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Leveraging the interplay of nanotechnology and neuroscience: Designing new avenues for treating central nervous system disorders

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ABSTRACT

Nanotechnology has the potential to open many novel diagnostic and treatment avenues for disorders of the central nervous system (CNS). In this review, we discuss recent developments in the applications of nanotechnology in CNS therapies, diagnosis and biology. Novel approaches for the diagnosis and treatment of neuroinflammation, brain dysfunction, psychiatric conditions, brain cancer, and nerve injury provide insights into the potential of nanomedicine. We also highlight nanotechnology-enabled neuroscience techniques such as electrophysiology and intracellular sampling to improve our understanding of the brain and its components. With nanotechnology integrally involved in the advancement of basic neuroscience and the development of novel treatments, combined diagnostic and therapeutic applications have begun to emerge. Nanotheranostics for the brain, able to achieve single-cell resolution, will hasten the rate in which we can diagnose, monitor, and treat diseases. Taken together, the recent advances highlighted in this review demonstrate the prospect for significant improvements to clinical diagnosis and treatment of a vast array of neurological diseases. However, it is apparent that a strong dialogue between the nanoscience and neuroscience communities will be critical for the development of successful nanotherapeutics that move to the clinic, benefit patients, and address unmet needs in CNS disorders.

Contents

Abbreviations: AD, Alzheimer's disease; AuNP, Gold Nanoparticle; BBB, blood brain barrier; CED, convection enhanced delivery; CNS, central nervous system; CP, cerebral palsy; DBS, deep brain stimulation; ECM, extracellular matrix; GBM, glioblastoma multiforme; HIE, Hypoxic Ischemia Encephalopathy; LBSL, Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation; MS, multiple sclerosis; NP, nanoparticle; NT, neurotransmitter; PAMAM, polyamidoamine; PD, Parkinson's disease; QD, quantum dot; SERS, surface-enhanced Raman scattering; TBI, traumatic brain injury; VTA, ventral tegmental area.

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1. Introduction

Nanomedicine has begun to show the potential for addressing the complex and diverse needs of neurological disease and illness. Until recently, most nanotechnology research for brain disorders has been focused on overcoming the blood-brain barrier (BBB), which is an important step in addressing the unmet clinical needs. However, crossing the BBB is just the first step in creating effective nanotherapies. While the need to cross the BBB is a critical commonality of most brain-related diseases (Fig. 1), there are many other facets of disease left to address. Localizing in cells of interest, preventing cell loss/death, promoting regrowth, removing toxic pathologies, and sustaining therapeutic effects are also important, yet not equally so between classes of neurological disease. Understanding the unique biological/pathological contributions allows us to appreciate the diversity of needs and to address them appropriately. For instance, in chronic and degenerative diseases, neuronal function is compromised and is accompanied by the accumulation of toxic aggregates and reactive oxygen species, whereas in cases of acute inflammation due to a traumatic event (hypoxia ischemia, traumatic brain injury, stroke), the natural immune response becomes pathological and requires swift, glia-focused intervention. The tailorable and multimodal aspects of many nanoplatforms make it possible to address some of these concerns concurrently. Additionally, nanotechnology can create new experimental methodologies to understand disease mechanisms. Combination of these two ideas, understanding the disease and treating the relevant aspects of each disease, may give rise to effective nanotherapies. Here we highlight recent advances showing translational promise in (1) bio-inspired treatments of disease, (2) nanoscale innovations in basic neuroscience techniques and diagnostic tools, and (3) their subsequent convergence into nanotheranostics, the promising future of medicine.

2. Novel nanomedicines for the treatment of central nervous system disorders

2.1. Acute neuroinflammation and the role of microglia

Neuroinflammation is the natural response of the brain to injury, and is a vital component to the healing process in most neurological disorders. However, when left unmitigated, the neuroinflammatory response can lead to increased damage, cell death, and loss of function, resulting in a more severe injury than the original insult may have induced. Chronic neuroinflammation is implicated in many neurodegenerative diseases; however, its role and relationship with other pathologies and resulting cell death is not fully understood. Following infection or injury, the neuroinflammatory response is more acute and a direct cause of cell death. In indications such as traumatic brain injury (TBI) [1,2], tubercular meningitis [3,4], hypoxic ischemic encephalopathy (HIE) [5], and cerebral palsy (CP) [6,7], where neuroinflammation plays a central role, early treatment of this neuroinflammation correlates with improved recovery, and is the focus of this section.

Activated microglia and macrophages are key mediators of neuroinflammation, which can be beneficial (early after injury) or detrimental when allowed to continue chronically. Therefore, appropriate timing of the therapeutic intervention is critical. Early after injury microglia typically facilitate the clearance of debris and tissue reorganization. Vexler *et al*., have shown that intervening early after acute neonatal focal stroke and ablating microglia can be harmful [8–11]. However, after the early phase of injury the microglia typically transition to a more chronic inflammatory response and become harmful as opposed to reparative [2,12,13]. In major acute brain insults such as HIE, stroke, and TBI, this perpetuated inflammatory response results in neural cell dysfunction and death.

Current therapeutic avenues for treating acute neuroinflammation have had a moderate effect, leaving significant opportunities for new advances. In neonatal HIE, therapeutic hypothermia is widely used, producing a positive effect in mild but not moderate or severe cases of neonatal HIE [14–16]. Traditional pharmaceutical approaches to treating neuroinflammation lack efficacy due to poor bioavailability and poor brain penetration requiring large, sometimes toxic, doses to reach therapeutic levels within the brain [17,18]. Even if these obstacles for brain delivery as a whole are overcome, delivering drugs to the specific cells that need them would be helpful to improve efficacy and reduce side effects. Intervening during this proinflammatory response is beneficial.

It is clear that accessing and manipulating these microglia will be a major weapon for treating and better understanding CNS disorders where neuroinflammation is a key component. The pharmaceutical industry also acknowledges that microglia could be the key to curing many of these disorders with Genentech dedicating research funding to better understanding microglia genetic variation in the search for understanding microglia and inflammation-mediated CNS disorders [19–21]. Recently, Denali Therapeutics received $1.2 billion in collaboration with Takeda Pharmaceutical to pursue clinical translation of their technology, which is a microglia RIP1K inhibitor and has entered phase I clinical trials as a potential therapeutic for Alzheimer's Disease (AD) by mediating microglial phagocytic responses and activation to a disease state in AD [22]. It has been recently shown that by only regulating the microglia, one can additionally impact astrocytes and potentially delay the onset of AD [23]. However, the Denali compound is not specific to microglia.

With the goal of accessing activated microglia residing behind a comparatively intact BBB, Gonzalez-Carter and colleagues have shown

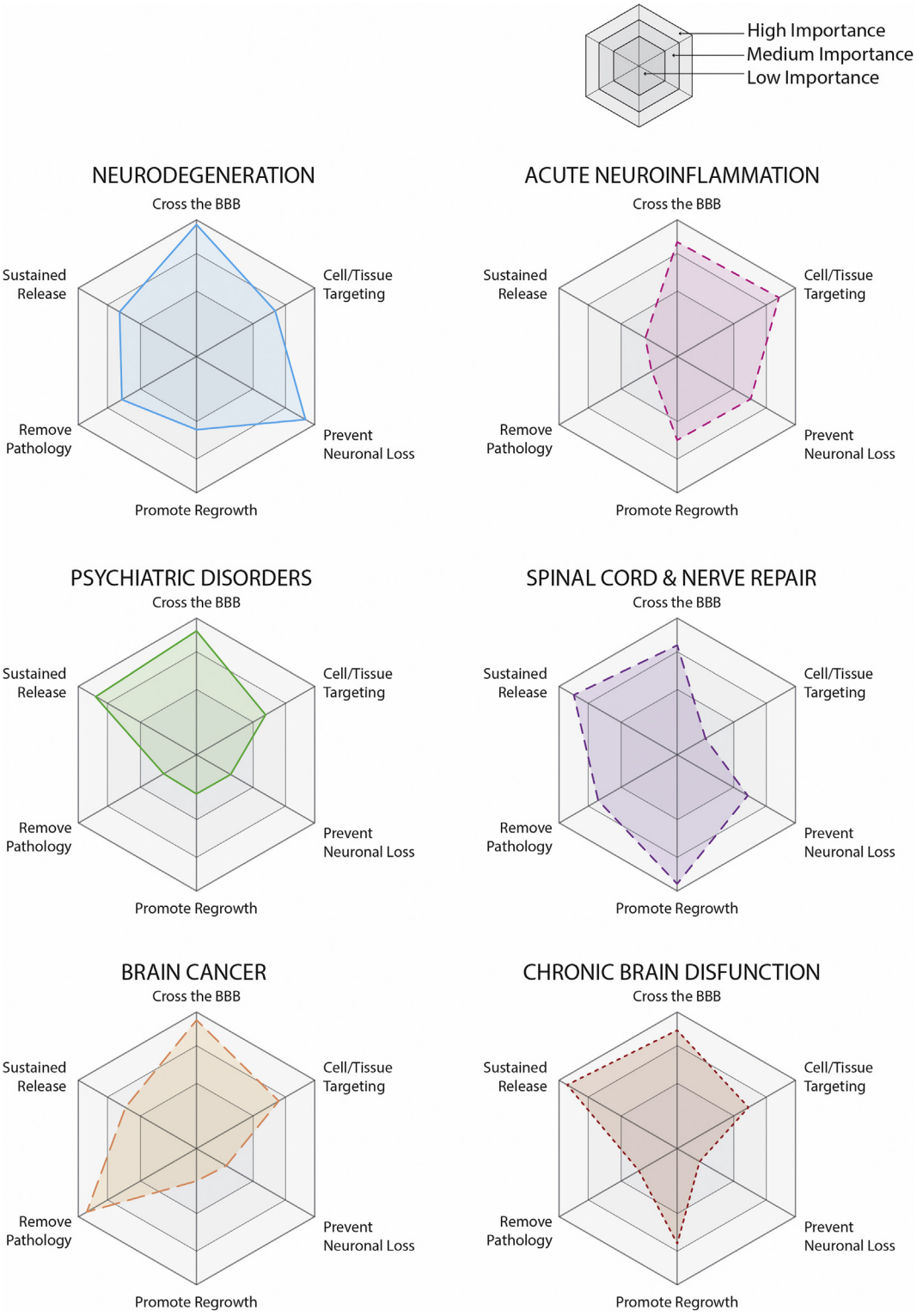

Fig. 1. Schematic representation of the varying needs of neurological illnesses.

in vitro that L-DOPA functionalized gold nanoflowers (AuNFs) can cross human brain endothelial cell monolayers, and are then internalized by mouse microglia [24]. Further *in vivo* work is necessary to confirm the microglia-targeting capacity of these AuNFs is maintained in an appropriate disease model, but if true would generate much interest in L-DOPA functionalization as a method to get nanoparticles (NPs) across the healthy BBB [25]. This study highlights the importance of penetrating the BBB; however, it does not investigate the ability of these AuNFs to perfuse freely through the brain parenchyma to reach activated microglia in the region of injury *in vivo*. Yoo *et al.* recently showed that their cross-linked PS80 NP does perfuse freely into the region of injury in a controlled cortical impact mouse model of TBI [26]. Upon systemic administration their NP rapidly accumulates in the region of injury and scavenges reactive oxygen species, resulting in improved clinical outcomes such as reduced lesion volume.

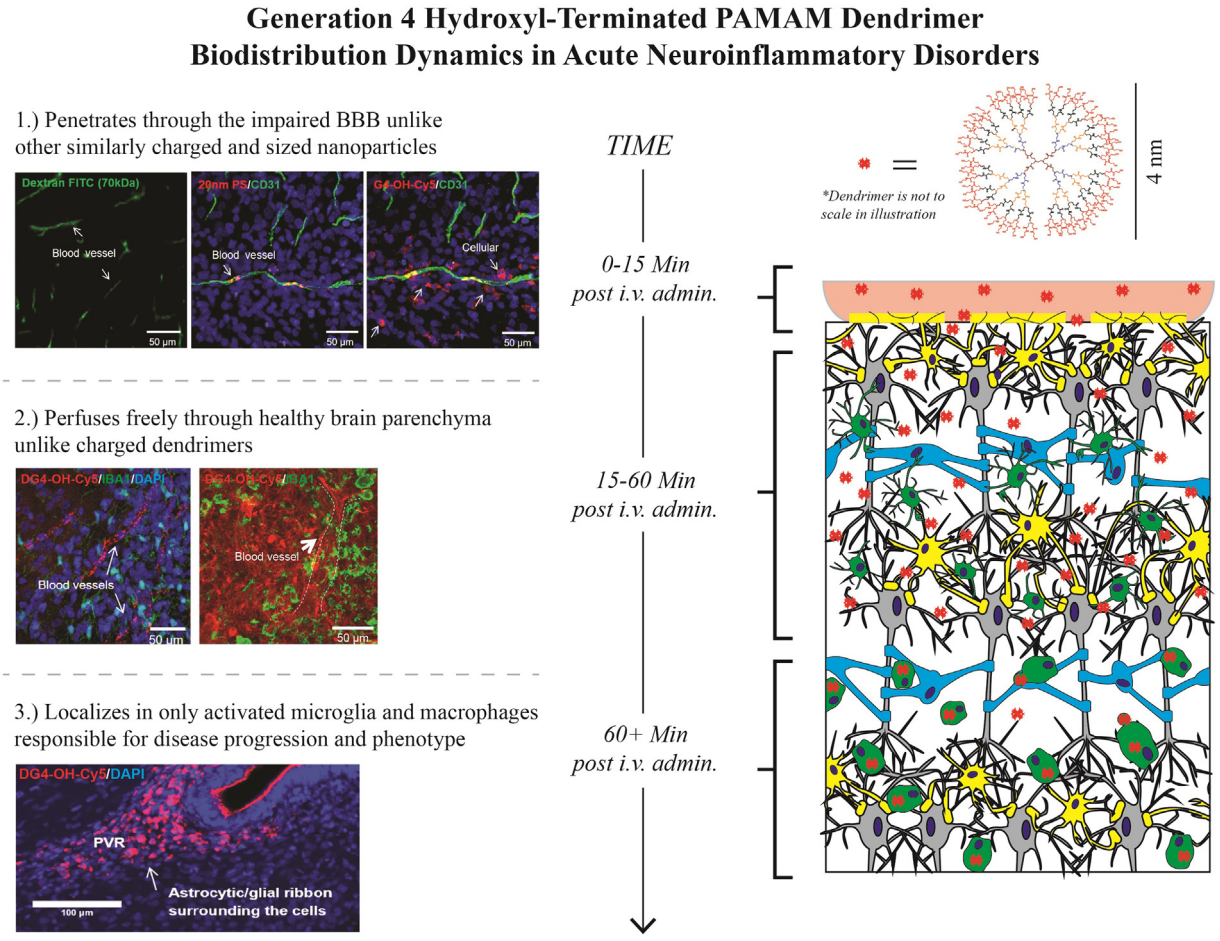

Fig. 2. PAMAM dendrimer CNS transport mechanism. Confocal images and schematic highlighting the characteristics of generation 4 hydroxyl-terminated PAMAM dendrimer transport into and through CNS tissues to target activated microglia and macrophages. Confocal images adapted with permission from Nance *et al. Biomaterials.* (2016) [42] and Zhang *et al. Biomaterials.* (2015) [38].

A class of nanoparticles that has more recently demonstrated robust microglia-specific uptake is dendrimers. Different dendrimers exhibit the abilities necessary to effectively access and treat activated glia: (1) cross the minimally compromised BBB, (2) perfuse freely through brain parenchyma to reach the region of injury, and (3) internalize within activated glia to deliver their payload (Fig. 2). One of the only nanoparticles shown to possess all of these capabilities in addition to being non-toxic is the hydroxyl-terminated PAMAM dendrimer. These dendrimers can specifically target activated microglia and macrophages (and to a lesser extent activated astrocytes) in the CNS upon systemic administration, without the need for any additional ligands [27,28]. The Kannan labs have shown that intravenously and intraperitoneally delivered dendrimers selectively localize in activated microglia/astrocytes in the CNS in mouse, rat, rabbit, canine and primate models (Table 1), and deliver drugs to the site of injury producing positive therapeutic outcomes [27,29,38,39,30–37]. Minimal cellular uptake is observed in the brains healthy animals, even when injected into the sub-arachnoid space [40]. The mechanism for this selective uptake, not seen with other NPs, appears to be related to the ability of this hydroxyl dendrimer to cross the impaired blood-brain barrier (BBB), and diffuse well in brain tissue, for eventual uptake by increasingly phagocytic/endocytotic activated glia (Fig. 2). Such localization into injured glia was not seen in linear dextran, PEG, and 20 nm PS NPs. The 'neutral' hydroxyl end groups appear to be the key to for accessing neuroinflammation as opposed these dendrimers' anionic and cationic counterparts, which have increased cell binding capabilities, but lack the biocompatibility and activated microglia internalization properties of neutral, hydroxyl-terminated dendrimers [41,42].

These dendrimers are highly tailorable and multifunctional, enabling conjugation of different drugs, imaging agents, and targeting ligands. When conjugated to the dendrimer surface at the appropriate payload, drugs take on the pharmacokinetics/biodistribution properties of the dendrimer, allowing their delivery to activated microglia and macrophages [27,43–45]. A generation 4 hydroxyl-terminated dendrimer conjugated to anti-inflammatory agent, N-acetyl cysteine, (D-NAC) has been applied to attenuate pro-inflammatory processes in several animal models including in rabbit model of cerebral palsy [31], a mouse model of Rett syndrome [29], and a canine model of hypothermic circulatory arrest [32,34] (Table 1, Fig. 3). A single dose of D-NAC, administered systemically in a rabbit model of CP, during the pro-inflammatory phase of the injury, produced remarkable neurological improvements, improved myelination, attenuated inflammation and oxidative stress, and dampened the pro-inflammatory phenotype of the microglia [31]. The same conjugate also showed promising responses in other etiologies of CP. This conjugate is undergoing clinical development for the treatment of childhood cerebral adrenoleukodystrophy in humans, with healthy volunteer studies already underway [46]. The results from over a decade of research from the Kannan labs have shown that by simply delivering drug directly to the activated glia and macrophages of the CNS from the spinal cord, to the hippocampus, to the retina, that they can have a major impact on cellular activity, disease propagation, and overall animal phenotype/outcome.

Amine-terminating cationic dendrimers are the most commonly used type of dendrimer, but can be cytotoxic and trigger immune response at moderate doses [47,48]. This could be mitigated to some extent by forming a tectodendrimer by conjugating the amine

Table 1
Disease models in which generation 4 hydroxyl-terminated PAMAM dendrimers have been evaluated for microglial/macrophage uptake (mi/ma) along with neuropathological and neurobehavior outcomes of dendrimer-N-acetyl cysteine (D-NAC) administration.

Disease	Species	Model	Administration route	Dendrimer Localization in Activated Mi/ma	D-NAC lowers pro-inflammatory cytokine expression	Major phenotype impact of D-NAC	References
Adreno-leukodystrophy	Human	patient-derived monocytes	n/a	Yes	Yes (TNFa)	N/A	Turk et al. (2018) [33]
Cerebral palsy	Rabbit	intrauterine LPS injection	*i.v.*, intra-amniotic, subarachnoid	Yes	Yes (TNFa)	Reduced mortality rate, improved motor function, hindlimb tone, myelination, and decreased oxidative damage	Dai et al. (2010) [40]; Kannan et al. (2012) [31]; Sharma et al. (2018) [162]; Nance et al. (2016) [42]; Zhang et al. (2016) [240]
Hypothermic circulatory arrest (HCA)	Dog	90 min HCA	*i.v.*	Yes	N/A	Trend of improved neurobehavior score 24 hours after HCA	Mishra et al. (2014) [32]; Zhang et al. (2017) [34]
Hypoxia ischemia (HI)	Mouse	P6 and P10 carotid ligation	*i.p.*	Yes	Yes (TNFa, IL-18, IL-6, IL-12)	Improved myelination	Nance et al. (2015) [241]
Necrotizing enterocolitis	Mouse	Transplant of NEC bacteria isolated from human samples	oral	Yes	N/A	Prevented myelin loss, reduced protein nitration, restored normal cognitive function	Niño et al. (2018) [242]
Rett Syndrome	Mouse	Mecp2-knockout	*i.p.*	Yes	N/A	Improved behavioral phenotype, decreased NAC toxicity mortality	Nance et al. (2017) [29]
Corneal inflammation	Rat	alkali burn	subconjunctival injectable gel	Yes	N/A	N/A	Soiberman et al. (2017) [35]
Dry eye	Rabbit	induced autoimmune dacryoadenitis	subconjunctival	Yes	N/A	N/A	Lin et al. (2018) [243]
Gliosarcoma	Rat	intracanial 9L gliosarcoma implantation	*i.v.*	Yes	N/A	N/A	Zhang et al. (2015) [36]
Hypoxic ischemia encephalopathy (HIE)	Mouse	carotid ligation and oxygen deprivation	*i.p.*	Yes	N/A	N/A	Nemeth et al. (2017) [27]
Ischemia/Reperfusion	Mouse	90 min ischemia	*i.v.*, intravitreal	Yes	N/A	N/A	Kambhampati et al. (2015) [37]
Optic Neuropathy	Rat, Rhesus Monkey	NAION	*i.v.*, intravitreal	Yes	N/A	N/A	Guo et al. (2016) [38]
Preterm birth	Mouse	intrauterine LPS administration	intra-amniotic, *i.p.*	Yes	N/A	N/A	Burd et al. (2014) [230]; Lei et al. (2017) [229]
Retinal degeneration	Rat	Royal College of Surgeons congenital model	intravitreal	Yes	N/A	N/A	Iezzi et al. (2012) [244]

dendrimer to a carboxylic acid dendrimer, which has been used in a preclinical model of rat ischemia [49,50]. Replacing parts of the amine surface by hydroxyl groups could also address toxicity to some extent [51]. Dendrimer charge, size, and composition have been shown to determine whether there are hemolytic effects [52,53], complement activation [54,55], and immunogenicity [56,57], as shown for amine-terminated dendrimers. While the generation 4 hydroxyl-terminated PAMAM dendrimer has not been shown to be toxic or immunogenic as summarized in a 2017 review by Dobrovolskaia [58], it is important to keep in mind the potential systemic consequences of dendrimer administration. In some cases, when side effects occur, some have been shown to be transient, with repeated intravenous administrations of a phosphorus-based dendrimer capped with anionic AzaBisPhosphonate groups (ABP dendrimer) in a macaque model resulting in temporarily increased liver aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels that returned to baseline within 2-3 days after injection, and later injections did not result in a cumulative effect [59]. This was followed by a study by Durrocher *et al.* who reported that injections of G0-G3 amine-terminated PAMAM dendrimers in a mouse air pouch model of inflammation caused a pro-inflammatory response, marked by significantly increased leukocyte infiltration following dendrimer administration [60]. Further discussion of the potential pro-inflammatory responses to anti-inflammatory dendrimers is provided in a review by Fruchon and Poupot [61].

The relative importance and the prominent role of microglia in the disease progression of neuroinflammatory disorders is receiving increased recognition in the field of neuroscience and clinical translation [13,62]. Now, nanotechnology has provided the tools to access these cells, which could lead to the development of innovative treatments as well as analyses of the biological processes these cells participate in, allowing a deeper understanding of neuroinflammation and how researchers and clinicians can continue addressing it in the future.

2.2. Neurodegenerative brain disorders

2.2.1. Oxidative stress

As of late, significant progress has been made in understanding the underlying pathological mechanisms of neurodegenerative diseases including Parkinson's disease (PD) and Alzheimer's disease; however, very few new therapies for these mechanisms have proven successful clinically. Neurodegenerative diseases have many pathological components including genetic mutations, oxidative stress, and aggregations of proteins, all leading to cell dysfunction and death which creates a vicious, self-perpetuating cycle in the cases of AD and PD. There have been many promising drug therapies developed to address these aspects of neurodegenerative disease pathology, but most have been met with limited clinical success. The pitfalls that stopped these therapies from

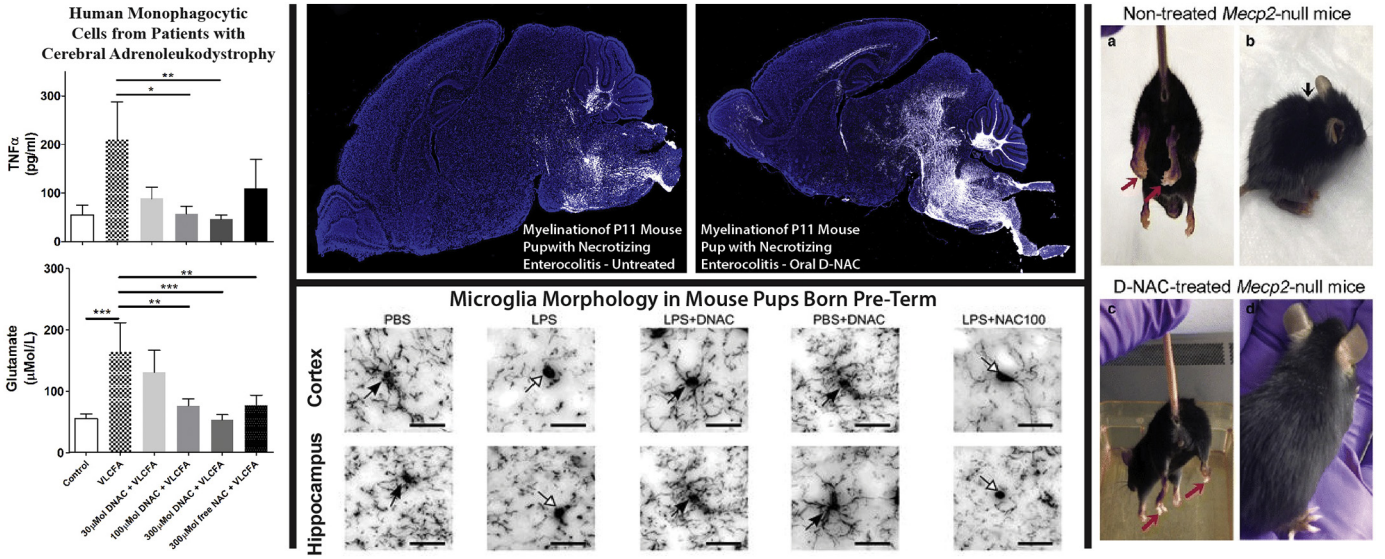

Fig. 3. Examples of phenotypic recovery after administration of D-NAC *in vivo* in various animal models of CNS disorders. *Left* – Human cells recovered from ccALD patients treated with very long chain fatty acids (VLCFA) express increased levels of pro-inflammatory cytokine TNFα and glutamate, both of which return to healthy levels with D-NAC treatment. Reprinted from Turk *et al. Annals of Neurology*. (2018) [35] *Upper Center* – mouse pups exposed to the bacteria causing necrotizing enterocolitis myelination as imaged through the presence of myelin basic protein (white) is diminished (left). Myelination catches up to that of healthy control pups within 30 days after a single oral dose of D-NAC (right). Reprinted with permission from Niño *et al. Science Translational Medicine*. (2018) [242]. *Right* – In an Mecp2 knockout mouse model of Rett syndrome mice display the characteristic paw clasping and hunching as is typical of human patients (top); however, D-NAC therapy has been shown to reverse the phenotype (bottom). Reprinted from Nance *et al. Journal of Neuroinflammation*. (2017) [29]. *Bottom* – Microglia morphology is highly indicative of activation state, with mice in a model of LPS-induced preterm birth possessing many activated M1 microglia (ameboid). Following D-NAC treatment these cells return to a healthy, non-active morphology (ramified). Scale bars are 5μm. Reprinted from Lei *et al. Scientific Reports*. (2017) [229].

reaching the clinic can potentially be overcome through advances from NP-mediated drug delivery to photothermal therapy.

Recently, there have been numerous clinical trials for antioxidants and anti-inflammatories for AD and PD that have had minimal success [63–68]. The most promising of the studies showed that NSAID usage could decrease the risk of PD by 15%, and a controlled clinical trial showed orally administered Vitamin E improved some aspects of cognitive function in AD [69,70]; however, other antioxidants and anti-inflammatories have shown little-to-no efficacy [66,71]. The reason for this collective failure has not been definitively ascertained but some have hypothesized that drug concentrations in the brain may be suboptimal [72,73]. In an attempt to overcome these bioavailability shortcomings, the field of nanotechnology has pursued several avenues for the creation of more bioavailable and better brain-penetrating antioxidants. Firstly, nanoformulations of antioxidants such as curcumin, ginsenosides and resveratrol have been pursued to facilitate entry into the brain with good success preclinically [74]. Secondly, loading antioxidants in or on NPs has also been pursued. Solid lipid nanoparticles, liposomes, and PLGA-NPs loaded with an antioxidant (commonly curcumin) are designed to scavenge ROS and have been reviewed previously [74]. These NP-loaded antioxidants show better antioxidant efficacy and increased uptake to the brain (and much as 30x) as well as longer half-life within the brain than delivery of free drug/antioxidant [74,75]. Lastly, bioactive nanoparticles are also in development. In this case, cerium oxide-NPs, boron cluster-containing NPs, and nitroxide radicals-containing NPs with PEG backbones have been developed to scavenge ROS [76]. These NPs are showing improved efficacy preclinically compared to freely delivered antioxidants [77,78].

2.2.2. Protein aggregates and toxic pathology

Even though oxidative stress represents one critical element of most neurodegenerative disorders, other pathologies occurring in tandem also play a key role. Commonly, proteins that have a specific function within the brain and body become pathological and form aggregates that are unable to be broken down and cleared from either within or outside the cell. Recent evidence suggests that removal of these pathological aggregations may improve outcome measures; however, clinically translating these ideas has been difficult because these proteins (alpha synuclein and amyloid) in their non-aggregated forms are integral synaptic proteins making non-specific inhibition of these proteins a non-viable thereapeutic avenue [79–85]. Instead, specific inhibition of these aggregates and/or facilitating their clearance is what is needed. Many strategies have been designed and tested to either prevent or break apart amyloid-β (Aβ) fibrils and alpha-synuclein aggregates (i.e. Lewy bodies). Apolipoprotein E3-reconsituted high density lipoprotein (ApoE3-rHDL), PEG-PLA with targeting peptides, PEG-Au, and AuNPs, and phosphorus dendrimers have all been developed for this purpose [86–88]. In some cases, including carboxyl-conjugated AuNPs, the NP is designed to destabilize Aβ fibrils [89]. While these carboxyl-conjugated AuNPs successfully break apart Aβ fibrils, they subsequently aggregate not as fibrils but as aggregated species. Even though these species are less toxic, it is unclear what the ramifications of the production of these new species are, and if this level of de-aggregation is sufficient for improvements in neural and behavioral outcomes [89]. Others have taken an arguably more efficient strategy to enhance established biological mechanisms for Aβ clearance including glial-mediated degradation of the fibrils. Song *et al* demonstrated that Apolipoprotein E3 conjugated to high density lipoprotein binds to Aβ oligomers and fibrils and after intravenous administration, this nanostructure facilitates lysosomal transport of fibrils into microglia and astrocytes in a mouse model [90]. With daily administration, these mice show functional improvements in spatial working memory paradigms [90].

Photothermal therapy is also an effective way to break apart these aggregates. To bypass this issue, NPs that can specifically bind to these fibrils and generate heat when near-infrared light is applied are being explored. NP candidates for photothermal therapy must have good NIR absorption as well good conductivity. As of late, two that fit this criteria are graphene oxide and WS2 nanosheets [91,92]. Both have shown early proof of concept and are capable of effectively breaking down Aβ in experimental preparations but their long-term viability as a therapeutic avenue remains to be seen as recently it has been shown that heavy metal NPs can cause damage to DNA with prolonged exposure [93,94]. However, translation of these technologies to the clinic is

still an issue. Failures in Aβ -based clinical trials have demonstrated that there is greater complexity to this disease neuropathology than is currently understood (i.e. role of Aβ, timing of pathology/treatment, role of neuroinflammation) [25,95] but regardless encourage continued study and the development of multi-faceted treatment strategies.

2.2.3. Non-invasive deep brain stimulation

Deep brain stimulation (DBS) has become one of many therapeutic options for restoring motor function in PD. Recently it has also begun to gain traction for the improvement of cognitive function in AD and other disorders characterized by cognitive dysfunction. To do this, the probe is placed in the white matter tract leading to the hippocampus called the fornix [96,97], or the nucleus basalis of Meynert [98] instead of where it is placed in PD patients for recovery of motor function (e.g. the subthalamic nucleus) [99,100]. It has been demonstrated that stimulation of these areas can improve cognitive deficits via enhancement of hippocampal function in many rodent neurodegenerative (e.g. AD) [96,101,102] as well as neurodevelopmental models [103–105]. However, even in PD, DBS is an invasive procedure that requires the precise and delicate placement of a probe almost at the base of the brain. Making such treatments safer and less invasive would be highly beneficial. NPs that can be delivered systemically and then activated from outside the skull with either magnetic stimulation or near infrared light are currently being developed to bypass this invasive electrode implantation. In one scenario, iron oxide magnetic NPs are delivered systemically to mice, and then alternating magnetic pulses (100 kHz – 1 MHz) are given to the skull (Fig. 4A, B). This causes the magnetic NPs to generate heat high enough to activate temperature sensitive TRPV1 receptors (cation channels), but not high enough to cause cell damage [106]. Chen an colleagues transfected ventral tegmental area neurons with AAVs containing TRPV1 and mCherry (for labeling). Then, magnetic NPs were delivered systemically and up to one month later, placing the mouse head in a magnetic field resulted in the activation this receptor with heat generated by the magnetic NPs as measured by an increase in the immediate early gene c-fos (Fig. 4C, D, E). In other scenarios, upconverting nanoparticles that emit blue light are being utilized to activate cells transfected with AAVs containing channel rhodopsin. When UNCPs are delivered intracerebrally to the VTA one month after AAV transfection, near-infrared light lead to UCNPs emitting blue light, activating VTA neurons, and causing an increase in dopamine release from these neurons [107]. While these technologies require further assessment in multiple animal models, it is an exciting step towards less invasive brain stimulation as well as a new, less invasive, more controlled method by which to study neural function and circuitry.

2.3. Chronic brain dysfunction and autoimmune disorders

2.3.1. Targeting neurons for chronic brain dysfunction

Treating chronic brain illness presents many challenges. Many times, prolonged treatment results in undesirable and sometimes intolerable side effects. In other cases, treatments are simply suboptimal or ineffective due to lack of specificity for the target cells, which in many of these scenarios are neurons. NP-mediated drug delivery to neurons could improve efficacy of these drugs. However, to date, there has been little success in targeted delivery/uptake in neurons without the use of adeno-associated viruses. While this technology is incredibly useful for genetic transfection of neurons and even subpopulations of neurons in nervous system [108–110], AAVs are suboptimal drug delivery devices as they do not regularly carry cargo. Walters *et al.* (2015) have demonstrated that negatively charged quantum dots are more likely to enter neurons by using a polyampholyte coating that includes a negatively heterocharged ligand on a PEG-appended DHLA (dishydrolipoic acid) [111,112]. It seems that a more viable route instead of changing the inherent characteristics of NPs is to use targeting ligands to facilitate neuronal uptake using mechanisms that are neuron-specific. For example, Tet1, the peptide responsible for the binding of tetanus toxin has been pursued as it naturally (preferentially) binds to motor neuron axons, and is subsequently retrogradedly transported to the soma [113]. Tet-1-HPMA-co-oligolysine copolymers [114,115] showed 80% uptake into neurons after intravenous administration in a rodent model of TBI [116] as well as significant silencing of the gene coding for Caspase 3 (shown to be detrimental in TBI [117]) when appropriate siRNA is loaded to the peptide NP. While neurobehavioral efficacy of this

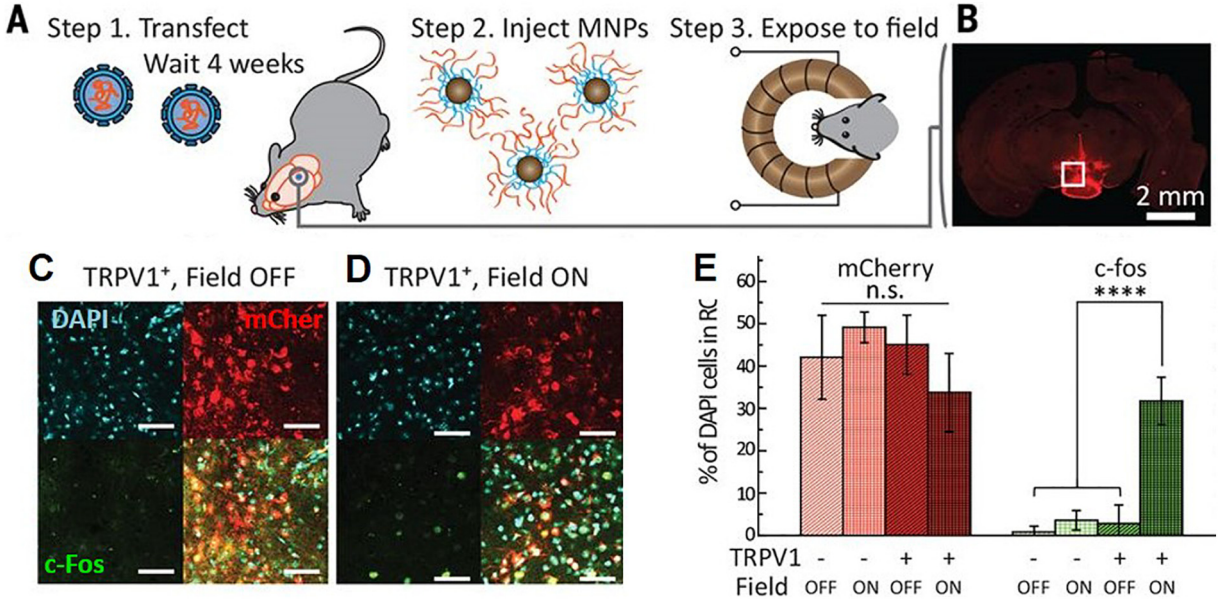

Fig. 4. Wireless magnetothermal stimulation *in vivo*. (A) In vivo experimental scheme. Mice were intracranially injected with AAV-mCherry-TRPV1. After recovery, mice were then systemically injected with magnetic nanoparticles (MNPs). Then mice were exposed to a magnetic field. (B) Confocal image of a coronal slice representative of the TRPV1-p2A-mCherry expression profile in the ventral tegmental area (VTA). (C) Without magnetic stimulation of MNPs, TRPV1 is not activated and neuronal activity measured via c-fos is low. (D) With magnetic field stimulation in TRPV1 is activated and neuronal activity (c-fos) is increased. DAPI (cyan), mCherry (red), and c-fos (green). Scale bar = 25 μm. (E) Percentage of c-fos-positive neurons within cell population was significantly increased in mice with TRPV1 transfection and magnetic field stimulation of MNPs. Adapted with permission from Chen *et al. Science*. Copyright 2015 The American Association for the Advancement of Science [107].

therapeutic intervention has yet to be established, this is an exciting first step towards designing NPs for neuron-targeted drug delivery.

2.3.2. Nanoparticle-mediated inverse vaccines for autoimmune disorders

In autoimmune disorders such as multiple sclerosis (MS), the body's immune system attacks myelin and the cells facilitating myelination within the CNS (i.e. oligodendrocytes). 'Inverse vaccines' (i.e. teaching the immune system *not* to respond to various antigens) have been created to prevent the body's immune system from attacking myelin instead of priming/teaching the body's immune response to attack as is done with traditional vaccines. However, they have been found to hasten disease progression [118]. Using NPs to enhance delivery of antigens to create immune tolerance for myelin has been exciting progress for this therapeutic approach. PLGA NPs encapsulated with the tolerogenic myelin proteolipid protein sequence ($PLP_{139-151}$) has been shown to prevent or delay onset neurobehavioral symptoms in an experimental model of MS called experimental autoimmune encephalitis (EAE). In one version, poly(ethylene-*co*-maleic acid) was added as surfactant which reduced EAE phenotype presence and severity (both prophylactically and after pathology onset) [119]. PLG-$PLP_{139-151}$ has also been created with the inclusion of rapamycin and has been shown to have a synergistic therapeutic effect. And even with several immune challenges, no induction of EAE was seen in these mice [120]. AuNPs encapsulated in PEG have also been used to deliver tolerogenic molecule 2-(1′ H-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE) and T-cell antigen myelin oligodendrocyte glycoprotein (MOG_{35-55}) to immune cells. The attachment of both ITE and MOG_{35-55} showed superior performance (as compared to unmodified AuNPs) in the induction of tolerogenic dendritic cells, differentiation of regulatory T-cells, and EAE suppression [121].

2.4. Psychiatric Illness

Psychiatric conditions such as depression, bipolar disorder, anxiety, and schizophrenia represent a significant opportunity for nanomedicine. Psychiatric conditions have the unique problem of patient non-compliance even when the drug therapy is effective. In some cases, patients have severely altered mental status rendering them incapable of self-care or seeking assistance [122–124]. With drug addiction, cravings and habits can be extremely difficult to overcome even in the best of scenarios [125,126]. Further, patients may discontinue effective treatment regimens under the belief that it is no longer needed [123]. However, the most marked and universal phenomenon across patient populations is that patients may discontinue drug treatment because of unpleasant side effects[127]. Recent strides have been taken to improve psychotropic medication to overcome these issues using NP-mediated drug delivery.

2.4.1. Improving efficacy of psychotropic medication

Anti-depressants, anxiolytics, and anti-psychotic drug classes are all prescribed commonly and are frequently not well tolerated. Side effects can range from undesired weight gain/loss, sleep disturbances, loss of motivation, and sexual dysfunction that can negatively impact a patient's life. Overall, 40–60% of patients are nonadherent or discontinue medication for mood disorders, anxiety disorders, and psychosis for various reasons but one persistent reason is dissatisfaction with the side effect profiles of these drugs [128–130] . NP-mediated drug delivery for the enhancement of brain uptake has been studied as a means to increase bioavailability and lower dosage to potentially decrease drug side effects [131,132]. Intranasal administration of anti-depressants or anti-psychotics using alginate NPs, thiolated-chitosan NPs, and PGLA-chitosan NPs have shown greater efficacy in preclinical models as compared to oral administration due to direct uptake to the brain, and bypassing the BBB and first pass metabolism [133–137]. A critical next step, however, is to validate improved efficacy in conjunction with reduced side effects of intranasal nanotherapies in clinically relevant animal models, and to evaluate if intranasal-brain transport is viable in humans.

A unique hurdle of psychotropic medication is non-compliance with an effective treatment regimen. To combat this, slow-release/long-acting oral and injectable drug formulations that have redosing intervals from 2 weeks to 3 months utilizing prodrugs or microsphere formulations have become commercially available [138]. Iqbal *et al.* have created a nano-based transdermal patch loaded with solid lipid NPs conjugated to Precirol able to match this release time frame of 2 weeks while also bypassing the need for intramuscular injections [139]. Another group has chosen to build off the current standard of care of long-acting injections of the antipsychotic, olanzapine by developing an intramuscular injection of mesoporous hydroxy-apatite-olanzipine that has a more consistent, slow drug release profile than the other currently available therapeutic option, Risperdal Consta ®, which is an *i.m.* injection of microspheres loaded with risperidone. Once in circulation, mesoHAP-olanzapine was endocytosed by blood macrophages then degraded inside lysosomes. These NPs were of varying sizes (900–2800 nm) to prolong the time to break them down, with smaller NPs being endocytosed first. Once the endosome merged with a lysosome, Ca^{2+} and H_3PO_4 were released and caused degradation of the lysosome and release of olanzapine into the cytosol. The increase in cytoplasmic calcium concentration then causes exocytosis (i.e. release) of the olanzapine from the cell and into the blood (Fig. 5). Using this novel mechanism of sustained release within the bloodstream, constant levels of olanzapine can be maintained in the bloodstream for weeks. Further, mesoHAP-olanzapine improves depressive behavior (locomotion, forced swim test) in Reserpine-injected rats as compared to untreated Reserpine-injected rats but has yet to be tested against the currently clinically available long-acting injectable olanzapine [140,141].

2.4.2. Nanomedicine for addiction and drug abuse

There have also been recent endeavors to apply nanomedicine to the field of addiction and drug abuse. Nicotine vaccines for smoking cessation are currently in various stages of clinical translation, but have shown limited success [142–144]. This treatment approach relies on priming the immune system to attack nicotine so it cannot bind to acetylcholine receptors in the brain and subsequently cannot have a hedonic effect. One of the criticisms of this method has been the lack of specificity (and subsequent efficacy) of the vaccine to nicotinic acetylcholine receptors [143,144]. Phase II clinical trials of two anti-nicotine vaccines have shown no improvement in 'quit rate' in tobacco smokers [142]. Evidence suggests that this may be linked to the high variability in antibody titer as it was shown that the participants with a high antibody titer had a greater quit rate that participants with a low antibody titer [142–144]. NP-mediated nicotine vaccines have been developed as a next-generation attempt to increase specificity and antibody titer. Using a PGLA core and a lipid outer layer, nicotine haptens are incorporated along with targeting ligands/adjuvants including Keyhole Limpet Hemocyanin (carrier protein for antibodies), and Toll-like receptor targeting molecules found on immune cells such as monophosphoryl lipid A (MPLA). Using these targeting molecules as well as incorporating the nicotine haptens into the core and shell to create a 100 nm particle leads to approximately 60% less nicotine entering the brain than non-nano-mediated vaccines. However, it is unknown if this decrease is sufficient to reduce addictive potential/hedonic value [145–147].

Opioid addiction has also begun to be tackled by nanomedicine. Opiate drug abuse has been labeled a public health crisis in the United States [125], and even with these high rates of abuse, opiates still remain the most effective and frequently prescribed drugs for chronic or post-surgical pain [126,148]. In one realm, NP-mediated delivery of non-opioid analgesics is being pursued to slow and sustain release of non-opioid analgesics for various intractable pain in the hope of making them more effective alternatives [149]. There has also been an effort to use nanotechnology as a means by which to decrease the addictive quality of opioids and their derivatives. With opioids, the dose interval

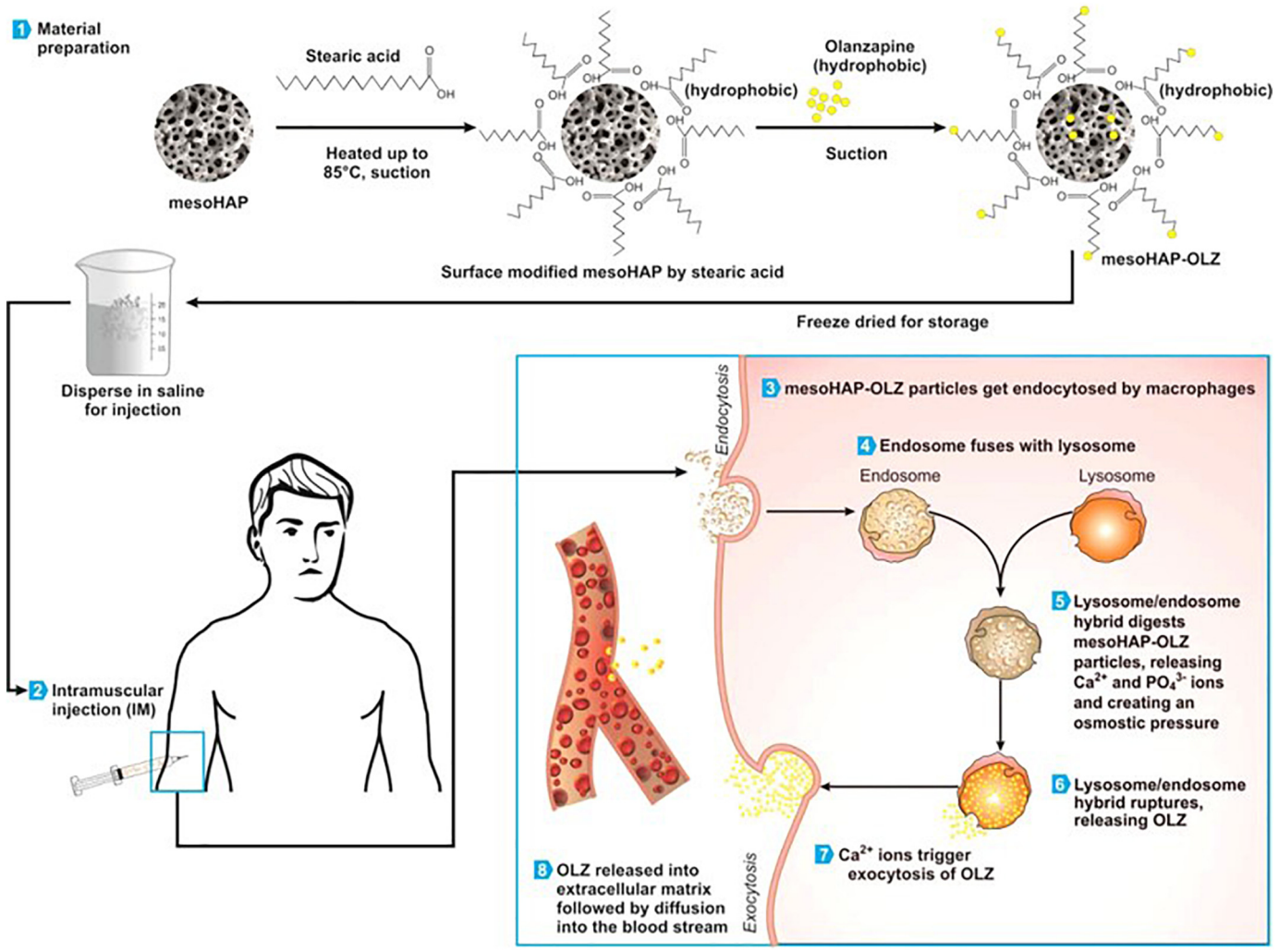

Fig. 5. Nanoparticle-mediated sustained release of the antipsychotic olanzipine. MesoHAP is conjugated with olanzipine, an antipsychotic and formulated in saline. Once delivered by IM, the mesoHAP-OLZ is taken up by macrophages in the blood via endosomes. Once in the lysosome, CA^{2+} and PO_4^{3-} ions are released triggering the rupture of the lysosome. The calcium release then triggers exocytosis and the payload is released into blood. Reprinted with permission from Shyong *et al. Journal of Medicinal Chemistry*. Copyright 2015 American Chemical Society [140].

and amount escalates quickly to continue to maintain the hedonic effect of the drug (i.e. tolerance), and if switching to a different opioid, this pharmacological tolerance is maintained (i.e. cross tolerance). Thus, people can become addicted to pain medication very quickly. There has been a movement towards finding alternatives either in different pain targets or changes in current drug formulations to decrease their addictive properties. Intranasally-administered glycochitosan NPs delivered a delta-selective opioid receptor agonist, Leucine^5-enkephalin hydrochloride (NM0127-LENK), and prevented tolerance and cross tolerance from occurring, which is a great improvement over traditional opiates like morphine, which shows rapid tolerance and cross tolerance [150]. When given to intact animals in a conditioned place preference paradigm, there was no preference for the space associated with NM0127-LENK injection suggesting this nanoformulation has no inherent hedonic value (i.e. no high, less abuse potential) however no mechanism for this has been suggested. While much more preclinical work is needed to further develop this approach, nanotechnology is offering exciting new avenues for making opioid usage for pain management safer.

2.5. Brain cancer

2.5.1. The current landscape of brain cancer treatment

While cancers of the brain and CNS (hereby referred to as 'brain cancer') statistically occur far less frequently than most other types of cancer, they are still a major health risk [151]. Glioblastoma multiforme (GBM) has received much of the focus in the design of novel treatments because it accounts for 46% of malignant brain cancers [152], giving patients only a median survival of 15 months after diagnosis even after treatment [153]. The current standard of care is maximum possible resection of the tumor followed by radiotherapy and chemotherapy with temozolomide, which is a potent antineoplastic alkylating agent. The limited scale of success with brain cancer treatments is due to the inherent biology of the disease providing major obstacles, such as tumor residence in critical tissue behind the BBB, difficulty penetrating the dense solid tumor tissue, and diffuse tumor borders making it difficult to remove all tumor during surgery. The genetic variability between tumors results in diverse patient responses to treatment, and the resilience of cancer cells requires sustained treatment and monitoring. The tumor is also comprised of both its own heterogeneous cancer cells, cancer stem cells (CSCs), and co-opted host immune cells, such as tumor-associated macrophages (TAMs) [154] and dysfunctional T cells [155] that both protect the tumor from the native immune response and help recruit new blood vessels and nutrients to support further tumor growth [156]. These facets of the disease and a lack of a biological focus in the development of new nanotherapies have thwarted many new therapies in the clinical and preclinical stages of development [157], which has kept the landscape of brain cancer standard of care

relatively unchanged as only three new therapies for brain cancer approved in this millennium so far.

2.5.2. Nanoparticle-mediated immunotherapy

In preclinical studies, a wide range of NP delivery systems have been combined with approved chemotherapies to improve drug delivery to brain cancer whether through cell/brain targeting, increased circulation, or improved BBB penetration, which can also lead to decreasing unwanted side effects. Several of the nanoplatforms show appreciable success in *in vitro* and *in vivo* models of brain cancer from killing tumor cells, to delivering drugs to tumor-associated macrophages (TAMs), to minimizing off-site toxicity and accumulation. However, these advances in drug delivery have not been very successful in translating to the clinic and will not be the focus of this review, but they have been reviewed extensively elsewhere [158–160].

Apart from just the safe delivery of chemotherapies, with nanomedicine comes the potential for developing effective cancer immunotherapies due to the ability of some NPs to target specific cell populations within the brain tumor. As discussed in section 2.2.1, generation 4 PAMAM dendrimers excel at targeting pro-inflammatory activated microglia and macrophages in the CNS, which holds true TAMs in a rat model of gliosarcoma [36]. TAMs are functionally equivalent to anti-inflammatory alternatively activated microglia and have greater phagocytic activity [161], which have shown dendrimer uptake in previous experiments [162], so uptake in TAMs is in agreement with the established PAMAM dendrimer literature. Within 15 minutes following systemic administration, dendrimers perfuse uniformly through the solid tumor region, but by four hours post injection, dendrimer is retained mainly in activated TAMs and microglia. TAMs are responsible for promoting tumor cell proliferation, maintaining cancer stem cells (CSCs), promoting angiogenesis to supply the tumor with nutrients, and blocking the host immune response by suppressing T cells [163]. Therefore, suppressing TAMs could both halt tumor growth and allow the host's immune system to begin attacking the tumor cells. Additionally, as these dendrimers are administered systemically, they could target TAMs in both primary and secondary tumors, but the application of PAMAM dendrimers to tumor immunotherapy requires significant additional research.

Another potential route for nanoimmunotherapy in brain cancer lies outside of the brain itself, and instead in peripheral dendritic and T cells. Dendritic cell based immunotherapy for GBM is a promising field that seeks to diminish the immunosuppression expressed by GBM through the secretion of glioma-cell mediators, which include various growth factors and signaling molecules, that incapacitate native T cells, preventing an immune response. Dendritic cells activate T cells by presenting antigens that inform the T cells how to identify and subsequently destroy foreign substances and afflicted cells. Dendritic cell therapy involves the differentiation of blood monocytes into dendritic cells *ex vivo* after which they are exposed to GBM antigens and reintroduced to the body where they present the antigens to native T cell which then cross the BBB and attack glioma cells, and is undergoing translation with completed phase I/II trials and an ongoing phase III trial [164]. Dendritic cell therapy has already been approved in prostate cancer with modest improvements to life expectancy. To increase the anti-tumor immune response achieved through dendritic cell therapy by improving activation of dendritic cells and increasing potency of the antigens against GBM, Li *et al.* recently developed a doxorubicin-polyglycerol-nanodiamond (Nano-DOX). When the Nano-DOX was loaded in dendritic cells *ex vivo* and reintroduced to the body along with lymphocytes increased immune cell activation and infiltration into the brain in a human GBM xenograft mouse model [165]. This approach had also been applied to TAMs previously where they found that after loading murine TAMs with Nano-DOX *ex vivo* and injecting them into the same mouse model, the injected TAMs delivered Nano-DOX to the tumor within 24 hours [166]. The nanodiamonds delivered to the tumor by the dendritic cells and macrophages were able to induce autophagy in immunogenic cells in the tumor, potentially allowing for a host immune response to the tumor. However, both studies were performed with immune compromised mice, resulting in no effect on survival following treatment, but these preliminary results indicate that there could be major improvements to GBM immunotherapy via nano-mediated cell therapy. The cellular specificity of these nanomedicines, whether achieved through systemic administration or *ex vivo* loading, enables them to modulate the host immune system to take control back from the tumor, resetting the host cells to defeat the disease.

2.5.3. Nanoparticle-mediated gene delivery

Gene therapies have historically met with many difficulties in the past ranging from therapeutic hurdles, such as effective transfection, to those of public perception. The approval of Kymriah (Novartis) for treatment of acute lymphoblastic leukemia in 2017 [167] has demonstrated that there are now techniques to successfully perform gene therapy in patients, thus providing a starting road map for success in brain cancer. As reviewed recently by William Kaemmerer, one of the most significant challenges the field of gene delivery faces, apart from issues with clinical trials and intellectual property, is enhancing delivery [168]. Enhancing gene delivery is multifaceted, requiring stability of the formulation, minimization of off-target transfection, and delivery to specific cell populations, which can all be addressed by nanotechnology. While many NPs have been utilized to deliver chemotherapies to tumors, delivering biologics is an even more complex task due to the additional requirements for stability and specificity, which results in many nanotechnology gene delivery systems that cannot pass preclinical stages [169]. Taking into account the previous failures of gene therapy translation for brain cancer, Mastorakos *et al.* recently developed a brain-penetrating polymer-DNA nanocomplex (PBAE-BPN), which they validated in two different rat brain cancer models: F98 glioblastoma (GBM) and 9L gliosarcoma (GS)[170]. In both models the PBAE-BPNs were able to localize specifically in tumor cells throughout the brain, not restricted to the peritumor, providing a 35% increase in lifespan in the rat F98 GBM model and an 86% increase in the 9L GS model upon convection enhanced delivery (CED). CED is an emerging strategy for delivering therapeutics to the brain that relies on injecting therapeutics directly into the tumor resection cavity under a constant pressure gradient that helps drive therapeutics well past the resection border into the brain parenchyma [171], which has made it a component of multiple ongoing clinical trials [172]. Many NPs, especially lipid-based and high molecular weight compounds, cannot diffuse rapidly through tumor tissue, even when administered intratumorally [160], so CED is a viable method for overcoming that limitation.

One of the greatest struggles with any form of cancer is reoccurrence following treatment. There exist many hypotheses as to how this arises with the prevailing theory being that CSCs possessing the ability to produce all other cancer cell types, survive treatment, and resume the tumor-growing process at a later date. Therefore, shutting down these CSCs should be of utmost importance. The Green group utilized CSC inhibiting miRNA to block the stem-like properties of GBM CSCs to prevent self-renewal and growth *in vitro* and *in vivo* (Fig. 6) [173]. Mice implanted with Oct4/Sox2-induced cancer stem cells (a highly aggressive model of GBM) were treated with nano-miR intratumorally, which was found to have a profound impact on tumor growth and the development of necrosis, indicating tumor cell death, when nano-miR containing a mixture of CSC inhibiting miRNAs was utilized. Animals treated with the combination nano-miR presented tumors about ten-fold smaller than control animals on day 42 post implantation (Fig. 6A) and caused a greater amount of tumor cell death with over 75% of tumor tissue treated with the combination nano-miR identified as necrotic. This treatment also dramatically increased lifespan with over 60% of treated animals living until the end of the study (Fig. 6C), almost doubling the lifespan of untreated control animals. These types of treatments are now real possibilities for clinical translation due to the

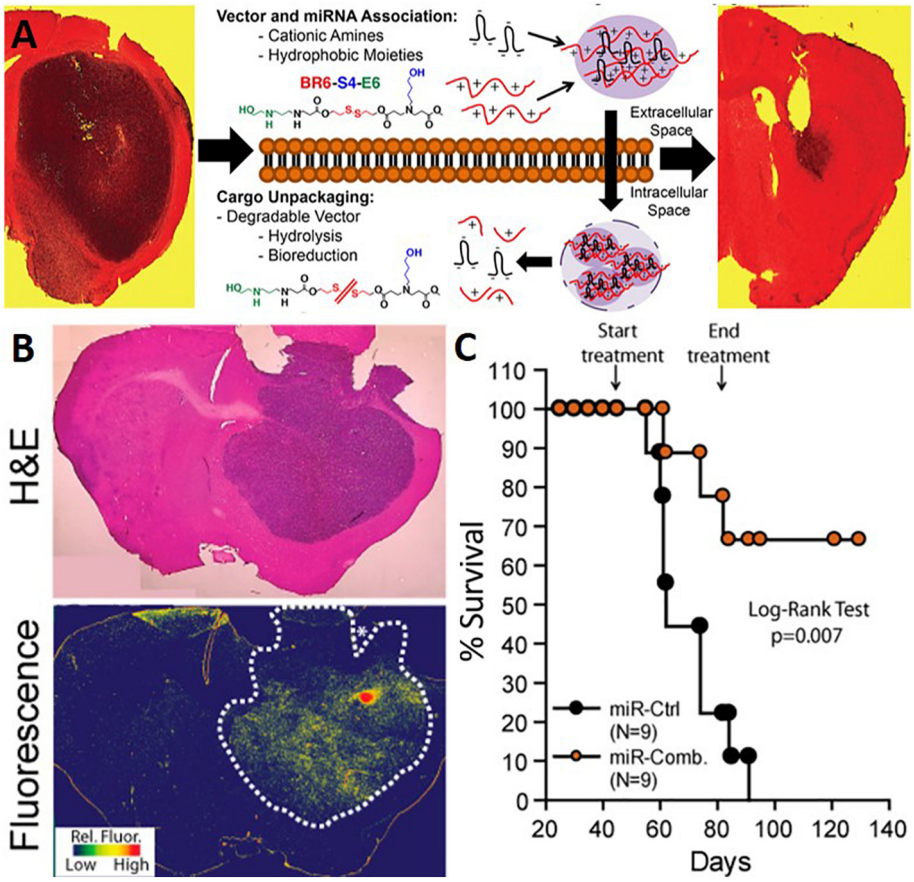

Fig. 6. Nano-miR inhibition of CSCs for the treatment of GBM *in vivo*. (A) Nanoparticle synthesis and delivery mechanism resulting in significant shrinking of tumor size after 28 days of treatment. (B) Localization of control miR loaded nanoparticles administered intratumorally in an orthotopic model of human GBM. (C) Survaival data of animals treated with combination of CSC-inhibiting miRNA loaded nano-miR compared with nano-miR loaded with control miRNA. Adapted with permission from Lopez-Bertoni *et al.* Copyright 2018 American Chemical Society [173].

preclinical successes seen with nano-mediated therapies [174]. While the landscape of brain cancer treatment has not changed significantly in recent years, there is hope for more effective and innovative brain cancer therapies through nanomedicine.

2.6. Spinal cord injury and peripheral nerve repair

Injuries in which the spinal cord or peripheral nerves are transected have historically had very few therapeutic avenues. Autologous grafts for peripheral nerve injury are generally successful but patients are frequently plagued with unwanted effects from the donor site. More severe and chronic injuries of peripheral nerves (>3 cm transection) and severe spinal cord transections usually have no successful treatment. Some patients have improved motor function after rigorous physical therapy or arduous spinal cord stimulation but still do not return to normal function. Recently, hollow conduits made of polyglycolic acid (PLGA) and collagen have become commercially available for small-to-medium (less-severe) nerve transections (<3 cm) with some success (NeuraGen, Intergra). However, nerve and spinal cord injuries can be extremely diverse and require treatment strategies that can be similarly complex. Crush or transection size is highly variable as well as the location of injury (i.e. which nerve and location of injury along nerve). Furthermore, nerve or spinal cord regeneration requires several types of interventions for proper nerve function to resume, including encouraging growth of damaged axon(s), promoting myelination of said axon(s), and facilitation of a growth-promoting extracellular matrix (ECM).

When the spinal cord is severely damaged or even transected, it may be necessary to introduce exogenous cells to the site of injury to enable regeneration; however, it is well known that cells 2D culture behave dramatically differently than cells *in vivo* in part due to the design and mechanical properties of the substrate [175,176]. Finer control over material and surface properties could therefore lead to increased control over cell morphology, phenotype, and fate, which has led to the pursuit of nanobiopatterning as a way of manipulating cells *in vitro* for implantation *in vivo*, particularly in regards to stem cell differentiation [177]. Nanopattering has provided many new techniques for differentiating stem cells in spinal cord implants, promoting Schwann cell proliferation, and encouraging neuronal regeneration. Nanoripples can guide Schwann cell growth direction and nanotopography can influence neural network establishment *in vitro* [178,179]. *In vivo*, nerve conduits and scaffolds with nanopatterning improve cell growth and proliferation as well as improve axonal guidance towards the proximal end [180]. Simply encouraging repair via nanoscale topography is sometimes not enough and these platforms must promote myelination and ECM development in other ways. Recently, growth factors and Schwann cells or stem cells have been incorporated in the scaffold/conduit to improve cell adhesion, migration, and proliferation through and around the nanodevice with varied success [181]. For example, loading multi-walled carbon nanotubes (MWCNTs)/PLA nanoscaffolds with erythropoetin (for the promotion of cell proliferation) and Schwann cells together lead to functional recovery comparable to the gold-standard autograft [182].

Both peripheral nerve and spinal cord repair can take upwards of one year, and the materials have to be chosen to minimize toxicity and adverse reactions while also maximizing nerve repair. As peripheral nerves and spinal cord repairs are a slow process, scaffolds must also maintain their structure for a prolonged period of time to fully support and encourage repair/regrowth of these axons. Recent studies have begun to systematically evaluate the degradation of these nanoscale

Table 2
Resolution improvements to basic neuroscience techniques with nanotechnology

Neuroscience technique	Conventional sensitivity	Nano-enabled sensitivity	Conventional time course	Nano-enabled time course	Example nanomaterials
In vivo extracellular recording	2–3 electrodes per probe	16 electrodes per probe	Days–weeks	>6 months	Flexible nanoprobe with conductive ink [190,191]
Intracellular electrophysiology	1 probe per cell	3–5 probes per cell	Hours	Days	SiO2 nanotubes, nanopillars [192]
Microdialysis (i.e. in vivo extracellular sampling)	1 analyte per probe	2-5 analytes per probe, multiple modalities	-	n/a	graphene quantum dots [197,198], Au SERS probes [205,206]
In vitro extracellular sampling	20 sensors per cell	20,000 sensors per cell	Hours	n/a	SWCNTs with corona phase recognition [200–202]
In vitro intracellular sampling	n/a	3–10 probes per cell	n/a	Days	Nanostraw cell culture surface [208]

scaffolds. Graphene nanoscaffolds loaded with Schwann cells were evaluated 18 weeks post-implantation and found there was little-to-no degradation of the nanoscaffold [183]. Meanwhile, scaffolds comprised of poly(ε-caprolactone-co-ethyl ethylene phosphate) (PCLEEP) and placed in a hydrogel and then applied *in vivo* to a spinal cord injury showed a much faster degradation rate of 50% mass loss at approximately 14-15 weeks, and 100% release of NT-3 and 30% release of miRNA for axonal growth at this same time point [184]. Thus, PCLEEP scaffolds in hydrogels may require further optimization for delayed release of soluble factors and for slower degradation of the scaffold. Mohamadi *et al*. also showed that a PCL/Collagen/Nanobioglass mat had only 20% mass loss after 3 months further demonstrating the appeal of nanobioglass inclusion for controlled degradation [185]. More assessments on systemic tolerability and the host immune response to these devices over a prolonged period will help in translation, as has been reviewed previously [186]. Highlighting the potential toxicity of degradation products of these types of scaffolds, Gholamine and colleagues recently demonstrated that both single-walled carbon nanotubes (SWCNTs) and MWCNTs (both of which have been utilized as implants for nerve and spinal cord repair) [181,187] injected *once* at 80 and 800 mg/kg *i.p.* into rats resulted in depressive and anxiogenic effects as well as altered brain-derived neurotropic factor concentrations [188]. Thus, developing a nanoscaffold that is able to retain its structure on the scale months and still have a subsequent safe degradation profile is critical.

While, as a field, nanotechnology for the treatment of nerve injury has progressed in many ways, it has been hampered by the constitutive use of severe models of nerve injury. Large axotomies or full transections of the nerve are less likely to occur and are generally considered the most severe form of injury. Compression injuries that do not result in transection are less utilized and most certainly have very different needs than a full nerve or spinal cord transection [189]. Furthermore, most of these treatments are provided immediately after the insult is inflicted. In reality, there is a gap of time between injury and treatment and that can change the physiological landscape significantly. There may already be an increased inflammatory response and toxic factors in the extracellular space or in the case of delayed treatment, scar tissue or axonal stump pathology may have already developed [189], suggesting that a combination of treatments may be required. It is apparent that not all nerve or spinal cord injuries are the same in scope or severity and as such, varied and tailorable biology-based treatment approaches for these diverse needs to should be developed.

3. Nanotechnology for basic neuroscience research and neurodiagnostics

Nanotechnology may help further basic neuroscience research in cells, animals, and humans. Many neuroscience techniques developed to understand and assess various aspects of brain function do not allow longitudinal or multiple simultaneous assessments on the same animal (or cells), and instead rely on invasive, irreversible manipulation the brain or its cells for analyses. By using nanotechnology, we can enhance the quality and quantity of information gained from research aimed at understanding the mechanisms of healthy brain function and subsequent pathological changes (Table 2). This richer knowledge base will then facilitate and better inform the design of future diagnostic techniques and subsequent treatment approaches.

3.1. Less destructive and higher sensitivity intracellular and extracellular electrophysiology recording

Typically, electrophysiology as a technique to measure electrical activity of neurons is conducted using micropipette probes that only measure electrical impedance. In the case of intracellular measurement techniques, including patch-clamp electrophysiology, the micropipette is forced through the cell membrane and kept there for the duration of the recording. Even when performed under ideal conditions, cells can burst, and when they do not, their function can only be recorded for several hours before they begin to deteriorate. Nanoscale probes can be inherently less destructive when inserted through the cell membrane. For example, SiO_2 nanotubes integrated with branched intracellular nano-tube field-effector transistors and silicon nanowire field-effect transistors are able to have a probe tip diameter of 3 nm and can even accommodate multiple probes within the same cell [190,191] which would allow for averaging of the signal to improve the signal-to-noise ratio and possibly assessments of the spatial relationship and dynamics of intracellular function. Further, when compared to standard patch-clamp probes, action potential dynamics showed less noise and finer temporal resolution [190]. Others have taken to using electroporation to create a completely non-invasive probe making it possible to record a cell indefinitely. Using a nanopillar adhered to the cell membrane, extracellular field potentials can be measured. Then a series of 2.5 V 200 μs biphasic pulses can be delivered directly to the site of cell contact to disrupt/open the cell membrane and measure intracellular action potentials for several minutes. This effect is transient with the membrane reconstituting within 10 minutes [192].

Extracellular recordings are also used to study neural (i.e. action potential) dynamics *ex vivo* in organotypic slice culture and *in vivo* with anesthetized and/or restrained animals, and gallium phosphide nanowires have been used to create nanoscale extracellular recording electrodes. Similar to other probes discussed above, by moving to the nanoscale, there is greatly improved resolution and decreased destruction of the tissue [193]. However, long-term real-time neural signal recording *in vivo* has been historically difficult and impractical because not only must the electrode stay in the correct location in the brain, the mount atop the animal's head must remain intact. Fu and colleagues have developed a system that overcomes these difficulties by using flexible mesh electronics consisting of 16 recording or stimulating electrodes sandwiched by insulating and biocompatible polymer layers that are injected into the brain region of interest [194–196]. Once injected, printed conductive ink is used to connect the mesh to a lightweight, flexible, flat cable that sits externally on top of the rodent's head. Using this technology, local field potentials from single neurons were able to be detected and recorded reliably for 8 months continuously [195].

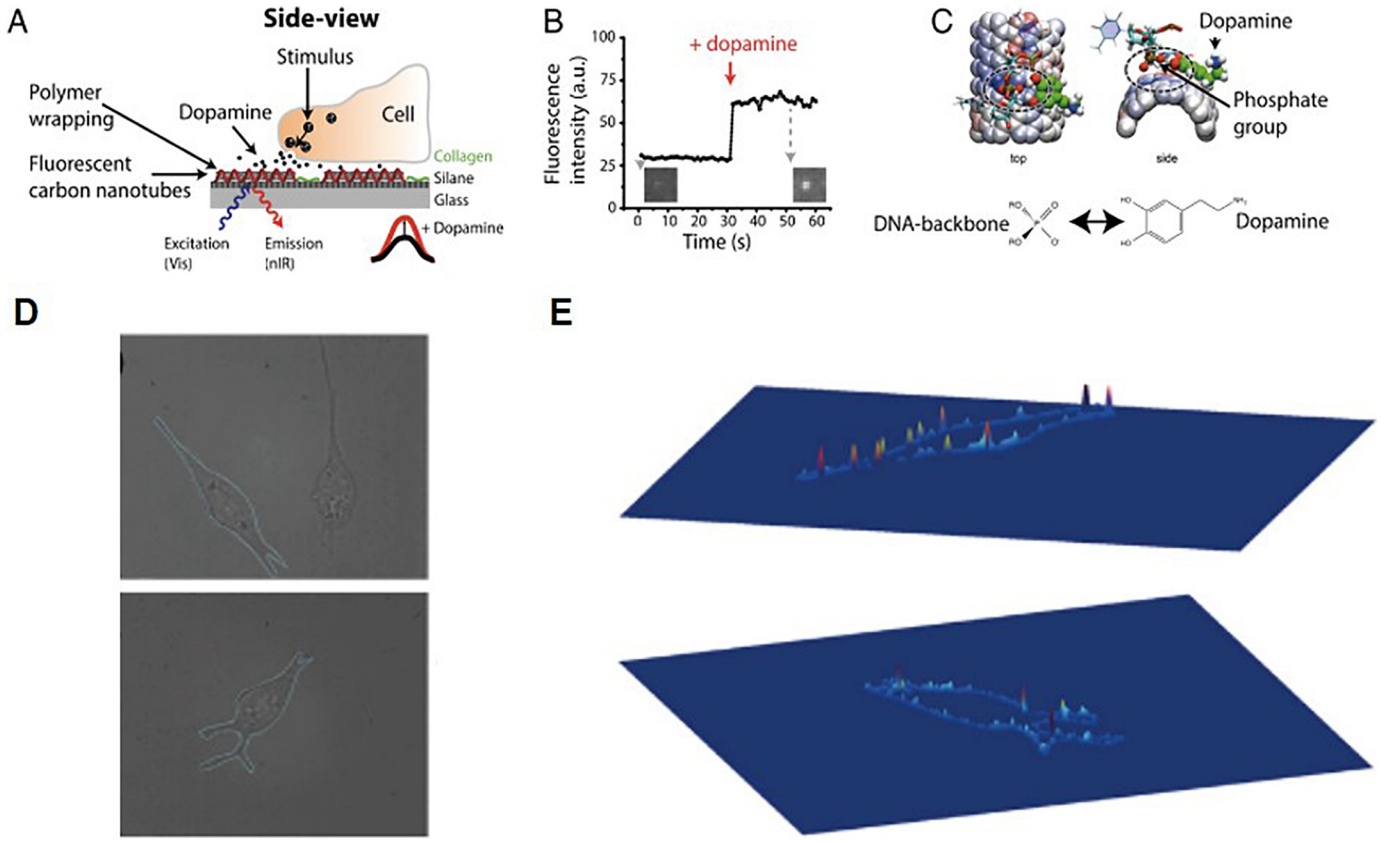

Fig. 7. Dopamine-sensing nanotubes. (A) Cells are cultured atop nanotubes. (B,C) When nanotubes interact with dopamine, dopamine pulls phosphate groups to the surface reducing quenching sites and increasing fluorescence intensity. (D) Brightfield image of dopamine neuron cultured on top of these carbon nanotubes. (E) Heatmap of dopamine release from the edge of the cell as detected by carbon nanotubes. Adapted from Kruss *et al. PNAS.* (2017) [200].

Recording many local field potentials simultaneously within a brain area over longer periods of time in awake animals allows us to study the activity of single neurons under various conditions and during different behaviors or vigilance states. Previously, awake and behavioral recordings have been difficult to attain and maintain. When tested for 8 months continuously in freely behaving mice, no long-term inflammation surrounding the site of the electrodes was detected [194,195]. Testing for this length of time *in vivo* is unprecedented and will allow for new information about neural function over long periods of time with the authors being the first to demonstrate changes in the functionality of the same neurons over a 14-week time period as the mice aged [195]. Previously, recordings in separate animals at discrete timepoints would have been conducted to understand neural function over time however by being able to record from the same neurons in the same animal, fewer variables/less variability is introduced and allows for more precise data and reliable conclusions to be reached.

3.2. Improved measurement of ions, neurotransmitters, and proteins

Similar to the difficulties in conducting electrophysiology, methods of *in vivo* or *ex vivo* measurement of ions responsible for action potentials, and neurotransmitter (NT) and protein release are hampered by scale. Generally, techniques such as microdialysis are employed to sample extracellular content. One difficulty is in detection of these proteins as the quantity of dialysate is generally very small. Graphene quantum dots have been developed for fluorescent sensing of copper as a marker of cell health from microdialysate [197,198]. In addition to copper, potassium nanosensors have been developed using PEG-lyated PAMAM dendrimer with a potassium sensitive dye (Asante Potassium Green 4) [199] . In this case, the dendrimer is suspended in a sol-gel and applied to tissue culture for real-time imaging of potassium changes. What is particularly useful is that the dye is restorative as it returns to baseline when potassium is washed out. This technique has the potential to be systemically administered and detected *in vivo/ex vivo*.

SWCNTs have also been attached to the ends of micropipettes or microarrays to enhance sensitivity to analytes such as ascorbate, glutamate, and dopamine [200]. In the case of dopamine, near-infrared SWCNTs were wrapped with DNA selectively reactive for dopamine by using a technique called corona phase molecule recognition [201,202]. When bound to dopamine, these SWCNTs fluoresced (Fig. 7B, C) making dopamine quantitation possible using 2-photo imaging. Because the SWCNTs are placed on the glass in a systematic array fashion, cells can be cultured on top and dopamine concentration can be measured at many points simultaneously as shown in Fig. 7D, E [200]. Traditionally, sensors such as this are no more than 20 per cell [203,204]. Here, there can be up to 20,000 per cell allowing for much greater spatial resolution.

Nano-enabled probes are also being developed for quantification of multiple analytes or multiple modes of analysis. Using dynamic surface-enhanced Raman spectroscopy (SERS) and AuNPs coated to glass micropipettes, multiple neurotransmitters including glutamate, acetylcholine, GABA, and dopamine along with ATP can be measured simultaneously [205,206]. Further, dual probes that can sense neurotransmitters and electrochemical signals have also been developed using microelectrode arrays modified with Platinum NPs and Nafion [207]. As proof-of-concept, these probes were implanted into unilaterally dopamine-depleted monkeys (a model of PD) and using this recording array, neural spike frequency and dopamine concentration changes were detected in real-time simultaneously and effectively detected changes under various therapeutic regimens including stimulation of the subthalamic nucleus (deep brain stimulation).

In single-cell monitoring experiments, it is highly desirable to monitor the intracellular environment without disruption and over a prolonged time. Cao and colleagues have developed a new technique for intracellular sampling *in vitro* for multiple days [208]. They embedded nanostraws in a substrate and placed a polymer membrane above it with openings for the nanostraws, on top of which cells could grow. When intracellular samples were desired, small holes were opened in the cell using electric current delivered by the nanostraw through which cytoplasmic solution was also collected. A 150 nm diameter straw was chosen to avoid the damage that happens from larger probes and spontaneous membrane rupture caused by smaller diameters. At 150 nm, the straw will be engulfed by the cell membrane but not penetrate into the cytosol. Using this method, cells can be sampled for multiple days.

3.3. Translating quantitative techniques for clinical diagnostic use.

Through the development of better *in vivo* and *ex vivo* techniques, we may be able to not only improve our understanding of CNS disorders, but also improve their diagnosis. One of the hurdles in assessing biological samples for biomarkers or other analytes is the poor detection limit, making it difficult to obtain data from small samples especially ones given by children. More sensitive detection of biomarkers or other analytes in real time from blood, plasma, and urine could enable us to correlate these to neural function, and improve their value for diagnosis and longitudinal assessment of therapies. For example, nanobiosensors for amyloid β detection have been developed using zinc oxide nanoflowers [209], both in preclinical settings and human samples [210]. Other sensors have been created for the testing of biological samples such as screen-printed graphene and carbon nanocomposites for dopamine and serotonin detection and carbon nanodot immunoassay for GFAP quantification [211,212].

Lastly, some have begun to develop up-converted NP (UCNPs) based sensors to detect the concentration of analytes in blood or other biological samples. The goal was to design a sensor for the rapid assessment of drug presence in the blood. Using UCNPs embedded in paper, cocaine can be detected immediately with a lower detection limit of 10 nM [213]. In this design, single strand DNA is coupled to poly(ethylenimine) modified oleic acid-coated UCNPs emitting green light and the complement of single strand DNA is couple to AuNPs. When cocaine is present, the single strands of DNA associate with each other and the AuNPs quench the luminescence from the PEI-UCNPs. These NPs were then immobilized on paper. When a patient sample (e.g. blood) is applied to the paper, the UCNP signal will be quenched in a dose dependent fashion, and by using a smartphone, the amount of luminescence (or lack of luminescence) can be quantified and calculated to determine the concentration of cocaine [213]. While this sensor has demonstrated proof-of-concept for first-responder assessments for drug detection, it could also be readily adapted for markers of various neurological events. To be able to begin diagnostic work in the field would greatly improve the time it takes to begin treating a patient with neurologic injury once they arrive in the hospital.

4. Nanotheranostic approaches for CNS disorders

As scientists and clinicians look forward to the translation of nanomedicines, it would be beneficial to synthesize nanodevices that can both treat disease and provide feedback to help diagnose disease progression and design additional treatment. These new nanotheranostics could both effectively treat patients while providing clinicians with new metrics to analyze disease progression in addition to what can be ascertained by conventional means.

4.1. Nano-enabled imaging modalities

Magnetic resonance imaging (MRI) has led to advances in patient care and diagnosis, but significant improvements could be achieved through increased resolution and site specificity of contrast agents. Integration of contrast agents into NPs has been widely studied, as most contrast agents are small molecules or single metal atoms that can be chelated to or contained within NPs. One example is the gold-silica "nanomastryoka" (NM) recently developed by the Halas group [214]. The nanomastroyka contains Gd(III) in a layer of silica between an Au shell and core. The NM showed improved T_1 MRI resolution and decreased relaxation, which would increase the potential imaging time and imaging quality. This NM platform was further improved by replacing the Gd(III) with Fe(III) (Fe-NM), which would be safer for potential translation and improve the signal as Fe(III) has been reported to have almost double the relaxivity of Gd(III) [215] . The Fe-NM was observed to internalize in macrophages *in vitro* and showed strong T_1 MRI contrast signal *in vivo*. Another example of coupled MRI imaging and therapy is a PLGA brain-penetrating NP similar to that described in Section 2.5.3. This NP relies on CED (see Section 2.5.3) to readily cross the BBB and accumulate at the site of injury [160,172,216]. Expanding on the success at localization at the site of CNS injury, the researchers added MRI capabilities by integrating superparamagnetic iron oxide into the NP [217] making the particle a strong contrast agent and providing specificity to the site of injury in the brain with minimal toxicity. This could be used in combination with chemotherapies for brain cancer by using previously validated PLGA particles containing chemoagents.

The concept of isolating and visualizing individual molecules is no longer out of reach as shown by Varela *et al*. with a new quantum dot (QD) platform for tracking and imaging dopamine receptors in *ex vivo* brain slices flowing intracranial administration [218]. The QDs were delivered through the brain ventricular system and localized in the neocortex, allowing them to track the migration of CFP-dopamine D1R, a key dopamine receptor in PD. They also postulate that this technology could be extended to *in vivo* imaging through additional modifications, which is promising, but would require the development of new techniques to synthesize QDs affordably on an economical scale conducive to *in vivo* and clinical applications. Nanoprobes offer enhanced investigations of basic neuroscience, which can reveal new pathways and functionalities critical to the design of new nanomedicine strategies for treating diseases like PD that we still understand very little and which have no current treatments (see section 3.2 for further discussion).

4.2. Nanotheranostics for brain cancer

There are many opportunities for improvement in the treatment of brain cancer, as has been shown through examples of nanoimaging techniques in the previous subsection. The facets of brain cancer that make it so difficult to treat such as genetic heterogeneity, drug resistance, and disease recurrence, necessitate novel treatment strategies that offer both treatment and longitudinal assessment of the treatment. Here we investigate emerging nanotheranostics that offer therapy and disease monitoring in one incorporated package as opposed to other particles which solely offer either drug delivery or imaging capabilities.

Carbon nanodots are undergoing validation in preclinical models of glioblastoma (as discussed briefly in Section 4.1). While specifications vary, they are generally small (<15 nm), crystalline carbon spheres with functionalized surfaces, hollow interiors, and intriguing optical/thermal properties. Carbon nanodots have previously been synthesized that serve as carriers for chemotherapeutic agents, which, paired with the optical properties of carbon nanodots, allowed for reporting of drug payload delivery by utilizing the fluorescence intensity of the quantum dots to determine NP concentration and therefore the quantity of drug delivered based on the loading [219]. One of the biggest challenges with some brain cancers

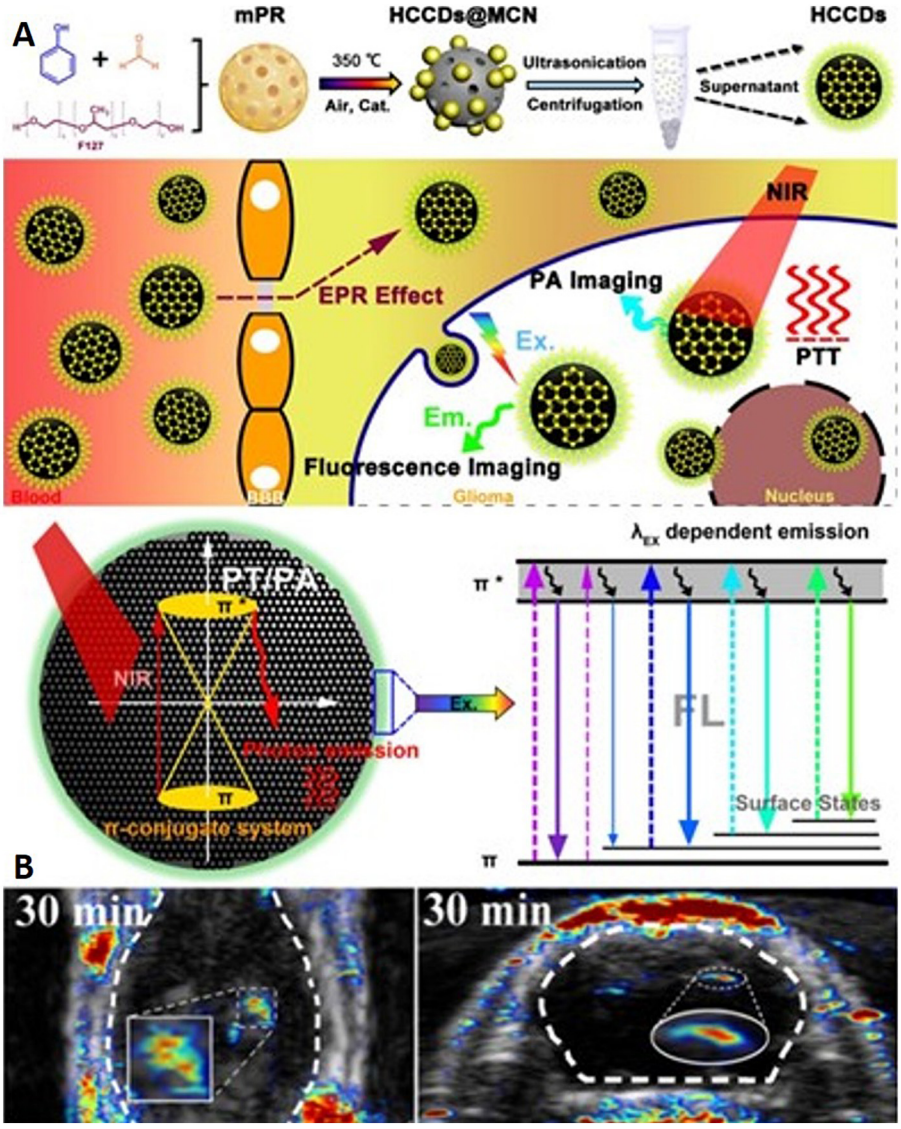

Fig. 8. Highly crystalline carbon dots for brain cancer photoacoustic-guided photothermal therapy. (A) Design of highly crystalline carbon nanodots by Qian *et al.* and summary of photoacoustic and photothermal properties for the siumultaneous imaging and treatment of gliomas. (B) *In vivo* photoacoustic images of a glioma-bearing mouse 30 minutes after an intravenous administration of nanodots. Adapted with permission from Qian *et al.* Copyright 2018 American Chemical Society [220].

is their resistance to drugs, so some groups have utilized the inherent photothermal/photoacoustic properties of carbon nanodots to turn the nanodots into tumor-killing agents themselves, without any chemoagent payload. Qian *et al.* have recently synthesized a carbon nanodot that serves as an imaging agent with fluorescence that can be tuned based on the carbon crystallization process, as well as photoacoustic properties for high resolution *in vivo* imaging and photothermal properties that kill tumor cells when exposed to higher power near-IR lasers (Fig. 8) [220]. The fluorescence and photoacoustic properties of the HCCD allowed for precise photothermal treatment at the appropriate time point and brain region in a mouse model of glioma following systemic administration. The photoacoustic-guided photothermal therapy resulted in 40% animal survival and an almost doubling of survival time overall compared to untreated control animals. In addition to efficacy, the carbon nanodot used in this study was synthesized in a scalable manner and was composed of only FDA-approved materials, which is a major advance in nanodot synthesis and may speed up the potential clinical translation.

Photoacoustic and photothermal technology has shown great promise coupled with other NPs as well, since they can be incorporated into the structure of NPs without requiring the conjugation of potentially harmful or cleavable imaging agents. These properties rely on the available sp2 orbitals and pi-pi bonds in the structure of the NP, allowing for the absorption of light, which is then converted to either heat or a detectable acoustic signal based on the wavelength of light and the laser power. They have both been utilized with success in both upconverting silica core/shell NPs [221], AuNPs [222], and polymeric NPs [223], providing a strong indication that this technology could be a viable path towards nanotheranostic treatment of brain cancer.

4.3. Nanotheranostics for neuroinflammation

Many of the technologies discussed for the treatment of neuroinflammation in Section 2.2 have the potential to become viable nanotheranostic tools. The multifunctionality of dendrimers allows for the conjugation of imaging agents, targeting ligands, and therapeutic agents to the surface [162,224], which could make them a powerful diagnostic tool as hydroxyl-terminated PAMAM dendrimers show minimal transport across the healthy BBB in the absence of neuroinflammation. When coupled with therapeutic agents, the

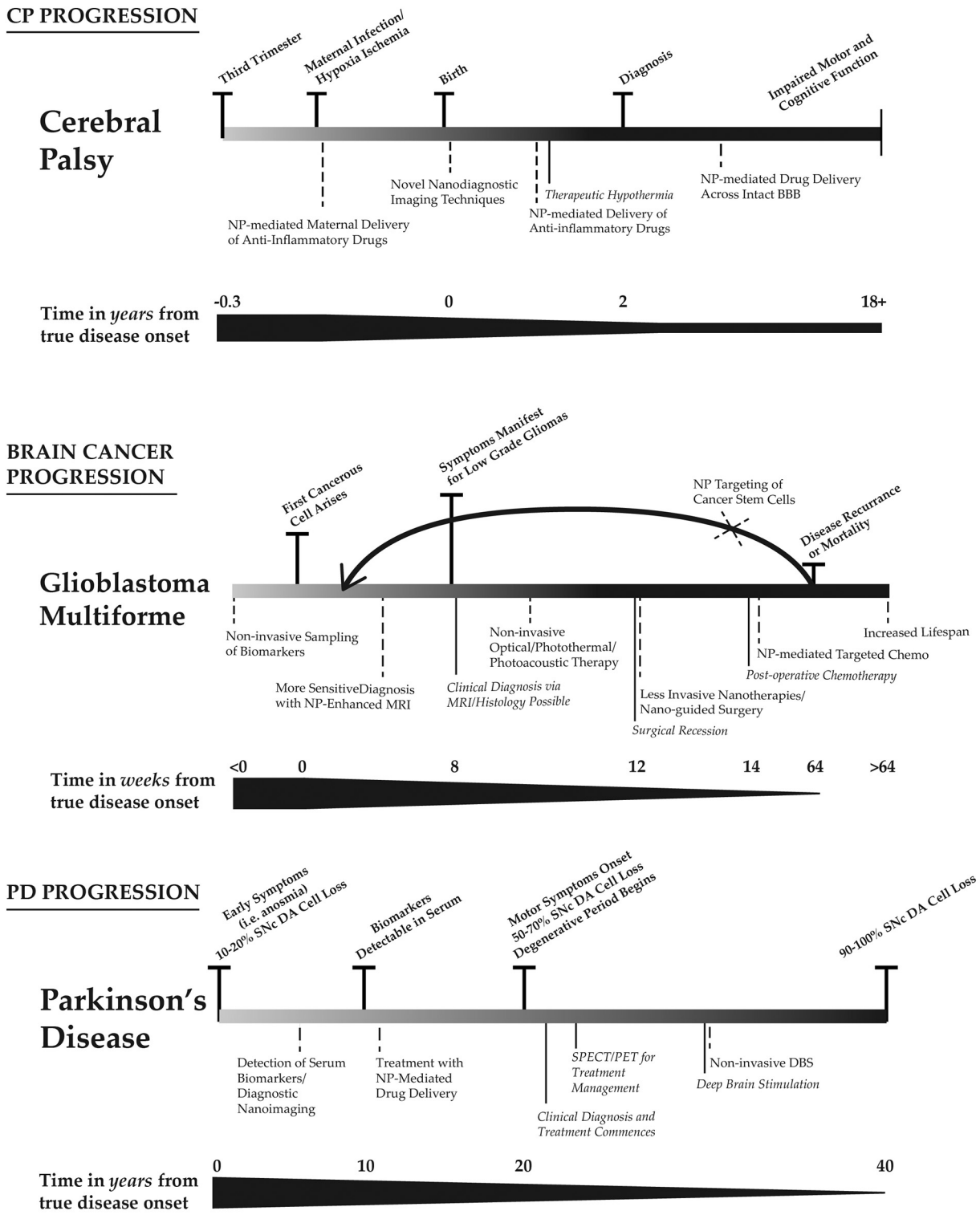

Fig. 9. Schematic representation of disease progression of cerebral palsy (top), Glioblastoma (middle), and Parkinson's disease (bottom). Standards of care for these diseases are noted below the timelines in solid lines and discussed nano-enabled treatments and diagnostic tools are noted with dotted lines.

dendrimers could be a first defense against chronic, difficult to detect neuroinflammation.

While dendrimers rely on passive diffusion to enter the brain in neuroinflammatory disorders, Zhang *et al.* have chosen to utilize the body's own immune response to shut neuroinflammation down by employing a NP with high internalization in neutrophils that then shuttle the particles to the sites of inflammation, brain lesions, following ischemia [225]. They had previously designed a NP that targeted monocytes that then carried the NP across the BBB and to the site of injury, but the delivered drug payload was not sufficient due to the small population size of monocytes [226]. These new NPs (cl PGP-PEG-DGL/CAT-Aco), consist of a dendrigraft generation 2 poly-l-lysine core to which PEG is attached and capped with tripeptide N-acetyl Pro-Gly-Pro (PGP) to promote neutrophil uptake, after which the dendritic molecule

is further functionalized with SPDP for improved stability. These were then complexed with CAT-aco and cross-linked to each other to make complexes about 50 nm in diameter.

The NPs were actively taken up by neutrophils *in vitro* and *in vivo* via multiple pathways, but most significantly through CXCR2 receptor-mediated endocytosis as blocking experiments with CXCR2 antagonist showed a significantly decreased uptake of the NPs compared to controls. The neutrophil transfer of the NPs to neurons *in vitro* was suggested to occur mainly through cell-to-cell contact, with some transfer occurring through exosomal exchange as well. In mouse and rat models of cerebral ischemia via middle cerebral artery occlusion, systemically administered NPs quickly associated with neutrophils in the blood stream with >15% of neutrophils isolated *ex vivo* containing NPs just 5 minutes post injection. These neutrophils then infiltrated the region of damage in the brain and were visible via in vivo fluorescence imaging within 15 minutes of injury in both neutrophils and neurons. This method of targeting injury behind the BBB without further disruption of the barrier allows both the diagnosis of potentially mild neuroinflammation, but also permits delivery of anti-inflammatory and other therapeutic compounds offering a streamlined platform for assessing and addressing acute neuroinflammation *in vivo*.

5. Conclusion: implications of nanotherapies, nanodiagnostics, and nanotheranostics for the clinic

From the early stages of brain development, to the diseases of healthy adult CNS tissue, to degenerative diseases of aging, nanomedicine can improve standards of patient care across the board by allowing earlier diagnosis and treatment of disease, improved longitudinal imaging of disease progression, novel treatment techniques, and less invasive methods of monitoring and diagnosis (Fig. 9). Here we discuss the potential clinical impact these advances can have on three extensively discussed diseases, neonatal brain injury, glioblastoma, and Parkinson's disease.

With diseases that affect the developing brain, where the initial insult sometimes occurs *in utero*, there is a critical need to diagnose the disease early on when patients have not yet suffered the debilitating deficiencies in development that many report lead to severely decreased quality of life, and even decreased life span in cases of more severe injury [227]. Considering CP as an example for these types of diseases with a range of phenotypes manifested in the clinic, nanomedicine offers many opportunities to improve patient care. Less severe cases of cerebral palsy can take up to two years to diagnose [228], which bypasses the current treatment window [14,15]. However, with novel nanodiagnostic tools, acute inflammation could be assessed through noninvasive techniques like PET and SPECT imaging to diagnose the problem earlier. This could even be packaged into a theranostic particle that delivers an anti-inflammatory compound to treat the identified neuroinflammation and brain injury. In cases where it is known that the infant is at risk for CP, such as cases of maternal infection or HIE, some therapeutics (*e.g.* Dendrimer-NAC) could be administered intra-amniotically or even systemically to the mother to quell neuroinflammation prior to birth [229,230].

Similar to CP, earlier diagnosis is critical to improving outcomes for patient with glioblastoma. It is already known that with many types of cancer (ovarian, skin, colorectal, etc.) the greatest indicator of patient survival is time-to-surgery [231–236], so allowing earlier identification of cancerous cells in the brain could dramatically improve outcomes. NPs that serve as more effective contrast agents for MRI fit well into the current clinical landscape as brain cancer as diagnosis is already performed via MRI. Stronger, more specific contrast agents such as those discussed in section 4.1 would allow for earlier diagnosis by identifying smaller tumors. Additional theranostic imaging platforms such as the highly crystalline carbon dots discussed in section 4.2 could be used to kill cancer cells in addition to highlighting their presence, but if surgical removal of the tumor remains necessary, then nanotechnology offers opportunities to make the surgery less invasive and damage less healthy tissue through additional nano-mediated imaging techniques. After surgery patients will still need to undergo chemotherapy, but with NP delivery of chemoagents, more of the active drugs can be delivered to the tumor site, improving efficacy and decreasing side effects potentially allowing a faster recovery and increasing patient's quality of life. Even after successful surgery and chemotherapy, recurrence is still a major problem with brain cancers, but novel nanoimmunotherapy treatments can target cancer stem cells to minimize the potential for the disease to return, and nanoimaging techniques can once again aid in the sensing of new tumors to begin treatment as early as possible.

Neurodegenerative disorders still pose several challenges that impede our ability to treat them effectively. In the case of PD, there may be up to a 20-year prodromal period in which some symptoms like loss of smell, depression, sleep disturbances appear but are not readily attributable to PD [237]. Frustratingly, by the time PD can be diagnosed (i.e. motor symptoms develop), the deterioration is already very pronounced [238,239]. With continued work to understand this period of PD and improved diagnostics with nanotechnology via biomarker detection or via imaging of pathological hallmarks, we may be able to intervene years before the disease has progressed to the stage of motor symptom onset and loss of 50% of nigral dopamine neurons [238,239]. However, the more immediate issue is developing effective therapies for the current therapeutic window (i.e. after motor symptom onset). NP guided delivery of antioxidants and anti-inflammatories as well as NP-mediated alpha synuclein removal may improve efficacy of these promising pharmacological targets.

The promise of recent preclinical advances has the potential to change the landscape of diagnosis and treatment of neurological disorders in ways traditional medicine has been unable. In this review we have discussed recent preclinical and clinical innovations that indicate that while there has yet to be success in the translation of nanomedicine for CNS disorders, successes may be around the corner. This is due to the growing understanding of the interplay between nanotechnology and neurobiology. Looking forward, the regulatory process for nanotechnology should consider both the risk and the reward in a balanced manner, to enable translation. In some cases, there are currently no viable therapeutic avenues, making the promised rewards of nanomedicine even more consequential.

Disclosure

Rangaramanujam M. Kannan is a co-inventor on the dendrimer platform technology and on related patents described in parts of this review paper. He and his wife Sujatha Kannan are co-founders of Ashvattha Therapeutics, Orpheris Inc., and RiniSight Inc., start ups that are leading the clinical development of the platform.

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