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## Core-shell PLA nanofibers@SPIONs nanocomposites with enhanced properties for biomedical imaging and magnetic applications

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### Introduction

Composites combining superparamagnetic iron oxide nanoparticles (SPIONs) and polymers are largely present in modern (bio)materials [1,2]. However, while SPIONs embedded in polymer matrices are classically reported, this approach fails in the case of electrospun nanocomposites where the incorporation of SPIONs results not only in beaded defects and a larger distribution in the diameter of the fibers, but also strongly impacts their mechanical and degradation properties, as well as the magnetic properties. Therefore, the controlled anchoring of SPIONs on polymer surfaces is still a major challenge. Herein, we propose an efficient strategy for the direct and uniform anchoring of SPIONs on the surface of functionalized-poly(lactide) (PLA) nanofibers via a simple free ligand exchange procedure to design PLA@SPIONs core@shell nanocomposites to be used as multifunctional scaffolds with magnetic and imaging properties [3]. A long term in vivo evaluation of the magnetic nanocomposites in terms of MRI visualization and tissue integration is discussed.

### Experimental Methods

Electrospun PLA nanofibers are chemically modified to generate alkyne surface groups [4]. Bifunctional thiol-phosphonic ligand is covalently bound to the surface by thiol-yne photoaddition. Finally, SPIONs are anchored on the PLA fibers via a free ligand exchange procedure. PLA@SPIONs hybrid biomaterials are characterized by electron microscopy (SEM and TEM) and EDXS analysis, to probe the morphology and detect elements present at the organic/inorganic interface, respectively. Magnetic properties are assessed in vitro by using a Quantum Design MPMS-XL SQUID magnetometer working in the 1.8–350 K temperature range with the applied magnetic field up to 7 T. MR imaging was performed on a Bruker Biospec 70/20 system operating at a magnetic field of 7T (Bruker, Wissembourg, France) using a 72-mm diameter birdcage resonator and a respiratory triggered RARE sequence

(effective repetition time TR ~ 2000 ms; rat breathing rate 40-50/min; effective echotime TE<sub>eff</sub> = 23 ms; RARE factor = 8; FOV = 55mm × 55mm; matrix 256 × 256, slice thickness= 1 mm and 8 accumulations). Host-tissue morphologic response to the presence of the scaffolds was assessed by histopathology with hematoxylin-eosin-suffran (HES) and Perls staining.

### **Results and Discussion**

The morphology and core-shell structure of the PLA@SPIONs nanocomposites were fully characterized by electron microscopy (SEM and TEM) and EDXS, revealing the homogeneous coverage of the nanofiber surface by a quasi-monolayer of SPIONs corresponding to 8 wt% of SPIONs. In contrast to classic magnetic composites, magnetization experiments proved that the magnetic properties of the SPIONs are well-preserved after their anchoring on the PLA fibers and that no aggregation occurred. Following an initial cytotoxicity study showing no toxicity of the PLA@SPIONs nanocomposites, their implantation in rats was performed to confirm the high sensitivity of detection obtained in vitro using standard T2-weighted spin echo sequence. PLA@SPIONs were easily detected using the same sequence in a pre-clinical MR scanner with a clear hypointensity due to the SPIONs anchored at the surface of the PLA fibers and acting as superparamagnetic contrast agents. Even at 6 months post-implantation, the PLA@SPIONs were easily detected and were still clearly distinct from the surrounding tissues. Histological data highlighted a moderate chronic inflammatory reaction that was similar for both PLA and PLA@SPIONs nanofibers. Thanks to Perls staining, the role of macrophages in the degradation of the scaffolds and in the elimination of the SPIONs was clarified. Finally, it also showed similar degradation/integration behavior for the PLA@SPIONs nanofibers compared to PLA fibers thus confirming our initial hypothesis that the herein proposed strategy allows obtaining magnetic nanocomposites without alteration of the degradation properties of the nanofibers.

### **Conclusion**

This set of data confirms the soundness of the proposed strategy that, through an efficient anchoring of SPIONs at the surface of PLA nanofibers, yields magnetic core shell nanocomposites with i) maintained magnetic properties compared to free SPIONs, ii) that allow a clear and long-term MRI visualization despite low SPIONs content, iii) whose tissue integration and degradation are similar to the ones of pure PLA. Overall it confirms the potential of this new class of core-shell magnetic nanocomposites that opens new opportunities in the field of magneto-scaffolds.

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