# IRON OXIDE NANOPARTICLES FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES

## Introduction

Reading Time: 12 minutes

Dementia, a syndrome that impairs cognitive function, is ranked 7th among the leading causes of death worldwide. According to the latest report by World Health Organization (WHO) in 2020, dementia entered the top 10 in last 20 years, affecting millions of people worldwide.[1] This kind of neurological disease called neurodegenerative disease (ND) occurs when neurons in the brain or the peripheral nervous system slowly lose function and ultimately degenerate and decline.[2] Although medical science is well advanced today to tackle the diseases affecting the brain, the limitation for the treatment of neurological diseases is the difficulty in delivering drugs to the brain. Human brain is covered by Brain-blood barrier (BBB) which works effectively as a defense mechanism in preventing the majority of molecules, including drugs from entering into brain.[3] Figure 1 shows a representation of the BBB. The BBB protects the brain from toxic molecules and at the same time, maintains the brain homeostasis by regulating ion and nutrient transport.[4]

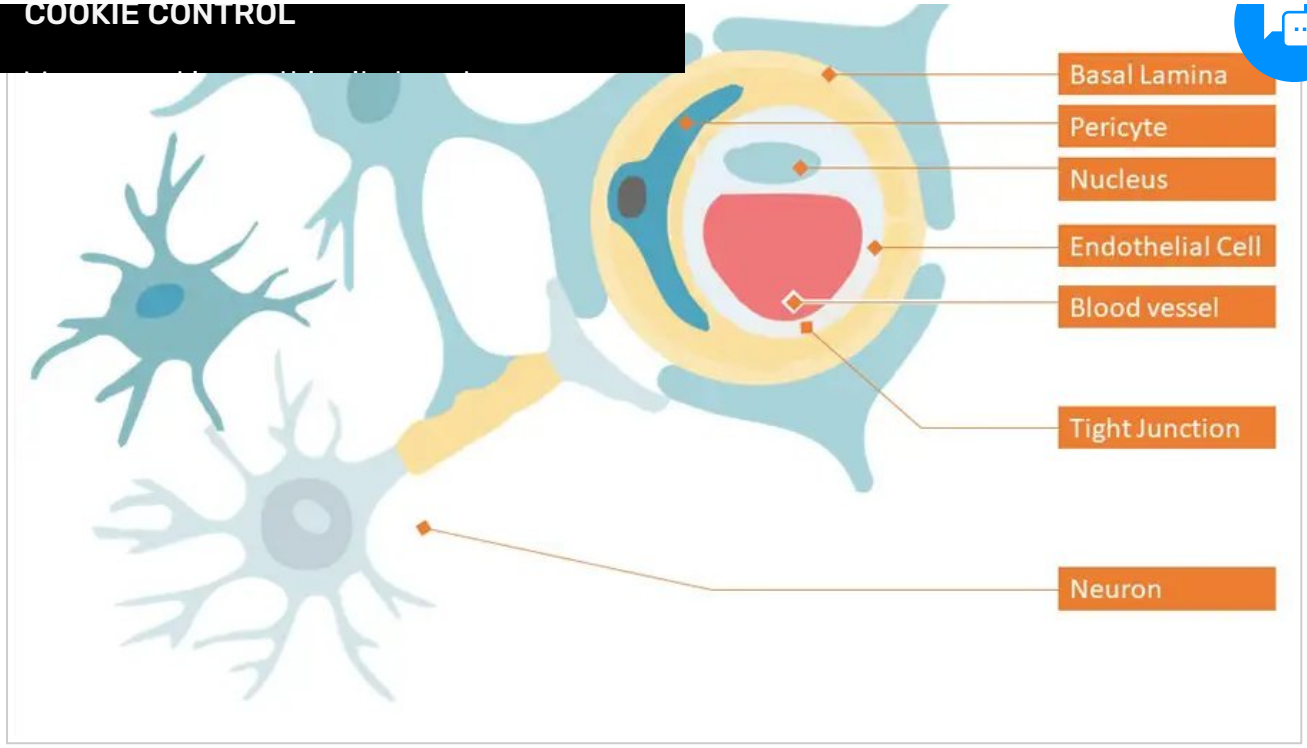



**Figure 1**. Illustration of the blood–brain barrier (BBB).

Crossing the BBB is a challenge when it comes to delivering necessary medicine to the brain for the treatment of NDs. The complex nature of the BBB demands better design and delivery of drugs to the brain to achieve maximum effectiveness. To cross the BBB without loss or accumulation, one method is to load the drug in nanoparticles (NPs) which can pass through the BBB. Nanoparticles have found applications in various biomedical fields such as drug delivery, biosensors, wound healing, etc.[5,6] A new field of research called "neuronanomedicine" has recently emerged, where nanomaterials are designed and engineered to interact with, and act as carriers of drugs to, the biological systems in molecular level.[7] This combination of neurology and nanotechnology is a promising field for the treatment of central nervous system disorders especially NDs, because of the capability of nanoparticles to permeate through BBB. The perfectly engineered nanomaterials can interact with the target area more effectively with less accumulation and toxicity.[8] A recent review on neuronanomedicine provides a summary of nanocarriers developed recently as drug delivery agents to the brain.[9] Nanoparticles coated with targeting ligands enable the NPs to interact effectively with the receptors on the target cells thereby improving the therapeutic action.[10] Although the coated NPs could be used for targeted drug delivery to many parts of the body, there is still lack of development when it comes to cross the BBB because of necessity of higher dose to achieve high concentration on the target site which

will in turn cause accumulation and toxicity in the brain. To avoid unwanted accumulation, attain maximum effect with minimum dosage, and to continuously maintain the drug for slow release on the target site, magnetic nanoparticles, which can be controlled externally by a magnetic field, can be used.[11] Iron oxide nanoparticles (IONPs) are the most widely used magnetic nanoparticles because of easy preparation and functionalization, stability, and biocompatibility.[12] Table 1 depicts the different ways of application of IONPs in diagnosis and treatment of Alzheimer's disease (AD).[13]

| Environment | Iron nanoparticles conjugated with | Application |
|---|---|---|
| In vitro | Anti-Aβ-40 & Anti-Aβ-42 antibodies | Detect Aβ in the blood |
| | Aβ oligomer aptamer | Measure the Aβ oligomer in the artificial cerebrospinal fluid |
| | Diazodinitrophenol (DDNP) | Detect $A\beta_{(1-40)}$ aggregates by fluorophotometry |
| In vivo | Ile-Pro-Leu-Pro-Phe-Tyr-Asn (PHO) | Mark on amyloid plaques in the NMRI mice brain |
| | Anti-Aβ protein precursor (AβPP) antibody | Visualize the number of plaques in APP/PS1 transgenic mice |
| | Diazodinitrophenol (DDNP) | Decrease signal intensity in the hippocampal area in rat AD model |
| | Curcumin | Detect amyloid plaques in Tg2576 mice brains |
| | Fibrin γ377–395 peptide | Inhibit the microglial cells in rTg4510 tau-mutant mice |
| | Antiferritin antibody | Detect ferritin protein in areas with a high amount of amyloid plaques in rat AD model brain |

**Table 1**. The application of iron oxide nanoparticles (IONPs) in diagnosis and treatment of Alzheimer's disease (AD). Adapted from [13]

Superparamagnetic iron oxide nanoparticles (SPIONs) are relatively new choice of nanomaterials for the targeted drug delivery.[14] Unlike ferromagnetic materials, they are small single-domain iron oxide nanoparticles, preferably below 20 nm in size, and their net magnetic effect is zero when the external field is removed. Many factors affect the passage of nanoparticles through the BBB especially the material, size, charge and other surface properties.[15] Due to their smaller size, SPIONs can easily pass through the BBB and this can be achieved by different strategies like encapsulation, external magnetic field and local heating. SPION cores coated with biocompatible materials like silica,

polymers, etc., can be functionalized with drugs or proteins and can be controlled externally using magnetic field to deliver to specific areas in the brain.[16] SPIONs are usually made of magnetite ($Fe_3O_4$) or maghemite ($\gamma$-$Fe_2O_3$).[17] They generate heat when external magnetic field is applied (magnetic hyperthermia) enabling opening of the BBB or destruction of cancer cells.[18] SPIONs can be easily detected in brain using magnetic resonance imaging (MRI).[19] They also show low toxicity and hence preferred over other magnetic materials.[20,21] In this whitepaper, we cover the recent advances in the utilization of SPIONs as targeted drug delivery system for the treatment of neurodegenerative diseases, focusing mainly on Alzheimer's disease and Parkinson's disease.

Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common neurodegenerative diseases among the aged population.[22] AD is a progressive degenerative disease where the brain shrinks and neurons die slowly causing a continuous decline in a person's cognitive thinking and behavior ultimately lead to the person's ability to think and function independently.[23-25] The important cause of this slow cell death (apoptosis) is found to be associated with the fibrillation of Amyloid $\beta$ (A$\beta$) peptides and the accumulation of amyloid plaque in the brain.[26,27] PD is another major neurodegenerative disorder that affects predominately the dopamine-producing neurons in a specific area of the brain called substantia nigra.[28] This disease also progresses slowly through years. The lack of understanding about the cause of NDs leads to lack of treatments of these diseases, although currently found medications can control and slow down the symptoms. Continuous research on drug delivery has helped improve drug delivery systems to the brain and hence better medication for the NDs. SPIONs are promising drug carriers to improve brain drug delivery. But, as for any other drug carriers, stability, biocompatibility and cytotoxicity of SPIONs should also be taken care of.

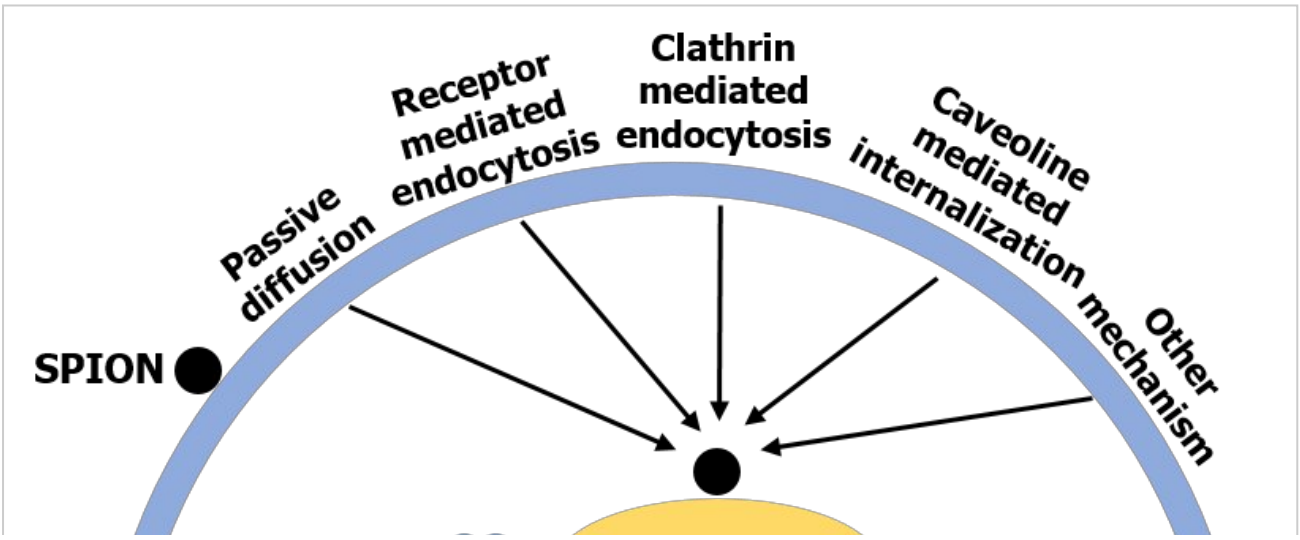
**Colloidal stability of SPIONs**

Colloidal stability refers to the resistance of the particles in a colloid to aggregate. Colloidal stability for SPIONs is important for in vivo applications because their superparamagnetic properties are lost once aggregated and they become permanent magnets.[29] Several factors affect the colloidal stability and potential application as a drug delivery agent in the central nervous system

(CNS). Some important factors are, the size of the particles, Brownian motion of particles, temperature of the medium which in turn determines the viscosity, concentration of the nanoparticles, forces between the particles and other components, etc. These factors play an important role in designing SPIONs for targeted drug delivery.[30]

**Toxicity considerations of SPIONs**

The toxicity of SPIONs is low compared to other nanoparticles because their iron oxide core disintegrates to low-molecular-weight iron containing molecules which can be comparatively easily removed by macrophages and microglia in the CNS.[31,32] However, research has proved that naked SPIONs exhibit more toxicity than those coated with functional molecules, due to the increased tendency of naked SPIONs to absorb amino acids, nutrients and ions causing the composition changes in cells.[33] Research conducted on in-vitro neurotoxicity study of bare, amine- and acid-functionalized SPIONs on human neuroblastoma cell lines, both in cellular and molecular levels, showed that the human neuroblastoma cells were more prone to toxicity effects induced by SPIONs when compared to the heart and kidney cells.[34] It was also found that the toxicity of iron oxide nanoparticles released from SPIONs is concentration dependent as they induce oxidative stress due to enhanced reactive oxygen species (ROS) generation when used in high concentration.[35] Figure 2 portrays possible mechanisms of SPIONs interaction and SPIONs-induced toxicity at cellular level.[35] Surface modification or functionalization reduces the toxicity and at the same time, increases the biocompatibility and blood half-life. Surface coating can be carried out with natural or synthetic polymers, ligands, antibodies, silica, liposomes, and other nanoparticles.



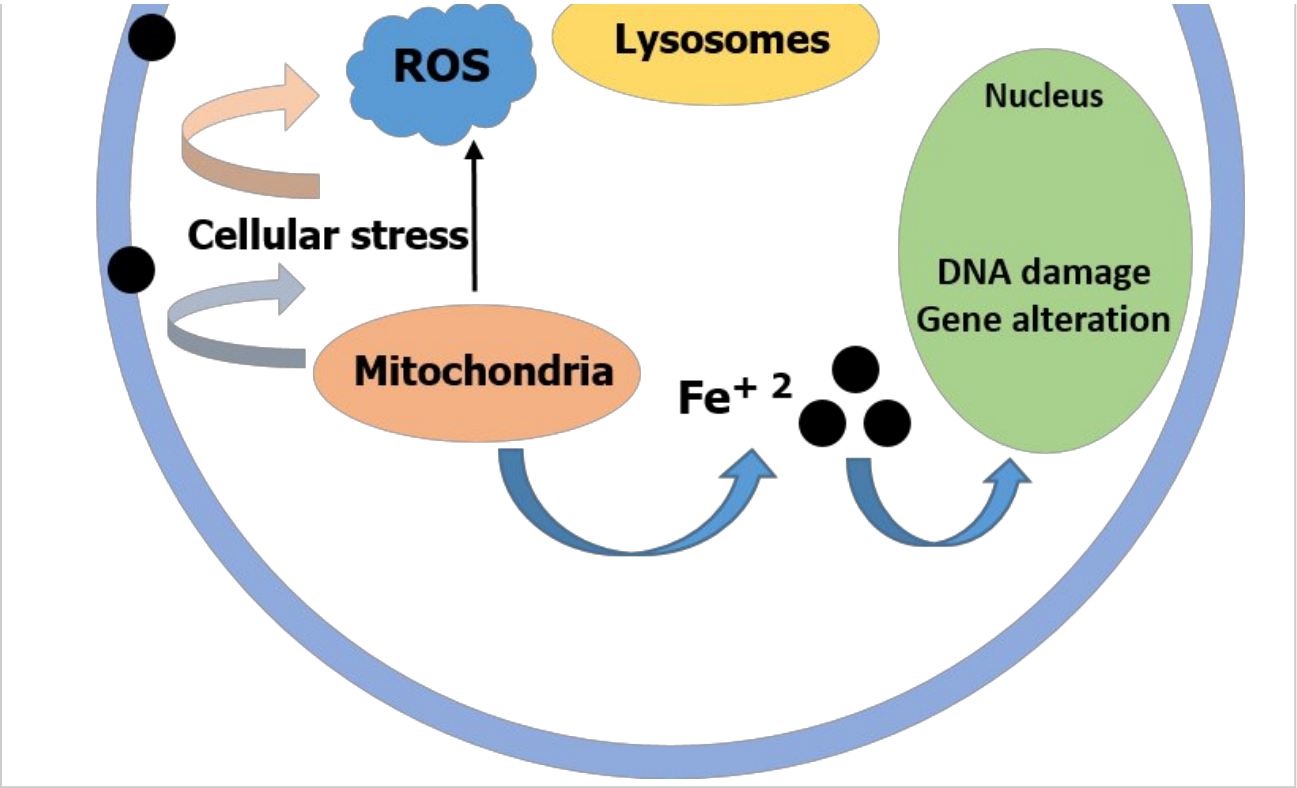



**Figure 2**. Schematic representation of possible mechanism of SPIONs interaction and SPION-induced toxicity at cellular level. Adapted from [35]

## Surface functionalization of SPIONs

Recent advances in targeted drug delivery using SPIONs with coating and/or surface functionalization have enabled it to specifically cross the BBB and deliver necessary dosage of drug to the brain for the treatment of NDs. Studies showed that SPIONs coated with polymers exhibit better desired properties for targeted drug delivery.[36] For example, polyethylene glycol (PEG) coating improves the stability, bioavailability and resists the interaction of the nanoparticles with the components during circulation. Another study involving the in-vivo effect of PEGylated SPIONs on the progression of Alzheimer's disease (by injecting Aβ 1- 42 intrahippocampally) on a Wistar rat model established that spatial memory deficits were improved potentially by PEGylated SPIONs.[37] SPIONs made better impacts on the redirection of Aβ fibrillation kinetics, thereby reducing the devastating effects of fibrils on cAMP response element-binding protein (CREB), brain-derived neurotrophic factor (BDNF), and stromal interaction molecules 1 and 2 (STIM1 and STIM2). Studies on coating SPIONs showed that SPIONs coated with PEG and co-coated with polyvinyl pyrrolidone (PVP) showed pH sensitive drug release capability.[38] Researchers found that the release rate of doxorubicin from drug loaded SPIONs is highly improved at acidic environment. The COO– group of oxidized

PEG-COOH can be utilized to attach to the SPIONs, while the carbonyl oxygen on PVP may be used to bind on the surface of the SPIONs. By coordination interactions between PEG and PVP, like Van der Waals interaction and hydrogen bond, PEG and PVP are strongly bound to the surface of the SPIONs. PVP coated iron oxide nanoparticles show no aggregation, better biocompatibility and less cytotoxicity than bare iron oxide NPs.[39]

**Targeted drug delivery to the brain**

While discussing the targeted drug delivery to the brain, the different methods of drug administration to the brain need to be mentioned. Mainly, there are 3 paths for delivering drug to the brain viz. local delivery, intranasal delivery and systemic delivery.[40] Local delivery, which is highly invasive, refers to delivery of drugs directly to brain by injection using a catheter and involves surgery. Intranasal delivery involves bypassing the BBB through nasal cavity. The drug carried by nanoparticles can be transported directly to the brain through the olfactory bulb and the trigeminal nerve. Nasal mucosa would affect the dose of drug and hence high dose may be required most of the time.

The most favored and most-researched route is the systemic pathway. For effective systemic pathway by crossing the BBB, the best method is to use nanoparticles with surface modification. SPIONs, with their superparamagnetic properties, can be surface modified to fit the occasion.

**Recent advances in targeted drug delivery for neurodegenerative diseases using SPIONs**

Different formulations of SPION-based drug delivery systems have been reported, including SPION hydrogels, liposomes, micelles, microspheres and nanospheres, and surface modifications with RNAs and peptides.[14] Integrated usage of SPIONs and drugs embedded in hydrogels allow target-specific and appropriate release of the drugs by making use of external magnetic field-triggered shrinkage or swelling of hydrogel. Similarly, by adjusting the size of micro or nanospheres coated over drug-loaded SPIONs, drugs can be selectively discharged to specific cells.

To overcome the BBB, drug-loaded SPIONs are used by surface modification or coating. Research has been carried out to investigate the ability of SPIONs to

cross the BBB to reach human brain microvascular endothelial cells (HBMECs) with the help of an external magnet.[32] The research result suggests a possible application of SPIONs to pass and deliver drugs even to the neurons present deeper in the brain without damaging the cells. The red dots present in confocal microscopy images of a monolayer of brain capillary endothelial cells (BCECs) cultured in an in vitro BBB model in Figure 3 indicates the ability of SPIONs to enter the deeper parts of the brain.[32]

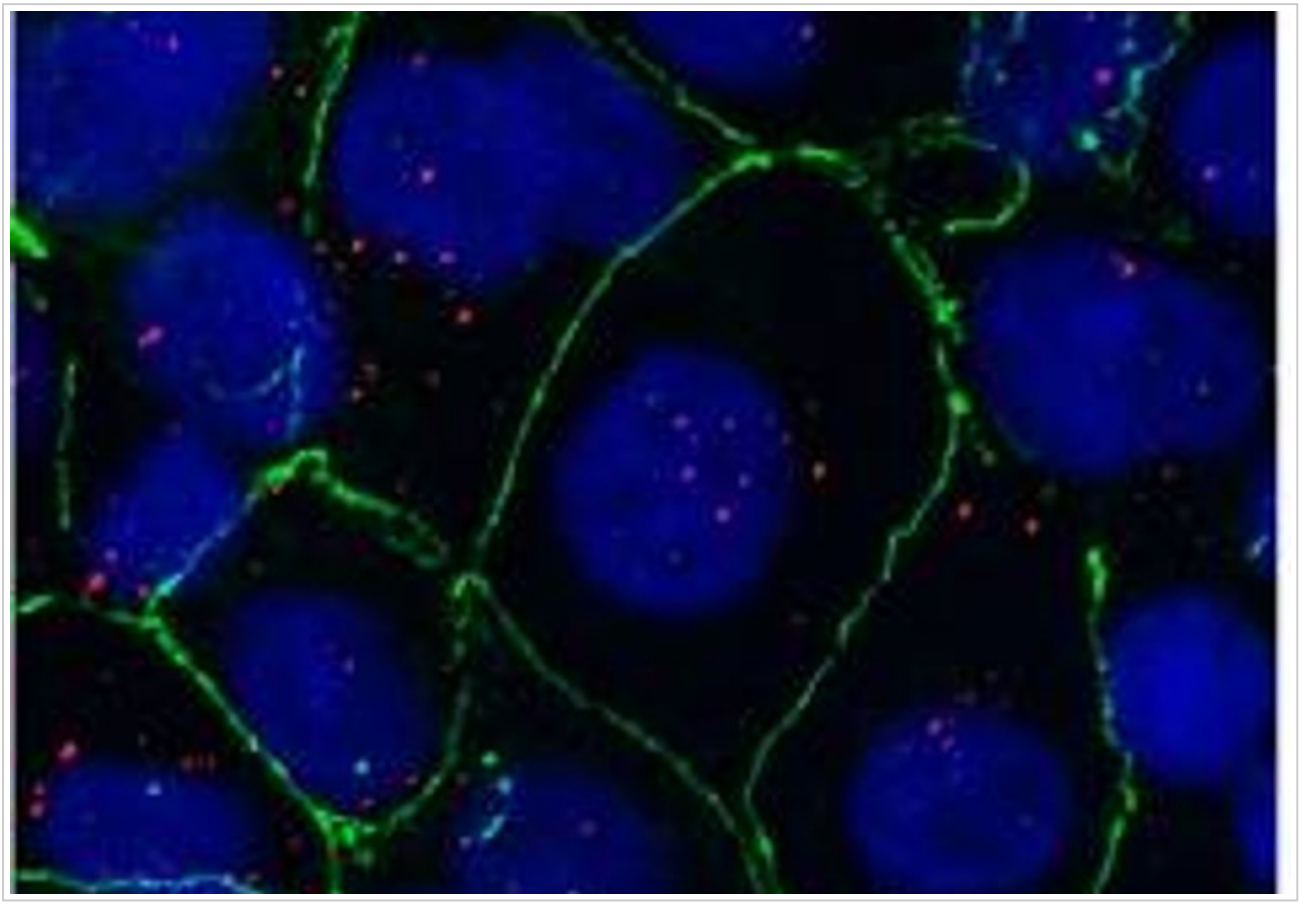


**Figure 3**. SPIONs are found inside the cells (red dots) within the cell boundaries, indicating that SPIONs are taken up by the BCECs.[32]

There have been some research into the diagnosis of Alzheimer's disease making use of the amyloid β (Aβ) plaques detection property of SPIONs recently. Simulation studies conducted by following the pharmacokinetics of SPIONs for the detection and imaging of Aβ plaques suggested that Aβ42 was inhibited with the addition of SPIONs as SPIONs showed good binding energy with Aβ42 peptide.[41]

Surface modified SPIONs have also been used for imaging and detecting the Aβ plaques. Curcumin, which is a known medicine to fight inflammation, cancer and AD, was conjugated with SPIONs to make use of its ability to connect Aβ42 plaques and with iron, thereby acting as a good candidate to detect Aβ42

plaques in Alzheimer's infected brain.[42] The Curcumin-SPION particles were coated with a block copolymer of polylactic acid (PLA) for stability and polyvinyl pyrrolidone (PVP) for hydrophilicity. Figure 4 illustrates the step-wise process of making Curcumin-Magnetic Nanoparticles (Curcumin-MNPs).[42]

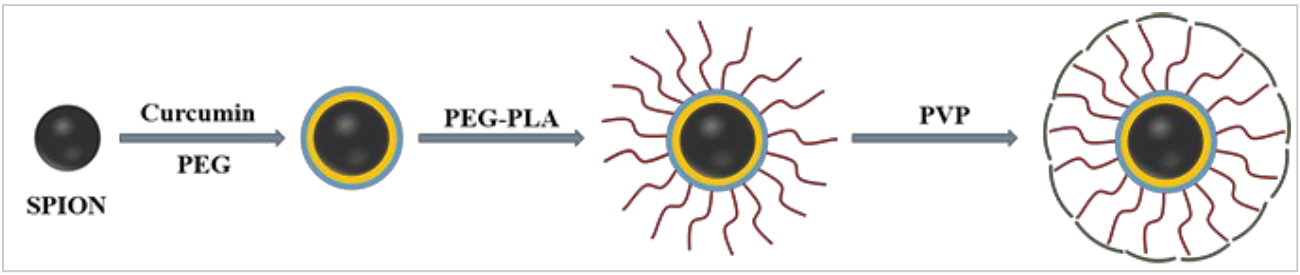



**Figure 4**. Step-wise process of making Curcumin-MNPs. Adapted from [42]

SPIONs, due to their ability to cross BBB and high contrast properties, are being used to stain mesenchymal stem cells (MSCs) and track their movement to brain. SPIONs can be surface modified to contain human neural stem cells and allow tracking the cells in crossing BBB and inside the brain by MRI without compromising the cell damage for several months.[43] Magnetic targeted cell delivery technique (MTCD) has been proved as an alternative to direct injection to brain for MSC-based regenerative medicine approach for the treatment of AD.[44] The study delivered Wharton's jelly-derived MSC to the hippocampus area of AD rat's brain to check the cognitive memory development. The MRI scans of rat's brain before and after the injection proved the presence of SPION-MSC in hippocampus area. After eight weeks of stem cell therapy, rat model was tested for learning and memory capabilities by passive avoidance response and Morris water maze (MWM) tests.[45,46] The results showed that Wharton's jelly (WJ)-derived MSCs cause cognitive improvement. The results are shown in Figure 5.[44]

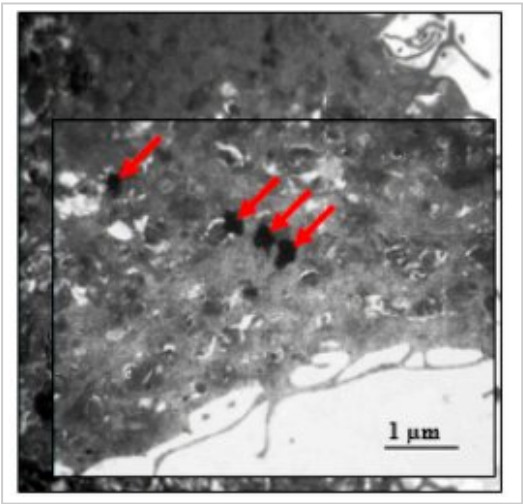


**Figure 5**. TEM image of SPIONs-labeled hWJ-MSCs showing entry of NPs into cells.[44]

Core-shell nanoparticles were synthesized for the controlled drug release in non-invasive neuroregeneration using a smart nanocarrier of superparamagnetic iron oxide-gold (SPIO-Au) core-shell (CS) nanoparticles (NPs) in conjugation with porous coordination cages (PCCs) through thiol bridging using retinoic acid (RA) as the growth promoter.[47] The structure suggested the new smart nanocarrier can have multiple applications, viz. intracellular targeting, controlled drug release and potential neuroregeneration.

Research on stem cell therapy for PD using SPION labelled adipose-derived stem cells (ADSCs) with the help of external magnetic field in a rat model were carried out recently.[48] Apart from stem cells, SPIONs can also be used in combination with lipids, proteins, genes, antibodies, etc. to the brain for the diagnosis and treatment of NDs. In a recent study, SPIONs in conjugation with single chain variable fragment (scFv) antibody W20 and scavenger receptor activator (XD4) were prepared for the detection of Aβ oligomer (AβO) as a viable biomarker for early diagnosis of AD.[49]

Work using polyvinyl pyrrolidone (PVP)-stabilized SPION modified with 1,2-Dimyristoyl-sn-glycero-3- hosphocholine (DMPC) phospholipid has also been reported. Modified SPIONs were added to rat adrenal pheochromocytoma (PC-12) cells to investigate the effect of DMPC on the distribution of SPIONs in cells and further injected to substantia nigra of rat model to check the distribution of DMPC/PVP-SPIONs in the tumor area.[50] Figure 6 shows the successful distribution of DMPC/PVP-SPIONs on the axon membranes. The use of phospholipids with SPIONs could facilitate transport of NPs and loaded drugs in brain because of biomimetic structures of phospholipids to cell membranes.

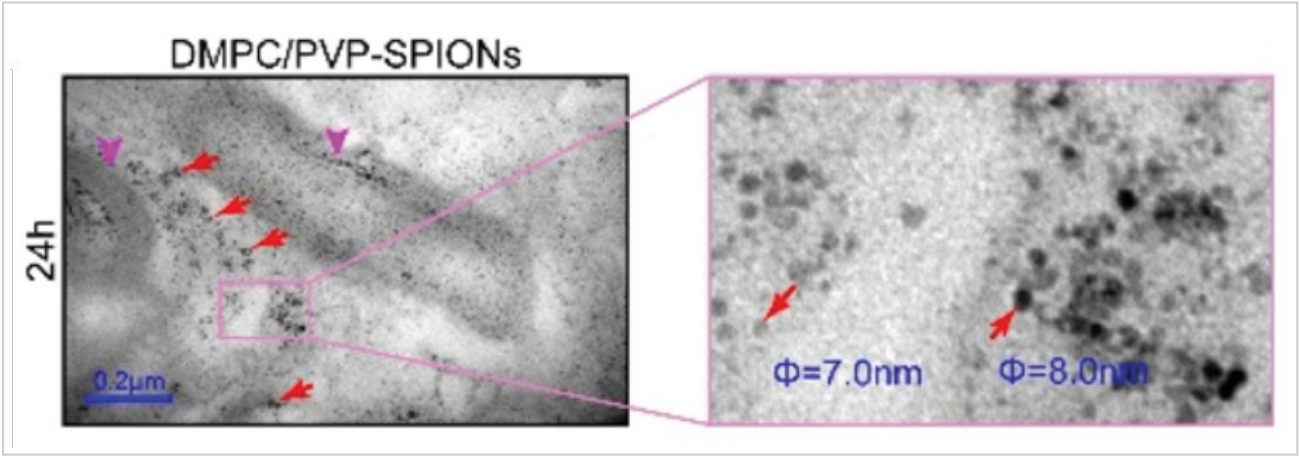


**Figure 6**. Distribution of nanoparticles in the substantia nigra after 24 h injected with DMPC/PVP-SPIONs.[50]

Another study showed that hydrogel-coated SPIONs carrying short hairpin RNA (shRNA) could repair in a PD model in vivo and in vitro by blocking the expression of α-synuclein (α-syn), which is a major component of Lewy bodies which in turn are the main pathological characteristics of PD and prevent further apoptosis.[51]

Other recent researches and reviews include, use of anti-oxidant quercetin in conjugation with SPIONs to slow down the AD progression by reducing the oxidative stress in affected neurons[52]; phenothiazine based fluorescent dyes combined with PEGylated SPIONs, where phenothiazine, at the same time acts as near infrared (NIR) fluorescent probe and inhibitor for β-amyloid aggregation[53]; different methods of synthesis, surface modification and drug delivery capability of SPIONs[13]; and emergence of "neuronanomedicine" that demonstrates the importance and relevance of the application of SPIONs in the diagnosis and treatment of NDs.[54-56]

## Challenges of SPIONs as targeted drug delivery carriers

In spite of the fact that SPIONs solved crucial problems in the treatment of neurodegenerative diseases, for instance, crossing the BBB and detecting the Aβ plaques, there are still many challenges and limitations in this field. Cytotoxicity is one of the challenges faced by all drug delivery agents and SPIONs are no exception. Since the cytotoxicity and transfer through BBB greatly depends upon several factors like size, surface charge and dosage of the drug carrier, extreme care must be taken while designing and applying the SPIONs in drug delivery. The distinctive features of the designed SPIONs may lead to unpredictable biological responses in the body. Iron disintegrated from the SPIONs are shown to cause neurotoxic effects like oxidative stress, alteration in synaptic transmission and nerve conduction leading to neuroinflammation and apoptosis.[57] These unpredictable responses, especially in the brain causes malfunction of BBB and could lead to permanent or reversible effects on CNS or on the whole body. BBB is very dynamic and unpredictable in nature. Although the usage of different drug delivery system is established after trials done on rat models, clinical trials have never been done on human body. The effects of the nanomaterials system on human brain

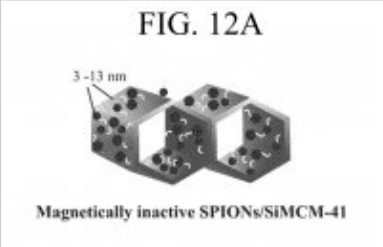
may be different than on rats. The development in this regard is limited by the lack of standardized model system, assays and in-vivo monitoring system to test the toxicity and other effects. Clinical trials without complete understanding of the disease and the effect of SPIONs in the body is not suggestible.

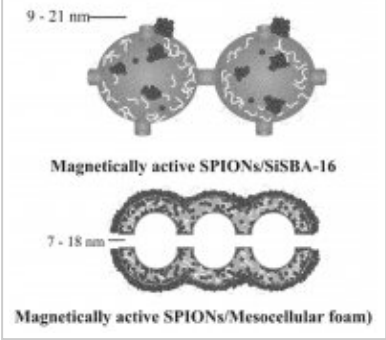
**Recent Patent Publications**

US11478433B2 – **Yale University** has developed supramolecular nanoparticles based on isolated medicinal natural products (MNPs)- diterpene resin acid, phytosterol, lupane-type pentacyclic triterpene, oleanane-type pentacyclic triterpene, and lanostane-type triterpene for delivery of therapeutic, prophylactic, or diagnostic agents. The supramolecular particles enhance the drug delivery by combining compounds based on MNPs and superparamagnetic iron oxide nanoparticles (SPIONs), thus convert compounds with low bioavailability to different routes of administration. By encapsulating the natural compounds with SPIONs, it ensures biocompatibility and guaranteed passage through the blood-brain-barrier. These MNPs can be extracted and isolated in a medium containing SPIONs, thus forming efficient drug carrier and can be manipulated using a magnet from outside the body.

US11471542B2 – **Imam Abdulrahman Bin Faisal University** has developed a composition containing hybrid nanocarriers formed by mesostructured silica foam nanoparticles, superparamagnetic iron oxide nanoparticles (SPIONs) and curcumin, formed through an adsorption technique.

The hybrid nano system can be loaded with drug and administered intravenously. The nanocarrier system can be made more biocompatible by the modification with chitosan, or poly (D, L-lactide-co-glycolide). The presence of SPIONs allow the system to be controlled from outside the body to reach desired area for release of the drug molecules. Combined effect of nano silica, SPIONs and curcumin is made use in effective permeability through blood-brain-barrier and treatment of neurodegenerative diseases.






The nature of SPIONs deposition over different structured silicas

EP3016671B1 – **University of Barcelona and Private Foundation Biomedical Research Institute** have collaboratively developed a novel peptide compound which can be transported through the blood-brain-barrier for delivery of molecules which are otherwise not possible. The peptide is attached to a bioactive substance including superparamagnetic iron oxide nanoparticles (SPIONs) for easy control of the movement of the drug carrier inside the body.

**Future perspective**

Further research to understand a complete picture of the disease, effect of the drugs and the drug delivery agents is inevitable. The developments in the technology side, in particular Artificial Intelligence (AI), robotics, lab-on-a-chip and simulation studies provide better, fast and accurate predictions and result on the disease and the efficacy of carrier and drug in the future. [58-60] Recent developments in neuronanomedicine in neuroregeneration as discussed previously gives hope for better medication and treatment. Finding better solution for early diagnosis and therapy monitoring of NDs could eventually bring down the rate of affecting and death due to NDs.

**Conclusion**

Superparamagnetic iron oxide nanoparticles (SPIONs) seem to be promising target drug carriers due to their smaller size, which can easily pass through the BBB by encapsulation, external magnetic field, or local heating. However, stability, biocompatibility and cytotoxicity are the major challenges of SPIONs as drug carriers. These can be addressed by surface functionalization of SPIONs. The SPIONs coated with polymers exhibit better desired properties for targeted drug delivery. A meagre number of patents published in this research field suggest plenty of room for innovation. Future lies in the development of

artificial intelligence in understanding the disease and predicting the possible structure and efficacy of drug delivery agents, which alleviate major problems associated with the diagnosis and treatment of NDs.

**Reference:**


1. THE GLOBAL HEALTH OBSERVATORY
   Source

2. Clinical Neurology and Epidemiology of the Major Neurodegenerative Diseases
   Michael G Erkkinen, Mee-Ohk Kim, Michael D Geschwind
   *Cold Spring Harb. Perspect. Biol.* 2018, **10(4)**, a033118;
   Source

3. Overcoming the Blood–Brain Barrier: The Role of Nanomaterials in Treating Neurological Diseases
   Denzil Furtado, Mattias Björnmalm, Scott Ayton, Ashley I. Bush, Kristian Kempe, Frank Caruso
   *Advanced Materials* 2018, **30**, 1801362;
   Source

4. The blood-brain barrier/neurovascular unit in health and disease
   Brian T Hawkins, Thomas P Davis
   *Pharmacol. Rev.* 2005, **57**, 173–185;
   Source

5. Nanoparticles in drug delivery: past, present and future
   P Couvreur
   *Adv. Drug Deliv. Rev.* 2013, **65**, 21–23;
   Source

6. A review on nanoparticle based treatment for wound healing
   Naresh Kumar Rajendran, Sathish Sundar Dhilip Kumar, Nicolette Nadene Houreld, Heidi Abrahamse
   *Drug Deliv. Sci. Tech.* 2018, **44**, 421–430;
   Source

7. Nanoparticles as carriers for drug delivery of macromolecules across the blood-brain barrier Giovanni Tosi, J. T. Duskey, Jörg Kreuter
   *Expert Opin Drug Deliv.* 2015, **12**, 1041–1044;

Source

8. Nano-particle mediated inhibition of Parkinson's disease using computational biology approach Aman Chandra Kaushik, Shiv Bharadwaj, Sanjay Kumar, Dong-Qing Wei
*Sci. Rep.* 2018, **8**, 1–8;
Source

9. Neuronanomedicine: An Up-to-Date Overview
Daniel Mihai Teleanu, Cristina Chircov, Alexandru Mihai Grumezescu, Raluca Ioana Teleanu
*Pharmaceutics* 2019, **11**, 101;
Source

10. Targeting Strategies for Multifunctional Nanoparticles in Cancer Imaging and Therapy
Mi Kyung Yu, Jinho Park, Sangyong Jon
*Theranostics* 2012; **2(1)**, 3–44;
Source

11. Nanomaterial based drug delivery systems for the treatment of neurodegenerative diseases
Shima Masoudi Asil, Jyoti Ahlawat, Gileydis Guillama Barroso, Mahesh Narayan
*Biomater. Sci.* 2020, **8**, 4109-4128;
Source

12. Iron Oxide Nanoparticles for Biomedical Applications: A Perspective on Synthesis, Drugs, Antimicrobial Activity, and Toxicity
Laís Salomão Arias, Juliano Pelim Pessan, Ana Paula Miranda Vieira, Taynara Maria Toito de Lima, Alberto Carlos Botazzo Delbem, Douglas Roberto Monteiro
*Antibiotics* 2018, **7**, 46;
Source

13. Application of Iron Oxide Nanoparticles in the Diagnosis and Treatment of Neurodegenerative Diseases With Emphasis on Alzheimer's Disease
Luo Shen, Ma Chi, Zhu Ming-Qin, Ju Wei-Na, Yang Yu, Wang Xu
*Front. Cell. Neurosci.* 2020, **14**, Article 21;
Source

14. Superparamagnetic iron oxide nanoparticle-based delivery systems for biotherapeutics
Hyejung Mok & Miqin Zhang

*Expert Opin. Drug Deliv*. 2013 10(1), 73–87;
Source

15. Nanoparticles for Brain Drug Delivery
    Massimo Masserini
    *ISRN Biochemistry* 2013, **2013**, 1–18;
    Source

16. Superparamagnetic nanoparticles for biomedical applications: Possibilities and limitations of a new drug delivery system
    Tobias Neuberger, Bernhard Schöpf, Heinrich Hofmann, Margarete Hofmann, Brigitte von Rechenberg
    *Magn. Magn. Mater.* 2005, **293**, 483–496;
    Source

17. Magnetic iron oxide nanoparticles: Synthesis and surface coating techniques for biomedical applicationsSun Sheng-Nan, Wei Chao, Zhu Zan-Zan, Hou Yang-Long, Venkatraman Subbu S, Xu Zhi-Chuan*Chin. Phys. B.* 2014, **23**, 037503; Source

18. Functionalized Superparamagnetic Iron Oxide Nanoparticles (SPIONs) as Platform for the Targeted Multimodal Tumor Therapy
    Christina Janko, Teresa Ratschker, Khanh Nguyen, Lisa Zschiesche, Rainer Tietze, Stefan Lyer, Christoph Alexiou
    *Front. Oncol.* 2019, **9:59**, 1–9;
    Source

19. Cancer Nanotheranostics: Improving Imaging and Therapy by Targeted Delivery Across Biological Barriers
    Forrest M. Kievit,
    Miqin Zhang
    *Adv. Mater*. 2011, **23**, H217–247;
    Source

20. Functionalisation of magnetic nanoparticles for applications in biomedicine
    Catherine C Berry and Adam S G Curtis
    *Phys. D: Appl. Phys*. 2003, **36**, R198;
    Source

21. Functional magnetic particles for medical application
    Masashige Shinkai

*Biosci. Bioeng*. 2002, **94**, 606–613;
Source

22. Nanotechnology—novel therapeutics for CNS disorders
Maya Shrikanth, John A. Kessler
*Nat. Rev. Neurol.* 2012, **8(6)**, 307–318;
Source

23. Nanotechnology-based drug delivery systems for the treatment of Alzheimer's disease
Fonseca-Santos B, Gremião MPD, Chorilli M.
*Int. J. Nanomedicine* 2015, **10**, 4981–5003;
Source

24. Emerging Therapeutic Promise of Ketogenic Diet to Attenuate Neuropathological Alterations in Alzheimer's Disease
Md. Sahab Uddin, Md. Tanvir Kabir, Devesh Tewari, Abdullah Al Mamun, George E. Barreto, Simona G. Bungau, May N. Bin-Jumah, Mohamed M. Abdel-Daim, Ghulam Md. Ashraf
*Mol. Neurobiol.* 2020, **57(12)**, 4961–4977;
Source

25. Exploring Potential of Alkaloidal Phytochemicals Targeting Neuroinflammatory Signaling of Alzheimer's Disease
Md. Sahab Uddin, Md. Tanvir Kabir, Abdullah Al Mamun, Tapan Behl, Rasha A Mansouri, Akram Ahmed Aloqbi, Asma Perveen, Abdul Hafeez, Ghulam Md. Ashraf
*Curr. Pharm. Des.* 2021, **27**, 357–366;
Source

26. Multifarious roles of mTOR signaling in cognitive aging and cerebrovascular dysfunction of Alzheimer's disease
Md. Sahab Uddin, Md. Ataur Rahman, Md. Tanvir Kabir, Tapan Behl, Bijo Mathew, Asma Perveen, George E. Barreto, May N. Bin-Jumah, Mohamed M. Abdel-Daim, Ghulam Md. Ashraf
*IUBMB Life* 2020, **72(9)**, 1843–1855;
Source

27. Fibrillation of β amyloid peptides in the presence of phospholipid bilayers and the consequent membrane disruption

Wei Qiang, Wai-Ming Yau, Jürgen Schulte
*Biochimica et Biophysica Acta* 2015, **1848**, 266–276;
Source

28. What is Parkinson's?
source

29. Magnetic interactions between nanoparticles
Steen Mørup, Mikkel Fougt Hansen, Cathrine Frandsen
*Beilstein J. Nanotechnol.* 2010, **1**, 182–190;
Source

30. Colloidal stability of superparamagnetic iron oxide nanoparticles in the central nervous system: a review
Pierre-Olivier Champagne, Harrison Westwick, Alain Bouthillier, Mohamad Sawan
*Nanomedicine (Lond.)* 2018, **13(11)**, 1385–1400;
Source

31. The design and utility of polymer-stabilized iron-oxide nanoparticles for nanomedicine applications
Cyrille Boyer, Michael R Whittaker, Volga Bulmus, Jingquan Liu, Thomas P Davis
*NPG Asia Mater.* 2010, **2**, 23–30;
Source

32. Uptake and Transport of Superparamagnetic Iron Oxide Nanoparticles through Human Brain Capillary Endothelial Cells
L. B. Thomsen, T. Linemann, K. M. Pondman, J. Lichota, K. S. Kim, R. J. Pieters, G. M. Visser, T. Moos
*ACS Chem. Neurosci.* 2013, 4(10), 1352–1360;
Source

33. Nanoneuromedicine for management of neurodegenerative disorder
Nitin Dwivedi, Jigna Shah, Vijay Mishra, Murtaza Tambuwala, Prashant Kesharwani
*Drug Deliv. Sci. Technol.* 2019, **49**, 477–490;
Source

34. Toxicity Evaluations of Superparamagnetic Iron Oxide Nanoparticles: Cell "Vision" versus Physicochemical Properties of Nanoparticles
Morteza Mahmoudi, Sophie Laurent, Mohammad A. Shokrgozar, Mohsen Hosseinkhani
*ACS Nano* 2011, **5**, 7263–7276;

Source

35. Comprehensive cytotoxicity studies of superparamagnetic iron oxide nanoparticles
Rakesh M.Patil, Nanasaheb D. Thorat, Prajkta B. Shete, Poonam A. Bedge, Shambala Gavde, Meghnad G. Joshi,
Syed A. M. Tofail, Raghvendra A. Bohara
*Biochem. Biophys. Rep.* 2018, **13**, 63–72;
Source

36. Multimodal tumor imaging by iron oxides and quantum dots formulated in poly (lactic acid)-d-alpha-tocopheryl polyethylene glycol 1000 succinate nanoparticles
Yang Fei Tan, Prashant Chandrasekharan, Dipak Maity, Cai Xian Yong, Kai-Hsiang Chuang, Ying Zhao, Shu Wang, Jun Ding, Si-Shen Feng
*Biomaterials* 2011, **32(11)**, 2969–78;
Source

37. PEGylated superparamagnetic iron oxide nanoparticles (SPIONs) ameliorate learning and memory deficit in a rat model of Alzheimer's disease: Potential participation of STIMs
Mehdi Sanati, Samaneh Aminyavari, Fariba Khodagholi, Mohammad Javad Hajipour, Payam Sadeghi, Marzieh Noruzi, Aynaz Moshtagh, Homayoon Behmadi, Mohammad Sharifzadeh
*Neurotoxicology* 2021, **85**, 145–159;
Source

38. Synthesis of poly(ethylene glycol) and poly(vinyl pyrrolidone) co-coated superparamagnetic iron oxide nanoparticle as a pH-sensitive release drug carrier
Zhijiang Tu, Baolin Zhang, Gao Yang, Ming Wang, Fangyuan Zhao, Dian Sheng, Jun Wang
*Colloids Surf A: Physicochem. Eng. Asp* 2013, **436**, 854–861;
Source

39. Core–shell hybrid nanomaterials based on $CoFe_2O_4$particles coated with PVP or PEG biopolymers for applications in biomedicine
Cristina Ileana Covaliu, Ioana Jitaru, Gigel Paraschiv, Eugeniu Vasile, Sorin-Ştefan Biriş, Lucian Diamandescu, Valentin Ionita, Horia Iovu
*Powder Technol.* 2013, **237,** 415–426;
Source

40. Key for crossing the BBB with nanoparticles: the rational design
Sonia M. Lombardo, Marc Schneider, Akif E. Türeli, Nazende Günday Türeli
*Beilstein J. Nanotechnol.* 2020**, 11**, 866–883;
Source

41. Deciphering the Biochemical Pathway and Pharmacokinetic Study of Amyloid βeta-42 with Superparamagnetic Iron Oxide Nanoparticles (SPIONs) Using Systems Biology Approach
Aman Chandra Kaushik, Ajay Kumar, Vivek Dhar Dwivedi, Shiv Bharadwaj, Sanjay Kumar, Kritika Bharti, Pavan Kumar, Ravi Kumar Chaudhary & Sarad Kumar Mishra
*Mol. Neurobiol.* 2018, **55(4)**, 3224–3236;
Source

42. Curcumin-conjugated magnetic nanoparticles for detecting amyloid plaques in Alzheimer's disease mice using magnetic resonance imaging (MRI)
Kwok Kin Cheng, Pui Shan Chan, Shujuan Fan, Siu Ming Kwan, King Lun Yeung, Yì-Xiáng J Wáng, Albert Hee Lum Chow, Ed X Wu, Larry Baum
*Biomaterials* 2015, **44**, 155–172;
Source

43. Tracking and Quantification of Magnetically Labeled Stem Cells Using Magnetic Resonance Imaging
Forrest T. Goodfellow, Gregory A. Simchick, Luke J. Mortensen, Steven L. Stice, Qun Zhao
*Adv. Funct. Mater.* 2016, **26**, 3899–3915;
Source

44. Magnetic targeted delivery of the SPIONs-labeled mesenchymal stem cells derived from human Wharton's jelly in Alzheimer's rat models
Farshid Qiyami Hour, Amir Johari Moghadam, Ali Shakeri-Zadeh, Mehrdad Bakhtiyari, Ronak Shabani, Mehdi Mehdizadeh
*Contr. Rel.* 2020, **321**, 430–441;
Source

45. Passive Avoidance Task
Source

46. Morris water maze: procedures for assessing spatial and related forms of learning and memory

Charles V Vorhees, Michael T Williams
*Nat. Protoc.* 2006, **1(2)**, 848–858;
Source

47. Superparamagnetic iron oxide–gold nanoparticles conjugated with porous coordination cages: Towards controlled drug release for non-invasive neuroregeneration
Muzhaozi Yuan, Tian-Hao Yan, Jialuo Li, Zhifeng Xiao, Yu Fang, Ya Wang, Hong-Cai Zhou, Jean-Philippe Pellois
*Nanomed: Nanotech. Biol. Med.* 2021, **35,** 102392;
Source

48. Homing of Super Paramagnetic Iron Oxide Nanoparticles (SPIONs) Labeled Adipose-Derived Stem Cells by Magnetic Attraction in a Rat Model of Parkinson's Disease
Moayeri A, Darvishi M, Amraei M.
*Int. J. Nanomedicine* 2020, **15**, 1297–1308;
Source

49. Multifunctional Superparamagnetic Iron Oxide Nanoparticles Conjugated with Aβ Oligomer-Specific scFv Antibody and Class A Scavenger Receptor Activator Show Early Diagnostic Potentials for Alzheimer's Disease
Liu XG, Zhang L, Lu S, Liu DQ, Zhang LX, Yu XL, Liu RT
*Int. J. Nanomedicine* 2020, **15,** 4919–4932;
Source

50. 1,2-Dimyristoyl-sn-glycero-3-phosphocholine promotes the adhesion of nanoparticles to bio-membranes and transport in rat brain
Dong Han, Baolin Zhang, Jianghui Dong, Boning Yang, Yuntao Peng, Junfeng Wang, Liping Wang
*RSC Adv.* 2021, **11**, 35455;
Source

51. Inhibition by Multifunctional Magnetic Nanoparticles Loaded with Alpha-Synuclein RNAi Plasmid in a Parkinson's Disease Model
Shuiqin Niu, Ling-Kun Zhang, Li Zhang, Siyi Zhuang, Xiuyu Zhan, Wu-Ya Chen, Shiwei Du, Liang Yin, Rong You, Chu-Hua Li, Yan-Qing Guan
*Theranostics* 2017, **7(2)**, 344–356;
Source

52. Quercetin-Conjugated Superparamagnetic Iron Oxide Nanoparticles Protect $AlCl_3$-Induced Neurotoxicity in a Rat Model of Alzheimer's Disease viaAntioxidant Genes, APP Gene, and miRNA-101
Amanzadeh Jajin Elnaz, Esmaeili Abolghasem, Rahgozar Soheila, Noorbakhshnia Maryam
*Front. Neurosci.* 2021, **14**, Article 598617;
Source

53. Ultrasmall superparamagnetic iron oxide nanoparticles-bound NIR dyes: Novel theranostic agents for Alzheimer's disease
Jing Cai, Pascal Dao, Huixiong Chen, Longjia Yan, Yong Liang Li, Wanzheng Zhang, Li Li, Zhiyun Du, Chang-Zhi Dong, Bernard Meunier
*Dyes Pigm.* 2020, **173**, 107968;
Source

54. Iron Oxide Nanoparticles for Biomedical Applications: A Perspective on Synthesis, Drugs, Antimicrobial Activity, and Toxicity
Laís Salomão Arias, Juliano Pelim Pessan, Ana Paula Miranda Vieira, Taynara Maria Toito de Lima, Alberto Carlos Botazzo Delbem, Douglas Roberto Monteiro
*Antibiotics* 2018, **7**, 46;
Source

55. Superparamagnetic Iron Oxide Nanoparticles—Current and Prospective Medical Applications
Joanna Dulińska-Litewka, Agnieszka Łazarczyk, Przemysław Hałubiec, Oskar Szafrański, Karolina Karnas, Anna Karewicz
*Materials* 2019, **12**, 617;
Source

56. Use of Super Paramagnetic Iron Oxide Nanoparticles as Drug Carriers in Brain and Ear: State of the Art and Challenges
Caroline Guigou, Alain Lalande, Nadine Millot, Karim Belharet, Alexis Bozorg Grayeli
*Brain Sci.* 2021, **11**, 358;
Source

57. Are iron oxide nanoparticles safe? Current knowledge and future perspectives
Vanessa Valdiglesias, Natalia Fernández-Bertólez, Gözde Kiliç, Carla Costa, Solange Costa, Sonia Fraga, Maria Joao Bessa, Eduardo Pásaro, João Paulo Teixeira, Blanca Laffon

*Trace Elem. Med. Biol.* 2016, **38**, 53–63;
Source

58. Artificial intelligence in drug discovery and development
Debleena Paul, Gaurav Sanap, Snehal Shenoy, Dnyaneshwar Kalyane, Kiran Kalia, Rakesh K. Tekade
*Drug Discov. Today* 2020, **26(1),** 80–93;
Source

59. Insights into Infusion-Based Targeted Drug Delivery in the Brain: Perspectives, Challenges and Opportunities
Asad Jamal, Tian Yuan, Stefano Galvan, Antonella Castellano, Marco Riva, Riccardo Secoli, Andrea Falini, Lorenzo Bello, Ferdinando Rodriguez y Baena, Daniele Dini
*Int. J. Mol. Sci.* 2022, ***23*(6)**, 3139;
Source

60. Lab-on-a-Chip Platforms as Tools for Drug Screening in Neuropathologies Associated with Blood–Brain Barrier Alterations
Cristina Elena Staicu, Florin Jipa, Emanuel Axente, Mihai Radu, Beatrice Mihaela Radu, Felix Sima
*Biomolecules* 2021, **11(6),** 916;
Source



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## AUTHORS

**Dr. Kiran Jathavedan**
**Dr. John Kathi**

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