



## Neurotheranostics as personalized medicines

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### ABSTRACT

The discipline of neurotheranostics was forged to improve diagnostic and therapeutic clinical outcomes for neurological disorders. Research was facilitated, in largest measure, by the creation of pharmacologically effective multimodal pharmaceutical formulations. Deployment of neurotheranostic agents could revolutionize staging and improve nervous system disease therapeutic outcomes. However, obstacles in formulation design, drug loading and payload delivery still remain. These will certainly be aided by multidisciplinary basic research and clinical teams with pharmacology, nanotechnology, neuroscience and pharmaceutical expertise. When successful the end results will provide “optimal” therapeutic delivery platforms. The current report reviews an extensive body of knowledge of the natural history, epidemiology, pathogenesis and therapeutics of neurologic disease with an eye on how, when and under what circumstances neurotheranostics will soon be used as personalized medicines for a broad range of neurodegenerative, neuroinflammatory and neuroinfectious diseases.

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## 1. Theranostics as personalized medicines

Until recently, the traditional approach to treating medical maladies has been to first make a diagnosis and then to administer a form of therapy. In line with this approach, medical research has primarily been focused on characterizing diseases followed by developing a therapeutic agent effective in treating disease. However, it is clear that this two-part strategy is not always effective for the most devastating of diseases. These are often times diverse in clinical presentation and underlying pathology [1]. Because of this fact, many of the so-called best treatments work for only certain affected subpopulations. Additionally, disease progression is also complex making it difficult to design treatments effective at all disease stages [2]. Indeed, the more we understand complex diseases such as cancer, human immunodeficiency virus (HIV), and inflammatory bowel disease among others the more apparent it is that a one size fits all approach to treatment is not uniformly effective [3–5].

With these concerns in mind the concept of combining a therapeutic agent with a diagnostic tool to produce personalized treatments was birthed. Protocols emerged that could provide improved prognoses than what is now standard treatments [6]. Personalized medicines based on nuclear and molecular imaging have emerged as a new therapeutic strategy. Such approaches can help physicians in pinpointing precise diagnoses leading to more efficient medical or surgical treatments [7]. This growing area of research has been coined "theranostics" defined as the combination of diagnostic and therapeutic agents placed into a single platform and enabling both to be delivered together. This allows the diseases to be treated and monitored effectively at the same time [8]. It is also one of the key strategies for the emergence of personalized medicines. Coined by John Funkhouser (Chief Executive Officer of PharmaNetics) in 2002, the term theranostics describes agents employed for combined applications [9]. *First*, theranostics can be used to identify subgroups of patients with specific clinical profiles likely to respond to specific treatment regimens. In kind the same subgroups likely to have adverse reactions to these treatments can also be identified so that the optimal therapies are chosen and administered. *Second*, disease-combating agents can be used to monitor disease progression in real time by diagnostic imaging [10].

Historically, the principle of theranostics was first employed in the 1940s with the imaging and treatment of thyroid cancers using radioactive iodine [11–13]. Similarly, long-acting  $^{131}\text{I}$  was used for therapeutic management of Grave's disease [12]. With a half-life of 8 days  $\beta$  and  $\gamma$ -particles are omitted with each radioactive decay. The  $\gamma$ -particles of  $^{131}\text{I}$  result in scatter and image blurring. However,  $^{123}\text{I}$  can be used solely as a diagnostic tool since it does not emit a  $\beta$ -particle. In contrast,  $^{131}\text{I}$  collides with atomic nuclei to elicit cell damage that produces a

therapeutic effect. As  $^{131}\text{I}$  is effective in treatment of thyroid disease, it became the first US Food and Drug Administration (FDA) approved radiopharmaceutical in 1951 [14]. With continued progress in molecular biology and biochemistry the elucidation of functional disease signatures allowed identification and treatments for a number of cancers [15,16]. This included recognition of specific surface receptors found to be expressed in abundance on tumor cells [17]. With such information in hand theranostics was applied to identify differences between normal and cancerous cells in order to identify molecular targets for delivery of sensitive and specific cytotoxic payloads for tumor cell elimination [18,19]. With such molecular targeting agents in hand a plethora of radioactive, fluorescence and paramagnetic imaging agents were subsequently developed for use by positron emission tomography (PET) and single photon emission computed tomography (SPECT/CT), optical imaging and magnetic resonance imaging (MRI) [20–22]. These types of imaging modalities using specific theranostic probes allow the attending physician to visualize the disease target, assess its location and size and determine the best means to control or eliminate it [23–25]. In the larger picture such approaches could be used as personalized medicines by using the probe to determine in any given patient the use of the therapeutic modality for patient screening. These works could also guide clinical trial enrollment and determine therapeutic effectiveness [26–28].

Advances in radioactive tracers have led to the development of 2D scintigraphy to facilitate disease localization. This technology greatly improved our understanding of disease markers and laid the groundwork for the advent of 3D and 4D radiographic imaging techniques [29]. An example of the clinical use of such theranostic probes is the targeting of human epidermal growth factor receptor (HER-2) expressed in metastatic breast cancer lesions with poor prognoses [30,31]. A diagnostic test can identify patients with HER-2 containing tumors. This has enabled image guided therapeutics using HER-2 monoclonal antibodies to target and eliminate cancer cells [31,32]. In 2004, the Pittsburgh compound B (PiB) discovery for PET imaging in amyloid in Alzheimer's disease (AD) patients led to major advances in bioimaging field [33].

Yet another theranostic is peptide receptor scintigraphy (PRS) and peptide receptor radionuclide therapy (PRRT) used for rapid diagnosis and treatment of pancreatic cancers. This technology came to the forefront in the late 1980s when  $^{123}\text{I}$ -labeled Tyr<sup>3</sup>-octreotide was used for the localization of carcinoid tumors, paragangliomas and pancreatic tumors [34]. This was followed by the development of  $^{111}\text{In}$ -pentetate, which had better sensitivity and specificity and became the first FDA approved peptide-based radiopharmaceutical in 1994 [35,36]. However, this approach yielded only a modest shrinkage of the tumor and there was an associated risk of development of melody

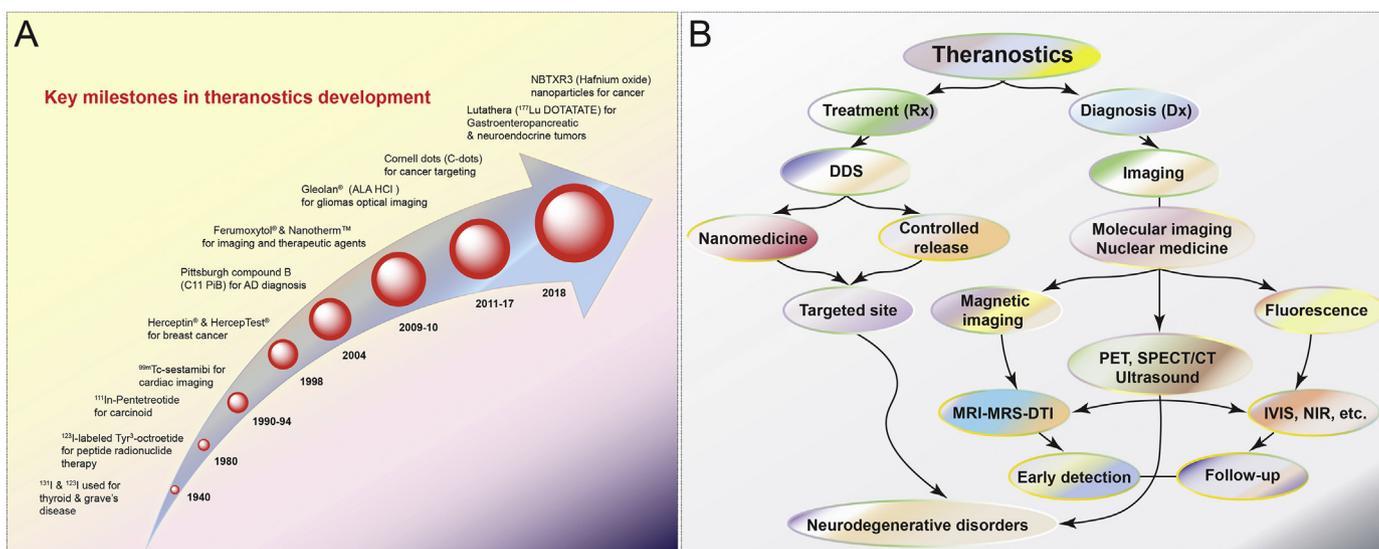
'plastic syndrome or leukemia [37]. This paved the way for the use of  $^{90}\text{Y}$ -Peptide Receptor Radionuclide Therapy (PRRT) and radiolabeled metal DOTA-chelated peptides [38]. However, significant renal uptake of the radionuclide was observed, and further research was needed to identify ways to preclude such events [39]. By the early 1990s, the Erasmus MC lysine-arginine formulation was discovered (Erasmus University Medical Center, Netherlands) and found to impart renal protection [40]. Renal protection with any PRRT with  $\beta$ -emitting radionuclides became a standard protocol since Novartis launched the  $^{90}\text{Y}$ -labeled DOTA, Tyr<sup>3</sup>-octreotide (DOTATOC) in 1997 which was more effective than  $^{111}\text{In}$ -pentetreotide although it also led to higher renal toxicity [41,42]. Around the same time, the first gallium labeled peptide imaging was fashioned by  $^{68}\text{Ga}$ -DOTATOC PET [43]. At the turn of the millennium [ $^{177}\text{Lu}$ -DOTA, Tyr<sup>3</sup>] octreotate was made and administered in conjunction with adequate amounts of supplemental amino acids to preclude amino acid renal toxicity [44]. It proved to be an effective therapeutic treatment and improved the survival rate of patients in clinical trials and it is presently under review by the FDA and European regulatory agencies. Numerous animal studies with various radionuclides have demonstrated that  $^{90}\text{Y}$ -PRRT is more effective with larger tumors than  $^{177}\text{Lu}$ -PRRT while the scenario is reversed for small tumor treatments [45]. Researchers have also looked into combination treatment with [ $^{177}\text{Lu}$ -DOTA, Tyr<sup>3</sup>] octreotate and a chemotherapeutic agent, which is referred to as peptide receptor chemoradionuclide therapy [46,47]. Another major innovation in theranostics is NETest, a gene transcript measure [48]. Concurrent advances in biomaterial science has enabled the creation of small nanoparticles capable of possessing both passive imaging agents for MRI or CT, as well as active agents for PET or SPECT/CT which creates an imaging agent that can maximize the strengths of each imaging technique while diminishing their inherent weaknesses [49]. Currently several nanoparticle and imaging agent constructs have been FDA approved for various disease treatments.

The most common radioisotope used in these nanoparticles is  $^{99\text{m}}\text{Tc}$ , which has a half-life of about six hours before decaying into  $^{99\text{m}}\text{Tc}$  and releasing a 140-keV  $\gamma$ -ray, which makes it ideal for  $\gamma$ -cameras and SPECT/CT imaging [50].  $^{99\text{m}}\text{Tc}$  has been incorporated into many FDA-approved colloidal nanoparticle platforms. These platforms include, sulfur, albumin, stannous fluoride ( $\text{SnF}_2$ ), and rhenium heptasulfide ( $\text{Re}_2\text{S}_7$ ) colloids, which are used mainly for lymphoscintigraphy, gastrointestinal or inflammation imaging [51]. Additionally, nanoparticles based on the superparamagnetic properties of iron oxide have been

FDA-approved as excellent MRI contrast agents. These, superparamagnetic iron oxide nanoparticles (SPIONS) have a large magnetic moment that reduces the signal seen on a MRI on T2 and T2\*-weighted images [52]. Dextran coated SPIONS have been used for lymph node, perfusion, and mononuclear phagocyte system imaging while carbodextran and polyglucose sorbitol carboxymethylether coated SPIONS are employed for hepatocellular carcinoma and iron-deficiency anemia, respectively [51]. Recently, FDA approved imaging agents and iron replacement therapies based on the nanoparticles are available for clinical applications; Venofer,  $^{\text{®}}$ Ferrlecit $^{\text{®}}$  INFed,  $^{\text{®}}$ Dexferrum,  $^{\text{®}}$ Nanotherm,  $^{\text{TM}}$  and Feraheme $^{\text{®}}$  [53,54]. In the future, more pace for FDA approval of nanoparticle constructs for medical imaging and therapeutic applications could accelerate their development and implementation. The complete historical evaluation of the theranostic discipline are pictured in Fig. 1.

As discussed, theranostic approaches have been successfully engaged in treatment of specific types of cancer and have been used effectively to localize and destroy the disease. Without doubt, the intersection between theranostics and personalized medicine is quite clear. Whether cancer, degenerative or infectious diseases theranostic approaches allow a physician to intervene most effectively to combat disease. Successful treatment is dependent on the disease lesion, as demonstrated with certain cancer types, on genetic parameters, and on parameters specific to the disease as well as to monitor disease progression and severity and predict therapeutic responses [55–57]. Thus, the use of the name "personalized" is very much linked to the actual therapeutic index and host factors that would determine efficacy. Indeed, in each and every instance, any implementation of theranostics brings the "concept" of personalized medicine to actual utility and often does affect overall morbidity and disease mortality [56]. This is based on the effectiveness of the developed modality to effectively combine therapeutics and diagnostics into single platforms [58,59]. The unique nature of such an approach is based on specific biological pathways to acquire images for the diagnosis as well as formulations that could be developed that serve to improve delivery of therapeutic agents, ultimately leading to the effectiveness of specific targeted therapies [59–63].

Thus, the overarching concept of theranostics is to deliver medicines at levels capable of eliminating a disease-causing agent, leading to cure. For nearly all applications diagnostic and therapeutic agents are co-delivered in nanoparticles. Thus, nanotechnology has had a dominant role in the field of theranostics in general. A theranostic platform allows



**Fig. 1.** A historical overview of theranostics. (A) Important events during the development of theranostics. (B) The role of theranostics in the diagnosis, staging and treatment of neurodegenerative diseases are outlined in this chart. Abbreviations are as follows: DDS; drug delivery system, MRI; magnetic resonance imaging, MRS; magnetic resonance spectroscopy, DTI; diffusion tensor Imaging, PET; positron emission tomography, SPECT/CT; single photon emission computed tomography, IVIS; *in vivo* optical imaging system and NIR; near infrared fluorescence.

encasements of multiple targeting and imaging modalities into a single formulation to optimize biodistribution of active agents [64].

## 2. Creating biomaterials for biomedical applications

Over the past decade, a vast array of multifunctional nanoparticles “*theranostic nanoparticles*” have emerged as promising candidates for such biomedical applications due to their physicochemical properties, chemical stability and engineered biocompatibility. As the term “*nano*” suggests, these particles have at least one dimension  $<1 \mu\text{m}$  and can be as small as atomic scale lengths of about 0.2 nm [65,66]. A plethora of theranostic platforms have been explored and developed including polymer-drug conjugates, dendrimers, polymeric particles, magnetic particles, solid lipid particles, gold nanoparticles and carbon nanomaterials [67]. Many nanoparticles such as gold particles, iron oxide particles, and carbon nanotubes have intrinsic theranostic capabilities. Others such as micelles, dendrimers and inorganic nanoparticles can be surface functionalized to express diagnostic properties as well as targeting moieties. Such nanoparticles can be altered to meet any desired physicochemical features. Preparations of aqueous nanosuspensions can be achieved through small molecules, surfactants, macromolecules and polymers [68]. However, nanoparticles are readily taken up by the liver and cleared from the systemic circulation. Therefore, modifications are required to extend drug half-life and circulation times. A modifiable surface can also serve to facilitate particle crossing of the BBB. Additionally, functionalization of nanoparticles with targeting moieties can be explored to deliver a particle to disease relevant cell and tissue sites of injury, inflammation or infection [69–74]. Therefore, the fabrication and development of aqueous-stable, stimuli-responsive, biocompatible, targeted nanoparticles with controllable sizes remains a focus of much research. Such nanoparticles are classified based on their size, shape, chemical properties and surface charge [75,76]. The selected classes of nanoparticles are illustrated in Fig. 2 and discussed below.

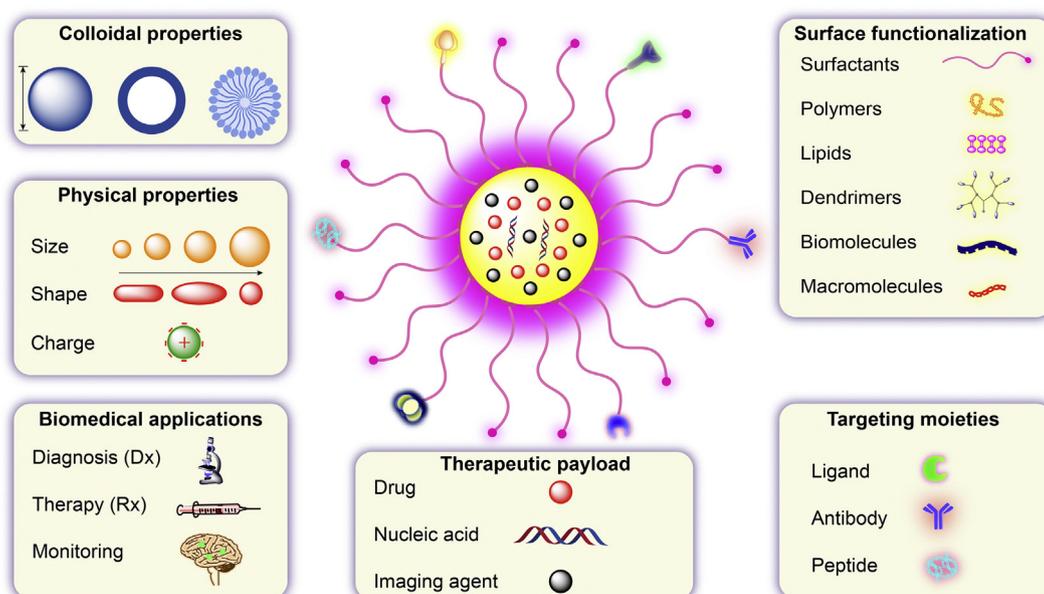
### 2.1. Drug nanocrystals and nanosuspensions

Aggregation and stability (Ostwald ripening) presents major challenges in the delivery of hydrophobic and lipophilic drugs to disease sites after systemic administration [77]. Formulation of such drugs in

forms of drug nanocrystals or nanosuspensions improves their stability and abilities to distribute to tissues of interest [71,78]. A variety of techniques have been employed for large-scale production of drug nanoparticles including precipitation, high-pressure homogenization, freeze-drying, wet stirring and milling [71,78–81]. Amphiphilic stabilizers are typically used in the preparation of nanosuspensions stable in an aqueous media [72,82,83]. Nanosuspensions can maintain therapeutic efficacy and increase drug half-lives by protecting them from rapid systematic metabolism [84,85]. Surface modified nanosuspensions with molecules to recognize receptors on the BBB can facilitate outcomes for neurodegenerative diseases [86,87].

### 2.2. Polymeric nanoparticles

A wide variety of biocompatible and biodegradable nanoparticles have been fabricated using polymeric entities [88,89]. Designing nanopatforms for drug delivery to the nervous system is pivotal importance. To this end, a variety of polymers have been screened for their suitability for brain delivery applications. These include, but are not limited to, poly(butyl cyanoacrylate) (PBCA), poly(isohexyl cyanoacrylate) (PIHCA), poly(lactic acid) (PLA), poly(glycolic acid) (PGA) or copolymers of poly(lactide-co-glycolide) (PLGA), human serum albumin (HSA) and chitosan. All have proven to be promising nanomaterials for human use due to their unique physicochemical properties, biocompatibility, rapid biodegradability, and ease of drug encapsulation. These polymeric nanoparticles provide a specific set of internal and surface properties which: (i) govern encapsulation interactions in the nanoparticle interior between the polymer and the drug(s), (ii) can be further modified by various surfactants to modulate their interactions with other materials post administration, and (iii) are utilized to anchor targeting ligands, glycoproteins or antibodies. For example, peptide decorated cationic nanogels encapsulating-triphosphates of nucleoside reverse transcriptase inhibitors (NRTIs) were created to target the brain-specific apolipoprotein E receptor [90]. In addition, model fluorescently tagged polystyrene nanoparticles were successfully designed to localize in cells (for example hCMEC/D3) as well as enable CNS delivery [91,92]. Studies have shown that the particle size and surface functionalization plays an important role in biodistribution following intravenous administration [93]. Polystyrene nanoparticles were further modified by a viral fusion peptide (gH625), which significantly enhanced the



**Fig. 2.** Design, physicochemical properties and applications of multimodal theranostic nanoparticles. An outline is provided of the physicochemical properties, payload options, imaging agent labeling and surface decoration designed to improve clinical outcomes.

nanoparticle permeation across the BBB [94]. It has been hypothesized that functionalizing nanoparticles with antibodies against cell surface receptors on brain endothelial cells could facilitate increased penetration of compounds delivered in nanoparticles. In one attempt to improve drug penetration across the BBB, researchers used polysorbate-80 functionalized PLGA nanoparticles covalently linked to a transferrin receptor-targeting antibody (8D3). Transferrin receptors are found in abundance on brain endothelial cells and are responsible for the uptake of iron into the CNS [95]. To demonstrate the enhanced BBB crossing of their particles, researchers studied central analgesia in rodents using a classic test of supraspinal responses to pain, the hot-plate test, in which an animal is placed onto a warm (~54 °C) plate and the time which the animal produces a nociceptive response is recorded [96]. As a model drug, the researchers used loperamide, a unique morphine-like opioid receptor agonist that, as a substrate for P-glycoprotein efflux transporters, does not accumulate in the CNS [97]. The maximal possible anti-nociceptive effect (MPE, in %) after injection with transferrin targeted, polysorbate-80 functionalized, loperamide loaded, PLGA nanoparticles was approximately 50% better than controls and twice as great as nanoparticles without the 8D3 antibody (~25%). However, researchers did not actually measure drug levels in any tissue during this study so it is not possible to conclude that more drug actually crossed the BBB and accumulated in the CNS [98]. This is further complicated by the fact that loperamide has a high affinity for both  $\mu$ -opioid receptors and peripheral  $\delta$ -opioid receptors so the increased analgesic effects seen could be mediated through increased peripheral opioid receptor activation [99]. To add further confusion to interpretation of the data, loperamide alone was never used as a control and thus comparison between native loperamide and nanoparticle delivered loperamide was not studied. In fact, the most interesting data from this study was that the greatest MPE was seen after administration of loperamide in 15 wt% of polysorbate-80. This indicates that if loperamide is crossing the BBB in this system, it may be doing so mainly through inactivation of P-glycoprotein efflux pumps by polysorbate-80 [100]. Elsewhere, PLGA nanoparticles modified with a "g7" peptide to target high molecular weight drugs for lysosomal storage disorders in the CNS have been developed [101]. Polymers have also been synthesized for efficient gene delivery across the BBB [102]. Dendrimers, another class of ordered, hyperbranched, macromolecular polymers, are also efficient drug delivery vectors for CNS disorders [103,104]. Studies have shown that fluorescent phosphorus dendrimers can be used for macrophage imaging and diagnosis of spinal cord injuries [105]. Stimuli responsive polymeric nanosystems, known as microbubbles, have gained considerable interest in recent years in the area of image-guided drug delivery vehicles [106–108]. Microbubbles have been found to be efficient delivery vectors, responsive towards focused ultrasound, and enable localized noninvasive imaging of the brain. Unlike other polymeric nanoparticles, they are able to combine various modalities of therapeutics and diagnostics into a single nanosystem [109].

### 2.3. Lipid nanoparticles

Lipid-based nanosystems have been extensively evaluated as nanocarriers for various biomedical applications [110] including treatment of neurodegenerative disorders [111]. Lipids have been known to form multiple varieties of vesicular architectures in aqueous media such as solid lipid nanoparticles (SLNs), monolayer micelles, and bilayer liposomes. SLNs have been successful in delivering various bioactive compounds across the BBB to the desired brain region [112,113]. Their unique vesicular structural properties, biocompatibility and stability make them suitable for delivery of drugs, nucleic acids and other therapeutic molecules. SLNs have also been widely used as theranostic agents due to their high multi component loading efficiency and ease of functionalization for targeted delivery [114]. SLNs are commonly prepared by hot and cold homogenization techniques.

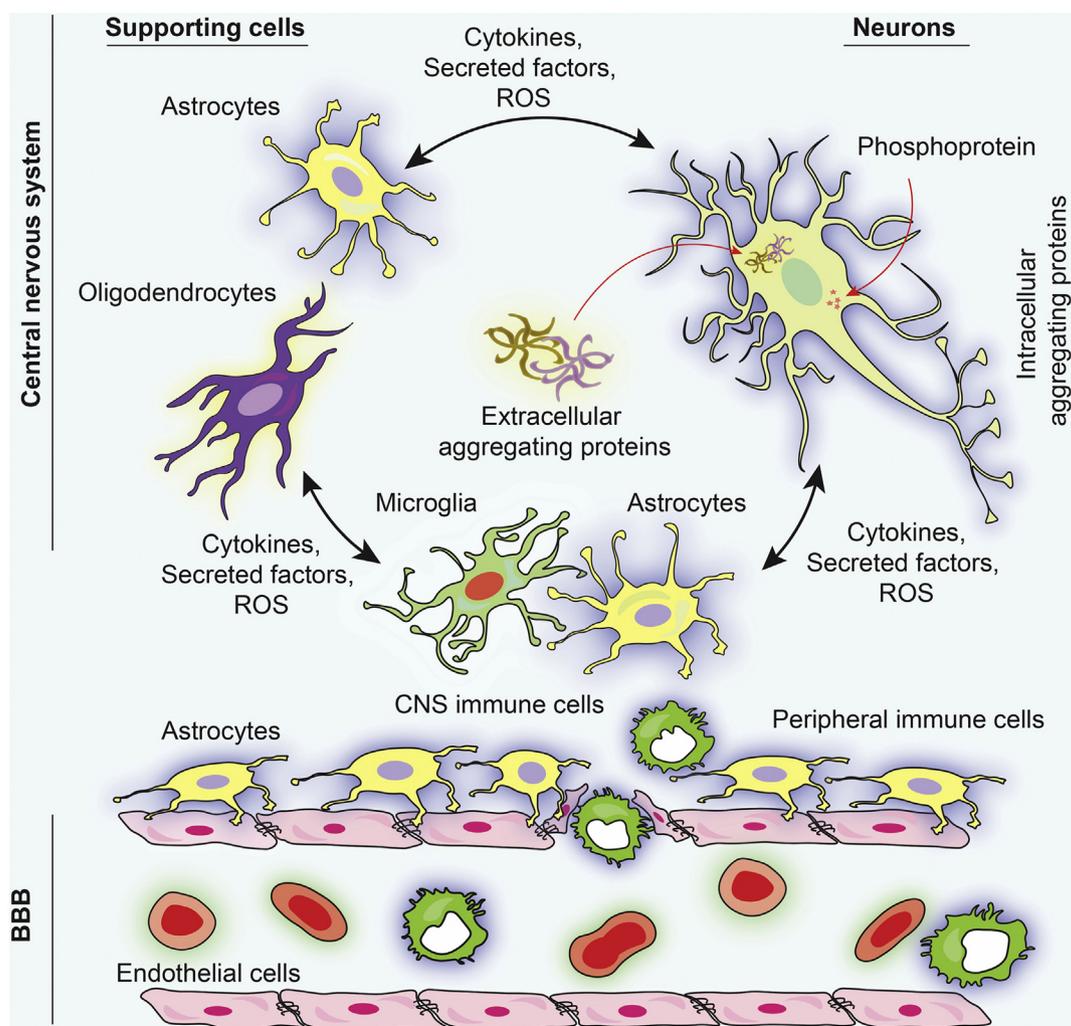
Bae et al., reported on the preparation of quantum dots (QDs) incorporated SLNs with a stable low-density lipoprotein core and paclitaxel incorporated shell with electrostatic complexation of siRNA on the surface of the SLNs. The strong fluorescence from the QDs enables *in vivo* visualization [115]. Liposomes are another type of lipid nanoparticles that have high potential for use as theranostic platforms due to their versatility for functionalization and therapeutic or imaging moiety can be either encapsulated within the hydrophilic core, embedded in the lipophilic bilayer or conjugated to the surface of the liposome. Their small size, hydrophobic and hydrophilic character, biodegradability, biocompatibility, low toxicity and immunogenicity make them effective theranostic platforms [116]. Liposomes are prepared mainly by mechanical dispersions, solvent dispersions and detergent removal. Xu et al., reported on the preparation of theranostic liposomes (QSC-Lip) integrated with SPIONS, QDs and the therapeutic peptide cilengitide (CGT) all encapsulated into a PEGylated liposome for dual-image guided cancer surgery. These liposomes were prepared by a process of film hydration followed by sequential extrusion to obtain particle sizes of about 100 nm [117]. For example, a pharmaceutical liposomal formulation loaded with the amphipathic weak base tempamine was developed for treatment of neurodegenerative disorders [118]. While drug-loaded SLNs were designed to reduce amyloid induced oxidative stress in the case of AD by targeting the hippocampus [119], further improvements were made through intranasal delivery of encapsulated SLNs [120]. Both non-targeted and targeted liposomes have proven efficient in delivery of biomolecules to the brain [121]. Non-targeted liposomal nanocarriers are known to successfully encapsulate hydrophobic drugs but fall short in selective localization. These liposomes showed random biodistribution, which led to accumulation in undesired tissues and development of secondary toxicities. This also results in the requirement of high doses to achieve therapeutic drug levels in tissues. Due to these shortcomings and considering the challenge for blood-brain barrier (BBB) transport, a wide variety of targeting strategies are being tested for CNS delivery. Small molecule ligands such as glutathione have been explored as targeting molecules conjugated to the liposomal surface [122]. For example, one study demonstrated that glutathione-modified drug-loaded liposomes were specifically taken up by brain capillary endothelial cells [123]. They subsequently crossed the BBB successfully, localized in brain tumor cells, initiated tumor regression and increased the survival rate of the experimental mice. Tissue homing peptides have been used in modifying the liposomal surface for improved localization across the BBB [124]. Liposomes loaded with the novel peptide H102 exhibited increased brain penetration when delivered through the intranasal route and localized to the hippocampus. These liposomes showed significant neuroprotective effects [125]. In another study, various peptides were synthesized and characterized for use as targeting ligands for drug-loaded liposomes [126]. These liposomes were able to transport the therapeutic load across the BBB and successfully initiated tumor regression of intracranial glioma. A bi-ligand system was also developed by conjugating transferrin to a cationic polypeptide as a targeting moiety for enhanced localization of labeled liposomes containing a plasmid DNA into the brain [127]. These results support the ability of liposomal nanocarriers to carry macromolecules across the BBB. Using a similar approach, investigators used a dually targeted liposomal nanocarrier for delivery of neuroprotective drug to ischemic neurons [128]. A stroke-homing peptide enabled the liposomal carrier to cross the BBB and a second peptide enabled specific targeting of ischemic neurons. A similar design of dual targeting has been successfully explored by many researchers for BBB transport of therapeutic molecules [129]. The combination of multiple targeting platforms and the fabrication of polymeric-lipoplexes for delivery of neuroprotective and neurotherapeutic agents has been studied [130]. On similar lines, a lipid-protein complex (lipoprotein) was recently developed for combination neuroprotective AD therapies [131].

#### 2.4. Inorganic nanoparticles

The nanoplatforms discussed have proven to be very promising as vehicles to transport therapeutic agents across the BBB. They are primarily dependent on optically active fluorescent molecules as imaging modalities. These fluorescent probes are known to be "photosensitive" and chemically-labile and the images obtained are optically compromised due to the scattering of light originating from signal in deep-seated tissues. In order to combine delivery, diagnostic, and imaging modalities into a single nanoplatform, inorganic nanoparticles have been studied as promising alternatives [61,132–134]. Multifunctional theranostics nanoparticles have been designed, for the most part, as image contrast agents to track the progression of disease and drug intervention [59,135]. New generations of merged particles utilize biocompatible and biodegradable materials and are widely used for concurrent monitoring/imaging of nanotherapeutics [59,136]. Despite challenges posed by the BBB in brain-targeted therapeutics, inorganic nanoparticles have been developed to facilitate delivery of therapeutic agents to the CNS for a variety of neurodegenerative disorders and tumors [137–139]. Among a wide range of theranostics nanoparticles, magnetic and gold nanoparticles have attracted significant interest in biomedical applications due to their unique abilities to respond to an external magnetic field and high X-ray attenuation coefficients. Due to the colloidal nature of metal nanoparticles, their synthesis has been challenging. Although numerous methods have been used to synthesize magnetic nanoparticles of suitable size and disparity, the most efficient method is the chemical co-precipitation technique of iron salts [140] followed by dispersion in an aqueous phase. However, a major limitation of dispersions is the ability to control the process to produce desired particle size and shape. Newer methods of synthesis have been explored such as the laser ablation method, which is very effective in producing small sized particles [141]. The particles are produced as a fine powder with a particle size of 20 to 50 nm and a narrow polydispersity. In another study, Dai et al., used an iron precursor to synthesize SPIONS *via* a polyol process involving high temperature thermal decomposition. These particles were readily dispersible in water with a hydrodynamic diameter of 11.7 nm and a narrow polydispersity [142]. Other types of theranostic particles have been developed that consist of highly magnetic sensitive particles using a multimodal europium doped cobalt ferrite nanoparticles synthesized by solvothermal techniques [59,64]. These particles were coated with a polymer-lipid core shell structure and then functionalized with folic acid to impart macrophage-targeting properties. The particles were further optimized for nuclear imaging by intrinsic labeling with radioactive nuclides,  $^{177}\text{Lu}$  and  $^{111}\text{In}$ , for rapid assessment of biodistribution and pharmacokinetics of antiretroviral drugs [59]. Gold nanoparticles (GNPs) have also been successfully used for theranostic applications. GNPs are commonly synthesized by chemical treatment of hydrogen tetrachloroaurate [67]. GNPs have a core size of about 1.5 to 10 nm and can be chemically conjugated to drugs and targeting ligands to advance therapeutic capabilities. Chen et al., designed smart theranostic GNPs, wherein doxorubicin was conjugated to the nanoparticles *via* a gold-sulfide (Au—S) bond [143]. In order to evaluate size dependent theranostic performances, studies were carried out with insulin-coated GNPs as potential drug carriers across the BBB [144]. Biodistribution and localization of these nanoparticles functionalized for AD was assessed by non-invasive 3D imaging [145].

Neurotheranostics is a new subfield of theranostics that is being developed for neurological disorders. Recent advances in the fields of nanotechnology and bioimaging have enabled the development of a wide array of multifunctional therapeutic platforms capable of transporting drugs across the BBB. For example, attempts were made to functionalize nanoparticles to target specific cell types, releasing drug in a controlled manner, enabling visualization of drug delivery

and uncovering altered functional brain states [146–149]. The field of theranostics, by bridging drug delivery and bioimaging is being applied to identify at-risk patients earlier and as such provide more effective treatments. Regenerative, protective, immune modulatory, anti-inflammatory and imaging agents are readily incorporated into nanoparticles designed to facilitate the delivery of medications to the brain [150]. However, in order to accomplish this the agents must cross the BBB. Based on this need, a variety of colloidal and physical properties along with surface decorations are provided to facilitate drug-encased particle delivery across the BBB (Fig. 2). Drug-loaded magnetic nanoparticles for targeting neurodegenerative diseases such as AD and PD have been well studied [151,152]. Also, optimal magnetic field parameters, which facilitate and dictate crossing of the BBB by these nanoparticles, have been assessed and supported by simulation and mathematical studies [153]. These nanoparticles have also been applied to delivery of RNAi [139]. Magnetic responsive carriers have emerged as the most promising contrast agents for MRI. Kirschbaum and colleagues assessed the performance and efficacy of multifunctional, multimodal theranostic magnetic nanoparticles for imaging of immune cells in a murine model of Multiple Sclerosis (MS) [154]. Peptide-targeted, lipid-modified magnetic nanoparticles have also been developed as multimodal-imaging platforms for molecular imaging of glycoproteins in the brain of epileptic rats [155]. Inherent properties of inorganic nanoparticles such as magnetism, photoluminescence and surface plasmon resonance have broadened their application in theranostic particles [156]. Upconverting luminescent tertiary nanoparticles conjugated with 2-dimensional graphene oxide have been developed as biosensors for specific RNA biomarkers of AD [157]. In addition to imaging, *in vivo* studies have also demonstrated that upconverting luminescent nanoparticles have the potential to capture  $\text{Cu}^{2+}$  ions to minimize aggregation of amyloid  $\beta$ (A $\beta$ ) proteins in AD [158,159]. Self-targeting carbon dots have been developed for localization of agents in the brain tissue, and could also be used for non-invasive imaging [160]. Rare earth metal oxides have been reported to not only localize in the brain tissue, but also can target sub-cellular compartments (mitochondria) in an AD transgenic mouse model [161]. Although there exists a vast pool of functional nanomaterials, promising alternatives include secondary, tertiary and quaternary nanoparticles, insulator-semiconductor quantum dots, molybdenum disulfide, graphene, cerium oxide, and yttrium oxide. Several have found application in the treatment and diagnostics of AD and PD [157,162–171]. Among a vast number of suitable options, magnetic nanoparticles, rare earth oxides, semiconductors, and metallic nanoparticles can be used as theranostic nanoparticles [59,64,162,172–174]. By modulating their shape, size and crystal structure they have been successfully used in clinical settings. Despite their encouraging success in the treatment of diseases such as cancer, bone repair, tissue regeneration, cardiac and vascular diseases, diabetes, arthritis, among others, these theranostic nanoparticles face a major challenge for treatment [6,175]. Current research is focused primarily on brain targeting and localization and brain subregional delivery [176]. While theranostic nanoparticles present opportunities for neurodegenerative disease treatments [177] the challenge that exists is in bypassing the BBB comprised of sealed cell-to-cell contacts and an extensive network of blood capillaries [178,179]. For neurodegenerative diseases therapies must include the means to prevent or eliminate protein aggregates that are known to accumulate in brain subregions [180]. The intracellular protein aggregation consists of misfolded tau,  $\alpha$ -synuclein, Huntingtin protein and superoxide dismutase-1 (SOD1) in the case of AD, PD, HD and ALS, respectively (Fig. 3) [181,182]. Each of these proteins are actively involved in the induction of reactive oxygen species (ROS) and pro-inflammatory responses that play key roles in affecting synaptic function and neuronal vitality [183]. Each of these protein aggregates affect glial (microglial, astrocyte and oligodendrocyte) activation responses or induce circulating immunocytes to affect neuronal function [184].



**Fig. 3.** Molecular mechanisms of neurodegenerative diseases: Role of protein aggregation and neuronal network dysfunction. Protein aggregates deposited in brain subregions are a common characteristic of neurodegenerative diseases [180]. Extracellular and intracellular protein aggregates are commonly observed. The intracellular protein aggregation consists of (a) tau, (b)  $\alpha$ -synuclein, (c) huntingtin protein, (d) SOD1 and (e) self-harm to neurons [181,182]. Each of these proteins are actively involved with cellular processes that play key roles in affecting microtubule and synaptic function [183]. However, amyloid- $\beta$ ,  $\alpha$ -synuclein, and tau are also part of extracellular protein aggregates and stimulate astrocyte and oligodendrocyte responses. These occur with immunocytes to affect neuronal function and vitality [184]. Astrocytes, microglia and oligodendrocyte cytokines and ROS generate a spectrum of immune cell responses that leads to BBB, neural and glial damage [184,200]. Schematic illustration concept was adopted from [201].

### 3. Natural history, pathobiology and therapies for neurodegenerative diseases

Neurodegenerative diseases (for example, Alzheimer's disease (AD) and Parkinson's disease (PD), Multiple sclerosis (MS), Huntington's disease (HD) and Amyotrophic lateral sclerosis; ALS), share in common significant morbidities, high prevalence and mortality rate [185–187]. All are incurable and present enormous and still growing medical, social and economic burdens. Unmet needs are considerable. Thus, the need for improved diagnostics and therapeutic options are immediate. The emergence of theranostics (combinations of diagnosis and therapy) for the nervous system (coined neurotheranostics) is timely in serving to fill an important void based on its potential to facilitate improved disease outcomes. Indeed, making precise and timely diagnoses can facilitate early treatment intervention and as such offers hope to patients in combating disease associated motor, behavioral and cognitive dysfunctions. Notably and in parallel to the suffering lies a prolific financial burden. Indeed, successful therapeutic outcomes would lead to savings of billions of dollars in health care costs that occur with the personal anguish from the disease complex affecting family and friends [188]. Indeed as of 2018, there is essentially nothing the medical industrial

complex can offer the patient in affecting the disease itself as treatments remain symptomatic [189,190].

The challenges in finding improved diagnostic tools and treatments for neurodegenerative diseases are substantive. Indeed, AD and PD are particularly worrisome as they are rapidly increasing in occurrence and frequency. They are both persistent and progressive with links to region specific neuronal impairments and inflammation. Depending on individual disease characteristics both the central and peripheral nervous systems (CNS and PNS) can be engaged and affect cell drop-out [191]. The more common of the two is AD which currently affects approximately 6 million Americans and this number is expected to exceed 14 million by 2050 as the "baby boomers" age [192]. While PD, ALS, HD and MS are less common each still affects large numbers of people. For example, over a million Americans are living with PD [193], 400,000 with MS [194], 30,000 with ALS [195] and another 30,000 with HD [196]. From an economic standpoint alone, the costs associated with caring for patients is staggering. In 2018, medical costs billed to Medicare and Medicaid associated only with AD exceeded \$186 billion and accounted for 67% of associated costs. An additional \$90 billion of the total costs came from patients or their families. If left unchecked the total medical expenditures

(including out of pocket expenses, Medicare and Medicaid) will exceed \$1 trillion by 2050 [197,198].

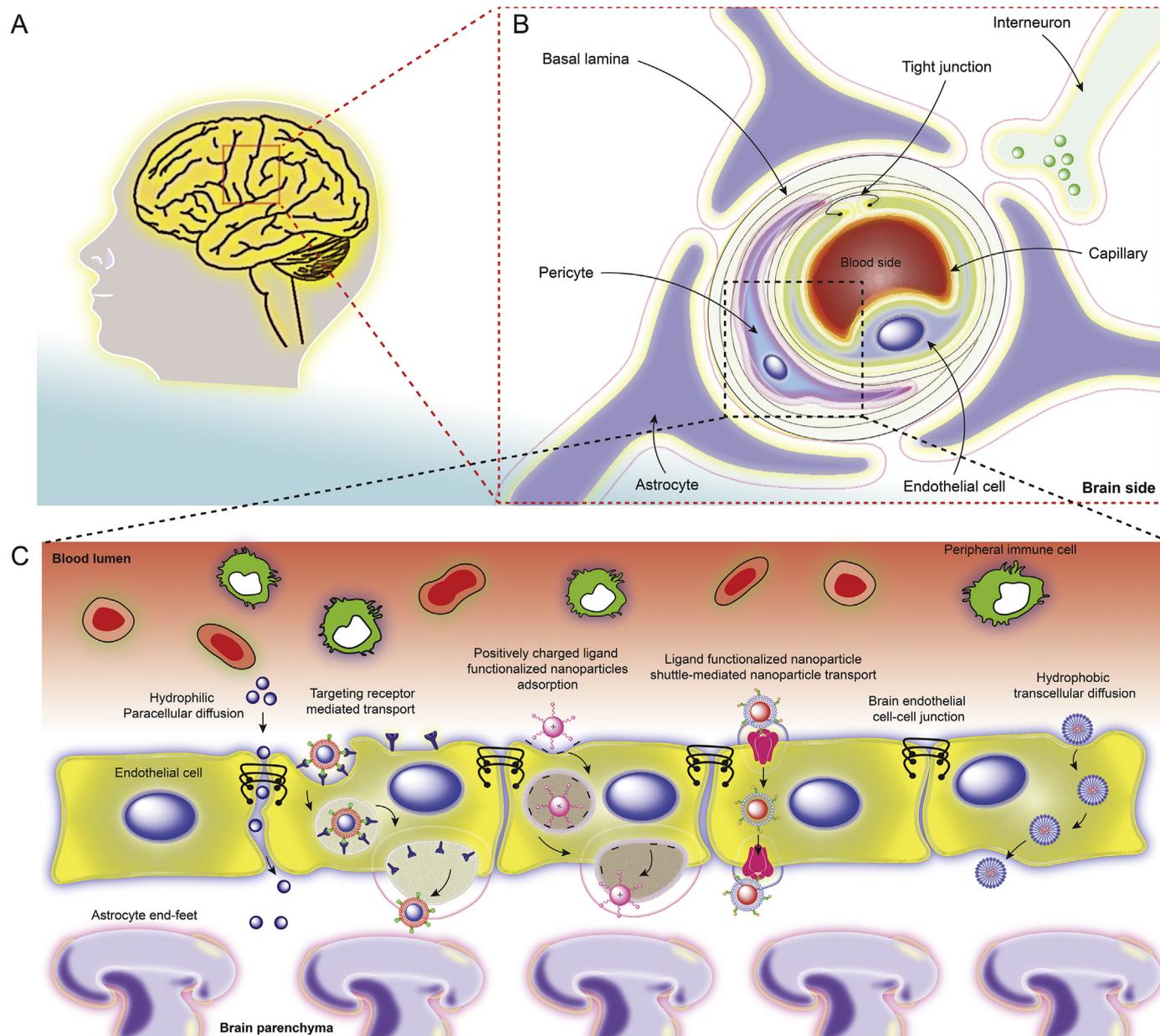
In many cases, current treatments are inadequate to affect disease progression or even ameliorate symptoms of neurodegeneration. In addition, diagnosis of disease may not occur until such time that the disease course is no longer alterable. The futility of current treatments and diagnostic strategies to combat underlying neurological pathologies demands a solution, as it constitutes an enormous psychological, economic and physical burden on patients and caregivers. In addition to ongoing investigations to uncover the underlying etiology of neurodegenerative diseases, the fight against these diseases is hindered by the BBB [199]. Because of this anatomical and functional barrier, current attempts to treat neurodegenerative disorders usually involve flooding the peripheral blood system with therapeutic agents in the hope that a percentage will make its way into the CNS. This approach, though, is inefficient, expensive, and leads to a number of off target toxicities. While blood vessels that vascularize, the nervous system tightly regulate the movement of ions, molecules, and cells from the blood to the brain. This controls brain homeostasis and facilitates functional neuronal control while at the same time protecting neural tissue from toxins and pathogens. Changes in BBB biology also underlie disease pathology and progression within the nervous system. The physiological barrier is coordinated by endothelial cells. These form the walls of blood vessels. What regulates BBB function are the vascular, lymphatic immune, glial and neuronal cell interactions and secretory factors. Affecting each or all of these cell populations can regulate BBB function during disease. The end result is BBB and neuronal damage [184,200] that affects ingress of cells, drug and macromolecules and can be harnessed for therapeutic gain.

### 3.1. Blood brain barrier (BBB)

The BBB as a concept was first introduced to explain a 19<sup>th</sup> century observation that basic dyes, when injected into blood, do not enter the brain. It was hypothesized that some barrier existed between the blood and brain. Indeed, in the 1960s the arterioles, venules and capillaries of the brain were found to differ from those structures located elsewhere in the body in a few important ways. *First*, tight junctions between blood capillary endothelial cells drastically reduce the space between cells forming a tight wall [202]. *Second*, the endothelial cells of the brain capillaries have greatly reduced pinocytosis making the uptake of molecules into these cells more challenging [202]. *Third*, cellular fenestrations and other forms of intracellular gaps are virtually non-existent. These three features ensure that plasma proteins such as albumin do not travel from the blood into the CNS [203]. Selectively located pericytes within the basement membrane also provide support and metabolic functions (Fig. 4) [204,205]. It is also important to note that the vascular BBB is not the only part of the conceptual BBB. The choroid plexus consists of similarly modified ependymal cells that act as a blood-cerebral spinal fluid barrier [206]. The tanycytic barriers that regulate hormonal passage from the hypothalamus to the blood stream along with specialized barriers in the retina and the cranial/spinal nerves are more recently discovered components of the BBB [207,208]. The BBB has a complex ultrastructure and is a gatekeeper for outgoing and incoming molecules as well as vitamins, minerals, biomolecules and hormones. It acts as a rate limiting diffusion barrier between the brain and the rest of the body. As such, the BBB is a significant obstacle for entry of any particulate matter into the brain, which makes treatment of neurodegenerative diseases very challenging. Even at high doses, localization of nanoparticles in diseased areas of the brain is minimal. There are several reasons for the limited success rate of nanoparticles targeted to the brain. The most common reasons are: (a) injected nanoparticles undergo modifications by proteins and enzymes and bind to other macromolecules leading to off-site targeting which results in "nonspecific uptake by healthy cells and tissues" [209–211]; (b) complex nanoparticle fluid dynamics in blood vessels [212]

and instability of target molecules on nanoparticles [213]; (c) limited number of and variability in cell-targeted biomarkers on diseased cells [214], highly selective barriers [215,216], and limited selected transporters for specific cells [214]; and (d) biochemical variables, such as pH differences, in tissues and targeted organs [217]. Therefore, a basic understanding of the functional and structural properties of the BBB plays a crucial role in the design of theranostic nanomedicine targeted to the brain [91]. The complex structure of the BBB, therefore, poses a significant obstacle that nanoparticles must overcome to reach sites within the brain [218]. In addition to restricting drug transport, the selective nature of the BBB limits disease diagnosis. This is based on the fact that 100% of the macromolecular drugs and over 98% of the small-molecule drugs are incapable of crossing the BBB [219,220]. However, the population of patients with brain disease is increasing and has generated a significant unmet need for the development of nanomedicine platforms that can facilitate drug transport across the BBB and localize the therapeutic molecules effectively to target sites within the CNS. To combat this problem, theranostic platforms are being evaluated and developed to improve brain delivery [221–223]. These present opportunities for use as a real-time non-invasive bioimaging platform for early diagnostics, evaluation of drug biodistribution and localization and treatments. The multimodal nature of the developed nanoparticles has been used to successfully target brain drug delivery by various researchers [224,225].

The movement of any drug(s) or therapeutic molecules across the BBB can occur through well-described mechanisms that include paracellular, transcellular transport and adsorptive transcytosis. Paracellular transport occurs passively between endothelial cells, utilizing co-transport of small ions and solutes and its rate is dictated by an electrochemical gradient. The presence of tight junctions between the endothelial cells severely limits the passive transport of any nanoscale agents across the BBB. Water-soluble, small molecules, such as carbon dioxide, oxygen, and small lipid soluble molecules can cross the BBB by transcellular diffusion. During active transport across the BBB, the passage of molecules depends largely on the presence and type of transmembrane glycoprotein receptors. This process can facilitate the crossing of nanoparticles, macromolecules, proteins and peptides having high surface charge, polarity and lipophilicity. Thus, the surface functionality of the nanoparticle, apart from size, will play an important role in identifying the specific receptors and facilitating the passage of any agent across the BBB [144]. A third way for molecules and drugs to cross the BBB is through receptor-mediated endocytosis by the way of caveolae and clathrin-mediated endocytosis [226,227]. Caveolae-mediated endocytosis occurs through specialized "microdomains" within the plasma membrane which are referred to as caveolae [228]. Caveolae are small flask-shape pits (approximately 50 nm in diameter) in the membrane that resemble the shape of a cave. The principal membrane components of caveolae are the caveolin proteins whose expression induce and are required for the formation of caveolae [230]. Although the function of these structures has yet to be fully elucidated, they have been implicated in the endocytosis of certain metabolites [229,230]. Clathrin-mediated endocytosis is a process by which high-affinity transmembrane receptors and their bound ligands are concentrated into "coated pits" on the plasma membrane. These coated pits are formed by the assembly of cytosolic coat proteins, the main component being the protein, clathrin [231]. These coated pits invaginate and with the help of scission proteins, pinch off to form endocytic vesicles that are encapsulated by the polygonal clathrin coat protein that will carry receptor-ligand complexes into the cell [232,233]. Some drugs are also transported via ATP-binding cassette transporters (ABCs) [234]. It has been observed that hydrophilic nanoparticles prefer paracellular diffusion via the tight junctions while hydrophobic nanoparticles prefer transcellular transport. Positively charged nanoparticles are transported via negatively charged plasma membrane caveolae of endothelial cells. Some researchers have used negatively charged quantum rods (QRs) for selective targeting of inorganic nanoparticles to



**Fig. 4.** The structural and functional components of the BBB. (A) Human brain cross-section and (B) cellular structure, and schematic representation of the BBB including, endothelial cells, astrocytes, tight junctions and transporters. (C) Several putative mechanisms for theranostic nanoparticles trafficking across the BBB. This includes, but is not limited to, passive transport of hydrophilic nanoparticles by paracellular diffusion and limited by endothelial tight junctions. Targeting insulin and transferrin receptors mediates transcytosis by functionalization of nanoparticles with antibody and ligands [73,236]. Nanoparticles with high positive zeta potential ( $> 15$  mV) show facilitated BBB passage [237–239]. Smaller hydrophobic and lipophilic nanoparticles cross the BBB by diffusion across endothelial cells [240,241].

neurons. They observed that negatively charged QRs administered at a low concentration (10 nM) interact with the neuronal membrane, whereas positively and neutrally charged QRs never localize to neurons. They proposed that the presence of negatively charged QRs on neuronal cell membranes influences the excitability of neurons by causing an increase in the amplitude and frequency of spontaneous postsynaptic currents at the single cell level and an increase of both the spiking activity and synchronous firing at the neural network level. To this effect, negatively charged QRs of different lengths and diameters were added to primary hippocampal neurons. A fluorescent signal was seen within 10 min of treatment suggesting rapid localization of the QRs to the neuronal cell membrane. Similar results were observed with spherical quantum dots, suggesting a primary role for the negative charge in neuronal localization. Experiments conducted to observe the interaction with neurons showed that nanoparticles interact solely with the

neuronal membrane and this interaction is mediated by neuronal spiking activity. It was also shown that negatively charged nanoparticles not only increase the global spiking activity of the network but also the spiking synchronicity of the network, up to a plateau of about  $-20$  mV. It was also noted that negatively charged nanoparticles are able to trigger an overall increase in neuronal and synaptic activity. A theoretical simulation model explained that the potential on the outer neuron surface only retains negative nanoparticles. These observations suggest that electric activity most likely plays a role in the specificity of the nanoparticle–neuron interaction [235]. The nanoparticles, which are functionalized with targeting moieties, initiate the receptor-mediated transport across the BBB [135]. Adsorptive-mediated transcytosis can also facilitate delivery of medicines that are encased in nanoparticles across the BBB. This is notable as the BBB allows binding and uptake of cationic molecules to the luminal surface of endothelial cells. Once

binding occurs exocytosis can then be facilitated at the abluminal surface. These possible mechanisms involved in nanoparticle trafficking across the BBB are schematically summarized in Fig. 4.

#### 4. Neurotheranostics for degenerative disorders

##### 4.1. Alzheimer's disease and associated dementias

In 1906 a German neuropathologist and psychiatrist named Alois Alzheimer gave a lecture at the Southwest German Psychiatrists meeting in Tübingen, Germany. In his talk, he detailed the clinical history of a relatively young patient he had treated. The patient suffered from a chronic, progressive neurological disorder that caused cognitive impairment, hallucinations, delusions, and social deficits. There was rapid loss of memory, disorientation in time and space that progressed to the patient becoming bedridden and incontinent before proceeding to death in just 4.5 years after onset of symptoms [242,243]. Upon autopsy, a novel observation in the form of neurofibrillary plaques in the neurons of the patient's cortex was made [244]. Plaques like these had not previously been associated with dementia and from further research a new concept emerged that perhaps senile dementia was a treatable disease instead of a normal unstoppable event associated with aging [243]. As more patients were diagnosed with senile dementia, a greater number were identified with symptoms characteristic of AD.

Today, AD is the most commonly diagnosed neurological disorder affecting millions of people worldwide. In the United States alone, it is estimated that 5.2 million people over the age of 65 have AD [245]. This number is expected to increase drastically by mid-century as more of the "baby-boomer" generation reaches the seventh and eighth decades of life [246]. Among developed nations, the chance of being diagnosed with AD doubles every five years after 65 years of age. Further, 10% of people aged 65 or older are affected by some form of dementia and this proportion increases to 33% after age 85 [247]. Around the world, roughly 26 million people were living with AD in 2006 and the number is expected to increase to over 100 million by 2050 [248]. AD and other dementias currently represent an extreme economic burden to society, which will only become more profound over time. In 2018, total healthcare payments related to AD in the US are estimated to be \$277 billion dollars [249]. If the number of people with AD quadruples by 2050 as projected, the total costs related to AD care could reach over \$1 trillion. It is anticipated that even modest advancements in the preventive and therapeutic strategies could slow the onset and progression of the disease and result in a significant reduction of the economic burden [250]. Early in the disease, symptoms are usually mild and are often overlooked. The most common early signs include a disruption of daily life by memory loss, especially forgetting recently learned information, reduced primacy effect (enhanced ability to recall the first item in a list), and an impaired priming ability (the memory gained from prior exposure to a stimulus) [251]. As the disease progresses, deficits in spoken and written language appear. Patients begin using simpler grammatical structures in their speech as their semantic memory and executive control of verbal fluency deteriorates [252] until mutism and echolalia ensues. Executive dysfunction also manifests relatively early in the disease. Patients have challenges in planning and solving problems, increasing difficulty with familiar tasks, trouble understanding images and spatial relationships, as well as poor judgement [249]. Behavioral symptoms include withdrawal from work and social life, agitation, anxiety, irritability, apathy, increased confusion, wandering, aberrant motor behavior and vocalizations, delusions, hallucinations, dysphoria, and insomnia [253].

The clinical diagnosis of AD relies upon family history, symptoms of dementia, and a plethora of AD imaging and blood biomarkers [254]. Physicians look for pathological levels of A $\beta$  or tau (tubulin-associated unit) protein in cerebrospinal fluid. Additionally, PET is employed to identify amyloid deposits in the brain [255,256]. However, a definitive diagnosis can only be obtained by post-mortem examination [257].

Detection of extracellular A $\beta$ -peptide fibrils, intracellular neurofibrillary tangles, and high levels of phosphorylated tau protein are needed to fully confirm an AD diagnosis [258]. AD is characterized by the functional and numerical loss of neurons affected by increase in tau protein tangles and loss in neural receptors [259]. These diminish neurotransmission and affect cognitive function [260,261]. The tangles and the accumulation of amyloid plaques affect neuroinflammation commonly present in AD brains, which are known to affect memory formation and recall of recent tasks and life events [262]. All are associated with reductions in synaptic proteins in brain subregions, resulting in behavioral impairment associated with changes in the brain's microenvironment as well as neuronal cytoskeletal changes and cell death [263]. Indeed, the pathological hallmarks of AD are synaptic loss and neuronal loss, decreases in neurotransmitters, and the abundance of extracellular amyloid  $\beta$ -peptide (A $\beta$ ) fibrils and intracellular neurofibrillary tangles [264]. An AD neuropathological hallmark is neurofibrillary tangles that include intraneuronal-paired helical filaments of hyperphosphorylated tau and A $\beta$ , a 40–43 amino acids fragment of the amyloid precursor protein (APP) [265,266]. APP is expressed in the brain, spinal cord, retina, thymus, spleen, all types of muscle, kidney, lung, gut, pancreas, prostate gland and thyroid gland [267,268]. APP has the characteristics of a cell surface receptor, with the A $\beta$  domain found within the cell membrane. However, the normal function of APP is not completely known, although there is evidence that it plays a role in synaptic formation and plasticity [269]. APP is cleaved by  $\alpha$ - or  $\beta$ -secretases, both of which produce an extracellular soluble APP fragment [270]. The  $\alpha$ -secretase cleavage site lies within the A $\beta$  domain while the  $\beta$ -secretase cleavage site lies outside this domain. This is an important difference because in the next step,  $\gamma$ -secretase cleaves the  $\alpha$ -secretase product into a harmless fragment termed the p3 fragment [271]. However,  $\gamma$ -secretase cleaves the  $\beta$ -secretase product into disordered peptides of 38–42 amino acids collectively referred to as A $\beta$  [272]. The most common isoforms are A $\beta$ <sub>40</sub> and A $\beta$ <sub>42</sub>, which consist of 40 and 42 amino acids respectively. The best evidence for A $\beta$ 's involvement in disease comes from the study of patients with early-onset disease [273,274]. These patients generally have mutations in one of three genes; *APP*, *PSEN1* or *PSEN2* [275]. All three lead to an overproduction A $\beta$ <sub>42</sub> which can undergo conformational changes that induce aggregation of soluble peptide fragments into large fibrils that become insoluble plaques [272](Fig. 3). A $\beta$  plaque toxicity is mediated by multiple mechanisms that include, but are not limited to, oxidative stress, mitochondrial dysfunction, increased membrane permeability, microglial activation, synaptic dysfunction, and excitotoxicity [276–280]. The A $\beta$  plaques first form in the basal cortex but spread gradually to most associative neocortical regions with the exception of the hippocampus [281]. Sensory and motor areas are generally spared until the very late stages of the disease [260,266].

In addition to the extracellular A $\beta$  accumulation, AD is characterized by an intracellular accumulation of hyper-phosphorylated tau protein [282]. Tau is a microtubule-associated protein that functions to stabilize neuronal cytoskeleton microtubules and is mainly localized to axons [283]. Hyperphosphorylated tau does not associate with microtubules as strongly as its unphosphorylated counterpart, resulting in destabilization of microtubules [284]. The abnormal phosphorylation of tau makes the protein much more prone to aggregation. However, phosphorylation of tau alone is not enough to induce aggregation indicating that a second insult may work in an additive or synergistic manner with hyperphosphorylation of tau to affect aggregation [285,286]. Apolipoprotein E (*APOE*) and its polymorphic alleles are the strongest genetic risk factor for developing the sporadic form of AD [287]. *APOE* is responsible for lipid and protein homeostasis and is primarily produced by astrocytes and microglia in the brain [288]. *APOE* was first found to be associated with AD when *APOE* immunoreactivity was observed in A $\beta$  deposits and tangles [289]. There are 3 common isoforms of *APOE*; *APOE2*, *APOE3*, and *APOE4* which differ by only one or two amino acids. The population prevalence of the *APOE3* isoform is roughly 78%,

with *APOE4* at 15% and 7% for *APOE2* [290]. Relatively few studies have investigated the role of *APOE2* in relation to AD. Most studies indicate that *APOE2* is a neuroprotective agent, however, there are studies that indicate the opposite effect. Nagy et al., found that *APOE2* provided protection against both amyloid deposition and neurofibrillary tangle formation in AD patients [291]. Similarly studies suggest that *APOE2* plays a major role in A $\beta$  clearance and can reduce the risk of cognitive destruction [292]. In contrast, Berlau et al., found that *APOE2* expression is related to a decreased risk of dementia but increased AD neuropathology [293]. Population studies suggest a 3-fold increase in the risk of developing AD if one allele of *APOE4* is present in an individual's genome and a 12-fold increase if there are two alleles [294]. Conversely, experiments in mouse models have shown that *APOE3* decreases A $\beta$  accumulation relative to whether there are one or two alleles of *APOE3* present [295]. In *APOE* knock-in mice, clearance of A $\beta$  from the CNS to the plasma depends on which alleles are present in the genome. *APOE4* isoforms lead to the slowest clearance of A $\beta$  and are dose-dependently associated with increased A $\beta$  deposits [296]. Studies like this indicate that *APOE* may act as a chaperone for clearing A $\beta$  from the CNS and any changes in the rate of this clearance can be detrimental to cellular physiology.

Currently there are only five medications approved by the FDA to combat AD. Four are cholinesterase inhibitors (tacrine, donepezil, rivastigmine, galantamine) and the fifth is an *N*-methyl-D-aspartate receptor antagonist (memantine) [297]. These drugs are short lived, their efficacy varies from person to person, and they cannot stop the progression of neuronal damage and loss [298]. Incidentally, the discovery of new drugs has been challenging. In fact, between 2002 and 2012 only one drug (memantine), out of 244 drug candidates, successfully completed clinical trials and was granted approval by the FDA [297]. There are many reasons for the very high failure rate. In addition to doubts that animal models faithfully recapitulate AD in humans, most drug candidates have been unable to provide any added benefit over placebo, cause unacceptable toxicities, or fail to cross the BBB well enough to relieve neurological symptoms [299]. Recently, Becker and Greiga published several reviews on flaws in AD clinical trials and provided a detailed rationale for why such failures occurred. *First*, there are many differences in how studies are conducted among clinical trial centers. *Second*, there are problems in identifying homogeneous groups and managing large numbers of subjects in a clinical trial. *Third*, there is a lack of knowledge of the pharmacological effects of new drugs. *Fourth*, there are flaws in study design, management and methodology, for example, poor design of testable hypotheses that can clearly explain the AD conditions, timing of AD neuropathologies and lack of clinical efficacy of drugs used. Finally, misinterpretation of drug effects can affect the study's conclusions [300–302].

Nanotheranostics provides an exciting opportunity to overcome these limitations. Research into nanotechnology and targeted drug delivery has revealed some general considerations for getting nanoparticles across the BBB; they should be relatively small (<500 Da), lipid soluble and have a neutral surface charge [303]. Indeed, small lipid molecules are favored for transport. Here we review current research into using nanotheranostic approaches for effective drug release/targeting [304–306], surface-engineered nanoparticles for imaging/diagnosis purposes [307–310], and finally surface-engineered nanoparticles investigated as theranostics (simultaneous drug therapy and imaging for AD [310–312]).

## 4.2. AD and theranostics

### 4.2.1. AD diagnosis

The staging and treatment of AD remains limited despite it being the most prevalent neurodegenerative disease [313,314]. Early diagnosis in AD, before the start of clinical symptoms, is a crucial step in preventing the irreversible neuronal damage that eventually leads to dementia and ultimately death [315,316]. Presently, two types of approaches are

practiced clinically for the diagnosis of AD; first being *in vivo* brain imaging of brain amyloid, or inflammation [317], and the second being neuropsychological, cognitive, and neurological assays [318,319] such as measurement of A $\beta$  (specifically A $\beta$ 42), total tau or phosphorylated tau levels in cerebrospinal fluid (CSF) [320]. Since there is no single test or method available for the real time detection of AD progression, there is an urgent need for crucial biomedical technology to facilitate rapid detection of specific biomarkers and proteins that demonstrate the location and density of amyloid plaques in the human brain [321]. Theranostic nanoparticles can serve as nucleation centers for amyloid fibrillation. The interaction of the nanoparticles with amyloid proteins can lead to the formation of intermediate structures that can accelerate or decelerate amyloid fibrillation and hence used as an important device to manipulate fibril formation and provide therapeutic potential. They also have superparamagnetic properties and have been shown to cross the BBB and accumulate in regions of the brain in measurable concentrations [322].

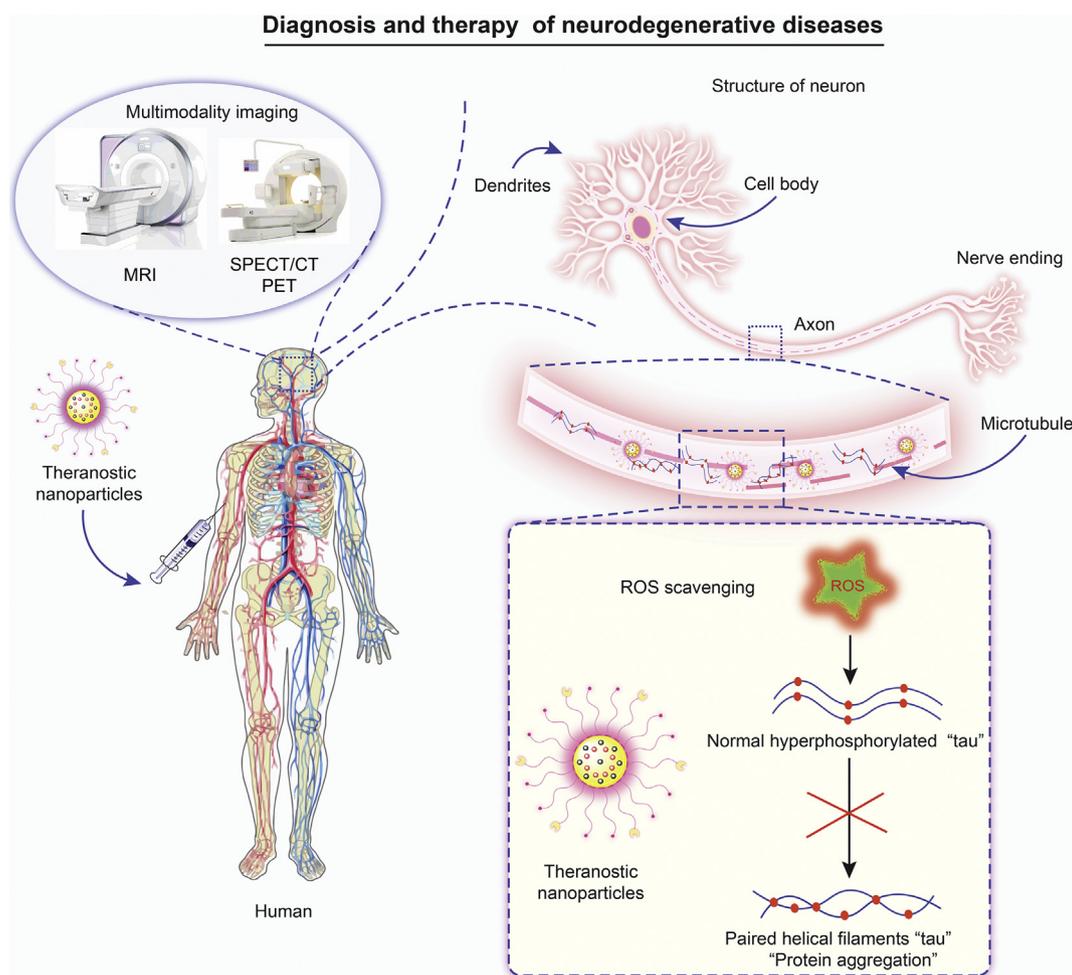
**4.2.1.1. Brain Imaging.** In the last few decades, considerable research has been focused on the development of nanoparticle-based imaging techniques using modalities such as MRI, single-photon emission computed tomography (SPECT) and PET to visualize amyloid plaques in AD patients [317]. Imaging of A $\beta$  and tau pathology with SPECT/CT and MRI has not been well-studied, however, Zhu et al., propose that these techniques could greatly improve our understanding of the pathophysiology and treatment of AD which would better guide physicians in the treatment of each patient [323]. PET scanning was recently approved by the FDA for clinical imaging of both A $\beta$  and tau [324], which will contribute significantly to the early diagnosis, differential diagnosis, and the tracking of disease progression during the preclinical, prodromal, and clinical stages of AD. MRI is a key tool in distinguishing between AD and other degenerative causes of dementia [325]. Skaat et al., recently developed a novel method for selective marking of A $\beta$ 40 fibrils by fluorescent-maghemite nanoparticles for early detection of plaques using MRI and fluorescence microscopy for *in vivo* diagnosis of AD [326]. Similarly, Bingbing et al., reported a system based on the magnetic properties of iron oxide nanoparticles for MRI detection of amyloid plaques and targeted delivery of AD therapeutic agents. To obtain iron oxide nanoparticles, oleic acid coated magnetic iron oxide particles were synthesized. 1, 2-distearoyl-sn-glycero-3-phosphoethanolamine-poly (ethylene glycol) (DSPE-PEG)-Congo red and DSPE-PEG-phenylboronic acid were used to improve the biocompatibility of these oleic acid coated nanoparticles *via* micelle formation. The hydrophilic drug rutin was then grafted onto the surface of the nanoparticles *via* conjugation chemistry. Congo red/rutin-magnetic nanoparticles, when co-administered with mannitol, could penetrate the BBB of APPswe/PS1dE9 transgenic mice and bind to amyloid plaques enabling detection of these plaques by MRI and achieving targeted drug delivery [327]. Other investigators used magnetic nanoparticles conjugated with curcumin that specifically bind to amyloid plaques. These nanoparticles were used to visualize amyloid plaques by *ex vivo* T2\*-weighted MRI in Tg2576 mouse brains [328]. Similarly, bovine serum albumin (BSA) coated high magnetic relaxivity nanoparticles have been developed and further functionalized with sialic acid (nanoformulated NBSAx-Sia) for A $\beta$  imaging [329]. T2\*-weighted MRI showed that NBSAx-Sia binds with A $\beta$  in a sialic acid dependent manner with high selectivity towards A $\beta$  deposited in neuronal cells. Moreover, investigators used an A $\beta$  oligomer-specific antibody conjugated to nitro-dopamine (nDOPA) and PEG-stabilized 12 to 16 nm magnetic nanostructures (MNS). MNS-antibody conjugates can detect AD causing toxic oligomers on nerve cell surfaces by MRI [330]. Similarly, Yang et al., investigated decoration of ultras-small superparamagnetic iron oxide (USPIO) particles with an A $\beta$  targeting peptide for detection of AD plaques using T2\*-weighted microimaging. The T2\* values demonstrated significant contrast-injected in APP/PS1 mice compared to control mice after injected with USPIO-A $\beta$ 1–42 [331]. Recently, other investigators used

different types of polymeric and metal ion complexes as MRI contrast agents in AD diagnostics. For example, biodegradable nanocarrier systems composed of poly(*n*-butyl cyanoacrylate) dextran polymers coated with polysorbate-80 have been used to deliver their payloads across the BBB. Whole brain MRI can be used to visualize amyloid plaques in a mouse model of human disease [332]. Investigators developed nanoparticles with ET6–21 (E)-2,2'-(4-(2-(pyrimidin-4-yl)vinyl)phenyl)azanediyldiethanol) conjugated to detect amyloid pathology in mouse models [333]. Chelated gadolinium and indocyanine green were included in the particles for visualization by MRI and near-infrared microscopy. Their studies demonstrated elevated signal in the brains of mice with amyloid plaques using magnetic resonance imaging (T1-MRI) that was conducted 4 days post-injection. Functional alterations in the AD patient's brain assessed by SPECT and PET could provide diagnosis that is more efficient at monitoring progression of AD [334]. One can visually detect soluble A $\beta$  by PET (Fig. 5).

Images of the brain can visualize disease using PET scans administered with radiolabeled mAb158 [335]. The transferrin receptor antibody facilitated receptor-mediated transcytosis across the BBB. These investigators observed that the PET signal increased with age and correlated with brain A $\beta$  levels. Similarly, investigators fabricated ultrasmall ceria nanocrystals (CeNCs) and iron oxide nanocrystals (IONCs) based on a multifunctional nanocomposite to target hyperphosphorylated tau protein. These multifunctional nanocomposites were functionalized with amino-T807 and grafted onto the surface of mesoporous silica

particles for active hyperphosphorylated tau targeting. This novel tracer was labeled with  $^{68}\text{Ga}$  for monitoring tau protein *in vivo* by MR/PET imaging [336] (Fig. 5). The SPECT images of A $\beta$  plaques in rhesus monkeys using oligoethyleneoxy- $^{99\text{m}}\text{Tc}$ -labeled probes showed significantly enhanced brain uptake [337]. However, SPECT imaging is limited clinically in diagnosing AD compared to PET imaging due to the variable prognostic precision of SPECT images [338]. Development of multi-modal imaging technologies using various particles for design and decoration of targeting ligands will assist in rapid and precise AD diagnosis.

**4.2.1.2. Disease biomarkers.** Identification of biomarkers for diagnosis of AD and associated dementia have become increasingly important. At present, detection of A $\beta$ 1–42, total tau and phospho-tau-181 in CSF by ELISA assay is the most common clinical technique. Sensitivity and specificity of AD diagnosis is made possible by combining all three CSF biomarkers [339]. However, it is a huge challenge to detect and quantify specific biomarkers in CSF and blood using nanoprobe technology. Antibody labeled magnetic nanoparticles is a sensitive and highly specific method for early detection of AD biomarkers. Recently, magnetic biofunctionalized nanoparticles were developed employing antibodies as immunomagnetic reducing reagent against  $\beta$ -amyloid-40 (A $\beta$ -40) [340]. The detection limit for A $\beta$ s using the magnetic nanoparticles *via* immunomagnetic reduction was determined to be  $\sim 10$  ppt (10 pg/mL). Using this detection system, they showed a significant difference between A $\beta$ 40 and A $\beta$ 42 concentrations in human plasma from



**Fig. 5.** Schematic representation of the clinical role of theranostic nanoparticles. Schematic representation of tau pathogenesis with theranostic nanoparticles: Formation of neurofibrillary tangles by the tau protein in Alzheimer's disease (AD) tauopathies. In pathological states tau becomes hyperphosphorylated and detaches from microtubules. Phosphorylated tau then aggregates to form paired helical filaments and neurofibrillary tangles. Here multifunctional theranostic nanoparticles injected into an AD patient precisely target hyperphosphorylated tau. Particles can have ROS scavenging, drug release and bioimaging capabilities. These nanoparticles can scavenge ROS to inhibit hyperphosphorylation of tau, aggregation and release drug. This leads to neuroprotection from ROS mediated cell damage.

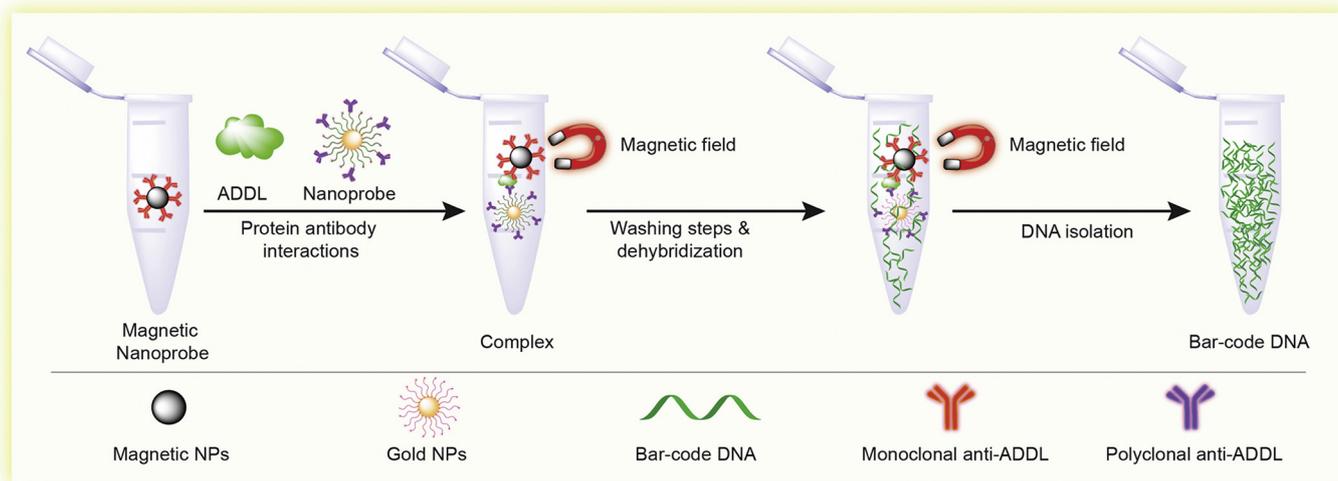
normal individuals and AD patients. Similarly, monoclonal anti-tau antibody-coated gold nanoparticles were employed with a two-photon scattering assay to develop a detection method with 16 times greater sensitivity than previously reported detection methods for AD tau protein. The detection limit was as low as 1 pg/mL and orders of magnitude lower than cutoff values (195 pg/mL) for tau protein in CSF [341]. Gold nanoparticle based dot-blot immunoassay was also developed and demonstrated detection of AD related A $\beta$  peptide 1–42 (A $\beta$ 1–42) at a concentration as low as 50 pg/mL [342]. A novel immuno-polymerase chain reaction (Nano-iPCR) method was developed where gold nanoparticle-tagged tau-specific monoclonal antibodies and oligonucleotide templates are used to quantitate tau protein in human CSF. Nano-iPCR is more sensitive compared to a commercial ELISA kit [343]. Another novel method used A $\beta$ -targeted fluorescent conjugated liposomes in which the targeting moiety was the highly specific A $\beta$  plaque ligand (methoxy-XO4) [344]. These particles were tested in an AD mouse model (APP/PSEN1 transgenic mice) to determine their ability to bind amyloid plaque deposits. They observed that the particles bound to synthetic A $\beta$  aggregates with greater specificity to the free ligand, and selectively bound A $\beta$  plaque deposits in brain tissue sections with high efficiency. However, most of the reported techniques are generally expensive, laborious with low sensitivity. Currently, electrochemical biosensors are extensively used in clinical diagnosis due to their ease of use, high sensitivity and rapid results [345]. Recently, a shape-code biosensor was made for detection of AD core biomarkers by using localized surface plasmon resonance (LSPR). They determined a detection limit of 34.9 f. for A $\beta$ 40, 26 f. for A $\beta$ 42 and 23.6 f. for tau protein corresponding to the ~ 1.0, 2.23 and 3.12 nm of Rayleigh scattering peak shift on a shape-code plasmon system for each biomarker, respectively, in mimicked blood [346]. Another study described a gold-capped nanoparticle LSPR-based immunoassay for detection of 10 pg/mL tau in CSF. This technique was much more sensitive compared to ELISA and could analyze up to 300 samples per chip in a single run [347]. Similarly, others used direct label-free detection of 17-beta-hydroxysteroid dehydrogenase types 10 (17 $\beta$ -HSD10) peptide, a mitochondrial enzyme that is involved in AD pathogenesis using a surface plasmon resonance (SPR) biosensor. They used alkythiolates and amino coupling chemistry for functionalization of A $\beta$  immobilized on the sensor surface or polyclonal antibody against a 17 $\beta$ -HSD10 peptide. The 17 $\beta$ -HSD10-enzyme assay tested in artificial CSF buffer could detect ng/ml levels by high affinity binding of A $\beta$ 40 to 17 $\beta$ -HSD10 enzymes [348]. Other investigators used multi-walled carbon nanotubes

(MWCNTs) modified with a secondary antibody for detection of tau protein using SPR. They used MWCNTs-antibody conjugate to develop a sandwich-based bioassay with the capability to increase the SPR signal around 100-fold compared to direct detection and conventional unconjugated sandwich assays [349]. The oligomeric forms of A $\beta$  called A $\beta$ -derived diffusible ligands (ADDLs) produced from APP are most toxic to brain neurons [350]. The brain, CSF and blood of AD patients were found to have high levels of ADDLs making it a reliable and noninvasive diagnostic biomarker. The bio-barcode amplification system is illustrated as an example of ADDL detection (Fig. 6).

Interestingly, an ultrasensitive bio-barcode assay for measurement of ADDLs concentrations in the CSF was developed. The bio-barcode assay was designed by functionalization of gold nanoparticles and magnetic micro particles with antibodies to ADDLs and used for specific antigen isolation by a sandwich process. They found that ADDLs concentrations for subjects diagnosed with AD were consistently higher than controls. This study was a step towards development of a diagnostic tool based on soluble pathogenic markers for AD [351] (Fig. 6). In a separate study, researchers developed a novel biosensor using an electrochemical redox-generating hydroxyapatite probe to measure the activity of the protease BACE1 (the  $\beta$ -site amyloid precursor protein cleaving enzyme-1) with detection limits as low as 0.1 U/mL BACE1 catalyzes the first step in the synthesis of A $\beta$  peptides that accumulate in the brain in AD [352]. Apart from A $\beta$ , several investigators also looked into using total tau and phospho-tau biomarkers as alternative tools for AD diagnosis. Recently, a highly sensitive and selective assay for acetylcholinesterase (AChE) detection was created based on rhodamine B-modified gold nanoparticles. The uniqueness of this assay was dual readouts by colorimetric and fluorometric techniques. They used the assay to monitor AChE levels in the CSF of transgenic mice with AD, with a detection limit of 0.1 mU/mL. This technology has potential use for early diagnostics and prognostics of AD [353]. Among all the above-mentioned techniques, biosensors have proven to be the most advanced technology for detection of biomarkers, as they are highly sensitive, precise, facilitate rapid analysis over a wide range of concentrations, and enable real time monitoring of specific biomarkers.

#### 4.2.2. AD treatment

Presently, there are no direct therapy or treatment options available for AD patients. However, cognitive and behavioral symptomatic treatments by using various therapeutic approaches may be realistic. Many investigators are working on alternative treatments to slow and change



**Fig. 6.** Bio-barcode amplification. This assay was developed with the aim to isolate amyloid- $\beta$ -derived diffusible ligands (ADDLs) concentrated in the CSF. First step, anti ADDLs mAbs were decorated onto magnetic nanoparticles. Second step, double-stranded DNA functionalized gold nanoparticles were allowed to bind the target antigen to create a magnetic nanoparticles complex. Last step, the sandwich complexes were then magnetically separated and collected as barcode DNA (Concept of assay from [351]).

the progression of the disease and improve the quality of life of people with dementia. Moreover, drug delivery with the help of therapeutic nanoparticles with ultra-small size (1– to 100 nm) can efficiently pass the BBB [354]. Recently, a "redox silence" approach was employed to treat AD. This was achieved by synthesizing a prototype nanoparticle–chelator conjugate (Nano-N2PY). These particles demonstrated an ability to protect human brain cells from A $\beta$  related toxicity by Nano-N2PY–chelator conjugates that inhibited A $\beta$  aggregate formation [355]. Similarly, other investigators used graphene oxide nanoparticles (GO) for AD treatment by using heat from NIR laser irradiation to dissociate amyloid aggregates. Further, functionalized GO–thioflavin-S (ThS) showed a robust ability in mouse CSF to dissociate amyloid deposits and thus protect cells from A $\beta$ -related toxicity upon NIR irradiation. Disaggregation of A $\beta$  fibrils was shown by fluorescence [170]. Thioflavin (ThT) and another fluorescent marker N1AD-4 were also used to detect and help in removal of amyloid protein aggregates by NIR [356]. Similarly, graphene quantum dots (GQDs) covalently linked to tramiprosate, exhibited great ability to reverse aggregation of A $\beta$  peptides by breakdown of the  $\beta$ -sheet structure and reduction of A $\beta$ -related cytotoxicity [162]. Fernández et al., demonstrated that a nanoconjugate composed of magnetic nanoparticles bound to an anti-ferritin antibody, recognized and bound specifically to the ferritin protein and accumulated in the subiculum area in the hippocampus in the brain in an AD mouse model [357]. Delivery of fluorescent carboxyl magnetic Nile Red particles (FMNPs) to the brains of normal mice using a functionalized magnetic field (FMF) composed of positive- and negative-pulsed magnetic fields. Nanoparticles successfully reached the cortex and hippocampus of the brain. Under the same FMF conditions, dextran-coated Fe<sub>3</sub>O<sub>4</sub> magnetic nanoparticles loaded with osmotin (OMNP) were transported into the brains of A $\beta$ 42-treated mice. Compared to native osmotin, the OMNP potently attenuated A $\beta$ 42-induced synaptic deficits, A $\beta$  accumulation, BACE-1 expression and tau hyperphosphorylation [358]. Brain-targeting sulfur nanoparticles were also used to check the effect of different particle morphologies on Cu<sup>2+</sup>-induced A $\beta$  aggregation and neurotoxicity. *In vitro* results showed that spherical nanoparticles maximally reduced A $\beta$ -Cu<sup>2+</sup> complex aggregation and increased cell viability by 92.4% [359]. Cerium oxide nanoparticles also showed a similar effect by formation of amyloid peptides and copper ion complexes and protected against neuronal cytotoxicity [168]. A few other research teams have shown similar results [163,360]. Another research group successfully engineered selenium nanoparticles (SeNPs) with two targeting peptides for inhibiting A $\beta$  aggregation and crossing the BBB [361]. Curcumin is a yellow-colored, plant-derived, polyphenolic compound that has potent pro-inflammatory and anti-inflammatory activities. Detailed experimental studies in recent years have demonstrated that curcumin can be used as a potential drug in the treatment of AD due to its novel property of disaggregating A $\beta$  plaques. To overcome the poor aqueous solubility of curcumin, a polymeric nanoparticle encapsulated curcumin (NanoCurc<sup>TM</sup>) formulation was developed. Neuronally differentiated human neuroblastoma (SK-N-SH) cells were protected from ROS induced oxidative damage by treatment with a range of concentrations of NanoCurc<sup>TM</sup>. Furthermore, NanoCurc<sup>TM</sup> was found to protect and preserve the neuronal phenotype from ROS mediated damage in NanoCurc<sup>TM</sup> treated cells in a dose-dependent manner. *In vivo* studies in athymic mice showed curcumin levels of about 0.322 ng/mg of brain tissue upon intraperitoneal injection suggesting that this formulation is capable of crossing the BBB. NanoCurc<sup>TM</sup> may also be able to provide an intracellular protective redox environment. Hence, this study showed that NanoCurc<sup>TM</sup> treatment has a unique capacity to protect, preserve and rescue human neuronal cells against oxidative damage and can ameliorate ROS-mediated damage in both cell culture and in animal models. This ability of NanoCurc<sup>TM</sup> to achieve significant intracerebral concentrations and offer neuronal protection against oxidative damage, renders it a unique formulation for the treatment of AD [362]. More recently, Luo et al., demonstrated the design of a self-destructive nanoparticles that rely on the multifunctional ability of

peptide-polymers. Acrylate-modified chitosan particles were linked with two functional peptide analogs. Cytotoxicity assays indicated that these particles were non-toxic at a concentration of 20  $\mu$ g/ml. The synergistic effects of the two functional peptides, KLVFF (m) and beclin-1 (n), were explored at different peptide ratios; it was found that structure M3 with peptide ratios of m = 0.5, n = 0.5 enhanced the anti-A $\beta$  toxicity effect. Thioflavin T fluorescence assay was used to confirm the capturing ability of A $\beta$ 42 by the KLVFF peptide on the nanosweeper surface. Transmission electron microscopy (TEM) confirmed the binding effect of M3 particles to A $\beta$ 42. To confirm the internalization efficiency of these particles, *in vitro* studies in N2a cells indicated that the co-assembly of M3 and A $\beta$ 42 not only inhibited the A $\beta$ 42 fibril formation, but also increased the internalization of A $\beta$ 42. Further experiments validated that M3 activated autophagy without blockade of the autophagic flux, suggested the possibility of autophagic degradation of A $\beta$ 42. *In vivo* studies to assess the BBB crossing efficiency and autophagic activity of these particles confirmed brain accumulation and autophagic activity. These findings therefore indicate that multifunctional nanosweepers are capable of specifically capturing A $\beta$ , delivering it into cells and promoting its degradation by upregulating autophagy. This novel technology serves as a promising therapeutic agent for the treatment of AD [363]. An alternative method for AD treatment was described in a recently published report by Kuo et al., and showed that rosmarinic acid had strong antioxidant activity against peroxynitrite radicals, which are responsible for increasing the amounts of amyloid fibrils in the brain of AD patients. They further formulated quercetin and rosmarinic acid in liposomes functionalized with phosphatidic acid (PA) and ApoE to prevent cerebral neurodegeneration [364]. QU acts as antioxidant flavonoid that has been shown to protect neurons against oxidative stress and improve cognitive function in AD rat models [365]. PA and ApoE have been shown to improve the *in vitro* A $\beta$  binding of associated drug carriers [364,366]. *In vivo* studies have shown that quercetin and rosmarinic acid-loaded PA liposomes reduced AChE activity, a prominent marker of A $\beta$  plaque formation in the AD brain. It was also found that addition of Tween-80 and ApoE led to further inhibition of AChE due to improved BBB penetration and neuronal targeting [364]. Taken together, theranostic approaches are more than capable to solve this protein aggregation problem, provide protection from ROS and neuroregeneration and can also cross the BBB.

Alternative treatments based on gene-silencing antisense therapy for AD have also been developed. Farr et al., designed antisense oligonucleotides that can easily bind with the messenger RNA (mRNA) of specific gene targets and then balanced natural protein to toxic protein ratio for reversal of AD symptoms [367]. They demonstrated the successful use of antisense treatment in an AD mouse model by showing reduction in a glycogen synthase kinase (GSK)-3 $\beta$  (GSK-3 $\beta$ ). They observed that after treatment with antisense oligonucleotide (GAO) mice showed improved learning and memory. More recently, DeVos et al., designed and showed successful application of a Tau antisense oligonucleotide (Tau ASO-12) in mice and nonhuman primates [368]. They observed that after treatment with Tau ASO-12, tau levels were decreased in AD mice and brain and spinal cord tau levels were reduced in nonhuman primates. Another alternative treatment is the use of monoclonal antibodies (mAbs) to treat AD by passive immunization. Several studies demonstrated that mAbs are effective at removing toxic A $\beta$  components *via* microglia, complement activation, prevention of the amyloid cascade and inhibition of neurodegeneration and cognitive impairment [369–371]. Banks et al., developed L11.3 and HyL5 human IgM antibodies to A $\beta$  and assessed their ability to cross the BBB in SAMP8 mice a murine model of AD. They observed that L11.3, was effectively taken up into the hippocampus and improved cognition in the aged SAMP8 mouse after direct administration into the brain. These results suggested that L11.3 or other human anti-A $\beta$  antibodies might be effective in the treatment of AD [367]. While there is no direct correlation of treatment with antibodies and clearance of A $\beta$  antibodies could reduce the association of A $\beta$  with the brain microvasculature

[372]. Finke et al., demonstrated that the surface sialic acid modified the monoclonal antibodies (4G8) has high uptake compared to non-modified in the brain of AD patients [373].

#### 4.3. Parkinson's disease and associated synucleinopathies

##### 4.3.1. Parkinson's disease

It's been over 200 years since the second most common neurodegenerative and most common movement disorder was first described in 1817. James Parkinson, an English surgeon and paleontologist, penned the monograph "An Essay on the Shaking Palsy" where he described "paralysis agitans", a condition later renamed PD [374,375]. A century later, in 1912, Frederick Lewis first described the characteristic intraneuronal inclusions (now termed "Lewy Bodies") found in post-mortem brains of patients who had PD [376]. The disease is also typified histopathologically by specific losses of dopaminergic neurons in the substantia nigra pars compacta leading to profound dopamine deficiency [377,378]. This progressive loss of dopaminergic neurons leads to profound motor and neurological symptoms, including static tremors, postural imbalance, bradykinesia, muscle rigidity, impaired olfaction, sleep disorders, gastrointestinal problems and cardiovascular dysfunction [379].

PD affects 2–3% of people older than 65 years of age, with men affected more than women [380]. Although the exact pathological mechanism driving PD is unknown, evidence from population based studies suggest that a variety of genetic and environmental factors contribute to disease progression [381]. Roughly 95% of cases appear to occur sporadically and risk peaks after 65 years of age. The other 5% of cases generally strike before the patient reaches 40 years of age and is termed familial PD. Monogenic mutations have been associated with over 50% of familial and 5% of sporadic PD occurrences [379]. These genes have elucidated key aspects of the pathogenesis of the disease. The first genetic mutation found to be associated with familial PD was a missense mutation in the protein  $\alpha$ -synuclein, encoded by the *SNCA/PARK1* gene [382]. Importantly,  $\alpha$ -synuclein is the main component in Lewy bodies and becomes phosphorylated, which facilitates synuclein fibril uptake by neurons and accelerates the progression of PD [383]. Misfolded, aggregated  $\alpha$ -synuclein among other proteins, neuroinflammation, glial activation and ROS production can all affect disease progression [384]. The highest risk for developing familial PD occurs in carriers of a genetic mutation in the *LRKK2/PARK8* gene, which encodes the Rab GTPase/kinase leucine-rich repeat kinase 2 (LRKK2) protein [385]. Other genetic mutations can occur in genes involved in mitochondria quality control (*PINK1*), ubiquitin ligases (*PARK2*), endoplasmic/golgi protein sorting (*VPS35*), antioxidants (*DJ-1*), glycolipid catabolism (*GBA1*), P-type ATPases (*ATP13A2*), and microtubule associated protein tau (*MAPT*) [386]. The function of these genes and their contribution to PD pathogenesis remain to be fully elucidated.

Similarly, toxins such as herbicides and pesticides, in conjunction with host genetics and aging, are directly implicated as disease inciting events [387,388]. One such toxin was discovered serendipitously and has led to the development of a very popular mouse model of PD. In 1976 a chemistry student trying to create a synthetic heroin, instead produced 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which is a potent and specific toxin to dopaminergic neurons [389]. Other heroin users made the mistake of using this synthetic drug and quickly developed PD like symptoms. Many of these patients were seen by Dr. William Langston, (a California based movement disorder specialist) who saw the potential for this toxin to create a disease model of PD [390]. The first published report that identified MPTP as the cause of permanent parkinsonism in heroin abusing patients with linked toxicities to the zona compacta of the substantia nigra appeared in the journal Science in 1983 [391]. The link between PD and MPTP was established based on the clinical findings and later substantiated by neuropathology identifying the trademark loss of nigral neurons and degeneration of their terminal connections in the striatum [392,393].

However, MPTP shows less of an effect in mouse models than primates, although the C57Bl/6 mouse strain is sensitive to MPTP [394]. Another limitation is that this model causes rapid and transient deterioration of dopaminergic neurons and therefore cannot replicate the chronic pathogenesis of PD [395]. Interestingly, MPTP is structurally similar to a variety of known environmental toxins that have been used to generate other toxin-mediated models of PD such as the herbicide paraquat and the insecticide/fish toxin rotenone [396,397].

Treatments for PD remain symptomatic and none can stop the loss of dopaminergic neurons and associated motor deficits. Initial treatment strategies for dopamine replacement initiated in the 1960s focused on improvement of motor, gait and postural symptoms linked to disease pathophysiology [398]. Levodopa (L-DOPA) is currently the gold standard treatment option for PD and nearly all PD patients will at some point require dopamine replacement by systemic administration of L-DOPA [399]. However, long term L-DOPA treatment is complicated by the development of L-DOPA induced motor complications (*i.e.* dyskinesias) [400]. Other treatment strategies include catechol-O-methyltransferase inhibitors to prevent peripheral metabolism of dopamine [401], monoamine oxidase type B inhibitors to prevent oxidative stress in glial cells [402], and deep brain stimulation using high-frequency (100–200 Hz) electrical signals to stimulate the subthalamic nucleus [403].

##### 4.3.2. Synucleinopathies

Incidentally, PD belongs to the group of neurodegenerative disorders referred to as "synucleinopathies" which are characterized by fibrillary aggregates of  $\alpha$ -synuclein observed pathologically in the cytoplasm of selective populations of neurons and glia [404]. Apart from PD, synucleinopathies also include dementia with Lewy bodies (DLB), pure autonomic failure (PAF), and multiple system atrophy (MSA) [405–408]. As a group, they clinically have in common chronic and progressive signs and symptoms and include, but are not limited to, decline in motor, cognitive, behavior, and autonomic functions [408]. The nature of disease is dependent on the brain subregions affected and the extent affected neuronal populations are damaged or destroyed [405]. There is clinical overlap between the different disorders making a precise diagnosis difficult [404]. Motor, gait, agility and coordination deficits are dominant symptoms but differ in severity and duration for PD, DLB and MSA [409]. Autonomic dysfunction, operative in PAF is common in PD, MSA and DLB. Symptom onset and severity is most significant in MSA and DLB [404]. These along with visual hallucinations characterized by widespread cortical pathologies and dementia are less common in PD [410,411]. However, the deposition of aggregates of synuclein in neurons and glia underlies a common pathogenic mechanism among all the disorders [412]. Although synuclein plays an important role in disease development the variant symptom complex, prognosis and management that characterize each disorder suggest that the extent, commonality and severity of the synucleinopathy itself may have limited predictive and diagnostic value in staging disease [404,412,413].

Theranostic nanoparticles and personalized medicine may be uniquely poised to better treat neurological disorders like PD and even aid in the development of novel strategies for earlier diagnosis and screening [414]. PD is most likely a multifactorial disease with both upstream and downstream pathogenesis that differ from patient to patient and may affect disease outcome. Indeed, PD symptomatology, disease course and neuropathology varies between patients [380]. Nanotheranostics can be developed to differentially screen PD patients for selection of the optimal treatment strategy. Additionally, experimental therapies such as gene therapy, which have shown both promise and failure, are currently delivered *via* adeno-associated viral vectors or by direct injection into the putamen [415–417]. One way to overcome this limitation would be to package the gene editing technology into lipid nanoparticles capable of crossing the BBB and targeting

appropriate cells in the substantia nigra, delivering treatment directly to where it is needed [414].

#### 4.4. PD and theranostics

The molecular changes in PD patients have been well characterized by imaging modalities in clinical practice [418–420]. This technology permits *in vivo* quantification of critical physiological factors such as gene and protein functions, protein–protein interactions, glucose metabolism [421] and neuroreceptor binding, allowing better understanding of the molecular pathophysiology of PD [418,422]. A variety of specific imaging agents have been investigated in order to increase the early diagnosis and therapeutic treatment of PD. Diagnosis using PET by injection of radioisotopes bound to specific tracers is a common technique. Antonini et al., discovered, for the first time, the relationship between striatal DOPA decarboxylase capacity, D2 dopamine receptor binding, and energy metabolism in PD patients by using PET with radioisotope tracers such as  $^{18}\text{F}$ -fluorodeoxyglucose (FDG),  $^{6-18}\text{F}$ -fluoro-L-dopa (FDOPA), and  $^{11}\text{C}$ -raclopride (RACLO) [420]. Similarly,  $^{123}\text{I}$ -ioflupane or DaTSCAN was used for dopamine transporter (DAT) imaging with SPECT for early diagnosis of psychogenic parkinsonism [423,424]. Nowadays, nanoparticle based novel approaches are used for the diagnosis of PD. Recently, McDonagh et al., developed manganese oxide nanoparticles functionalized with L-DOPA that gradually released  $\text{Mn}^{2+}$  ions and L-DOPA. The former moiety gave a positive contrast in MRI and may be useful for the diagnosis and treatment of PD patients [425]. Accumulation of advanced glycation end products in the extracellular space from activated microglial cells is a key factor in pathogenesis of PD and other neurodegenerative diseases [426–428]. Other researchers demonstrated that AGE-albumin could prove useful as a targeting biomarker for theranostic applications [429]. The most common treatment strategy that is employed in PD is the administration of L-DOPA [430]. However, nearly half of the patients who receive this treatment present with complications within the first five years [431]. Presently, nanomedicine has shown promise as a new direction for the better treatment of PD patients. Because of advancements in nanomedicine drugs, research has been focused on the development of therapeutic nanocarriers that can easily cross the BBB. Mead et al., developed new techniques for delivery of the glial cell-line derived neurotrophic factor (GDNF) by use of MRI guided focused ultrasound (FUS) and brain-penetrating nanoparticles (BPN). These particles carried the GDNF plasmid (~4 kB) for sufficient expression of the therapeutic protein at targeted brain tissue areas where MRI is applied with FUS. This study examined the striatum of a 6-hydroxydopamine (6-OHDA)-induced rat model of PD for up to 10 weeks and the strategy was successful in restoring dopamine levels, dopaminergic neuron density and reversed behavioral indicators of PD-associated motor dysfunction [432]. Niu et al., also used novel dual targeted magnetic nanoparticles carrying an shRNA plasmid which could interfere with  $\alpha$ -synuclein synthesis and effectively repair affected brain regions *in vivo* PD models by inhibiting further apoptosis [139]. Interestingly, PEG-PLGA nanoparticles conjugated with odorran lectin were used to develop a nose-to-brain delivery for PD. The therapeutic efficacy of these particles was tested on hemiparkinsonian rats following intranasal administration. The odorran lectin conjugated to PEG-PLGA increased the brain delivery of nanoparticles and enhanced the therapeutic effects of urocortin peptide loaded nanoparticles in PD [433]. Similarly, lactoferrin-conjugated PEG-PLGA nanoparticles were used to cross the BBB *via* clathrin-mediated endocytosis. These particles were tested in rats and found to be effective in decreasing striatal lesions [434]. Pahuja et al., also developed dopamine-loaded PLGA nanoparticles to deliver dopamine to the brain. These particles were shown to successfully cross the BBB and release drug in the brain parenchyma following systemic IV infusion in a 6-OHDA-induced rat model of PD. The investigators further confirmed competency of PLGA nanoparticles in restoring neurobehavioral and neurochemical deficits in

parkinsonian rats [435]. Similar findings were observed in another study where pramipexole dihydrochloride loaded chitosan nanoparticles enhanced antioxidant status by increasing superoxide dismutase and catalase activities, and elevating dopamine levels in the brain in a PD rat model [436]. Chung et al., showed that dextran-coated iron oxide nanoparticles helped to protect dopaminergic neurons damage [437]. Most recently, Hu et al., developed a technique using plasmid DNA (pDNA)-loaded gold nanoparticle (GNP) composites. These GNPs *via* neural growth factor receptor-mediated endocytosis were able to suppress the expression of  $\alpha$ -synuclein, inhibiting the apoptosis of PC12 cells and substantia nigra and striatal dopaminergic neurons. Further efficacy of GNPs was confirmed in PD rodent models [438]. Oral administration of apocyanin, a plant-derived molecule, has been shown to be effective in preventing early PD-like symptoms in PD mouse models. Apocyanin has antioxidant and NADPH oxidase inhibiting properties and has been studied in pre-clinical models of PD, while its dimer diapocyanin has been shown to have neuroprotective and anti-neuroinflammatory effects [439]. In the same context, treatment with diapocyanin was found to greatly improve locomotor activity, restore dopamine levels and provide protection to dopaminergic neurons against further degeneration in pre-clinical models of PD. Interestingly, it was also shown that early administration of diapocyanin restored neurochemical deficits and halted disease progression in a chronic mouse model of PD [440]. Similarly, resveratrol, a plant-derived polyphenolic compound, has been shown to relieve oxidative stress and mitochondrial dysfunction in PD models [441]. Due to low aqueous solubility and slow dissolution rate, the clinical use of this drug has been greatly limited. However, Palle et al., examined resveratrol nanoparticles (NRSV) as a novel drug delivery system for improved bioavailability. NRSV were prepared by antisolvent precipitation method and their neuroprotective efficacy was analyzed by behavioral quantifications. Rotarod performance and other test results indicated increased efficiency of NRSV to ameliorate rotenone-induced PD symptoms, behavioral alterations, oxidative stress and mitochondrial dysfunction in rats compared to free resveratrol [442]. Brenza et al., implemented the neuroprotective properties of apocyanin to synthesize a folic acid (FA) functionalized lipophilic mitochondria-targeted apocyanin (Mito-Apo) nanoparticles. The antioxidant efficacy of these Mito-Apo nanoparticles was tested in primary cortical neurons and the results indicated effective inhibition of  $\text{H}_2\text{O}_2$  induced cell-death by FA functionalized Mito-Apo nanoparticles. The neuroprotective effect of these Mito-Apo nanoparticles was studied in mesencephalon-derived neuronal LUHMES cells and it was found that FA functionalized Mito-Apo nanoparticles were effective in protecting against mitochondrial damage and preventing cell death [443]. These results indicated that FA could be used as an effective targeting ligand for neuronal delivery systems. In conclusion, nanotheranostics applications for PD diagnosis and treatment could be improved by using the new-targeted particles with multiple drug payloads.

#### 4.5. Prion diseases

Prion diseases, also known as transmissible spongiform encephalopathies (TSEs), are a unique group of fatal neurodegenerative disorders that include Kuru, Creutzfeldt-Jakob Disease (CJD), Gerstmann-Sträussler-Scheinker, and fatal familial insomnia [444]. Prion diseases can be hereditary, infectious or sporadic [445]. Pathologically, all are marked by spongiform vacuolation, neuronal loss, astrocytosis and misfolded protein aggregation [446]. British sheep farmers reported the first cases of TSEs in the 1750's, concerned that imported Spanish merino sheep were spreading an unknown disease commonly termed "scrapie" [447]. Scrapie is a fatal, degenerative disease that selectively affects the nervous system of sheep or goats [448]. It is the one of several TSEs related to bovine spongiform encephalopathy (BSE or "mad cow disease") [449]. The sole diagnostic test that is specific requires brain or lymphoid tissue biopsies making disease detection difficult

[450,451]. Sheep typically live 1 to 6 months after the onset of symptoms and are commonly found dead. Although, symptoms may not appear until years after the disease was initially contracted. The common signs and symptoms in animals include behavior changes (nervousness or aggression), excessive self-rubbing, and motor dysfunctions that progress to immobility and death [452]. In addition, tremors of the head and neck, "star gazing," weight loss with change in appetite, wool pulling, and hyperesthesia are common [453]. In humans, broad motor and cognitive symptoms (cerebellar ataxia, oculomotor disturbances, peripheral nerve pain, pyramidal syndrome) followed by dementia are associated with disease and, for example, CJD [454].

For 250 years after the description of the disorder, the nature of the scrapie agent remained unknown [455]. The study of prion biology has led to a new category of infectious and/or heredity agents [456]. Prions are the only known example of an infectious and/or heredity pathogen devoid of nucleic acid [457]. As infectious agents were nearly exclusively assumed to be microbial or viral in nature, the lack of identity of microbial nucleic acids in scrapie infected plasma or tissues made agent associations difficult [458]. Indeed, no microbial or viral agents were found at that time. However, biochemical techniques and our understanding of protein biology advanced significantly and finally in the late 1970s and -80s, research intensified after it was discovered that several rare human TSEs were transmissible to non-human primates [459]. This was followed closely by the Mad Cow epidemic in the 1980s [460]. By that time, observations that TSEs could last for years before symptoms appeared, did not incite inflammation, were resistant to formalin fixation, and could not be inactivated by DNases and RNases [461] were made. These findings led Dr. Stanley Pruisner and colleagues to propose that toxic, infectious, misfolded proteins, which he termed "prions" [461], caused TSEs. The idea that an infectious agent could be devoid of nucleic acid was met with a great deal of skepticism at first, but it is now widely accepted that infectious proteins termed "prions" cause TSEs.

Another pivotal discovery was the finding that cells in the brain [462] constitutively expressed the prion protein. Additionally, prion diseases, are unique in that the causative agent acts as a template to change the conformation of recruited benign forms of the agent into the disease state which has a substantially different conformation from that of its precursor, PrPC. Prion diseases are also exceptional in that they can be acquired in several ways either from genetic mutations of the PrPC gene, sporadic conformational changes in the PrPC protein, or through ingestion of the altered PrPSc [463]. Under healthy conditions, the cellular prion protein (PrPC) assumes a three-dimensional conformation composed of mainly  $\alpha$ -helices with very few  $\beta$ -sheets. These proteins cause disease when they assume an unnatural conformation that is enriched in  $\beta$ -sheets [464]. The abnormal protein is termed prion protein (PrP)-scrapie or PrPSc. The abnormal PrPSc acts as a corruptive seed or template that can recruit the previously benign PrPC and induce the diseased conformation [465]. The self-propagating mechanism leads to ever increasing amounts of PrPSc in cells. Additionally, PrPSc is very prone to self-aggregation and as these aggregates grow in size they can impair normal cellular functions, activate surrounding microglial cells leading to harmful neuroinflammation, and splinter and spread to other cells, irreversibly leading to widespread neurodegeneration [445].

#### 4.6. Prion disease and theranostics

There is currently no appropriate technology for early diagnosis of prion diseases [466]. These diseases are detected through conventional methods by *ex-vivo* tissue analysis after noticeable symptomatic signs of the disease in animals. The *ex-vivo* tissue analysis test includes identification of prion proteins, quantification by ELISA, immunohistochemistry, conformation-dependent immunoassay and cyclic amplification of misfolded protein. These detection assays are time consuming, costly and laborious [467–470]. For example, a serial cyclic amplification of

misfolded protein assay cycle requires approximately three days [471]. Thus, a sensitive and time effective technology for detection of prion protein would be helpful in early accurate diagnosis of these diseases.

To date, there are no effective treatments for human prion diseases [466]. Although animal models exist for many prion diseases, none of the proposed anti-prion therapies have shown efficacy in treating CJD-infected mouse models [472]. However, efforts to find a therapeutic intervention have intensified because there is an increased understanding that more common neurodegenerative diseases like AD and PD also proceed through the self-propagation and aggregation of misfolded proteins [473]. The cellular prion protein (PrPSc) is considered the main target of the anti-prion treatments [474]. There are five different types of approaches that have been used to treat prion diseases. These include (a) small molecule inhibitors such as thioflavine, amphotericin B, quinacrine, pentosan, polysulfate, Congo red, anthracyclines, and memantine [475]; (b) immunotherapies by engineering of anti-prion antibodies [476]; (c) prion gene disruption by using a CRISPR/Cas9 system [477]; (d) targeting of the unfolded protein response; and (e) heterologous prion proteins [478].

These therapeutic approaches for longer treatment of prion diseases are not effective. However, in the last few years, theranostics technology has significantly advanced and has facilitated the easy detection of some complex molecular mechanisms of these diseases. This should prove helpful in providing improved early diagnosis and precise treatments for prion diseases [466,479,480]. Theranostic nanoparticles such as magnetic and gold nanoparticles were demonstrated to bind with prion proteins and were used for imaging [480,481]. Recently, Miller et al., reported that superparamagnetic iron oxide nanoparticles bound to PrPSc molecules efficiently and specifically, permitting magnetic separation of prions from a sample mixture for protein misfolding cyclic amplification reactions to improve detection [466]. Similarly, Irudayaraj's group demonstrated that streptavidin-conjugated gold-coated magnetic nanoparticles functionalized with biotinylated aptamer could be used for prion protein detections [482]. Another study demonstrated use of silver nanoparticle-aptamer conjugates for anti-prion protein detections [483]. Design of nanoparticle-labeled aptamers linked to PrP antibody was shown to be a major development in the diagnosis of prion diseases. Recently, Zhang et al., demonstrated detection of prion protein by construction of a simple biosensor that used protein aptamer and gold nanoparticles. The principle of this assay was binding of the prion protein on the target molecule followed by signal amplification by gold nanoparticles and detection using resonance light scattering [484]. Other investigators have reported development of a surface-modified fluorescence nanoparticle labeled antibody assay for the detection of the conserved sequence of PrP. The surface-modified fluorescence nanoparticle produced a signal when it formed a complex with PrP in samples [485]. In short, there is no actual treatment to date for prion diseases. However, Calvo et al., created a long-circulating PEGylated particle [methoxy poly (ethylene glycol) cyanoacrylate-co-hexadecyl cyanoacrylate] (PEG-PHDCA), which demonstrated higher uptake in target tissues of PrP (brain and spleen) in scrapie-infected animals [486]. Thus, these theranostic technologies will improve upon conventional management of prion diseases due to their ability to cross the BBB and their capability to perform simultaneous diagnosis and long-term treatment monitoring options.

#### 4.7. Motor neuron diseases (MNDs)

Diseases of motor neurons are often regarded as the most devastating adult onset neurodegenerative disorder and are characterized by loss of upper and lower motor neurons [487]. Upper motor neurons originate in the cortical motor regions and their role is to transfer signals to the lower motor neurons, which are derived from the anterior horn of the spinal column and extend to innervate specific skeletal muscle groups throughout the body at junctions termed neuromuscular junctions [488]. A motor unit is comprised of a motor neuron, its axon, the

neuromuscular junction and all the muscle fibers it innervates [489]. In MNDs, the affected neuronal somas undergo apoptosis and this causes the associated axon to degenerate resulting in the destruction of the neuromuscular junction [490]. This destruction leads to rapidly worsening muscular atrophy in the arms, legs, trunk and bulbar region inevitably leading to paralysis and shortly thereafter, death, often by respiratory failure [487]. The risk of developing MND peaks between age 50 and 75 years and most patients succumb to symptoms within 3–5 years of diagnosis, although a fraction of patients do survive into the second decade after diagnosis [487].

Common MNDs include ALS, primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), progressive bulbar palsy (PBP), and pseudobulbar palsy [491]. Among these, ALS is the most common and is often synonymous with MND [492]. It has a widely diverse clinical presentation and the symptoms depend on which motor neurons are affected. Roughly 60% of patients present with weakness in one or multiple limbs, which could be due to upper motor neuron dysfunction in the motor cortex [493]. Around 30% present with difficulty in swallowing (dysphagia) or pronouncing words (dysarthria), which indicate that the lower motor neurons of the medulla oblongata are primarily affected. Up to 5% of patients present with frontal temporal dementia or respiratory weakness [487]. As the disease progresses, symptoms include cramps, stiffness, shortness of breath, swallowing difficulties, insomnia, loss of appetite, uncontrollable laughing or crying, fasciculation, anxiety, pain, fatigue and depression [494].

There are no treatments available for ALS and other MNDs other than symptomatic relief since like other neurodegenerative disorders its cause and pathophysiology are poorly understood [495]. Identification of causative environmental risk factors have also been ineffective to date. About 90–95% of ALS cases present sporadically with no identifiable genetically inherited component [496]. However, in the other 5–10% of cases, there is a genetic linkage and such research has provided insights into the neurodegenerative processes [497]. Clinically it can be difficult to separate familial from sporadic ALS but advancements made in the fields of genetic sequencing and molecular biology technologies indicate that there are up to 20 genes that are affected which increase susceptibility to disease [498]. The most common of these are *SOD1*, *C9ORF72*, *TARDBP*, *FUS*, *VAPB*, and *UBQLN2* [499] and inheritance is primarily autosomal dominant [500]. These genes are linked to antioxidant defense, RNA metabolism, protein homeostasis, and cytoskeletal dynamics [501]. *SOD1* and *C9ORF72* mutations account for the majority of familial ALS but their frequency varies [502]. For example, mutations in *C9ORF72* represent the majority of familial ALS cases in Europe (~40%), but in Asia <10% of familial ALS cases can be linked to a mutation in *C9ORF72* [503].

In 1993, mutations in the Cu/Zn superoxide dismutase gene (*SOD1*) were found associated with familial ALS and this discovery led directly to the formation of the first mouse model of human disease. Since that study, over 150 mutations in *SOD1* have been described and these contribute to 20% of familial ALS and up to 3% of sporadic ALS [504,505]. This observation indicated the critical importance of the *SOD1* gene encoding a homodimeric metalloenzyme that catalyzes the reaction of toxic  $O_2^-$  into  $O_2$  and  $H_2O_2$  [505]. Indeed, the role of ROS mediated toxicity in neurodegeneration [505] is well studied. Nonetheless, treatments aimed at reducing oxidative stress have not been successful in treating ALS or other motor neuron diseases.

Since the mid-1990s, research has supported a broader role of factors beyond *SOD1* for the cause of ALS [505]. Indeed, mutant *SOD1* (mutSOD1), for example, does not lose enzymatic activity [506] and a simple knock down of wild type *SOD1* fails to cause motor neuron degeneration, at least in mouse models of human disease [507]. Studies have also shown that overexpressing mutSOD1 specifically in neurons is not enough to fully cause disease [508–510]. Some researchers changed their focus to the role of mutSOD1 in non-neuronal cells in the CNS. A study in 2003 found that motor neurons with wild type *SOD1* developed ALS type pathology when surrounded by mutSOD1-

expressing microglia but neurons expressing mutSOD1 surrounded by wild type microglia appeared normal [511]. Research has shown that microglia harboring mutSOD1 are more activated, produce more ROS, and affect more motor neurons than microglia with wild type *SOD1* [512]. In addition, inhibition of the production of cytokines reduces neuron toxicity [513]. Thus mutSOD1 results in overproduction of microglial ROS and apoptosis in nearby neurons [514].

The mechanism that causes the microglia to become activated is debated but post-mortem studies found large aggregates that stain for mutSOD1 and other ALS related proteins in the cytoplasm of affected neurons [515]. This supports the hypothesis that an accumulation of mutSOD1 protein aggregates in diseased neurons may activate microglia, which over produce inflammatory cytokines leading to neurodegeneration in a vicious cycle. However, for *C9ORF72*, pathogenic expansions in the non-coding region of a G4C2 (GGGGCC) repeat can occur. In healthy individuals, the number of G4C2 repeats is <25, but in ALS-affected individuals hundreds or thousands of such repeats are present [516]. This is observed in approximately 40% of familial ALS and even 5–10% of sporadic ALS cases [517]. Due to this mutations' association with familial and sporadic ALS, extensive research has been done to find out the correlation between repeat expansion mutation and disease. In relation to this mutation, three broad mechanisms have been proposed to explain neuron death. Firstly, the existence of this large repeat in the promoter region leads to down regulation of *C9ORF72* and a loss of its cellular functions [518]. Secondly, RNA transcripts with many short repetitive sequences in a row can be trapped in cellular nuclei as they recruit an abnormal amount of cellular machinery leading to "RNA foci" which are accumulations of proteins and RNA transcripts that do not make it to the cytoplasm for translation [519]. These RNA foci have been found in ALS patients harboring this mutation [520]. The third proposed mechanism comes from observations that *C9ORF72* mutation carriers show accumulations of dipeptide repeat proteins in their brains and spinal cords [521]. These proteinaceous inclusions have been shown to impair nucleus to cytoplasm transport in affected cells leading to cytotoxicity and cell death [522]. However, more research is required to determine how and to what extent each of these mechanisms may contribute to neuronal death in motor neuron diseases.

#### 4.8. Theranostics for MND

There are currently no curative treatments for MND, and there are only a couple of options for palliative care. For over 20 years, the only drug that could effectively slow down the progression of neuromuscular degeneration was riluzole, a glutamate release inhibitor [523]. But at the time of diagnosis, 50% of affected motor neurons are already lost and treatment with riluzole only prolongs life by about 3 months compared to placebo [524]. Finally, in 2015 edaravone, a neuroprotective agent with known free radical scavenging properties, was approved for the treatment of ALS in Japan and South Korea and in 2017 in the United States [525]. The FDA approved this drug for clinical use to treat ALS patients [526]. Originally, edaravone was developed as an intravenous treatment for acute ischemic stroke, but showed promising results in a mouse model of genetic ALS [527]. However, a double blind, placebo controlled phase two study using intravenous edaravone treatment in patients with ALS did not show a significant difference between control and treatment groups, but a post-hoc analysis revealed a select sub-set of patients who may have benefited from the treatment [528]. Based on this data, phase 3 studies were conducted in patients who were recruited under strict criteria. In this 24-week study, the progression of ALS was slowed significantly in patients given edaravone compared to controls [528]. Because of these stringent criteria, <10% of ALS patients are expected to benefit from such treatment. It is also worth noting that because of the relatively short duration of phase 3 studies, the efficacy of edaravone in the long-term management of ALS and MNDs is not known [529].

Overall >30 agents have been tested to treat or cure MNDs such as ALS, but the only successful treatments are edavarone and riluzole [530]. Hence the research focus has shifted to discovery of biomarkers of MND that could lead to earlier treatment intervention. Such a biomarker would also greatly help the search for new and better medications, as it would provide a real disease-associated end point for clinical trials [531]. The reasons for so many treatment failures include, targeting the wrong target, inability of the drug to cross the BBB and accumulate in the brain at therapeutic concentrations, or because of poor oral bioavailability [532]. There is currently no treatment for ALS or a clear pathway to stop its progression and the inability to make a conclusive diagnosis is a major drawback in designing an effective therapy. Although some drugs have been proposed for the treatment of ALS, their poor bioavailability and inability to cross biological barriers have hindered effective treatment of ALS [533]. Packaging these treatments or prospective treatments into nanoparticle carriers capable of crossing the BBB could prove to be beneficial in the treatment of MNDs and other neurodegenerative illnesses [530]. Recently, Chen et al., demonstrated the development of calcium phosphate nanoparticles (CaP-lipid NPs) for delivery of SOD1-ASO (superoxide dismutase 1-antisense oligonucleotides) to motor neurons. These particles have uniform spherical core-shell morphology and an average size of 30 nm. *In vitro* experiments demonstrated that the negatively charged ASO-loaded CaP-lipid NPs could effectively deliver SOD1-targeted ASO into a mouse motor neuron-like cell line (NSC-34) through endocytosis and significantly down-regulated SOD1 expression in HEK293 cells. Further studies showed that ASO-loaded CaP-lipid NPs significantly increased SOD1 knockdown. To assess *in vivo* delivery of these nanoparticles, empty CaP-lipid NPs were microinjected into live zebrafish larvae. Overall, this study demonstrates that CaP-lipid NPs can circulate freely within the bloodstream following systemic delivery into zebrafish and diffuse throughout the brain and spinal cord after direct injection, suggesting that these nanoparticles could be a useful tool to promote gene delivery for ALS therapy [534].

#### 4.9. Huntington's disease

In 1872, George Huntington reported the first case of hereditary dementia and chorea symptoms in adults between 30 and 40 years of age in the US. This condition, referred to as HD [535,536], is a particularly devastating neurodegenerative disease that affects about 1 in 7300 individuals in Europe and the Americas [537]. Inherited in an autosomal dominant fashion, patients are generally diagnosed between ages 30 and 45, although there is a juvenile form of the disease in which symptoms appear before 20 years of age. The course of the disease is unstoppable and invariably ends with death of the patient within ~20 years of symptom onset [538,539]. HD results in a triad of severe physical, cognitive, and physiological abnormalities. Physical symptoms tend to be the most noticeable and include, but are not limited to, dystonia, abnormal eye movements, impaired gait, posture and balance, difficulty in speaking and swallowing, and most commonly involuntary jerking or writhing movements (chorea) [540]. Cognitively, affected individuals show difficulties in organizing or prioritizing tasks, learning and processing thoughts [541,542], tend to get stuck in loops of thought, behavior or action and lack impulse control. Psychologically, HD leads to depression, social withdrawal insomnia, obsessive-compulsive disorder, mania, or bi-polar disorder [543,544]. A decade of research has provided key insights into the pathobiology of HD and has generated promising therapeutic targets, but to date no curative treatment exists. Thus, treatment of the disease is limited to attempting to maximize the patient's quality of life and functional capabilities. The key symptom of HD is involuntary shaking of the arms, shoulders, hips, and head. It also causes a weakening of the thought processes by slowdown of reasoning skills, loss of memory, and difficulty in focusing, common decision-making issues, and unorganized lifestyle [545,546].

HD is one of nine related conditions termed polyglutamine (polyQ) disorders. PolyQ disorders are monogenic and caused by an expansion of CAG trinucleotides in the affected gene's coding region that are translated into a long string of glutamine amino acids in the protein product [547]. Notably, all nine disorders primarily affect the CNS with almost no effect on peripheral organs or systems (immune, hematologic, or endocrine). In the case of HD, the affected gene, HTT, is located on chromosome 4 and encodes the protein, huntingtin [548]. The normal function of this protein is currently unknown [549]. However, it is well known that the number of polyQ repeats found near the amino terminus of the protein positively correlates with disease severity and age of onset [550,551]. Normal huntingtin protein contains between 6 and 35 of such repeats and when expanded to  $\geq 40$  repeats, the disease phenotype becomes highly penetrant [552,553]. Generally, one allele of the gene will contain a longer repeat than the other and this allele determines the disease progression and age of onset. The long CAG repeats cause the gene to become "fragile" during meiotic cell division and is almost exclusively passed down through fathers, potentially indicating that CAG expansion occurs during spermatogenesis [554].

While normal huntingtin protein does not have a well-characterized biochemical function, studies have shown that it has critical roles in the early development of the nervous system, the production of brain-derived neurotrophic factor, and in cell adhesion [555,556]. It is still not completely understood how polyQ expansion leads to a toxic gain-of function in huntingtin protein, though it is known that the protein is susceptible to proteolytic fragmentation [557]. In particular, a small N-terminal fragment is produced from the first exon containing the polyQ repeat sequence [558]. Interestingly, a large body of evidence now shows that HTT exon 1 can readily form a variety of aggregation structures [559,560] which links HD to other neurological disorders like AD, PD, and ALS.

Fragmentation and aggregation of huntingtin protein forms the foundation of the pathobiology of HD. Fragments of huntingtin protein can be detected in all brain regions of huntingtin mouse models before the appearance of cellular inclusions [561,562]. The likelihood that the fragments will aggregate and cause cytotoxicity is primarily determined by the expression level of the huntingtin protein [563]. Expression of the protein is highest in CNS tissues, which may explain why the symptoms are primarily CNS related [564].

#### 4.10. HD and theranostics

HD is usually diagnosed based on clinical outcomes from family medical history, genetic testing and neuropsychological examinations. There is no treatment that can suppress symptoms or reverse HD progression [565]. Over the last two decades substantial research efforts have focused on the development of an effective HD treatment. Though some small molecules exhibited potential positive results in animal studies, they were unable to produce the same effect clinically. Tetrabenazine is the only single molecule that has been approved by the FDA for symptomatic treatment of HD-associated chorea [566]. Currently, theranostic nanoparticle-based strategies have played a significant role in the rapid diagnosis and prevention of HD [164,567–570]. For example poly(trehalose) nanoparticles that can prevent amyloid/polyglutamine aggregation under extra-/intracellular conditions, reduce such aggregation-derived cytotoxicity, and prevent polyglutamine aggregation [568].

While there are no curative treatments for HD, symptomatic medicines can improve some signs of movement and psychiatric disorders. Various attempts have been made to deliver these neuroprotective and/or neurocorrective therapies to the brain [571,572]. For example, Pradhan et al., utilized the protein aggregation inhibiting ability of osmolytes to prepare glutamine/proline-conjugated zwitterionic nanoparticles. Iron oxide nanoparticles were used as the core and coated with a polymeric shell covalently functionalized with glutamine and proline. *In vitro* studies demonstrated that glutamine and proline can

be 1000 to 10,000 times more effective in inhibiting protein aggregation when employed in their nanoparticle forms. Further results demonstrated that glutamine-functionalized particles were able to block the aggregation of polyglutamine expanded mutant huntingtin protein in a HD model cell line [573]. Bhatt et al., fabricated solid lipid nanoparticles for encapsulation and intranasal delivery of rosmarinic acid. Interestingly, rosmarinic acid is known to have neuroprotective effects, which are undertaken for the prevention of oxidative stress, and intracellular  $\text{Ca}^{2+}$  overload in the neurons [574]. On the other hand, Godinho et al., followed a neuro-corrective approach via siRNA to silence the mutant protein expression in HD. They encapsulated the nucleic acid in a sugar-based ( $\beta$ -cyclodextrin) nanoparticle and observed encouraging results in a rat brain model [575]. In other studies, Debnath et al., developed poly(trehalose) nanoparticles that can reduce amyloid-polyglutamine aggregation and aggregation-derived cytotoxicity in the brain of a HD model mouse. These investigators successfully demonstrated the use of trehalose nanoparticles for efficient brain targeting, entry into neuronal cells, and suppression of mutant huntingtin aggregation [568].

#### 4.11. Spinocerebellar ataxia (SCA)

Spinocerebellar ataxia (SCA) is among a class of neurodegenerative disorders that can be described as progressive, degenerative and monogenic. It has an autosomal dominant pattern of inheritance and affects both males and females equally [576]. There are different types of SCA which are classified based on the mutated gene which is responsible for each specific type. SCA3, referred to as Machado-Joseph disease, is the most common type and the signs and symptoms of most types can develop at any age. The most common symptoms in such patients are difficulty in maintaining coordination and balance, unstable gait, slurred speech, poor hand-eye coordination, dysarthria, dysphagia, vision problems, brisk tendon reflexes, etc. With increasing age, muscle atrophy sets in along with chorea, dystonia, and cognitive impairment, among other symptoms [577]. In the majority of SCA types, the genetic change that causes the condition is CAG repeat expansion. However, there are other repeat expansions as well, such as CTG for SCA8, ATTCT repeat expansion for SCA10 and a point mutation in the PRKCG gene in SCA14 [578,579]. This is the basis on which the diagnosis of SCA is established. In addition, the use of CT and MRI have revealed cerebellar atrophy and loss of brain stem gray matter while PET demonstrated hypometabolism in individuals with ATXN1 trinucleotide expansion [580,581]. There is no specific treatment for SCA which relies currently upon rehabilitative management of physical symptoms. Several groups have studied the neuropathology of the disease in order to guide development of new therapeutic approaches. Alves et al., developed a lentiviral vector model in the rat to study the pathological features in different regions of the brain with emphasis on the substantia nigra, cortex and striatum. They concluded that delivery of mutant ataxin-3 is a new genetic model of SCA3, which could pave the way for development of effective therapeutic strategies [582]. Scoles et al., have explored the possibility of RNA-targeted therapies in two mouse models (ATXN2-Q127 and BAC-Q72) of SCA2. Their target was the ATXN2 gene, which is associated with protein instability and conformational changes in SCA. Using the antisense oligonucleotide (ASO7), they demonstrated that ASO7 could reduce the expression of ATXN2 mRNA and protein, which in turn delayed the onset of SCA2 in both mouse models [583].

#### 4.12. Theranostic potential for SCA

The pathophysiology of SCA is multifaceted, suggesting a series of possible options that are advisable for symptomatic relief. Neurotransmitters such as serotonin, norepinephrine, acetylcholine, dopamine, and histamine are responsible for natural cerebellar function. These molecules are not used as first-line therapy, however some treatments

use small molecules such as riluzole, antiglutaminergics, nicotine receptor agonists, serotonergic therapy,  $\gamma$ -aminobutyric acid (GABA) therapy and insulin-like growth factor-1 (IGF-1) as second-line treatments [584]. There have been several reports on development of anti-SCA therapeutic agents but these have not translated into clinical applications. Only a few reports have described the use of nanoparticles for treatment and diagnosis of SCA. Interestingly, Malhotra et al., developed peptide-tagged PEGylated chitosan nanoparticles for siRNA delivery for use in SCA1. The nanoparticles were tested to deliver a functional siRNA against the ataxin-1 gene in an established model of a neurodegenerative SCA1 over-expressing ataxin protein. The results indicated successful suppression of the SCA1 protein following 48 h of transfection [585]. Prior works employed a gene therapy strategy whereby dopamine D2 receptor was used as a reporter gene and imaged by radioiodinated IBF (5-iodo-7-N-[(1-ethyl-2-pyrrolidinyl)methyl]carboxamide-2,3-dihydro-benzofuran) making it an effective tool for monitoring the progression of SCA [586]. Although there is no effective treatment for SCA, many attempts have been made to deliver the neuroprotective and neurotherapeutic agents packaged in nanocarriers to the affected brain tissue [585,587,588]. The development of theranostic nanoparticles for the rapid assessment of disease progression and design of improved treatment would be of great benefit for treatment of this disease.

#### 4.13. Spinal muscular atrophy (SMA)

Spinal muscular atrophy is an autosomal recessive neuromuscular disorder which is characterized by degeneration of the alpha motor neurons of the spinal cord anterior horn cells [589]. This in turn results in progressive proximal muscle weakness, atrophy and paralysis. In addition, patients also present with the symptoms such as loss of strength of the respiratory muscles, fasciculations of the tongue, difficulty in maintaining posture and dysphagia [590]. SMA has a relatively high incidence rate of 1 in 6000 to 10,000 births and is categorized into types I–IV based on the motor function and age of onset. This incidence rate makes it the second most common autosomal recessive disorder after cystic fibrosis and is almost comparable to Duchenne's muscular dystrophy and ALS [591]. Unlike most neurologic disorders, there is a specific causative factor for SMA and that is mutations in or deletion of the survival motor neuron (*SMN1*) gene [592]. This gene is responsible for the formation of the SMN protein and though *SMN2*, which differs from the former by a single nucleotide, also produces the same protein, it is in very low amounts. The functions carried out by SMN are significant as it facilitates biogenesis and metabolism of various ribonucleoprotein complexes involved in mRNA transport and regulation along with loss of alpha motor neurons of the spinal cord [593–596]. Numerous animal models of SMA have been studied which has provided information about the pathophysiology and molecular pathways of the SMN gene [597]. Although the signs and symptoms provide a clear indication of the condition, diagnosis is confirmed through genetic testing of the SMN gene.

#### 4.14. SMA and theranostics

Most of the current treatment options for SMA are designed to improve the muscle weakness and general health of the patient or to provide orthopedic support [598,599]. Currently, the only approved medication for treatment of SMA is the antisense oligonucleotide nusinersen [600]. Since there is lack of a specific strategy for clinical therapy for SMA, various researchers are exploring nanoplatforms for delivery of interfering or silencing nucleic acids for identification and suppression of mutant protein expression. Shi et al., studied the combinatorial effects of elevated ROS and lack of SOD1 and have attempted to identify molecular targets involved in SMA in mouse models [601]. As an attempt towards targeted SMA therapeutics, Shabanpoor et al., reported a synthetic peptide capable of crossing the BBB and delivering the splice-switching phosphorodiamidate morpholino oligonucleotide

which is targeted towards the motor neurons in the brain [602]. Although various treatment modalities are being explored, gene therapy promises to be the most viable option through insertion of a whole gene or cDNA sequence into the genome of patients with SMA [603]. The diagnosis of SMA uses the McDonald criteria which is based upon clinical, laboratory and radiological evidence of lesions in different brain regions and at different times [604]. Some of the most commonly employed diagnostic tools are neuroimaging-using MRI with gadolinium used as a contrast agent, analysis of CSF for oligoclonal bands of IgG and sensory and visual evoked potentials [605,606]. Recently, gold nanoparticles were used as a colorimetric-based technique for diagnosis of SMA [607]. Taking a cue from this diagnostic tool, it would be advantageous to combine theranostics with gene therapy, as it will be able to directly monitor gene expression and assess therapeutic efficiency simultaneously.

#### 4.15. Multiple sclerosis

MS is a chronic inflammatory condition whereby the immune cells attack the nervous system resulting in demyelization and destruction of myelinated axons in the central nervous system. The hallmark of this condition is the formation of plaques consisting of demyelinated nerve cells in the nervous system. MS is also known as disseminated sclerosis and encephalomyelitis and is a progressive autoimmune disorder resulting in impaired and delayed nerve signaling [608–610]. The symptoms are normally found to develop between the second and fourth decade of life and affect about 2.5 million people worldwide [611]. The etiology of MS is still not well understood, but a number of theories as to its cause have been proposed, including a combination of genetics, immune infections, and environmental factors such as sunlight, UV radiation, Epstein-Barr virus, and vitamin D deficiency. [612,613]. These factors result in an adverse immune response and damage to the myelin sheath. However, the role of genetics is undeniable as there is a 20 to 40-fold increased risk of MS in first-degree relatives of patients. HLA-DRB1\*1501 haplotype is the primary genetic factor which increases the risk of MS susceptibility and is present in about 20 to 30% of the individuals [614]. There is marked gender preponderance in MS as women are found to be affected twice as often as men except in the primary progressive form of MS. Geographically, MS is more prevalent in northern parts of Europe and North America [611]. Depending on the cause and progression of the disease, MS is classified into four groups such as relapsing-remitting MS, primary progressive MS, secondary progressive MS and progressive-relapsing MS. Among all the groups, the first category is the most common and accounts for about 85% of MS patients [615]. MS is a persistent disease, which relapses at intermittent periods and results in diffuse changes in the gray and white matter. In order to study the immunological pathways involved in MS, studies have used experimental autoimmune encephalomyelitis (EAE) animal models. At the same time, studies on the CSF and serum of such patients have revealed an accumulation of iron, which is characteristic of peripheral venous disorders [616–618]. Damage to the myelin sheath occurs as a result of the action of a combination of inflammatory cytokines, proteases and free radicals produced by pro-inflammatory T helper cells, B cells and macrophages [619]. These immunocytes are generated after autoreactive T cells bind to adhesion molecules on the endothelial cells of CNS venules. This in turn enables the cells to cross the BBB with the help of proteases and chemokines [620–622].

#### 4.16. MS and theranostics

There is no cure for MS and therapies are designed to provide symptomatic management and improve the quality of life of the affected patient. However, there are a number of FDA-approved disease-modifying medications, such as interferon  $\beta$ 1a and  $\beta$ 1b, glatiramer acetate and natalizumab, which slow disease progression [623]. Hence, various

research groups have explored the use of nanotechnology and nanoparticles for diagnostic as well as therapeutic applications for MS. Several studies have confirmed that dimethyl fumarate (DMF) has immune modulatory characteristic by minimizing cytokine production. Oral DMF has been approved by the FDA as a first-line monotherapy for MS [624]. Interestingly, Karaborni et al., developed nanoparticle compositions of DMF which in turn resulted in high concentrations of the mono compound in MS patients [625]. Nanoparticles have also been used for improved neuroimaging through the use of engineered molecular imaging probes. Santamaria and coworkers recently developed a therapeutic composition consisting of a MS related antigen for treatment [626]. Theranostics platforms can open up a new avenue for perceiving more efficient targeted medication, early diagnosis and precisely monitoring of MS progression. All together theranostics can provide the opportunities to better treatments for MS patients.

### 5. Therapeutics for neuroprotection and neuroregeneration

Despite abundant developments in understanding the basic biology of neurodegenerative diseases, there are no current treatments that have produced significant outcomes. Neuroprotection has been widely explored as an effective treatment strategy to prevent neuronal degeneration in diseases like AD, PD and MS. Contribution of oxidative stress to progression of neurodegenerative disease is suggested by numerous studies. Indeed, overproduction of ROS is a common observation in neurodegenerative disease patients and may lead to neuronal loss [627, 628].

Neuroprotection reflects the preservation of neuronal structure by reducing the rate of neuron loss over time. As an intervention it influences the etiology or the pathogenesis of underlying neurodegenerative diseases, thus preventing or delaying the onset or the progression of the disease [628,629]. Using effective neuroprotection strategies, disease progression can be slowed or prevented to a considerable extent. The primary mechanisms underlying neuroprotection are the same, immaterial of the disease condition. These mechanisms include mitochondrial dysfunction, increased levels of oxidative stress, inflammatory changes, excitotoxicity, and protein accumulation such as A $\beta$  aggregation and fibril formation in AD. Most neuroprotective approaches involve suppression of oxidative stress and excitotoxicity which work synergistically to accelerate neuronal cell death and degradation. Oxidative stress can be reduced in neurodegenerative diseases through the use of antioxidant supplements [629,630] or other "neuroprotective agents" [631]. While some antioxidants can readily cross the blood brain barrier, including vitamins C and E and N-acetylcysteine [632–634], other available antioxidants cannot [635]. To improve antioxidant penetration across the BBB nanoparticle-based delivery of antioxidants or nanoparticles themselves are being developed for neuroprotection [163]. Cerium oxide nanoparticles (CNPs) have been widely explored as therapeutic drug delivery systems due to their antioxidant potential and potential for treating oxidative stress related conditions [636]. CNPs have unique regenerative properties due to the low reduction potential of the co-existing Ce<sup>3+</sup> and Ce<sup>4+</sup> redox system on their surface, which is an efficient scavenger of free radicals involved in oxidative stress. CNPs are well tolerated *in vitro* and *in vivo*, making them suitable for application in neuroprotection and regeneration [167]. To utilize the antioxidant properties of CNPs, Schubert et al., developed cerium and yttrium oxide nanoparticles. Yttrium nanoparticles were studied due to the high free energy of oxide formation from elemental yttrium. Experimental results showed that cerium and yttrium oxide particles were non-toxic to HT22 neuronal cells and had antioxidant properties that could promote cell growth and survival under oxidative stress conditions. It was noted that the neuroprotective efficacy of these particles was related to their structure and did not depend on their elemental composition [166]. In another study, Das et al., synthesized ultrafine, non-agglomerated CNPs by a microemulsion process for neuroprotective applications in spinal cord injury and neurodegenerative disease.

*In vitro* studies in a serum-free cell culture model of adult rat spinal cord indicated a significantly higher cell survival in CNP-treated cultures compared to control cultures. Immuno-staining showed significantly higher numbers of neuronal cells in CNP-treated cultures compared to control cultures. The reversible nature of the  $Ce^{3+}/Ce^{4+}$  redox system on the surface of the CNPs confers an autocatalytic property onto these particles. A hydrogen peroxide-induced oxidative injury model utilizing the adult spinal cord model system was used to demonstrate the autocatalytic property of CNPs. The results indicated that the CNP-treated cultures had a significantly higher peroxide detoxification ability suggesting neuroprotective property. The autocatalytic property of these particles, which enables them to regenerate their antioxidant effect, appears to be responsible for their neuroprotective action [637]. CNPs also decrease ischemia through reduction of the levels of 3-nitrotyrosine, a tyrosine modification caused by peroxy-nitrite radicals. Using an *in vitro* model of brain ischemia, Estevez et al., studied the neuroprotective efficacy and extent of cellular localization of CNPs in a rat model of ischemia. Investigators were demonstrated the primary underlying mechanism by which CNPs exert their antioxidant effect involves a significant reduction in peroxy-nitrite, which in turn is responsible for the formation of 3-nitrotyrosine [165]. More recently researchers found that epigallocatechin-3-gallate (EGCG), a polyphenolic compound present in green tea, has potent antioxidant activity [638]. Several studies have been carried out to examine the interaction of EGCG with a large number of amyloid-forming proteins such as A $\beta$ ,  $\alpha$ -synuclein, transthyretin, and huntingtin, all of which are involved in neurodegeneration [639–646]. EGCG is a promising drug delivery system as it is able to redirect the amyloid formation pathways and promote the assembly of low-toxicity aggregates to a certain extent [647,648]. However, EGCG has poor aqueous solubility, which limits its bioavailability and efficiency of targeted cellular uptake. Selenium (Se) is a trace element that is essential to the system and plays a significant role in assisting cells to resist oxidative damage. "Se" is present biologically in the form of selenoproteins, which play important roles in cellular redox regulation, detoxification and immune system protection [649]. Due to its high expression in the brain, it is thought that Se may be responsible for neuroprotection *via* antioxidation [650]. In order to utilize the therapeutic potential of EGCG and Se, EGCG-stabilized SeNPs (EGCG@Se) were synthesized. These particles were then coated with Tet-1 peptide due to the affinity and binding characteristics of Tet-1 peptide to neurons (Tet-1 EGCG@SeNPs). *In vitro* results indicated that the introduction of nanoparticles into A $\beta$  substantially inhibits A $\beta$  aggregation. Cytotoxicity and ultra-structural analysis assays show significant evidence of the ability of Tet-1 EGCG@SeNPs to effectively mitigate A $\beta$  fibrillation. Studies performed to assess the disaggregation of preformed A $\beta$  fibrils by Tet-1 EGCG@SeNPs, suggested that these nanoparticles are able to successfully convert  $\beta$ -sheet-rich fibrils into amorphous aggregates. It was also found that these nanoparticles were capable of transforming A $\beta$  fibrils into structures with reduced ROS producing capability. Hence, these results suggest that Tet-1 EGCG@SeNPs are promising candidates for A $\beta$  disaggregation and can mitigate A $\beta$  fibrillation. These results suggest that EGCG and Se have the potential to serve as effective therapeutic agents in the treatment of AD [651]. In other studies, Esteves et al., used retinoic acid (RA) loaded nanoparticles as a neuroprotective drug delivery system for an *in vivo* PD model [652]. RA is important for midbrain dopaminergic (mDA) neurons because its receptors and RA-synthesizing enzymes are abundantly expressed in these neurons and their target regions. *In vitro* and *in vivo* studies in a mouse model of PD showed significant neuroprotective effects upon intra-striatal injections of RA nanoparticles (RA-NPs) *via* decreased levels of Nurr1 mRNA expression. These RA-NPs were also found to support dopaminergic neuronal projections present in the striatum [652]. Future studies will require illuminating the neurological mechanism of action of the theranostic nanoparticles and other agents. The combination of theranostic nanoparticles with

other antioxidants demonstrates a favorable course of action as it prevents events that lead to neurodegenerative injury.

## 6. Nanoparticles and Neurotoxicity

With the surge in research and development, nanoparticles have increasingly been featured in the diagnosis, therapy and monitoring of disease progression in humans. Animal models have shown that nanoparticles such as zinc oxide and iron oxide are able to translocate into the brain by virtue of their size and ability to be surface modified depending on the purpose for which it was fabricated [653–655]. Since the delivery of drugs into the CNS through the BBB is hindered due to various factors, coated nanoparticles such as PEG, transferrin, thiamine, glutathione, and others have proven to be ideal choices as drug carriers [656–659]. Nanoparticles have been extensively used in the development of nanoscaffolds for neuronal growth; carbon nanotubes have proven to be particularly effective in this application [660]. Apart from therapeutic applications, nanoparticles are also used for diagnostic purposes such as nanoelectromechanical systems for the assessment of parameters such as intracranial pressure and cerebrospinal fluid [661]. Although, the application of nanoparticles as contrast agents in medical imaging technologies has shown extraordinary progress further development is needed to enable their use as early diagnostic tools [64,69,174,662,663].

Despite the fact that these properties of nanoparticles make them an attractive choice as drug carriers into the CNS, there is an undeniable risk of toxicity, which in turn could result in neurotoxic defects [664]. Hirst et al., had studied the biodistribution and the anti-oxidant effects of CNPs and they found CNPs induced liver toxicity in mice [169]. Similarly, Repar et al., observed that citrate coated silver nanoparticles (AgSCs) were toxic to human embryonic stem cell-derived neurons and astrocytes [665]. Morphological and biochemical assays indicated that AgSCs reduced neurite outgrowth, decreased postsynaptic density protein 95 and synaptophysin expression, and induced neurodegeneration *via* the glycogen synthase kinase-3 and caspase pathways. Results also showed that at low concentrations, AgSCs promote astrogenesis, increasing the astrocyte/neuron ratio. Though there has been no direct correlation between nanoparticles and CNS diseases in humans, studies in mice indicate the potential for neurotoxic effects [665]. Mirasattari et al., reported that repeated oral ingestion of silver nanoparticles led to the development of myoclonic status epilepticus in a 71-year-old male [666]. There have also been reports that nanoparticle exposure in mothers may be harmful to fetal development [667]. Interestingly, Shimizu et al., observed toxicity of titanium oxide nanoparticles on mice brain development associated genes [667]. Similarly, studies by Mohammadipour, et al., indicated that titanium oxide nanoparticles impaired memory and learning in fetal mice [668]. In addition, zinc oxide nanoparticles induced necrosis and apoptosis in murine macrophages through p47phox and NADPH oxidase regulated ROS formation [669]. These studies together indicate that, although nanoparticles have a host of advantages, significant research still needs to be done to ensure that neurotoxicity is negated.

## 7. Macrophages and Bioimaging

Macrophage (cell)-based imaging is of increasing interest for diagnostic as well as therapeutic applications, through their ability to deliver nanometer sized contrast and therapeutic agents to disease sites for theranostics [670]. In fact, macrophage based theranostic platforms have emerged as promising bioimaging tools for overcoming limitations in assessment of drug pharmacokinetic and biodistribution [2,671,672]. Many physicochemical factors are important for nanoparticulate drug biodistribution, such as particle surface charge, size, shape, hydrophobicity, surface functionalization or composition of coating material, and protein binding ability [673,674]. Current studies have shown the effects of nanoparticle size and shape on macrophage uptake

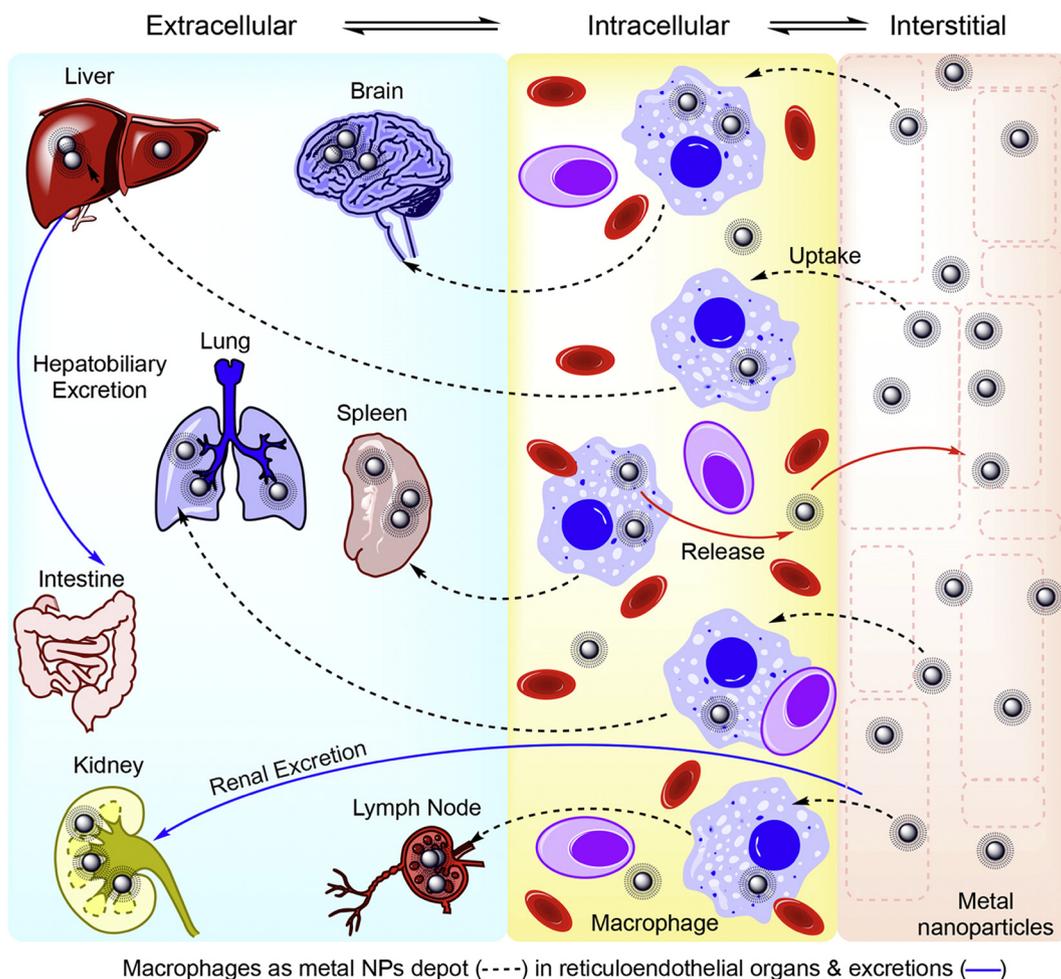
[675,676]. These sizes and shapes define precise biological topographies in the interaction with macrophage receptors [676]. Macrophages phagocytose large amounts of nanoparticles and store them in subcellular compartments for long-term systemic circulation and depot formation in reticuloendothelial organs [212,677–679].

Macrophages can also release metallic nanoparticles from their intracellular compartments into plasma (reverse metabolism) in response to systemic requirements [64,174]. In short, metal nanoparticles are rapidly taken up by blood circulating monocytes and establish drug depots in the reticuloendothelial system (spleen, lymph nodes and liver), creating flexibility for imaging these tissues for rapid and real-time assessment of biodistribution of drug or biomolecules [670,676] (Fig. 7). Imaging nanoparticles loaded in macrophages provide a tool of choice to monitor the participation of macrophages in inflammatory processes of various diseases and release particles at sites of inflammation. Macrophage-loaded nanoparticles retained within reticuloendothelial system organs can be easily detected by modern imaging techniques (MRI, [64,174], CT, PET [670], SPECT [684] and fluorescence [685,686]).

Macrophage-based imaging has unlocked new horizons for diagnosis and therapeutics, as well as predictions of disease progression and design of personalized therapeutic approaches [687]. Two major classes of nanoparticles have been reported for cell based bioimaging applications, based on particle type; (i) inorganic nanoparticles such as metal (silver, gold) [688], metal oxides (iron oxide and cobalt ferrite) [689], rare earth doped nanoparticles, metal-doped silica nanoparticles [174,688], gadolinium [690] semiconductor nanocrystals (e.g. quantum

dots (QDs) and more recently up-conversion nanoparticles [688,691], and (ii) organic nanoparticles (e.g. dye labeled polymeric as well as lipid particles and dye labeled drug nanocrystals) [680,692,693].

Magnetic nanoparticles (MNPs) have attracted extensive attention due to their widespread applications that include magnetic separation, magnetic hyperthermia, and use as contrast agents for MRI [682,683,690]. In particular, iron oxide nanoparticles (IONPs) have attracted extensive interest due to their superparamagnetic properties [682,683,690]. IONPs with diameters between 1 and 100 nm are most widely used in biological systems [694,695] and are mainly in the forms of magnetite ( $\text{Fe}_3\text{O}_4$ ) and its oxidized derivative maghemite ( $\gamma\text{-Fe}_2\text{O}_3$ ) [674]. Other types of MNPs that are used in bioimaging include other forms of ferrite [64,174], dysprosium, manganese [690,696,697], neodymium [698], and gadolinium [699]. More recently, MNPs have been modified to enhance their biocompatibility and ease attachment of targeting moieties to trace disease progression as well as therapeutic applications. Silica coated cobalt ferrite nanoparticles have been applied as multimodal probes for tracking antiretroviral drug biodistribution, utilizing macrophages as carrier vehicles [64,174]. After intravenous administration of MNPs to animals, they are taken up by macrophages *via* clathrin-mediated endocytosis in addition to phagocytosis and macropinocytosis [700]. The uptake of MNPs by macrophages creates a unique *in vivo* tool by which imaging techniques can be used for screening of macrophage involvement in inflammatory processes, such as HIV infection, HIV-1 associated encephalitis [701,702], bacterial infections [703], CNS diseases [704,705], tumors [706,707] and

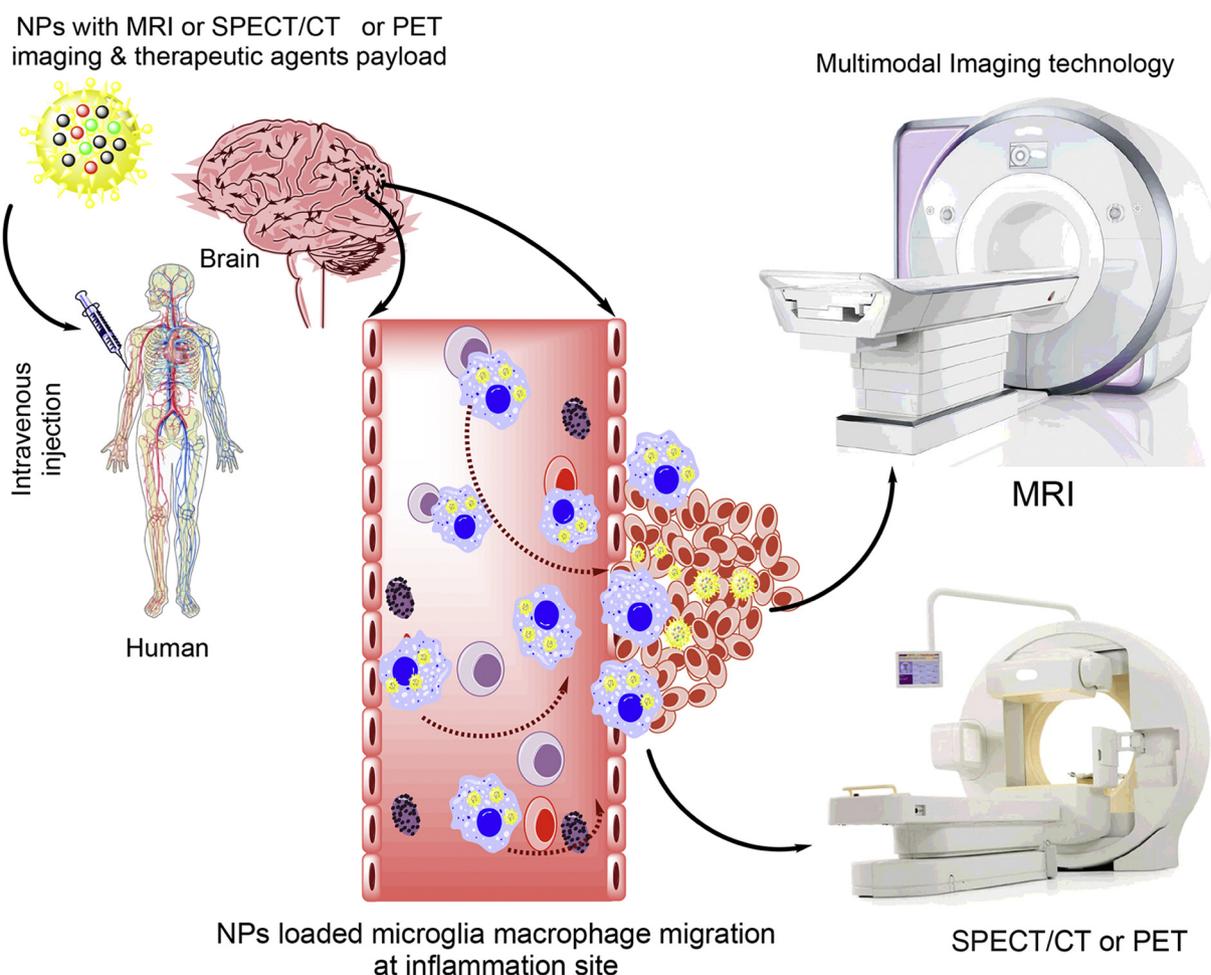


**Fig. 7.** Schematic illustration of theranostic nanoparticle biodistribution. Biodistribution of multifunctional theranostic nanoparticles loaded in cells. Metal nanoparticle-loaded macrophages are shown here. Nanoparticle loaded macrophages are transported through the intestinal epithelium and are capable of systematic biodistribution to organs susceptible to infection including lung, liver, spleen and lymph nodes. The ultimate fate of theranostic nanoparticles depends on their specific physicochemical properties, targeting moieties on nanoparticles, and the route of administration, as well as altered biochemical processes in disease states [678,680–683].

atherosclerosis [708,709]. Our laboratory has recently reported the development of europium-doped cobalt ferrite nanoparticles for rapid assessment of drug biodistribution by MRI and SPECT/CT in rodents and non-human primates [59,64]. Moreover, by using folic acid and alendronate functionalized IONPs, tagged macrophages were visualized *in vitro* and *in vivo* by MRI after their injection in mice [69]. Recently, PEG-coated IONPs in bone marrow-derived M1 and M2 macrophages were assessed for uptake, labeling efficiency, biocompatibility, and *in vivo* MRI detection. The authors reported that carboxylate modified IONPs showed higher uptake compared to PEGylated IONPs in M2 subsets [710]. A similar study demonstrated that IONPs used as MRI contrast agents undergo a specific mechanism of chemically activated macrophage uptake by using competition experiments with specific ligands of scavenger receptors SRA-I/II [711]. In addition, IONPs have been used to track the progression of atherosclerosis based on macrophage imaging in rabbits [712]. Lipinski et al., used gadolinium-containing lipid-based nanoparticles for MRI detection of high-risk human plaques prior to use of an atherothrombotic by targeting macrophage-specific (CD36) [713]. Bagalkot et al., have shown lipid-latex hybrid nanoparticles targeting, controlled drug release and imaging by MRI of M1 macrophages for inflammation in atherosclerosis [714]. For ischemic stroke, Wiart et al., reported *in vivo* magnetic labeling of macrophages and use of MRI to assess macrophage involvements in post-ischemic inflammatory responses [715]. In a separate study, the migration of iron-labeled polarized M1 and M2 macrophages to the lung in a lipopolysaccharide-induced chronic obstructive pulmonary disease animal model and the polarization state of the macrophages once they reached the sites of lung inflammation were assessed. Biodistribution

of iron labeled macrophages in abdominal organs and homing to the site of inflammation in the lung was tracked by MRI and used to visualize inflammation in the lungs [716]. Daldrup-Link, et al., showed by MRI that IONPs are preferentially phagocytosed by tumor-associated macrophages but not by malignant tumor cells [707]. Based on their observation, the authors concluded that IONPs might serve as a new cancer biomarker for long-term prognosis and for evaluation of new immune-targeted therapies [707]. Such non-invasive MRI of TAM using imaging nanoparticles has a huge potential for designing treatment regimens and monitoring effectiveness of chemotherapy, radiation and immunotherapy for cancer patients with primary and metastatic tumors. Dousset et al., reported IONP-loaded macrophage imaging for assessment of allergic encephalomyelitis by MRI and found a low MRI signal intensity related to IONP-loaded macrophages in the CNS in all animals [717]. Representative schematic of cell based multimodal nanoparticles bio imaging were shown in Fig. 8.

Unlike MRI-based imaging technologies, nuclear imaging modalities such as SPECT and PET, are highly sensitive, have unlimited tissue penetration depth and are quantitative [59, 684,718-720]. These qualities of nuclear imaging have enabled scientists to design nanoparticles that can diagnose disease, track therapeutic efficacy and deliver large payloads of therapeutics to disease sites using macrophages *in vivo* [709,722]. Commonly used isotopes for PET include  $^{18}\text{F}$ ,  $^{64}\text{Cu}$ ,  $^{68}\text{Ga}$ ,  $^{11}\text{C}$ ,  $^{86}\text{Y}$ ,  $^{124}\text{I}$ , and  $^{89}\text{Zr}$  [721-726]. The decay of these isotopes results in the emission of a positron. In tissues, these positrons travel a short distance before they collide with an electron resulting in the emission of two 511 keV photons 180 degrees apart from one another. A PET scanner can detect



**Fig. 8.** Cell-based bioimaging. Schematic illustration of multimodal cell based bioimaging. Theranostic nanoparticles loaded into cells can be monitored for brain distribution by using SPECT/CT, PET, and MRI.

the emissions “coincident” in time and thus determine the location of the radionuclide [727].

Yet another dual modality platform for macrophage targeted USPIO core particles were produced. The particles were coated in aminated and carboxylated PEG, functionalized with diethylenetriaminepentacetate acid, and targeted using annexin-V that can be imaged by SPECT and MRI. The combination of the two modalities resulted in an imaging platform that combines the high resolution of MRI with the high specificity of SPECT imaging [59,728–730]. Venneti et al., used PET imaging with the  $^{11}\text{C}$ -labeled R-enantiomer form of PK11195 ( $^{11}\text{C}$ -(R)-PK11195) to detect brain macrophages in simian immunodeficiency virus-infected rhesus macaques. They found that increased PK11195 binding *in vivo* and in postmortem brain tissue correlated with the relative abundance of macrophages but not astrocytes. PET  $^{11}\text{C}$ -(R)-PK11195 imaging can be used to detect the presence of macrophages in simian immunodeficiency virus encephalitis *in vivo* and may be useful in predicting the development of human immunodeficiency virus encephalitis [730]. This type of bioimaging technology may help in identification of macrophage subpopulations at disease sites and quantification, rapid assessment of pharmacokinetics and drug biodistribution, design of future therapy and real time monitoring of clinical outcomes of patients after treatment with therapeutic agents [59].

## 8. Personalized medicine and its perspectives

Incomplete and incorrect understanding of neurodegenerative diseases is one of the reasons for failure of current lines of treatment. In the development of a treatment strategy for these disorders, the ability of the therapeutic molecules to cross the BBB is of paramount importance. Nanotechnology-based alternative therapeutic approaches present more promise than the conventional treatment strategies, however, their potential has yet to be fully explored. There is ample evidence in support of the ability of nanotechnology to deliver and localize therapeutically significant amounts of drug, however, no products have yet been approved for clinical use. This may be due in part to that although they show enhanced performances; they also encounter similar difficulties in trafficking across the BBB for effective treatment as do conventional therapies. This increases the complexity of development of these approaches and efficient management of the neurodegenerative diseases. It has been established that the behavior and biodistribution of these nanocarriers largely depend on their surface characteristics. Thus, newer molecules and approaches are required to tailor the particle surface to achieve selective brain localization and minimal clearance by other organs. These tailorable surfaces can ensure the enhanced adhesion of these nanocarriers to the BBB and their subsequent brain influx. A better understanding of the molecular expression on the endothelial lining of the BBB would in the effective development and utilization of this strategy. The nanocarriers developed on a laboratory scale face difficulty in their large-scale fabrication, which in turn compromises the architectural integrity, stability and shelf-life of the formulations. Another key factor to maintaining their shelf-life is the fragility and reduced activity of the targeting molecules, including antibodies, which are employed both during production and usage.

Personalized medicine afforded by neurotheranostics technology may enable delivery of effective treatments with reduced side effects through the design of treatment strategies for individual patients. Recent advancements in multimodal nanoparticles design and delivery technologies may promote molecular and nuclear imaging as clinical tools for rapid diagnosis and therapeutics for NDs. The complex structure of the blood brain barrier has limited theranostics use for personalized treatment, thus, it may be some time before bench-scale technology of neurotheranostics can be adapted for clinical applications.

## 9. Summary and conclusions

Despite considerable advances in the understanding and treatment of diseases of the CNS, development of clinically significant treatment faces many challenges. Limitations in correct and timely diagnosis of disease and delivery of neurotherapeutic drugs to the brain are responsible for the high morbidity and mortality rates in patients suffering from neurodegenerative disorders. Moreover, most of the neurotherapeutic and neuroprotective molecules suffer from poor aqueous stability, which results in low bioavailability and limited clinical utility. While the BBB imposes limitations to the delivery of high concentrations of drugs to the brain, the liver plays a major role in their rapid clearance from the systemic circulation. Thus, many potential therapeutic molecules fail to reach their molecular targets in the brain, limiting their clinical efficiency. Recent years have seen an exponential increase in attempts to develop effective strategies to cross the BBB and deliver the therapeutic molecule to the site of interest. This review presents a consolidated clinical scenario of various neurodegenerative diseases with focus on the current status of research in the field of theranostics for brain delivery. In addition, the molecular details in disease progression and mechanisms of BBB transport have also been discussed.

A promising approach to enhance the delivery of effective drug levels to the brain is the use of colloidal nanocarriers such as nanocrystals, polymeric nanoparticles, conjugate inorganic nanoparticles, oligosaccharides, and lipids. While movement of naked therapeutic molecules across the BBB faces severe restrictions, transport and targeted delivery of nanocarrier-mediated delivery has shown great potential as a viable therapeutic strategy. These nanocarriers can be loaded with drugs, peptides, nucleic acids, and other neurotherapeutic molecules and can facilitate their transport across the BBB. These nanocarriers can also successfully protect their therapeutic payload from the external environment, where its deactivation or degradation occurs. They have been engineered using various strategies to modify their physicochemical properties and their fate *in vivo*. They have been decorated by various ligands and antibodies, which have been reported to enhance binding to the cerebrovascular endothelium and enable penetration across the BBB in order to specifically, target the brain tissue and enhance localized drug levels. It should be noted that both the surface properties of these nanocarriers and their targeting specificities are essential in combination to achieve an effective targeted brain delivery. Finally, the accessibility of targeting ligands, their systemic circulation time, and their localization efficiency all play important roles in successful targeting of these nanocarriers.

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