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Thermosensitive Magnetic Nanoparticles for Self-Controlled Hyperthermia Cancer Treatment

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Magnetic nanoparticles show remarkable phenomena such as superparamagnetism, high field irreversibility and high saturation magnetization [1]. The study of magnetic nanoparticles has been a very active research field due to many important applications such as drug delivery, imaging and hyperthermia cancer treatment [2]. Hyperthermia has been used for many years to treat a wide variety of tumors in patients and used as well as an adjunct to cancer radiotherapy or chemotherapy [3,4]. Its use is based on the fact that tumor cells are more sensitive to temperature in the range of 42–45°C (which yields necrosis, coagulation, or carbonization) than normal tissue cells. This temperature range has become critical for cancer treatment due to damaging the cancerous cells without altering the healthy cells by selective heating (up to 45°C) and controlling heating rate and time.

Basically, hyperthermia increases perfusion and oxygenation of neoplastic hypoxic cells, which are more resistant to ionizing radiation than normal cells [5]. Moreover, increased tumor tissue perfusion facilitates the absorption of chemotherapeutic drugs through cell membrane without being more toxic [6-8]. As a result, the action of combination of hyperthermia with radiotherapy or chemotherapy becomes more efficient. Consequently, hyperthermia allows reducing of tumors resistant to various chemotherapeutic drugs such as doxorubicin, cisplatin, bleomycin, nitrosoureas, and cyclophosphamide. It has been demonstrated that hyperthermia also has an anti-angiogenic action and an immunotherapeutic role, due to thermal shock proteins, which are produced by stressed tumor cells [9,10]. This method has found clinical application mostly in Europe and Asia [4,8]. While in the United States, microwave hyperthermia in conjunction with radiation has received approval from the Food and Drug Administration (FDA), it still remains mostly as an experimental method due to possible overheating and necrosis of normal tissue [11,12]. There is an urgent need for development of new hyperthermia heating agents and treatment methodologies that will be more effective than those currently available and help to unlock the full potential of the technology that can have a significant impact on management of cancer patients. Thus, it is of paramount importance to develop new nanostructured media, which would enable selective heating of tumor cells and vasculature avoiding excessive damage to healthy tissue structures.

Magnetic fluids based on iron oxide (Fe_3O_4), stabilized by biocompatible surfactants are typically used as heating agent in magnetic hyperthermia [13,14]. In the presence of AC magnetic field, magnetic nanoparticles show three different types of losses - Hysteresis, Ne´el, and Brownian, which are responsible for heat generation. However, significant limitations of using commercial available magnetic nanoparticles are non-selectivity and overheating of surrounding normal tissues. For most nanoparticles suggested so far for cancer hyperthermia treatment, uniform controlled induction heating and selectivity remain as major challenges.

There is increasing number of research articles for self-controlled hyperthermia and development of nanoparticles with Curie Temperature (T_c) in the range of 45-50°C that are not affected by alternating magnetic fields above 50°C in order to prevent overheating of normal cells [15-26]. Various nanoparticles were synthesized using physical as well as chemical methods. For example, ultrafine alumina coated particles of substituted ferrite $Co_{1-x}Zn_xFe_2O_4$ and yttrium–iron garnet $Y_3Fe_{5-x}Al_xO_{12}$ have been proposed to tailor T_c at ~50°C [16]. Copper nickel (CuNi) alloy nanoparticles with varying T_c from 40 to 60°C were synthesized by several techniques [17]. *In vitro* and *in vivo* animal experiments have demonstrated the feasibility of the temperature-controlled heating of the tissue, laden with the particles, by an external alternating magnetic field. Nickel-Chromium ($Ni_{1-x}Cr_x$) particles with varying compositions have been investigated as thermoseeds for use in localized self controlled hyperthermia treatment of cancer [18]. A series of Ni-Cr alloys, have been prepared to find the specific composition that has Curie temperature in range of 43-44°C. The samples were cast by arc melting technique then annealed at 850°C for 5 hours in sealed quartz tubes. The Curie temperatures of the alloys decreased almost linearly with increasing Cr concentration from 4.54 to 5.9 wt %. The results showed that $Ni_{1-x}Cr_x$ alloys might be good candidates for self controlled magnetic hyperthermia applications.

Structural and magnetic properties have been studied for $Gd_5(Si_{1-}xGex)_4$ and $(Gd_{1-}xRx)_5Si_4$ series, with R = Ce Nd, Er, and Ho, in the context of their use as magnetic materials in the self-controlled hyperthermia treatment of cancer [19]. The study shows that these materials have high magnetization values and their magnetic ordering temperatures can be varied linearly over a broad range by adjusting the composition of the constituent elements. The high magnetization and optimal T_c values of these composites meets self-controlled hyperthermia requirements.

La-Ag and La-Na perovskite manganites were proposed [20] as smart mediators for self-controlled isothermal heating in magnetic hyperthermia. It shows that dissipation of the alternating magnetic field energy causes heating of aqueous suspensions to terminate at 42-48°C without external temperature control. Ferromagnetic $La_{0.73}Sr_{0.27}MnO_3$ nanoparticles (20–100 nm) showed saturation magnetization ~38 emu/g at 20 kOe with T_C value of 45°C [21]. Unaggregated $La_{0.8}2Sr_{0.18}MnO_{3+\delta}$ perovskite nanoparticles with a mean crystallite size of 22 nm were successfully synthesized through an aqueous combustion synthesis, which takes advantage of exothermic, fast and self-sustaining chemical reactions between metal nitrates and glycine [22]. Fast calcination and milling process were used to

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enhance crystallinity of the nanoparticles and their desaggregation. The heating experiments of magnetic fluid suspended $La_{0.8}2Sr_{0.18}MnO_{3+\delta}$ nanoparticles in AC magnetic field demonstrated that the particles can be used for self-controlled hyperthermia application, considering their maximum heating temperature ~43°C. Recently, it was shown that complex ferrites nanoparticles with formula $Mg_{1+x}Fe_{2-2x}Ti_xO_4$, (where 0≤x≤0.5) can be meet self-controlled hyperthermia requirements with T_c in range of 45-50°C [23-24]. Furthermore, authors [25] confirmed that Curie temperature for Zn doped Mn-ferrite, $Mn_{1-x}Zn_xO$ and the Gd doped Zn-ferrite, $ZnGd_xFe_{2-x}O_4$ nanoparticles can be tuned to the optimum temperature of 43°C. The Mg-Fe-Ti compositions are very promising, since all the elements biocompatible. Magnetic nanocomposite $Ni_{0.2}Ca_{0.8}Gd_{0.08}Fe_{1.92}O_4$ encapsulated by poly vinyl alcohol and synthesized by a two steps chemical reaction including sol-gel combustion and solvent casting technique also can be applicable for self controlled hyperthermia [26].

Thus, the magnetic materials with Curie temperature ~45°C, having sufficient biocompatibility are the best candidates for effective cancer hyperthermia treatment to avoid overheating. Because of unique capability of turning on and off the magnetic properties depending on temperature, the tumors will be continuously heated at a self-controlled temperature equal to the Curie temperature of the magnetic nanoparticles. This approach will allow to heat the tumor cells and vasculature selectively and to prevent overheating with subsequent damage to neighboring healthy tissues. Additionally, the self-controlled method might allow in situ MRI monitoring and selective hyperthermic therapy.

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