Towards MRI-Controlled Ferromagnetic and MC-1 Magnetotactic Bacterial Carriers for Targeted Therapies in Arteriolocapillar Networks Stimulated by Tumoral Angiogenesis

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Abstract— The delivery of a therapeutic agent through controlled carriers directly to the tumoral lesion can enhance treatment efficacy by reducing dosage while minimizing systemic circulation of toxic compounds through healthy tissues. As such, the induction of a feedback controlled steering force on ferromagnetic carriers from magnetic gradients generated by an upgraded clinical Magnetic Resonance Imaging (MRI) system has been demonstrated by our group. But the gradient strengths required in some sections of the capillary network may be technologically very difficult to achieve for human due mainly to the size and cooling issues of additional gradient coils embedded in the MRI bore. As such, the use of MC-1 Magnetotactic Bacteria (MTB) pushing microbeads with a therapeutic agent may provide complementary means of propulsion in smaller capillaries. Based on preliminary experimental results, carriers and a new method combining the induction of force in a ferromagnetic material with the thrust provided by MTB for direct targeting to the tumor mass are proposed.

Keywords—**Ferromagnetic, magnetotactic bacteria, MRI system, targeted drug delivery, angiogenesis capillary network.**

I. INTRODUCTION

Angiogenesis represents for many cancer treatments such as chemotherapy, the accessibility or routes to the targeted tumor. It refers to the formation of blood vessels from a pre-existing vasculature and occurs in many instances including tumor growth. New treatments of cancer use tumor-induced angiogenesis. It is also used as a prognostic tool. As such, anti-angiogenesis therapies are being developed as potential non-invasive treatments against the spread of cancer. As for chemotherapy, since such therapy may also in the future benefits from improved targeting of the anti-angiogenic inhibitors, enhancing Direct Targeting (DT) (i.e. with external control resulting in non-systemic circulation) towards the tumoral lesion has the potential to play an important role for such therapies. There are also several other types of cancer treatment which are presently used individually or in combination depending on each patient's medical condition and the type of cancer. In general, surgery, chemotherapy and radiation therapy are considered as common types of cancer treatment but they present their proper limits and negative side effects. Hence, improving DT towards the tumor cells may play an important complementary role to enhance the efficacy of many of these treatment strategies.

For chemotherapy, the disadvantages could potentially be avoided or reduced if drugs are administered by controlled carriers since better targeting offers the potential to reduce dosage while minimizing systemic circulation of toxic compounds through healthy tissues.

For embolization, DT may help reaching specific blood supplies with the use of carriers slightly larger than the targeted blood vessels and hence, enhance the efficacy of the treatment. For chemo-embolization, the same as for embolization applies but with carriers with slowed dissolving substance containing chemotherapeutic drugs. Direct targeting here should significantly enhance the efficacy of the treatment.

Besides the above treatments, numerous efforts to reduce side effects and enhance treatment effectiveness have been done for some therapeutic procedures such as biological therapy, laser treatment, gene therapy, photodynamic therapy, and hyperthermia. In particular, hyperthermia is presently considered as an emerging therapeutic procedure. When used in combination with other treatments such as chemotherapy and radiation therapy, it can provide an increase of the response rate of some tumors. Hyperthermia is a procedure to raise the temperature of tumor loaded tissues or organs artificially to temperatures between 41 – 46ºC with the aim of therapeutic benefits. It has been shown that the use of hyperthermia can enhance the delivery of monoclonal antibodies to tumors with resultant improvement in anti-tumor effects. But a number of challenges remain before hyperthermia can be considered standard cancer treatment since no method simultaneously provides all the essential main factors that influence the effectiveness of hyperthermia treatment namely, non-invasive control of the thermal dose distribution and deeper penetration depth.

But another recent promising approach to hyperthermia is Magnetic Fluid Hyperthermia (MFH) cancer treatment that involves injecting a fluid containing magnetic nanoparticles, also known as ferrofluid, directly into the tumor. When placed in AC magnetic fields with FM radiofrequencies, the magnetic particles are heated and the temperatures of surrounding tumor cells (size: 10-100 µm)

are elevated and can be killed. It is well known that these cancer cells absorb magnetic particles. The advantages of this method are that therapeutic temperature can be directly delivered to the tumor and unnecessary heating in normal tissues can be avoided. In other words, magnetic nanoparticles contribute to the precise control of temperature distribution. However there are still two main problems to resolve. First, the development of a reliable delivery method that can go deep in the body is required and second, a reliable non-invasive thermal monitoring method to maintain heating within precise temperature levels is essential. Today, temperature control in hyperthermia treatment is typically achieved by using invasive temperature measurements, which give very limited knowledge about temperature distribution throughout the volume. On the other hand, temperature sensitivity of Magnetic Resonance (MR) parameters such as T1, proton frequency shift or the diffusion coefficient are known to be the basis for monitoring thermo-therapies with MRI leading to the recent development of an hybrid system for simultaneously MRI and RF hyperthermia. This alone coped with efforts to advance this novel magnetic targeting technique as described in this paper while opening huge opportunities in combined cancer therapies, justify the use of a clinical MRI system instead of any other medical platforms.

II. MAGNETIC TARGETING

Typical magnetic targeting methods control particles from external magnets. Although it was demonstrated that with such magnetic targeting methods coped with a drug release mechanism that complete tumor remission was drastically improved with a reduction of toxicity since lower dosages were used, the use of external magnets has limitations for targeting purpose. For instance, it restricts the targeting possibilities to organs that are close to the skin and does not allow precise control of the particles.. As such, unlike presently known magnetic targeting techniques, the imaging feedbacks and computerized control of 3D magnetic gradient generations (instead of a DC magnetic field) provided by a clinical MRI system coped with a carrier based on an agglomeration of particles made of materials with high saturation magnetization, potentially allow for precise delivery and targeting of a tumor located deeply in the body. Such claim is reinforced by the fact that our group demonstrated experimentally that the propulsion of a ferromagnetic core in the human cardiovascular network through an induced force generated by an MRI system is possible [1, 2]. It then becomes technological feasible, although very challenging, to apply this method to navigate particles in a 3D space in order to reach the tumor cells through an anarchic arteriolocapillar network stimulated by tumoral angiogenesis.

The targeting efficacy can be optimized by maximizing three main parameters, namely: 1. the magnetic gradient

strengths, 2. the effective volume of the ferromagnetic body in the carriers, and 3. by selecting a ferromagnetic material to be embedded in the carriers with the highest magnetization saturation level. The first parameter relies on upgrading the clinical MRI system with additional steering coils while parameters 2 and 3 will affect the design of the carriers.

Applications for targeting tumors in regions outside the human torso (e.g. the head) would simplify coil design dramatically through a reduction of space constraints, and potentially yield higher gradient strengths. But for targeting deeply in regions such as in the torso, a 150mT/m may be a realistic limit being fixed by constraints such as space in the MRI bore and cooling issues, but also by the use of clinical amplifiers limiting the maximum inductance of the coil and hence, the gradient strength. Although dedicated amplifiers for steering could be used to increase gradient strengths, it is not clear at the present time if issues such as space and cooling for the coils could be dealt with appropriately for such applications considering physiological and technological constraints such as capillary network topologies, pulsating flow rates, and maximum duty cycles allowable for the generation of magnetic gradients to allow adequate cooling of the coils.

III. FERROMAGNETIC CARRIERS

Although several designs are possible, micro-carriers acting under the influence of magnetic gradients would typically consist of magnetic nanoparticles and an anticancer agent loaded onto a biodegradable polymer. Magnetic nanoparticles instead of microparticles are used in similar applications such as MRI contrast agents for many reasons and they are suited here for the ease of incorporating them in polymer-based microparticles without causing structural weaknesses while providing a valuable delivery vehicle for targeted hyperthermia (~9-30 nm particles can be heated within constraints of RF wavelengths). To increase the magnitude of the induced force for targeting purpose, both the effective volume of ferromagnetic nanoparticles in each micro-carrier and the material properties, and in particular the level of saturation magnetization of the ferromagnetic nanoparticles, must be maximized. But even with the highest saturation magnetization level, not sufficient force for arteriole entry (just beyond the reaching limits of modern minimally invasive interventional tools that can be used to release the carriers in the cardiovascular system) can be induced in a single micro-carrier, due to the small volume of ferromagnetic material that can be embedded, to deal with the relatively high blood flow rate in larger diameter vessels. Hence, an agglomeration of such microparticles in the form of a ferrofluid, providing the required mechanical compliance properties for entry from larger to smaller diameter vessels, must be used. Sufficient induced force can be realized since the interactions between the microparticles

are governed according to the theories of colloids and ferrohydrodynamics through the potentials of London Van Der Waals, double electrostatic layers, magnetic dipole, by Stokes equations for the drag forces and corrected for the effects of the vascular walls, and by less significant influences due to gravity and Brownian motion. Although Fe_3O_4 nanoparticles can be used since its biocompatibility has been proven in many studies, Fe-Co nanoparticles coated with titanium, oleic acid, or other substances for biocompatibility issues would be preferred here due to the excellent magnetic properties of this material. Such nanoparticles can be loaded by double-emulsion in microparticles made of a therapeutic drug release biodegradable polymer such as poly (D,L-lactic acid) (PLA) or poly(D,L-lactic-co-glycolic acid) (PLGA) that are already approved by the FDA.
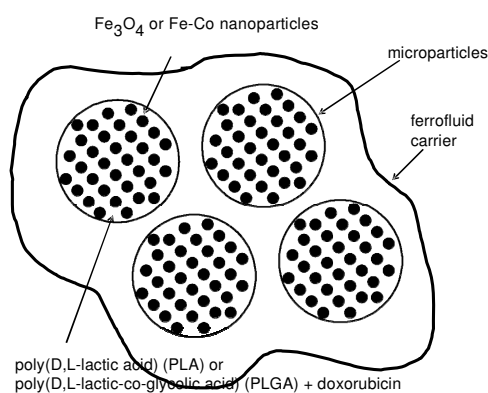
Fig. 1. – Simple diagram of an experimental magnetic carrier showing just a few microparticles with doxorubicin acting as the therapeutic agent (not to scale)

IV. BACTERIAL CARRIERS

Non-pathogenic anaerobic bacteria that preferentially localize and proliferate in the hypoxic regions of tumors have been investigated for many years as treatments for tumors with mixed success. But in our knowledge, the use of Magnetotactic Bacteria (MTB) [3, 4] to help for the treatment of tumor has never been investigated yet, especially as a complementary means of propulsion in smaller vessels. The MC-1 bacterium is of particular interest for this application. It is a polar bacterium (i.e. it swims persistently in one direction along a magnetic field) with a diameter of ~1.0 µm and it is the fastest MTB that we know so far with swimming speeds in the range of ~80-200 µm/s.

We have shown that the displacement path of a swarm of MTB could be controlled by magnetotaxis under homemade computer software that gives the local magnetic field direction as depicted in Fig. 2a. Furthermore, the swimming path of a single MTB pushing a microbead can be modified by computer software by re-orienting the lines of a magnetic field as shown in Fig. 2b with a close-up view of the bacterium pushing the bead in Fig. 2c.
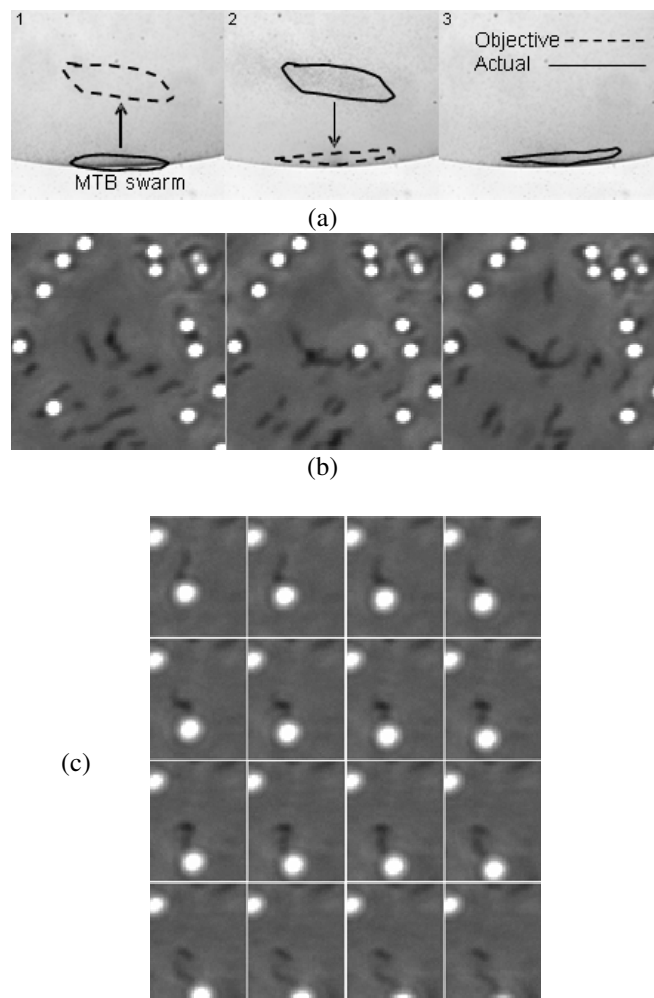
Fig. 2. – (a) Directional control indicated by the black arrows of a swarm of MC-1 MTB swimming in an aqueous solution at an average speed of 130µm/s. (b) Directional control of a 3µm bead being pushed by a single MTB with a controlled directional change of the swimming path occurring after 2.5 sec.(small dashed lines indicate the field direction) (c) Close-up view of a single MTB pushing a microbead.

We also demonstrated through preliminary experimental results that MC-1 MTB could swim efficiently in human blood for a few minutes. Furthermore, a swarm of these bacteria pushing ferromagnetic microbeads could potentially be detected for real-time MR-tracking. Our preliminary experiments also show that a single MC-1 MTB can provide a thrust of ~4.6 pN (unpublished data). Such results as depicted in Fig. 3 and Fig. 4 are very promising in sight of using them in human capillary networks.
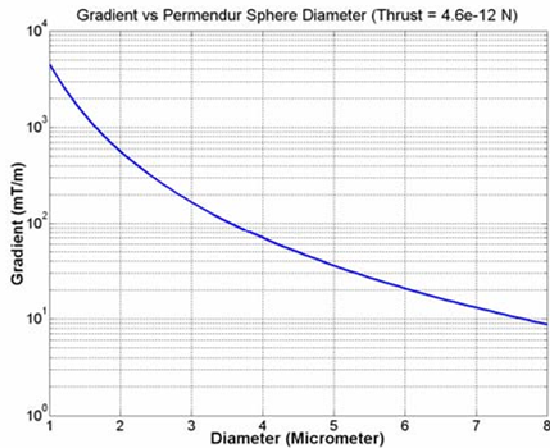
Fig. 3. – Gradient strengths - Permendur sphere diameter indicates that with a gradient limit of 150mT/m, the smallest sphere diameter for a corresponding induced thrust of 4.6e-12 N corresponding the thrust provided buy a single MC-1 bacterium is slightly larger than 3 micrometers.
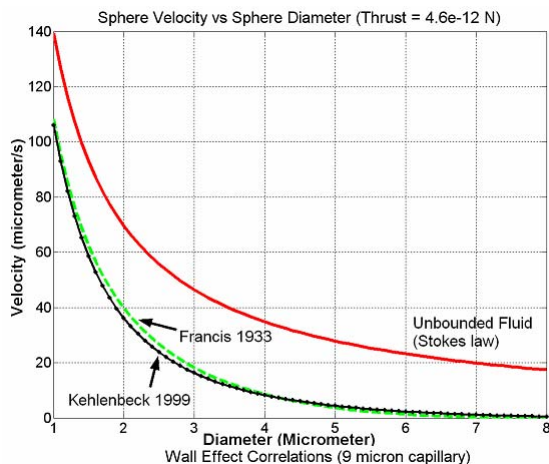

Fig. 4. – With a thrust equivalent to the MC-1 bacteria, for the same diameter sphere, the steering speed would correspond to 18 microns/s (from models taking into account retarding effects from the blood vessel walls) being the maximum expected diameters of capillaries in human. It is to note that blood transit time in the capillaries is 1 s.

The typical 1.5 T DC magnetic field of clinical MRI systems complicates the directional control of such bacteria compared to a platform where an X-ray system could be upgraded with peripheral permanent or electromagnets. Nonetheless, the use of an MRI system has many advantages in term of imaging modalities and the lack of radiation. Although such approach need to be confirmed experimentally in an MRI system, the swimming direction of MTB in the MRI bore could potentially be changed by pulsed magnetic field created by the propulsion/steering coils.

Finally, for effective delivery through the arterioles where additional force is required, MTB must be encapsulated in ferromagnetic carriers prior to be released in the capillary network where the blood flow is much lower.

This is turn will influence the design of the combined ferromagnetic and magnetotactic bacterial carriers.

VI. CONCLUSIONS

The use of special devices combining ferromagnetic materials and magnetotactic bacteria to be propelled in the human blood vessels could allow or improve many medical tasks such as on-site delivery of MRI contrast agents, highly localized drug delivery for chemotherapy and chemo-embolization, thermal treatment of tumors at selected sites, and for biosensing applications, to name but a few applications. Such potential impact is due mainly to the fact that presently, many remote locations within the human body are out of reach. With the proposed carriers being navigated through the human blood circulatory system, efficacy in targeted therapies could potentially be improved.

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