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An Eye on Extracellular Vesicles: Trends and Clinical Translations in Vision Research

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Purpose: To perform a review of research, funding, and clinical translation efforts for extracellular vesicles (EVs) within vision science.

Design: Retrospective analysis of publication, funding, and clinical trials data.

Methods: A pretrained large language model (Jina2) was used to create semantic embeddings for 41 282 abstracts from articles related to EVs archived on EMBASE and published between January 1966 and January 2024. The articles were projected and clustered according to semantic embedding similarity, and research subdomains for EVs were determined through inspection of term frequency-inverse document frequency weighted word clouds. Mann−Kendall trend analysis was performed to identify current areas of growth within EV research. Additionally, National Institutes of Health funding data from RePORT Expenditures and Results and clinical trials data from ClinicalTrials.gov were analyzed to correlate publication trends with funding support and clinical translation efforts.

Results: Unsupervised clustering and Mann−Kendall trend analysis identified wound healing/regeneration ($P = 0.030$) and neurodegenerative disease ($P = 0.049$) as significantly accelerating in growth of publication over time. Ophthalmology-restricted subset analysis identified that publications in age-related macular degeneration ($P = 0.191$) and clinical applications ($P = 0.086$) are no longer growing at a significant rate. Analysis of funding data identified that the National Cancer Institute was the top funding institution overall, but that the National Institute on Aging is rapidly advancing in terms of funding EV research and trials. Analysis of ClinicalTrials.gov data highlights a dearth of clinical trials within ophthalmology despite a growing number of studies in other medical subfields.

Conclusions: Extracellular vesicles remain a promising substrate for both the identification and treatment of vision-threatening diseases. A better understanding of the current landscape of research and funding trends should help to inform future funding and translational efforts.

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Extracellular vesicles (EVs) refer to nano- to micro-sized heterogeneous group of particles released from cells, surrounded by a lipid bilayer, and lacking the ability to self-replicate (i.e., devoid of a functional nucleus). Extracellular vesicles, containing a diverse cargo of lipids, proteins, and nucleic acids, serve as indicators of their cell of origin, influencing the functions and phenotypes of other cells.[1−3] Alongside the expanding studies in the fundamental biology of EVs, there has been a growing interest in their application in various clinical practices—ranging from using EVs in biofluids as biomarkers to delivering either naive or bioengineered EVs as bioactive therapeutics directly to target tissues.[4] Therefore, there has been growing interest in translating EV research into effective patient care across various branches of medicine. Currently, a wide variety of EV therapeutics are being developed to combat a multitude of diseases. For example, treatments are being developed for dermatological disorders and skin repair (Aegle Therapeutics, XOStem Inc, Exogenus Therapeutics), as well as cancer (Aethlon Medical, Unicyte AG, TAVEC Pharmaceuticals, Puretech Health, EV Therapeutics Inc, Anjarum Biosciences, Codiak Biosciences) and neurological disorders/diseases (Stemcell Medicine Ltd, Puretech Health, Evox Therapeutics, Codiak Biosciences).[5,6]

Meanwhile, the field of ophthalmology presents a compelling prospect for the development of EV-based diagnostics and therapeutics. The distinctive characteristics of the eye, including its unique anatomy on a relatively small scale, the presence of specialized cell types, immune-privileged organ physiology with blood-ocular barriers, the accessibility to its own biofluid, and feasibility for local drug delivery, have positioned vision research at the forefront of technological advancements. This is exemplified by notable innovations in ophthalmology such as OCT, intraocular drug delivery therapy, and intraocular cell and gene therapy.[7−10] Furthermore, several reports have underscored the production of EV by ocular tissues, emphasizing their significance in the normal homeostatic maintenance of structures like the cornea and retina.[11,12] Additionally, EVs have been implicated in the pathophysiology of several important diseases of the visual system, including age-related macular degeneration (AMD). Several studies have

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implicated EV-mediated signaling in the retinal pigment epithelium as a potential driver of protein secretion and drusen development.[13,14] In retinoblastoma, tumor-associated CD63+/CD81+ EVs have been identified in the aqueous humor, representing a possible target for liquid biopsy.[15] In the anterior segment of the eye, EVs containing thrombospondin-1 and fibronectin have been identified that may modulate corneal myofibroblast differentiation and migration—key drivers of corneal scarring and opacification.[16] Treating the cornea with EVs, especially those derived from human corneal stromal stem cells, may have antifibrotic and regenerative effects to reverse vision-threatening corneal disease.[17] Within the eye, a diverse array of EVs within the aqueous humor may also serve as a rich messaging channel between the loci of aqueous production at the ciliary body and aqueous outflow through the trabecular meshwork and uveoscleral pathways, with implications for pressure regulation in the development and management of glaucoma.[18] This recognition of the potential utility of EVs in vision science led to the organization of the inaugural Extracellular Vesicle Workshop by the National Eye Institute (NEI) in 2023, which brought together a diverse group of experts in EV research. The workshop aimed to assess current EV studies and pinpoint critical knowledge gaps, needs, and opportunities for investigating EVs in eye health and disease. Besides these scientific strides and promising prospects, there remains significant untapped potential related to practical aspects such as the lack of EV communities, funding, and focused clinical trials (https://www.nei.nih.gov/about/goals-and-accomplishments/nei-research-initiatives/regenerative-medicine/extracellular-vesicle-workshop).[19]

In this study, we performed an unbiased review of the scientific literature to identify trends in publications related to EVs. We analyze these trends to highlight current areas of active investigation across EVs and ophthalmology, aiming to provide a fact-check that highlights the necessities and opportunities for advancing EV applications in this field.

Methods

Overview of Data Gathering and Data Sources

To derive insights regarding scientific research, funding availability, and clinical translation, we gathered data regarding EVs from several orthogonal data sources. Specific procedures, access times, data representation formats, and analysis performed are documented below for each data source. This study was reviewed by the University of Southern California Institutional Review Board and was determined to be exempt from Institutional Review Board approval because it did not involve human subjects as defined by federal regulations.

Publication Data Were Gathered through EMBASE

To obtain publication data, we queried the EMBASE library using the University of Southern California library access to search for all articles pertaining to EVs that were indexed as part of MEDLINE. The following query was used: "('exosomes'/exp OR exosomes OR 'microvesicle'/exp OR microvesicle OR 'extracellular vesicle'/exp OR 'extracellular vesicle') AND [medline]/lim." This search was executed on February 2, 2024, and resulted in a total of 41 282 independent publication items returned. These items were exported to a comma-separated-value format and processed by a series of custom python and R scripts (R Foundation for Statistical Computing) for subsequent analysis. Publications were identified as ophthalmology-focused by regular expression search of the publication abstracts and titles for the substrings: "eye," "ocular," "retina," "cornea," "glaucoma," and "ophth." Any publication containing any of these substrings was included as an ophthalmology focused publication in further analysis.

Funding Data Were Gathered through the National Institutes of Health RePORT Expenditures and Results

The National Institutes of Health (NIH) RePORT Expenditures and Results (RePORTER) platform was searched to identify public funding from all NIH-affiliated funding administering institutes and centers. All funding entries containing the keywords "extracellular vesicle" OR "microvesicle" OR "exosome" were queried from all financial year data stored in the database. The query was executed on January 27, 2024 and resulted in a total of 6462 items returned. These data were also exported to a comma-separated-value format and analyzed using python and R language tools as described here.

Clinical Trials Data Were Gathered through ClinicalTrials.gov

The ClinicalTrials.gov database was searched to identify current and historical clinical trials related to EVs. The database was queried using the terms "extracellular vesicle OR exosome OR microvesicle" on January 29, 2024. The query identified a total of 643 study records, which were exported to a comma-separated-value format and analyzed using python and R.

Geographic Annotation of Publications for Author Nationality

To associate publication records with country-of-origin for authorship nationality annotation and geographic attribution of EV research, regular expression string searching was used on EMBASE-documented author affiliation strings for each publication. The UNICODE Common Locale Data Repository standard list of country names was used, along with tooling from the countrycode library in the R.[20]

Semantic Embedding and Clustering of Publication Abstracts

The development of language models pretrained on large natural language corpuses has dramatically expanded methods for analyzing textual data.[21] These tools enable

automated clustering and similarity measures that capture the semantics of publication abstract data in a far richer way than keyword or other language-component based methods.[22,23] To analyze and subdivide the thousands of abstracts identified by our literature search, we employed the Jina2 long context model for semantic embedding of abstract text.[24] Pretrained models for the Jina2 architecture were loaded from the hugging face public repository maintained by the original authors.[25] Abstract embeddings were clustered using the Louvain algorithm with the igraph package in R, after principal components analysis, a linear dimensionality reduction method.[20,21] To capture higher order structure within 2 dimensions for improved human interpretability, visualization of these embeddings was performed using uniform manifold approximation and projection, a nonlinear dimensionality reduction method.[22,23]

Generation of Word Clouds for Abstract Subdomains

Abstract texts were split into bag-of-words representations using the text mining "TM" library in R.[26] Standard English stop words were discarded, and words were reweighted according to the term frequency-inverse document frequency scoring system.[27] The wordcloud package in R was used to generate the word cloud visualizations with the parameters min.freq = 1, max.words = 50, rot.per = 0.35, scale from 3 to 0.2, and color mapping to the first 8 colors of the "Dark2" palette from RColorBrewer.[28,29]

Graphics and Rendering

Free icons were downloaded and used from flaticon.com. These icons were used in the rendering of Figure 1. All data visualizations were generated using Inkscape and the ggplot2 and cowplot libraries in R.[30,31]

Statistics and Hypothesis Testing

Standard summary statistics generation such as mean and standard deviation were calculated using the R statistical programming language base utilities and library functions. Average annual growth rate was calculated throughout as the arithmetic mean of the year-over-year percentage growth rate for the specified time period. Nonparametric Mann−Kendall trend tests were employed in the analysis of publication growth data. In general, 2 types of Mann−Kendall trend tests were employed: (1) a test of "growth," where raw values of publication numbers were supplied to the Mann−Kendall test, and (2) a test of "acceleration," where year-over-year changes in publications were supplied to the Mann−Kendall test. Intuitively, these tests correspond roughly to first and second-derivative estimates of publication rate as a function of time. One-tailed tests with an alternative hypothesis corresponding to growth of publications over time were employed, based on the time period specified. Multiple comparisons correction was performed using the Bonferroni method.[32]

Results

Data Gathering and Queries

Comprehensive data gathering from EMBASE, NIH RePORTER, and ClinicalTrials.gov was performed between January 27, 2024 and February 2, 2024. The queries identified 41 282 publication records from EMBASE, 6462 funding records from NIH RePORTER, and 643 study records from ClinicalTrials.gov (Fig 1). Additionally, the full NIH EXPORTER dataset was obtained to perform analysis of the amount of funding accorded to EV-associated research as a percentage of the total annual budget of each NIH institute. Each record in EMBASE corresponded to a single publication. Each record in NIH RePORTER corresponded to a single funding event. Each record in ClinicalTrials.gov corresponded to a single study, either observational or interventional. These data were used for subsequent analysis.

The United States and China Remain Leading Contributors in EV Research

Country-of-origin analysis of all publication records retrieved from EMBASE identified that the top contributors

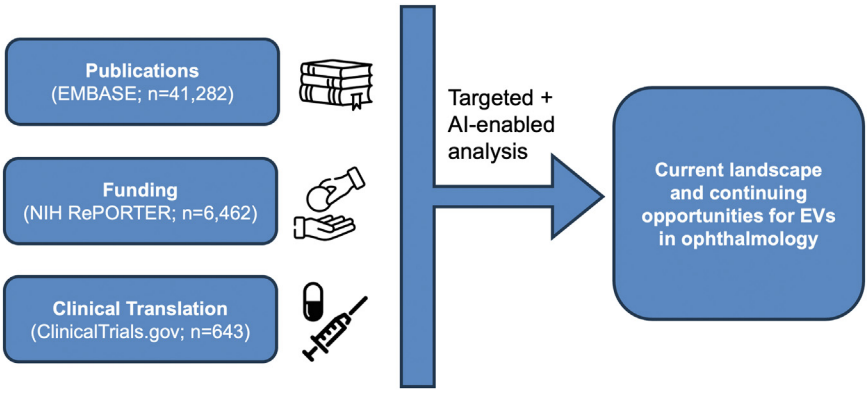


Figure 1. Overview of study design. Publication, funding, and clinical translation data were gathered from the EMBASE, NIH RePORTER, and ClinicalTrials.gov databases respectively to produce a comprehensive view of current trends and future opportunities for EVs within ophthalmology. AI = artificial intelligence; EV = extracellular vesicle; NIH = National Institutes of Health; RePORTER = RePORT Expenditures and Results.

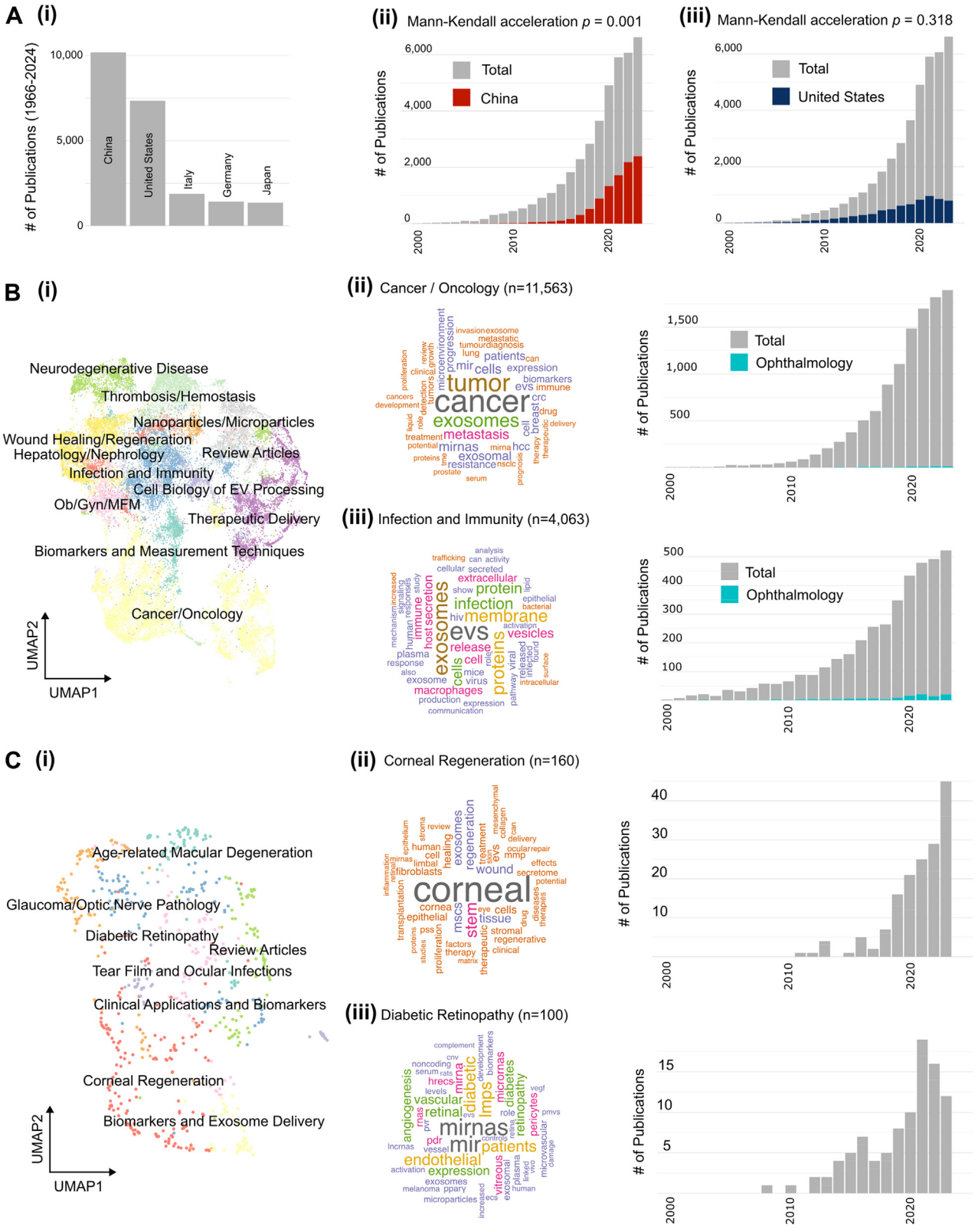


Figure 2. Analysis of publication trends in EV research at large and within ophthalmology. **A (i),** The nations with the most number of publications are China and the United States. **A (ii–iii),** While the number of publications per year continues to grow in China, it has plateaued in the United States. **B (i),** Semantic embedding and clustering analysis reveals key research subdomains. **B (ii),** Term frequency-inverse document frequency weighted term occurrence matrix rendered as a word cloud highlights key terms within the oncology subdomain. The total number of publications in this subdomain is growing over

Table 1. Overview of Clusters Identified in all EV-Associated Publications Using Semantic Embedding

Cluster	Total # (1966-2024)	AAGR (10 yrs) (% ± SD)	Mann–Kendall Growth (10 yrs)	Mann–Kendall Acceleration (10 yrs)
Cancer/Oncology	11 563	27.7 ± 15.1	$P < 0.001$*	$P = 1.449$
Therapeutic Delivery	4536	40.0 ± 36.9	$P < 0.001$*	$P = 0.370$
Infection and Immunity	4063	18.1 ± 11.4	$P < 0.001$*	$P = 4.532$
Wound Healing/Regeneration	**3960**	**43.1 ± 27.2**	**$P < 0.001$***	**$P = 0.030$***
Thrombosis/Hemostasis	3366	2.4 ± 14.1	$P = 0.951$	$P = 10.722$
Review Articles	2736	22.7 ± 12.6	$P < 0.001$*	$P = 0.113$
Neurodegenerative Disease	**2632**	**30.8 ± 21.3**	**$P < 0.001$***	**$P = 0.049$***
Obstetrics/Gynecology/MFM	1693	34.4 ± 34.9	$P < 0.001$*	$P = 6.373$
Biomarkers and Measurement Techniques	1658	46.8 ± 43.6	$P < 0.001$*	$P = 0.521$
Hepatology/Nephrology	1120	34.8 ± 27.1	$P < 0.001$*	$P = 0.076$
Cell Biology of EV Processing	1038	9.0 ± 31.1	$P = 1.261$	$P = 6.000$
Nanoparticles/Microparticles	648	14.9 ± 24.2	$P = 0.002$*	$P = 0.606$

AAGR = average annual growth rate; EV = extracellular vesicle; MFM = maternal-fetal medicine; SD = standard deviation.
Bonferroni-corrected Mann–Kendall trend test *P* values are reported. Clusters with statistically significantly accelerating trends are highlighted in bold.
*Statistically significant *P* values.

to EV research were authors from China, the United States, Italy, Germany, and Japan (Fig 2A.i). Of these, authors from China and the United States contributed more than double that of authors from Italy, suggesting growth opportunities for additional research in other countries (Fig 2A.i). While the total number of publications related to EVs has grown over the past decade in both China and the United States, the growth of EV research continues to accelerate in China (Mann–Kendall acceleration trend $P = 0.001$; Fig 2A.ii), while growth has slowed in the United States (Mann–Kendall acceleration trend $P = 0.318$; Fig 2A.iii).

Natural Language Processing of Publication Abstracts Identifies Semantic Subdomains

Embedding of publication abstracts using the Jina2 long context model followed by unsupervised Louvain clustering identified 24 clusters. These clusters were manually annotated as 12 semantically coherent research subdomains by inspection of cluster-specific term frequency-inverse document frequency weighted word clouds. The identified subdomains were (in order of decreasing publication volume): cancer/oncology (n = 11 563), therapeutic delivery (n = 4563), infection and immunity (n = 4063), wound healing/regeneration (n = 3960), thrombosis/hemostasis (n = 3366), review articles (n = 2736), neurodegenerative disease (n = 2632), obstetrics/gynecology/maternal-fetal medicine (n = 1693), biomarkers and measurement techniques (n = 1658), hepatology/nephrology (n = 1120), cell biology of EV processing (n = 1038), and nanoparticles/microparticles (n = 648) (Fig 2B; Table 1). Analysis of publication growth over the last 10 years (2013–2023) identified that almost all subdomains showed statistically significant growth, except for thrombosis/hemostasis and basic cell biology of EV processing (Table 1). However, accelerating publication volume was only identified in 2 domains: wound healing/regeneration and neurodegenerative disease (Table 1).

A parallel analysis of ophthalmology-focused publications identified in EMBASE identified 9 clusters by unsupervised Louvain clustering, which were annotated as 8 distinct subdomains. The identified subdomains were (in order of decreasing publication volume): corneal regeneration (n = 160), diabetic retinopathy (n = 100), tear film and ocular infection (n = 97), glaucoma/optic nerve pathology (n = 91), review articles (n = 79), AMD (n = 68), clinical applications and biomarkers (n = 42), and biomarkers and exosome delivery (n = 40) (Fig 2C; Table 2). While no subdomains within ophthalmology showed statistically significant acceleration of research growth, all subdomains except AMD and clinical applications showed statistically significant growth over the last 10 years (Table 2).

Analysis of EV Funding from the NEI and Other Institutions Shows Opportunity for Growth

Aggregation and visualization of funding data provided by the NIH RePORTER database identified that the greatest amount of funding disbursed to EV-related projects from 1994 to 2024 was from the National Cancer Institute (NCI) (Fig 3A). While the NCI has continued to lead other administering institutes and centers within the NIH in terms of the number of awards granted annually, the National Institute on Aging has recently surpassed the NCI in terms of the total dollar value of awards given annually (Fig 3B-C). When funding data are analyzed as a proportion of the total budget of the administering institute per year, the NEI remains behind other institutes

time, with very few publications in ophthalmology. **B (iii),** Parallel analysis for the infection and immunity research subdomain highlights key terms. Ophthalmology research in this subdomain is growing. **C (i),** Semantic embedding and clustering analysis of ophthalmology-focused publications identifies key research subdomains. **C (ii–iii),** Word clouds and publications-per-year trends for corneal regeneration and diabetic retinopathy, the largest subdomains identified. EV = extracellular vesicle; MFM = maternal-fetal medicine; UMAP = Uniform Manifold Approximation and Projection.

Table 2. Overview of Cluster Identified in Ophthalmology-Focused Extracellular Vesicle-Associated Publications Using Semantic Embedding

Cluster	Total # (1966-2024)	AAGR (10 yrs) (% ± SD)	Mann–Kendall Growth (10 yrs)	Mann–Kendall Acceleration (10 yrs)
Corneal Regeneration	160	104.0 ± 163.0	$P = 0.001$*	0.16
Diabetic Retinopathy	100	25.6 ± 45.4	$P = 0.006$*	4.25
Tear Film and Ocular Infection	97	56.3 ± 69.5	$P < 0.001$*	0.28
Glaucoma/Optic Nerve Pathology	91	58.2 ± 132.1	$P = 0.006$*	1.37
Review Articles	79	19.2 ± 68.0	$P = 0.001$*	0.19
Age-related Macular Degeneration	**68**	**60.2 ± 114.4**	**$P = 0.191$**	**4.50**
Clinical Applications and Biomarkers	**42**	**65.8 ± 50.0**	**$P = 0.086$**	**4.00**
Biomarkers and Exosome Delivery	40	21.2 ± 69.9	$P = 0.002$*	0.53

AAGR = average annual growth rate; SD = standard deviation.
Bonferroni-corrected Mann–Kendall trend test P values are reported. Clusters without statistically significantly growing trends are highlighted in bold.
*Statistically significant P values.

in the NIH, but the difference is of a lower magnitude (Fig 3D). While the NEI continues to increase annual funding and awards for research in EVs, both the number of awards and total funding remain behind the NCI, National Institute on Aging, and others (Fig 3).

While There Are a Growing Number of Clinical Trials Investigating EVs, Ophthalmology Continues to Lag Behind

Data from ClinicalTrials.gov showed an overall increase in the number of registered studies year-over-year pertaining to EVs (Fig. 4A). However, of these studies, only a total of 9 were identified within ophthalmology (Fig 4A-B). Of these, 2 studies pertained to macular degeneration, 3 to diabetic eye disease, 2 to dry eye disease, 1 to uveitis, and 1 to allergic conjunctivitis (Fig 4B). Only a few studies (NCT05839938, NCT05738629, NCT04213248, and NCT01523314) were interventional in nature while the rest of studies were observational (Fig 4B).

Discussion

The past decade has shown an explosion of research into EVs, led by the field of oncology, but also within vision science. Extracellular vesicles hold the promise of tremendous diversity in clinical application, from serving as circulating biomarkers of health, to flexible payloads for targeted therapeutic intervention. From our unbiased examination of the scientific literature to identify the current status in publications related to EVs, a global pattern in EV research emerges, with China leading in the number of publications, followed by the United States, Italy, Germany, and Japan. Although we did not assess the academic impact and quality of these publications, it is worth noting that the growth of EV research in China mirrors the overall global trend, indicating ongoing acceleration. In contrast, EV research in the United States appears to remain on a plateau. These findings may be compared to other cutting-edge research in stem cell and gene therapy[33,34] where the United States has been leading the field, suggesting a potential lag in EV research in the United States.

Using state-of-the-art natural language processing to decompose and landscape of 41 282 publications written regarding EVs, we identified wound healing/regenerative medicine and neurodegenerative disease as 2 areas where research progress continues to accelerate. Within ophthalmology, prevalent studies in cornea and glaucoma reflect the active research in wound healing and neurodegenerative diseases in and outside of ophthalmology.[17,35] However, studies investigating AMD, the most common ocular neurodegenerative disease and a leading cause of blindness worldwide, have not kept pace with research in other subdomains.[36] Our results suggest that new research into EVs in neurodegeneration at large may anticipate possibilities for cross-domain translation and application to AMD. For example, gasdermin D knockdown has been described to reduce exosomal IL-1beta production, with a neuroprotective effect.[37] VEGF receptor mRNA has also been shown to be secreted in the exosomes of stressed retinal pigment epithelium cells, with proangiogenic effects in nearby endothelial cells.[38] Aging retinal pigment epithelium may also signal to retinal microglia through EVs-microRNA, initiating a cascade of chronic inflammation that may exacerbate a number of age-related pathologies including macular degeneration.[39]

Other important areas highlighted by our analysis for EVs within ophthalmology include corneal regeneration, tear film and ocular infections, and glaucomatous optic neuropathy. Corneal regeneration has been an especially active area of research using exosomes and several trials are now underway exploring the potential for exosome use as a therapeutic agent in corneal pathology (NCT05738629; NCT04213248). These translational applications run hand-in-hand with an emerging literature demonstrating that corneal niches are highly sensitive to EVs, and that EVs may serve a physiological role in signaling by limbal stem cells.[40] Extracellular vesicles may play a role in the development and progression of important viral infections of the eye, including herpes simplex virus keratitis, where tear exosomes have been described as a site of viral persistence.[41] Further, in glaucoma, EV-mediated signaling between the trabecular

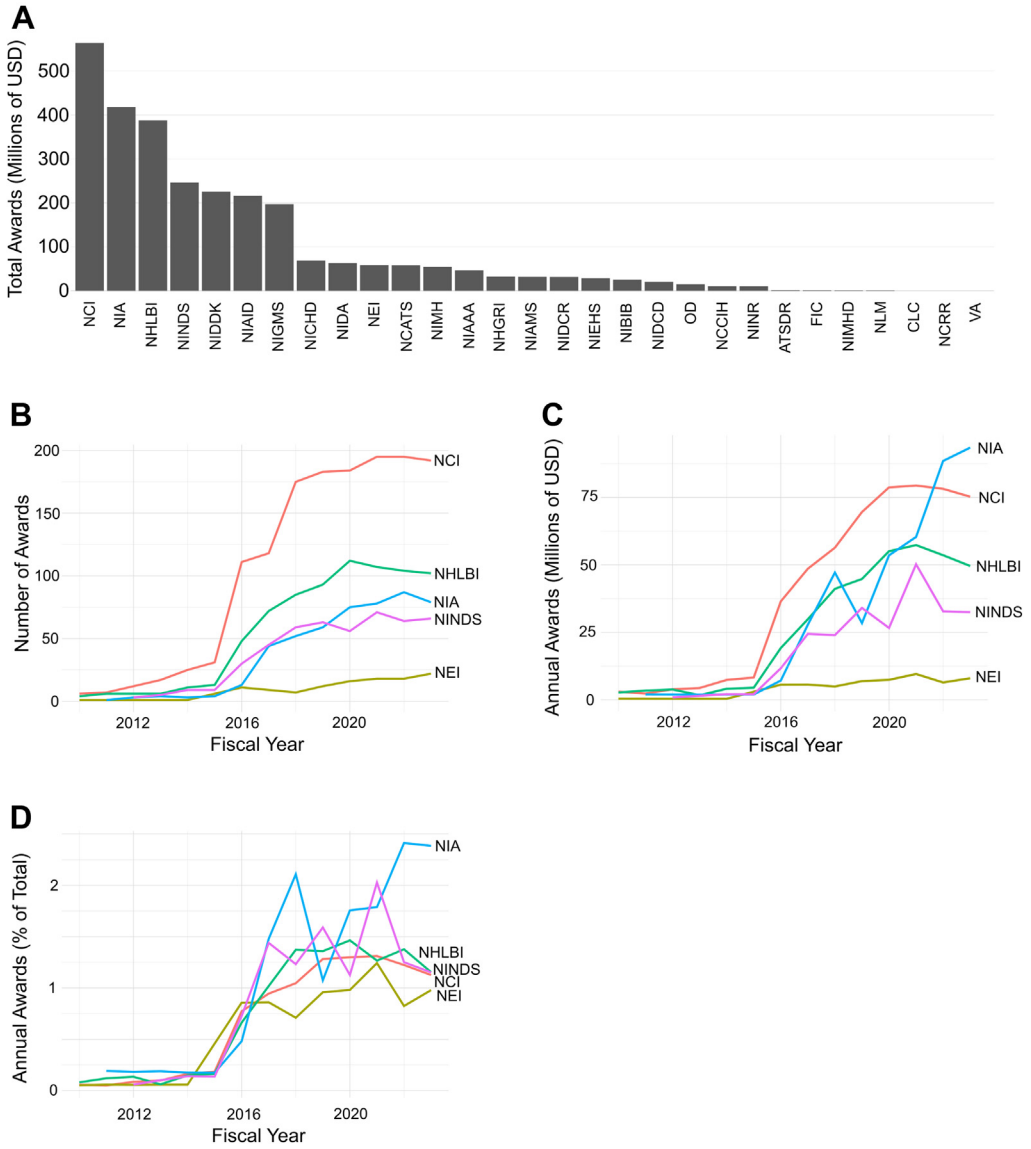
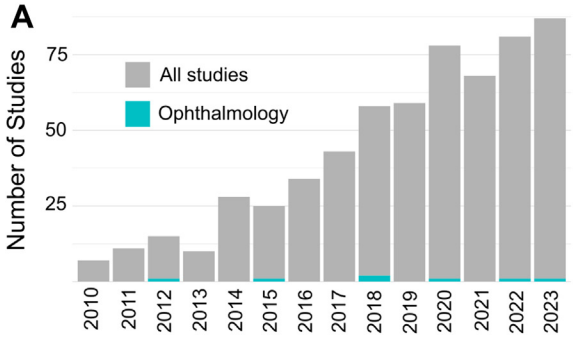


Figure 3. Analysis of United States governmental funding supporting research and clinical trials pertaining to EVs. **A,** Total monetary amount of all awards given to support EV research across each administering institute/center (standard abbreviations are used, from the official NIH abbreviations glossary). **B,** Plot of the total number of EV-related awards given per year for the top 4 funders and the NEI. **C,** Plot of the total monetary value of all EV-related awards given per year for the top 4 funders and the NEI. **D,** Plot of monetary value of all EV-related awards expressed as a percentage of the annual budget for the administering institution each year. ATSDR = Agency for Toxic Substances and Disease Registry; CLC = Clinical Center; EV = extracellular vesicle; FIC = Fogarty International Center; NCATS = National Center for Advancing Translational Sciences; NCCIH = National Center for Complementary and Integrative Health; NCI = National Cancer Institute; NCRR = National Center for Research Resources; NEI = National Eye Institute; NHGRI = National Human Genome Research Institute; NHLBI = National Heart, Lung, and Blood Institute; NIA = National Institute on Aging; NIAAA = National Institute on Alcohol Abuse and Alcoholism; NIAID = National Institute of Allergy and Infectious Diseases; NIAMS = National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIBIB = National Institute of Biomedical Imaging and Bioengineering; NICHD = National Institute of Child Health and Human Development; NIDA = National Institute on Drug Abuse; NIDCD = National Institute on Deafness and Other Communication Disorders; NIDCR = National Institute of Dental and Craniofacial Research; NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases; NIEHS = National Institute of Environmental Health Sciences; NIGMS = National Institute of General Medical Sciences; NIMH = National Institute of Mental Health; NIMHD = National Institute on Minority Health and Health Disparities; NINDS = National Institute of Neurological Disorders and Stroke; NINR = National Institute of Nursing Research; NLM = National Library of Medicine; OD = Office of Director; USD = United States dollars; VA = Veterans Affairs.

meshwork and Schlemm's canal endothelial cells may play a role in modifying the facility of trabecular outflow.[42] Extracellular vesicles may also hold promise in promoting retinal ganglion cell and optic nerve regeneration through Müller glia through modulation of Yamanaka factors and activation of Wnt signaling.[43,44]



B

NCT Trial Number	Ophthalmic Disease	Start Date (YYYY-MM)
NCT00331331	Uveitis	2007-02
NCT01523314	Diabetic Macular Edema	2012-03
NCT02863640	Age-related Macular Degeneration	2015-12
NCT03415984	Age-related Macular Degeneration	2018-01
NCT03264976	Diabetic Retinopathy	2018-07
NCT04213248	Dry Eye	2020-02
NCT05839938	Allergic Conjunctivitis	2022-08
NCT05738629	Dry Eye	2023-03
NCT06198543	Diabetic Retinopathy	2024-01

Figure 4. Analysis of clinical trials investigating extracellular vesicles in ophthalmology and other domains. **A,** The number of studies listed on ClinicalTrials.gov, grouped by year of start date. **B,** Callout table showing all ophthalmology focused studies registered with ClinicalTrials.gov, ordered by start date. NCT = National Clinical Trial.

Additionally, our work identifies a gap in research on EVs, particularly regarding their clinical applicability, which presents an active opportunity within the United States, including support from the NIH/NEI. The potential of EV therapeutics in vision science precisely aligns with the strategic plan for the NEI titled "Vision for the Future," where EV research is listed as a priority, especially within regenerative medicine, demonstrating the importance of continued growth in this field.[45] However, the translation of EV research into clinical applications in ophthalmology lags behind, as indicated by trends in clinical trials.

To expedite the translation of EVs in ophthalmology, whether as diagnostics or therapeutics, it is imperative to not only pursue funding opportunities but also to foster a deeper understanding of EV biology within the eye. Additionally, rigorous validation of established biological knowledge in EV will be crucial for advancing this field. These efforts collectively will establish a robust evidence base and foundation, laying the groundwork for initiating the first human clinical trials focused on therapeutics for vision-threatening diseases, while also facilitating compliance with necessary regulatory requirements. It may be premature to discuss the potential disadvantages of translating EVs in ophthalmology, although important, because the field is still in its early stages. However, it is necessary to acknowledge the challenges related to the inherent nature of EVs for their translation, drawing lessons from outside the ophthalmology field, such as their heterogeneity and limited understanding of their mechanisms of action. These factors should be considered in ophthalmology as well.

Several limitations to the current study should be noted. First, our study did not evaluate the academic impact and quality of publications during our semantic subclustering analysis. Instead, we used an unbiased analysis to identify core themes within the data, which were then further explored and analyzed to identify important areas for future growth and research. Furthermore, we did not perform investigation of private funding sources or funding from non-United States governmental agencies which may provide significant support, especially for research and clinical translation efforts taking place outside of the United States. Additionally, while our study was able to obtain a much broader picture of the overall research landscape by making use of automated semantic interpretation by large language models, the segmentation assigned by unsupervised clustering of these data may not correspond exactly to subdomains annotated de novo by a human domain expert.

Despite these limitations, this study offers an up-to-date overview of several key trends in EV research and clinical translation reflected in ophthalmology. Moreover, we contextualize the current efforts within ophthalmology as part of broader initiatives across various medical fields, aiming to identify potential synergies that could benefit from cross-domain technology, such as advancement in EV bioengineering technology and single particle analysis along with knowledge transfer.

In summary, EVs remain a promising avenue for both detection of and intervention on cellular phenotypes for the prevention and reversal of vision-threating pathology. Our survey results advocate continued attentions from EV and vision scientists, funding agencies, and industry.

Footnotes and Disclosures

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This material has not been presented at a meeting.

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HUMAN SUBJECTS: No human subjects were included in this study.

This study was reviewed by the University of Southern California Institutional Review Board and was determined to be exempt from Institutional Review Board approval because it did not involve human subjects as defined by federal regulations.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Dhodapkar, Jung, Lee

Data collection: Dhodapkar, Jung, Lee

Analysis and interpretation: Dhodapkar, Jung, Lee

Obtained funding: Lee

Overall responsibility: Dhodapkar, Jung, Lee

Abbreviations and Acronyms:
AMD = age-related macular degeneration; **EV** = extracellular vesicle; **NCI** = National Cancer Institute; **NEI** = National Eye Institute; **NIH** = National Institutes of Health; **RePORTER** = RePORT Expenditures and Results.

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References

1. Buzas EI. The roles of extracellular vesicles in the immune system. *Nat Rev Immunol*. 2023;23:236−250.
2. Zhang Y, Liu Y, Liu H, Tang WH. Exosomes: biogenesis, biologic function and clinical potential. *Cell Biosci*. 2019;9:1−18.
3. Welsh JA, Goberdhan DC, O'Driscoll L, et al. Minimal information for studies of extracellular vesicles (MISEV2023): from basic to advanced approaches. *J Extracell Vesicles*. 2024;13:e12404.
4. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science*. 2020;367:eaau6977.
5. Meng W, He C, Hao Y, et al. Prospects and challenges of extracellular vesicle-based drug delivery system: considering cell source. *Drug Deliv*. 2020;27:585−598.
6. Claridge B, Lozano J, Poh QH, Greening DW. Development of extracellular vesicle therapeutics: challenges, considerations, and opportunities. *Front Cell Dev Biol*. 2021;9:734720.
7. Bouma BE, de Boer JF, Huang D, et al. Optical coherence tomography. *Nat Rev Methods Prim*. 2022;2:79.
8. Thomas D, Duguid G. Optical coherence tomography—a review of the principles and contemporary uses in retinal investigation. *Eye*. 2004;18:561−570.
9. Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. *Lancet*. 2017;390:849−860.
10. Humayun MS, Lee SY. Advanced retina implants. *Ophthalmol Retina*. 2022;6:899−905.
11. McKay TB, Yeung V, Hutcheon AE, et al. Extracellular vesicles in the cornea: insights from other tissues. *Anal Cell Pathol*. 2021;2021:9983900.
12. Sun F, Xu W, Qian H. The emerging role of extracellular vesicles in retinal diseases. *Am J Transl Res*. 2021;13:13227.
13. Kurzawa-Akanbi M, Whitfield P, Burté F, et al. Retinal pigment epithelium extracellular vesicles are potent inducers of age-related macular degeneration disease phenotype in the outer retina. *J Extracell Vesicles*. 2022;11:12295.
14. Flores-Bellver M, Mighty J, Aparicio-Domingo S, et al. Extracellular vesicles released by human retinal pigment epithelium mediate increased polarised secretion of drusen proteins in response to AMD stressors. *J Extracell Vesicles*. 2021;10:e12165.
15. Pike S, Peng CC, Neviani P, et al. CD63/81 small extracellular vesicles in the aqueous humor are retinoblastoma associated. *Invest Ophthalmol Vis Sci*. 2023;64:5.
16. McKay TB, Hutcheon AE, Zieske JD, Ciolino JB. Extracellular vesicles secreted by corneal epithelial cells promote myofibroblast differentiation. *Cells*. 2020;9:1080.
17. Deng SX, Dos Santos A, Gee S. Therapeutic potential of extracellular vesicles for the treatment of corneal injuries and scars. *Transl Vis Sci Technol*. 2020;9:1.
18. Dismuke WM, Challa P, Navarro I, et al. Human aqueous humor exosomes. *Exp Eye Res*. 2015;132:73−77.
19. Sanghani A, Andriesei P, Kafetzis KN, et al. Advances in exosome therapies in ophthalmology−From bench to clinical trial. *Acta Ophthalmol*. 2022;100:243−252.
20. Arel-Bundock V, Enevoldsen N, Yetman C. Countrycode: an R package to convert country names and country codes. *J Open Source Softw*. 2018;3:848.
21. Zhao WX, Zhou K, Li J, et al. A survey of large language models. *arXiv*. 2023. https://doi.org/10.48550/arXiv.2303.18223.
22. Guesmi M, Chatti MA, Kadhim L, et al. Semantic interest modeling and content-based scientific publication recommendation using word embeddings and sentence encoders. *Multimodal Technol Interact*. 2023;7:91.
23. Alexandrov M, Gelbukh A, Rosso P. *An approach to clustering abstracts*. Berlin, Germany: Springer; 2005:275−285.
24. Günther M, Ong J, Mohr I, et al. Jina embeddings 2: 8192-token general-purpose text embeddings for long documents. *arXiv*. 2023. https://doi.org/10.48550/arXiv.2310.19923.
25. Wolf T, Debut L, Sanh V, et al. Huggingface's transformers: state-of-the-art natural language processing. *arXiv*. 2019. https://doi.org/10.48550/arXiv.1910.03771.
26. Feinerer I, Hornik K, Meyer D. Text mining infrastructure in R. *J Stat Software*. 2008;25:1−54.
27. Beel J, Gipp B, Langer S, Breitinger C. Paper recommender systems: a literature survey. *Int J Digit Libr*. 2016;17:305−338.
28. Fellows I, Fellows MI, Rcpp L, Rcpp L. Package 'wordcloud'. *R package version*. 2018;2:331.
29. Neuwirth E. Package 'RColorBrewer', 2014, ColorBrewer. https://doi.org/10.32614/CRAN.package.RColorBrewer. Accessed October 2, 2024.
30. Wilke CO. Package 'cowplot', In: *Streamlined plot theme and plot annotations for 'ggplot2*, 2019, 1. https://doi.org/10.32614/CRAN.package.cowplot. Accessed October 2, 2024.

31. Wilkinson L. *ggplot2: Elegant Graphics for Data Analysis by Wickham, H*. Oxford, United Kingdom: Oxford University Press; 2011.
32. Armstrong RA. When to use the Bonferroni correction. *Ophthalmic Physiol Opt*. 2014;34:502−508.
33. Ginn SL, Amaya AK, Alexander IE, et al. Gene therapy clinical trials worldwide to 2017: an update. *J Gene Med*. 2018;20:e3015.
34. Liu M, Yang F, Xu Y. Global trends of stem cell precision medicine research (2018−2022): a bibliometric analysis. *Front Surg*. 2022;9:888956.
35. Mead B, Amaral J, Tomarev S. Mesenchymal stem cell−derived small extracellular vesicles promote neuroprotection in rodent models of glaucoma. *Invest Ophthalmol Vis Sci*. 2018;59:702−714.
36. Fleckenstein M, Keenan TD, Guymer RH, et al. Age-related macular degeneration. *Nat Rev Dis Prim*. 2021;7:31.
37. ekar R, Wooff Y, Cioanca AV, et al. Impairing Gasdermin D-mediated pyroptosis is protective against retinal degeneration. *J Neuroinflammation*. 2023;20:239.
38. Atienzar-Aroca S, Flores-Bellver M, Serrano-Heras G, et al. Oxidative stress in retinal pigment epithelium cells increases exosome secretion and promotes angiogenesis in endothelial cells. *J Cell Mol Med*. 2016;20:1457−1466.
39. Morris DR, Bounds SE, Liu H, et al. Exosomal MiRNA transfer between retinal microglia and RPE. *Int J Mol Sci*. 2020;21:3541.
40. Yeung V, Boychev N, Farhat W, et al. Extracellular vesicles in corneal fibrosis/scarring. *Int J Mol Sci*. 2022;23:5921.
41. Huang H, Liu S, Zhao X, et al. Role of tear exosomes in the spread of herpes simplex virus type 1 in recurrent herpes simplex keratitis. *Eye*. 2023;37:3180−3185.
42. Takahashi E, Saruwatari J, Fujimoto T, et al. The effects of exosomes derived from trabecular meshwork cells on Schlemm's canal endothelial cells. *Sci Rep*. 2021;11:21942.
43. Gao Y, Li H, Qin C, et al. Embryonic stem cells-derived exosomes enhance retrodifferentiation of retinal Müller cells by delivering BDNF protein to activate Wnt pathway. *Immunobiology*. 2022;227:152211.
44. Ke Y, Fan X, Hao R, et al. Human embryonic stem cell-derived extracellular vesicles alleviate retinal degeneration by upregulating Oct4 to promote retinal Müller cell retrodifferentiation via HSP90. *Stem Cell Res Ther*. 2021;12:1−14.
45. Chiang MF. The 2021 national eye institute strategic plan: driving innovation in eye and vision research. *Invest Ophthalmol Vis Sci*. 2021;62:2.