Sucrose acetate isobutyrate based nanogels as liquid fiducial tissue markers with potential use in image guided radiotherapy

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SUMMARY
Sucrose Acetate IsoButyrate (SAIB)-based radiopaque fiducial tissue markers containing coated gold nanoparticles (AuNPs) have been developed. One of these formulations, the PNIPAM (poly(N-isopropyl acrylamide))-AuNP-SAIB based gel, was assessed to be a suitable marker for image guided radiotherapy (IGRT).

INTRODUCTION
IGRT is an important tool used to visualize tumors during radiation treatment. Tumors rarely display a fixed position during irradiation or within a treatment period due to breathing motion, changes in organ filling and tumor size. Radiopaque fiducial tissue markers are therefore of great interest to place within - or around tumors in order to achieve high precision in IGRT. Better markers will enable improved tumor coverage i.e. the destruction of all cancer tissue. Furthermore, it is important to have a safer and more accurate setup for tumor treatment in radiotherapy - including adaptation of online “tumor-tracking” – thereby delivering high radiation doses to tumors with minimal damage to surrounding healthy tissue [1].

EXPERIMENTAL METHODS
The poster presents the development of novel injectable liquid fiducial markers based on formulations of SAIB and polylactide (PLA) containing coated AuNPs. A mixture of SAIB/EtOH/PLA (75:20:5) was used as matrix due to its high biocompatibility, low viscosity, as well as its ability to form a stable, biodegradable gel depot upon injection [2]. Three different AuNP coating systems were tested – a dithiolane functionalized SAIB derivative, synthesized in four steps starting from sucrose, together with PEG- and PNIPAM polymers, respectively. The AuNPs were synthesized by a three step seeding protocol using chloroauric acid as Au+3 source and trisodium citrate as reductant and stabilizer. In vitro release from SAIB gels was studied in PBS-buffer at 37°C. Gels (200µL) containing SAIB/EtOH/PLA (75:20:5) + 30mg PNIPAM-AuNPs mL-1 or 10mg PEG-AuNPs mL-1 were injected subcutaneously at the upper left flank of immunocompetent NMRI-mice using hypodermic 25G needles. The gel-depots were visualized by micro-CT imaging.

RESULTS AND DISCUSSION
The dithiolane functionalized SAIB derivative was discarded as a coating option due to irreversible aggregation of the formed nanoparticles. The SAIB gels containing PEGylated AuNPs provided high CT contrast in vivo, however it suffered from AuNP migration towards the gel-boundaries resulting in an inhomogeneous distribution of contrast agent. The PNIPAM-coated-AuNP-SAIB gel provided both excellent CT contrast and high in vivo stability. Furthermore, the PNIPAM-coated-AuNPs are easy to handle, as they can be lyophilized and stored as an air stable powder, which is readily dispersible in ethanol.

CONCLUSION
The PNIPAM-AuNP-SAIB gel showed high stability, biocompatibility and provided high CT contrast in vivo. This gel is a viable alternative to existing liquid fiducial markers.

REFERENCES