of the disease in vitro. This approach will likely serve to model other monogenetic or polygenetic cardiovascular disorders in the future. Moreover, test platforms based on patient-specific iPSC could be used to test the potential of drug candidates to induce QT-interval prolongation or other unwanted side effects, screen for novel cardiovascular drugs, or to tailor medical therapy to the specific needs of a single patient.

Dolatshad, H., et al. (2019). "Application of induced pluripotent stem cell technology for the investigation of hematological disorders." Adv Biol Regul **71**: 19-33.

Induced pluripotent stem cells (iPSCs) were first described over a decade ago and are currently used in various basic biology and clinical research fields. Recent advances in the field of human iPSCs have opened the way to a better understanding of the biology of human diseases. Disease-specific iPSCs provide an unparalleled opportunity to establish novel human cell-based disease models, with the potential to enhance our understanding of the molecular mechanisms underlying human malignancies, and to accelerate the identification of effective new drugs. When combined with genome editing technologies, iPSCs represent a new approach to study single or multiple disease-causing mutations and model specific diseases in vitro. In addition, genetically corrected patient-specific iPSCs could potentially be used for stem cell based therapy. Furthermore, the reprogrammed cells share patient-specific genetic background, offering a new platform to develop personalized therapy/medicine for patients. In this review we discuss the recent advances in iPSC research technology and their potential applications in hematological diseases. Somatic cell reprogramming has presented new routes for generating patient-derived iPSCs, which can be differentiated to hematopoietic stem cells and the various downstream hematopoietic lineages. iPSC technology shows promise in the modeling of both inherited and acquired hematological disorders. A direct reprogramming and differentiation strategy is able to recapitulate hematological disorder progression and capture the earliest molecular alterations that underlie the initiation of hematological malignancies.

Drummond, R. J., et al. (2011). "Induced pluripotent stem cell technology and stem cell therapy for diabetes." Exp Ther Med **2**(1): 3-7.

Although diabetes can be managed clinically with the use of insulin injections, it remains an incurable and inconvenient disorder. In the long-term, it is associated with a number of clinical complications, such as cardiovascular disease, resulting in a desire for the development of new methodologies to replace defective cells and provide a lasting normality without the need for drug treatment. Stem cells, including induced pluripotent stem cells, offer the possibility of generating cells suitable for transplantation due to their capacity to differentiate into all tissue lineages. However, many issues must be addressed before this type of treatment becomes a reality, including the need for a greater understanding of the underlying biology involved in the onset of diabetes.

Duelen, R. and M. Sampaolesi (2017). "Stem Cell Technology in Cardiac Regeneration: A Pluripotent Stem Cell Promise." EBioMedicine **16**: 30-40.

Despite advances in cardiovascular biology and medical therapy, heart disorders are the leading cause of death worldwide. Cell-based regenerative therapies become a promising treatment for patients affected by heart failure, but also underline the need for reproducible results in preclinical and clinical studies for safety and efficacy. Enthusiasm has been tempered by poor engraftment, survival and differentiation of the injected adult stem cells. The crucial challenge is identification and selection of the most suitable stem cell type for cardiac regenerative medicine. Human pluripotent stem cells (PSCs) have emerged as attractive cell source to obtain cardiomyocytes (CMs), with potential applications, including drug discovery and toxicity screening, disease modelling and innovative cell therapies. Lessons from embryology offered important insights into the development of stem cell-derived CMs. However, the generation of a CM population, uniform in cardiac subtype, adult maturation and functional properties, is highly recommended. Moreover, hurdles regarding tumorigenesis, graft cell death, immune rejection and arrhythmogenesis need to be overcome in clinical practice. Here we highlight the recent progression in PSC technologies for the regeneration of injured heart. We review novel strategies that might overcome current obstacles in heart regenerative medicine, aiming at improving cell survival and functional integration after cell transplantation.

Egawa, N., et al. (2020). "From in vitro to in vivo reprogramming for neural transdifferentiation: An approach for CNS tissue remodeling using stem cell technology." J Cereb Blood Flow Metab **40**(9): 1739-1751.

Advances in stem cell technology have provided three approaches to address the demanding issue of the treatment of intractable neurological disease. One of the approaches is the screening of compounds attenuating pathological phenotypes in stem-cell based models. A second approach consists of exogenous-targeted cell supplementation to the lesion with stem cell-derived differentiated cells. A third approach involves in vivo direct programming to transdifferentiate endogenous somatic cells and to boost CNS tissue remodeling. In this review, we outline research advances in stem cell technology of direct reprogramming in vitro and in vivo and discuss the future challenge of tissue remodeling by neural transdifferentiation.

Elbadry, M. I., et al. (2017). "Induced pluripotent stem cell technology: A window for studying the pathogenesis of acquired aplastic anemia and possible applications." Exp Hematol **49**: 9-18.

Recent progress in human induced pluripotent stem cells (iPSCs) has opened the door to a better understanding of the biology of human diseases, especially rare disorders such as acquired aplastic anemia, in which the target hematopoietic tissues are depleted. The advent of somatic cell reprogramming has presented new routes for generating hematopoietic stem cells from patient-derived iPSCs and their differentiation into hematopoietic lineages. The purpose of this review is to discuss the recent advances in iPSC research technology and their potential applications in disease modeling for understanding the pathogenesis of bone marrow failure syndrome and the potential clinical utility of iPSC-derived cells.

Emery, D. W. and D. M. Bodine (2002). "The third conference on hematopoietic stem cell gene therapy: biology and technology." Mol Ther **5**(6): 658-663.

Fan, P., et al. (2012). "[The changes of cardioelectrical activity of rat with myocardial infarction receiving sarcoplasmic reticulum Ca(2+)-ATPase gene modified bone marrow stem cell transplantation by microelectrode array technology]." Zhonghua Xin Xue Guan Bing Za Zhi **40**(9): 729-735.

OBJECTIVE: Therapy effects and cardiac electrical activity comparison of bone marrow stem cells (BMSCs) transplantation and sarcoplasmic reticulum Ca(2+)-ATPase (SERCA2a) gene modified BMSCs transplantation after acute myocardial infarction (AMI) in rats. METHODS: Rats with AMI were divided into 4 groups (n = 30) randomly: normal group (n = 6), saline group (control group, n = 8), BMSCs transplantation group (BMSCs group, n = 8) and SERCA2a gene modified BMSCs transplantation group (BMSCs + rAd.SERCA2a group, n = 8). After 14 days, cardiac function was evaluated by echocardiography and heart electrical activity was evaluated by electrocardiogram and microelectrode array (MEA) technology. RESULTS: (1) The transduction ratio of rAd.SERCA2a to BMSCs were 80% to 90%. (2) Left ventricular ejection fraction on 14 days after therapy was significantly higher in BMSCs group and BMSCs + rAd.SERCA2a group than in control group (all $P < 0.05$). (3) QT duration was significantly shorter [(80.30 +/- 6.53) ms vs. (105.31 +/- 21.89) ms, $P < 0.05$] and ventricular premature beats less frequent in BMSCs + rAd. SERCA2a group than in the control group. (4) MEA results suggested that isolated heart beat was significantly slowed down and frequent ventricular arrhythmias and atrioventricular block were recorded in control group. The maximum field potential and field potential duration on infarcted myocardium area in BMSCs group and BMSCs + rAd.SERCA2a group were significantly longer than those in control group[the maximum field potential: (0.51 +/- 0.15), (0.55 +/- 0.16), (0.23 +/- 0.10) mV; field potential duration:

(104.5 +/- 25.43), (107.67 +/- 24.01), (63.00 +/- 20.34) ms; all P < 0.05]. (5) The conduction time was the shortest and the cardiac electrical conduction consistency in myocardial infarction tissue was significantly improved in BMSCs + rAd.SERCA2a group. CONCLUSIONS: BMSCs and SERCA2a gene modified BMSCs transplantation could significantly improve cardiac function and BMSCs + rAd.SERCA2a could also effectively improve electrical conduction of infarcted myocardium and attenuate the incidence of arrhythmia after myocardial infarction in rats.

Fauer, A. J., et al. (2019). "Impact of a health information technology tool addressing information needs of caregivers of adult and pediatric hematopoietic stem cell transplantation patients." Support Care Cancer **27**(6): 2103-2112.

PURPOSE: We developed BMT Roadmap, a health information technology (HIT) application on a tablet, to address caregivers' unmet needs with patient-specific information from the electronic health record. We conducted a preliminary feasibility study of BMT Roadmap in caregivers of adult and pediatric HSCT patients. The study was registered on ClinicalTrials.gov (NCT03161665; NCT02409121). METHODS: BMT Roadmap was delivered to 39 caregivers of adult and pediatric patients undergoing first-time HSCT at a single study site. We assessed person-reported outcome measures (PROMs) at baseline (hospital admission), discharge, and day 100: usefulness of BMT Roadmap (Perceived Usefulness); activation (Patient Activation Measure-Caregiver version [PAM-C]); mental health ([POMS-2(R)]: depression, distress, vigor, and fatigue); anxiety (State-Trait Anxiety Inventory); and quality of life (Caregiver Quality of Life Index-Cancer [CQOLC]). To identify determinants of caregiver activation and quality of life, we used linear mixed models. RESULTS: BMT Roadmap was perceived useful and activation increased from baseline to discharge (p = 0.001). Further, burden decreased through discharge (p = 0.007). Overall, a pattern of increasing vigor and decreasing depression, distress, fatigue, and anxiety was apparent from baseline to discharge. However, overall quality of life lowered at discharge after accounting for BMT Roadmap use, depression, anxiety, and fatigue (p = 0.04). CONCLUSIONS: BMT Roadmap was a feasible HIT intervention to implement in HSCT caregivers. BMT Roadmap was associated with increased activation and decreased burden, but quality of life lowered across hospitalization. Findings support the need to further develop caregiver-specific self-directed resources and provide them both inpatient and outpatient across the HSCT trajectory.

Feng, R. and C. Lengner (2013). "Application of Stem Cell Technology in Dental Regenerative Medicine." Adv Wound Care (New Rochelle) **2**(6): 296-305.

SIGNIFICANCE: In this review, we summarize the current literature regarding the isolation and characterization of dental tissue-derived stem cells and address the potential of these cell types for use in regenerative cell transplantation therapy. RECENT ADVANCES: Looking forward, platforms for the delivery of stem cells via scaffolds and the use of growth factors and cytokines for enhancing dental stem cell self-renewal and differentiation are discussed. CRITICAL ISSUES: We aim to understand the developmental origins of dental tissues in an effort to elucidate the molecular pathways governing the genesis of somatic dental stem cells. The advantages and disadvantages of several dental stem cells are discussed, including the developmental stage and specific locations from which these cells can be purified. In particular, stem cells from human exfoliated deciduous teeth may act as a very practical and easily accessibly reservoir for autologous stem cells and hold the most value in stem cell therapy. Dental pulp stem cells and periodontal ligament stem cells should also be considered for their triple lineage differentiation ability and relative ease of isolation. Further, we address the potentials and limitations of induced pluripotent stem cells as a cell source in dental regenerative. FUTURE DIRECTIONS: From an economical and a practical standpoint, dental stem cell therapy would be most easily applied in the prevention of periodontal ligament detachment and bone atrophy, as well as in the regeneration of dentin-pulp complex. In contrast, cell-based tooth replacement due to decay or other oral pathology seems, at the current time, an untenable approach.

Fernandes, A. R. and D. M. Chari (2016). "Part I: Minicircle vector technology limits DNA size restrictions on ex vivo gene delivery using nanoparticle vectors: Overcoming a translational barrier in neural stem cell therapy." J Control Release **238**: 289-299.

Genetically engineered neural stem cell (NSC) transplant populations offer key benefits in regenerative neurology, for release of therapeutic biomolecules in ex vivo gene therapy. NSCs are 'hard-to-transfect' but amenable to 'magnetofection'. Despite the high clinical potential of this approach, the low and transient transfection associated with the large size of therapeutic DNA constructs is a critical barrier to translation. We demonstrate for the first time that DNA minicircles (small DNA vectors encoding essential gene expression components but devoid of a bacterial backbone, thereby reducing construct size versus conventional plasmids) deployed with magnetofection achieve the highest, safe non-viral DNA transfection levels (up to 54%) reported so far for primary NSCs. Minicircle-functionalized magnetic nanoparticle (MNP)-mediated gene delivery also resulted in sustained gene expression for up to four weeks. All

daughter cell types of engineered NSCs (neurons, astrocytes and oligodendrocytes) were transfected (in contrast to conventional plasmids which usually yield transfected astrocytes only), offering advantages for targeted cell engineering. In addition to enhancing MNP functionality as gene delivery vectors, minicircle technology provides key benefits from safety/scale up perspectives. Therefore, we consider the proof-of-concept of fusion of technologies used here offers high potential as a clinically translatable genetic modification strategy for cell therapy.

Forte, L. and A. C. Berardi (2013). "Stem cell technologies based on hemangioblast technology focusing on human blood cells." Recent Pat Drug Deliv Formul **7**(1): 4-8.

The in vitro generation of hematopoietic stem cells (HSCs) and mature hematopoietic cells from hemangioblast derived from embryonic stem (ES) or induced pluripotent stem (iPS) cells promises to provide an alternative source of cells that could replace total bone marrow cells or HSC-enriched fractions. This mini-review deals with innovation related to hemangioblast-based methods for blood cells production as disclosed in recent patent literature and current barriers to clinical translation are discussed.

Friel, R., et al. (2006). "Embryonic stem cell technology: applications and uses in functional genomic studies." Stem Cell Rev **2**(1): 31-35.

In this postgenomic era, the role of functional genomics is becoming increasingly important and playing a key role in this field are embryonic stem cells. These cells are capable of proliferating indefinitely in a pluripotent state and have the potential to differentiate into all somatic cell types. Through a combination of their ease of genetic manipulation and directed in vitro differentiation they have proved themselves to be an extremely valuable tool in functional genomics. Here, some of their applications in functional genomic studies are discussed.

Fujii, Y., et al. (2018). "Bone regeneration by human dental pulp stem cells using a helioxanthin derivative and cell-sheet technology." Stem Cell Res Ther **9**(1): 24.

BACKGROUND: Human dental pulp stem cells (DPSCs), which have the ability to differentiate into multiple lineages, were recently identified. DPSCs can be collected readily from extracted teeth and are now considered to be a type of mesenchymal stem cell with higher clonogenic and proliferative potential than bone marrow stem cells (BMSCs). Meanwhile, the treatment of severe bone defects, such as fractures, cancers, and congenital abnormalities, remains a great challenge, and novel bone regenerative techniques are highly anticipated. Several studies have previously shown that 4-(4-methoxyphenyl)pyrido[40,30:4,5]thieno[2,3-b]pyridine-2-carboxamide (TH), a helioxanthin derivative, induces osteogenic differentiation of preosteoblastic and mesenchymal cells. However, the osteogenic differentiation activities of TH have only been confirmed in some mouse cell lines. Therefore, in this study, toward the clinical use of TH in humans, we analyzed the effect of TH on the osteogenic differentiation of DPSCs, and the in-vivo osteogenesis ability of TH-induced DPSCs, taking advantage of the simple transplantation system using cell-sheet technology. METHODS: DPSCs were obtained from dental pulp of the wisdom teeth of five healthy patients (18-22 years old) and cultured in regular medium and osteogenic medium with or without TH. To evaluate osteogenesis of TH-induced DPSCs in vivo, we transplanted DPSC sheets into mouse calvaria defects. RESULTS: We demonstrated that osteogenic conditions with TH induce the osteogenic differentiation of DPSCs more efficiently than those without TH and those with bone morphogenetic protein-2. However, regular medium with TH did not induce the osteogenic differentiation of DPSCs. TH induced osteogenesis in both DPSCs and BMSCs, although the gene expression pattern in DPSCs differed from that in BMSCs up to 14 days after induction with TH. Furthermore, we succeeded in bone regeneration in vivo using DPSC sheets with TH treatment, without using any scaffolds or growth factors. CONCLUSIONS: Our results demonstrate that TH-induced DPSCs are a useful cell source for bone regenerative medicine, and the transplantation of DPSC sheets treated with TH is a convenient scaffold-free method of bone healing.

Gentile, C. (2016). "Filling the Gaps between the In Vivo and In Vitro Microenvironment: Engineering of Spheroids for Stem Cell Technology." Curr Stem Cell Res Ther **11**(8): 652-665.

Engineering of in vitro three-dimensional cultures of stem cells and their progenies has offered promising alternatives to recapitulate the in vivo microenvironment, or stem cell niche, and has provided more specific cues for proper stem cell differentiation, maintenance and culture. In particular, tissue spheroids are cellular aggregates with defined cellular and extracellular features and have provided optimal conditions for stem cell technology, both in culture and for potential engraftment. Recent studies have focused on spheroid formation and the developmental roles played by cellular and extracellular signals necessary for cellular aggegation into spheroids. This review will provide insights into the factors that regulate in vitro spheroid formation by comparing them with their developmental counterparts in vivo. At the same time, we will identify cellular and extracellular signals that could be used to bioengineer spheroids with improved features according to their application. Finally, this

review will provide an overview of the applications to date of spheroid cultures of stem cells and their progenies, providing insights for future studies.

Gerlach, J. C., et al. (2010). "Interwoven four-compartment capillary membrane technology for three-dimensional perfusion with decentralized mass exchange to scale up embryonic stem cell culture." Cells Tissues Organs **192**(1): 39-49.

We describe hollow fiber-based three-dimensional (3D) dynamic perfusion bioreactor technology for embryonic stem cells (ESC) which is scalable for laboratory and potentially clinical translation applications. We added 2 more compartments to the typical 2-compartment devices, namely an additional media capillary compartment for countercurrent 'arteriovenous' flow and an oxygenation capillary compartment. Each capillary membrane compartment can be perfused independently. Interweaving the 3 capillary systems to form repetitive units allows bioreactor scalability by multiplying the capillary units and provides decentralized media perfusion while enhancing mass exchange and reducing gradient distances from decimeters to more physiologic lengths of <1 mm. The exterior of the resulting membrane network, the cell compartment, is used as a physically active scaffold for cell aggregation; adjusting intercapillary distances enables control of the size of cell aggregates. To demonstrate the technology, mouse ESC (mESC) were cultured in 8- or 800-ml cell compartment bioreactors. We were able to confirm the hypothesis that this bioreactor enables mESC expansion qualitatively comparable to that obtained with Petri dishes, but on a larger scale. To test this, we compared the growth of 129/SVEV mESC in static two-dimensional Petri dishes with that in 3D perfusion bioreactors. We then tested the feasibility of scaling up the culture. In an 800-ml prototype, we cultured approximately 5 x 10(9) cells, replacing up to 800 conventional 100-mm Petri dishes. Teratoma formation studies in mice confirmed protein expression and gene expression results with regard to maintaining 'stemness' markers during cell expansion.

Ghita, A., et al. (2015). "Applications of Raman micro-spectroscopy to stem cell technology: label-free molecular discrimination and monitoring cell differentiation." EPJ Tech Instrum **2**(1): 6.

Stem cell therapy is widely acknowledged as a key medical technology of the 21st century which may provide treatments for many currently incurable diseases. These cells have an enormous potential for cell replacement therapies to cure diseases such as Parkinson's disease, diabetes and cardiovascular disorders, as well as in tissue engineering as a reliable cell source for providing grafts to replace and repair diseased tissues. Nevertheless, the progress in this field has been difficult in part because of lack of techniques that can measure non-invasively the molecular properties of cells. Such repeated measurements can be used to evaluate the culture conditions during differentiation, cell quality and phenotype heterogeneity of stem cell progeny. Raman spectroscopy is an optical technique based on inelastic scattering of laser photons by molecular vibrations of cellular molecules and can be used to provide chemical fingerprints of cells or organelles without fixation, lysis or use of labels and other contrast enhancing chemicals. Because differentiated cells are specialized to perform specific functions, these cells produce specific biochemicals that can be detected by Raman micro-spectroscopy. This mini-review paper describes applications of Raman micro-scpectroscopy to measure moleculare properties of stem cells during differentiation in-vitro. The paper focuses on time- and spatially-resolved Raman spectral measurements that allow repeated investigation of live stem cells in-vitro.

Gnecchi, M., et al. (2017). "Induced pluripotent stem cell technology: Toward the future of cardiac arrhythmias." Int J Cardiol **237**: 49-52.

The development of human induced pluripotent stem cell (iPSC) technology has revitalized the efforts made in the last decade to exploit the potential of human embryonic stem cells (ESCs) for scientific research. In the field of cardiac arrhythmias, the possibility of generating an unlimited amount of patient-specific cardiomyocyte-like cells (iPSC-CMs) has clear advantages compared with the use of ESC-derived cardiac cells. In particular, with the introduction and implementation of the large-scale precision medicine initiative, we anticipate that the iPSC technology will play an important role in the advancement of cardiovascular research and medicine. This platform is not free from technical limitations that must be carefully taken into account; however, the utility of iPSC-CMs in disease modeling and drug testing studies is hardly questionable. Here, we summarize some of the progresses made in the field of iPSC technology applied to inherited cardiac arrhythmias, with particular emphasis on the use of iPSC-CMs for modelling the long QT syndrome and for the development of personalized drug and molecular therapies. The growing role of iPSC technology in the practice of precision medicine will also be discussed.

Goldstein, L. S., et al. (2015). "Probing the secrets of Alzheimer's disease using human-induced pluripotent stem cell technology." Neurotherapeutics **12**(1): 121-125.

Our understanding of Alzheimer's disease (AD) is still incomplete and, as a result, we lack effective therapies. Reprogramming to generate human-induced pluripotent stem cells provides a new approach to the generation of human neurons that carry

the genomes of people with familial or sporadic AD. Differentiation of such stem cells to human neurons is already providing new insights into AD and molecular pathways that may provide new targets for effective therapy. These pathways include typical amyloid response pathways, as well as pathways leading from altered behavior of amyloid precursor protein to the elevated phosphorylation of tau protein. There is also a need for standardization of models so that isogenic lines differing only in the familial AD mutation can be compared.

Gomathi, M. and V. Balachandar (2017). "Novel therapeutic approaches: Rett syndrome and human induced pluripotent stem cell technology." Stem Cell Investig **4**: 20.

Recent advances in induced pluripotent stem cell (iPSC) technology target screening and discovering of therapeutic agents for the possible cure of human diseases. Human induced pluripotent stem cells (hiPSC) are the right kind of platform for testing potency of specific active compounds. Ayurveda, the Indian traditional system of medicine developed between 2,500 and 500 BC, is a science involving the intelligent formulations of herbs and minerals. It can serve as a "goldmine" for novel neuroprotective agents used for centuries to treat neurological disorders. This review discusses limitations in screening drugs for neurological disorders and the advantages offered by hiPSC integrated with Indian traditional system of medicine. We begin by describing the current state of hiPSC technology in research on Rett syndrome (RTT) followed by the current controversies in RTT research combined with the emergence of patient-specific hiPSC that indicate an urgent need for researchers to understand the etiology and drug mechanism. We conclude by offering recommendations to reinforce the screening of active compounds present in the ayurvedic medicines using the human induced pluripotent neural model system for research involving drug discovery for RTT. This integrative approach will fill the current knowledge gap in the traditional medicines and drug discovery.

Gopalan, N., et al. (2020). "Regulation of Stem Cell Technology in Malaysia: Current Status and Recommendations." Sci Eng Ethics **26**(1): 1-25.

Stem cell technology is an emerging science field; it is the unique regenerative ability of the pluripotent stem cell which scientists hope would be effective in treating various medical conditions. While it has gained significant advances in research, it is a sensitive subject involving human embryo destruction and human experimentation, which compel governments worldwide to ensure that the related procedures and experiments are conducted ethically. Based on face-to-face interviews with selected Malaysian ethicists, scientists and policymakers, the objectives and effectiveness of the current Guideline for Stem Cell Research and Therapy (2009) are examined. The study's findings show that the guideline is rather ineffective in ensuring good ethical governance of the technology. A greater extent of unethical conduct is likely present in the private medical clinics or laboratories offering stem cell therapies compared with the public medical institutions providing similar services, as the latter are closely monitored by the governmental agencies enforcing the relevant policies and laws. To address concerns over malpractices or unethical conduct, this paper recommends a comprehensive revision of the current stem cell guideline so that adequate provisions exist to regulate the explicit practices of the private and public stem cell sectors, including false advertising and accountability. The newly revised Malaysian stem cell guideline will align with the Guidelines for Stem Cell Research and Clinical Translation (2016) of the International Society for Stem Cell Research (ISSCR) containing secular but universal moral rules. However, a regulatory policy formulated to govern the technology remains the main thrust of empowering the guideline for compliance among the stakeholders.

Gratwohl, A., et al. (2010). "Changes in the use of hematopoietic stem cell transplantation: a model for diffusion of medical technology." Haematologica **95**(4): 637-643.

BACKGROUND: Innovations in hematology spread rapidly. Factors affecting the speed of introduction, international diffusion, and durability of use of innovations are, however, poorly understood. DESIGN AND METHODS: We used data on 251,106 hematopoietic stem cell transplants from 591 teams in 36 European countries to analyze the increase and decrease in such transplants for breast cancer and chronic myeloid leukemia and the replacement of bone marrow by peripheral blood as the source of stem cells as processes of diffusion. Regression analyses were used to measure the quantitative impact of defined macro- and microeconomic factors, to look for significant associations (t-test), and to describe the coefficient of determination or explanatory content (R(2)). RESULTS: Gross national income per capita, World Bank category, team density, team distribution, team size, team experience and, team innovator status were all significantly associated with some or all of the changes. The analyses revealed different patterns of associations and a wide range of explanatory content. Macro- and micro-economic factors were sufficient to explain the increase of allogeneic hematopoietic stem cell transplants in general (R(2) = 78.41%) and for chronic myeloid leukemia in particular (R(2) = 79.39%). They were insufficient to explain the changes in stem cell source (R(2) =26.79% autologous hematopoietic stem cell transplants; R(2) = 9.67%

allogeneic hematopoietic stem cell transplants) or the decreases in hematopoietic stem cell transplants (R(2) =10.22% breast cancer; R(2)=33.17% chronic myeloid leukemia). CONCLUSIONS: The diffusion of hematopoietic stem cell transplants is more complex than previously thought. Availability of resources, evidence, external regulations and, expectations were identified as key determinants. These data might serve as a model for diffusion of medical technology in general.

Groot, M. T., et al. (2004). "[The role of cost analysis in the evaluation of the development of medical technology. The case of allogenic stem-cell transplantation]." Ned Tijdschr Geneeskd **148**(10): 480-484.

OBJECTIVE: To estimate the real costs of allogeneic haematopoetic stem-cell transplantation and to compare these with the historically determined budgets that are made available for this purpose ([symbol: see text] 70,038 for genetically related donors and [symbol: see text] 76,826 for unrelated donors). DESIGN: Cost analysis. METHODS: In the period 1994-1999, the direct medical costs (price level of 1998) of bone-marrow transplantation from related donors (BMT), stem-cell transplantation from unrelated donors (VUD-SCT) and allogeneic peripheral-blood stem-cell transplantation (PBSCT) from related donors were determined on the basis of data on adult patients with either acute myeloid leukaemia (n = 66) or acute lymphocytic leukaemia (n = 31). First, the medical resource use by these patients was determined and multiplied by the unit costs of each of the items. Second, a structural programme for allogeneic stem-cell transplantation brings along costs that are not evident from the registration of the medical resource use (e.g., the costs of pretransplantation screening and the selection of the donor). The costs of these items were calculated by taking inventory in the hospitals and assessed by experts. RESULTS: The average costs per transplanted patient were [symbol: see text] 98,334 (BMT), [symbol: see text] 151,754 (VUD-SCT) and [symbol: see text] 98,977 (PBSCT) during the first two years after transplantation. The greater part of the costs was incurred in the transplantation phase. In VUD-SCT, one-third of the total cost was due to the costs of finding a suitable donor. CONCLUSION: The current budget for allogeneic stem-cell transplantation is insufficient to perform the transplantations adequately. Periodic evaluation of the budgets for complicated procedures based on cost analyses has added value for the evaluation of the development of these procedures in time and can thereby contribute to the quality and continuity of care.

Halpern, W., et al. (2011). "Stems to GEMs: impact of stem cell technology on engineered animal models." Vet Pathol **48**(5): 1041-1043.

Collectively, these presentations introduced the audience to the roles of ES cells in generating phenotypes of transgenic animals,and they provided examples where the GEMs were used to define molecular mechanisms of disease or where ES cells were used as a therapeutic modality. Points of discussion among audience members reinforced the importance of strain-associated background lesions in animal models, technological advances in imaging functional biology, opportunities for stem cell therapies, and ubiquitination in regulation of cell proliferation. The 2012 American College of Veterinary Pathologists symposium "Evolutionary Aspects of Animal Models" will focus on the proper selection of a relevant animal model in biomedical research as critical to investigative success. Recent work characterizing rapid evolutionary changes and differences in physiology between species questions the validity of some comparative models. Dr. Robert Hamlin will be speaking on cardiovascular disease in "Animals as Models of Human Cardiovascular Disease: Or the Search to Overcome Outdated Evolutionary Homeostatic Mechanisms." Dr. Stefan Niewiesk will discuss evolutionary factors that affect modeling the human immune system in "Of Mice and Men: Evolutionarily, What Are the Best Rodent Models of the Human Immune System for Infectious Disease Research?" Dr. Steven Austad will consider evolution in "Evolutionary Aspects of Animal Models of Aging."Finally, Dr. Elizabeth Uhl will conclude the session with "Modeling Disease Phenotypes: How an Evolutionary Perspective Enhances the Questions."

Hasegawa, K., et al. (2010). "Current technology for the derivation of pluripotent stem cell lines from human embryos." Cell Stem Cell **6**(6): 521-531.

Technology for the derivation, propagation, and characterization of pluripotent stem cell lines from the human embryo has undergone considerable refinement and improvement since the first published description of human embryonic stem cells in 1998. In particular, there has been extensive effort to optimize protocols and develop defined culture systems with a view toward future clinical applications of embryonic stem cell-derived products. Here, we review the current status of methodology for human embryonic stem cell derivation and culture, and we highlight the challenges that remain for workers in the field.

Hashemi, M. and F. Kalalinia (2015). "Application of encapsulation technology in stem cell therapy." Life Sci **143**: 139-146.

Stem cells are characterized by their capacity for self-renewal and their ability to differentiate into specific cell types under the influence of their microenvironment. These cells are potent therapeutic

tools to treat various regenerative diseases based on their ability to produce a therapeutic protein or restore natural tissue function with minimal side effects. However, a major problem that must be overcome is to find a suitable stem cell delivery system. Cell encapsulation is a novel concept in which cells are immobilized inside a biocompatible and semi-permeable natural or synthetic matrix. The purpose of encapsulation is to protect the cell from the host's immune system, improve cell expansion and maintain cell viability, self-renewal potency and direct cell differentiation toward a desired lineage. This review will provide an overview of the application of encapsulation technology for phenotypic and functional improvement of stem cells and using these encapsulated cells to treat various diseases.

Hengstler, J. G., et al. (2005). "Generation of human hepatocytes by stem cell technology: definition of the hepatocyte." Expert Opin Drug Metab Toxicol **1**(1): 61-74.

Since 1999, numerous articles have reported the generation of hepatocytes from different types of extrahepatic stem or precursor cells. This opens exciting new possibilities for pharmacology and toxicology, as well as for cell therapy. Hepatocyte marker expression, including albumin, cytokeratin 18, c-met, alpha-fetoprotein and cytochrome P450 3A4 and -2B6, has been observed after transplantation of different types of human stem cells into the liver of laboratory animals or in vitro after incubation with cytokines. These intriguing observations have prompted scientists to classify stem cell-derived cell populations as hepatocytes. However, this conclusion may be premature. It has been shown that factors of the liver microenvironment can induce expression of a limited number of hepatocyte marker genes in nonhepatic cell types. To conclude on the grounds of a limited number of markers that these cells are true hepatocytes is not indicated. In this case one should carefully evaluate crucial hepatocyte-defining enzymatic properties. The present article: i) reviews studies describing the fate of extrahepatic human stem and precursor cells in livers of laboratory animals, including the possibility of cell fusion; and ii) critically discusses the phenotype of stem cells after application of various differentiation protocols aimed at generating human hepatocytes. In addition, the necessary criteria needed for defining a true hepatocyte are suggested. Establishing the necessary properties for stem cell-derived hepatocytes is timely and reasonable, and thus avoids further misleading semantic confusion. Finally, it is essential to understand that the definition of a bona fide hepatocyte should not be limited to qualitative assays, such as reverse transcriptase polymerase chain reaction and immunohistochemistry, but has to include a quantitative analysis of enzymatic activities, which allows direct comparison with primary hepatocytes. Although the stem cell-derived-hepatocyte does not yet exist there is a good chance that this aim may be achieved in the future.

Hester, J. (2000). "Peripheral blood stem cell collection: the interaction of technology, procedure, and biological factors." Transfus Sci **23**(2): 125-132.

Centrifugal technology, continuous flow and discontinuous flow, has served as the technology platform for extracting cell concentrates of interest from peripheral blood (PB) for patient therapy for the past 35-40 yr. Models for procedure outcome exist for collection of normal donor (ND) platelet and granulocyte concentrates that integrate: (1) biological variables (pre-procedure PB cell concentration, the total circulating quantity of cells, donor/patient blood volume (BV)), (2) device efficiency, and (3) procedure parameters such as total blood processed (TBP), and in the case of cytoreductions - the volume collected. (cf. Hester J, Kellogg R, Mulzet A, et al., Blood (54) (1979) 254; Hester J, Ventura G, J Clin Apheresis (4) (1988) 188.) To date, no predictive CD34+ yield algorithm integrating these three variables has been formulated that could be applied prospectively for individual ND or patients (PT). There are economic, toxicity and statistical comparison benefits to be derived from generating such an algorithm.A small pilot study is presented with a brief review of current publications that suggest the circulating quantity of CD34+ cells available to be collected and the quantity mobilized during leukapheresis are the major contributing factors to CD34+ yield, somewhat obscuring the role of the total blood processed (TBP). Intraprocedure CD34+ cell mobilization, incompletely characterized to date, appears to be a dynamic nonlinear process, as the harvested yield does not rise proportionally as the fraction of BV processed increases. And, like the pre-procedure PB CD34+ concentration and total circulating quantity, CD34+ mobilization during leukapheresis probably relates to prior treatment and the priming regimen. Studies that provide: (1) separate analyses of PT populations divided according to chemotherapy toxicity factors; (2) design and implementation of optimal priming regimens with respect to dose 'intensity' of both growth factors and chemotherapy; and (3) standardization of laboratory assays of CD34+ enumeration seem essential to generating a predictive algorithm.

Hill, A. B. T., et al. (2019). "Applications of mesenchymal stem cell technology in bovine species." Stem Cell Res Ther **10**(1): 44.

Mesenchymal stem cells (MSCs) have received a great deal of attention over the past 20 years mainly because of the results that showed regeneration potential and plasticity that were much stronger than expected in prior decades. Recent findings in this field

have contributed to progress in the establishment of cell differentiation methods, which have made stem cell therapy more clinically attractive. In addition, MSCs are easy to isolate and have anti-inflammatory and angiogenic capabilities. The use of stem cell therapy is currently supported by scientific literature in the treatment of several animal health conditions. MSC may be administered for autologous or allogenic therapy following either a fresh isolation or a thawing of a previously frozen culture. Despite the fact that MSCs have been widely used for the treatment of companion and sport animals, little is known about their clinical and biotechnological potential in the economically relevant livestock industry. This review focuses on describing the key characteristics of potential applications of MSC therapy in livestock production and explores the themes such as the concept, culture, and characterization of mesenchymal stem cells; bovine mesenchymal stem cell isolation; applications and perspectives on commercial interests and farm relevance of MSC in bovine species; and applications in translational research.

Hook, L. A. (2012). "Stem cell technology for drug discovery and development." Drug Discov Today **17**(7-8): 336-342.

Stem cells have enormous potential to revolutionise the drug discovery process at all stages, from target identification through to toxicology studies. Their ability to generate physiologically relevant cells in limitless supply makes them an attractive alternative to currently used recombinant cell lines or primary cells. However, realisation of the full potential of stem cells is currently hampered by the difficulty in routinely directing stem cell differentiation to reproducibly and cost effectively generate pure populations of specific cell types. In this article we discuss how stem cells have already been used in the drug discovery process and how novel technologies, particularly in relation to stem cell differentiation, can be applied to attain widespread adoption of stem cell technology by the pharmaceutical industry.

Housler, G. J., et al. (2012). "Compartmental hollow fiber capillary membrane-based bioreactor technology for in vitro studies on red blood cell lineage direction of hematopoietic stem cells." Tissue Eng Part C Methods **18**(2): 133-142.

Continuous production of red blood cells (RBCs) in an automated closed culture system using hematopoietic stem cell (HSC) progenitor cell populations is of interest for clinical application because of the high demand for blood transfusions. Previously, we introduced a four-compartment bioreactor that consisted of two bundles of hollow fiber microfiltration membranes for transport of culture medium (forming two medium compartments), interwoven with one bundle of hollow fiber membranes for transport of oxygen (O(2)), carbon dioxide (CO(2)), and other gases (forming one gas compartment). Small-scale prototypes were developed of the three-dimensional (3D) perfusion cell culture systems, which enable convection-based mass transfer and integral oxygenation in the cell compartment. CD34(+) HSC were isolated from human cord blood units using a magnetic separation procedure. Cells were inoculated into 2- or 8-mL scaled-down versions of the previously designed 800-mL cell compartment devices and perfused with erythrocyte proliferation and differentiation medium. First, using the small-scale 2-mL analytical scale bioreactor, with an initial seeding density of 800,000 cells/mL, we demonstrated approximately 100-fold cell expansion and differentiation after 7 days of culture. An 8-mL laboratory-scale bioreactor was then used to show pseudocontinuous production by intermediately harvesting cells. Subsequently, we were able to use a model to demonstrate semicontinuous production with up to 14,288-fold expansion using seeding densities of 800,000 cells/mL. The down-scaled culture technology allows for expansion of CD34(+) cells and stimulating these progenitors towards RBC lineage, expressing approximately 40% CD235(+) and enucleation. The 3D perfusion technology provides an innovative tool for studies on RBC production, which is scalable.

Huang, H. P., et al. (2012). "Induced pluripotent stem cell technology for disease modeling and drug screening with emphasis on lysosomal storage diseases." Stem Cell Res Ther **3**(4): 34.

The recent derivation of disease-specific induced pluripotent stem cells (iPSCs) from somatic cells of patients with familial and sporadic forms of diseases and the demonstration of their ability to give rise to disease-relevant cell types provide an excellent opportunity to gain further insights into the mechanisms responsible for the pathophysiology of these diseases and develop novel therapeutic drugs. Here, we review the recent advances in iPSC technology for modeling of various lysosomal storage diseases (LSDs) and discuss possible strategies through which LSD-iPSCs can be exploited to identify novel drugs and improve future clinical treatment of LSDs.

Ikeda, M., et al. (2014). "Acceleration of peripheral nerve regeneration using nerve conduits in combination with induced pluripotent stem cell technology and a basic fibroblast growth factor drug delivery system." J Biomed Mater Res A **102**(5): 1370-1378.

Various modifications including addition of Schwann cells or incorporation of growth factors with bioabsorbable nerve conduits have been explored as options for peripheral nerve repair. However, no reports of nerve conduits containing both supportive cells and growth factors have been published as a regenerative therapy for peripheral nerves. In the

present study, sciatic nerve gaps in mice were reconstructed in the following groups: nerve conduit alone (control group), nerve conduit coated with induced pluripotent stem cell (iPSc)-derived neurospheres (iPSc group), nerve conduit coated with iPSc-derived neurospheres and basic fibroblast growth factor (bFGF)-incorporated gelatin microspheres (iPSc + bFGF group), and autograft. The fastest functional recovery and the greatest axon regeneration occurred in the autograft group, followed in order by the iPSc + bFGF group, iPSc group, and control group until 12 weeks after reconstruction. Thus, peripheral nerve regeneration using nerve conduits and functional recovery in mice was accelerated by a combination of iPSc-derived neurospheres and a bFGF drug delivery system. The combination of all three fundamental methodologies, iPSc technology for supportive cells, bioabsorbable nerve conduits for scaffolds, and a bFGF drug delivery system for growth factors, was essential for peripheral nerve regenerative therapy.

Jeong, Y., et al. (2014). "Technology advancement for integrative stem cell analyses." Tissue Eng Part B Rev **20**(6): 669-682.

Scientists have endeavored to use stem cells for a variety of applications ranging from basic science research to translational medicine. Population-based characterization of such stem cells, while providing an important foundation to further development, often disregard the heterogeneity inherent among individual constituents within a given population. The population-based analysis and characterization of stem cells and the problems associated with such a blanket approach only underscore the need for the development of new analytical technology. In this article, we review current stem cell analytical technologies, along with the advantages and disadvantages of each, followed by applications of these technologies in the field of stem cells. Furthermore, while recent advances in micro/nano technology have led to a growth in the stem cell analytical field, underlying architectural concepts allow only for a vertical analytical approach, in which different desirable parameters are obtained from multiple individual experiments and there are many technical challenges that limit vertically integrated analytical tools. Therefore, we propose--by introducing a concept of vertical and horizontal approach--that there is the need of adequate methods to the integration of information, such that multiple descriptive parameters from a stem cell can be obtained from a single experiment.

Jiang, Z., et al. (2017). "Laminin-521 Promotes Rat Bone Marrow Mesenchymal Stem Cell Sheet Formation on Light-Induced Cell Sheet Technology." Biomed Res Int **2017**: 9474573.

Rat bone marrow mesenchymal stem cell sheets (rBMSC sheets) are attractive for cell-based tissue engineering. However, methods of culturing rBMSC sheets are critically limited. In order to obtain intact rBMSC sheets, a light-induced cell sheet method was used in this study. TiO2 nanodot films were coated with (TL) or without (TN) laminin-521. We investigated the effects of laminin-521 on rBMSCs during cell sheet culturing. The fabricated rBMSC sheets were subsequently assessed to study cell sheet viability, reattachment ability, cell sheet thickness, collagen type I deposition, and multilineage potential. The results showed that laminin-521 could promote the formation of rBMSC sheets with good viability under hyperconfluent conditions. Cell sheet thickness increased from an initial 26.7 +/- 1.5 mum (day 5) up to 47.7 +/- 3.0 mum (day 10). Moreover, rBMSC sheets maintained their potential of osteogenic, adipogenic, and chondrogenic differentiation. This study provides a new strategy to obtain rBMSC sheets using light-induced cell sheet technology.

Jones, J. M. and J. A. Thomson (2000). "Human embryonic stem cell technology." Semin Reprod Med **18**(2): 219-223.

Undifferentiated human embryonic stem (ES) cells can be cultured indefinitely and yet maintain the potential to form almost every cell in the adult human body. Therefore ES cells provide a model for understanding the differentiation and function of human tissue, offer new strategies for drug discovery and testing, and have the potential to provide new transplantation therapies for the treatment of a wide variety of human diseases. In this article, we describe the origin and properties of human ES cells, distinguish ES cells from other pluripotent stem cell lines, and discuss their implications for basic research and human medicine.

Kane, N. M., et al. (2011). "Pluripotent stem cell differentiation into vascular cells: a novel technology with promises for vascular re(generation)." Pharmacol Ther **129**(1): 29-49.

Several types of stem and progenitor cells are currently under investigation for their potential to accomplish vascular regeneration. This review focuses on embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). We will discuss the technologies allowing for their derivation, culture expansion and maintenance in a pluripotent status. Moreover, both ESCs and iPSCs can be differentiated in endothelial cells (ECs) and mural cell, including vascular smooth muscle cells (VSMCs). Here, we will describe the involvements of growth factors (vascular endothelial growth factors-VEGFs-, platet-derived growth factors-PDGFs-), Wnt and Notch signal pathways, reactive oxygen species (ROS), histone deacetylases (HDACs), and microRNAs (miRNAs) in vascular cell differentiation from pluripotent stem cells.

We will additionally describe the therapeutic potential of stem cells for vascular medicine.

Karagiannis, P., et al. (2018). "Bringing Induced Pluripotent Stem Cell Technology to the Bedside." JMA J **1**(1): 6-14.

Induced pluripotent stem cells (iPSCs) describe somatic cells that have been reprogrammed to the pluripotent state. From a scientific perspective, their discovery has provided a molecular roadmap for turning on and off cell identities, effectively allowing any cell type to have its identity changed into any other cell type. They also act as a human model for understanding the development of every cell and organ in the body. In addition, because they can be prepared from patients, iPSCs offer a unique human model for studying disease development, including many diseases that are generally diagnosed at a late stage of their development. These models have provided new insights on the pathogenesis and new targets to prevent or reverse the disease development process. Indeed, clinical studies on compounds based on drug screening hits in human iPSC disease models have begun. Because of their proliferation and differentiation capacity, iPSCs can also be used to prepare cells for transplantations, and related clinical studies using iPSC-based cell therapies are ongoing. The combination of iPSCs with other technologies or therapeutic strategies is expected to expand their medical benefits. In this review, we consider medical accomplishments based on iPSC research and future ones that can be anticipated.

Karastaneva, A., et al. (2014). "Dynamics of Graft Function Measured by DNA-Technology in a Patient with Severe Aplastic Anemia and Repeated Stem Cell Transplantation." Case Rep Med **2014**: 576373.

Although bone marrow transplantation (BMT) from an HLA identical sibling is considered as treatment of choice in pediatric patients with severe aplastic anemia (SAA), a significant number of them experience graft failure (GF) after BMT. We report a case of an 8-year-old male patient with SAA who presented with a complicated posttransplant course due to parvovirus B19 infection and GF. A subsequent attempt to support the graft by antithymocyte globulin (ATG) and a peripheral stem cell boost resulted in transitory autologous recovery of hematopoiesis followed by mixed chimerism, supported by donor lymphocyte infusions (DLIs) and finally graft rejection with relapse of SAA. Permanent complete chimerism was achieved by a second BMT. Dynamics of graft function, measured by a single nucleotide polymorphism (SNPs) analysis, are discussed.

Kiatpongsan, S. (2008). "Policy roadmap for stem cell technology in Thailand." J Med Assoc Thai **91**(1): 124-128.

Policy and technology roadmaps have been long and widely used in industry and business sectors. The primary objective of the roadmap is to be a policy and technology planning tool helping to deal with an increasingly competitive environment. The obvious benefit of roadmapping is to provide information to make better technology investment decisions by identifying critical technologies and technology gaps and identifying methods to improve research and development (R&D) investments. It can also be used as a marketing tool. Roadmapping is critical and necessary when the technology investment decision is not straightforward. This occurs when it is not clear which alternative to pursue, how soon the technology is needed, or when there is a need to coordinate the development of multiple technologies. Stem cell technology is still in its nascent stage and one of the technologies with obvious uncertainties. Moreover it involves many issues from bioethical, legal and public policy perspectives. Then, development of national policy and technology roadmap for stem cell technology is definitely required and crucial to make most benefit from this promising technology for Thailand. The present article will provide perspectives on stem cell policy roadmap and propose critical action plans for the next five-year period.

Kiatpongsan, S. (2008). "Science and society: a stem cell technology model." J Med Assoc Thai **91**(2): 268-271.

Stem cell technology has been recognized as an emerging technology that could transform current supportive approach toward curing many chronic disorders and degenerative conditions. Regenerative medicine is the promising area of medical practice in the coming decade. However, stem cell technology also brings up controversial issues from the bioethical perspective such as the destruction of human embryos to derive embryonic stem cells or putting the egg donors at risk when retrieving oocytes used in somatic cell nuclear transfer technique. Recently, scientists have discovered a novel method to derive human embryonic stem cell-like cells (iPS; induced pluripotent stem cells) from human skin cells. This innovative approach would not only be a breakthrough discovery to advance the knowledge of stem cell research and the landmark for future stem cell-based therapy but will also provide viable solutions for social concerns on bioethical issues.

Kiatpongsan, S., et al. (2006). "Future cancer management with stem cell knowledge and technology." J Med Assoc Thai **89**(8): 1322-1332.

Cancer has been proposed as a result of abnormal control of growth and development of stem cells for more than century. This is the "cancer stem cell hypothesis". Both cancer and stem cells share many common especial properties. They are immortal

and have good differentiation potential. In addition, organogenesis and carcinogenesis are very similar processes. Recently, more evidence and convincing data from stem cell biology research are supporting this concept. Furthermore, the research provides new promising approaches for cancer diagnosis and treatment based on stem cell knowledge and technology. Upcoming data and evidence may revolutionize cancer management, making it more effective and safer.

Kiki, I. (2017). "What is the role of apheresis technology in stem cell transplantation?" Transfus Apher Sci **56**(6): 788-794.

Since the demonstration that hematopoietic cells are present in circulating blood, peripheral blood stem cell transplantation (PBSCT) has become an area of interest. The invention of growth factors such as the granulocyte colony-stimulating factor (G-CSF) and the availability of apheresis techniques allowed the wide application of peripheral blood stem cells (PBSC) in both autologous and allogeneic hematopoietic stem cell transplantation settings. It has been since 1986 that clinically introduced, peripheral blood stem cells replaced bone marrow as a stem-cell source to nearly 100% in the autologous and to approximately 75% in the allogeneic transplantation setting. During this period of time, remarkable development occurred in both stem cell mobilizing agents (i.e. CXCR4 antagonists) and apheresis techniques. Currently, apheresis technology is being increasingly used in not only for collection of PBSC or blood product support, but also for treatment and/or prevention of several transplantations related complications. Apheresis technology also allows to manipulate stem cells and thus provides opportunity to curative treatment of certain diseases.

Kim, J., et al. (2019). "Modeling Host-Virus Interactions in Viral Infectious Diseases Using Stem-Cell-Derived Systems and CRISPR/Cas9 Technology." Viruses **11**(2).

Pathologies induced by viral infections have undergone extensive study, with traditional model systems such as two-dimensional (2D) cell cultures and in vivo mouse models contributing greatly to our understanding of host-virus interactions. However, the technical limitations inherent in these systems have constrained efforts to more fully understand such interactions, leading to a search for alternative in vitro systems that accurately recreate in vivo physiology in order to advance the study of viral pathogenesis. Over the last decade, there have been significant technological advances that have allowed researchers to more accurately model the host environment when modeling viral pathogenesis in vitro, including induced pluripotent stem cells (iPSCs), adult stem-cell-derived organoid culture systems and CRISPR/Cas9-mediated genome editing. Such technological breakthroughs have ushered in a new era in the field of viral pathogenesis, where previously challenging questions have begun to be tackled. These include genome-wide analysis of host-virus crosstalk, identification of host factors critical for viral pathogenesis, and the study of viral pathogens that previously lacked a suitable platform, e.g., noroviruses, rotaviruses, enteroviruses, adenoviruses, and Zika virus. In this review, we will discuss recent advances in the study of viral pathogenesis and host-virus crosstalk arising from the use of iPSC, organoid, and CRISPR/Cas9 technologies.

Kokubu, C. and J. Takeda (2014). "When half is better than the whole: advances in haploid embryonic stem cell technology." Cell Stem Cell **14**(3): 265-267.

Recent advances in embryonic stem cell (ESC) derivation and genome editing offer efficient platforms for genetic screening. In this issue, Li et al. and Leeb et al., respectively, expand such applications by generating haploid rat ESCs for screening, mutagenesis, and CRISPR-Cas-mediated gene targeting and by developing a forward genetic screen for interrogating haploid mESCs.

Kramer, A. S., et al. (2013). "Systematic review of induced pluripotent stem cell technology as a potential clinical therapy for spinal cord injury." Cell Transplant **22**(4): 571-617.

Transplantation therapies aimed at repairing neurodegenerative and neuropathological conditions of the central nervous system (CNS) have utilized and tested a variety of cell candidates, each with its own unique set of advantages and disadvantages. The use and popularity of each cell type is guided by a number of factors including the nature of the experimental model, neuroprotection capacity, the ability to promote plasticity and guided axonal growth, and the cells' myelination capability. The promise of stem cells, with their reported ability to give rise to neuronal lineages to replace lost endogenous cells and myelin, integrate into host tissue, restore functional connectivity, and provide trophic support to enhance and direct intrinsic regenerative ability, has been seen as a most encouraging step forward. The advent of the induced pluripotent stem cell (iPSC), which represents the ability to "reprogram" somatic cells into a pluripotent state, hails the arrival of a new cell transplantation candidate for potential clinical application in therapies designed to promote repair and/or regeneration of the CNS. Since the initial development of iPSC technology, these cells have been extensively characterized in vitro and in a number of pathological conditions and were originally reported to be equivalent to embryonic stem cells (ESCs). This review highlights emerging evidence that suggests iPSCs are not necessarily indistinguishable from ESCs and may occupy a different "state" of pluripotency with differences in

gene expression, methylation patterns, and genomic aberrations, which may reflect incomplete reprogramming and may therefore impact on the regenerative potential of these donor cells in therapies. It also highlights the limitations of current technologies used to generate these cells. Moreover, we provide a systematic review of the state of play with regard to the use of iPSCs in the treatment of neurodegenerative and neuropathological conditions. The importance of balancing the promise of this transplantation candidate in the light of these emerging properties is crucial as the potential application in the clinical setting approaches. The first of three sections in this review discusses (A) the pathophysiology of spinal cord injury (SCI) and how stem cell therapies can positively alter the pathology in experimental SCI. Part B summarizes (i) the available technologies to deliver transgenes to generate iPSCs and (ii) recent data comparing iPSCs to ESCs in terms of characteristics and molecular composition. Lastly, in (C) we evaluate iPSC-based therapies as a candidate to treat SCI on the basis of their neurite induction capability compared to embryonic stem cells and provide a summary of available in vivo data of iPSCs used in SCI and other disease models.

La Spada, A., et al. (2014). "Application of Tissue Microarray Technology to Stem Cell Research." Microarrays (Basel) **3**(3): 159-167.

There is virtually an unlimited number of possible Tissue Microarray (TMA) applications in basic and clinical research and ultimately in diagnostics. However, to assess the functional importance of novel markers, researchers very often turn to cell line model systems. The appropriate choice of a cell line is often a difficult task, but the use of cell microarray (CMA) technology enables a quick screening of several markers in cells of different origins, mimicking a genomic-scale analysis. In order to improve the morphological evaluations of the CMA slides we harvested the cells by conventional trypsinization, mechanical scraping and cells grown on coverslips. We show that mechanical scraping is a good evaluation method since keeps the real morphology very similar to those grown on coverslips. Immunofluorescence images are of higher quality, facilitating the reading of the biomarker cellular and subcellular localization. Here, we describe CMA technology in stem cell research.

Liu, Y. and W. Deng (2016). "Reverse engineering human neurodegenerative disease using pluripotent stem cell technology." Brain Res **1638**(Pt A): 30-41.

With the technology of reprogramming somatic cells by introducing defined transcription factors that enables the generation of "induced pluripotent stem cells (iPSCs)" with pluripotency comparable to that of embryonic stem cells (ESCs), it has become possible to use this technology to produce various cells and tissues that have been difficult to obtain from living bodies. This advancement is bringing forth rapid progress in iPSC-based disease modeling, drug screening, and regenerative medicine. More and more studies have demonstrated that phenotypes of adult-onset neurodegenerative disorders could be rather faithfully recapitulated in iPSC-derived neural cell cultures. Moreover, despite the adult-onset nature of the diseases, pathogenic phenotypes and cellular abnormalities often exist in early developmental stages, providing new "windows of opportunity" for understanding mechanisms underlying neurodegenerative disorders and for discovering new medicines. The cell reprogramming technology enables a reverse engineering approach for modeling the cellular degenerative phenotypes of a wide range of human disorders. An excellent example is the study of the human neurodegenerative disease amyotrophic lateral sclerosis (ALS) using iPSCs. ALS is a progressive neurodegenerative disease characterized by the loss of upper and lower motor neurons (MNs), culminating in muscle wasting and death from respiratory failure. The iPSC approach provides innovative cell culture platforms to serve as ALS patient-derived model systems. Researchers have converted iPSCs derived from ALS patients into MNs and various types of glial cells, all of which are involved in ALS, to study the disease. The iPSC technology could be used to determine the role of specific genetic factors to track down what's wrong in the neurodegenerative disease process in the "disease-in-a-dish" model. Meanwhile, parallel experiments of targeting the same specific genes in human ESCs could also be performed to control and to complement the iPSC-based approach for ALS disease modeling studies. Much knowledge has been generated from the study of both ALS iPSCs and ESCs. As these methods have advantages and disadvantages that should be balanced on experimental design in order for them to complement one another, combining the diverse methods would help build an expanded knowledge of ALS pathophysiology. The goals are to reverse engineer the human disease using ESCs and iPSCs, generate lineage reporter lines and in vitro disease models, target disease related genes, in order to better understand the molecular and cellular mechanisms of differentiation regulation along neural (neuronal versus glial) lineages, to unravel the pathogenesis of the neurodegenerative disease, and to provide appropriate cell sources for replacement therapy. This article is part of a Special Issue entitled SI: PSC and the brain.

Longo, V. D. and S. Cortellino (2016). "Enhancing Stem Cell Transplantation with "Nutri-technology"." Cell Stem Cell **19**(6): 681-682.

It is necessary to employ myeloablative irradiation or chemotherapy to deplete the HSC niche to optimize hematopoietic stem cell transplantation. In a recent issue of Science, Taya and colleagues provide evidence for an alternative to the toxic chemoirradiative procedure by showing that a valine-restricted diet is sufficient to empty the bone marrow niche.

Lowenthal, J. and S. Gerecht (2016). "Stem cell-derived vasculature: A potent and multidimensional technology for basic research, disease modeling, and tissue engineering." Biochem Biophys Res Commun **473**(3): 733-742.

Proper blood vessel networks are necessary for constructing and re-constructing tissues, promoting wound healing, and delivering metabolic necessities throughout the body. Conversely, an understanding of vascular dysfunction has provided insight into the pathogenesis and progression of diseases both common and rare. Recent advances in stem cell-based regenerative medicine - including advances in stem cell technologies and related progress in bioscaffold design and complex tissue engineering - have allowed rapid advances in the field of vascular biology, leading in turn to more advanced modeling of vascular pathophysiology and improved engineering of vascularized tissue constructs. In this review we examine recent advances in the field of stem cell-derived vasculature, providing an overview of stem cell technologies as a source for vascular cell types and then focusing on their use in three primary areas: studies of vascular development and angiogenesis, improved disease modeling, and the engineering of vascularized constructs for tissue-level modeling and cell-based therapies.

Lu, J., et al. (2010). "A novel technology for hematopoietic stem cell expansion using combination of nanofiber and growth factors." Recent Pat Nanotechnol **4**(2): 125-135.

Hematopoietic stem cell transplantation has been applied as a standard procedure of treatment for hematological disorders like multiple myeloma and leukemia for several decades. Various sources of stem cells like bone marrow, peripheral blood and umbilical cord blood are used for the transplantation. Among these umbilical cord blood is currently preferred due to the primitiveness of the derived stem cells and minimal possibilities of graft versus host disease or development of graft induced tumors. One of the problems for these sources is the procurement of sufficient number of donor stem cells. Inadequate number of cells may lead to delayed recovery and decrease survivability of the patient. Thus to overcome the limitation of stem cell number, development of an ex-vivo expansion technology is critically important. The recent emerging technology using nanofiber in combination with growth factors has made a significant improvement to the field of regenerative medicine and a couple of patents have been filed. In this review, we will focus on factors regulating hematopoietic stem cell self-renewal and expansion emphasizing on nanofiber as a supporting matrix.

Lui, P. P. (2015). "Stem cell technology for tendon regeneration: current status, challenges, and future research directions." Stem Cells Cloning **8**: 163-174.

Tendon injuries are a common cause of physical disability. They present a clinical challenge to orthopedic surgeons because injured tendons respond poorly to current treatments without tissue regeneration and the time required for rehabilitation is long. New treatment options are required. Stem cell-based therapies offer great potential to promote tendon regeneration due to their high proliferative, synthetic, and immunomodulatory activities as well as their potential to differentiate to the target cell types and undergo genetic modification. In this review, I first recapped the challenges of tendon repair by reviewing the anatomy of tendon. Next, I discussed the advantages and limitations of using different types of stem cells compared to terminally differentiated cells for tendon tissue engineering. The safety and efficacy of application of stem cells and their modified counterparts for tendon tissue engineering were then summarized after a systematic literature search in PubMed. The challenges and future research directions to enhance, optimize, and standardize stem cell-based therapies for augmenting tendon repair were then discussed.

Lunn, J. S., et al. (2011). "Stem cell technology for the study and treatment of motor neuron diseases." Regen Med **6**(2): 201-213.

Amyotrophic lateral sclerosis and spinal muscular atrophy are devastating neurodegenerative diseases that lead to the specific loss of motor neurons. Recently, stem cell technologies have been developed for the investigation and treatment of both diseases. Here we discuss the different stem cells currently being studied for mechanistic discovery and therapeutic development, including embryonic, adult and induced pluripotent stem cells. We also present supporting evidence for the utilization of stem cell technology in the treatment of amyotrophic lateral sclerosis and spinal muscular atrophy, and describe key issues that must be considered for the transition of stem cell therapies for motor neuron diseases from bench to bedside. Finally, we discuss the first-in-human Phase I trial currently underway examining the safety and feasibility of intraspinal stem cell injections in amyotrophic lateral sclerosis patients as a foundation for translating stem cell therapies for various neurological diseases.

Lunn, J. S., et al. (2011). "Stem cell technology for neurodegenerative diseases." Ann Neurol **70**(3): 353-361.

Over the past 20 years, stem cell technologies have become an increasingly attractive option to investigate and treat neurodegenerative diseases. In the current review, we discuss the process of extending basic stem cell research into translational therapies for patients suffering from neurodegenerative diseases. We begin with a discussion of the burden of these diseases on society, emphasizing the need for increased attention toward advancing stem cell therapies. We then explain the various types of stem cells utilized in neurodegenerative disease research, and outline important issues to consider in the transition of stem cell therapy from bench to bedside. Finally, we detail the current progress regarding the applications of stem cell therapies to specific neurodegenerative diseases, focusing on Parkinson disease, Huntington disease, Alzheimer disease, amyotrophic lateral sclerosis, and spinal muscular atrophy. With a greater understanding of the capacity of stem cell technologies, there is growing public hope that stem cell therapies will continue to progress into realistic and efficacious treatments for neurodegenerative diseases.

Lysaght, M. J. and A. L. Hazlehurst (2003). "Private sector development of stem cell technology and therapeutic cloning." Tissue Eng **9**(3): 555-561.

Based on data collected in June 2002, more than 30 biotechnology startup firms in 11 countries are pursuing commercial development of stem cell technology and therapeutic cloning. These firms employ 950-1000 scientists and support staff and spend just under $200 million on research and development each year. The field has the look and feel of a high-tech cottage industry, with about half the startups employing fewer than 15 FTEs (full time equivalents). Funding is mostly from venture capitalists and private investors. Participants are geographically dispersed, with about 40% of the activity outside the United States. Focus is equally split between embryonic and adult stem cells. Taken as a whole, both the structure and scope of the private sector in stem cell research seem appropriate to the promise and development time frames of this important new technology.

Mack, D. L., et al. (2014). "Disease-in-a-dish: the contribution of patient-specific induced pluripotent stem cell technology to regenerative rehabilitation." Am J Phys Med Rehabil **93**(11 Suppl 3): S155-168.

Advances in regenerative medicine technologies will lead to dramatic changes in how patients in rehabilitation medicine clinics are treated in the upcoming decades. The multidisciplinary field of regenerative medicine is developing new tools for disease modeling and drug discovery based on induced pluripotent stem cells. This approach capitalizes on the idea of personalized medicine by using the patient's own cells to discover new drugs, increasing the likelihood of a favorable outcome. The search for compounds that can correct disease defects in the culture dish is a conceptual departure from how drug screens were done in the past. This system proposes a closed loop from sample collection from the diseased patient, to in vitro disease model, to drug discovery and Food and Drug Administration approval, to delivering that drug back to the same patient. Here, recent progress in patient-specific induced pluripotent stem cell derivation, directed differentiation toward diseased cell types, and how those cells can be used for high-throughput drug screens are reviewed. Given that restoration of normal function is a driving force in rehabilitation medicine, the authors believe that this drug discovery platform focusing on phenotypic rescue will become a key contributor to therapeutic compounds in regenerative rehabilitation.

Madden, L. M., et al. (2016). "Response to: "Technology and Long-Term Health-Related Quality-of-Life Outcomes in Children with Nonmalignant Disorders after Reduced-Intensity Conditioning and Stem Cell Transplantation"." Biol Blood Marrow Transplant **22**(9): 1734.

Mahabadi, J. A., et al. (2018). "Application of induced pluripotent stem cell and embryonic stem cell technology to the study of male infertility." J Cell Physiol **233**(11): 8441-8449.

Stem cells (SCs) are classes of undifferentiated biological cells existing only at the embryonic, fetal, and adult stages that can divide to produce specialized cell types during fetal development and remain in our bodies throughout life. The progression of regenerative and reproductive medicine owes the advancement of respective in vitro and in vivo biological science on the stem cell nature under appropriate conditions. The SCs are promising therapeutic tools to treat currently of infertility because of wide sources and high potency to differentiate. Nevertheless, no effective remedies are available to deal with severe infertility due to congenital or gonadotoxic stem cell deficiency in prepubertal childhood. Some recent solutions have been developed to address the severe fertility problems, including in vitro formation of germ cells from stem cells, induction of pluripotency from somatic cells, and production of patient-specific pluripotent stem cells. There is a possibility of fertility restoration using the in vitro formation of germ cells from somatic cells. Accordingly, the present review aimed at studying the literature published on the medical application of stem cells in reproductive concerns.

Maiers, M., et al. (2010). "Information technology and the role of WMDA in promoting standards for international exchange of hematopoietic stem cell

donors and products." Bone Marrow Transplant **45**(5): 839-842.

Nearly half of the unrelated hematopoietic SCTs facilitated worldwide involves an exchange of products between countries. The process is information intensive and requires coordination through regional hubs of complex data transactions of demographic, clinical and genetic information, laboratory samples and results. Each registry has developed its own unique systems for representing data and process leading to transplantation. The WMDA Information Technology Working Group was formed in the autumn of 2001 as a forum to discuss and develop standards for information technology (IT) in support of hematopoietic stem cell registries. Its membership includes experts in IT from the WMDA member registries. The group has focused its standardization efforts on three areas: Standardized reference data sets for validation and plausibility controls for HLA and other data domains. Matching algorithm standards for determining histocompatibility. Communication standards between registries.

Maioli, M., et al. (2016). "REAC technology and hyaluron synthase 2, an interesting network to slow down stem cell senescence." Sci Rep **6**: 28682.

Hyaluronic acid (HA) plays a fundamental role in cell polarity and hydrodynamic processes, affording significant modulation of proliferation, migration, morphogenesis and senescence, with deep implication in the ability of stem cells to execute their differentiating plans. The Radio Electric Asymmetric Conveyer (REAC) technology is aimed to optimize the ions fluxes at the molecular level in order to optimize the molecular mechanisms driving cellular asymmetry and polarization. Here, we show that treatment with 4-methylumbelliferone (4-MU), a potent repressor of type 2 HA synthase and endogenous HA synthesis, dramatically antagonized the ability of REAC to recover the gene and protein expression of Bmi1, Oct4, Sox2, and Nanog in ADhMSCs that had been made senescent by prolonged culture up to the 30(th) passage. In senescent ADhMSCs, 4-MU also counteracted the REAC ability to rescue the gene expression of TERT, and the associated resumption of telomerase activity. Hence, the anti-senescence action of REAC is largely dependent upon the availability of endogenous HA synthesis. Endogenous HA and HA-binding proteins with REAC technology create an interesting network that acts on the modulation of cell polarity and intracellular environment. This suggests that REAC technology is effective on an intracellular niche level of stem cell regulation.

Maniangou, B., et al. (2018). "Next-generation sequencing technology a new tool for killer cell immunoglobulin-like receptor allele typing in hematopoietic stem cell transplantation." Transfus Clin Biol **25**(1): 87-89.

Killer cell Immunoglobulin-like Receptor (KIR) genes are a family of genes located together within the leukocyte receptor cluster on human chromosome 19q13.4. To date, 17 KIR genes have been identified including nine inhibitory genes (2DL1/L2/L3/L4/L5A/L5B, 3DL1/L2/L3), six activating genes (2DS1/S2/S3/S4/S5, 3DS1) and two pseudogenes (2DP1, 3DP1) classified into group A (KIR A) and group B (KIR B) haplotypes. The number and the nature of KIR genes vary between the individuals. In addition, these KIR genes are known to be polymorphic at allelic level (907 alleles described in July 2017). KIR genes encode for receptors which are predominantly expressed by Natural Killer (NK) cells. KIR receptors recognize HLA class I molecules and are able to kill residual recipient leukemia cells, and thus reduce the likelihood of relapse. KIR alleles of Hematopoietic Stem Cell (HSC) donor would require to be known (Alicata et al. Eur J Immunol 2016) because the KIR allele polymorphism may affect both the KIR(+) NK cell phenotype and function (Gagne et al. Eur J Immunol 2013; Bari R, et al. Sci Rep 2016) as well as HSCT outcome (Boudreau et al. JCO 2017). The introduction of the Next Generation Sequencing (NGS) has overcome current conventional DNA sequencing method limitations, known to be time consuming. Recently, a novel NGS KIR allele typing approach of all KIR genes was developed by our team in Nantes from 30 reference DNAs (Maniangou et al. Front in Immunol 2017). This NGS KIR allele typing approach is simple, fast, reliable, specific and showed a concordance rate of 95% for centromeric and telomeric KIR genes in comparison with high-resolution KIR typing obtained to those published data using exome capture (Norman PJ et al. Am J Hum Genet 2016). This NGS KIR allele typing approach may also be used in reproduction and to better study KIR(+) NK cell implication in the control of viral infections.

Martin, P. A., et al. (2006). "Commercial development of stem cell technology: lessons from the past, strategies for the future." Regen Med **1**(6): 801-807.

This paper presents historical and contemporary survey data on the commercial development of stem cell technology from the 1990s to the present day. We describe the first wave of industrial investment in hematopoietic stem cells during the 1990s and contrast this with the more recent expansion of the sector. In particular, we explore the cell types used, diseases targeted and business models adopted by firms. We conclude, by arguing that the commercial prospects for stem cell technologies remain highly uncertain and that innovative public policies should be adopted to prevent 'market failure'.

Matapurkar, B. G. (2002). "A new physiological phenomenon of mammalian body for organ and tissue neo-regeneration in vivo: adult stem cell technology in

the perspective of literature." Indian J Exp Biol **40**(12): 1331-1343.

A new phenomenon by which adult developed mammalian and human body, can neo-regenerate its own tissue/organ in vivo, is recognized as "Desired Metaplasia". Reserve stem cells present in the tissues of adult developed body, are responsible for repair and replacement of lost tissues and cells during life, is plasia. Chronic tissue damage, due to long-standing causative factor, is taken care of and protected by forming resistant tissues, is metaplasia. Both these changes take place at the anatomical abode of the tissues. When stem cells of one tissue are colonized with another tissue/organ system, away from its anatomical abode, the neo-organo-histogenesis takes place by a phenomenon of desired metaplasia. This being new is critically, analytically and scientifically studied and discussed with reference to the available literature. An attempt has been made to establish the scientific account of the phenomenon. The laws of nature and embryology, as well as the basic philosophy responsible for neo-regeneration of tissues and organs in vivo, are discussed. In conclusion, the mammalian and human bodies can neo-regenerate their tissues and organs in vivo by desired metaplasia, provided certain criteria of embryological organogenesis are strictly observed.

McGivern, J. V. and A. D. Ebert (2014). "Exploiting pluripotent stem cell technology for drug discovery, screening, safety, and toxicology assessments." Adv Drug Deliv Rev **69-70**: 170-178.

In order for the pharmaceutical industry to maintain a constant flow of novel drugs and therapeutics into the clinic, compounds must be thoroughly validated for safety and efficacy in multiple biological and biochemical systems. Pluripotent stem cells, because of their ability to develop into any cell type in the body and recapitulate human disease, may be an important cellular system to add to the drug development repertoire. This review will discuss some of the benefits of using pluripotent stem cells for drug discovery and safety studies as well as some of the recent applications of stem cells in drug screening studies. We will also address some of the hurdles that need to be overcome in order to make stem cell-based approaches an efficient and effective tool in the quest to produce clinically successful drug compounds.

Megaw, R., et al. (2015). "Use of induced pluripotent stem-cell technology to understand photoreceptor cytoskeletal dynamics in retinitis pigmentosa." Lancet **385 Suppl 1**: S69.

BACKGROUND: Retinitis pigmentosa, which affects one in 3000 people, causes blindness and has no treatment. Mutations in the retinitis pigmentosa GTPase regulator (RPGR) gene cause 20% of all cases. Recent work suggests that RPGR, localised to the photoreceptor connecting cilium, regulates rhodopsin transport to the outer segment through its effect on the turnover of actin. We set out to establish a novel model for RPGR disease to test the hypothesis that RPGR mutations lead to retinal degeneration due to a dysregulation of the actin cytoskeleton. METHODS: Patients with RPGR mutations and their unaffected relatives were recruited and skin biopsy samples taken. Fibroblast lines were established and reprogrammed to generate induced pluripotent stem cell (iPSC) lines. A three-dimensional organogenesis protocol was optimised whereby embryoid bodies were formed and patterned towards an eye field fate in a 100-day retinal differentiation protocol, allowing three-dimensional optic cups to form. RPGR-mutated cultures were compared with their healthy controls. FINDINGS: Mutant and wild-type iPSC lines were generated and characterised. Differentiation of all lines resulted in the generation of optic cups in a self-organising manner after 100 days in culture. These cultures contained mature photoreceptors, as evidenced by morphology and both RNA and protein expression. Photoreceptor cultures from RGPR-mutated iPSCs had increased actin polymerisation compared with controls (mean confocal pixel intensity count 59.02 [SD 16.24] vs 23.70 [8.20], p=0.0081). This finding was confirmed by assessment of F-actin with western blot. Pathways regulating actin turnover were explored; western blot analysis showed a reduction in both Src and ERK phosphorylation in RGPR-mutated photoreceptor cultures. An unbiased protein array confirmed this reduction in ERK and Src activation. Several other pathways were also shown to be dysregulated in the RGPR-mutated photoreceptor cultures. INTERPRETATION: This study supports the hypothesis that RPGR mutations lead to actin dysregulation. We have identified several pathways that are interrupted in RPGR-mutant photoreceptor cultures and could be contributing to disease. This study is the first use, to our knowledge, of human iPSCs with retinitis pigmentosa-causing mutations to look at pathophysiology of disease. FUNDING: Wellcome Trust.

Mohamet, L., et al. (2014). "Familial Alzheimer's disease modelling using induced pluripotent stem cell technology." World J Stem Cells **6**(2): 239-247.

Alzheimer's disease (AD) is a progressive neurodegenerative disease in which patients exhibit gradual loss of memory that impairs their ability to learn or carry out daily tasks. Diagnosis of AD is difficult, particularly in early stages of the disease, and largely consists of cognitive assessments, with only one in four patients being correctly diagnosed. Development of novel therapeutics for the treatment of AD has proved to be a lengthy, costly and relatively unproductive process with attrition rates of > 90%. As

a result, there are no cures for AD and few treatment options available for patients. Therefore, there is a pressing need for drug discovery platforms that can accurately and reproducibly mimic the AD phenotype and be amenable to high content screening applications. Here, we discuss the use of induced pluripotent stem cells (iPSCs), which can be derived from adult cells, as a method of recapitulation of AD phenotype in vitro. We assess their potential use in high content screening assays and the barriers that exist to realising their full potential in predictive efficacy, toxicology and disease modelling. At present, a number of limitations need to be addressed before the use of iPSC technology can be fully realised in AD therapeutic applications. However, whilst the use of AD-derived iPSCs in drug discovery remains a fledgling field, it is one with immense potential that is likely to reach fruition within the next few years.

Moriguchi, H. (2015). "The development of statin-based therapy for patients with hepatitis C virus (HCV) infection using human induced pluripotent stem (iPS) cell technology." Clin Res Hepatol Gastroenterol **39**(5): 541-543.

Human induced pluripotent stem (iPS) cells may transform drug discovery. Here I show an example of the development of statin (HMG-CoA reductase inhibitors)-based therapy for patients with hepatitis C virus (HCV) infection using human iPS cell technology. When Shimada et al. considered the two reports on the antiviral effects of pitavastatin for HCV infection in vitro by Moriguchi et al., they conducted a randomized controlled trial. As a result, a proof-of-concept for the antiviral effect of pitavastatin against HCV infection using human iPS cell technology by Moriguchi et al. was confirmed in the randomized controlled trial by Shimada et al. in 2012. Therefore, above-mentioned a series of studies became to the first to report the clinical application of human iPS cells. Furthermore, here I propose that new clinical research methods using human iPS cell technology will be able to circumvent the limitations of conventional randomized controlled trials (RCTs) for the purpose of personalized medicine in the clinical setting.

Morizane, A. and J. Takahashi (2012). "[A challenge towards the clinical application of induced pluripotent stem cell technology for the treatment of Parkinson's disease]." Brain Nerve **64**(1): 29-37.

Parkinson's disease has been so far commonly treated with medication therapy. Although the medication works effectively in the initial phase, it turns out to be less effective at the later stage of the disease. Recently, induced pluripotent stem (iPS) cells have attracted much attention because of their potential to cure diseases such as Parkinson's disease. Due to the accumulating clinical experiences of cell transplantation procedures with aborted fetal tissues, Parkinson's disease has become one of the most promising targets for the clinical application of this iPS cell technology. In this review, we will summarize the ongoing research in the field of iPS cells and Parkinson's disease. The method for establishing iPS cells has advanced rapidly that can be applied in the clinical stage in terms of avoiding the use of viral vectors, xenogenic materials, etc. The differentiation protocol to derive the dopamine neurons from iPS cells has also been improved. However, several issues, such as the risk of tumor formation and the poor survival of the grafted dopamine neurons in vivo remain to be solved before these cells can be used in the clinical settings. Other than cell transplantations, iPS cell technology can also provide a valuable platform for disease analysis and drug development with in vitro systems of human cells. Several lines of iPS cells have already been established from Parkinson's disease patients with either sporadic or genetic background. For patients to achieve maximum benefits of this technology, further research must be conducted in both fields, that is, cell transplantation and the disease modeling with patient-derived iPS cells.

Morse, M. A. (1999). "Technology evaluation: Stem-cell therapy, Aastrom Biosciences Inc." Curr Opin Mol Ther **1**(6): 745-752.

The expansion of human stem cells and their genetic manipulation represent areas of increasing interest in the field of stem cell transplantation. Previously, stem cell transplantation has been accomplished by using cellular products obtained by large volume bone marrow or peripheral blood harvest. Difficulties with this approach include inadequate cell numbers and tumor cell contamination. Furthermore, for gene transfer modalities requiring proliferating progenitor cells, low gene expression would be expected in these products. To address these difficulties, the AastromReplicell System has been developed as a fully closed and automated system for expanding hematopoietic cells. Investigators at Aastrom have evaluated the conditions needed for optimal growth including the need for unpurified bone marrow or cord blood mononuclear cells, high cell densities, serum-containing medium and certain types of plastic surfaces. Studies have now been initiated to demonstrate the feasibility of generating enough cells to fully reconstitute hematopoiesis from small volumes of cellular progenitors. It has also been demonstrated that tumor cell contamination passively decreases during the culture period. It now remains to be shown in a direct comparison that this approach yields greater efficacy and a lower cost than transplantation with unmanipulated large volume marrow or peripheral blood stem cell products.

Mouhayar, Y. and F. I. Sharara (2017). "G-CSF and stem cell therapy for the treatment of refractory thin lining in assisted reproductive technology." J Assist Reprod Genet **34**(7): 831-837.

PURPOSE: The study aims to describe two promising therapeutic options for resistant "thin" endometrium in fertility treatment: granulocyte colony-stimulating factor (G-CSF) and stem cell therapy. METHODS: A review of the scientific literature related to patients with thin endometrium undergoing fertility treatment. RESULTS: Sufficient endometrial growth is fundamental for embryo implantation. Whether idiopathic or resulting from an underlying pathology, a thin endometrium of <7 mm is associated with lower probability of pregnancy; however, no specific thickness excludes the occurrence of pregnancy. We specifically reviewed two relatively new treatment options for resistant thin lining: intrauterine G-CSF and stem cell therapy. The majority of the reviewed trials showed a significant benefit for intrauterine G-CSF infusion in improving endometrial thickness and pregnancy rates. Early results of stem cell therapy trials seem promising. CONCLUSIONS: EMT <7 mm is linked to lower probability of pregnancy in assisted reproductive technology. Intrauterine G-CSF infusion appears to be a potentially successful treatment option for resistant cases, while stem cell therapy seems to be a promising new treatment modality in severely refractory cases.

Mulder, P., et al. (2018). "Predicting cardiac safety using human induced pluripotent stem cell-derived cardiomyocytes combined with multi-electrode array (MEA) technology: A conference report." J Pharmacol Toxicol Methods **91**: 36-42.

Safety pharmacology studies that evaluate drug candidates for potential cardiovascular liabilities remain a critical component of drug development. Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) have recently emerged as a new and promising tool for preclinical hazard identification and risk assessment of drugs. Recently, Pluriomics organized its first User Meeting entitled 'Combining Pluricyte(R) Cardiomyocytes & MEA for Safety Pharmacology applications', consisting of scientific sessions and live demonstrations, which provided the opportunity to discuss the application of hiPSC-CMs (Pluricyte(R) Cardiomyocytes) in cardiac safety assessment to support early decision making in safety pharmacology. This report summarizes the outline and outcome of this Pluriomics User Meeting, which took place on November 24-25, 2016 in Leiden (The Netherlands). To reflect the content of the communications presented at this meeting we have cited key scientific articles and reviews.

Nagata, N. and S. Yamanaka (2014). "Perspectives for induced pluripotent stem cell technology: new insights into human physiology involved in somatic mosaicism." Circ Res **114**(3): 505-510.

Induced pluripotent stem cell technology makes in vitro reprogramming of somatic cells from individuals with various genetic backgrounds possible. By applying this technology, it is possible to produce pluripotent stem cells from biopsy samples of arbitrarily selected individuals with various genetic backgrounds and to subsequently maintain, expand, and stock these cells. From these induced pluripotent stem cells, target cells and tissues can be generated after certain differentiation processes. These target cells/tissues are expected to be useful in regenerative medicine, disease modeling, drug screening, toxicology testing, and proof-of-concept studies in drug development. Therefore, the number of publications concerning induced pluripotent stem cells has recently been increasing rapidly, demonstrating that this technology has begun to infiltrate many aspects of stem cell biology and medical applications. In this review, we discuss the perspectives of induced pluripotent stem cell technology for modeling human diseases. In particular, we focus on the cloning event occurring through the reprogramming process and its ability to let us analyze the development of complex disease-harboring somatic mosaicism.

Nair, M., et al. (2017). "Induced Pluripotent Stem Cell Technology: A Paradigm Shift in Medical Science for Drug Screening and Disease Modeling." Curr Med Chem **24**(39): 4368-4398.

BACKGROUND: Induced Pluripotent Stem Cell (IPSC) Technology is the most advanced research as it offers an attractive alternative for establishing patient-specific IPSCs to recapitulate phenotypes of not only monogenic diseases (viz. Thalassaemia, Sickle cell anemia, Haemophilia, Tay-Sachs disease), but also late-onset polygenic diseases (viz. Parkinson's disease, Alzheimer's disease, schizophrenia). Over the hindsight, numerous studies of the past and current scientists have led to the production, maturation and understanding of induced pluripotent stem cell technology and its use in basic and clinical research. METHODS: A systematic search of peer-reviewed scientific literature and clinical trials in public databases were carried out to summarize the evidence on the use of IPSC. RESULTS: Current review sheds light upon the use of patient-derived iPSC models in drug toxicity, screening and discovery which have been derived after referring to more than 200 articles in literature. Furthermore, their use as disease models was also studied signifying the versatility of iPSC lines. CONCLUSION: Through this review, we describe the advent of iPSC technology, where we comprehensively cover the generation of iPSCs and their characterization along with their prospective

applications using IPSC banks in disease modeling and drug screening.

Nakatsuji, N. (2000). "[Stem cell technology: overview]." Tanpakushitsu Kakusan Koso **45**(13 Suppl): 2037-2039.

Nakayama, M. (2009). "Cell Therapy Using Induced Pluripotent Stem (iPS) Cells Meets Next-Next Generation DNA Sequencing Technology." Curr Genomics **10**(5): 303-305.

The recent development of induced pluripotent stem (iPS) cell technology brings cell and gene therapies to patients one large step closer to reality. Technical improvements in various research fields sometimes come together fortuitously, leading to approaches to treating disease. If iPS cell technology continues to progress smoothly as expected and is actually applied to patients, the next logical step to ensuring the success of iPS cell therapy is to make use of next-next generation DNA sequencing technology and bioinformatics of recipient genomes. Before a patient-derived iPS cell colony is used for clinical therapy in a patient, the colony should undergo whole-genome DNA sequencing, thus avoiding risks associated with spontaneously mutagenized iPS cells. Researchers participating in the Human Genome Project need to take full advantage of both technologies-iPS cell technology and DNA sequencing-as doing so will help us achieve the original long-term goal of the project: developing therapies that will benefit human health.

Nikolov, N. P. and S. Z. Pavletic (2008). "Technology Insight: hematopoietic stem cell transplantation for systemic rheumatic disease." Nat Clin Pract Rheumatol **4**(4): 184-191.

Hematopoietic stem cells (HSCs) have the capacity for self-renewal and the potential to differentiate into all types of hematopoietic and immune system cells. These features have been successfully used to treat a multitude of hematologic malignancies and nonmalignant diseases such as aplastic anemia, hemoglobinopathies, inborn errors of metabolism and congenital immunodeficiency states. The application of HSC transplantation has been expanded over the past decade to include immune-mediated diseases such as multiple sclerosis, treatment-refractory rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis. Transplantation of HSCs for the treatment of autoimmune diseases aims to fundamentally correct the dysregulated immune system, which could result in sustained clinical remission or potential cure. The use of this approach is currently restricted to clinical research, as there is no standard conditioning regimen to attain these aims in autoimmune diseases. HSC transplantation is associated with inherent morbidity and mortality, both treatment-related and disease-related, and selecting the correct group of patients with the best risk:benefit ratio is a challenging task.

Nishimura, K. and J. Takahashi (2013). "Therapeutic application of stem cell technology toward the treatment of Parkinson's disease." Biol Pharm Bull **36**(2): 171-175.

Parkinson's disease (PD) is one of the candidate diseases for cell transplantation therapy, since successful clinical experiments have accumulated using human fetal tissue grafting for PD patients. Although some grafted PD patients have shown drastic improvements, several issues still remain with regard to using human fetal tissue. This review highlights the recent advances in stem cell technology toward clinical applications using human pluripotent stem cells. In particular, pluripotent stem cells, such as embryonic stem cells and induced pluripotent stem cells (iPSCs), are the focus as a source of cell transplantation therapy that can be used instead of human fetal tissues. Additionally, efficient methods for stem cell maintenance and differentiation have been developed and improved toward the clinical transition. These advances in the basic technologies have helped accelerate the realization of regenerative medicine. We also review the current topics regarding disease modeling and drug screening using iPSC technology. Finally, we also describe the future prospects of these stem cell research fields toward clinical application.

Ohgushi, H. and A. I. Caplan (1999). "Stem cell technology and bioceramics: from cell to gene engineering." J Biomed Mater Res **48**(6): 913-927.

Mesenchymal stem cells reside in bone marrow and, when these cells are incorporated into porous ceramics, the composites exhibit osteo-chondrogenic phenotypic expression in ectopic (subcutaneous and intramuscular) or orthotopic sites. The expressional cascade is dependent upon the material properties of the delivery vehicle. Bioactive ceramics provide a suitable substrate for the attachment of the cells. This is followed by osteogenic differentiation directly on the surface of the ceramic, which results in bone bonding. Nonbioactive materials show neither surface-dependent cell differentiation nor bone bonding. The number of mesenchymal stem cells in fresh adult bone marrow is small, about one per one-hundred-thousand nucleated cells, and decreases with donor age. In vitro cell culture technology can be used to mitotically expand these cells without the loss of their developmental potency regardless of donor age. The implanted composite of porous ceramic and culture-expanded mesenchymal stem cells exhibits in vivo osteo-chondrogenic differentiation. In certain culture conditions, these stem cells differentiate into osteoblasts, which make bone matrix on the ceramic surface. Such in vitro prefabricated bone within the ceramic provides immediate new bone-forming

capability after in vivo implantation. Prior to loading of the cultured, marrow-derived mesenchymal stem cells into the porous ceramics, exogenous genes can be introduced into these cells in culture. Combining in vitro manipulated mesenchymal stem cells with porous ceramics can be expected to effect sufficient new bone-forming capability, which can thereby provide tissue engineering approaches to patients with skeletal defects in order to regenerate skeletal tissues.

Ohnishi, H., et al. (2010). "Stem cell technology using bioceramics: hard tissue regeneration towards clinical application." Sci Technol Adv Mater **11**(1): 014110.

Mesenchymal stem cells (MSCs) are adult stem cells which show differentiation capabilities toward various cell lineages. We have already used MSCs for treatments of osteoarthritis, bone necrosis and bone tumor. For this purpose, culture expanded MSCs were combined with various ceramics and then implanted. Because of rejection response to allogeneic MSC implantation, we have utilized patients' own MSCs for the treatment. Bone marrow is a good cell source of MSCs, although the MSCs also exist in adipose tissue. When comparing osteogenic differentiation of these MSCs, bone marrow MSCs show more extensive bone forming capability than adipose MSCs. Thus, the bone marrow MSCs are useful for bone tissue regeneration. However, the MSCs show limited proliferation and differentiation capabilities that hindered clinical applications in some cases. Recent advances reveal that transduction of plural transcription factors into human adult cells results in generation of new type of stem cells called induced pluripotent stem cells (iPS cells). A drawback of the iPS cells for clinical applications is tumor formation after their in vivo implantation; therefore it is difficult to use iPS cells for the treatment. To circumvent the problem, we transduced a single factor of either SOX2 or NANOG into the MSCs and found high proliferation as well as osteogenic differentiation capabilities of the MSCs. The stem cells could be combined with bioceramics for clinical applications. Here, we summarize our recent technologies using adult stem cells in viewpoints of bone tissue regeneration.

Okano, T., et al. (2015). "Regenerative therapy by fusion of medicine and engineering: First-in-human clinical trials with induced pluripotent stem cells and cell sheet technology: A report of the Symposium of Regenerative Medicine for Patients." Regen Ther **2**: 2-5.

The Symposium of Regenerative Medicine for Patients, organized by the Japanese Society for Regenerative Medicine, was held on 28 September 2014 in Tokyo, Japan. The event provided an overview of the important areas of cell-based medicine, and highlighted the first-in-human clinical trial of induced pluripotent stem cell (iPSC)-derived products. Recent advances in regenerative medicine were also discussed, especially regarding the use of somatic cells such as chondrocytes, skeletal myocytes and cardiomyocytes under both the Act on the Safety of Regenerative Medicine, and the Pharmaceuticals, Medical Devices and Other Therapeutic Products Act.

Oltra, J. A. E. (2020). "Improving Therapeutic Interventions of Schizophrenia with Advances in Stem Cell Technology." Clin Psychopharmacol Neurosci **18**(3): 352-361.

Although historic documents posit schizophrenia to the beginnings of mankind, its diagnosis remains poorly defined, currently relying on unspecific clinical symptoms; and controversies still maintain its origin under intense debate. This review aimed at quantitatively assessing the preferential forefronts of clinical trials towards the treatment of schizophrenia from inception till present, according to clinicaltrials.gov database registry. Towards that end study status and study phase classifications were used as criteria for progress in the field. Study groups by sex and age together with countries and organisms involved in the studies were used as indicators of the populations studied and as evidence of main promoter institutions, in both, pharmacological and drug-free protocols. The findings clearly show a decline of active clinical research with small synthetic compounds and limited numbers of novel initiatives, mostly based on drug-free alternatives with expected reduced secondary effects. A paucity of sex- and age-oriented designs is detected, and it is proposed that future clinical trials should set their basis on data obtained from patient-derived induced pluripotent stem cells, brain organoid systems and human brain circuitry platforms. Only individual precision medical approaches may turn effective for the treatment of this complex and highly incapacitating disease.

Otsuka, R., et al. (2020). "Immune reaction and regulation in transplantation based on pluripotent stem cell technology." Inflamm Regen **40**: 12.

The development of pluripotent stem cell (PSC)-based technologies provides us a new therapeutic approach that generates grafts for transplantation. In order to minimize the risk of immune reaction, the banking of induced pluripotent stem cells (iPSCs) from donors with homozygous human leukocyte antigen (HLA) haplotype is planned in Japan. Even though pre-stocked and safety validated HLA-homozygous iPSCs are selected, immunological rejection may potentially occur because the causes of rejection are not always due to HLA mismatches. A couple of studies concerning such immunological issues have reported that genetic ablation of HLA molecules from PSC combined with gene transduction of several immunoregulatory molecules may be

effective in avoiding immunological rejection. Also, our research group has recently proposed a concept that attempts to regulate recipient immune system by PSC-derived immunoregulatory cells, which results in prolonged survival of the same PSC-derived allografts. PSC-based technologies enable us to choose a new therapeutic option; however, considering its safety from an immunological point of view should be of great importance for safe clinical translation of this technology.

Passweg, J. R., et al. (2000). "Increased stem cell dose, as obtained using currently available technology, may not be sufficient for engraftment of haploidentical stem cell transplants." Bone Marrow Transplant **26**(10): 1033-1036.

The best strategies for haploidentical stem cell transplants are not known. We used a standard myeloablative pretransplant conditioning regimen (30 mg/kg VP-16, 120 mg/kg cyclophosphamide, and 12 Gy of TBI in six fractions), an increased peripheral stem cell dose of > 10 x 10(6) CD34+ cells/kg, T cell depletion (with CD34+ cell selection and CD4/CD8 depletion steps) to < 1 x 10(5) CD3+ cells/kg and cyclosporine post transplant. Ten patients (7M/3F, median age 11 (3-33) years) with high-risk leukemia (AML in 4, MDS in 2, CML in 1 and T-ALL in 3) received a hemopoietic stem cell transplant (HSCT) from a haploidentical father or sibling. The median number of CD34+ cells was 12.9 (9.5-45.7) x 10(6) cells/kg; median number of CD3+ cells was 0.41 (0.09-1.89) x 10(5) CD3+ cells/kg. All patients initially achieved 0.5 x 10(9)/l neutrophils at a median 12 (10-21) days. Graft failure in two consecutive patients out of four on the original protocol led to a modification adding ATG pretransplant and OKT3 post transplant. Graft failure was observed in one out of six subsequent patients. Acute GVHD > or = grade II was observed in three patients. Three of 10 patients are alive in CR at > 24 and >3 (2) months after transplant. Seven patients died: four of transplant related complications and three of relapse. Increased stem cell dose (> or = 10 x 10(6) CD34+ cells/kg) as obtained using currently available technology may not be sufficient to ensure stable engraftment in patients with high-risk leukemia using standard myeloablative conditioning regimens.

Payne, A. G. (2004). "Using immunomagnetic technology and other means to facilitate stem cell homing." Med Hypotheses **62**(5): 718-720.

If stem cell therapy is to be maximally effective, it is vital that progenitor (stem) cells get to the target tissue(s) and/or organ(s). Three methods of facilitating stem cell homing to target tissues are explored in this paper: (1) cobalt compounds such as cobalt phthalocyanines could be magnetically delivered to target tissue(s) and/or organ(s), and then subject to a brief pulsed magnetic field or ultrasound exposure suitable to induce mild hyperthermia with the result being the synthesis of cytokines that are chemoattractants to progenitor (stem) cells; (2) ferromagnetic nanobead particles could be tagged with antibodies specific to the target tissue(s) and/or organ(s) and infused into patients, followed by introduction of progenitor (stem) cells tagged with antibody-bound magnetic nanoparticles. This should result in passive attachment (stem cells to tagged tissue or organ); and (3) Reticulose, which stimulates the synthesis of the stem cell chemoattractant IL-8, could be magnetically guided to target tissue(s) and/or organ(s).

Pei, D., et al. (2010). "Induced pluripotent stem cell technology in regenerative medicine and biology." Adv Biochem Eng Biotechnol **123**: 127-141.

The potential of human embryonic stem cells (ESCs) for regenerative medicine is unquestionable, but practical and ethical considerations have hampered clinical application and research. In an attempt to overcome these issues, the conversion of somatic cells into pluripotent stem cells similar to ESCs, commonly termed nuclear reprogramming, has been a top objective of contemporary biology. More than 40 years ago, King, Briggs, and Gurdon pioneered somatic cell nuclear reprogramming in frogs, and in 1981 Evans successfully isolated mouse ESCs. In 1997 Wilmut and collaborators produced the first cloned mammal using nuclear transfer, and then Thomson obtained human ESCs from in vitro fertilized blastocysts in 1998. Over the last 2 decades we have also seen remarkable findings regarding how ESC behavior is controlled, the importance of which should not be underestimated. This knowledge allowed the laboratory of Shinya Yamanaka to overcome brilliantly conceptual and technical barriers in 2006 and generate induced pluripotent stem cells (iPSCs) from mouse fibroblasts by overexpressing defined combinations of ESC-enriched transcription factors. Here, we discuss some important implications of human iPSCs for biology and medicine and also point to possible future directions.

Peloso, A., et al. (2018). "Regenerative Medicine and Diabetes: Targeting the Extracellular Matrix Beyond the Stem Cell Approach and Encapsulation Technology." Front Endocrinol (Lausanne) **9**: 445.

According to the Juvenile Diabetes Research Foundation (JDRF), almost 1. 25 million people in the United States (US) have type 1 diabetes, which makes them dependent on insulin injections. Nationwide, type 2 diabetes rates have nearly doubled in the past 20 years resulting in more than 29 million American adults with diabetes and another 86 million in a pre-diabetic state. The International Diabetes Ferderation (IDF) has estimated that there will be almost 650 million adult diabetic patients worldwide at the end of the next 20 years (excluding patients over the age of 80). At this time, pancreas transplantation is the only

available cure for selected patients, but it is offered only to a small percentage of them due to organ shortage and the risks linked to immunosuppressive regimes. Currently, exogenous insulin therapy is still considered to be the gold standard when managing diabetes, though stem cell biology is recognized as one of the most promising strategies for restoring endocrine pancreatic function. However, many issues remain to be solved, and there are currently no recognized treatments for diabetes based on stem cells. In addition to stem cell resesarch, several beta-cell substitutive therapies have been explored in the recent era, including the use of acellular extracellular matrix scaffolding as a template for cellular seeding, thus providing an empty template to be repopulated with beta-cells. Although this bioengineering approach still has to overcome important hurdles in regards to clinical application (including the origin of insulin producing cells as well as immune-related limitations), it could theoretically provide an inexhaustible source of bio-engineered pancreases.

Pino, C. J. and H. D. Humes (2010). "Stem cell technology for the treatment of acute and chronic renal failure." Transl Res **156**(3): 161-168.

Acute and chronic renal failure are disorders with high rates of morbidity and mortality. Current treatment is based upon conventional dialysis to provide volume regulation and small solute clearance. There is growing recognition that renal failure is a complex disease state requiring a multifactorial therapy to address the short-comings of the conventional monofactorial approach. Kidney transplantation remains the most effective treatment, however, organ availability lags far behind demand. Many key kidney functions including gluconeogenesis, ammoniagenesis, metabolism of glutathione, catabolism of important peptide hormones, growth factors, and cytokines critical to multiorgan homeostasis and immunomodulation are provided by renal tubule cells. Therefore, cell-based therapies are promising multifactorial treatment approaches. In this review, current stem cell technologies including adult stem cells, embryonic stem cells and induced pluripotent stem cells will be discussed as cell sources for the treatment of acute and chronic renal failure.

Preffer, F. and D. Dombkowski (2009). "Advances in complex multiparameter flow cytometry technology: Applications in stem cell research." Cytometry B Clin Cytom **76**(5): 295-314.

Flow cytometry and cell sorting are critical tools in stem cell research. Recent advances in flow cytometric hardware, reagents, and software have synergized to permit the stem cell biologist to more fully identify and isolate rare cells based on their immunofluorescent and light scatter characteristics. Some of these improvements include physically smaller air-cooled lasers, new designs in optics, new fluorescent conjugate-excitation pairs, and improved software to visualize data, all which combine to open up new horizons in the study of stem cells, by enhancing the resolution and specificity of inquiry. In this review, these recent improvements in technology will be outlined and important cell surface and functional antigenic markers useful for the study of stem cells described.

Prelle, K., et al. (2002). "[Application of stem cell technology and nuclear transfer in animal models]." Z Arztl Fortbild Qualitatssich **96**(6-7): 434-440.

Pluripotent embryonic stem (ES) cells established from undifferentiated cells of early embryos together with embryonic germ (EG) cells derived from primordial germ cells are used for gene transfer into the germ lines of mice. ES cells are also capable of in vitro differentiation into embryo-like aggregates (embryoid bodies) consisting of meso-, ecto- and endodermal cells. Except in chicken in no other vertebrate species pluripotent cell lines equivalent to murine ES cells are established. Recently, isolated human pluripotent cells originating from spare IVF embryos or aborted human foetuses have successfully been differentiated into somatic cells and may at some point serve as cellular grafts for transplantation. In therapeutic cloning somatic cells can be reprogrammed by fusion with an enucleated oocyte. Later the established autologous ES cells from the resulting nuclear transfer embryo can be differentiated into the specific cell type needed for tissue therapy.

Rabinovitch, M. (2013). "Combining induced pluripotent stem cell with next generation sequencing technology to gain new insights into pathobiology and treatment of pulmonary arterial hypertension." Pulm Circ **3**(1): 153-155.

Raghunath, J., et al. (2005). "Advancing cartilage tissue engineering: the application of stem cell technology." Curr Opin Biotechnol **16**(5): 503-509.

The treatment of cartilage pathology and trauma face the challenges of poor regenerative potential and inferior repair. Nevertheless, recent advances in tissue engineering indicate that adult stem cells could provide a source of chondrocytes for tissue engineering that the isolation of mature chondrocytes has failed to achieve. Various adjuncts to their propagation and differentiation have been explored, such as biomaterials, bioreactors and growth hormones. To date, all tissue engineered cartilage has been significantly mechanically inferior to its natural counterparts and further problems in vivo relate to poor integration and deterioration of tissue quality over time. However, adult stem cells--with their high rate of proliferation and ease of isolation--are expected to greatly further the development and usefulness of tissue engineered cartilage.

Rahmi, G., et al. (2016). "Designing 3D Mesenchymal Stem Cell Sheets Merging Magnetic and Fluorescent Features: When Cell Sheet Technology Meets Image-Guided Cell Therapy." Theranostics **6**(5): 739-751.

Cell sheet technology opens new perspectives in tissue regeneration therapy by providing readily implantable, scaffold-free 3D tissue constructs. Many studies have focused on the therapeutic effects of cell sheet implantation while relatively little attention has concerned the fate of the implanted cells in vivo. The aim of the present study was to track longitudinally the cells implanted in the cell sheets in vivo in target tissues. To this end we (i) endowed bone marrow-derived mesenchymal stem cells (BMMSCs) with imaging properties by double labeling with fluorescent and magnetic tracers, (ii) applied BMMSC cell sheets to a digestive fistula model in mice, (iii) tracked the BMMSC fate in vivo by MRI and probe-based confocal laser endomicroscopy (pCLE), and (iv) quantified healing of the fistula. We show that image-guided longitudinal follow-up can document both the fate of the cell sheet-derived BMMSCs and their healing capacity. Moreover, our theranostic approach informs on the mechanism of action, either directly by integration of cell sheet-derived BMMSCs into the host tissue or indirectly through the release of signaling molecules in the host tissue. Multimodal imaging and clinical evaluation converged to attest that cell sheet grafting resulted in minimal clinical inflammation, improved fistula healing, reduced tissue fibrosis and enhanced microvasculature density. At the molecular level, cell sheet transplantation induced an increase in the expression of anti-inflammatory cytokines (TGF-ss2 and IL-10) and host intestinal growth factors involved in tissue repair (EGF and VEGF). Multimodal imaging is useful for tracking cell sheets and for noninvasive follow-up of their regenerative properties.

Ramakrishna, R. R., et al. (2020). "Stem cell imaging through convolutional neural networks: current issues and future directions in artificial intelligence technology." PeerJ **8**: e10346.

Stem cells are primitive and precursor cells with the potential to reproduce into diverse mature and functional cell types in the body throughout the developmental stages of life. Their remarkable potential has led to numerous medical discoveries and breakthroughs in science. As a result, stem cell-based therapy has emerged as a new subspecialty in medicine. One promising stem cell being investigated is the induced pluripotent stem cell (iPSC), which is obtained by genetically reprogramming mature cells to convert them into embryonic-like stem cells. These iPSCs are used to study the onset of disease, drug development, and medical therapies. However, functional studies on iPSCs involve the analysis of iPSC-derived colonies through manual identification, which is time-consuming, error-prone, and training-dependent. Thus, an automated instrument for the analysis of iPSC colonies is needed. Recently, artificial intelligence (AI) has emerged as a novel technology to tackle this challenge. In particular, deep learning, a subfield of AI, offers an automated platform for analyzing iPSC colonies and other colony-forming stem cells. Deep learning rectifies data features using a convolutional neural network (CNN), a type of multi-layered neural network that can play an innovative role in image recognition. CNNs are able to distinguish cells with high accuracy based on morphologic and textural changes. Therefore, CNNs have the potential to create a future field of deep learning tasks aimed at solving various challenges in stem cell studies. This review discusses the progress and future of CNNs in stem cell imaging for therapy and research.

Ramirez-Solis, R. and A. Bradley (1994). "Advances in the use of embryonic stem cell technology." Curr Opin Biotechnol **5**(5): 528-533.

Embryonic stem cells have become versatile genetic vehicles. Two-step recombination protocols have been used to modify endogenous mouse genes, and yeast artificial chromosomes containing human genes have been transmitted into the mouse germline. Recently, it has become possible to evaluate homozygous deficiencies in specific developmental compartments either through the use of chimeras or by activating recombination in vivo using potent recombinases.

Rao, M. and J. M. Gottesfeld (2014). "Introduction to thematic minireview series: Development of human therapeutics based on induced pluripotent stem cell (iPSC) technology." J Biol Chem **289**(8): 4553-4554.

With the advent of human induced pluripotent stem cell (hiPSC) technology, it is now possible to derive patient-specific cell lines that are of great potential in both basic research and the development of new therapeutics for human diseases. Not only do hiPSCs offer unprecedented opportunities to study cellular differentiation and model human diseases, but the differentiated cell types obtained from iPSCs may become therapeutics themselves. These cells can also be used in the screening of therapeutics and in toxicology assays for potential liabilities of therapeutic agents. The remarkable achievement of transcription factor reprogramming to generate iPSCs was recognized by the award of the Nobel Prize in Medicine to Shinya Yamanaka in 2012, just 6 years after the first publication of reprogramming methods to generate hiPSCs (Takahashi, K., Tanabe, K., Ohnuki, M., Narita, M., Ichisaka, T., Tomoda, K., and Yamanaka, S. (2007) Cell 131, 861-872). This minireview series highlights both the promises and challenges of using iPSC technology for disease

modeling, drug screening, and the development of stem cell therapeutics.
Riemens, R. J. M., et al. (2017). "Stem Cell Technology for (Epi)genetic Brain Disorders." Adv Exp Med Biol **978**: 443-475.

Despite the enormous efforts of the scientific community over the years, effective therapeutics for many (epi)genetic brain disorders remain unidentified. The common and persistent failures to translate preclinical findings into clinical success are partially attributed to the limited efficiency of current disease models. Although animal and cellular models have substantially improved our knowledge of the pathological processes involved in these disorders, human brain research has generally been hampered by a lack of satisfactory humanized model systems. This, together with our incomplete knowledge of the multifactorial causes in the majority of these disorders, as well as a thorough understanding of associated (epi)genetic alterations, has been impeding progress in gaining more mechanistic insights from translational studies. Over the last years, however, stem cell technology has been offering an alternative approach to study and treat human brain disorders. Owing to this technology, we are now able to obtain a theoretically inexhaustible source of human neural cells and precursors in vitro that offer a platform for disease modeling and the establishment of therapeutic interventions. In addition to the potential to increase our general understanding of how (epi)genetic alterations contribute to the pathology of brain disorders, stem cells and derivatives allow for high-throughput drugs and toxicity testing, and provide a cell source for transplant therapies in regenerative medicine. In the current chapter, we will demonstrate the validity of human stem cell-based models and address the utility of other stem cell-based applications for several human brain disorders with multifactorial and (epi)genetic bases, including Parkinson's disease (PD), Alzheimer's disease (AD), fragile X syndrome (FXS), Angelman syndrome (AS), Prader-Willi syndrome (PWS), and Rett syndrome (RTT).

Rinaldi, S., et al. (2014). "Stem cell senescence. Effects of REAC technology on telomerase-independent and telomerase-dependent pathways." Sci Rep **4**: 6373.

Decline in the gene expression of senescence repressor Bmi1, and telomerase, together with telomere shortening, underlay senescence of stem cells cultured for multiple passages. Here, we investigated whether the impairment of senescence preventing mechanisms can be efficiently counteracted by exposure of human adipose-derived stem cells to radio electric asymmetrically conveyed fields by an innovative technology, named Radio Electric Asymmetric Conveyer (REAC). Due to REAC exposure, the number of stem cells positively stained for senescence associated beta-galactosidase was significantly reduced along multiple culturing passages. After a 90-day culture, REAC-treated cells exhibited significantly higher transcription of Bmi1 and enhanced expression of other stem cell pluripotency genes and related proteins, compared to unexposed cells. Transcription of the catalytic telomerase subunit (TERT) was also increased in REAC-treated cells at all passages. Moreover, while telomere shortening occurred at early passages in both REAC-treated and untreated cells, a significant rescue of telomere length could be observed at late passages only in REAC-exposed cells. Thus, REAC-asymmetrically conveyed radio electric fields acted on a gene and protein expression program of both telomerase-independent and telomerase-dependent patterning to optimize stem cell ability to cope with senescence progression.

Roessler, R., et al. (2013). "Induced pluripotent stem cell technology and direct conversion: new possibilities to study and treat Parkinson's disease." Stem Cell Rev Rep **9**(4): 505-513.

Recent developments in in vitro disease modeling and regenerative medicine have placed induced pluripotent stem cells (iPSCs) in the center of attention as a unique source to study Parkinson's disease. After only 5 years of intensive research, human iPSCs can be generated without viral integration and under xeno-free conditions. This, combined with increasingly sophisticated methods to differentiate iPSCs into functional dopaminergic (DA) neurons, led us to recapitulate the most important findings concerning the use of iPSC technology as a prospective tool to treat symptoms of Parkinson's disease as well as to obtain insight in disease related cell pathogenesis. Moreover, we touch upon some of the latest discoveries in which patient-derived autologous DA neurons come into even more direct reach thanks to a method that allows transdifferentiation of fibroblasts into DA neurons.

Ross, S. B., et al. (2018). "Induced pluripotent stem cell technology and inherited arrhythmia syndromes." Heart Rhythm **15**(1): 137-144.

Inherited arrhythmia syndromes, including familial long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome, can cause life-threatening arrhythmias and are responsible for a significant proportion of sudden deaths in the young. Identification of genetic mutations and pathophysiological changes that underlie disease development can inform clinical practice and guide novel drug development. However, disease mechanisms in a large number of patients remain elusive and pharmacologic treatment is suboptimal, so many patients rely on implantable cardioverter-defibrillator therapy. Induced pluripotent stem cell models of disease facilitate analysis of disease

mechanisms in patient-specific cardiomyocytes, overcoming limitations of animal models and human tissue restrictions. This review outlines how studies using induced pluripotent stem cell-derived cardiomyocytes are contributing to our understanding of the mechanisms that underpin disease pathogenesis and their potential to facilitate new pharmacologic therapies and personalized medicine.

Rossbach, B., et al. (2016). "WITHDRAWN: Generation of a human induced pluripotent stem cell line from urinary cells of a healthy donor using integration free Sendai technology." Stem Cell Res **16**(1): 133-136.

The Publisher regrets that this article is an accidental duplication of an article that has already been published in Stem Cell Res., 16 (2016) 133-136, http://dx.doi.org/10.1016/j.scr.2015.12.021. The duplicate article has therefore been withdrawn. The full Elsevier Policy on Article Withdrawal can be found at http://www.elsevier.com/locate/withdrawalpolicy.

Rossbach, B., et al. (2017). "Generation of a human induced pluripotent stem cell line from urinary cells of a healthy donor using integration free Sendai virus technology." Stem Cell Res **21**: 167-170.

We have generated a human induced pluripotent stem cell (iPSC) line derived from urinary cells of a 28year old healthy female donor. The cells were reprogrammed using a non-integrating viral vector and have shown full differentiation potential. Together with the iPSC line, the donor provided blood cells for the study of immunological effects of the iPSC line and its derivatives in autologous and allogeneic settings. The line is available and registered in the human pluripotent stem cell registry as BCRTi005-A.

Rozwadowski, M., et al. (2020). "Promoting Health and Well-Being Through Mobile Health Technology (Roadmap 2.0) in Family Caregivers and Patients Undergoing Hematopoietic Stem Cell Transplantation: Protocol for the Development of a Mobile Randomized Controlled Trial." JMIR Res Protoc **9**(9): e19288.

BACKGROUND: Cancer patients who undergo allogeneic hematopoietic stem cell transplantation are among the most medically fragile patient populations with extreme demands for caregivers. Indeed, with earlier hospital discharges, the demands placed on caregivers continue to intensify. Moreover, an increased number of allogeneic hematopoietic stem cell transplantations are being performed worldwide, and this expensive procedure has significant economic consequences. Thus, the health and well-being of family caregivers have attracted widespread attention. Mobile health technology has been shown to deliver flexible, and time- and cost-sparing interventions to support family caregivers across the care trajectory. OBJECTIVE: This protocol aims to leverage technology to deliver a novel caregiver-facing mobile health intervention named Roadmap 2.0. We will evaluate the effectiveness of Roadmap 2.0 in family caregivers of patients undergoing hematopoietic stem cell transplantation. METHODS: The Roadmap 2.0 intervention will consist of a mobile randomized trial comparing a positive psychology intervention arm with a control arm in family caregiver-patient dyads. The primary outcome will be caregiver health-related quality of life, as assessed by the PROMIS Global Health scale at day 120 post-transplant. Secondary outcomes will include other PROMIS caregiver- and patient-reported outcomes, including companionship, self-efficacy for managing symptoms, self-efficacy for managing daily activities, positive affect and well-being, sleep disturbance, depression, and anxiety. Semistructured qualitative interviews will be conducted among participants at the completion of the study. We will also measure objective physiological markers (eg, sleep, activity, heart rate) through wearable wrist sensors and health care utilization data through electronic health records. RESULTS: We plan to enroll 166 family caregiver-patient dyads for the full data analysis. The study has received Institutional Review Board approval as well as Code Review and Information Assurance approval from our health information technology services. Owing to the COVID-19 pandemic, the study has been briefly put on hold. However, recruitment began in August 2020. We have converted all recruitment, enrollment, and onboarding processes to be conducted remotely through video telehealth. Consent will be obtained electronically through the Roadmap 2.0 app. CONCLUSIONS: This mobile randomized trial will determine if positive psychology-based activities delivered through mobile health technology can improve caregiver health-related quality of life over a 16-week study period. This study will provide additional data on the effects of wearable wrist sensors on caregiver and patient self-report outcomes. TRIAL REGISTRATION: ClinicalTrials.gov NCT04094844; https://www.clinicaltrials.gov/ct2/show/NCT04094844. INTERNATIONAL REGISTERED REPORT IDENTIFIER (IRRID): PRR1-10.2196/19288.

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

Quantum dots (QDs) are a new class of fluorescent labeling for biological and biomedical applications. In this study, we detected prostate stem cell antigen (PSCA) expression correlated with tumor grade and stage in human prostate cancer by QDs-based immunolabeling and conventional immunohistochemistry (IHC), and evaluated the sensitivity and stability of QDs-based immunolabeling

in comparison with IHC. Our data revealed that increasing levels of PSCA expression accompanied advanced tumor grade (QDs labeling, $r = 0.732$, $p < 0.001$; IHC, $r = 0.683$, $p < 0.001$) and stage (QDs labeling, $r = 0.514$, $p = 0.001$; IHC, $r = 0.432$, $p = 0.005$), and the similar tendency was detected by the two methods. In addition, by comparison between the two methods, QDs labeling was consistent with IHC in detecting the expression of PSCA in human prostate tissue correlated with different pathological types ($K = 0.845$, $p < 0.001$). During the observation time, QDs exhibited superior stability. The intensity of QDs fluorescence remained stable for two weeks ($p = 0.083$) after conjugation to the PSCA protein, and nearly 93% of positive expression with their fluorescence still could be seen after four weeks.

Sales, K. M., et al. (2005). "Advancing vascular tissue engineering: the role of stem cell technology." Trends Biotechnol **23**(9): 461-467.

Atherosclerosis and heart disease are still the leading causes of morbidity and mortality worldwide. The lack of suitable autologous grafts has produced a need for artificial grafts but the patency of such grafts is limited compared to natural materials. Tissue engineering, whereby living tissue replacements can be constructed, has emerged as a solution to some of these difficulties. This, in turn, is limited by the availability of suitable cells from which to construct the vessels. The development of prosthesis using progenitor cells and switching these into endothelial cells is an important and exciting advance in the field of tissue engineering. Here, we describe recent developments in the use of stem cells for the development of replacement vessels. These paradigm shifts in vascular engineering now offer a new route for effective clinical therapy.

Sauer, V., et al. (2016). "Human Urinary Epithelial Cells as a Source of Engraftable Hepatocyte-Like Cells Using Stem Cell Technology." Cell Transplant **25**(12): 2221-2243.

Although several types of somatic cells have been reprogrammed into induced pluripotent stem cells (iPSCs) and then differentiated to hepatocyte-like cells (iHeps), the method for generating such cells from renal tubular epithelial cells shed in human urine and transplanting them into animal livers has not been described systematically. We report reprogramming of human urinary epithelial cells into iPSCs and subsequent hepatic differentiation, followed by a detailed characterization of the newly generated iHeps. The epithelial cells were reprogrammed into iPSCs by delivering the pluripotency factors OCT3/4, SOX2, KLF4, and MYC using methods that do not involve transgene integration, such as nucleofection of episomal (oriP/EBNA-1) plasmids or infection with recombinant Sendai viruses. After characterization of stable iPSC lines, a three-step differentiation toward hepatocytes was performed. The iHeps expressed a large number of hepatocyte-preferred genes, including nuclear receptors that regulate genes involved in cholesterol homeostasis, bile acid transport, and detoxification. MicroRNA profile of the iHeps largely paralleled that of primary human hepatocytes. The iHeps engrafted into the livers of Scid mice transgenic for mutant human SERPINA1 after intrasplenic injection. Thus, urine is a readily available source for generating human iHeps that could be potentially useful for disease modeling, pharmacological development, and regenerative medicine.

Sawada, M., et al. (2018). "A Japanese Bioventure Company's Application of Stem Cell Technology in Regenerative Medicine." Clin Ther **40**(11): 1801-1806.

Regenerative medicine mediated by the transplantation of somatic stem cells and functional cells derived from induced pluripotent stem cells has great potential in the treatment of currently incurable diseases and thus has attracted significant public attention. To put this into practice, several functional cell lines were developed and laws regarding regenerative medicine were put in force in Japan. In this report, we introduce recent efforts of a bioventure company with special attention to the case of Healios K.K.

Scheel, O., et al. (2014). "Action potential characterization of human induced pluripotent stem cell-derived cardiomyocytes using automated patch-clamp technology." Assay Drug Dev Technol **12**(8): 457-469.

Recent progress in embryonic stem cell (ESC) and induced pluripotent stem cell (iPSC) research led to high-purity preparations of human cardiomyocytes (CMs) differentiated from these two sources-suitable for tissue regeneration, in vitro models of disease, and cardiac safety pharmacology screening. We performed a detailed characterization of the effects of nifedipine, cisapride, and tetrodotoxin (TTX) on Cor.4U((R)) human iPSC-CM, using automated whole-cell patch-clamp recordings with the CytoPatch 2 equipment, within a complex assay combining multiple voltage-clamp and current-clamp protocols in a well-defined sequence, and quantitative analysis of several action potential (AP) parameters. We retrieved three electrical phenotypes based on AP shape: ventricular, atrial/nodal, and S-type (with ventricular-like depolarization and lack of plateau). To suppress spontaneous firing, present in many cells, we injected continuously faint hyperpolarizing currents of -10 or -20 pA. We defined quality criteria (both seal and membrane resistance over 1 GOmega), and focused our study on cells with ventricular-like AP. Nifedipine induced marked decreases in AP duration (APD): APD90 (49.8% and 40.8% of control values at 1 and 10 muM, respectively),

APD50 (16.1% and 12%); cisapride 0.1 muM increased APD90 to 176.2%; and tetrodotoxin 10 muM decreased maximum slope of phase to 33.3% of control, peak depolarization potential to 76.3% of control, and shortened APD90 on average to 80.4%. These results prove feasibility of automated voltage- and current-clamp recordings on human iPSC-CM and their potential use for in-depth drug evaluation and proarrhythmic liability assessment, as well as for diagnosis and pharmacology tests for cardiac channelopathy patients.

Schlotzer-Schrehardt, U., et al. (2017). "[The emerging technology of tissue engineering : Focus on stem cell niche]." Ophthalmologe **114**(4): 327-340.

Limbal stem cells reside in a highly specialized complex microenvironment that is known as the stem cell niche, an anatomically protected region at the bottom of the Palisades of Vogt, where the stem cells are located and where their quiescence, proliferation and differentiation are maintained in balance. Besides the epithelial stem and progenitor cell clusters, the limbal niche comprises several types of supporting niche cells and a specific extracellular matrix mediating biochemical and biophysical signals. Stem cell-based tissue engineering aims to mimic the native stem cell niche and to present appropriate microenvironmental cues in a controlled and reproducible fashion in order to maintain stem cell function within the graft. Current therapeutic approaches for ex vivo expansion of limbal stem cells only take advantage of surrogate niches. However, new insights into the molecular composition of the limbal niche and innovative biosynthetic scaffolds have stimulated novel strategies for niche-driven stem cell cultivation. Promising experimental approaches include collagen-based organotypic coculture systems of limbal epithelial stem cells with their niche cells and biomimetic hydrogel platforms prefunctionalized with appropriate biomolecular and biophysical signals. Future translation of these novel regenerative strategies into clinical application is expected to improve long-term outcomes of limbal stem cell transplantation for ocular surface reconstruction.

Schutgens, F., et al. (2016). "Pluripotent stem cell-derived kidney organoids: An in vivo-like in vitro technology." Eur J Pharmacol **790**: 12-20.

Organoids are self-organizing, multicellular structures that contain multiple cell types, represent organ structure and function, and can be used to model organ development, maintenance and repair ex vivo. Organoids, derived from embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) or adult stem cells, are cultured in extracellular matrix (ECM). Organoid cultures have been developed for multiple organs and for the kidney, pluripotent stem cell (PSCs) derived organoid technology has rapidly developed in the last three years. Here, we review available PSC differentiation protocols, focusing on the pluripotent stem cells to initiate the organoid culture, as well as on growth factors and ECM used to regulate differentiation and expansion. In addition, we will discuss the read out strategies to evaluate organoid phenotype and function. Finally, we will indicate how the choice of both culture parameters and read out strategy should be tailored to specific applications of the organoid culture.

Secher, J. O., et al. (2015). "Optimization of three-dimensional imaging on in vitro produced porcine blastocysts and chimeras for stem cell testing: a technology report." Stem Cells Dev **24**(9): 1141-1145.

Differential staining is an immunocytochemical staining that visualizes trophectoderm (TE) and the inner cell mass (ICM) of the blastocysts. It is used to determine the blastocyst quality, but could also be a useful tool to assess the integration site of injected cells into the early embryo. This is relevant for testing of presumed pluripotent stem cells. The gold standard for pluripotent stem cells is to test if the cells are capable of contributing to germline chimeras. Differential staining can be used to evaluate the possibility of chimeric contribution; if the cells are located in the area of the ICM they are likely to contribute to the fetus and if they are located in the area of the TE they are likely to contribute to the fetal membranes. In this article, we optimize on methods for embryo staining and mounting so that the exact location of injected stem cells within preimplantation porcine embryos can be evaluated.

Selich, A., et al. (2016). "Massive Clonal Selection and Transiently Contributing Clones During Expansion of Mesenchymal Stem Cell Cultures Revealed by Lentiviral RGB-Barcode Technology." Stem Cells Transl Med **5**(5): 591-601.

UNLABELLED: Mesenchymal stem (or stromal) cells (MSCs) have been used in more than 400 clinical trials for the treatment of various diseases. The clinical benefit and reproducibility of results, however, remain extremely variable. During the in vitro expansion phase, which is necessary to achieve clinically relevant cell numbers, MSCs show signs of aging accompanied by different contributions of single clones to the mass culture. Here we used multicolor lentiviral barcode labeling to follow the clonal dynamics during in vitro MSC expansion from whole umbilical cord pieces (UCPs). The clonal composition was analyzed by a combination of flow cytometry, fluorescence microscopy, and deep sequencing. Starting with highly complex cell populations, we observed a massive reduction in diversity, transiently dominating populations, and a selection of single clones over time. Importantly, the first wave of clonal constriction already occurred in the early passages

during MSC expansion. Consecutive MSC cultures from the same UCP implied the existence of more primitive, MSC culture-initiating cells. Our results show that microscopically homogenous MSC mass cultures consist of many subpopulations, which undergo clonal selection and have different capabilities. Among other factors, the clonal composition of the graft might have an impact on the functional properties of MSCs in experimental and clinical settings. SIGNIFICANCE: Mesenchymal stem cells (MSCs) can easily be obtained from various adult or embryonal tissues and are frequently used in clinical trials. For their clinical application, MSCs have to be expanded in vitro. This unavoidable step influences the features of MSCs, so that clinical benefit and experimental results are often highly variable. Despite a homogenous appearance under the microscope, MSC cultures undergo massive clonal selection over time. Multicolor fluorescence labeling and deep sequencing were used to demonstrate the dynamic clonal composition of MSC cultures, which might ultimately explain the variable clinical performance of the cells.

Semi, K. and Y. Yamada (2015). "Induced pluripotent stem cell technology for dissecting the cancer epigenome." Cancer Sci **106**(10): 1251-1256.

Cancer arises through the accumulation of both genetic and epigenetic alterations. Although the causal role of genetic mutations on cancer development has been established in vivo, similar evidence for epigenetic alterations is limited. Moreover, mutual interactions between genetic mutations and epigenetic alterations remain unclear. Cellular reprogramming technology can be used to actively modify the epigenome without affecting the underlying genomic sequences. Here we introduce recent studies that have utilized this property for cancer research. We propose that just as it has potential for regenerative medicine and disease modeling, cell reprogramming could also be a powerful tool for dissecting the role of the cancer epigenome in the development and maintenance of cancer cells.

Shi, Y., et al. (2017). "Induced pluripotent stem cell technology: a decade of progress." Nat Rev Drug Discov **16**(2): 115-130.

Since the advent of induced pluripotent stem cell (iPSC) technology a decade ago, enormous progress has been made in stem cell biology and regenerative medicine. Human iPSCs have been widely used for disease modelling, drug discovery and cell therapy development. Novel pathological mechanisms have been elucidated, new drugs originating from iPSC screens are in the pipeline and the first clinical trial using human iPSC-derived products has been initiated. In particular, the combination of human iPSC technology with recent developments in gene editing and 3D organoids makes iPSC-based platforms even more powerful in each area of their application, including precision medicine. In this Review, we discuss the progress in applications of iPSC technology that are particularly relevant to drug discovery and regenerative medicine, and consider the remaining challenges and the emerging opportunities in the field.

Staquicini, F. I., et al. (2010). "Phage display technology for stem cell delivery and systemic therapy." Adv Drug Deliv Rev **62**(12): 1213-1216.

Advances in the technology for phage display in vivo have set the stage for a new ligand-directed pharmacology with broad implications for both treatment and molecular imaging of patients, and for the elucidation of molecular mechanisms of action, particularly in carcinogenesis. This technology identifies specific molecular complexes, mainly small peptide and gene-based therapeutic and imaging agents, effective in experimental animals and patients. The unbiased identification of molecular targets on the surfaces of blood vessels and parenchymal cells in preselected specific organs and tissues raises the prospect of an increased understanding of animal and human cellular and vascular proteomics. In this review, we focus on the delivery of phage-based agents via stem and progenitor cells, important delivery vehicles contributing to the growing impact of phage display on modern medicine.

Stenn, K. S. and G. Cotsarelis (2005). "Bioengineering the hair follicle: fringe benefits of stem cell technology." Curr Opin Biotechnol **16**(5): 493-497.

Recent advances in epithelial stem cell biology have resulted in the isolation of hair follicle stem cells, which generate hair follicles when injected into immunodeficient mice. These isolated hair follicle epithelial stem cells must be combined with 'inductive' dermal cells to produce new hair follicles. The advent of techniques for cultivating inductive dermal cells and competent epithelial stem cells creates the opportunity to bioengineer hair follicles for the treatment of hair loss.

Stingl Jankovic, K., et al. (2019). "Quantitative polymerase chain reaction technology in chimerism monitoring after hematopoietic stem cell transplantation: One center experience." HLA **94 Suppl 2**: 16-20.

Chimerism status evaluation is a routine test performed in post-hematopoietic stem cell transplantation (HSCT) period. The aim of the study was to evaluate a quantitative polymerase chain reaction (qPCR) method (GenDx, Utrecht, the Netherlands) applicability for this purpose. The study included 74 recipient/donor pairs tested for informative markers: median of four and six informative markers was found for patients (related and unrelated donor, respectively). Higher sensitivity of qPCR method was confirmed by analysis of recipient post-HSCT samples

(N = 800) among which microchimerism (0.1%-1% recipient DNA) was detected in 21.8% of cases. The ability to detect less than 1% of minor population, as opposed to the short tandem repeat (STR) method for which 1% is the limit, translated into earlier identification of a disease relapse for four patients in our study sample.

Suh, C. Y., et al. (2014). "Advancements in Induced Pluripotent Stem Cell Technology for Cardiac Regenerative Medicine." J Cardiovasc Pharmacol Ther **19**(4): 330-339.

Cardiovascular diseases remain the leading causes of morbidity and mortality in the developed world. Cellular-based cardiac regenerative therapy serves as a potential approach to treating cardiovascular diseases. Although various cellular types have been tested, induced pluripotent stem cells (iPSCs) are regarded as a promising cell source for therapy. In this review, we will highlight some of the advances in generating iPSCs and differentiation to cardiac cells. We will also discuss the progress in modeling cardiovascular diseases using iPSCs-derived cardiac cells. As we continue to make progress in iPSC and cardiac differentiation technology, we will come closer to the application of cardiac regenerative medicine.

Sultan, S., et al. (2018). "Stem Cell Smart Technology, where are we now and how far we have to go?" Vascular **26**(2): 216-228.

Approximately eight million people in the United States have peripheral arterial disease, which increases exponentially with age. There have been a plethora of available treatments including surgery, angioplasty, atherectomy, laser technology, and cell-based therapies. Cell-based therapies were developed in the hope of translating laboratory-based technology into clinical successes. However, clinical results have been disappointing. Infusion or injection for stem cell therapy is still considered experimental and investigational, and major questions on safety and durability have arisen. In no option patients, how can they be treated safely and successfully? In this article, we review contemporary practice for cell therapy, its pitfalls and breakthroughs, and look at the future ahead. We introduce a novel smart system for minimally invasive delivery of cell therapies, which exemplifies the next generation of endovascular solutions to stem cell technology and promises safety, efficacy, and reliability.

Sun, S., et al. (2017). "Bringing the age-related macular degeneration high-risk allele age-related maculopathy susceptibility 2 into focus with stem cell technology." Stem Cell Res Ther **8**(1): 135.

Age-related macular degeneration (AMD) is a major cause of blindness in older adults in developed countries. It is a multifactorial disease triggered by both environmental and genetic factors. High-temperature requirement A serine peptidase 1 (HTRA1) and age-related maculopathy susceptibility 2 (ARMS2) are two genes that are strongly associated with AMD. Because ARMS2 is an evolutionarily recent primate-specific gene and because the ARMS2/HTRA1 genes are positioned at a locus on chromosome 10q26 in a region with strong linkage disequilibrium, it is difficult to distinguish the functions of the individual genes. Therefore, it is necessary to bring these genes into focus. Patient-specific induced pluripotent stem cell (iPSC)-derived retinal pigment epithelium (RPE) provides direct access to a patient's genetics and allows for the possibility of identifying the initiating events of RPE-associated degenerative diseases. In this paper, a review of recent epidemiological studies of AMD is offered. An argument for a definite correlation between the ARMS2 gene and AMD is presented. A summary of the use of ARMS2 genotyping for medical treatment is provided. Several ARMS2-related genetic models based on such stem cells as iPSCs are introduced. The possibility of applying gene-editing techniques and stem-cell techniques to better explore the mechanisms of the ARMS2 high-risk allele, which will lead to important guidance for treatment, is also discussed.

Takasuna, K., et al. (2017). "Comprehensive in vitro cardiac safety assessment using human stem cell technology: Overview of CSAHi HEART initiative." J Pharmacol Toxicol Methods **83**: 42-54.

Recent increasing evidence suggests that the currently-used platforms in vitro IKr and APD, and/or in vivo QT assays are not fully predictive for TdP, and do not address potential arrhythmia (VT and/or VF) induced by diverse mechanisms of action. In addition, other cardiac safety liabilities such as functional dysfunction of excitation-contraction coupling (contractility) and structural damage (morphological damage to cardiomyocytes) are also major causes of drug attrition, but current in vitro assays do not cover all these liabilities. We organized the Consortium for Safety Assessment using Human iPS cells (CSAHi; http://csahi.org/en/), based on the Japan Pharmaceutical Manufacturers Association (JPMA), to verify the application of human iPS/ES cell-derived cardiomyocytes in drug safety evaluation. The main goal of the CSAHi HEART team has been to propose comprehensive screening strategies to predict a diverse range of cardiotoxicities by using recently introduced platforms (multi-electrode array (MEA), patch clamp, cellular impedance, motion field imaging [MFI], and Ca transient systems) while identifying the strengths and weaknesses of each. Our study shows that hiPS-CMs used in these platforms have pharmacological responses more relevant to humans in comparison with existent hERG, APD or Langendorff (MAPD/contraction) assays, and not only MEA but

also other methods such as impedance, MFI, and Ca transient systems would offer paradigm changes of platforms for predicting drug-induced QT risk and/or arrhythmia or contractile dysfunctions. Furthermore, we propose a potential multi-parametric platform in which field potential (MEA)-Ca transient-contraction (MFI) could be evaluated simultaneously as an ideal novel platform for predicting a diversity of cardiac toxicities, namely whole effects on the excitation-contraction cascade.

Temkin, A. M. and D. D. Spyropoulos (2014). "Induced pluripotent stem cell technology and aquatic animal species." Comp Biochem Physiol C Toxicol Pharmacol **163**: 3-13.

Aquatic animal species are the overall leaders in the scientific investigation of tough but important global health issues, including environmental toxicants and climate change. Historically, aquatic animal species also stand at the forefront of experimental biology, embryology and stem cell research. Over the past decade, intensive and high-powered investigations principally involving mouse and human cells have brought the generation and study of induced pluripotent stem cells (iPSCs) to a level that facilitates widespread use in a spectrum of species. A review of key features of these investigations is presented here as a primer for the use of iPSC technology to enhance ongoing aquatic animal species studies. iPSC and other cutting edge technologies create the potential to study individuals from "the wild" closer to the level of investigation applied to sophisticated inbred mouse models. A wide variety of surveys and hypothesis-driven investigations can be envisioned using this new capability, including comparisons of organism-specific development and exposure response and the testing of fundamental dogmas established using inbred mice. However, with these new capabilities, also come new criteria for rigorous baseline assessments and testing. Both the methods for inducing pluripotency and the source material can negatively impact iPSC quality and bourgeoning applications. Therefore, more rigorous strategies not required for inbred mouse models will have to be implemented to approach global health issues using individuals from "the wild" for aquatic animal species.

Teramura, T., et al. (2018). "Laser-assisted cell removing (LACR) technology contributes to the purification process of the undifferentiated cell fraction during pluripotent stem cell culture." Biochem Biophys Res Commun **503**(4): 3114-3120.

Purification of undifferentiated cells by removing differentiated parts is an essential step in pluripotent stem cell culture. This process has been traditionally performed manually using a fine glass capillary or plastic tip under a microscope, or by culturing in a selective medium supplemented with anti-differentiation inhibitors. However, there are several inevitable problems associated with these methods, such as contamination or biological side-effects. Here, we developed a laser-assisted cell removing (LACR) technology that enables precise, fast, and contact-less cell removal. Using LACR combined with computational image recognition/identification-discriminating technology, we achieved automatic cell purification (A-LACR). Practicability of A-LACR was evaluated by two demonstrations: selective removal of trophoblast stem (TS) cells from human iPS and TS cell co-cultures, and purification of undifferentiated iPS cells by targeting differentiated cells that spontaneously developed. Our results suggested that LACR technology is a novel approach for stem cell processing in regenerative medicine.

Terzic, A., et al. (2011). "Regenerative medicine: a reality of stem cell technology." Minn Med **94**(5): 44-47.

Regenerative medicine aims to restore homeostasis through a broad spectrum of strategies ranging from transplantation of donor organs to augmentation of innate healing processes. Its first clinical application emerged five decades ago when bone marrow-derived stem cells were used to replace defective progenitor cells. Since then, a variety of technological advances have expanded its scope. Most recently, the advent of natural or bioengineered stem cell products for tissue repair has inspired hope that the toughest obstacles in transplant medicine--the shortage of organs and organ rejection--might be overcome.This article describes the evolution of regenerative medicine and some of the ways it is being used in research and clinical practice.

Titmarsh, D. M., et al. (2014). "Concise review: microfluidic technology platforms: poised to accelerate development and translation of stem cell-derived therapies." Stem Cells Transl Med **3**(1): 81-90.

Stem cells are a powerful resource for producing a variety of cell types with utility in clinically associated applications, including preclinical drug screening and development, disease and developmental modeling, and regenerative medicine. Regardless of the type of stem cell, substantial barriers to clinical translation still exist and must be overcome to realize full clinical potential. These barriers span processes including cell isolation, expansion, and differentiation; purification, quality control, and therapeutic efficacy and safety; and the economic viability of bioprocesses for production of functional cell products. Microfluidic systems have been developed for a myriad of biological applications and have the intrinsic capability of controlling and interrogating the cellular microenvironment with unrivalled precision; therefore, they have particular relevance to overcoming such barriers to translation.

Development of microfluidic technologies increasingly utilizes stem cells, addresses stem cell-relevant biological phenomena, and aligns capabilities with translational challenges and goals. In this concise review, we describe how microfluidic technologies can contribute to the translation of stem cell research outcomes, and we provide an update on innovative research efforts in this area. This timely convergence of stem cell translational challenges and microfluidic capabilities means that there is now an opportunity for both disciplines to benefit from increased interaction.

Uchida, S., et al. (2016). "Treatment of spinal cord injury by an advanced cell transplantation technology using brain-derived neurotrophic factor-transfected mesenchymal stem cell spheroids." Biomaterials **109**: 1-11.

Curing spinal cord injury (SCI) is challenging because of the onset of multiple and irreversible pathological responses to such injury. To suppress the responses, we employed an advanced cell transplantation technology integrating three-dimensional spheroid cell transplantation with non-viral gene transfection using biodegradable polycations. Brain-derived neurotrophic factor (BDNF)-transfected mesenchymal stem cell (MSC) spheroids were transplanted at thoraces level (Th9) to SCI region in mice. BDNF-transfected MSC spheroid transplantation led to a significantly enhanced recovery of hindlimb motor function in acute phase of SCI with myelinated axons preserved at the SCI region, while use of either technology in isolation, BDNF transfection or spheroid culture, exerted only a limited therapeutic effect, demonstrating the importance of integrated approaches. Secretion of endogenous therapeutic proteins, such as anti-inflammatory factors, was greater in MSC spheroids than in monolayer culture MSCs, and these factors appeared to act synergistically alongside BDNF secretion in SCI treatment. This study forms a basis for cell therapy regulating complex pathophysiologic processes.

Valenti, M. T., et al. (2019). "CRISPR/Cas system: An emerging technology in stem cell research." World J Stem Cells **11**(11): 937-956.

The identification of new and even more precise technologies for modifying and manipulating the genome has been a challenge since the discovery of the DNA double helix. The ability to modify selectively specific genes provides a powerful tool for characterizing gene functions, performing gene therapy, correcting specific genetic mutations, eradicating diseases, engineering cells and organisms to achieve new and different functions and obtaining transgenic animals as models for studying specific diseases. Clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 technology has recently revolutionized genome engineering. The application of this new technology to stem cell research allows disease models to be developed to explore new therapeutic tools. The possibility of translating new systems of molecular knowledge to clinical research is particularly appealing for addressing degenerative diseases. In this review, we describe several applications of CRISPR/Cas9 to stem cells related to degenerative diseases. In addition, we address the challenges and future perspectives regarding the use of CRISPR/Cas9 as an important technology in the medical sciences.

Vallazza, B., et al. (2015). "Recombinant messenger RNA technology and its application in cancer immunotherapy, transcript replacement therapies, pluripotent stem cell induction, and beyond." Wiley Interdiscip Rev RNA **6**(5): 471-499.

In recent years, the interest in using messenger RNA (mRNA) as a therapeutic means to tackle different diseases has enormously increased. This holds true not only for numerous preclinical studies, but mRNA has also entered the clinic to fight cancer. The advantages of using mRNA compared to DNA were recognized very early on, e.g., the lack of risk for genomic integration, or the expression of the encoded protein in the cytoplasm without the need to cross the nuclear membrane. However, it was generally assumed that mRNA is just not stable enough to give rise to sufficient expression of the encoded protein. Yet, an initially small group of mRNA aficionados could demonstrate that the stability of mRNA and the efficiency, by which the encoded protein is translated, can be significantly increased by selecting the right set of cis-acting structural elements (including the 5'-cap, 5'- and 3'-untranslated regions, poly(A)-tail, and modified building blocks). In parallel, significant advances in RNA packaging and delivery have been made, extending the potential for this molecule. This paved the way for further work to prove mRNA as a promising therapeutic for multiple diseases. Here, we review the developments to optimize mRNA regarding stability, translational efficiency, and immune-modulating properties to enhance its functionality and efficacy as a therapeutic. Furthermore, we summarize the current status of preclinical and clinical studies that use mRNA for cancer immunotherapy, for the expression of functional proteins as so-called transcript (or protein) replacement therapy, as well as for induction of pluripotent stem cells.

Van der Jeught, M., et al. (2015). "The post-inner cell mass intermediate: implications for stem cell biology and assisted reproductive technology." Hum Reprod Update **21**(5): 616-626.

BACKGROUND: Until recently, the temporal events that precede the generation of pluripotent embryonic stem cells (ESCs) and their equivalence with specific developmental stages in vivo was poorly

understood. Our group has discovered the existence of a transient epiblast-like structure, coined the post-inner cell mass (ICM) intermediate or PICMI, that emerges before human ESC (hESCs) are established, which supports their primed nature (i.e. already showing some predispositions towards certain cell types) of pluripotency. METHODS: The PICMI results from the progressive epithelialization of the ICM and it expresses a mixture of early and late epiblast markers, as well as some primordial germ cell markers. The PICMI is a closer progenitor of hESCs than the ICM and it can be seen as the first proof of why all existing hESCs, until recently, display a primed state of pluripotency. RESULTS: Even though the pluripotent characteristics of ESCs differ from mouse (naive) to human (primed), it has recently been shown in mice that a similar process of self-organization at the transition from ICM to (naive) mouse ESCs (mESCs) transforms the amorphous ICM into a rosette of polarized epiblast cells, a mouse PICMI. The transient PICMI stage is therefore at the origin of both mESCs and hESCs. In addition, several groups have now reported the conversion from primed to the naive (mESCs-like) hESCs, broadening the pluripotency spectrum and opening new opportunities for the use of pluripotent stem cells. CONCLUSIONS: In this review, we discuss the recent discoveries of mouse and human transient states from ICM to ESCs and their relation towards the state of pluripotency in the eventual stem cells, being naive or primed. We will now further investigate how these intermediate and/or different pluripotent stages may impact the use of human stem cells in regenerative medicine and assisted reproductive technology.

Verlinsky, Y., et al. (2006). "Repository of human embryonic stem cell lines and development of individual specific lines using stembrid technology." Reprod Biomed Online **13**(4): 547-550.

A human embryonic stem cell (HESC) line repository has been established, containing HESC lines with normal and abnormal genotypes, providing the source for studying the primary mechanisms of genetic disorders at the cellular level. Because the outcome of HESC transplantation treatment depends on access to human leukocyte antigen identical stem cells, the development of individual specific HESC was initiated, using the original stembrid technology, which is based on the hybridization of adult somatic cells with cytoplast of HESC lines. The data presented here demonstrate feasibility of this approach in the future development of HESC transplantation treatment of genetic and acquired disorders. The established HESC repository presently contains 166 HESC lines, including 127 with normal genotype and 39 with genetic and chromosomal disorders.

Vissers, C., et al. (2019). "Nanoparticle technology and stem cell therapy team up against neurodegenerative disorders." Adv Drug Deliv Rev **148**: 239-251.

The convergence of nanoparticles and stem cell therapy holds great promise for the study, diagnosis, and treatment of neurodegenerative disorders. Researchers aim to harness the power of nanoparticles to regulate cellular microenvironment, improve the efficiency of cell and drug delivery to the brain, and enhance the survival of stem cell transplants. Understanding the various properties of different nanoparticles is key to applying them to clinical therapies; the many distinct types of nanoparticles offer unique capacities for medical imaging, diagnosis, and treatment of neurodegeneration disorders. In this review we introduce the biology of Alzheimer's, Parkinson's Disease, and amyotrophic lateral sclerosis, and discuss the potentials and shortcomings of metal, silica, lipid-based, polymeric, and hydrogel nanoparticles for diagnosis and treatment of neurodegenerative disorders. We then provide an overview of current strategies in stem cell therapies and how they can be combined with nanotechnology to improve clinical outcomes.

Vyas, V. and P. D. Lambiase (2013). "The investigation of sudden arrhythmic death syndrome (SADS)-the current approach to family screening and the future role of genomics and stem cell technology." Front Physiol **4**: 199.

SADS is defined as sudden death under the age of 40 years old in the absence of structural heart disease. Family screening studies are able to identify a cause in up to 50% of cases-most commonly long QT syndrome (LQTS), Brugada and early repolarization syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT) using standard clinical screening investigations including pharmacological challenge testing. These diagnoses may be supported by genetic testing which can aid cascade screening and may help guide management. In the current era it is possible to undertake molecular autopsy provided suitable samples of DNA can be obtained from the proband. With the evolution of rapid sequencing techniques it is possible to sequence the whole exome for candidate genes. This major advance offers the opportunity to identify novel causes of lethal arrhythmia but also poses the challenge of managing the volume of data generated and evaluating variants of unknown significance (VUS). The emergence of induced pluripotent stem cell technology could enable evaluation of the electrophysiological relevance of specific ion channel mutations in the proband or their relatives and will potentially enable screening of idiopathic ventricular fibrillation survivors combining genetic and electrophysiological studies in derived myocytes. This also could facilitate the assessment of

personalized preventative pharmacological therapies. This review will evaluate the current screening strategies in SADS families, the role of molecular autopsy and genetic testing and the potential applications of molecular and cellular diagnostic strategies on the horizon.

Wakayama, S., et al. (2005). "Propagation of an infertile hermaphrodite mouse lacking germ cells by using nuclear transfer and embryonic stem cell technology." Proc Natl Acad Sci U S A **102**(1): 29-33.

Animals generated by systematic mutagenesis and routine breeding are often infertile because they lack germ cells, and maintenance of such lines of animals has been impossible. We found a hermaphrodite infertile mouse in our colony, a genetic male with an abnormal Y chromosome lacking developing germ cells. We tried to clone this mouse by conventional nuclear transfer but without success. ES cells produced from blastocysts, which had been cloned by using somatic cell nuclear transfer (ntES cells) from this mouse, were also unable to produce offspring when injected into enucleated oocytes. Although we were able to produce two chimeric offspring using these ntES cells by tetraploid complementation, they were infertile, because they also lacked developing germ cells. However, when such ntES cells were injected into normal diploid blastocysts, many chimeric offspring were produced. One such male offspring transmitted hermaphrodite mouse genes to fertile daughters via X chromosome-bearing sperm. Thus, ntES cells were used to propagate offspring from infertile mice lacking germ cells.

Wallner, K., et al. (2018). "Stem cells and beta cell replacement therapy: a prospective health technology assessment study." BMC Endocr Disord **18**(1): 6.

BACKGROUND: Although current beta cell replacement therapy is effective in stabilizing glycemic control in highly selected patients with refractory type 1 diabetes, many hurdles are inherent to this and other donor-based transplantation methods. One solution could be moving to stem cell-derived transplant tissue. This study investigates a novel stem cell-derived graft and implant technology and explores the circumstances of its cost-effectiveness compared to intensive insulin therapy. METHODS: We used a manufacturing optimization model based on work by Simaria et al. to model cost of the stem cell-based transplant doses and integrated its results into a cost-effectiveness model of diabetes treatments. The disease model simulated marginal differences in clinical effects and costs between the new technology and our comparator intensive insulin therapy. The form of beta cell replacement therapy was as a series of retrievable subcutaneous implant devices which protect the enclosed pancreatic progenitors cells from the immune system. This approach was presumed to be as effective as state of the art islet transplantation, aside from immunosuppression drawbacks. We investigated two different cell culture methods and several production and delivery scenarios. RESULTS: We found the likely range of treatment costs for this form of graft tissue for beta cell replacement therapy. Additionally our results show this technology could be cost-effective compared to intensive insulin therapy, at a willingness-to-pay threshold of $100,000 per quality-adjusted life year. However, results also indicate that mass production has by far the best chance of providing affordable graft tissue, while overall there seems to be considerable room for cost reductions. CONCLUSIONS: Such a technology can improve treatment access and quality of life for patients through increased graft supply and protection. Stem cell-based implants can be a feasible way of treating a wide range of patients with type 1 diabetes.

Wang, Z., et al. (2020). "Generation of a MCPH1 knockout human embryonic stem cell line by CRISPR/Cas9 technology." Stem Cell Res **49**: 102105.

Human MCPH1 (Microcephalin 1) encodes a DNA damage response protein. Mutations in this gene have been associated with Primary Autosomal Recessive Microcephaly and premature chromosome condensation syndrome. To further understand the roles of MCPH1 in neural differentiation and brain development, here we generated a MCPH1 knockout human embryonic stem cell line by CRISPR/Cas9 genome editing technology. This cell line maintained a normal karyotype and typical undifferentiated state in terms of morphology, pluripotent gene expression, and had differentiation potential in vitro. This cell line provides a good resource to study the role of MCPH1 gene in neurogenesis and regulation of the size of the cerebral cortex in vitro.

Watson, L. M., et al. (2015). "Induced pluripotent stem cell technology for modelling and therapy of cerebellar ataxia." Open Biol **5**(7): 150056.

Induced pluripotent stem cell (iPSC) technology has emerged as an important tool in understanding, and potentially reversing, disease pathology. This is particularly true in the case of neurodegenerative diseases, in which the affected cell types are not readily accessible for study. Since the first descriptions of iPSC-based disease modelling, considerable advances have been made in understanding the aetiology and progression of a diverse array of neurodegenerative conditions, including Parkinson's disease and Alzheimer's disease. To date, however, relatively few studies have succeeded in using iPSCs to model the neurodegeneration observed in cerebellar ataxia. Given the distinct neurodevelopmental phenotypes associated with certain types of ataxia, iPSC-based models are likely to provide significant insights, not only into

disease progression, but also to the development of early-intervention therapies. In this review, we describe the existing iPSC-based disease models of this heterogeneous group of conditions and explore the challenges associated with generating cerebellar neurons from iPSCs, which have thus far hindered the expansion of this research.

Wu, C. L. and Y. M. Zhang (2014). "[Progress and potential applications of induced pluripotent stem cell technology]." Zhongguo Shi Yan Xue Ye Xue Za Zhi **22**(4): 883-888.

Differentiated somatic cells can be reprogrammed to a pluripotent state through ectopic expression of specific transcription factors. These reprogrammed cells, which were designated as induced pluripotent stem (iPS) cells, are detected to exhibit unlimited self-renewal capacity and pluripotency. This breakthrough in stem cell research provides a powerful and novel tool for the studies on pathogenesis of diseases, reprogramming mechanism and development of new therapies. For this reason, the iPSC technology has currently become one of the hot topics in stem cells research. Recently, major progress in this field has been achieved: initially, researchers succeeded in inducing the reprogramming of mouse fibroblasts by retroviral transduction of four specific transcription factors; in succession, the accelerated development of iPSC technology by employing non-integrating viral vectors, non-viral vectors or removing the introduced foreign genes via gene knock-out has ensured the yields of much safer iPSC; meanwhile, some researches discovered the proofs that a number of micro molecular compounds were potent in accelerating the cellular reprogramming. For a prospect, iPSC are highly promising for regenerative medicine, disease modeling and drug screening. In this review, the recent progress in the generation of iPSC, prospects of their possible clinical applications and problems in the iPSC research are summarized and discussed.

Xu, C., et al. (2020). "Generation of a DAPK1 knockout first (conditional ready) human embryonic stem cell line (ZSSYe001-A) by CRISPR-Cas9 technology." Stem Cell Res **43**: 101693.

Death-associated protein kinase 1 (DAPK1) is a Ca(2+)/calmodulin regulated Ser/Thr kinase involved in various cellular processes including cell death, autophagy and inflammation. Its dysregulation has been linked to tumour metastasis, anti-viral responses, Alzheimer's disease and other neurological disorders. To further investigate the role of DAPK1 in these processes, we generated a DAPK1 knockout first (conditional ready) human embryonic stem (hES) cell line in which the endogenous DAPK1 can be easily restored with expression of FLPe. This cell line provides an ideal model to study the role of DAPK1 in human development and various pathologies related to DAPK1 dysregulation in vitro.

Xue, Y., et al. (2019). "Establishment of an ectodermal dysplasia related gene EDA Knockout human embryonic stem cell line (WAe001-A-22) by CRISPR-Cas9 technology." Stem Cell Res **34**: 101379.

EDA is a gene located at Xq13.1. It encodes different isoforms of tumor necrosis factor (TNF) superfamily member ectodysplasin A. Ectodysplasin A is a transmembrane protein which can be cleaved to form a secreted form and interact with EDA receptor to mediate the development of ectoderm. Mutations of the EDA gene are related to ectodermal dysplasia and tooth agenesis. Here, we report the establishment of the EDA gene knockout human embryonic stem (hES) cell line by CRISPR-Cas9 technology. This cell line provides good materials for further studies of the roles ectodysplasin A plays in ectoderm differentiation and tooth development.

Xue, Y., et al. (2017). "Establishment of a congenital tooth agenesis related gene MSX1 knockout human embryonic stem cell lines by CRISPR-Cas9 technology." Stem Cell Res **24**: 151-154.

Human MSX1 gene is mapped to chromosome 4 and encodes a 303aa homeobox protein MSX1. MSX1 expression appears during early tooth development of vertebrate embryogenesis. Mutations in this protein are related to human tooth anomalie, cleft lip and palate and congenital ectodermal dysplasia syndrome. Most of the confirmed pathogenic mutations are located in exon2 encoded homeobox domain. Here, we report the establishment of MSX1 gene knockout human embryonic stem (hES) cell lines by CRISPR-Cas9 technology. These cell lines provide good materials for further studies of the roles MSX1 plays in human tooth development and congenital tooth agenesis.

Yamada, Y., et al. (2010). "A feasibility of useful cell-based therapy by bone regeneration with deciduous tooth stem cells, dental pulp stem cells, or bone-marrow-derived mesenchymal stem cells for clinical study using tissue engineering technology." Tissue Eng Part A **16**(6): 1891-1900.

This study investigated the effect of bone regeneration with dental pulp stem cells (DPSCs), deciduous tooth stem cells (DTSCs), or bone-marrow-derived mesenchymal stem cells (BMMSCs) for clinical study on hydroxyapatite-coated osseointegrated dental implants, using tissue engineering technology. In vitro, human DPSCs and DTSCs expressed STRO-1, CD13, CD29, CD 44, CD73, and osteogenic marker genes such as alkaline phosphatase, Runx2, and osteocalcin. In vivo, prepared bone defect model was implanted using graft materials as follows: platelet-rich plasma (PRP), PRP and canine BMMSCs (cBMMSCs), PRP and canine DPSCs (cDPSCs), PRP and puppy

DTSCs (pDTSCs), and control (defect only). After 8 weeks, the dental implants were installed, and 16 weeks later the sections were evaluated histologically and histometrically. The cBMMSCs/PRP, cDPSCs/PRP, and pDTSCs/PRP groups had well-formed mature bone and neovascularization. Histometrically, the bone-implant contact was significantly different between the cBMMSCs/PRP, cDPSCs/PRP, pDTSCs/PRP groups, and the control and PRP groups ($p < 0.01$). These results demonstrated that these stem cells with PRP have the ability to form bone, and this bone formation activity might be useful for osseointegrated hydroxyapatite-coated dental implants with good levels of bone-implant contact.

Yashiro, Y. (2011). "[Stem cell research and science and technology policy in Japan]." Nihon Rinsho **69**(12): 2251-2256.

In this paper I review the present condition of the regeneration medicine research using pluripotency and a somatic stem cell, and I describe the subject of the science and technology policy in Japan towards realization of regeneration medicine. The Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) supported research promotion by the prompt action in 2007 when establishment of the iPS cell was reported by Shinya Yamanaka. Although the hospitable support of the Japanese government to an iPS cell is continued still now, there are some problems in respect of the support to other stem cell researches, and industrialization of regeneration medicine. In order to win a place in highly competitive area of investigation, MEXT needs to change policy so that funds may be widely supplied also to stem cell researches other than iPS cell research.

Yasuda, K. (2010). "[On-chip Cellomics technology for drug screening system using cardiomyocyte cells from human stem cell]." Yakugaku Zasshi **130**(4): 545-557.

Limitation of conventional human Ether-a-go-go Related Gene (hERG) assay and QT prolongation testing for accurate prediction of Torsades de Pointes (TdP) by compounds showed us the necessity of a new approach to evaluate global cardiac safety. As one of the advanced applications of an on-chip cellomics system, on-chip cardiomyocyte cell network-based re-entry model assay has the potential to measure the TdP probability as a pre-clinical test for cardiac safety. This system also can estimate the heart pressure, Na, K, and Ca ion channel conditions using a single cell-based optical/electrical measurement system. In this presentation, we present the system setup and then its possible application for drug discovery and toxicology.

Yousef, M. A. A., et al. (2017). "Long-term Radiological and Clinical Outcomes After Using Bone Marrow Mesenchymal Stem Cells Concentrate Obtained With Selective Retention Cell Technology in Posterolateral Spinal Fusion." Spine (Phila Pa 1976) **42**(24): 1871-1879.

STUDY DESIGN: Retrospective study. OBJECTIVE: The aim of this study was to evaluate the long-term clinical and radiological outcomes of the use of bone marrow mesenchymal stem cell concentrate obtained with selective cell retention technology using Cellect with a particular collagen scaffold, Healos for posterolateral spinal fusion. SUMMARY OF BACKGROUND DATA: With the increasing rate of spinal fusion, the problem of pseudarthrosis, which contributes to recurrent pain with patient disability, is considered to be the most common cause of revision lumbar spine surgery. Intensive research is being carried out to develop an alternative source of bone grafting and improve the spinal fusion rate. METHODS: A retrospective review of hospital records was performed. Identified patients were contacted to have a clinical and radiological evaluation follow-up. Clinical outcome was evaluated using visual analog scales for the back pain (VAS), Oswestry Disability Index (ODI) scores, and quality of life (EQ-5D) questionnaire. Radiological outcome was evaluated by performing dynamic flexion/extension lateral views and calculation of segmental Cobb angle. Any implant-associated complication was reported. Computed tomography (CT) scans were also performed. RESULTS: Twenty-one patients were included and all patients achieved successful fusion. The mean difference of the segmental Cobb angle was 0.48 degrees (range 0.3 degrees -0.7 degrees). Computed tomography scans showed solid bilateral fusion with bridging bone (Grade I) in all patients, but solid unilateral fusion with bridging bone (Grade II) was detected for one patient at one level. Patients started to resume working activities within a mean period of 3.5 months. The VAS score for the residual back pain was 4.1 +/- 2.1, whereas the ODI was 10.5 +/- 5.6 points, and the mean disability index was 21.1%. CONCLUSION: The use of bone marrow mesenchymal stem cell concentrate obtained with selective cell retention technology could be considered as an effective means for augmenting spinal fusion. LEVEL OF EVIDENCE: 3.

Yu, Y. (2018). "Application of Stem Cell Technology in Antiaging and Aging-Related Diseases." Adv Exp Med Biol **1086**: 255-265.

Stem cells are one kind of cells that have the potential of proliferation and differentiation. The human beings are originated from a totipotential stem cell-fertilized egg. After birth, the proliferation and differentiation of stem cells contribute to the development and maturation of individual tissues and organs. After maturation, aging is a phases of the life process, the stem cells within the individual's tissues ensure the metabolism of different cells and tissues,

such as the hematopoietic stem cells in the bone marrow, which ensure there are still enough red blood cells (RBCs) being responsible for the mission of transporting oxygen after a single RBC has completed its 120-day physiological life cycle. After pathological damage and necrosis occurring on the intestinal epithelial cells or tubular epithelial cells, there will be regenerative epithelial cells continuing to maintain the integrity of the structure and function of the intestine and renal tubules. The role of stem cells in the regeneration and repair of tissues and organs is not only because of the ability of proliferation and differentiation of stem cells but also of the secretion function of stem cells, which secrete various growth factors and cytokines to regulate the tissue microenvironment. For example, mesenchymal stem cells derived from bone marrow are important regulators in bone marrow hematopoietic stem cell niche. Mesenchymal stem cells maintain the "stemness" of hematopoietic stem cells by secreting various cytokines.Aging is a phases of the life process, and all creatures obey this rule of nature. Different organs of the body have different time of entering into aging. Aging is reflected in structural changes and reduced function. Among them, the reduction of regeneration and repair capacity is the main feature of aging. As we age, the aging of stem cells in human tissues is a major cause of the decline in tissue regeneration capacity. Therefore, the elderly's ability of regenerate and repair can be improved by application of advance stem cell technology. It can delay the aging process and treat aged diseases (showed in Fig. 16.1).

Zhang, B. Y., et al. (2018). "Evaluation of the Curative Effect of Umbilical Cord Mesenchymal Stem Cell Therapy for Knee Arthritis in Dogs Using Imaging Technology." Stem Cells Int **2018**: 1983025.

Objective: The aim of this study was to assess the efficacy of canine umbilical cord mesenchymal stem cells (UC-MSCs) on the treatment of knee osteoarthritis in dogs. Methods: Eight dogs were evenly assigned to two groups. The canine model of knee osteoarthritis was established by surgical manipulation of knee articular cartilage on these eight dogs. UC-MSCs were isolated from umbilical cord Wharton's jelly by 0.1% type collagenase I and identified by immunofluorescence staining and adipogenic and osteogenic differentiation in vitro. A suspension of allogeneic UC-MSCs (1 x 10(6)) and an equal amount of physiological saline was injected into the cavitas articularis in the treated and untreated control groups, respectively, on days 1 and 3 posttreatment. The structure of the canine knee joint was observed by magnetic resonance imaging (MRI), B-mode ultrasonography, and X-ray imaging at the 3rd, 7th, 14th, and 28th days after treatment. Concurrently, the levels of IL-6, IL-7, and TNF-alpha in the blood of the examined dogs were measured. Moreover, the recovery of cartilage and patella surface in the treated group and untreated group was compared using a scanning electron microscope (SEM) after a 35-day treatment. Results: Results revealed that the isolated cells were UC-MSCs, because they were positive for CD44 and negative for CD34 surface markers, and the cells were differentiated into adipocytes and osteoblasts. Imaging technology showed that as treatment time increased, the high signal in the MRI T2-weighted images decreased, the echo-free space in B ultrasonography images disappeared basically, and the continuous linear hypoechoic region at the trochlear sulcus thickened. On X-ray images, the serrate defect at the ventral cortex of the patella improved, and the low-density gap of the ventral patella and trochlear crest gradually increased in the treated group. On the contrary, the high signal in the MRI T2-weighted images and the echo-free space in B ultrasonography images still increased after a 14-day treatment in the untreated control group, and the linear hypoechoic region was discontinuous. On the X-ray images, there was no improvement in the serrate defect of the ventral cortex of the patella. Results for inflammatory factors showed that the blood levels of IL-6, IL-7, and TNF-alpha of the untreated control group were significantly higher than those of the treated group ($P < 0.05$) 7-14 days posttreatment. The result of SEM showed that the cartilage neogenesis in the treated group had visible neonatal tissue and more irregular arrangement of new tissue fibers than that of the untreated control group. Furthermore, more vacuoles but without collagen fibers were observed in the cartilage of the untreated control group, and the thickness of the neogenetic cartilage in the treated group (65.13 +/- 5.29, 65.30 +/- 5.83) and the untreated control group (34.27 +/- 5.42) showed a significant difference ($P < 0.01$). Conclusion: Significantly higher improvement in cartilage neogenesis and recovery was observed in the treated group compared to the untreated control group. The joint fluid and the inflammatory response in the treated group decreased. Moreover, improved recovery in the neogenetic cartilage, damaged skin fascia, and muscle tissue around the joints was more significant in the treated group than in the untreated control group. In conclusion, canine UC-MSCs promote the repair of cartilage and patella injury in osteoarthritis, improve the healing of the surrounding tissues, and reduce the inflammatory response.

Zhang, F., et al. (2011). "Prospects of induced pluripotent stem cell technology in regenerative medicine." Tissue Eng Part B Rev **17**(2): 115-124.

Induced pluripotent stem (iPS) cells are derived from adult somatic cells via reprogramming with ectopic expression of four transcription factors

(Oct3/4, Sox2, c-Myc and Klf4; or, Oct3/4, Sox2, Nanog, and Lin28), by which the resultant cells regain pluripotency, namely, the capability exclusively possessed by some embryonic cells to differentiate into any cell lineage under proper conditions. Given the ease in cell sourcing and a waiver of ethical opponency, iPS cells excel embryonic pluripotent cells in the practice of drug discovery and regenerative medicine. With an ex vivo practice in regenerative medicine, many problems involved in conventional medicine dosing, such as immune rejection, could be potentially circumvented. In this article, we briefly summarize the fundamentals and status quo of iPS-related applications, and emphasize the prospects of iPS technology in regenerative medicine.

Zhang, J., et al. (2018). "Generation of a human induced pluripotent stem cell line from urinary cells of a patient with primary congenital glaucoma using integration free Sendai technology." Stem Cell Res **29**: 162-165.

We have generated a human induced pluripotent stem cell (iPSC) line derived from urinary cells of a 10years old patient with primary congenital glaucoma (PCG). The cells were reprogrammed with the human OSKM transcription factors using the Sendai-virus delivery system and shown to have full differentiation potential. The line is available and registered in the human pluripotent stem cell registry as BIOi001-A.

Zheng, G., et al. (2020). "Recent advances of single-cell RNA sequencing technology in mesenchymal stem cell research." World J Stem Cells **12**(6): 438-447.

Mesenchymal stem cells (MSCs) are multipotent stromal cells with great potential for clinical applications. However, little is known about their cell heterogeneity at a single-cell resolution, which severely impedes the development of MSC therapy. In this review, we focus on advances in the identification of novel surface markers and functional subpopulations of MSCs made by single-cell RNA sequencing and discuss their participation in the pathophysiology of stem cells and related diseases. The challenges and future directions of single-cell RNA sequencing in MSCs are also addressed in this review.

Zhong, C. and J. Li (2017). "Efficient Generation of Gene-Modified Mice by Haploid Embryonic Stem Cell-Mediated Semi-cloned Technology." Methods Mol Biol **1498**: 121-133.

Haploid embryonic stem cells can be derived from androgenetic embryos produced by injection of sperm into enucleated oocytes or by removal of the female pronucleus from zygotes. These cells, termed AG-haESCs, can be used in place of sperm to produce the so-called semi-cloned (SC) mice. Importantly, AG-haESCs carrying H19-DMR and IG-DMR knockouts (DKO-AG-haESCs) can efficiently and stably support the generation of SC mice via intracytoplasmic AG-haESCs injection (ICAHCI), which provides a new route to obtain genetically modified mice. In this chapter, we describe the procedures for AG-haESCs culturing, enrichment of haploid cells by FACS, genomic manipulation in DKO-AG-haESCs by CRISPR/Cas9 and generation of live SC mice with gene-modified DKO-AG-haESCs.

Zhou, H. and S. Ding (2010). "Evolution of induced pluripotent stem cell technology." Curr Opin Hematol **17**(4): 276-280.

PURPOSE OF REVIEW: Induced pluripotent stem cell (iPSC) technology, which uses defined transcription factors to reprogram somatic cells to become pluripotent cells, offers a significant technical simplicity and enables generation of patient-specific pluripotent stem cells with reduced ethical concerns. This review will focus on recent progresses in understanding of iPSCs and improved methods of generating iPSCs. RECENT FINDINGS: Whereas iPSCs generated from a variety of cell sources were found to be nearly identical functionally to embryonic stem cells, some differences were also identified and remain to be characterized. Meanwhile, new methods of generating iPSCs with minimal or no exogenous genetic modifications to cells have advanced rapidly. SUMMARY: iPSC technology provides unprecedented opportunities in biomedical research and regenerative medicine. However, there remain a great deal to learn about iPSC safety, the reprogramming mechanisms, and better ways to direct a specific reprogramming process. The iPSC field will flourish on its mechanistic studies, iPSC-based disease modeling, and identification of new small molecules that modulate reprogramming.

Zhou, S., et al. (2020). "The Fabrication and Evaluation of a Potential Biomaterial Produced with Stem Cell Sheet Technology for Future Regenerative Medicine." Stem Cells Int **2020**: 9567362.

To date, the decellularized scaffold has been widely explored as a source of biological scaffolds for regenerative medicine. However, the acellular matrix derived from natural tissues and organs has a lot of defects, including the limited amount of autogenous tissue and surgical complication such as risk of blood loss, wound infection, pain, shock, and functional damage in the donor part of the body. In this study, we prepared acellular matrix using adipose-derived stem cell (ADSC) sheets and evaluate the cellular compatibility and immunoreactivity. The ADSC sheets were fabricated and subsequently decellularized using repeated freeze-thaw, Triton X-100 and SDS decellularization. Oral mucosal epithelial cells were seeded onto the decellularized ADSC sheets to evaluate the cell replantation ability, and silk fibroin was used as the control. Then, acellular matrix was transplanted

onto subcutaneous tissue for 1 week or 3 weeks; H&E staining and immunohistochemical analysis of CD68 expression and quantitative real-time PCR (qPCR) were performed to evaluate the immunogenicity and biocompatibility. The ADSC sheet-derived ECM scaffolds preserved the three-dimensional architecture of ECM and retained the cytokines by Triton X-100 decellularization protocols. Compared with silk fibroin in vitro, the oral mucosal epithelial cells survived better on the decellularized ADSC sheets with an intact and consecutive epidermal cellular layer. Compared with porcine small intestinal submucosa (SIS) in vivo, the homogeneous decellularized ADSC sheets had less monocyte-macrophage infiltrating in vivo implantation. During 3 weeks after transplantation, the mRNA expression of cytokines, such as IL-4/IL-10, was obviously higher in decellularized ADSC sheets than that of porcine SIS. A Triton X-100 method can achieve effective cell removal, retain major ECM components, and preserve the ultrastructure of ADSC sheets. The decellularized ADSC sheets possess good recellularization capacity and excellent biocompatibility. This study demonstrated the potential suitability of utilizing acellular matrix from ADSC sheets for soft tissue regeneration and repair.

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

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