Archives of Medical Research

Archives of Medical Research 56 (2025) 103085

REVIEW ARTICLE

Theranostics Advances in the Treatment and Diagnosis of Neurological and Neurosurgical Diseases

Wireko Andrew Awuah,[a,*] Arjun Ahluwalia,[b,*] Joecelyn Kirani Tan,[c] Vivek Sanker,[d] Sakshi Roy,[b] Adam Ben-Jaafar,[e] Devansh Mitesh Shah,[f] Pearl Ohenewaa Tenkorang,[g] Nicholas Aderinto,[h] Toufik Abdul-Rahman,[a] Oday Atallah,[i] and Athanasios Alexiou[j,k,l,m]

[a] *Faculty of Medicine, Sumy State University, Sumy, Ukraine*
[b] *School of Medicine, Queen's University Belfast, Belfast, United Kingdom*
[c] *Faculty of Medicine, University of St Andrews, St. Andrews, Scotland, UK*
[d] *Department of Neurosurgery, Stanford University, CA, USA*
[e] *University College Dublin, School of Medicine, Belfield, Dublin 4, Ireland*
[f] *School of Medicine, Dentistry and Nursing, University of Glasgow, Glasgow, UK*
[g] *University of Ghana Medical School, Accra, Ghana*
[h] *Internal Medicine Department, LAUTECH Teaching Hospital, Ogbomoso, Nigeria*
[i] *Department of Neurosurgery, Hannover Medical School, Carl-Neuberg-Strasse 1, Hannover, Germany*
[j] *University Centre for Research and Development, Chandigarh University, Chandigarh-Ludhiana Highway, Mohali, Punjab, India*
[k] *Department of Research and Development, Funogen, Athens, Greece*
[l] *Department of Research and Development, AFNP Med, Wien, Austria*
[m] *Department of Science and Engineering, Novel Global Community Educational Foundation, Hebersham, Australia*

Received for publication December 10, 2023; accepted September 3, 2024 (ARCMED-D-23-00996).

Theranostics represents a significant advance in the fields of neurology and neurosurgery, offering innovative approaches that combine the diagnosis and treatment of various neurological disorders. This innovation serves as a cornerstone of personalized medicine, where therapeutic strategies are closely integrated with diagnostic tools to enable precise and targeted interventions. Primary research results emphasize the profound impact of theranostics in Neuro Oncol. In this context, it has provided valuable insights into the complexity of the tumor microenvironment and mechanisms of resistance. In addition, in the field of neurodegenerative diseases (NDs), theranostics has facilitated the identification of distinct disease subtypes and novel therapeutic targets. It has also unravelled the intricate pathophysiology underlying conditions such as cerebrovascular disease (CVD) and epilepsy, setting the stage for more refined treatment approaches. As theranostics continues to evolve through ongoing research and refinement, its goals include further advancing the field of precision medicine, developing practical biomarkers for clinical use, and opening doors to new therapeutic opportunities. Nevertheless, the integration of these approaches into clinical settings presents challenges, including ethical considerations, the need for advanced data interpretation, standardization of procedures, and ensuring cost-effectiveness. Despite these obstacles, the promise of theranostics to significantly improve patient outcomes in the fields of neurology and neurosurgery remains a source of optimism for the future of healthcare.

Key Words: Theranostics, Neuro Oncol, Neurodegenerative diseases, Cerebrovascular diseases, Epilepsy and seizure, Nuclear medicine, Neurology, Neurosurgery.

* These authors contributed equally to this work.

Address reprint requests to: Chandigarh-Ludhiana Highway, Mohali, Punjab 140413, India; E-mail: alexiou@funogen.com

https://doi.org/10.1016/j.arcmed.2024.103085

Introduction

Theranostics, a term originally introduced by Funkhouser in 1998, represents the integration of therapeutic and diagnostic functions, allowing for the simultaneous administration of treatment and monitoring of its effects (1). The origins of this concept can be traced back to the 1940s, when radioactive iodine played a dual role in the diagnosing and treatment of thyroid cancer, laying the foundation for the basic principles of theranostics (2).

The development of nanotechnology and advances in bioimaging have accelerated the emergence of nanoparticles (NPs) capable of penetrating the formidable blood-brain barrier (BBB). These engineered particles are designed to target specific cell types, deliver therapeutics with precision, and simultaneously facilitate real-time imaging to reveal the pathophysiological aspects of brain diseases (3,4). By integrating therapeutic and diagnostic modalities, neurotheranostics has the potential to identify individuals at an elevated risk of disease progression or poor prognosis at an earlier stage, thereby offering the opportunity for more effective interventions.

Currently, diagnostic imaging plays an essential role in the preparation for neurological interventions, serving as a crucial diagnostic and assessment step prior to any surgical procedure. However, the emerging field of neurotheranostics has the potential to transform this process by integrating diagnosis with therapeutic interventions. This innovative approach aims to increase the availability of neurosurgical procedures and improve patient outcomes. By combining diagnosis and treatment, it not only reduces the frequency of hospital visits but also streamlines the use of medical technologies, reducing the need for complex treatment protocols. The resulting benefits include improved patient compliance, increased accessibility, and cost-effectiveness of neurosurgical care (5).

In the field of neurological diseases, especially neurodegenerative diseases (NDs), the need for advanced diagnostic and therapeutic strategies is both urgent and critical. Timely and accurate diagnoses are essential to facilitate prompt interventions and potentially reduce the various motor, behavior, and cognitive impairments that reduce not only life expectancy but also quality of life. Moreover, improved therapeutic outcomes resulting from early diagnosis could alleviate the financial burden on the support networks of affected individuals (6). This innovative area of research sets the stage for innovative diagnostic and therapeutic approaches, but the translation of such research into effective and cost-effective theranostics applications remains a challenge (7).

The emergence of nanotheranostics represents a disruptive innovation that serves as a bridge between current diagnostic and therapeutic approaches, and the envisioned future characterized by improved therapeutic outcomes in the fields of neurology and neurosurgery (6). The purpose of this article is to explore the potential of neurotheranostics to reshape the landscape of neurological and neurosurgical care and to usher in a transition to integrated, patient-centred treatment methods.

Methodology

This narrative review presents a comprehensive framework for assessing theranostics in the fields of neurology and neurosurgery. Inclusion criteria for this review encompassed full-text articles in the English language, with no specific limitations on publication date. However, more emphasis was placed on recent studies in order to accurately assess the progress in the field. A thorough literature search was conducted using multiple databases, including PubMed, EMBASE, Google Scholar, the Cochrane Library, and Scopus. Key search terms like “theranostics,” “neurology,” and “neurosurgery” were consistently used, along with additional terms such as “neurodegenerative diseases,” “cerebrovascular disorders,” “epilepsy and seizures,” “brain tumors,” and “spinal cord tumors.”

To broaden the search strategy, additional sources were identified by manual screening of references in recent disease-specific reviews. A stringent set of exclusion criteria was applied resulting in the exclusion of stand-alone abstracts, case reports, posters, and unpublished or non-peer-reviewed studies. These criteria were established to ensure the inclusion of high-quality, reliable evidence.

With regard to the scope of the review, there was no predefined limit on the number of papers included. This approach was adopted to ensure a comprehensive understanding of the topic. The evaluation covers a wide range of research methodologies, including descriptive studies, animal model studies, cohort studies, and observational studies. It also includes studies conducted in both pre-clinical and clinical settings, providing a broad perspective on the use of scRNA-seq in neurosurgery and neurology research. A summary of the approach is provided in Table 1.

General Overview of Theranostics

History and Development of the Technology

As previously mentioned, the term “neurotheranostics” was coined a little more than 20 years ago, while the concept of theranostics dates back to the 1940s (1,2) (Figure 1). Different neurotheranostic modalities have their own distinct timelines of development. An illustrative example is neurotheranostics for Alzheimer’s disease (AD).

In 2008, NP-assisted magnetic resonance imaging (MRI) enabled the visualization of early stages of amyloid β self-assembly in AD. These stages were reversible, meaning that surface engineering of NPs for diagnostic applications had the potential to facilitate earlier disease detection and diagnosis (8). Subsequently, in 2012, poly

Table 1. A summary of the methodology

Methodology steps	Description
Literature search	Scopus, MEDLINE, EMBASE, and the Cochrane Library
Inclusion criteria	Full-text articles published in the English language without a specific time frame were selected. A diverse range of study designs, including observational studies, case-control investigations, cohort studies, cross-sectional analyses, and randomized controlled trials. Studies involving paediatric and adult populations.
Exclusion criteria	Stand-alone abstracts and unpublished studies.
Search terms	Precise terms such as "theranostics" and "neurology", 'neurosurgery' were utilized in all searches, accompanied by additional terms including "neurodegenerative disorders", "cerebrovascular disorders", "epilepsy and seizures", "neuro-oncological disorders", "brain tumors", and "spinal cord tumors".
Additional search	A manual search was systematically undertaken to identify references pertaining to recently published reviews.
Sample size requirement	No strict sample size requirement.

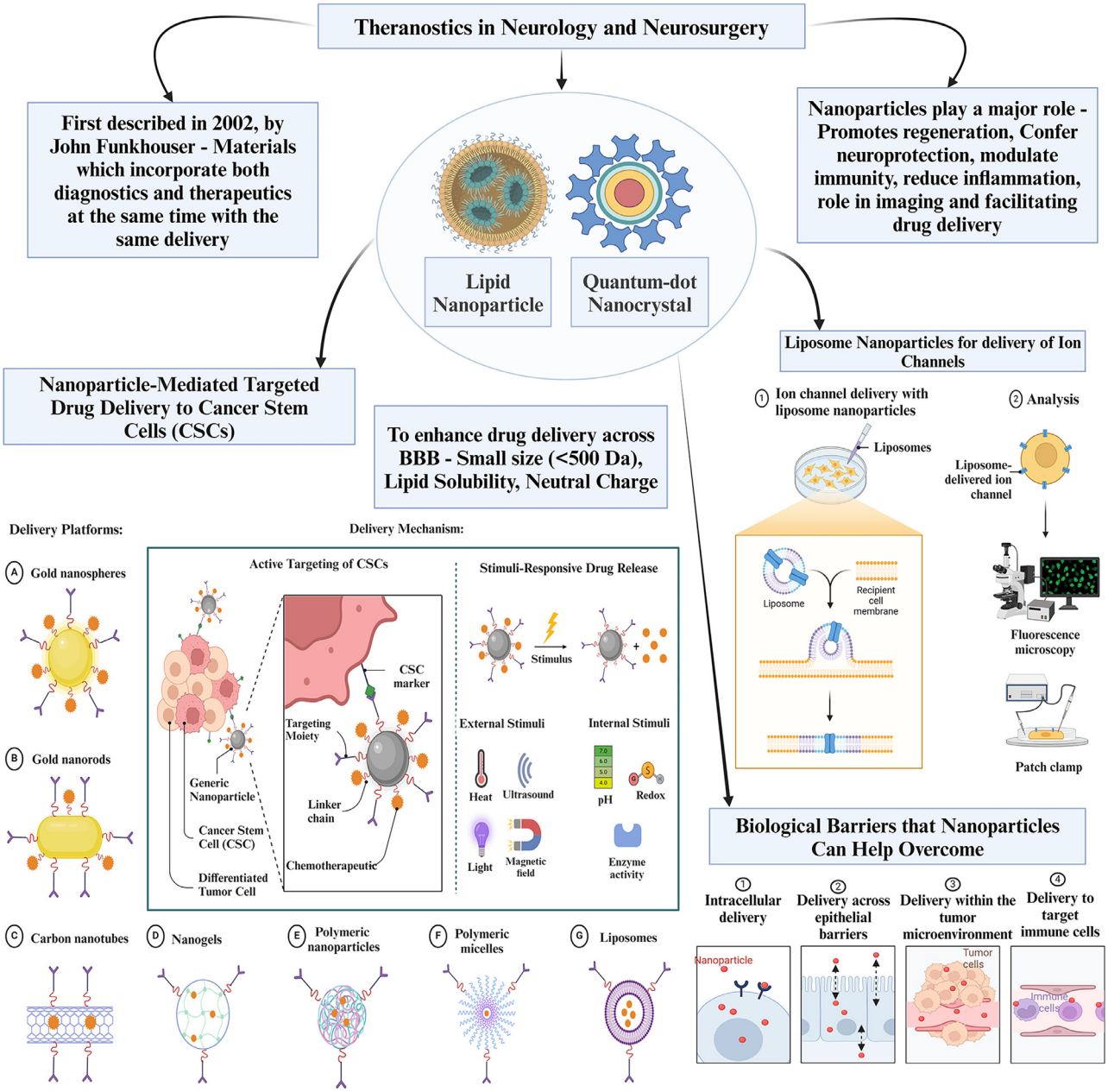

Figure 1. General overview of the applications of theranostics in neurology and neurosurgery. BBB: blood brain barrier.

(lactic-co-glycolic acid) (PLGA) NPs conjugated with Tet-1 peptides and loaded with curcumin were used as an approach for precise drug targeting and release in AD-affected structures (9). Furthermore, in 2014, dual-function NPs were used to target amyloid plaques in the brains of mice with AD. These engineered NPs not only contributed to imaging but also enhanced drug delivery to the target tissue, potentially achieving a theranostic effect for the disease (10).

In recent advances, the integration of artificial intelligence (AI) with theranostic platforms has facilitated the development of highly sensitive diagnostic tools and personalized treatment strategies, further refining the precision and efficacy of interventions (11). The future holds great promise for innovations that promote this revolutionary method of personalized medicine, particularly in the areas of neurology and neurosurgery.

Mechanism of Action and Probe Design

Nanotheranostics has spearheaded the development of advanced neurotheranostics capable of simultaneously diagnosing, evaluating, and treating patients. Research into targeted drug delivery has identified specific criteria for NPs to cross the BBB: a) they must be relatively small (<500 Da); b) they should be lipid soluble; and c) they must carry a net surface charge of 0 (12). These NPs can be categorized based on their size, shape, chemical properties, and surface charge (Figure 2).

In the last decade, a wide range of multifunctional NPs has emerged, all of which show promise for biomedical applications. These "theranostic NPs" exhibit stable chemical structures, compatibility with biological systems, and physicochemical properties that make them suitable for various applications. They can have at least one dimension of less than a micrometer, and their sizes can even reach about 0.2 nanometers, comparable to many atomic-scale lengths (13). Various NPs such as polymer-drug conjugates, dendrimers, polymeric particles, magnetic particles, solid lipid particles, gold NPs, and carbon nanomaterials have been developed and explored for theranostic purposes (14). Some particles, such as iron oxide particles, gold NPs, and carbon nanomaterials, already possess intrinsic theranostic properties, while micelles, dendrimers, and inorganic NPs can be surface-modified to achieve similar properties. The preparation of these theranostic nanomolecules into aqueous nanosuspensions for administration can be achieved using small molecules, surfactants, macromolecules, and polymers (15).

However, these particles are often rapidly cleared from the body's circulation by the liver, necessitating changes that extend their half-life and circulation time. Such alterations facilitate the ability of the particles to cross the BBB and reach cells and tissues affected by diseases characterized by injury, inflammation, or infection (16). Thus, the ongoing focus of theranostic research remains the production of NPs that are stable in aqueous solutions, responsive to stimuli, biocompatible, and of appropriate size (17).

Many neurological disorders are associated with cerebrovascular dysfunction that prevent the delivery of existing medications across the BBB. Overcoming this challenge remains a primary criterion for any therapy (18). Smart NPs with magnetic properties (MNPs) have proven effective in achieving this through efficient magnetoporation of the BBB endothelium (19). The size, coating, and shape of NPs influence the magnetic forces applied to them, and it has been discovered that slower blood flow enhances the magnetic targeting of neurotheranostic NPs to target tissues and cells (20).

In all of the above cases, it has been proposed that MRIs can be employed to monitor the penetration of MNPs into deeper tissues in real time, providing an imaging and diagnostic perspective on these treatments (21).

The overview, mechanism of action, and probe design of theranostics in neurology and neurosurgery are summarized in Figure 1.

Current Trends in Theranostics in Diagnostics and Treatment of

Neuro-oncological Disorders

Brain Tumors. In the field of Neuro Oncol, theranostics has played a pivotal role in addressing the challenges posed by brain tumors, which include gliomas, meningiomas, and spinal tumors (22). The intricate characteristics of these tumor types and the need for precise interventions have been the driving force behind the progress of theranostics in the field of Neuro Oncol (22).

Gliomas. In the quest for precision in glioma treatment, several studies have explored theranostic approaches designed to target specific molecular markers on glioma cells (23,24). In particular, gold NPs functionalized with monoclonal antibodies that specifically target the epidermal growth factor receptor (EGFR), a molecule frequently overexpressed in glioma cells, have been used (25). These NPs are tailored to recognize and bind to EGFR, based on the molecular interaction between the antibodies and EGFR. This interaction not only aids in accurate tumor diagnosis but also serves as a vehicle for the precise delivery of therapeutic agents directly to the tumor site (26). Similarly, liposomes loaded with monoclonal antibodies against vascular endothelial growth factor (VEGF) have been designed to selectively bind to VEGF molecules within the glioma microenvironment, disrupting the tumor's ability to stimulate angiogenesis (27). Iron oxide NPs (IONPs) with glioma-specific ligands have been used as both imaging agents and drug carriers, allowing precise molecular local-

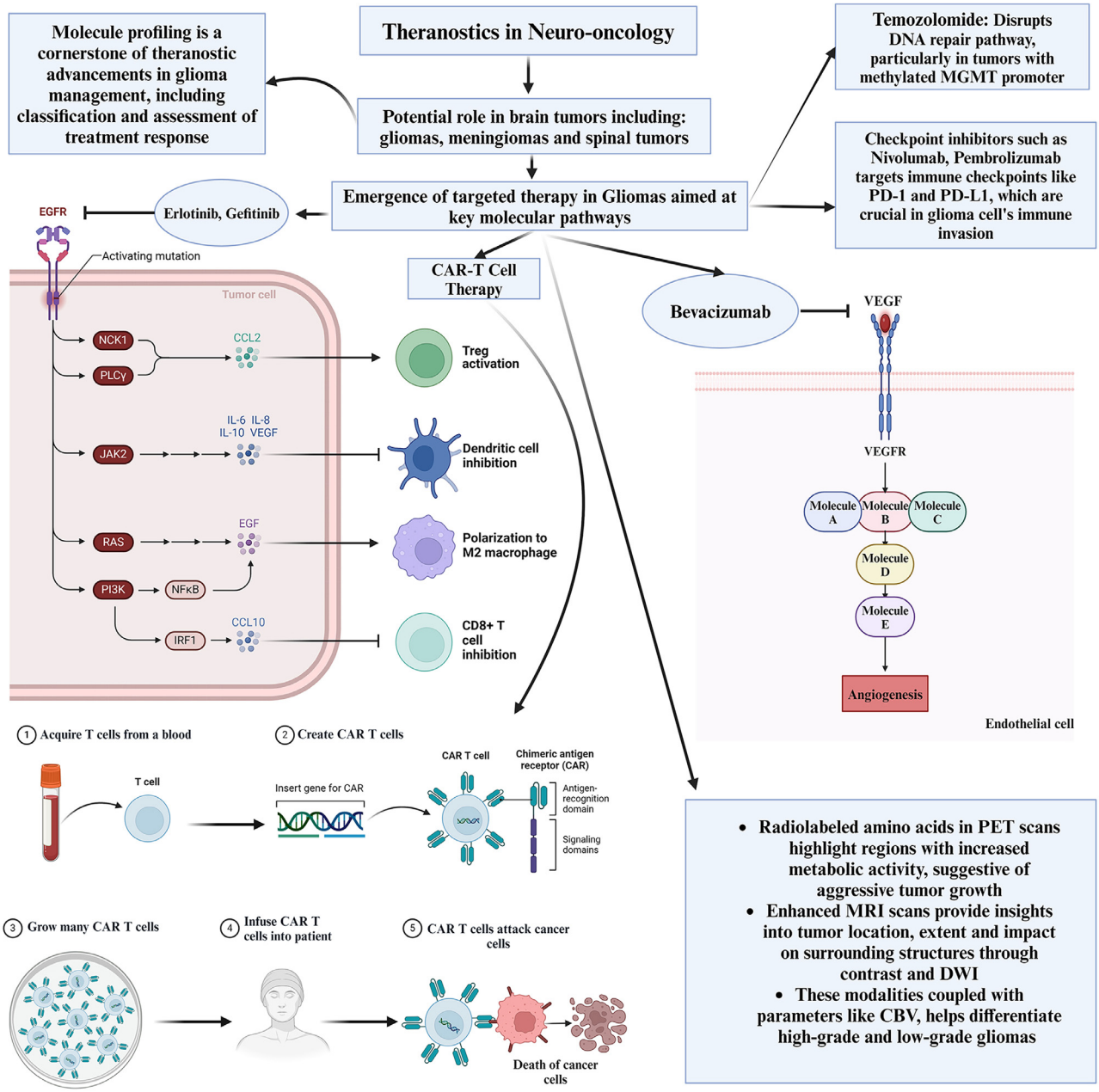

Figure 2. Overview of the application of theranostics in Neuro Oncol. CBV: cerebral blood volume; MRI: magnetic resonance imaging; DWI: diffusion-weighted imaging; PET: positron emission tomography; CAR-T cell: chimeric antigen receptor T-cell; VEGF: vascular endothelial growth factor; EGFR: epithelial growth factor receptor; DNA: deoxyribonucleic acid; MGMT: O6-methylguanine-DNA methyltransferase; PD-1: programmed cell death-1 receptor; PD-L1: programmed cell death ligand.

ization of the tumor by imaging techniques and targeted delivery of therapeutic agents (28).

Mesoporous silica NPs (MSNs) modified with glioma-specific ligands provide a versatile platform for combining diagnostics and therapy (29). Their porous, molecular-level structure allows them to carry diagnostic agents for imaging and therapeutic agents for precise drug delivery to glioma cells (29). In the field of neuroimaging, superparamagnetic iron oxide NPs (SPIONs) coated with monoclonal antibodies targeting EGFR have shown promise (30). These NPs possess superparamagnetic properties that enhance MRI contrast by interacting at the molecular-level with the surrounding magnetic field. Their anti-EGFR coating ensures specific molecular targeting of glioma cells, resulting in accurate tumor localization at the molecular level during MRI scans (30).

Furthermore, gadolinium-based NPs with molecular surface modifications have been developed to enhance MRI

contrast (31). These NPs are carefully designed to selectively bind to specific molecular markers on glioma cells, effectively distinguishing glioma tissue from healthy brain tissue (31). For optical imaging, quantum dots (QDs) with tunable emission spectra have been utilized due to their unique optical properties at the molecular level. These NPs emit robust fluorescence, facilitating precise tumor localization at the molecular level during imaging. Their tunable emission spectra make them adaptable to different molecular-level imaging needs (32). To enhance drug delivery with molecular precision, PEGylated liposomes loaded with therapeutic drugs have demonstrated promise in efficiently crossing the BBB (33). Molecular-level PEGylation enhances their stability and brain-targeting ability (33).

Meningiomas. Significant advances in the field of theranostics for meningiomas have centred on the use of superparamagnetic IONPs, known for their exceptional superparamagnetic properties (34). These IONPs are designed with antibodies or ligands that specifically target receptors found in meningiomas (34). For instance, monoclonal antibodies such as octreotide or pasireotide that target the somatostatin receptor subtype 2 (SST2), are commonly used (35). These antibodies bind to SST2 receptors, allowing IONPs carrying them to selectively interact with meningioma cells that overexpress SST2 receptors (35). This precise molecular targeting enables them to visualize and localize meningiomas with remarkable accuracy, thereby optimizing both diagnostic and treatment procedures.

Moreover, QDs have opened up new possibilities for optical imaging of meningiomas. These tiny particles are coated with materials that selectively bind to meningioma-specific markers, enabling highly precise real-time visualization of meningioma tissue during surgical or imaging procedures. QDs are coated with ligands that selectively bind to MUC1, allowing highly specific targeting and exceptionally accurate visualization of meningiomas (36).

NPs, particularly polymeric liposomes, have emerged as a promising avenue for the precise delivery of therapeutic agents tailored for meningioma-specific targeting. PEGylated liposomes loaded with doxorubicin serve as a prime example of this approach (37). PEGylation not only enhances the stability of the liposomes but also improves their brain-targeting capabilities, while doxorubicin acts as a potent anticancer agent (37). Additionally, liposomes encapsulating temozolomide have been developed for selective delivery to meningioma cells (38). Solid lipid NPs (SLNs) and polymeric NPs have shown potential to cross the BBB and facilitate targeted drug delivery (39).

Astrocytomas. In the field of astrocytoma theranostics, there has been an exploration of iron oxide nanoparticles tailored with monoclonal antibodies and peptides (40). These nanoparticles are designed to specifically target and bind to the EGFR present on the surface of astrocytoma cells (41). Cetuximab, a monoclonal antibody specifically designed to target EGFR, has been the subject of a study to evaluate its efficacy in the treatment of astrocytoma (41). In addition, short peptides inspired by the epidermal growth factor (EGF) receptor ligand have been studied to functionalize these nanoparticles. These peptides are designed to mimic the natural ligand's capacity to effectively bind to EGF. For instance, the GE11 peptide is a novel ligand known for its high affinity for the EGFR (42). This ligand can be used to functionalize nanosystems for precise targeting of EGFR (43).

Furthermore, multifunctional NPs have found utility in the treatment of astrocytomas. These NPs, typically composed of gold, are modified with molecular imaging agents such as fluorescent dyes or Raman tags (44). Their unique optical properties make them well suited for advanced imaging techniques such as surface-enhanced Raman spectroscopy (SERS) (44). Consequently, these short ligands and monoclonal antibodies that enhance IONPs form the basis for astrocytoma theranostics. They simultaneously achieve therapeutic goals and allow imaging for diagnostic purposes (40,41).

Spinal Tumors

NP-targeted therapies have emerged as a promising avenue in the treatment of spinal tumors. These NPs, often based on liposomes or polymer NPs, are designed to encapsulate therapeutic agents, such as paclitaxel (45). For example, there are doxorubicin-loaded polymeric NPs modified with a peptide ligand, which allows them to target specific surface receptors that are overexpressed in spinal tumor cells (46). This innovative approach has demonstrated a significant improvement in the therapeutic effects of doxorubicin while reducing off-target toxicity (46).

Other targeted therapies have been developed for spinal tumors, such as multiple myeloma, a primary spinal tumor. For example, Sn2 lipase-labile phospholipid prodrugs designed for contact-facilitated drug delivery to target the b-HLHZ transcription factor c-Myc (MYC) have shown promising results (47).

Similarly, VLA-4-targeted liposomal carfilzomib (CFZ) NPs (TNP-CFZ) have been designed to specifically target VLA-4-expressing multiple myeloma cells (48). *In vitro* studies have shown that both NP-CFZ and TNP-CFZ exhibited enhanced cytotoxicity compared to free CFZ. These NPs-induced apoptosis effectively inhibited spinal tumor growth *in vivo* (48). Taking advantage of the abundant presence of proteoglycans (PG) in chondrosarcomas, a quaternary ammonium (QA) compound has been used as a carrier to selectively deliver therapeutic drugs or imaging agents to extracellular matrix (ECM)-rich tissues (49). Additionally, 111In-SRP@QA has shown promise as a radiobiological approach for the treatment of highly radioresistant PG-rich tumors such as chondrosarcomas. It also provides multimodal imaging capabilities for these tumors (49).

Cerebrovascular Disorders

Theranostics has ushered in a transformative era in the diagnosis and treatment of cerebrovascular diseases (CVDs)—conditions that affect the blood vessels and cerebral circulation in the brain. The advent of theranostics in this field has the potential to streamline personalized treatment protocols while providing innovative methods of cellular mapping.

The use of NPs in the field of cerebrovascular theranostics has been analyzed for a variety of disorders and has proven to be a new avenue in theranostics in cerebrovascular health. Current treatments for conditions such as cerebral amyloid angiopathy, which are definitively diagnosed by pathological examination, are often associated with significant systemic side effects, making them less suitable for long-term use (50). To overcome this challenge, researchers have developed theranostic nanovehicles equipped with antibody cores specifically designed to target the amyloid deposits within blood vessels (50).

Moreover, novel nanoparticles such as t-PA@iRNP, which encapsulate tissue plasminogen activator (t-PA) in antioxidants, improve drug stability and reduce oxidative stress, targeting only the affected cells and sparing the healthy ones (51). Similarly, NPs have been developed to target macrophages to prevent arterial atherosclerotic plaque formation more effectively than traditional drugs (52). In addition, theranostic immunoliposomes, guided by molecular markers such as HSP72 and tracked by MRI and computed tomography (CT), deliver treatments such as citicoline directly to the stroke-damaged regions, minimizing lesion size in affected brains (53). These nanotechnological advances integrate therapy and diagnosis, offering targeted, safer, and more effective treatment options for stroke and other CVDs.

Exosomes have emerged as potential theranostic tools for the treatment of brain ischemia due to their ability to penetrate the BBB and deliver targeted treatments. Modified to carry rabies virus glycoprotein or specific peptides, these nanovesicles facilitate the delivery of therapeutic ribonucleic acid (RNA) and anti-inflammatory agents such as curcumin directly to the site of injury, promoting neurogenesis and reducing damage (54,55). Additionally, stromal cell-derived exosomes, enriched with chemokine receptor type 4 (CXCR4), significantly boost angiogenesis, which is essential for tissue repair after stroke. Moreover, the incorporation of glucose-coated gold NPs into exosome tracking allows clinicians to monitor these nanocarriers using CT imaging (56). This combination of targeted delivery and advanced imaging underscores the dual role of exosomes in improving neuroregenerative therapies and providing diagnostic insights and represents a potential strategy to combat the long-term effects of cerebral ischemia.

Employment of aggregation-induced emission (AIE) technology represents a significant step forward in the theranostic landscape, providing diagnostic clarity and informing the development of targeted therapeutic interventions for cerebrovascular health challenges. AIE-based organic dots exhibit robust, high-intensity fluorescence that enables the precise *in vivo* identification of lipid-rich tissues, which is critical for understanding and labeling the impact of atherosclerotic plaques in the cerebral vasculature (57). Moreover, the integration of AIE technology with gadolinium, to produce AIE-Gd dots provides a composite tool for detailed imaging of the cerebral vasculature (58). This is instrumental in assessing the integrity of the BBB, a critical factor in the progression of various CVDs and NDs. Theranostics applications in CVDs are summarized in Figure 3.

Neurodegenerative Disorders

The field of theranostics offers promising prospects for NDs - a type of pathologies characterized by progressive neuronal loss with devastating clinical manifestations, including AD, Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS). Given the multifactorial pathogenesis of NDs, theranostics offers a tailored therapeutic regimen based on individual pathophysiological profiles, thereby potentially improving treatment efficacy and monitoring.

QDs are becoming pivotal in AD research, providing a way to detect and track the accumulation of amyloid-β peptides. These NPs, when tagged with specific antibodies, can light up amyloid deposits in mouse brain models and distinguish diseased from healthy tissue with enhanced fluorescence (59). Furthermore, graphene QD-based probes exceed traditional dyes in sensitivity, enabling both detailed observation of amyloid formation and non-invasive *in vivo* imaging (60). This dual diagnostic and tracking capability positions QDs as a promising tool for early detection and therapeutic monitoring of AD. Additionally, theranostic therapies for AD exploit the potential to disrupt the mechanisms of the disease. Conjugated polymers with amyloid-like structures have shown promise in disrupting harmful aggregation of amyloid-β proteins, suggesting a way to reduce the neuronal toxicity that drives disease progression (61). Simultaneously, multifunctional nanocomposites have emerged that target the pathological tau proteins and alleviate symptoms by counteracting oxidative stress and preventing cell death (62). Moreover, specially designed ceria NPs are being developed to counteract the damaging reactive oxygen species in neurons, with some designed to specifically target mitochondria (63). Additionally, chelator-conjugated NPs are exploring strategies to mitigate the effects of metal ion accumulation, which is associated with amyloid-β interactions that exacerbate AD's pathology (64). These NP-based approaches represent a

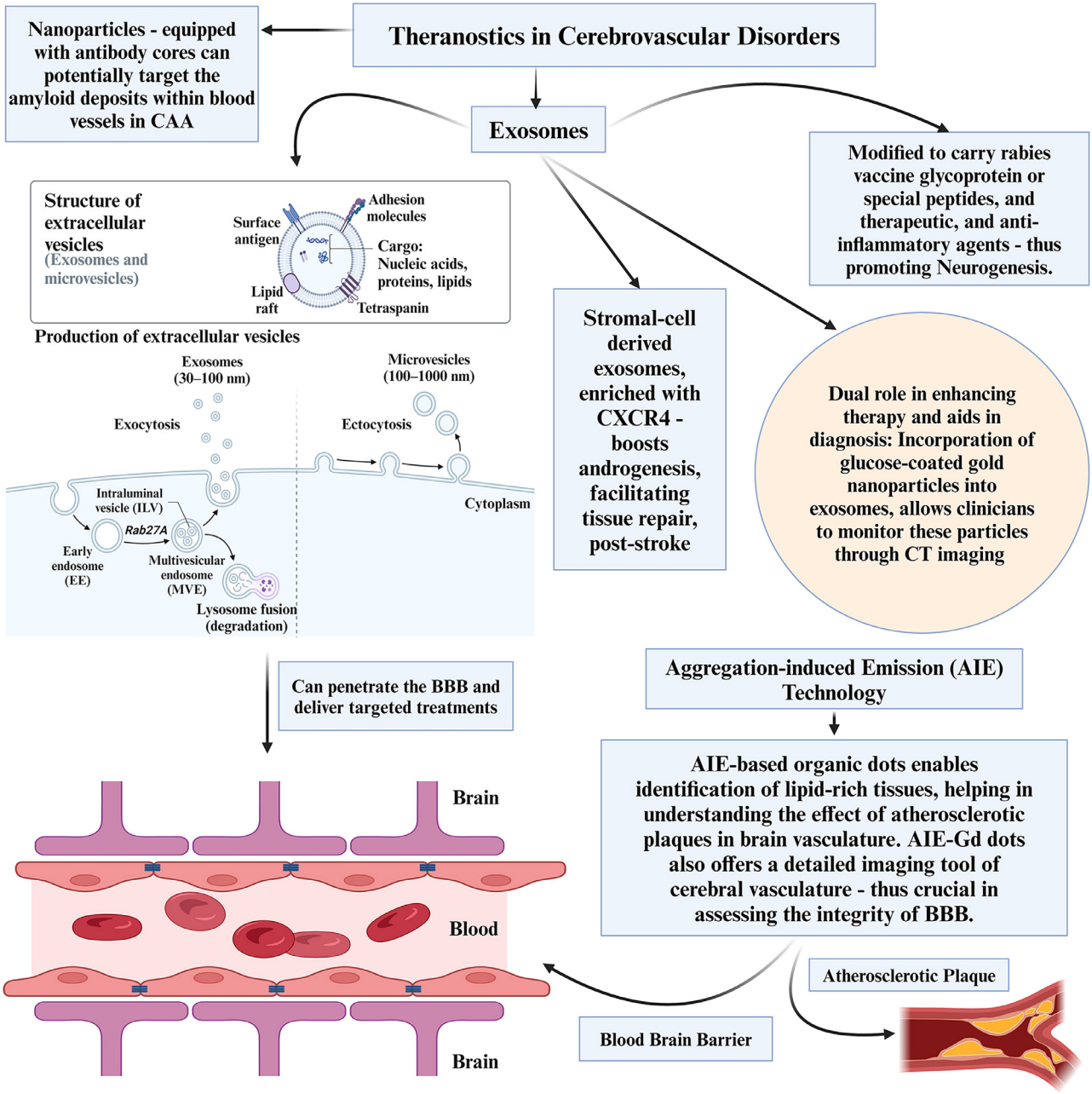

Figure 3. Overview of the application of theranostics in cerebrovascular disorders. BBB: blood-brain barrier; CAA: cerebral amyloid angiopathy; CT: computed tomography; CXCR4: Chemokine receptor type 4.

promising frontier for both diagnosing and combating the complex pathology of AD with precision.

NPs are revolutionizing the approach to PD, serving as innovative theranostic tools that simultaneously diagnose, image, and deliver targeted therapies. For instance, NPs are being engineered to cross the traditionally impenetrable BBB, providing non-invasive routes to transport neuroprotective compounds such as neurotrophic factors and curcumin directly to affected brain regions, significantly improving motor function and dopamine levels in PD models (65,66). Techniques such as MRI guide these NPs to diseased sites, while MNPs allow precise drug delivery under external magnetic fields, enhancing the therapeutic efficacy of drugs such as resveratrol (67). Furthermore, these NPs are being used to modulate the expression of harmful proteins such as α-synuclein, leveraging gene therapy for targeted intervention (68). Collectively, these advanced nanotechnologies are paving the way for breakthroughs in the diagnosis and treatment of PD, promising more effective management of this ND.

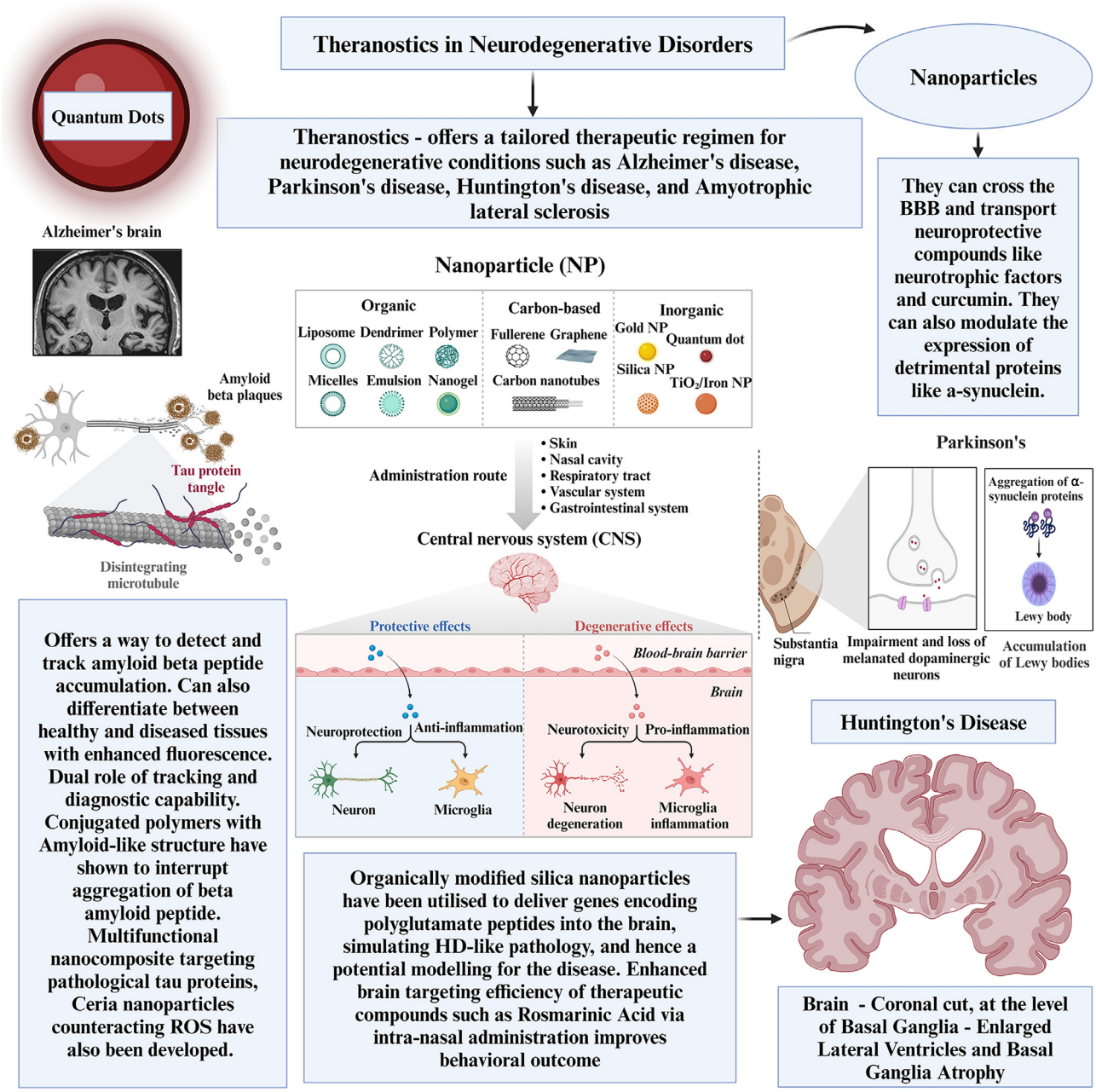

Figure 4. Overview of the application of theranostics in neurodegenerative disorders. HD: Huntington's disease; ROS: reactive oxygen species; BBB: blood brain barrier.

NPs have emerged as a breakthrough theranostic tool against HD, a genetic ND. Organically modified silica NPs have been used to deliver genes encoding polyglutamine peptides into the brain, successfully inducing HD-like cellular pathologies and motor deficits, highlighting their potential for disease modeling and evaluation of gene therapies (69). Furthermore, extracellular vesicles loaded with microRNAs (miRNAs) restore synaptic functions by reversing synaptic deficits in HD-affected neurons (70). Solid lipid NPs have shown promise in enhancing the brain targeting efficiency of therapeutic compounds such as rosmarinic acid via intranasal administration, leading to improved behavioral outcomes and reduced oxidative damage in HD models (71). Theranostics applications in NDs are summarized in Figure 4.

Epilepsy and Seizure Disorders

Theranostic NPs represent a breakthrough in the treatment of epilepsy by precisely targeting and treating the inflamed regions of the brain that cause seizures. These devices, tailored with specific antibodies, can both deliver anti-

inflammatory drugs directly to the source of epilepsy and provide real-time MRI monitoring of treatment efficacy.

For the treatment of drug-resistant epilepsy, by using superparamagnetic IONPs with specialized antibodies, researchers have created a targeted therapeutic system that crosses the BBB, concentrates in the affected brain areas, and provides simultaneous diagnostic imaging via MRI. This magnet-directed drug delivery system targets the inflammation characteristic of temporal lobe epilepsy and directly delivers therapeutics to treat it (72). Similarly, MNPs with non-radioactive α-methyltryptophan have demonstrated their ability to localize to the regions of seizure origin in both the acute and chronic stages of animal epilepsy models, as confirmed by MRI and intracranial EEG, enabling them to determine the exact location of epileptic activity with high accuracy (73).

Innovations in epilepsy treatment are harnessing the power of precise drug delivery mechanisms. One such breakthrough is the creation of a flexible chip using a positron emission tomography (PET) substrate embedded with NPs to control the release of ethosuximide, an antiepileptic drug, by manipulating magnetic fields (74). Electro-responsive hydrogel NPs have also been developed that efficiently penetrate the BBB to distribute drugs such as phenytoin sodium directly to the brain (75).

Moreover, when potent anticonvulsants are encapsulated in NPs and coated with polysorbate 80, they show extended release and efficacy in the central nervous system, significantly prolonging their anticonvulsant action (76). Furthering this innovation, researchers have developed a dual-function NP that can detect changes in brain pH and deliver an anticonvulsant drug precisely when needed. These pH-sensitive NPs have demonstrated the ability to both identify seizure-prone environments and reduce seizure severity in animal models (77). These approaches represent a sophisticated fusion of targeted delivery and responsive release, offering the promise of more effective, personalized epilepsy treatment with improved patient compliance and fewer side effects. Theranostics applications in epilepsy and seizures are summarized in Figure 5.

Challenges and Limitations of the Technology

Theranostics technology, which combines diagnostic and therapeutic functions, represents a promising avenue in neurology and neurosurgery. However, its successful application faces technical, developmental, and accessibility challenges that must be addressed to realize its full potential.

Technical Challenges

A crucial technical challenge revolves around the development of highly specific and sensitive imaging agents tailored to neurological disorders. Achieving accurate diagnosis and precise treatment monitoring depends on these agents, as the BBB targets specific molecular markers associated with conditions such as brain tumors and NDs (78,79).

The integration of theranostic agents with advanced imaging modalities, such as PET, MRI, and CT, presents challenges such as variable receptor expression, limited optical depth, and spatial resolution issues in PET/single-photon emission CT (SPECT). Coordination of imaging with therapy, varying sensitivities, and selection of appropriate techniques require careful planning in cancer therapy (80,81). In addition, optical coherence tomography (OCT), which provides non-invasive real-time imaging of brain tissue, has challenges such as limited differentiation between healthy and cancerous tissue, minimizing the surgeon's tremor effect during laser ablation, and effectively performing imaging throughout the procedure (82).

Another theranostic tool, confocal laser endomicroscopy (CLE), which allows subcellular resolution imaging during surgery, also presents challenges. Interpretation of CLE images, which are typically grayscale fluorescence images, can be a difficult task for an untrained user. Moreover, CLE images are affected by motion artifacts, signal problems and interference from blood cells (83). More recently, innovative approaches such as liquid biopsy combined with photoacoustic flow cytometry for CSF analysis to detect circulating tumor cells and other biomarkers have also been evaluated with limited sensitivity for early detection. As the integration of theranostic approaches with liquid biopsies is still in its infancy, more sensitive and specific detection technologies will be important in the development of this approach (84).

Furthermore, the complex task of designing multifunctional theranostic nanoparticles capable of controlled drug release poses a formidable technical challenge. Achieving optimal drug delivery, minimizing off-target effects, and ensuring controlled release kinetics require meticulous engineering and formulation strategies (85).

Difficulties in Development and Implementation

The development and implementation of theranostics in neurology and neurosurgery involves several challenges ranging from preclinical validation to regulatory approval and clinical adoption. Extensive preclinical testing and validation are essential to establish the safety, efficacy, and specificity of theranostic agents before moving on to clinical trials (86–88).

Navigating the regulatory landscape for approval and securing reimbursement for these innovative therapies presents additional challenges. The specialized equipment required for theranostic procedures can complicate the regulatory approval process and limit patient access due to reimbursement issues (89).

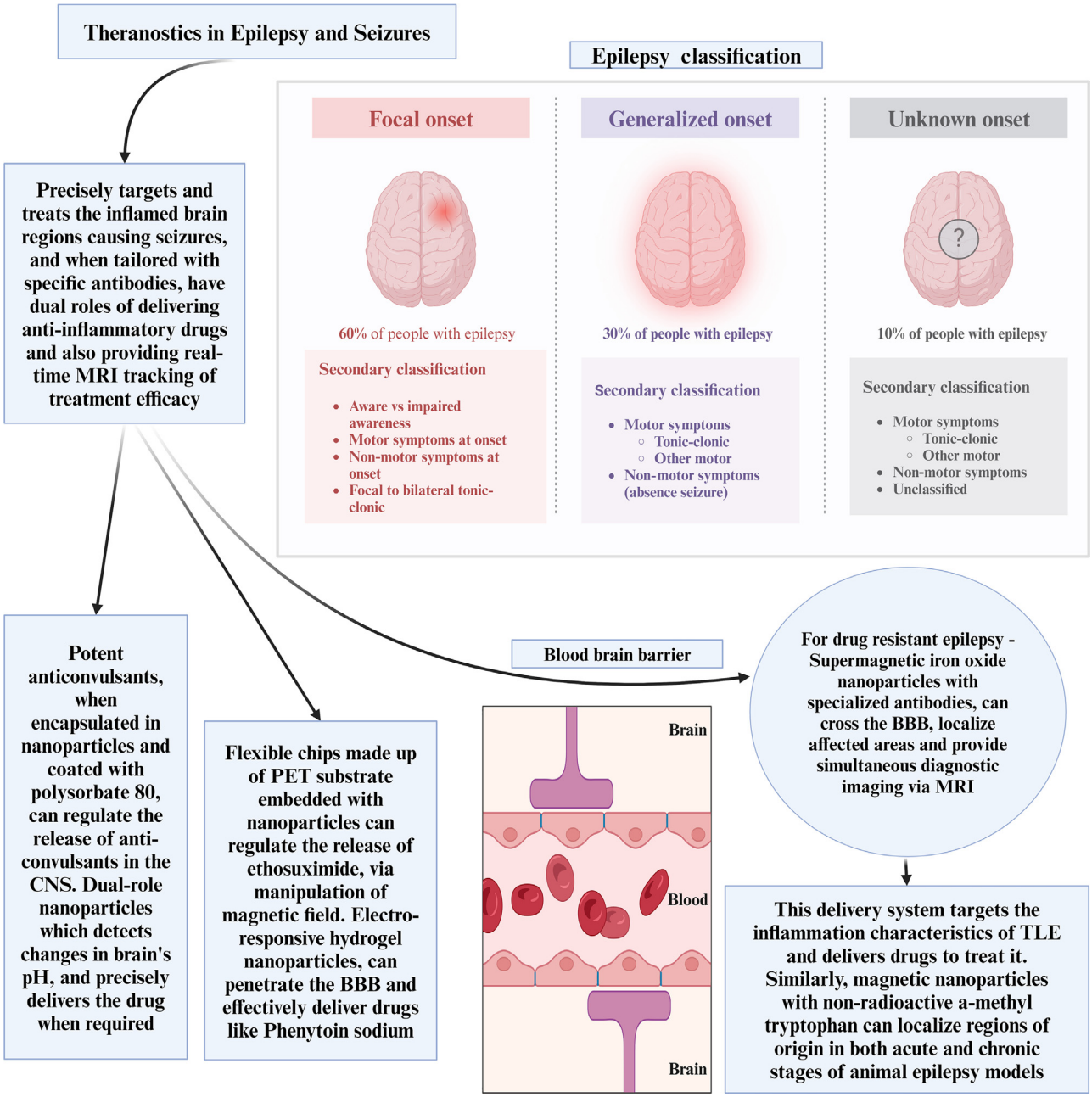

Figure 5. Overview of the application of theranostics in epilepsy and seizure. TLE: Temporal lobe epilepsy; BBB: Blood brain barrier; MRI: Magnetic resonance imaging; PET: Positron emission tomography; CNS: Central nervous system.

Another key challenge for theranostic implementation is the application of inorganic nanoparticles (INPs) to the CNS. INPs are particularly effective for drug delivery due to their ability to cross the BBB, but this also increases the potential for neurotoxicity. Studies have shown that following traumatic brain injury, the temporary breakdown of the BBB allows nanoparticles to accumulate in injured brain tissue. This accumulation is size dependent, with smaller nanoparticles showing increased retention in the brain, which could exacerbate neurotoxic effects (90). While acute toxicities may be of concern, the long-term effects of nanoparticle exposure pose an even greater challenge. Very few studies discuss the long-term effects of INPs on the CNS. However, general research suggests that the chronic toxicity of iNPs is influenced by several factors, including their composition, size, surface charge and route of administration. Long-term exposure to these nanoparticles may result in tissue and blood toxicity, immunotoxicity, and even genotoxicity, leading to potential long-term health problems (86). Furthermore, in the con-

Table 2. Theranostics technology challenges in neurology and neurosurgery

Challenges	Description
Technical challenges (78–85)	- Challenges in development of specific and sensitive imaging agents targeting the BBB - Issues with variable receptor expression, limited optical depth, and spatial resolution in PET/SPECT -Difficulty in technicalities regarding designing multifunctional nanoparticles for controlled drug release
Difficulties in development and implementation (86–91)	- Challenges in developing and implementing theranostics in neurology and neurosurgery entails various challenges spanning preclinical validation, regulatory approvals, and clinical adoption. - Securing reimbursement and approval poses as additional challenges. - The specialized equipment required for theranostic procedures can complicate the regulatory approval process and limit patient access due to reimbursement issues.
Cost and inaccessibility (86,5,92–94)	- High costs associated with development, production, and clinical use. Prohibitive expenses potentially limiting widespread adoption. - Geographical disparities in accessibility leading to challenges in theranostics in low-resource regions.

BBB: blood-brain barrier; PET: positron emission tomography; SPECT; single-photon emission computed tomography.

text of neurodegenerative diseases, the long-term presence of INPs in the brain could trigger unintended side effects, such as neuroinflammation and neuronal damage (91).

Cost and Inaccessibility

Cost is a major limitation of theranostics technology. The development, production, and clinical use of specialized theranostic agents and equipment can be prohibitively expensive, potentially limiting widespread adoption (86). Even the most cost-effective theranostic tools are often inaccessible. For example, the cost-effectiveness of stereotactic radiosurgery (SRS) has been compared with that of traditional surgical resection in the treatment of solitary metastatic brain tumors. It was concluded that although SRS was still more cost-effective at baseline, there were significant upfront costs that discouraged healthcare providers from offering these more advanced therapies (92).

However, the cost of implementation is not the only concern. Although studies have discussed the evolving role of theranostics and highlighted its cost-effective potential to optimize patient outcomes, the initial investment required for the necessary technology and training can be prohibitive, particularly in low-resource settings (5). In addition, geographic disparities in accessibility may hinder equitable access to care. The concentration of advanced theranostic centers and expertise in certain regions can pose challenges for patients in remote or underserved areas, limiting their access to these transformative technologies (86). Advanced theranostic procedures require sophisticated equipment and specialized expertise. For example, theranostic methods such as optical coherence tomography or peptide receptor radionuclide therapy, while promising, may be hampered by the need for exclusive, high-precision, costly equipment and highly specialized centers for long-term care (93,94). The challenges of theranostics technology in neurology and neurosurgery are summarized in Table 2.

Ethical Considerations

In the innovative field of theranostics for neurology and neurosurgery, ethical governance is crucial. The Declaration of Helsinki underpins this field, safeguarding the rights and safety of participants (95). The authorization of new neurosurgical theranostic tools is subject to the scrutiny of ethics committees, which ensure that any advancement is as ethically sound as it is scientifically valid. This includes strict informed consent protocols and protection of patient confidentiality. Additionally, liability insurance is mandatory, reinforcing an ethos of foresight and accountability (95).

In the context of theranostics, the consent process is particularly nuanced, given the high stakes and complexity of neurological diseases. Patients must make informed decisions in the midst of rapidly evolving therapeutic options, highlighting the need for a consent framework that is both comprehensive and sensitive to the setting (96). Communication between clinicians and patients must prioritize clarity and empathy, with a focus on aligning treatment choices with patient values and ensuring that therapeutic advances are pursued with ethical diligence and a patient-centered approach.

Theranostics involving nanoparticles pose another set of ethical concerns, particularly in the area of patient privacy and data integrity. These sophisticated nanomedical devices promise an unprecedented level of detail in health monitoring at the subcellular level, offering real-time, continuous health data collection (97). This capability raises critical ethical questions about the readiness of current health information systems to securely handle, pro-

Table 3. Discussion and prospects of theranostics potential in transforming the neurological and neurosurgical field

Section	Key technologies/Strategies	Potential impact
Overview of evolving technologies (104–117)	- Neurotheranostics in neuro-oncology. - Advanced imaging (fMRI, DTI, PET). - Liquid biopsies. - AI in data interpretation. - Theranostic radiometals.	- Revolutionizing diagnosis and treatment of brain/spinal tumors. - Non-invasive tumorigenesis monitoring. - Personalized therapy planning.
Advancements in neuro treatment (108–114)	- Theranostic pairs (*e.g.*, 177-lutetium-somatostatin). - Heteromultivalent ligands. - Radioligand cocktails. - PET/CT imaging. - Novel agents (177-lutetium-PSMA, 225-actinium-PSMA).	- Higher tumor radiation doses. - New standards in cancer diagnosis/management. - Tailored neuro-oncological treatments.
Gaps and future exploration (97,98,105,106,115–117)	- Long-term safety/efficacy data. - Addressing disease heterogeneity. - Long-term follow-up studies. - Equitable access. - Ethical implications of AI/big data. - Biocompatible/biodegradable agents. - Multicenter clinical trials.	- Essential for validating long-term outcomes - Bridging healthcare disparities. - Protecting patient privacy/security. - Enhancing accessibility and equity in treatment.

fMRI: Functional MRI; DTI: Diffusion tensor imaging; PET: Positron emission tomography; AI: Artificial intelligence; CT: Computed tomography.

cess, and analyze the flood of sensitive health information. There is an urgent need to develop and strengthen health information infrastructures that are capable of supporting this advanced data while maintaining the highest standards of privacy (97). Ethical stewardship of these data is essential to maintaining patient trust and safeguarding the very essence of personalized medicine in the theranostic approach.

Discussions and Future Directions

The integration of diagnostics and therapeutics through theranostics had a remarkable impact on healthcare, highlighted by the USD 3.9 billion acquisition of Advanced Accelerator Applications by Novartis (98). In neurology, neurotheranostics leverage NPs with a high surface-area-to-mass ratio, enhancing drug interactions and efficacy (99,100). These NPs, including cerebrolysin-loaded PLGA with CW800 imaging agents, show promise in overcoming challenges such as BBB repair after trauma (101,102). Additionally, liposome-encapsulated therapies with peptides have shown superior efficacy with fewer side effects compared to traditional drugs (103). However, the rapid development of neurotheranostic radiopharmaceuticals presents a challenge for traditional drug approval frameworks.

Overview of the Evolving Technologies to Improve Theranostics

The field of neurotheranostics, particularly in Neuro Oncol, is advancing rapidly, heralding a new era in the precise diagnosis and treatment of brain and spinal tumors. Advanced imaging technologies such as functional MRI (fMRI), diffusion tensor imaging (DTI), and PET, enhanced with radiolabeled tracers, are providing complex information about tumors (104). Liquid biopsies are emerging as non-invasive methods to track tumor evolution through biomarkers in body fluids (105). Furthermore, AI and machine learning are refining data analysis for more accurate treatment planning and personalization (106). The introduction of novel theranostic radiometals also offers promising synergistic therapeutic options (107). However, the application of these innovative approaches requires careful, tailored implementation in the complex landscape of neurology and neurosurgery.

Exploring How other Technological Advances in Neurology and Neurosurgery Could Transform Theranostics

Advances in theranostics are set to transform neurology and neurosurgery, with theranostic pairs such as 177-lutetium-somatostatin receptor antagonists offering higher-dose, targeted radiotherapy for neuroendocrine tumors with dense receptor co-expression (108,109). Exploratory strategies involving heteromultivalent ligands and radioligand combinations aim to further improve treatment efficacy (110). The introduction of different radiometals enables personalized neuro-oncological treatments, while PET/CT imaging has become a cornerstone for cancer diagnosis and treatment (111). In particular, novel agents like 177-lutetium-PSMA and 225-actinium-PSMA show promise for advanced neuroendocrine prostate cancer, marking

a hopeful advancement for this challenging condition (112–114).

Identification of Gaps in Current Knowledge and Areas Needing Further Exploration

Despite advances in theranostics, significant knowledge gaps remain, particularly in the long-term safety and efficacy of nanomaterial-based agents. The diversity of NDs complicates the creation of universal theranostics applications (115). As theranostic treatments improve survival rates for brain and spinal tumor patients, thorough long-term studies are essential to understand the lasting effects and quality of life outcomes (105). Ensuring that all patients have access to these advanced treatments is a critical challenge that addresses disparities in healthcare (106). Ethical concerns, particularly regarding the security of patient data in AI applications, must be carefully considered (97). Moreover, reducing the cost of theranostic technologies is essential for broader access and treatment equity (116).

Future research should prioritize the development of safe, biocompatible theranostic agents and the validation of their efficacy through multicenter trials in diverse patient groups (98). This is essential for the continued refinement and success of theranostic approaches in neurology and neurosurgery. The discussion and prospects of the potential of theranostics in transforming the fields of neurology and neurosurgery are summarized in Table 3.

Conclusion

In conclusion, theranostics demonstrates the potential of integrating diagnostic and therapeutic strategies to improve patient outcomes in neurosurgery and neurology. Advances in nanotechnology and bioimaging, as detailed, offer promising avenues for crossing the blood-brain barrier and targeting disease states with precision. Although the field is advancing with innovations, the review underscores the need for continued research in both preclinical and clinical settings to optimize the delivery and efficacy of these novel treatments. The promising findings encourage further exploration of theranostics as a cornerstone for future neurological and neurosurgical interventions, with a focus on patient accessibility, cost-effectiveness, and improved quality of life.

Ethics Approval

As this is a narrative review, ethics approval is not applicable.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Conflict of Interests

The authors have no relevant financial or non-financial interests to disclose.

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