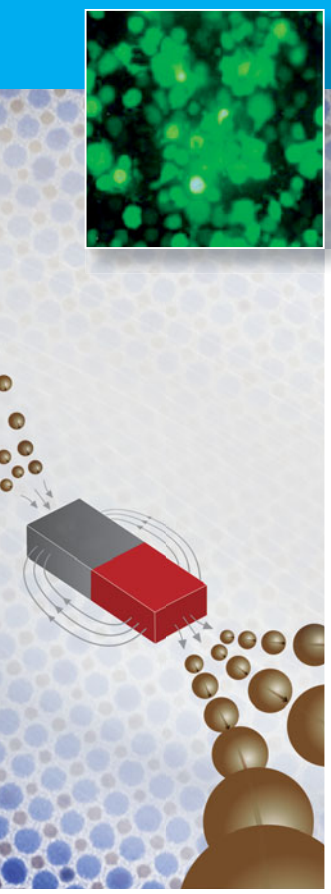


Biomedical applications of mesoscale magnetic particles

Bettina Kozissnik and Jon Dobson

Mesoscale (nanometers to microns) magnetic particles are becoming increasingly important in biomedical applications both *in vitro* for cell and tissue-based research and *in vivo* for clinical imaging and therapy. These applications generally rely on the fact that, while the body is relatively transparent to magnetic fields, magnetic particles within the body, or in *ex vivo* biological samples, will couple strongly to applied external fields. By synthesizing biofunctionalized, biocompatible polymer/magnetic particle composites, this remote coupling provides a mechanism for the precisely targeted actuation of cell signaling pathways, delivery of genes, targeted transmission of thermal energy, generation of tissue matrix, and imaging (via magnetic resonance imaging), among others. This article explores a variety of biomedical applications of mesoscale magnetic particles, some of which are routinely used in the clinic and in biomedical laboratories, with others approaching the realm of science fiction.

Introduction

The use of magnetic micro- and nanoparticles in biological and biomedical applications goes back nearly 100 years. In the early 20th century, Heilbronn and Seifritz used magnetic forces on iron and nickel microparticles embedded within slime molds and cellular cytoplasm to probe their rheological properties.[1,2] More than 60 years ago, Nobel Laureate Francis Crick, along with Arthur Hughes, expanded on these studies using well-characterized iron oxide microparticles.[3] In the decades since, the use of magnetic micro- and nanoparticles in biomedical applications has undergone rapid growth, with exponential growth in both publications and citations in this field since the early 2000s. Research in this area is growing at a remarkable pace. Novel applications that exploit the most fundamental principle of magnetism and magnetic particles—action at a distance—are being developed that have the potential to revolutionize fields as diverse as cancer therapy, gene therapy, developmental biology, and tissue engineering.

Most magnetic particles used in biomedical applications are superparamagnetic iron oxides, particularly for *in vivo* applications. Iron oxide is well tolerated by living organisms; in fact, virtually all living organisms, including humans, store iron in the form of iron oxide. However, aggregations of magnetic particles circulating within the bloodstream of a human or animal can have catastrophic consequences, as the clusters can block the flow of blood. By coating superparamagnetic iron oxides with biocompatible polymers such as dextran or polyethyleneglycol or synthesizing multiple superparamagnetic crystallites within a polymer matrix, it is possible to prevent particle aggregation (and the associated potential for embolism formation when the particles are introduced intravenously) as well as attenuate any immune response, facilitating longer circulation times. Here we explore both established and emerging biomedical applications of mesoscale magnetic particles.

Magnetic cell separation

One of the most widely used applications for mesoscale magnetic particles is magnetic cell separation to isolate a specific cell population from a heterogeneous sample. Cells are labeled with antibody-conjugated magnetic particles targeted to specific proteins or peptides (antigens) displayed on the surface of the desired cell population. Magnetically labeled cells can then be separated from the rest of the (non-labeled) cell population using a high gradient magnetic separator (**Figure 1**).

In 1990, Miltenyi et al.[4] introduced a magnetic cell separation system that employed fluorescently labeled, antibody-conjugated magnetic microparticles in combination with a separation column filled with steel wool. A static magnetic field magnetizes the steel wool, enabling trapping of the magnetically labeled cells. With the magnetic field in place, unlabeled cells are washed through the column. After removing the magnetic field, the labeled cells are released from the steel wool in

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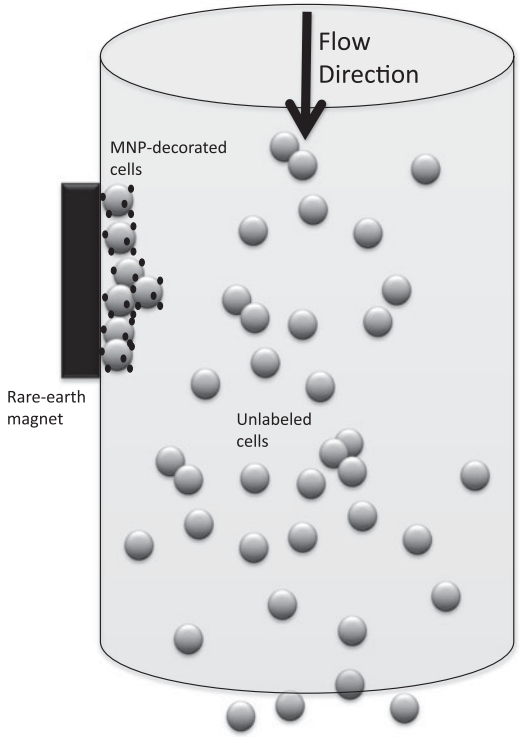


Figure 1. Principles of magnetic cell separation. Cells in suspension decorated with magnetic micro- or nanoparticles are attracted to the magnet as they pass through the column. Unlabeled cells pass through without being captured. After the sample has cleared the column, the magnet is removed, and the supernatant is washed out with the target cells. Note: MNP, magnetic nanoparticle.

a simple washing step, allowing for efficient, rapid cell separation with excellent cell viability.

In order to address challenges, such as low target antigen expression levels on the surface of some cells, McCloskey et al.[5] modeled three different scenarios to enhance the magnetophoretic mobility (the movement of magnetic particles, and the cells to which they are attached, along a field gradient). It was found that microparticles (particles with hydrodynamic diameters of more than 1 μm) improve the magnetophoretic mobility of cells by several orders of magnitude in comparison to nanoparticles (<100 nm). However, when dealing with cells expressing low numbers of antigens, indirect antibody labeling is recommended. This is done by grafting multiple polyclonal antibodies (antibodies that bind multiple sites on the cell surface antigen) onto magnetic nanoparticles.[6]

MRI contrast enhancement

The first routinely used clinical application of magnetic nanoparticles was as negative contrast agents in magnetic resonance imaging (MRI). Field inhomogeneities introduced by the presence of the magnetic particles promote rapid dephasing of protons in nearby water molecules, resulting in negative contrast in T_2-weighted MR images.[7,8]

It is worth noting that despite their potential, superparamagnetic iron oxide nanoparticles (SPIONs) are not routinely used for most clinical MRI examinations. This is primarily because SPIONs are negative contrast agents, making clinical diagnosis somewhat more difficult. In addition, negative contrast may also arise from metal deposits, calcification, and bleeding, further confusing diagnosis.

Hence, while until recently, several brands of SPION MRI contrast agents were available, most of them have been discontinued to give way for ultrasmall iron oxide nanoparticles, such as Supravist and gadolinium-based contrast agents, such as Magnevist, which require lower doses.

Nevertheless, there are currently exciting developments with SPIONs in MRI. Recently, Carroll et al. demonstrated that magnetite nanoparticles coated with co-polyethers, when "clustered" (MBIClusters), improved their T_2 relaxivities by a factor of 1.7 in comparison to the commercial contrast agent Feridex.[7] This was taken a step further when the same group showed that the loading of these MBIClusters with the antibiotic gentamicin did not affect their high MRI sensitivity, highlighting the "theranostic" (combined diagnostic and therapeutic) potential of these particles by combining imaging with drug delivery.[9]

Magnetic drug targeting

In the late 1970s, Widder et al. introduced the concept of magnetic drug delivery using mesoscale magnetic particles as carriers of chemotherapy compounds (**Figure 2**).[10] The group conjugated the cytotoxic drug "adriamycin" (better known as doxorubicin) to magnetic microspheres and, using a high-gradient magnetic field, targeted them to a specific site in a rat model. This resulted in a localized drug concentration that, if achieved through systemic intravenous delivery, would require a 100-fold higher dose of the free drug.[10]

Although these first results were promising and there has been progress with the loading and release of drugs from magnetic particles (e.g., through the use of thermoresponsive

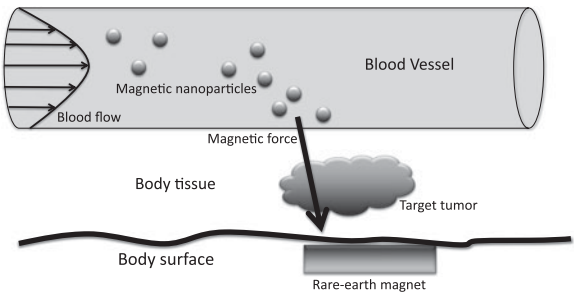


Figure 2. Principles of magnetic targeting for drug delivery. Magnetic nanoparticles carrying a therapeutic agent (not to scale) are pulled from circulation by a high gradient magnetic field positioned at the target site (such as a tumor). The magnetic nanoparticles collect at the target site and exit the vasculature via an enhanced permeability and retention effect.

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polymers[9]), magnetic drug delivery has yet to fulfill its early potential. This is primarily due to the fact that the magnetic field strength and gradient decrease exponentially with distance from the magnet, making targeting sites deep within tissue difficult. Also, the hydrodynamic drag on the particles in rapidly flowing blood competes with the magnetic force. In addition, ballistic effects of proteins and cells traveling within the blood make particle capture more difficult.

One of the main requirements of magnetic nanoparticles (MNPs) for magnetic targeting is that they are very small (<100–200 nm hydrodynamic diameter), so the iron oxide cores are superparamagnetic, and the MNP/composite particle can evade the reticuloendothelial system—the body's immune surveillance system. With current magnetic materials being used for these applications (primarily iron oxides), this small size means that the magnetic moment of the particle—which is composed of both iron oxide and diamagnetic polymer matrix—is not sufficiently large to experience a magnetic force larger than the hydrodynamic drag on the individual particles in most cases.

Several groups are investigating techniques for overcoming these issues, such as implanting magnetic meshes near the target site,[11,12] using novel, high-gradient magnet arrays such as Halbach—so-called "one-sided flux"—arrays,[13] using MNP-doped cells as carriers in order to generate a larger force while eliminating any immune response,[14] and a concept called "magnetic pushing" based on the geometric interaction of multiple field sources to create null field points.[15]

Nanomagnetic gene transfection

An important and useful biomedical application of MNPs that had its genesis in the principles of magnetic drug targeting is nanomagnetic transfection (non-viral introduction of exogenous genes into a cell) for gene delivery. Magnetic microparticles were first used by our group in 2000 to deliver genes into cells by linking a viral vector to the particles. By placing a NdFeB magnet beneath a culture dish, a microparticle/virus complex was targeted to a specific area of cells growing in the culture, resulting in enhanced transduction of those cells, while non-targeted cells showed little evidence of fluorescent reporter gene expression (**Figure 3**).[16,17]

More recently, *in vitro* transfection efficiency and protein expression have been further enhanced for both DNA and small-interfering RNA delivery by mechanical stimulation through the use of oscillating magnet arrays and pulsed electromagnets.[18–20] In this case, MNP/biomolecule complexes are introduced into cell cultures. Arrays of NdFeB magnets placed below the cell culture plate are attached to microprocessor controlled stepper motor/slide assemblies. These slide assemblies oscillate along the slide axis, essentially "dragging" the particles over the surface of the cells. Mechanical stimulation of the cell surface promotes endocytosis (the uptake of materials into the cell via membrane engulfment) of the MNP/biomolecule complex, improving uptake.[21] This motion also appears to increase protein yield, perhaps via enhanced activation of the cell's transcription machinery.

Another approach for gene delivery combines nanomagnetic transfection with ultrasound and nanoparticle loaded microbubbles.[22] This technique is interesting not only for transfection, but also potentially for drug delivery and imaging. Depending on the design, nanoparticles or drugs can be incorporated within the bubble coating or be loaded into the bubble itself, depending on the acoustic field. Different applied physical effects, such as microjetting, may improve drug delivery, opening an array of possible theranostic applications.[23,24]

Magnetic fluid hyperthermia

The concept of magnetic fluid hyperthermia (MFH) was first proposed by Gilchrist[25] in 1957 and relies on coupling magnetic nanoparticles to a radio frequency (RF) magnetic field, generally at frequencies between 100 KHz and 1 MHz, to generate heat at a targeted site within the body. As the human body is primarily transparent to magnetic fields, energy can be delivered to MNPs targeted to tumors within the body via MFH. This energy can be dissipated as heat via two mechanisms—(1) frictional heating due to Brownian rotation of magnetically

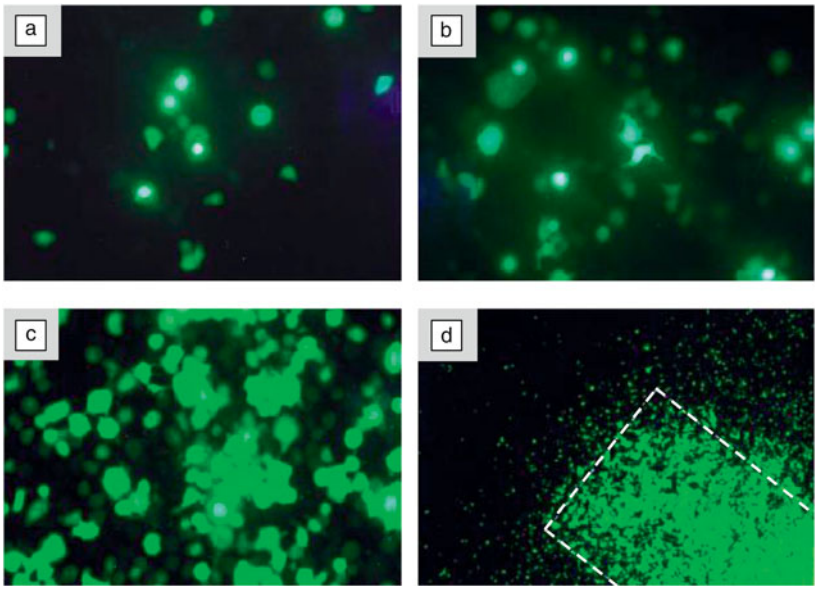


Figure 3. *In vitro* transduction of green fluorescent protein (GFP) reporter genes into C12S cells. The C12S cells were transduced using microparticle/virus complexes. (a) Control 1: Non-magnetic, polystyrene microsphere-conjugated rAAV encoding GFP. (b) Control 2: Magnetic microsphere conjugated-rAAV encoding GFP with no magnet. (c–d) Magnet-assisted transduction of magnetic microsphere conjugated-rAAV encoding GFP (magnet placement indicated by white dotted line). Reprinted with permission from Reference 16. © 2002 Nature Publishing Group.

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blocked particles within the tissue, and (2) Néel relaxation, or phase lag of the electron spin orientations, in superparamagnetic particles as they attempt to follow the changing field vector (there are other possible sources such as eddy currents and hysteretic heating, but these are negligible in comparison).[7] Therefore, the heating potential of a nanoparticle suspension is strongly dependent on magnetic particle core size and composition, as well as its hydrodynamic diameter and size distribution, in addition to the magnetic field strength and frequency.[26] By heating tumor cells above ~42°C for a period of time, a process known generally as "hyperthermia," cellular apoptosis (programmed cell death), or necrosis may be induced. Additionally, the heated cells are more susceptible to chemotherapy and radiotherapy in this stressed state.

Although MFH has been used as complementary therapy in cancer treatment, and there are a number of studies that indicate synergistic effects when hyperthermia is applied in combination with chemo- and radiation therapy, it was not until the end of the last decade that the first clinical MFH trials were started.[27–29] Since then, the MFH community has focused primarily on improvements in the heating potential of magnetic nanoparticles. To date, the most significant heating has been achieved by iron oxide nanocubes, with a specific absorption rate of up to 2,452 W/g at 520 kHz and 29 kA/m.[30] Additionally, magnetically more favorable core materials have also been investigated, such as $CoFe_2O_4$-coated $MnFe_2O_4$.[31] However, toxicity of these particles may be an issue for *in vivo* applications.

Despite these successes, the biological consequences of MFH are not properly understood. Following the original experiments by Gilchrist, it was assumed that a macroscopic increase in temperature (hyperthermia) would be required to enable cell death.[32] However, there is a growing body of evidence indicating the presence of highly localized heating effects affecting cells in the absence of a detectable, macroscopic temperature increase.[33]

Nanomagnetic actuation of cell surface receptors

Targeted, remote magnetic manipulation of specific cell surface receptors is a relatively recent development with potential implications for tissue engineering and regenerative medicine, developmental biology, and cancer therapy. The technique, which grew out of work on magnetic twisting cytometry[34,35] and magnetic microparticle-based cell membrane stretching experiments,[36,37] is based on coupling magnetic nanoparticles to specific cell surface receptors via antibodies or other receptor-specific targeting molecules (such as arginine-glycine-aspartic acid targeting integrin receptors).

It is possible to induce conformational changes in cell surface receptor proteins by "pulling" on magnetic nanoparticles attached to them (**Figure 4**). This "activates" biochemical signaling pathways within the cell, inducing a response in the cell that may be, for example, the production of a specific type of tissue matrix, differentiation of a stem cell down a specific lineage, initiation of cell division, or activation of apoptosis pathways to kill the cell. Targeted nanomagnetic actuation of specific cell surface receptors was first demonstrated by our group in 2002, and later expanded to target and magnetically activate specific cell signaling pathways both for tissue matrix production and to remotely activate and control stem cell differentiation both *in vitro* and *in vivo*.[38–42]

Recently, the technique has been adapted to manipulate signaling pathways that are activated via receptor clustering. Many so-called "death receptors" are activated via clustering, opening up the potential for remotely triggering apoptosis pathways in cancer cells. Mannix et al. first demonstrated magnetically triggered receptor clustering by coating superparamagnetic nanoparticles with monovalent ligands targeting transmembrane receptors to activate specific cell signaling pathways.[43] The application of a high gradient magnetic field

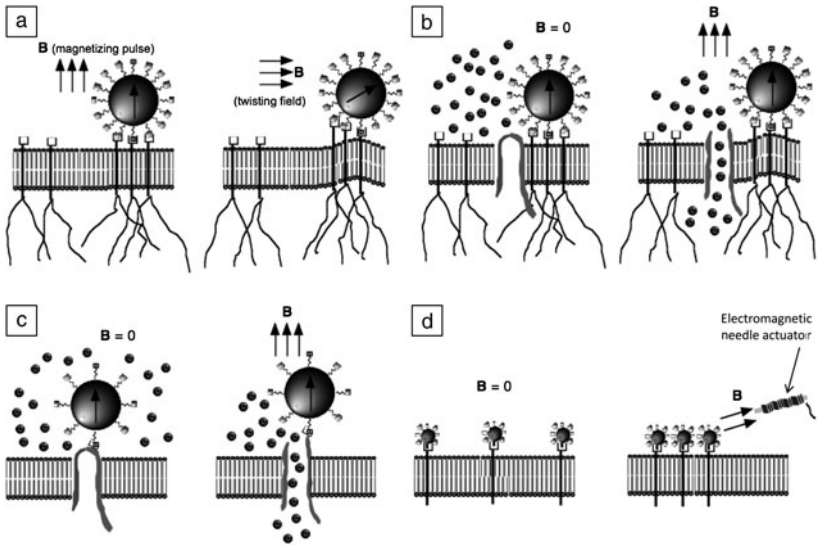


Figure 4. Magnetic actuation of cell surface receptors. (a) Magnetic twisting: Large (micron-sized) magnetic particles coated with arginine-glycine-aspartic acid (RGD) molecules attach to integrin receptors on the cell membrane. The receptors are linked to actin filaments (black lines). A magnetizing pulse gives the particle a remanent magnetization (**B** = magnetic field vector). A torque is then applied to the particle via a "twisting field." The force required to twist the particle is related to the mechanical properties of the actin filaments. (b) Mechanosensitive (MS) ion-channel activation: Mesoscale magnetic particles are bound to the integrin receptors and, upon the application of a high-gradient magnetic field, the particles are pulled toward the field, deforming the cell membrane and activating nearby MS ion channels. (c) Targeted ion-channel activation: Magnetic nanoparticles are attached to an ion channel via an antibody. Upon activation of a high-gradient magnetic field source, the ion channel is forced open. (d) Receptor clustering: Magnetic nanoparticles are bound to receptor complexes. In the absence of a magnetic field, the receptors are spaced along the membrane surface. When a high-gradient field is applied with a magnetic needle, the receptors are pulled toward the field source, initiating receptor clustering that can, for example, trigger intracellular signaling. Reproduced with permission from Reference 39. © 2008 Nature Publishing Group.

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via a magnetic needle induced clustering between the nanoparticles and therefore between the bound receptors, directly stimulating a signaling cascade within the cell. In a more recent article, Cho et al. adapted this idea *in vivo* and demonstrated the initiation of apoptosis in the tail region of zebrafish embryos by targeting and clustering tumor necrosis factor-related apoptosis inducing ligands.[44]

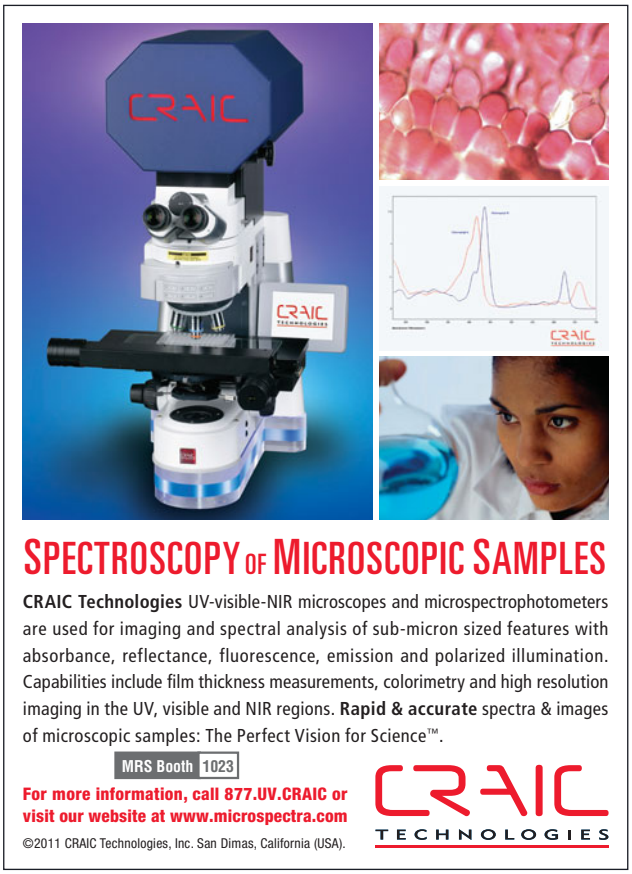
Concluding remarks

The use of mesoscale magnetic particles for biomedical applications is growing rapidly. Though few of these applications have reached the clinic, the potential is great, particularly as iron oxides are found naturally in the body. Current research focuses not only on the development of novel particles with enhanced biocompatibility and magnetic properties but also on applications that, through the coupling of particles *in vivo* to external fields, open up potential for magnetically actuated remote control of human physiology.

Currently, there are several challenges that must be overcome before mesocale magnetic particles can realize their full biomedical potential. Enhanced magnetic materials with higher moments and zero- or near-zero-remanance ground states are required for generating higher forces in order to develop more effective *in vivo* transducers and targeting agents. Improved biocompatibility and biomolecular surface functionalization for cell targeting will enable longer circulation times and improved activation of cell signaling pathways to control cell behavior. Finally, it is necessary to develop models and experiments that improve our understanding of the interactions of mesoscale magnetic structures with the complex biological environment *in vivo* and how magnetic energy can be deposited and transduced to activate and control biological or physiological processes.

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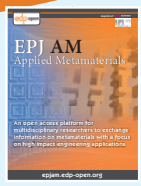
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