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Review

PRNANO

Precis. Nanomed. 2022;5(2):897-910

ANDOVER HOUSE

SPION based nanoformulations: bio-inspired design and functionalization strategies for applications in medicine

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Submitted: December 21, 2021 Accepted: May 9, 2022 Published: May 12, 2022

Abstract

Biomedical applications in medicine are an area of research studied in great breadth, covering the various potential applications. Mimicking natural processes promises to be a successful strategy for several reasons. For example, physiological structures can generate drug delivery platforms that are better tolerated by the immune system. Furthermore, physiological movement patterns in flagella or contracting motions, which originate from unicellular organisms, are imitated. Further examples are stimuli-responsive tissue structures that serve the regeneration of bone material by stimulating pre-osteoblasts to proliferate. The examples of bioinspired SPIONs discussed in this review span the fields of drug delivery, imaging/diagnostics, nano/micromotion, and tissue engineering. All these concepts need to be evaluated regarding their technical feasibility and translatability into the clinic. Therefore, this text concludes with a general consideration for clinically proving such developments.

Keywords:

bioinspired, SPION, surface functionalization

Purpose and Rationale:

Attempts to place overview articles in the general area of biomedical applications for magnetic iron oxide nanoparticles have long been hampered by the flood of contributions. However, the focus on bioinspired applications also runs the risk of becoming too excessive, especially if strict attention has not been paid to the appropriate use of the term "bioinspired." Unfortunately, several examples show that a certain vagueness in using the terminology is accepted. Therefore, a conceptual clarification was first formulated based on the selected works in this review.

The origins of the terms bioinspired and biomimetic are challenging to pin down. The neologism "biomimetic" is attributed to Otto Schmidt, who used it to describe the use of artificial electrical stimuli administered to an octopus, thereby mimicking the organism's natural nerve impulse [1]. These terms refer to material properties that are based on natural functionalities. A good and useful definition is provided by Naik R. and Singamaneni S., according to which bioinspiration can be described as a learning process based on natural design principles [2]. Here, there seems to be a gradual but important difference between biomimetic and bioinspired. Biomimetic, composed of the words *bios* (βίος, ancient Greek for life) and *mimesis* (μίμησις, ancient Greek for to copy), thus suggests the mere imitation of natural physiological processes. "Bioinspired" can be interpreted much more broadly since here nature is merely taken as a model and artificial modifications are permissible accordingly. Thus, the area of bioinspiration is naturally larger [1]. In this review, the term is intended to be applied preferably to superparamagnetic iron oxide nanoparticles (SPIONs), and all other particle systems are therefore left unmentioned. Likewise, bioinspired synthesis, applications, or theoretical considerations will be presented. Finally, the work presented here will be limited to the medical field, although it is impossible to avoid addressing disciplines such as biochemistry, molecular biology, and pharmacology.

Another challenge was to find out precisely what the principle referred to as bioinspired consists of. Often this is brought into the context of coating or grafting materials, which

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merely show their origin as a natural material but mechanistically remain artificially technical. In this respect, numerous publications offer, for instance, dopamine grafting or coating as bioinspired because these substances are also found in nature.

Introduction

Drug delivery

The challenge of an effective medication is often a targeted enrichment of the active substance to maximize the effect and, at the same time to spare other body regions as much as possible. This applies most prominently to oncological chemotherapy and other diseases such as arteriosclerosis or localized inflammation. As a result, various SPION-based concepts have been developed, especially for drug delivery [3-5].

One work whose "bioinspired" terminology refers primarily to mussel protein-derived adhesion of the coating to the SPION surface is the development by Saskila et al. [6]. Here, SPIONs are very stably coated with polymers by implementing catechols and then functionalized with bortezomib for drug delivery purposes.

Although it means its slight modification of the title term "SPIONs," a work on magnetic greigite particles originating from magnetotactic bacteria shall be mentioned here [7]. Years ago, more and more occurrences of this mineral were discovered in living organisms [8]. These particles have magnetic properties comparable to nano-particulate magnetite (Fe_3O_4), but, likely, they are structurally less prone to oxidation over the storage time, and therefore their properties are conserved. Nevertheless, these particles also possess disadvantages such as strong hydrophobicity, complicating potential biomedical applications. Feng et al. made this water suspendable via a polyethylene glycol and β-cyclodextrin coating. In addition, the particles were readily imageable on MRI ($r_2 = 94.8$ $mM^{-1}s^{-1}$), and the chemotherapeutic drug doxorubicin could be transported, which could provide an additional therapeutic option.

An interesting approach is developing a nanofluidic system for controlling the transport of ions and molecules [9]. Wang, C., and coworkers drew inspiration for this from the operation of cellular ion channels. This is achieved by the controlled deformation of ferrofluids located on superhydrophilic nanochannels, allowing the transport of substances in these channels.

However, most papers in which bioinspired drug delivery concepts have been developed are based on particulate nanoscale vehicles. One example is superparamagnetic hybrid nanobeads derived from a bioinspired mineralization process consisting of iron-doped apatite heterogenically crystallized from an alginate matrix [10]. As a result, these particles exhibit biomimetic composition and adequate swelling properties in a physiological-like environment and superparamagnetic properties suitable for bioresorbable drug delivery systems with magnetic properties. To make drug transport more effective by imitating proven biological structures is the claim of Zhao et al. with their idea to use the morphology of viruses [11]. Here, Fe_3O_4/Au@C particles are hydrothermally synthesized to form spiky nanoparticles that have a similar appearance to coronaviruses. Subsequently, an additional coating with PEG-doxorubicin enables drug transport, characterized by a significantly higher cell internalization, whereas the spherical control particles were less well absorbed. The targeted use of immunocompetent cells for the purpose of a better immune response against tumors is being pursued by Boosz et al. [12]. For this purpose, T cells are labeled with the help of citrate-coated SPIONs and thus made magnetically controllable. In this way, tumors that are deficient in lymphocytes are made immunologically susceptible again in the first place. In this work, SPIONs are successfully bound to the plasma membrane of the cells or taken up intracellularly, and the cell hybrids are then magnetically enriched while retaining their function. A therapy concept using tumor-specific structures can be even more targeted if homologous tumor cell membrane components are used to recruit the specific immune defense, as shown by the approach of tumor self-targeting [13].

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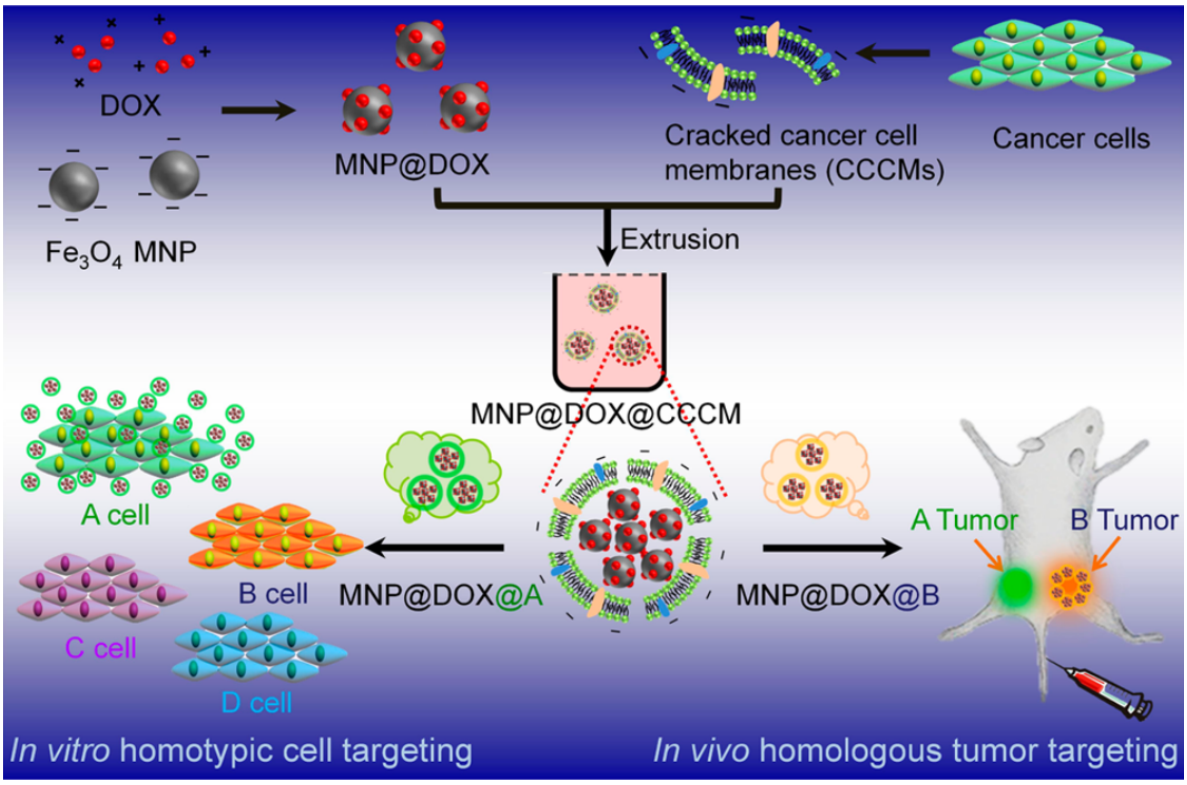

Figure 1: https://doi.org/10.1021/acs.nanolett.6b02786: Preparation of cancer cell membrane-cloaked magnetic nanoparticles and illustration of preferential cancer cell self-recognition and tumor self-targeting.

Here, tumor cell membranes are fragmented and used as structural components of liposomal doxorubicin-containing encapsulation of magnetic nanoparticles. The result is an effective concerted action by massive particle internalization and simultaneous invasion of immunocompetent cells into the tumor area. Another attribute of this system is the visibility in MRI, which makes precise therapy control possible.

An exactly opposite system of designing the nature of the drug carrier so that they are not recognized by the body's own defense mechanisms is also used. Camouflage using endogenous structures is a very successful strategy in this respect. For example, the stealth magneto nano micelles developed by Zhang et al. have long circulation behavior in the blood due to self-peptide decoration of paclitaxel-carrying poly(lactide-glycolide)–poly(ethylene glycol) (PLGA–PEG) encapsulated iron oxide nanoparticles. The self-peptide interacts with SIRPα-receptor, expressed on phagocytes [14]. As a result, the nano vehicles are not recognized by the phagocytes, which avoids premature MPS-mediated immune clearance.

In a special approach to visualize arteriosclerotic lesions, magnetic nanoclusters are coated with leukocyte membrane components and thus transmigrate into intimal foam cells [15]. In this way, initial lesions are visualized by appropriately applied MRI. Furthermore, as shown in Wu et al., simultaneously transported simvastatin and ligated apolipoprotein A-I mimetic 4F peptides can exert a therapeutic benefit.

Imaging/Diagnostics

Therapy and diagnostics are the most important areas in the medical field. Therefore, in addition to drug delivery concepts, various systems are also being developed that are dedicated to diagnostics. Often both concepts, i.e., therapy and diagnostics, are implemented simultaneously, as shown at the end of the last chapter with the work of Wu et al. [15]. The image capability for the MRI described here as a secondary aspect of the therapeutic approach plays a primary role in other works. Because MR imaging of SPIONs is based on their intrinsic properties, the surface can be more or less freely designed to incorporate additional attributes such as functional imaging.

An example of this is provided by the work of Li et al., which aims to illuminate specially designed particles ultra-small metastases [16]. This is accomplished by functionalizing SPIONs with the tumor-specific ligand CREKA.

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This peptide binds to fibronectin, a hallmark of epithelial to mesenchymal transition in the extracellular matrix of high-risk breast cancer and its metastasis. Inspired by the natural principle of "immunosurveillance," a metastasis chemotactic nanoprobe was developed in this work, which after specific binding to the metastases causes a specific release of large amounts of Mn^{2+} ions. This area of increased magnesium ion concentration can be visualized very well in t1 weighted MR imaging

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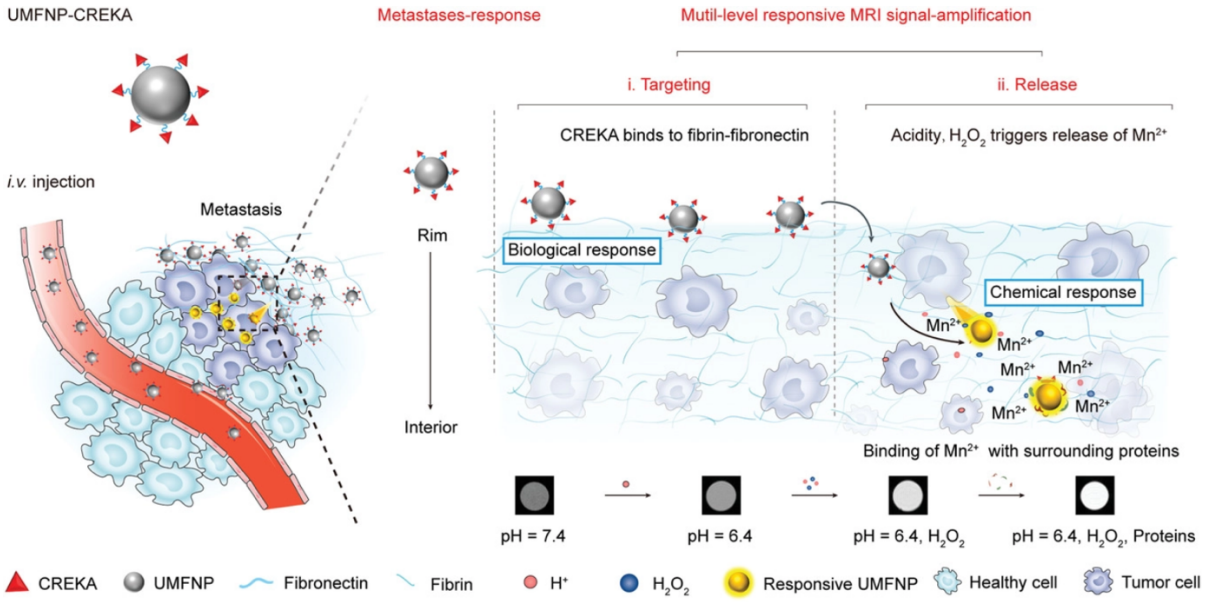

Figure 2: https://doi.org/10.1002/adma.201906799: In response to the biological parameters in the metastasis microenvironment, the UMFNP-CREKA nanoprobe is recruited to the periphery of the metastasis via CREKA binding to the abundant fibrin-fibronectin complexes present. Subsequently, the UMFNPs respond to the chemical parameters of the unique pathological environment of metastases and release Mn^{2+} that rapidly permeates to the cancerous tissues in response to the chemoattractant (mild acidity and elevatedH_2O_2). Subsequently, the T_1-weighted MR signal in the metastasis is further enhanced when Mn^{2+} ions interact with surrounding proteins.

It is well known that SPIONs are suitable as T2 contrast agents in MRI, and for a long time, there were correspondingly widely available products under the name Resovist® or the frequently used off-label Rienso®. Both were SPIONs coated with dextran derivatives suitable for MR imaging. Currently, mainly gadolinium-containing contrast agents are used, but they are based on the principle of T1 relaxivity. Early efforts were made to lower the inherently high signal threshold of paramagnetic contrast agents to improve imaging properties accordingly. The development of Gd^{3+} contrast agents is always confronted with the trade-off of good relaxivity with high complex binding constants. Thus, the molecular architecture of a good approach of water molecules to the central ion as opposed to a complex as stable as possible for low toxicity of gadolinium. In the work of Allen et al., Gd^{3+} are packed as tightly as possible inside a viral envelope [17]. The protein cage of cowpea chlorotic mottle virus offers promise in this regard, as it contains 180 metal-binding sites. The rationale behind using viral envelopes is that they can be easily modified both chemically and genetically and can thus be biotechnologically produced rapidly in large quantities. The result was Gd^{3+} carriers with a T1 relaxivity of 202 mM-1 s-1, which is incomparably higher than, for example, in gadolinium-containing albumin adducts. [18].

Frequently, different diagnostic techniques are combined, and multifunctional SPIONs are used to detect a comprehensive pattern of possible disease patterns. In connection with the MRI capabilities in the T1 weighting, the work of Zhang et al. can be mentioned here as an example, which combines photoacoustic imaging with MRI [19].

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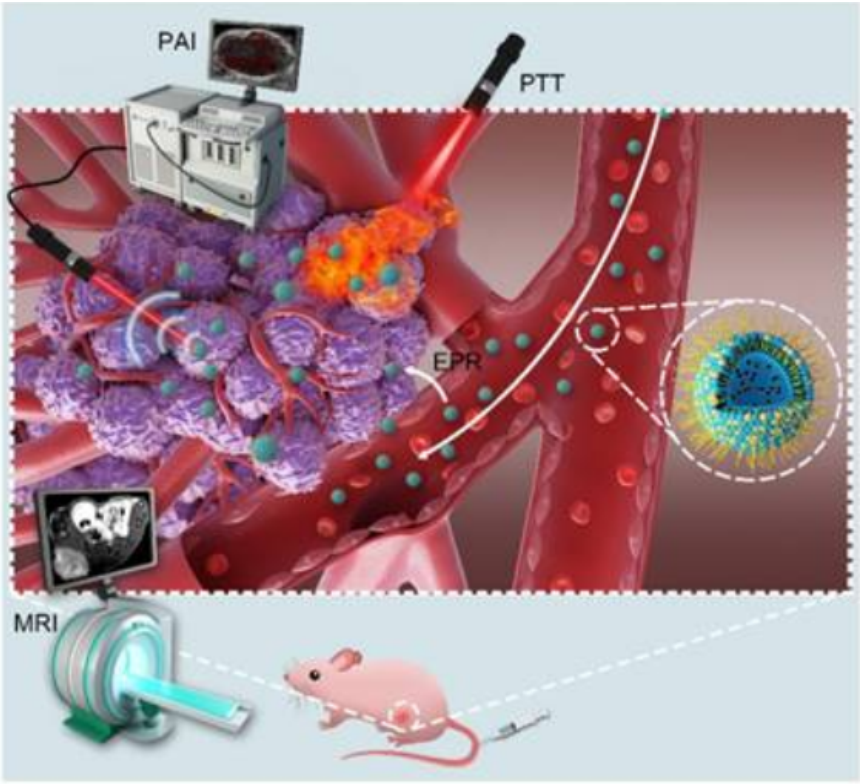

Figure 3: htpps://doi.org/10.7150/thno.22430: Schematic illustration of the theranostic functions of as-synthesized Lip-Mel, including their passive accumulation into the tumor tissue via the typical EPR effect followed by PA/MR imaging-guided PTT ablation of the tumor.

For this approach, melanin-based nanoliposomes are synthesized. Melanin is a pigment that occurs in almost all living organisms and in humans is responsible for the brown coloration of the skin and hair color and serves as a natural protective filter for harmful ultraviolet radiation. The molecule is characterized indole-containing copolymer and offers special photochemical properties such as a broad absorption spectrum due to the high degree of conjugation of the molecule. The darkness of the pigment is because a large part of the visible spectrum is absorbed. The lowest energy quantum transitions are transitions from nonbonding to antibonding π-orbitals (n-4), which occur predominantly in carbonyl bonds (*C*=O), which exist in most melanins [20]. This makes the substance per se interesting for optical diagnostic methods [21]. The melanin-based nanoliposomes of Zhang et al. offer, in addition to the diagnosis of tumors, the further ability to thermally destroy tumor cells by photothermal conversion after infrared laser application.

Photoacoustic imaging is also the focus of the work of Nima et al. and their development of nanoparticles derived from magnetotactic bacteria [22]. These nanoparticles of natural origin are used for concerted, highly sensitive single-cell analysis using photoacoustics and single-cell therapy using photomechanics. The SPIONs in this work are combined with gold nanorods for the correspondingly high quantum yield required and functionalized with folic acid for specific tumor cell detection. These hybrids show adsorption capability in the spectral range around 530 nm and 700-900 nm and associated transverse and longitudinal plasmonic resonance, respectively. The photoacoustic contrast is also sufficient for molecular diagnosis and targeted therapy of single cancer cells.

The work described in this section uses costly scanners as imaging technology, which are not available in many medical facilities, especially in underdeveloped countries. The developers are well aware of this, and so there are also different approaches to detect diseases via a simple point of care diagnostic. This also plays a role where quick decisions are necessary. A prime example in this context is infection diagnostics, as described in the concept of Kanitthamniyom [23]. There, magnetic digital microfluid platforms are used. Analyte droplets can be controlled on superhydrophobic surfaces

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and placed on areas functionalized with bioinspired polydopamine surfaces. Various process steps such as particle extraction, liquid dispensing, liquid shaping, and cross-platform transfer are possible in a very small space on this platform. The hepatitis B virus surface antigen is used here as a diagnostic proof of principle. Its presence in the test fluid is determined by using complementary binding capture antibody-conjugated dynabeads and the horseradish peroxidase-labeled detector antibody.

Nano/micromotion

The visualized concepts of actuator motion patterns in gels and other hybrid materials, equipped with magnetic particles and performing various motion sequences, are impressive. Complex motion sequences such as flagellar movements for the propulsion of micro- or nanoscale objects have also become established. Thus, nano or micromotors have great potential in various fields of nanotechnology and especially in bionanotechnology. There are multiple approaches to the conception of these motors. Systems have been developed whose biomimetic approaches are based on the movement of bacteria, the structure of water-bearing vessels in plants, or the organization of swarms.

In Yu at. al. [24], the flagellar movement of E. coli is to be transferred for locomotion using a microfluidic-spin helical microfiber template. The vehicle consists of a SPION-doped polymer matrix composed of alginate/poly (ethylene glycol diacrylate/methacrylate gelatin. On this base, the micromotors' morphologies can easily be tailored because of the highly controllable and reliable fabrication process. Furthermore, materials based on this principle could be used as cell carriers suitable for cell seeding and further cultivation, with magnetic nanoparticles providing the kinetic properties of the material.

Similarly, Peters et al. are trying to combine superparamagnetic nanoparticles and a poly (ethylene glycol)-based matrix to produce a helical microrobot platform inspired by *E. coli* [25]. The locomotion is based on a corkscrew movement. Special attention was paid to the cytotoxicity of the degradation products.

To mimic specific structures and functionalities of living organisms was the aim of developing soft microrobots. The challenge was to create a precisely controllable and directly responsive vehicle. The approach from the study [26] uses soft robots produced by magnetotactic bacteria with SPIONs (embedded inside non-swelling microgels) to treat microvascular thrombosis. This was achieved by the cargo of tissue plasminogen activator (tPA), which could be precisely navigated to the blood clot. The microrobots were propelled by the flagellar motion of E. coli. The helical micromotors are used as dynamic cell microcarriers.

Another interesting bioinspired approach has the spiral water-bearing structure of various aquatic plants as a model[27]. The microswimmer comprises fragments of xylem fibers that are coated by a thin layer of magnetic material. The precise control of the propulsion of a plant-based microswimmer is achieved using three orthogonal Helmholtz coil pairs that create a uniform rotating magnetic field. In this approach, low-cost and mass-producible magnetic microswimmers can be produced that can reach speeds of 250 μm/s as well as powerful locomotion in biological media such as human serum.

Helices are widely present in from microscopic and DNA, bacterial flagella, and viral capsids to macroscopic seed pods and plant vasculatures are well-known examples. Artificial structural analogs seem to be very suitable nano or micro-scale tools. Many works address this development. The principle is a multi-compartment architecture to achieve remote control of the objects by external influences like magnetic fields. In the work of Yu et al., helical microfibers are created whose magnetic properties are obtained by implementing N-isopropylacrylamide (NIPAM) coated SPIONs [28]. A coaxial capillary microfluidic system with consecutive spinning and spiraling functions for the scalable generation of helical microfibers was presented. These microfibers could be stretched by a magnet, showing a noticeable increase in their helical pitch. However, they shrank and recovered their original pitches when the magnet was moved away. Various applications, for instance, force indicators, are possible. This would have applicability for a force indication in cardiomyocyte contraction.

Ahmed et al. developed self-assembled micro-floats through acoustic and magnetic fields[29]. This could achieve upstream movement as occurs in bacteria, sperm, and plankton that take advantage of the non-slip boundary

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conditions of the wall to exhibit upstream propulsion. Based on this, they designed self-assembled microswarms that can execute upstream motility and, therefore, consider cooperative qualities of the single objects that afford more sophisticated steering devices. Nevertheless, this opens possibilities for targeted therapies and non-invasive surgery.

Nano-swarms, as strikingly futuristic as they appear, are tangible developments in nanomedicine. A particular challenge is to control the mutual interactions of the individual objects while at the same time maintaining the cooperative direction of preference. Heterogeneous colloidal systems based on natural swarm intelligence were used by Jin et al.[30]

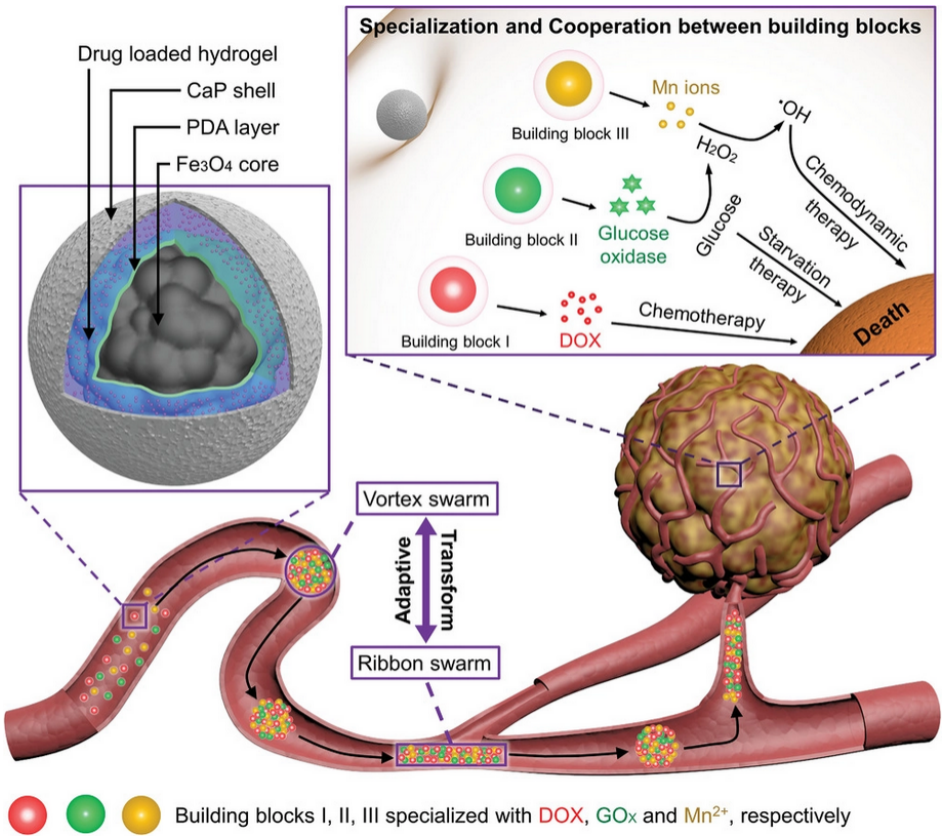

Figure 4: https://doi.org/10.1002/adma.202100070: The swarm is composed of millions of nanosized intelligent building blocks. Each building block consists of a Fe_3O_4 core, a middle layer of the smart hydrogel as a drug reservoir, and a pH-responsive CaP shell for on-demand drug release. A team of building blocks is synchronously navigated to the target position with adaptive morphology to different environments by alternating the programmed magnetic fields. Different subgroups of building blocks are separately functionalized with DOX, GO_X, and Mn^{2+} and then perform cooperation upon the internalization by cancer cells. At this time, chemotherapy is achieved by the released DOX, while the GO_X-mediated reaction consumes the glucose to starve cancer cells and produces abundant H_2O_2 to be converted to highly toxic ·OH via an Mn^{2+}-mediated Fenton-like reaction, thus achieving a domino reaction enabled combination therapy.

Adaptive and heterogeneous colloidal magnetic micro-swarms achieve cooperative functions encoded by domino reactions. Through programming and external magnetic fields, the system self-organizes into two swarm states, vortex and ribbon microswarms, which can switch between each other reversibly within seconds. From a clinical perspective, this could interrupt cancer cells' growth pathways.

Tissue engineering

The incorporation of magnetic nano- or microparticles into novel bioinspired materials has led to new developments in tissue engineering. The focus thereby is to remotely activate or control the materials by using magnetic fields or the potential magnetic conductivity. Using a bio-inspired mineralization process, Patricio et al. [31] synthesized bone-like microspheres with magnetic properties. This magnetic material obtained by heterogeneous nucleation of Fe2+/Fe3+-doped hydroxyapatite nanocrystals can be magnetically controlled and used in medical applications for bone tissue regeneration using a hydrothermal treatment for the

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crosslinking of the matrix. Lin et al. presented magnetoactive elastomers that can be used as the magnetoactive drivers applied in soft robotic applications that can be used in heart implants [32]. They achieved synchronous pumping using soft magnetic iron microparticles with radial chains that can be formed in one piece, achieve 3-D deformation and cooperate between multiple micro elastic elastomers under single homogeneous stimuli. Synchronous pumping behavior of the heart and muscle expansion under applied homogeneous magnetic fields were demonstrated, achieving a flow rate and total pumping volume of 200.1 and 52.3 mL/min, respectively, under a harmonic magnetic field of 120 BPM with an amplitude of 0-300 mT.

In the field of tissue engineering of cartilage, Brady et al. presented a method to produce a three-layer nanocomposite hydrogel (ferrogel) that could react to external stimuli [33]. Bovine chondrocytes were seeded into the ferrogels and cultured for up to 14 days with good cell viability. They used a variable number of magnetic nanoparticles as carriers for growth factors. This way, it was possible to achieve a zonal differentiation of mesenchymal stem cells. Furthermore, applying time-varying magnetic fields made it possible to apply dynamic loading to increase cartilage formation.

Another arising field of interest is synthetic conductive materials line the biopolymers like the injectable hybrid networks presented by Xu et al. These networks were based on polysaccharide-based conductive hydrogel crosslinked through noncovalent, reversible covalent reactions [34]. This material exhibits rheological properties associated with dynamic networks such as self-healing and stress relaxation. The heparin-containing electroconductive adhesive showed high biocompatibility in immunocompetent mice showing high potential for the fields of cardiovascular diseases and wound dressing.

Pöttler et al. pursue a very straightforward approach by marking vocal folds with magnetic particles to construct a tissue substitute for damaged or destroyed vocal folds. In this way, scaffolds can be dispensed with, which allows great freedom in the design of the engineered tissue material [35].

Finally, it is worth mentioning the bone tissue repair strategy using magneto-responsive nanocomposites by Fernandes et al. Here, those scaffolds obtained through the development of nanocomposites comprised of a piezoelectric polymer poly(vinylidene fluoride) (PVDF) and magnetostrictive particles of $CoFe_2O_4$. These scaffolds respond to magnetic stimuli due to the mechanical deformation of magnetostrictive particles, and it was found that pre-osteoblasts proliferate under these conditions.

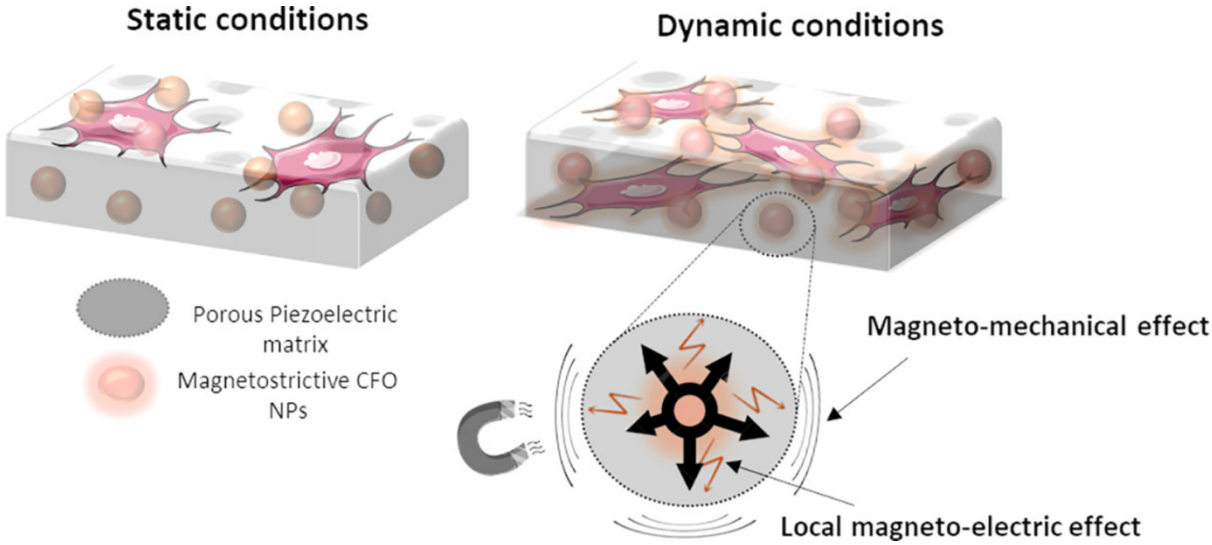

Figure 5: https://doi.org/10.1021/acsami.9b14001. Magnetomechanical and Local Magnetoelectrical Properties of 3D Scaffolds upon the Application of Magnetic Stimuli.

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Clinical Translational considerations

Clinical applications of SPIONs which passed clinical applications are still scarce. Up to now, no magnetic drug delivery agent has reached the clinics. The rare formulations consider the fields of MRI, magnetic hyperthermia, and treatment of iron deficiency treatment [36]. The clinical translation of successful developments in SPIONs for various applications is and remains the most important prerequisite, which has already been discussed intensively in the past [37]. First of all, there are difficulties that all drug developments, including classical ones, have to face during the approval process. In addition, there are specific requirements for nanoparticles that are to be applied intravascularly. These are among others:

- Comprehensive characterization of the physical properties of the nanoscale material.
- Investigation of the general safety of the application, including toxicological studies
- Unraveling specific toxicity with the aspects of immunological toxicity, genotoxicity carcinogenicity, and neurotoxicity
- Studies on the mode of application, biodistribution, metabolism, and excretion, especially nanoscale material.

Recently, J. Metselaar and T. Lammers defined the most important five challenges to overcome for successful clinical translation [38]. These are, therefore, commercial, and practical feasibility. This means that both the improved therapeutic potential for the patient and the size of the patient population that would benefit are essential. The clearer these advantages are, the easier it will be to enter the market later. The next aspect concerns the feasibility of clinical development. New drugs advertised as safer and more effective have to prove their qualities in long-lasting and thus capital-intensive clinical trials. Here, a careful study design with meaningful endpoints and control plays a vital role in adequately reflecting the improved benefit for patients afterward. The next challenge concerns the translation of preclinical efficacy into clinical outcomes. Here, the specific difficulty of nanomedicine is that predictions of therapeutic efficacy and response rate are more challenging to make, especially when dealing with molecular targeting, which by its very nature can have idiosyncratic responses. Bridging the gap between preclinical toxicology and real-world patient safety is another important criterion for a successful new drug. The uncertainty lies in the fact that the pharmacology of the transported active ingredient can change fundamentally compared to classical drug formulations. In addition, there are often excipients from the nanoparticle synthesis. There is sometimes insufficient experience from a pharmaceutical point of view. Finally, there are unpredictable immunological reactions that are difficult to predict for the entire nanoformulation. The last challenge to clinical translation is the production of the new nano-drug as well as quality assurance management. Here, both classical product qualities and nanomaterial-specific parameters such as particle size, surface morphology, active ingredient loading, and release behavior must be closely controlled since the product quality to be guaranteed depends significantly on this. Therefore, the manufacturing process must be reliable and scalable to meet production requirements according to good manufacturing practice guidelines. The possible fulfillment of these conditions must consequently take place as early as possible to not be confronted with insurmountable difficulties later on [39].

In the meantime, due to the Sars-CoV2 pandemic, it became possible to find various shortcuts in the approval process, without which it would not have been possible to supply the world with vaccines in such a timely manner. In their commentary, S. Friedrich and D. Bowmann express confidence that nanotechnology has now found an established approach in the approval process of new drugs [40]. Feeding this hope is the development, approval, and manufacture of numerous vaccines at an unprecedented pace, representing unprecedented hand-in-hand collaboration in the “triple helix of government-industry-university interaction” that we hope will become so established.

Discussion

SPIONs associated with the terminology bio-inspired can be found in a wide variety of application areas, and the examples presented here represent only a section of the whole. In

Table 1, the original papers described are listed and divided into two groups. In the first

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group, the term bio-inspired refers to the material's design or composition, while in the second group, the term is associated with the intended mechanism of action. Furthermore, a brief assessment was made of how the concepts could be implemented in a clinical application environment. Working with a "bio-inspired" design could be somewhat easier to implement due to the lower synthesis complexity and a simpler application scenario. Many concepts whose mechanism is "bio-inspired" are still far from practice.

Table 1: Overview of bio-inspired studies in this review

Ref.	Approach	Assessment
	Bioinspired design/composition	
[6]	Mussel-inspired adhesion of polymers on particles surfaces of SPIONs	Translation ability: moderate Approvability: high Application expenses: moderate
[7]	Drug targeting using hydrophilic modified greigite crystals.	Translation ability: high Approvability: high Application expenses: moderate
[10]	Iron-substituted hydroxyapatite nanophase by bioinspired mineralizing a self-assembling alginate matrix for drug delivery	Translation ability: moderate Approvability: moderate Application expenses: moderate
[11]	A virus-like Fe_3O_4/Au@C nanovector as a programmable drug delivery vehicle	Translation ability: low Approvability: low Application expenses: moderate
[17]	Polymer coating derived from virus protein of cowpea chlorotic mottle virus.	Translation ability: moderate Approvability: moderate Application expenses: moderate
[19]	Melanin-based nanoliposomes as theranostic agents for simultaneous photoacoustic- and T1-weighted MR imaging-guided photothermal ablation of tumors	Translation ability: low Approvability: low Application expenses: high
[23]	Magnetic digital microfluid platform using polydopamine adhesion inspired mussels for point-of-care diagnostics	Translation ability: high Approvability: high Application expenses: moderate
[31]	Heterogeneous nucleation of Fe2+/Fe3+-doped hydroxyapatite nanocrystals for bone-like microspheres	Translation ability: moderate Approvability: high Application expenses: moderate
[33]	Trilayered nanocomposite hydrogel (ferrogel) with a gradient in compressive modulus for cartilage tissue engineering	Translation ability: moderate Approvability: moderate Application expenses: moderate
	Bioinspired strategy	
[9]	Artificial cellular ion channels nanofluidic transportation channels.	Translation ability: low Approvability: low Application expenses: high
[12]	Magnetically labeled T-cells for targeted immune tumor therapy	Translation ability: high Approvability: high Application expenses: moderate

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[13]	Nanoparticles coated with the source cancer cell membrane for tumor self-recognition	Translation ability: low Approvability: low Application expenses: high
[14]	Drug loaded stealth magneto-nanomicelle antiphagocytic delivery system modified with self-peptides for the receptor SIRPα	Translation ability: low Approvability: low Application expenses: high
[15]	A nanovehicle with leukocyte camouflage acquiring inherently targeting and transmigrating capabilities	Translation ability: low Approvability: low Application expenses: high
[16]	Nanoprobe with tumor-specific ligand CREKA.	Translation ability: moderate Approvability: low Application expenses: moderate
[24]	*E.Coli* inspired propelling of microcarrier	Translation ability: low Approvability: low Application expenses: moderate
[25]	SPIONs embedded in a biodegradable polymer helical microrobot locomotion based on corkscrew propulsion enable drug delivery	Translation ability: low Approvability: low Application expenses: moderate
[26]	Locomotion using soft robots inspired by magnetotactic bacteria	Translation ability: low Approvability: low Application expenses: moderate
[27]	Bioinspired helical Microswimmers Based on Vascular Plants	Translation ability: low Approvability: low Application expenses: moderate
[28]	Helical microfibers consisting of N-isopropylacrylamide (NIPAM) coated SPIONs	Translation ability: low Approvability: low Application expenses: moderate
[29]	Self-assembled micro-floats acousto-magnetic microswarm Robots with Upstream Motility	Translation ability: low Approvability: low Application expenses: moderate
[30]	Colloidal magnetic microswarm with domino reaction encoded cooperative functions	Translation ability: low Approvability: low Application expenses: moderate
[32]	Magnetoactive elastomers that can for magnetoactive driver applied in the soft robotic applications	Translation ability: low Approvability: low Application expenses: high
[34]	Cytocompatible, Injectable, and electroconductive Soft Adhesives polysaccharide-based conductive hydrogel	Translation ability: moderate Approvability: low Application expenses: moderate
[35]	Magnetic Tissue Engineering of the Vocal Fold Using Superparamagnetic Iron Oxide Nanoparticles	Translation ability: low Approvability: moderate Application expenses: moderate

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Conclusion

In the field of bioinspired SPIONs for medical applications, a trend increasingly relies on multimodal concepts, mirroring the development of all conventional SPIONs systems in this field. Here, as in many other areas of nanomedicine, it has become confusing to maintain a complete overview of what is currently happening. Many examples in this review are decidedly futuristic and extraordinarily intriguing. In this context, however, it remains to be seen to what extent the gap between sophisticated basic research and actual clinical application potential will continue to widen here, as the complexities of regulatory approval processes continue to increase, and such multi-step syntheses and complex modes of action further complicate realistic clinical translation. Other concepts not mentioned in the subheadings may represent more tangible developments. Here, surfaces are coated according to the pattern of plant defense strategies to avoid bacterial colonization [41]. This is very easy to realize as a possibility for inerting medical products. Selective enrichment concepts based on proven broad-spectrum pattern recognition motifs of the mucosa, which serve as host defense against pathological invaders in the organism, can contribute to selective, highly efficient sample preparation in medical diagnostics [42]. It is exciting to follow the diverse concepts in bioinspired SPIONs, which are finally medically successful.

Acknowledgment

The authors thank the Manfred Roth-Stiftung, Fürth and the Forschungsstiftung Medizin am Universitätsklinikum Erlangen (Germany) for their support.

Conflict of interest

The authors declare no conflict of interest in the work done.

Refer to this article as Tietze R and Alexiou C, SPION based nanoformulations: bio-inspired design and functionalization strategies for applications in medicine Precis. Nanomed. 2022;5(2):897-910, https://doi.org/10.33218/001c.35650

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