

**Euro Biopharma 2018- Nanobiotechnology-based drugs for treatment of neurological disorders- Alain L. Fymat- International Institute of Medicine and Science,****Alain L. Fymat,***International Institute of Medicine and Science, California, U.S.A*

There are approximately 400 known neural disorders, some being due to a disruption or failure of the blood brain barrier (BBB) such as, e.g., meningitis, epilepsy, multiple sclerosis, prion and prion-like diseases (Parkinson's, Alzheimer's), HIV encephalitis, and systemic inflammation (sterile or infectious). As a consequence of the growing aging population, many such neurodegenerative diseases, cancer, and infections of the brain will become more prevalent. Unfortunately, the developmental process for new drugs has not kept pace with progress in molecular neuroscience because most of the new drugs discovered are unable to cross the BBB. This clinical failure may be largely attributed to a lack of appropriate drug delivery systems. Of interest here are those disorders requiring treatment by delivery of nanobiotechnology (NBT)-based drugs through the BBB - one of the most promising applications in clinical neuroscience. Nanoparticles, utilized as drug delivery agents, could potentially carry out multiple tasks in a predefined sequence. They can be effective carriers in delivery of conventional drugs, recombinant proteins, vaccines, etc. The following nanotechnologies are available: liposomes, peptides, radiolabeled polyethylene glycol coated hexadecylcyanoacrylate nanospheres, Polyalkylcyanoacrylate or poly-lactic-co-glycolic acid (PLGA) nanoparticles with polysorbate 80 or poloxamer, and magneto-electric nanoparticles (MENs). Localized and controlled delivery of drugs at their desired sites of action is preferred because it reduces toxicity

and increases treatment efficiency. I will discuss the various strategies that have been explored to increase drug delivery into the brain and their attending difficulties, with particular emphasis on NBT-based drug delivery systems. However, although the use of nanotechnology is expected to reduce the need for invasive procedures for delivery of therapeutics, some devices such as implanted catheters and reservoirs will still be needed. Further, there is some concern about the safety of nanoparticle entry in the brain and this needs to be resolved before human use.

Research into treatments for diseases of the CNS has made magnificent advances in the past few years, but therapeutic choices are restricted for many patients with CNS disorders. Nanotechnology has come out as a promising and exciting new means of treating neurological disease, with the elementary changes the way we approach CNS-targeted therapeutics. Molecules are nanoengineered to cross the blood-brain barrier, signalling systems or target specific cell response to endogenous stimuli, or act as vehicles for gene delivery, or as a matrix to develop axon elongation and support cell endurance. The different variety of nanotechnologies confess the selection of a nanoscale material with the quality best suited to the therapeutic challenges posed by an individual CNS disorder. In this inspection, we describe current advances in the development of nanotechnology for the treatment of neurological disorders—in particular, neurodegenerative disease and malignant brain tumours—and for the promotion of neuroregeneration.

## Introduction

A number of obstacles present substantial challenges when attempting to treat CNS disorders. For example, systemically delivered products must pass through the blood–brain barrier (BBB), and substances delivered intracranially must withstand the substantial dynamic force of cerebrospinal fluid (CSF) flow in the brain interstitium.<sup>1</sup> In addition, the complex cellular organization of the brain and spinal cord complicates the targeted treatment of specific cell populations. Nanotechnology presents a potential solution to these problems. The term ‘nanotechnology’ refers to the engineering of materials on the nanoscale, with functional organization of less than 100 nm in at least one dimension. The scale of nanoengineered materials enables the structures to interact with biological substrates at a molecular level, providing these materials with the potential to effect change in biological systems in unprecedented ways. As such, nanotechnologies can be broadly applied in the diagnosis, imaging and treatment of neurological disorders.

Nanoengineered materials are relevant, and indeed advantageous, for the treatment of CNS disease for a number of reasons. First and foremost, the materials can permeate the BBB—a common obstacle for CNS-targeted therapies. Nanomaterials can also be engineered to interact with defined cellular subsets or molecules, thereby affording specificity of treatment. Furthermore, inclusion of enzyme cleavage sequences in the nanomaterial enables modification of activity in response to biological stimuli, such as pH-sensitive modification or cation-triggered self-assembly. Nanofibres and nanoscaffolds can provide structural as well as trophic support for either endogenous or transplanted cells. Importantly, nanoengineered materials are multifaceted; multiple features can be incorporated into the structures to provide simultaneous targeting,

bioactivity, gene delivery and imaging capabilities in a single material.

In this Review, we provide an overview of nanotechnologies that have been investigated in the context of neurological disease, discuss the evidence for efficacy and toxicity of nanomaterials in specific disorders of the CNS, and highlight the potential for translation of nanotechnology to the clinic.

## Examples of nanotechnologies

Many different forms of nanotechnology exist (Figure 1), each of which provides unique properties that can be utilized for CNS therapeutics. Nanoparticles are highly stable 3D polymeric encapsulation systems that can be loaded with drugs and functionalized with targeting ligands or antibodies, and can be used as nanocarriers to deliver drugs to the CNS. Nanomicelles and nanoliposomes are also used for CNS-targeted drug delivery; nanomicelles comprise a hydrophilic phospholipid monolayer (or polymer) with a hydrophobic core, whereas nanoliposomes have a lipid bilayer structure similar to that of a vesicle. Dendrimers are highly organized structures with repeatedly branched polymers that arise from a central core that can also be loaded with drugs. Aptamers are single-stranded DNA or RNA molecules that are folded into specific 3D structures that can bind to targets with high affinity. Nanofibres are long, linear arrangements of nanomaterials that can self-assemble and provide structural support and guidance to neighbouring cells. This form of nanomaterial can be organized into nanogels that serve as 3D scaffolds to organize transplanted cells as well as promote cell adhesion and growth. Nanoscale materials can also be engineered from carbon; for example, fullerenes and their derivatives are spherical assemblies of 60 carbon atoms arranged in the same pattern as a soccer ball. A subset of fullerenes includes carbon nanotubes—hexagonal arrays of carbon that are similar in

structure to graphite. This extensive variety of technologies enables the choice of a nanoscale material with the quality best suited to the therapeutic challenges by an individual CNS disorder, and is one of the main advantages provided by nanotechnology.

### **Neurodegenerative diseases**

Neurodegenerative diseases are among the most debilitating of CNS disorders. Over 6 million Americans are affected by the two most common neurodegenerative diseases—Alzheimer disease (AD) and Parkinson disease (PD)—and this number can only rise as the population continues to age.<sup>2,3</sup> Although advances have been made with regard to understanding the aetiology of these diseases, currently available treatments for CNS disorders are only able to temporarily alleviate symptoms, and delivery of therapeutics to the brain remains a considerable challenge. As such, novel approaches to the treatment of AD and PD have become a focus of nanotechnology research

#### **Alzheimer disease**

The pathological hallmarks of AD—the leading cause of dementia worldwide—include plaques of amyloid- $\beta$  ( $A\beta$ ) and neurofibrillary tangles of hyperphosphorylated tau. The peptides and aggregates of  $A\beta$  are neurotoxic and have been proposed as the inciting insult in AD, although tau aggregates are also neurotoxic and can impair cognition. The pathological features of AD are accompanied by increased oxidative stress, elevated levels of metal ions, and the eventual death of many neuronal subsets such as basal forebrain cholinergic neurons, which are among the earliest neurons affected by AD pathology.

#### **Drug delivery**

##### **Generic nanocarriers**

As access to the brain is a considerable impediment to the application of standard chemotherapeutics for CNS neoplasms, nanocarriers that usher systemic drugs across the BBB have been extensively investigated.

Examples of such nanocarriers include PBCA nanoparticles, which have been used to optimize the delivery of methotrexate<sup>96</sup> and temozolomide<sup>97</sup> to the brain, resulting in significantly increased intracerebral drug concentrations compared with treatment with the drugs alone.

### **Biography**

Dr. Alain L. Fymat is the current President/CEO and Professor at the International Institute of Medicine and Science with a previous appointment as Executive Vice President, Chief Operating Officer and Professor at the Weil Institute of Critical Care Medicine, both Institutes located in Rancho Mirage, California, USA. He was formerly Professor of Radiology, Radiological Sciences, Radiation Medicine (Oncology), and Physics at several U.S. and European Universities (University of California at Los Angeles, University of Southern California, Loma Linda University, California; University of Lille, France). Previously, he was Deputy Director (Western Region) of the U.S. Department of Veterans Affairs, Veterans Health Administration (Office of Research Oversight), and Director of the Magnetic Resonance Imaging Center and for a time Acting Chair of Radiology at its Loma Linda, California Medical Center.

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