



OPEN ACCESS

This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Institute of Molecular Biology and Biotechnology, Bahauddin Zakariya University, Multan, Pakistan

Correspondence to:

Muhammad Imran Qadir,
mimranqadir@hotmail.com

Additional material is published online only. To view please visit the journal online.

Cite this as: Qadir MI and Altaf A. Nanoparticles Crossing the Blood–Brain Barrier: A Hope for Central Nervous System Disorders. Premier Journal of Neuroscience 2025;4:100011

DOI: <https://doi.org/10.70389/PJN.100011>

Peer Review

Received: 3 June 2025

Last revised: 24 July 2025

Accepted: 24 July 2025

Version accepted: 2

Published: 22 August 2025

Ethical approval: N/a

Consent: N/a

Funding: No industry funding

Conflicts of interest: N/a

Author contribution:

Muhammad Imran Qadir and Ayesha Altaf – Conceptualization, Writing – original draft, review and editing

Guarantor: Muhammad Imran Qadir

Provenance and peer-review:

Unsolicited and externally peer-reviewed

Data availability statement: N/a

Nanoparticles Crossing the Blood–Brain Barrier: A Hope for Central Nervous System Disorders

Muhammad Imran Qadir and Ayesha Altaf

ABSTRACT

It has been estimated that about 1.5 million deaths occur due to central nervous system disorders. The problem is overcome by modern pharmaceutical technology by manufacturing nanoparticles. These are small particles that have an advantage over other drugs because they have the ability to pass through the blood–brain barrier, which is a structure in the brain that maintains the transport of substances and drugs between blood and brain. Nanoparticles are of different types. They may be polymeric, liposomal, or solid lipid nanoparticles. The main aim of nanoparticles is the target-specific delivery of drugs.

Keywords: Nanoparticles, Blood-brain barrier, CNS disorders, Drug delivery, Liposomal nanoparticles

Introduction

The development of nanoparticles for the central nervous system (CNS) is an effective field of study in the recent century. It is focusing on the delivery of large pharmaceutical molecules such as antisense drugs, recombinant proteins and antibiotics, due to some problems in the functional platform of the CNS that is why the large molecules cannot be targeted properly and its effect cannot occur efficiently with other modern technologies the problem has been overcome by the development of the nanoparticles.¹

Nanoparticles, which are small particles with a size ranging from 1 to 100 nm and may be organic or inorganic in nature, are similar to DNA plasmids and antibodies. In past decades, significant work has been done in the field of nanotechnology, and nanoparticles are being used to deliver drugs across the blood–brain barrier (BBB) and are site-specific.²

Proper functioning of nanoparticles depends on the size of the nanoparticles and their ability to cross the BBB.² The BBB is a regulated interface between the CNS and peripheral circulations, the BBB is the cerebral microvascular endothelium which together with the pericytes, neurons, extracellular matrix and the astrocytes forms “neurovascular unit,” which is essential for the proper functioning of a CNS there is a tight junction between the endothelial cells of the BBB which restrict the diffusion of substances between blood and brain, the impairment of the BBB and tight junctions can effect CNS.³

It has been estimated that about 1.5 million deaths occur due to malfunctioning of CNS diseases like encephalitis and meningitis, and neurodegenerative diseases such as glioblastoma, Alzheimer’s disease, and Parkinson’s disease. There is a demand for effective treatment, so nanoparticles are being used as site-specific target drugs.⁴

In CNS, nanoparticles-targeted drug therapy provides better penetration of the therapeutic drug or agent, and it also reduces the chance of biodegradability. It is also possible to deliver drugs across the BBB, with controlled release of the drug. In aqueous solution, many therapeutic drugs or agents are poorly soluble or insoluble, oral or parental delivery of the drug is of a great challenge. However, these therapeutic compounds became beneficial through nanoparticle technology. The targeted drug delivery is basically the delivery of drugs or a therapeutic agent to a specific site in the body. In this review, we will study the nanoparticle-targeted drug delivery system and its work in the BBB.

Anatomy of BBB

The BBB, which separates the circulating blood from the extracellular fluid, is a selective membrane in the CNS. The BBB comprises endothelial cells, an adherens junction, and a tight junction, which form the first line of defense in endothelial barrier disruption, which may cause cell death.⁵

The main factor that promoted the development of the BBB was the protection of neurons in the brain and the spinal cord. The flow of plasma components in both directions, which is the delivery of nutrients to the brain and the removal of metabolic products, is controlled by the specific transport system. The brain is protected by the P-glycoprotein, which provides protection against lipophilic compounds entering through the gastrointestinal tract (Figure 1).

For the proper functioning of the BBB, the operative features must be taken into account, which include physical, immunologic, transportation, and metabolic features. The physical barrier can be defined as the presence of adherens junctions and tight junctions between adjacent endothelial cells.⁶ The metabolic junction is the combination of intracellular and extracellular enzymes.⁷ The transport barrier includes para-transcellular routes, and the transcellular route plays an important role in the penetration of substances through the BBB.⁸

Microglia, mast cells, and perivascular macrophages form the immunological barrier and provide limited penetration of immune cells such as lymphocytes.⁹

The function of the BBB is to protect the brain against the bacterial infections, and it allows the diffusion of water, gases, and lipid molecules. The main function of the BBB is to protect the brain from the harmful toxins that are present in the brain. Active metabolism and carrier-mediated transportation occur due to the BBB.

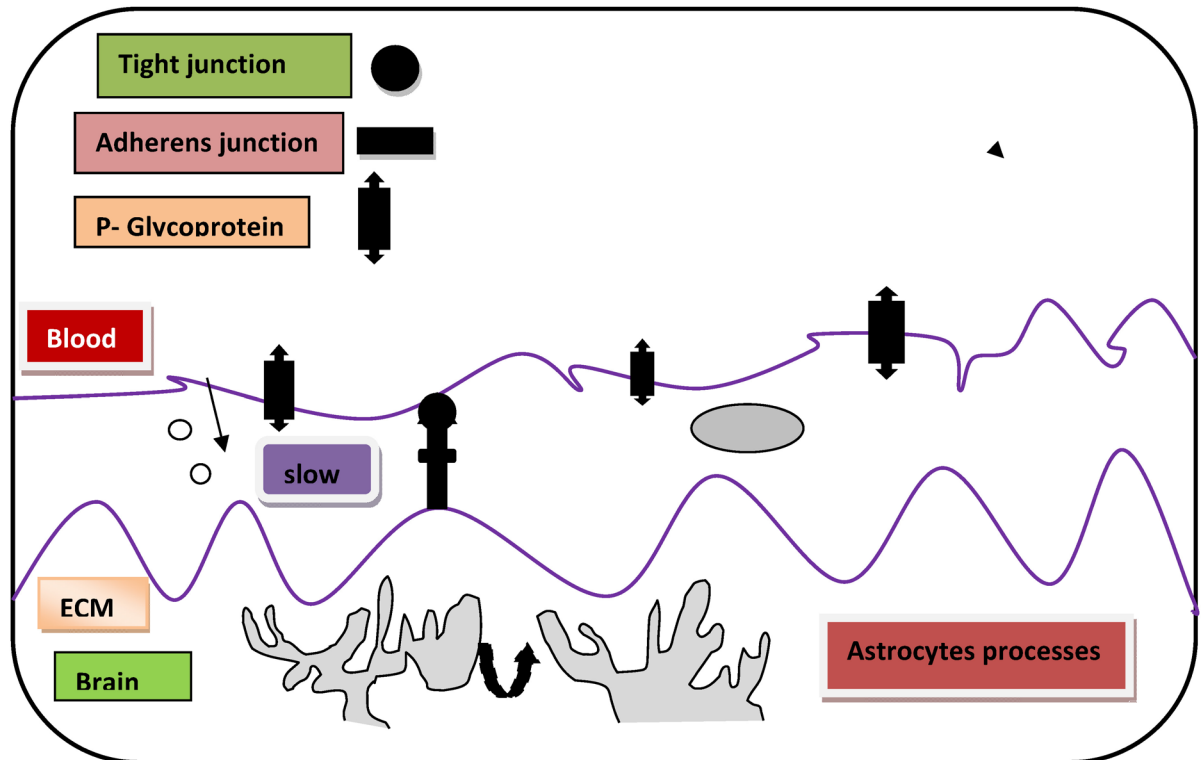


Fig 1 | Anatomical structure of BBB

Nanoparticles for Drug Delivery

Nanoparticles are small organic and inorganic molecules similar to DNA plasmid and antibody. The nanoparticles are influencing fields like nanobiotechnology, biosensors, drug delivery, and microarrays to tissue engineering.² Different types of nanoparticles have been designed for the specific delivery of nanoparticles, which includes organic, polymeric, liposomes, and metallic nanoparticles.¹⁰

Targeted site-specific drug delivery is an important function of nanomedicines. The ability to eliminate tumorous outgrowth without any damage is possible through nanoparticles, and the delivery systems are based on functionalized nanoparticles, with a nanometer range in size, and can enhance the delivery of the drug by biodistribution.¹¹ Modification of the nanoparticles for their delivery in the BBB is a great success in this field, for example, doxorubicin does not cross the BBB, but its integration with the polysorbate can enhance its delivery across the brain.¹² Nanoparticles have the ability to efficiently penetrate deep into the cells and tissues.¹³ Nanoparticles have increased the scope of the pharmacokinetics for insoluble drugs.

Nanoparticles Targeted to the Brain

Neurological disorders are an important cause of death, and it has been estimated that 12% deaths occur due to neurological disorders globally. Nanoparticles, if they cross the BBB, are easily targeted to the brain. They are lipid soluble and mostly active in

passive diffusion. Nanoparticles are objects ranging in size from 1 to 100 nm, and they work as a whole unit when it comes to their transport and properties. Among all therapies, nanotherapy is an important therapy to reduce the mortality rate due to CNS disorders.

The nanoparticles are targeted to the brain in the following steps:

The nanoparticle drug concentration increases on the surface of the BBB cells, and a concentration gradient is established between the blood and the brain. This gradient will increase the passive diffusion of the drug. The next step that nanoparticles have to pass through is the capillary cells of the brain and their passage through the BBB.^{4,6}

Types of Nanoparticles Targeted to the Brain

Generally, nanoparticles are composed of inorganic and polymeric materials, but different types of nanoparticles that are being targeted to the BBB are the following:

Lipid-Based Nanoparticles

Liposomes

Liposomes are made from cholesterol and phospholipids and are small artificial vesicles of spherical shape. Because of their size and characteristics (hydrophobic and hydrophilic), liposomes are considered the first generation of the nanoparticulate drug delivery system, and they constitute one or more vesicular bilayers composed of lipids. The liposomes are widely used to

treat brain tumors for the delivery of opioid peptides.¹⁴ In the treatment of cerebrovascular system disorders, the substances prepared in liposomal form are very beneficial.

The nerve growth factor (NGF) is a peptide that was considered beneficial for the treatment of damaged neurons, but it cannot pass through the BBB. The same NGF becomes effective in liposome form.¹⁵

The hydrophobic and hydrophilic compounds can be trapped by the liposome, which will avoid the decomposition of the entrapped combinations and release them at a specific targeted place.¹⁶

Cationic Liposomes

The positively charged particles, named as cationic liposomes, have been developed and used as a vehicle to transfer genetic material into the cells, avoiding the lysosomal digestion. An example of the cationic liposome is bolaamphiphiles in which hydrophobic group is surrounded by the hydrophilic group and strengthen the nanovesicles containing the drug.¹⁷

Solid Lipid Nanoparticles (SLNs)

SLNs are stable lipid-based nanoparticles that have a solid core made of hydrophobic lipid in which a drug can be dissolved or dispersed. These SLNs are made up of waxes, fatty acids, and triglycerides; they are small in size and can pass through the BBB. The solid core of SLN is usually hydrophobic and is covered by a phospholipid layer. The attachment of the ligand facilitates the penetration across the BBB.¹⁸ The permeability of the SLNs can be increased by polyethylene glycol. The advantage of SLNs is the controlled release of the drug.¹⁹

Polymer-Based Nanoparticles

Polymeric Nanoparticles

Polymeric nanoparticles represent a solid colloidal system composed of biocompatible copolymers that have low water solubility; the nanoparticles are prepared from synthetic polymers. As the name suggests, the nanoparticles are made up of polymers.

The drug is dispersed in nanospheres, which have dense polymeric matrices; the polymeric shell is surrounded by a nanocapsule. The most important technique involved in monomer polymerization is the addition of monomers into the dispersed phase of an emulsion or dissolved in a nonsolvent polymer.¹⁹

There are two approaches for the preparation of nanoparticles by synthetic polymers; the first theory involves emulsification of a water-immiscible organic solution of the polymer. The second approach follows the precipitation of a polymer after the addition of a nonsolvent to the polymer.

The mechanism of nanoparticle uptake by the brain involves the following steps:

1. The enhanced retention in the brain blood capillaries with adsorption to the capillary walls increasing the concentration across the BBB

2. The junction opens due to the presence of the nanoparticles
3. Transcytosis of nanoparticles through the endothelium

The advantage of polymeric nano particles is the stability of the pharmaceutical agent and delivery of higher concentration to the targeted site.

MicroRNA-Loaded Exosomes

MicroRNA (miRNA)-loaded exosomes have emerged as a promising nanoparticle-based delivery system capable of crossing the BBB with high efficiency and specificity. Exosomes are naturally occurring, nanosized extracellular vesicles that facilitate intercellular communication and possess inherent biocompatibility and low immunogenicity. When engineered to carry therapeutic miRNAs, they can modulate gene expression in targeted brain cells, offering potential treatments for neurodegenerative diseases, brain tumors, and other CNS disorders. By surface-modifying exosomes with targeting ligands or peptides, such as rabies virus glycoprotein, researchers have enhanced their ability to cross the BBB via receptor-mediated transcytosis. This delivery approach not only protects the miRNA cargo from degradation in circulation but also ensures controlled, targeted release within the brain microenvironment. The convergence of nanotechnology and exosome engineering thus holds significant promise for advancing noninvasive, gene-regulatory therapies for neurological conditions.^{20,21}

Transferrin-Modified Polymeric Micelles

Transferrin-modified polymeric micelles represent a cutting-edge approach in nanoparticle-mediated drug delivery across the BBB. These nanoscale carriers are engineered by decorating the surface of polymeric micelles with transferrin, a glycoprotein that binds to transferrin receptors abundantly expressed on the endothelial cells of the BBB. This modification enables receptor-mediated endocytosis, facilitating efficient and targeted transport of therapeutic agents into the brain. Polymeric micelles, typically composed of amphiphilic block copolymers, offer advantages such as high drug-loading capacity, stability in circulation, and controlled release profiles. When functionalized with transferrin, these micelles exhibit enhanced BBB permeability and cellular uptake, making them highly suitable for delivering chemotherapeutics, neuroprotective agents, or gene therapies to treat brain tumors, neurodegenerative diseases, and other CNS disorders. This strategy exemplifies the synergy between receptor-targeted delivery and nanotechnology to overcome the physiological barriers of the brain.^{22,23}

Advancements in the Current Era

Recent advancements in nanotechnology have significantly improved the ability of nanoparticles to cross the BBB, a major obstacle in treating CNS disorders. Researchers have developed surface-engineered nanoparticles—such as those coated with targeting ligands, peptides, or antibodies—that can interact

with specific receptors on the BBB, enabling receptor-mediated transcytosis. Additionally, stimuli-responsive nanoparticles that react to changes in pH, temperature, or enzymes offer controlled drug release once inside the brain. Innovations in lipid-based carriers, dendrimers, and polymeric nanoparticles have further enhanced biocompatibility and drug-loading capacity. These breakthroughs hold promising potential for more effective treatments of neurodegenerative diseases, brain tumors, and other neurological conditions by enabling the precise delivery of therapeutic agents directly to the brain.^{24–26}

CRISPR-Cas Delivery Across the BBB

Nanoparticle-based delivery systems have emerged as a powerful strategy for transporting clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein (CRISPR-Cas) components across the BBB, addressing one of the critical challenges in gene editing for neurological disorders. Traditional delivery methods, such as viral vectors, often face limitations in safety and BBB permeability, whereas nanoparticles—especially lipid-based, polymeric, and inorganic formulations—offer customizable, non-viral platforms with improved biocompatibility and reduced immunogenicity. By functionalizing nanoparticles with targeting ligands or peptides that exploit receptor-mediated transport mechanisms (e.g., transferrin or insulin receptors), researchers have achieved efficient translocation of CRISPR-Cas9 ribonucleoproteins or plasmids into brain tissue. Furthermore, stimuli-responsive and biodegradable nanoparticles enhance control over release kinetics and protect CRISPR components from enzymatic degradation. These innovations are paving the way for precise, minimally invasive genome editing therapies for conditions such as Huntington's disease, glioblastoma, and Alzheimer's disease.^{27,28}

Conclusion

In the above discussion, the importance of nanoparticles is discussed. Nanotechnology is used for the treatment of CNS disorders. Nanoparticles have the advantage for drug delivery, such as reduced side effects, increased drug half-life, and the possibility to enhance drug crossing across the BBB. Therefore, the aim of nanotechnology is to reduce the mortality rate due to CNS disorders.

References

- Debnath B, JashimUddin M, Maiti D. Nanoparticle (NP) as a targeting drug delivery system to blood-brain barrier (BBB): a review. *PharmaTutor*. 2015;3(8):30–7.
- Mirza AZ, Siddiqui FA. Nanomedicine and drug delivery: a mini review. *Int Nano Lett*. 2014;4(1):94–7. <https://doi.org/10.1007/s40089-014-0094-7>
- Hawkins BT, Davis TP. The blood-brain barrier/neurovascular unit in health and disease. *Pharmacol Rev*. 2005;57(2):173–85. <https://doi.org/10.1124/pr.57.2.4>
- Mohanraj V, Chen Y. Nanoparticles-a review. *Trop J Pharm Res*. 2006;5(1):561–73. <https://doi.org/10.4314/tjpr.v5i1.14634>
- Yang Y, Rosenberg GA. Blood–brain barrier breakdown in acute and chronic cerebrovascular disease. *Stroke*. 2011;42(11):3323–8. <https://doi.org/10.1161/STROKEAHA.110.608257>
- Hosoya K-I, Ohtsuki S, Terasaki T. Recent advances in the brain-to-blood efflux transport across the blood–brain barrier. *Int J Pharm*. 2002;248(1):15–29. [https://doi.org/10.1016/S0378-5173\(02\)00457-X](https://doi.org/10.1016/S0378-5173(02)00457-X)
- Abbott NJ, Rönnebeck L, Hansson E. Astrocyte–endothelial interactions at the blood–brain barrier. *Nat Rev Neurosci*. 2006;7:41–53. <https://doi.org/10.1038/nrn1824>
- Chen Y, Liu L. Modern methods for delivery of drugs across the blood–brain barrier. *Adv Drug Deliv Rev*. 2012;64(7):640–65. <https://doi.org/10.1016/j.addr.2011.11.010>
- Daneman R, Rescigno M. The gut immune barrier and the blood-brain barrier: are they so different? *Immunity*. 2009;31(5):722–35. <https://doi.org/10.1016/j.immuni.2009.09.012>
- Bala I, Hariharan S, Kumar MNVR. PLGA nanoparticles in drug delivery: the state of the art. *The State of the Art*. 2004;21(5):387–442. <https://doi.org/10.1615/CritRevTherDrugCarrierSyst.v21.i5.20>
- Yokoyama M, Okano T, Sakurai Y, Ekimoto H, Shibazaki C, Kataoka K. Toxicity and antitumor activity against solid tumors of micelle-forming polymeric anticancer drug and its extremely long circulation in blood. *J Contr Release*. 1991;51(12):3229–36.
- Kabanov AV, Lemieux P, Vinogradov S, Alakhov V. Pluronic® block copolymers: novel functional molecules for gene therapy. *Adv Drug Deliv Rev*. 2002;54(2):223–33. [https://doi.org/10.1016/S0169-409X\(02\)00018-2](https://doi.org/10.1016/S0169-409X(02)00018-2)
- Ishii T, Asai T, Oyama D, Agato Y, Yasuda N, Fukuta T, et al. Treatment of cerebral ischemia-reperfusion injury with PEGylated liposomes encapsulating FK506. *FASEB J*. 2013;27(4):1362–70. <https://doi.org/10.1096/fj.12-221325>
- Xie Y, Ye L, Zhang X, Cui W, Lou J, Nagai T, et al. Transport of nerve growth factor encapsulated into liposomes across the blood–brain barrier: in vitro and in vivo studies. *J Contr Release*. 2005;105(1–2):106–19. <https://doi.org/10.1016/j.jconrel.2005.03.005>
- Shehata T, Ogawara K-I, Higaki K, Kimura T. Prolongation of residence time of liposome by surface-modification with mixture of hydrophilic polymers. *Int J Pharm*. 2008;359(1):272–9. <https://doi.org/10.1016/j.ijpharm.2008.04.004>
- Hwang SR, Kim K. Nano-enabled delivery systems across the blood–brain barrier. *Arch Pharmacol Res*. 2014;37(1):24–30. <https://doi.org/10.1007/s12272-013-0272-6>
- Martins S, Tho I, Reimold I, Fricker G, Souto E, Ferreira D, et al. Brain delivery of camptothecin by means of solid lipid nanoparticles: formulation design, in vitro and in vivo studies. *Int J Pharm*. 2012;439(1–2):49–62. <https://doi.org/10.1016/j.ijpharm.2012.09.054>
- Kaur IP, Bhandari R, Bhandari S, Kakkar V. Potential of solid lipid nanoparticles in brain targeting. *J Contr Release*. 2008;127(2):97–109. <https://doi.org/10.1016/j.jconrel.2007.12.018>
- Soppimath KS, Aminabhavi TM, Kulkarni AR, Rudzinski WE. Biodegradable polymeric nanoparticles as drug delivery devices. *J Contr Release*. 2001;70(1–2):1–20. [https://doi.org/10.1016/S0168-3659\(00\)00339-4](https://doi.org/10.1016/S0168-3659(00)00339-4)
- Chen YF, Luh F, Ho YS, Yen Y. Exosomes: a review of biologic function, diagnostic and targeted therapy applications, and clinical trials. *J Biomed Sci*. 2024;31(1):67. <https://doi.org/10.1186/s12929-024-01055-0>
- Das N, Bhat S, Fugo P, Dhawan A. miRNA as neuro-oncologic therapeutics: a narrative review. *Mol Ther*. 2025;33(6):2740–52. <https://doi.org/10.1016/j.jymthe.2024.12.045>
- Kumar LA, Pattnaik G, Satapathy BS, Mohanty DL, Zafar A, Warsi MH, et al. Transferrin-modified gemcitabine encapsulated polymeric nanoparticles persuaded apoptosis in U87MG cells and improved drug availability in rat brain: an active targeting strategy for treatment of glioma. *J Oleo Sci*. 2025;74(3):261–74. <https://doi.org/10.5650/jos.ess24085>
- Kakinen A, Jiang Y, Davis TP, Teesalu T, Saarna M. Brain targeting nanomedicines: pitfalls and promise. *Int J Nanomed*. 2024;19:4857–75. <https://doi.org/10.2147/IJN.S454553>
- Dong N, Ali-Khiavi P, Ghavamikia N, Pakmehr S, Sotoudegan F, Hjadi A, et al. Nanomedicine in the treatment of Alzheimer's disease: bypassing the blood-brain barrier with cutting-edge nanotechnology. *Neurol Sci*. 2025;46(4):1489–507. <https://doi.org/10.1007/s10072-024-07871-4>
- Agaram Sundaram V, Saravanan B, Durairaj JR, Balamurugan BS, Chinnakannu Marimuthu MM, et al. Nanoparticles for overcoming blood-brain barrier challenges in neurodegenerative illness.

- Biomed Eng Commun. 2025;4(4):22. <https://doi.org/10.53388/BMEC2025022>
- 26 Alqudah A, Aljabali AA, Gammoh O, Tambuwala MM. Advancements in neurotherapeutics: nanoparticles overcoming the blood–brain barrier for precise CNS targeting. *J Nanopart Res.* 2024;26(6):123. <https://doi.org/10.1007/s11051-024-05983-8>
- 27 Tashima T. Non-invasive delivery of CRISPR/Cas9 ribonucleoproteins (Cas9 RNPs) into cells via nanoparticles for membrane transport. *Pharmaceutics.* 2025;17(2):201. <https://doi.org/10.3390/pharmaceutics17020201>
- 28 Rawal S, Khodakiya A, Prajapati BG. Nanotechnology-based delivery for CRISPR-Cas 9 cargo in Alzheimer's disease. In: *Alzheimer's disease and advanced drug delivery strategies.* Prajapati BG, Chellappan DK, Kendre PN (eds.). Cambridge. Academic Press; 2024. p. 139–52. <https://doi.org/10.1016/B978-0-443-13205-6.00012-1>