We are IntechOpen, the world’s leading publisher of Open Access books. Built by scientists, for scientists.

5,700 Open access books available
139,000 International authors and editors
175M Downloads

154 Countries delivered to
TOP 1% Our authors are among the most cited scientists
12.2% Contributors from top 500 universities

We are IntechOpen, the world’s leading publisher of Open Access books.
Built by scientists, for scientists.

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected. For more information visit www.intechopen.com
1. Introduction

1.1 Stem cell (SC) therapy is not a new concept. In the aftermath of the bombings of Hiroshima and Nagasaki in 1945, researchers discovered that bone marrow transplanted into irradiated mice produced hematopoiesis (Lorenz, 1951). Hematopoietic stem cells (HSCs) were first identified in 1961 and their ability to migrate and differentiate into multiple cell types was documented (Till, 1961).

Distinct SC types have been established from embryos and identified in the fetal tissues and umbilical cord blood (UCB) as well as in specific niches in many adult mammalian tissues and organs such as bone marrow (BM), brain, skin, eyes, heart, kidneys, lungs, gastrointestinal tract, pancreas, liver, breast, ovaries, prostate and testis (Siqueira, 2010). All SCs are undifferentiated cells that exhibit unlimited self-renewal and can generate multiple cell lineages or more restricted progenitor populations which can contribute to tissue homeostasis by replenishing the cells or to tissue regeneration after injury (Lanza, 2004; Mimeault, 2006).

Several investigations (Mimeault, 2004; Ortiz-Gonzalez, 2004; Trounson, 2006) have been carried out with isolated embryonic, fetal and adult SCs in a well-defined culture microenvironment to define the sequential steps and intracellular pathways that are involved in their differentiation into the specific cell lineages. More particularly, different methods have been developed for the in vitro culture of SCs, including the use of cell feeder layers, cell-free conditions, extracellular matrix molecules such as collagen, gelatin and laminin and diverse growth factors and cytokines (Mimeault, 2004; Siqueira, 2010).

1.2 Overview of the retinal anatomy

The retina is approximately 0.5 mm thick and lines the back of the eye. The optic nerve contains ganglion cell axons running to the brain and incoming blood vessels that open into the retina to vascularize the retinal layers and neurons. A radial section of a portion of the retina reveals that the ganglion cells (the output neurons of the retina) lie innermost in the retina closest to the lens and front of the eye, and the photosensors (the rods and cones) lie outermost in the retina against the retinal-pigment epithelium (RPE) and choroid. Light must, therefore, travel through the thickness of the retina before striking and activating the rods and cones. Subsequently, the absorption of photons by the visual pigment of the photoreceptors is translated first into a biochemical message and then into an electrical
message that stimulates all of the succeeding neurons of the retina. The retinal message concerning the photic input and some preliminary organization of the visual image into several forms of sensation are transmitted to the brain from the spiking discharge pattern of the ganglion cells (Kolb, 2005).

RPE cells support photoreceptor survival and are involved in, for example, ion and nutrient transport, formation of the blood-retina barrier and light absorption. They are also responsible for phagocytosis of the photoreceptor outer segments, which is important for the renewal of photoreceptor membranes. Interestingly, it has been demonstrated in a chicken model that, RPE in the postnatal stage of life is similar to that found in the embryonic retina with regard to specific gene expression.

Furthermore, the generation and ex vivo expansion of RPE from human embryonic stem cells (hESCs) has been extensively studied and characterized. Moreover, hESC-derived RPE cells have been demonstrated to be functional in ex vivo conditions. More recently, the in vitro differentiation of RPE and photoreceptors from human induced pluripotent stem (iPS) cell cultures provide another potential tool for transplantation purposes and additionally enables avoidance of host immune reactions (Machalinska, 2009).

1.3 Retinal diseases

Age-related macular degeneration (AMD), glaucoma and diabetic retinopathy are the three most common causes of visual impairment and legal blindness in developed countries (Bunce, 2006). One common denominator of these conditions is progressive loss of the neural cells of the eye [photoreceptors, interneurons and retinal ganglion cells (RGC)] and essential supporting cells such as the RPE. Retinal dystrophies [retinitis pigmentosa (RP), Stargardt’s disease, Best disease, Leber congenital amaurosis, etc.] all evolve with early loss of photoreceptors and subsequent loss of RGC. Recent years have seen enormous progress in the treatment options that stop the progression of AMD from a neovascular state to fibrosis, that slow down the progression of glaucoma by reducing intraocular pressure, and that prevent progression of diabetic retinopathy by optimizing glycemic control and treat retinal neovascularization early (Chakravarthy, 2010; Maier, 2005; O’Doherty, 2008; Mohamed, 2007). However, irreversible visual loss still occurs in a significant proportion of cases. Research is aimed at developing novel treatments using neuroprotective and regenerative strategies.

SCs can potentially be used for both neuroprotection and cell replacement. Intravitreal delivery of neurotrophic factors slows down photoreceptor degeneration in rodent models of RP, RGC loss in glaucoma models and optic nerve and optic tract trauma, but the effect may be temporary. Slow-release preparations and gene therapy approaches used to induce retinal cells to secrete neurotrophic factors are two ways to induce longer-term effects. A third option is to use SC as long-term delivery agents, possibly encapsulated in a device, because many SC either secrete neurotrophins naturally or can be genetically engineered to do so (Otani, 2004; Dahlmann-Noor, 2010).

Progress has also been made in the field of photoreceptor, RPE and RGC replacement by SC and progenitor cells, although long-term restoration of visual function has been confirmed. The recent discoveries that human fibroblasts can be “reprogrammed” to behave like embryonic SC and that adult eyes harbor retinal progenitor cells, also increase the potential availability of SC for transplantation, including autologous transplantation and stimulate intrinsic “self-regeneration,” which could potentially overcome a lot of the problems associated with non-autologous transplantation in humans (Dahlmann-Noor, 2010).
2. Potential sources of stem cells for cell therapy in retinal diseases

2.1 Bone marrow-derived stem cells

Bone marrow-derived SCs have been proposed as a potential source of cells for regenerative medicine (Machalinska, 2009; Enzmann, 2009). This is based on the assumption that HSCs isolated from BM are plastic and are able to “transdifferentiate” into tissue-committed SCs for other organs (e.g., heart, liver or brain). Unfortunately, the concept of SC plasticity was not confirmed in recent studies and previously encouraging data demonstrating this phenomenon in vitro could be explained by a phenomenon of cell fusion or, as believed by our group, by the presence, of heterogeneous populations of SCs in BM (Müller-Sieburg, 2002; Spangrude 1988). The identification of very small, embryonic-like SCs in BM supports the notion that this tissue contains a population of primitive SCs, which, if transplanted together with HSCs, would be able to regenerate damaged tissues in certain experimental settings. Cells from BM are easily and safely aspirated. After administering local anesthesia, about 10 mL of the BM is aspirated from the iliac crest using a sterile BM aspiration needle; subsequently mononuclear bone marrow SCs are separated using the Ficoll density separation method (Siqueira, 2010) (Figure 1).

![Fig. 1. Sequence of photos showing the collection of bone marrow (A) and the initial separation of the mononuclear cells using Ficoll-Hypaque gradient centrifugation (B) (C) (D) (Siqueira RC 2010)](image-url)

www.intechopen.com
SC-based therapy has been tested in animal models for several diseases including neurodegenerative disorders, such as Parkinson disease, spinal cord injury, and multiple sclerosis. The replacement of lost neurons that are not physiologically replaced is pivotal for therapeutic success. In the eye, degeneration of neural cells in the retina is a hallmark of such widespread ocular diseases as AMD and RP. In these cases the loss of photoreceptors that occurs as a primary event as in RP or secondary to loss of RPE, as in AMD, leads to blindness (Machalinska 2009; Siqueira 2010).

BM is an ideal tissue for studying SCs because of its accessibility and because proliferative dose-responses of bone marrow-derived SCs can be readily investigated. Furthermore, there are a number of well-defined mouse models and cell surface markers that allow effective studies of hematopoiesis in healthy and injured mice. Because of these characteristics and the experience of BM transplantation in the treatment of hematological cancers, bone marrow-derived SCs have also become an important tool in regenerative medicine. The BM harbors at least two distinct SC populations: HSCs and multipotent marrow stromal cells (MSC).

2.1.1 Hematopoietic stem cells

HSCs are multipotent SCs that give rise to all the blood cell types including myeloid (monocytes and macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets, dendritic cells), and lymphoid lineages (T-cells, B-cells, NK-cells). HSCs are found in the BM of adults, which includes in femurs, hips, ribs, the sternum and other bones. Cells can be obtained directly from the hip using a needle and syringe (Figure 1), or from the blood following pretreatment with cytokines, such as G-CSF (granulocyte colony stimulating factors), that induce cells to be released from the BM compartment. Other sources for clinical and scientific use include UCB and placenta (Ratajczak, 2004; Müller-Sieburg 2002).

In reference to phenotype, HSCs are identified by their small size, lack of lineage markers, low staining (side population) by vital dyes such as rhodamine 123 (rhodamine-dull, also called rholo) or Hoechst 33342 and presence of various surface antigenic markers, many of which belong to the cluster of differentiation series: CD34, CD38, CD90, CD133, CD105, CD45 and also c-kit and SC factor receptor (Müller-Sieburg, 2002; Nielsen, 2009; Kuçi, 2009; Challen 2009; Voltarelli 2000; Voltarelli 2003). Otani (2004) demonstrated that whenever a fraction of mouse or human adult bone marrow-derived SCs [lineage-negative hematopoietic stem cells (Lin-HSCs)] containing endothelial precursors stabilizes and rescues retinal blood vessels that would ordinarily completely degenerate, a dramatic neurotrophic rescue effect is also observed. Retinal nuclear layers are preserved in two mouse models of retinal degeneration, rd1 and rd10, and detectable, albeit severely abnormal, electroretinogram recordings are observed in rescued mice at times when they are never observed in control-treated or untreated eyes. The normal mouse retina consists predominantly of rods, but the rescued cells after treatment with Lin-HSCs are nearly all cones. Microarray analysis of rescued retinas demonstrates significant upregulation of many antiapoptotic genes, including small heat shock proteins and transcription factors.

Some reports have demonstrated the clinical feasibility of the intravitreal administration of autologous bone marrow-derived mononuclear cells (ABMC) in patients with advanced degenerative retinopathies (Jonas, 2008 and 2010). More recently, our group conducted a prospective phase I trial to investigate the safety of intravitreal ABMC in patients with retinitis pigmentosa or cone-rod dystrophy, with promising results (Siqueira, 2011).
2.1.2 Multipotent Mesenchymal Stromal Cells (Mesenchymal Stem Cells)

Mesenchymal stem cells (MSCs) are progenitors of all connective tissue cells. In adults of multiple vertebrate species, MSCs have been isolated from BM and other tissues, expanded in culture and differentiated into several tissue-forming cells such as bone, cartilage, fat, muscle, tendon, liver, kidney, heart, and even brain cells.

According to the International Society for Cellular Therapy (Horwitz, 2005), there are three minimum requirements for a population of cells to be classified as MSCs. The first is that MSCs are isolated from a population of mononuclear cells on the basis of their selective adherence to the surface of the plastic of culture dishes, differing in this respect to bone marrow hematopoietic cells, a disadvantage of this method of identification is the possible contamination by hematopoietic cells and cellular heterogeneity with respect to the potential for differentiation. The second criteria is that CD105, CD73 and CD90 are present and that CD34, CD45, CD14 or CD11b, CD79, or CD19 and HLA-DR are not expressed in more than 95% of the cells in culture. Finally, the cells can be differentiated into bone, fat and cartilage (Phinney, 2007).

A number of studies have shown that bone-marrow-derived MSCs can differentiate into cells expressing photoreceptor proteins when injected into the subretinal space (Gong, 2008; Castanheira, 2008). Interestingly, it has been suggested that rat MSCs can be made to express photopigment (rhodopsin) in vitro simply by adding epidermal growth factor to the culture media (Zhang, 2008). Additionally, though other retina-relevant cell types have been engineered, a number of studies have shown that BM or adipose tissue MSCs are converted to RPE (Gong, 2008; Arnhold, 2006; Vossmerbaeumer 2009). As with work on other neuronal phenotypes, however, there has now been a reassessment of the ability of MSCs to differentiate into functionally useful retinal cells. Some studies have shown that transplanted bone marrow MSCs do not differentiate into neural retinal cells (YU, 2006). In an in vitro rat retina-explant model, untreated MSCs seemed to transdifferentiate into microglia in a way reminiscent of earlier work on MSC transplants in other neurological tissue (Azizi 1998). Some limited improvement was seen with pre-treatment with BDNF, NGF, and bFGF in terms of morphological differentiation into retinal neurons and expression of NF200, GFAP, PKC-alpha, and recoverin, but these cells did not express Rhodopsin (Erices, 2000).

In an ischemic retina rodent model, MSCs injected into the vitreous cavity have been shown to mature (with expression of neuron-specific enolase and neurofilament) and secrete CNTF, bFGF, and BDNF for at least 4 weeks (Li, 2009). Animal studies have also demonstrated that subretinal transplantation of MSCs delays retinal degeneration and preserves retinal function through a trophic response (Inoue, 2007). UCB-derived MSCs have also been shown to be neuroprotective of rat ganglion cells (Zwart, 2009). Very recently, the intravenous administration of bone marrow-derived MSCs was shown to prevent photoreceptor loss and preserve visual function in the RCS rat model of RP.

A role for genetically-modified MSCs may emerge in the treatment of subretinal neovascularization. It has been shown that bone-marrow-derived MSCs accumulate around subretinal membranes induced by retinal laser burns. Intravenous injection of mouse bone-marrow MSCs genetically engineered to secrete pigment epithelium derived factor resulted in smaller neovascular complexes (Hou, 2010).

2.2 Induced pluripotent stem cells

Current methods of producing SCs from adult somatic cells offer an alternative cell source for transplantation. Induced pluripotent stem (iPS) cells are morphologically identical to
Embryonic Stem Cells, display similar gene expression profiles and epigenetic status and have the potential to form any cell in the body (Takahashi, 2006 and 2007; Yu, 2007). These cells have been employed to generate cells for the treatment of various diseases including diabetes, cardiovascular disease, sickle cell anemia, Parkinson's disease and hemophilia (Zhang, 2009; Hanna, 2007; Xu, 2009; Wernig, 2008). Meyer et al. 2009 recently showed that iPS cells can differentiate into retinal cell types whilst a paper by Buchholz et al. 2009 showed that human iPS cells can be differentiated into retinal pigment epithelial cells which display functionality in vitro.

Carr (2009) demonstrated that iPS cells can be differentiated into functional iPS-RPE and that transplantation of these cells can facilitate the short-term maintenance of photoreceptors through phagocytosis of photoreceptor outer segments. Long-term visual function is maintained in this model of retinal disease even though the xenografted cells are eventually lost, suggesting a secondary protective host cellular response. While this particular line of iPS-RPE cells cannot be used as a direct therapy due to viral insertions of pluripotency genes, recent advances in iPS cell reprogramming technology, including the use of small molecules (Huangfu, 2008; Shi, 2008; Li, 2009), piggyBac transposition (Woltjen, 2009; Kaji, 2009), non-integrating episomal vectors (Yu, 2009) and manipulation of endogenous transcription factors (Balasubramanian, 2009) should eliminate the risks associated with the integration of SC genes into the genome. Furthermore, the finding that blood cells can be used to derive iPS cells (Loh, 2009) may remove the need for the invasive biopsies required to collect somatic cells and accelerate the ethical production of SC-derived tissue for therapeutic use.

2.3 Human Embryonic Stem Cells

The human embryonic stem cell (hESC) is defined as a cell that can both renew itself by repeated division and differentiate into any one of the 200 or more adult cell types in the human body. An hESC cell arises from the eight-cell stage morula. Outside of normal development, hESCs have been differentiated in vitro into neural cell types and even pigmented epithelium, although controlling their differentiation has proven challenging. Several hESC lines exist and are supported by public research funds. The use of hESCs has significant limitations, including ethical issues, and a risk of teratoma formation, but the chief problem is that we are still struggling to understand the developmental cues that differentiate hESCs into the specific adult cell types required to repair damaged tissues (MacLaren, 2007).

Nistor et al. (2010) showed for the first time that three-dimensional early retinal progenitor tissue constructs can be derived from hESCs. Three-dimensional tissue constructs were developed by culturing hESC-derived neural retinal progenitors in a matrix on top of hESC-derived RPE cells in a cell culture insert. An osmolarity gradient maintained the nutrition of the three-dimensional cell constructs. Cross-sections through hESC-derived tissue constructs were characterized by immunohistochemistry for various transcription factors and cell markers. Tissue constructs derived from hESC expressed transcription factors characteristic of retinal development, such as Pax6, Otx2, Chx10, retinal RAX, Brm3b (necessary for differentiation of retinal ganglion cells) and crx and nrl (role in photoreceptor development). Many cells expressed neuronal markers including nestin, beta-tubulin and microtubule-associated protein.

Assessments of safety and efficacy are crucial before hESC therapies can move into the clinic. Two important early potential hESC applications are the use of retinal pigment
Stem-cell therapy for retinal diseases, an untreatable form of macular dystrophy that leads to early-onset blindness. Long-term safety and function of RPE from hESCs in preclinical models of macular degeneration was demonstrated by Lu et al. (2009).

They showed long-term functional rescue using hESC-derived RPE in both RCS rats and Elov14 mice, which are animal models of retinal degeneration and Stargardt’s disease, respectively. Good manufacturing practice-compliant hESC-RPE survived subretinal transplantation in RCS rats for prolonged periods (> 220 days). The cells sustained visual function and photoreceptor integrity in a dose-dependent fashion without teratoma formation or untoward pathological reactions.

Near-normal functional measurements were recorded at > 60 days survival in RCS rats. To further address safety concerns, a Good laboratory practice-compliant study was carried out in the NIH III immune-deficient mouse model. Long-term data (spanning the life of the animals) showed no gross or microscopic evidence of teratoma/tumor formation after subretinal hESC-RPE transplantation.

These results suggest that hESCs could serve as a potentially safe and inexhaustible source of RPE for the efficacious treatment of a range of retinal degenerative diseases.

In 2010, the US Food and Drug Administration (FDA) granted Orphan drug designation for RPE cells of Advanced Cell Technology, Inc. (ACT) to initiate its Phase 1/2 clinical trials.

Fig. 1. Intravitreal injection of autologous bone marrow–derived stem cells in a patient with retinitis pigmentosa (Siqueira RC, 2010)
using retinal pigment epithelial (RPE) cells derived from hESCs to treat patients with Stargardt’s Macular Dystrophy (SMD). Moreover, in 2011 the company received a positive opinion from the Committee for Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA) towards designation of this product as an orphan medicinal product for the treatment of Stargardt’s disease.

| Name                  | Type of study                      | Type of injury or illness                          | Route used            | Type and source of cells                                      |
|-----------------------|------------------------------------|---------------------------------------------------|-----------------------|-------------------------------------------------------------|
| Atsushi Otani et al.  | Experimental study in animals      | Mice with retinal degenerative disease            | Intravitreous         | Adult bone marrow–derived lineage-negative hematopoietic stem cells |
| Wang S et al.         | Experimental study in animals      | Retinitis pigmentosa                              | Tail vein             | Pluripotent bone marrow–derived mesenchymal stem cells       |
| Li Na & Li Xiao-rong & Yuan Jia-qin | Experimental study in animals | Rat injured by ischemia/reperfusion                | Intravitreous         | Bone marrow mesenchymal stem cells                           |
| Uteza Y, Rouillot JS, Kobetz A, et al. | Experimental study in animals | Photoreceptor cell degeneration in Royal College of Surgeon rats | Intravitreous         | Encapsulated fibroblasts                                     |
| Zhang Y, Wang W       | Experimental study in animals      | Light-damaged retinal structure                    | Subretinal space      | Bone marrow mesenchymal stem cells                           |
| Tomita M              | Experimental study in animals      | Retinas mechanically injured using a hooked needle| Intravitreous         | Bone marrow–derived stem cells                               |
| Meyer JS et al.       | Experimental study in animals      | Retinal degeneration                               | Intravitreous         | Embryonic stem cells                                         |
| Siqueira RC et al.    | Experimental study in animals      | Chorioretinal injuries caused by laser red diode 670N-M | Intravitreous         | Bone marrow–derived stem cells                               |
| Wang HC et al.        | Experimental study in animals      | Mice with laser-induced retinal injury             | Intravitreous         | Bone marrow–derived stem cells                               |
| Johnson TV et al.     | Experimental study in animals      | Glaucoma                                           | Intravitreous         | Bone marrow–derived mesenchymal stem cell                    |
| Castanheira P et al.  | Experimental study in animals      | Rat retinas submitted to laser damage             | Intravitreous         | Bone marrow–derived mesenchymal stem cell                    |
| Jonas JB et al.       | Case report                        | Patient with atrophy of the retina and optic nerve| Intravitreous         | Bone marrow–derived mononuclear cell transplantation          |
| Type of study      | Type of injury or illness                              | Route used          | Type and source of cells                          |
|-------------------|--------------------------------------------------------|---------------------|--------------------------------------------------|
| Jonas JB et al.   | Case report Three patients with diabetic retinopathy, age related macular degeneration and optic nerve atrophy (glaucoma) | Intravitreous transplantation | bone marrow-derived mononuclear cell transplantation |
| Siqueira RC et al. | Clinical Trial Phase I Five patients with retinitis pigmentosa | Intravitreous transplantation | bone marrow-derived mononuclear cell transplantation |
| Siqueira RC et al. | Clinical trial Phase II 50 patients with retinitis pigmentosa | Intravitreous transplantation | bone marrow-derived mononuclear cell transplantation |
| Siqueira RC et al. | Clinical trial Phase I/II Ten patients with macular degeneration | Intravitreous transplantation | bone marrow-derived mononuclear cell transplantation |
| Advanced Cell Technology | Clinical trial Phase I/II 12 patients with Stargardt’s Macular Dystrophy | Subretinal transplantation | retinal pigment epithelial (RPE) cells derived from human embryonic stem cells (hESCs) |

Table 1. Clinical and experimental studies using cell therapy for retinal diseases

3. Conclusion

Stem cells maintain the balance between somatic cell populations in various tissues and are responsible for organ regeneration. The remarkable progress of regenerative medicine in the last few years indicates promise for the use of stem cells in the treatment of ophthalmic disorders. Based on the above mentioned mechanisms, experimental and human studies with intravitreal bone marrow-derived stem cells have begun (Table 1). The history starts to be written in this very promising therapeutic field.

4. Acknowledgment

Júlio Cesar Voltarelli, André Marcio Vieira Messias, Rodrigo Jorge from São Paulo University - USP, Ribeirão Preto, SP, Brazil.

5. References

[1] Lorenz E, Congdon C, Uphoff ED, R. Modification of acute irradiation injury in mice and guinea-pigs by bone marrow injections. Radiology. 1951; 58:863-77.
[2] Till JE, McCulloch EA. A direct measurement of the radiation sensitivity of normal mouse bone marrow cells. Radiat Res. 1961; 14:213-22.
[3] Lanza R, Rosenthal N. The stem cell challenge. Sci Am. 2004; 290:93-9.
Mimeault M, Batra SK. Concise review: recent advances on the significance of stem cells in tissue regeneration and cancer therapies. Stem Cells. 2006; 24 (11):2319-45.

Ortiz-Gonzalez XR, Keene CD, Verfaillie C, Low WC. Neural induction of adult bone marrow and umbilical cord stem cells. Curr Neurovasc Res. 2004; 1 (3):207-13.

Trounson A. The production and directed differentiation of human embryonic stem cells. Endocr Rev. 2006; 27 (2):208-19. Review.

Schuldiner M, Yanuka O, Itskovitz-Eldor J, Melton DA, Benvenisty N. Effects of eight growth factors on the differentiation of cells derived from human embryonic stem cells. Proc Natl Acad Sci U S A. 2002; 97 (21):11307-12.

Siqueira RC, Voltarelli JC, Messias AM, Jorge R. Possible mechanisms of retinal function recovery with the use of cell therapy with bone marrow-derived stem cells. Arq Bras Oftalmol. 2010 Oct; 73 (5):474-9.

Siqueira RC, Messias A, Voltarelli JC, Scott I, Jorge R. Autologous bone marrow-derived stem cells transplantation for retinitis pigmentosa. Cytotherapy. 2010; 12 Suppl 1:58.

ClinicalTrials.gov. [Internet]. Autologous Bone Marrow-Derived Stem Cells Transplantation for Retinitis Pigmentosa. NCT01068561. [cited 2010 July 30]. Available at: http://clinicaltrial.gov/

Siqueira RC. Autologous transplantation of retinal pigment epithelium in age related macular degeneration. Arq Bras Oftalmol. 2009; 72 (1):123-30

Siqueira RC, Abad L, Benson G, Sami M. Behaviour of stem cells in eyes of rabbits with chorioretinal injuries caused by laser red diode 670N-M. In: Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO), 2008, Fort Lauderdale. Invest Ophthalmol Vis Sci. 2008; 49:536.

Siqueira RC. Cell therapy in ophthalmology diseases. Rev. Bras. Hematol. Hemoter. 2009, vol. 31, suppl. 1, pp. 120-127.

Kolb H. Simple Anatomy of the Retina. The Organization of the Retina and Visual System [Internet]. Salt Lake City (UT): University of Utah Health Sciences Center; 1995-. 2005 May 1.

Machalinska A, Baumert B, Kuprianowicz L, Wiszniewska B, Karczewicz D, Machalinski B. Potential application of adult stem cells in retinal repair–challenge for regenerative medicine. Curr Eye Res. 2009 Sep; 34 (9):748-60. Review.

Dahlmann-Noor A, Vijay S, Jayaram H, Limb A, Khaw PT. Current approaches and future prospects for stem cell rescue and regeneration of the retina and optic nerve. Can J Ophthalmol. 2010 Aug; 45 (4):333-41.

Bunce C, Wormald R. Leading causes of certification for blindness and partial sight in England & Wales. BMC Public Health 2006; 6:58.

Chakravarthy U, Evans J, Rosenfeld PJ. Age related macular degeneration. BMJ 2010; 340:c981.

Maier PC, Funk J, Schwarzer G, Antes G, Falck-Ytter YT. Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials. BMJ 2005; 331:134.

O’Doherty M, Dooley I, Hickey-Dwyer M. Interventions for diabetic macular oedema: a systematic review of the literature. Br J Ophthalmol 2008; 92:1581–90.

Mohamed Q, Gillies MC, Wong TY. Management of diabetic retinopathy: a systematic review. JAMA 2007; 298:902–16.
Stem-Cell Therapy for Retinal Diseases

[22] Enzmann V, Yolcu E, Kaplan HJ, Ildstad ST. Stem cells as tools in regenerative therapy for retinal degeneration. Arch Ophthalmol. 2009; 127 (4):563-71.

[23] Crisóstomo PR, Markel TA, Wang Y, Meldrum DR. Surgically relevant aspects of stem cell paracrine effects. Surgery. 2008; 143 (5):577-81.

[24] Vandervelde S, van Luyn MJ, Tio RA, Harmsen MC. Signaling factors in stem cell-mediated repair of infarcted myocardium. J Mol Cell Cardiol. 2005; 39 (2):363-76.

[25] Oh JY, Kim MK, Shin MS, Lee HJ, Ko JH, Wee WR, Lee JH. The anti-inflammatory and anti-angiogenic role of mesenchymal stem cells in corneal wound healing following chemical injury. Stem Cells. 2008; 26 (4):1047-55.

[26] Gomei Y, Nakamura Y, Yoshihara H, Hosokawa K, Iwasaki H, Suda T, Arai F. Functional differences between two Tie2 ligands, angiopoietin-1 and -2, in the regulation of adult bone marrow hematopoietic stem cells. Exp Hematol. 2010; 38 (2):82-9.

[27] Li N, Li XR, Yuan JQ. Effects of bone-marrow mesenchymal stem cells transplanted into vitreous cavity of rat injured by ischemia/reperfusion. Graefes Arch Clin Exp Ophthalmol. 2009; 247 (4):503-14.

[28] Markel TA, Wang Y, Herrmann JL, Crisóstomo PR, Wang M, Novotny NM, et al. VEGF is critical for stem cell-mediated cardioprotection and a crucial paracrine factor for defining the age threshold in adult and neonatal stem cell function. Am J Physiol Heart Circ Physiol. 2008; 295 (6):H2308-14.

[29] Markel TA, Crisóstomo PR, Wang M, Herring CM, Meldrum DR. Activation of individual tumor necrosis factor receptors differentially affects stem cell growth factor and cytokine production. Am J Physiol Gastrointest Liver Physiol. 2007; 293 (4):G657-62

[30] Harris JR, Brown GA, Jorgensen M, Kaushal S, Ellis EA, Grant MB, Scott EW. Bone marrow-derived cells home to and regenerate retinal pigment epithelium after injury. Invest Ophthalmol Vis Sci. 2006; 47 (5):2108-13.

[31] Zhang P, Li J, Liu Y, Chen X, Kang Q, Zhao J, Li W. Human neural stem cell transplantation attenuates apoptosis and improves neurological functions after cerebral ischemia in rats. Acta Anaesthesiol Scand. 2009; 53 (9):1184-91.

[32] Cheng AS, Yau TM. Paracrine effects of cell transplantation: strategies to augment the efficacy of cell therapies. Semin Thorac Cardiovasc Surg. 2008; 20 (2):94-101.

[33] Harris JR, Fisher R, Jorgensen M, Kaushal S, Scott EW. CD133 progenitor cells from the bone marrow contribute to retinal pigment epithelium repair. Stem Cells. 2009; 27 (2):457-66.

[34] Tomita M, Adachi Y, Yamada H, Takahashi K, Kuchiki K, Oyaizu H, et al. Bone marrow-derived stem cells can differentiate into retinal cells in injured rat retina. Stem Cells. 2002; 20 (4):279-83.

[35] Otani A, Dorrell MI, Kinder K, Moreno SK, Nusinowitz S, Banin E, et al. Rescue of retinal degeneration by intravitreally injected adult bone marrow-derived lineage-negative hematopoietic stem cells. J Clin Invest. 2004; 114 (6):765-74. Comment in: J Clin Invest. 2004; 114 (6):755-7.

[36] Otani A, Kinder K, Ewalt K, Otero FJ, Schimmel P, Friedlander M. Bone marrow-derived stem cells target retinal astrocytes and can promote or inhibit retinal angiogenesis. Nat Med. 2002; 8 (9):1004-10. Comment in: Nat Med. 2002; 8 (9):932-4.
[37] Meyer JS, Katz ML, Maruniak JA, Kirk MD. Embryonic stem cell-derived neural progenitors incorporate into degenerating retina and enhance survival of host photoreceptors. Stem Cells. 2006; 24 (2):274-83.

[38] Binder S, Stanzel BV, Krebs I, Glittenberg C. Transplantation of the RPE in AMD. Prog Retin Eye Res. 2007 Sep; 26 (5):516-54. Epub 2007 Mar 6. Review.

[39] Lu B, Malcuit C, Wang S, Girman S, Francis P, Lemieux L, Lanza R, Lund R. Long-term safety and function of RPE from human embryonic stem cells in preclinical models of macular degeneration. Stem Cells. 2009 Sep; 27 (9):2126-35.

[40] Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006; 126:663–676.

[41] Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007; 131:861–872.

[42] Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, et al. Induced pluripotent stem cell lines derived from human somatic cells. Science. 2007; 318:1917–1920.

[43] Zhang D, Jiang W, Liu M, Sui X, Yin X, et al. Highly efficient differentiation of human ES cells and iPS cells into mature pancreatic insulin-producing cells. Cell Res. 2009; 52:615–621.

[44] Zhang J, Wilson GF, Soerens AG, Koonce CH, Yu J, et al. Functional cardiomyocytes derived from human induced pluripotent stem cells. Circ Res. 2009; 104:e30–41.

[45] Hanna J, Wernig M, Markoulaki S, Sun CW, Meissner A, et al. Treatment of sickle cell anemia mouse model with iPS cells generated from autologous skin. Science. 2007; 318:1920–1923.

[46] Xu D, Alipio Z, Fink LM, Adcock DM, Yang J, et al. Phenotypic correction of murine hemophilia A using an iPS cell-based therapy. Proc Natl Acad Sci U S A. 2009; 106:80

[47] Wernig M, Zhao JP, Pruszak J, Hedlund E, Fu D, et al. Neurons derived from reprogrammed fibroblasts functionally integrate into the fetal brain and improve symptoms of rats with Parkinson’s disease. Proc Natl Acad Sci U S A. 2008; 105:5856–5861.

[48] Meyer JS, Shearer RL, Capowski EE, Wright LS, Wallace KA, et al. Modeling early retinal development with human embryonic and induced pluripotent stem cells. Proc Natl Acad Sci U S A. 2009; 106:

[49] Buchholz DE, Hikita ST, Rowland TJ, Friedrich AM, Hinman CR, et al. Derivation of Functional Retinal Pigmented Epithelium from Induced Pluripotent Stem Cells. Stem Cells. 2009; 27:2427–2434.

[50] Carr AJ, Vugler AA, Hikita ST, Lawrence JM, Gias C, Chen LL, Buchholz DE, Ahmedo A, Semo M, Smart MJ, Hasan S, da Cruz L, Johnson LV, Clegg DO, Coffey PJ. Protective effects of human iPS-derived retinal pigment epithelium cell transplantation in the retinal dystrophic rat. PLoS One. 2009 Dec 3; 4 (12):e8152.

[51] Huangfu D, Osafune K, Maehr R, Guo W, Eijkelenboom A, et al. Induction of pluripotent stem cells from primary human fibroblasts with only Oct4 and Sox2. Nat Biotechnol. 2008; 26:1269–1275.

[52] Shi Y, Desponts C, Do JT, Haeh HS, Scholer HR, et al. Induction of pluripotent stem cells from mouse embryonic fibroblasts by Oct4 and Klf4 with small-molecule compounds. Cell Stem Cell. 2008; 3:568–574.

[53] Li W, Zhou H, Abujaour R, Zhu S, Joo JY, et al. Generation of Human Induced Pluripotent Stem Cells in the Absence of Exogenous Sox2. Stem Cells 2009.
[54] Woltjen K, Michael IP, Mohseni P, Desai R, Mileikovsky M, et al. piggyBac transposition reprograms fibroblasts to induced pluripotent stem cells. Nature. 2009; 458:766–770.
[55] Kaji K, Norrby K, Paca A, Mileikovsky M, Mohseni P, et al. Virus-free induction of pluripotency and subsequent excision of reprogramming factors. Nature. 2009; 458:771–775.
[56] Yu J, Hu K, Smuga-Otto K, Tian S, Stewart R, et al. Human Induced Pluripotent Stem Cells Free of Vector and Transgene Sequences. Science. 2009; 324:797–801.
[57] Müller-Sieburg CE, Cho RH, Thoman M, Adkins B, Sieburg HB. Deterministic regulation of hematopoietic stem cell self-renewal and differentiation. Blood. 2002; 100 (4):1302-9.
[58] Balasubramanian S, Babai N, Chaudhuri A, Qiu F, Bhattacharya S, et al. Non Cell-Autonomous Reprogramming of Adult Ocular Progenitors: Generation of Pluripotent Stem Cells Without Exogenous Transcription Factors. Stem Cells. 2009.
[59] Loh YH, Agarwal S, Park IH, Urbach A, Huo H, et al. Generation of induced pluripotent stem cells from human blood. Blood. 2009; 113:5476–5479.
[60] Spangrude GJ, Heimfeld S, Weissman IL. Purification and characterization of mouse hematopoietic stem cells. Science. 1988; 241 (4861):58-62. Erratum in: Science. 1989;244 (4908):1030.
[61] Ratajczak MZ, Kuca Z, Majka M, Janowska-Wieczorek A, Ratajczak J. Stem cell plasticity revisited: CXCR4-positive cells expressing mRNA for early muscle, liver and neural cells 'hide out' in the bone marrow. Leukemia. 2004; 18 (1):29-40.
[62] Müller-Sieburg CE, Cho RH, Thoman M, Adkins B, Sieburg HB. Deterministic regulation of hematopoietic stem cell self-renewal and differentiation. Blood. 2002; 100 (4):1302-9.
[63] Nielsen JS, McNagny KM. CD34 is a key regulator of hematopoietic stem cell trafficking to bone marrow and mast cell progenitor trafficking in the periphery. Microcirculation. 2009; 16 (6):487-96.
[64] Kuči S, Kuči Z, Latifi-Pupovci H, Niethammer D, Handgretinger R, Schumm M, et al. Adult stem cells as an alternative source of multipotential (pluripotential) cells irregenerative medicine. Curr Stem Cell Res Ther. 2009; 4 (2):107-17.
[65] Challen GA, Boles N, Lin KK, Goodell MA. Mouse hematopoietic stem cell identification and analysis. Cytometry A. 2009; 75 (1):14-24. Review.
[66] Voltarelli JC, Ouyang J. Hematopoietic stem cell transplantation for autoimmune diseases in developing countries: current status and future perspectives. Bone Marrow Transplant. 2003; 32 Suppl 1:S69-71.
[67] Voltarelli JC. Applications of flow cytometry to hematopoietic stem cell transplantation. Mem Inst Oswaldo Cruz. 2000; 95 (3):403-14.
[68] Horwitz EM, Le Blanc K, Dominici M, Mueller I, Slaper-Cortenbach I, Marini FC, Deans RJ, Krause DS, Keating A; International Society for Cellular Therapy. Clarification of the nomenclature for MSC: The International Society for Cellular Therapy position statement. Cytotherapy. 2005; 7 (5):393-5.
[69] Phinney DG, Prockop DJ. Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair-current views. Stem Cells. 2007; 25 (11):2896-902.
[70] Gong L, Wu Q, Song B, et al. Differentiation of rat mesenchymal stem cells transplanted into the subretinal space of sodium iodate-injected rats. Clin Experiment Ophthalmol. 2008; 36:666–671.

[71] Castanheira P, Torquetti L, Nehemy MB, et al. Retinal incorporation and differentiation of mesenchymal stem cells intravitreally injected in the injured retina of rats. Arq Bras Oftalmol. 2008; 71:644–650.

[72] Zhang ZQ, Dong FT. In vitro differentiation of rat mesenchymal stem cells into photoreceptors. Zhonghua Yan Ke Za Zhi. 2008; 44:540–544.

[73] Vossmerbaeumer U, Ohnesorge S, Kuehl S, et al. Retinal pigment epithelial phenotype induced in human adipose tissue-derived mesenchymal stromal cells. Cytotherapy. 2009; 11:177–188.

[74] Arnhold S, Heiduschka P, Klein H, et al. Adenovirally transduced bone marrow stromal cells differentiate into pigment epithelial cells and induce rescue effects in RCS rats. Invest Ophthalmol Vis Sci. 2006; 47:4121–4129.

[75] Yu S, Tanabe T, Dezawa M, et al. Effects of bone marrow stromal cell injection in an experimental glaucoma model. Biochem Biophys Res Commun. 2006; 344:1071–1079.

[76] Azizi SA, Stokes D, Augelli BJ, et al. Engraftment and migration of human bone marrow stromal cells implanted in the brains of albino rats—Simpilicities to astrocyte grafts. Proc Natl Acad Sci U S A. 1998; 95:3908–3913.

[77] Erices A, Congel P, Minguell JJ. Mesenchymal progenitor cells in human umbilical cord blood. Br J Haematol. 2000; 109:235–242.

[78] Li N, Li XR, Yuan JQ. Effects of bone-marrow mesenchymal stem cells transplanted into vitreous cavity of rat injured by ischemia/reperfusion. Graefes Arch Clin Exp Ophthalmol. 2009; 247:503–514.

[79] Inoue Y, Iriyama A, Ueno S, et al. Subretinal transplantation of bone marrow mesenchymal stem cells delays retinal degeneration in the RCS rat model of retinal degeneration. Exp Eye Res. 2007; 85:234–241.

[80] Zwart I, Hill AJ, Al-Allaf F, et al. Umbilical cord blood mesenchymal stromal cells are neuroprotective and promote regeneration in a rat optic tract model. Exp Neurol. 2009; 216:439–448.

[81] Hou HY, Liang HL, Wang YS, et al. A Therapeutic strategy for choroidal neovascularization based on recruitment of mesenchymal stem cells to the sites of lesions. Mol Ther. 2010 Jul 20. [Epub ahead of print]

[82] Jonas JB, Witzens-Harig M, Arseniev L, Ho AD. Intravitreal autologous bone marrow-derived mononuclear cell transplantation: a feasibility report. Acta Ophthalmol. 2008; 86 (2):225-6.

[83] Jonas JB, Witzens-Harig M, Arseniev L, Ho AD. Intravitreal autologous bone marrow-derived mononuclear cell transplantation. Acta Ophthalmol. 2010; 88 (4):e131-2.

[84] Siqueira RC, Messias A, Voltarelli JC, Scott IU, Jorge R. Intravitreal injection of autologous bone marrow-derived mononuclear cells for hereditary retinal dystrophy: a phase I trial. Retina. 2011 Feb 2. [Epub ahead of print]

[85] Nistor G, Seiler MJ, Yan F, Ferguson D, Keirstead HS. Three-dimensional early retinal progenitor 3D tissue constructs derived from human embryonic stem cells. J Neurosci Methods. 2010 Jun 30; 190 (1):63-70. Epub 2010 May 4.

[86] MacLaren R E, Pearson R A. Stem cell therapy and the retina. Eye (2007) 21, 1352–1359
The ultimate clinical implementation of embryonic stem cells will require methods and protocols to turn these unspecialized cells into the fully functioning cell types found in a wide variety of tissues and organs. In order to achieve this, it is necessary to clearly understand the signals and cues that direct embryonic stem cell differentiation. This book provides a snapshot of current research on the differentiation of embryonic stem cells to a wide variety of cell types, including neural, cardiac, endothelial, osteogenic, and hepatic cells. In addition, induced pluripotent stem cells and other pluripotent stem cell sources are described. The book will serve as a valuable resource for engineers, scientists, and clinicians as well as students in a wide range of disciplines.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Rubens Camargo Siqueira (2011). Stem-Cell Therapy for Retinal Diseases, Embryonic Stem Cells - Differentiation and Pluripotent Alternatives, Prof. Michael S. Kallos (Ed.), ISBN: 978-953-307-632-4, InTech, Available from: http://www.intechopen.com/books/embryonic-stem-cells-differentiation-and-pluripotent-alternatives/stem-cell-therapy-for-retinal-diseases
