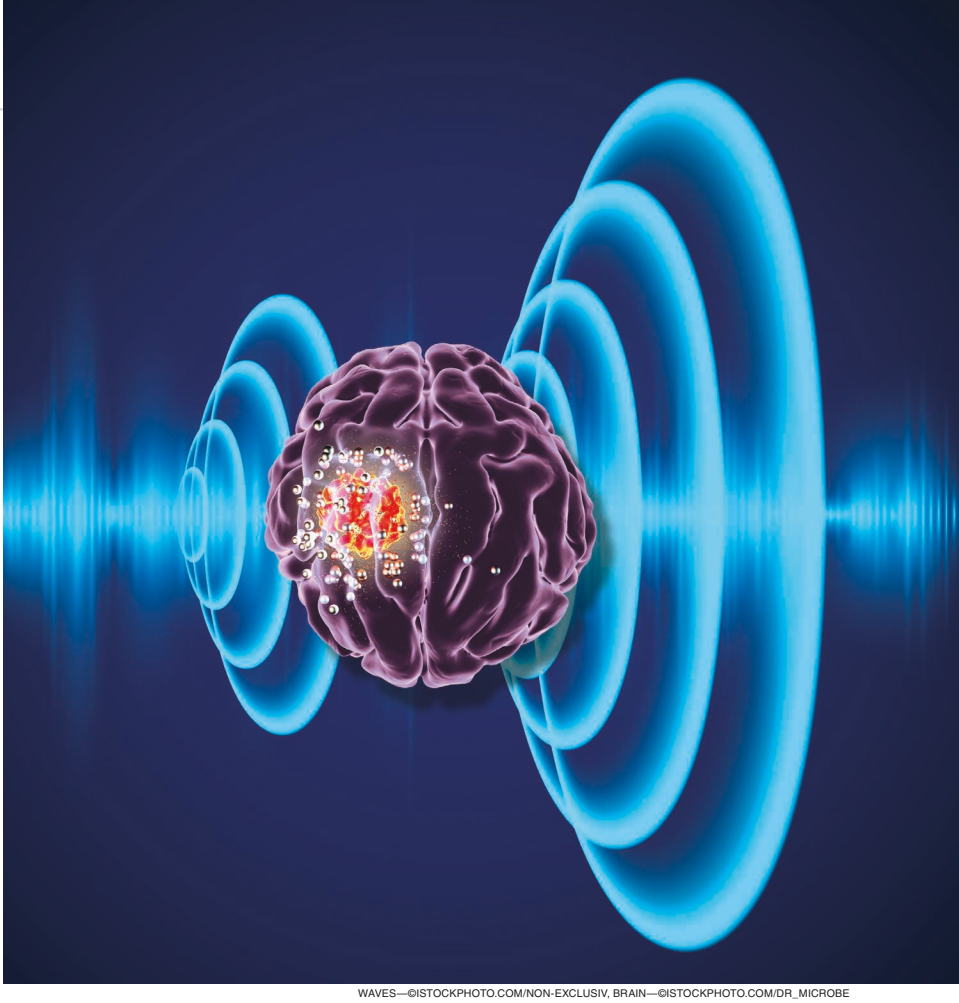

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Engineering Future Medicines With Magnetoelectric Nanoparticles

Wirelessly controlled, targeted therapies.

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NANOMEDICINE, AN EMERGING field at the intersection of medicine and nanotechnology, has the potential to be revolutionary. The human body is an extremely complex engineering system optimized through many years of evolution. It involves trillions of interconnected cells; intrinsic electric fields at the subcellular level play an important role in these interactions and, ultimately, define fundamental physiological mechanisms.

Magnetoelectric nanoparticles (MENPs) allow cells to wirelessly connect at the nanoscale, thereby unlocking unprecedented capabilities. By controlling the intrinsic electric fields that underlie inter- and intracellular interactions, MENPs are instrumental for the development of imaging and therapeutic methods that can eliminate the collateral damage of and significantly increase the efficacy of modern therapies. This article provides an overview of the current development of MENP-based medical research and discusses applications for diagnosing and treating cancer, human immunodeficiency virus (HIV)/acute immunodeficiency syndrome, neurodegenerative conditions, and other diseases.

MULTIMODAL MENPs

Much of the recent progress in medicine has, to a great extent, been driven by nanotechnology. The field at the crossroads of medicine and nanotechnology,

Nanomedicine enables medical treatment at the nanoscale and, thus, addresses diseases at fundamental subcellular and molecular levels.

widely known as *nanomedicine*, is vital to enabling the essential goals of precision and personalized medicine [4], [12], [29]. Nanomedicine enables medical treatment at the nanoscale and, thus, addresses diseases at fundamental subcellular and molecular levels. Traditionally, nanomedicine has rapidly advanced through biotechnology. For example, one of the most popular biotechnology techniques has relied on tagging nanoparticles with biomolecules to target disease-specific biomarkers [27] In conjunction with the rapidly growing areas of bioinformatics and big data, nanomedicine has shown great promise for providing highly specific, targeted treatment, leading to successful therapies with significantly reduced adverse effects.

However, despite this undeniable progress, many open questions remain due to the inadequate understanding of the human body as an engineering system. The physics underlying inter- and intracellular field interactions during physiological processes is barely understood. The ability to wirelessly detect and control these fields at the nanoscale could create possibilities for medical prevention and treatment and shed light on the concept of the human body as an engineering system.

The human body is an extremely sophisticated engineering system designed and optimized by nature through billions of years of evolution. Currently, we do not understand all of the underlying science; however, we can learn a great deal from reverse engineering the naturally designed system and then build on this knowledge. The engineering system of the human body involves trillions of interacting cells. Each cell is an intricate engineering machine, far more complicated than a state-of-the-art CMOS chip. At the system level, the collective behavior of these cells follows nature-designed communications algorithms that are substantially more complex than, for example, those in the modern Internet. Therefore, no ideal medicine will ever be possible until this engineering system of the human body is well understood.

Reciprocally, technology itself, as a discipline, could greatly benefit from this approach. Understanding the human body, particularly the human brain, as an engineering system can pave the way for next-generation technology development. One example is the reemerging concept of neuromorphic computing [18]. To date, no computer technology can compare with the computational power and energy efficiency of the human brain. One can only imagine how useful artificial intelligence (AI) will become when it is powered by neuromorphic computing.

To treat the human body as an engineering system, we need to understand how its basic elements work individually and together. Fundamental molecular-level interactions are governed by electric fields; therefore, the ability to control these electric fields at the nanoscale would allow for the control of the intrinsic molecular mechanisms underlying fundamental biological processes. Consequently, a straightforward engineering task would be to learn how to read and write electrical signals from any one basic element in this system of tens of trillions of cells. However, it is challenging to achieve this goal with electric fields wirelessly, that is, without establishing physical contacts/implants, due to significant interference from the rest of the electrical system.

According to the U.S. Food and Drug Administration (FDA), magnetic fields could be wirelessly controlled without causing any damage to the electrical circuitry of the body as long as the field strength and frequency are smaller than established safe limits. Therefore, to combine the electric field's advantage of intrinsic connection to intracellular processes and the magnetic field's advantage of wireless penetration into the human body, MENPs have been introduced into medical applications.

Because of their ME properties, unlike any other currently known nanoparticles, MENPs allow for wireless sensing and control of electric fields at the nanoscale, anywhere in the human body, via magnetic fields. Furthermore, MENPs enable harvested energy to be carried by other fields as well (e.g., by acoustic/ultrasound and/or electromagnetic waves in a wide frequency range, such as in the near infrared) and, thus, can convert this energy carried by multiple fields into electric fields and vice versa. Due to this ability to combine multiple fields, MENPs present a perfect platform to exploit the merits of some fields to mitigate the limitations of others.

MENPs

What distinguishes MENPs from other nanoparticles, including traditional magnetic nanoparticles, is the presence of the ME effect. As a result, MENPs can couple intrinsic molecular-level electric fields to externally controlled magnetic fields and, thus, allow wireless control of fundamental biological mechanisms at the molecular level. The relationship between the magnetic and electric fields can be described thermodynamically with the Landau theory [17], which states that the second-order free energy cross term, including both electric and magnetic fields, is given as

$$G(E,H) = -\alpha_{ij} E_i H_j, \qquad (1)$$

where $\boldsymbol{E}$ and $\boldsymbol{H}$ are the electric and magnetic fields, respectively, and α_{ij} is the ME coefficient tensor, which in most cases is diagonal. Then,

$$P_i = -dG/dE_i = -\alpha_{ii} H_i \quad \text{and} \qquad (2)$$
$$M_i = -dG/dH_i = \alpha_{ii} E_i, \qquad (3)$$

where $\boldsymbol{P}$ and $\boldsymbol{M}$ are the polarization and magnetization of the nanoparticles, respectively. Therefore, the MENPs' magnetization can be induced via application

of an electric field and vice versa, that is, their electric polarization can be induced via application of a magnetic field. There are different types of ME materials, including 1) single-phase multiferroic crystal structures, in which the magnetoelectricity is due to quantum-mechanical coupling between adjacent sites [Figure 1(a)], and 2) nanocomposite heterostructures, in which the ME effect originates at the interface of lattice-matched piezoelectric and magnetostrictive components [Figure 1(b)] [23].

A popular example of composite MENPs is core–shell structures, such as $CoFe_2O_4$–$BaTiO_3$ nanoparticles made of the magnetostrictive spinel core $CoFe_2O_4$ and the piezoelectric perovskite shell $BaTiO_3$ [2]. The size of these nanostructures can be controlled in a range from fewer than 20 to more than 100 nm through myriad chemical process, such as coprecipitation, thermal decomposition, and others. Their key properties (i.e., the ME coefficient, saturation magnetization, and magnetic anisotropy) can also be controlled in wide ranges through both thermally controlled synthesis and composition. For the latter, it is normal to see the cobalt element in the core structure substituted with another transition metal, such as nickel.

The most important physical parameter for MENPs is the ME coefficient; for the 30-nm $CoFe_2O_4$–$BaTiO_3$ MENPs, a typical ME value would be on the order of 100 $mV{\cdot}cm^{-1}{\cdot}Oe^{-1}$. For these 30-nm nanoparticles, the core diameter is approximately 15 nm. Despite the relatively small size, due to the core's generally high magnetic anisotropy, the nanoparticles still do not fall into the superparamagnetic state at room temperature. It is possible that the ME coupling between the core and the shell can further increase the magnetic anisotropy of the core. These MENPs have been extensively studied for their toxicity and been shown to be safe, at a proper dosage, through in vitro and in vivo experiments [13]. In general, in mouse studies, a dose of MENPs of fewer than approximately 10 μg per 1 g of body mass was shown to be safe. For comparison, visible positive effects with regard to stimulation and drug delivery were achieved at a dose of 1 μg per 1 g of body mass.

> MENPs represent just the first step in using multiferroic nanostructures in medicine.

Ideally, MENPs can be made of many different materials and compositions. In addition, MENPs represent just the first step in using multiferroic nanostructures in medicine. It is possible that nanoparticles with more than two ferroics will be eventually implemented, for example, by combining the ME effect with an optical property to add the advantage of optogenetics to the MENP-based approach [33]. Also, it is very likely that wirelessly controlled biodegradable nanoparticles will be used in the future [26].

MEDICAL APPLICATIONS OF MENPs

Next, we provide a few examples of medical applications of MENPs. According to (2) and (3), MENPs can be used for both writing and reading back local intrinsic electric fields, which, in turn, can be used for advanced medical treatment and diagnostic methods, as detailed in this section.

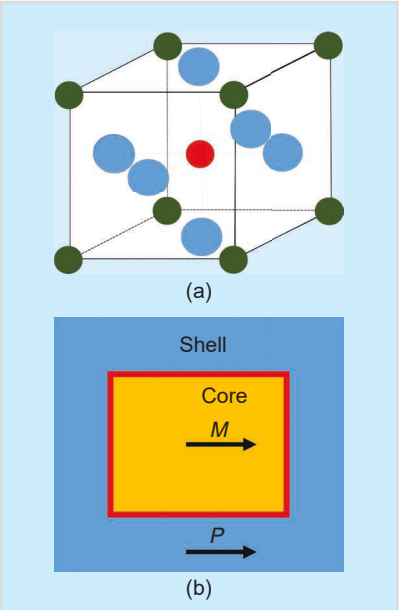

FIGURE 1 (a) A typical oxide perovskite multiferroic single-phase ME crystal structure. The green and red circles indicate A and B sites, respectively, and the blue circles represent oxygen sites. The magnetoelectricity is due to the quantum-mechanical coupling between the perovskite sites. (b) A core–shell MENP configuration made of a magnetostrictive core and a piezoelectric shell. The magnetoelectricity is the result of lattice matching at the interface of the two components.

Especially with the rapid emergence of AI and augmented learning, it is just a matter of time before machines will be able to work in sync with the human brain to revolutionize quality of life and the state of health care. Arguably, to achieve these milestones, we need to create an adequate brain–machine interface (BMI). Most current efforts to create a BMI focus on using a finite number of wired implants. Such an approach is fundamentally limited because the task of establishing wired contacts to all of the 80 billion neurons in the brain would be unachievable. In contrast, owing to the ME effect, MENPs, for the first time, provide the opportunity to create a wireless, noninvasive BMI with single-neuron precision and real-time temporal resolution.

By "writing" information, some kind of temporary or permanent modification of cellular properties is implied. For example, for neurons in the brain, deep-brain stimulation (DBS) of the neural network is a well-established approach to treating patients with Parkinson disease, epilepsy, essential tremor, major depression, and other neurodegenerative disorders by forcefully inducing a certain neural activity through application of an electric potential difference between two electrodes, often surgically implanted [16]. Such induced activation is believed to at least partially repair the brain's neural circuitry [37]. This approach works even when no drug-based therapy is effective, and it is one of the few FDA-approved neurological surgeries based on blinded studies.

According to the traditional DBS approach, wired electrodes are used to apply a periodic train (5–20 Hz) of relatively narrow voltage pulses (approximately

> Metastable physics can be used to deliver MENPs to any point(s) deep in the brain without surgical intervention.

100 μs) with an amplitude above a threshold value (approximately 10 mV) to trigger action potentials. However, despite its many advantages, DBS, in the traditional sense, has a limited spatial resolution (approximately 1 cm) due to the need to establish direct physical contact with neurons. Alternatively, transcranial magnetic stimulation (TMS) is a wireless approach that uses a time-varying magnetic field to induce electric currents in the brain according to the Faraday theory [3]. However, TMS provides an even worse spatial resolution, not to mention relatively high and fast-changing magnetic fields (approximately 1 T); thus, it has therapeutic effects of relatively low efficacy.

MENPs can fill this gap by providing a means to wirelessly stimulate any one neuron or many selected neurons with an adequately high efficacy to enable certain specific functions on demand (Figure 2), which is an approach that was theoretically proposed by Yue et al. [38]. MENP-based wireless stimulation of neurons in mice was discussed by Guduru et al. [9]. According to one implementation, 30-nm MENPs are administrated into the blood stream through an intravenous injection. Then, after MENPs cross the blood–brain barrier (BBB), by application of a magnetic field gradient of greater than 1,000 Oe/cm, MENPs are pulled across the BBB [21].

In the brain, the nanoparticles can be moved into a certain specific location via the concept of metastable physics [22]. According to this idea, the magnetic field is being varied in time so that the MENPs' magnetic moments continuously remain oppositely oriented with respect to the applied magnetic field [19]. In this metastable diamagnetic state, the nanoparticles move toward a magnetic field minimum (not a maximum, as in the traditional, nonmetastable case) when they remain in their stable ferromagnetic state.

There is no mathematical solution for achieving a field maximum anywhere outside the source boundary; minimum points, however, can be easily achieved. Thus, metastable physics can be used to deliver MENPs to any point(s) deep in the brain without surgical intervention. To maintain MENPs in this metastable state, the field variation period should be matched to the characteristic magnetic moment switching time, which, in turn, depends on the magnetic force and the drag force acting on the nanoparticles in the cellular microenvironment or, alternatively, the magnetic force and the spin relaxation force due to the spin-orbit coupling in the nanoparticle.

An option for improving the localization into a specific brain region, characterized by a certain biomarker, is to coat the nanoparticles with the target antibody. Finally, when they are at the target site in the brain, which can be confirmed via an image-guided technique [e.g., magnetic resonance imaging (MRI), magnetic particle imaging (MPI), or an in vivo imaging system (IVIS)], the nanoparticles' electric moments can be varied in time to generate a local ac electric field via application of an ac magnetic field, according to the aforementioned Landau theory described in (2) [5], [6], [24]. To electrically stimulate the region, the induced local electric field across the membrane should be high enough to overcome the membrane potential threshold (approximately 10 mV) and, thus, fire an action potential [1]. Finally, this principle of the MENP-based wireless controlled electric stimulation of selected small regions or even individual cells can be extended to any organ in the body.

According to the principle of reciprocity, MENPs can also be used to read back electric fields due to intrinsic cellular activity. Again, using the example of the brain, neural activity deep in the brain could be read back (recorded) wirelessly with a spatial resolution limited by the nanoparticle size. In this case, according to (3), the local electric field in the vicinity of a nanoparticle leads to a change of the nanoparticle's magnetic moment, which, in turn, can be detected through magnetic imaging. The temporal resolution of MRI is limited to approximately 1 ms by the characteristic relaxation time of the nuclear spin. As

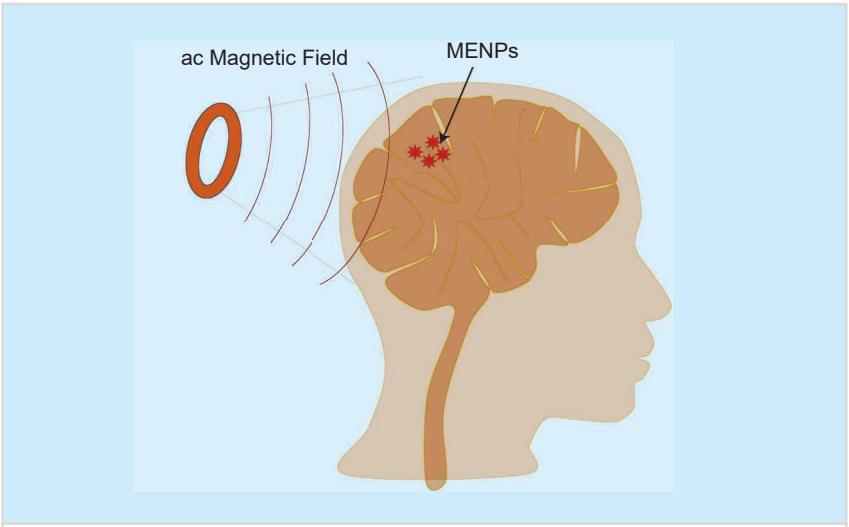

FIGURE 2 The "writing" of information into a selected region deep in the brain wirelessly using localized MENPs. An ac magnetic field is applied to induce local intrinsic electric fields in the vicinity of MENPs sufficiently high to trigger action potentials.

for MPI, its temporal resolution is limited by the ferromagnetic resonance of the nanoparticle's electron spin, which is determined by the magnetic anisotropy energy of the nanostructure and, thus, can be faster than 1 μs [35].

A theoretical study in which MENPs were used to sense electric-field activity in a cellular microenvironment was described in by Guduru et al. [10], who compared MPI conducted with MENPs to MPI conducted with traditional magnetic nanoparticles, such as gadolinium or superparamagnetic iron oxide nanoparticles. These traditional nanoparticles have been widely used as MRI contrast-enhancement agents and, thus, are approved by the FDA. They reflect the material's density and, therefore, mostly enhance the structural information of the imaged region. In contrast, MENPs detect both structural and electric-field information. For example, a process of neuroinflammation, accompanied by a change of the local electric-field profile, could be detected with MENP-based MRI. Furthermore, if coupled with the ultrafast technique of MPI, MENPs could be used to monitor neural activity deep in the brain in real time.

The concept of direct observation of a propagating action potential through an axon in the central nervous system (CNS) or peripheral nervous system (PNS) via detection of the MENPs' magnetization is illustrated in Figure 3. Guduru et al. [10] hypothesized that because the MENP-enhanced MPI provides intrinsic electric-field information at the molecular level, it could reflect the degree of neuroinflammation in specific regions deep in the brain, which could be used as a detectable biomarker for early disease screening and prevention.

Obviously, this principle of operation with MENPs could be used for the imaging and treatment, at the subcellular level, not only of brain-related conditions but also of other diseases. In fact, in general, electric-field profiles in the cellular microenvironment depend on the specific disease and, thus, can be used for its signature identification. For example, Nagesetti et al. [20] used MENPs in combination with the nuclear magnetic resonance (NMR) technique to identify different cancer cells in vitro. They showed that, owing to the ME effect of these nanoparticles, a cellular medium mixed with MENPs provided a signature NMR spectrum specific to the imaged cell line. They argued that the intrinsic electric fields at the cellular membrane of the imaged cells specifically changed the magnetic moments of the nanoparticles, which, in turn, modulated the net magnetic field, resulting in signature NMR spectra.

> The electric field generated by each MENP can be controlled by an externally applied magnetic field.

Using this diagnostic approach, Nagesetti et al. [20] successfully distinguished cancer cells from their normal counterparts as well as distinguish between different cancers. For example, they studied different ovarian and breast cancer cell lines, glioblastomas, and several normal cell lines and compared 30-nm MENPs with traditional magnetic nanoparticles. Given the fundamental nature of sensing the intrinsic electric-field profiles of cells, the MENP-based diagnostic approach could be used for early screening in an in vitro setting for many other diseases, not just cancers.

In general, cancer cells have different membrane potentials compared with their normal counterparts [36]. In most cases, with few exceptions, cancer cells have smaller potential values than normal cells of the same type. This difference in the membrane potential is the basis for the well-known approach of high-specificity targeted delivery known as *electroporation* [25]. This technique allows delivery of certain biomolecules specifically into cancer cells by application of an electric voltage sufficiently high to overcome the membrane potential in the cancer cell but too weak for the normal cells. For example, for ovarian cancer cells, the cancer and normal cell membrane potentials are on the order of –5 and –50 mV, respectively. Because MENPs allow us to tap in into this difference at the subcellular, nanoscale level, they enable us to scale the high-specificity-delivery approach down into the nanoscale. Hence, the term *nanoelectroporation* was introduced by Guduru et al. [7].

Due to the ME effect, the electric field generated by each MENP can be controlled by an externally applied magnetic field. Therefore, there is always a magnetic field at which the nanoparticles

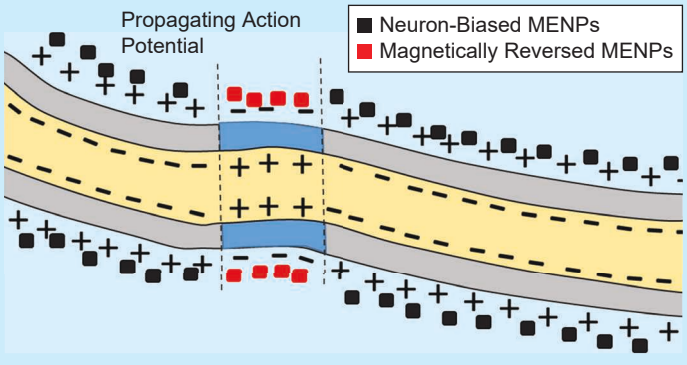

FIGURE 3 The use of MENPs for direct observation of a propagating action potential through axons in the CNS or PNS. As an electric field, due to the action potential, reverses the electric dipole moment of the nanoparticle, its magnetic moment also changes owing to the ME effect; thus, this event can be detected through a magnetic imaging technique, such as MPI.

With MEMPS, a relatively strong chemistry can be used to attach the drug to the nanoparticles during the conjugation process.

will induce an electric field sufficiently high to enter cancer cells while sparing equivalent normal cells in the same region. Through an in vitro study, Guduru et al. [7] showed that drug-loaded MENPs could specifically enter the ovarian cancer cell line SKOV-3 while keeping the normal ovarian cell line HOMEC intact when they applied a magnetic field with a strength as high as 300 Oe in a near-dc frequency range of up to 1,000 Hz. They used the fluorescent version of the popular mitotic inhibitor paclitaxel, Flutax-2, as the drug in their delivery studies.

Similar studies to deliver drugs into CNS cells were conducted by Kaushik et al. [14]. A groundbreaking in vivo study to confirm the high-specificity delivery by MENPs in mice was described by Rodzinski et al. [28]. In that comprehensive study, in which mice were cured after subcutaneously inoculation with ovarian cancer, the researchers proved that only the targeted cancer cells were affected by this treatment. They compared the MENP-based delivery to other approaches, including targeted delivery with traditional magnetic nanoparticles, nanoparticle-based delivery grounded on the enhanced permeability and retention effect, and delivery with antibodies specific to the characteristic protein overexpressed in the cancer cell membranes, human epidermal growth factor receptor 2. Only the MENP-based delivery led to complete cure, and the investigators argued that this was due to the unprecedented high specificity of the MENP-based delivery approach. They confirmed their findings with a detailed tissue-level compositional analysis using the energy-dispersive spectroscopy (EDS) mode of scanning electron microscopy (SEM).

The EDS-SEM approach to studying the biodistribution and clearance of MENPs was described in detail by Hadjikhani et al. [11]. This approach combines 1) an elemental compositional quality comparable to that of the popular mass spectroscopy technique and 2) the high spatial resolution of SEM. Through studying clearance from different organs of nanoparticles ranging in size from 10 to 600 nm, the researchers showed that most nanoparticles were excreted from the system within approximately one month after administration. The optimal size for clearance was found to be between 30 and 100 nm.

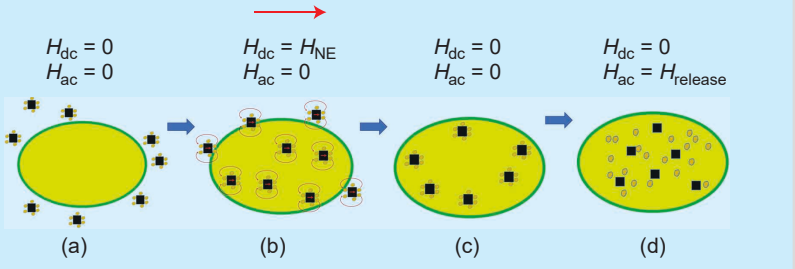

FIGURE 4 The wirelessly controlled separation of functions of high-specificity MENP-based drug delivery into cancer cells and release. (a) When $H_{dc} = 0$ and $H_{ac} = 0$, drug-loaded MENPs cannot cross cell membranes from extracellular space. (b) When $H_{dc} = H_{NE}$ (the nanoelectroporation field) and $H_{ac} = 0$, drug-loaded MENPs enter cells with the membrane potential equal to or smaller than the electric potential generated by the nanoparticles due to the ME effect, as a result of the application of the threshold dc magnetic field required for nanoelectroporation to begin. (c) When $H_{dc} = 0$ and $H_{ac} = 0$, drug-loaded MENPs are inside the selected cells, and the drug is not active. (d) When $H_{dc} = 0$ and $H_{ac} = H_{release}$, the drug is released from the nanoparticles inside the selected cells to regain its bioactivity.

To underscore the significance of the MENPs' ability to enable wireless control of electric fields at the nanoscale, these nanoparticles can be used not only for targeted drug delivery but also for wirelessly controlled release of a drug. The latter is a very important capability in the field of nanomedicine. Often, when nanoparticles are used for drug delivery, especially in the brain, they rely on superficial release mechanisms, such as different pH levels in target sites. As a result, to ensure a successful release, the energy to keep the drug on the nanoparticles' surface has to be kept relatively weak during the preparation of the drug-loaded nanoparticles.

However, because of this, the nanoparticles drop most of the drug into the blood circulation by the time they reach the target site. In contrast, with MENPs, due to the improved remote control of the interaction between the nanoparticles and the drug, a relatively strong chemistry can be used to attach the drug to the nanoparticles during the conjugation process. Then, owing to the ME effect, after the nanoparticles reach the target site, a special signal can be sent to the nanoparticles remotely, via application of an ac magnetic field, to release the drug on demand.

It is critical to release the drug from the nanoparticles for it to be bioactive [34]. Therefore, MENPs allow separation of these two important functions, the drug delivery and the drug release, via application of dc magnetic field gradients and ac magnetic fields, respectively. The physics of the wirelessly controlled release of the drug on demand was first described and demonstrated in an in vitro study by Nair et al. [21]. The idea of the separation of the delivery and release processes is illustrated in Figure 4. The researchers used 30-nm MENPs for wirelessly controlled delivery across the in vitro BBB model and release of the antiretroviral therapy AZTTP to eradicate HIV-1 virus hidden in the brain.

An in vitro study to wirelessly control the release of special antitumor peptides

developed to kill glioblastoma cell lines was described by Stewart et al. [30]. This wirelessly controlled release mechanism was also exploited in the aforementioned in vivo study to cure mice subcutaneously inoculated with ovarian cancer cells [28]. The physics of the high-specificity MENP-based targeted anticancer drug delivery was described Stimphil et al. [31]. They considered the interplay between wirelessly controlled magnetic and electric dipole moments of MENPs and the surface charge due to the dual-layer chemistry of nanoparticles in a cellular microenvironment and the effects of the magnetically controlled nanoparticles' electric fields on cellular membranes.

In conclusion, MENPs provide a way to wirelessly control and detect intrinsic electric fields that underlie the state of a disease at the subcellular level. Because of the unprecedented control of fundamental biological mechanisms, MENPs can serve as a powerful tool to enable superior and highly personalized medical treatment as well as help answer many existing questions about the physics of the human body as a complex engineering system.

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