**Name of Journal:** *World Journal of Stem Cells*

**Manuscript NO:** 90578

**Manuscript Type:** REVIEW

**Unlocking the versatile potential: Adipose-derived mesenchymal stem cells in ocular surface reconstruction and oculoplastics**

Surico PL *et al*. MSCs in oculoplastics

Pier Luigi Surico, Anna Scarabosio, Giovanni Miotti, Martina Grando, Carlo Salati, Pier Camillo Parodi, Leopoldo Spadea, Marco Zeppieri

**Pier Luigi Surico,** Schepens Eye Research Institute of Mass Eye and Ear, Harvard Medical School, Boston, MA 02114, United States

**Pier Luigi Surico,** Department of Ophthalmology, Campus Bio-Medico University, Rome 00128, Italy

**Anna Scarabosio, Giovanni Miotti, Pier Camillo Parodi,** Department of Plastic Surgery, University Hospital of Udine, Udine 33100, Italy

**Martina Grando,** Department of Internal Medicine, Azienda Sanitaria Friuli Occidentale, San Vito al Tagliamento 33078, Italy

**Carlo Salati, Marco Zeppieri,** Department of Ophthalmology, University Hospital of Udine, Udine 33100, Italy

**Leopoldo Spadea,** Eye Clinic, Policlinico Umberto I, “Sapienza” University of Rome, Rome 00142, Italy

**Co-first authors:** Pier Luigi Surico, Anna Scarabosio.

**Author contributions:** Surico PL and Scarabosio A contributed equally to the manuscript as co-first authors. Surico PL, Scarabosio A, Miotti G, Grando M, Salati C, Parodi PC, Spadea L, and Zeppieri M wrote the outline; Surico PL and Scarabosio A did the research and writing of the manuscript; Miotti G, Grando M, Salati C, Parodi PC, Spadea L, and Zeppieri M assisted in the writing of the paper; Zeppieri M was responsible for the conception and design of the study and completed the English and scientific editing (a native English speaking MD, PhD); Surico PL, Scarabosio A, Miotti G, Grando M, Salati C, Parodi PC, Spadea L, and Zeppieri M assisted in the editing and making critical revisions of the manuscript; and all authors provided the final approval of the article.

**Corresponding author: Marco Zeppieri, MD, PhD, Doctor,** Department of Ophthalmology, University Hospital of Udine, p.le S. Maria della Misericordia 15, Udine 33100, Italy. markzeppieri@hotmail.com

**Received:** December 7, 2023

**Revised:** January 6, 2024

**Accepted:** January 29, 2024

**Published online:**

**Abstract**

This review comprehensively explores the versatile potential of mesenchymal stem cells (MSCs) with a specific focus on adipose-derived MSCs. Ophthalmic and oculoplastic surgery, encompassing diverse procedures for ocular and periocular enhancement, demands advanced solutions for tissue restoration, functional and aesthetic refinement, and aging. Investigating immunomodulatory, regenerative, and healing capacities of MSCs, this review underscores the potential use of adipose-derived MSCs as a cost-effective alternative from bench to bedside, addressing common unmet needs in the field of reconstructive and regenerative surgery.

**Key Words:** Stem cells; Adipose stem cell; Ocular therapy; Oculoplastics; Regenerative

Surico PL, Scarabosio A, Miotti G, Grando M, Salati C, Parodi PC, Spadea L, Zeppieri M. Unlocking the versatile potential: Adipose-derived mesenchymal stem cells in ocular surface reconstruction and oculoplastics. *World J Stem Cells* 2024; In press

**Core Tip:** Mesenchymal stem cells (MSCs) have great have shown great therapeutic potential in all fields of medicine. Adipose-derived MSCs are advantageous, abundant, and relatively safe when considered in treatment regimes. Ophthalmic and oculoplastic surgery that involve procedures for periocular enhancement can benefit from this treatment option for tissue restoration, functional and aesthetic refinement and aging. Adipose-derived MSCs offer immunomodulatory, regenerative, and healing, thus addressing common unmet needs in the field of reconstructive and regenerative surgery. Patient outcomes, success of therapy, prevention of complications and management of patients depend on proper surgical option for individualized tailored needs.

**INTRODUCTION**

The field of oculoplastic surgery, which encompasses a wide array of procedures to enhance the form and function of the eye and its surrounding structures, has long been a domain of meticulous precision and innovative approaches. From repairing damaged ocular tissues to restoring the aesthetic aspects of periocular regions, oculoplastics demand novel solutions that promote both efficacy and safety. Mesenchymal stem cells (MSCs) emerge as a beacon of hope in this intricate landscape. These versatile cells, well-known for their regenerative abilities in various medical disciplines, hold immense promise in oculoplastics. The human eye and its adjacent tissues are an intricately interconnected system comprising muscle, adipose tissue, ocular surface, and skin. Each component plays a vital role in ocular health, appearance, and function.

In recent years, the field of regenerative medicine has witnessed a paradigm shift in the quest for innovative therapeutic strategies, particularly in the realm of ocular surface reconstruction and oculoplastics. Among the various cell types under investigation, adipose-derived MSCs have emerged as promising candidates due to their unique characteristics, including easy accessibility, abundant supply, and robust regenerative properties. This comprehensive review aims to unravel the versatile potential of MSCs in the context of ocular surface reconstruction and oculoplastics, shedding light on their mechanisms of action, preclinical and clinical applications, and the current challenges and prospects in harnessing their therapeutic efficacy.

Understanding the multifaceted roles of MSCs in ocular tissue regeneration is paramount for advancing clinical interventions and enhancing patient outcomes. The review was performed by using PubMed (<https://pubmed.ncbi.nlm.nih.gov>) and *Reference Citation Analysis* (*RCA*) (<https://www.referencecitationanalysis.com>). As we delve into the intricate interplay between MSCs and the ocular microenvironment, this review will explore the molecular and cellular mechanisms underlying their immunomodulatory effects, paracrine signaling, and differentiation capacities. Furthermore, a critical examination of the existing preclinical studies and clinical trials will provide a comprehensive overview of the safety and efficacy profiles of MSC-based therapies, paving the way for a nuanced understanding of their translational potential in the field of ophthalmology.

**MSCS**

In 2006, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy issued a position statement with the intent of providing clarity regarding the terminology “multipotent mesenchymal stromal cells”. They established specific criteria for the identification of MSCs, requiring that these cells exhibit characteristics such as adherence to plastic surfaces, clonogenic ability, the presence of certain cell surface markers (CD73, CD90, CD105), and the absence of hematopoietic and endothelial markers (CD45, CD34, CD14, CD11b, CD79α, CD19, HLA-DR)[1]. Additionally, these MSCs must demonstrate the potential for *in vitro* differentiation into mesodermal cell lineages[2,3].

MSCs, renowned for their remarkable plasticity, have long been a subject of interest due to their potential for tissue repair and regeneration[4,5]. These versatile cells can be harvested from a wide array of sources, including bone marrow, nervous tissue, adipose tissue, amniotic fluid, placenta, and the Wharton’s jelly of the umbilical cord[6-11]. MSCs possess an impressive capacity for self-renewal, maintaining their characteristics over multiple passages without significant alteration[12,13].

MSCs exhibit the unique ability to differentiate into various mesenchymal lineages, encompassing adipocytes, chondrocytes, and osteocytes[14]. Notably, it has been demonstrated that specific MSC-like cells from both mice and humans can be induced to differentiate into cells of neuroectodermal and endodermal lineages, including neurons, endothelial cells, and hepatocytes[15-18].

Furthermore, MSCs exhibit a notable inclination to target areas of tissue injury or inflammation upon intravenous administration[19-21]. This characteristic enhances their appeal, particularly in the context of tissue repair and the maintenance of immune homeostasis. Their substantial immunoregulatory capacities, which involve the secretion of anti-inflammatory factors, empower MSCs to finely tune both innate and adaptive immune responses, ultimately facilitating a state of immunosuppression[19,22].

Interestingly, MSCs are known to secrete numerous substances into the medium in which they are cultured[23]. This cocktail of secretions is referred to as the MSC secretome and comprises soluble factors (cytokines, chemokines, growth factors, immunomodulatory proteins, and mitogenic factors) and membrane-bound vesicles (microvesicles and exosomes)[24]. MSCs-secretome treatment has been successfully and safely tested in several fields such as wound healing, myocardial infarction, liver injury, cerebral ischemic disease, spinal cord injury, lung diseases, urologic disorders, ocular diseases inflammatory arthritis, and bone defects[25-33].

**ADIPOSE-DERIVED MSCs**

Adipose tissue offers a more abundant supply of MSCs and is relatively easier to access compared to bone marrow, making it an appealing choice for clinical applications. However, it’s worth noting that reports suggest variations in the properties of MSCs derived from these two tissue sources. Inconsistencies in the findings across studies can be attributed to the diversity in cell preparations, which may result from differences in extraction methods, culture conditions, as well as the age and gender of the donors[34,35].

Adipocytes represent only 25% of the total number of cells in fat tissue, despite accounting for 80% to 90% of its volume. The remaining 75% of the cells, known as the stromal vascular fraction (SVF), are rich in adipose-derived stem cells, endothelial cells, granulocytes, monocytes, macrophages, and lymphocytes[35-37].

However, the significant advantage of adipose tissue lies in its potential to yield a substantially higher number of stem cells - estimated to be 100 to 500-fold greater than that obtained from bone marrow aspirate[38]. This characteristic has piqued the interest of plastic surgeons, and various methods for isolating cells from lipoaspirate or fat tissue have become available[39,40].

In plastic surgery, procedures involving stem cell-containing tissue transplants, such as fat grafts, cell-enriched lipoaspirate, or the so-called SVF, are typically performed in the operating theatre. However, this approach often hinders the in-depth characterization of MSCs within the cell or tissue graft, including immunophenotyping, differentiation potential, assessment of senescence, and determining the proportional contribution of stem cells to the graft as a whole[40].

In addition, it has been demonstrated that the abundance of colony-forming unit-fibroblast in the adipose-derived MSCs is significantly greater than in that of bone marrow-derived MSCs, suggesting again their stronger potential in the field of plastic surgery[41]. Despite these advantages of adipose-derived MSCs, there is still a need for further research toward standardized clinical procedures.

**ADIPOSE-DERIVED MSCs IN PLASTIC SURGERY**

Adipose stem-cell regenerative and anti-inflammatory properties make them a promising candidate in plastic surgery. Numerous applications are described, in particular in the tissue regeneration field[42,43]. MSCs are capable of enhancing the survival and integration of fat grafts in procedures like lipofilling or fat transfer improving graft retention and promoting better tissue integration[44]. As already mentioned, MSCs play a certain role in tissue repair and wound healing[43]. Their ability to modulate the immune response and stimulate the formation of new blood vessels can contribute to improved healing outcomes in plastic surgery procedures. These staminal cells also have anti-inflammatory properties, which can be beneficial in reducing inflammation and promoting a more favorable healing environment. This is particularly relevant in procedures where inflammation can impact outcomes, such as tissue reconstruction or scar revision like breast surgery[45]. Moreover, the regenerative properties of MSCs may contribute to minimizing scar formation[46]. Research suggests that MSCs can modulate the collagen production and remodeling process, potentially leading to less noticeable scars[47].

MSCs demonstrated to play a role also in the cosmetic area of plastic surgery for their potential to stimulate collagen production and improve skin quality[42,48]. In procedures involving bone or cartilage reconstruction, such as craniofacial surgery or rhinoplasty, MSCs may be used to enhance the regenerative capacity of the implanted tissues. Otherwise, it is important to note that while there is promising research in these areas, the use of MSCs in plastic surgery is still an evolving field and more clinical studies are needed to establish the safety and efficacy of these approaches.

**APPLICATION OF ADIPOSE-DERIVED MSCs IN OCULOPLASTICS**

Adipose-derived MSCs do have a great potential for application in oculoplastics surgery. This encompasses a variety of subfields starting with eyelid reconstruction, going through lacrimal gland development, and ending with cosmetic surgery. Possible applications may be potentially endless. Stem cell biology in oculoplastic is still at the beginning of its path but is already a central topic[49] (Table 1).

Stem cells mean regeneration. This concept is extremely interesting in the ocular area in which we find highly specialized tissue that is difficult to replace in other ways. In plastic surgery the main concept is “like-to-like” reconstruction or replacement. This is our mantra whenever a flap is raised and set. What if there are no similar tissues? Stem cells may be the only appropriate answer. And adipose-derived MSCs are incredibly important in the topic. Due to the high variety of applications these may have in oculoplastic, in our review two main chapters have been identified: (1) Ocular surface reconstruction; and (2) Periocular.

In ocular surface MSCs have shown great promise in the treatment of ocular surface disorders. These cells may have anti-inflammatory and regenerative properties, making them potential candidates for conditions like dry eye syndrome or chemical burns affecting the ocular surface[49]. Periocular applications are even wider but probably even less explored.

It is important to note that while the potential applications of stem cells in oculoplastic are promising, research in this field is ongoing, and many aspects, including safety and long-term effectiveness, are still being explored. Additionally, ethical considerations and regulatory frameworks surrounding the use of stem cells need to be carefully addressed. As with any medical advancement, the translation of stem cell research into clinical practice requires rigorous testing and validation through well-designed clinical trials before becoming standard treatments.

**OCULAR SURFACE RECONSTRUCTION**

The ocular surface constitutes a complex system perpetually exposed to a multitude of stimuli capable of disturbing its equilibrium. Damage to the ocular surface can arise from various sources, including external factors such as mechanical traumas, chemical burns, adverse effects of topical medications, or may result from inflammatory processes that encompass conditions such as mucous membrane pemphigoid (MMP), Stevens-Johnson Syndrome, and graft-*versus*-host disease, all of which can engender substantial damage to the ocular surface, particularly affecting corneal transparency[62-66]. Such damage may also extend to the associated ocular structures, involving the conjunctiva and eyelids, resulting in cicatricial alteration of the ocular surface[62].

An additional and formidable consequence of these alterations to the ocular surface is the impairment of limbal stem cells located in the corneal limbus, a condition known as limbal stem cell deficiency (LSCD)[67]. Impairment of these stem cells’ regenerative capacity can lead to conjunctivalization of the cornea, resulting in the loss of transparency and, consequently, visual function, requiring optimization of the ocular surface by a wide range of treatments from medical management to eyelid, corneal, and conjunctival reconstruction[68].

Corneal transplantation and stem cell transplantation stand as pivotal surgical procedures within ocular surface reconstruction, addressing a range of conditions and playing a critical role in vision restoration[69,70]. However, they can be characterized by a risk of rejection, a challenge that poses complexity in managing the postoperative phase[71,72].

Furthermore, akin to other organs within the human body, the ocular surface undergoes the natural aging process, which can manifest in various forms, with the most common disorder being dry eye syndrome[73]. These aging processes can have a significant impact on patients’ quality of life. In this complex field, MSCs represent a promising novel regenerative approach to such a wide range of pathologies, requiring more in-depth characterization of their function in the different clinical subsets[74].

***Chemical injuries***

Chemical injuries to the cornea are the most common type of ocular and periocular injury and can vary widely in severity[75,76]. These injuries range from minor damage that affects only the outer layer of the corneal surface to more severe burns that penetrate deep into the layers of the cornea[77], resulting in inflammation, scarring, and impairment of vision[76]. Consequently, immediate assessment and treatment of chemical burns are crucial to restore and preserve ocular surface integrity[78]. Notably, alkali burns are particularly concerning. Unlike acid burns, alkalis penetrate the tissues by causing membrane lipid saponification and collagen matrix denaturation, leading to tissue necrosis and further damage by disrupting the balance between pro-oxidant and antioxidant substances[79].

MSCs, when transferred to the damaged corneal surface, ameliorate alkali-induced oxidative damage, reducing apoptosis, matrix metalloproteinases, and pro-inflammatory cytokines[50]. Moreover, adipose-derived MSCs showed the ability to suppress corneal inflammation and neovascularization while significantly expediting corneal healing following alkali burn in various animal models[50,51,80].

It has been reported that MSCs, when combined with polysaccharide scaffold demonstrated an additive effect[81]. This effect was observed in the upregulation of anti-inflammatory cytokines, specifically transforming growth factor beta (TGF-β), and antiangiogenic cytokine thrombospondin 1[53]. Moreover, adipose-derived MSCs have been associated with a concurrent downregulation of pro-inflammatory cytokines like tumor necrosis factor alpha (TNF-α), chemotactic factors such as macrophage inflammatory protein-1alpha and monocyte chemoattractant protein-1 (MCP-1), as well as pro-angiogenic factors like vascular endothelial growth factor (VEGF) and MMP-2, showing promising result for a new therapeutic use of MSCs[52,82].

Using an *in vivo* mouse model of ocular injury, it has been shown that MSCs have the capacity to restore corneal transparency by secreting high levels of hepatocyte growth factor (HGF) and subsequently inhibiting myofibroblast generation. Interestingly, in the same study HGF alone was able to restore corneal transparency, an observation that supports the rationale of using specific MSC-secreted factors to treat ocular diseases[83].

Hence, in addition to their primary anti-inflammatory role in the context of chemical burns, the regenerative function of adipose-derived MSCs has been demonstrated in promoting the regeneration of the corneal epithelium[54]. Specifically, adipose-derived MSCs have clearly shown this regenerative potential[54,55,84-86].

***LSCD***

In the treatment of unilateral limbal stem cell loss, autologous limbal cell transplantation has been widely validated as a therapeutic option[87]. However, in cases of bilateral damage, allogeneic limbal cell transplantation is indicated[68], however, it presents a high risk of rejection and requires prolonged systemic immunosuppressive therapy[88]. Therefore, within this field, MSCs have been demonstrated to offer a genuine alternative to these limitations[89]. Specifically, adipose-derived MSCs have been shown to be modulated to promote wound healing and reduce inflammation[86,90]. It has been demonstrated that adipose-derived MSCs topically administrated in a rat corneal burn model rapidly reach the corneal epithelium and stroma after the application of the cells[56]. Human adipose-derived MSCs, when transplanted onto the ocular surface of rabbits with partial and total LSCD models, promoted the expression of corneal epithelial cell markers such as CK3 and E-cadherin, and the limbal epithelial cell markers CK15 and p63[86]. Adipose-derived MSCs exhibited good tolerance, migrated to inflamed areas, diminished inflammation, and hindered the progression of corneal neovascularization and opacity, enhancing the corneal healing process.

Interestingly, priming human adipose-derived MSCs with a specific medium optimized for limbal stem cell conditions enhanced their ability to improve corneal wound healing, suppressing inflammation with the downregulation of proinflammatory TNF-α, MMP-2, interleukin (IL)-6, and MCP1. The fact that MSCs function in a paracrine context-dependent manner makes it promising to enhance their capacity *in vitro* to improve the healing of ocular surface wounds[90].

When examining the *in vitro* differentiation of MSCs into corneal epithelial and limbal stem cells, it has been demonstrated that adipose-derived MSCs exhibit a foundational expression of corneal epithelial cell markers like ABCG2, p63, CK12, and CK16[91,92]. Moreover, several studies have indicated their differentiation into these cells in response to specific media[90,93].

Another concept that has to be investigated regarding the mechanism of MSCs function is the epithelial-mesenchymal transition (EMT). EMT refers to the transformation of polarized epithelial cells into mesenchymal- or myofibroblast-like cells[94,95]. This process contributes to tissue homeostasis maintenance. However, a prolonged inflammatory state or excessive EMT can lead to tissue fibrosis in organs, as often observed in the context of LSCD[96]. There is also evidence suggesting the involvement of EMT in ocular surface diseases such as pterygium[97] and corneal subepithelial fibrosis[95]. Therefore, suppressing EMT on the ocular surface could be an effective treatment for EMT-related ocular surface diseases to maintain homeostasis. In this regard, it has been demonstrated that the adipose-derived secretome attenuated TGF-β1-induced EMT phenotypes in corneal epithelial cells[57].

Similarly, in the realm of reducing fibrosis in skin wound healing, it has been shown that the paracrine action of MSCs delivered by microspheres could serve as a promising strategy to boost tissue repair and curb excessive TGF-β mediated fibrosis in cutaneous wound healing[98], suggesting a multifaceted and promising role in harnessing the potent paracrine action of adipose-derived MSCs in ocular and periocular applications[99].

***Corneal transplantation***

Due to their immunomodulatory traits, MSCs offer potential in corneal allograft transplantation which remains a main procedure in the field of ocular surface reconstruction. While corneal allografts boast high survival rates due to immune privilege, the risk of immune rejection remains the primary cause of graft failure[71,100].

Moreover, MSCs’ paracrine function shows promising potential in corneal transplantation by influencing the environment and immunoregulation adipose-derived MSCs secrete growth factors such as platelet-derived growth factor, VEGF, HGF, and TGFβ1[101,102]. These factors induce neovascularization, beneficial in ischemic conditions[103,104] but concerning in avascular corneal transplants, elevating the risk of rejection[72]. Despite adipose-derived MSCs also secreting IL-6 and IL-8, their impact, including the potential for rejection responses, appears to vary based on the environment, underlining the contextual influence of adipose-derived MSCs therapy and its role in suppressing inflammation and immune reaction signaling[93]. Across several investigations, the several routes of administration of adipose-derived MSCs topically[105], subconjunctivally[106], using amniotic membranes, or utilizing other substrates like contact lenses have been established[105,106].

Human adipose-tissue MSCs have been proven to be effective in restoring and enhancing corneal and limbal epithelial cell function in animal LSCD models[74,86,105]. These results indicate that MSCs contribute to the recovery of the corneal epithelium with paracrine mechanism rather than by a trans-differentiation process. Moreover, given the low-immunogenic proprieties of adipose-derived MSCs, they appear to be a potential solution for complex cases of ocular surface failure that require transplantation, representing a cost-effective alternative to the current therapies.

Various evidence suggests a preventive role of MSCs in corneal transplant rejection. Infusing MSCs with cyclosporine post-surgery extends graft survival by inhibiting T helper type 1 (Th1) cytokine production and enhancing regulatory T cell immunosuppressive function[107]. Another study highlighted pre-surgical MSC administration’s ability to diminish surgery-related inflammation, extending graft survival by reducing rejection immune response[58]. However, a pig-to-rat corneal transplantation model showed no benefit from MSC infusion, potentially due to increased Th2 cytokine production[108]. Despite the need for further studies, applying adipose-derived MSCs as cell therapy for graft-rejection prevention remains a promising area to explore, potentially extendable to fields like skin transplantation, particularly relevant in oculoplastic practice[109].

***Ocular surface ageing***

The ocular surface undergoes the effects of aging due to continual exposure to environmental elements and various irritants and dry eye disease (DED) is the most prevalent age-related ocular surface condition, which poses challenges in treatment, demanding a multifaceted therapeutic approach[110,111]. In the elderly, the immune system often exhibits a chronic, mild inflammatory condition known as inflammaging[73,112]. This state is linked to the dysregulation of the immune system referred to as immunosenescence[113,114]. Additionally, it reduces the resilience and capacity of aged bodies to withstand internal or external stressors. In this scenario, although oculoplastic procedures aid in the anatomical, mechanical, and aesthetic restoration of the ocular and periocular region, they can stress the ocular surface, especially in older individuals[115]. Consequently, stabilizing the ocular surface before and after any ophthalmic, ocular, or periocular procedure becomes crucial[115-117]. Current treatment approaches predominantly encompass artificial tear replacement therapy, anti-inflammatory interventions, and localized immunosuppressive strategies[118].

While the exact pathogenesis of DED remains not entirely comprehended, it is acknowledged that inflammation and the breakdown of ocular surface immunoregulation significantly contribute to the advancement of the disease[119,120]. Considering the ability of MSCs to aid in tissue repair by suppressing inflammation, recent investigations have delved into the therapeutic prospects of MSCs within the realm of DED[121]. Previous studies have shown that the number of conjunctival goblet cells increases after treatment with adipose-derived MSCs in animal dry eye models[122,123].

Studies have shown that adipose-derived MSCs can significantly promote lacrimal gland regeneration and increase tear secretion[124]. Injecting adipose-derived MSCs into the lacrimal glands of dogs with dry eyes led to an improvement in dry eye signs and good tolerance[59,125]. A clinical trial in which allograft adipose derived-MSCs were administered into the lacrimal glands of patients with severe lacrimal defects. The results similarly showed that MSCs are well tolerated and promote improvement in ocular surface signs and symptoms[60]. Additionally, derived-MSCs exosomes treated dry eye in a murine model and have been able to decrease pro-inflammatory cytokines, promote corneal epithelial repair, and increase tear secretion by inhibiting pro-inflammatory and apoptotic pathways[126].

Finally, it has also been shown that therapy using MSCs conditioned media may enhance the effectiveness of dry eye treatment through the suppression of inflammation and apoptosis, as well as by encouraging tear secretion and fostering the proliferation of corneal epithelial cells, highlighting the potential of MSCs secretome[31].

Further studies are necessary to validate adipose-derived MSCs therapy in the domain of the ocular surface. However, by consolidating these outcomes, they may potentially play a significant role as a therapy that amalgamates a multidisciplinary approach in the treatment of the ocular surface, particularly intriguing in the field of oculoplastic surgery.

**PERIOCULAR SURGERY**

***Applications***

The application of stem cells in the periocular area involves various techniques[49,127]. First of all, stem cell or stem cell-derived products may be applied topically to the skin in the periocular region[128]. This could involve the use of creams, gels, or serums containing stem cells or their derivatives. The idea is that these products may stimulate skin regeneration, improve elasticity, and contribute to a more youthful appearance[128]. MSCs can be injected directly into the periocular tissues. This may be done using various injection techniques, such as microinjections or more targeted approaches. The injected stem cells could potentially contribute to tissue regeneration and the improvement of skin quality. These therapies may be combined with other cosmetic or reconstructive procedures in the periocular area. For example, these could be applied in conjunction with eyelid surgery to enhance the overall aesthetic outcome and promote better tissue healing[129,130]. Promoting wound healing after periocular surgeries or injuries may become a game changer in this field, particularly in reducing the retraction effect.

***Indications***

The periocular region, which includes the area around the eyes, eyebrows, and temples, is of particular interest in the field of regenerative medicine and stem cell research. The periocular application of stem cells holds promise for various therapeutic purposes, including both cosmetic and reconstructive procedures.

***Cosmetic***

As previously mentioned, stem cells stand for regeneration. The cosmetic field has itself a regenerative effort: Restoring something that time had changed. Therefore, stem cell treatment may become a cornerstone.

***Rejuvenation***

The regenerative properties of stem cells could contribute to skin renewal, reducing wrinkles, and improving skin elasticity. This might involve the application of stem cells directly to the skin or in conjunction with other cosmetic procedures. In particular eyelid rejuvenation is one of the most frequently requested procedures[49,131].

***Scar treatment***

In the last decade, numerous procedures have been proposed to improve scars. There in the periocular region may be particularly challenging to treat because of the highly functional demand. Surgery is commonly useful to major retraction areas but stem cell treatment may be also explored. The regenerative properties of stem cells could aid in tissue repair and promote a more natural and aesthetically pleasing outcome[43,46,129].

***Hair restoration***

For individuals experiencing hair loss in the eyebrows or eyelashes, stem cells might be investigated for their role in promoting hair follicle regeneration and improving hair density in the periocular area[132,133].

***Reconstructive***

Similarly, reconstructive surgery is deeply connected to stem cell treatment. MSCs have already demonstrated their capacity to stimulate wound healing, neovascularization, and tissue regeneration[43,44,61,134]. These, through fat grafting, are already a well-established procedure to improve radiotherapy-damaged skin. The same principle may also be applied to ocular/periocular cancers. In these patients, good skin quality is essential to be able to wear an ocular prosthesis when needed. Eyelid malposition correction may be combined with fat grafting to improve the outcome and to apply a regenerative boost[135]. In some cases, micro fat grafting applied to the upper lid seems to improve levator palpebrae superioris muscle in mild ptosis[130]. This application needs to be explored.

**OTHER KINDS OF MSCs**

MSCs are highly heterogeneous multipotent stromal cells that can be found in various tissues throughout the body. Autologous adult stem cells have consistently served as the primary cell type employed in various applications due to their immuno-compatibility, and their utilization poses minimal ethical concerns[136]. This stands in stark contrast to the use of embryonic stem cells (ESCs), umbilical cord MSCs (UCMSCs), and induced pluripotent stem cells (iPSCs), each of which has encountered substantial limitations in clinical practice[137]. These constraints primarily revolve around issues concerning cellular regulation and the potential for teratoma formation, ethical dilemmas, immunogenicity (in the case of ESCs), genetic manipulation complexities (associated with iPSCs), and difficulties related to the long-term preservation of UCMSCs[138,139]. In this review, we included studies about different sources of MSCs to support the wide array of functions that MSCs can potentially express in the field of ocular surface reconstruction and oculoplastics. However, the main focus stays on adipose-derived MSCs, since adipose tissue offers a more abundant supply of MSC cells and is relatively easier to access compared to other sources[38].

**ACCELERATING THE CLINICAL USE OF MSCs**

As of today, the primary issue in the application of MSCs appears to be their inability to survive at the site of administration. We should likely focus on this aspect to assess their actual clinical efficacy. Various factors contribute to this challenge and understanding them is crucial for developing strategies to enhance the survival and therapeutic potential of MSCs in clinical settings. Further investigation into the survival mechanisms, interaction with the host microenvironment, and optimization of delivery methods may provide valuable insights for addressing this critical concern in MSC-based therapies. Various clinical trials are ongoing.

**CONCLUSION**

In conclusion, this review illuminates the versatile potential applications of adipose-derived MSCs in oculoplastics, emphasizing their ease of harvesting, cost-effectiveness, safety, and efficacy. While the current evidence suggests their promising role in various clinical scenarios, further studies are warranted to elucidate the precise mechanisms of action and functions of MSCs, particularly in the context of wound healing, inflammation, and regenerative and reconstructive procedures in ophthalmology and plastic surgery. Optimizing and standardizing protocols for the application of MSC-based cell therapy will be crucial for unlocking their full therapeutic potential in addressing the intricate challenges posed by ocular surface and periocular conditions. Moreover, the main issue to untangle consists of their effective survival in the donor area. Many unsatisfactory clinical results may be due to the poor survival rate. Further high-quality basic and clinical studies are needed to finally be able to apply MSCs successfully in our daily clinical practice.

**REFERENCES**

1 **Dominici M**, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop Dj, Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* 2006; **8**: 315-317 [PMID: 16923606 DOI: 10.1080/14653240600855905]

2 **Uccelli A**, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. *Nat Rev Immunol* 2008; **8**: 726-736 [PMID: 19172693 DOI: 10.1038/nri2395]

3 **Costela-Ruiz VJ**, Melguizo-Rodríguez L, Bellotti C, Illescas-Montes R, Stanco D, Arciola CR, Lucarelli E. Different Sources of Mesenchymal Stem Cells for Tissue Regeneration: A Guide to Identifying the Most Favorable One in Orthopedics and Dentistry Applications. *Int J Mol Sci* 2022; **23** [PMID: 35683035 DOI: 10.3390/ijms23116356]

4 **Brown C**, McKee C, Bakshi S, Walker K, Hakman E, Halassy S, Svinarich D, Dodds R, Govind CK, Chaudhry GR. Mesenchymal stem cells: Cell therapy and regeneration potential. *J Tissue Eng Regen Med* 2019; **13**: 1738-1755 [PMID: 31216380 DOI: 10.1002/term.2914]

5 **Guillamat-Prats R**. The Role of MSC in Wound Healing, Scarring and Regeneration. *Cells* 2021; **10** [PMID: 34359898 DOI: 10.3390/cells10071729]

6 **Tavakoli S**, Ghaderi Jafarbeigloo HR, Shariati A, Jahangiryan A, Jadidi F, Jadidi Kouhbanani MA, Hassanzadeh A, Zamani M, Javidi K, Naimi A. Mesenchymal stromal cells; a new horizon in regenerative medicine. *J Cell Physiol* 2020; **235**: 9185-9210 [PMID: 32452052 DOI: 10.1002/jcp.29803]

7 **Li H**, Ghazanfari R, Zacharaki D, Lim HC, Scheding S. Isolation and characterization of primary bone marrow mesenchymal stromal cells. *Ann N Y Acad Sci* 2016; **1370**: 109-118 [PMID: 27270495 DOI: 10.1111/nyas.13102]

8 **Huang SJ**, Fu RH, Shyu WC, Liu SP, Jong GP, Chiu YW, Wu HS, Tsou YA, Cheng CW, Lin SZ. Adipose-derived stem cells: isolation, characterization, and differentiation potential. *Cell Transplant* 2013; **22**: 701-709 [PMID: 23068312 DOI: 10.3727/096368912X655127]

9 **Wang Y**, Pan J, Wang D, Liu J. The Use of Stem Cells in Neural Regeneration: A Review of Current Opinion. *Curr Stem Cell Res Ther* 2018; **13**: 608-617 [PMID: 30027853 DOI: 10.2174/1574888X13666180720100738]

10 **Beeravolu N**, McKee C, Alamri A, Mikhael S, Brown C, Perez-Cruet M, Chaudhry GR. Isolation and Characterization of Mesenchymal Stromal Cells from Human Umbilical Cord and Fetal Placenta. *J Vis Exp* 2017 [PMID: 28447991 DOI: 10.3791/55224]

11 **Ding DC**, Shyu WC, Lin SZ. Mesenchymal stem cells. *Cell Transplant* 2011; **20**: 5-14 [PMID: 21396235 DOI: 10.3727/096368910X]

12 **Kolf CM**, Cho E, Tuan RS. Mesenchymal stromal cells. Biology of adult mesenchymal stem cells: regulation of niche, self-renewal and differentiation. *Arthritis Res Ther* 2007; **9**: 204 [PMID: 17316462 DOI: 10.1186/ar2116]

13 **Mazzella M**, Walker K, Cormier C, Kapanowski M, Ishmakej A, Saifee A, Govind Y, Chaudhry GR. Regulation of self-renewal and senescence in primitive mesenchymal stem cells by Wnt and TGFβ signaling. *Stem Cell Res Ther* 2023; **14**: 305 [PMID: 37880755 DOI: 10.1186/s13287-023-03533-y]

14 **Pittenger MF**, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, Moorman MA, Simonetti DW, Craig S, Marshak DR. Multilineage potential of adult human mesenchymal stem cells. *Science* 1999; **284**: 143-147 [PMID: 10102814 DOI: 10.1126/science.284.5411.143]

15 **Summer S**, Rossmanith E, Pasztorek M, Fiedler C, Gröger M, Rauscher S, Weber V, Fischer MB. Mesenchymal stem cells support human vascular endothelial cells to form vascular sprouts in human platelet lysate-based matrices. *PLoS One* 2022; **17**: e0278895 [PMID: 36520838 DOI: 10.1371/journal.pone.0278895]

16 **Christ B**, Dollinger MM. The generation of hepatocytes from mesenchymal stem cells and engraftment into the liver. *Curr Opin Organ Transplant* 2011; **16**: 69-75 [PMID: 21150616 DOI: 10.1097/MOT.0b013e3283424f5b]

17 **Jiang Y**, Jahagirdar BN, Reinhardt RL, Schwartz RE, Keene CD, Ortiz-Gonzalez XR, Reyes M, Lenvik T, Lund T, Blackstad M, Du J, Aldrich S, Lisberg A, Low WC, Largaespada DA, Verfaillie CM. Pluripotency of mesenchymal stem cells derived from adult marrow. *Nature* 2002; **418**: 41-49 [PMID: 12077603 DOI: 10.1038/nature00870]

18 **Mawrie D**, Bhattacharjee K, Sharma A, Sharma R, Bhattacharyya J, Bhattacharjee H, Deori N, Kumar A, Jaganathan BG. Human orbital adipose tissue-derived mesenchymal stem cells possess neuroectodermal differentiation and repair ability. *Cell Tissue Res* 2019; **378**: 531-542 [PMID: 31377878 DOI: 10.1007/s00441-019-03072-0]

19 **Huldani H**, Margiana R, Ahmad F, Opulencia MJC, Ansari MJ, Bokov DO, Abdullaeva NN, Siahmansouri H. Immunotherapy of inflammatory bowel disease (IBD) through mesenchymal stem cells. *Int Immunopharmacol* 2022; **107**: 108698 [PMID: 35306284 DOI: 10.1016/j.intimp.2022.108698]

20 **Liu Z**, Mikrani R, Zubair HM, Taleb A, Naveed M, Baig MMFA, Zhang Q, Li C, Habib M, Cui X, Sembatya KR, Lei H, Zhou X. Systemic and local delivery of mesenchymal stem cells for heart renovation: Challenges and innovations. *Eur J Pharmacol* 2020; **876**: 173049 [PMID: 32142771 DOI: 10.1016/j.ejphar.2020.173049]

21 **Nakagawa T**, Sasaki M, Kataoka-Sasaki Y, Yotsuyanagi T, Radtke C, Kocsis JD, Honmou O. Intravenous Infusion of Mesenchymal Stem Cells Promotes the Survival of Random Pattern Flaps in Rats. *Plast Reconstr Surg* 2021; **148**: 799-807 [PMID: 34550936 DOI: 10.1097/PRS.0000000000008327]

22 **Wang Y**, Chen X, Cao W, Shi Y. Plasticity of mesenchymal stem cells in immunomodulation: pathological and therapeutic implications. *Nat Immunol* 2014; **15**: 1009-1016 [PMID: 25329189 DOI: 10.1038/ni.3002]

23 **Eleuteri S**, Fierabracci A. Insights into the Secretome of Mesenchymal Stem Cells and Its Potential Applications. *Int J Mol Sci* 2019; **20** [PMID: 31533317 DOI: 10.3390/ijms20184597]

24 **Harrell CR**, Jovicic N, Djonov V, Arsenijevic N, Volarevic V. Mesenchymal Stem Cell-Derived Exosomes and Other Extracellular Vesicles as New Remedies in the Therapy of Inflammatory Diseases. *Cells* 2019; **8** [PMID: 31835680 DOI: 10.3390/cells8121605]

25 **Cho YJ**, Song HS, Bhang S, Lee S, Kang BG, Lee JC, An J, Cha CI, Nam DH, Kim BS, Joo KM. Therapeutic effects of human adipose stem cell-conditioned medium on stroke. *J Neurosci Res* 2012; **90**: 1794-1802 [PMID: 22535477 DOI: 10.1002/jnr.23063]

26 **Wang Y**, Wang X, Zou Z, Hu Y, Li S, Wang Y. Conditioned medium from bone marrow mesenchymal stem cells relieves spinal cord injury through suppression of Gal-3/NLRP3 and M1 microglia/macrophage polarization. *Pathol Res Pract* 2023; **243**: 154331 [PMID: 36738517 DOI: 10.1016/j.prp.2023.154331]

27 **Su VY**, Lin CS, Hung SC, Yang KY. Mesenchymal Stem Cell-Conditioned Medium Induces Neutrophil Apoptosis Associated with Inhibition of the NF-κB Pathway in Endotoxin-Induced Acute Lung Injury. *Int J Mol Sci* 2019; **20** [PMID: 31060326 DOI: 10.3390/ijms20092208]

28 **Nahar S**, Nakashima Y, Miyagi-Shiohira C, Kinjo T, Toyoda Z, Kobayashi N, Saitoh I, Watanabe M, Noguchi H, Fujita J. Cytokines in adipose-derived mesenchymal stem cells promote the healing of liver disease. *World J Stem Cells* 2018; **10**: 146-159 [PMID: 30631390 DOI: 10.4252/wjsc.v10.i11.146]

29 **Zhang C**, Xiao J, Fa L, Jiang F, Jiang H, Zhou L, Xu Z. Advances in the applications of mesenchymal stem cell-conditioned medium in ocular diseases. *Exp Eye Res* 2023; **233**: 109560 [PMID: 37385531 DOI: 10.1016/j.exer.2023.109560]

30 **Giorgino R**, Albano D, Fusco S, Peretti GM, Mangiavini L, Messina C. Knee Osteoarthritis: Epidemiology, Pathogenesis, and Mesenchymal Stem Cells: What Else Is New? An Update. *Int J Mol Sci* 2023; **24** [PMID: 37047377 DOI: 10.3390/ijms24076405]

31 **Bouche Djatche WH**, Zhu H, Ma W, Li Y, Li Z, Zhao H, Liu Z, Qiao H. Potential of mesenchymal stem cell-derived conditioned medium/secretome as a therapeutic option for ocular diseases. *Regen Med* 2023; **18**: 795-807 [PMID: 37702008 DOI: 10.2217/rme-2023-0089]

32 **Liu X**, Li X, Zhu W, Zhang Y, Hong Y, Liang X, Fan B, Zhao H, He H, Zhang F. Exosomes from mesenchymal stem cells overexpressing MIF enhance myocardial repair. *J Cell Physiol* 2020; **235**: 8010-8022 [PMID: 31960418 DOI: 10.1002/jcp.29456]

33 **Ma H**, Lam PK, Siu WS, Tong CSW, Lo KKY, Koon CM, Wu XX, Li X, Cheng W, Shum WT, Leung PC. Adipose Tissue-Derived Mesenchymal Stem Cells (ADMSCs) and ADMSC-Derived Secretome Expedited Wound Healing in a Rodent Model - A Preliminary Study. *Clin Cosmet Investig Dermatol* 2021; **14**: 753-764 [PMID: 34234501 DOI: 10.2147/CCID.S298105]

34 **Mohamed-Ahmed S**, Fristad I, Lie SA, Suliman S, Mustafa K, Vindenes H, Idris SB. Adipose-derived and bone marrow mesenchymal stem cells: a donor-matched comparison. *Stem Cell Res Ther* 2018; **9**: 168 [PMID: 29921311 DOI: 10.1186/s13287-018-0914-1]

35 **Chun SY**, Lim JO, Lee EH, Han MH, Ha YS, Lee JN, Kim BS, Park MJ, Yeo M, Jung B, Kwon TG. Preparation and Characterization of Human Adipose Tissue-Derived Extracellular Matrix, Growth Factors, and Stem Cells: A Concise Review. *Tissue Eng Regen Med* 2019; **16**: 385-393 [PMID: 31413942 DOI: 10.1007/s13770-019-00199-7]

36 **La Padula S**, Ponzo M, Lombardi M, Iazzetta V, Errico C, Polverino G, Russo F, D'Andrea L, Hersant B, Meningaud JP, Salzano G, Pensato R. Nanofat in Plastic Reconstructive, Regenerative, and Aesthetic Surgery: A Review of Advancements in Face-Focused Applications. *J Clin Med* 2023; **12** [PMID: 37445386 DOI: 10.3390/jcm12134351]

37 **Khazaei S**, Keshavarz G, Bozorgi A, Nazari H, Khazaei M. Adipose tissue-derived stem cells: a comparative review on isolation, culture, and differentiation methods. *Cell Tissue Bank* 2022; **23**: 1-16 [PMID: 33616792 DOI: 10.1007/s10561-021-09905-z]

38 **Kilinc MO**, Santidrian A, Minev I, Toth R, Draganov D, Nguyen D, Lander E, Berman M, Minev B, Szalay AA. The ratio of ADSCs to HSC-progenitors in adipose tissue derived SVF may provide the key to predict the outcome of stem-cell therapy. *Clin Transl Med* 2018; **7**: 5 [PMID: 29417261 DOI: 10.1186/s40169-018-0183-8]

39 **Casteilla L**, Planat-Benard V, Laharrague P, Cousin B. Adipose-derived stromal cells: Their identity and uses in clinical trials, an update. *World J Stem Cells* 2011; **3**: 25-33 [PMID: 21607134 DOI: 10.4252/wjsc.v3.i4.25]

40 **Weyand B**, Vogt PM. Potential of mesenchymal stem cell applications in plastic and reconstructive surgery. *Adv Biochem Eng Biotechnol* 2013; **130**: 55-67 [PMID: 23128957 DOI: 10.1007/10\_2012\_162]

41 **Vishnubalaji R**, Al-Nbaheen M, Kadalmani B, Aldahmash A, Ramesh T. Comparative investigation of the differentiation capability of bone-marrow- and adipose-derived mesenchymal stem cells by qualitative and quantitative analysis. *Cell Tissue Res* 2012; **347**: 419-427 [PMID: 22287041 DOI: 10.1007/s00441-011-1306-3]

42 **Tran DK**, Phuong TNT, Bui NL, Singh V, Looi QH, Koh B, Zaman UMSBM, Foo JB, Wu CC, Show PL, Chu DT. Exploring the Potential of Stem Cell-Based Therapy for Aesthetic and Plastic Surgery. *IEEE Rev Biomed Eng* 2023; **16**: 386-402 [PMID: 34905495 DOI: 10.1109/RBME.2021.3134994]

43 **Kosaric N**, Kiwanuka H, Gurtner GC. Stem cell therapies for wound healing. *Expert Opin Biol Ther* 2019; **19**: 575-585 [PMID: 30900481 DOI: 10.1080/14712598.2019.1596257]

44 **Sterodimas A**, de Faria J, Nicaretta B, Boriani F. Autologous fat transplantation versus adipose-derived stem cell-enriched lipografts: a study. *Aesthet Surg J* 2011; **31**: 682-693 [PMID: 21813882 DOI: 10.1177/1090820X11415976]

45 **Caputo G**, Scarabosio A, Di Filippo J, Contessi Negrini F, Albanese R, Mura S, Parodi PC. Optimizing Acellular Dermal Matrix Integration in Heterologous Breast Reconstructive Surgery: Surgical Tips and Post-Operative Management. *Medicina (Kaunas)* 2023; **59** [PMID: 37512043 DOI: 10.3390/medicina59071231]

46 **Spiekman M**, van Dongen JA, Willemsen JC, Hoppe DL, van der Lei B, Harmsen MC. The power of fat and its adipose-derived stromal cells: emerging concepts for fibrotic scar treatment. *J Tissue Eng Regen Med* 2017; **11**: 3220-3235 [PMID: 28156060 DOI: 10.1002/term.2213]

47 **Boháč M**, Csöbönyeiová M, Kupcová I, Zamborský R, Fedeleš J, Koller J. Stem cell regenerative potential for plastic and reconstructive surgery. *Cell Tissue Bank* 2016; **17**: 735-744 [PMID: 27604466 DOI: 10.1007/s10561-016-9583-4]

48 **Prantl L**, Brix E, Kempa S, Felthaus O, Eigenberger A, Brébant V, Anker A, Strauss C. Facial Rejuvenation with Concentrated Lipograft-A 12 Month Follow-Up Study. *Cells* 2021; **10** [PMID: 33800325 DOI: 10.3390/cells10030594]

49 **Daniel MG**, Wu AY. Applications of stem cell biology to oculoplastic surgery. *Curr Opin Ophthalmol* 2016; **27**: 428-432 [PMID: 27206262 DOI: 10.1097/ICU.0000000000000288]

50 **Chen M**, Chen X, Li X, Wang J, Wu J, Wang Q, Huang Y, Li Z, Wang L. Subconjunctival Administration of Mesenchymal Stem Cells Alleviates Ocular Inflammation in a Murine Model of Corneal Alkali Burn. *Stem Cells* 2023; **41**: 592-602 [PMID: 37061809 DOI: 10.1093/stmcls/sxad027]

51 **Hussein Abed H**, Hameed Fathullah Al-Bayati A. Clinical and Histopathological Study of the Effect of Adipose-Derived Mesenchymal Stem Cells on Corneal Neovascularization following Alkali Burn in a Rabbit Model. *Arch Razi Inst* 2022; **77**: 1715-1721 [PMID: 37123111 DOI: 10.22092/ARI.2022.357998.2136]

52 **Cejkova J**, Trosan P, Cejka C, Lencova A, Zajicova A, Javorkova E, Kubinova S, Sykova E, Holan V. Suppression of alkali-induced oxidative injury in the cornea by mesenchymal stem cells growing on nanofiber scaffolds and transferred onto the damaged corneal surface. *Exp Eye Res* 2013; **116**: 312-323 [PMID: 24145108 DOI: 10.1016/j.exer.2013.10.002]

53 **Ke Y**, Wu Y, Cui X, Liu X, Yu M, Yang C, Li X. Polysaccharide hydrogel combined with mesenchymal stem cells promotes the healing of corneal alkali burn in rats. *PLoS One* 2015; **10**: e0119725 [PMID: 25789487 DOI: 10.1371/journal.pone.0119725]

54 **Yu F**, Gong D, Yan D, Wang H, Witman N, Lu Y, Fu W, Fu Y. Enhanced adipose-derived stem cells with IGF-1-modified mRNA promote wound healing following corneal injury. *Mol Ther* 2023; **31**: 2454-2471 [PMID: 37165618 DOI: 10.1016/j.ymthe.2023.05.002]

55 **Bandeira F**, Goh TW, Setiawan M, Yam GH, Mehta JS. Cellular therapy of corneal epithelial defect by adipose mesenchymal stem cell-derived epithelial progenitors. *Stem Cell Res Ther* 2020; **11**: 14 [PMID: 31900226 DOI: 10.1186/s13287-019-1533-1]

56 **Zeppieri M**, Salvetat ML, Beltrami AP, Cesselli D, Bergamin N, Russo R, Cavaliere F, Varano GP, Alcalde I, Merayo J, Brusini P, Beltrami CA, Parodi PC. Human adipose-derived stem cells for the treatment of chemically burned rat cornea: preliminary results. *Curr Eye Res* 2013; **38**: 451-463 [PMID: 23373736 DOI: 10.3109/02713683.2012.763100]

57 **Shibata S**, Hayashi R, Okubo T, Kudo Y, Baba K, Honma Y, Nishida K. The secretome of adipose-derived mesenchymal stem cells attenuates epithelial-mesenchymal transition in human corneal epithelium. *Regen Ther* 2019; **11**: 114-122 [PMID: 31312693 DOI: 10.1016/j.reth.2019.06.005]

58 **Oh JY**, Lee RH, Yu JM, Ko JH, Lee HJ, Ko AY, Roddy GW, Prockop DJ. Intravenous mesenchymal stem cells prevented rejection of allogeneic corneal transplants by aborting the early inflammatory response. *Mol Ther* 2012; **20**: 2143-2152 [PMID: 22929658 DOI: 10.1038/mt.2012.165]

59 **Villatoro AJ**, Fernández V, Claros S, Rico-Llanos GA, Becerra J, Andrades JA. Use of adipose-derived mesenchymal stem cells in keratoconjunctivitis sicca in a canine model. *Biomed Res Int* 2015; **2015**: 527926 [PMID: 25802852 DOI: 10.1155/2015/527926]

60 **Møller-Hansen M**, Larsen AC, Toft PB, Lynggaard CD, Schwartz C, Bruunsgaard H, Haack-Sørensen M, Ekblond A, Kastrup J, Heegaard S. Safety and feasibility of mesenchymal stem cell therapy in patients with aqueous deficient dry eye disease. *Ocul Surf* 2021; **19**: 43-52 [PMID: 33253910 DOI: 10.1016/j.jtos.2020.11.013]

61 **Naderi N**, Combellack EJ, Griffin M, Sedaghati T, Javed M, Findlay MW, Wallace CG, Mosahebi A, Butler PE, Seifalian AM, Whitaker IS. The regenerative role of adipose-derived stem cells (ADSC) in plastic and reconstructive surgery. *Int Wound J* 2017; **14**: 112-124 [PMID: 26833722 DOI: 10.1111/iwj.12569]

62 **Faraj HG**, Hoang-Xuan T. Chronic cicatrizing conjunctivitis. *Curr Opin Ophthalmol* 2001; **12**: 250-257 [PMID: 11507337 DOI: 10.1097/00055735-200108000-00003]

63 **Tung CI**. Graft versus host disease: what should the oculoplastic surgeon know? *Curr Opin Ophthalmol* 2017; **28**: 499-504 [PMID: 28598869 DOI: 10.1097/ICU.0000000000000400]

64 **Baudouin C**, Labbé A, Liang H, Pauly A, Brignole-Baudouin F. Preservatives in eyedrops: the good, the bad and the ugly. *Prog Retin Eye Res* 2010; **29**: 312-334 [PMID: 20302969 DOI: 10.1016/j.preteyeres.2010.03.001]

65 **Barrientez B**, Nicholas SE, Whelchel A, Sharif R, Hjortdal J, Karamichos D. Corneal injury: Clinical and molecular aspects. *Exp Eye Res* 2019; **186**: 107709 [PMID: 31238077 DOI: 10.1016/j.exer.2019.107709]

66 **Alves M**, Asbell P, Dogru M, Giannaccare G, Grau A, Gregory D, Kim DH, Marini MC, Ngo W, Nowinska A, Saldanha IJ, Villani E, Wakamatsu TH, Yu M, Stapleton F. TFOS Lifestyle Report: Impact of environmental conditions on the ocular surface. *Ocul Surf* 2023; **29**: 1-52 [PMID: 37062427 DOI: 10.1016/j.jtos.2023.04.007]

67 **Deng SX**, Borderie V, Chan CC, Dana R, Figueiredo FC, Gomes JAP, Pellegrini G, Shimmura S, Kruse FE; and The International Limbal Stem Cell Deficiency Working Group. Global Consensus on Definition, Classification, Diagnosis, and Staging of Limbal Stem Cell Deficiency. *Cornea* 2019; **38**: 364-375 [PMID: 30614902 DOI: 10.1097/ICO.0000000000001820]

68 **Deng SX**, Kruse F, Gomes JAP, Chan CC, Daya S, Dana R, Figueiredo FC, Kinoshita S, Rama P, Sangwan V, Slomovic AR, Tan D; and the International Limbal Stem Cell Deficiency Working Group. Global Consensus on the Management of Limbal Stem Cell Deficiency. *Cornea* 2020; **39**: 1291-1302 [PMID: 32639314 DOI: 10.1097/ICO.0000000000002358]

69 **Tan DT**, Dart JK, Holland EJ, Kinoshita S. Corneal transplantation. *Lancet* 2012; **379**: 1749-1761 [PMID: 22559901 DOI: 10.1016/S0140-6736(12)60437-1]

70 **Yin J**, Jurkunas U. Limbal Stem Cell Transplantation and Complications. *Semin Ophthalmol* 2018; **33**: 134-141 [PMID: 29172876 DOI: 10.1080/08820538.2017.1353834]

71 **Zhu J**, Inomata T, Di Zazzo A, Kitazawa K, Okumura Y, Coassin M, Surico PL, Fujio K, Yanagawa A, Miura M, Akasaki Y, Fujimoto K, Nagino K, Midorikawa-Inomata A, Hirosawa K, Kuwahara M, Huang T, Shokirova H, Eguchi A, Murakami A. Role of Immune Cell Diversity and Heterogeneity in Corneal Graft Survival: A Systematic Review and Meta-Analysis. *J Clin Med* 2021; **10** [PMID: 34682792 DOI: 10.3390/jcm10204667]

72 **Di Zazzo A**, Kheirkhah A, Abud TB, Goyal S, Dana R. Management of high-risk corneal transplantation. *Surv Ophthalmol* 2017; **62**: 816-827 [PMID: 28012874 DOI: 10.1016/j.survophthal.2016.12.010]

73 **Di Zazzo A**, Coassin M, Surico PL, Bonini S. Age-related ocular surface failure: A narrative review. *Exp Eye Res* 2022; **219**: 109035 [PMID: 35307396 DOI: 10.1016/j.exer.2022.109035]

74 **Sahu A**, Foulsham W, Amouzegar A, Mittal SK, Chauhan SK. The therapeutic application of mesenchymal stem cells at the ocular surface. *Ocul Surf* 2019; **17**: 198-207 [PMID: 30695735 DOI: 10.1016/j.jtos.2019.01.006]

75 **Pargament JM**, Armenia J, Nerad JA. Physical and chemical injuries to eyes and eyelids. *Clin Dermatol* 2015; **33**: 234-237 [PMID: 25704943 DOI: 10.1016/j.clindermatol.2014.10.015]

76 **Bizrah M**, Yusuf A, Ahmad S. An update on chemical eye burns. *Eye (Lond)* 2019; **33**: 1362-1377 [PMID: 31086244 DOI: 10.1038/s41433-019-0456-5]

77 **Alemi H**, Dehghani S, Forouzanfar K, Surico PL, Narimatsu A, Musayeva A, Sharifi S, Wang S, Dohlman TH, Yin J, Chen Y, Dana R. Insights into mustard gas keratopathy- characterizing corneal layer-specific changes in mice exposed to nitrogen mustard. *Exp Eye Res* 2023; **236**: 109657 [PMID: 37722586 DOI: 10.1016/j.exer.2023.109657]

78 **Dua HS**, Ting DSJ, Al Saadi A, Said DG. Chemical eye injury: pathophysiology, assessment and management. *Eye (Lond)* 2020; **34**: 2001-2019 [PMID: 32572184 DOI: 10.1038/s41433-020-1026-6]

79 **Said DG**, Dua HS. Chemical burns acid or alkali, what's the difference? *Eye (Lond)* 2020; **34**: 1299-1300 [PMID: 31848459 DOI: 10.1038/s41433-019-0735-1]

80 **Soleimani M**, Masoumi A, Momenaei B, Cheraqpour K, Koganti R, Chang AY, Ghassemi M, Djalilian AR. Applications of mesenchymal stem cells in ocular surface diseases: sources and routes of delivery. *Expert Opin Biol Ther* 2023; **23**: 509-525 [PMID: 36719365 DOI: 10.1080/14712598.2023.2175605]

81 **Holan V**, Javorkova E. Mesenchymal stem cells, nanofiber scaffolds and ocular surface reconstruction. *Stem Cell Rev Rep* 2013; **9**: 609-619 [PMID: 23733704 DOI: 10.1007/s12015-013-9449-0]

82 **Yao L**, Li ZR, Su WR, Li YP, Lin ML, Zhang WX, Liu Y, Wan Q, Liang D. Role of mesenchymal stem cells on cornea wound healing induced by acute alkali burn. *PLoS One* 2012; **7**: e30842 [PMID: 22363499 DOI: 10.1371/journal.pone.0030842]

83 **Mittal SK**, Omoto M, Amouzegar A, Sahu A, Rezazadeh A, Katikireddy KR, Shah DI, Sahu SK, Chauhan SK. Restoration of Corneal Transparency by Mesenchymal Stem Cells. *Stem Cell Reports* 2016; **7**: 583-590 [PMID: 27693426 DOI: 10.1016/j.stemcr.2016.09.001]

84 **Li F**, Zhao SZ. Mesenchymal stem cells: Potential role in corneal wound repair and transplantation. *World J Stem Cells* 2014; **6**: 296-304 [PMID: 25126379 DOI: 10.4252/wjsc.v6.i3.296]

85 **Venkatakrishnan J**, Saeed Y, Kao WW. Trends in using mesenchymal stromal/stem cells (MSCs) in treating corneal diseases. *Ocul Surf* 2022; **26**: 255-267 [PMID: 36240995 DOI: 10.1016/j.jtos.2022.10.003]

86 **Galindo S**, Herreras JM, López-Paniagua M, Rey E, de la Mata A, Plata-Cordero M, Calonge M, Nieto-Miguel T. Therapeutic Effect of Human Adipose Tissue-Derived Mesenchymal Stem Cells in Experimental Corneal Failure Due to Limbal Stem Cell Niche Damage. *Stem Cells* 2017; **35**: 2160-2174 [PMID: 28758321 DOI: 10.1002/stem.2672]

87 **Khan-Farooqi H**, Chodosh J. Autologous Limbal Stem Cell Transplantation: The Progression of Diagnosis and Treatment. *Semin Ophthalmol* 2016; **31**: 91-98 [PMID: 26959134 DOI: 10.3109/08820538.2015.1114862]

88 **Chotikavanich S**, Poriswanish N, Luangaram A, Numnoi P, Thamphithak R, Pinitpuwadol W, Uiprasertkul M, Chirapapaisan C, Sikarinkul R, Prabhasawat P. Genetic analysis of allogenic donor cells after successful allo-limbal epithelial transplantation in simple and cultivated limbal epithelial transplantation procedures. *Sci Rep* 2023; **13**: 4290 [PMID: 36922551 DOI: 10.1038/s41598-023-31261-z]

89 **Huang Y**, Wu Q, Tam PKH. Immunomodulatory Mechanisms of Mesenchymal Stem Cells and Their Potential Clinical Applications. *Int J Mol Sci* 2022; **23** [PMID: 36077421 DOI: 10.3390/ijms231710023]

90 **Nieto-Nicolau N**, Martínez-Conesa EM, Fuentes-Julián S, Arnalich-Montiel F, García-Tuñón I, De Miguel MP, Casaroli-Marano RP. Priming human adipose-derived mesenchymal stem cells for corneal surface regeneration. *J Cell Mol Med* 2021; **25**: 5124-5137 [PMID: 33951289 DOI: 10.1111/jcmm.16501]

91 **Martínez-Conesa EM**, Espel E, Reina M, Casaroli-Marano RP. Characterization of ocular surface epithelial and progenitor cell markers in human adipose stromal cells derived from lipoaspirates. *Invest Ophthalmol Vis Sci* 2012; **53**: 513-520 [PMID: 22199247 DOI: 10.1167/iovs.11-7550]

92 **Nieto-Miguel T**, Galindo S, Reinoso R, Corell A, Martino M, Pérez-Simón JA, Calonge M. In vitro simulation of corneal epithelium microenvironment induces a corneal epithelial-like cell phenotype from human adipose tissue mesenchymal stem cells. *Curr Eye Res* 2013; **38**: 933-944 [PMID: 23767776 DOI: 10.3109/02713683.2013.802809]

93 **Alió Del Barrio JL**, De la Mata A, De Miguel MP, Arnalich-Montiel F, Nieto-Miguel T, El Zarif M, Cadenas-Martín M, López-Paniagua M, Galindo S, Calonge M, Alió JL. Corneal Regeneration Using Adipose-Derived Mesenchymal Stem Cells. *Cells* 2022; **11** [PMID: 36010626 DOI: 10.3390/cells11162549]

94 **Kalluri R**, Neilson EG. Epithelial-mesenchymal transition and its implications for fibrosis. *J Clin Invest* 2003; **112**: 1776-1784 [PMID: 14679171 DOI: 10.1172/JCI200320530]

95 **Shu DY**, Lovicu FJ. Myofibroblast transdifferentiation: The dark force in ocular wound healing and fibrosis. *Prog Retin Eye Res* 2017; **60**: 44-65 [PMID: 28807717 DOI: 10.1016/j.preteyeres.2017.08.001]

96 **Domdey M**, Kluth MA, Maßlo C, Ganss C, Frank MH, Frank NY, Coroneo MT, Cursiefen C, Notara M. Consecutive dosing of UVB irradiation induces loss of ABCB5 expression and activation of EMT and fibrosis proteins in limbal epithelial cells similar to pterygium epithelium. *Stem Cell Res* 2022; **64**: 102936 [PMID: 36242878 DOI: 10.1016/j.scr.2022.102936]

97 **Kato N**, Shimmura S, Kawakita T, Miyashita H, Ogawa Y, Yoshida S, Higa K, Okano H, Tsubota K. Beta-catenin activation and epithelial-mesenchymal transition in the pathogenesis of pterygium. *Invest Ophthalmol Vis Sci* 2007; **48**: 1511-1517 [PMID: 17389479 DOI: 10.1167/iovs.06-1060]

98 **Huang S**, Wu Y, Gao D, Fu X. Paracrine action of mesenchymal stromal cells delivered by microspheres contributes to cutaneous wound healing and prevents scar formation in mice. *Cytotherapy* 2015; **17**: 922-931 [PMID: 25939802 DOI: 10.1016/j.jcyt.2015.03.690]

99 **Sikora B**, Skubis-Sikora A, Prusek A, Gola J. Paracrine activity of adipose derived stem cells on limbal epithelial stem cells. *Sci Rep* 2021; **11**: 19956 [PMID: 34620960 DOI: 10.1038/s41598-021-99435-1]

100 **Yin J**. Advances in corneal graft rejection. *Curr Opin Ophthalmol* 2021; **32**: 331-337 [PMID: 33989234 DOI: 10.1097/ICU.0000000000000767]

101 **De Miguel MP**, Fuentes-Julián S, Blázquez-Martínez A, Pascual CY, Aller MA, Arias J, Arnalich-Montiel F. Immunosuppressive properties of mesenchymal stem cells: advances and applications. *Curr Mol Med* 2012; **12**: 574-591 [PMID: 22515979 DOI: 10.2174/156652412800619950]

102 **Le Blanc K**, Ringdén O. Immunomodulation by mesenchymal stem cells and clinical experience. *J Intern Med* 2007; **262**: 509-525 [PMID: 17949362 DOI: 10.1111/j.1365-2796.2007.01844.x]

103 **Xiao Y**, Zhang Y, Li Y, Peng N, Liu Q, Qiu D, Cho J, Borlongan CV, Yu G. Exosomes Derived From Mesenchymal Stem Cells Pretreated With Ischemic Rat Heart Extracts Promote Angiogenesis via the Delivery of DMBT1. *Cell Transplant* 2022; **31**: 9636897221102898 [PMID: 35726847 DOI: 10.1177/09636897221102898]

104 **Sun J**, Shen H, Shao L, Teng X, Chen Y, Liu X, Yang Z, Shen Z. HIF-1α overexpression in mesenchymal stem cell-derived exosomes mediates cardioprotection in myocardial infarction by enhanced angiogenesis. *Stem Cell Res Ther* 2020; **11**: 373 [PMID: 32859268 DOI: 10.1186/s13287-020-01881-7]

105 **Agorogiannis GI**, Alexaki VI, Castana O, Kymionis GD. Topical application of autologous adipose-derived mesenchymal stem cells (MSCs) for persistent sterile corneal epithelial defect. *Graefes Arch Clin Exp Ophthalmol* 2012; **250**: 455-457 [PMID: 22012407 DOI: 10.1007/s00417-011-1841-3]

106 **Galindo S**, de la Mata A, López-Paniagua M, Herreras JM, Pérez I, Calonge M, Nieto-Miguel T. Subconjunctival injection of mesenchymal stem cells for corneal failure due to limbal stem cell deficiency: state of the art. *Stem Cell Res Ther* 2021; **12**: 60 [PMID: 33441175 DOI: 10.1186/s13287-020-02129-0]

107 **Jia Z**, Jiao C, Zhao S, Li X, Ren X, Zhang L, Han ZC, Zhang X. Immunomodulatory effects of mesenchymal stem cells in a rat corneal allograft rejection model. *Exp Eye Res* 2012; **102**: 44-49 [PMID: 22800963 DOI: 10.1016/j.exer.2012.06.008]

108 **Oh JY**, Kim MK, Ko JH, Lee HJ, Lee JH, Wee WR. Rat allogeneic mesenchymal stem cells did not prolong the survival of corneal xenograft in a pig-to-rat model. *Vet Ophthalmol* 2009; **12** Suppl 1: 35-40 [PMID: 19891650 DOI: 10.1111/j.1463-5224.2009.00724.x]

109 **Al-Jaibaji O**, Swioklo S, Connon CJ. Mesenchymal stromal cells for ocular surface repair. *Expert Opin Biol Ther* 2019; **19**: 643-653 [PMID: 30979344 DOI: 10.1080/14712598.2019.1607836]

110 **Bonini S**, Di Zazzo A, Surico PL, Balzamino BO, Luccarelli V, Niutta M, Coassin M, Micera A. Inflammation and Dry Eye-like Symptoms as Concomitant Manifestations of Laryngo-Pharyngeal Reflux. *Curr Eye Res* 2023; **48**: 724-730 [PMID: 37092761 DOI: 10.1080/02713683.2023.2207210]

111 **Bron AJ**, de Paiva CS, Chauhan SK, Bonini S, Gabison EE, Jain S, Knop E, Markoulli M, Ogawa Y, Perez V, Uchino Y, Yokoi N, Zoukhri D, Sullivan DA. TFOS DEWS II pathophysiology report. *Ocul Surf* 2017; **15**: 438-510 [PMID: 28736340 DOI: 10.1016/j.jtos.2017.05.011]

112 **Franceschi C**, Capri M, Monti D, Giunta S, Olivieri F, Sevini F, Panourgia MP, Invidia L, Celani L, Scurti M, Cevenini E, Castellani GC, Salvioli S. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. *Mech Ageing Dev* 2007; **128**: 92-105 [PMID: 17116321 DOI: 10.1016/j.mad.2006.11.016]

113 **Franceschi C**, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann N Y Acad Sci* 2000; **908**: 244-254 [PMID: 10911963 DOI: 10.1111/j.1749-6632.2000.tb06651.x]

114 **Franceschi C**, Bonafè M, Valensin S. Human immunosenescence: the prevailing of innate immunity, the failing of clonotypic immunity, and the filling of immunological space. *Vaccine* 2000; **18**: 1717-1720 [PMID: 10689155 DOI: 10.1016/S0264-410X(99)00513-7]

115 **Zhao S**, Song N, Gong L. Changes of Dry Eye Related Markers and Tear Inflammatory Cytokines After Upper Blepharoplasty. *Front Med (Lausanne)* 2021; **8**: 763611 [PMID: 34957146 DOI: 10.3389/fmed.2021.763611]

116 **Yan Y**, Zhou Y, Zhang S, Cui C, Song X, Zhu X, Fu Y. Impact of Full-Incision Double-Eyelid Blepharoplasty on Tear Film Dynamics and Dry Eye Symptoms in Young Asian Females. *Aesthetic Plast Surg* 2020; **44**: 2109-2116 [PMID: 32696159 DOI: 10.1007/s00266-020-01874-0]

117 **Hollander MHJ**, Pott JWR, Delli K, Vissink A, Schepers RH, Jansma J. Impact of upper blepharoplasty, with or without orbicularis oculi muscle removal, on tear film dynamics and dry eye symptoms: A randomized controlled trial. *Acta Ophthalmol* 2022; **100**: 564-571 [PMID: 34612583 DOI: 10.1111/aos.15036]

118 **Tsubota K**, Pflugfelder SC, Liu Z, Baudouin C, Kim HM, Messmer EM, Kruse F, Liang L, Carreno-Galeano JT, Rolando M, Yokoi N, Kinoshita S, Dana R. Defining Dry Eye from a Clinical Perspective. *Int J Mol Sci* 2020; **21** [PMID: 33291796 DOI: 10.3390/ijms21239271]

119 **Chauhan SK**, El Annan J, Ecoiffier T, Goyal S, Zhang Q, Saban DR, Dana R. Autoimmunity in dry eye is due to resistance of Th17 to Treg suppression. *J Immunol* 2009; **182**: 1247-1252 [PMID: 19155469 DOI: 10.4049/jimmunol.182.3.1247]

120 **Chen Y**, Dana R. Autoimmunity in dry eye disease - An updated review of evidence on effector and memory Th17 cells in disease pathogenicity. *Autoimmun Rev* 2021; **20**: 102933 [PMID: 34509656 DOI: 10.1016/j.autrev.2021.102933]

121 **Jiang Y**, Lin S, Gao Y. Mesenchymal Stromal Cell-Based Therapy for Dry Eye: Current Status and Future Perspectives. *Cell Transplant* 2022; **31**: 9636897221133818 [PMID: 36398793 DOI: 10.1177/09636897221133818]

122 **Lee MJ**, Ko AY, Ko JH, Lee HJ, Kim MK, Wee WR, Khwarg SI, Oh JY. Mesenchymal stem/stromal cells protect the ocular surface by suppressing inflammation in an experimental dry eye. *Mol Ther* 2015; **23**: 139-146 [PMID: 25152016 DOI: 10.1038/mt.2014.159]

123 **Beyazyıldız E**, Pınarlı FA, Beyazyıldız O, Hekimoğlu ER, Acar U, Demir MN, Albayrak A, Kaymaz F, Sobacı G, Delibaşı T. Efficacy of topical mesenchymal stem cell therapy in the treatment of experimental dry eye syndrome model. *Stem Cells Int* 2014; **2014**: 250230 [PMID: 25136370 DOI: 10.1155/2014/250230]

124 **Chen W**, Yu Y, Ma J, Olsen N, Lin J. Mesenchymal Stem Cells in Primary Sjögren's Syndrome: Prospective and Challenges. *Stem Cells Int* 2018; **2018**: 4357865 [PMID: 30305818 DOI: 10.1155/2018/4357865]

125 **Park SA**, Reilly CM, Wood JA, Chung DJ, Carrade DD, Deremer SL, Seraphin RL, Clark KC, Zwingenberger AL, Borjesson DL, Hayashi K, Russell P, Murphy CJ. Safety and immunomodulatory effects of allogeneic canine adipose-derived mesenchymal stromal cells transplanted into the region of the lacrimal gland, the gland of the third eyelid and the knee joint. *Cytotherapy* 2013; **15**: 1498-1510 [PMID: 23992828 DOI: 10.1016/j.jcyt.2013.06.009]

126 **Wang G**, Li H, Long H, Gong X, Hu S, Gong C. Exosomes Derived from Mouse Adipose-Derived Mesenchymal Stem Cells Alleviate Benzalkonium Chloride-Induced Mouse Dry Eye Model via Inhibiting NLRP3 Inflammasome. *Ophthalmic Res* 2022; **65**: 40-51 [PMID: 34530425 DOI: 10.1159/000519458]

127 **Wu AY**, Daniel MG. Using stem cell biology to study and treat ophthalmologic and oculoplastic diseases. *Taiwan J Ophthalmol* 2017; **7**: 77-81 [PMID: 29018761 DOI: 10.4103/tjo.tjo\_16\_17]

128 **Zarei F**, Abbaszadeh A. Stem cell and skin rejuvenation. *J Cosmet Laser Ther* 2018; **20**: 193-197 [PMID: 29394110 DOI: 10.1080/14764172.2017.1383615]

129 **Lupo F**, Ioppolo L, Pino D, Meduri A, d'Alcontres FS, R Colonna M, Delia G. Lipograft in cicatricial ectropion. *Ann Ital Chir* 2016; **87**: 466-469 [PMID: 27842016]

130 **Benslimane F**, Pessoa Ladvocat Cintra H. 15 Years of Upper Eyelid Micro-fat Graft: the Good, the Bad and the Ugly. *Aesthetic Plast Surg* 2021; **45**: 1035-1046 [PMID: 32944851 DOI: 10.1007/s00266-020-01946-1]

131 **Zoumalan CI**, Roostaeian J. Simplifying Blepharoplasty. *Plast Reconstr Surg* 2016; **137**: 196e-213e [PMID: 26710052 DOI: 10.1097/PRS.0000000000001906]

132 **Shimizu Y**, Ntege EH, Sunami H, Inoue Y. Regenerative medicine strategies for hair growth and regeneration: A narrative review of literature. *Regen Ther* 2022; **21**: 527-539 [PMID: 36382136 DOI: 10.1016/j.reth.2022.10.005]

133 **Gentile P**, Garcovich S. Advances in Regenerative Stem Cell Therapy in Androgenic Alopecia and Hair Loss: Wnt pathway, Growth-Factor, and Mesenchymal Stem Cell Signaling Impact Analysis on Cell Growth and Hair Follicle Development. *Cells* 2019; **8** [PMID: 31100937 DOI: 10.3390/cells8050466]

134 **Suh A**, Pham A, Cress MJ, Pincelli T, TerKonda SP, Bruce AJ, Zubair AC, Wolfram J, Shapiro SA. Adipose-derived cellular and cell-derived regenerative therapies in dermatology and aesthetic rejuvenation. *Ageing Res Rev* 2019; **54**: 100933 [PMID: 31247326 DOI: 10.1016/j.arr.2019.100933]

135 **Korn BS**, Kikkawa DO, Cohen SR, Hartstein M, Annunziata CC. Treatment of lower eyelid malposition with dermis fat grafting. *Ophthalmology* 2008; **115**: 744-751.e2 [PMID: 18067964 DOI: 10.1016/j.ophtha.2007.06.039]

136 **Zhou T**, Yuan Z, Weng J, Pei D, Du X, He C, Lai P. Challenges and advances in clinical applications of mesenchymal stromal cells. *J Hematol Oncol* 2021; **14**: 24 [PMID: 33579329 DOI: 10.1186/s13045-021-01037-x]

137 **Golchin A**, Chatziparasidou A, Ranjbarvan P, Niknam Z, Ardeshirylajimi A. Embryonic Stem Cells in Clinical Trials: Current Overview of Developments and Challenges. *Adv Exp Med Biol* 2021; **1312**: 19-37 [PMID: 33159303 DOI: 10.1007/5584\_2020\_592]

138 **Tan Y**, Ooi S, Wang L. Immunogenicity and tumorigenicity of pluripotent stem cells and their derivatives: genetic and epigenetic perspectives. *Curr Stem Cell Res Ther* 2014; **9**: 63-72 [PMID: 24160683 DOI: 10.2174/1574888X113086660068]

139 **Ben-David U**, Benvenisty N. The tumorigenicity of human embryonic and induced pluripotent stem cells. *Nat Rev Cancer* 2011; **11**: 268-277 [PMID: 21390058 DOI: 10.1038/nrc3034]

**Footnotes**

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** December 7, 2023

**First decision:** December 31, 2023

**Article in press:**

**Specialty type:** Cell and tissue engineering

**Country/Territory of origin:** Italy

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Li YH, China **S-Editor:** Wang JJ **L-Editor:** A **P-Editor:**

**Table 1 Studies included from literature about mesenchymal stem cells applications in ocular and periocular reconstructive surgery**

|  |  |  |  |
| --- | --- | --- | --- |
| **Therapy** | **Model** | **Outcomes** | **Ref.** |
| hP-MSCs | Corneal alkali burn in mice | Subconjunctival administration of MSCs exerted anti-inflammatory and anti-apoptotic effects in the cornea, anterior uvea, and retina after corneal alkali burn | Chen *et al*[50], 2023 |
| Adipose-derived MSCs | Corneal alkali burn in rabbits | Subconjunctival administration of MSCs significantly decreased corneal neovascularization and improved re-epithelialization | Hussein Abed *et al*[51], 2022 |
| Nanofiber scaffolds seeded with MSCs | Corneal alkali burn in rabbits | Topical application of MSCs growing on nanofiber scaffolds reduced oxidative stress in the cornea, apoptotic cell death, and decreased matrix metalloproteinase levels as well as the induction of pro-inflammatory cytokines, accelerating wound healing | Cejkova *et al*[52], 2013 |
| Polysaccharide hydrogel combined with MSCs | Corneal alkali burn in rats | Subconjunctival injections of MSCs increased TGF-β and reduced the expression of TNF-α, MIP-1α, and MCP-1 and suppressed VEGF and MMP-2 expression in alkali-injured corneas. These effects were significantly enhanced by polysaccharides | Ke *et al*[53], 2015 |
| modIGF1-engineered adipose-derived MSCs | Human injured cornea and *in-vitro* | Subconjunctival injection of MSCmodIGF1 treatment could achieve the most extensive recovery of corneal morphology and function when compared not only with simple MSCs but also IGF-1 protein eyedrops, which was reflected by the healing of corneal epithelium and limbus, the inhibition of corneal stromal fibrosis, angiogenesis, and lymphangiogenesis, and also the repair of corneal nerves | Yu *et al*[54], 2023 |
| Human adipose-derived MSCs | LSCD in rats | Topical application of human adipose-derived MSCs epithelial-like cells, *via* mesenchymal-epithelial transition, recovered the corneal epithelium from epithelial defect associated with LSCD | Bandeira *et al*[55], 2020  |
| Human adipose-derived MSCs | Corneal alkali burn in rats | Topical treatment with human adipose-derived MSCs improved ocular surface healing contributing to re-epithelization with less inflammatory cells and limited fibroblast activation structure compared with the control eyes | Zeppieri *et al*[56], 2013  |
| Adipose-derived MSCs secretome | *In-vitro* | The secretome of adipose-derived MSCs can inhibit TGF-β-induced epithelial-mesenchymal transition in human corneal epithelial cells | Shibata *et al*[57], 2019 |
| Human MSCs | Cornea transplantation in mice | Intravenous injections of hMSCs improve the survival of corneal allografts without engraftment and primarily by secreting TSG-6 which acts by aborting early inflammatory responses | Oh *et al*[58], 2012 |
| Allogeneic adipose-derived MSCs | Dry eye in a canine model | Adipose-derived MSCs around lacrimal glands have been found as an effective therapeutic alternative to treat dogs with dry eye disease. Implanted cells were well tolerated and were effective in reducing clinical signs of dry eye with a sustained effect during the study period | Villatoro *et al*[59], 2015 |
| Adipose-derived MSCs | Humans with dry eye disease | Injection of allogeneic adipose-derived MSCs into the lacrimal glands is a safe and feasible treatment for patients with severe aqueous-deficient dry eye disease | Møller-Hansen *et al*[60], 2021 |
| Adipose-derived MSCs | Oculoplastic surgery | The identification and characterization of endogenous stem cell populations in the eye makes it possible to obtain specific tissues through induced pluripotent stem cell differentiation, permitting their use in transplants for oculoplastic surgery | Daniel *et al*[49], 2016 |
| Adipose-derived stem cell | Application in plastic surgery | Clinical applications of adipose-derived MSCs are broadly ranged; the ease of cell harvest and high yield with minimal donor-site morbidity make them an ideal cell source. Additionally, the multi-lineage potential of these cells demonstrates the significant opportunities they present within the field of tissue engineering | Naderi *et al*[61], 2017 |
| Stem-cell therapy | Application in plastic and aesthetic surgery | Stem cell-associated therapies are widely used because of their potential for self-renewable and multipotent differentiation ability. Stem cells have become more attractive for aesthetic uses and plastic surgery, including scar reduction, breast augmentation, facial contouring, hand rejuvenation, and anti-aging. The current preclinical and clinical studies of stem cells for aesthetic uses also showed promising outcomes | Tran *et al*[42], 2023 |

MSC: Mesenchymal stem cell; TGF-β: Transforming growth factor beta; TNF-α: Tumor necrosis factor alpha; MIP-1α: Macrophage inflammatory protein-1alpha; MCP-1: Monocyte chemoattractant protein-1; VEGF: Vascular endothelial growth factor; MMP-2: Mucous membrane pemphigoid; IGF-1: Insulin-like growth factor-1; LSCD: Limbal stem cell deficiency; hMSC: Human mesenchymal stem cell; TSG-6: Tumor necrosis factor-alpha-stimulated gene/protein-6; modIGF1: Insulin-like growth factor-1 modRNA; hP-MSCs: Human placenta-derived mesenchymal stem cell.