Towards cancer nanoradiopharmaceuticals – radioisotope nanocarrier system for prostate cancer theranostics based on radiation-synthesized polymer nanogels

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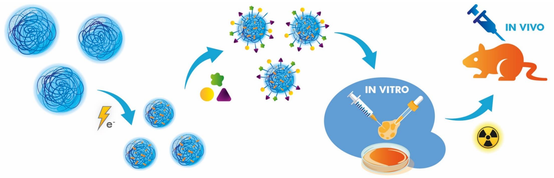
Introduction

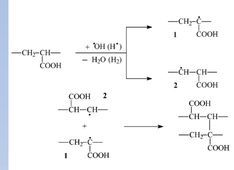
Despite many efforts, cancer remains a major challenge for medicine professionals and scientists around the world. According to data published by University of Oxford in cooperation with Global Change Data Lab, cancer is the second leading cause of death worldwide. Therefore, there is a constant need for new therapeutic and diagnostic modalities which can improve the situation.



Nanotechnology is believed to bring about change in the field of oncology and revolutionize current cancer management strategies. Therefore, in our research we synthesize state-of-the-art biocompatible polymer nanostructures in the process of preparative pulse radiolysis. We start with dilute aqueous solution of poly(acrylic acid) (PAA), which forms nanogels (NG) upon irradiation. Next, we functionalize these nanogels with ligands containing targeting moieties and radionuclide chelators. So prepared nanocarriers are finally radiolabeled with therapeutic and theranostic isotopes and tested on *in-vitro* prostate cancer model (human prostate adenocarcinoma cell line PC-3), as well as *in-vivo* (Balb/c mice - biodistribution).

Poly(acrylic acid) nanogels

Nanogel synthesis is driven by the reactive species generated during water radiolysis. They lead to changes in molecular structure of poly(acrylic acid) and formation of internal crosslinks within the polymer coils.



We use 2 batches of linear PAA with nominal Mw 250kDa and 450kDa. Upon pulse irradiation with 6 MeV electrons from a linear accelerator, we obtain colloidally stable nanogels of ca. 50 nm and 90 nm size, respectively.

S. Kadlubowski, *Macromolecules*, vol. 36, no. 7, pp. 2484–2492, 2003.

Data - nanogels

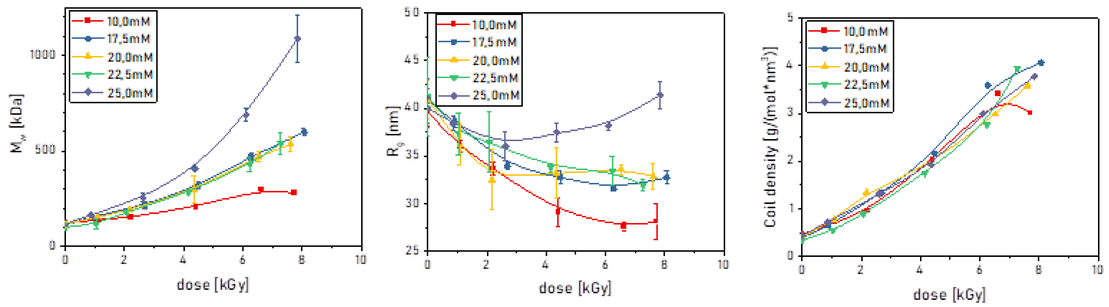
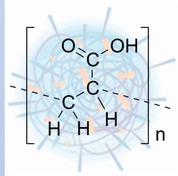
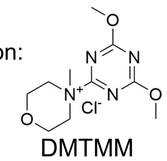


Figure 1: (A) Molecular mass (Mw), (B) radius of gyration (Rg) and (C) coil density of PAA structures as a function of absorbed dose for electron beam irradiated samples in Ar-saturated solutions.

Data - functionalization



COOH activation:

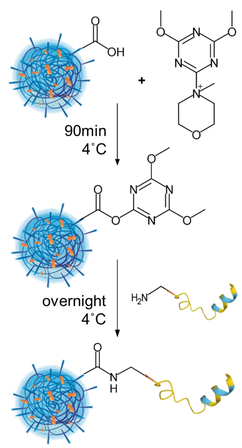


DMTMM

4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl-morpholinium chloride

Reaction steps:

- COOH activation & ligand conjugation
  pH 5.5 (MES buffer)
- Purification
  3 x PBS rinsing
- Recovery
  concentrated sample in PBS
  YIELD ~ 100%!



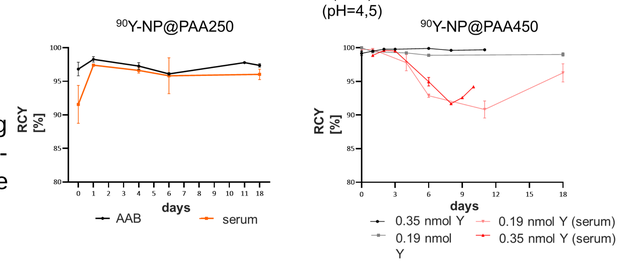
Schematic representation of coupling reaction

Functionalization of nanogels towards functional nanocarriers is achieved in one-pot synthesis. Among various conjugation chemistries tested, triazine-based procedure allows best coupling yield – virtually 100% of peptide is successfully bound to carboxylic groups present in PAA nanostructures, as assessed with BCA protein assay.

Data – active targeting and radiolabeling

DOTA-BBN-NG+ ^{90}Y/^{177}Lu → (15min. 90ºC, ascorbic acid buffer (AAB) (pH=4,5)) → **^{90}Y/^{177}Lu–DOTA-BBN-NG**

Active targeting towards prostate cancer cells and radiolabeling is enabled by using engineered ligand - bombesinderivative (DOTA-BBN).



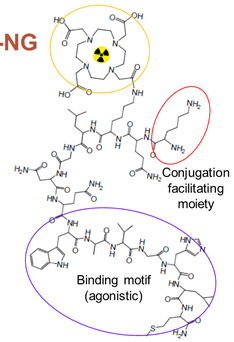
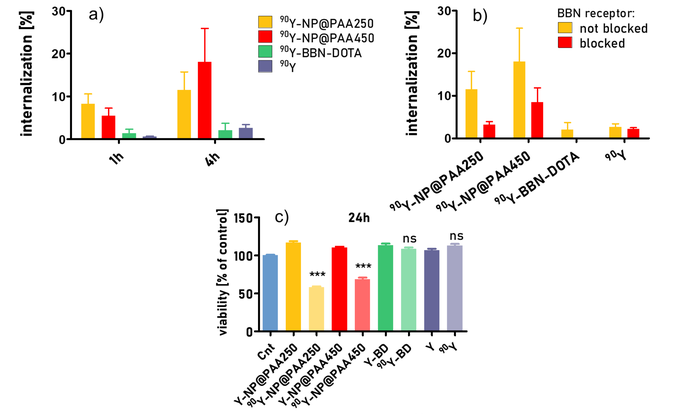
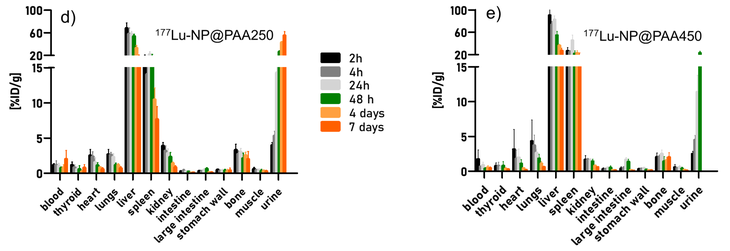


Figure 2: Radiolabeling stability (in ascorbic acid buffer at RT and in serum solution at 37°C); RCY – radiochemical purity.

Results/Conclusions





Nanocarriers improve radioisotope internalization in PC-3 cells (a), and this effect is greatly driven by the conjugated targeting ligand (b). Significant decrease of PC-3 cells viability shows therapeutic potential of radiolabelled carriers in comparison to their carrier-free and non-radioactive counterparts (c). *In-vivo* studies (d, e) in general show i.a. elimination with urine, and low retention in bones (which proves stability of the radiolabeling). Size of nanoparticles clearly influences the biodistribution, however high retention of both carriers in liver and spleen suggests the need for further optimization of the construct.

Acknowledgements/References

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Learn more about prostate cancer active targeting, nanogels and its functionalization