EXOSOMES: THE RISING STAR IN DRUG DELIVERY AND DIAGNOSTICS

CAS
A division of the
American Chemical Society

Introduction

For a long time, synthetic drug nanocarriers such as lipid nanoparticles (LNPs) have held a recognized position in mainstream drug delivery systems. However, despite the advantages of drug delivery via LNPs, their clinical application has seen substantial difficulties, including low bioavailability, toxicity, clearance from the bloodstream, off-target accumulation, and triggering of innate immune responses.[1]

Considering these limitations, researchers are increasingly turning their attention towards exosomes, which are a type of membrane-contained nanosized extracellular vesicle (EV) released from cells as part of their normal physiology or under certain pathologies.[2,3] Exosomes are produced in the endosomal compartment of most eukaryotic cells and are subsequently released into the extracellular space by fusion with the plasma membrane. Upon release from the parent cell, exosomes have been shown to provide a means of efficient intercellular communication and signaling.[4,5] Crucially, exosomes are also able to transport bioactive molecules such as proteins, lipids, and nucleic acids between cells and across biological barriers.[4,5]

As a natural carrier system, exosomes have the potential to overcome several of the limitations associated with other drug delivery systems: they can be readily metabolized, elicit minimal immune responses, exhibit minimal tumorigenicity,[6] and can cross the blood-brain barrier (BBB).[7] Due to these properties, exosomes have emerged as a contender to lipid nanoparticles (LNPs) as prospective drug carriers. In addition to their promise in drug delivery, exosomes are an attractive tool in clinical diagnostics and biomarker discovery. Additionally, prospective applications of exosomes in cosmetics and food are being explored.

In this Insight Report, we analyze the CAS Content Collection™ to provide a unique landscape of exosome-related research, including current knowledge in the field of clinical applications of these natural carrier systems. We also highlight the current knowledge gaps and the remaining challenges to overcome for us to fully harness the potential of this nanotechnology.

Exosome characterization and function

Understanding the exosome pathway

To ensure the successful development of exosome-based clinical products, it's important to first understand exosome biology, including their formation, structure, and eventual release from parent cells. Exosomes are a population of EVs secreted by most cell types through the endocytic pathway. They are produced in the endosomal compartment of most eukaryotic cells, including dendritic cells, macrophages, various kinds of stem cells, and even cancer cells.[8] Once produced, exosomes are subsequently released into the extracellular space by fusion with the plasma membrane (**Figure 1**).

With a diameter of between ~30–150 nm, exosomes are the smallest of the EVs released from cells, dwarfed by microvesicles or ectosomes (100 nm–1 µm) and apoptotic bodies (50 nm–5 µm).[2,3] Exosomes are surrounded by a lipid membrane, which encapsulates their cargo (e.g., peptides, small proteins, and nucleic acids) in an inner aqueous medium. Though similar in structure to liposomes, exosomes are more complex, containing a large variety of integral and peripheral membrane proteins.[9] In fact, nearly 100,000 proteins and over 1,000 lipids have been discovered to be linked with exosomes, along with a multitude of messenger RNAs (mRNAs) and microRNAs (miRNAs).[10–13] Among these are heat shock proteins, membrane transport and fusion proteins, as well as a multitude of tetraspanins, a transmembrane protein family.[14,15] Exosomes are also enriched with lipids including cholesterol, sphingomyelin, saturated phosphatidylcholine, and phosphatidylethanolamine (**Figure 1**; inset).[16]

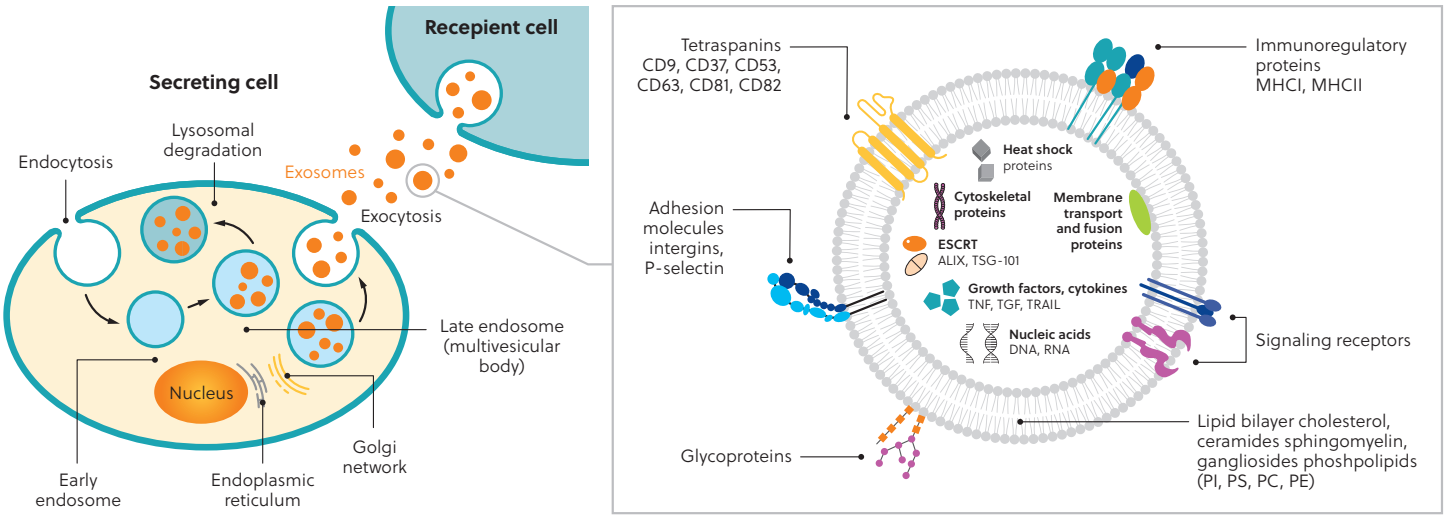


Figure 1. Schematic representation of exosome biogenesis and secretion. The inset shows the molecular constituents of the exosomes

The complex array of proteins and lipids present in exosomes are essential for them to exert their activity upon release from the parent cell. Once released, exosomes must undergo significant changes in their environment, moving from the cytoplasm and cell surface to the extracellular fluids. Exosomes are present in a variety of biological fluids such as blood, urine, saliva, breast milk, amniotic, synovial, cerebrospinal fluids, and even tears. To preserve and protect their cargo, exosomes must adjust to these varying conditions so they can deliver functional cargo to the designated location.[17]

The extracellular circulation half-life of exosomes is estimated to be approximately 2–30 min according to reported pharmacokinetic profiles.[18] Although researchers are gaining an understanding of exosome biogenesis and how they are secreted, there is still a limited understanding of how exosomes elicit a response in their target cells. Generally, exosomes transmit messages to recipient cells through several mechanisms, including surface receptor interaction and membrane fusion, as well as receptor-mediated endocytosis, phagocytosis, and/or micropinocytosis.[3]

Exosomes in health and disease

The functions of exosomes are still largely unknown. However, their important roles in physiological and pathophysiological processes are gradually being uncovered. Exosomes are key players in cell-to-cell communication, signal transduction, extracellular matrix support and remodeling, and various other important physiological activities. As such, the exosome pathway of intercellular traffic plays a significant role in essential cellular processes, including immunity, tissue homeostasis, and regeneration. Conversely, this same pathway is also involved in the pathogenesis of the diseases such as cancer, as well as neurodegenerative and cardiovascular disorders. **Table 1** summarizes the roles of exosomes in both health and disease.

Table 1. The roles of exosome in health and disease

Exosome role	Details and references
Cell-to-cell communication	Exosomes can participate in autocrine, paracrine, or endocrine communication, reaching their target cells via systemic or local circulation. They play a vital role in cell migration, proliferation, and senescence.[19,20]
Immune response	The cells of the immune system (e.g., dendritic cells and macrophages) are known to release exosomes.[21] Exosomes act to mediate immune modulation, including both immunosuppression and immunostimulation.[22]
Signal transduction	Exosomes mediate intercellular communication among several types of cells, regulating gene expressions and cellular signaling pathways of recipient cells by delivering their components, such as specific lipids, proteins, and RNAs.[23–25]
Material (cargo) transport	Exosomes transport their constituents (e.g., proteins, nucleic acids, lipids, and metabolites) between cells. This can occur not only in close vicinity of the parent cell, but also at distant sites in the body via biofluids. This material transport can trigger a variety of responses in the recipient cell, such as modifying gene expression and cellular function.[26,27]
Pathogenesis	Viruses are known to make use of exosome biogenesis pathways to release a variety of pathogenic factors.[28] Exosomes also play multiple roles in the progression of cancer via autocrine, paracrine, and endocrine communications. They can manipulate both the local tumor environment and the systemic environment to support tumor cell growth, dissemination, and metastasis.[29] Exosomes are more frequently released by tumor cells than by healthy ones, facilitating communication within the tumor microenvironment.[30]
Blood-to-brain communication	Studies have shown that exosomes are able to cross the BBB in both directions – from the brain to the bloodstream and from the blood to the central nervous system (CNS). Moreover, exosomes can interact with the BBB leading to changes in the properties of the barrier.[7]
Target cell delivery	The delivery of cargo such as bioactive RNAs, proteins, metabolites, and/or lipids makes the capture of exosomes by target cells of vital importance in a variety of key biological processes such as angiogenesis,[31] bone development,[32] and cell migration.[33]

Methods for exosome isolation and purification

To effectively utilize exosomes in research and clinical practice, it is crucial that these nano-sized particles are precisely distinguished and isolated from the wide spectrum of cellular debris and interfering components found in biological samples. Though there is no single standardized approach to exosome separation and analysis, several methods are available, with each approach providing a unique set of strengths and limitations (summarized in **Table 2**).[34–38]

Table 2. Major methods of exosome isolation/purification

Method	Principle	Advantages	Disadvantages
Ultrafiltration	Utilizing filter membrane with defined size-exclusion limit or molecular weight cut-off	– Low cost – Time efficient – Simple	– Potential damage ofexosomes – Membrane clogging and blockage
Ultracentrifugation	Density and size-based sequential separations	– Suitable for large-volume samples – No other markers introduced – Low cost	– High equipment cost – Labor-intensive – Potential damage of exosomes – Low yield
Immunoaffinity	Exosome capture based on antigen–antibody specific recognition and binding	– High specificity – Simple – Scalability	– Potential damage of exosome integrity – Expensive reagents – Nonspecific binding
Polymer precipitation	Hydrophilic water-excluding polymer adhering and precipitating exosomes	– Broad applicability – Simple and rapid – No exosome deformation	– Lack of specificity and selectivity – Low purity – Contamination with polymers
Size-exclusion chromatography	Exosome separation based on hydrodynamic radii	– Preserve biological activity – No preprocessing	– Potential contamination – High equipment cost
Microfluidics	Immunoaffinity, size, density	– High efficiency – Fast sample processing – High portability – Easy automation and integration	– Large amounts of starting materials – Low sample capacity

Ultracentrifugation was once considered the gold standard approach due to its affordability and ease of use. Yet in recent years, precipitation and microfluidic methods have gained popularity due to their ability to purify exosomes without causing potential damage. There is no single approach that can solve all the associated challenges, such as batch-to-batch variation, limited yield, and/or low purity. A combination of several of these methods has been suggested as a promising strategy for improvement of the isolation outcome, to provide exosome subsets with high purity, in particular with respect to size, morphology, concentration, presence of exosome-enriched markers, and the lack of contaminants.[34]

Applications of exosomes

Due to their natural properties and diverse roles in health and disease, exosomes have been subject to a burst of research interest. To identify the research trends emerging in exosomes, we analyzed the CAS Content Collection to build a picture of the exosome research landscape over the past two decades.

The CAS Content Collection[39] is the largest human-curated collection of published scientific knowledge, empowering quantitative analysis of global scientific publications against variables such as time, research area, application, disease association, and chemical composition. Currently, there are over 40,000 scientific publications (journal articles and patents) in the CAS Content Collection related to exosomes/extracellular vesicles. Our analyses revealed a steady, exponential growth of these documents over time (**Figure 2A**). The number of documents (journal articles and patents) originating from organizations in the USA has been correlated with funding from the National Institutes of Health (NIH), which is the primary agency of the United States government responsible for biomedical and public health research,[40] increasing sharply after 2015 (**Figure 2B**).

To better reveal the rising trends in this research area, we analyzed the presence and trends of certain key concepts in scientific publications relevant to exosome applications in drug delivery and diagnostics (**Figure 3**). With respect to the cumulative number of documents, "targeting" and "biomarker" appear as top concepts in the area (**Figure 3A**), reflecting the rising interest in the application of exosomes in therapeutics with specificity and diagnostics.

In the following sections, we will explore some of the key applications for exosomes, including the latest research findings in each area.

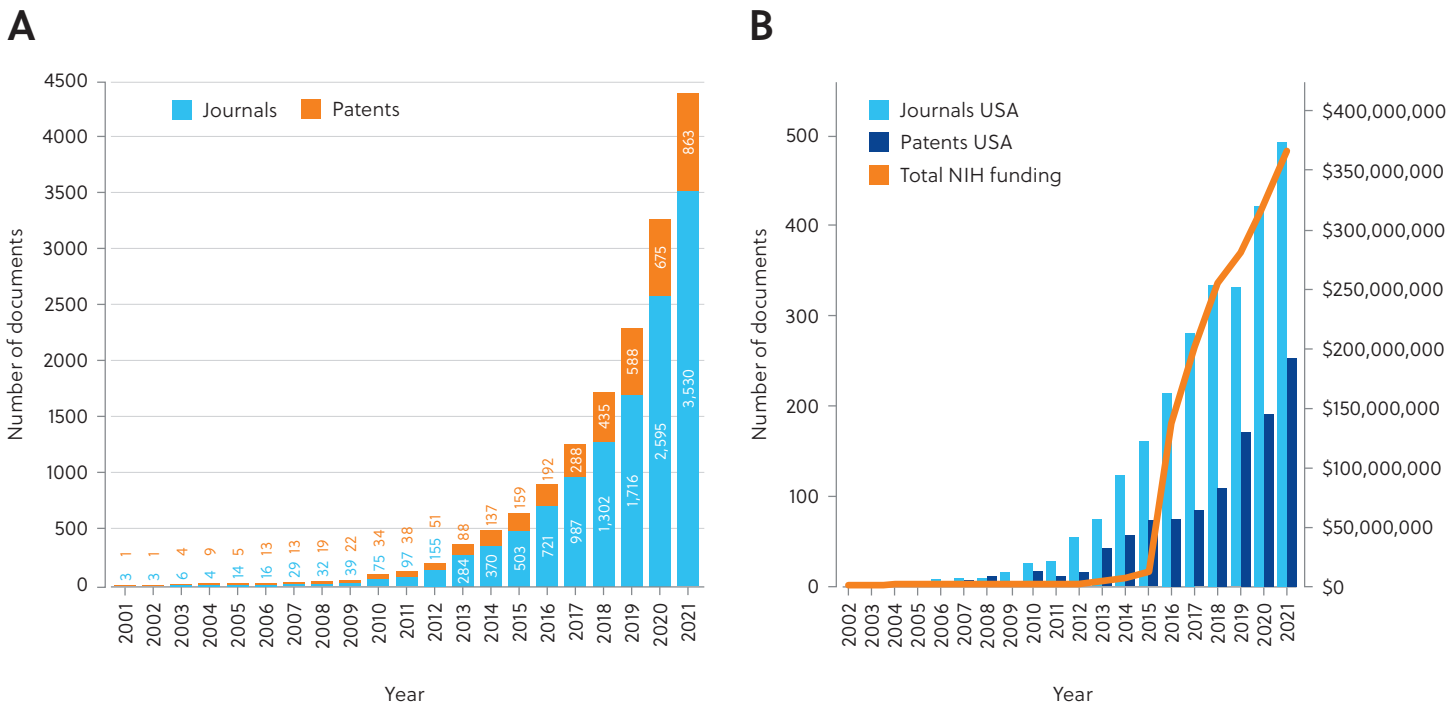


Figure 2. Journal and patent publication trends of exosome research in drug delivery and diagnostics and the association with research funding. (A) Trends in the number of publications related to exosomes in drug delivery and diagnostics, including journal articles and patents. (B) Number of documents originating from organizations in the USA as correlated with the annual NIH funding

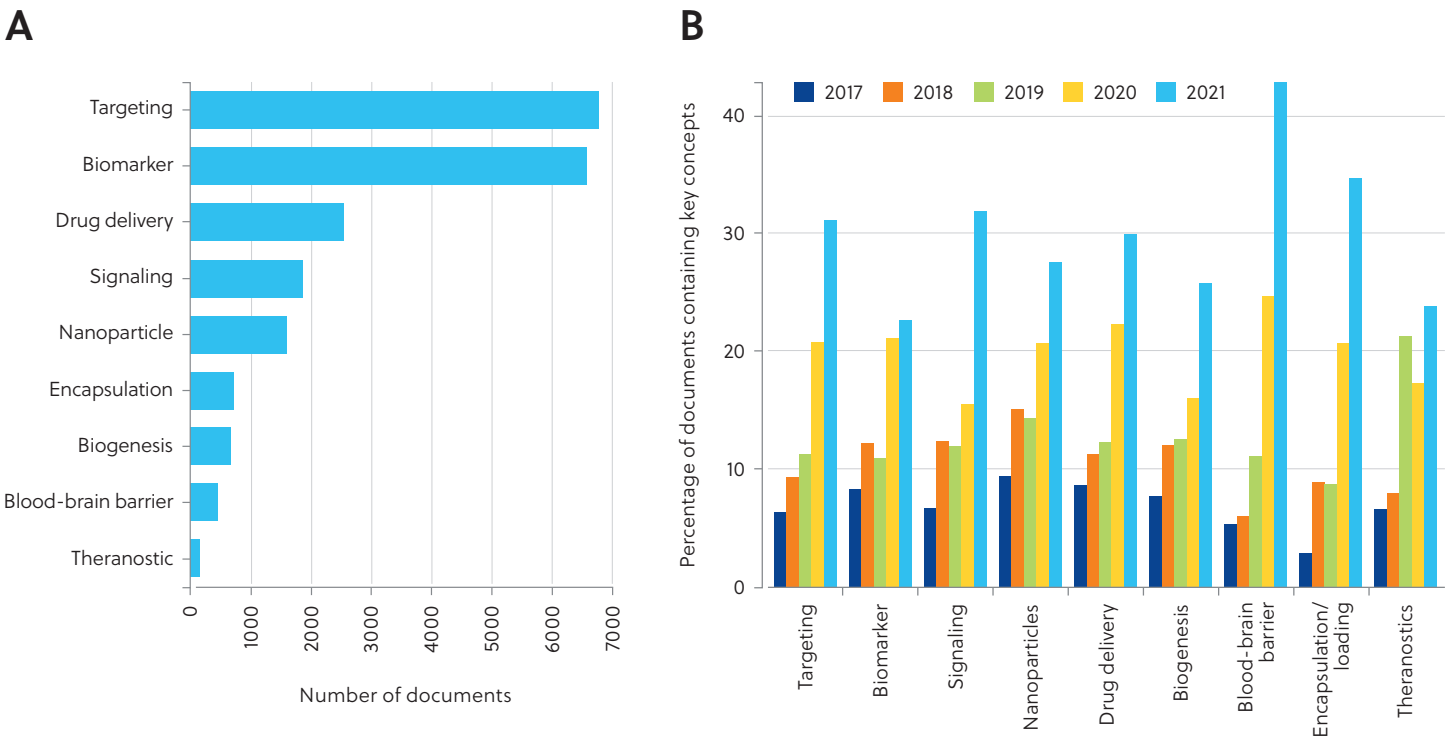


Figure 3. Key concepts in the scientific publications relevant to the exosome applications in drug delivery and diagnostics. (A) Number of publications exploring key concepts related to exosome applications in therapy and diagnostics. (B) Trends in key concepts presented in the articles related to exosome applications in therapy and diagnostics during the years 2017–2021. Percentages are calculated with yearly publication numbers for each key concept, normalized by the total number of publications for the same concept in the same period

Exosomes as drug delivery vehicles

The unique properties of exosomes make them highly effective drug carriers. Their lipid composition is rich in non-lamellar forming lipids, which may give rise to favorable curvatures in their lipid bilayer, and that has been proven beneficial in drug delivery. Furthermore, the exosome lipid bilayer is highly asymmetrical, which could be particularly advantageous for their interaction with the plasma membrane and especially with their target cells.[9] Finally, the large variety of integral and peripheral membrane proteins found in exosomes enables efficient delivery of therapeutic cargo via cell-to-cell communications.[41] These proteins can be modified through their parent cells to express targeting moiety on their surface, making exosomes highly amenable to modification for targeted delivery. Another feature that makes exosomes desirable as drug delivery vehicles is the ability to deliver diverse cargo. Exosomes can be supplemented with a range of therapeutic cargos (e.g., small molecule drugs, nucleic acids, proteins, peptides, and various nanomaterials) to elicit a desired biological activity.

Indeed, researchers are beginning to recognize the advantages that exosomes hold over other drug carrier systems. In the last 3–4 years, exosomes have become preferable over lipid nanoparticles as prospective drug carriers and the number of documents, both patents and journal articles, related to exosomes applied in drug delivery has significantly surpassed that of lipid nanoparticles, as revealed by a search in the CAS Content Collection (**Figure 4**).[39]

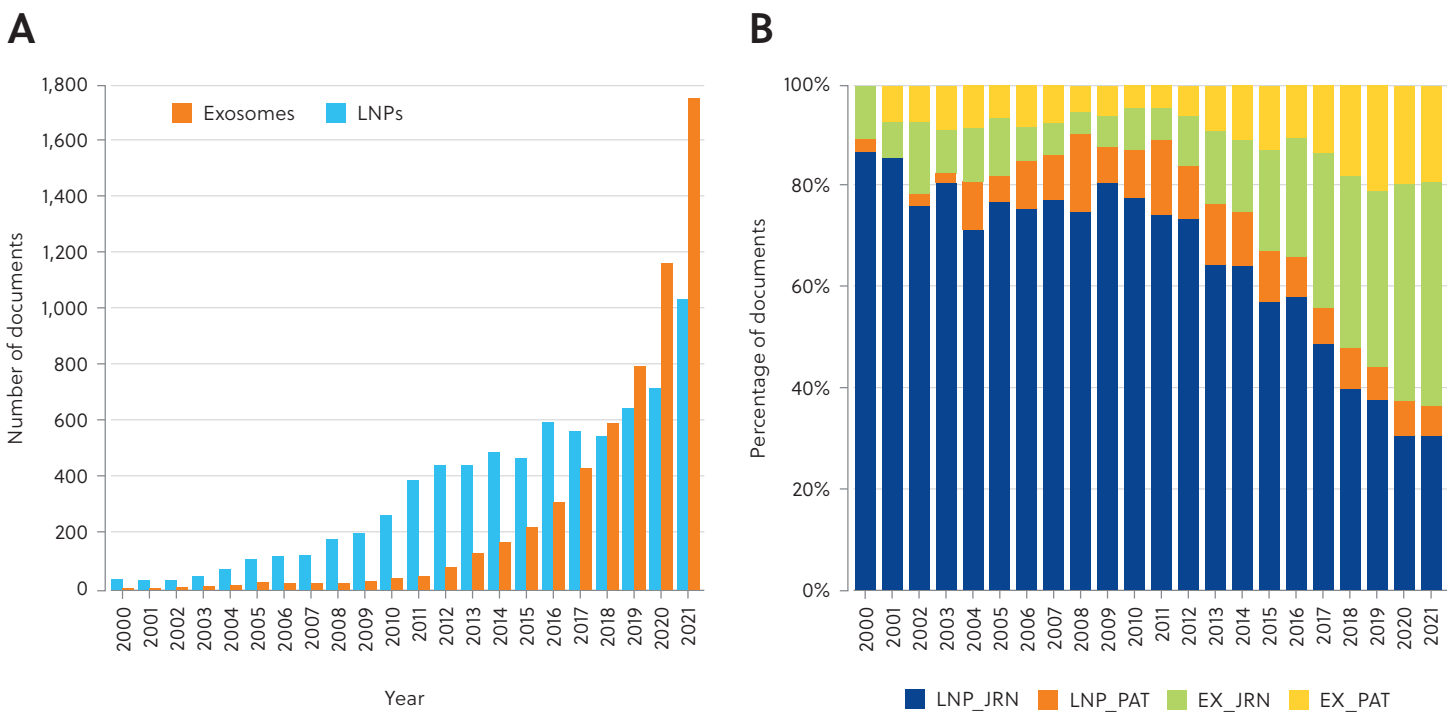


Figure 4. Publication trends of exosomes and lipid nanoparticles applied to drug delivery. (A) Comparison of the trends in the number of publications related to exosomes and lipid nanoparticles. (B) Corresponding percentages of publications related to exosomes (EX) and lipid nanoparticles (LNP) in journal articles (JRN) and patents (PAT) are compared

Cargo loading

A key factor to consider is how to load cargo into exosomes in the first place. Efficient encapsulation strategies are essential for the favorable delivery of therapeutic cargo. Multiple approaches utilizing physical, chemical, and biological techniques have been developed for achieving this to achieve diverse therapeutic effects and optimum efficiency.

Cargo loading techniques are broadly divided into those that incorporate cargo into exosomes either before, or after, exosome isolation.[3,41–43] A key example of the latter is cell transfection, which is the most widely used approach for loading nucleic acids, proteins, and peptides into exosomes.[44,45] However, this method can lead to cytotoxicity of recipient cells. Post-isolation loading methods incorporate the drug after the exosome collection and isolation. Examples of these techniques include direct co-incubation, sonication, electroporation, freeze-thaw cycles, and extrusion.[43,46]

Using data from the CAS Content Collection, we evaluated the distribution of documents in the CAS Content Collection related to exosome applications in therapy and diagnostics with respect to the applied exosome loading methods (**Figure 5**). While all methods are appropriate for different cargo loadings, the analysis revealed that physical methods — electroporation, freeze-thaw, sonication, and extrusion — are more popular than chemical and biological methods such as transfection and incubation.

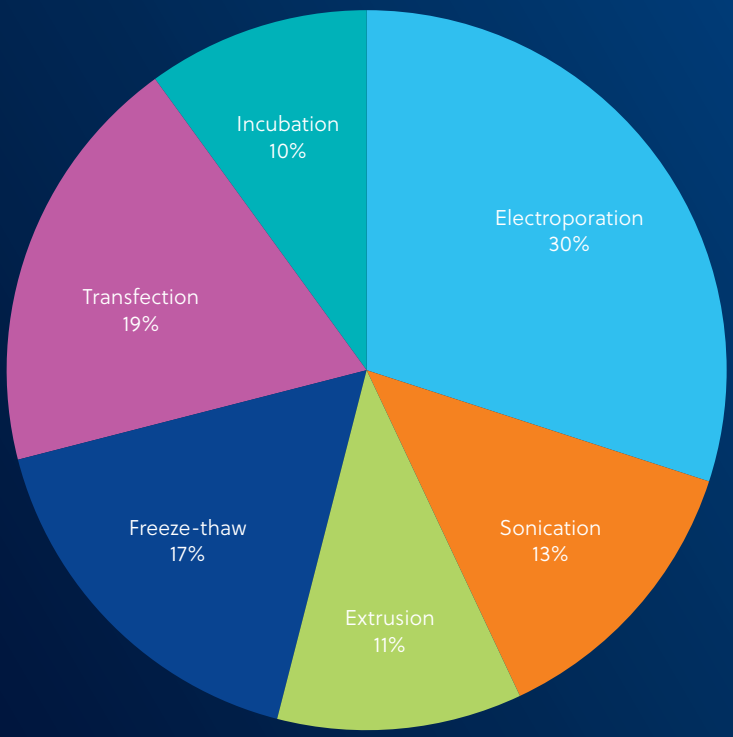


Figure 5. Percentages of documents related to exosome applications in therapy and diagnostics concerning various exosome loading methods

Properties of different cell-derived exosomes

From macrophages to mast cells, T lymphocytes to tumor cells, exosomes are secreted by a wide variety of cell types. Exosomes secreted by different tissues and cells exhibit unique properties. For example, tumor-derived exosomes have been found to impact tumor properties, such as growth, angiogenesis, invasion, and metastasis.[47,48] In contrast, exosomes from mesenchymal stem cells (MSCs) have properties that make them ideal for use as adjuvants to support and complement other therapeutic modalities.[49] Understanding the properties of different cell-derived exosomes can help us to harness their full potential. In addition, a deeper understanding of these various cell-derived exosomes can unveil novel insights into the pathogenic mechanisms of various diseases.

An analysis of the number of documents in the CAS Content Collection shows that tumor cells and MSCs are the most frequently used exosome sources (**Figure 6**). We also examined the correlation between the exosome donor cells and the diseases to which they have been applied to, as represented by the number of documents in the CAS Content Collection (**Figure 7**). Our analysis revealed that cancer studies clearly dominate, followed by inflammation and infection studies. Antigen-presenting cells and natural killer cells have been the most frequently used exosome donor cells in cancer studies, while macrophages and stem cells are the most frequently used in inflammation, and antigen-presenting cells and T-cells are frequently used in infection.

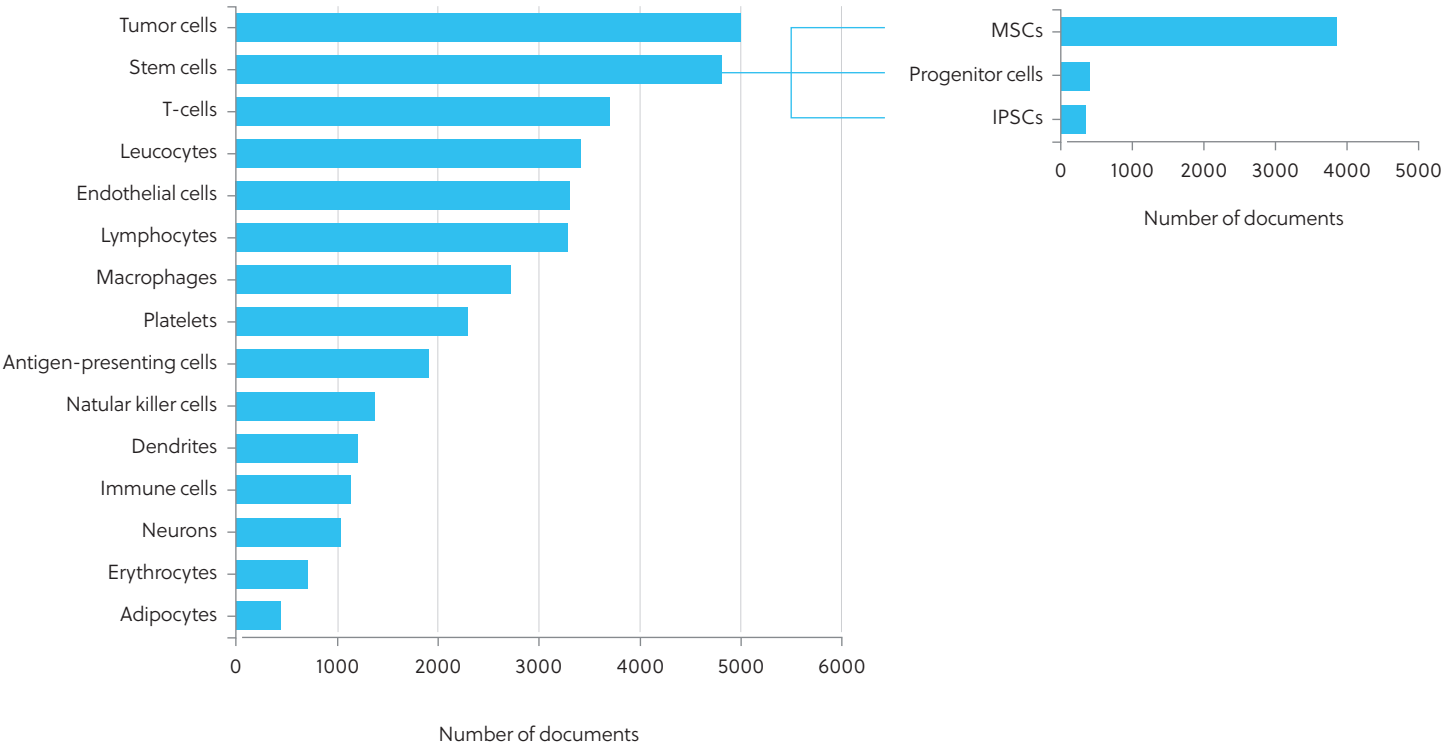


Figure 6. Number of documents related to exosome applications in therapy and diagnostics, in which various types of cells have been used as exosome donors. Abbreviations: MSCs = Mesenchymal Stromal Cells; IPSCs = Induced Pluripotent Stem Cells

	Dendrites	Leucocytes	Endothelial cells	Antigen-presenting cells	Stem cells	Erythrocytes	Platelets	Lymphocytes	Immune cells	T-cells	Natular killer cells	Macrophages	Adipocytes
Cancer	50	41	39	56	37	35	37	46	49	46	57	39	33
Inflammation	18	26	24	14	28	20	25	24	25	21	14	31	26
Infection	15	15	9	18	9	14	11	15	13	17	12	13	7
Cardiovascular disease	4	6	13	3	9	9	11	4	4	4	5	6	10
Neurodegeneration	2	2	2	2	4	4	3	2	2	2	4	2	1
Alzheimer disease	5	3	3	2	4	6	5	3	2	3	3	3	3
Parkinson disease	2	2	2	2	3	5	3	2	1	2	3	2	2
Diabetes	3	4	8	4	6	8	6	4	3	4	2	5	17

Figure 7. Correlation between exosome donor cells and the diseases to which the exosomes have been applied to in the studies related to exosome in therapy and diagnostics, as represented by the number of documents in the CAS Content Collection

Exosome modification for targeted delivery

The inherent properties of different cell-derived exosomes mean they are naturally able to exhibit selectivity, with preferential uptake of exosomes derived from specific cells by the corresponding type of tissue.[50,51] This phenomenon can be exploited to develop new specific vectors for advanced therapies. Moreover, exosomes can also be further modified to enhance their targeted deliverability. To facilitate the delivery of desired cargos into specific tissues or cells, methodologies that augment the natural targeting capacity of exosomes have been developed.

One approach developed for this purpose is ligand-receptor binding-based targeted delivery. In this technique, ligands are added onto the exosomal surface either via transfection-based ectopic expression or direct chemical assembling. This enables exosomes to better recognize their specific receptors on target cells. This approach has been successfully applied to exosomes carrying the chemotherapeutic doxorubicin, significantly inhibiting tumor growth.[52] Another method developed to augment natural targeting capacity is pH gradient/surface-charge driven targeted delivery. Different organs, tissues, and cellular compartments have different pH values. For instance, acidic metabolic waste products accumulate in the tumor microenvironment because of high metabolic activity and insufficient perfusion. Based on this principle, exosomes can be engineered with a pH targeting strategy to enhance specificity and delivery efficiency.

Exosomes as therapeutics

Exosomes are garnering attention as a drug delivery system due to their unique structure and composition, allowing them to be used as efficient, natural nanocarriers. Yet, another rapidly expanding and noteworthy application of exosomes is their use as therapeutic agents. Exosome systems have been applied as therapeutic or diagnostic tools to a wide range of disorders. These systems may offer advantages over stem cell-based transplantation due to their low tumorigenic potential and low immunogenicity.[6,53]

Our analysis of the CAS Content Collection shows that while most publications are associated with cancer, neurodegenerative, inflammatory, and cardiovascular diseases are also represented (**Figure 8**). Some of the key findings in these areas are summarized below.

Cancer: One of the most widely researched treatment applications for exosomes has been in cancer, where exosomes may act as biological reprogramming agents for tumor cells.[54] It has been reported that exosomes can control tumor growth due to certain proteins and RNAs that are transferred to the malignant cells. Exosomal miRNAs have been shown to inhibit cancer cell proliferation, migration, and invasion. This approach has been explored in various malignant cell subtypes, including those for bladder,[55] colorectal,[56,57] and breast cancer.[58]

Neurodegenerative disease: Due to their ability to cross the BBB, exosomes have enormous therapeutic potential in neurological disorders. For instance, analysis of exosomal miRNAs derived from MSCs has been shown to improve various brain disorder pathologies, including Alzheimer's disease (miR-21, miR-29b and miR-146a), subarachnoid hemorrhage (miR-21 and miR-193b) and traumatic brain injury (miR-216a).[59] A study in a mouse model of Parkinson's disease showed that treating cells with exosomes enriched with miR-188-3p suppressed autophagy, which is believed to be involved in the pathogenesis of the condition.[60]

Cardiovascular disease: Exosomes have been reported to play a role in the treatment of cardiovascular diseases. Recent studies have demonstrated that exosomes secreted by stem cells stimulate angiogenesis, provide cytoprotection, and modulate apoptosis.[6,61] In a separate study, exosomes secreted by cardiac-derived progenitor cells (CDCs) were packed with miRNAs known to promote cardioprotective effects. In an animal model of ischemia-perfusion injury, exosomes transmitted to macrophages after reperfusion were associated with a reduction of the infarct size.[62] Another in vivo study showed that exosomes from CDCs significantly protected against ischemic injury and improved cardiac function after myocardial infarction (MI) compared with the control (mice treated with exosomes from mouse embryonic fibroblasts).[63]

Indeed, exosomes offer exciting potential in the diagnosis and treatment of various diseases. Still, a better understanding of their biological functions, as well as verification of the sensitivity and specificity of each biomarker under well-defined conditions, are needed to fully achieve their potential.

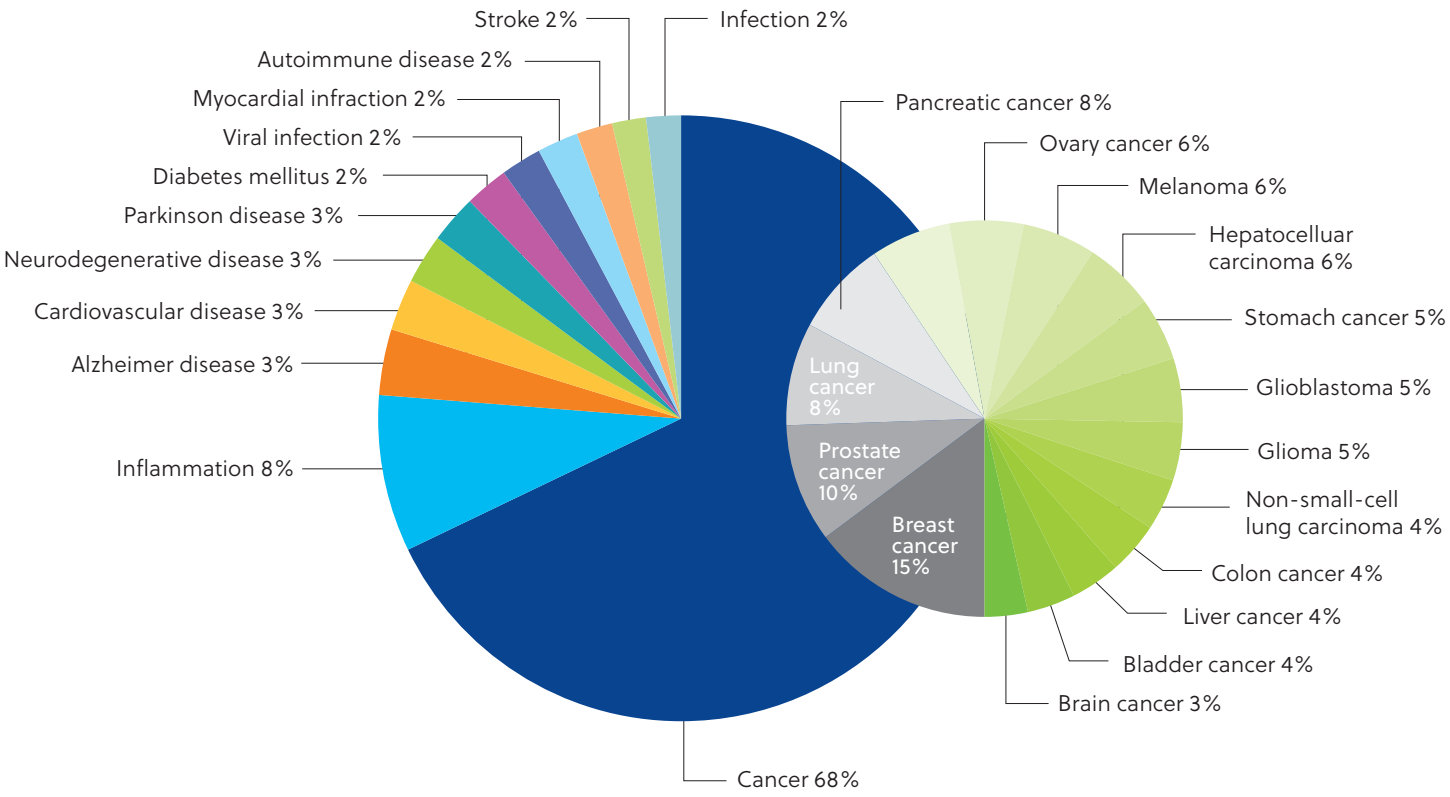


Figure 8. Distribution of the publications in the CAS Content Collection related to exosome applications in therapy and diagnostics with respect to the target diseases

Exosomes versus lipid nanoparticles — how do they compare?

Exosomes have several properties that make them ideal tools for diagnosis and drug delivery. Firstly, their small size, flexibility, and the presence of adhesive proteins on their surface enables them to cross the BBB. Furthermore, their endogenous origin and the presence of a cellular lipidic bilayer minimize immunogenicity and toxicity, supporting their stabilization in blood circulation. Additionally, the application of exosomes both as diagnostic and therapeutic tools is deeply correlated to their long in vivo blood circulation and biodistribution.

However, many of these strengths can also be limitations. For example, the endogenous origins of exosomes mean that, in contrast to liposomes, their yield is highly dependent on the parent cells that produce them. The yield of exosomes is also severely limited by the difficulty and cost of large-scale cell culture, as well as the time-consuming and low-efficient methods of exosome isolation and purification. Together these create barriers to full industrial production of exosomes.[64]

While exosomes can carry several types of cargo, their loading capacity and efficiency is limited due to the natural proteins and nucleic acids present within them. In contrast, LNPs have a simpler structure that allows for great cargo loading.[65]

Finally, another limitation of exosomes compared to LNPs is the increased difficulty in quality control. Exosomes, even those generated from a single type of cells, are highly heterogenic. Due to the lack of sensitive high-throughput analyses for low copy number nucleic acids and proteins in single-exosome dimension, we are unable to separate the heterogeneous exosome population into a homogeneous one.[2] It's also important to note that an important function of exosomes is to remove harmful or unwanted substances from the parent cells. Thus, there is the potential for exosomes to pass these undesired macromolecules into the recipient cell.[66] Approaches to precisely modify the contents of exosomes are still in short supply.

Exosomes in diagnostics

To be feasible in clinical use, a peripheral biomarker should be easy to assess, cost effective, specific for the targeted disease, highly sensitive, and easily and reliably measured. Exosomes show superiority to conventional serum-based biomarkers, especially in their higher diagnostic sensitivity and accuracy, making them an attractive tool in clinical diagnostics and biomarker discovery.

The properties that make exosomes a promising vehicle for drug delivery also make them attractive biomarkers. Firstly, nucleic acids, proteins, lipids, and other bioactive substances present within exosomes have been shown to be altered during disease progression. Therefore, exosomes can provide an insight into the pathological status of the cells.[67,68] Exosomes can also be isolated from urine, blood, saliva, and even tears, providing a rapid yet non-invasive diagnostic approach.[69,70] Exosomes are also innately stable, able to circulate even within a harsh tumor microenvironment.[69,71]

The potential of exosomes in diagnostics has already been widely recognized, and exosomes are drawing intense attention for their promise as diagnostic biomarkers in cancer, neurodegenerative, infectious, and metabolic diseases.[72–78] In particular, exosomal proteins and nucleic acids have drawn researchers' attention in recent years. Numerous exosomal protein biomarkers have shown promise in the diagnosis of cancer,[79] central nervous system diseases,[80] urinary tract diseases,[81] and beyond. To date, several candidate protein biomarkers have been reported for diagnostic applications. Exploration of exosomal RNAs as diagnostic biomarkers has been triggered by the finding that exosomes contain RNAs. Among all exosomal cargo substances, miRNA has drawn researchers' attention in recent years due to its complex roles in regulating the cancer microenvironment, involving angiogenesis, cell proliferation, and metastasis. Its roles in regulating cellular behaviors in situ or in the remote recipient cells are under intensive investigation.[82–84]

A search of the CAS Content Collection found extensive growth of the number of documents related to exosome applications in diagnostics (**Figure 9A**). A comparison with the therapy-related exosome documents demonstrates that although at present they outnumber the diagnostic-related documents (**Figure 9A, B**), the annual growth of the diagnostic exosome documents has begun to dominate (**Figure 9A**, inset).

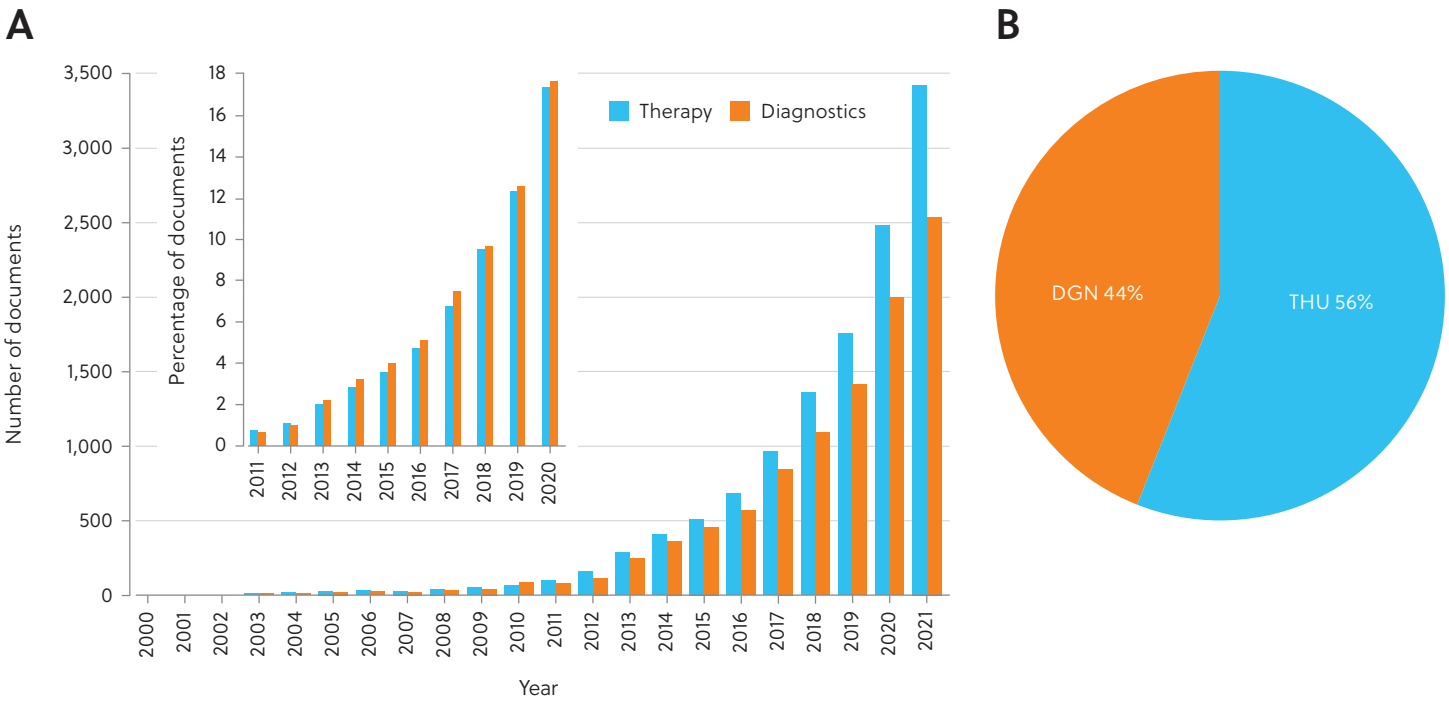


Figure 9. Diagnostic vs therapeutic application of exosomes. (A) Comparison of the number of documents related to exosome applications in therapy vs diagnostics; Inset: Annual growth of the number of documents related to exosome applications in therapy vs diagnostics. (B) Comparison of the number of documents related to exosome applications in therapy vs diagnostics with respect to their role indicators (THU, therapeutic; DGN, diagnostic)

Exosomes as therapeutic targets

Exosomes are involved in the pathogenesis of diseases such as cancer, neurodegeneration, and cardiovascular disease, among others. Therefore, a successful therapeutic strategy may involve reducing exosome production and circulation to normal levels to prevent disease progression.[85–88] Several ongoing studies are exploring the impacts of modulating the exosome pathway at various steps, including its production, release, and uptake.[89] Several approaches are being explored to achieve this, including:

- Inhibiting exosome formation by targeting pathways involved in endosomal sorting and exosome production.
- Inhibiting exosome release is another approach being investigated to modulate extracellular exosome levels.
- Exosome uptake inhibition is another way to modulate exosome activity. By blocking the uptake of exosomes by target cells, researchers hope to modulate exosome-mediated disease progression.
- Physical elimination of exosomes has also been explored in cancer cells.[90] This elimination may help to hamper the communication between tumor cells that contributes to tumor progression.

While early studies exploring these strategies are promising, a clear understanding of the disease-specific mechanisms of exosome pathways is required to identify specific therapies mediated by targeting exosomes.[91]

Other applications of exosomes

In addition to their application in drug delivery, diagnostics and therapeutics, a search of the CAS Content Collection has revealed a sharp increase in the number of documents related to the application of exosomes in cosmetics and food (**Figure 10**).

Stem cell derived exosomes have a key place in skin cosmetology such as wound healing, skin aging, and scar formation. Several studies have explored the potential of stem cell-derived exosomes for alleviating skin aging.[92–93] In terms of food, exosomes have demonstrated enormous potential as carriers of food-related bioactive compounds such as polyphenols, vitamins, and polyunsaturated fatty acids, helping to improve their bioavailability. Furthermore, emerging evidence suggests that plant cells may release EVs such as exosomes. Exosomes from ginger and aloe are being tested for the treatment of polycystic ovary syndrome (NCT03493984),[94] while grape exosomes are being evaluated as an anti-inflammatory agent to reduce the incidence of oral mucositis during radiation and chemotherapy treatment for head and neck tumors (NCT01668849).[95]

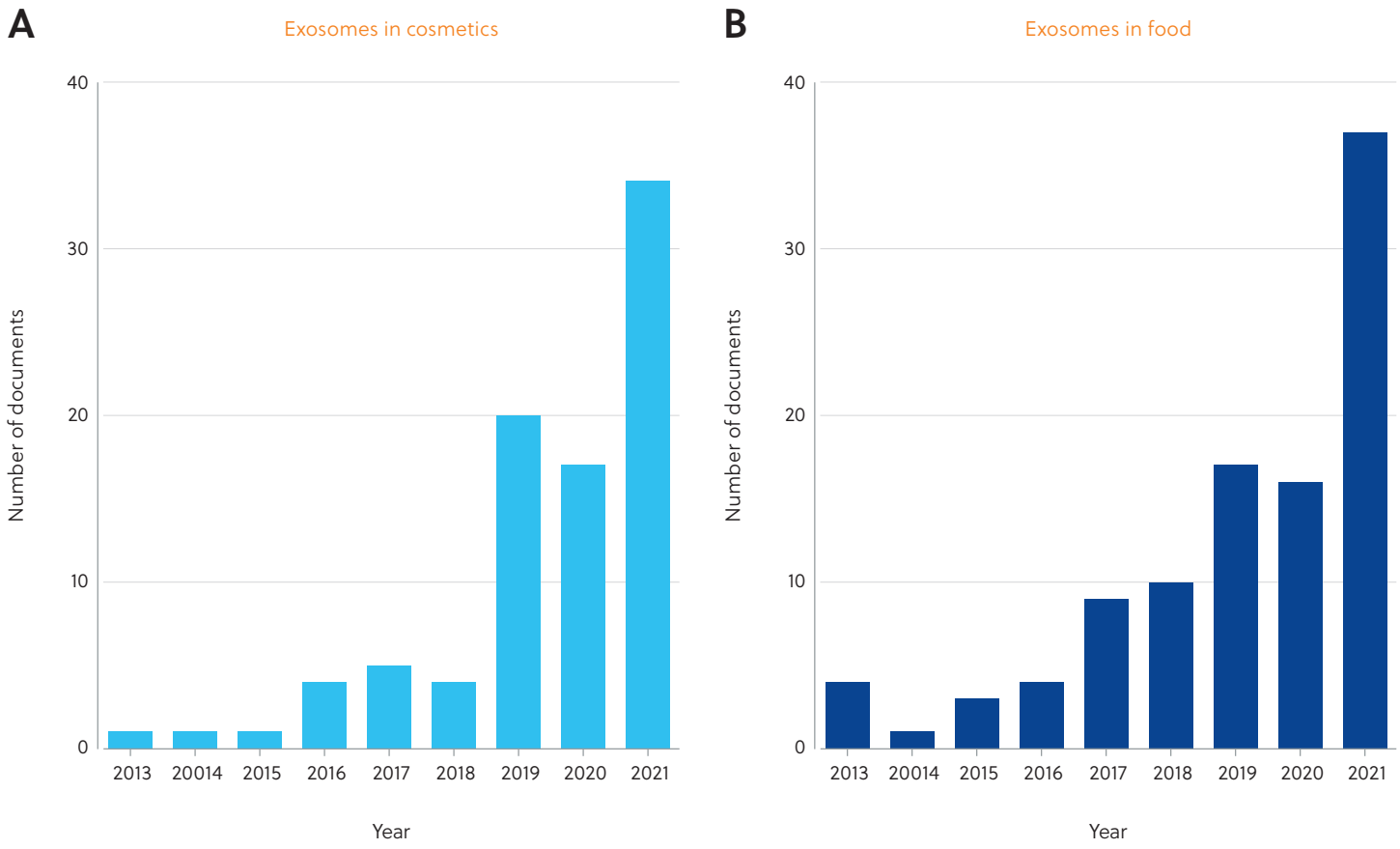


Figure 10. Annual trend of the number of documents in the CAS Content Collection related to the exosome applications in cosmetics (A) and food (B)

Progressing exosome research from conception to commercialization

Several companies, medical centers, universities, and research organizations are looking to utilize exosomes for therapy and diagnostics to target diseases with high unmet needs. Both pre-clinical and clinical companies are progressing exosome therapeutics through their pipelines. A thorough review of exosome therapeutic companies reveals that the most highly represented targeted diseases are cancer, neurological and neurodegenerative diseases, lung diseases, and wound healing (**Figure 11**).

A growing number of companies are researching exosomes in the hopes of advancing their therapeutic discoveries to the clinic. While historically MSC-derived exosomes were researched for therapy, companies are starting to shift their focus towards organ-specific exosomes (e.g., cardiac-derived exosomes or neural-derived exosomes) for more targeted specificity in treating diseases. **Table 3** displays the selected preclinical companies focusing their research efforts on the highly represented targeted diseases.

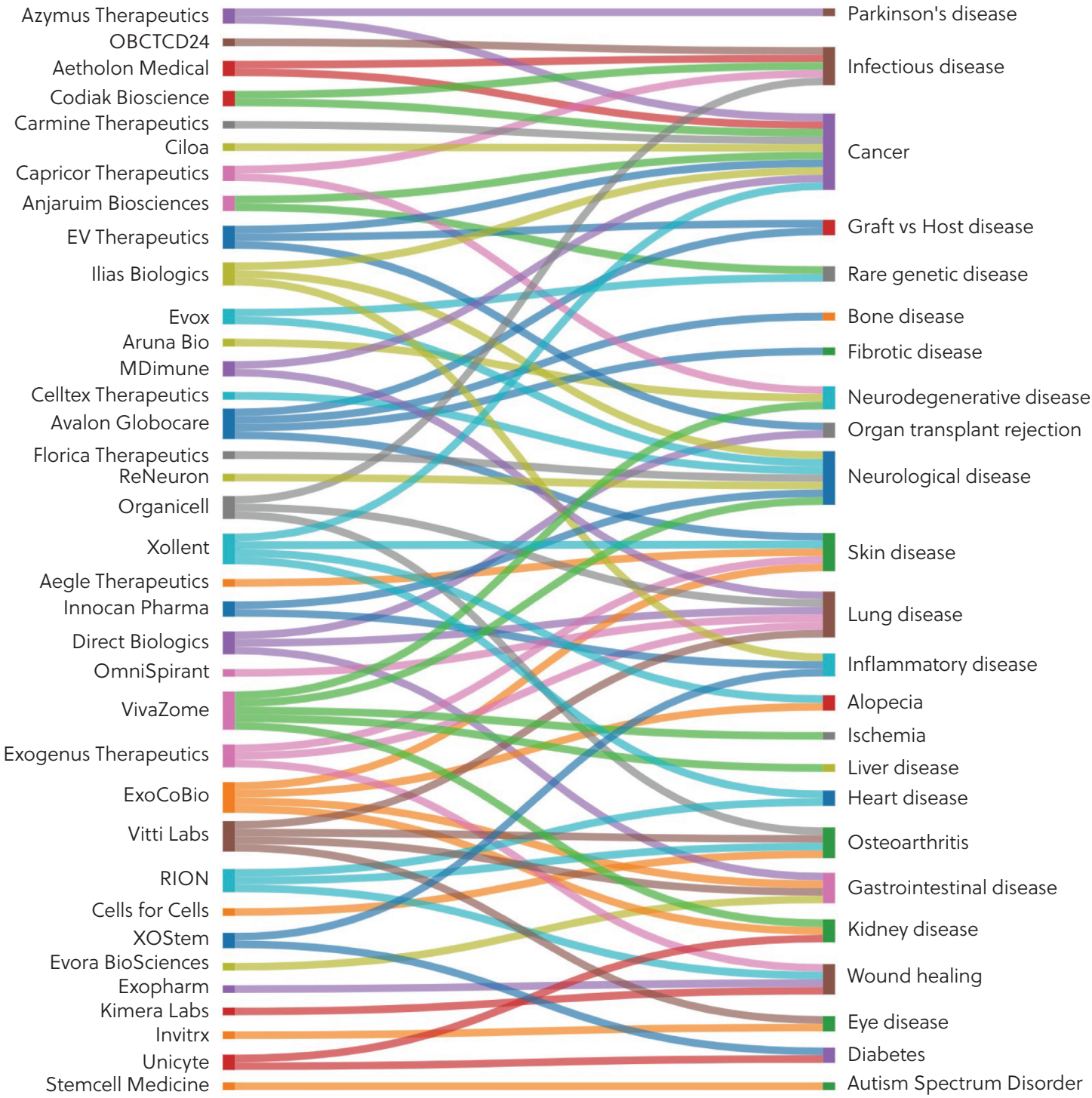
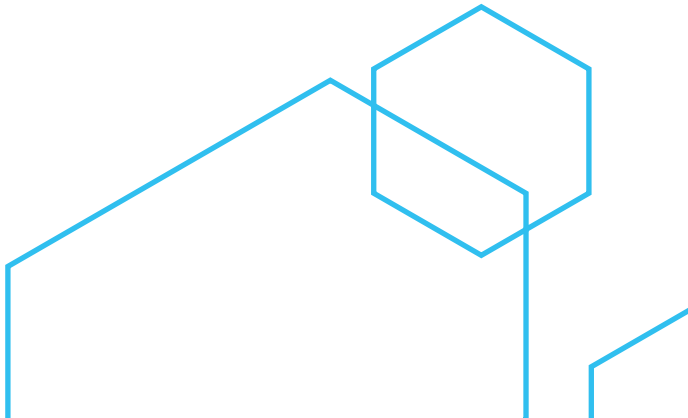


Figure 11. Promising exosome therapeutic companies and targeted diseases

Table 3. Highlighted preclinical therapeutic and cosmetic exosome companies along with their summaries

Company (Location)	Summary
Anjarium Biosciences (Switzerland)	Anjarium is researching and developing precision exosome therapeutics. Their Hybridosome platform utilized nanotechnology and biochemistry to increase the efficiency of exosome loading with therapeutic cargo.[96] Anjarium is looking to use its exosome-based therapy platform to treat cancers and rare genetic diseases.
Carmine Therapeutics (USA)	Carmine Therapeutics utilizes red blood cell exosomes.[97] Their Red Cell EV Gene Therapy (REGENT) platform will be used to generate a pipeline of therapies for the treatment of a wide range of diseases.[98]
Ilias Biologics (South Korea)	Ilias developed the platform EXPLOR that allows the loading of proteins into exosomes in a more controlled manner than conventional passive loading.[99] Ilias's lead compound, ILB-202, consists of an exosome loaded with anti-inflammatory protein super-repressor IkB, targeting both acute and chronic inflammatory diseases. This lowers the risk of off-target effects by targeting core inflammation signals.[100]
Aruna Bio (USA)	Aruna Bio is transforming treatment for neurological and neurodegenerative diseases. They utilize neural exosomes derived from neural stem cells that have CNS specificity and the ability to cross the BBB. Their candidate AB126 shows high uptake in the cerebellum and basal ganglia showing treatment potential for diseases such as stroke and neurodegenerative diseases.[101] Their pipeline shows that AB126 can be loaded with different cargoes including siRNA, ASO, progranulin, and tripeptidyl-peptidase 1.[102]
Capricor (USA)	Capricor is developing multiple exosome platforms including cardiosphere-derived cell-exosomes (CDC-exosomes), engineered exosomes, and an exosome-based vaccine. They are currently researching the use of CDC-exosomes for the treatment of Duchenne Muscular Dystrophy and have engineered Exosomes for RNA and protein delivery in trauma-related injuries and conditions in collaboration with the U.S. Army Institute of Surgical Research. They are also in preclinical trials for an exosome-based multivalent vaccine for COVID-19 and other infectious diseases.[103]
Evox (United Kingdom)	Evox is an exosomal therapeutic company using its DeliverEX platform to deliver proteins and nucleic acids to treat a variety of rare diseases. Their internal program is researching rare metabolic disorders. They have partnered with Takeda to treat lysosomal storage disease and other undisclosed rare diseases. Evox has recently partnered with Lilly to research neurological treatment.[104]
Innocan Pharma (Israel)	Innocan is a pharmaceutical company researching cannabidiol (CBD) drugs, working to enhance their targeting due to their low bioavailability. Innocan is researching, in partnership with Tel Aviv University, the development of CBD-loaded exosomes to target inflammatory diseases and diseases of the CNS.[105]
Xollent (USA)	Xollent is advancing a diversified pipeline of therapeutics, including exosome therapeutics that treat myocardial infarction through an intravenous patch, alopecia through a spray, and skin aging through a needless injection.[106]
Exogenus Therapeutics (Portugal)	Exogenus's lead candidate Exo-101 is produced from umbilical cord blood mononuclear cells. It has been shown to have regenerative, anti-inflammatory, and immunomodulatory properties. Exo-101 is being investigated for treatment in inflammatory skin diseases such as psoriasis, inflammatory lung disorders such as COVID-19 acute respiratory distress syndrome,[107] and chronic wound healing.[108]

Company (Location)	Summary
OmniSpirant (Ireland)	OmniSpirant's platform technology is based on inhalation and is very efficient at delivering cargos to treat respiratory diseases. The mucus-penetrating exosomes will be used to develop a regenerative gene therapy for cystic fibrosis and other respiratory diseases.[109]
Kimera Labs (USA)	Kimera specializes in the use of perinatal MSC-derived exosome products for both cosmetics and scientific research.[110] Their cosmetic products are XoGlo, XOGloPro, and Vive. They also produce a veterinarian wound healing agent called Equisome HC.[111]
Exocel Bio (USA)	Exocel utilizes placental MSC-derived exosomes for both skin care and hair care. Their products include the Evovex line called Evovex Restore, Evovex Revive, Evovex Renew, and Evovex Reveal.[112] These products are used in conjunction with facial and scalp micro needling and energy-based aesthetic device treatments to enhance results and improve recovery time.[113]
Regen Suppliers (USA)	Regen Suppliers developed an exosome product called ReBellaXO, derived from umbilical stem cell tissue and Wharton's Jelly used for regenerative aesthetic procedures involving hair, facial, and sexual rejuvenation.[114]
ExoCoBio (Republic of Korea)	ExoCoBio is focusing on stem cell-derived exosomes to develop therapeutic and cosmetic products. They have developed ExoSCRT Exosome for the treatment of atopic dermatitis,[115] irritable bowel syndrome, acute kidney injury, and alopecia.[116] An immune-oncology drug based on exosomes derived from immune cells is also in their pipeline.
MDimune (Republic of Korea)	MDimmune developed a platform technology called BioDrone that uses cell-derived vesicles for targeted drug delivery.[117] Their internal pipeline includes treatment for chronic obstructive pulmonary disease and an undisclosed rare disease with therapeutics BDR-231 and BDR-331, respectively. They have partnered with Ildong, Kainos Medicine, and NeoCura for the treatment of cancer using various mRNAs and small molecules for cargo for therapeutic products BDR-165, BDR-166, and BDR-167. They are also partnered with Reyon for a vaccine with therapeutic BDR-761 and treatment of an undisclosed rare disease with therapeutic BDR-762 using mRNA as cargo.[118]
EV Therapeutics (USA)	EV Therapeutics is developing modified exosomes (mEVs) (miR-424i and MiR-424KO) in combination with an immune checkpoint inhibitor for the treatment of metastatic colorectal cancer and other gastrointestinal cancers.[119] mTEV is a CD-28-CD80/86 co-stimulatory pathway technology platform that functions in combination with checkpoint inhibitors to enhance T-cell immunomodulation to prevent solid tumor cancer recurrence.[120]
Evora BioSciences (France)	The EVOGEX therapeutic platform was developed by Evora. Their lead product, EVOGEX-Digest, aims to treat digestive fistula and improve patient outcomes.[121]
Florica Therapeutics (USA)	Florica Therapeutics aims to use hypothalamus stem-cell-derived exosome therapeutics to increase lifespan and deter neurological diseases of aging.[122]



Companies, medical centers, and universities are also focusing their research efforts on discovering exosome biomarkers and representative tests for the diagnosis of hard-to-treat diseases earlier, to help aid in the treatment success and patient survival. **Table 4** explores promising preclinical companies, medical centers, and universities researching exosome disease diagnosis.

Table 4. Highlighted preclinical companies and universities researching exosomes as biomarkers for diagnosis of various diseases and their summaries

Company (Location)	Summary
Craif (Japan)	Craif developed a medical device consisting of a zinc oxide nanowire embedded in a microfluidic channel that collects urinary miRNA for exosome-based liquid biopsy. They are using machine learning technology to analyze miRNA profiles with their original miRNA database to identify biomarkers for early cancer detection.[123]
Mercy Bioanalytics (USA)	Mercy developed the Halo test for early cancer detection with an initial focus on hard-to-treat cancers such as ovarian and lung cancers.[124] Preliminary results from studies researching Halo detection of both early-stage ovarian and lung cancers were positive.[125,126]
University of Texas MD Anderson Cancer Center (USA)	Researchers identified a cell surface proteoglycan, glypican-1 (GPC1), specifically enriched on cancer-cell-derived exosomes. GPC1(+) circulating exosomes may serve as a potential diagnostic and screening biomarker for assays to detect initial stages of pancreatic cancer.[127]
Harvard Medical School (USA) / Wenzhou Medical University (China)	Researchers have developed an incorporated tear-exosome analysis via a rapid-isolation system (iTEARS) through nanotechnology to discover if exosomes from tears can diagnose ocular disorders and systemic diseases. Data shows that iTEARS might be used to improve the molecular diagnostics of dry eye disease, along with diabetic retinopathy.[17] There is also a possibility that iTEARS could be used to detect other neurodegenerative diseases and cancer.
Frankfurt University Hospital (Germany)	Researchers discovered how CD81 is increased in the exosomal serum of patients with chronic hepatitis C, and appears to be associated with inflammatory activity and severity of liver fibrosis.[128]
Aarhus University Hospital (Denmark)	Researchers discovered that the biomarkers CD151, CD171, and tetraspanin 8 were the strongest separators of patients with non-small cell lung cancer of all histological subtypes vs patients without cancer.[129]
UCSF Medical Center (USA)	Researchers discovered that levels of P-S396-tau, P-T181-tau, and Aβ1–42 from neural-derived blood exosomes can predict the development of Alzheimer's disease up to 10 years before clinical onset of symptoms.[68]
Osako University (Japan)	Researchers discovered that three p53-responsive microRNAs, miR-194, miR-34a, and miR-192 are elevated in the exosomes of patients with acute myocardial infarction, suggesting that these miRNAs function as circulating regulators of heart failure. They feel that these three miRNAs are worth further exploration as biomarkers for ischemic heart failure after acute myocardial infarction.[130]

The future of exosomes: challenges and growth opportunities

As demonstrated by the data analysis of the CAS Content Collection, the interest in exosome research has increased dramatically in recent years. With substantial research being dedicated to exosome applications — in drug delivery, diagnostics, as therapeutic targets, or as therapeutics themselves — it is vital to review and recapitulate the progress made, along with the persisting challenges.

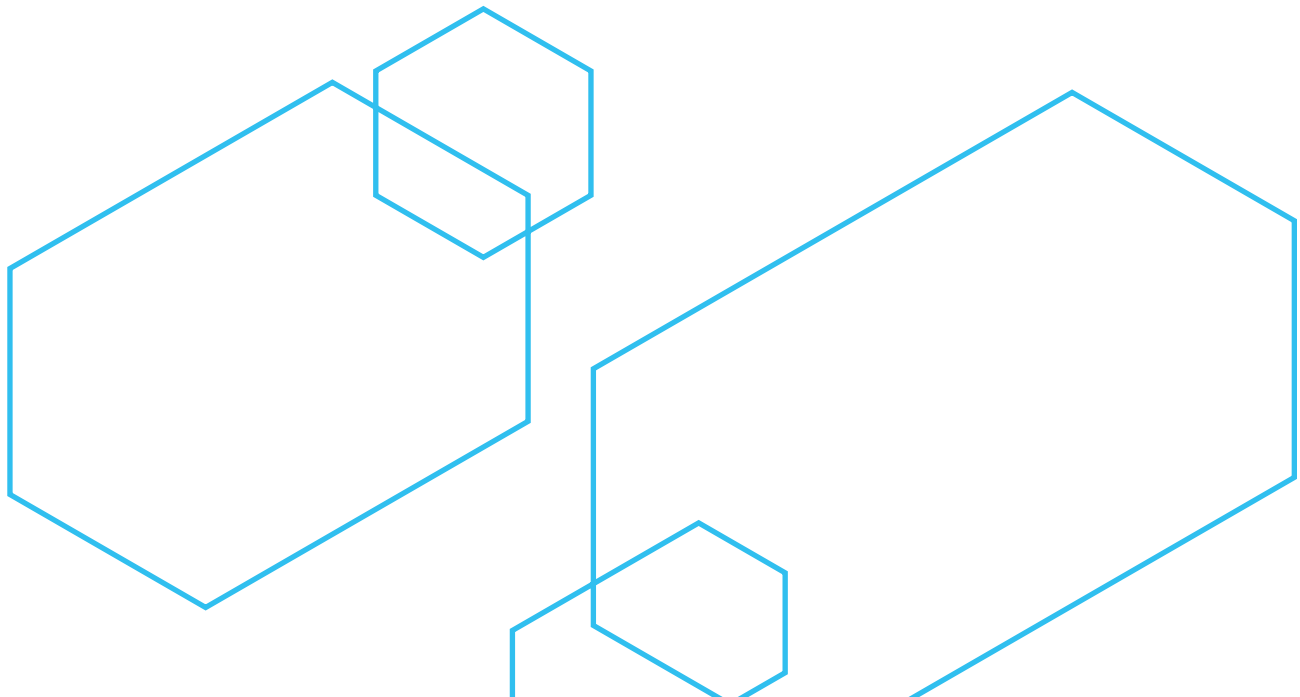
Although our knowledge of exosomes has evolved in recent years, our analysis has revealed some appealing challenges in exosome knowledge, including:

- **The need for robust isolation methods** that do not compromise the purity of the isolate. Such methods will pave the way for exosomal large-scale application in medical practice.
- **Elucidation of the exact mechanisms** involved in the biogenesis, secretion, and fusion of exosomes, as well as a greater understanding. of how exosomes selectively communicate with target cells. This knowledge is essential for the development of effective targeted therapeutics and for the development of engineered exosome-derived therapeutic vehicles.
- Optimization and improvement of **exosome loading capacity and targeting** is another prerequisite for large-scale application in clinic.
- **Standardization** of exosome preparation, including source selection, isolation, characterization, drug loading, stability, targeting, and quality control, in compliance with good manufacturing practice, are all important aspects in the clinical application of exosomes and need to be advanced.
- Advanced knowledge on the **pharmacokinetic profile and biodistribution of exosomes** is still particularly insufficient and is a required step toward their practical utility in clinics.

Conclusions

As demonstrated by the data analysis of the CAS Content Collection, the interest in exosome research has increased dramatically in recent years. A growing number of studies provide valuable knowledge regarding this remarkable subtype of EVs. Indeed, exosomes exhibit unique functions as intercellular messengers, the ability to alter recipient cell bioactivities, and therapeutic potential in disease diagnostics and targeted drug delivery. This, along with advantages over traditional pharmaceutical nanocarriers, distinguishes exosomes as a rising star in both therapeutics and diagnostics.

However, breakthroughs in technologies and instruments are still needed to catapult the large-scale production of purified and quality-controllable drug-loaded exosomes, in compliance with good manufacturing practice. Furthermore, the clinical applications of exosomes, although highly promising, are hindered by gaps in exosome knowledge. Only by addressing these challenges can the full potential of exosomes be realized, creating a tangible patient benefit.



References

1. van der Meel, R.; Fens, M. H.; Vader, P.; van Solinge, W. W.; Eniola-Adefeso, O.; Schiffelers, R. M. Extracellular vesicles as drug delivery systems: lessons from the liposome field. *J. Controlled. Release.* **2014**, *195*, 72–85. DOI: 10.1016/j.jconrel.2014.07.049.
2. Pegtel, D. M.; Gould, S. J. Exosomes. *Annu. Rev. Biochem.* **2019**, *88*, 487–514.
3. Chen, H.; Wang, L.; Zeng, X.; Schwarz, H.; Nanda, H. S.; Peng, X.; Zhou, Y.; Exosomes, a New Star for Targeted Delivery. *Front. Cell. Dev. Biol.* **2021**, *9*. DOI: 10.3389/fcell.2021.751079.
4. Su, S.-A.; Xie, Y.; Fu, Z.; Wang, Y.; Wang, J.-A.; Xiang, M. Emerging role of exosome-mediated intercellular communication in vascular remodeling. *Oncotarget.* **2017**, *8*, 25700–25712. DOI: 10.18632/oncotarget.14878.
5. Théry, C. Exosomes: secreted vesicles and intercellular communications. *F1000 Biol. Rep.* **2011**, *3*, 15. DOI: 10.3410/B3-15.
6. Dougherty, J. A.; Kumar, N.; Noor, M.; Angelos, M. G.; Khan, M.; Chen, C. A.; Khan, M. Extracellular Vesicles Released by Human Induced-Pluripotent Stem Cell-Derived Cardiomyocytes Promote Angiogenesis. *Front. Physiol.* **2018**, *9*, 1794. DOI: 10.3389/fphys.2018.01794.
7. Saint-Pol, J.; Gosselet, F.; Duban-Deweer, S.; Pottiez, G.; Karamanos, Y. Targeting and Crossing the Blood-Brain Barrier with Extracellular Vesicles. *Cells.* **2020**, *9*, 851–864. DOI: 10.3390/cells9040851
8. Morishita, M.; Takahashi, Y.; Nishikawa, M.;Takakura, Y. Pharmacokinetics of Exosomes-An Important Factor for Elucidating the Biological Roles of Exosomes and for the Development of Exosome-Based Therapeutics. *J. Pharm. Sci.* **2017**, *106*, 2265–2269. DOI: 10.1016/j.xphs.2017.02.030.
9. Koynova, R.; Tenchov, B.;MacDonald, R. C. Nonlamellar Phases in Cationic Phospholipids, Relevance to Drug and Gene Delivery. *ACS Biomater. Sci. Eng.* **2015**, *1*, 130–138. DOI: 10.1021/ab500142w.
10. *ExoCarta - Exosome Protein, RNA and Lipid Database.* http://www.exocarta.org/ (accessed 2022-10-10).
11. Mathivanan, S.; Fahner, C. J.; Reid, G. E.; Simpson, R. J. ExoCarta 2012: database of exosomal proteins, RNA and lipids. *Nucleic. Acids. Res.* **2012**, *40*, D1241–1244. DOI: 10.1093/nar/gkr828.
12. *Vesiclepedia.* http://www.microvesicles.org/ (accessed 2022-10-10).
13. Kim, D. K.; Kang, B.; Kim, O. Y.; Choi, D. S.; Lee, J.; Kim, S. R.; Go, G.; Yoon, Y. J.; Kim, J. H.; Jang, S. C.; Park, K. S.; Choi, E. J.; Kim, K. P.; Desiderio, D. M.; Kim, Y. K.; Lötvall, J.; Hwang, D.;Gho, Y. S. EVpedia: an integrated database of high-throughput data for systemic analyses of extracellular vesicles. *J. Extracell. Vesicles.* **2013**, *2*, 20384. DOI: 10.3402/jev.v2i0.20384.
14. Tschuschke, M.; Kocherova, I.; Bryja, A.; Mozdziak, P.; Angelova Volponi, A.; Janowicz, K.; Sibiak, R.; Piotrowska-Kempisty, H.; Iżycki, D.; Bukowska, D.; Antosik, P.; Shibli, J. A.; Dyszkiewicz-Konwińska, M.; Kempisty, B. Inclusion Biogenesis, Methods of Isolation and Clinical Application of Human Cellular Exosomes. *J. Clin. Med.* **2020**, *9*, 436–445. DOI: 10.3390/jcm9020436.
15. Mukherjee, A.; Bisht, B.; Dutta, S.; Paul, M. K. Current advances in the use of exosomes, liposomes, and bioengineered hybrid nanovesicles in cancer detection and therapy. *Acta. Pharmacol. Sin.* **2022**. DOI: 10.1038/s41401-022-00902-w.
16. Villarroya-Beltri, C.; Baixauli, F.; Gutiérrez-Vázquez, C.; Sánchez-Madrid, F.; Mittelbrunn, M. Sorting it out: regulation of exosome loading. *Semin. Cancer. Biol.* **2014**, *28*, 3–13. DOI: 10.1016/j.semcancer.2014.04.009.
17. Hu, L.; Zhang, T.; Ma, H.; Pan, Y.; Wang, S.; Liu, X.; Dai, X.; Zheng, Y.; Lee, L. P.; Liu, F. Discovering the Secret of Diseases by Incorporated Tear Exosomes Analysis via Rapid-Isolation System: iTEARS. *ACS Nano.* **2022**. DOI: 10.1021/acsnano.2c02531.
18. Yang, Z.; Shi, J.; Xie, J.; Wang, Y.; Sun, J.; Liu, T.; Zhao, Y.; Zhao, X.; Wang, X.; Ma, Y.; Malkoc, V.; Chiang, C.; Deng, W.; Chen, Y.; Fu, Y.; Kwak, K. J.; Fan, Y.; Kang, C.; Yin, C.; Rhee, J. et al. Large-scale generation of functional mRNA-encapsulating exosomes via cellular nanoporation. *Nat. Biomed. Eng.* **2020**, *4*, 69–83. DOI: 10.1038/s41551-019-0485-1.
19. Théry, C.; Ostrowski, M.; Segura, E. Membrane vesicles as conveyors of immune responses. *Nat. Rev. Immunol.* **2009**, *9*, 581–593. DOI: 10.1038/nri2567.
20. Zduriencikova, M.; Gronesova, P.; Cholujova, D.; Sedlak, J. Potential biomarkers of exosomal cargo in endocrine signaling. *Endocr. Regul.* **2015**, *49*, 141–150. DOI: 10.4149/endo_2015_03_141.

21. Raposo, G.; Nijman, H. W.; Stoorvogel, W.; Liejendekker, R.; Harding, C. V.; Melief, C. J.; Geuze, H.J. B lymphocytes secrete antigen-presenting vesicles. *J. Exp. Med.* **1996**, *183*, 1161–1172. DOI: 10.1084/jem.183.3.1161.

22. Leone, D. A.; Rees, A. J.; Kain, R. Dendritic cells and routing cargo into exosomes. *Immunol. Cell. Biol.* **2018**. DOI: 10.1111/imcb.12170

23. Skotland, T.; Hessvik, N. P.; Sandvig, K.;Llorente, A. Exosomal lipid composition and the role of ether lipids and phosphoinositides in exosome biology. *J. Lipid Res.* **2019**, *60*, 9–18. DOI: 10.1194/jlr.R084343.

24. Skryabin, G. O.; Komelkov, A. V.; Savelyeva, E. E.; Tchevkina, E. M. Lipid Rafts in Exosome Biogenesis. *Biochemistry (Moscow).* **2020**, *85*, 177–191. DOI: 10.1134/S0006297920020054.

25. Marat, A. L.; Haucke, V. Phosphatidylinositol 3-phosphates-at the interface between cell signalling and membrane traffic. *EMBO J.* **2016**, *35*, 561–579. DOI: 10.15252/embj.201593564.

26. O'Brien, K.; Breyne, K.; Ughetto, S.; Laurent, L. C.; Breakefield, X. O. RNA delivery by extracellular vesicles in mammalian cells and its applications. *Nat. Rev. Mol. Cell. Biol.* **2020**, *21*, 585–606. DOI: 10.1038/s41580-020-0251-y.

27. Kawamura, Y.; Yamamoto, Y.; Sato, T. A.; Ochiya, T. Extracellular vesicles as trans-genomic agents: Emerging roles in disease and evolution. *Cancer. Sci.* **2017**, *108*, 824–830. DOI: 10.1111/cas.13222.

28. Schorey, J. S.; Cheng, Y.; Singh, P. P.; Smith, V. L. Exosomes and other extracellular vesicles in host–pathogen interactions. *EMBO reports.* **2015**, *16*, 24–43. DOI: 10.15252/embr.201439363.

29. Hood, J. L.; San, R. S.; Wickline, S. A. Exosomes released by melanoma cells prepare sentinel lymph nodes for tumor metastasis. *Cancer. Res.* **2011**, *71*, 3792–3801. DOI: 10.1158/0008-5472.CAN-10-4455.

30. Iero, M.; Valenti, R.; Huber, V.; Filipazzi, P.; Parmiani, G.; Fais, S.; Rivoltini, L. Tumour-released exosomes and their implications in cancer immunity. *Cell. Death. Differ.* **2008**, *15*, 80–88. DOI: 10.1038/sj.cdd.4402237.

31. Ribeiro, M. F.; Zhu, H.; Millard, R. W.; Fan, G. C. Exosomes Function in Pro- and Anti-Angiogenesis. *Curr. Angiogenes.* **2013**, *2*, 54–59. DOI: 10.2174/22115528113020020001.

32. Cui, Y.; Luan, J.; Li, H.; Zhou, X.; Han, J. Exosomes derived from mineralizing osteoblasts promote ST2 cell osteogenic differentiation by alteration of microRNA expression. *FEBS Lett.* **2016**, *590*, 185–192. DOI: 10.1002/1873-3468.12024.

33. Sung, B. H.; Ketova, T.; Hoshino, D.; Zijlstra, A.; Weaver, A. M. Directional cell movement through tissues is controlled by exosome secretion. *Nat. Commun.* **2015**, *6*, 7164. DOI: 10.1038/ncomms8164.

34. Liu, W. Z.; Ma, Z. J.; Kang, X. W. Current status and outlook of advances in exosome isolation. *Anal. Bioanal. Chem.* **2022**, *414*, 7123–7141. DOI: 10.1007/s00216-022-04253-7.

35. Sidhom, K.; Obi, P. O.; Saleem, A. A Review of Exosomal Isolation Methods: Is Size Exclusion Chromatography the Best Option? *Int. J. Mol. Sci.* **2020**, *21*, 6466. DOI: 10.3390/ijms21186466.

36. Ferreira, D.; Moreira, J. N.; Rodrigues, L. R. New advances in exosome-based targeted drug delivery systems. *Crit. Rev. Oncol. Hematol.* **2022**, *172*, 103628. DOI: 10.1016/j.critrevonc.2022.103628.

37. Yang, D.; Zhang, W.; Zhang, H.; Zhang, F.; Chen, L.; Ma, L.; Larcher, L. M.; Chen, S.; Liu, N.; Zhao, Q.; Tran, P. H. L.; Chen, C.; Veedu, R. N.; Wang, T. Progress, opportunity, and perspective on exosome isolation - efforts for efficient exosome-based theranostics. *Theranostics.* **2020**, *10*, 3684–3707. DOI: 10.7150/thno.41580.

38. Ayala-Mar, S.; Donoso-Quezada, J.; Gallo-Villanueva, R. C.; Perez-Gonzalez, V. H.; González-Valdez, J. Recent advances and challenges in the recovery and purification of cellular exosomes. *Electrophoresis.* **2019**, *40*, 3036–3049. DOI: 10.1002/elps.201800526.

39. *CAS Content Collection.* https://www.cas.org/about/cas-content (accessed 2022-10-10).

40. *NIH RePORTER.* https://reporter.nih.gov/ (accessed 2022-10-10).

41. Batrakova, E. V.; Kim, M. S. Using exosomes, naturally-equipped nanocarriers, for drug delivery. *J. Control. Release.* **2015**, *219*, 396–405. DOI: 10.1016/j.jconrel.2015.07.030.

42. *Cargo Loading into Exosomes.* https://www.creative-biolabs.com/exosome/cargo-loading-into-exosomes.htm? gclid=Cj0KCQjw3eeXBhD7ARIsAHjssr8jAvBATTlmPXiuVhOO0cHVvbQ925eo WMXRUiPSWY tJQtQCze12NYQaAlwoEALw_wcB%20;%20https://doi.org/10.3389/fbioe.2020.586130 (accessed 2022-10-10).

43. Xi, X. M.; Xia, S. J.; Lu, R. Drug loading techniques for exosome-based drug delivery systems. *Pharmazie*. **2021**, *76*, 61–67. DOI: 10.1691/ph.2021.0128.

44. Ran, N.; Gao, X.; Dong, X.; Li, J.; Lin, C.; Geng, M.; Yin, H. Effects of exosome-mediated delivery of myostatin propeptide on functional recovery of mdx mice. *Biomaterials*. **2020**, *236*, 119826. DOI: 10.1016/j.biomaterials.2020.119826.

45. Vakhshiteh, F.; Rahmani, S.; Ostad, S. N.; Madjd, Z.; Dinarvand, R.; Atyabi, F. Exosomes derived from miR-34a-overexpressing mesenchymal stem cells inhibit in vitro tumor growth: A new approach for drug delivery. *Life. Sci.* **2021**, *266*, 118871. DOI: 10.1016/j.lfs.2020.118871.

46. Fitts, C. A.; Ji, N.; Li, Y.; Tan, C. Exploiting Exosomes in Cancer Liquid Biopsies and Drug Delivery. *Adv. Healthcare Mater.* **2019**, *8*, 1801268. DOI: 10.1002/adhm.201801268.

47. Shin, K.; Fogg, V. C.; Margolis, B. Tight junctions and cell polarity. *Annu. Rev. Cell Dev. Biol.* **2006**, *22*, 207-235. DOI: 10.1146/annurev.cellbio.22.010305.104219.

48. Yang, H.; Fu, H.; Wang, B.; Zhang, X.; Mao, J.; Li, X.; Wang, M.; Sun, Z.; Qian, H.; Xu, W. Exosomal miR-423-5p targets SUFU to promote cancer growth and metastasis and serves as a novel marker for gastric cancer. *Mol. Carcinog.* **2018**, *57*, 1223–1236. DOI: 10.1002/mc.22838.

49. *Direct Biologics clinical trials.* https://clinicaltrials.gov/ct2/results?cond=&term=exoflo&cntry=&state=&city=&dist=&Search=Search (accessed 2022-10-10).

50. Sancho-Albero, M.; Navascués, N.; Mendoza, G.; Sebastián, V.; Arruebo, M.; Martín-Duque, P.; Santamaría, J. Exosome origin determines cell targeting and the transfer of therapeutic nanoparticles towards target cells. *J. Nanobiotechnol.* **2019**, *17*, 16. DOI: 10.1186/s12951-018-0437-z.

51. Hazan-Halevy, I.; Rosenblum, D.; Weinstein, S.; Bairey, O.; Raanani, P.; Peer, D. Cell-specific uptake of mantle cell lymphoma-derived exosomes by malignant and non-malignant B-lymphocytes. *Cancer. Lett.* **2015**, *364*, 59–69. DOI: 10.1016/j.canlet.2015.04.026.

52. Tian, Y., Li, S., Song, J., Ji, T., Zhu, M., Anderson, G. J., Wei, J.,Nie, G. A doxorubicin delivery platform using engineered natural membrane vesicle exosomes for targeted tumor therapy. *Biomaterials.* **2014**, *35*, 2383-2390.

53. Bradley, J. A.; Bolton, E. M.; Pedersen, R. A. Stem cell medicine encounters the immune system. *Nat. Rev. Immunol.* **2002**, *2*, 859–871. DOI: 10.1038/nri934.

54. Nicolini, A.; Ferrari, P.; Biava, P. M. Exosomes and Cell Communication: From Tumour-Derived Exosomes and Their Role in Tumour Progression to the Use of Exosomal Cargo for Cancer Treatment. *Cancers (Basel).* **2021**, *13*, 822. DOI: 10.3390/cancers13040822.

55. Jia, Y.; Ding, X.; Zhou, L.; Zhang, L.; Yang, X. Mesenchymal stem cells-derived exosomal microRNA-139-5p restrains tumorigenesis in bladder cancer by targeting PRC1. *Oncogene.* **2021**, *40*, 246–261. DOI: 10.1038/s41388-020-01486-7.

56. Liu, D.; Chen, C.; Cui, M.; Zhang, H. miR-140-3p inhibits colorectal cancer progression and its liver metastasis by targeting BCL9 and BCL2. *Cancer. Med.* **2021**, *10*, 3358–3372. DOI: 10.1002/cam4.3840.

57. Tang, Y.; Zong, S.; Zeng, H.; Ruan, X.; Yao, L.; Han, S.; Hou, F. MicroRNAs and angiogenesis: a new era for the management of colorectal cancer. *Cancer. Cell. Int.* **2021**, *21*, 221. DOI: 10.1186/s12935-021-01920-0.

58. Yue, S.; Ye, X.; Zhou, T.; Gan, D.; Qian, H.; Fang, W.; Yao, M.; Zhang, D.; Shi, H.; Chen, T. PGRN(-/-) TAMs-derived exosomes inhibit breast cancer cell invasion and migration and its mechanism exploration. *Life. Sci.* **2021**, *264*, 118687. DOI: 10.1016/j.lfs.2020.118687.

59. Nakano, M.; Fujimiya, M. Potential effects of mesenchymal stem cell derived extracellular vesicles and exosomal miRNAs in neurological disorders. *Neural Regen. Res.* **2021**, *16*, 2359–2366. DOI: 10.4103/1673-5374.313026.

60. Li, Q.; Wang, Z.; Xing, H.; Wang, Y.; Guo, Y. Exosomes derived from miR-188-3p-modified adipose-derived mesenchymal stem cells protect Parkinson's disease. *Mol. Ther. – Nucleic Acids.* **2021**, *23*, 1334–1344. DOI: 10.1016/j.omtn.2021.01.022.

61. Dougherty, J. A.; Mergaye, M.; Kumar, N.; Chen, C.-A.; Angelos, M. G.; Khan, M. Potential Role of Exosomes in Mending a Broken Heart: Nanoshuttles Propelling Future Clinical Therapeutics Forward. *Stem Cells Int.* **2017**, *2017*, 5785436. DOI: 10.1155/2017/5785436.

62. Couto, G. d.; Gallet, R.; Cambier, L.; Jaghatspanyan, E.; Makkar, N.; Dawkins, J. F.; Berman, B. P.; Marbán, E. Exosomal MicroRNA Transfer into Macrophages Mediates Cellular Postconditioning. *Circulation.* **2017**, *136*, 200–214. DOI: 10.1161/circulationaha.116.024590.

63. Kwon, J.-S.; Schumacher, S. M.; Gao, E.; Chuprun, J. K.; Ibetti, J.; Roy, R.; Khan, M.; Kishore, R.; Koch, W. J. Characterization of βARKct engineered cellular extracellular vesicles and model specific cardioprotection. *Am. J. Physiol. Heart. Circ. Physiol.* **2021**, *320*, H1276–H1289. DOI: 10.1152/ajpheart.00571.2020.

64. Soltani, F.; Parhiz, H.; Mokhtarzadeh, A.; Ramezani, M. Synthetic and Biological Vesicular Nano-Carriers Designed for Gene Delivery. *Curr. Pharm. Des.* **2015**, *21*, 6214–6235. DOI: 10.2174/1381612821666151027153410.

65. Das, C. K.; Jena, B. C.; Banerjee, I.; Das, S.; Parekh, A.; Bhutia, S. K.; Mandal, M. Exosome as a Novel Shuttle for Delivery of Therapeutics across Biological Barriers. *Mol. Pharm.* **2019**, *16*, 24–40. DOI: 10.1021/acs.molpharmaceut.8b00901.

66. Karpman, D.; Ståhl, A.-l.; Arvidsson, I. Extracellular vesicles in renal disease. *Nat. Rev. Nephrol.* **2017**, *13*, 545–562. DOI: 10.1038/nrneph.2017.98.

67. Fiandaca, M. S.; Kapogiannis, D.; Mapstone, M.; Boxer, A.; Eitan, E.; Schwartz, J. B.; Abner, E. L.; Petersen, R. C.; Federoff, H. J.; Miller, B. L.; Goetzl, E. J. Identification of preclinical Alzheimer's disease by a profile of pathogenic proteins in neurally derived blood exosomes: A case-control study. *Alzheimers. Dement.* **2015**, *11*, 600-607.e601. DOI: 10.1016/j.jalz.2014.06.008.

68. Saman, S.; Kim, W.; Raya, M.; Visnick, Y.; Miro, S.; Saman, S.; Jackson, B.; McKee, A. C.; Alvarez, V. E.; Lee, N. C. Y.; Hall, G. F. Exosome-associated Tau Is Secreted in Tauopathy Models and Is Selectively Phosphorylated in Cerebrospinal Fluid in Early Alzheimer Disease *J. Biol. Chem.* **2012**, *287*, 3842–3849. DOI: 10.1074/jbc.M111.277061.

69. Yu, D.; Li, Y.; Wang, M.; Gu, J.; Xu, W.; Cai, H.; Fang, X.; Zhang, X. Exosomes as a new frontier of cancer liquid biopsy. *Mol. Cancer.* **2022**, *21*, 56. DOI: 10.1186/s12943-022-01509-9.

70. Liu, J., Chen, Y., Pei, F., Zeng, C., Yao, Y., Liao, W., Zhao, Z., Extracellular Vesicles in Liquid Biopsies: Potential for Disease Diagnosis. *Biomed Res Int.* **2021**, *2021*, 6611244.

71. Boukouris, S.; Mathivanan, S. Exosomes in bodily fluids are a highly stable resource of disease biomarkers. *Proteomics: Clin. Appl.* **2015**, *9*, 358–367. DOI: 10.1002/prca.201400114.

72. Lin, J.; Li, J.; Huang, B.; Liu, J.; Chen, X.; Chen, X.-M.; Xu, Y.-M.; Huang, L.-F.; Wang, X.-Z. Exosomes: Novel Biomarkers for Clinical Diagnosis. *Sci. World. J.* **2015**, *2015*, 657086. DOI: 10.1155/2015/657086.

73. Manterola, L.; Guruceaga, E.; Pérez-Larraya, J. G.; González-Huarriz, M.; Jauregui, P.; Tejada, S.; Diez-Valle, R.; Segura, V.; Samprón, N.; Barrena, C.; Ruiz, I.; Agirre, A.; Ayuso, Á.; Rodríguez, J.; González, Á.; Xipell, E.; Matheu, A.; López de Munain, A.; Tuñón, T.; Zazpe, I.; et al. A small noncoding RNA signature found in exosomes of GBM patient serum as a diagnostic tool. *Neuro. Oncol.* **2014**, *16*, 520–527. DOI: 10.1093/neuonc/not218.

74. Kalluri, R.; LeBleu, V. S. The biology, function, and biomedical applications of exosomes. *Science.* **2020**, *367*, aau6977. DOI: 10.1126/science.aau6977.

75. Mosquera-Heredia, M. I.; Morales, L. C.; Vidal, O. M.; Barceló, E.; Silvera-Redondo, C.; Vélez, J. I.; Garavito-Galofre, P. Exosomes: Potential Disease Biomarkers and New Therapeutic Targets. *Biomedicines.* **2021**, *9*. DOI: 10.3390/biomedicines9081061.

76. Li, A.; Zhang, T.; Zheng, M.; Liu, Y.; Chen, Z. Exosomal proteins as potential markers of tumor diagnosis. *J. Hematol. Oncol.* **2017**, *10*, 175. DOI: 10.1186/s13045-017-0542-8.

77. Hu, C.; Jiang, W.; Lv, M.; Fan, S.; Lu, Y.; Wu, Q.; Pi, J. Potentiality of Exosomal Proteins as Novel Cancer Biomarkers for Liquid Biopsy. *Front. Immunol.* **2022**, *13*. DOI: 10.3389/fimmu.2022.792046.

78. Nonaka, T.; Wong, D. T. W. Saliva-Exosomics in Cancer: Molecular Characterization of Cancer-Derived Exosomes in Saliva. *Enzymes.* **2017**, *42*, 125–151. DOI: 10.1016/bs.enz.2017.08.002.

79. Bao, M.; Huang, Y.; Lang, Z.; Zhao, H.; Saito, Y.; Nagano, T.; Kawagoe, I.; Divisi, D.; Hu, X.; Jiang, G. Proteomic analysis of plasma exosomes in patients with non-small cell lung cancer. *Transl. Lung. Cancer. Res.* **2022**, *11*, 1434–1452. DOI: 10.21037/tlcr-22-467.

80. Rajendran, L.; Honsho, M.; Zahn, T. R.; Keller, P.; Geiger, K. D.; Verkade, P.; Simons, K. Alzheimer's disease β-amyloid peptides are released in association with exosomes. *Proc. Natl. Acad. Sci.* **2006**, *103*, 11172–11177. DOI: 10.1073/pnas.0603838103.

81. Zhou, H.; Cheruvanky, A.; Hu, X.; Matsumoto, T.; Hiramatsu, N.; Cho, M. E.; Berger, A.; Leelahavanichkul, A.; Doi, K.; Chawla, L. S. Urinary exosomal transcription factors, a new class of biomarkers for renal disease. *Kidney. Int.* **2008**, *74*, 613–621. DOI: 10.1038/ki.2008.206.

82. Taylor, D. D.; Gercel-Taylor, C. MicroRNA signatures of tumor-derived exosomes as diagnostic biomarkers of ovarian cancer. *Gynecol. Oncol.* **2008**, *110*, 13–21. DOI: 10.1016/j.ygyno.2008.04.033.

83. Mitchell, P. S.; Parkin, R. K.; Kroh, E. M.; Fritz, B. R.; Wyman, S. K.; Pogosova-Agadjanyan, E. L.; Peterson, A.; Noteboom, J.; O'Briant, K. C.; Allen, A. Circulating microRNAs as stable blood-based markers for cancer detection. *Proc. Natl. Acad. Sci.* **2008**, *105*, 10513–10518. DOI: 10.1073/pnas.0804549105.

84. Hunter, M. P.; Ismail, N.; Zhang, X.; Aguda, B. D.; Lee, E. J.; Yu, L.; Xiao, T.; Schafer, J.; Lee, M.-L. T.; Schmittgen, T. D. Detection of microRNA expression in human peripheral blood microvesicles. *PLoS One.* **2008**, *3*, e3694. DOI: 10.1371/journal.pone.0003694.

85. Simpson, R. J.; Lim, J. W.; Moritz, R. L.; Mathivanan, S. Exosomes: proteomic insights and diagnostic potential. *Expert Rev. Proteomics.* **2009**, *6*, 267–283. DOI: 10.1586/epr.09.17.

86. Silva, J.; Garcia, V.; Rodriguez, M.; Compte, M.; Cisneros, E.; Veguillas, P.; Garcia, J. M.; Dominguez, G.; Campos-Martin, Y.; Cuevas, J.; Peña, C.; Herrera, M.; Diaz, R. Mohammed, N.;Bonilla, F. Analysis of exosome release and its prognostic value in human colorectal cancer. *Genes, Chromosomes and Cancer.* **2012**, *51*, 409–418. DOI: 10.1002/gcc.21926.

87. Friel, A. M.; Corcoran, C.; Crown, J.; O'Driscoll, L. Relevance of circulating tumor cells, extracellular nucleic acids, and exosomes in breast cancer. *Breast Cancer Res. Treat.* **2010**, *123*, 613–625. DOI: 10.1007/s10549-010-0980-2.

88. Rashed M.H.; Bayraktar, E.; G, K. H.; Abd-Ellah, M. F.; Amero, P.; Chavez-Reyes, A.; Rodriguez-Aguayo, C. Exosomes: From Garbage Bins to Promising Therapeutic Targets. *Int. J. Mol. Sci.* **2017**, *18*. DOI: 10.3390/ijms18030538.

89. Raposo, G.; Stoorvogel, W. Extracellular vesicles: exosomes, microvesicles, and friends. *J. Cell Biol.* **2013**, *200*, 373–383. DOI: 10.1083/jcb.201211138.

90. Marleau, A. M.; Chen, C.-S.; Joyce, J. A.; Tullis, R. H. Exosome removal as a therapeutic adjuvant in cancer. *J. Transl. Med.* **2012**, *10*, 134. DOI: 10.1186/1479-5876-10-134.

91. Barnie, P. A.; Afrifa, J.; Gyamerah, E. O.; Amoani, B. Extracellular Vesicles as Biomarkers and Therapeutic Targets in Cancers. In *Extracellular Vesicles*, Paul, M. K.; Ed. IntechOpen: London, 2022.

92. Shen, X.; Song, S.; Chen, N.; Liao, J.; Zeng, L. Stem cell-derived exosomes: A supernova in cosmetic dermatology. *J. Cosmet. Dermatol.* **2021**, *20*, 3812–3817. DOI: 10.1111/jocd.14438.

93. Li, L.; Ngo, H. T. T.; Hwang, E.; Wei, X.; Liu, Y.; Liu, J.; Yi, T. H. Conditioned Medium from Human Adipose-Derived Mesenchymal Stem Cell Culture Prevents UVB-Induced Skin Aging in Human Keratinocytes and Dermal Fibroblasts. *Int. J. Mol. Sci.* **2019**, *21*. DOI: 10.3390/ijms21010049.

94. *Plant Exosomes and Patients Diagnosed With Polycystic Ovary Syndrome (PCOS) 17.* https://clinicaltrials.gov/ct2/show/NCT03493984 (accessed 2022-10-10).

95. *Edible Plant Exosome Ability to Prevent Oral Mucositis Associated With Chemoradiation Treatment of Head and Neck Cancer.* https://clinicaltrials.gov/ct2/show/NCT01668849 (accessed 2022-10-10).

96. *Anjarium Biosciences.* https://www.anjarium.com/ (accessed 2022-10-10).

97. *Carmine Therapeutics* https://www.carminetherapeutics.com/ (accessed 2022-10-10).

98. Usman, W. M.; Pham, T. C.; Kwok, Y. Y.; Vu, L. T.; Ma, V.; Peng, B.; Chan, Y. S.; Wei, L.; Chin, S. M.; Azad, A.; He, A. B.-L.; Leung, A. Y. H.; Yang, M.; Shyh-Chang, N.; Cho, W. C.; Shi, J.; Le, M. T. N. Efficient RNA drug delivery using red blood cell extracellular vesicles. *Nat. Commun.* **2018**, *9*, 2359.

99. *Ilias Biologics - Platform Technology.* https://www.iliasbio.com/our/platform.php (accessed 2022-10-10).

100. *Ilias Biologics - Pipeline - ILB-202.* https://www.iliasbio.com/pipeline/srIkB.php (accessed 2022-10-10).

101. Webb, R. L.; Kaiser, E. E.; Scoville, S. L.; Thompson, T. A.; Fatima, S.; Pandya, C.; Sriram, K.; Swetenburg, R. L.; Vaibhav, K.; Arbab, A. S.; Baban, B.; Dhandapani, K. M.; Hess, D. C.; Hoda, M. N.; Stice, S. L. Human Neural Stem Cell Extracellular Vesicles Improve Tissue and Functional Recovery in the Murine Thromboembolic Stroke Model. *Transl. Stroke. Res.* **2018**, *9*, 530–539. DOI: 10.1007/s12975-017-0599-2.

102. *Aruna Bio.* https://www.arunabio.com/aruna-bio-our-platform (accessed 2022-10-10).

103. *Capricor.* https://capricor.com/exosomes/ (accessed 2022-10-10).

104. *Evox Pipeline.* https://www.evoxtherapeutics.com/Pipeline (accessed 2022-10-10).
105. *Innocan Pharma.* https://innocanpharma.com/cell-therapy/ (accessed 2022-10-10).
106. *Xollent Biotech.* https://www.xollentbio.com/pipeline (accessed 2022-10-10).
107. *Exogenus Therapeutics.* https://www.exogenus-t.com/pipeline-2/ (accessed 2022-10-10).
108. Henriques-Antunes, H.; Cardoso, R. M. S.; Zonari, A.; Correia, J.; Leal, E. C.; Jiménez-Balsa, A.; Lino, M. M.; Barradas, A.; Kostic, I.; Gomes, C.; Karp, J. M.; Carvalho, E.; Ferreira, L. The Kinetics of Small Extracellular Vesicle Delivery Impacts Skin Tissue Regeneration. *ACS Nano.* **2019**, *13*, 8694–8707.
109. *OmniSpirant Therapeutics.* https://www.omnispirant.com/ (accessed 2022-10-10).
110. *Kimera Labs.* https://kimeralabs.com/ (accessed 2022-10-10).
111. *Kimera Labs products.* https://kimeralabs.com/products/ (accessed 2022-10-10).
112. *Exocel Bio* - Exosome Products. https://www.exocelbio.com/products (accessed 2022-10-10).
113. *Exocel Bio.* https://www.exocelbio.com/ (accessed 2022-10-10).
114. *Regen Suppliers.* https://www.regensuppliers.com/rebellaxo.html (accessed 2022-10-10).
115. Cho, B. S.; Kim, J. O.; Ha, D. H.; Yi, Y. W. Exosomes derived from human adipose tissue-derived mesenchymal stem cells alleviate atopic dermatitis. *Stem Cell. Res. Ther.* **2018**, *9*, 187. DOI: 10.1186/s13287-018-0939-5.
116. *ExoCoBio.* http://www.exocobio.com/default/eng/02/02.php (accessed 2022-10-10).
117. *MDimune - BioDrone Platform.* http://www.mdimune.com/en/m62.php (accessed 2022-10-10).
118. *MDimune Pipeline.* http://www.mdimune.com/en/m71.php (accessed 2022-10-10).
119. *EV Therapeutics - gallery.* https://www.evtherapeutics.com/gallery (accessed 2022-10-10).
120. *EV Therapeutics - platform.* https://www.evtherapeutics.com/about-us (accessed 2022-10-10).
121. *Evora BioSciences.* https://www.evorabio.com/ (accessed 2022-10-10).
122. *Florica Therapeutics.* https://floricatherapeutics.com/ (accessed 2022-10-10).
123. *Craif.* https://craif.com/en/science/ (accessed 2022-10-10).
124. *Mercy Bioanalytics.* https://mercybio.com/the-mercy-halo-test/ (accessed 2022-10-10).
125. Bortolin, L. T.; Salem, D. P.; Banerjee, S. Preliminary results for a novel single extracellular vesicle assay for early stage ovarian cancer: The power of co-localized detection of surface biomarkers. In *AACR Anual Meeting*, New Orleans, 2022.
126. Salem, D. P.; Bortolin, L. T.; Banerjee, S. Preliminary results for a novel single extracellular vesicle assay for early lung cancer: The power of co-localized detection of surface biomarkers. In *AACR Annual Meeting*, New Orleans, 2022.
127. Melo, S. A.; Luecke, L. B.; Kahlert, C.; Fernandez, A. F.; Gammon, S. T.; Kaye, J.; LeBleu, V. S.; Mittendorf, E. A.; Weitz, J.; Rahbari, N.; Reissfelder, C.; Pilarsky, C.; Fraga, M. F.; Piwnica-Worms, D.; Kalluri, R. Glypican-1 identifies cancer exosomes and detects early pancreatic cancer. *Nature.* **2015**, *523*, 177–182. DOI: 10.1038/nature14581.
128. Welker, M.-W.; Reichert, D.; Susser, S.; Sarrazin, C.; Martinez, Y.; Herrmann, E.; Zeuzem, S.; Piiper, A.; Kronenberger, B. Soluble Serum CD81 Is Elevated in Patients with Chronic Hepatitis C and Correlates with Alanine Aminotransferase Serum Activity. *PLoS One.* **2012**, *7*, e30796. DOI: 10.1371/journal.pone.0030796.
129. Sandfeld-Paulsen, B.; Jakobsen, K. R.; Bæk, R.; Folkersen, B. H.; Rasmussen, T. R.; Meldgaard, P.; Varming, K.; Jørgensen, M. M.; Sorensen, B. S. Exosomal proteins as diagnostic biomarkers in lung cancer. *J. Thorac. Oncol.* **2016**, *11*, 1701–1710. DOI: 10.1016/j.jtho.2016.05.034.
130. Matsumoto, S.; Sakata, Y.; Suna, S.; Nakatani, D.; Usami, M.; Hara, M.; Kitamura, T.; Hamasaki, T.; Nanto, S.; Kawahara, Y.; Komuro, I. Circulating p53-Responsive MicroRNAs Are Predictive Indicators of Heart Failure After Acute Myocardial Infarction. *Circ. Res.* **2013**, *113*, 322–326. DOI: 10.1161/CIRCRESAHA.113.301209.

For more details on the research progression of Exosomes, see our publication in ACS Nano at cas.org/exosomes

CAS is a leader in scientific information solutions, partnering with innovators around the world to accelerate scientific breakthroughs. CAS employs over 1,400 experts who curate, connect, and analyze scientific knowledge to reveal unseen connections. For over 100 years, scientists, patent professionals, and business leaders have relied on CAS solutions and expertise to provide the hindsight, insight, and foresight they need so they can build upon the learnings of the past to discover a better future. CAS is a division of the American Chemical Society.

Connect with us at cas.org

CAS
A division of the
American Chemical Society

CASGENENGWHP100864221028