Review Article

Cellular Camouflage for Brain Delivery: Living Cells and Cell-Derived Vesicles as Therapeutic Carriers

Anusha Dasari*, Tavitinaidu Mudadla, Sravani Lakkamraju, Lakshmi Kalyani Bai Banavathu, Manisha Bogolu, Siva Reddy Chinakondu
Malineni Perumallu Pharmacy College, Pulladigunta, Guntur, Andhra Pradesh 522017, India.
***Corresponding author's E-mail:** dasarianusha1221@gmail.com

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ABSTRACT

Drug development for central nervous system (CNS) disorders continues to face a major delivery problem: many potentially useful medicines do not reach the brain at concentrations high enough to produce a therapeutic effect. The blood–brain barrier (BBB) is the main obstacle. Conventional solutions, including increasing drug lipophilicity, using receptor-directed transport, temporarily opening the barrier, or packaging drugs in synthetic nanoparticles, can improve delivery in selected settings, but they also introduce limitations such as rapid clearance, off-target distribution, immune recognition, and toxicity. A different approach is to use biological carriers that already possess the ability to circulate, recognise diseased tissue, and interact with the BBB. This review examines mesenchymal, neural, and adipose-derived stem cells; immune cells such as neutrophils, monocytes/macrophages, and T cells; and cell-derived vesicles including exosomes, microvesicles, and engineered membrane vesicles. Particular attention is given to how these carriers cross or interact with the BBB, how therapeutic cargo can be incorporated, and what has been demonstrated in glioma, neurodegenerative disorders, and stroke. Although preclinical findings are encouraging, cell-derived carriers have not yet achieved routine regulatory approval for neurological indications. Major barriers to translation include reproducible manufacturing, appropriate potency testing, long-term safety assessment, biodistribution, immunogenicity, and regulatory classification

Keywords: Blood–Brain Barrier; Cellular Camouflage; Trojan-Horse Delivery; Mesenchymal Stem Cells; Neural Stem Cells; Adipose-Derived Stem Cells; Extracellular Vesicles; Exosomes; Therapeutic Payloads; Glioblastoma; Neurodegenerative Disease; Ischaemic Stroke.

1. INTRODUCTION

1.1 The unmet need in CNS therapeutics

Neurological disorders such as Alzheimer's disease, Parkinson's disease, stroke, and glioblastoma remain difficult to treat despite major advances in molecular biology and medicinal chemistry. One important reason is not the lack of therapeutic targets, but the difficulty of getting an effective amount of drug to those targets inside the brain. This delivery problem contributes to high attrition and long development timelines for CNS medicines. [1,2] The BBB is central to this problem. It protects neural tissue from potentially harmful substances circulating in the blood, but the same protective function also restricts many therapeutic compounds. As a result, a drug may show strong activity against a molecular target in laboratory studies yet produce little benefit in the brain if adequate exposure cannot be achieved. The delivery strategies discussed in this review are therefore aimed primarily at overcoming or exploiting this access barrier. [2]

The organisation and principal exclusion mechanisms of the blood-brain barrier are illustrated in Figure 1.

1.2 Anatomy and physiology of the barrier

The BBB is best understood as a coordinated component of the neurovascular unit rather than as a simple physical wall. Cerebral endothelial cells form the inner lining of brain capillaries and are connected by tight junctions involving proteins such as claudins, occludin, and junctional adhesion molecules. Pericytes are associated with the vascular basement membrane, while astrocytic end-feet surround the outer surface of the vessels. Perivascular immune and glial cells also contribute to barrier function. Together, these components regulate physical passage, transport processes, metabolism, and local immune responses. [2,8]

These mechanisms work together to restrict the entry of many circulating substances into brain tissue. [2]

Tight junctions strongly limit movement through the spaces between endothelial cells, while selective transport systems control which substances can cross the endothelial layer. Efflux proteins, particularly P-glycoprotein (P-gp/ABCB1) and breast cancer resistance protein (BCRP/ABCG2), can return transported compounds to the blood. Low vesicular transport and enzymatic activity at the endothelial interface further reduce exposure of the brain to many macromolecules. Consequently, only a relatively small proportion of conventional drug candidates achieve therapeutically useful concentrations in the CNS. [2]

The barrier is not equally restrictive under every pathological condition. Tumours, neuroinflammation, and cerebral ischaemia can alter endothelial behaviour, increase local permeability, and promote expression of adhesion molecules that recruit circulating leukocytes. These disease-associated changes provide an opportunity for biological carriers to use pathways that are already active at the affected site. [2,6]

The conceptual basis of the Trojan-horse approach is illustrated in Figure 2.

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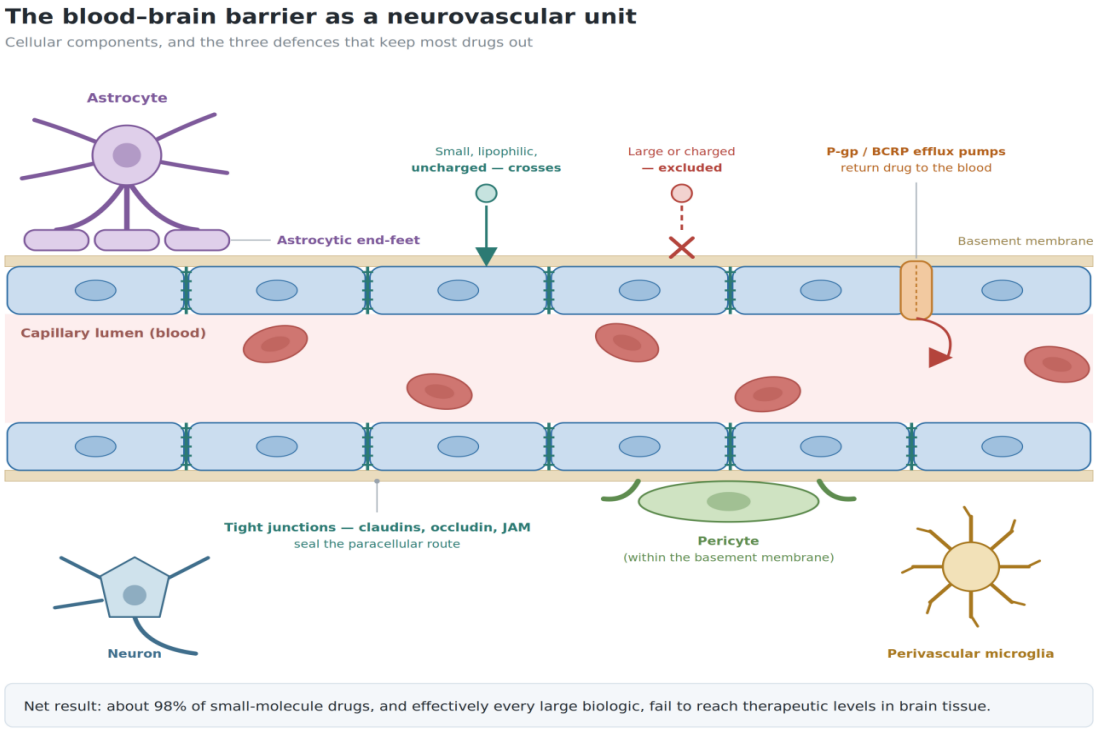


Figure 1: Organisation of the blood–brain barrier within the neurovascular unit. Endothelial cells joined by continuous tight junctions are invested by pericytes and astrocytic end-feet, with perivascular microglia positioned externally. The three principal exclusion mechanisms are indicated: paracellular sealing, efflux mediated by P-gp and BCRP, and exclusion on the basis of size and charge. [2]

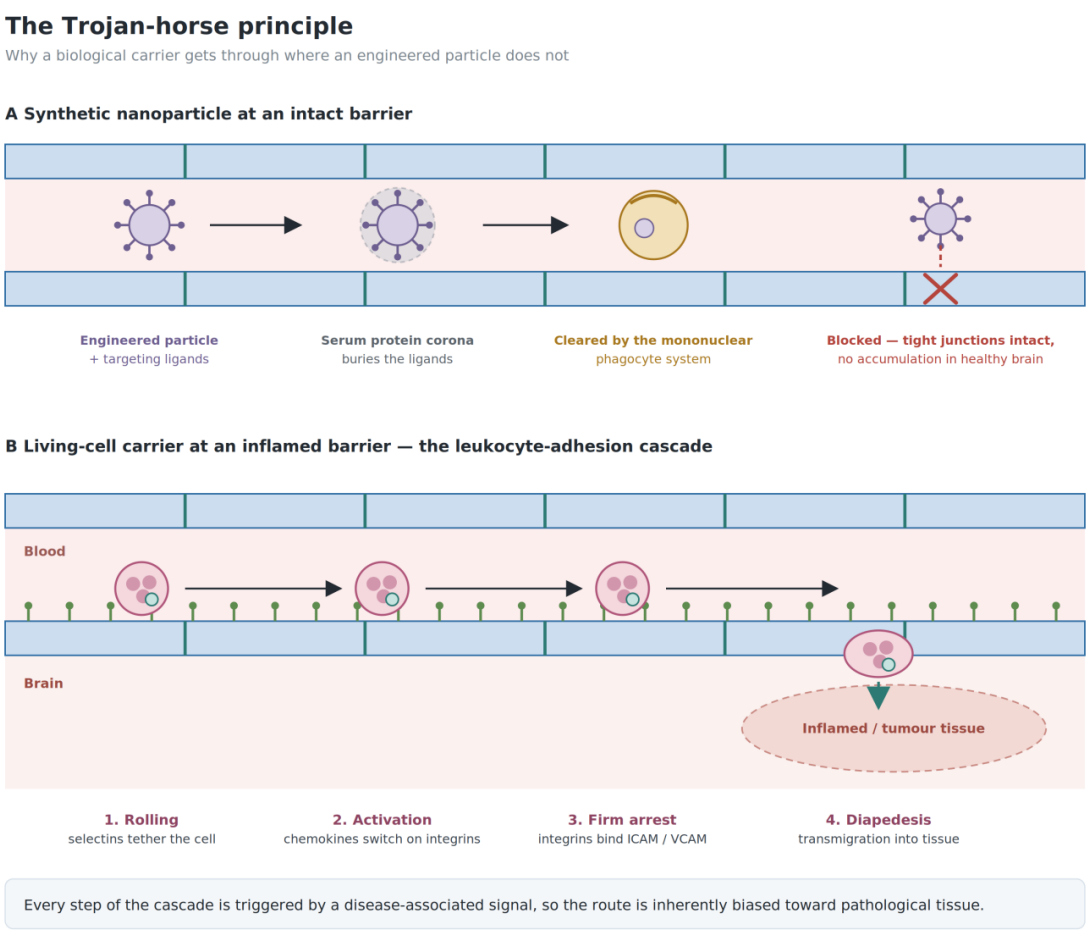


Figure 2: Conceptual basis of the Trojan-horse approach. [1,9,6]

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1.3 Limitations of conventional delivery strategies

A number of strategies have been developed to improve brain exposure, but each has disadvantages. Altering drug properties or using prodrugs may increase BBB penetration, yet the same changes can affect distribution and toxicity in peripheral tissues. Direct approaches such as intrathecal or intracerebroventricular administration, convection-enhanced delivery, osmotic opening, and focused ultrasound can produce high local concentrations but require specialised procedures and may be difficult to repeat for long-term treatment. Receptor-mediated transcytosis uses endogenous transport systems, including transferrin-, insulin-, or LRP1-related pathways, but receptor availability and competition from peripheral tissues can limit efficiency. [2,5,10,11,12,13]

Synthetic nanoparticles provide substantial flexibility in drug formulation and can be modified with targeting ligands. However, they may be removed by the mononuclear phagocyte system, acquire a protein corona that changes their surface behaviour, trigger immune responses, or show limited accumulation in regions where the BBB remains relatively intact. These limitations have encouraged interest in carriers that inherit biological recognition and trafficking functions from cells rather than having to reproduce them synthetically. [5,10,11,12,13]

This concept shifts the design strategy from making a synthetic carrier behave like a cell to using the cell, or a material derived from it, as the delivery platform. [1,5,10,11]

Exosome biogenesis, cargo composition, and targeted entry into the CNS are summarised in Figure 3.

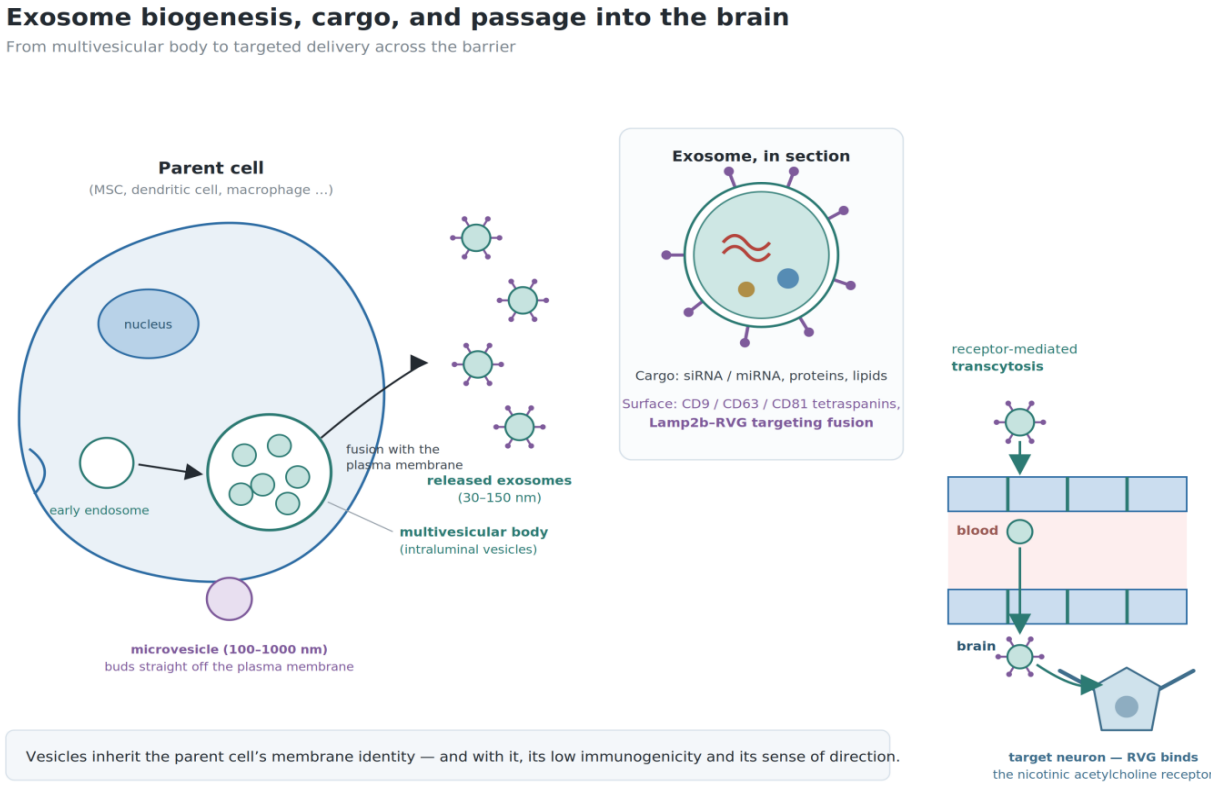


Figure 3: Exosome biogenesis, cargo composition, and entry into the CNS. Intraluminal vesicles are generated within multivesicular bodies; fusion of these compartments with the plasma membrane liberates exosomes measuring 30 to 150 nm and containing proteins, lipids, and nucleic acids derived from the parent cell. Surface modification, exemplified by a Lamp2b–RVG fusion construct, directs the vesicles across the barrier towards neurons. [14,3,4]

1.4 The Trojan-horse concept and the scope of this review

The Trojan-horse concept is based on using a carrier that the body already recognises and knows how to traffic. Living cells and their vesicles contain biological surface features that can reduce rapid immune clearance and, depending on the source cell, can direct the carrier towards inflammation, injury, or tumour tissue. Instead of relying entirely on the physicochemical properties of the drug, the therapeutic payload can therefore benefit from the natural behaviour of its carrier. This approach does not remove the BBB problem; rather, it attempts to use existing biological transport and recruitment mechanisms to negotiate it. [1,9,6]

The review first discusses living-cell carriers and the mechanisms that allow them to reach the CNS. It then considers cell-derived vesicles from mammalian, plant, and milk sources, followed by approaches for payload loading and surface modification. The therapeutic evidence in brain tumours, neurodegenerative disease, and stroke is subsequently reviewed, before comparing biological and synthetic carrier classes and discussing the manufacturing, safety, and regulatory issues that influence clinical translation.

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2. Living Cells as Therapeutic Carriers

Living-cell delivery uses viable cells as transport vehicles for therapeutic agents. Stem cells and leukocytes are particularly attractive because they can remain in circulation, respond to disease-associated signals, and interact with the BBB through physiological trafficking pathways. Their ability to migrate toward pathological tissue can provide a targeting function that is difficult to reproduce with a conventional nanoparticle. The major disadvantage is that the biological complexity of a living cell also creates greater challenges for manufacturing, storage, safety, and quality control. [1,9,6]

2.1 Stem-cell carriers

2.1.1 Mesenchymal stem cells (MSCs)

Mesenchymal stem cells (MSCs) are among the most studied cellular carriers for CNS delivery. They can be expanded outside the body, generally show relatively low immunogenicity, and display migration toward injured and tumour-bearing tissues. Chemokine signalling, including the SDF-1α/CXCR4 axis, contributes to this tropism. MSCs can also internalise drug-loaded nanoparticles, allowing therapeutic and imaging functions to be combined in a single carrier. Preclinical studies have reported greater tumour accumulation when nanoparticles are transported by MSCs than when comparable nanoparticles are administered without the cellular carrier. [1,15,16,9]

2.1.2 Neural stem cells (NSCs)

Neural stem cells (NSCs) also show migration toward intracranial tumours and have the added advantage of being naturally associated with the CNS. One important strategy is to engineer NSCs to express an enzyme capable of converting a systemically administered inactive prodrug into an active cytotoxic compound at the tumour site. This approach can concentrate drug activation within the lesion and reduce exposure of surrounding healthy tissue. NSC-based strategies have therefore attracted considerable interest for targeted treatment of brain tumours. [9,17]

2.1.3 Adipose-derived stem cells (ADSCs)

Adipose-derived stem cells (ADSCs) are another potential source of cellular carriers. Adipose tissue is relatively accessible, and cells obtained from it can be expanded and used for drug or gene delivery. Like other MSC populations, ADSCs can respond to chemokine signals associated with tumours and tissue injury and can be combined with nanoparticle-based cargo. Their accessibility also makes them relevant to approaches in which autologous cells are considered. [15,16]

2.2 Immune-cell carriers

Leukocytes provide a particularly interesting delivery platform because their normal function already involves movement from the circulation into inflamed or damaged tissues. During inflammation, endothelial adhesion molecules and chemokine signals promote leukocyte recruitment and can increase local barrier permeability. A therapeutic cargo associated with these cells may therefore benefit from a naturally occurring route into pathological regions of the CNS. [6,9]

2.2.1 Neutrophils

Neutrophils are abundant circulating leukocytes and are rapidly recruited to sites of acute inflammation. Their ability to cross activated endothelium has been used to transport nanoparticle or liposomal drugs to brain lesions. In glioma models, neutrophils carrying chemotherapy have been investigated for targeting the inflammatory environment that remains after tumour resection. This strategy is particularly interesting because postoperative inflammation can act as the signal that draws the carrier toward residual tumour tissue. [7]

2.2.2 Monocytes and macrophages

Monocytes and macrophages can migrate along chemokine gradients associated with tumours and tissue injury and can carry therapeutic cargo without necessarily losing their transport function. Their role may extend beyond simple delivery. Depending on their phenotype and the therapeutic material used, macrophages can also influence the tumour microenvironment and inflammatory signalling. Thus, the carrier itself may contribute to treatment while simultaneously transporting a drug or nanoparticle. [6]

2.2.3 T cells

T lymphocytes can enter inflamed CNS regions and can be modified to carry genes or particulate therapeutic materials. Techniques such as electroporation can be used to introduce cargo, while the natural antigen-recognition properties of T cells provide a potential route for disease-specific targeting. However, T-cell-based delivery to the brain remains less developed than MSC-, NSC-, neutrophil-, or macrophage-based approaches, and additional work is required to establish its safety and reproducibility. [6]

2.3 Mechanisms of barrier transit by cellular carriers

Cellular carriers, particularly leukocytes, can use the multistep adhesion and migration pathway that normally moves immune cells from blood into inflamed tissue. Selectins first support transient attachment and rolling along activated endothelium. Chemokines then activate integrins, allowing firm binding to endothelial ICAM and VCAM molecules. The cell subsequently migrates along the endothelial surface and crosses the vessel wall by diapedesis. Because these signals increase in diseased tissue, the process can provide a degree of pathological targeting. Stem cells use overlapping adhesion and chemokine systems and can also take advantage of changes in BBB permeability associated with tumours or injury. [6,9]

The principal living-cell carriers, their homing signals, routes of BBB transit, and representative CNS applications are summarised in Table 1.

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Table 1: Living-cell carriers: homing signals, routes of BBB transit, and representative CNS applications. [1,15,16,9,6,7]

Carrier cell	Principal homing signal	Route of BBB transit	Representative CNS application
Mesenchymal stem cells	SDF-1α/CXCR4; tropism for injury and tumour	Paracellular and transcellular	Nanoparticle delivery to glioma; imaging [15,16]
Neural stem cells	Tumour-secreted chemokines	Native migration within the CNS	Enzyme–prodrug therapy in glioma [17,9]
Adipose-derived stem cells	SDF-1α/CXCR4	Paracellular and transcellular	Transport of genes and nanoparticles [15,16]
Neutrophils	Inflammatory chemokines (e.g. the CXCL family)	Adhesion cascade with diapedesis	Post-surgical glioma; liposomal drug carriage [7]
Monocytes/macrophages	CCL2/CCR2 and related axes	Adhesion cascade with diapedesis	Chemotherapy delivery with TME reprogramming [6]
T cells	Antigen recognition plus inflammatory cues	Adhesion cascade with diapedesis	Gene delivery; targeted therapy [6]

3 Cell-Derived Vesicles as Therapeutic Carriers

The use of cell-derived vesicles follows naturally from the cellular-carrier concept. If the useful properties of a cell could be retained in a smaller, non-viable structure, some of the practical difficulties associated with living cells might be reduced. [1,3]

Cell-derived vesicles are membrane-enclosed particles released by cells and can retain proteins, lipids, and nucleic acids associated with their source cells. They can therefore preserve aspects of parental-cell biocompatibility and targeting while avoiding the risks associated with maintaining a viable cell in the patient. Their small size and non-replicating nature can also simplify storage and formulation. These characteristics make extracellular vesicles attractive candidates for brain delivery, although their biological heterogeneity and the difficulty of achieving consistent large-scale production remain important limitations. [1,8,3]

3.1 EV biology and nomenclature

Extracellular vesicles (EVs) comprise several populations of membrane-bound particles with different origins and sizes. Exosomes are generally described as small vesicles formed through the endosomal pathway and released when multivesicular bodies fuse with the plasma membrane. Microvesicles arise by outward budding of the plasma membrane, while apoptotic bodies are produced during programmed cell death. EVs carry proteins, lipids, and nucleic acids from their cells of origin and naturally participate in cell-to-cell communication. Because isolation procedures may produce overlapping EV populations, current work places increasing emphasis on operational definitions and detailed characterisation rather than relying only on size or presumed biogenesis. [8,3,4]

3.2 Exosomes and intrinsic tropism for the CNS

Exosomes have received particular attention for brain delivery because of their small size, flexible membrane, and surface molecules inherited from the parent cell. Their targeting behaviour can be retained from the source cell or modified by engineering the vesicle surface. In an influential study, exosomes were modified with a rabies virus glycoprotein (RVG)-derived targeting peptide using the exosomal membrane protein Lamp2b. After systemic administration, the engineered vesicles delivered siRNA to the mouse brain and produced sequence-specific gene silencing. This work provided important proof that exosomes could be adapted for non-invasive delivery of nucleic acids to the CNS and helped establish the broader strategy of targeted exosomal transport. [14,8,3,4]

3.3 Vesicles by parent-cell source

3.3.1 Stem-cell-derived EVs

EVs produced by MSCs and NSCs can retain some of the biological activities associated with their parent cells while avoiding the use of a viable cell. In preclinical studies, MSC-derived vesicles have shown anti-inflammatory and neuroprotective effects and have been investigated for reducing amyloid-related pathology in Alzheimer's disease models. Their surfaces can also be modified with targeting ligands such as RVG or cRGD to improve interaction with brain or tumour-associated targets. Because these vesicles may act both as carriers and as bioactive products, they are of particular interest for CNS therapy. [18,19,17]

3.3.2 Immune-cell-derived EVs

Vesicles released by dendritic cells, macrophages, and other immune-cell populations can transport small molecules, proteins, and nucleic acids. Experimental studies have explored dendritic-cell vesicles for delivery of agents such as curcumin and siRNA, while macrophage-derived vesicles carrying neurotrophic factors have been investigated in Parkinson's disease models. Their potential advantage is that some of the inflammatory or tissue-homing characteristics of the parent immune cell can be retained after the cell itself is removed. [18,19,6]

3.3.3 Tumour-cell-derived EVs

Tumour-derived EVs can show strong affinity for tumour tissue, which makes them potentially useful for glioma targeting. The same origin, however, creates a major safety concern because these vesicles may contain oncogenic or

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immunosuppressive components. Any therapeutic strategy using tumour-derived vesicles would therefore require careful control or removal of undesirable native cargo. This additional safety requirement currently makes other EV sources more attractive for clinical development. [8,3]

3.3.4 Plant-derived vesicles

Plant-derived nanovesicles are being investigated as alternative biological carriers because they can be produced from relatively accessible sources and may offer advantages in cost, stability, and scalability. Studies using vesicles from plants such as grapefruit have explored their ability to transport therapeutic cargo and reach tissues beyond the gastrointestinal tract. Their use could reduce some concerns associated with mammalian cell culture, although source variability, purification, composition, and batch-to-batch consistency must still be addressed. [1,4,20]

3.3.5 Milk-derived vesicles

Milk-derived EVs are another potentially scalable source of biological vesicles. Their relative abundance and ability to remain stable during gastrointestinal passage have encouraged interest in oral delivery. If milk-derived vesicles can be loaded reproducibly and shown to transport CNS-directed cargo safely, they could offer a practical option for repeated treatment. As with other biological vesicles, however, controlled sourcing, purification, composition, and quality testing are essential before clinical translation.[20]

The major cell-derived vesicle sources and their advantages and limitations are compared in Table 2.

Table 2: Comparison of cell-derived vesicle sources for delivery to the brain. [1,18,20,8,3]

Vesicle source	Principal advantages	Principal limitations and cautions	Distinguishing feature
MSC / NSC EVs	Inherited homing; intrinsic therapeutic activity; low immunogenicity	Standardisation of yield and potency	Functions as carrier and drug simultaneously [18,19,17]
Immune-cell EVs	Inflammation-directed homing; versatile cargo	Donor-to-donor variability	Dendritic-cell and macrophage payloads [18,19,6]
Tumour-cell EVs	Pronounced tumour tropism	Oncogenic and immunosuppressive cargo	Requires removal of native cargo [8,3]
Plant-derived	Low cost; scalable; stable; intrinsically bioactive	Variability of botanical source	Grapefruit vesicles achieve barrier transit [1,4,20]
Milk-derived	Abundant; low cost; survives gastrointestinal transit	Sourcing and purity controls	Possible oral administration [20]

4 Drug Loading, Surface Engineering, and Payload Design

The therapeutic value of a carrier depends not only on its ability to reach the brain but also on how reliably it can hold and release its payload. Loading methods influence the amount and integrity of cargo, the viability of living cells, the stability of vesicles, and the reproducibility of the final product. These factors are closely linked to manufacturing and regulatory requirements because the loading process can change the biological properties of the carrier. [21,4,3]

4.1 Loading living-cell carriers

- Phagocytosis or endocytosis can allow cells to take up drug-loaded nanoparticles directly. When appropriately optimised, this approach can preserve cell viability and use the cell's natural uptake machinery. Particle size, surface chemistry, and intracellular stability must nevertheless be controlled to prevent loss of carrier function. [15,16]
- Electroporation creates temporary membrane pores that allow macromolecules, including nucleic acids, to enter cells. It is useful when direct intracellular delivery is required, but excessive electrical exposure can reduce cell viability or alter cell behaviour. Optimisation is therefore necessary to balance loading efficiency with preservation of the carrier's biological functions. [21,4,3]
- Surface coupling attaches a therapeutic molecule or nanoparticle to the outside of the cell through a linker, such as a peptide or antibody-based interaction. This method keeps the payload accessible without requiring intracellular uptake, but the attachment must remain stable during circulation and should not interfere with the cell's ability to migrate or interact with the BBB. [5,10,11]
- Electrostatic adsorption uses charge-based interactions to associate nanocarriers with the cell membrane. The method is comparatively straightforward, but the strength and stability of the interaction can vary in biological fluids. Loss of the payload during circulation therefore needs to be evaluated before this strategy can be considered reliable. [4,21]

Across these approaches, the main challenge is to achieve sufficient payload loading without damaging the carrier. For living cells, premature drug release or excessive intracellular accumulation may reduce viability or impair migration. A useful formulation must therefore maintain the functions that make the cell an effective delivery vehicle in the first place. [1,15,16]

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4.2 Loading cell-derived vesicles

Endogenous loading takes place before vesicle isolation. The parent cell can be transfected or otherwise engineered to express a therapeutic protein or RNA, after which the desired material is incorporated into the vesicles released by the cell. This approach can provide efficient biological packaging, although it is mainly suited to cargoes that the parent cell can produce and load into EVs. [21,4,3]

Exogenous loading is performed after vesicles have been isolated. Depending on the cargo, methods include passive incubation, sonication, electroporation, freeze–thaw treatment, extrusion, and chemical conjugation. These techniques expand the range of possible payloads, including small molecules and preformed nucleic acids, but they can also cause membrane damage, aggregation, or changes in vesicle surface properties. Process conditions therefore need careful optimisation and characterisation. [21,4,3]

4.3 Surface engineering for targeting

Surface engineering can add a second layer of targeting to the natural behaviour of a cell or vesicle. RVG-derived ligands have been used to promote interaction with neuronal receptors, while cRGD-based approaches can improve recognition of integrin-rich tumour-associated vasculature. Other ligands can exploit receptor-mediated transport pathways at the BBB. Cell-membrane coating provides a related biomimetic strategy in which a synthetic nanoparticle is wrapped with membrane obtained from a selected cell type, combining a controllable nanoparticle core with biological surface functions. [14,21,22,5,10]

The main payload-loading methods and their associated risks are summarised in Table 3.

Table 3: Payload-loading methods: applicability, suitable cargo, and principal risks. [21,4,3]

Method	Applicable to	Best-suited payloads	Principal risk
Co-incubation	Vesicles	Lipophilic small molecules	Low and variable loading efficiency [4,3,21]
Electroporation	Cells and vesicles	Nucleic acids	Damage to membrane or vesicle; aggregation [21,4,3]
Sonication	Vesicles	Small molecules and proteins	Structural disruption [21,4]
Freeze–thaw	Vesicles	Proteins and small molecules	Moderate loading; aggregation [21,4]
Parent-cell transfection	Vesicles	Proteins and RNA	Restricted to expressible cargo [21,4]
Surface conjugation	Cells and vesicles	Targeting ligands and particles	Altered surface properties; immunogenicity [5,10,11]

5. Therapeutic Applications

Preclinical evidence is most developed in three broad areas: brain tumours, neurodegenerative disorders, and cerebrovascular disease. These conditions are particularly suitable for cellular and vesicular carriers because tumours, inflammation, and tissue injury generate biological signals that can recruit or retain specific carrier populations. [1,18,19,15,6,7]

5.1 Primary brain tumours (glioblastoma)

Glioblastoma is a demanding target for drug delivery because of its aggressive growth, diffuse infiltration into surrounding tissue, heterogeneous microenvironment, and frequent recurrence after surgery. In addition, portions of the BBB may remain functional around the tumour, limiting drug penetration. [1,9,7]

Cellular and vesicular carriers have been investigated against several of these barriers at the same time. MSCs carrying drug-loaded nanoparticles have shown increased tumour accumulation compared with free nanoparticles in preclinical models. Neutrophils can be recruited to the inflammatory environment that follows tumour resection and have been used to transport chemotherapy toward residual tumour cells. Macrophage-derived vesicles have been explored for delivery of gene-silencing cargo, while engineered NSCs can localise prodrug-activating enzymes to tumour tissue. Although the individual platforms differ, their common feature is the use of biological trafficking signals to improve delivery to the tumour. [15,16,7,3]

5.2 Neurodegenerative disease

In neurodegenerative disease, cell-derived vesicles are being explored both as delivery vehicles and as sources of therapeutic biological activity. MSC-derived EVs have shown reductions in amyloid-related pathology and neuroinflammatory responses in experimental Alzheimer's disease. Other studies have investigated dendritic-cell or macrophage-derived vesicles for delivery of agents relevant to Parkinson's disease. RVG-targeted exosomes carrying siRNA have also been used to suppress disease-associated genes after systemic administration. A major attraction of these systems is the possibility of repeated administration without the invasive procedures required by direct intracranial delivery. [18,19,4]

5.3 Cerebrovascular disease (ischaemic stroke) [23,4]

Ischaemic stroke produces a strong inflammatory response that can attract cellular carriers to the injured region. Experimental studies have investigated neutrophils for targeted delivery and platelet- or cell-membrane-based systems for preferential accumulation at damaged vascular sites. Brain-targeted exosomes carrying therapeutic siRNA, including approaches directed against HMGB1, have also shown beneficial effects in experimental stroke models. These findings suggest that inflammation and vascular

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injury can provide useful biological signals for directing delivery, although translation to human treatment will require careful assessment of timing, safety, and therapeutic window. [23,7,5]

Representative therapeutic applications of cell- and vesicle-based brain-delivery systems are summarised in Table 4.

6 Comparative Synthesis: Cells, Vesicles, and Synthetic Carriers

There is no universally optimal carrier. The most appropriate platform depends on the disease-associated signals available for targeting, the type and amount of therapeutic cargo, the required dosing schedule, and the practical demands of manufacturing and regulation. [1,21,3,5,10,15,6]

Living cells generally provide strong active homing and may contribute therapeutic effects of their own, but they are also the most biologically complex option and are difficult to manufacture, store, and characterise consistently. Cell-derived vesicles retain several advantages of their parent cells while being non-viable and potentially easier to formulate and standardise; however, their cargo capacity and active migration may be more limited. Synthetic and membrane-camouflaged nanoparticles offer greater control over composition and scale-up, but their biological recognition and targeting properties must be deliberately engineered rather than inherited from a living source. [1,21,3,5,10,15]

The principal attributes of living cells, cell-derived vesicles, and synthetic/camouflaged carriers are compared in Table 5.

Table 4: Representative therapeutic applications of cell- and vesicle-based delivery systems for the brain. [1,14,23,18,19,4,15,7]

Indication	Carrier / payload example	Reported outcome	Signal exploited
Glioblastoma	MSCs + drug nanoparticles	Increased intratumoural accumulation	Tumour tropism [15,16]
Glioblastoma	Neutrophils + liposomal chemotherapy	Delayed post-surgical recurrence	Surgery-associated inflammation [7]
Alzheimer's disease	MSC-derived exosomes	Reduced amyloid-β; attenuated neuroinflammation	Intrinsic bioactivity [18,19]
Parkinson's disease	Macrophage exosomes + GDNF	Rescue of dopaminergic neurons	Inflammation-directed homing [18,19]
Parkinson's/general	RVG-exosomes + siRNA	Gene knockdown across the BBB	Neuronal RVG target [14,4]
Ischaemic stroke	Brain-targeting exosomes + siRNA	Neuroprotection; extended time window	Ischaemia-associated inflammation [23,4]

Table 5: Comparative attributes of the three principal carrier classes. [1,21,3,5,10,15]

Attribute	Living cells	Cell-derived vesicles	Synthetic / camouflaged
Active homing	Strongest (active chemotaxis)	Inherited, largely passive	Engineered ligands only [1,15,16,9,6]
Intrinsic therapeutic effect	Frequently present	Often present	Absent [1,21,3,5,10,15]
Payload capacity	High	Low to moderate	High and tunable [1,21,3,5,10]
Storage and stability	Challenging (viable cells)	More favourable	Most favourable [1,21,3,5,10]
Manufacturing control	Low	Moderate	High [1,21,3,5,10]
Immunogenicity risk	Low (autologous)	Low	Variable [1,5,10]
Biosafety burden	Highest	Intermediate	Lower on biological grounds [1,5,10,6]
Regulatory precedent	Cell-therapy frameworks	Emerging and unsettled	Established for nanoparticle products[1,21,5,10]

CONCLUSION

The evidence reviewed here supports the use of cells and cell-derived vesicles as promising biological carriers for brain delivery. Instead of attempting to reproduce every targeting and trafficking function synthetically, these systems make use of properties that cells already possess, including biocompatibility, immune interactions, and migration toward diseased tissue. Studies in glioma, neurodegenerative disease, and stroke show that such carriers can improve brain exposure to different classes of therapeutic cargo in experimental models. At the same time, most of the evidence remains preclinical, and successful BBB transit does not by itself establish clinical effectiveness.

The major barriers to translation are now increasingly practical as well as biological. Cell and vesicle products must be manufactured reproducibly at useful scale, characterised with reliable identity and potency assays, and evaluated for biodistribution, immunogenicity, toxicity, and long-term safety. For products that combine biological materials with engineered nanoparticles or therapeutic cargo, the regulatory pathway may also be complex. Addressing these issues will be essential if promising laboratory findings are to become clinically useful CNS therapies.

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At present, cell-derived nanocarriers have not become established approved therapies for neurological disease. Future progress will depend on better standardisation, robust quality-control procedures, well-defined manufacturing processes, and stronger safety and efficacy evidence. Continued collaboration between researchers, manufacturers, clinicians, and regulatory agencies will be important for determining which cellular camouflage strategies can move successfully from experimental models to patients.

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