

ENRICHMENT AND BIODISTRIBUTION OF A MAGNETICALLY TARGETED DRUG CARRIER

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INTRODUCTION: Biocompatible ferrofluids are superparamagnetic nanoparticles, that may be used as a delivery system for anticancer agents in locoregional tumor therapy, called “magnetic drug targeting.” Through this form of target directed drug application, one attempts to concentrate a pharmacological agent at its site of action in order to minimize unwanted side effects in the organism and to increase its loco-regional effectiveness [1]. Ferrofluids have been used in medicine since the 1960’s for magnetically controlled metallic thrombosis of intracranial aneurysms [2] and magnetically guided selective embolization of the renal artery in case of a renal tumor [3], for example. Ferrofluids have also been used as a contrast agent for MRI in the diagnostic evaluation of liver and spleen tumors [4]. Furthermore ferrofluids have been used for a specific cell separation method called “immuno-magnetic cell separation” for the early detection of cancer [5], and have also been an important subject in the development of an implantable artificial heart [6].

application no. 19624426.9) and consisted of a colloidal dispersion of iron oxides and hydroxides. The particles were surrounded by starch polymers for stabilization under various physiological conditions and to allow ionic binding to chemotherapeutic agents or to form a complex with iodine [7].

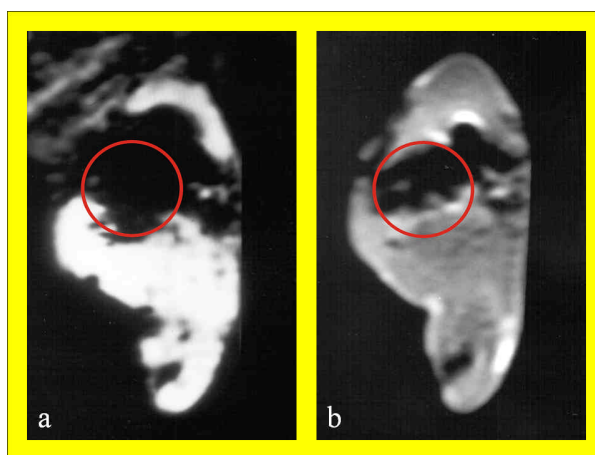


Fig. 2: Magnetic resonance imaging of rabbit’s left hind limb following intraarterial ferrofluid application; (a) T2-weighted, (b) T1-weighted imaging technique.

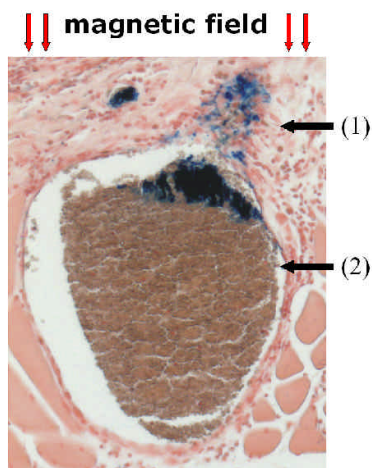


Fig. 1: Section of the tumor removed after treatment with ferrofluids stained with Prussian blue. The orientation of the ferrofluid to the gradient of the magnetic field is clearly visible in the tumor tissue (1) and in the vascular lumen (2).

MATERIALS AND METHODS: The ferrofluids used in the experiments were obtained from Chemicell (Berlin, Germany; German patent

The ferrofluids were injected into the tumor supplying artery (femoral artery) of tumor bearing rabbits (squamous cell carcinoma at the medial portion of the hind limb). An external magnetic field was focused on the tumor for 60 min. Enrichment of ferrofluids in tumor tissue was documented in vivo by histological analysis (five μm thick paraffin sections of the tumor were cut and stained with Prussian Blue) (Fig. 1) and by magnetic resonance imaging (T1- and T2-weighted MRI) using an electro-magnetic field with a strength of 1.7 Tesla (Fig. 2). Biodistribution was studied semi-quantitatively by the use of ^{123}I -labeled nanoparticles focused by an external magnetic field (permanent magnet) of 0.6 Tesla (Fig. 3), and quantitatively with radioactive ^{59}Fe -ferrofluids using an external magnetic field of 1.7 Tesla (electromagnet) (Fig. 4).

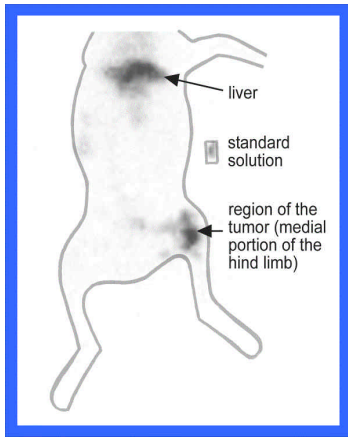


Fig. 3: Enrichment of ^{123}I -labeled nano-particles in the region of interest (VX2-tumor) after “Magnetic Drug Targeting.” This image was taken 10 minutes after application, still showing stable concentration of ferrofluids in the tumor region. Sedimentation characteristics of ferrofluids were investigated in vitro. A ^{125}I -ferrofluid suspension was incubated in 96-well-plates in magnetic field strengths of 0, 0.2 and 0.4 Tesla. Activities of the upper and the lower phases were determined (Fig. 5).

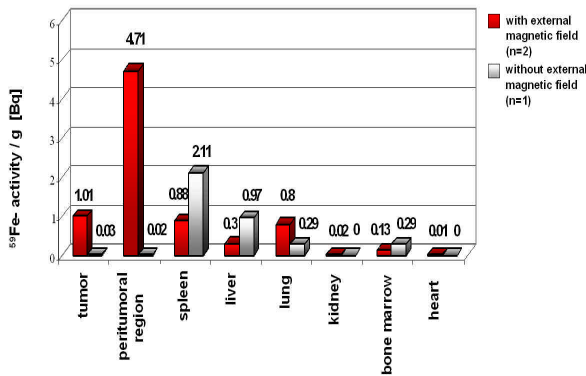


Fig. 4: Radioactive ^{59}Fe -distribution 60 minutes after intraarterial application.

RESULTS: In histological investigations, we could demonstrate enrichment of ferrofluids in tumor tissue (Fig. 1). MRI investigation revealed a definitive extinction of signal in the area of the tumor, which was caused by the enrichment of ferrofluids due to the magnetic field (Fig. 2). The scintigraphically detected ^{123}I -signal has been shown to be significantly higher in the magnetically focused region compared to application without magnetic field (Fig. 3).

^{59}Fe -ferrofluids could be concentrated in the tumor area by a factor of 235 using an external magnetic

field compared to the absence of a magnetic field. In vitro studies using ^{125}I -labeled ferrofluids showed sedimentation to be dependent on magnetic field strength (Fig. 5). No sedimentation was found with gravitation alone (triangles). By using permanent magnets a logarithmic dependency was observed. The fraction of sedimentation was not doubled by doubling the strength of the magnetic field.

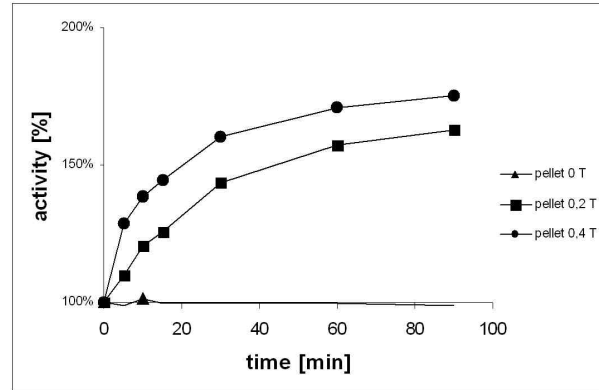


Fig. 5: Activity of sedimentary ^{125}I -labeled nanoparticles in dependence on magnetic field strength and time in the lower phase.

DISCUSSION & CONCLUSIONS: Besides conventional investigation (i.e. histological cross sections and MRI), the biodistribution studies with radioactive labeling showed enrichment of ferrofluids targeted by a focused magnetic field and also, semi-quantitatively and quantitatively, a high and selective concentration in the tumor region. In vitro data indicate a strong dependency of sedimentation on the magnetic field strength.

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