HHS Public Access

Author manuscript

Mol Aspects Med. Author manuscript; available in PMC 2023 February 01.

Published in final edited form as:

Mol Aspects Med. 2022 February ; 83: 101046. doi:10.1016/j.mam.2021.101046.

Recent advances, status, and opportunities of magneto-electric nanocarriers for biomedical applications

Nagesh Kolishetti[*,a,b], **Arti Vashist**[a,b], **Adriana Yndart Arias**[a,b], **Venkata Atluri**[a,b], **Shanta Dhar**[c,d], **Madhavan Nair**[*,a,b]

[a]Department of Immunology and Nano-Medicine, Herbert Wertheim, College of Medicine, Florida International University, Miami, FL, 33199

[b]Institute of Neuroimmune Pharmacology, Herbert Wertheim College of Medicine, Florida International University, Miami, FL, 33199

[c]Department of Biochemistry and Molecular Biology, University of Miami Miller School of Medicine, Miami, FL 33136

[d]Sylvester Comprehensive Cancer Center, Miller School of Medicine, University of Miami, Miami, FL 33136

Abstract

Magnetoelectric (ME) materials with core-shell architecture where the core is made of magnetic materials have emerged as an attractive nanomaterial due to the coupling of magnetic and electric properties in the same material and the fact that both fields can be controlled which allows an on-demand, transport and release of loaded cargo. Over the last decade, biomedical engineers and researchers from various interdisciplinary fields have successfully demonstrated promising properties ranging from therapeutic delivery to sensing, neuromodulation using magnetoelectric materials. In this review, we systematically summarize developments in various biomedical fields using the nanoforms of these materials. Herein, we highlight various promising biomedical applications where the ME nanocarriers are encapsulated in other materials such as gels and liposomes and their potential for promising therapeutics and diagnostic applications.

Introduction

Discoveries of micro and nanoparticle (NP) properties and their formulations have dominated the biomedical field in the last few decades. This has resulted in tremendous efforts by next-generation researchers to keep designing and developing new smart materials which can be studied for their unique properties and synthesized into nanomaterials with unique functional abilities. In the area of drug delivery and development, often these

[*]To whom correspondence should be addressed. nkolishe@fiu.edu; nairm@fiu.edu.

Conflict of Interest:
The authors declare no conflict of interest.

properties are focused on controlled release of therapeutics, attachment of novel targeting ligands on surfaces for targeted drug delivery. Organic nanoformulations from polymers and lipids have dominated the drug development and delivery research areas. Metallic nanoformulations such as gold, iron oxide, and quantum dots have been explored for drug delivery applications, but often they found success in diagnostic applications. In particular iron oxide and its derivatives have dominated the magnetic NP field and magnetic resonance imaging-related diagnostic applications and various theranostic applications involving imaging. The majority of the delivered therapeutic and diagnostic nanomaterials often end up in undesired locations, leading to unwanted side-effects to healthy cells and tissues, thus modification of materials with better pharmacokinetics (PK) and biodistribution (BioD) profiles is often explored and incorporate targeting ligands for targeted delivery of the therapeutics. This demand for targeted therapy has resulted in exploring stimuli-directed nanomaterials to a target location of interest. Magnetic drug delivery systems come under such technologies due to the feasibility of using magnetic fields to direct them to regions of interest. Magnetic nanoparticles are much explored inorganic particles since the 1980s and have gained a lot of attention since then (Kost and Langer, 1986; Widder et al., 1980). The NPs exhibiting the magnetic properties can find application in hyperthermic treatment, site-specific drug delivery, magnetic resonance imaging (MRI), and crossing tough biological barriers. Multiple review articles in the recent literature have highlighted the importance of magnetic particles or paramagnetic particles and/or superparamagnetic particles and discussed how the research revolutionized with new core-shell structures being discovered and many applied towards cancer diagnostics and therapies(Gupta and Gupta, 2005; Pankhurst et al., 2003; Sun et al., 2008). These materials are weakly attracted by the externally applied magnetic field and generate an induced magnetic field in the direction of the applied magnetic field. The property of paramagnetic is retained in materials due to the presence of unpaired electrons and those materials having incompletely filled atomic orbitals fall in this category. The magnetic permeability of these materials is generally higher than 1 and thus these are attracted by the magnetic fields. (Toy and Karathanasis, 2016). These MNPs got a lot of attention for their use in targeted MRI for multifunctional imaging and have acted as a potential candidate for tumor therapy by hyperthermia and triggered therapeutic release. Moreover, the large surface areas of MNPs and their ability to be controlled by external magnetic field resulted, these NPs as candidates for targeted drug delivery applications (Xie et al., 2008). Core-shell materials containing a magnetic core and shell with a coating of materials such as polyethylene glycol (PEG) have been often explored to escape the RES system and avoid clearance from the body(Ghosh Chaudhuri and Paria, 2012; Kumar and Mohammad, 2011) (Kreuter, 1994). Specific functionalization of MNPs is further explored for isolation of specific cells, organelles, and membranes and during biochemical assays and screening(Banik et al., 2016; Banik and Dhar, 2017; Tchikov et al., 2010; Zhang et al., 2017). In addition, the incorporation of material with electrical properties as a shell is also explored. As a natural evolution of magnetic materials and core-shell technologies, a few years ago, researchers have developed a next-generation core-shell magnetic material known as magneto-electro (ME) material. The magnetoelectric property comes from the interaction between magnetic and electric subsystems in material and has additional properties which are typically not present in either magnetic and/or electric parts of the individual materials. This property offers a targeting and trigger mechanism to build

nanoparticles (NPs) or nanoformulations from these materials and to take them to choose of the region in the body with an external trigger without generating heat.

Magnetoelectric Nanoparticles (MENPs):

Magnetoelectric nanoparticles (MENPs) or Magnetoelectric nanocarriers (MENCs) are mostly employed for the delivery of therapeutics through targeting and triggering mechanisms for delivering anticancer and antiviral therapeutics to target locations. Further, these materials are also explored for use for deep brain stimulation for modulation of brain activity and also as sensors. In this review article, we discuss materials employed in preparing these MENPs, the type of coating to improve their biomedical properties, and various examples where these MENPs were successfully employed for a specific disease such as cancer or viral diseases and other neuro diseases (Figure 1) (Guduru and Khizroev, 2014; Guduru et al., 2015; Kaushik et al., 2019a; Kaushik et al., 2019b; Nair et al., 2013; Nguyen et al., 2021; Singer et al., 2020; Stewart et al., 2018).

Cobalt ferrite (CFO) or $CoFe_2O_4$ is a very commonly used magnetic component of the MENPs, which is magnetostrictive and Barium titanate (BTO) or BaTiO3 is the electric part of the MENPs, which is piezoelectric and generates electrical charge upon application of certain stimuli. MENPs are made using a core-shell strategy, where CFO is magnetic core and BTO is the electric shell (Khizroev and Liang, 2020; Nagesetti et al., 2017). This $CoFe_2O_4$ and $BaTiO_3$ combination is the most extensively used MENP material combination in the literature of biomedical applications (Hadjikhani et al., 2017b; Singer et al., 2020; Stimphil et al., 2017b; Truong et al., 2020). A quick literature search using MENPs or MENs revealed over 1600 hits comprising of research articles, patents, reviews, and conference abstracts. The majority of them deal with the physical properties and characterization while only 80 of these literature articles have explored these materials for biomedical applications. Here, we have summarized some of the notable work in the biomedical application areas.

MENP Synthesis and Characterization methods:

Cobalt ferrite (CFO)-is the most employed material as core in MENPs due to its excellent magnetic properties, and tunable size, morphology, surface, and magnetic properties. This material can be made using calcination of Ferrous and cobalt salts using their chorine, nitrate, or sulfate precursors at 400–800 °C by adjusting the ionic strength of the solution between 125–5M and at a constant alkaline pH. The hydrodynamic size of these NPs can be easily tuned from 10 to 60 nm by varying the ionic strength and pH, while the magnetization and morphology are controlled by calcination temperature and concentration of metals (Malinowska et al., 2020). Barium titanate (BTO) shell is made by mixing a solution of barium acetate or barium carbonate and titanium butoxide or titanium isopropoxide in acids such as glacial acetic acid or stearic acid or citric acid in ethanol and adding to CFO NPs at a 1:3 (BTO: CFO) or higher ratio. This combined mixture was stirred at 60 °C and concentrated, and the final mixture is calcinated at high temperatures such as 600 – 800 °C to result in the core-shell MENPs or MENCs (Guduru and Khizroev, 2014; Kozielski et al.,

2021; Nair et al., 2013; Yue et al., 2012). The resultant MENPs are typically characterized by a combination of techniques based on the application used.

MENPs are characterized by dynamic light scattering (DLS) for hydrodynamic size and zeta potential in various media such as water, saline, serum, cell culture media, etc. Scanning electron microscopy (SEM) (Guduru and Khizroev, 2014), and Transmission electron microscopy (TEM) (Nair et al., 2013) is routinely employed for shape and size, inductively coupled plasma (ICP) mass spectroscopy (ICP-MS), or ICP optical emission spectroscopy (ICP-OES), and energy dispersion spectroscopy (EDS) (Nair et al., 2013) or electron energy loss spectroscopy for quantitative elemental composition and molar percentages of each material. X-ray powder diffraction is used for identifying the crystal structure of the BTO and CFO components of the MENPs (Guduru and Khizroev, 2014; Guduru et al., 2013; Kaushik et al., 2019a; Kaushik et al., 2019b). The magnetoelectric properties characterizations include studying traditional magnetic and electric properties and their combination use AC and DC magnetic fields (Guduru et al., 2013). Magnetization and oscillation range, electromagnetic output, magnetoelectric coefficients, voltage outputs at various AC magnetic fields, and frequency using magnetometer and VSM probe(Kaushik et al., 2016; Kozielski et al., 2021; Pandey et al., 2021). Micro sense EZ VSM is typically used as a DC magnetic field source with an additional Helmholtz coil connected to a voltage amplifier (Kaushik et al., 2016).

In addition to the above-indicated characterization methods, when a drug is loaded onto the MENP surface, it is often characterized with additional techniques such as FT-IR, UV-visible, Raman spectroscopy, and HPLC methods to understand the amount of drug binding, release aspects in a respective MENP-Drug formulation (Guduru and Khizroev, 2014; Kaushik et al., 2019a; Nair et al., 2013; Rodriguez et al., 2017).

Therapeutic applications against NeuroHIV:

Antiretroviral therapy (ART) has reduced the mortality associated with HIV and AIDS, but the resurgence due to treatment interruption, and lack of the complete eradication of the virus from the body, and various viral reservoirs in the peripheral and central nervous system is a challenge. The brain is one such location where it is difficult to reach viral reservoirs in the body and it has been a challenging problem to develop treatment options for neuroHIV and very few reports in the literature address this problem (Surnar et al., 2021; Velichkovska et al., 2019). One area where NPs have generated a lot of attention in tackling these difficult to reach areas to address the problems, but oftentimes the administered NPs end up in major organs such as the liver, lungs, and lymphoid organs due to clearance from the reticuloendothelial system when the NPs are over 200 nm and filtration by kidney if the NPs are small (Kolishetti et al., 2011; Mamo et al., 2010; Marrache et al., 2013; Surnar et al., 2021). Hence the search for methods such as targeted delivery or external stimuli-directed delivery of NPs to the brain has gained significant attention (Barbu et al., 2009; Cena and Jativa, 2018; Marrache et al., 2013; Rodzinski et al., 2016b; Saraiva et al., 2016; Stimphil et al., 2017a; Surnar et al., 2021; Velichkovska et al., 2019).

MENPs offered a unique advantage of delivering the drug to the target region and can be released using a low magnetic field. Nair et. al have taken advantage of intrinsic magnetoelectricity properties of these MENPs to load 3'-azido-3'-deoxythymidine (AZTTP), a nucleotide reverse transcriptase inhibitor (NRTI) against HIV (Nair et al., 2013). In this study AZTTP loaded MENPs with a size of 30 nm were translocated across the blood-brain barrier (BBB) using an external magnetic field of 40 Oe for 3 h and a gradient of ~22 Oe cm^{-1} in *in vitro* BBB model followed by the release of AZTTP from MENPs through the application of an a.c. magnetic field of 66 Oe at 100 Hz. Further, this study explains the mechanism of drug release, optimization of drug release, and its dependence on field strength and time at various frequencies (Nair et al., 2013). This study further explains how the drug AZTTP binds to MENPs via an ionic bond, which can only be triggered by varying the magnetic field, and a detailed mechanism of drug release and underlying physics is shown in figure 2 below.

In another study, Nair and co-workers have used the electroporation approach to show uptake of drug-free MENPs in human microglial cells with over 92% cell viability post electroporation and application of 60 Oe ac-magnetic field. The cell morphology was significantly affected at the 80 Oe ac-magnetic field due to heat generation(Kaushik et al., 2017). Numerical simulation studies have been employed to show this Nano-electroporation of MENPs results in penetration of the particles through electrically induced nanopores for 40 ms (Kaushik et al., 2017).

Kaushik et al, have developed a similar 20 nm size MENCs known as BaTiO3@CoFe2O4, where cobalt ferrite as core and barium titanate as shell and characterized using standard methods (Figure 3). Authors studied MENCs *in vitro* toxicity in human astrocytes and SKNMC, a human neuroblastoma cell line, and found the MENCs were not toxic up to 0.25 mg/mL demonstrating their utility for neuro applications at such concentrations. However, at 1 mg/mL concentration, viability of ~80% was observed indicating higher concentrations might be toxic (Kaushik et al., 2016). Further, they tested the toxicity of these nanocarriers upon intravenous injection in mice at 10 mg/kg and found no toxicity in the liver, kidney, or brain using histology studies and clinical chemistry in the brain. Authors also analyzed uptake of MENCs using in-situ TEM imaging (Fig. 4A, B) and confirmed that MENCs were capable of crossing the BBB (Fig. 4A, a control vs Fig. 4B, a) and found them localized into various brain cells, (Fig. 4A, a–c), and blood cells (Fig. 4B, a) and smooth muscle cells (Fig. 4B,e). Neurobehavioral studies such as grip strength, rotating rod confirmed that sensorimotor activities were not affected by these MENCS indicating at this dose and up to 7 days after the injection neurobehavior functioning is in comparison to control mice. These MENCs were uniformly distributed inside the brain and other major organs. ICP-MS analysis indicated MENCs presence at 38 ug/g tissue, while no quantification or comparison to % injected dose was provided in this study (Kaushik et al., 2016).

In a follow-up *in vivo* study, the team studied the feasibility of delivery of MENPs using magnetic resonance imaging instrument to the brain of a large primate, such as a baboon (Kaushik et al., 2019a). The authors injected MENPs at a dose of 1.69 mg/kg intravenously into a single baboon and placed the baboon under a static magnetic field of MRI for 3 h. The distribution of MENPs in various regions of the brain and peripheral organs was analyzed

using T_2 values. Significant reduction in T_2 values observed in basal ganglia, hemisphere and vertex, liver and kidney, and spleen demonstrating accumulation of the MENPs in those regions (Figure 5) and translation of this novel technology into large vertebrates (Kaushik et al., 2019a). Histopathology and clinical studies did not reveal any observable toxicity in this animal post-MENP administration.

Beclin1 is a key protein in the regulation of autophagy and shown to be regulating viral replication and associated inflammation in HIV-1 infected microglia. Rodriguez et al, have loaded a siRNA targeting Beclin1 onto the MENPs and tested their ability in reducing the viral infection and associated inflammation markers in an *in vitro* BBB model(Rodriguez et al., 2017). MENP-siBeclin1 was transmigrated across the BBB using 3 h exposure of 0.8 Tesla static magnetic field, followed by the release of siRNA with an a.c. magnetic field application for 30 min using the electromagnetic coil. The release of siBeclin1 successfully attenuated HIV-1 replication and reduced the viral inflammation through STAT1/NF-kB pathway, without compromising the BBB integrity in this study(Rodriguez et al., 2017). The time-lapse analysis of neuronal viability after treatment with MENP-siBeclin1 also indicated similar viability to that of control cells over a period of 72 h.

Recently developed revolutionary technique in the gene editing is CRISPR technology, an abbreviation for clustered regulatory interspaced short palindromic repeat (CRISPR) -associated 9 (cas9), to edit a specific part of the genome using cas9 was employed by Nair and workers in combination with MENP against viral diseases such as HIV-1 (Kaushik et al., 2019b). In this work, a nanoformulation composed of cas9/RNA was bound with MENPs (Figure 6) and transported across an *in vitro* BBB to inhibit latent HIV-1 infection in HC69 microglial cells. A 60 Oe ac magnetic field was employed to release cas9/gRNA from the MENP surface and results showed a reduction in HIV-LTR expression comparison to unbound cas9/gRNA nanoformulations in these HC69 cells. In the same article authors also demonstrated the toxicity of both free MENPs and MENP-cas9/gRNA in 4 different CNS cell lines, namely, human astrocytes (HA), human brain microvascular endothelial cells (HBMEC), Human pericytes (HP), and microglial cells (CHEM-5), and found that up to 50 ug MENPs or the csa9 bound MENPs were not toxic to the cells, while there is significant toxicity at 100 *ug* (Kaushik et al., 2019b).

With numerous research articles (Kaushik et al., 2016; Kaushik et al., 2017; Kaushik et al., 2019a; Kaushik et al., 2019b; Nair et al., 2013; Rodriguez et al., 2017; Yue et al., 2012) on delivery of different antiretroviral drugs or CRISPR/cas9 and Beclin1 to tackle the HIV, controlled release of the drugs were utilized, but sustained release of drugs is yet to be explored in addition, unfortunately in all of these studies, the efficacy studies only carried out at *in vitro* level which a drug is involved. All the studies conducted *in vivo* were mostly done on the MENPs without therapeutic drug-loaded and with qualitative analysis on localization of the MENPs in the tissues. Hence demonstration of *in vivo* efficacy in a quantitative way is needed.

ME materials for Neural Stimulation:

Studying neural activity in various regions in the brain can result in understanding the progress of various brain-related diseases in patients. Lead zirconate titanate (PZT) based thin film systems were employed by Robinson and coworkers to generate wireless neural stimulation at therapeutic frequencies up to 100 Hz (Singer et al., 2020). Studies in mice and rats with these invasive thin-film implants have shown encouraging results (Luan et al., 2020; Singer et al., 2020). For this article, we are mainly focusing data on nanoparticles or nanocarriers involving magnetoelectric materials.

To address neurological and psychiatric disorders through wireless deep brain stimulation, Sitti and coworkers (Kozielski et al., 2021) have utilized MENPs of CFO@BTO of 224 nm size with 36% of BTO and 64% of CFO in mice. The authors studied the effect of magnetic stimulation of MENPs *in vitro* using neuronal cell activity *via* examining intracellular Ca2+ signaling in SHSY5Y cells. These studies found a significant increase in CA2+ transients when MENPs were stimulated with simultaneous AC and DC magnetic fields (Kozielski et al., 2021). Neuromodulation was assessed *in vivo*, using C57Bl/6J mice by injecting 100 *ug* of MENPs in mice subthalamic area using stereotactic injections. Behavioral testing such as the CatWalk test, and Rotarod testing revealed that *in vivo* magnetic stimulation using a custom coil system proved the potential of these MENPs as nanoelectrodes to modulate the deep brain targets *via* modulation of neuronal activity and changes the animal behavior. This demonstration provides promising prospects for wireless neural devices developments with such materials (Kozielski et al., 2021).

MENPs for Parkinson's Disease (PD):

Kun Yue et. al have studied the artificial stimulation of neural activity deep in the brain of PD patients using MENPs. The modeling indicated when 20nm MENPs delivered at a concentration of 3 X 10^6 particles/cc into four selective brain regions and stimulated in a non-invasive way used 300-Oe magnetic field of 80 Hz showed neural activity returning to levels of healthy person brain while the invasive deep brain stimulation procedure did not result in such activity levels (Yue et al., 2012). Such studies assist in the non-invasive monitoring of brain and related CNS diseases. In a follow-up study, the GMO coated MENPs were shown to be non-toxic up to 200 ug/mL concentration in peripheral blood mononuclear cells and 10ug of GMO-MENPs were administration *via* IV injection in ICR mice to test by electroencephalography using a head mount to control the neural activity (Guduru et al., 2015). Here again, post-MENPs administration, a 100 Oe magnetic field was applied in a frequency range from 0 to 30 Hz to modulate the electric waveforms deep in the brain of mice, while no such modulation was possible in control mice where no MENPs were administered (Guduru et al., 2015).

MENPS for Cancer applications:

Another major area in the magnetoelectric effect that has been exploited is for drug delivery to various difficult-to-reach cancers. Deep tumors are often difficult to reach and the magnetoelectric effect has been exploited for such applications. MENCs are explored

in literature in brain tumors, ovarian cancer, melanoma, and hepatocellular carcinoma, as many of them are difficult to reach due to the off-target distribution of the drugs upon administration.

Core-shell cobalt ferrite@barium titanate (CFO@BTO) based MENPs are also routinely employed for examining their applications in cancer therapies. Khizroev and co-workers have examined the use of 30 nm size CFO@BTO based MENPs for different types of cancer applications (Guduru and Khizroev, 2014; Guduru et al., 2013; Hadjikhani et al., 2017a; Khizroev and Liang, 2020; Khizroev et al., 2013; Nagesetti et al., 2017; Rodzinski et al., 2016a; Rodzinski et al., 2016b; Rodzinski et al., 2016c; Stewart et al., 2018; Stimphil et al., 2017a; Stimphil et al., 2017b). In one of the first studies, Khizroev and his coworkers made a magnetic field-controlled release of paclitaxel (PTXL) drug from functionalized MENPs (Guduru and Khizroev, 2014). In this study, the authors tried to address various factors that influence the release of drugs from the MENPs. The use of an external magnetic field to remotely control the forces between drug and MENCs is studied here and how it affects with specific functionalization of the surface of the MENPs. Intermediate layers of glycerol monooleate (GMO) or Tween-20 or ethyl-3-(3-dimethyl aminopropyl) carbodiimide (EDC), a popular coupling agent were coated and studied their effect on the loading, size, zeta potential variations, and release of PTXL. Size and zeta potentials did not significantly affect by coating GMO, Tween-20, EDC, or loading with PTXL. But the amount of PTXL bound on the MENPs is significantly increased with Tween-20 and moderately with EDC and EMO coating when compared with unfunctionalized MENPs (Guduru and Khizroev, 2014). FT-IR analysis confirmed the coating of the functionalized layers. Release of the PTXL by varying the magnetic field at low (<10 Oe), moderate (~100 Oe), and high (~200 Oe) was examined and found that the higher the magnetic field, the higher the release in all the cases. But the overall release from EDC-MENs and Tween20-MENs were less than 20% at these magnetic field and frequency treatments (Guduru and Khizroev, 2014). Cytotoxicity studies in human ovarian, SKOV-3 cells revealed EDC and Tween functionalized MENPs were toxic over 20 ug/mL concentration, while the GMO functionalized materials were non-toxic up to 50 ug/mL (Guduru and Khizroev, 2014).

In follow-up studies (Guduru et al., 2013; Rodzinski et al., 2016a) PTXL bound GMO-MENPs were examined for delivery into SKOV-3 cells using localized nano-electroporation (Figure 7) by systematically varying magnetic field from 12 Oe to 66 Oe and frequency of 0 Hz to 1000 Hz and the time of exposure from 1 min to 120 min (Figure 8). These studies found that at 66 Oe and /or 1000 Hz frequency and 120-minute exposure maximum drug release (>95%) was observed (Guduru et al., 2013). The uptake of MENPs was examined in both cancerous SKOV-3 cells and healthy ovarian cells, Human Ovarian Microvascular Endothelial Cells (HOMEC) at various field strengths, and found the uptake is significantly higher in the cancerous cells when compared to non-cancerous cells (Guduru et al., 2013). The *in vivo* efficacy of these PTXL loaded GMO-MENPs were examined in a SKOV-3 xenograft study in nude mice upon the weekly intravenous dose of 15 *ug* of PTXL and respective NPs. For mice where MENPs will be injected a high-moment neodymium magnetic coin was attached with a tissue adhesive over the tumor. This magnet can generate a d.c. field on the order of 100 Oe. The formulations with MENPs followed by the magnetic field treatment group showed a significant reduction in tumor size in

three months of continuous weekly treatments (Rodzinski et al., 2016a). Interestingly subcutaneous administration of PTXL by MENPs only showed a reduction in tumor size in the first 40 days, but the tumor size increased significantly in the last 30 days of the study. One significant drawback of these studies is the number of mice (n=2) used per group, as one cannot generate statistically significant data with this low number of animals (Rodzinski et al., 2016a).

Biodistribution and clearance of the CFO@BTO based MENPs ware also examined using energy dispersive spectroscopy (EDS) in major tissues of female SCID mice upon administration of 10 nm, 30 nm, 100 nm, and 600 nm MENPs intravenously (Hadjikhani et al., 2017b). Mice were injected 5 mg of GMO-coated MENPs by lateral tail vein injection and sacrificed at 1 day, 1 week, 4 weeks, and 8 weeks and observed the distribution in kidneys, liver, spleen, lungs, and brain without the use of a magnetic field to direct the MENPs to any specific location. The net clearance rates were 90, 86, 85, and 61% for 10-, 30– 100- and 600 nm MENPs respectively, when compared with MENPs in all the organs 1-week post-injection to that of subsequent 7 weeks (Hadjikhani et al., 2017b). This clearance trend is similar for small NPs of other types in literature, where the smaller NPs are known to be easily cleared by splenic and kidney filtration, while the clearance for large particles has been non-linear and depends on surface groups, chain-end functionalities, the charge of the particle, etc (Kolishetti et al., 2011). Overall, the number of larger MENPs decreased in the lungs, and increased in the liver and spleen for larger NPs with time, unfortunately, this study also did not address a more quantitative analysis of the fate of these NPs, such as half-life, clearance, the effect of the magnetic field, etc.

In another work, Pardo et al have examined the abilities of MENPs of different sizes *via* intranasal administration for examining the use for targeted brain localization to explore the utility for brain-related complications. One of the objectives of this study was to evaluate the efficacy difference in the delivery to the brain *via* intranasal (IN) and intravenous (IV) injections by varying the size and concentration of the MENPs. 30 and 60 nm sizes CFO@BTO, MENPs were synthesized *via* the hydrothermal method and conjugated with a 680 XL fluorochrome dye, a red dye for tracking *via* IVIS studies (Pardo et al., 2021). These MENPs were injected into NSG mice *via* IN and IV methods at 5 *ug* or 60 *ug* dose per mice. The application of a magnetic field significantly increased the radiance signal from the IVIS imaging at the top of the brain, but no such difference in signal was observed at the bottom of the brain (Pardo et al., 2021). Further 30 nm size MENPs showed a significantly higher amount than the 60 nm MENPs. Post euthanasia analysis of cortex, amygdale indicated similar results as of IVIS imaging. H&E staining and caspase 3 stainings did not show any abnormalities in morphology or apoptosis. This study concluded 30 nm size MENPs were ideal for brain delivery applications (Pardo et al., 2021).

In recent work, Ali and coworkers have used CFO@BTO based MENPs to conjugate doxorubicin and methotrexate *via* traditional amide coupling and test them against hepatocellular carcinoma (HepG2) and melanoma (GT144) cells *in vitro* (Shahzad et al., 2021). The NPs used in this study was ~84 nm in size with a −30mV zeta potential. Conjugation of the drugs did not affect their zeta potential values, but the size was almost doubled to 160 nm with no change in the polydispersity index. Drug release kinetics was

studied by varying magnetic field intensities from 0–7mT using Helmholtz coils at room temperature and exposure times from 1 to 60 min. Electric dipoles that were formed due to magnetoelectric effect and the dipole charge density becomes comparable to ionic charge density in the shell of the NP and drug bond and in this example at 5 mT field and 20 min exposure drug and NP bonds are broken (Shahzad et al., 2021). Cytotoxicity studies revealed the drug-loaded NPs were relatively non-toxic to HepG2 and HT144 cells unless they are exposed to the magnetic field. The IC50 values showed a 6-to-8-fold difference depending on cell type and drug used in the study (Shahzad et al., 2021). Hemolysis was observed in erythrocytes at higher concentrations of methotrexate conjugated MENPs, demonstrating caution and need of examining further before employing them for *in vivo* applications.

In 2020, researchers from Taiwan, have developed nanohybrid material by mixing boron-doped graphene quantum dots (B-GQDs) loaded with doxorubicin, a DNA intercalator, and topoisomerase inhibitor, and a pH-sensitive dendrimer loaded with Palbociclib, a CDK4/6 inhibitor (Su et al., 2020). The nanohybrids were coated with rabies virus glycoprotein (RVG) to enhance delivery and transport. The drug release from this nanohybrid was achieved by placing them in High-frequency magnetic field (HFMF) coils of 2 cm at a frequency of 50 kHz and a 70 W power with a strength of 4 kA/m for 30 min. These RVG-nanohybrids did not show any cytotoxicity up to 20 ug/mL concentration in ALTS1C1 cells, while the drug-loaded nanohybrids showed extensive cytotoxicity at these concentrations and 15 min of HFMF indicating their use for cancer treatment (Su et al., 2020). In this study, an orthotopic intracranial tumor was developed using ALTS1C1 cells and RVG-nanohybrid was administered intravenously 14 days after tumor implantation and applied an HFMF for 30 min after 24 h and the biodistribution and efficacy and survival rate was studied. These studies revealed enhanced accumulation of these nanohybrids in the brain, spinal cord and improved the survival rate of 37 days in the treatment groups compared to 17 days in the saline treatment group showing the utility of such systems (Su et al., 2020). Other magnetoelectric materials made from Nickel, Lead Zirconate Titanate (piezoelectric ceramic material or PZT) (Babu et al., 2009) are not employed in biomedical applications due to toxicity issues from the lead.

Other applications of MENPs:

A 3D-printed biodegradable hydrogel was made from gelatin-methacryloyl was used to load CFO@BTO based MENPs and generate microswimmers, which were used for differentiation of neuron-like cells using SHSY-5Y cells and through magnetic stimulation (Dong et al., 2020). Study authors envision these devices will provide avenues for targeted cell therapies for traumatic brain injuries. In addition, Magnetoelectric (ME) transducers were being explored for use as wireless power transfer systems (WPTS) to employ in biomedical implants (Truong et al., 2020), wireless deep brain stimulation for neuromodulation (Kozielski et al., 2021), micromachines (Chen et al., 2016), and sensor applications (Murzin et al., 2020).

Although this MENP technology is mainly studied for neuroHIV, Parkinson and ovarian cancer-related applications, the same Idea can be extended to other viruses which affect the brain such as coxsackievirus, poliovirus, echovirus, herpes simplex virus, varicella-zoster

virus, Epstein-Barr virus, cytomegalovirus, adenovirus, rubella, measles, ZIKA virus, and SARS-Corona virus, etc. Also, this MENP technology can be employed to other difficult to reach cancers such as pancreatic cancer, and brain cancers, or in diseases with organ-specific therapeutics.

Potential of magneto-electro nanogels and nanoliposomes for promising therapeutics and diagnostic applications:

The advancements in the metallic NP research and their surface functionalization have resulted in the exploration of less toxic core-shell magnetic materials where these MENPs or MENCs were packaged into liposomes or nanogels, which provided a competitive solution in this area, where the core is made from magnetic component and the shell using biocompatible lipids or polymers which are crosslinked to form a gel. Liposomes and Nanogels have already shown potential clinical applications and widened the applications of these materials for drug delivery and diagnostics applications. Hydrogel systems have gained attention due to their soft structure which has human tissue resemblance, their high biocompatibility, and biodegradable characteristics (Madhavan et al., 2020; Vashist et al., 2020b). Our research group has been working with the development of auto-fluorescent Micro/ Nanogels for therapeutic and diagnostic applications (Vashist et al., 2020a; Vashist et al., 2019). We envision, that the magnetoelectric nanogels based nanocarriers find potential for targeted therapy for various diseases including HIV, ovarian cancer and other cancer disorders, and neurodegenerative medicines. The hydrogel matrix will enhance the stability of the nanoformulation as well as add on to the biocompatibility and biodegradability of magnetic- electro nanogels. The magnetic core will enhance the specific targeting and the electric core will facilitate the on-demand release and will open avenues for controlled release systems. We believe that the more aspects of magnetic and ME drug delivery systems are still to be explored which requires extensive study on the mechanism of the route of delivery and their degradation pathways. This recent strategy to develop magneto electric nanogels will be promising and requires the combined effort from materials chemists, physicists, biologists, pharmacologists and clinical scientists for translation to the clinic.

Perceived roadblocks and mitigations for MENP related advances:

Current roadblocks to advancing the MENP technology are mainly coming from physicochemical aspects, mainly generating reproducible size, charge particles without aggregation in biological media, ability to scale up to multi-gram level. The focus on physicochemical properties of MENP such as hydrodynamic size, surface zeta potential in the human circulatory system, enhancing the biodegradation by functionalization with biopolymers, and reducing its toxicity aspects would be a breakthrough for the real translation of MENP based therapeutics. The optimized hydrodynamic sizes and surface charge will play a leading role in improved and advanced applications. Moreover, the functionalization of the surface charge by biocompatible materials will be of utmost importance. The real utilization of the magnetic simulating characteristics of MENP will be possible if the green route of synthesis is opted to make it safe and effective and keeping in mind patient compliance. The excellent feature of on-demand drug release and targeted

therapy by MENP functionalized materials will be most suitable once we make them highly compatible to be well tolerated by the human body and can be excreted/degraded with time. And many of these roadblocks have been faced by other nano and biotechnologies and have been able to overcome by extensive research by various groups across the globe. Hence by embracing this technology and exploring the research by more researchers will solve the problems associated with MENPs.

Summary:

In summary, the promise of magnetoelectric nanomaterials is demonstrated in cancer, HIV, neurodegenerative diseases, Parkinson disease, cell differentiation, sensors, and neuromodulation through proof-of-concept studies by various research groups across the globe (Guduru and Khizroev, 2014; Guduru et al., 2015; Kaushik et al., 2019a; Kaushik et al., 2019b; Nair et al., 2013; Nguyen et al., 2021; Singer et al., 2020; Stewart et al., 2018). Many of these reported studies need increased sample size in their experiments, especially in *in vivo* studies for rigorous analysis and a better understanding of their potential. These advancements have demonstrated the safety, efficacy of these materials under different contexts for the respective applications. Authors predict significant new advances with these materials in other diseases and during the coming decades, there will be significant interest from academia and industry due to their untapped potential.

Outlook:

There are numerous biomedical applications where MENP can lead to improvement in efficacy and advancements. In the last few years, magnetic particles have become potential candidates for targeted delivery systems and imaging modalities. Mapping the neuronal activity in the brain is the biggest challenge. To well understand the diverse functions of the brain, it is important to map the activity in the brain which will be very helpful in diagnostics and treatment of brain diseases. In this regard, MENP has demonstrated a great potential to overcome the drawbacks associated with the non-invasive mapping of the brain and adds to the quality assessment of neuronal activity (Guduru, 2013). Our understanding is that despite the significant advances, the present state of the art can be improved for a robust and clinical translation of MENP for biomedical applications and to be in the market.

Acknowledgments:

M.N. thanks support from the National Institutes of Health (NIH) grants DA042706, DA040537, DA037838, DA034547, and N.K. thanks support from H&N Wertheim Research Pilot Project from Florida International University, and A.V. thanks support from FIU Foundation *via* grant number AWD0011094.

References:

Babu SN, Siddeshwar A, Srinivas K, Suryanarayana SV, Bhimasankaram T, 2009. Magnetoelectric properties of Ni/PZT/Ni layered composite for low field applications. J. Mater. Sci 44 (15), 3948–3951.

Banik B, Askins BW, Dhar S, 2016. Mito-magneto: a tool for nanoparticle mediated mitochondria isolation. Nanoscale 8 (47), 19581–19591. [PubMed: 27735003]

Banik B, Dhar S, 2017. Centrifugation-free magnetic isolation of functional mitochondria using paramagnetic iron oxide nanoparticles. Curr. Protoc. Cell Biol 76, 25 24 21–25 24 20. [PubMed: 28862341]

Barbu E, Molnar E, Tsibouklis J, Gorecki DC, 2009. The potential for nanoparticle-based drug delivery to the brain: overcoming the blood-brain barrier. Expert Opin Drug Deliv 6 (6), 553–565. [PubMed: 19435406]

Cena V, Jativa P, 2018. Nanoparticle crossing of blood-brain barrier: a road to new therapeutic approaches to central nervous system diseases. Nanomedicine (Lond) 13 (13), 1513–1516. [PubMed: 29998779]

Chen XZ, Shamsudhin N, Hoop M, Pieters R, Siringil E, Sakar MS, Nelson BJ, Pane S, 2016. Magnetoelectric micromachines with wirelessly controlled navigation and functionality. Mater. Horiz 3 (2), 113–118.

Dong M, Wang XP, Chen XZ, Mushtaq F, Deng SY, Zhu CH, Torlakcik H, Terzopoulou A, Qin XH, Xiao XZ, Puigmarti-Luis J, Choi H, Pego AP, Shen QD, Nelson BJ, Pane S, 2020. 3D-Printed Soft Magnetoelectric Microswimmers for Delivery and Differentiation of Neuron-Like Cells. Adv. Funct. Mater 30 (17).

Ghosh Chaudhuri R, Paria S, 2012. Core/shell nanoparticles: classes, properties, synthesis mechanisms, characterization, and applications. Chem. Rev 112 (4), 2373–2433. [PubMed: 22204603]

Guduru R, 2013. Bionano Electronics: Magneto-Electric Nanoparticles for Drug Delivery, Brain Stimulation and Imaging Applications FIU Electronic Theses and Dissertations 10.25148/etd.fi13112201979.

Guduru R, Khizroev S, 2014. Magnetic Field-Controlled Release of Paclitaxel Drug from Functionalized Magnetoelectric Nanoparticles. Part. Part. Syst. Char 31 (5), 605–611.

Guduru R, Liang P, Hong J, Rodzinski A, Hadjikhani A, Horstmyer J, Levister E, Khizroev S, 2015. Magnetoelectric 'spin' on stimulating the brain. Nanomedicine (Lond) 10 (13), 2051–2061. [PubMed: 25953069]

Guduru R, Liang P, Runowicz C, Nair M, Atluri V, Khizroev S, 2013. Magneto-electric Nanoparticles to Enable Field-controlled High-Specificity Drug Delivery to Eradicate Ovarian Cancer Cells. Sci. Rep 3.

Gupta AK, Gupta M, 2005. Synthesis and surface engineering of iron oxide nanoparticles for biomedical applications. Biomaterials 26 (18), 3995–4021. [PubMed: 15626447]

Hadjikhani A, Rodzinski A, Wang P, Nagesetti A, Guduru R, Liang P, Runowicz C, Shahbazmohamadi S, Khizroev S, 2017a. Biodistribution and clearance of magnetoelectric nanoparticles for nanomedical applications using energy dispersive spectroscopy. Nanomedicine-UK 12 (15), 1801–1822.

Hadjikhani A, Rodzinski A, Wang P, Nagesetti A, Guduru R, Liang P, Runowicz C, Shahbazmohamadi S, Khizroev S, 2017b. Biodistribution and clearance of magnetoelectric nanoparticles for nanomedical applications using energy dispersive spectroscopy. Nanomedicine (Lond) 12 (15), 1801–1822. [PubMed: 28705034]

Kaushik A, Jayant RD, Nikkhah-Moshaie R, Bhardwaj V, Roy U, Huang Z, Ruiz A, Yndart A, Atluri V, El-Hage N, Khalili K, Nair M, 2016. Magnetically guided central nervous system delivery and toxicity evaluation of magneto-electric nanocarriers. Sci. Rep 6, 25309. [PubMed: 27143580]

Kaushik A, Nikkhah-Moshaie R, Sinha R, Bhardwaj V, Atluri V, Jayant RD, Yndart A, Kateb B, Pala N, Nair M, 2017. Investigation of ac-magnetic field stimulated nanoelectroporation of magneto-electric nano-drug-carrier inside CNS cells. Sci. Rep 7, 45663. [PubMed: 28374799]

Kaushik A, Rodriguez J, Rothen D, Bhardwaj V, Jayant RD, Pattany P, Fuentes B, Chand H, Kolishetti N, El-Hage N, Khalili K, Kenyon NS, Nair M, 2019a. MRI-Guided, Noninvasive Delivery of Magneto-Electric Drug Nanocarriers to the Brain in a Nonhuman Primate. ACS Appl. Bio Mater 2 (11), 4826–4836.

Kaushik A, Yndart A, Atluri V, Tiwari S, Tomitaka A, Gupta P, Jayant RD, Alvarez-Carbonell D, Khalili K, Nair M, 2019b. Magnetically guided non-invasive CRISPR-Cas9/gRNA delivery across blood-brain barrier to eradicate latent HIV-1 infection. Sci. Rep 9 (1), 3928. [PubMed: 30850620]

Khizroev S, Liang P, 2020. Engineering future medicines with magnetoelectric nanoparticles: Wirelessly controlled, targeted therapies. IEEE Nanotechnol. Mag 14 (1), 23–29.

Khizroev S, Yue K, Guduru R, Liang P, Hong J, Nair M, 2013. Magneto-Electric Nanoparticles for Non-Invasive Brain Stimulation. J. Neuroimmune Pharm 8 (2), 388–389.

Kolishetti N, Alexis F, Pridgen EM, Farokhzad OC, 2011. Biodistribution and Pharmacokinetics of Nanoprobes. Nanoplatform-Based Molecular Imaging, 75–104.

Kost J, Langer R, 1986. Advances in drug delivery-magnetically modulated drug delivery systems. Pharmacy International 7 (3), 60–63.

Kozielski KL, Jahanshahi A, Gilbert HB, Yu Y, Erin O, Francisco D, Alosaimi F, Temel Y, Sitti M, 2021. Nonresonant powering of injectable nanoelectrodes enables wireless deep brain stimulation in freely moving mice. Sci. Adv 7 (3).

Kreuter J, 1994. Drug targeting with nanoparticles. Eur J Drug Metab Pharmacokinet 19 (3), 253–256. [PubMed: 7867668]

Kumar CS, Mohammad F, 2011. Magnetic nanomaterials for hyperthermia-based therapy and controlled drug delivery. Adv. Drug Deliv. Rev 63 (9), 789–808. [PubMed: 21447363]

Luan L, Robinson JT, Aazhang B, Chi T, Yang K, Li X, Rathore H, Singer A, Yellapantula S, Fan Y, Yu Z, Xie C, 2020. Recent Advances in Electrical Neural Interface Engineering: Minimal Invasiveness, Longevity, and Scalability. Neuron 108 (2), 302–321. [PubMed: 33120025]

Madhavan N, Raymond A, Vashist A, 2020. Biotherapy for viral infections using biopolymer based micro/nanogels. Google Patents

Malinowska I, Ryzynska Z, Mrotek E, Klimczuk T, Zielinska-Jurek A, 2020. Synthesis of CoFe2O4 Nanoparticles: The Effect of Ionic Strength, Concentration, and Precursor Type on Morphology and Magnetic Properties. J. Nanomater 2020.

Mamo T, Moseman EA, Kolishetti N, Salvador-Morales C, Shi J, Kuritzkes DR, Langer R, von Andrian U, Farokhzad OC, 2010. Emerging nanotechnology approaches for HIV/AIDS treatment and prevention. Nanomedicine (Lond) 5 (2), 269–285. [PubMed: 20148638]

Marrache S, Pathak RK, Darley KL, Choi JH, Zaver D, Kolishetti N, Dhar S, 2013. Nanocarriers for tracking and treating diseases. Curr. Med. Chem 20 (28), 3500–3514. [PubMed: 23834187]

Murzin D, Mapps DJ, Levada K, Belyaev V, Omelyanchik A, Panina L, Rodionova V, 2020. Ultrasensitive Magnetic Field Sensors for Biomedical Applications. Sensors-Basel 20 (6).

Nagesetti A, Rodzinski A, Stimphil E, Stewart T, Khanal C, Wang P, Guduru R, Liang P, Agoulnik I, Horstmyer J, Khizroev S, 2017. Multiferroic coreshell magnetoelectric nanoparticles as NMR sensitive nanoprobes for cancer cell detection. Sci. Rep 7.

Nair M, Guduru R, Liang P, Hong J, Sagar V, Khizroev S, 2013. Externally controlled on-demand release of anti-HIV drug using magneto-electric nanoparticles as carriers. Nat. Commun 4, 1707. [PubMed: 23591874]

Nguyen T, Gao JH, Wang P, Nagesetti A, Andrews P, Masood S, Vriesman Z, Liang P, Khizroev S, Jin XM, 2021. In Vivo Wireless Brain Stimulation via Non-invasive and Targeted Delivery of Magnetoelectric Nanoparticles. Neurotherapeutics

Pandey P, Ghimire G, Garcia J, Rubfiaro A, Wang X, Tomitaka A, Nair M, Kaushik A, He J, 2021. Single-Entity Approach to Investigate Surface Charge Enhancement in Magnetoelectric Nanoparticles Induced by AC Magnetic Field Stimulation. ACS Sens 6 (2), 340–347. [PubMed: 32449356]

Pankhurst QA, Connolly J, Jones SK, Dobson J, 2003. Applications of magnetic nanoparticles in biomedicine. J. Phys. D Appl. Phys 36 (13), R167–R181.

Pardo M, Roberts ER, Pimentel K, Yildirim YA, Navarrete B, Wang P, Zhang E, Liang P, Khizroev S, 2021. Size-dependent intranasal administration of magnetoelectric nanoparticles for targeted brain localization. Nanomedicine-UK 32, 102337.

Rodriguez M, Kaushik A, Lapierre J, Dever SM, El-Hage N, Nair M, 2017. Electro-Magnetic Nano-Particle Bound Beclin1 siRNA Crosses the Blood-Brain Barrier to Attenuate the Inflammatory Effects of HIV-1 Infection in Vitro. J. Neuroimmune Pharm 12 (1), 120–132.

Rodzinski A, Guduru R, Liang P, Hadjikhani A, Stewart T, Stimphil E, Runowicz C, Cote R, Altman N, Datar R, Khizroev S, 2016a. Targeted and controlled anticancer drug delivery and release with magnetoelectric nanoparticles. Sci. Rep 6.

Rodzinski A, Guduru R, Stimphil E, Stewart T, Liang P, Runowicz C, Khizroev S, 2016b. Targeted, controlled anticancer drug delivery and release with magnetoelectric nanoparticles. Cancer Res 76.

Rodzinski A, Hadjikhani A, Stewart T, Stimphil E, Guduru R, Liang P, Runowicz C, Khizroev S, 2016c. A novel mechanism for field-controlled high-specificity targeted anticancer drug delivery and on-demand release using magnetoelectric nanoparticles. Cancer Res 76.

Saraiva C, Praca C, Ferreira R, Santos T, Ferreira L, Bernardino L, 2016. Nanoparticle-mediated brain drug delivery: Overcoming blood-brain barrier to treat neurodegenerative diseases. J Control Release 235, 34–47. [PubMed: 27208862]

Shahzad K, Mushtaq S, Rizwan M, Khalid W, Atif M, Din FU, Ahmad N, Abbasi R, Ali Z, 2021. Field-controlled magnetoelectric core-shell CoFe2O4@BaTiO3 nanoparticles as effective drug carriers and drug release in vitro. Mat. Sci. Eng. C Mater 119.

Singer A, Dutta S, Lewis E, Chen Z, Chen JC, Verma N, Avants B, Feldman AK, O'Malley J, Beierlein M, Kemere C, Robinson JT, 2020. Magnetoelectric Materials for Miniature, Wireless Neural Stimulation at Therapeutic Frequencies. Neuron 107 (4), 631–643 e635. [PubMed: 32516574]

Stewart TS, Nagesetti A, Guduru R, Liang P, Stimphil E, Hadjikhani A, Salgueiro L, Horstmyer J, Cai RZ, Schally A, Khizroev S, 2018. Magnetoelectric nanoparticles for delivery of antitumor peptides into glioblastoma cells by magnetic fields. Nanomedicine-UK 13 (4), 423–438.

Stimphil E, Nagesetti A, Guduru R, Stewart T, Rodzinski A, Liang P, Khizroev S, 2017a. Physics considerations in targeted anticancer drug delivery by magnetoelectric nanoparticles. Appl. Phys. Rev 4 (2).

Stimphil E, Nagesetti A, Stewart TS, Rodzinski A, Guduru R, Liang P, Runowicz C, Khizroev S, 2017b. Magnetoelectric nanoparticles for high-specificity treatment of cancer. Cancer Res 77.

Su YL, Kuo LW, Hsu CH, Chiang CS, Lu YJ, Chang SJ, Hu SH, 2020. Rabies virus glycoprotein-amplified hierarchical targeted hybrids capable of magneto-electric penetration delivery to orthotopic brain tumor. J. Control. Release 321, 159–173. [PubMed: 32045622]

Sun C, Lee JSH, Zhang MQ, 2008. Magnetic nanoparticles in MR imaging and drug delivery. Adv Drug Deliver Rev 60 (11), 1252–1265.

Surnar B, Shah AS, Park M, Kalathil AA, Kamran MZ, Ramirez Jaime R, Toborek M, Nair M, Kolishetti N, Dhar S, 2021. Brain-Accumulating Nanoparticles for Assisting Astrocytes to Reduce Human Immunodeficiency Virus and Drug Abuse-Induced Neuroinflammation and Oxidative Stress. ACS Nano

Tchikov V, Fritsch J, Kabelitz D, Schutze S, 2010. Immunomagnetic Isolation of Subcellular Compartments. Method Microbiol 37, 21–33.

Toy R, Karathanasis E, 2016. Paramagnetic Nanoparticles, in: Lu Z-R, Sakuma S (Eds.), Nanomaterials in Pharmacology Springer New York, New York, NY, pp. 113–136.

Truong BD, Andersen E, Casados C, Roundy S, 2020. Magnetoelectric wireless power transfer for biomedical implants: Effects of non-uniform magnetic field, alignment and orientation. Sensor Actuat. A-Phys 316.

Vashist A, Atluri V, Raymond A, Kaushik A, Parira T, Huang Z, Durygin A, Tomitaka A, Nikkhah-Moshaie R, Vashist A, 2020a. Development of multifunctional biopolymeric auto-fluorescent micro-and nanogels as a platform for biomedical applications. Front. Bioeng. Biotech 8, 315.

Vashist A, Kaushik A, Madhavan N, 2019. Micro/nano magnetic hydrogels with autofluorescence for therapeutic and diagnostic applications. Google Patents

Vashist A, Walters R, Nair M, 2020b. Challenges and Future Prospects Associated with Smart Hydrogels for Drug Delivery and Imaging, Intelligent Hydrogels in Diagnostics and Therapeutics CRC Press, pp. 135–144.

Velichkovska M, Surnar B, Nair M, Dhar S, Toborek M, 2019. Targeted Mitochondrial COQ10 Delivery Attenuates Antiretroviral-Drug-Induced Senescence of Neural Progenitor Cells. Mol Pharm 16 (2), 724–736. [PubMed: 30592424]

Widder KJ, Senyei AE, Ranney DF, 1980. In vitro release of biologically active adriamycin by magnetically responsive albumin microspheres. Cancer Res 40 (10), 3512–3517. [PubMed: 7438037]

Xie J, Chen K, Lee H-Y, Xu C, Hsu AR, Peng S, Chen X, Sun S, 2008. Ultrasmall c(RGDyK)-Coated Fe3O4 Nanoparticles and Their Specific Targeting to Integrin αvβ3-Rich Tumor Cells. J. Am. Chem. Soc 130 (24), 7542–7543. [PubMed: 18500805]

Yue K, Guduru R, Hong J, Liang P, Nair M, Khizroev S, 2012. Magneto-electric nano-particles for non-invasive brain stimulation. PLoS One 7 (9), e44040. [PubMed: 22957042]

Zhang W, Yu ZL, Wu M, Ren JG, Xia HF, Sa GL, Zhu JY, Pang DW, Zhao YF, Chen G, 2017. Magnetic and Folate Functionalization Enables Rapid Isolation and Enhanced Tumor-Targeting of Cell-Derived Microvesicles. ACS Nano 11 (1), 277–290. [PubMed: 28005331]

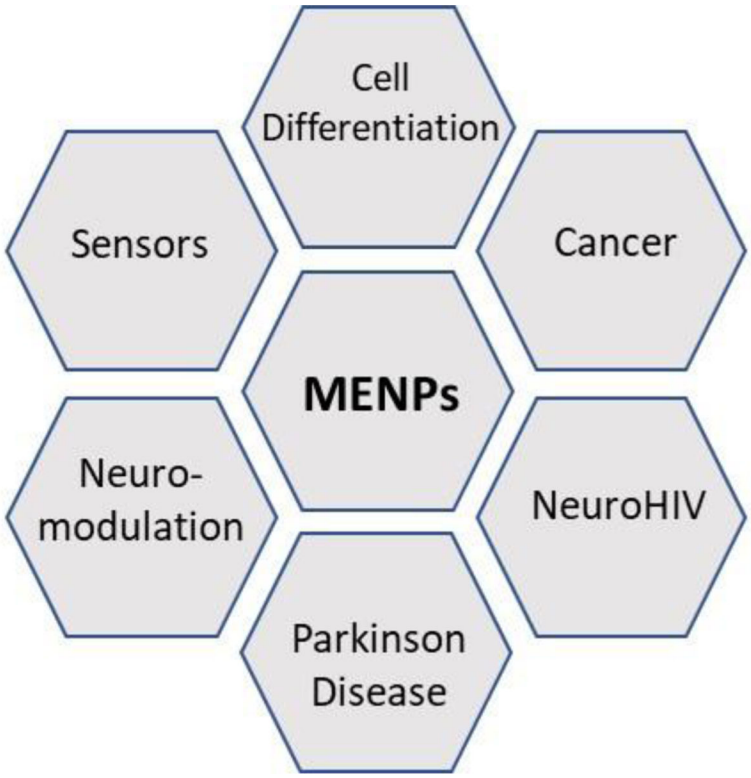

Figure 1:
Research areas in which magnetoelectric materials have been explored and shown promising results.

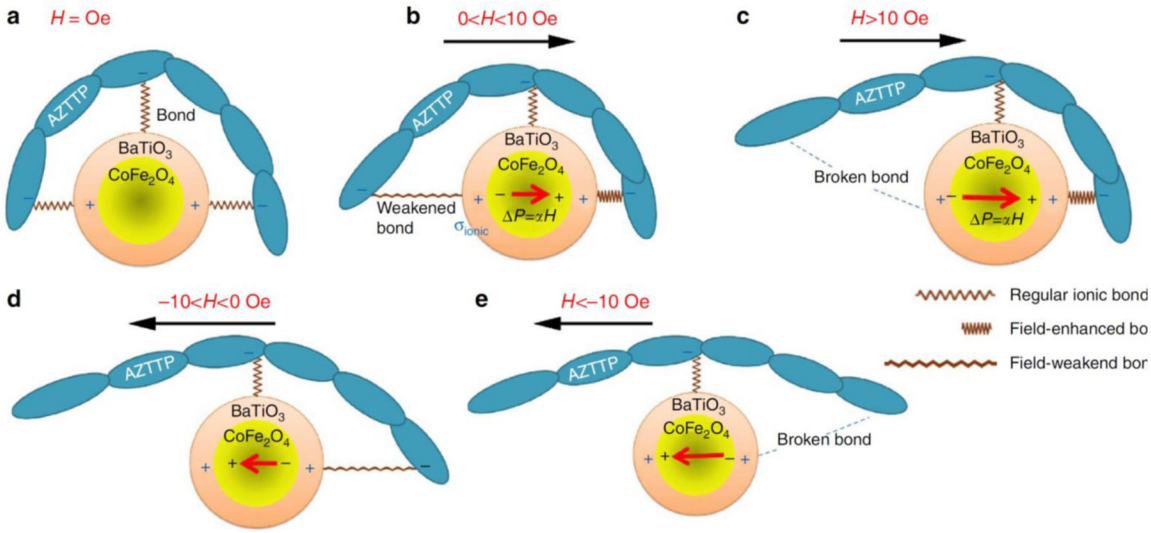

Figure 2:

Underlying physics of the triggered on-demand drug (AZTTP) release by MENs stimulated by a.c. magnetic field. (a) At zero field, only the ionic charge is present in the MEN shell. (b) An additional dipole moment (proportional to the magnetic field) breaks the original symmetry of the charge distribution in the shell. (c) As the field is increased above the threshold value, the bond on one side is broken. (d,e) The field is reversed to break the bond on the opposite side of the NP. The red arrows show the electric dipole due to the ME effect. In practice, owing to the random configurations of nanoformulations with respect to the field, the effect is present along with every central bond orientation. Adapted from Nair, M. et al. Externally controlled on-demand release of anti-HIV drug-using magneto-electric nanoparticles as carriers. Nat. Commun. 4:1707; doi: 10.1038/ncomms2717 (2013).

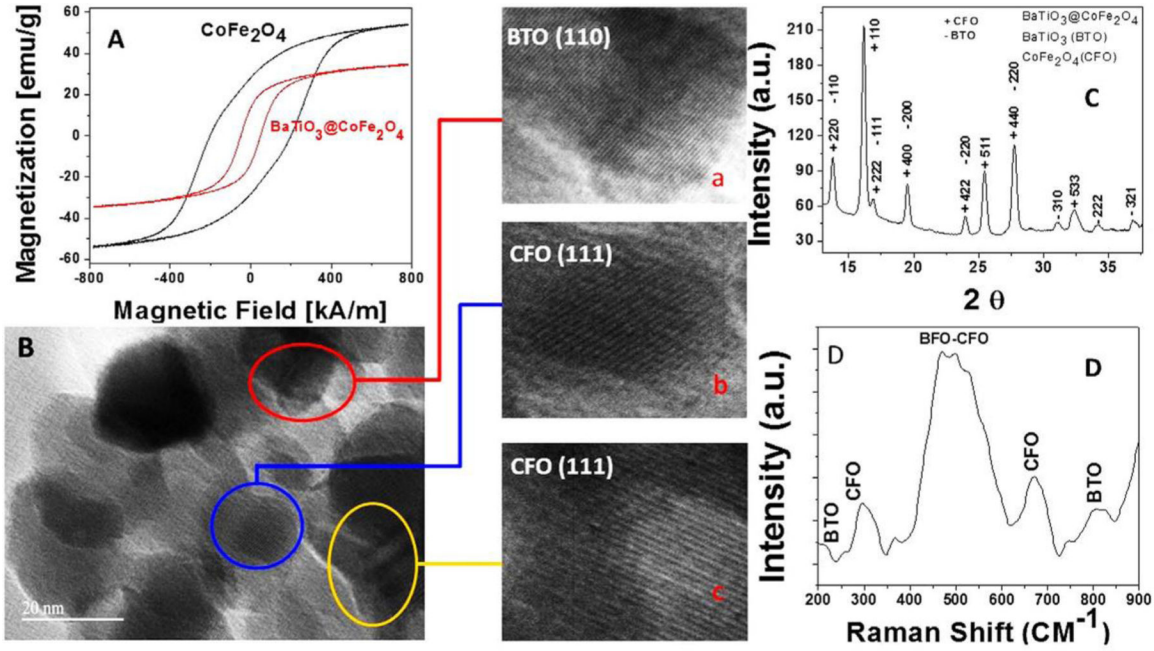

Figure 3:

Characterization of MENCs. (A) VSM study of CoFe2O4 and MENCs (BaTiO3@CoFe2O4). (**B**) TEM image of synthesized MENCs, atomic planes with respect to BTO (a) and CFO (b–c) reveals the formation of MENCs. (**C**) X-ray diffraction pattern of MENCs to explain phase purity and crystallinity of MENCs, (**D**) Raman spectra of MENCs to explain the functionality of MENCs. Kaushik, A. *et al.* Magnetically guided central nervous system delivery and toxicity evaluation of magneto-electric nanocarriers. *Sci. Rep.* **6**, 25309; doi: 10.1038/srep25309 (2016).

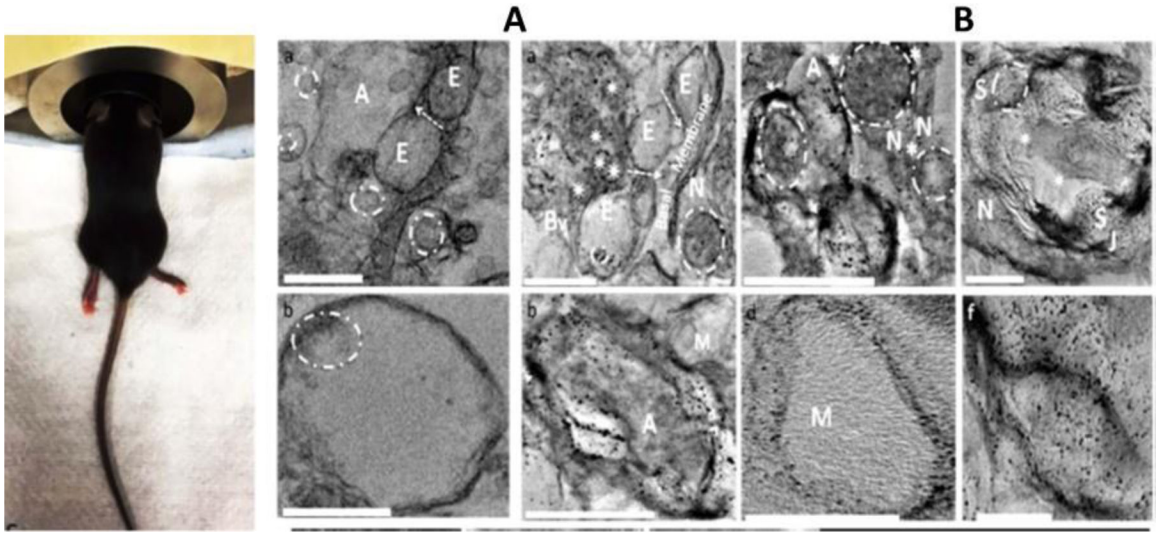

Figure 4.

TEM analysis of MENCs navigation across BBB in mice. (**A, B)** *In situ* TEM image of mouse's brain tissue without MENCs injection (A, control) and after MENCs injection (B, treatment). MENCs are capable of navigating across BBB (**A**, a vs **B**, a), direction of movement across tight junctions of endothelial (E) cells layer is indicated by arrows. MENCs are able to reach target sites, including neurons (N), astrocytes (A), and microglia (M), and are also observed in smooth muscle cells (S), and endothelial cells (E). Most MENCs are uniformly distributed in brain tissue/cells and are able to reach the nucleus (dotted circles), but some agglomeration of MENCs in cell membranes and their entrapment in endosomes is also observed (solid arrowheads). * represent synapses (**B**,c), J represents the neuromuscular junction between S and at (axon terminal, B,e), A layer of Schwann cells (sc) surrounding at is also observed (**B**,c). Scale bars: 1 μ m (A,a; B,a,b,e) and 0.5 μ m **(A**,b; **B**,c,d,f). Adapted from Kaushik, A. *et al.* Magnetically guided central nervous system delivery and toxicity evaluation of magneto-electric nanocarriers. *Sci. Rep.* **6**, 25309; doi: 10.1038/srep25309 (2016).

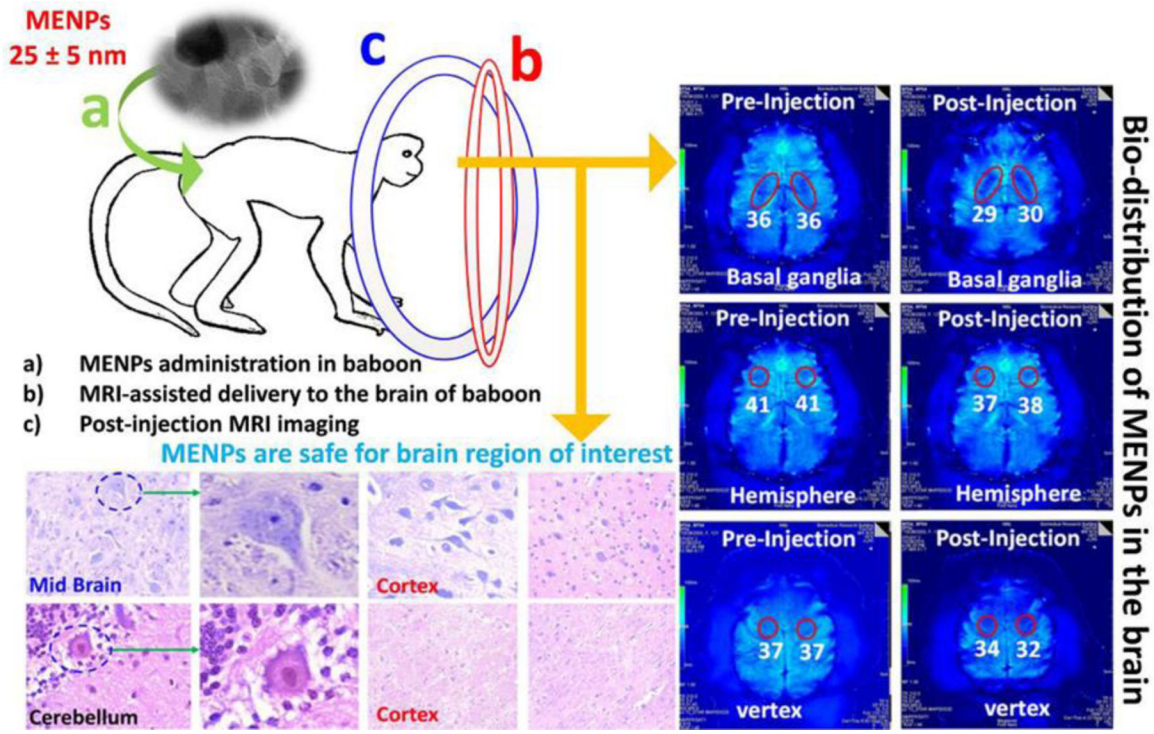

Figure 5.

MRI-assisted brain delivery MENPs intravenously administrated in the baboon. MRI brain imaging of the MENP-injected baboon showed a significant reduction in T2* value at the basal ganglia, hemisphere, and vertex and confirmed MRI-assisted brain delivery (right). Histopathology analysis for morphological assessment of MENP-injected baboon organs using hematoxylin-eosin staining (bottom) from different regions of the brain, including the midbrain, cerebellum, and frontal cortex at 20 X magnification. Adapted from Kaushik, A. *et al.* MRI-Guided, Noninvasive Delivery of Magneto-Electric Drug Nanocarriers to the Brain in a Nonhuman Primate, *ACS Appl. Bio Mater.* 2019, 2, 11, 4826–4836.

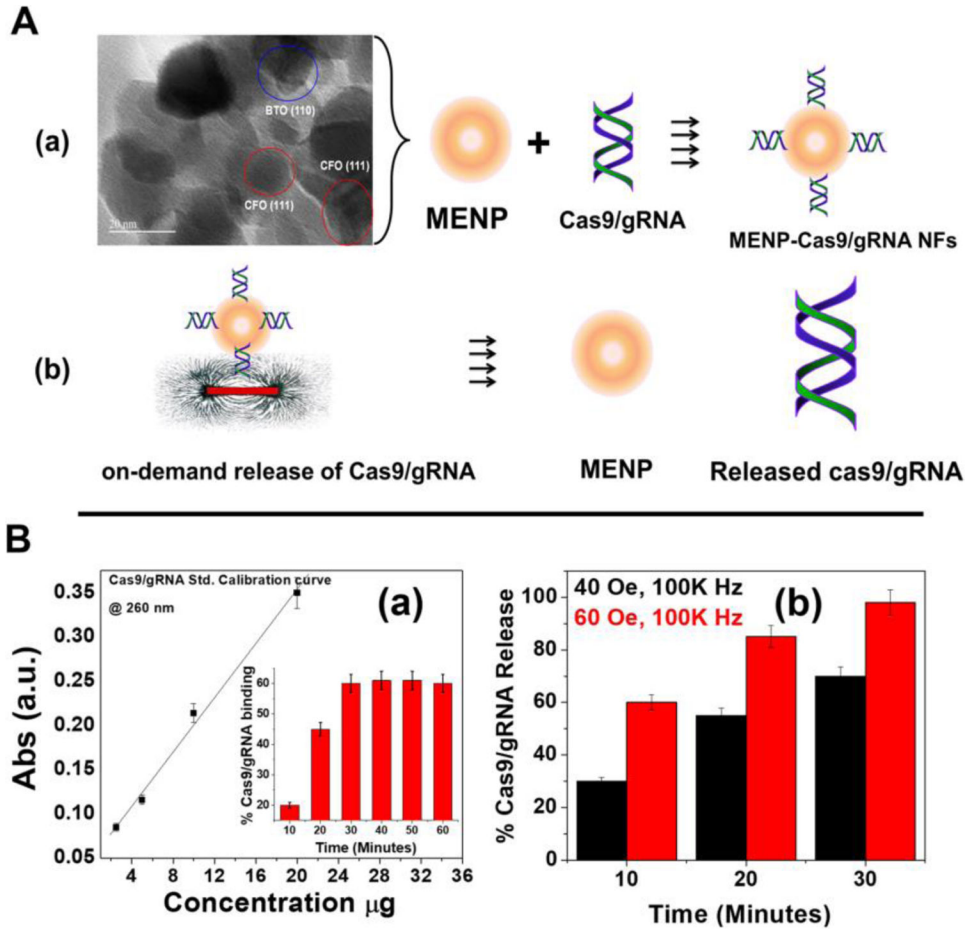

Figure 6.

(**A**) Schematic presentation of NF preparation. Surface charged MENPs of size 25 ± 5 nm bind (as demonstrated by representative TEM image) with Cas9/gRNA *via* electrostatic binding due to differences in surface charge (a). On applying ac-magnetic field stimulation *via* an electromagnetic coil (60 Oe for 30 minutes), the change in polarization on MENPs causes MENPs-Cas9/gRNA bond length contraction and expansion. This rapid phenomenon occurred repeatedly and at some points, the bond between MENPs and Cas9/gRNA broke down. (**B**) Cas9/gRNA and binding and release profile. (a) Calibration curve plotted between Cas9/gRNA absorption at 260 nm as a function of Cas9/gRNA concentrations. This calibration curve was used to estimate the unknown concentration of Cas9/gRNA. Cas9/gRNA % binding with MENPs (50 μg) as a function of time is shown in inset (a). (b) On-demand release of Cas9/gRNA from MENPs surface as a function of externally applied ac-magnetic field and time at a constant frequency (1 kHz). Adapted from Kaushik, A., Yndart, A., Atluri, V. *et al.* Magnetically guided non-invasive CRISPR-Cas9/gRNA delivery across the blood-brain barrier to eradicate latent HIV-1 infection. *Sci Rep* **9,** 3928 (2019). https://doi.org/10.1038/s41598-019-40222-4.

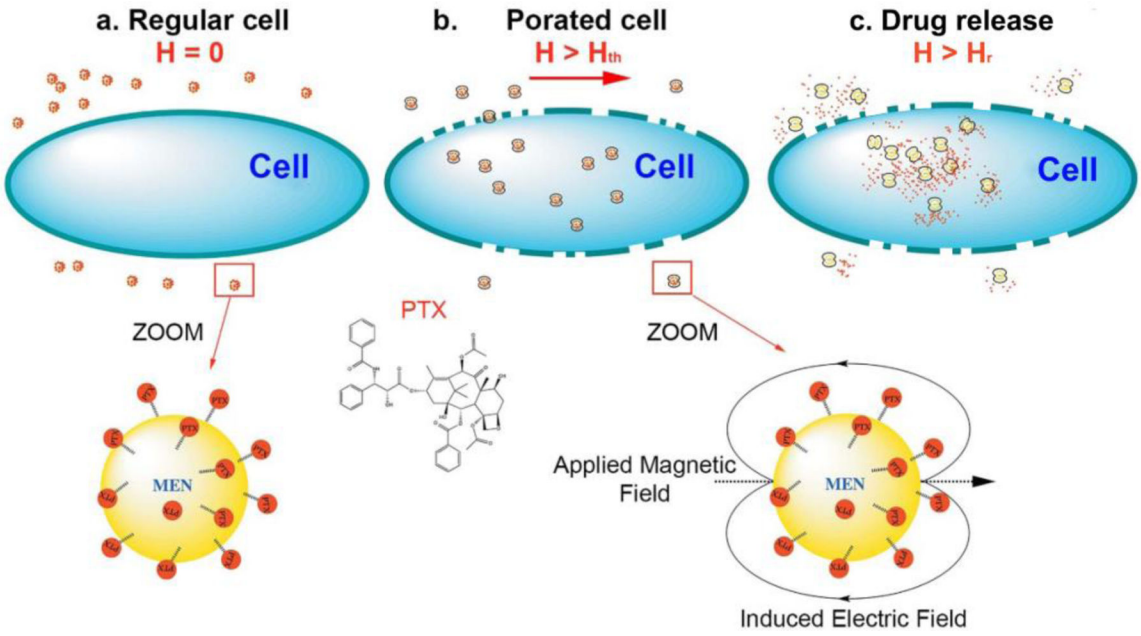

Figure 7.

Hypothesis illustration: MENs as field-controlled nano-electroporation sites to let the drug through the cancer cell membranes. Adapted from Guduru, R. et al. Magneto-electric Nanoparticles to Enable Field-controlled High-Specificity Drug Delivery to Eradicate Ovarian Cancer Cells. Sci. Rep. 3, 2953; DOI:10.1038/srep02953 (2013).

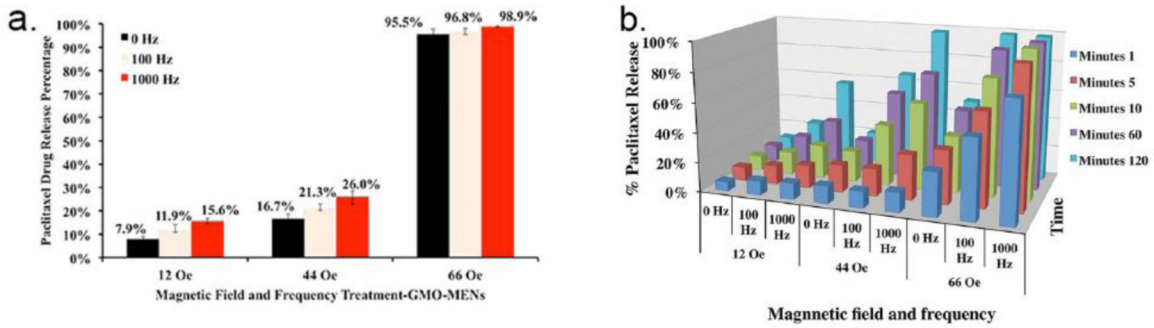

Figure 8.

Photo-absorption measurements of the release kinetics. A) drug release from absorption spectrophotometry experiments after a 1-minute exposure to a magnetic field at three strengths, 12, 44, and 66 Oe, respectively, for three different frequencies, 0, 100, and 1000 Hz, B) Kinetics of the field-strength-frequency dependence of the release for the five values of the field exposure times, 1, 5, 10, 60, and 120 minutes. Adapted from Guduru, R. et al. Magneto-electric Nanoparticles to Enable Field-controlled High-Specificity Drug Delivery to Eradicate Ovarian Cancer Cells. Sci. Rep. 3, 2953; DOI:10.1038/srep02953 (2013)