Impact of molecular weight and structural design of HPMA-based drug carrier systems on body distribution and tumor uptake *in vivo*

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Objectives: "Polymer therapeutics" became an emerging field in both, chemical and medical science over the last four decades [1]. Designed to improve the therapeutic index of (chemo)therapeutic drugs, advantageous key attributes of macromolecular drug delivery systems are the reduction of toxic side effects of the chemotherapeutic agent in healthy tissue, their passive accumulation in tumor tissue due to the EPR effect [2] and a longer blood circulation time compared to the solely anticancer agent.

In this field poly-*N*-(2-hydroxypropyl)methacrylamide poly(HPMA) is a promising polymeric backbone that has been widely used for preclinical as well as clinical testing being non-toxic, non-immunogenic and biocompatible.

Nevertheless, for any medical application it is essential to understand how structural modifications resulting in modified polymer characteristics are influencing the *in vivo* behavior.

Methods: Defined HPMA-based homopolymers and co-polymers –exhibiting laurylmethacrylate sidechains– were synthesized using RAFT polymerization technique, with molecular weights below and above the renal threshold for each polymer architecture. Polymers were labeled by means of [^{18}F]FETos [3] and body distribution and tumor uptake was studied in tumor bearing rats (AT1 prostate and Walker-256 carcinoma) using *ex vivo* biodistribution measurements and non-invasive µPET imaging [4].

Results: ^{18}F-Fluoroethylation was successfully applied to a new series of HPMA homopolymers (P1*, 12 kDa; P2*, 77 kDa) and random copolymers (P3*, 14 kDa; P4*, 55 kDa), exhibiting hydrophobic laurylmethacrylate side-chains. ^{18}F-P1* showed highest activity levels at 2 h p.i. in kidneys (15.2 % ID/g tissue) and liver (1.6 %ID/g tissue). In contrast, the high molecular weight (M_w) homopolymer ^{18}F-P2* was accumulated less pronounced in kidneys, whereas liver uptake was four times higher compared to ^{18}F-P1*. The low M_w copolymer ^{18}F-P3* was predominantly found in kidney, liver and blood. The high M_w copolymer ^{18}F-P4* showed increased levels in blood with lower kidney and liver uptake (Fig. 1). Independent of the M_w, the HPMA-*ran*-LMA copolymer exhibited longer biological half-life in the blood compartment in comparison to the homopolymeric system. µPET images visualized different distribution patterns of P1*-P4* in high spatial resolution. Studies on the uptake of P1*-P4* in two different tumor models showed poor accumulation of all polymers in AT1 dunning prostate carcinoma model. Here, neither polymer structure nor M_w had a relevant impact on tumor uptake. In Walker-256 tumors, the uptake was depending on the polymer architecture and the M_w with intratumoral concentration of the large copolymer P4* being more than four times higher than for the high M_w homopolymer P2*.

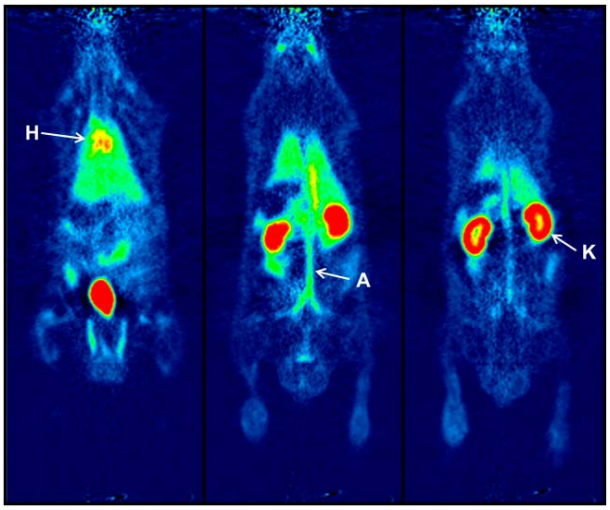

Figure 1: Representative coronar µPET images of HPMA-*ran*-LMA copolymer ^{18}F-P4* 2 h after i.v. injection. K: kidneys; H: heart; A: aorta.

Conclusions: The variations in structure showed major impact on the biodistribution pattern *in vivo*. Random copolymer P4* exhibited increased enrichment in the blood pool, underlining its potential as transport vehicle for therapeutics *in vivo*. These results underline the significance of both (1) a good characterization of the polymers and their aggregates and (2) the use of non-invasive imaging modalities to evaluate the potential of biocompatible polymers as potential drug carriers.

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