# A Topical Review of Magnetic Fluid Hyperthermia

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## Introduction

The human body naturally uses heat to fight disease. For example, viruses and bacteria proliferate at normal body temperatures, so the body instinctively defends itself by increasing its temperature several degrees to slow the rapid multiplication of such disease-causing agents. This phenomenon, commonly called a fever, gives the body an advantage while fighting the infection. Fevers form one subset of hyperthermia, an abnormally high body temperature. Hyperthermia also refers to body temperatures elevated for therapeutic reasons. The use of hyperthermia to treat cancer has been a recent topic of research. Magnetic fluid hyperthermia offers particularly promising capabilities for treating several types of cancer.

## Essentials of Hyperthermia Cancer Treatment

The body maintains a normal temperature of 37°C. Healthy cells, however, can survive temperatures up to 42°C. According to the National Cancer Institute, hyperthermia cancer treatment kills cancerous cells by elevating their temperatures to the therapeutic temperature range, 42-45°C. This approach can destroy tumors with minimal damage to healthy tissues and, therefore, limit negative side effects. Currently, oncologists often use hyperthermia cancer treatment in combination with radiotherapy and chemotherapy. In addition to eliminating many cancerous cells, hyperthermia can make resistant cells more vulnerable to other treatments.

Hyperthermia can treat specific locations, larger regions, or the entire body. Local hyperthermia may be applied externally to treat tumors near the skin's surface or with probes to reach deep-seated cancerous tissues. For larger tumors or multiple tumor locations, regional hyperthermia focuses microwave, laser, or ultrasound energy on diseased tissues. Whole-body hyperthermia treats cancers that have spread to several regions by using thermal chambers to elevate a patient's body temperature to just below 42°C (National Cancer Institute).

## Challenges of Hyperthermia Cancer Treatment

Regional hyperthermia treatments can effectively heat tumors. However, healthy tissues also absorb microwave, laser, and ultrasound energy. Heating healthy tissues between the external energy source and tumor is therefore unavoidable. Temperatures above 42°C in healthy tissues can cause burns, blisters, and discomfort. Consequentially, temperatures must be closely monitored during hyperthermia cancer treatment.

Regional hyperthermia treatments are also limited by the ability of microwave, laser, and ultrasound energy to penetrate body tissues. Shallow penetration can prevent the treatment of deep-seated tumors including brain and pelvic tumors.

## Magnetic Materials in Hyperthermia Treatment

Gilchrist and others proposed the use of magnetic materials in hyperthermia in 1957. The particles used in hyperthermia exhibit ferro- or ferrimagnetic properties. Ferro- and ferrimagnetic particles display magnetism even in the absence of an applied magnetic field (Pankhurst *et al*.). Consider a magnetic stir bar (a ferromagnetic material) resting on a stir plate. The stir bar can be reoriented by applying a physical force (twisting the bar by hand, for example) or by introducing a stronger magnetic field. Both processes require energy, which is released when the external force is removed and the stir bar returns to its original position. Likewise, the magnetic particles used in hyperthermia have permanent magnetic orientations or moments. An applied alternating magnetic field can provide the energy necessary to reorient the particles' magnetic moments. This magnetic energy, when dissipated, is converted to thermal energy (Hergt *et al*.). In addition to causing changes in the magnetic moments, this energy can force the nanoparticles to physically rotate. Hyperthermia cancer treatment uses the heat generated by this conversion to destroy cancerous tissues. The friction created as the nanoparticles rotate through viscous fluids to return to their equilibrium

positions also generates heat. Frictional heating, however, contributes much less than magnetic heating to the particles' total heat generation.

Pankhurst and others also describe heating in magnetic nanoparticles. Particles with diameters of 10 nanometers or less typically demonstrate superparamagnetic properties. The magnetic moments of superparamagnetic nanoparticles are randomly reoriented by the thermal energy of their environment and do not display magnetism in the absence of a magnetic field. Unlike ferro- and ferrimagnetic materials, they do not aggregate after exposure to a magnetic field (Berry and Curtis). Aggregation can hinder the body's efforts to remove the nanoparticles. Therefore, superparamagnetic nanoparticles are ideal candidates for hyperthermia cancer treatment.

The use of magnetic nanoparticles can improve hyperthermia cancer treatment. Cancerous cells typically have diameters of 10 to 100 micrometers and have been shown to absorb magnetic particles. This increases the effectiveness of hyperthermia by delivering therapeutic heat directly to cancerous cells. Nanoparticles can also effectively cross the blood-brain barrier, an essential step in treating brain tumors (Koziara *et al*.). Finally, nanoparticles can be coupled with viruses (20-450 nm), proteins (5-50 nm), and genes (10-100 nm long) (Pankhurst *et al*.). The advantages of these techniques will be discussed as topics of future research.

## Magnetic Fluid Hyperthermia Cancer Treatment

Magnetic fluid hyperthermia (MFH) cancer treatment involves injecting a fluid containing magnetic nanoparticles directly into tumors. When placed in an alternating magnetic field with frequencies similar to FM radio signals, the nanoparticles generate heat and destroy the tumors. This minimally invasive procedure, unlike laser, microwave, and ultrasound hyperthermia, prevents unnecessary heating in healthy tissues because only the magnetic nanoparticles absorb the magnetic field.

Magnetic fluids generally consist of magnetic nanoparticles dispersed in water or a hydrocarbon fluid (Tartaj *et al*.). For medical applications, the biocompatibility of both the fluid and nanoparticles must be considered. The fluid must have a neutral pH and physiological salinity. The particles should remain evenly dispersed throughout the fluid, and must therefore be small enough to avoid precipitation due to gravitational forces (Tartaj *et al*.). In addition, the magnetic material should not be toxic. The established biocompatibility of magnetite ($Fe_3O_4$) makes it a common choice.

Synthesis methods focus on generating magnetic nanoparticles of uniform size and shape. The most common approaches include solution chemistry and aerosol/vapor techniques. Homogeneous precipitation reactions are used to prepare nanoparticles from solutions. To create consistent nanoparticles, the reaction occurs in two stages: particle formation and growth. Ideally, a single group of particles form when the solution reaches the critical saturation point. The particles then grow as solutes adhere to their surfaces. The formation of new particles should be avoided during the growth phase (Tartaj *et al*.).

Traditional aerosol/vapor methods include spray and laser pyrolysis. Spray pyrolysis begins with an aerosol droplet generator that creates fine droplets of a solution. These droplets pass through a series of reactors that evaporate the solvent and pyrolize the resulting nanoparticles. The ultrafine nanoparticles created by this technique often collect to form larger particles. Laser pyrolysis, however, can almost eliminate nanoparticle aggregation and achieve narrower particle size distributions. This technique employs a continuous wave carbon dioxide laser to initiate nanoparticle formation reactions. Both of these methods provide straightforward means for rapidly producing large quantities of magnetic nanoparticles for hyperthermia treatments (Tartaj *et al*.).

Once synthesized, the magnetic fluids are localized in tumors for MFH treatment. Several methods for delivering the fluids exist. For identified tumor locations, direct injection concentrates fluid in the diseased tissue. Alternatively, the fluid can be injected into an artery that supplies the tumor with blood (Berry and Curtis). Treating groups of small tumors whose locations cannot be pinpointed requires a different approach. An intravascular injection delivers magnetic nanoparticles throughout the body. The heating can be localized, however, by applying the magnetic field only to the region containing the

tumors (Pankhurst *et al*.). Attaching targeting antibodies to the magnetic nanoparticles could make MFH treatment via intravascular injection more selective. Instead of circulating throughout the body, the antibodies and nanoparticles would concentrate in the cancerous cells with receptors for the antibody. This method will be discussed as an area of future research.

**Low-Curie Temperature Nanoparticles**

Magnetic fluid hyperthermia cancer treatments must maintain therapeutic temperatures in diseased tissues for approximately 30 minutes (Pankhurst *et al*.). Excessive heating, however, can cause unwanted charring. Nanoparticles with low-Curie-temperatures – defined as the temperature when the material loses its magnetic moment – heat until they reach the Curie temperature and then remain ineffective unless their temperature falls below the Curie temperature. Nanoparticles with Curie temperatures near the therapeutic range can efficiently maintain temperatures between 42 and 45°C and therefore enhance magnetic fluid hyperthermia. These self-regulating nanoparticles ensure diseased tissues reach the necessary temperatures while preventing excessive heating and damage to surrounding healthy tissues.

**Magnetic Fluid Hyperthermia Applications**

Many studies have confirmed the feasibility of magnetic fluid hyperthermia cancer treatment. Hergt and others performed *in vitro* experiments to evaluate the heating effects of commercially available magnetite ($Fe_3O_4$) particles. Study samples consisted of a sphere of compressed magnetite particles embedded in a large volume of KCl/Currageenan-gel. The samples were exposed to an alternating magnetic field (H = 18 kA/m, frequency = 300 kHz) and the surface temperatures of the particle spheres were recorded. The heat generated depended heavily on particle size and microstructure. The results proved that even small amounts of particles with suitable properties can generate the heat required for magnetic fluid hyperthermia.

Hilger and others used magnetic fluid hyperthermia to treat breast cancer in mice. Fluid containing iron oxide particles was injected into tumors grown from human breast adenocarcinoma cells. Tumor and healthy tissue temperatures were monitored throughout the 4-minute application of the alternating magnetic field (H = 6.5 kA/m, frequency = 400 kHz). Therapeutic temperatures were obtained, but regions of insufficient heating were also observed. Cool spots were consistent with lower concentrations of magnetic fluid, emphasizing the importance of fitting the magnetic fluid distribution to the tumor's shape.

Jordan and others also explored the effects of magnetic fluid hyperthermia on mammary carcinoma in mice. Magnetic fluid containing magnetite ($Fe_2O_3/Fe_3O_4$) particles was delivered by intratumoral injection (0.015 mg magnetite/$mm^3$). Post-injection examination of the cancerous tissues showed deep fluid penetration. An alternating magnetic field (H = 6 – 12.5 kA/m, frequency = 520 kHz) was applied for 20 – 30 minutes. Widespread death of cancerous cells was observed after MFH treatment. This study also tracked tumor growth in the 50 days following treatment. MFH treatment halted growth in some tumors, but did not impede growth in others. These differences were attributed to the inconsistent distribution of the magnetic fluid in the tumors.

**Modeling Magnetic Fluid Hyperthermia**

In addition to *in vitro* and *in vivo* studies, computer simulations aid researchers in understanding and improving MFH cancer treatment. The model developed by Bagaria and Johnson (Bagaria and Johnson) consists of two finite concentric spherical regions. The inner sphere represents cancerous tissue containing magnetic particles, and the outer sphere represents healthy tissue. Penne's bioheat transfer equation describes the temperature in the diseased and healthy tissues as functions of the heat generated by the particles, the heat conducted through the tissues, and the heat removed by blood perfusion. The model showed the proper distribution of magnetic particles throughout the tumor could minimize the damage to the surrounding healthy tissue while still maintaining a therapeutic temperature in the tumor.

The same model can be used to define the ideal particle properties suggested by the experiments of Hergt and others. Nanoparticles with these characteristics would convert magnetic energy to thermal energy more efficiently. Such advances

would reduce the number of nanoparticles required and therefore minimize the side effects of MFH. The self-regulating effects of low-Curie-temperature nanoparticles can also be confirmed. Finally, the model can be used to find ways to apply the magnetic field to minimize damage to healthy tissues and the patient's exposure to the field.

Future computer simulations could assist doctors in determining how and where to place the magnetic fluids. Precise treatments would increase the likelihood of eliminating the tumor while decreasing the side effects of heating healthy tissue.

## Future Research

Promising areas for future MFH research include low-Curie-Temperature nanoparticles and cancer-specific binding agents. Low-Curie-temperature nanoparticles with ideal sizes and magnetic properties would heat efficiently and maintain therapeutic temperatures. Iron-platinum (FePt) and nickel-palladium (NiPd) nanoparticles could potentially meet these criteria. Figure 1 shows a transmission electron microscope image of a self-assembled film of FePt nanoparticles.

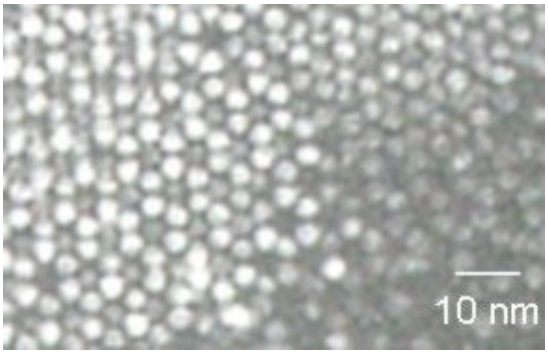


**Figure 1: Iron-platinum magnetic nanoparticles.**

Attaching cancer-specific binding agents to magnetic nanoparticles would make MFH treatment much more selective than traditional chemotherapy and radiation treatments. Chemotherapy destroys a wide range of rapidly dividing cells, including many types of cancer. However, chemotherapy also damages healthy cells with rapid multiplication rates, such as those found in hair, bone marrow, and the lining of the gastrointestinal tract. The side effects are compounded by the high systemic doses required to achieve local effective concentrations. Likewise, external beam radiation treatments can eliminate tumors but also harm healthy tissues between the tumor and radiation source. In contrast, MFH uses frequencies that pass harmlessly through the body and only generate heat in tissues containing magnetic nanoparticles. Attaching cancer-specific binding agents to these nanoparticles would enable doctors to target both a specific chemical profile and physical location. The side effects associated with healthy tissue damage would be significantly reduced. This approach would also treat small tumors that might otherwise be missed.

Cancer-specific binding agents could include hormones, antibodies, and viruses. Several types of cancers have hormone receptors. Some forms of breast cancer, for example, have estrogen receptors. Current breast cancer treatments often include anti-estrogen drugs such as tamoxifen. Magnetic particles coupled with estrogen would therefore target hormone-sensitive breast cancer. Similarly, testosterone and thyroid hormone could be used in MFH treatments for prostrate cancer and thyroid cancer, respectively.

Monoclonal antibodies can also be used to target cancer. These antibodies react with matching antigens on cancerous cells, and can be produced for many types of cancer. According to the American Cancer Society, Monoclonal antibodies have been successfully coupled with chemotherapy drugs and radioactive particles. These tagged antibodies increase the effectiveness of chemotherapy and radiation therapy by delivering therapeutic agents to cancerous sites. In principle, the same benefits could be achieved by coupling antibodies with magnetic nanoparticles.

Finally, attaching magnetic nanoparticles to viruses (Fig. 2) has promising implications for MFH cancer treatment. Viruses can be modified to latch onto receptors on several types of cancerous cells. The genetic material contained in the viruses can also be replaced with chemotherapy drugs. These viruses can then be engineered to release the drugs at elevated temperatures. Viruses coupled to magnetic particles could therefore locate cancerous cells and deliver heat and therapeutic drugs directly to these locations.

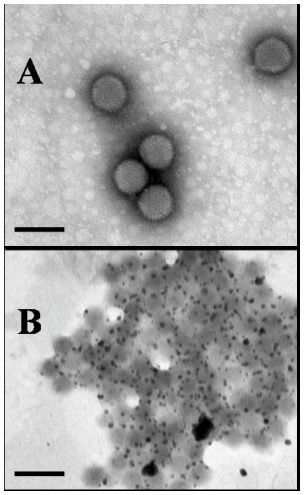


**Figure 2: A) Scanning electron microscope (SEM) image of normal adenoviruses. B) SEM image of viruses with silver-stained gold nanoparticles attached to the virus capsid.**

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