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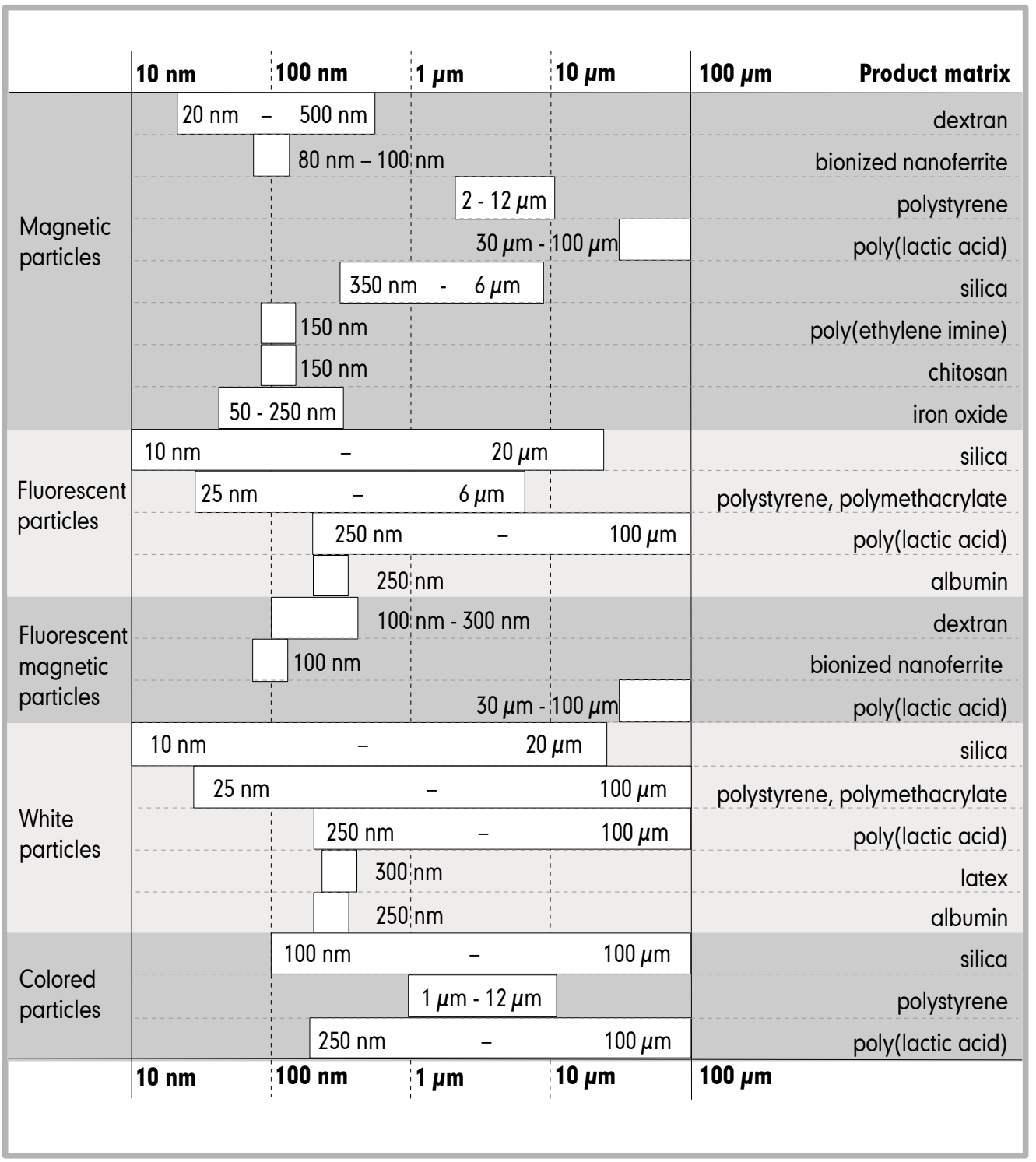

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8 Targeting applications with magnetic nanoparticles

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8.1 Magnetic nanoparticles for targeted magnetic resonance imaging (MRI) applications

The high spatial resolution of magnetic resonance imaging (MRI) is ideally suited for detection of cancer and assessment of response to therapy. Up to now MRI has found limited application in tumor imaging due to a lack of sensitivity. Advances in the use of magnetic nanoparticles (MNP) have the potential to address this limitation. Due to their large magnetic moments MNPs significantly increase MRI R_1 and R_2 relaxivities, leading to a marked reduction in T_1 and T_2 times. This allows sensitive visualization *in vivo*. Clinical application of MNPs as contrast agents has been demonstrated with Endorem®, Feridex® and Resovist®. These MNPs are not tumor specific *per se* but instead provide positive contrast in tumors based on their uptake by healthy phagocytic cells in preference to cancerous cells [1]. The development of specific antibody labeled MNPs has a high potential to improve the selective MR imaging of tumor cells. Here we report on different strategies for the design of antibody conjugated MNPs for targeted MRI for different cancer cell types.

8.1.1 MR imaging of carcinoembryonic antigen (CEA)-expressing human tumor cells

Vigor et al. have generated antibody-functionalized MNPs using a single chain Fv antibody fragment (scFv) specific for carcinoembryonic antigen (CEA), an oncofoetal cell surface protein. Nanomag®-D-spio particles with diameters of 20 nm and 50 nm and different surface modifications were investigated. The antibody fragments were conjugated to the surface of the plain dextran particles via periodate activation of the dextran-OH groups or by carbodiimide (EDC)/ N-hydroxysuccinimide (NHS) activation of nanomag®-D-spio particles with PEG-COOH surface groups (Figure 1).

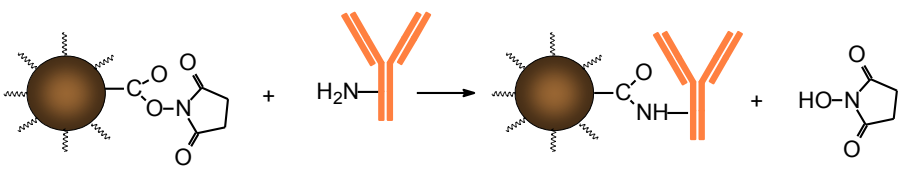

Figure 1. Activation of MNPs with COOH groups on the surface with EDC (1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide) and NHS (N-hydroxysuccinimide) for conjugation with amino groups of the antibody

The targeting was confirmed by ELISA, cellular iron uptake, confocal laser scanning microscopy and MRI. The results demonstrated that the scFv-conjugated MNPs bound specifically to CEA-expressing human tumor cells, generating selective image contrast in MRI. The cellular interaction of the MNPs was influenced by hydrodynamic size and surface coating [1].

8.1.2 MR imaging of lymphocytes

Luchetti et al. found that monoclonal antibodies conjugated with superparamagnetic nanoparticles allow MRI detection of lymphocytes in the mouse brain. Different types of MNPs were conjugated with anti-mCD3 or anti-mB220 antibodies. Therefore the binding of biotinylated antibodies to the surface of streptavidin-modified particles was compared with the direct covalent binding of non-modified antibodies to the surface of 50 nm nanomag®-D-spio, and 250 nm nanomag®-D particles by EDC/ NHS chemistry (Figure 1). These vectorialized MNPs were successfully employed to image B220+ cells in murine model of B-cell lymphoma. The specificity of the technique was confirmed by immunohistochemistry and electron microscopy. It was found that indirect antibody binding to streptavidin-modified MNPs allowed for enhanced particle vectorialization compared to covalent binding of the antibody to the particles [2].

8.1.3 MR imaging of prostate cancer cells

Many types of prostate cancer cells express high levels of prostate-specific membrane antigen (PSMA) on their cell surface. Abdolahi et al. studied the use of MNPs attached to an antibody that binds to the extracellular domain of PSMA, to specifically enhance the contrast of PSMA-expressing prostate cancer cells. Therefore the selective J591 mAb was conjugated to 20 nm nanomag®-D-spio particles with PEG-NH2 groups on the surface by maleimide chemistry (Figure 2.). These J591-nanoparticle conjugates were evaluated *in vitro* for specific detection of prostate cancer by MRI. Cell uptake experiments with two types of prostate cancer cell lines demonstrated the high potential of the antibody-nanoparticle conjugate as specific contrast agent for PSMA-expressing prostate cancer cells [3]

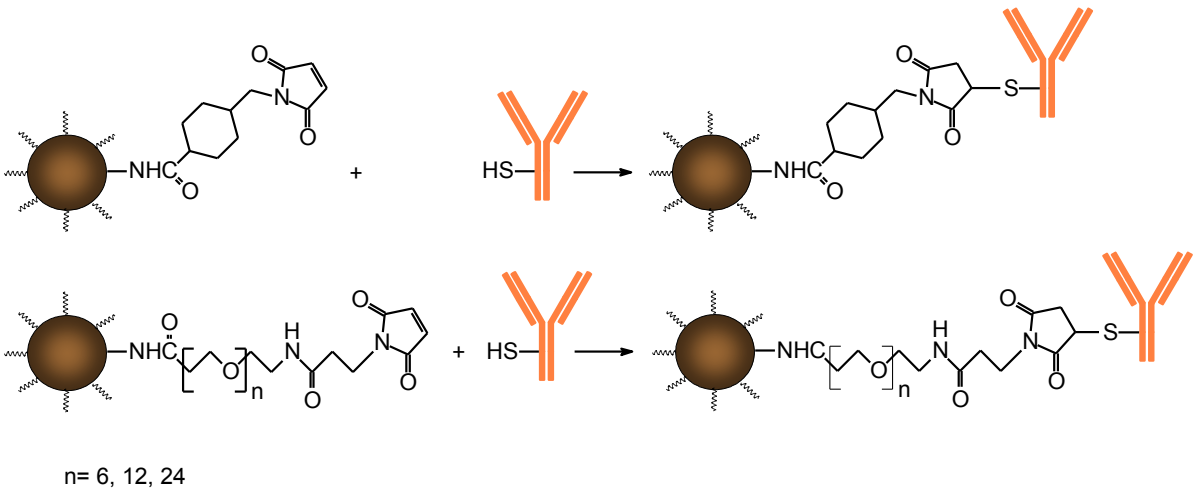

Figure 2. Functionalization of MNPs with amino groups on the surface with maleimide or PEG-maleimide groups for conjugation with thiol groups of the antibody

8.1.4 C595 antibody conjugated particles for MR imaging of ovarian and breast cancer cells

In another approach Shahbazi-Gahrouei and Abdolahi conjugated C595 mAb against MUC1-expressing ovarian cancer cells to the surface of 20 nm nanomag®-CLD-spio particles by maleimide chemistry (Figure 2). This potential MRI contrast agent for ovarian cancer detection was investigated *in vitro* and *in vivo* (mice). No cytotoxicity of the conjugate was found. MRI and biodistribution results showed good tumor accumulation and high sensitivity in detection [4, 5]. Shanehsazzadeh et al. also investigated C595 mAb conjugated 20 nm nanomag®-CLD-spio particles *in vitro* and *in vivo* for breast cancer imaging. In addition the antibody conjugated MNPs were radiolabeled with ^{99m}Tc for biodistribution studies. The conjugate showed considerable targeting yield for uptake in MUC1-positive breast cancer cell lines *in vitro*. In contrast to the results of the *in vivo* study of Shahbazi-Gahrouei and Abdolahi [5] the radiolabeled nanoprobe showed a high accumulation in liver and spleen demonstrating a significant reduction of the *in vivo* targeting. The reason for these different *in vivo* results could be the different tumor models (ovarian and breast cancer model) or a change of the surface properties of the nanoprobe by the radiolabeling process [6].

8.1.5 Detection of chronic obstructive pulmonary disease (COPD) by targeted MRI

Chronic obstructive pulmonary disease (COPD) was predicted to be the third leading cause of death by 2020. Al Faraj et al. studied the targeting and MR imaging of a specific alveolar macrophage subpopulation in lipopolysaccharide-induced COPD using antibody-conjugated MNPs [7]. The *in vivo* effect of pulmonary administration of MNPs on the polarization profile of macrophages was assessed, and a noninvasive free breathing MRI protocol with the use of antibody conjugated 20 nm nanomag®-CLD-spio particles was developed. CD86 or CD206 antibodies were covalently attached on the surface of PEG-NH_2 functionalized particles by maleimide chemistry (Figure 2). The MNPs were found to be biocompatible for lung administration in preclinical settings. Cluster of differentiation of CD86- and CD206-conjugated nanomag®-CLD-spio particles enabled successful noninvasive detection of M1 and M2 macrophage subpopulations. The particles were found to co-localize with inflammatory regions induced by lipopolysaccaride challenge and could offer a promising strategy for an early and better diagnosis of pulmonary inflammatory diseases using noninvasive MRI [7].

8.1.6 High specificity targeting and MR detection of human neuroblastoma using multifunctional anti-GD2 nanoparticles

Baiu et al. have developed biocompatible, tumor-specific multifunctional magnetic nanoparticles for the targeting of neuroblastoma, an aggressive pediatric malignancy [8]. Therefore clinical-grade humanized monoclonal antibody (hu14.18K322A) designed to target GD2 antigen on neuroblastoma with reduced nonspecific immune interactions was conjugated to 80 nm BNF-Starch nanoparticles by maleimide conjugation (Figure 2). The targeting capability *in vitro* and *in vivo* was assessed by immunofluorescence, electron microscopy, analytical spectrophotometry, histochemistry and magnetic resonance R2* relaxometry. The biocompatible nanoconstructs

demonstrated high tumor specificity *in vitro* and *in vivo*, and low background uptake in a mouse flank xenograft model. Specific accumulation in tumors enabled particle visualization and quantification by magnetic resonance R2* mapping (Figure 3). This anti-GD2 iron-oxide nanoconstruct was shown to be an interesting diagnostic and therapeutic scaffold for neuroblastoma and potentially other GD2-positive malignancies and should be further developed toward clinical application [8].

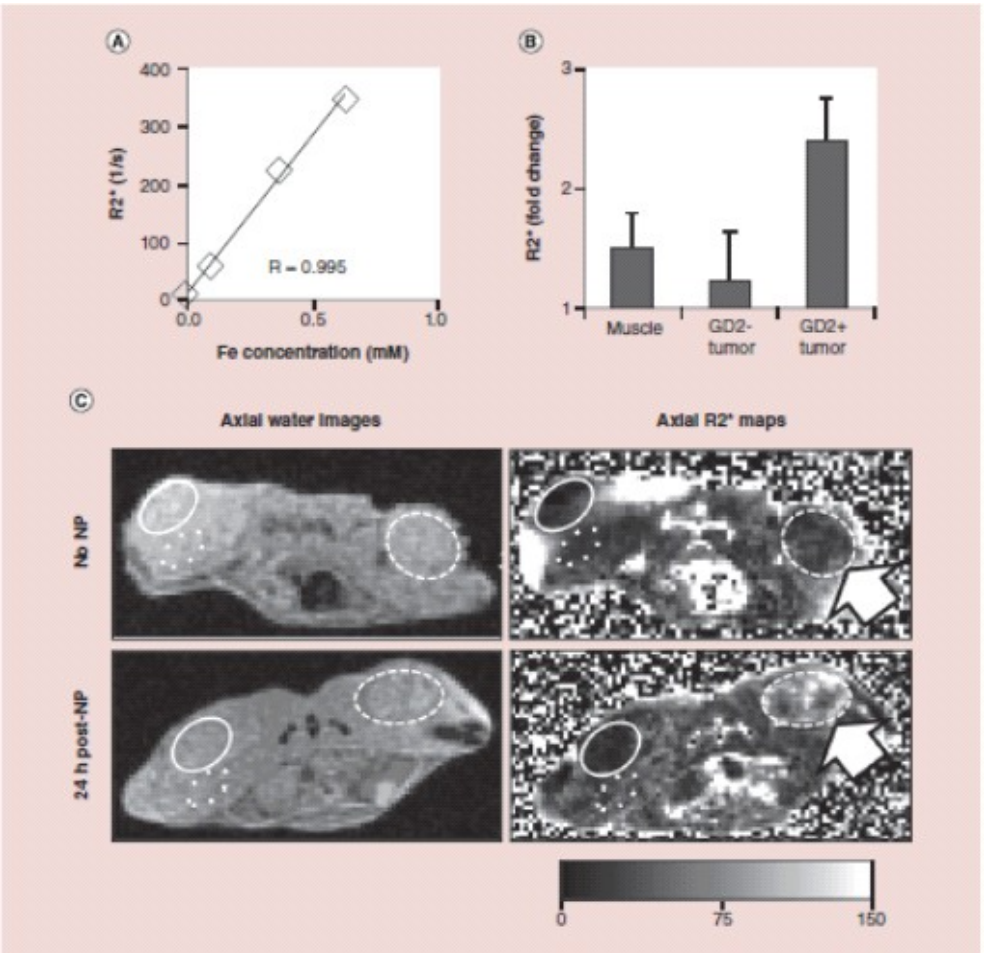

Figure 3. Iron oxide nanoparticles in GD2+ xenografts are detectable by magnetic resonance. (A) Correlation between MR R2* values and iron concentration for BNF nanoparticle phantoms (linear regression, coefficient R = 0.995). (B) R2* fold change in GD2+ tumors, GD2– tumors and muscle in mice 24 h after anti-GD2-BNF injection versus mice with no treatment. Averages ± standard deviation, n = 2. (C) MR images (method parameters B) of a noninjected mouse (upper panels) and a mouse 24 h after intravenous anti-GD2-BNF NP administration shows elevated R2* for the injected mouse in the GD2+ tumor (arrow). Region of interest defined on water images (left panels) and corresponding R2* images (right panels) circumscribe GD2+ xenografts (CHLA-20, dashed line), GD2–xenografts (PC-3, solid line) and control skeletal muscle (dotted). Representative images of two experiments with two separate anti-GD2-BNF batches.

8.1.7 Non-invasive detection of complement activation in placenta and foetal brain in an *in vivo in utero* model by MRI

Girardi et al. found that anti-complement C3-targeted 20 nm nanomag®-D-spio bind within the inflamed placenta and foetal brain cortical tissue, causing a shortening of the T2* relaxation time. Two mouse models of pregnancy complications were used in the study. The detection of C3 deposition in the placenta in the antiphospholipide syndrome (APS) model was associated with placental insufficiency characterized by increased oxidative stress, decreased vascular endothelial growth factor and placental growth factor levels and intrauterine growth restriction. The foetal brain C3 deposition was associated with cortical axonal cytoarchitecture disruption and increased neurodegeneration in both mouse models. Importantly, the C3-targeted nanomag®-D-spio particles did not affect pregnancy outcomes and liver function in the mother and the offspring, suggesting that this method may be useful for detecting complement activation *in vivo in utero* and predicting placental insufficiency and abnormal foetal neurodevelopment that leads to neuropsychiatric disorders [9].

8.1.8 Diagnosis and treatment of acute temporal lobe epilepsy with anti-IL-1b conjugated MNPs by MRI

Temporal lobe epilepsy (TLE) is the most prevalent form of adult focal onset epilepsy and is often associated with pharmacological resistance. A hallmark in the neuropathology of TLE is brain inflammation, in particular the activation of interleukin-1b (IL-1b) induced by activated glial cells, which has been considered a new mechanistic target for treatment. Fu et al. determined the feasibility of nanomag®-D-spio conjugated to anti-IL-1b monoclonal antibody to render MRI diagnoses and simultaneously provide targeted therapy with the neutralization of IL-1b overexpressed in epileptogenic zone of an acute rat model of TLE. This novel approach enhanced accumulation and the therapeutic effect of anti-IL-1b mAb by magnetic-targeted drug delivery system using MNPs [10].

8.2 MNPs for targeted magnetic particle imaging (MPI) applications

Atherosclerosis, or the formation of plaques in the arterial wall, leads to cardiovascular disease, the number one cause of death in the United States. Atherosclerosis develops through multiple stages, which makes it a particularly difficult disease to detect. Drews et al. have selectively targeted and deliver perimag® particles to atherosclerotic plaques through the use of peptides that bind to unique markers of plaque development and used MPI to diagnose atherosclerotic plaques [11].

8.3 MNPs for targeted multimodal imaging purposes

Multimodal imaging with targeted magneto-optical or magneto-radiolabeled probes allows for detection of a broad range of molecular-cellular targets through their modular design. Rimkus et al. described the construction of multimodal 20 nm nanomag®-CLD-spio particles addressing mVCAM-1 expression on endothelial cells as response to inflammatory factors [12]. The anti-

VCAM-1 antibody was fluorescence labeled with DY649, thiolated and conjugated to maleimide or PEG-maleimide functionalized nanomag®-CLD-spio particles (Fig. 4). Results of optical imaging and MRI showed that the multimodal MNPs can selectively address mVCAM-1 on endothelial cells in murine animal models [12].

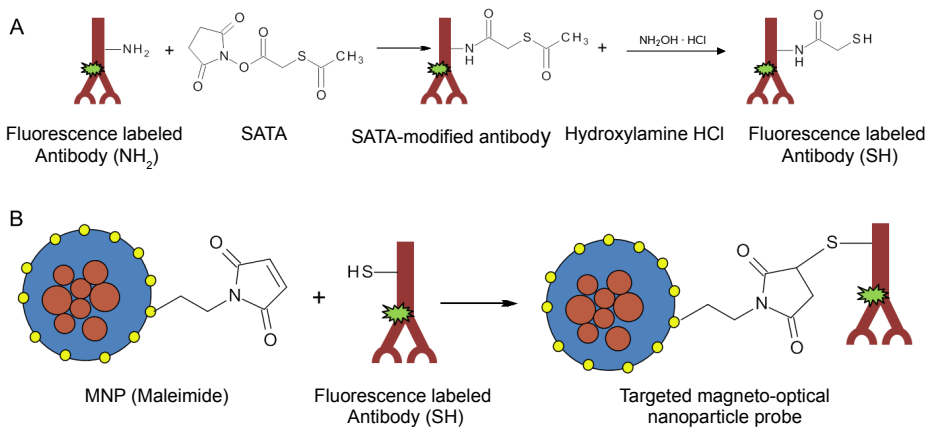

Figure 4. Reaction scheme of antibody-MNP conjugation using maleimide chemistry

Azad et al. have evaluated a PSMA-targeted BNF (Bionized NanoFerrite) nanoparticle in an experimental model for prostate cancer [13]. BNF-Starch particles with a diameter of 80 nm and amino groups on the surface were conjugated to a small-molecule PSMA inhibitor as well as to 1000 Da PEG chains. In addition the obtained nanoconjugate was labeled with the IRDye 800CW® for optical imaging or radiolabeled with ^{111}In for single photon emission computed tomography (SPECT). The conjugated BNF particles exhibit properties conductive to targeted imaging such as stealth, prolonged circulation time and enhanced clearance from non-target sites. Optical imaging of the targeted BNF particles *in vivo* indicates preferential accumulation in PSMA+ tumors 4 h post-injection, suggesting target specificity. On the other hand, non-targeted BNF particles exhibit lower uptake with similar accumulation in both PSMA+ and PSMA- tumors indicating tumor access without preferential accumulation. SPECT imaging and biodistribution studies indicated highest tumor accumulation at 48 h post-injection. *Ex vivo* fluorescence microscopy, Prussian blue staining, immunohistochemistry and biodistribution studies confirm enhanced BNF particle uptake in PSMA+ tumors compared to those not expressing PSMA. Thus the PSMA-targeted BNF particles are promising for PSMA-targeted imaging applications [13].

8.4 Magnetic nanoparticles for targeted hyperthermia applications

Heating living tissues to temperatures between 42°C and 46°C leads to inactivation of normal cellular processes in a dose-dependent manner described for decades as the classic hyperthermia response. External alternating magnetic fields (AMF) are an interesting possibility to induce heating of MNPs that are bound to the cancer cells. The degree to which this approach can be applied to cancer therapy depends on the MNPs, which after intravenous injection reach the cancer cells in effective concentrations for thermal ablation [14].

DeNardo et al. developed ^{111}In-Chimeric L6 (^{111}In-ChL6) monoclonal antibody conjugated nanomag®-D-spio particles for AMF cancer therapy (Fig. 5). The pharmacokinetics, tumor uptake, and the therapeutic effect of inductively heating these nanoconjugates by externally applied AMF were studied in athymic mice bearing human breast cancer HBT3477 xenografts. Tumor cell radioimmunotargeting of the bioprobes and therapeutic and toxic responses were determined.

The ^{111}In-ChL6 antibody was bound to 20 nm nanomag®-D-spio particles with PEG-COOH groups on the surface by EDC/ NHS chemistry (Figure 5). The conjugated MNPs remained in the blood circulation sufficiently long to allow significant tumor accumulation. The presence of the MNPs in the tumor xenografts was confirmed by quantitation of the tumor radiotracer in the pharmacokinetics study and by electron microscopy of the MNPs in the tumor. Treated tumors having MNP-conjugates activated by AMF, demonstrated tumor growth delay without normal tissue toxicity. This tumor response correlated with the calculated heat dose delivered [14, 15]. The study was extended by the comparison of tumor targeting of these ^{111}In-ChL6 conjugated 20 nm nanomag®-D-spio particles with corresponding larger BNF particles with diameters of 30 nm and 100 nm. The larger BNF particles targeted the tumor less than the 20 nm nanomag®-D-spio particles, but their heating capacity is typically 6 times greater, suggesting the 100 nm BNF particles could still deliver a better therapy with AMF [16]. For the development of a second generation radio-immuno nanoparticle the targeting ChL6 antibody was replaced with anti-Muc-1di-scFv-cysteine antibody fragment to provide more binding units per particle. The antibody fragment was bound to maleimide functionalized 20 nm nanomag®-CLD-spio particles via its terminal cysteine unit in analogy to Figure 2. This site-specific conjugation of the antibody fragment resulted in increased binding to breast cancer tumor cells in comparison to analogous particles with randomly oriented antibodies on the particle surface after conjugation with EDC/NHS chemistry (Figure 1) [17]. This result was confirmed by corresponding studies with model antibodies [18]. Further development of anti-Muc-1 di-scFv conjugated nanomag®-CLD-spio particles may provide uniquely high tumor targeting for AMF-driven tumor hyperthermia with less spleen and kidney accumulation [13].

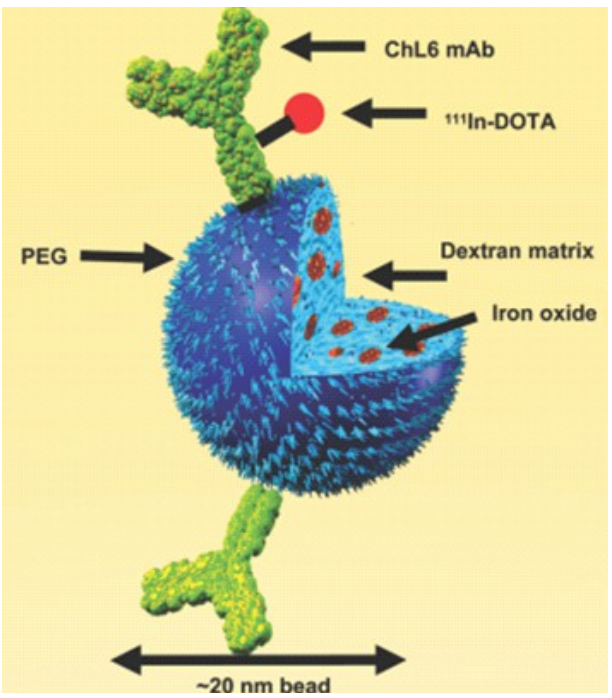

Figure 5. Schematic of ^{111}In-ChL6 antibody conjugated to PEG-COOH functionalized 20 nm nanomag®-D-spio particles

Herceptin, or Trastuzumab, is a high affinity engineered mouse-human-chimeric monoclonal antibody that was raised against the extracellular domain of human epidermal growth factor receptor 2 (HER-2). HER-2 is overexpressed in 20-30% of breast, lung, ovarian and gastric adenocarcinomas. Herceptin was approved by the FDA for the treatment of patients with HER-2 overexpressing breast cancer [19]. Zhang et al. have used the maleimide chemistry (Figure 2) for Herceptin conjugation on the surface of aminated 100 nm BNF-Starch particles. The Herceptin conjugated BNF particles bound selectively to the tumor cells *in vitro*. After AMF exposure th tumor cells died by apoptosis, quantifiable by Live/Dead and nuclear morphology assays. These Herceptin-directed BNF particles can selectively kill HER-2+ human mammary cancer cells (SK-BR-3) by AMF treatment [15].

NDong et al. have compared the tumor cell targeting of 30 nm MNPs and 100 nm nanomag®-D-spio particles that were conjugated with Herceptin *in vivo* and *in vitro*. *In vitro*, molecular targeting to the HER-2 receptor was the dominant factor driving cancer cell association. In contrast, size was found to be the key determinant of tumor accumulation *in vivo*, where molecular targeting increased tumor tissue concentration for 30 nm but not 100 nm MNPs. These results indicate that the *in vitro* advantages of molecular targeting may not consistently be extended to pre-clinical *in vivo* settings [20].

8.5 Delivery of therapeutic molecules and MNPs inside cells by nontransgenic approaches

Efficient delivery of therapeutic molecules inside cells by nontransgenic approaches is key as gene editing/correction, directed differentiation, and *in vivo* cell modulation/tracking are translated for regenerative medicine applications. Dixon et al. developed a peptide-based system to enhance the activity of cell-penetrating peptides to achieve exceptional intracellular transduction. Glycosaminoglycan-binding enhanced transduction (GET) uses peptides that interact with cell membrane heparan sulfates and promote cell-penetrating peptide-mediated endocytosis into cells. Thus enzymes, transcription factors, antibodies, native proteins, MNPs (250 nm nanomag®-D), and nucleic could be delivered in cell types considered hard to transduce, such as mouse embryonic stem cells (mESCs), human ESCs, and induced pluripotent stem cells (hiPSCs). Importantly, this approach does not affect cell proliferation and viability and can be used to deliver a plethora of functional cargoes [21].

8.6 Biomimetic amplification of nanoparticle homing to tumors

MNP-based diagnostics and therapeutics mainly depend on the ability to home to specific sites in the body. Simberg et al. have developed biomimetic particles that not only home to tumors, but also amplify their own homing. The system is based on a peptide that recognizes clotted plasma proteins and selectively homes to tumors, where it binds to vessel walls and tumor stroma. Nanomag®-D-spio particles and liposomes coated with this tumor-homing peptide accumulate in tumor vessels, where they induce additional local clotting thereby producing new binding sites for more particles. The system mimics platelets, which also circulate freely but accumulate at a

diseased site and amplify their own accumulation at that site. The self-amplifying homing is a novel function for nanoparticles that greatly enhances tumor imaging [22].

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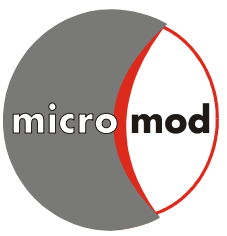

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