NANONEUROLOGY

Rodica Balasa[1,2]

[1]*Targu-Mures Clinical Emergency Hospital*
[2]*University of Medicine and Pharmacy, Targu-Mures*

ABSTRACT

In the last two decades, nanotechnology has acquired a new dimension in medicine and healthcare. Applications of nanotechnology to neurology complement other approaches for the research, diagnosis and treatment of the neurological diseases/disorders (nanoneurology). The clinical challenges imposed by the central nervous system (CNS) and the obstacles faced by anything designed to target and interface with CNS are a result of its unique anatomophysiology. In this context, we can mention the possibilities of nanoparticles (drugs, contrast agents) to cross through blood-brain-barrier. Once entered in CNS, the nanoparticles need to selectively target its intended cells or ligands and only then carry out its primary functions. A promising area that has seen marked progress involves nanoengineered technologies for imaging anatomofunctional structures and for tracking transplanted stem cells and related applications with high efficacy and at high spatial resolutions. Several "nano" formulations are being investigated as potential carries for drug of various classes to treat the neurological diseases (e.g.: demyelinating, degenerative, stroke, epilepsy). Other potential future applications of nanotechnology include the use of nanoengineered functional scaffold systems for promoting neural regeneration following both acute and chronic neurological injury. Applications of nanotechnology to neurology and to neuroscience more broadly, represent emerging next-generation basic research, diagnostic and therapeutic tools.

Keywords: nanotechnology, neuroimaging, brain drug delivery, blood-brain-barrier, neurological diseases

DEFINITIONS

Nanoneurology is part of nanomedicine/nanoneuroscience and represents the ensemble of the nanotechnologies used for research, diagnosis and therapy of neurological diseases/disorders (1-4).

Nanomedicine is defined as the application of nanotechnology in medicine. Its broad scope covers the use of nanoparticles, nanodevices and nanosystems in health-care. Safety, ethical and regulatory issues are also included (1-4).

Nanoneuroscience is a new discipline that bridges neuroscience and nanotechnology by concurrently addressing the fundamental goals of these two separate fields (1-4).

Nanotechnology (molecular engineering) is an emerging interdisciplinary area of science and engineering, which utilize materials, devices and systems through the control of matter on the nanometer-length scale at the level of atoms, molecules and supramolecular structures (dimensions from 1 to 100 nm, where unique phenomena enable novel applications). Nanotechnology involves imaging, measuring, modelling and manipulating matter at the nano length scale. Nanotechnology is important in medicine mostly because of increasing costs of healthcare and the demand for less invasive/more efficient medical procedures (1-4).

Nanotheranostics is the integration of nanodiagnosis (e.g.: molecular diagnostic) and nanotherapy (e.g.: targeted drug delivery) in one system using the benefits of nanotechnology. Nanotheranostics is extremely attractive for personalized medicine (5, 6,28).

Nanoparticles (NPs), named also nanocarriers, are defined as objects in the 1-100 nm range being used as a transport module for another substance (e.g.: contrast agents, drugs). The unique physicochemical properties of NPs find practical applications in many disciplines of medicine, including neurology. NPs are categorized into following platforms: a) nanopolymers (e.g.: colloidal semi-conductor nanocrystal surrounded by polymer shell – quantum dot); b) nanoscaffold (three-dimensional

Author for correspondence:
Rodica Balasa, First Neurological Clinic, Targu-Mures Clinical Emergency Hospital, 50 Gh. Marinescu Street, Targu-Mures

structure composed of polymer fibres); c) micelles (an aggregate of surfactant molecules dispersed in liquid colloid); d) liposomes (e.g.: liposomal-based gadolinium); e) peptides/proteins-based nanoparticles; f) metal complexes (e.g.: gadolinium-based endohedral metallo-fullerenes, iron oxide, silver, gold, platinum, yttrium and cerium nanoparticles); g) carbon platforms (e.g.: nanodiamonds, carbon nanotubes); h) dendrimers (e.g.: pegylated dendrimers) (7-17b, 43).

Nanotechnology for neurophysiological studies

Nanoscale devices incorporating silicon nanowires, carbon nanotubes and nanotransistors are used to record electrical activity from neurons. The nanoelectrodes have the following particular possibilities: a) recording from smaller structures; b) recording in vivo from more cells with less volume displacement; c) recording intracellular electrical activity from thousands of neurons simultaneously without perturbing their physiological properties (non-invasive); d) existence of intimate contact between cell and nanoelectrode simplifies signal source attribution (one electrode for one neuron) (18-20).

Microelectrode arrays can be used for in vivo monitoring of neuro-transmitters (21,22).

There are two general recording configurations: a) cell-penetrating electrodes; b) cell-engulfed electrodes. For both types of electrodes the crucial benefit is to control the interaction of the recording device with the cell, specifically the cell membrane (23-25).

Nanotechnology for neuroimaging

Ideal imaging contrast agents would exhibit: a) high binding affinity for the target; b) specific uptake; c) retention in the target; d) rapid clearance from non-target tissue; e) adequate capillary permeability; f) high stability; g) integrity in physiological conditions; h) safety/non-toxicity (1-3,12,26).

Peptides or peptidomimetic-based imaging probes can be directly or indirectly labelled with imaging moieties to provide or augment the imaging signal while maintaining their biological activity against specific receptors. Multimodal nanoprobes can be simultaneously analyzed (e.g.: MRI and PET/SPECT) (27,28).

Long circulating nanoparticle contrast agents (core-encapsulated gadolinium liposomes and dual mode gadolinium liposomes) are utilized for contrast-enhanced MRI and magnetic resonance angiography (MRA) (29,30).

Gold nanoparticles have become highly promising contrast agents for optical imaging of their unique resonance properties, biocompatibility and uncomplicated conjunction to biomolecules (31-34,44).

Ultrasmall superparamagnetic nanoparticles of iron oxide (USPION – 20-50 nm), due to their long blood half-life are readily phagocytosed by inflammatory cells and can detect inflammatory brain lesions by in vivo MRI (35-42).

Superparamagnetic nanoparticles (SPION – 0.9-4.5 μm), due to their high iron content, create significantly greater hypointense contrast effects than USPION on T2-weighted MRI and can enable in vivo detection of single cell (35-42).

Molecular MRI (mMRI) is a nanotechnology that utilizes contrast agents (USPION or SPION) for noninvasive detection and localisation of molecular disease markers, cells or therapeutic drugs (43).

Atomic force microscopy (AFM) is a very high-resolution type of scanning probe microscopy for biomolecular manipulation and single-molecule imaging (43a).

Fluorescence resonance energy transfer (FRET) microscopy is the physical process of energy transfer from an excited donor chromophore to a nearby acceptor chromophore and permits investigation into structural dynamics of an individual protein molecule, monitoring its behavior at different folding conformations (43b).

Computed tomography (CT) enables 3D anatomic imaging using gold nanoparticles as an X-ray contrast agent (43c).

Diffuse optical imaging is a method of imaging using near-infrared spectroscopy or fluorescence-based techniques for monitoring of blood perfusion and oxygenation in living tissue (43d).

Photoacoustic imaging is a nanotechnology obtained by using non-ionizing laser pulses which is delivered into biological tissues and some energy is absorbed and converted into ultrasonic emission (43e).

Nanoparticles for targeted brain drug delivery

Nanoparticles (NPs) for brain drug delivery are included in the process of passing therapeutically active molecules across blood-brain barrier (BBB) for the purpose of treating central nervous system (CNS) diseases (44-47).

The possibility for drug to reach the brain is based upon the fact that their crossing of BBB will depend completely on the physiochemical and biomimetic features of the NPs vehicle and will not depend anymore on the chemical structure of the drug, which is hindered inside the NPs (44-47).

The ideal characteristics of NPs are: a) it should be biochemical inert, nontoxic, biodegradable, biocompatible, non-thrombogenic and non-immunogenic; b) to avoid reticuloendothelial system and to have prolonged circulation time; c) it should be stable both physically and chemically in vitro and in vivo; d) it should have uniform distribution in the target; e) restrict drug distribution to non-target cells, tissues or organs; f) controllable and predicable rate of drug release; g) drug release should not affect drug action; h) carriers used must be biodegradable or readily eliminated from the body without any problem; i) no carrier induced modulation in disease state; j) the preparation of the delivery system should be easy/reasonable, simple, reproducible and cost effective (48-53).

The advantage of NPs are: a) possibility of conferring on them features such us high chemical and biological stability, feasibility of incorporating both hydrophilic and hydrophobic pharmaceuticals and the ability to be administered by a variety of routes (e. g.: oral, inhalational, parenteral); b) can be functionalized by covalent conjugation to various ligands (e.g.: antibodies, proteins) to target specific tissues; c) large surface-area-to volume ratio permits multiple copies of a ligand to be attached and to dramatically increase their binding affinity via multivalent functionalization; d) reduction of the specific therapeutic drug release amount and the frequency of the dosages; e) more uniform effect of the drug; f) the reduction of drug side effects; g) reduced fluctuation in circulating drug levels; h) avoids hepatic first pass metabolism. (48-53).

Lipid-based nanoparticles (liposomes and solid lipid nanoparticles) can improve the ability of the drugs to penetrate through the BBB and constituted a promising drug targeting system for the treatment of CNS disorders (54-56).

Polymer-based nanoparticles (polymeric micelles, dendrimers) has shown significant therapeutic potential and have made them ideal candidates for targeted drug delivery across the BBB (e.g.: chemicals, vaccine, antibiotics) (57,58).

NPs encapsulation has the potential to enhance many aspects of drug delivery to the brain. Encapsulation protects the targeted from degeneration en route to the CNS and effectively increasing its bioavailability (49-52).

Transport of nanoparticles across blood-brain barrier

Three principle barriers regulate and limit exchange between blood and neural tissue: a) BBB, formed primarly by capillary endothelial cells between the blood and neuronal tissue; b) choroid plexus epithelium, between blood and ventricular cerebrospinal fluid (CSF); c) arachnoid epithelium, between blood and subarachnoid CSF. The most important barrier, including for drug delivery, is BBB (59,60).

The BBB, as a regulated interface between the peripheral circulation and CNS, is a structure formed by a complex system of endothelial cells, astrocytic end feet and pericytes. BBB together with perivascular neurons constitute a neurovascular unit that is essential for function of the CNS (59-61).

The characteristics of the CNS microvasculature, which make the BBB highly impermeable, are: a) tight junctions (TJs) between adjacent endothelial cells, prohibiting paracellular transport; b) lack of fenestrations within endothelial cells, precluding transcellular transport; c) uniform thickness of cell cytoplasm; d) little vesicular transport; d) greater mitochondrial content than other organs; e) one endothelial cell encompasses the circumference of the capillary lumen, with the opposing ends meeting in a TJ; f) the basal side of the endothelial cells is directly linked to basal lamina through transmembrane protein focal adhesions (61,62).

The basal lamina is formed by three membranes, composed of different extracellular matrix molecules: a) structural proteins (collagen and elastin); b) specialized proteins (e.g.: fibronectin, occludin, laminin); c) proteogycans. Within the complex matrix, the basement membrane also includes receptors (e.g.: cell adhesion molecules, lipoprotein, transferrin) (62,63).

Pericytes are integrated within the basal lamina and regulate: a) endothelial cell proliferation, migration and differentiation; b) BBB adjustments in response to stressful stimuli (e.g.: conservation of the TJs) (62-64).

Astrocytic end feet contact the basal lamina and play a role in: a) tightness of TJs; b) expression of transporters; c) regulation of water fluxes within brain through expression of aquaporin 4 (a membrane water channel). Microglia and synaptic terminal boutons of nerve fibers are in the immediate perivascular space. Neurons play a crucial role in regulating the BBB in response to metabolic requirements by expression of enzymes that adjust vessel permeability (59,61-64).

The BBB plays physical, metabolic and immunologic roles to allow a separate and distinct extracellular fluid compartment (CSF). The BBB maintains a medium for optimal neuronal function, protecting the brain from different components of peripherally circulation (66,67).

Molecules cross the BBB either through a paracellular route (between cells) or a transcellular route (through cells). The majority of molecules pass transcellularly due to complexity of TJs. Endothelial cells contain membrane transporters (specific receptors) that regulate transcellular trafficking between the blood and the brain for essential molecules (e.g.: glucose, amino acids, hormones, insulin, antibiotics). When the target molecule binds to its respective receptor on the endothelial luminal surface, it is transcytosed, forming a vesicle that can be transported across the cell (60,62).

Endothelial cells regulate the concentration of toxins and waste products through efflux pumps, which is thought to be one of the major causes of chemotherapy drug resistance (67,68).

The BBB plays an important role in immune function (the CNS is considered immune privileged since BBB restricts the entry of lymphocytes into the brain and spinal cord parenchyma) (69,70).

CNS disorders can lead to increased BBB permeability (e.g.: tumors, ischemia, inflammation, infection, traumatic injury) (62-64).

The hyperosmolar solutions (e.g.: manitol) can led to increased capillary permeability (62-64).

The ideal method for the delivery of therapeutics across the BBB should have the following characteristics: a) to be controlled; b) not damage the barrier; c) to be biodegradable and not toxic; d) to be selective; e) to be targeted to the BBB and to the site of intended action in the brain; f) the drug load transported through the BBB should be adequate for reaching therapeutic concentrations in the brain; g) therapeutic concentrations should be maintained for a sufficient duration of time for the desired efficacy (48-53,70,71).

The mechanisms involved in drug NPs crossing the BBB: a) NPs open the TJs between endothelial cells and enable the drugs to penetrate the BBB either in free form or together with the nanocarriers (only NPs smaller than about 20 nm); b) NPs are transcytosed through the endothelial cell layer (adsorptive-mediated/receptor-mediated transcytosis); c) NPs are endocytosed by endothelial cells and release the drugs inside the cell; d) NPs inhibit the transmembrane efflux systems; e) NPs improve delivery to the brain by creating a concentration gradient that promotes transport across the endothelial cell layer; f) drug transport is enhanced by the solubilisation of the endothelial cell membrane lipids by surfactant effect; g) exploiting monocyte/macrophage infiltration in the CNS (e.g.: „Trojan" monocytes for NPs delivery to the brain, NPs mimicking activated monocytes); h) NPs may induce local toxic effects on the brain vasculature leading to a limited permeabilization of the brain endothelial cells (48-53,70-74).

Factors affecting NPs brain drug delivery: a) NPs diffusion inside of brain parenchyma (e.g.: presence of cellular obstructions, transient binding to cell membranes or extracellular matrix); b) „corona" of biomolecules on surfaces of NPs; c) BBB alteration in neurological diseases; d) size of NPs (75-79).

Different types of NPs were partly discarded after having demonstrated their cerebral toxicity when utilized in vivo (e.g.: carbon nanotubes, gold-based and iron-based nanoparticles). The cytokines can be utilized for evaluating the immunotoxicity of nanomaterials. The benefit-risk balance deriving from NPs intended for treatment of CNS diseases should be carefully evaluated for each type of NPs. (80-85).

Applications of nanotechnology in demyelinating diseases

Multiple sclerosis (MS) is the most prevalent inflammatory, autoimmune demyelinating disease involving CNS. A fundamental pathologic feature of MS is the formation of multifocal plaques in CNS, accompanied by a disruption of the BBB. Lesion within myelinated regions of the CNS, mediated by infiltrating T cells and autoantibodies, are a hallmark of the disease and lead to progressive neurologic dysfunction. Chronic inflammatory processes that continuously disturb neuroaxonal homeostasis drive neurodegeneration, so the clinical outcome probably depends on the balance of stressor load (inflammation) and any remaining capacity for neural self-protection (86,87).

Molecular MRI with SPION facilitates visualization of macrophage infiltration and provides complementary information to gadolinium enhancement for MS state assessment (88-90).

Magnetic NPs surfaces can be conjugated with antibodies such as anti-VCAM-1 or other endovascular targets implicated in BBB breakdown that could indicate the beginning of neuroinflammatory and/or demyelinating pathology (88-90).

Mesenchymal stem cells (MSCs) may dampen neuroimflammation reducing microglial activation. MSCs may differentiate into glial lineages such as oligodendrocytes or promote neurogenesis in the brain parenchyma, effectively mitigating the neurodegenerative arm of MS and experimental autoimmune encephalomyelitis (EAE). NPs can be used to track transplanted MSCs to ensure survival and function upon differentiation in the target tissue (91-95).

Liposome-encapsulated prednisolone was more effective than 5-fold higher dose of free prednisolone in terms of reducing T cells and macrophage infiltration, restoring BBB and ameliorating the clinical course of EAE (96).

Aquasomes (e.g.: myelin basic protein) represent a possible delivery vehicle for peptides in MS therapy (97).

Plasmid deoxyribonucleic acid (DNA) vaccines, which aim to induce tolerance in MS by encoding for one or more myelin antigens, show great potential for MS therapy (98,99).

Targeting micro ribonucleic acid (mRNA) by delivering a cognate antisense sequence represent a novel therapeutic strategy regulating pathogenic gene expression, relevant for MS, in which the expression of a particular mRNA correlates with disease severity (100).

Glatiramer acetate – GA (Copaxone) is a non-biologic (synthetic) complex drug and first-generation nanomedicine composed of a heterogeneous mixture of immunogenic polypeptides (L-glutamic acid, L-alanine, L-lysine and L-tyrosine) in nanoscale sizes and in a defined molar ratio as a colloidal solution. There are the same amino acids represented in myelin basic protein. Copaxone is included in the group of disease-modifying therapies for MS treatment. Copaxone has immunomodulatory effects at the T-cell level in MS patients: a) modifies the GA-reactive T-cell repertoire; b) reduces the proliferative reactivity of GA-specific CD4-positive T cells; c) restores GA-induced proliferation of CD8-positive T cells; d) stimulates a new population of Th2 CD4-positive T cells; e) produces neurotrophic factors. In EAE, GA-reactive Th2 cells were found in CNS. Clinically, Copaxone: a) reduces the frequency and severity of relapses; b) reduces the accumulation of lesions within brain and spinal cord as seen on MRI; c) slows down the accumulation of physical disability and cognitive deficits (100a-100e).

Pegylated interferon beta-1a (Plegridy) is an interferon beta-1a conjugated to a polyethylene glycol (PEG) molecule and can be used for the treatment of patients with relapsing-remitting MS. Plegridy (125 μg) utilized subcutaneous every 2 weeks significantly reduced the adjusted annualized relapse rate and disability progression with parallel sustained improvements in all MRI endpoints, compared with placebo. The drug might be an effective treatment for relapsing-remitting MS with less frequent administration than other injectable therapies (101-107).

Applications of nanotechnology in neurodegenerative diseases

Parkinson's disease (PD) is a progressive neurodegenerative disease and occurs primarily due to death of dopaminergic neurons in the substantia nigra pars compacta of nigrostriatal system. The most important mechanisms of neurons degeneration in PD are: a) abnormal accumulation of the protein alpha-synuclein bound to ubiquitin inside neurons forming Lewy bodies; b) proteosomal and liposomal system dysfunction; c) reduced mitochondrial activity; d) iron accumulation in the substantia nigra; e) oxidative stress. Chronic neuroinflammation may be a slow and steady reason for neuro-degeneration and neural dysfunction during the asymptomatic stage of PD. Familial forms of PD (less than 10%) are the results of mutations in specific genes: a) alpha-synuclein; b) parkin; c) dardarin (108-111).

Drug delivery systems (DDSs) in PD therapy are currently focused on: a) reformulation of existing drugs; b) reposition of compounds approved for other indications; c) development of novel small molecules, genes and cell-based approaches (112).

Existing antiparkinsonian drugs have been used in animal models through different routes (including via naso-brain), as nanoparticles: a) dopamine-loaded chitosan; b) succinyl dopamine; c) levodopa-α-lipoic acid; d) levodopa methyl ester/benserazide-polylactic-co-glycolic acid – PLGA); e) rotigotine-PLGA; f) apomorphine-tripalmitin; g) ropinirole-nanoemulsion; h) rasagiline-PLGA; i) bromocriptine-chitosan (113-122).

Neurotrophic factors have been proposed as an alternative therapy to prevent or slow down PD. In this context, were used genetic modified mesenchymal stem cells or specific nanoparticles for delivering of nerve growth factor (NGF), glial cell-derived neurotrophic factor (GDNF) and brain derived neurotrophic factor (BDNF) (123,124).

Nanoparticles can be injected by stereotaxy in discrete, precise and functional brain areas without damaging the surrounding tissue: a) nano-enabled scaffold device for dopamine; b) GDNF – PLGA; c) GDNF/BDNF – PLGA; d) plasmid-GDNF (125-129).

Vectors used are derived from adeno-associated viruses and lentiviruses. A possible approaches are: a) to induce 3,4-dihidroxiphenylalanine – DOPA and dopamine – DA biosynthesis in basal ganglia (delivery of tyrosine hydroxylase – TH and aromatic amino acid decarboxylase – AADC); b) to increase gamma-aminobutyric acid – GABA activity in subthalamic nucleus (delivery of glutamic acid decarboxylase – GAD); c) to protect neuronal func-

tions and halt disease (delivery of GDNF); c) to interfere with alpha-synuclein or parkin expression (130-140).

Alzheimer's disease (AD) is a progressive neurodegenerative dementia of old age with loss of neurons and synapses in the cerebral cortex and certain subcortical regions. The neuropathological hallmarks of AD are extracellular amyloid plaques and intracellular neurofibrillary tangles. Amyloid plaques are made up of small peptides, called beta-amyloid (Aβ), cleaved sequentially from a larger amyloid precursor protein (APP) by two enzymes (β-secretase and γ-secretase). If APP is cleaved by α-secretase rather β-secretase then Aβ is not formed. Neurofibrillary tangles comprise mainly of the tau protein which binds micro-tubules, thereby facilitating the neuronal transport system. Uncoupling of tau protein from microtubules and aggregation into tangles inhibits transport and results in microtubule disassembly. Apolipoprotein (Apo E4) has been genetically linked to late-onset (>60 years) familial and sporadic AD. Early-onset AD, the rare familial form, is the result of a mutation in AAP, presenilin 1 or presenilin 2. In the pathogenesis of AD are also involved: a) inflammatory and immune mechanisms; b) oxidative stress/free radicals (compounding with advancing age); c) mitochondrial dysfunction; d) cerebral amyloid angiopathy; e) decreased acetylcholine (Ach) and acetyl-choline-transferase (Acht); f) neuroinflammation; g) disruptions in homeostasis of metal ions (Fe^{++}, Zn^{++}, Cu^{++}) (141-144).

Application of nanotechnology in molecular detection of biomarkers is promising for very early diagnosis of AD. Potential application of nanotechnology in molecular diagnosis is mainly based on special physical, chemical and biological characteristics of certain multifunctional NPs (145,146).

It is possible to detect AD biomarkers (amyloid β-derived diffusible ligant or Aβ) in vitro and in vivo in both humans and animal models (147-154).

The therapeutic potential of nanotechnology includes disease-modifying therapy (neuroprotective/neuroregenerative) and symptomatic therapy. Several nanocarriers systems have been studied to increase the bioavailability, efficacy and safety of different AD therapeutic agents (146,154,155).

Nanotechnology-based approaches are capable of protecting neurons from: a) Aβ oligomeric species; b) uncoupling tau protein; c) oxidative stress; d) glutamate (Glu) excitotoxicity (156-168).

Nanocarrier systems have been used to transport drugs through BBB for AD therapy: a) Acht inhibitors (rivastigmine); b) neurotransmitters (Ach); c) antioxidants (curcumin, ferulic acid): d) neuroprotectors (estradiol, mifepristone, green tea polyphenol); e) metal chelators (d-penicillamine); f) genes (DNA, NGF) (169-180).

Huntington's disease (HD) is a progressive neurodegenerative genetic disease characterized by neuronal lesions mainly in striatum and cerebral cortex. The inherited mutation that causes HD is known as a CAG (cytosine, adenine and guanine) trinucleotide repeat expansion in the huntingtin (Htt) gene. Expanded Htt is unstable and induces a mutant Htt protein in brains and many of the body's tissue of HD patients and animal models. In HD, the proteolytic activity of ubiquitin proteasome system (UPS) is reduced in brain and other tissues. Neuropathological hallmark of HD is the presence of neuronal nuclear inclusions and cytoplasmic aggregates of misfolded mutant Htt (181-183).

Neuroprotective gene therapy had good results in HD using: a) polymer-encapsulated cells engineered to secrete GDNF in human; b) specific functional enhancements by proteasome activator of UPS in model cells (184-185).

The application of RNA interface/small interfering RNA technologies to silence mutant Htt has therapeutic potential in HD animal models (186-190).

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease due to degenerations of motor neurons in the primary motor cortex, brain stem and spinal cord (motor neuron disease). Most ALS cases are sporadic (sALS) but 5-10% are familial (fALS) and of these about 20% have a mutation of the Cu/Zn-superoxidase (SOD1) and about 2-5% have mutation of the transactive response DNA binding protein (TARDBP) gene. Mutations of both SOD1 and TARDBP induce inclusions (e.g.: ubiquitin-positive aggregates) in neurons. Excitotoxicity and apoptosis are other events contributing to motor degeneration and death. Also, oxidative stress is directly implicated in pathogenesis of ALS (191-193).

Proteomics and biomarkers of oxidative stress may be detected by nanotechnology in plasma, CSF or/and urine of both sALS and fALS, including in presymptomatic stage (194-199).

Metals nanoparticles can be excellent probes in order to monitor the biological assembly and its mechanism of ALS and SOD1 aggregates (200-202).

Nanoliposomes can be utilized as carriers for delivery of drugs and genes in ALS (203).

Applications of nanotechnology in stroke

Stroke is defined as an acute neurologic dysfunction of vascular origin with sudden or at least rapid occurrence of symptoms and signs corre-

sponding to the involvement of focal areas in the brain, lasting more than 24 hours. There are two essential types of strokes: a) ischemic stroke (~85%); b) hemorrhagic stroke (~15%). (204).

Ischemic stroke (IS) results when cerebral blood flow (CBF) to an area of brain is decreased or interrupted by stenosis, thrombosis, embolus (e.g.: cardiac or carotid arteries sources) or hemodynamic mechanisms (e.g.: low perfusion pressure, watershed) in intra/extra cerebral arteries and induce cerebral infarction. About 25% of all ischemic strokes are cryptogenetic. Transient ischemic attack (TIA) is an acute episode of temporary neurologic dysfunction, without acute infarction, that typically lasts less than one hour (204,205,214).

CBF thresholds of IS are: a) infarct core (<10 ml/100 g/min); b) reversible penumbra (10-18 ml/100 ml/min); c) normal tissue, including benign oligemia (>18 ml/100 g/min) (206).

Ischemia develops a complex cascade of dynamic pathological events that evolves over time, including: a) depletion of oxygen and glucose; b) depletion of cellular energy (e.g.: failure of mitochondria functions); c) anaerobic metabolism; d) disruption of BBB and extracellular matrix; e) loss of membrane ion pump (e.g.: influx of calcium, sodium and chloride plus efflux of potassium ions) followed by cytotoxic edema (potentially reversible) and vasogenic edema (irreversible); f) release of excitatory neurotransmitters (e.g.: glutamate); g) production of oxygen stress (reactive oxygen species); h) activation of platelet and coagulation cascade; i) induction of cell death in ischemic core and apoptosis in peripheral ischemic zone; j) robust inflammatory responses (e.g.: peripheral leukocyte influx into the cerebral parenchyma, activation of endogenous microglia, release of proinflammatory cytokines, chemokines and matrix metalloproteinases); k) activation of various neuroprotective mechanisms (e.g.: neurotrophins, interleukin-10, granulocyte-colony stimulating factor, angiogenesis). Status of cerebral collateral circulation could influence the effects of arterial occlusion (e.g.: ischemia reperfusion injury) (205-213).

Blood biomarkers of ischemic stroke are studied for stroke risk (e.g.: cardioembolic stroke), diagnosis, infarct volume, stroke severity, hemorrhagic transformation and stroke outcome (215).

Hemorrhagic stroke (HS) occurs due to rapid accumulation of blood within brain parenchyma (hemorrhagic transformation) induced by arterial hypertension, antiplatelet/anticoagulant therapy, cavernoma and/or amyloid angiopathy (216-221).

Depending on the dynamic of hematoma expansion, the primary damage is the result of mass effect. Secondary damage is induced by many parallel and in cascade pathological pathways, including: a) cytotoxicity of blood; b) hypoxia due to disrupted vascular supply; c) raised intracranial pressure; d) oxidative stress; e) disruption of BBB; f) inflammation; g) brain edema; h) massive brain cell death (216-218).

Hemorrhagic infarct (HI) is a secondary hemorrhage into initially IS and may appear as a result of: a) cerebral embolic infarct; b) thrombolytic/ anticoagulant therapy; c) cerebral venous infarct; d) rapid recanalisation/reperfusion of the occluded artery (e.g.: carotid endarterectomy, carotid artery stenting) (222,223).

Atherosclerosis (Aths) is a specific type of **arteriosclerosis** and affects large and medium sized arteries, inducing stenosis or occlusion. Aths is a slow and progressive arterial disease, which become dangerous in 6 or 7 of decades of life. Aths is due to a chronic inflammatory response of white blood cells (monocytes and T-lymphocytes – transformed in foam cells), lipoproteins, platelets and smooth muscle cells in the intimal and medial layers of arteries. Aths lesions (Aths plaques) are separated into two broad categories: a) stable; b) unstable (vulnerable). Aths plaques is followed by a) thrombus formation in carotid, vertebrobasilar and/or cerebral arteries (atherothrombotic stroke); b) downstream cerebral arterial embolism of atheroma debris (embolic stroke); c) lipohyalinosis which affects small vessels (lacunar stroke) (224-226).

Nanotechnologies (e.g.: USPION, fibrin-specific mMRI agents, gold nanoparticles, radionuclide tracers) can be used for detection of intracerebral thrombus or hemorrhage, early stage of ischemic stroke, ischemic penumbra, neural stem cell transplants, Aths plaque composition, reactive oxygen species and apoptosis (227-239).

Nanoparticles can be used in stroke therapy: a) recanalisation/thrombolysis (e.g.: tissue plasminogen activator – tPA, anti-fibrin monoclonal antibody, ultrasound plus tPA, urokinase); b) neuroprotection/neuro-regeneration (e.g.: human mesenchymal stem cells, vasoactive/neuroactive drugs, genes, antioxidant enzymes, cerebrolysin, anti-apoptotic agents, ion channel modulators, growth factors, anti-inflammatory agents); c) inhibition of atherosclerotic plaques growth (e.g.: statins, anti-inflammatory agents) (240-273).

Applications of nanotechnology in epilepsy

Epilepsy (Ep) is a chronic cerebral disease characterised as an enduring predisposition of the brain to generate unprovoked epileptic seizures, with

neurobiologic, cognitive, psychological and social consequences. Ep is not a singular disease, but is heterogeneous in terms of clinical expression, underlying etiologies and pathophysiology (274).

Epileptic seizure (ES) is defined as a transient occurrence of signs and/or symptoms due to abnormal excessive and hypersynchronous discharges of a group of neurons in the brain. ES are broadly classified according to their site of origin and pattern of spread in: a) partial seizures/secondary generalized seizures ; b) primary generalized seizures (274).

Epileptogenesis (development of Ep) refers to a process in which an initial brain-damaging insult triggers a complex, dynamic and heterogeneous cascade at multiple hierarchial levels of CNS (e.g.: molecular, cellular, neurotransmitters, synaptic, neuronal network) towards the generation of ES. Epileptogenesis can have genetic and/or acquired determinants. The changes after the first brain injury include cellular mitochondrial dysfunction, gliosis, neurogenesis, neurodegeneration, axonal damage, dendritic plasticity, BBB deterioration, recruitment of inflammatory cells into brain tissue, reorganisation of synapses, extracellular matrix and molecular architecture neuronal cells. At a basic level, an ES represents a disruption in normal balance between excitatory and inhibitory currents of neurotransmission in the CNS. These currents are mediated via two types of ion channels: a) voltage-gated ion channels are activated by changes in membrane potential (depolarizing currents are excitatory and are mediated by inward Na^+ and Ca^{++} conductances, while inhibitory, hyperpolarizing currents include inward Cl^- and outward K^+ conductances; b) ligand-gated ion channels are activated by binding of a neurotransmitter to an ionotropic receptor on the postsynaptic membrane (the primary excitatory neurotransmitter in the brain is Glu, while GABA is primary inhibitory neurotransmitter). Glial cells play an important role in epileptogenesis by: a) restoration of homeostasis after neural activity (particularly extracellular K^+); b) rapid and efficient removal of extracellular Glu; c) modulation of neural excitability (e.g.: regulation of extracellular pH). Paroxysmal depolarization shift (PDS) is the cellular correlate of the interictal epileptiform discharge (a hallmark of focal Ep). Abnormal neuronal circuitry is required for propagation of PDS to other neurons to produce discharge on EEG or a clinical ES. ES can result from different brain injuries that alter the balance between inhibition and excitation. Recurrent ES lead to subsequent decreased threshold to additional ES and is associated with psychosocial comorbidities (e.g.: impairment of cognition, behaviour and motor regulation). Absence seizures arises from alterations in thalamocortical circuitry. Cellular and electrophysiologic changes in developing brain make it vulnerable to epileptogenesis. Novel treatments (antiinflammatory, immunosuppressants and treatments that modify cellular adhesion, proliferation or neuronal plasticity) have demonstrated favourable effects on genetic and acquired epileptogenesis (275-281).

Ictogenesis describes the processes of transition from the interictal state to a ES and includes the involvement of pyramidal cells, interneurons, astrocytes, GABA-ergic and Glu-ergic signalling and ionic perturbations (282).

Biomarkers of epileptogenesis and ictogenesis could: a) predict the development of an Ep condition; b) identify the presence and severity of tissue capable of generating spontaneous ES; c) measure progression after the condition is established; d) follow-up potential antiepileptogenetic and antiseizure drugs and devices (283).

Action mechanisms of antiepileptic drugs (AEDs): a) AD that affect Na^+ channels (carbamazepine, lacosamide, lamotrigine, oxcarbazine, phenytoin, rufinamide); b) AD that affect Ca^{++} channels (ethosuximide); c) AD that affect inhibitory transmission (benzodiazepines, clobazam, phenobarbital, tiagabine, vigabatrin); d) AD that affect exitatory transmission (perampanel): e) AD that affect K^+ channels (ezogabine); f) AD with multiple action mechanisms (felbamate, gabapentin, levetiracetam, pregabalin, topiramate, valproate, zonisamide) (284,285).

Rational combination of drugs involves establishing the optimal dose of baseline agents and adding drug with multiple mechanisms and avoiding combining those with similar modes of action. A third drug may be added if there is partial response but seizure control remains suboptimal. Special attention should be paid to the overall drug load to avoid side-effects (286).

Drug-resistant epilepsy (refractory epilepsy) is recognized after failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drugs to achieve sustained seizure freedom. The mechanisms of drug resistance are variable and multifactorial according to the underlying cause and to the drug's site of action. Hypothesized biologic mechanisms of drug resistance in epilepsy operate at: a) BBB level (P-glycoprotein expression); b) altered expression or function of neuronal voltage-gated ion channels that are known targets of AD; c) mechanisms not targeted by current AD

(electrical coupling through gap junctions, mitochondrial dysfunction, antibodies to neuro-transmitter receptors) (287).

P-glycoprotein belongs to the CNS drug transporters and multidrug resistance-associated proteins 1 (MRP1). P-glycoprotein is an important protein of the cell membrane that functions as a biological barrier by extruding toxin and xenobiotics out of cells and plays a significant role in drug absorption and disposition. P-glycoprotein expression is increased at the BBB and sclerotic hippocampus levels in patients with pharmacoresistant Ep. P-glycoprotein inhibition enhances AD efficacy (288,289).

Nanotechnologies (e.g.: magnetonanoparticles, diffuse optical imaging, photoacoustic imaging) can be used to localize ES onset and epileptogenic zone. Nanoscale methods suggest that detection and prediction algorithms may be enhanced by recording signal at the neuronal and vascular level of resolution (290-299).

An alternative to delivering free AEDs to the brain is to encapsulate the drugs within a nanoscale delivery system. Drug delivery nanosystems may help to maintain the therapeutic concentration of AEDs in the brain tissue. Factors that regulate achieving and maintain of therapeutic AEDs concentration in the brain include BBB, active removal of AD from the brain to the vascular lumen by MRP1, systemic toxicity of drugs and drug phagocytosis by macrophages in the reticulo-endothelial system. In this context, it is possible to use AEDs and/or adjuvant drugs (carbamazepine, clonazepam, ethosuximide, gabapentin, oxcarbazepine, phenobarbital, phenytoin, valproic acid) as: a) polymeric NPs encapsulating an active substance or forming a drug-polymer complex; b) liposomes entrapping hydrophilic drugs in the aqueous core or binding hydrophobic/aminophilic drugs to the lipid layer; c) hydrogel NPs; d) chitosan solid lipid NPs; e) core-shell NPs (300-313).

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REFERENCES

1. **Silva G.A.** Neuroscience nanotechnology: progress, opportunity and challenges. *Nat Rev Neurosci* 2006; 7: 65-74.
2. **Jain K.K.** Current status and future prospects of nanoneurology. *J Nanoneurosci* 2009; 1: 56-64.
3. **Provenzale J.M., Mohs A.M.** Nanotechnology in neurology – current status and future possibilities. *US Neurology* 2010; 6: 12-17.
4. **Ventola C.L.** The nanomedicine revolution. Part 1: Emerging Concepts. *Pharm Therap* 2012; 37: 512-517.
5. **Kim T.H., Lee S., Chen X.** Nanotheranostics for personalized medicine. *Expert Rev Mol Diag* 2013; 13: 257-269.
6. **Muthu M.S., Leong D.T., Mei L., et al.** Nanotheranostics – Application and further development of nanomedicine strategies for advanced theranostics. *Theranostics* 2014; 4: 660-677.
7. **Zhang L., Gu F.X., Chan J.M., et al.** Nanoparticles in medicine: therapeutic applications and developments. *Clin Pharm Ther* 2008; 83: 761-769.
8. **Muthu M.S., Sing S.** Targeted nanomedicine: effective treatment modalities for cancer, aids and brain disorders. *Nanomed* (Lond) 2009; 4: 105-118.
9. **Blanco E., Kessinger C.W., Sumer B.D., et al.** Multifunctional micellar nanomedicine for cancer therapy. *Exp Biol Med* 2009; 234: 123-131.
10. **Torchilin.** Recent advances with liposomes as pharmaceutical carriers. *Nat Rev Drug Discov* 2005; 4: 145-160.
11. **Jain P.K., Lee K.S., El-Sayed I.H., et al.** Noble metals on the nanoscale: optical and photothermal properties and some applications in imaging, sensing, biology and medicine. *Acc Chem Res* 2008; 41: 1578-1586.
12. **McAteer M.A., Choudhury R.P.** Applications of nanotechnology in molecular imaging of the brain. *Prog Brain Res* 2009; 180: 72-96.
13. **Ando Y.** Carbon nanotube: the inside story. *J Nanosci Nanotechnol* 2010; 10: 3726-3738.
14. **Xiang Y., Dai L.** Nanodiamonds for nanomedicine. *Nanomed* (Lond) 2009; 4: 207-218.
15. **Gillies E.R., Frechet J.M.** Dendrimers and dendritic polymers in drug delivery. *Drug Discov Today* 2005; 10: 35-43.
16. **Mintzer M.A., Grinstaff M.W.** Biomedical applications of dendrimers: a tutorial. *Chem Soc Rev* 2011; 40: 173-190.
17. **Smith A.M., Duan H., Mohs A.M., et al.** Bioconjugated quantum dots for in vivo molecular and cellular imaging. *Adv Drug Deliv Res* 2008; 60: 1226-1240.

17a. **Emerich D.F., Thanos C.G.** Nanotechnology and medicine. *Expert Opin Biol Ther* 2003; 3: 655-663.

17b. **Kubik T., Bogunia-Kubik K., Sugisaka.** Nanotechnology on duty in medical applications. *Cur Pharm Biotechnol* 2005; 6: 17-33.

18. **Liopo A.V., Stewart M.P., Hudson J., et al.** Biocompatibility of native and functionalized single-walled carbon nanotubes for neuronal interface. *J Nanosci Nanotechnol* 2006; 6: 1365-1374.
19. **Misra N., Martinez J.A., Huang S.C., et al.** Bioelectronic silicon nanowire devices using functional membrane proteins. *Proc Natl Acad Sci USA* 2009; 106: 13780-13784.
20. **Qing Q., Pal S.K., Tian B., et al.** Nanowire transistor arrays for mapping neural circuits in acute brain slices. *Proc Natl Acad Sci USA* 2010; 107: 1882-1887.
21. **Burmeister J.J., Pomerleau F., Huettl P., et al.** Ceramic-based multisite microelectrode arrays for simultaneous measures of choline and acetylcholine in CNS. *Biosens Bioelectron* 2008; 23: 1382-1389.
22. **Stephens M.L., Pomerleau F., Huettl P., et al.** Real-time glutamate measurements in the putamen of awake rhesus monkeys using an enzyme-based human microelectrode array prototype. *J Neurosci Methods* 2010; 185: 264-272.
23. **Hai A., Shappir J., Spira M.E.** In-cell recordings by extracellular microelectrodes. *Nat Methods* 2010; 7: 200-202.
24. **Robinson J.T., Jorgolli M., Shalek A.K., et al.** Vertical nanowire electrode arrays as a scalable platform for intracellular interfacing to neuronal circuits. *Nat Nanotechnol* 2012; 7: 180-184.
25. **Spira M.E., Hai A.** Multi-electrode array technologies for nanoscience and cardiology. *Nat Nanotechnol* 2013; 8: 83-94.

26. **Rosen J.E., Yoffe S., Meerasa A., et al.** Nanotechnology and diagnostic imaging: new advances in contrast agent technology. *J Nanomed Nanotechnol* 2011; 2: 115.
27. **Reubi J.C., Maeke H.R.** Peptide-based probes for cancer imaging. *J Nucl Med* 2008; 49: 1735-1738.
28. **Fang C., Zhang M.** Nanoparticle-based theranostics: integrating diagnostic and therapeutic potentials in nanomedicine. *J Control Release* 2010; 146: 2-5.
29. **Ghaghada K.B., Hawley C., Kawaji K., et al.** T1 relaxivity of core-encapsulated gadolinium liposomal contrast agents – effect of liposome size and internal gadolinium concentration. *Acad Radiol* 2008; 15: 1259-1263.
30. **Ghaghada K.B., Ravoori M., Sabapathy D., et al.** New dual mode gadolinium nanoparticle contrast agent for magnetic resonance imaging. *PLOS ONE* 2009; 4: e7628.
31. **Huang X., Jain P.K., El-Sayed I., et al.** Gold nanoparticles: interesting optical properties and recent applications in cancer diagnostics and therapy. *Nanomed* 2007; 2: 681-693.
32. **Giljohann D.A., Seferos D.S., Daniel W.L., et al.** Gold nanoparticles for biology and medicine. *Angew Chem Int Ed Engl* 2010; 49: 3280-3284.
33. **Dykman L.A., Khlebtsov.** Gold nanoparticles in biology and medicine: recent advances and prospects. *Acta Nat* 2011; 3: 34-55.
34. **Tiwari P.M., Vig K., Dennis V.A., et al.** Functionalized gold nanoparticles and their biomedical applications. *Nanomater* 2011; 1: 31-63.
35. **Cheng M.M., Cuda G., Bunimovich Y.L.** Nanotechnologies for biomolecular detection and medical diagnostics. *Curr Opin Chem Biol* 2006; 10: 11-19.
36. **Pery K.G., Boiziau C., Dousset V., et al.** Magnetic resonance imaging of human brain macrophage infiltration. *J Am Soc Exp NeuroTherap* 2007; 4: 434-342.
37. **Slotkin J.R., Cahill K.S., Tharin S.A., et al.** Cellular magnetic resonance imaging: nanomer and micromer size particles for noninvasive cell localization. *J Am Soc Exp NeuroTherap* 2007; 4: 428-433.
38. **Wang Y.X.J.** Super paramagnetic iron oxide based MRI contrast agents: current status of clinical application. *Quant Imaging Med Surg* 2011; 1: 35-40.
39. **Li L., Jiang W., Song H., et al.** Superparamagnetic iron oxide nanoparticles as MRI contrast agents for non-invasive stem cell labelling and tracking. *Theranostics* 2013; 3: 595-615.
40. **Kolosnjaj-Tabi J., Wilhelm C., Clément O., et al**. Cell labelling with magnetic nanoparticles: opportunity for magnetic cell imaging and cell manipulation. *J Nanobiotech* 2013; 11 (Suppl 1): S7.
41. **Suffredini G., East J.E., Levy L.M.** New applications of nanotechnology for neuroimaging. *Am J Neuroradiol* 2014; 35: 1248-1253.
42. **Neuwelt A., Sidhu N., Hu C., et al.** Iron-based superparamagnetic nanoparticle contrast agents for MRI of infection and inflammation. *Am J Roent* 2015; 204: 302-313.
43. **Hengerer A., Grimm J.** Molecular magnetic resonance imaging. *Biomed Imag Interv* J 2006; 2: e8.

43a. **Engel A., Muller D.J.** Observing single biomolecules at work with the atomic force microscope. *Nat Struct Biol* 2000; 7: 715-718.

43b. **Sekar R.B., Periasamy A.** Fluorescence resonance energy transfer (FRET) microscopy imaging of live cell protein localizations. *J Cell Biol* 2003; 160: 629-633.

43c. **Cole L.E., Ross R.D., Tilley J.M., et al.** Gold nanoparticles as contrast agents in x-ray imaging and computed tomography. *Nanomed* (Lond) 2015; 10: 321-341.

43d. **Gibson A.P., Hebden J.C., Arridge S.R.** Recent advances in diffuse optical imaging. *Phys Med Biol* 2005; 50: 1-43.

43.e **Zhang H.F., Maslov K., Stoica G., et al.** Functional photoacustic microscopy for high-resolution and noninvasive in vivo imaging. *Nat Biotech* 2006; 24: 848-851.

44. **Bhaskar S., Tian F., Stoeger T., et al.** Multifunctional nanocarriers for diagnostics, drug delivery and targeted treatment across blood-brain barrier: perspectives on tracking and neuroimaging. *Part Fibre Toxicol* 2010; 7: 3.
45. **Pantic I., Paunovic, Dimitrijevic, et al.** Gold nanomaterials in contemporary neurophysiology, neurology and psychiatric research. *Rev Adv Mater Sci* 2015; 40: 257-261.
46. **Chen Y., Liu L.** Modern methods for delivery of drugs across the blood-brain barrier. *Adv Drug Deliv Rev* 2012; 64: 640-665.
47. **Kanwar J.R., Sriramoju B., Kanwar R.K.** Neurological disorders and therapeutics targeted to surmount the blood-brain barrier. *Int J Nanomed* 2012; 7: 3259-3278.
48. **Jenkins S.I., Roach P., Maitreyi D., et al.** Development of a nanomaterial bio-screening platform for neurological applications. *Nanomed Nanotech Biol Med* 2015; 11: 77-87.
49. **Barbu E., Molnár E., Tsibouklis J., et al.** The potential for nanoparticle-based drug delivery to the brain. *Exp Opin Drug Deliv* 2009; 6: 553-565.
50. **Provenzale J.M., Silva G.A.** Uses nanoparticles for central nervous system imaging and therapy. *Am J Neuroradiol* 2009; 30: 1293-1231.
51. **Vergoni A.V., Tosi G., Tacchi R., et al.** Nanoparticles as drug delivery agents specific for CNS: in vivo biodistribution. *Nanomed Nanotech Biol Med* 2009; 5: 369-377.
52. **Biddlestone-Thorpe L., Marchi N., Guo K., et al.** Nanomaterial-mediated CSN delivery of diagnostic and therapeutic agents. *Adv Drug Deliv Rev* 2012; 64: 605-613.
53. **Tosi G., Muresanu D.F., Sharma A.** Advances and perspectives for central nervous drug delivery: the interface between nanotechnology and neuroscience. *J Nanoneurosci* 2012; 2: 1-2.
54. **Ramos-Caber P., Campos F.** Lisosomes and nanotechnology in drug development: focus on neurological targets. *Int J Nanomed* 2013; 8: 951-960.
55. **Lai F., Fadda Am, Sinico C.** Liposomes for brain delivery. *Exp Opin Drug Deliv* 2013; 10: 1003-1022.
56. **Pardeshi C., Rajput P., Belgamwar V., et al.** Solid lipid based nanocarriers: an overview. *Acta Pharm* 2012; 62: 433-472.
57. **Patel T., Zhou J., Piepmeier J.M., et al.** Polymeric nanoparticles for drug delivery to central nervous system. *Adv Drug Deliv Rev* 2012; 64:701-705.
58. **Kreuter J.** Drug delivery to the central nervous system by polymeric nanoparticles: what do we know?. *Adv Drug Deliv Rev* 2014; 71: 2-14.
59. **Abbot N.J., Rönnbäck L., Hansson E.** Astrocyte-endothelial inter-actions at the blood-brain barrier. *Nat Rev Neurosci* 2006; 7: 41-53.
60. **de Boer A.G., Gaillard P.J.** Drug targeting to the brain. *Annu Rev Pharm Toxicol* 2007; 47: 323-355.
61. **Hawkins B.T., Davis T.P.** The blood-brain barrier/neurovascular unit in health and disease. *Pharm Rev* 2005; 57: 173-185.
62. **Cardoso F.L., Brites D., Brito M.A.** Looking at the blood-brain barrier: molecular anatomy and possible investigation approaches. *Brain Res Rev* 2010; 64: 328-363.
63. **Wolburg H., Noell S., Mack A., et al.** Brain endothelial cells and the glio-vascular complex. *Cell Tiss Res* 2009; 335: 75-96.
64. **Persidsky Y., Ramirez S.H., Haorah J., et al.** Blood-brain barrier: structural components and function under physiologic and pathologic conditions. *J Neuroimmun Pharm* 2006; 1: 223-236.
65. **Koziara J.M., Lockman P.R., Allen D.D., et al**. The blood-brain barrier and brain drug delivery. *Nanosci Nanotechnol* 2006; 6: 2712-2735.
66. **Begley D.J.** Delivery of therapeutic agents to the central nervous system: the problems and the possibilities. *Pharm Ther* 2004; 104: 29-45.
67. **Cecchelli R., Berezowski V., Lundquist S., et al.** Modelling of the blood-brain barrier in drug discovery and development. *Nat Rev Drug Discov* 2007; 6: 650-661.
68. **Weiss N., Miller F., Cazaubon S., et al.** The blood-brain barrier in brain homeostasis and neurological diseases. *Biochem Biophys Acta* 2009; 1788: 842-857.
69. **von Wedel-Parlow M., Schrot S., Lemmen J., et al.** Neutrophils cross the BBB primarly on transcellular pathways: an in vitro study. *Brain Res* 2011; 1367: 62-76.

70. **Tiwari S.B., Amiji M.M.** A review of nanocarriers-based CNS delivery system. *Curr Drug Deliv* 2006; 3: 219-232.
71. **Martin-Banderas L., Holgado A.** Nanostructures for drug delivery to the brain. *Curr Med Chem* 2011; 18: 5303-5321.
72. **Silva G.A.** Nanotechnology approaches to crossing the blood-brain barrier and drug delivery to the CNS. *BMC Neurosci* 2008; 9 (Suppl 3): S4.
73. **Park K.** Trojan monocytes for improved drug delivery to the brain. *J Control Release* 2008; 132: 75.
74. **Parodi A., Quattrocchi N., van de Ven A.l., et al.** Synthetic nanoparticles functionalized with biomimetic leukocyte membranes possess cell-like functions. *Nat Nanotech* 2013; 8: 61-68.
75. **Syková E., Nicholson C.** Diffusion in brain extracellular space. *Physiol Rev* 2008; 88: 1277-1340.
76. **Pathan S.A., Iqbal Z., Zaidi S.M., et al.** CNS drug delivery systems: novel approaches. *Recent Pat Drug Deliv Formul* 2009; 3: 71-89.
77. **Wolak D.J., Thorne R.G.** Diffusion of macromolecules in the brain: implications for drug delivery. *Mol Pharm* 2013; 10: 1492-1504.
78. **Mahon E., Salvati A., Baldelli F., et al.** Designing the nanoparticle-biomolecule interface for „targeting and therapeutic delivery". *J Control Release* 2012; 161: 164-174.
79. **Modi G., Pillay V., Choonara Y.E.** Advances in the treatment of neuro-degenerative disorders employing nanotechnology. *Ann NY Acad Sci* 2010; 1184: 154-172.
80. **Hutter E., Boridly S., Labrecque S., et al.** Microglial response to gold nanoparticles. *ACS NANO* 2010; 4: 2595-2606.
81. **Win-Shwe T.T., Fujimaki H.** Nanoparticles and neurotoxicity. *Int J Mol Sci* 2011; 12: 6267-6280.
82. **Rivet C.J., Yuan Y., Borca-Tasciuc D.A., et al.** Altering iron oxide nanoparticle surface properties induce cortical neuron cytotoxicology. *Chem Res Toxicol* 2012; 25: 153-161.
83. **Nunes A., Al-jamal K., Nakajima T., et al.** Application of carbon nanotubes in neurology: clinical perspectives and toxicological risks. *Arch Toxicol* 2012; 86: 1009-1020.
84. **Landsiedel R., Fabian E., Ma-Hock L., et al.** Toxico-biokinetics of nanomaterials. *Arch Toxicol* 2012; 86: 1021-1060.
85. **Elsabahy M., Wooley K.L.** Cytokines as biomarkers of nanoparticle immunotoxicity. *Chem Soc Rev* 2013; 42: 5552-5576.
86. **Frischer J.M., Bramow S., Dal-Bianco A., et al.** The relation between inflammation and neurodegeneration in multiple sclerosis brain. *Brain* 2009; 132: 1175-1189.
87. **Lassmann H. van Horssen J.** The molecular basis of neuro-degeneration in multiple sclerosis. *FEBS Lett* 2011; 585: 3715-3723.
88. **Dousset V., Brochet B., Deloire M.S.A., et al.** MR imaging of relapsing multiple sclerosis patients using ultra-small-particle iron oxide and compared with gadolinium. *Am J Neuroradiol* 2006; 27: 1000-1005.
89. **Velling M.M., Oude Engberink R.D., Seewann A., et al.** Pluriformity of inflammation in multiple sclerosis shown by ultra-small iron oxide particle enhancement. *Brain* 2008; 131: 800-807.
90. **Tysiak E., Asbach P., Aktas O., et al.** Beyond blood brain barrier breakdown – in vivo detection of occult neuroinflammatory foci by magnetic nanoparticles in high field MRI. *J Neuroinflamm* 2009; 6: 20.
91. **Karussis D., Kassis I.** The potential use stem cells in multiple sclerosis: an overview of the preclinical experience. *Clin Neurol Neurosurg* 2008; 110: 889-896.
92. **Gordon D., Pavlovska G., James B., et al**. Human mesenchymal stem cells infiltrate the spinal cord, reduce demyelination and localize to white matter lesions in experimental autoimmune encephalomyelitis. *J Neuropath Exp Neuro*l 2010; 69: 1087-1176.
93. **Freedman M.S., Bar-Or A., Atkins H.L., et al.** The therapeutic potential of mesenchymal stem cell transplantation as a treatment for multiple sclerosis: consensus report of the International MSCT Study Group. *Mult Scler* 2010; 16: 503-510.
94. **Uccelli A., Laroni A., Freedman M.S.** Mesenchymal stem cells for the treatment of multiple sclerosis and other neurological diseases. *Lancet Neurol* 2011; 10: 649-656.
95. **Cohen J.A.** Mesenchymal stem cell transplantation in multiple sclerosis. **J Neurol Sci** 2013; 333: 43-49.
96. **Schmidt J., Metaselaar J.M., Wauben M.H.M., et al.** Drug targeting by long-circulating liposomal glucocorticosteroids increases therapeutic efficacy in a model of multiple sclerosis. *Brain* 2003; 126: 1895-1904.
97. **Warren K.G., Catz I., Ferenczi L.Z., et al.** Intravenous synthetic peptide MBP8298 delayed disease progression in an HLA class II-defined cohort of patients with progressive multiple sclerosis: results of a 24-month double-blind placebo-controlled clinical trial and 5 years of follow-up treatment. *Eur J Neurol* 2006; 13: 887-895.
98. **Bar-Or A., Vollmer T., Antel J., et al.** Induction of antigen-specific tolerance in multiple sclerosis after immunization with DNA encoding myelin basic protein in a randomized, placebo-controlled phase 1/2 trial. *Arch Neurol* 2007; 64: 1407-1415.
99. **Fissolo N., Montalban X., Comabella M.** DNA-based vaccines for multiple sclerosis: current status and future directions. *Clin Immunol* 2012; 142: 76-83.
100. **Junker A., Hohfeld R., Meinl E.** The emerging role of microRNAs in multiple sclerosis. *Nat Rev Neurol* 2011; 7: 56-59.

100a. **Comi G., Filippi M., Wolinsky J.S., et al.** European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging – measured disease activity and burden in patients with relapsing multiple sclerosis. *Ann Neurol* 2001; 49: 290-297.

100b. **Farina C., Weber M.S., Meinl E., et al.** Glatiramer acetate in multiple sclerosis: update on potential mechanisms of action. *Lancet Neurol* 2005; 4: 567-575.

100c. **Rizvi S.A., Kim E., Moodie J.** Glatiramer in the treatment of multiple sclerosis. *Int J Nanomed* 2006; 1: 283-289.

100d. **Wolinski J.S.** The use of glatiramer acetate in the treatment of multiple sclerosis. *Adv Neurol* 2006; 98: 273-292.

100e. **La Mantia L., Munari L.M., Lovati R.** Glatiramer acetate for multiple sclerosis. Cochrane Database Syst Rev 2010; CD004678.

101. **Hu X., Miller L., Richman S., et al.** A novel PEGylated Interferon beta-1a for multiple sclerosis: safety, pharmacology and biology. *J Clin Pharm* 2012; 52: 798-808.
102. **Reus R.** PEGylated interferon beta-1a in the treatment of multiple sclerosis – an update. *Biologics Targ Ther;* 2013; 7: 131-138.
103. **Calabresi P.A., Keiseier B.C., Arnold D.L., et al.** Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomized, phase 3, double-blind study. *Lancet Neurol* 2014; 13: 657-665.
104. **Arnold D.L., Calabresi P.A., Kieseier B.C., et al.** Effect of peginterferon beta-1a on MRI measures and achieving no evidence of disease activity: results from a randomized controlled trial in relapsing-remitting multiple sclerosis. *BMC Neurol* 2014; 14: 240.
105. **Hoy S.M.** Peginterferon beta-1a: a review of its use in patients with relapsing-remitting multiple sclerosis. CNS Drugs 2015; 29: 171-179.
106. **Tolley K., Hutchinson M., You X., et al.** A network meta-analysis of safety of subcutaneous pegylated Interferon beta-1a versus other injectable therapies for the treatment of relapsing-remitting multiple sclerosis. *PLOS ONE* 2015; 10: e127960.
107. **Cocco E., Marrosu M.G.** Profile of PEGylated interferon beta in the treatment of relapsing-remitting multiple sclerosis. T*her Clin Risk Manag* 2015; 11: 759-766.
108. **Gandhi S., Wood N.W.** Molecular pathogenesis of Parkinson's disease. *Hum Mol Genet* 2005; 14: 2749-2755.
109. **Eriksen J.L., Wszolek Z., Petrucelli L.** Molecular pathogenesis of Parkinson's disease. *Arch Neurol* 2005; 62: 353-357.
110. **Moore D.J., West A.B., Dawson V.L., et al.** Molecular patho-physiology of Parkinson's disease. *Annu Rev Neurosci* 2005; 28: 57-87.
111. **Hirsch E.C., Hunot S.** Neuroinflammation in Parkinson's disease: a target for neuroprotection? *Lancet Neurol* 2009; 8: 382-397.
112. **Meissner W.G., Frasier M., Gasser T., et al.** Priorities in Parkinson's disease research. *Nat Rev Drug Disc* 2011; 10: 377-393.
113. **Trapani A., De Giglo E., Cafagna D., et al.** Characterization and evaluation of chitosan nanoparticles for dopamine brain delivery. *Int J Pharm* 2011; 419: 296-307.

114. **Malvidini MA, Di Corato R, Curcio A, et al.** Multiple functiona-lization of fluorescent nanoparticles for specific biolabeling and drug delivery of dopamine. *Nanoscale* 2011; 3: 5110-5119.
115. **D'Aurizio E., Sozio P., Cerasa L.S., et al.** Biodegradable microspheres loaded with an anti-Parkinson prodrug: an in vivo pharmaco-kinetic study. *Mol Pharm* 2011; 5: 2408-2415.
116. **Yang X., Zheng R., Cai Y., et al.** Controlled-release levodopa metyl ester/benserazide-loaded nanoparticles ameliorate levodopa-induced dyskinesia in rats. *Int J Nanomed* 2012; 7: 2077-2086.
117. **Wang A., Wang L., Sun K., et al.** Preparation of rotigotine-loaded microspheres and their combination use with L-DOPA to modify dyskinesias in 6-OHDA-lesioned rats. *Pharm Res* 2012; 29: 2367-2376.
118. **Tsai M.J., Huang Y.B., Wu P.C., et al.** Oral apomorphine delivery from solid lipid nanoparticles with different monostearate emulsifiers: pharmaco-kinetic and behavioral evaluations. *J Pharm Sci* 2011; 100: 547-557.
119. **Azeem A., Talegaonkar S., Negi L.M., et al.** Oil based nanocarriers system for transdermal delivery of ropinirole: a mechanistic, pharmacokinetic and biochemical investigation. *Int J Pharm* 2012; 422: 436-444.
120. **Fernández M., Negro S., Slowing K., et al.** An effective novel delivery strategy of rasagiline for Parkinson's disease. *Int J Pharm* 2011; 419: 271-280.
121. **Md S., Khan R.A., Mustafa G., et al.** Bromocriprine loaded chitosan nanoparticles intended for direct nose to brain delivery: pharmaco-dynamic, pharmacokinetic and scintigraphy study in mice model. *Eur J Pharm Sci* 2013; 14: 393-405.
122. **Kulkami A.D., Vanjari Y.H., Sancheti K.H., et al.** Nanotechnology-mediated nose to brain drug delivery for Parkinson's disease: a mini review. *J Drug Target* 2015; 11: 1-14.
123. **Géral C., Angelova A., Lesieur S.** From molecular to nanotechnology strategies for delivery of neurotrophins: emphasis on brain-derived neurotrophic factor (BDNF). *Pharmaceutics* 2013; 5: 127-167.
124. **Wyse R.D., Dumbar G.L., Rossignol J.** Use genetically modified mesenchymal stem cells to treat neurodegenerative diseases. *Int J Mol Sci* 2014; 15: 1719-1745.
125. **Pillay S., Pillay V., Choonara Y.E., et al.** Design, miometric simulation and optimization of a nano-enabled scaffold device for enhanced delivery of dopamine to the brain. *Int J Pharm* 2009; 382: 277-290.
126. **Garabayo E., Ansorena E., Lanciego J.L., et al.** Long-term neuroprotection and neurorestoration by glial-derived neurotrophic factor microspheres for the treatment of Parkinson's disease. *Mov Dis* 2011; 15: 1943-1947.
127. **Lampe K.J., Kern D.S., Mahoney M.J., et al.** The administration of BDNF and GDNF to the brain via PLGA microparticles patterned with a degradable PEG-based hydrogel: protein distribution and the glial response. **J Biomed Mater Res Part** A 2011; 96: 595-607.
128. **Delcroix G.J., Garbayo E., Sindji L., et al.** The therapeutic potential of human mesenchymal stromal cells combined with pharmacologically active microcarriers transplanted in hemi-parkinsonian rats. *Biomaterials* 2011; 32: 1560-1573.
129. **Yurek D.M., Fletcher A.M., Kowalczyk T.H., et al.** Compacted DNA nanoparticles gene transfer of GDNF to the rat striatum enhances the survival of grafted fetal dopamine neurons. *Cell Transplant* 2009; 18: 1183-1196.
130. **Björklund T., Carlsson T., Cederfjäll E.A., et al.** Optimized adeno-associated viral vector-mediated striatal DOPA delivery restores sensorimotor function and prevents dyskinesias in a model of advanced Parkinson's disease. *Brain* 2010; 133: 496-511.
131. **Manfredsson F.P., Burger C., Sulivan L.F., et al.** rAAV-mediated nigral human parkin over-expression partially ameliorates motor deficits via enhanced dopamine neurotransmission in a rat model of Parkinson's disease. *Exp Neurol* 2007; 207: 289-301.
132. **Sapru M.K., Yates J.W., Hogan S., et al.** Silencing of human alpha-synuclein in vitro and in rat brain using lentiviral-mediated RNAi. *Exp Neurol* 2006; 198: 382-390.
133. **McCormack A.L., Mak S.K., Henderson J.M., et al.** Alpha-synuclein suppression by targeted small RNA in the primate substantia nigra. *PLOS ONE* 2010; 11: e12122.
134. **Yamada M., Mizuno Y., Mochizuki H.** Parkin gene therapy for alpha-synucleinopathy: a rat model of Parkinson's disease. *Hum Gene Ther* 2005; 16: 262-270.
135. **Christine C.W,. Starr P.A., Larson P.S., et al.** Safety and tolerability of putaminal AADC gene therapy for Parkinson's disease. *Neurology* 2009; 73: 1662-1669.
136. **Hadaczek P., Eberling J.L., Pivirotto P., et al.** Eight years of clinical improvement in MPTP-lesioned primates after gene therapy with AAV2-hAADC. *Mol Ther* 2010; 18: 1458-1461.
137. **Luo J., Kaplitt M.G., Fizsimons H.L., et al.** Subthalamic GAD gene therapy in a Parkinson's disease rat model. *Science* 2002; 298: 425-429.
138. **Lang A.E., Gill S., Patel N.K., et al.** Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson's disease. *Ann Neurol* 2006; 59: 459-466.
139. **Marks Jr W.J., Batus R.T., Sifert J., et al.** Gene delivery of AAV2-neurturin for Parkinson's disease: a double-blind, randomized, controlled trial. *Lancet Neurol* 2010; 9: 1164-1172.
140. **LeWitt P.A., Rezai A.R., Leehery M.A., et al.** AAV2-GAD gene therapy for advanced Parkinson's disease: a double-blind, sham-surgery controlled, randomized trial. *Lancet Neurol* 2011; 10: 309-319.
141. **Yaari R., Corely-Bloom J**. Alzheimer's disease. *Semin Neurol* 2007; 27: 32-41.
142. **de Paula V.J.R., Guimarães F.M., Diniz B.S., et al.** Neurobiological pathways to Alzheimer's disease. Amiloid-beta, Tau protein or both? *Dementia Neuropsychol* 2009; 3: 188-194.
143. **Querfurfurth H.W., LaFerla F.M.** Alzheimer's disease. *New Engl J Med* 2010; 362: 329-344.
144. **Dong S., Duan Y., Hu Y., et al.** Advances in the pathogenesis of Alzheimer's disease: a re-evaluation of amyloid cascade hypothesis. *Trans Neurodegen* 2012; 1: 18.
145. **Nazem A., Mansoori G.A.** Nanotechnology solutions for Alzheimer's disease: advances in research tools, diagnostic methods and therapeutic agents. *J Alz Dis* 2008: 13: 199-223.
146. **Brambilla D., Le Droumaguet B., Nicolas J., et al.** Nano-technologies for Alzheimer's disease: diagnosis, therapy and safety issues. *Nanomed Nanotech Biol Med* 2011; 7: 521-540.
147. **Georganopoulou D.G., Chang L., Nam J.M., et al.** Nanoparticle-based detection in cerebral spinal fluid of a soluble pathogenic biomarker for Alzheimer's disease. *Proc Natl Acad Sci USA* 2005; 102: 2273-2276.
148. **Haes A.J., Chang L., Klein W.L., et al.** Detection of a biomarker for Alzheimer's disease from synthetic and clinical samples using nanoscale optical biosensor. *J Am Chem Soc* 2005; 127: 2264-2271.
149. **Kang D.Y., Lee J.H., Oh B.K., et al.** Ultra-sensitive immunosensor for beta-amyloid (1-42) using scanning tunneling microscopy-based electrical detection. *Biosens Bioelectron* 2009; 24: 1431-1436.
150. **Neely A., Perry .C, Varisli B., et al.** Ultrasensitive and highly selective detection of Alzheimer's disease biomarker using two-photon Rayleigh scattering properties of gold nanoparticles. *ACS NANO* 2009; 3: 2834-2840.
151. **Skaat H., Margel S.** Synthesis of fluorescent-maghemite nanoparticles as multimodal imaging agents for amyloid-beta fibrils detection and removal by magnetic field. *Biochem Biophys Res Commun* 2009; 386: 645-649.
152. **Wadghiri Y.Z., Sigurdsson E.M., Sadowski M., et al.** Detection of Alzheimer's amyloid in transgenic mice using magnetic resonance micro-imaging. *Magn Reson Med* 2003; 50: 293-302.
153. **Yang J., Wadghiri Y.Z., Hoang D.M., et al.** Detection of amyloid plaques targeted by USPIO-Aβ-42 in Alzheimer's disease transgenic mice using magnetic resonance microimaging. *Neuroimage* 2011; 55: 1600-1609.
154. **Nesterov E.E., Stoch J,. Hyman B.T., et al.** In vivo optical imaging of amyloid aggregates in brain: design of fluorescent markers. *Angew Chem Int Ed Engl* 2005; 44: 54525456.

155. **Cummings J.L.** Defining and labeling disease-modifying treatments for Alzheimer's disease. *Alz Dement* 2009; 5: 406-418.
156. **Ikeda K., Okada T., Sawada S.** Inhibition of the formation of amyloid beta-protein fibrils using biocompatible nanogels as artificial chaperones. *FEBS Lett* 2006; 580: 6587-6595.
157. **Podolski I.Y., Podlubnaya Z.A., Kosenko E.A., et al**. Effects of hydrated forms of C60 fullerene on amyloid 1-peptide fibrillization in vitro and performance of the cognitive task. *J Nanosci Nanotechnol* 2007; 7: 1479-1785.
158. **D'Angelo B., Santucci S., Benedetti E., et al.** Cerium oxide nano-particles trigger neuronal survival in a human Alzheimer's disease model by modeling BDNF pathway. *Curr Nanosci* 2009; 5: 167-176.
159. **Patel D.A., Henry J.E., Good T.A.** Attenuation of β-amyloid induced toxicity by sialic acid-conjugated dendrimers: role of sialic acid attachment. *Brain Res* 2007; 1161: 95-105.
160. **Kogan M.J., Bastus N.G., Amigo R., et al.** Nanoparticle-mediated local and remote manipulation of protein aggregation. *Nano Lett* 2008; 6: 110-115.
161. **Xue Y., Mansoori G.A.** Self-assembly of diamondoid molecules and derivates (MD simulation and DFT calculations). *Int J Mol Sci* 2010; 11: 288-303.
162. **Saraiva A.M., Cardoso I., Saraiva M.J., et al.** Randomization of amyloid-β-peptide (1-42) conformation by sulfonated and sulfated nanoparticles reduces aggregation and cytotoxicity. *Macromol Biosci* 2010; 10: 1152-1163.
163. **Rocha S., Thünemann A.F., do Campo Pereira M., et al.** Influence of fluorinated and hydrogenated nanoparticles on the structure and fibrillo-genesis of amyloid beta-peptide. *Biophys Chem* 2008; 137: 35-42.
164. **Pai A.S., Rubinstein I., Onyüsel H.** PEGylated phospholipid nano-micelles interact with beta-amyloid (1-42) and minigate its beta-sheet formation, aggregation and neurotoxicity in vitro. *Peptides* 2006; 27:2858-2866.
165. **Cabaleiro-Lago C., Quinian-Pluck F., Lynch I,. et al.** Inhibition of amyloid β protein fibrillation by polymeric nanoparticles. *J Am Chem Soc* 2008; 130: 15437-15443.
166. **Thakur G., Micic M., Yang Y., et al.** Conjugated quantum dots inhibit the amyloid β (1-42) fibrillation process. *Int J Alz Dis* 2011; ID 502386.
167. **Dou F., Netzer W.J., Tanemura K., et al.** Chaperones increase association of tau protein with microtubules. *Proc Natl Acad Sci* USA 2003; 100: 721-726.
168. **Boutajangout A., Ingadottir J., Davies P., et al.** Passive immunization targeting pathological phospho-tau protein in a mouse model reduces functional decline and clears tau aggregates from the brain. *J Neurochem* 2011; 118: 658-667.
169. **Wilson B., Samanta M.K., Santhi K., et al.** Poly(n-butylcyano-accrylate) nanoparticles coated with polysorbate 80 for the targeted delivery of rivastigmine into the brain to treat Alzheimer's disease. *Brain Res* 2008; 1200: 159-168.
170. **Mulik R.S., Mönkkönen J., Juvonen R.O., et al.** ApoE3 mediated poly(butyl) cyanoacrylate nanoparticles containing curcumin: study of enhanced activity of curcumin against beta amyloid induced cytotoxicity using in vitro cell culture model. *Mol Pharm* 2010; 7: 815-825.
171. **Sahni J.K., Doggui S. Ali J., et al.** Neurotherapeutic applications of nanoparticles in Alzheimer's disease. *J Control Release* 2011; 152: 208-231.
172. **Wang X., Chi N., Tang X.** Preparation of estradiol chitosan nanoparticles for improving nasal absorption and brain delivery. *Eur J Pharm Biopharm* 2008; 70: 735-740.
173. **He W., Horn S.W., Hussain M.D.** Improved bioavailability of orally administered mifepristone from PLGA nanoparticles. *Int J Pharm* 2007; 334: 173-178.
174. **Razai-Zadeh K., Arendash G.W., Hou H., et al.** Breen tea epigallo-catechin-3-gallate(EGCG) reduces beta-amyloid mediated cognitive impairment and modulates tau pathology in Alzheimer transgenic mice. *Brain Res;* 1214: 177-187.
175. **Liu G., Men P., Perry G., et al**. Metal chelators coupled with nanoparticles as potential therapeutic agents for Alzheimer's disease. *J Nanoneurosci* 2009; 1: 42-55.
176. **Cui Z., Lockman P.R., Atwood C.S., et al.** Novel D-penicillamine carrying nanoparticles for metal chelation therapy in Alzheimer's and other CNS diseases. *Eur J Pharm Biopharm* 2005; 59: 263-272.
177. **Bondi M.L., Montana G., Craparo E.F., et al.** Ferulic acid-loaded lipid nanostructures as drug delivery system for Alzheimer's disease: preparation, characterization and cytotoxicity studies. *Curr Nanosci* 2009; 5: 26-32.
178. **Miller V.M., Gouvion C.M., Davidson B.L., et al**. Targeting Alzheimer's disease genes with RNA interface: an efficient strategy for silencing mutant alleles. *Nucl Acids Res* 2004; 32: 661-668.
179. **Glat J.M., Offen D.** Cell and gene therapy in Alzheimer's disease. *Stem Cells Develop* 2013; 22: 1490-1496.
180. **Tuszynski M.H., Yang J.H., Barba D., et al.** Nerve growth factor gene therapy activation of neuronal responses in Alzheimer disease. *JAMA Neurol* 2015; DOI: 10100/jamaneurol.2015.1807.
181. **Cattaneo E., Rigamonti D., Goffredo D., et al.** Loss of normal huntingtin function: new developments in Huntington's disease research. *Trends Neurosci* 2001; 24: 182-188.
182. **Walker F.O.** Huntington's disease. Lancet 2007; 369: 218-228.
183. **van der Burg J.M.M., Björkqvist M., Brundin P.** Beyond the brain: widespread pathology in Huntington's disease. *Lancet Neurol;* 8: 765-674.
184. **Bloch J., Bachoud-Lévi A.C., Déglon N., et al.** Neuroprotective gene therapy for Huntington's disease, using polymer-encapsulated cells engineered to secrete human ciliary neurotrophic factors: results of a phase I study. *Hum Gene Ther* 2004; 15: 968-975.
185. **Seo H., Sonntag K.C., Kim W., et al.** Proteasome activator enhances survival of Huntington's disease neuronal model cells. *PLOS ONE* 2007; 2: e238
186. **Harper S.Q., Staber P.D., He X., et al.** RNA interference improves motor and neuropathological abnormalities in a Huntington's disease mouse model. *Proc Natl Acad Sci* USA; 102: 5820-5825.
187. **Wang Y.L., Liu W., Wada E., et al.** Clinico-pathological rescue of a model mouse Huntington's disease by siRNA. *Neurosci Res* 2005; 53: 221-252.
188. **McBride J.L., Pitzer M.R., Boudreau R.L., et al.** Preclinical safety of RNAi-mediated Htt suppression in the rhesus macaque as a potential therapy for Huntington's disease. *Mol Therap* 2011; 19: 2152-2162.
189. **Kordasiewicz H.B., Stanek L.M., Wancewicz E.V., et al.** Sustained therapeutic reversal of Huntington's disease by transient repression of huntingtin synthesis. *Neuron* 2012; 74: 1031-1044.
190. **Grondin R., Kaytor M.D., Ai Y., et al.** Six-month partial suppression of huntingtin is well tolerated in the adult rhesus striatum. *Brain* 2012; 135: 1197-1209.
191. **Rowland L.P., Shneider N.A.** Amyotrophic lateral sclerosis. *N Engl J Med* 2001; 344: 1688-1700.
192. **Wijesekera L.C., Leigh P.N.** Amyotrophic lateral sclerosis. *Orphanet J Rare Dis* 2009; 4: 3.
193. **Kiernan M.C., Vucic S., Cheach B.C., et al.** Amyotrophic lateral sclerosis. *Lancet;* 377: 942-955.
194. **Simpson E.P., Henry Y.K., Henkel J.S, et al.** Increased lipid peroxidation in sera of ALS patients. *Neurology* 2004; 62: 1758-1765.
195. **Chang Y., Kong Q., Shan X., et al.** Messenger RNA oxidation occur early in disease pathogenesis and promotes motor neuron degeneration in ALS. *PLOS ONE* 2008; 3: e2849.
196. **Bowser R., Lacomis D.** Applying proteomics to the diagnosis and treatment of ALS and related diseases. *Muscle Nerve* 2009; 40: 753-762.
197. **Ryberg H., An J., Darko S., et al.** Discovery and verification of amyotrophic lateral sclerosis biomarkers by proteomics. *Muscle Nerve* 2010; 42, 104-111.
198. **Benatar M., Wuu J.** Presymptomatic studies in ALS. *Neurology* 2012; 79: 1732-1739.
199. **Tower R.A., Smith N., Saunders D., et al.** In vivo detection of free radicals using molecular MRI and immuno-spin trapping in a mouse

model for amyotrophic lateral sclerosis. *Free Rad Biol Med* 2013; 63: 351-360.

200. Say R., Kilic G.A., Ozcan A.A., et al. Investigation of photosensitively bioconjugated quantum dots for the labeling of Cu/Zn superoxide dismutase in fixed cells and tissue sections. *Histochem Cell Biol* 2011; 135: 523-530.

201. Choi I., Song H.D., Lee S., et al. Direct observation of defects and increased ion permeability of a membrane induced by structurally disordered Cu/Zn-superoxide dismutase aggregates. *PLOS ONE* 2011; 6: e28982.

202. Hong S., Choi I., Lee S., et al. Sensitive and colorimetric detection of the structural evolution of superoxide dismutase with gold nanoparticles. *Anal Chem* 2009; 81: 1378-1382,

203. Wiley N.J., Madhankumar A.B., Mitchell R.M., et al. Lipopoly-saccharide modified liposomes for amyotrophic lateral sclerosis therapy: efficacy in SOD1 mouse model. *Adv Nanopartic* 2012; 1: 44-53.

204. Moustafa R.R., Baron J.C. Pathophysiology of ischaemic stroke: insights from imaging, and implications for therapy and drug discovery. *Brit J Pharm* 2008; 153: 544-554.

205. Hart R.G., Diener H.C., Coutts S.B., et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014; 13: 429-438.

206. Bandera E., Botteri M., Minelli C., et al. Cerebral blood flow threshold of ischemic penumbra and infarct core in acute ischemic stroke: a systematic review. *Stroke* 2006; 37: 1334-1339.

207. Mergenthaler P., Dirnagl U., Meisel A. Pathophysiology of stroke: lessons from animal models. *Metab Brain Dis* 2004; 19: 151-167.

208. Wang Q., Xian N.T., Yenari M.A. The inflammatory response in stroke. *J Neuroimmunol* 2007; 184: 53-68.

209. Deb P., Sharma S., Hassan K.M. Pathophysiologic mechanisms of acute ischemic stroke: a overview with emphasis on therapeutic significance beyond thrombolysis. *Pathophysiol* 2010; 17: 197-218.

210. Klijn C.J.M., Kappelle J. Haemodynamic stroke: clinical features, prognosis, and management. *Lancet Neurol* 2010; 9: 1008-1017.

211. Iadecola C., Anrather J. The immunology of stroke: from mechanisms to translation. *Nat Med* 2011; 17: 796-808.

212. Macrez R., Ali C., Toutirais O., et al. Stroke and the immune system: from pathophysiology to new therapeutic strategies. *Lancet Neurol* 2011; 10: 471-480.

213. Shuaib A., Butcher K., Mohamad A.A., et al. Collateral blood vessels in acute ischaemic stroke: a potential therapeutic target. *Lancet Neurol* 2011; 10: 909-921.

214. Fonseca A.C., Ferro J.M. Cryptogenetic stroke. *Eur J Neurol* 2015; 22: 618-623.

215. Jicking G.C., Sharp F.R. Blood biomarkers of ischemic stroke. *Neurother* 2011; 8: 349-360.

216. Steiner T., Rosand J., Diringer M. Intracerebral hemorrhage associated with oral anticoagulant therapy. *Stroke* 2006; 37: 256-262.

217. Qureshi A.I., Mendelow A.D., Hanley D.F. Intracerebral haemorrhage. *Lancet* 2009; 373: 1632-1644.

218. Aronowski J., Zhao X. Molecular pathophysiology of cerebral hemorrhage: secondary brain injury. *Stroke* 2011; 42: 1781-1786.

219. Cervera A., Amaro S., Chamorro A. Oral anticoagulant-associated intracerebral hemorrhage. *J Neurol* 2012; 259: 212-224.

220. Veltkamp R., Rizos T., Horstmann S. Intracerebral bleeding in patients on antithrombotic agents. *Semin Thromb Hemost* 2013; 39: 963-971.

221. Laurer A., Pfeilschifter W., Schaffer C.B., et al. Intracerebral haemorrhage associated with antithrombotic treatment: translational insights from experimental studies. *Lancet Neurol* 2013; 12: 394-405.

222. Paciaroni M., Agnelli G., Corea F., et al. Early hemorrhagic transformation of brain infarction: rate, predictive factors, and influence on clinical outcome. *Stroke* 2008; 39: 2249-2256.

223. Choi P.M.C., Ly J.V., Srikanth V., et al. Differentiating between hemorrhahic infarct and parenchymal intracerebral hemorrhage. *Radiol Res Pract* 2012; ID 475497.

224. Nagai Y., Kitagawa K., Sakaguchi M., et al. Significance of earlier carotid atherosclerosis for stroke subtypes. *Stroke* 2001; 32: 1780-1785.

225. Elkind M.S. Inflammation, atherosclerosis and stroke. *Neurologist;* 12: 140-148.

226. Holmstedt C., Turan T.N., Chimowitz M.I. Aterosclerotic intracranial arterial stenosis:risk factors, diagnosis and treatment. *Lancet Neurol* 2013; 12: 1106-1114.

227. Desestret V., Brisset J.C., Moucharrafie S., et al. Early-stage investigations of ultra superparamagnetic iron oxide-induced signal change after permanent middle cerebral artery occlusion in mice. *Stroke* 2009; 40: 1834-1841.

228. Modo M., Beech J.S., Meade T.J., et al. A chronic 1 year assessment of MRI contrastagent-labelled neural stem cell transplants in stroke. *Neuroimage* 2009; 47 (suppl 2):133-142.

229. Uppalo R., Ay I., Dai G., et al. Molecular MRI of intracranial thrombus in a rat ischemic stroke model. *Stroke* 2010; 41: 1271-1277.

230. Cormode D., Roessi Thran A., et al. Atherosclerotic plaque composition: analysis with multicolor CT and targeted gold nanoparticles. *Radiology* 2010; 256-782.

231. Marinescu M., Langer M., Durand A., et al. Synchrotron radiation X-ray phase micro-computed tomography as a new method to detect iron oxide nanoparticles in the brain. *Mol Imaging Biol* 2013; 15: 552-559.

232. Marinescu M., Chauveau F., Durand A., Riou A., et al. Monitoring therapeutic effects in experimental stroke by serial USPIO-enhanced MRI. *Eur Radiol* 2013; 23: 37-47.

233. Kim D.E., Kim J.Y., Sun I.C., et al. Hyperacute direct thrombus imaging using computed tomography and gold nanoparticles. *Ann Neurol* 2013; 73: 617-625.

234. Hyun H., Lee K., Min K.H., et al. Ischemic brain imaging using fluorescent gold nanoprobes sensitive to reactive oxygen species. *J Control Release* 2013; 170: 352-357.

235. Rahmer J., Antonelli A., Sfara C., et al. Nanoparticle encapsulation in red blood cells enables blood-pool magnetic particle imaging after injection. *Phys Med Biol* 2013; 58: 3965-3977.

236. Wen X., Wang Y., Zhang F., et al. In vivo monitoring of neural stem cells after transplantation in acute cerebral infarction with dual-modal MR imaging and optical imaging. *Biomaterials* 2014; 35: 4627-4635.

237. Dimitrev R.I., Borisov S.M., Kondrashina A.V., et al. Imaging oxygen in neural cell and tissue models by means of anionic cell-permeable phosphorescent nanoparticles. *Cell Mol Life Sci* 2015; 72: 367-381.

238. Blankenberg F.G. In vivo detection of apoptosis. *J Nucl Med* 2008; 49 (Suppl 2): 81-95.

239. Ishii T., Fukuta T., Agato Y., et al. Nanoparticles accumulate in ischemic core and penumbra region even when cerebral perfusion is reduced. *Biochem Biophys Res Commun* 2013; 430: 1201-1205.

240. Marsh J.N., Senpan A., Hu G., et al. Fibrin-targeted perfluocarbon nanoparticles for targeted thrombolysis. *Nanomed* (Lond) 2007; 2: 533-543.

241. Torno M.D., Kaminski M.D., Xie Y., et al. Improvement of in vitro thrombolysis employing magnetically-guided microspheres. *Thromb Res* 2008; 121: 799-811.

242. Marsh J.N., Hu G., Zhang H., et al. A fibrin-specific thrombolytic nanomedicine approach to acute ischemic stroke. *Nanomed* (Lond); 6: 605-615.

243. Flores R., Hennings L.J., Lowery J.D., et al. Microbubble augmented ultrasound sonothrombolysis decreases intracranial hemorrhage in a rabbit model of acute ischemic stroke. *Invest Radiol* 2011; 46: 419-424.

244. Chen J.P., Yang P.C., Ma Y.H., et al. Targeted delivery of tissue plasminogen activator by binding to silica-coated magnetic nanoparticles. *Int J Nanomed* 2012; 7: 5137-5149.

245. Cheng R., Huang W., Huang L., et al. Acceleration of tissue plasminogen activator-mediated thrombolysis by magnetically powered nanomotors. *ACS NANO* 2014; 8: 7746-7754.

246. Voros E., Cho M., Ramirez M., et al. TPA immobilization on oxide nanocubes and localized magnetic hyperthermia accelerate blood clot lysis. *Adv Funct Mat* 2015; 25: 1709-1718.

247.Luk Y.O., Cheng W.Y., Wong W.J., et al. Treatment of focal cerebral ischemia with liposomal nerve growth factor. *Drug Deliv* 2004; 11: 319-324.

248.Kolb B., Morshead C., Gonzales C., et al. Growth factor-stimulated generation of new cortical tissue and functional recovery after stroke damage to motor cortex of rats. *J Cereb Blood Flow Metab* 2007; 27: 983-997.

249.Dalpiaz A., Gavini E., Colombo G., et al. Brain uptake of an anti-ischemic agent by nasal administration of microparticles. *J Pharm Sci* 2008; 97: 4889-4903.

250.Kim D., Chung B.G., Kim Y.K., et al. In vivo tracking of human mesenchymal stem cells in experimental stroke. *Cell Transplant* 2008; 16: 1007-1012.

251.Reddy M.K., Labhasetwar V. Nanoparticle-mediated delivery of superoxide dismutase to the brain: an effective strategy to reduce ischemia-reperfusion injury. *FASEB J* 2009; 23: 1384-1395.

252.Klose D., Laprais M., Leroux V., et al. Fenofibrate-loaded PLGA microparticles: effects on ischemic stroke. *Eur J Pharm Sci* 2009; 37: 43-52.

253.Bible E., Chau D.Y., Alexander M.R., et al. The support of neural stem cells transplanted into stroke-induced brain cavities by PLGA particles. *Biomaterials* 2009; 30: 2985-2994.

254.Johnson T.A., Stasko N.A., Matthews J.L., et al. Reduced ischemia/reperfusion injury glutathione-initiated nitric oxide-relapsing dendrimers. *Nitric Oxide* 2010; 22: 30-36.

255.Hyun H., Won Y.W., Kim K.M., et al. Therapeutic effects of a reducible poly (oligo-D-arginine) carrier with the heme oxygenase-1 gene in the treatment of hypoxic-ischemic brain injury. *Biomaterials* 2010; 31: 9128-9134.

256.Kim C.K., Kim T., Choi I.Y., et al. Ceria nanoparticles that can protect against ischemic stroke. A*ngew Chem Int Ed Engl* 2012; 51: 11039-11043.

257.Takamiya M., Miyamoto Y., Yamashita T., et al. Strong neuro-protection with a novel platinum nanoparticle against ischemic stroke and tissue plasminogen activator-related brain damages in mice. *Neurosci* 2012; 221: 47-55.

258.Wang Y., Cooke M.J., Morshead C.M., et al. Hydrogel delivery of erythropoietin to the brain for endogenous stem cell stimulation after stroke injury. *Biomaterials* 2012; 33: 2681-2692.

259.Wang Y., Cooke M.J., Sachewsky N., et al. Bioengineered sequential growth factor delivery stimulates brain tissue regeneration after stroke. *J Control Release* 2013; 172: 1-11.

260.Ghosh A., Sarkar S., Mandal A.K., et al. Neuroprotective role of nanoencapsulated quercetin in combating ischemia-reperfusion induced neuronal damage in young and aged rats. *PLOS ONE* 2013; 8: e57735.

261.Liu X., An C., Jin P., et al. Protective effects of cationic bovine serum albumin-conjugated PEGylated tanshinone IIA nanoparticles on cerebral ischemia. *Biomaterials* 2013; 34: 817-830.

262.An S., Kuang Y., Shen T., et al. Brain-targeting delivery for RNAi neuroprotection against cerebral ischemia reperfusion injury. *Biomaterials* 2013; 34: 8949-8959.

263.Yun X., Maximov V.D., Yu J., et al. Nanoparticles for targeted delivery of antioxidant enzymes to the brain after cerebral ischemia and reperfusion injury. *J Cereb Blood Flow Metab* 2013; 33: 583-592.

264.Mdzinarishvili A., Sutariya V., Talasila P.K., et al. Engineering triiodothyronine (T3) nanoparticles for use in ischemic brain stroke. *Drug Deliv Transl Res* 2013; 3: 309-317.

265.Farr T.D., Lai C.H., Grünstein D., et al. Imaging early endothelial inflammation following stroke by core shell silica superparamagnetic glyconanoparticles that target selectin. *Nano Lett* 2014; 14: 2130-2134.

266.Lu Y.M., Huang J.Y., Wang H., et al. Targeted therapy of brain ischemia using Fas ligand antibody conjugated PEG-lipid nanoparticles. *Biomaterials* 2014; 35: 530-537.

267.Gaudin A., Yemisci M., Eroglu H., et al. Squalenoyl adenosine nanoparticles provide neuroprotection after stroke and spinal cord injury. *Nat Nanotechnol* 2014; 9: 1054-1062.

268.Joachin E., Kim I.D., Jin Y., et al. Gelatin nanoparticles enhance the neuroprotective effects of intranasally administered osteopontin in rat ischemic stroke model. *Drug Deliv Trans Res* 2014; 4: 395-399.

269.Kalani A., Kamat P.K., Kalani K., et al. Epigenetic impact of curcumin on stroke prevention. *Metab Brain Dis* 2015; 30: 427-435.

270.Nucci L.P., Silva H.R., Giampoli V., et al. Stem cells labeled with superparamagnetic iron oxide nanoparticles in a preclinical model of cerebral ischemia: a systematic review with meta-analysis. *Stem Cell Res Ther* 2015; 6: 27.

271.Ruozi B., Belletti D., Sharma H.S., et al. PLGA nanoparticles loaded cerebrolysin: studies on their preparation and investigation of the effect and serum stability with reference to traumatic brain injury. *Mol Neurobiol* 2015; 52: 899-912.

272.Duivenvoorden R., Tang J., Cormode D.P., et al. A statin-loaded reconstituted high-density lipoprotein nanoparticles inhibits atherosclerotic plaque inflammation. *Nat Commun* 2014; 5: 3065.

273.Tang J., Lobatto M.E., Hassing L., et al. Inhibiting macrophage proliferation suppresses atherosclerotic plaque inflammation. *Sci Adv* 2015; 1: e1400223.

274.Fisher R.S., van Emde Boas W., Blume W., et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005; 46: 470-472.

275.Moshé S.L., Perucca E., Ryvlin P., et al. Epilepsy: new advances. *Lancet* 2015; 385: 884-898.

276.Engelborghs S., D'Hooge R., De Deyn P.P. Pathophysiology of epilepsy. *Acta Neurol Belgica* 2000; 100: 201-213.

277.Pitkänen A., Lukasiuk K. Mechanisms of epileptogenesis and potential treatment targets. *Lancet Neurol* 2011; 10: 173-186.

278.Goldberg E.M., Coulter D.A. Mechanisms of epileptogenesis: a convergence on neural circuit dysfunction. *Nat Rev Neurosci* 2013; 14: 337-349.

279.International League Against Epilepsy Consortium on Complex Epilepsy. Genetic determinants of common epilepsies: a meta-analysis of genome-wide association studies. *Lancet Neurol* 2014; 13: 893-903.

280.Zsurka G., Kunz W.S. Mytochondrial dysfunction and seizures: the neuronal energy crisis. *Lancet Neurol* 2015; 14: 956-966.

281.Pitkänen A. Therapeutic approaches to epileptogenesis – hope on the horizon. *Epilepsia* 2010; 51 (Suppl 3): 2-17.

282.Blauwblomme T., Jiruska P., Huberfeld G. Mechanisms of ictogenesis. *Int Rev Neurobiol* 2014; 114: 155-185.

283.Engel J. jr, Pitkänen Loeb J.A., et al. Epilepsy biomarkers. *Epilepsia* 2013; 54 (Suppl 4): 61-69.

284.Brodie M.J., Kwan P. Staged approach to epilepsy management. *Neurology* 2002; 58 (Suppl 5): S2-S8.

285.Perucca E., Tomson T. The pharmacological treatment of epilepsy in adults. *Lancet Neurol* 2011; 10: 446-456.

286.Kwan P., Brodie M.J. Combination therapy in epilepsy. *Drugs* 2006; 66: 1817-1829.

287.Kwan P., Schachter S.C., Brodie M.J. Drug-resistant epilepsy. *N Engl J Med* 2011; 365: 919-926.

288.Feldmann M., Asselin M.C., Liu J., et al. P-glycoprotein expression and function in patients with temporal lobe epilepsy: a case-control study. *Lancet Neurol* 2013; 12: 777-785.

289.Potschka H., Luna-Munguia H. CNS transporters and drug delivery in epilepsy. *Curr Pharm Des* 2014; 20: 1534-1542.

290.Sokol D.K., Markand O.N., Daly E.C., et al. Near infrared spectroscopy (NIRS) distinguishes seizure types. *Seizure* 2000; 9: 323-327.

291.Watanabe E., Maki A., Kawaguchi F., et al. Noninvasive cerebral blood volume measurement during seizures using multichannel near infrared spectroscopic topography. *J Biomed Opt* 2000; 5: 287-290.

292.Iasemidis L.D., Shiau D.S., Chaovalitwongse W., et al. Adaptative epileptic seizure prediction system. IEEE Transact Biomed Engineer 2003; 50: 616-627.

293.Durduran T., Yu G., Burnett M.G., et al. Diffuse optical measurement of blood flow, blood oxygenation and metabolism in a human sensorimotor cortex activation. *Opt Lett* 2004; 29: 1766-1768.

294.Hilman E.M., Devor A., Bouchard M.B., et al. Depth-resolved optical imaging and microscopy of vascular compartment dynamics during somatosensory stimulation. *Neuroimage* 2007; 35: 89-104.
295.Gallagher A., Thériault M., Maclin E., et al. Near-infrared spectroscopy as an adaptative to the Wada test for language mapping in children, adults and special population. *Epileptic Dis* 2007; 9: 241-255.
296.Carney P.R., Myers S., Geyer J.D. Seizures prediction: methods. *Epilepsy Behav* 2011; 22 (Suppl 1): S94-S101.
297.Akhtari M., Bragin A., Moats R., et al. Imaging brain neural activity using functionalized magnetonanoparticles and MRI. *Brain Topography* 2012; 25: 374-388.
298.Cook M.J., O'Brien T.J., Berkovic S.F., et al. Prediction of seizure likelihood with long-term, implanted seizure advisory system in patients with drug-resistant epilepsy: a first-in-man study. *Lancet Neurol* 2013; 12: 563-571.
299.Ramgopal S., Thome-Sousa S., Jackson M., et al. Seizure detection, seizure prediction and closed-loop warning systems in epilepsy. *Epilepsy Behav* 2014; 37: 291-307.
300.Ryu J.G., Jeong Y.I., Kim I.S., et al. Clonazepam release from core-shell type nanoparticles of poly(ε-caprolactone)/poly(ethylene glycol)/poly(ε-caprolactone) triblock copolymers. *Int J Pharm* 2000; 200: 231-242.
301.Potschka H., Fedrowitz M., Löscher W. P-gycoprotein-mediated efflux of phenobarbital, lamotrigine and felbamate at the blood-brain barrier: evidence from microdialysis experiments in rats. *Neurosci Lett* 2002; 327: 173-176.
302.Madhusudhan B., Rambhau D., Apte S.S., et al. 1-0-alkylglycerol stabilized carbamazepine intravenous o/w nanoemulsions for drug targeting in mice. *J Drug Target* 2007; 15: 154-161.
303.Kelmann R.G., Kuminek G., Teixeira H.F., et al. Carbamazepine parenteral nanoemulsions prepared by spontaneous emulsification process. *Int J Pharm* 2007; 342: 231-239.
304.Li Z., Li Q., Simon S., et al. Formulation of spray-dried phenytoin loaded poly(epsilon-caprolactone) microcarrier intended for brain delivery to treat epilepsy. *J Pharm Sci* 2007; 96: 1018-1030.
305.Heredia-Cervera BE, Gonzáles SA, Rodriguez-Gattorno G, et al. Controlled release of phenytoin from nanostructured TiO_2 reservoirs. *Sci Adv Mater* 2009; 1: 63-68.
306.Eskandri S., Varshosaz J., Minaiyan M., et al. Brain delivery of valproic acid via intranasal administration of nanostructured lipid carriers: in vivo pharmacodynamic studies using rat electroshock model. *Int J Nanomed* 2011; 6: 363-371.
307.Nair R., Kumar A.C., Priya V.K., et al. Formulation and evaluation of chitosan lipid nanoparticles of carbamazepine. *Lipids Health Dis* 2012; 11: 72.
308.Lakshmi D., Nair R., Chakrapani M., et al. Solid lipid nanoparticle system for delivery of drugs to the brain. *Int J Biopharm* 2012; 3:70-77.
309.Hsiao M.H., Larsson M., Larsson A., et al. Design and characterization of a novel amphiphilic chitosan nanocapsule-based thermogelling biogel with sustained in vivo release of hydrophilic anti-epilepsy drug ethosuximide. *J Control Release* 2012; 161: 942-948.
310.Hamidi M., Azadi A., Mohamadi-Samani S., et al. Valproate-loaded hydrogel nanoparticles: preparation and characterization. *J Appl Polymer Sci* 2012; 124: 4686-4693.
311.Kumar P.A., Singh R., Kathick K., et al. Formulation and evaluation of sustained released niosomes containing pregabalin. *Int J Pharm Life Sci* 2013; 4: 2770-2774.
312.Sakthivel M., Kannan K., Manavalan R., et al. Formulation and in vivo evaluation of niosomes containing oxcarbazepine. *J Pharm Sci Res* 2013; 5: 8-11.
313.Tummala S., Satish Kumar M.N., Prakash A. Formulation and in vitro characterization of carbamazepine polymeric nanoparticles with enhanced solubility and sustained release for the treatment of epilepsy. *J Chem Pharm Res* 2015; 7: 70-79.