Controlling Nano-Ferrofluid Permeability with Surface Engineering and Their Future Applications

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Statement of Purpose: The blood-brain barrier acts as a wall that separates somatic circulating blood from the cerebrospinal fluid in the central nervous system (CNS). Previous research has demonstrated that small lipid-soluble-molecules which have a molecular weight less than 600 Da can be transported across the blood-brain barrier, suggesting a pathway to design novel nanoparticles which can either be inhibited or promoted to cross the blood brain barrier[1]. As there are concerns about both the delivery of drugs across the blood-brain barrier and the accumulation of ferrofluids in the body, this study controlled the ability of a new type of magnetic materials (ferrofluids) to pass through the blood-brain barrier. Here, an immortalized cell line, b.End3 cells, was used in a blood–brain barrier model to test several variations of magnetic nanoparticles in an effort to both increase blood-brain barrier passage (for neural drug delivery applications) and decrease blood-brain barrier passage (to minimize toxicity). Results provided significant promising evidence that a combination of bioactive ligands used during the *in situ* synthesis of ferrofluids determines whether they cross the blood brain barrier or not.

Methods: According to a patented process[2], five ferrofluids were synthesized by incubating a ferrous/ferric salt solution in phosphate-buffered saline supplemented with the additives of interest such as collagen, poly(vinyl) alcohol (PVA) and/or bovine serum albumin (BSA) using ammonium hydroxide under highly alkaline conditions. After synthesis, ferrofluids were centrifuged for a stability test so that the supernatant byproducts could be washed away. Dynamic light scattering and TEM were used to characterize their diameter and zeta potential was used to characterize the charge of those ferrofluids. An in vitro blood-brain barrier model based on b.End3 cells was then used to test the permeability of the various nanoparticles which were GGB (ferrofluid synthesized using glycine, glutamic acid and BSA), GGC (glycine, glutamic acid and collagen), GGP (glycine, glutamic acid and PVA), BPC (BSA, PEG and collagen) and CPB (collagen, PVA and BSA). For this, nanoparticles were diluted 1:19 with HBSS and then inserts were exposed to them for 2 hours. After 2 hours, a 100 µL solution was taken from each well and an iron assay kit was used to detect the iron concentration for each sample. Each experiment was conducted in triplicate and repeated at least three times[3]. TEM thin sections were used to inspect the mechanism of how the ferrofluids were being transported through the cell layers.

Results: Results showed that the highest permeability was obtained from CPB and the lowest permeability was obtained from GGB. Also ferrofluids synthesized using a combination of collagen and BSA generally had higher permeability than those synthesized using glycine and glutamic acid (Figure 1). These results suggest that for nanoparticles that need to be delivered through the BBB (i.e., for treating neurological diseases), ferrofluids (FF) should be coated with collagen while, on the other hand, FF should be coated with glycine and glutamic acid to keep the nanoparticles from penetrating the BBB (i.e., for whole body MRI imaging to decrease brain toxicity). Cytotoxicity assays were also used to test cytocompatibility of the ferrofluids.

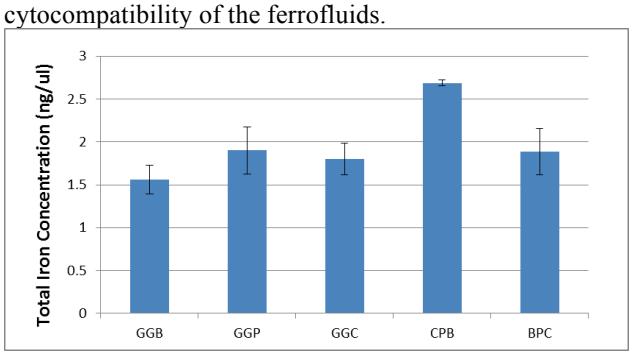

Figure 1. Blood–brain barrier permeability by sample. Data are shown as the mean ± SD, N=3. Abbreviations: GGB (glycine, glutamic acid and BSA), GGC (glycine, glutamic acid and collagen), GGP (glycine, glutamic acid and PVA), BPC (BSA, PEG and collagen) and CPB (collagen, PVA and BSA).

Conclusions: An in vitro model of the blood-brain barrier was established using b.End3 cells. As the permeability decreased with increasing exposure to serum-free medium, the model was confirmed by comparing the permeability of FITC-dextran in serum-free medium with previous research. With the successfully established model, the permeability of five magnetic nanoparticle ferrofluids was examined. The present results suggest a possibility to manipulate magnetic nanoparticle penetration across the blood–brain barrier by controlling the bioactive coatings. Such data lay the foundation for the modification of ferrofluids to be either coated with collagen to pass through blood-brain barrier, or to be coated with glycine and glutamic acid to avoid penetration. In addition, compared to a previous study that focused on characterizing nanoparticles with different combinations of PVA, BSA, glutamic acid and collagen, further affirmation can be stated that as coating candidates, collagen or PVA itself at a low concentration, or combined to glutamic acid or BSA, have good permeability through blood-brain barrier.

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