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Surface coating of Pharmaceutical Nanoparticles with SH-Proteins for Site-directed Drug Targeting and Radio-Therapy – Time-resolved SANS of Deuterium-matched Carriers

Nanoparticles circulating in the human blood depict a protein corona [Tenzer et al.]. This principle can be used for site specific drug targeting by receptor recognition after attachment of an artificial specific protein corona to drug loaded nanoparticles, lipoplexes, liposomes and polymers, which contain a protein-binding anchor component, and the therapeutic drug or mRNA.
We have studied the surface protein coating of PLGA polymer particles (w/o/w double emulsion) and liposomes bearing an activated binding thiol-component by coupling with proteins containing a SH-group. The Thiol-activated anchor component was synthetized from Amino-lipid, cholesterol or PLA-derivative (L. Krebs, Nanovel). The proteins for surface coating contained a SH-group by nature (BSA, HSA), or were equipped with this by conversion of a surface Lysine to a SH-derivative by Trout's reagent. The studied nanoparticle contained 2% of anchor group embedded in a host matrix of lecithin (DMPC, DOPC) or polymer (PLGA). The drug loads were hydrophobic drugs of the BCS classes 2 and 4 (Fenofibrate, Curcumin, Amphotericin B) or Lanthanide chelates (Gadolinium, Erbium, Lutetium -DTPA) as radiation absorber for indirect radiotherapy of cancer with photons (PT) or neutrons (NCT).
The drug nanoparticles were studied at ILL-D11 with SANS and DLS at site (same cuvettes). The particle structure details were distinguished by D2O-contrast variation. The protein surface coating process, i.e. the formation of a sulfur-bridge between activated anchor component and thiolated protein was studied with time resolved SANS of D2O-contrast matched PLGA nanoparticles with 2% activated PLA-anchor "P4". The size of the foam-like PLGA nanocarriers (100 nm) and the smaller proteins (BSA, SH-BSA, SH-Transferrin) required a SANS double shot strategy with cross-like distance changes (2m, 8m, 34m) after stopped flow mixing of the components (activated nanoparticle and protein solutions). As result the coupling was detected structurally in a time regime of 2h with sliding resolution. The result is important for the medical application, where the person and/or tissue specific protein or antibody coating can be attached to preformed drug/mRNA nanoparticles (stock) in the studied time window before the patient application.

Primary authors: Dr NAWROTH, Thomas (Gutenberg University Mainz); Mrs KREBS, Lidija (Gutenberg University, Pharmaceutical Technology); Mr WILHELMY, Christoph (Gutenberg University, Pharmaceutical Technology); Prof. LANGGUTH, Peter (Gutenberg University); Prof. SCHMIDBERGER, Heinz (Gutenberg University Clinics, Radiooncology); Dr SÄNGER, Markus (Gutenberg University Clinics, Radiooncology); Dr JOHNSON, Raphael (KNUST University); MATSARSKAIA, Olga; SCHWEINS, Ralf

Presenter: Dr NAWROTH, Thomas (Gutenberg University Mainz)