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In-Situ Forming Implant for Application of Local Hyperthermia in Cancer

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INTRODUCTION

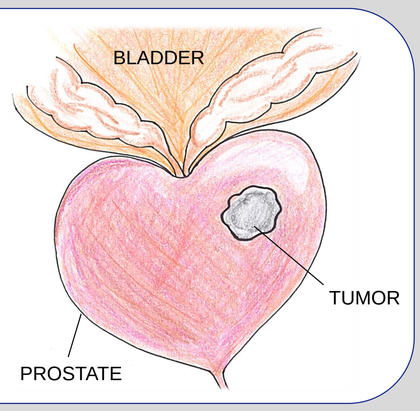
The aim of this work is to develop an *in-situ* forming implant as local, injectable tumor treatment by magnetically-induced hyperthermia based on iron oxide nanoparticles.

Superparamagnetic iron oxide nanoparticles (SPIONs) consist of one single magnetic domain randomly changing its magnetization direction. Submitted to an **alternating magnetic field**, SPIONs can dissipate **heat** as a form of energy loss during relaxation.

In contact with human tissue and reaching a threshold temperature of 42° C, apoptosis of surrounding cells will be provoked [1].

Prostate cancer shows the third highest mortality of cancerous diseases in men in Europe [2].

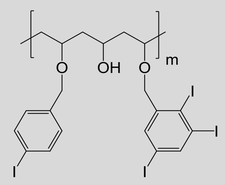
The optimal therapy scheme for locally confined prostate carcinoma is controversial, since common treatments like radical prostatectomy are accompanied by significant side effects.

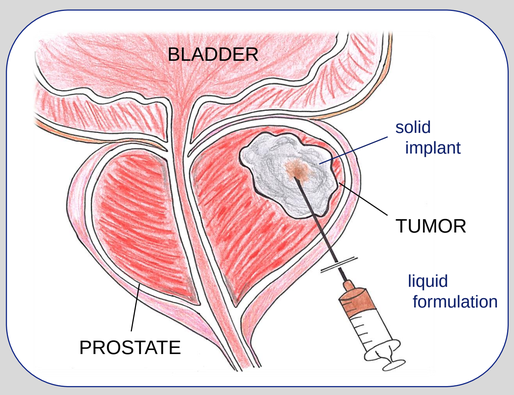


Radiopacity of the polymer is required for *in-vivo* real-time monitoring of implant distribution using X-ray imaging.

FORMULATION

SPIONs embedded in mesoporous silica, suspended in a solution of radiopaque mono-/ tri-iodo benzyl-ether polyvinylalcohol (**MTIB-PVA**) in DMSO.





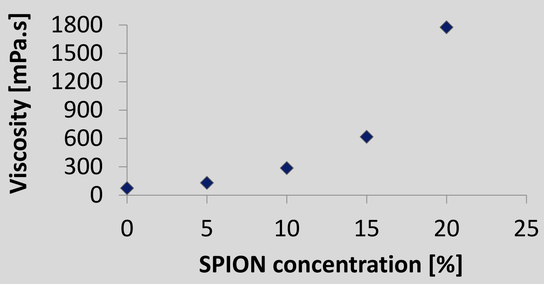
ROUTE OF ADMINISTRATION

Minimally invasive injection:

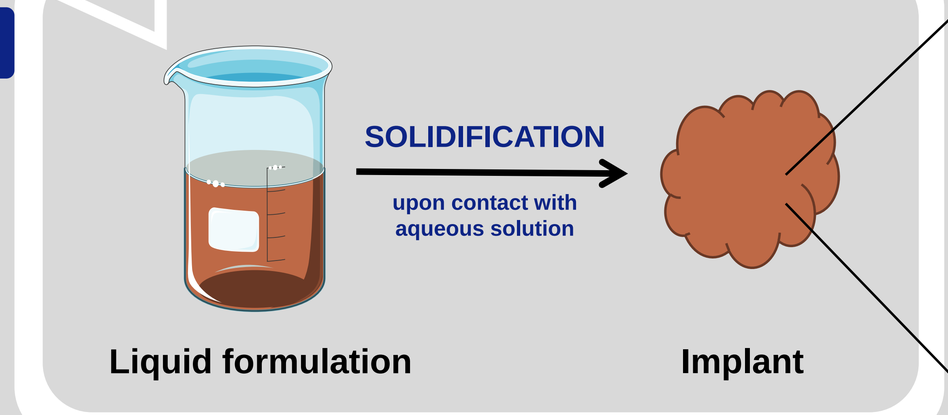
liquid formulation solidifying as a **semisolid implant** upon contact with body fluids due to the insolubility of the polymer in aqueous solution.

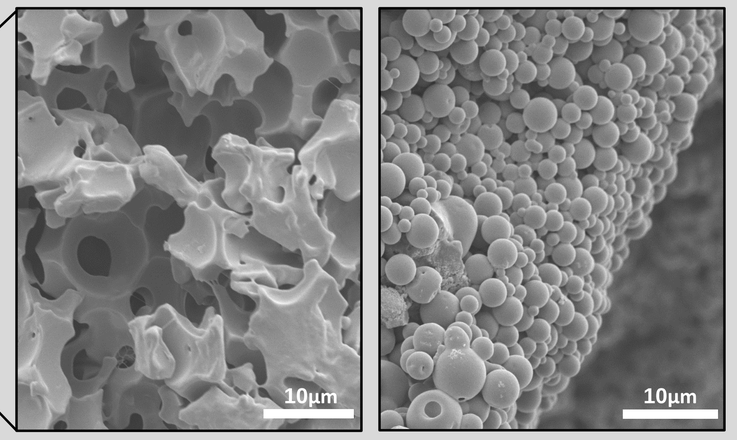
CHARACTERIZATION

INJECTABILITY



The concentration of SPIONs is limited by the viscosity of the formulation to ensure an appropriate injectability.



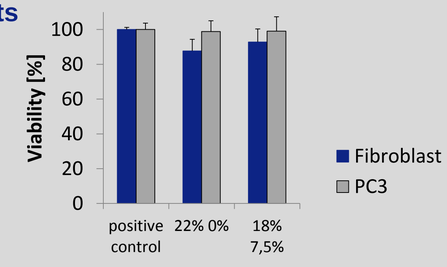


Scanning electron microscopy pictures of a precipitated implant and entrapped silica-SPION-beads

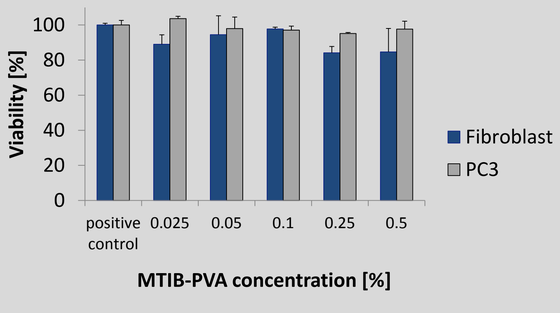
IN-VITRO CYTOTOXICITY

No significant cytotoxicity of two different implants and of the polymer MTIB-PVA was observed on human PC3 cells (prostate cancer cells) and fibroblasts (healthy cells), based on the threshold of 80% cell viabililty compared to untreated cells (positive control):

Implants

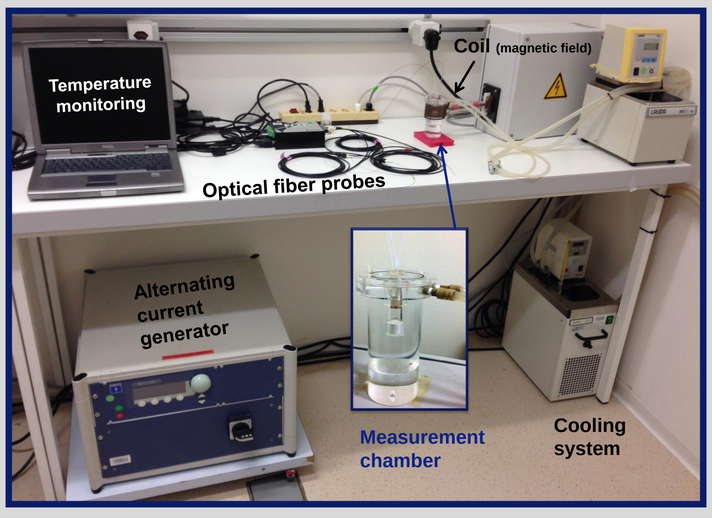


Polymer solution

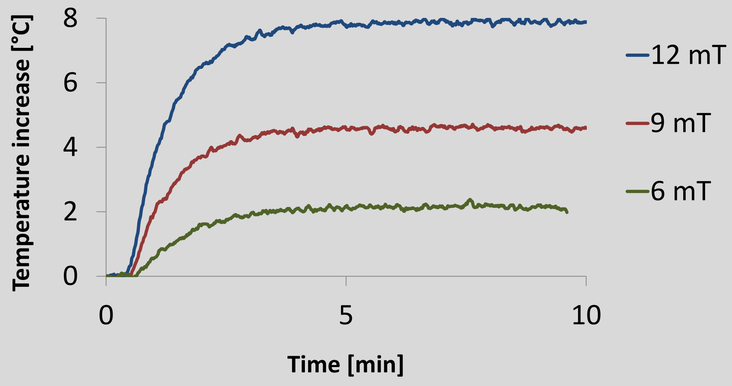


Cell viability measured by WST-1 after an exposure time of 48h

HEATING MEASUREMENTS



Experimental set-up for heating measurements



Temperature increase of implant exposed to alternating magnetic fields at 300 kHz

Mimicking *in-vivo* conditions by keeping the implant surrounded by circulating, thermostated water at 37° C, a SPION-induced temperature increase of the implant up to 8° C was measured, expected to locally induce cell apoptosis.

CONCLUSION

The formulation of SPIONs embedded in silica and suspended in a radiopaque polymer solution shows an **adequate injectability** and forms a **porous, homogeneous implant** upon contact with aqueous solution. This implant is able to dissipate the required heat for **local tumor thermotherapy**. Newly developped SPIONs are under investigation to reach the required temperature elevation at lower magnetic field strengths.

REFERENCES

[1] Hildebrandt B et al. Crit Rev Oncol Hematol 2002; 43: 33-56. [2] Malvezzi M et al. Ann Oncol 2014; 25: 1650-6.