Directed enzyme-prodrug therapies aim to improve conventional chemotherapy by activating a non-toxic prodrug into a toxic drug only at the site of the tumor. This considerably lowers the systemic toxicity associated with conventional chemotherapy. Directed enzyme-prodrug therapy involves two stages. In the first step the activating enzyme is directed to the tumor. In the second step the non-toxic prodrug is systemically administered. Subsequently, the prodrug is converted to a toxic drug by the prodrug activating enzyme resulting in high local concentrations of an anticancer drug at the tumor site. The targeting of the enzyme can either be mediated by antibodies, named antibody-directed enzyme-prodrug therapy (ADEPT) (Bagshawe et al., 2004) or by a gene-vector, named gene-directed enzyme-prodrug therapy (GDEPT) (Dachs et al., 2005). Both ADEPT and GDEPT suffer from several shortcomings such as immunogenicity of an antibody-enzyme conjugate in ADEPT or inefficient transfection, unsustained gene expression, pathogenesis of viral vectors and the risk of insertional mutagenesis in GDEPT.

Therefore we introduced a novel enzyme-prodrug strategy in which the prodrug activating enzyme is not directly linked to a tumor targeting antibody but encapsulated in a nanometer-sized vesicle, called nanoreactor. Such nanometer-sized reactors are composed of PMOXA-PDMS-PMOXA triblock copolymers. These triblock copolymers are able to self assemble into various aggregates such as vesicles, micelles, nanotubes and free standing films in aqueous solutions. Nucleoside Hydrolase of Trypanosoma vivax (TvNH), that catalyzes the hydrolysis of nucleoside(analogs) into ribose and the respective nucleobase(analogs), was encapsulated in the polymeric vesicles. To permeabilize the polymeric membrane for substrates and products, bacterial outermembrane proteins OmpF or Tsx were incapsulated.

In this project we were able to validate TvNH as a novel prodrug activating enzyme in combination with the prodrug 6-thioguanosine and we delivered a proof of principle that these polymeric nanoreactors show great potential as an alternative enzyme-prodrug therapy.

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