Protein Coating of Pharmaceutical Drug Carriers for Specific Cell Targeting

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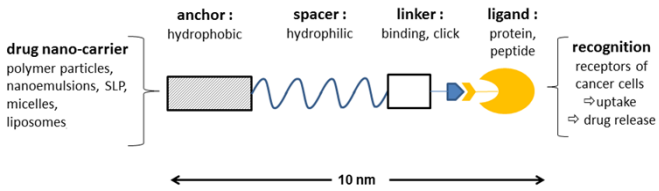
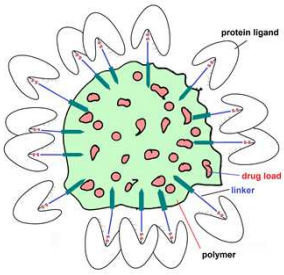
Targeting drug excipients for nanotherapy





paranteral

cancer therapy

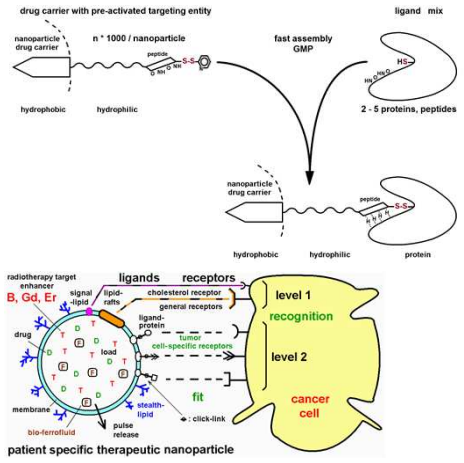


Fig.1: Targeting materials for oral drug delivery and nano-pharmaceuticals : The multi-targeting modifiers consist of four domains: 1) hydrophobic anchor, 2) hydrophilic spacer, 3) linker (two parts), and 4) receptor ligand (protein or bioorganic ligand), coupled by fast assembly.

Fig.2: The targeting materials can be applied for a) oral drug delivery (recognition by intestinal eceptors), or b) parenteral formulations for case- and person specific therapy and diagnosis by cell specific nano-pharmaceuticals (multi-targeting modifiers), e.g. cancer therapy. The final cell uptake signal is delivered in the second step by the novel targeting materials for a case specific therapy.

- Modular targeting materials [7, 2-4] bearing a ligand head (fig.1) can supply a cell or tumor receptor recognition to radiotherapy enhancers, hydrophobic drugs (BCS classes 2, 4), or nanoscaled drug carriers, e.g. liposomes, micelles and polymer particles. This drug / co-drug complex concept requires the synthesis of special modular targeting materials.
- The parenteral MultiTarget branch (fig.2, lower) shall improve therapy and diagnosis of severe diseases, e.g. cancer, by individual targeting of drug-loaded nano-pharmaceuticals towards cancer cells; while the oral targeting branch (fig.2, upper) enables a drug uptake by complexes of targeting material and hydrophobic drug. Specific ligands, which are recognized by the diseased cells, are bound to the nanoparticle surface, and thus capable of directing the drug carriers. In the current concept for cancer therapy (fig.2, lower) a multiple ligand set is coupled by a fast assembly technique (click link) in the very last step of the formulation. In the clinical application the ligands set (2-5 different) will be selected according to the biopsy analysis of the patient tissue e.g. from tumor.
- We synthesize multi-targeting modifiers of oral drug nano-intermediates and parenteral drug loaded nanoparticles which consist of four structure domains (fig.1) with lipid or hydrophobic polymer anchors (left). The components are varied and optimized in a case specific manner. The nanoparticles, e.g. intestinal lipid-bile nanoparticles [12-15], biodegradable polymer (PLGA), lipid particles as well as the anchor domain are hydrophobic, while iron oxide can be included for bio-medical manipulation [8-11]. With proteins as ligands, e.g. transferrin or albumin, the protein is transformed to an artificial membrane protein. The linker binds the ligand in two steps: adsorption and a fast covalent bond formation as terminal step. The hydrophilic spacer is essential for keeping the distance from the nanoparticles surface.
- The structure of the modified nanoparticles is analyzed by dynamic light scattering DLS, neutron small angle scattering SANS and metal specific X-ray scattering ASAXS, while the effect of the drug is proven in cell culture tests [1]. The multi-targeting modification is applied to lanthanide loaded polymer nanoparticles (PLGA, patent of the Gutenberg-University [5]) for radiation therapy [1,5,6] and liposomes as fast development system.

Patient and case- specific therapeutic Nanoparticles:

ILL-D11 and FRM-II-KWS2

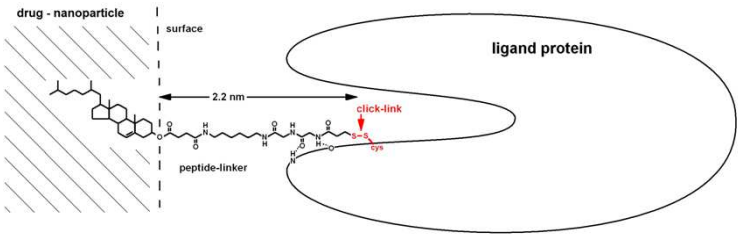


Fig.3: Target excipient or case- and person specific therapy and diagnosis by case specific nano-pharmaceuticals (multi-targeting modifiers), e.g. individual cancer therapy. The **case specific recognition** by **receptor ligands** at level 2 are bound as a mix by cleavable links with a fast **click-chemistry** (**S-S**). An unwanted early liver uptake is avoided by polyglycerol stealth lipids [2].

ASAXS of metal-liposomes and PLGA polymer particles for cancer therapy

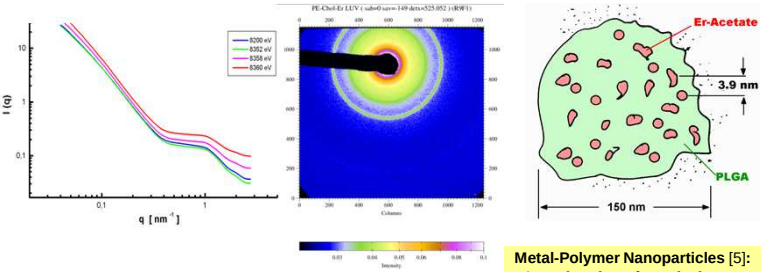


Fig.4: TR-SANS+DLS and ASAXS of **liposomes** for enhancer radiotherapy with entrapped beam-target (B, Gd, Er)

Metal-Polymer Nanoparticles [5]: A metal produces free radicals upon external irradiation (**γ**-photons, **N**)

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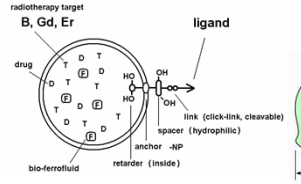
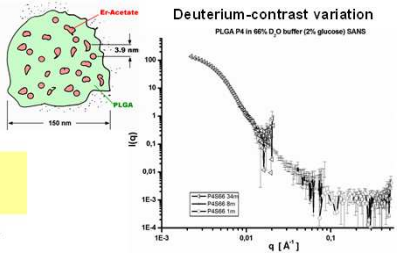
Bio-Targeting : targeting ligands/proteins at nanoparticle surface



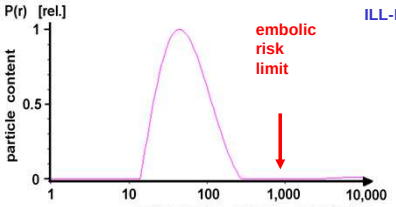
Neutron scattering SANS: nanoscale 1nm – 0.5µm

Polymer nanoparticles as drug carriers: **PLGA** w/o/w **triple NP**



Combination : DLS and Neutron scattering SANS

DLS: large particles 0.1 - 100 µm



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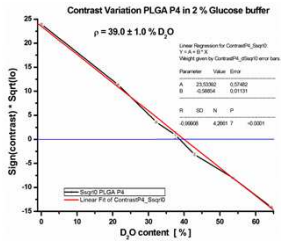

Fig.5: Concept of **Tumor-Case Specific target nanoparticles**: liposomes and polymer (PLGA) with surface bound targeting ligands (proteins) for cancer cell recognition: The overall structure is investigated by DLS, which also is a test for **medical shure** pruducts. Structure and protein loading is investigated by time-resolved and D-contrast variation neutron small angle scattering SANS.

Artificial protein corona of nanoparticles: Drug targeting and SANS - drug-liposomes by D-contrast variation

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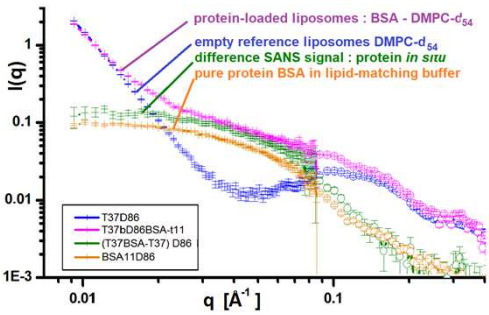

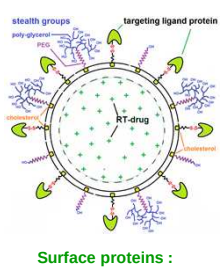

Surface proteins : SH-BSA, SH-Transferrin

Fig.6: The target excipient test and structure investigation is done by a combination of time resolved neutron scattering and dynamic light scattering (SANS + DLS). With neutrons the components of complex nanoparticles can be distinguished and localized by Deuterium-contrast variation.

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