Non-emulsion clinical gadolinium/perfluorocarbon nanoparticles for 19F MRI

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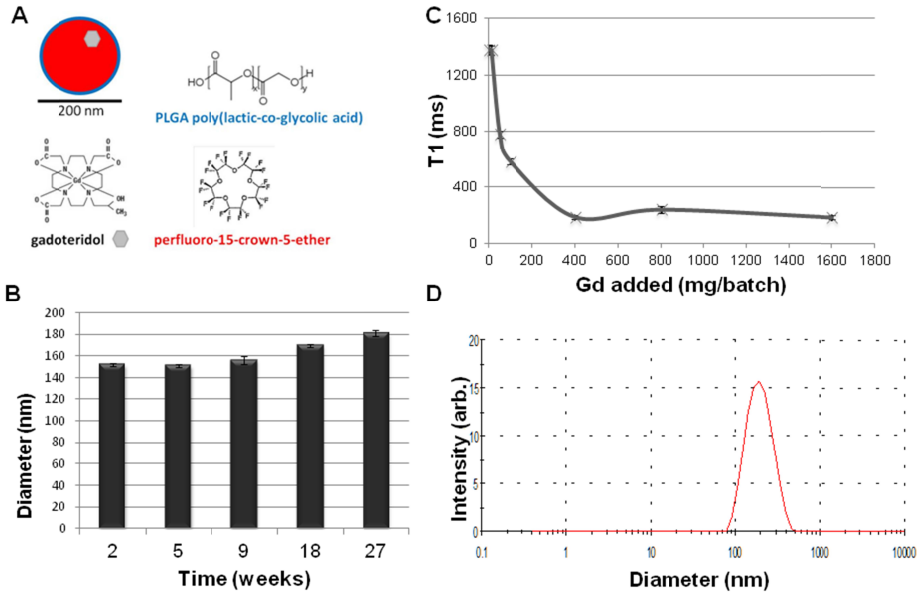
Introduction

^{19}F MRI for quantitative cell tracking may become a key tool for optimizing cellular therapies [1]. We have previously developed polymer-encapsulated perfluorocarbon (PFC) nanoparticles as customizable labels that are clinically applicable [2]. However, insufficient signal-to-noise within a reasonable imaging time is often a problem with ^{19}F MRI. Here, we use a commercial MRI contrast agent, i.e. a gadolinium chelate, to enhance the ^{19}F signal. The co-encapsulation of the hydrophobic perfluorocarbon and the hydrophilic Gd chelate forces close interactions between these nonmiscible compounds (A), and thus effectively changes the ^{19}F longitudinal relaxation time. We label dendritic cells (DCs), as used in clinical trials, with these particles and show the effective ^{19}F signal enhancement obtained.

Methods

Nanoparticles were synthesized as before [2], with the addition of Gd at the amounts stated in the figures (mg of Gd chelate per batch of particles). MRI was done on a horizontal bore 7T animal scanner using a ^{1}H/^{19}F transmit and receive volume coil. Particle stability was measured using dynamic light scattering and ^{19}F NMR. A gradient echo sequence was employed to obtain T1 values using standard techniques. Primary human DCs were cultured, as per standard protocols for DC vaccination trials [3].

Results and Discussion



The nanoparticles have a stable diameter and ^{19}F content, for at least 6 months after formulation (B; this data is for the highest concentration of Gd added). Incorporation of Gd itself had no effect on ^{19}F encapsulation, which remained at 10^{19} fluorines per mg of particles, with no significant difference between batches. There was also no effect on particle diameter, which remained at an average of just under 200nm. A representative diameter distribution is shown (D). We found that the addition of gadolinium decreased the dominant ^{19}F T_1 value (C). The particles are also detectable via their effect on the ^{1}H relaxivity. Finally, we found no effect of labeling on the DCs even at the highest concentration of Gd, which can otherwise be toxic to cells (not shown). We found maximum SNR enhancement at 3T, with the highest concentration of Gd (C; at 7T). This effect was lower at higher field strengths, as expected. Finally, we also found that Gd affected the ^{19}F T_2, although to a smaller extent. Gd has been shown previously to enhance ^{19}F signal in perfluorocarbon emulsions [4]. However, our use of nanoparticles ensures close contact between the Gd and ^{19}F nuclei and thus allows us to use commercial, clinically approved hydrophilic Gd chelates, without further modification (A).

Conclusion

Gd has previously been used to modify ^{19}F relaxivity [e.g. ref. 4]. However, the low miscibility of perfluorocarbons and Gd chelates has been a problem, affecting emulsion stability and reducing the efficacy of the Gd. Here, our use of a polymer coat to force close proximity between the compounds allows for a strong and stable effect on ^{19}F relaxivity, which was sustained for at least 6 months.

Acknowledgements

This research was supported by investment grants NWO VENI 700.10.409, middelgroot 40-00506-90-06021 and BIG (VISTA); ENCITE (HEALTH-F5-2008-201842); and Spinoza.

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