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Nanoneuromedicines for degenerative, inflammatory, and infectious nervous system diseases

Howard E. Gendelman[a,*], Vellareddy Anantharam, PhD[b], Tatiana Bronich[c], Shivani Ghaisas[b], Huajun Jin, PhD[b], Anumantha G. Kanthasamy, PhD[b], Xinming Liu[a,c], JoEllyn McMillan[a], R. Lee Mosley[a], Balaji Narasimhan, PhD[d], Surya K. Mallapragada, PhD[d,**]

[a]*Department of Pharmacology and Experimental Neuroscience, University of Nebraska Medical Center, Omaha, NE, USA*
[b]*Department of Biomedical Sciences, Iowa State University, Ames, IA USA*
[c]*Department of Pharmaceutical Sciences, University of Nebraska Medical Center, Omaha, NE, USA*
[d]*Department of Chemical and Biological Engineering, Iowa State University, Ames, IA USA*

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Abstract

Interest in nanoneuromedicine has grown rapidly due to the immediate need for improved biomarkers and therapies for psychiatric, developmental, traumatic, inflammatory, infectious and degenerative nervous system disorders. These, in whole or in part, are a significant societal burden due to growth in numbers of affected people and in disease severity. Lost productivity of the patient and his or her caregiver, and the emotional and financial burden cannot be overstated. The need for improved health care, treatment and diagnostics is immediate. A means to such an end is nanotechnology. Indeed, recent developments of health-care enabling nanotechnologies and nanomedicines range from biomarker discovery including neuroimaging to therapeutic applications for degenerative, inflammatory and infectious disorders of the nervous system. This review focuses on the current and future potential of the field to positively affect clinical outcomes.

From the Clinical Editor: Many nervous system disorders remain unresolved clinical problems. In many cases, drug agents simply cannot cross the blood-brain barrier (BBB) into the nervous system. The advent of nanomedicines can enhance the delivery of biologically active molecules for targeted therapy and imaging. This review focused on the use of nanotechnology for degenerative, inflammatory, and infectious diseases in the nervous system.

Key words: Nanoneuromedicine; Diagnostics; Neurodegenerative disorders; Nanotechnology; Drug development

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; ADDL, amyloid-β-derived diffusible ligand; ALS, amyotrophic lateral sclerosis; ApoE, apolipoprotein E; ART, antiretroviral therapy; BBB, blood–brain barrier; CNS, central nervous system; CSF, cerebral spinal fluid; CTE, chronic traumatic encephalopathies; EAE, experimental autoimmune encephalomyelitis; MOG, myelin oligodendrocyte glycoprotein; MP, mononuclear phagocyte; MPIO, microparticles of iron oxide; MRI, magnetic resonance imaging; MS, multiple sclerosis; NAC, *N*-acetyl cysteine; NGF, nerve growth factor; NRTI, nucleoside reverse transcriptase inhibitors; PAMAM, polyamidoamine; PBCA, poly(*n*-butyl cyanoacrylate); PD, Parkinson's disease; PEG, polyethylene glycol; PET, positron emission tomography; QD, quantum dots; RES, reticuloendothelial system; SLNs, solid lipid nanoparticles; SPIO, superparamagnetic iron oxide; STL, *Solanum tuberosum* lectin; Tregs, regulatory T cells; USPIO, ultra-small superparamagnetic iron oxide; VCAM, vascular cell adhesion molecule-1; VSPIO, very-small superparamagnetic iron oxide.

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*Correspondence to: H.E. Gendelman, Department of Pharmacology and Experimental Neuroscience, Omaha, NE, USA 68198-5880.
**Correspondence to: S.K. Mallapragada, Department of Chemical and Biological Engineering, Iowa State University, Ames, Iowa, USA.
E-mail addresses: hegendel@unmc.edu (H.E. Gendelman), suryakm@iastate.edu (S.K. Mallapragada).

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The field of nanoneuromedicine offers real opportunities to harness unique therapeutic approaches to address diseases of the nervous system where often few options exist. Because of the enormous potential of the field, it was chosen as the theme for the 2014 meeting of the American Society for Nanomedicine.[1] In addition to improved therapies, newer, safer and more sensitive-specific imaging modalities as well as improved diagnostics for disease detection are immediately needed.

Nervous system disorders, due to infection, trauma or degenerative disorders, represent a significant societal burden with parallel broad unmet needs. In many and sometimes most cases, current treatments are simply inadequate to affect disease progression or even ameliorate symptoms and signs of brain injury or degeneration. Significant challenges abound and are associated with the transport of therapeutic or imaging contrast agents across the blood–brain barrier (BBB) into the nervous system and retain the ability to achieve targeted delivery to appropriate brain or spinal cord subregions.[2] Nanomedicines can facilitate solutions to such problems. This and related enabling technologies, can increase drug–drug interactions, facilitate disease ameliorating immunomodulation, enable pathogen clearance and improve nervous system delivery of biologically active molecules. Included are multifunctional therapeutic, imaging and diagnostic devices currently referred to as theranostics.[3] However, limitations for improved drug delivery to the nervous system are not trivial, including the potential for secondary toxicities. Thus, any new formulation must balance a drug therapeutic index. This highlights a quite diverse and multifaceted field of research in biomarker discovery, bioimaging and theranostics. If successful, therapies to address neurodegenerative, immune and infectious diseases of the nervous system could be realized and more options would be available for human use.

Biomarker discovery, bioimaging and theranostics

The abilities to diagnose and monitor neurological diseases have seen considerable growth in the recent decades. Nonetheless, in understanding the mechanisms and pathology of neurodegenerative diseases, the development of strategies to detect neurological diseases at early stages and prior to the emergence of overt symptoms is still a challenge for scientists and physicians in the field. In this context, nanotechnology-based techniques have gained tremendous interest as a tool in the efforts to improve the effectiveness of the imaging of central nervous system (CNS) functions and disease states as well as to advance neurosurgical practice. Most notably is bioimaging. Magnetic resonance imaging (MRI) has emerged as the most important tool in the diagnosis of brain disorders. Positron emission tomography (PET) imaging is not far behind and has already allowed improved understanding of the time course of a range of nervous system disorders including for the pathophysiology of Alzheimer's disease (AD). This has been seen through the application of radiolabeled amyloid ligands.[4–6]

Nanoparticles containing iron, gadolinium and manganese were studied extensively as contrast agents. Among them superparamagnetic iron oxide (SPIO) nanoparticles have garnered interest due to their large surface area, magnetic properties and low toxicity. Biocompatible SPIO nanoparticles consist of a crystalline iron oxide core (in the form of magnetite, Fe_3O_4, or maghemite, γFe_2O_3) encased in polymer or a coated monomer (Figure 1, upper panel).[7,8] The particles can be classified according to their size in several categories: particles with a mean diameter of 50 to 180 nm, referred to as standard SPIOs (e.g. ferumoxides coated with dextran); ultra-small SPIO (USPIOs) nanoparticles with a diameter of 10 to 50 nm; and very-small SPIO (VSPIOs) nanoparticles less than 10 nm in diameter.[9] The nature of the surface coatings determines the physical and biologic properties such as the overall size, surface charge, coating density, toxicity and degradability. These affect the fate of SPIO in body fluids and cells[10]. The nonspecific uptake of SPIO nanoparticles by the reticuloendothelial system (RES) has found clinical application for imaging liver tumors[11,12] and lymph nodes.[13] Ferumoxytol, the USPIO nanoparticles coated with polyglucose sorbitol carboxymethyl ether approved for intravenous iron replacement therapy in patients with chronic kidney disease,[14] was recently investigated as an MR contrast for brain tumors.[15,16] Unlike gadolinium-based agents, contrast enhancement of brain malignancies with ferumoxytol requires intracellular uptake by mononuclear phagocytes (MPs; perivascular macrophages and microglia) and reactive astrocytes with maximal signal enhancement at 24-48 h after injection.[9] The extended USPIO residence time is believed to promote their uptake by circulating cells. This suggests that USPIOs, combined with perfusion-weighted imaging can accurately gauge tumor progression.

Since MPs are present in a range of intracranial pathologies from glial tumors to many inflammatory disorders, ferumoxytol and other USPIO may be useful for imaging diseases. Labeling of circulating monocytes by systemic administration of USPIO nanoparticles was applied to spatiotemporal profiles of MP infiltration in stroke models.[17,18] Studies demonstrated delayed influx of blood-borne monocytes in affected brain regions. The potential of using ferumoxtran-10 (USPIO coated with dextran) for imaging ischemic lesions in patients suffering from stroke was evaluated.[19] Contrast enhancement was observed primarily within the infarcted brain region attributed to the USPIO nanoparticle-labeled macrophage brain infiltration. The latter was supported by a combination of gadolinium-enhanced and USPIO nanoparticle-enhanced MRI.[17,18] Similar observations were reported by Beckmann et al[20] in studies of cerebral amyloid angiopathy in amyloid precursor protein mouse AD models. Systemic administration of SPIO improved the MRI detection of microvascular lesions in the brains of the mice, and also led to the labeling of additional microvascular alteration sites. For AD, it was suggested that monocytes take up SPIO nanoparticles in the circulation then penetrate the brain after attraction by chemokines produced by amyloid beta (Aβ)-stimulated glia. This is true in inflammatory diseases of the nervous system. Indeed, macrophage activity can be visualized with USPIO nanoparticles using MRI tests in patients with relapsing–remitting multiple sclerosis.[21] Alternatively to labeling circulating monocyte-macrophages, visualization of activity may be achieved with isolated cells loaded with SPIO nanoparticles through *in vitro*