Recent advances in SPIONs for use as Theranostics

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Superparamagnetic iron oxide nanoparticles (SPIONs) have the potential to be theranostic materials for the future of personalized medicine. Theranostics are materials that can serve as therapeutic and diagnostic materials. There are a variety of theranostic materials currently being investigated including liposomes, polymers, carbon-nanotubes, just to name a few all with the goal of someday facilitating personalized medicine by helping to determine and administer the right dose, for the right patient at the right time.[1] Currently, there are several commercially available SPIONs being used as contrast agents for magnetic resonance imaging (MRI).[2] However, there is plenty of work to be done to make SPIONs useful for imaging tumors in other organs and to serve as theranostics. Recent advances in SPIONs have focused on *in vivo* studies using SPIONs for MRI and magnetic hyperthermia treatment (MHT),[3] crossing the blood-brain barrier (BBB),[4] and using MHT as a trigger for drug delivery.[5]

Iron oxide nanoparticles are typically regarded as safe materials to use *in vivo*. In fact, SPIONs are biocompatible and currently commercially available as nanomedicine with a wide breadth of uses.[6] However, a great deal of work must be done to understand the technical details of using SPIONs as theranostics before they can be implemented in medicine.

Superparamagnetism, is similar to paramagnetism with the added benefit of high magnetic saturation, a measure of how well the spins of a magnetic material align with an external magnetic field. In paramagnetic materials, unpaired electrons of disordered atoms can align with an applied external magnetic field, but without any long range order, thermal motion prevents paramagnetic materials from establishing high magnetic saturation (Fig. 5a). If paramagnetic materials have enough long range structural order, such as bulk iron, thermal motion does not prevent them from achieving high magnetic saturation (Fig 5b). If paramagnetic materials have short range order, typically <10 nm, they have enough order that thermal motion does not prevent individual spins from aligning with the external magnetic field. Additionally, when an external magnetic field is removed, thermal motion randomizes the superparamagnetic grains thereby resulting in no permanent magnetization.

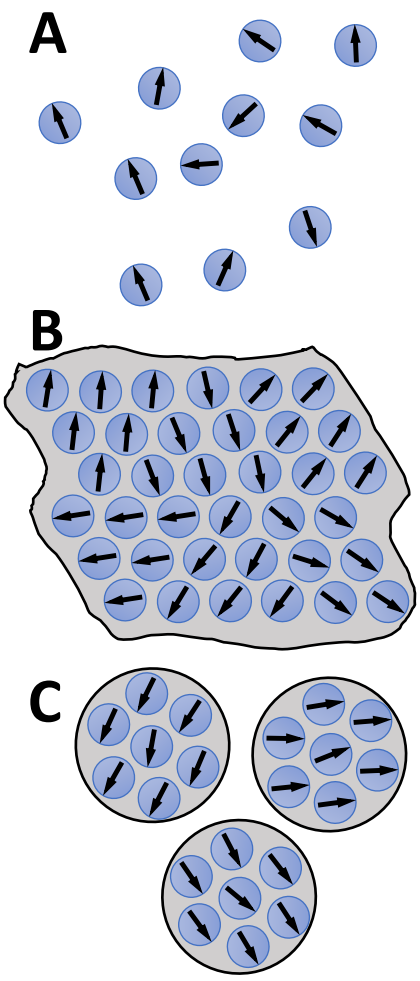

Figure 1. (A) Paramagnetic materials are unstructured individual spins. (B) Ferromagnetic and ferromagnetic materials have long range order. (C) Superparamagnetic materials have single magnetic grains.

In a 2013 *in vivo* study, Hayashi et al. synthesized SPION nanoclusters (NCs) that enhanced the negative contrast of MR images of tumors in rats and used MHT to stunt the growth of tumors in treated rats for 35 days.[3] Hayashi et al. used the synthesis shown in Figure 2 to synthesize SPION NCs coated with polyethyleneglycol (PEG), a biocompatible polymer known to increase the permeability and retention of materials in the blood compartment, using the thiol-ene click (TEC) reaction (Figure 2). This is a significant step because further functionalization of the SPIONs may degrade the macromolecular corona around the NCs unless the PEG has been

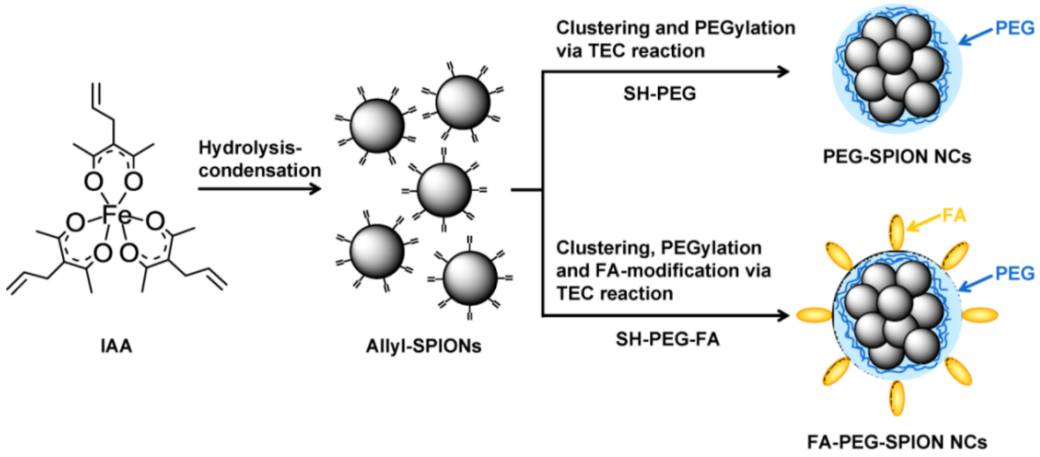

Figure 2: Hayashi et al. created nanoclusters to prevent leakage of SPIONs into undesired locations. They coated these NCs with PEG and FA to for biocompatibility and cancer targeting.

covalently bound to the NC.[7] After PEGylation, the NCs were coated with folic acid (FA) because FA has been found to actively target cancerous cells due to the overexpression of folic acid receptors on the surface of cancerous cells.[8]

In a more recent 2016 study, Huang et al. focused on crossing theranostic materials through the notoriously problematic blood-brain barrier (BBB).[4] The difficulty with entering the BBB stems from the interactions between the endothelial cells of blood vessels and the astrocytes that provide structural support for neurons and blood vessels in the brain. Studies have found that the interaction between endothelial cells of blood vessels and astrocytes in the brain releases signaling hormones that cause the tight junctions between endothelial cells to tighten

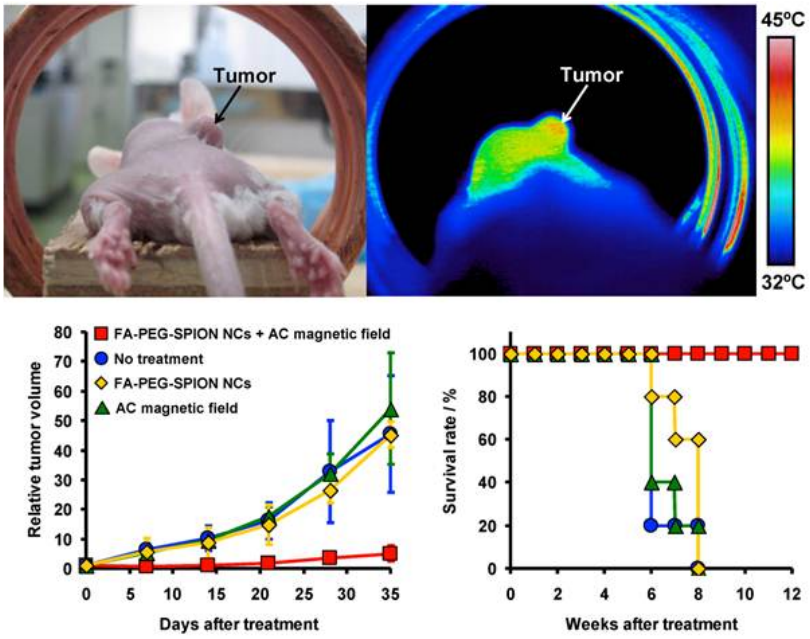

Figure 1: Hayashi et al. used MHT to suppress the tumor growth in rats. Untreated rats were euthanized when their tumors reached 3500 mm^3, whereas treated rats were euthanized after 12 weeks with significantly smaller tumors.

excessively thereby closing the extracellular gap and restricting access to the brain parenchyma to trans-cellular transport.[9] In order to cross the BBB, Huang et al. synthesized SPIONs coated with PEG, PEI, and Tween 80 based on a synthesis from an earlier study.[10] PEG and PEI are known to be biocompatible polymers that enhance the permeability and retention of nanoparticles in the blood compartment. Tween 80 is a detergent that has been found to permit trans-cellular transport of nanoparticles into the endothelial cells of blood vessels in the brain. Although it is not entirely understood how Tween 80 facilitates the passage of nanoparticles through the BBB, existing studies suggest that the mechanism involves the formation of an apolipoprotein corona around the nanoparticles, which may interact with low-density lipoprotein receptors in the BBB.[11]

In summary, this abstract has highlighted the recent work of two papers in the field of theranostic SPIONs. Hayashi *et al* have shown evidence of *in vivo* studies that show the efficacy of using FA-PEG-SPION NCs for MRI and MHT-based tumor suppression. Huang *et* al have shown evidence from *in vivo* studies of FA-PEG-SPIONs successfully crossing the blood brain barrier. Future directions for this work will focus on more rodent *in vivo* studies as there is a large gap in technical knowledge that must be gathered before human testing may begin. Additionally, more work has to be done in coating nanoparticles with drugs and using hyperthermia as a trigger for release as MHT has only been shown to suppress, not eliminate, tumor growth. Despite the obstacles that lie ahead for this field, researchers are confident that SPIONs will provide a medium for enhanced MRI, active targeting of tumors, and effective treatment of cancer with MHT and chemotherapy. As stated by Mornet *et al*, "Today, physicians, pharmacologists, biologists, chemists of organic molecules and macromolecules, physicists and chemists of solid state have to **dream** and to **dream together**."[12]

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