

## Development of Superparamagnetic Nanoparticles for Magnetic Imaging and as Drug Vectors for Therapy

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The use of Super Paramagnetic Iron Oxide Nanoparticles (SPIONs) (Fig.1) combined with MRI is under clinical evaluation to enhance detection of neurodegenerative diseases.

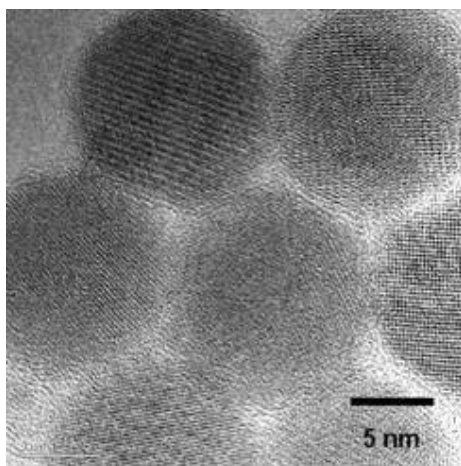


Fig. 1: Transmission electron micrograph (TEM) showing iron oxide particles in the 10 nm range.

A major improvement would be to link therapeutic drugs to the SPIONs to achieve targeted drug delivery, either at the cell surface or intracellularly, together with active disease detection, without inducing cell reaction. Our objectives are to define the characteristics of SPIONs able to achieve cell-specific interaction with brain-derived structures.

Our system consists in an ironoxide core (9-10 nm diameter) coated either with polyvinylalcohol (PVA) (native nanoparticles) or with PVA which has been functionalized on the hydroxyl groups with either amino (aminoPVA), carboxylate (carboxylatePVA) or thiol (thiolPVA) groups. We investigated the cellular uptake, the cytotoxicity and the interaction of these various nanoparticles with brain-derived endothelial cells, microglial cells and differentiating 3-dimensional aggregates.

Only aminoPVA-SPIONs were taken up by brain cells, but did not invade brain cell aggregates lower than the first cell layer. Fluorescent aminoPVA-SPIONs demonstrated cell interaction with brain-derived endothelial and microglial cells

and intracellular uptake by microglial cells using confocal microscopy. No cytotoxicity or inflammatory reaction was observed as determined by cell respiratory potential, death, the production of the inflammatory mediator nitric oxide or the expression of inflammatory markers. AminoPVA-SPIONs neither invaded brain cell aggregates lower than the first cell layer nor induced microglial cell activation in the aggregates.

In order to develop therapeutics-derivatized-SPIONs and to couple defined molecules for targeted detection and drug-delivery purposes, we have designed and synthesized a multivalent linker, to which drugs are covalently coupled via a biologically labile linkage before the preparation of derivatized SPIONs (Fig 2).

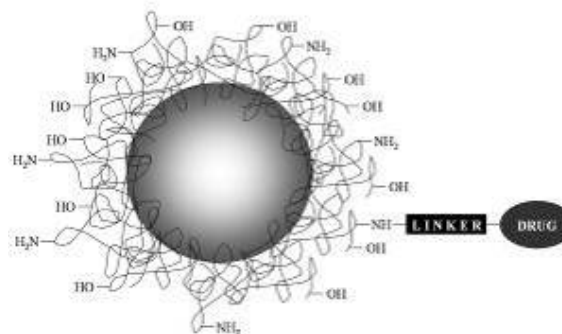


Fig. 2: Model SPIONs under evaluation, with a linker coupled to a therapeutic drug

**REFERENCES:** <sup>1</sup> M. Chastellain, A. Petri and H. Hofmann (2004) *J. Colloid and Interface Science* **278**: 353-360 <sup>2</sup>A. Petri-Fink, M. Chastellain, L. Juillerat-Jeanneret, et al. (2005) *Biomaterials* **26**: 2685-2694 <sup>3</sup>F. Cengelli, D. Maysinger, F. Tschuddi-Monnet, et al. (2006) *J. Pharm. Exp. Ther.*, in press.