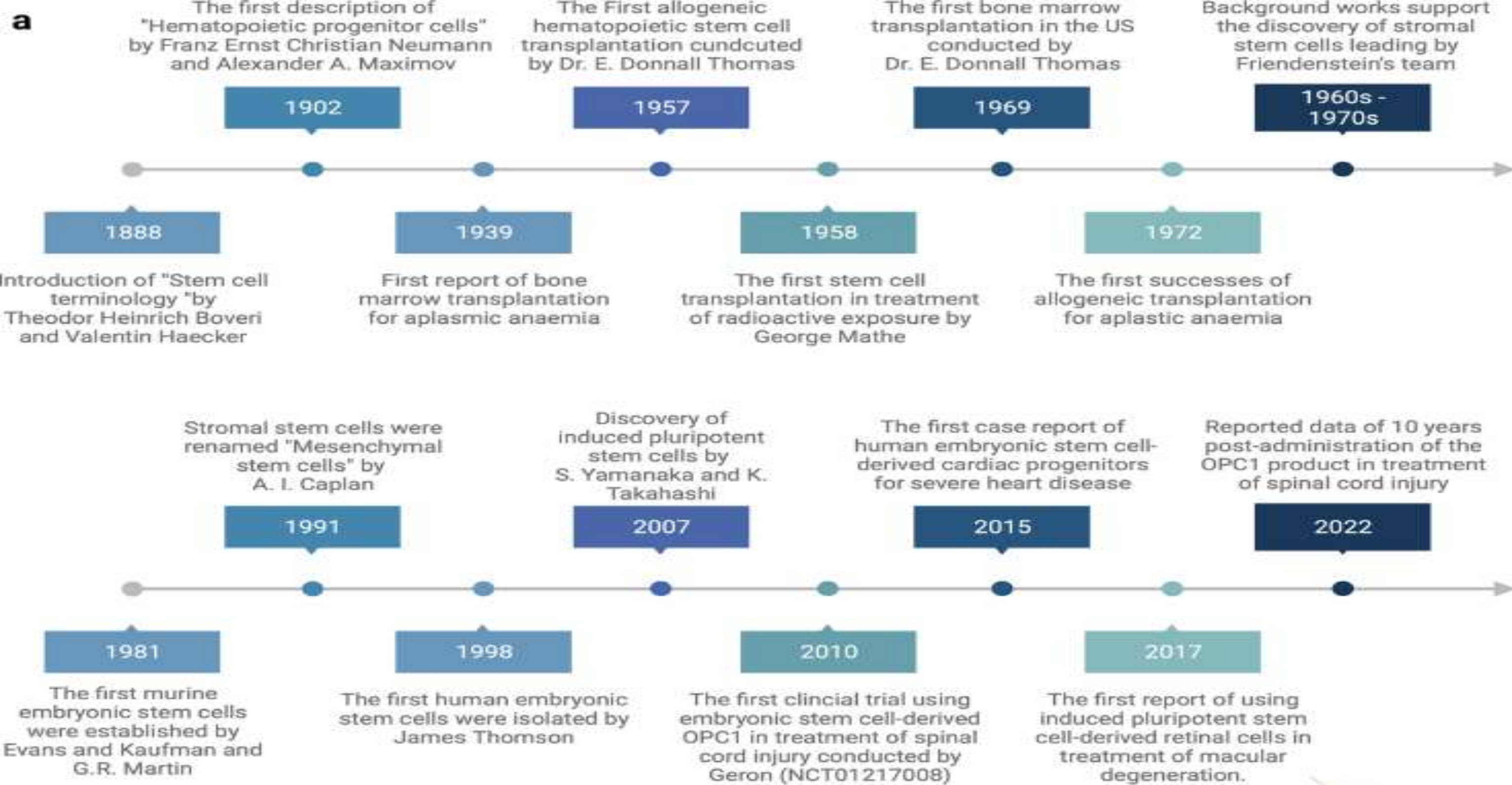


OCULAR REGENERATIVE MEDICINE

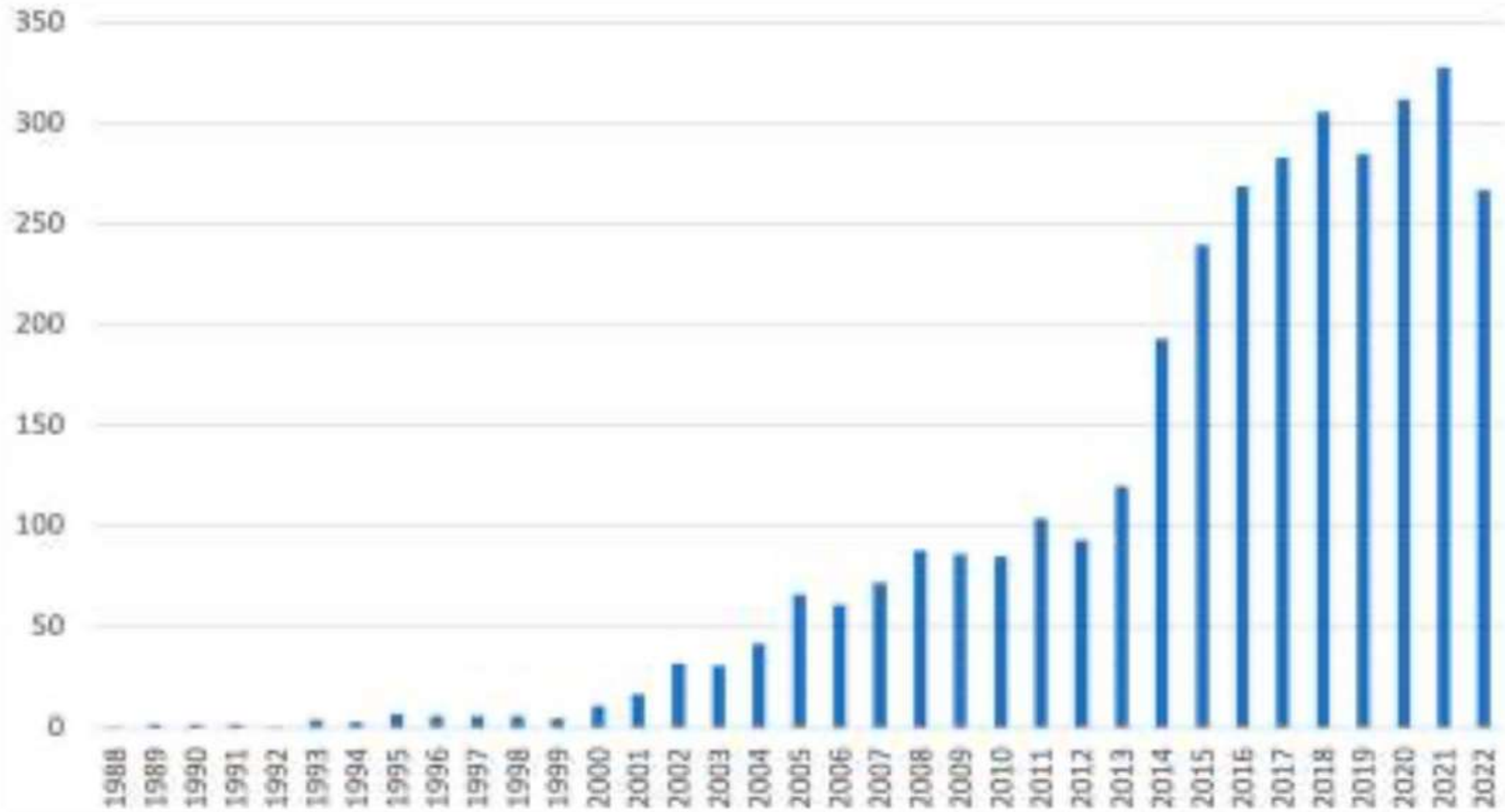
• دکتر حسین قاسمی مقدم

- متخصص داخلی و فوق تخصص خون و سرطان بالغین و فلوشیپ پیوند و سلول درمانی
- استادیار دانشگاه علوم پزشکی تبریز
- مدیر گروه رشته پزشکی بازساختی بالینی
- رئیس گروه بالینی مرکز سلول های بنیادی و پزشکی بازساختی قطب آذربایجان
- مدیر هماهنگی تحقق مرجعیت علمی جهت مهندسی ارگان شمال غرب ایران
- عضو کمیته سیاستگذاری سلول درمانی و پزشکی بازساختی معاونت درمان



b







Introduction to Ocular Regenerative Medicine

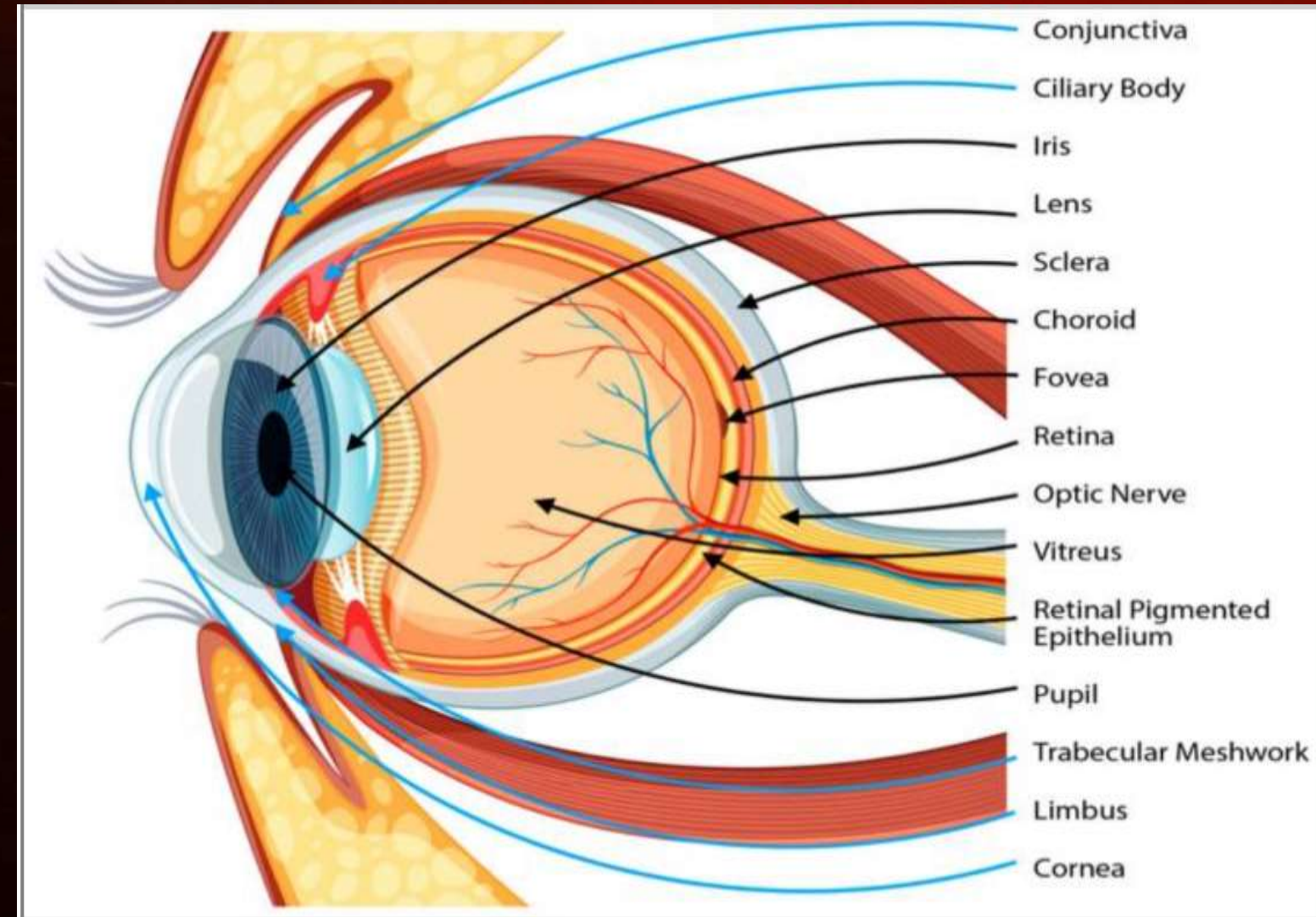
Ocular regenerative medicine offers groundbreaking solutions for various eye conditions and diseases. By harnessing the power of stem cells, gene therapy, and tissue engineering, this innovative field aims to restore vision, repair damaged ocular tissues, and ultimately transform the landscape of ophthalmic care.

Through cutting-edge research and technological advancements, ocular regenerative medicine holds the promise of not only treating but potentially curing debilitating eye disorders such as macular degeneration, retinitis pigmentosa, and corneal injuries. The potential impact of these developments extends not only to improving visual function but also enhancing the overall quality of life for countless individuals.



Understanding the eye's regenerative potential

The eye's regenerative potential is a fascinating area of research that holds promise for the treatment of various eye disorders and injuries. The retina, for example, has been a focus of exploration due to its complex structure and the potential for regrowth of damaged cells.



The exosome of MSCs shows potential for the treatment of various ocular diseases, including:

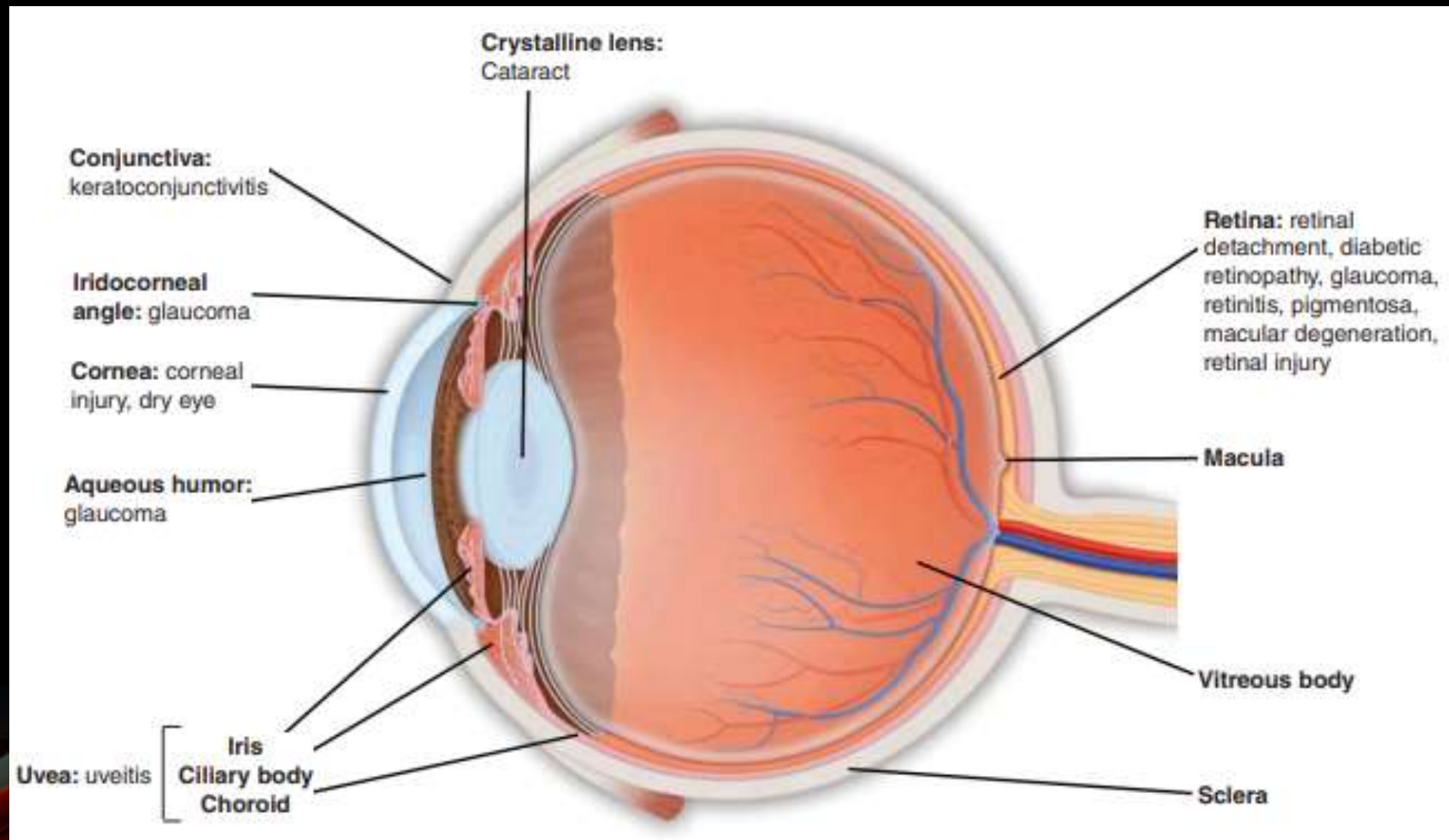
Corneal diseases ✓

Dry eye ✓

Glaucoma ✓

Retinal diseases ✓

Uveitis ✓



Current challenges in ocular regenerative medicine

- **Limited understanding of ocular microenvironment:** The complex and delicate nature of the ocular microenvironment presents a challenge in developing regenerative therapies tailored to the unique conditions of the eye.
- **Immune response and rejection:** Addressing the potential immune response and rejection of implanted or transplanted cells and tissues in the ocular context is a significant challenge.
- **Integration with host tissue:** Ensuring the seamless integration of regenerative treatments with the existing ocular tissue poses a key challenge in achieving long-term efficacy and functional restoration.

Promising Approaches and Technologies in Ocular Regenerative Medicine

1

Gene Therapy

Gene therapy is a groundbreaking approach that involves introducing genetic material into the eye to address inherited disorders or genetic mutations. This technology holds promise for treating conditions such as retinitis pigmentosa and Leber congenital amaurosis by targeting the underlying genetic causes, thereby potentially restoring vision.

2

Stem Cell-Based Therapies

Stem cell-based therapies utilise the regenerative potential of stem cells to repair or replace damaged ocular tissues. This approach includes the use of pluripotent stem cells, adult stem cells, and induced pluripotent stem cells, offering hope for conditions like age-related macular degeneration and corneal disorders through tissue regeneration and repair.

3

Artificial Intelligence and Machine Learning

Artificial intelligence and machine learning are revolutionising diagnostic and treatment strategies in ocular regenerative medicine. These technologies can analyse complex datasets to identify disease patterns and predict treatment outcomes, leading to personalised and more effective interventions for conditions such as glaucoma and diabetic retinopathy.



Clinical applications and success stories

Corneal Regeneration

One of the most significant success stories in ocular regenerative medicine is the development of techniques to regenerate the cornea. Through the use of stem cells and tissue engineering, researchers have been able to restore vision in individuals with corneal damage or disease. This has not only improved the quality of life for many patients but has also paved the way for further advancements in the field.

Retinal Cell Replacement Therapy

Another area of success in ocular regenerative medicine is the development of retinal cell replacement therapy. By transplanting healthy retinal cells into individuals with retinal degenerative diseases such as macular degeneration, researchers have been able to slow down or even reverse vision loss. These groundbreaking treatments have shown remarkable improvements in the visual function of patients.

Optic Nerve Regeneration

Advances in optic nerve regeneration have provided hope for individuals with optic nerve damage and diseases such as glaucoma. Through innovative approaches, including the use of neuroprotective agents and cell-based therapies, researchers have been able to stimulate nerve regeneration and restore visual function in preclinical studies, laying the foundation for future clinical applications.

OPHTHALMOLOGY FUNDS



CIRM Funded Clinical Trials

Retinal progenitor cells for treatment of retinitis pigmentosa

Disease Area:

Retinitis
Pigmentosa

Investigator:

Dr.
Henry
John
Klassen

Institution:

University
of
California,
Irvine

CIRM Grant:

DR2A-05739
(Closed)

Award Value:

\$17,144,825.00

Trial Sponsor:

jCyte

Trial Stage:

Phase 1/2

Trial Status:

Completed

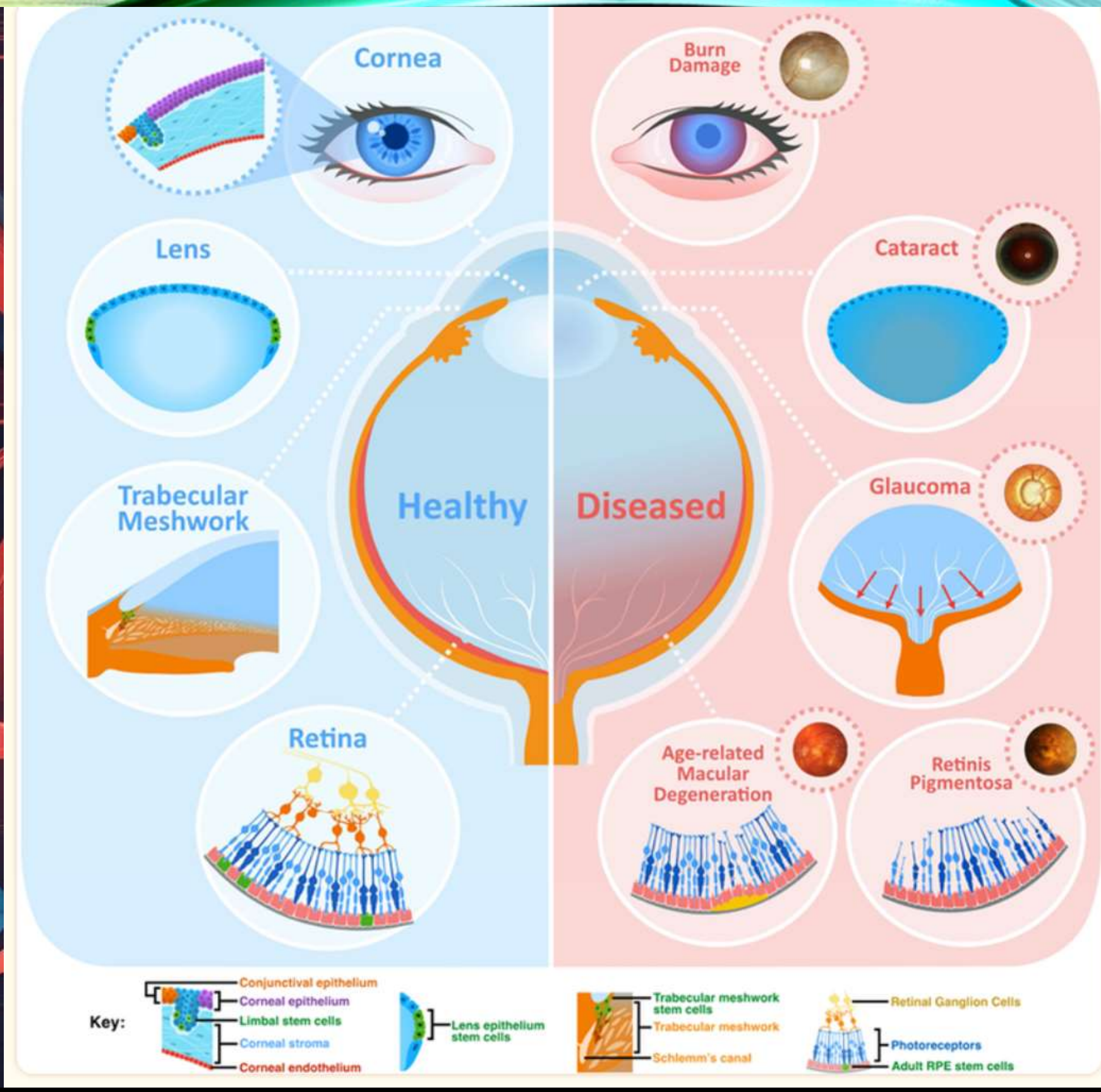
Targeted Enrollment:

28

ClinicalTrials.gov ID:

NCT02320812

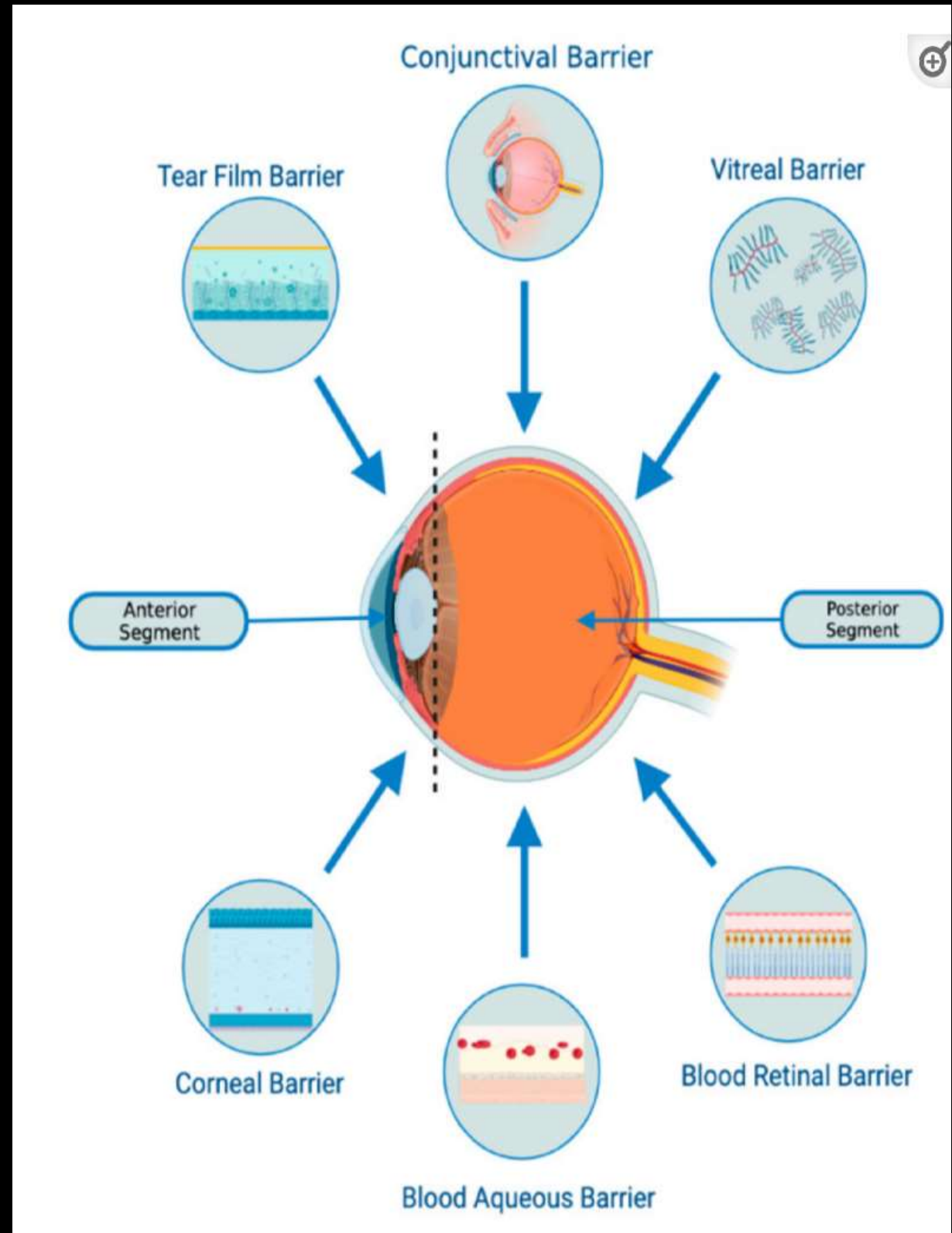






MSC-exosomes have shown efficacy in treating various immune-mediated ocular disorders, such as Sjögren's syndrome dry eye, corneal allograft rejection, and autoimmune uveitis, by modulating the overactive immune response that characterizes these pathologies.

EYE BARRIERS

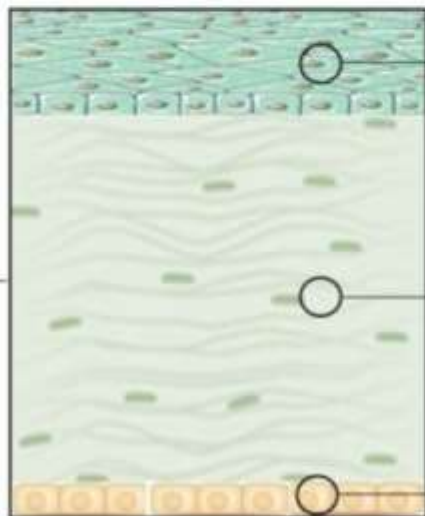


Corneal regeneration

Mesenchymal Stem Cells
with diverse sources



Repair of corneal
layers damage



Epithelium layer

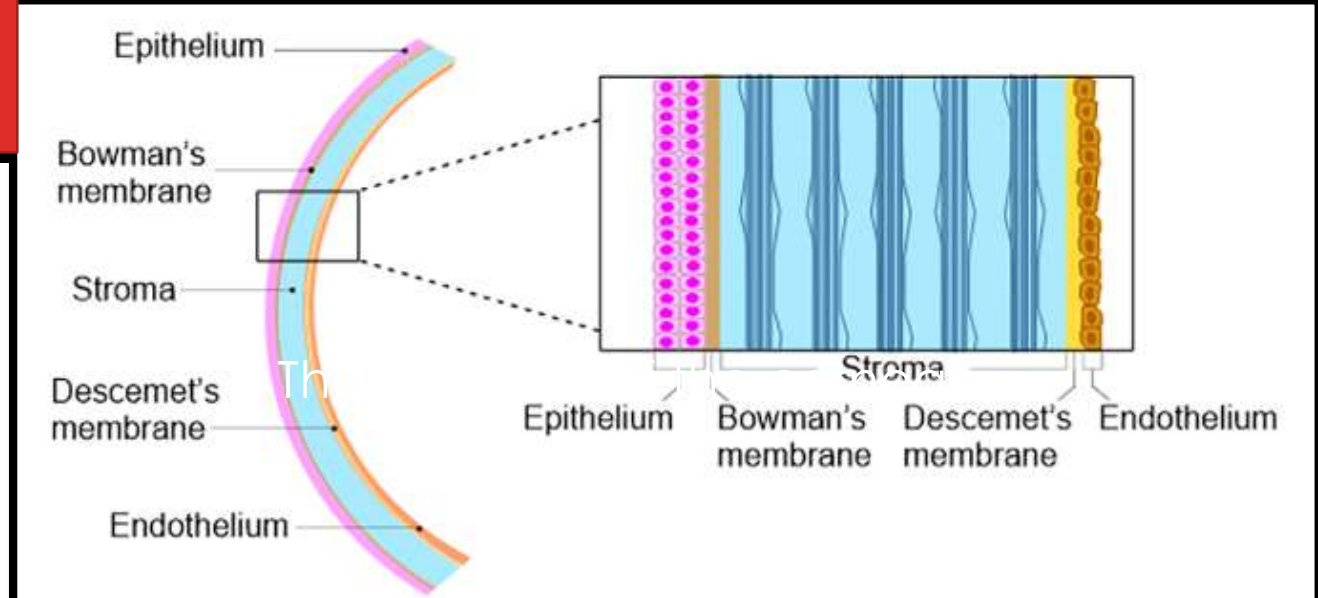
Stromal layer

Endothelial layer

Differentiation into epithelial cells invitro and invivo - Improve chemical burns and physical injury - Ability to selectively migrate to the underlying damaged tissue- Increase transparency

Corneal stroma reconstruction - Ability to produce keratocytes - Collagen production - increased expression of *keratocan* , *ALDH1* genes-Ability to increase cell viability, migration and ECM formation in damaged stroma

Ability to repair endothelial damage- Reduction of edema in the corneal epithelial layer - Increase corneal transparency



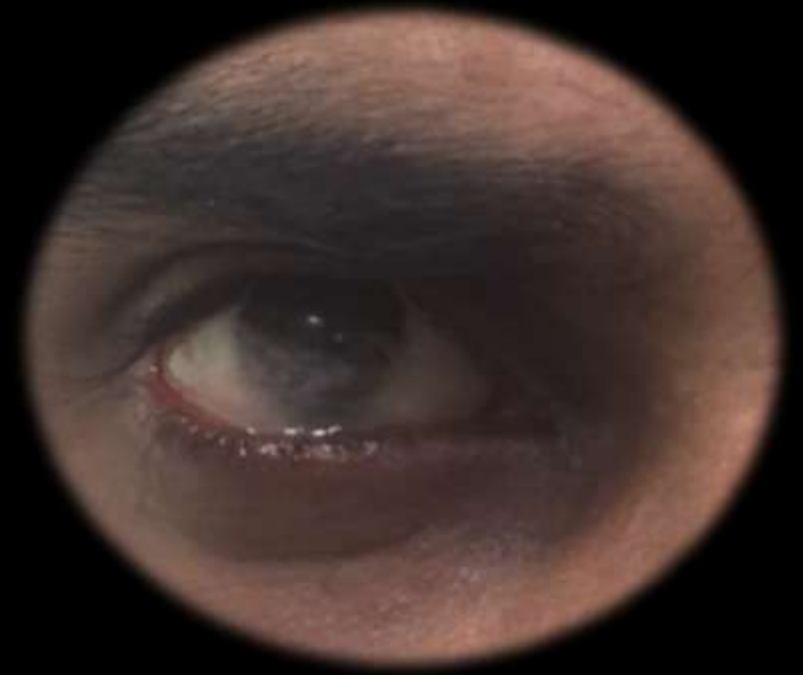
LIMBAL STEM CELL DEFICIENCY & EYE PROSTHESIS

Limbal stem cell deficiency (LSCD) is characterized by a loss or deficiency of the stem cells in the limbus that are vital for re-population of the corneal epithelium and to the barrier function of the limbus

When these stem cells are lost, the corneal epithelium is unable to repair and renew itself.

This results in epithelial breakdown and persistent epithelial defects, corneal conjunctivalization and neovascularization, corneal scarring, and chronic inflammation.

All of these contribute to loss of corneal clarity, potential vision loss, chronic pain, photophobia, and keratoplasty failure

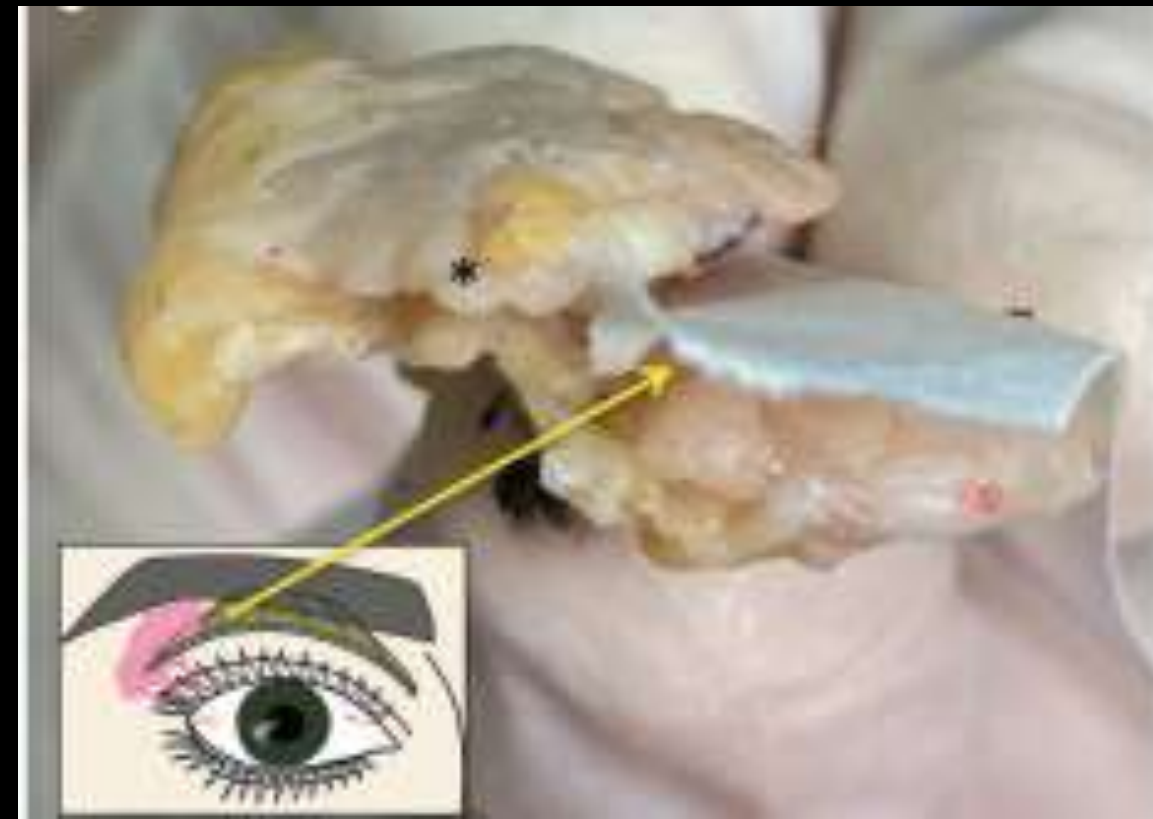


Classification of limbal epithelial stem cell transplants. The most common LESC transplantation techniques by stem cell source.

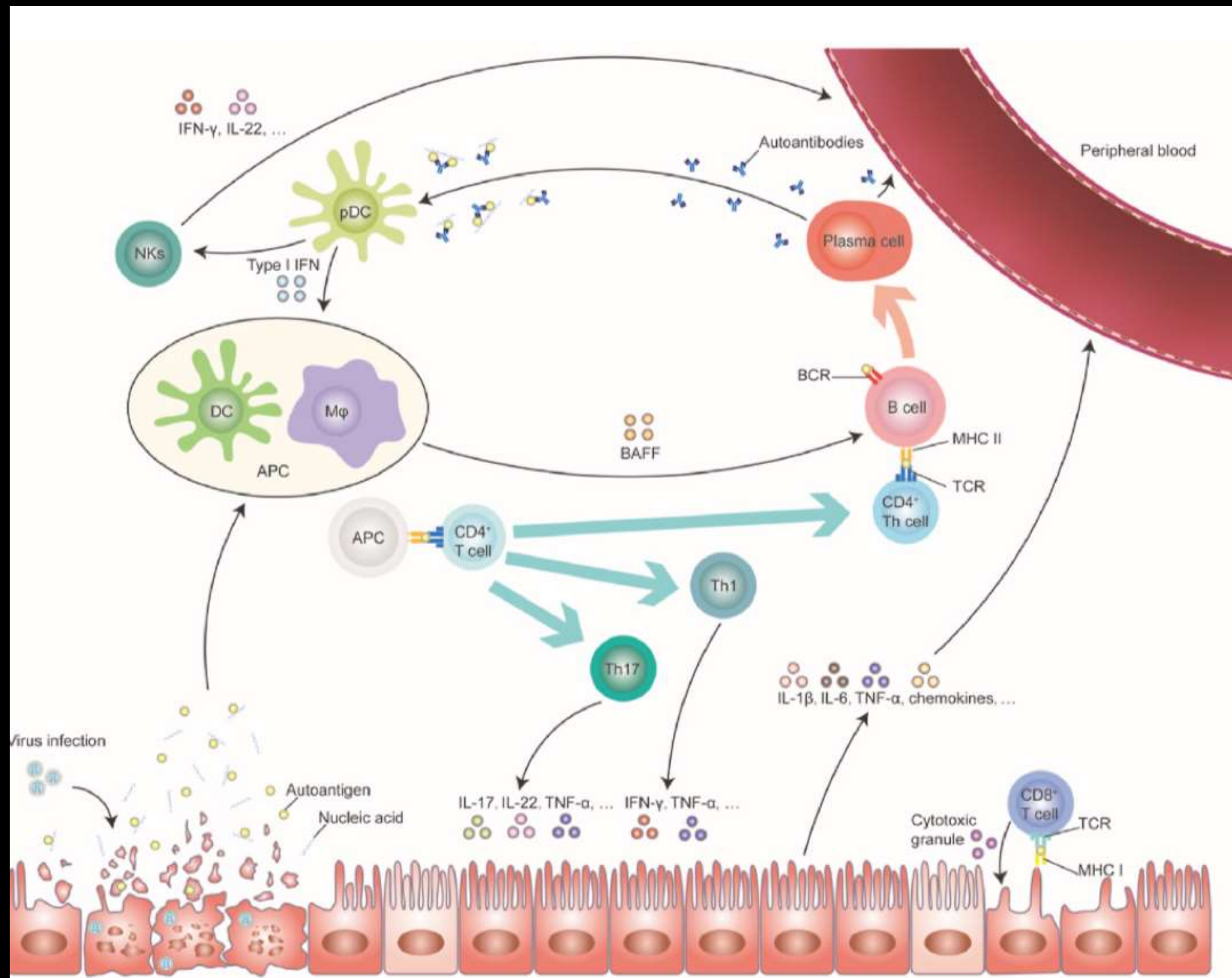
Limbal Autografts	Limbal Allografts	Non-LESCs Transplantation
• Conjunctival-limbal autograft (CLAU) • Cultured limbal epithelial transplantation (CLET) • Simple limbal epithelial transplantation (SLET)	• Keratolimbal allografts (KLAL) • Living-related conjunctival allograft (LR-CLAL) • Allogenic SLET	• Cultivated corneal mucosal epithelial transplantation (COMET)

HUMAN LACRIMAL GLAND DERIVED MESENCHYMAL STEM CELLS – ISOLATION, PROPAGATION, AND CHARACTERIZATION

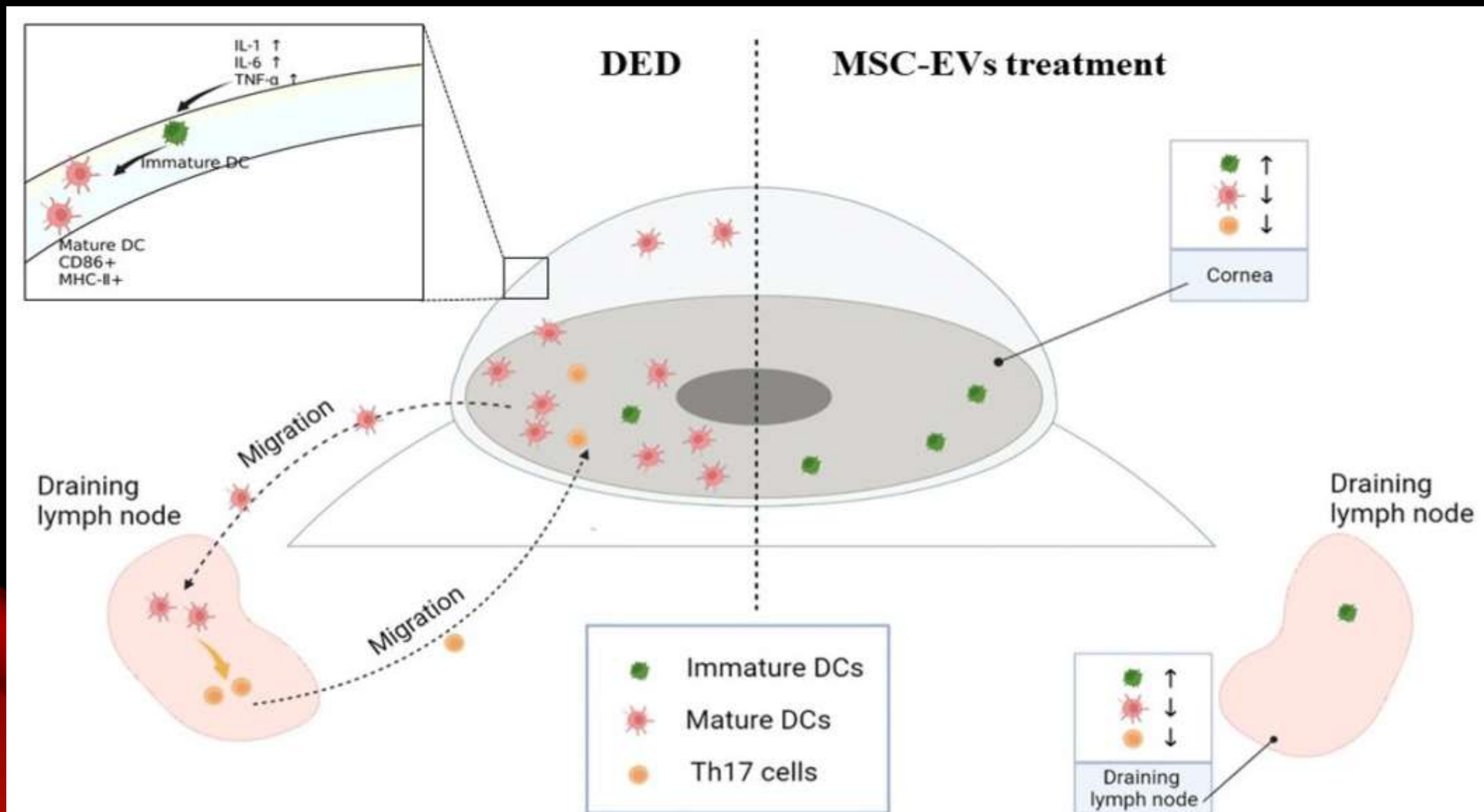
- The existing treatment options for dry eye disease (DED) due to lacrimal gland (LG) dysfunction are mainly palliative. Mesenchymal stem cells (MSCs) based therapies and 3D-LG organoids have been explored as a curative option for LG regeneration



PATHOGENESIS OF SJOGREN SYN



MSC-DERIVED EXTRACELLULAR VESICLES INHIBIT THE FUNCTIONS OF DENDRITIC CELLS IN DRY EYE DISEASE



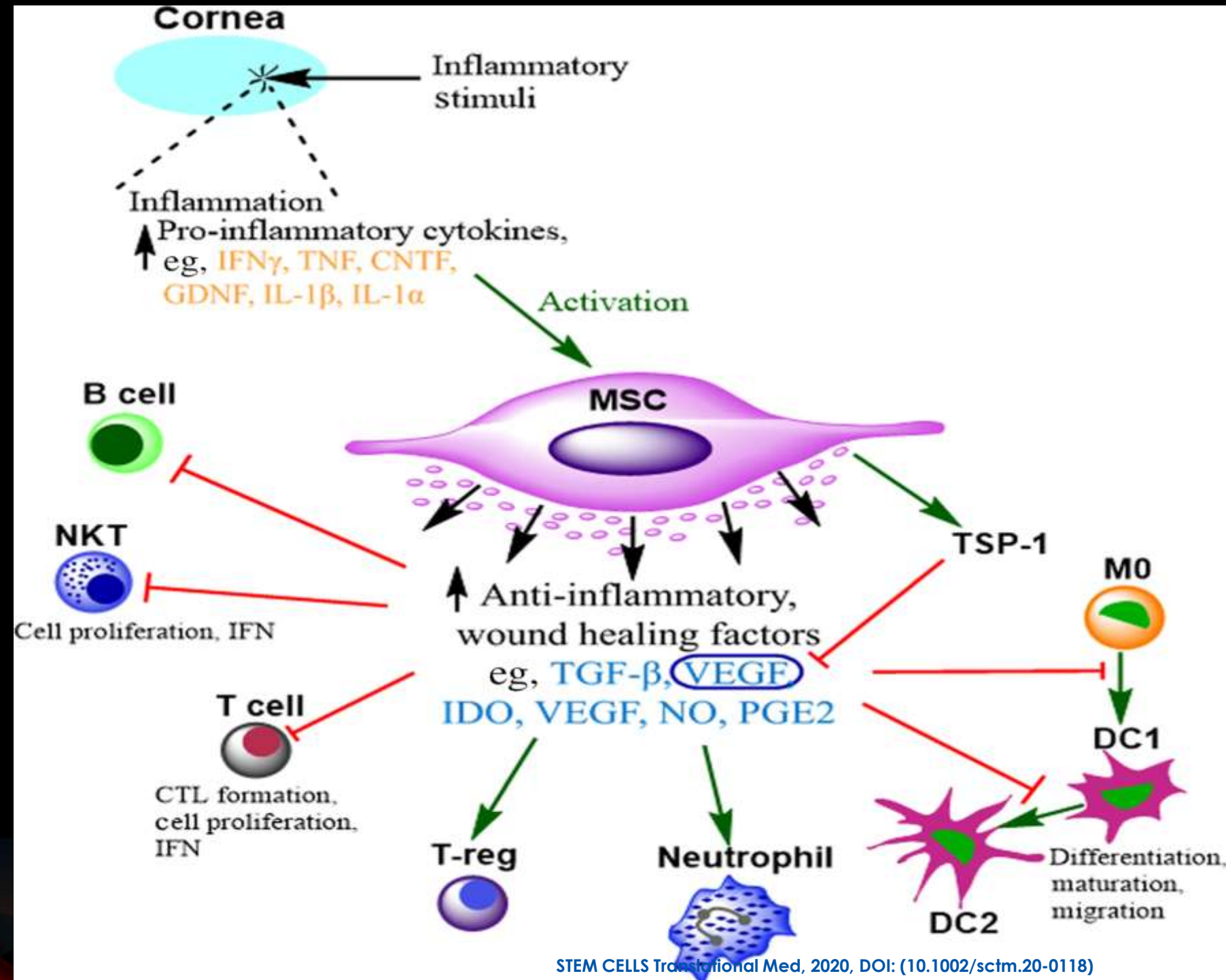
CORNEAL DISORDERS

Application of MSC-EVs in corneal disease.						
Year of publication	Mode of EV delivery	Sources of MSC-EVs	Treatment	Animal Model	Mechanism	References
2022	Subconjunctival injection	hUC-MSCs	30 µg q.o.d, for 5 doses	Rabbit autoimmune dacryoadenitis model (n = 6)	Promote M2 polarization; Increase Tregs via miR-100-5p.	Li et al. (2022)
2021	Eye drops	mADSCs	5 µl (12.5, 25 and 50 mg/mL) t.i.d. *7days	BAC-induced mouse dry eye model (n = 18)	Inhibit cell apoptosis; Anti-inflammatory effect; Reverse NLRP3 activation.	Wang et al. (2022)
2023	Eye drops	hUC-MSCs	1 µl (1.0 mg/ml) q.i. d. *11days	Scopolamine hydrobromide-induced mouse dry eye model (n = 4)	Anti-inflammatory effect; Inhibit DCs activation-mediated Th17 immune responses.	Guo et al. (2022)
2019	Eye drops	hCSCCs	0.5 µl (10 ¹⁰ /ml, 0.5 mg/ml) for 2 doses	Mouse corneal wound model (n = 6)	Decrease fibrotic genes COL3α1 and ACTA2; Block neutrophil infiltration; Restore normal tissue morphology.	Shojaati et al. (2019)
2023	Eye drops	ESCs	8 µl (0.5 mg/ml) (6doses/day) *5days	Rat model of corneal scarring by irrPTK (n = 38)	Promote wound closure; Reduce scar development; Anti-angiogenesis effect; Immunomodulation function.	Ong et al. (2023)
2022	Eye drops	hCECs	10 µl (10 ⁸ /ml) b.i.d. *5days	Alkali-burn mouse model (n = 3)	Modulate cell death; Anti-inflammatory effect; Modulate angiogenesis.	Saccu et al. (2022)
2019	Eye drops	hP-MSCs	10 µl (33.33 µg/L) t. i.d. *14days	Alkali-burn mouse model (n = 8)	Enhance proliferation; Anti-inflammatory effect; Suppress apoptosis.	Tao et al. (2019)
2018	Eye drops	hCSCCs	5 µl (1.0*10 ⁹ /ml) for 4doses (at 0/10/20/30 min)	Mouse epithelial mechanical injury model (n = 6)	Accelerate corneal epithelial wound healing.	Samaeekia et al. (2018)
2022	Subconjunctival injection	hUC-MSCs	40 µg for 1 dose	Rat corneal mechanical wound model (n = 8)	Promote the corneal epithelial repair; Inhibit PTEN by transferring miR-21.	Liu et al. (2022)
2023	Eye drops	hUC-MSCs	5 µl (3.0 mg/ml) q.i. d. *21days	scopolamine administration induced mouse dry eye model (n = 10)	Anti-inflammatory effect; Restore corneal surface homeostasis; Regulate the IRAK1/TAB2/NF-κB pathway via certain miRNAs.	Wang et al. (2023b)
2022	Eye drops	mBM-MSCs	5 µl (2.5*10 ¹⁰ /ml) b. i.d. *7days	BAC-induced mouse dry eye model/ NOD–Prkdc ^{em26Cd52} IL2rg ^{em26Cd22} Nju (NCG)–GVHD mouse (n = 12/n = 8)	Prevent corneal epithelium degeneration; Restore corneal structure; Promote M2 polarization; Regulate the IL-6/IL-6R/STAT3 pathway via miR-204.	Zhou et al. (2022b)
2022	Subconjunctival injection	Rat BM-MSCs	10 µg for 2 doses (at day0 and day2)	Wistar-Lewis rat corneal allograft rejection models (n = 6)	Inhibit Th1 pathway.	Jia et al. (2022)
2022	Eye drops	hUC-MSCs	50 µl (0.2 mg/ml) q. i.d. *14days	GVHD-associated dry eye disease patient (n = 14)	Promote M2 polarization; Regulate the IL-6/IL-6R/Stat3 pathway via miR-204.	Zhou et al. (2022b) NCT04212248

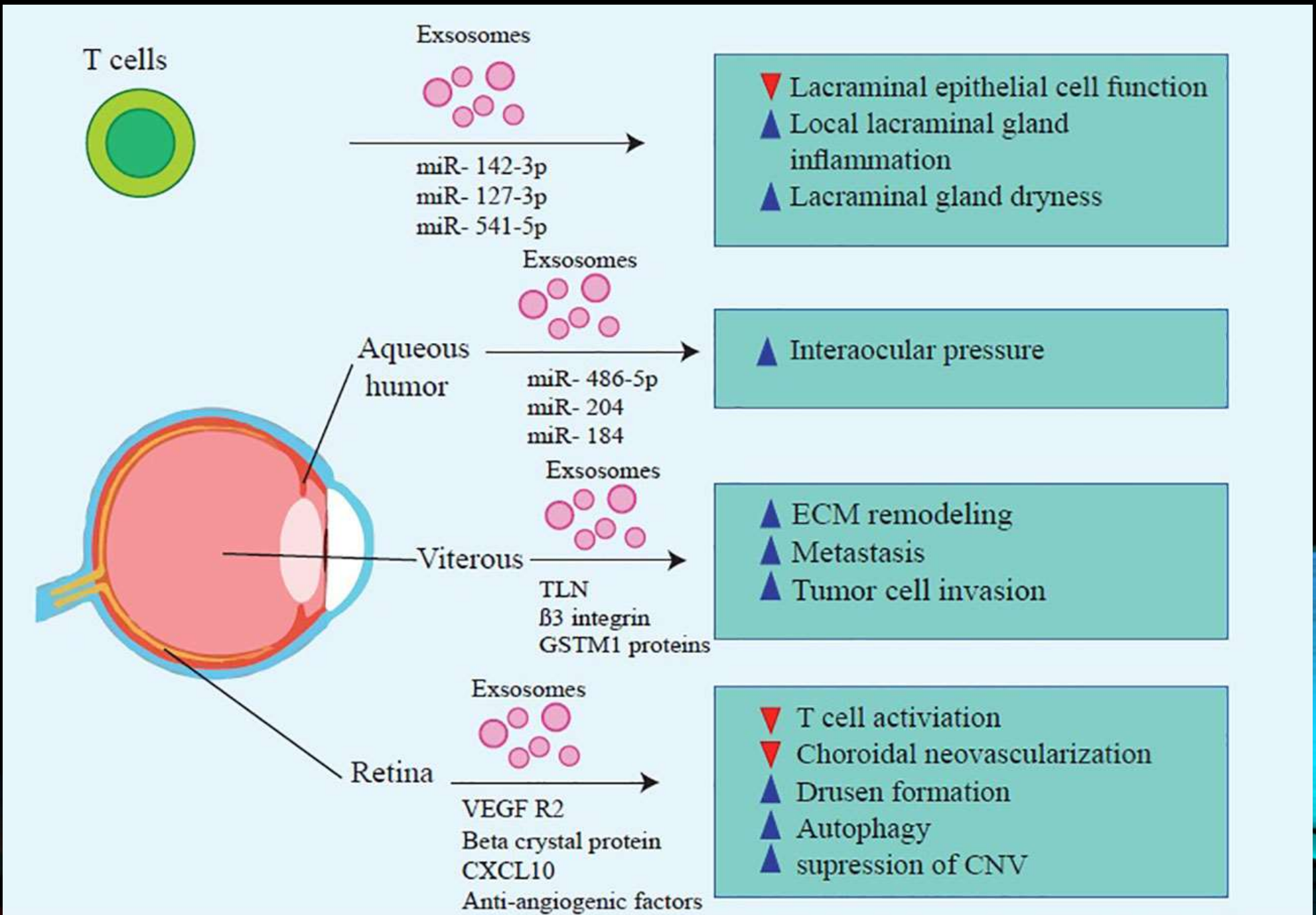
Table 2. Studies on the therapy of ocular diseases using MSC-EVs

Position	EV source	Administration route/dose	Results	Effector molecule
Cornea	BMSCs	Viscoelastic gel carrier/unclear	Enhance HCECs proliferation and wound healing; reduce scar formation, neovascularization, and hemorrhage	Unclear ^[96]
	BMSCs	Co-culture/unclear	Induce proliferation and migration of damaged HCECs; inhibit cell apoptosis	Unclear ^[97]
	ADSCs	Topical administration/unclear	Promote proliferation and migration of HCECs, reduce inflammatory cytokine levels, polarize infiltrating macrophages toward M2	Unclear ^[98]
	CSSCs	EVs drop/ 5.0×10^6 particles	Accelerate wound healing	Unclear ^[99]
	CSSCs	Topical fibrin gel/ 1×10^7 particles	Decreased expression of fibrotic genes Col3a1 and Acta2, blocked neutrophil infiltration	miRNA ^[100]
	ADSCs	Co-culture/ 1.61×10^{10} particles	Toxicological testing	Unclear ^[101]
	BMSCs	Co-culture/unclear	facilitate wound healing	Unclear ^[102]
Retina	UMSCs	IV/ $2.5 \mu\text{g}$	Inhibition of MCP-1	MCP-1 ^[28]
	BMSCs	IV/ 3×10^9 particles	Through miRNA dependent mechanisms	miRNA ^[56]
	UMSCs	Tail vein/ $55 \mu\text{g}$	MiR-126 expression and downregulating the HMGB1 signaling pathway	miR-126 ^[103]
	ADSCs	IS/unclear	Delivering microRNA-222 acts as mediators in retinal tissue repair	miRNA-222 ^[104]
	BMSCs	IV/ 4×10^9 particles	Reduce neuroinflammation and neuronal apoptosis	Unclear ^[105]
	BMSCs	Tail vein/ $30 \mu\text{g}$	Inhibit activation of antigen-presenting cells and suppress the development of Th1 and Th17 cells	Unclear ^[106]
	UMSCs	IV/ $0.05 \mu\text{g}$	Ameliorate retinal injury via downregulation of VEGF-A	Unclear ^[107]
	UMSCs	IV/ 1×10^9 particles	Promoting the RGCs survival and glia cells activation	Unclear ^[108]
	BMSCs	IV/ 1×10^9 particles	Preserving RGC numbers and protecting against axonal degeneration	Unclear ^[109]
	ES-MSCs	IO/ $15 \mu\text{g}$	Improved Brn3a+ RGCs survival and improved cognitive visual behavior	Unclear ^[110]

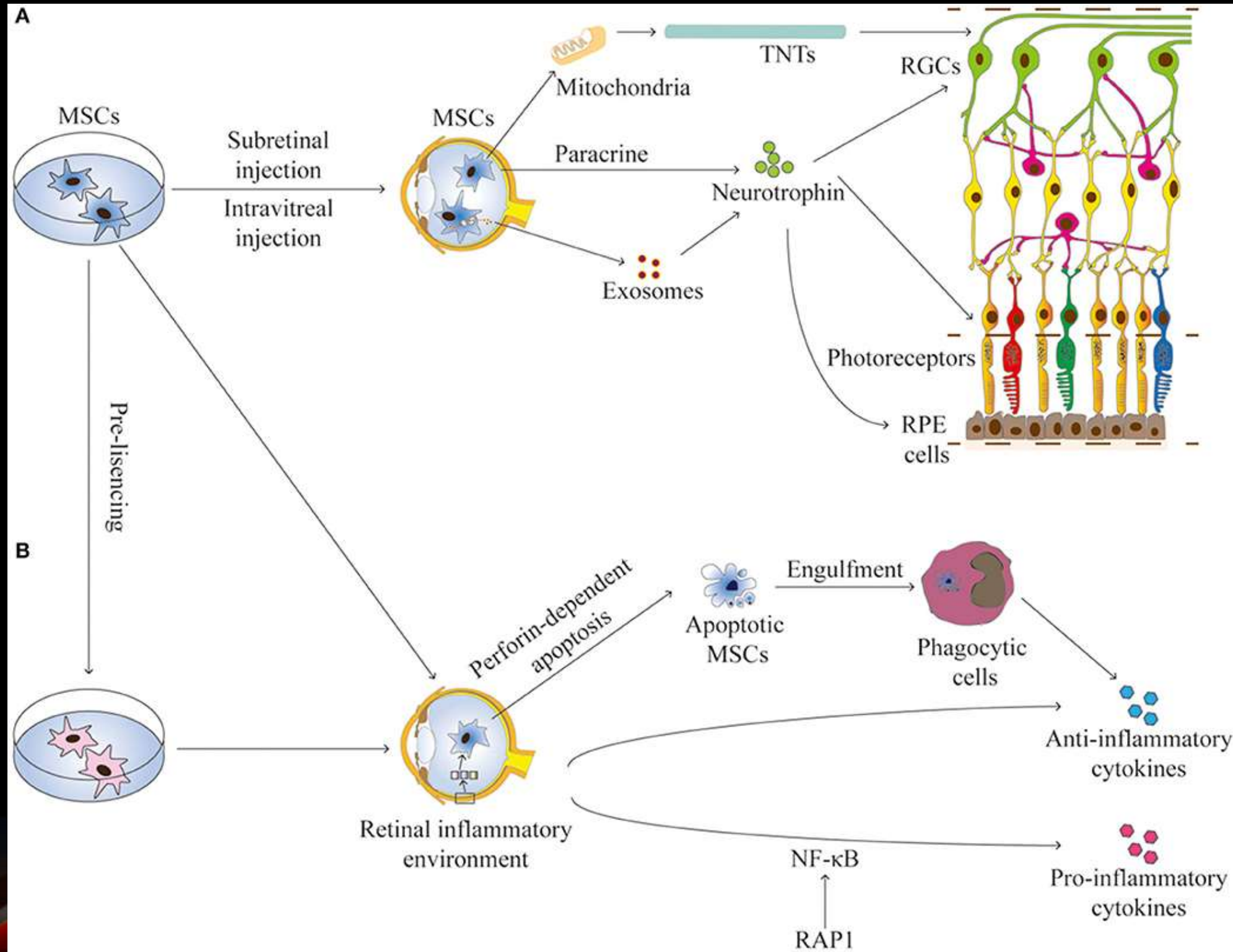
MSCS FOR OCULAR SURFACE INFLAMMATORY DISORDERS



MSC-EXOS' BENEFICIAL EFFECTS ON TREATING INFLAMMATORY OCULAR DISEASES



THE INTERACTIONS BETWEEN MSCs AND THE RETINAL ENVIRONMENT

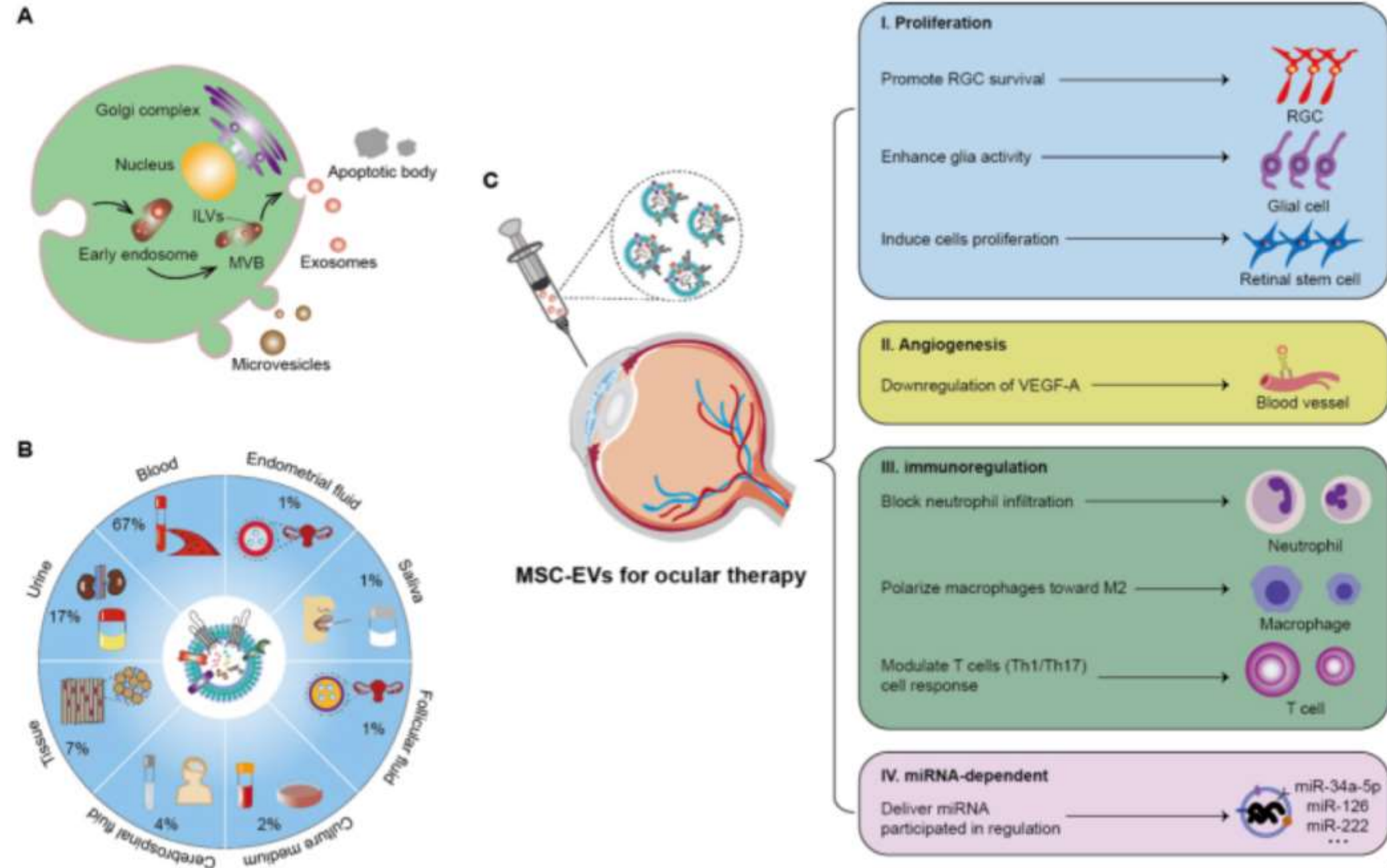


MSC-based treatment in clinical trials for retinal disease.

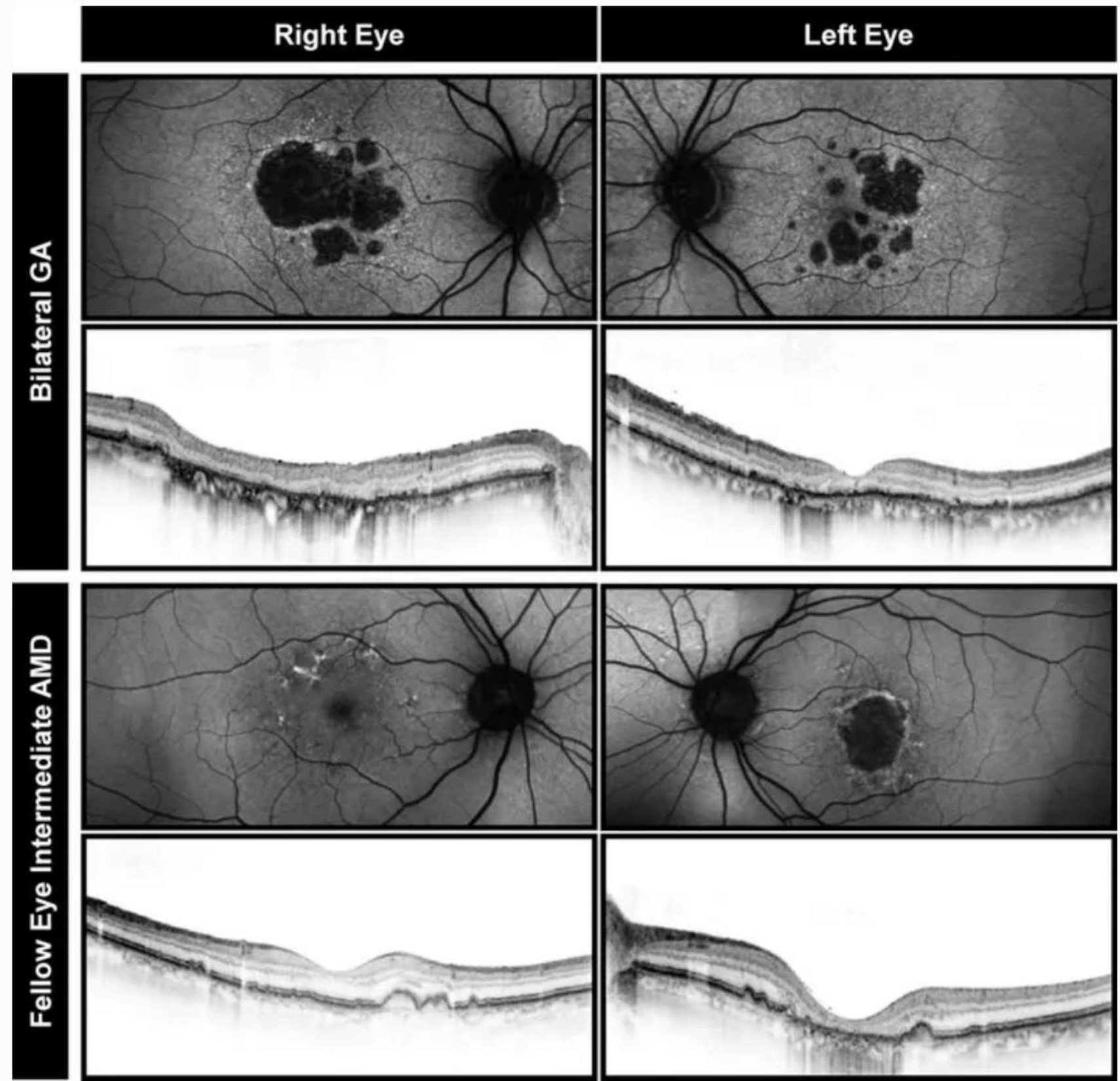
Study (Year)	Retinal Disease	Number of Patients	Cell Type	Route of Administration	Dosage	Phase of Study	Outcomes
Oner [10] (2016)	RP	11	AD-MSC	Subretinal	$2.47 \times 10^6 \pm 0.11$ cells/150 μ l	I	Minor ocular complications
Kahraman [11] (2020)	RP	82	UC-MSC	Suprachoroidal	5×10^6 cells/2 mL	III	Beneficial effect on BCVA, VF, and mfERG
Özmert [12] (2020)	RP	32	WJ-MSC	Subtenon	$2-6 \times 10^6$ cells/1.5 mL	III	No ocular or systemic adverse events
Weiss [13] (2018)	RP	17	BM-MSC	Retrobulbar, subtenon, intravitreal and intravenous	1.2×10^9 cells/14–15 cm ³	NA	Beneficial effect on visual acuity
Tuekprakhon [14] (2021)	RP	14	BM-MSC	Intravitreal	1×10^6 cells, 5×10^6 cells, 1×10^7 cells	I	Beneficial effect on visual acuity
Park [15] (2014)	IDRD	6	BM-MSC	Intravitreal	-	I	No ocular or systemic adverse events associated with treatment
Siqueira [16] (2011)	HRD	6	BM-MSC	Intravitreal	10×10^6 cells/0.1 mL	I	No ocular or systemic adverse events associated with treatment
Gu [17] (2018)	DR	17	BM-MSC	Intravenous	3×10^6 cells/kg	NA	Beneficial effect on macular thickness and visual acuity
Levy [18] (2015)	Optic nerve diseases	1	BM-MSC	Retrobulbar, subtenon, intravitreal, and intravenous	1.2×10^9 cells/14–15 cm ³	NA	Beneficial effect on visual acuity
Weiss [19] (2017)	NAION	10	BM-MSC	Retrobulbar, subtenon, intravitreal, and intravenous	1.2×10^9 cells/14–15 cm ³	NA	Beneficial effect on visual acuity
Kuriyan [20] (2017)	AMD	3	AD-MSC	Intravitreal	-	NA	Severe ocular complications

RP: retinitis pigmentosa; IDRD: ischemic and degenerative retinal disorders; BCVA: best-corrected visual acuity; VF: visual field; mfERG: multifocal electroretinography; HRD: hereditary retinal dystrophy; DR: diabetic retinopathy; NAION: nonarteritic ischemic optic neuropathy; AMD: age-related macular degeneration

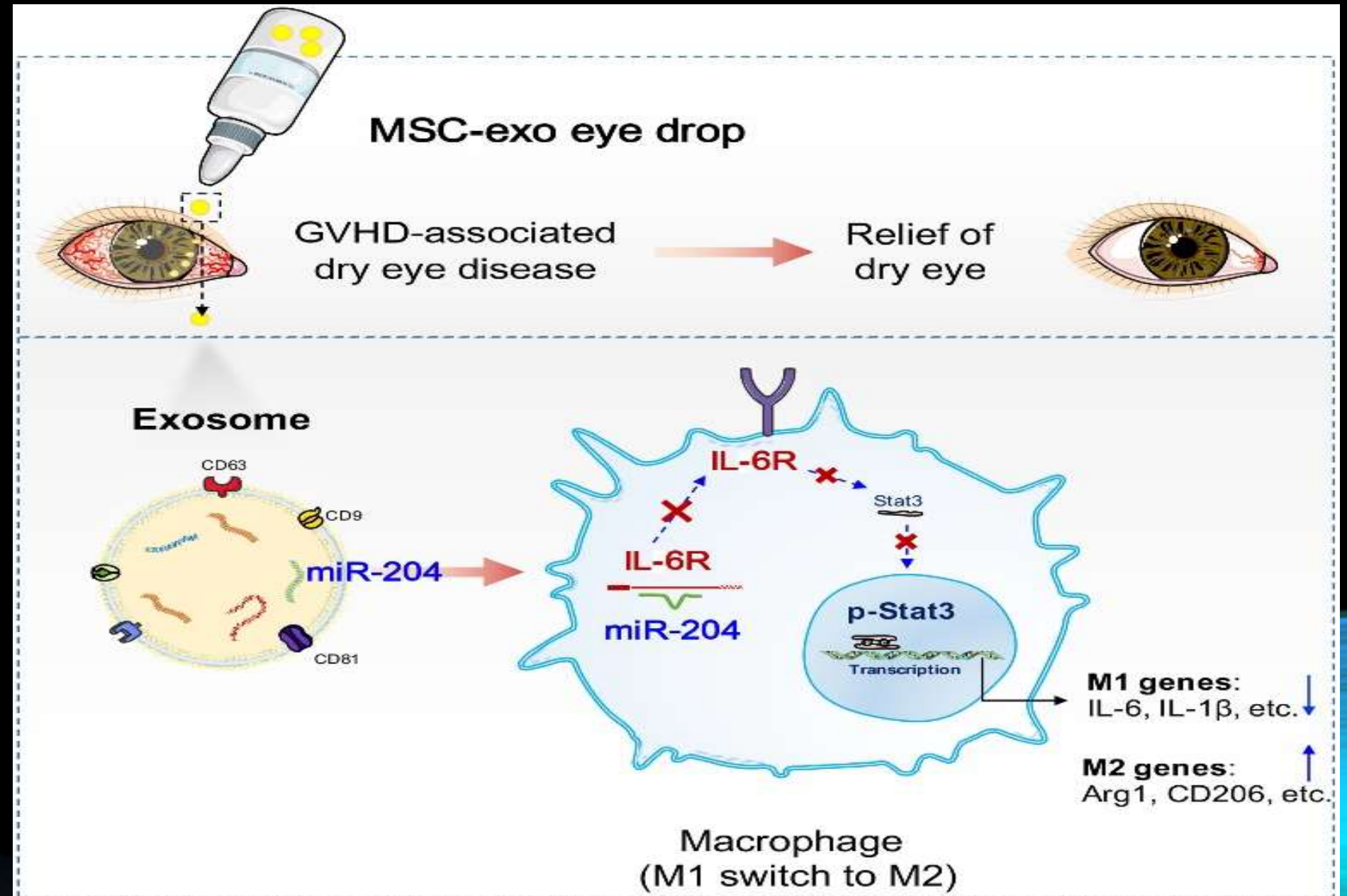
EFFICACY OF EXOSOMES

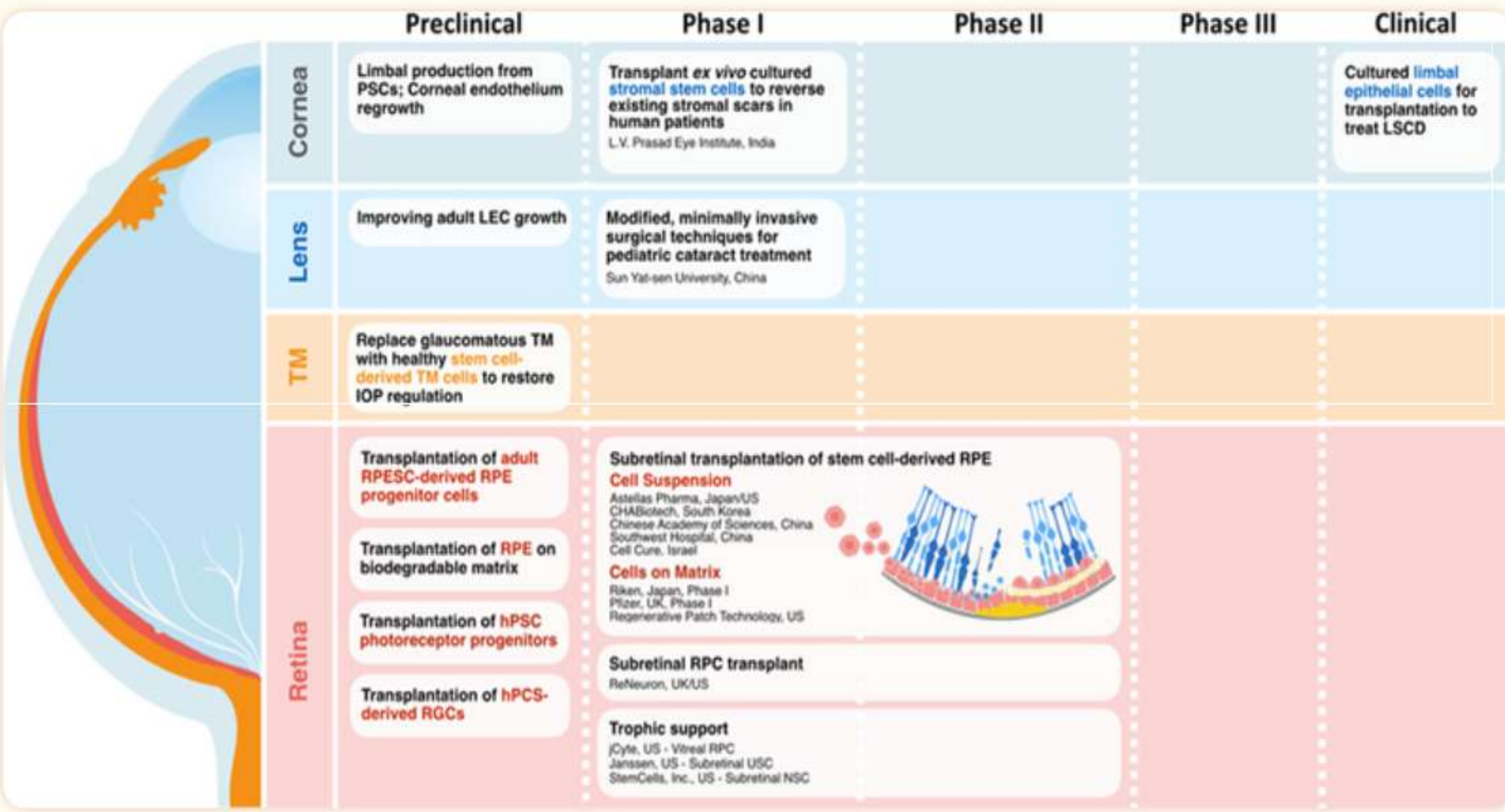


EXOSOME THERAPY IN AMD



GVHD-associated dry eye disease by reprogramming M1 macrophages to M2 via miR-204-mediated targeting of IL-6R/Stat3 pathway



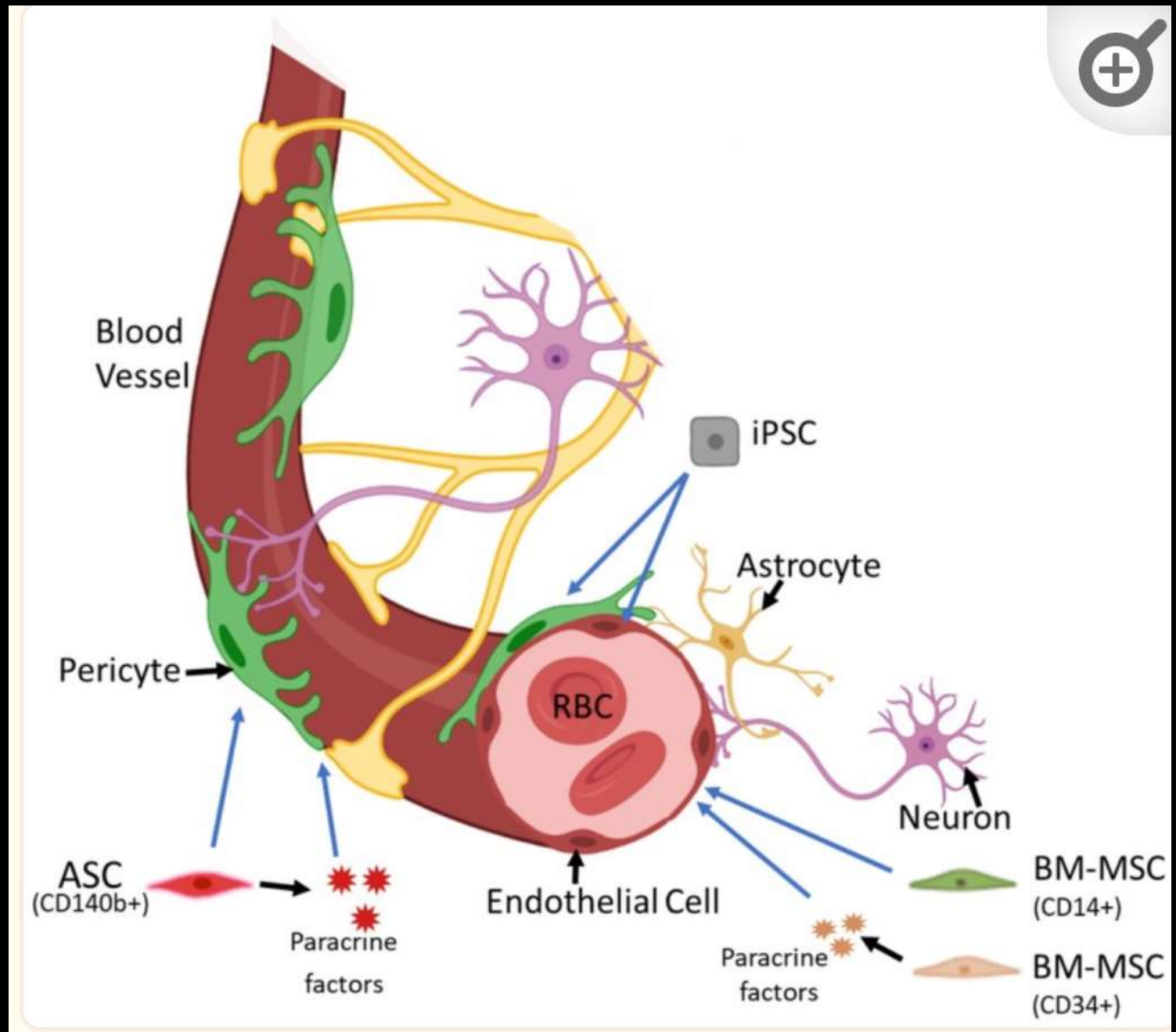


ROUTES OF MSC APPLICATION

Table 1 Effects of mesenchymal stem cell derived extracellular vesicles in ocular disorders.

Ref.	Origin	Delivery way	Biological function
Yu <i>et al</i> [74], 2016	Human umbilical cord derived MSCs	Intravitreal injection	Ameliorate retinal laser injury
Mead <i>et al</i> [64], 2017	Human bone marrow derived MSCs	Intravitreal injection	Promote RGC survival in optic nerve crush model
Kuroda <i>et al</i> [58], 2017	Human bone marrow derived MSCs	Intravenous injection	Prevent EAU development
Moisseiev <i>et al</i> [77], 2017	Human bone marrow derived MSCs	Intravitreal injection	Decrease the severity of retinal ischemia
Bai <i>et al</i> [57], 2017	Human umbilical cord derived MSCs	Periocular injection	Inhibit inflammatory cell migration in EAU
Shen <i>et al</i> [44], 2018	Rabbit adipose derived MSCs	In vitro	Contribute to the growth and plasticity of corneal stromal cells
Samaeekia <i>et al</i> [39], 2018	Human corneal MSCs	Topical application	Accelerate corneal epithelial wound healing
Mead <i>et al</i> [67], 2018	Human bone marrow derived MSCs	Intravitreal injection	Promote neuroprotection in glaucoma model
Safwat <i>et al</i> [72], 2018	Rabbit adipose derived MSCs	Intravenous, intraocular or subconjunctival injection	Attenuate retina degeneration in diabetic retinopathy
Zhang <i>et al</i> [71], 2018	Human umbilical cord derived MSCs	Intravitreal injection	Ameliorate hyperglycemia-induced retinal inflammation
Mathew <i>et al</i> [76], 2019	Human bone marrow derived MSCs	Intravitreal injection	Protect retinal cells from cell death in retinal ischemia

DIABETIC RETINOPATHY



Ethical Considerations and Future Implications



Benefit to Society

Ethical considerations in ocular regenerative medicine involve assessing the potential benefits to society. This includes evaluating the impact on public health, accessibility of treatments, and the ethical implications of prioritizing certain groups for treatment.



Equitable Access

Ensuring equitable access to advanced ocular regenerative therapies is a critical ethical consideration. Addressing disparities in access based on socioeconomic status, geography, and other factors is imperative for the ethical advancement of these treatments.



Regulatory Oversight

Future implications involve establishing robust ethical and regulatory frameworks to govern the development and deployment of ocular regenerative treatments. This includes considerations around safety, informed consent, and the ethical use of emerging technologies.



Patient Autonomy

Respecting patient autonomy is a core ethical consideration. Promoting informed decision-making, privacy, and patient rights in the context of ocular regenerative medicine is essential for upholding ethical standards.

Key players and collaborations in ocular regenerative medicine



Leading Researchers

Collaborations in ocular regenerative medicine are often spearheaded by leading researchers in the field. Their expertise and dedication drive the development of innovative treatments and breakthrough technologies, laying the foundation for successful partnerships.



Biotech Companies

Key players in ocular regenerative medicine frequently include biotech companies at the forefront of developing cutting-edge therapies. These collaborations bring together scientific knowledge and industry capabilities to translate research into tangible clinical solutions.



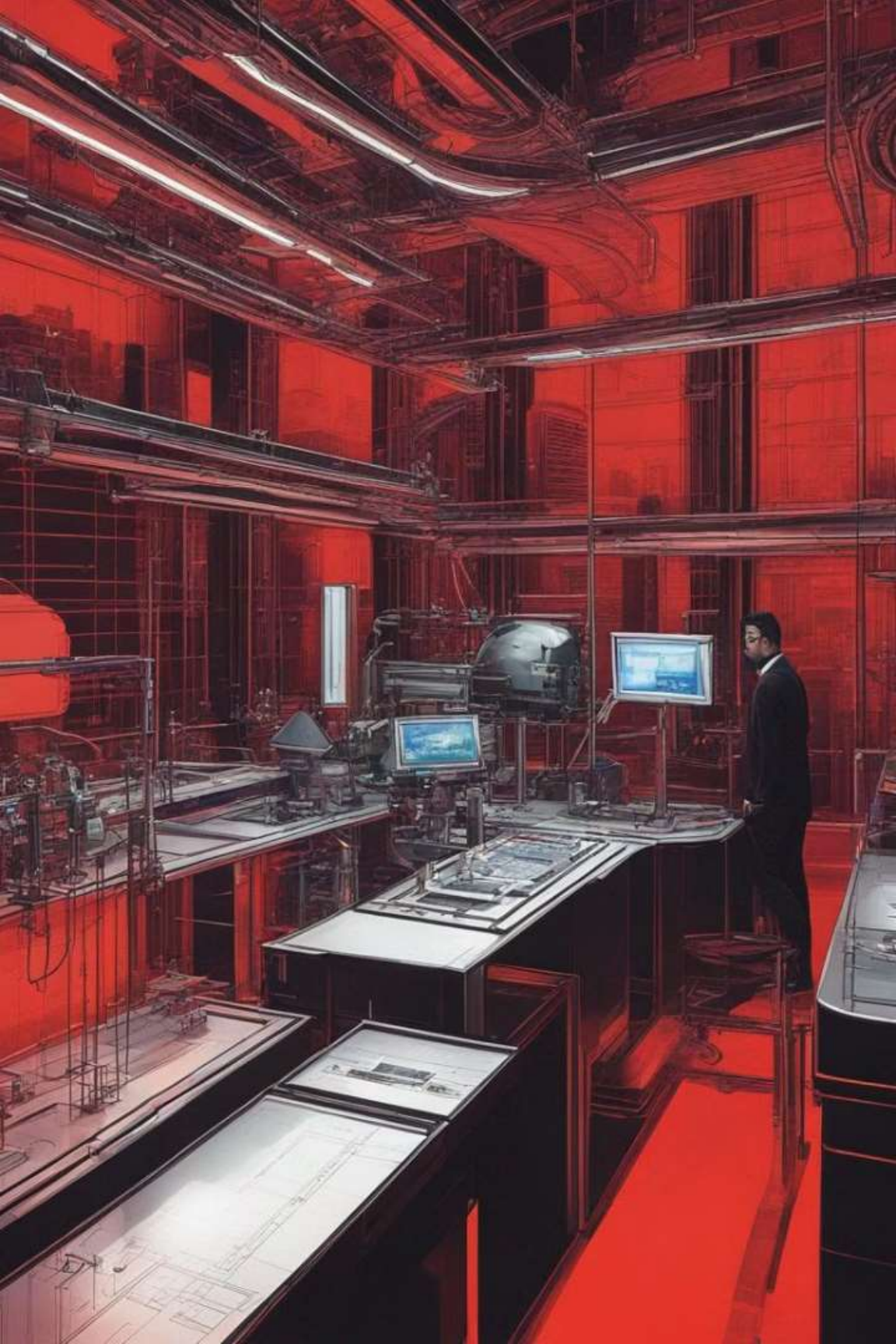
Academic Institutions

Universities and academic institutions play a pivotal role in fostering collaborations within ocular regenerative medicine. Their multidisciplinary approach and access to diverse resources contribute significantly to the advancement of innovative treatments and technologies.



Clinical Trials Partnerships

Collaborations in ocular regenerative medicine extend to clinical trials partnerships, where research institutions, industry leaders, and medical centers join forces to evaluate the safety and efficacy of novel regenerative therapies, accelerating their transition to clinical practice.

A futuristic laboratory with red lighting and advanced equipment. A person in a dark suit stands in the center, looking at a monitor. The room is filled with complex machinery, including large screens and intricate metal structures. The overall atmosphere is high-tech and innovative.

Conclusion and Future Directions

In conclusion, ocular regenerative medicine holds immense promise for the future of eye health. With advancements in stem cell research, tissue engineering, and gene therapy, the potential for restoring vision and treating ocular disorders is unprecedented. The integration of artificial intelligence and machine learning in diagnostic and treatment protocols further propels the field towards innovative solutions.

As we look towards the future, collaborative efforts between research institutions, biotechnology companies, and healthcare providers will be pivotal in translating scientific discoveries into practical clinical applications. Moreover, ongoing ethical discussions and regulatory frameworks will shape the landscape of ocular regenerative medicine, ensuring that patient safety and societal implications are carefully considered.

Cell Therapy in Ocular Disorders

Stem Cell Therapy

Stem cell therapy holds immense promise in the treatment of various ocular disorders. By harnessing the regenerative potential of stem cells, researchers aim to develop targeted therapies to repair damaged tissues and restore visual function. The ability of stem cells to differentiate into specific ocular cell types offers hope for addressing conditions such as retinal degeneration and corneal damage.

Gene Editing Techniques

Advancements in gene editing technologies, such as CRISPR-Cas9, have opened up new avenues for precision medicine in ocular disorders. By targeting specific genetic mutations associated with conditions like age-related macular degeneration and glaucoma, researchers can explore the potential of gene editing to correct underlying genetic defects at the cellular level.

Tissue Engineering Innovations

Tissue engineering approaches in ocular regenerative medicine involve the development of scaffolds, biomaterials, and bioengineered constructs to support the growth and integration of ocular tissues. These innovations have the potential to revolutionize the treatment of conditions such as corneal scarring and optic nerve damage, offering alternatives to traditional transplantation methods.



Mesenchymal stem cell application in eye disorders

Mesenchymal stem cells (MSCs) have garnered significant attention in the field of ocular regenerative medicine due to their remarkable regenerative and immunomodulatory properties. These multipotent stromal cells hold great promise in treating a wide range of eye disorders, including but not limited to corneal injuries, retinal degeneration, and optic nerve damage. Through their ability to differentiate into various cell types and release bioactive molecules, MSCs offer a potential solution for restoring vision and preventing further degeneration in affected individuals.

Moreover, the application of MSCs in eye disorders is not only limited to their regenerative potential but also extends to their ability to modulate the immune response, reducing inflammation, and promoting tissue repair. This multifaceted approach makes MSC-based therapy a comprehensive and promising strategy for addressing the complex pathology of ocular diseases.

These groundbreaking developments in ocular regenerative medicine have paved the way for extensive research and clinical trials to explore the safety and efficacy of MSC-based interventions. As the understanding of MSC biology and their interaction with ocular tissues continues to deepen, the future holds immense potential for innovative treatment modalities that harness the regenerative power of these remarkable cells to combat various eye disorders.

This image could depict a laboratory setting with scientists conducting experiments related to MSC application in eye disorders. The scene exudes an atmosphere of exploration and discovery, with bright, sterile lighting illuminating the dedicated researchers engaged in advancing the frontiers of ocular regenerative medicine.

