OCULAR REGENERATIVE MEDICINE

- متخصص داخلى و فوق تخصص خون و سرطان بالغين وفلوشيپ پيوند و سلول در مانى

 - رییس گروہ بالینی مرکز سلول ہای بنیادی و پزشکی بازساختی قطب آذربایجان
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Ectoderm

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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 \checkmark

Dry eye ✓ Glaucoma ✓ Retinal diseases ✓

Uveitis \checkmark



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

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.

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.

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 provide hope for individuals with or nerve damage and disease such as glaucoma. Throug innovative approaches, including the use of neuroprotective agents and cell-based therapies, researchers have been ab stimulate nerve regeneration and restore visual function preclinical studies, laying t foundation for future clinical applications.

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OPHTALMOLOGY FUNDS



California Institute for Regenerative Medicine

CIRM Funded Clinical Trials

Retinal progenitor cells for treatment of retinitis pigmentosa

Disease Area:

Investigator:

Institution:

CIRM Grant:

Award Value: Trial Sponsor: Trial Stage:

Trial Status:

Targeted Enrollment:

ClinicalTrials.gov ID:



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EYE BARRIERS

Conjunctival Barrier Tear Film Barrier Anterior Segment **Corneal Barrier**

Blood Aqueous Barrier





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 repopulation 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	Limbal		
Autografts	Allografts		
 Conjunctival- limbal autograft (CLAU) 	 Keratolimbal allografts (KLAL) 	•	
 Cultured limbal epithelial transplantation (CLET) 	 Living- related conjunctival allograft (LR-CLAL) 		
 Simple limbal epithelial transplantation (SLET) 	 Allogenic SLET 		

Non-LESCs Transplantatic

• Cultivated c mucosal epithelial transplantat (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











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



Draining lymph node

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	hCSSCs	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	hCSSCs	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- ĸB 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	Zhou et al. (2022b)

CORNEAL DISORDERS

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 fifibrin 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 μg	Inhibition of MCP-1	MCP-1 ^[28]
	BMSCs	IV/3 × 10 ⁹ particles	Through miRNA dependent mechanisms	miRNA ^[56]
	UMSCs	Tail vein∕55 μg	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 μg	Inhibit activation of antigen-presenting cells and suppress the development of Th1 and Th17 cells	Unclear ^[106]
	UMSCs	IV/0.05 μg	Ameliorate retinal injury via downregulation of VEGF-A	Unclear ^[107]
	UMSCs	$IV/1 \times 10^9$ 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	10/15 ug	Improved Brn3a+ RGCs survival and improved cognitive visual behavior	Unclear ^[110]

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

MSCS FOR OCULAR SURFACE INFLAMMATORY DISORDERS



MSC-EXOS' BENEFICIAL EFFECTS ON TREATING INFLAMMATORY OCULAR DISEASES



Lacraminal epithelial cell function

Choroidal neovascularization

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	Outcor
Oner [10] (2016)	RP	11	AD- MSC	Subretinal	2.47 × 10 ⁸ ± 0.11 cells/150 μl	I	Minor ocular co
Kahraman [11] (2020)	RP	82	UC- MSC	Suprachoroidal	5 × 10 ⁶ cells/2 mL	Ш	Beneficial effect on BC
Özmert [12] (2020)	RP	32	WJ- MSC	Subtenon	2-6 × 10 ⁶ cells/1.5 mL	Ш	No ocular or system
Weiss [13] (2018)	RP	17	BM- MSC	Retrobulbar, subtenon, intravitreal and intravenous	1.2 × 10 ⁹ cells/14-15 cm ³	NA	Beneficial effect o
Tuekprakhon [14] (2021)	RP	14	BM- MSC	Intravitreal	1×10^{6} cells, 5×10^{6} cells, 1×10^{7} cells	I	Beneficial effect o
Park [15] (2014)	IDRD	6	BM- MSC	Intravitreal	-	I	No ocular or system associated wit
Siqueira [16] (2011)	HRD	6	BM- MSC	Intravitreal	10 × 10 ⁸ cells/0.1 mL	I	No ocular or system associated wit
Gu [17] (2018)	DR	17	BM- MSC	Intravenous	3 × 10 ⁶ cells/kg	NA	Beneficial effect on ma visual a
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 o
Weiss [19] (2017)	NAION	10	BM- MSC	Retrobulbar, subtenon, intravitreal, and intravenous	1.2 × 10 ⁹ cells/14-15 cm ³	NA	Beneficial effect o
Kuriyan [20] (2017)	AMD	3	AD- MSC	Intravitreal	-	NA	Severe ocular o

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

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CVA, VF, and mfERG

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on visual acuity

on visual acuity

complications

EFFICACY OF EXOSOMES



RGC Glial cell Retinal stem cel Downregulation of VEGF-A **Blood vessel** Block neutrophil infiltration Neutrophil Polarize macrophages toward M2 Macrophage Modulate T cells (Th1/Th17) T cell

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



SCIENCE ADVANCES, 12 Jan 2022, Vol 8, Issue 2, DOI: 10.1126/sciedv.abj9617

		Preclinical	Phase I	Phase II
	Cornea	Limbal production from PSCs; Corneal endothelium regrowth	Transplant ex vivo cultured stromal stem cells to reverse existing stromal scars in human patients L.V. Prased Eye Institute, India	
	Lens	Improving adult LEC growth	Modified, minimally invasive surgical techniques for pediatric cataract treatment Sun Yat-sen University, China	
	TM	Replace glaucomatous TM with healthy stem cell- derived TM cells to restore IOP regulation		
	tina	Transplantation of adult RPESC-derived RPE progenitor cells Transplantation of RPE on	Subretinal transplantation of stem ce Cell Suspension Astellas Pharma, Japan/US CHABiotech, South Korea Chinese Academy of Sciences, China Southwest Hospital, China Cell Cure, Israel	III-derived RPE
		Transplantation of hPSC photoreceptor progenitors	Cells on Matrix Riken, Japan, Phase I Plaer, UK, Phase I Regenerative Patch Technology, US Subretinal RPC transplant	
	Re	Transplantation of hPCS- derived RGCs	ReNeuron, UK/US Trophic support JCyte, US - Vitreal RPC Janssen, US - Subretinal USC StemCells, Inc., US - Subretinal NSC	

Phase III

Clinical

Cultured limbal epithelial cells for transplantation to treat LSCD

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

ROUTES OF MSC APPLICATION

Ref.	Origin	Delivery way
Yu <i>et al</i> [<mark>74</mark>], 2016	Human umbilical cord derived MSCs	Intravitreal injection
Mead <i>et al</i> [<u>64</u>], 2017	Human bone marrow derived MSCs	Intravitreal injection
Kuroda <i>et</i> <i>al</i> [<mark>58</mark>], 2017	Human bone marrow derived MSCs	Intravenous injection
Moisseiev <i>et</i> <i>al</i> [<u>77</u>], 2017	Human bone marrow derived MSCs	Intravitreal injection
Bai <i>et al</i> [<u>57</u>], 2017	Human umbilical cord derived MSCs	Periocular injection
Shen <i>et al</i> [<u>44</u>], 2018	Rabbit adipose derived MSCs	In vitro
Samaeekia <i>et</i> <i>al</i> [<u>39</u>], 2018	Human corneal MSCs	Topical application
Mead <i>et al</i> [<u>67</u>], 2018	Human bone marrow derived MSCs	Intravitreal injection
Safwat <i>et</i> <i>al</i> [<u>72</u>], 2018	Rabbit adipose derived MSCs	Intravenous, intraocular or subconjunctival injection
Zhang <i>et</i> <i>al</i> [<mark>71</mark>], 2018	Human umbilical cord derived MSCs	Intravitreal injection
Mathew <i>et</i> <i>al</i> [<u>76</u>], 2019	Human bone marrow derived MSCs	Intravitreal injection

Biological function

Ameliorate retinal laser injury

Promote RGC survival in optic nerve crush model

Prevent EAU development

Decrease the severity of retinal ischemia

Inhibit inflammatory cell migration in EAU

Contribute to the growth and plasticity of corneal stromal cells

Accelerate corneal epithelial wound healing

Promote neuroprotection in glaucoma model

Attenuate retina degeneration in diabetic retinopathy

Ameliorate hyperglycemia-induced retinal inflammation

Protect retinal cells from cell death in retinal ischemia

DIABETIC RETHINOPATHY





E thical Considerations and Future Implications

Benefit to Society

E thical 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.

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.

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.

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 nartnorching

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Biotech Companies

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

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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.



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 agerelated 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. gurthie a Batto



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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.

