Systemic epidermal growth factor receptor-targeted gene delivery using the theranostic sodium iodide symporter (NIS) gene in an advanced orthotopic tumor model

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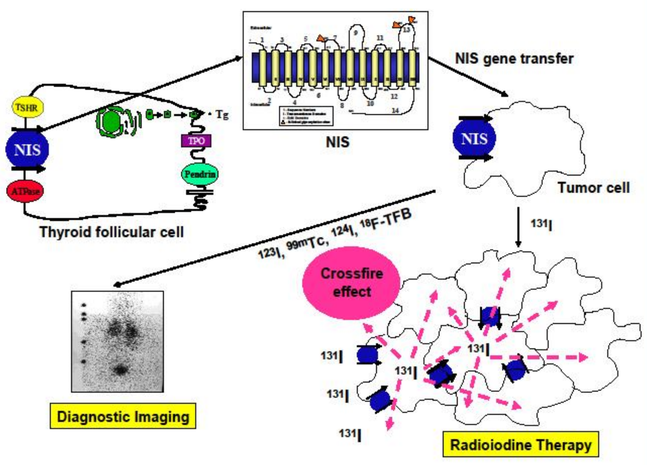
Introduction

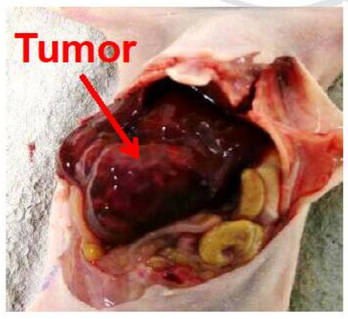
The well characterized sodium iodide symporter (NIS) in its dual function as reporter and therapy gene represents an outstanding tool to target different cancer types allowing non-invasive imaging of functional NIS expression and therapeutic radionuclide application. We recently reported induction of tumor-selective accumulation and therapeutic efficacy of radioiodide after systemic non-viral epidermal growth factor receptor (EGFR)- targeted NIS gene delivery in a subcutaneous hepatocellular cancer (HuH7) xenograft tumor model. As a next step towards clinical application, we are now investigating tumor specificity and transduction efficiency of EGFR-targeted polyplexes as systemic NIS gene delivery vehicles in an advanced orthotopic tumor model

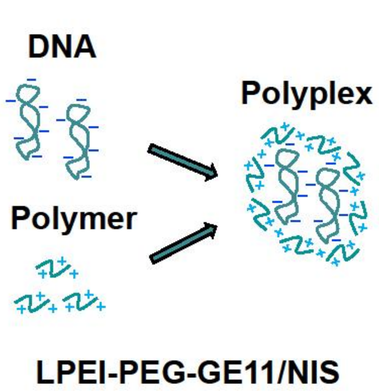


Spitzweg C & Morris JC, Thyroid, 2004; 14:424-34

Materials and Methods

- Orthotopic liver cancer model: HuH7 cells were injected directly into the liver leading to the development of orthotopic liver tumors
- Polymers based on linear polyethylenimine (LPEI) and polyethylene glycol (PEG) were coupled to the synthetic peptide GE11 as an EGFR-specific ligand (LPEI-PEG-GE11) and complexed with human NIS DNA
- Imaging studies: investigation of vector biodistribution and functional NIS expression measured by tumor specific accumulation of ^{124}I or ^{18}F-tetrafluoroborate (^{18}F-TFB) after application of 10 MBq of the respective radionuclide
- *Ex vivo* biodistribution: 24 hours after polyplex administration, mice received 18.5 MBq ^{123}I. 3h later, animals were sacrificed, organs dissected and measured in a gamma-counter



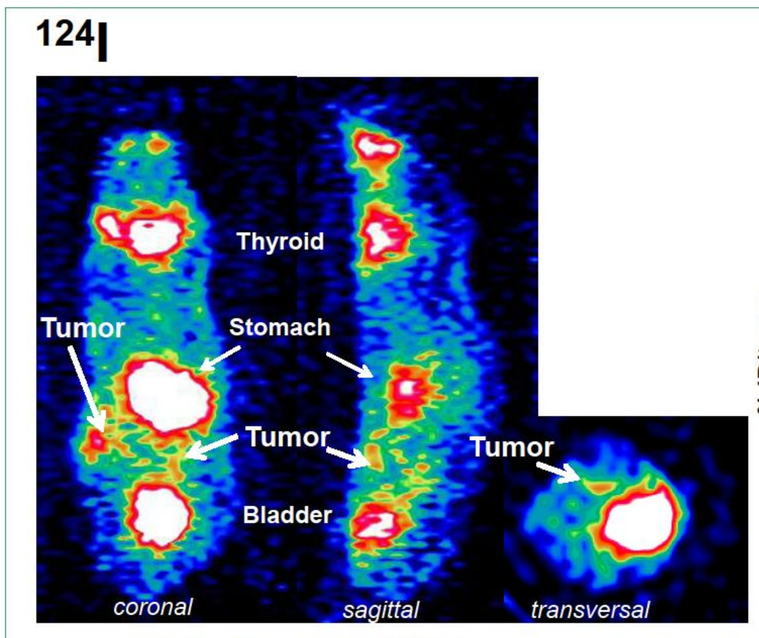


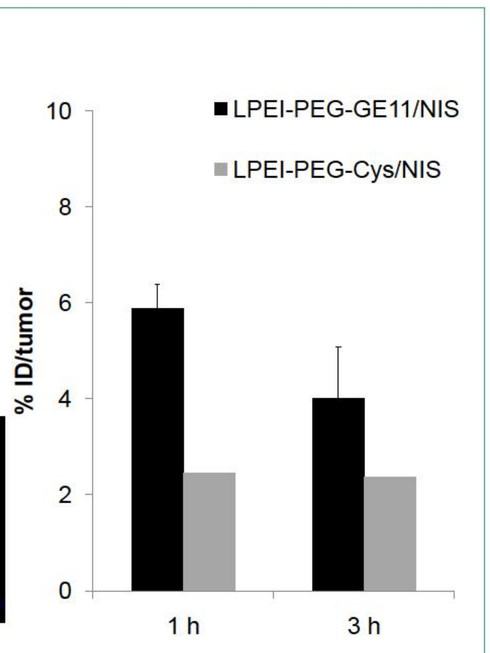
Results

PET-imaging

24h after intravenous injection of LPEI-PEG-GE11/NIS, mice with orthotopic HuH7 liver carcinomas showed high tumoral levels of functional NIS protein expression detected by either ^{124}I or ^{18}F-TFB PET-imaging. In contrast, far lower uptake levels were detected in animals treated with untargeted LPEI-PEG-Cys/NIS polyplexes confirming receptor-mediated gene-transfer. The two tracers, ^{124}I-PET and ^{18}F-TFB, which exhibit different pharmacodynamic and pharmacokinetic parameters, were compared: ^{124}I was found to be less sensitive and resulted in images with lower resolution compared to images obtained with the novel tracer ^{18}F-TFB. The higher resolution of ^{18}F-TFB allows a more precise and exact tumor localization for quantification of regions of interests.

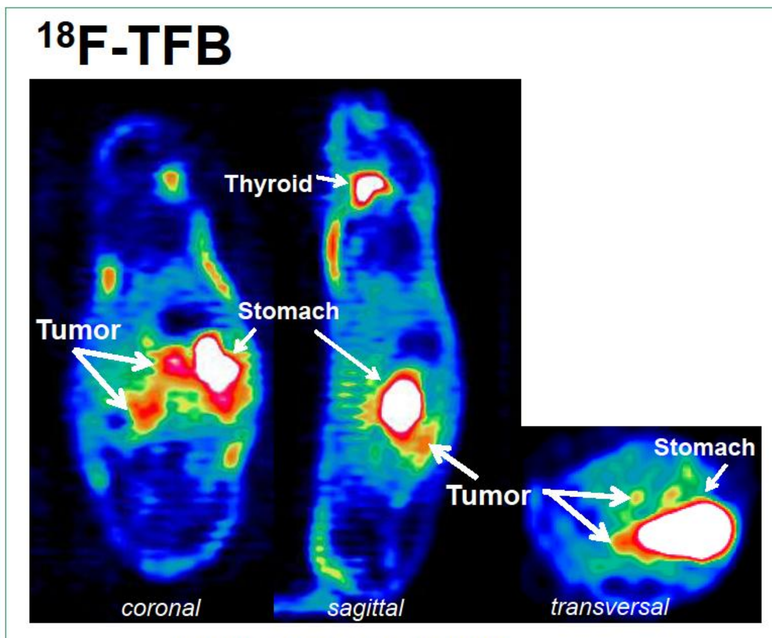
^{124}I

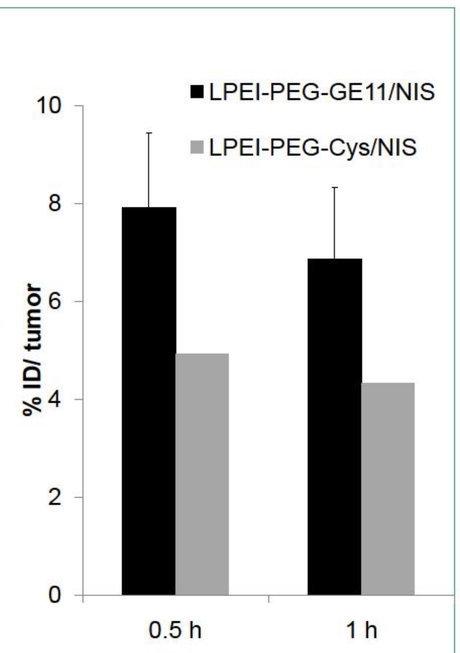




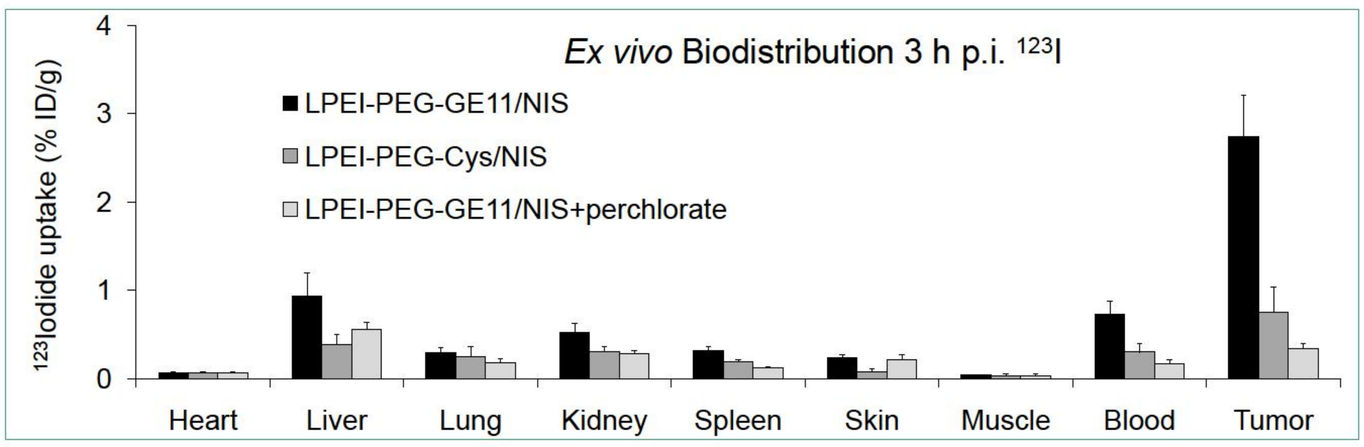
LPEI-PEG-GE11/NIS

^{18}F-TFB





LPEI-PEG-GE11/NIS



Ex vivo biodistribution

3h after application of ^{123}I, EGFR-targeted polyplex biodistribution and tumor specific NIS expression in orthotopic liver cancer was examined. LPEI-PEG-GE11/NIS-treated mice showed significant tumoral accumulation of iodide, whereas injection of control vectors (LPEI-PEG-Cys/NIS) as well as pretreatment with the NIS-specific inhibitor perchlorate resulted in significantly lower iodide uptake levels.

Summary and Conclusion

- *In vivo* ^{124}I- and ^{18}F-TFB-PET imaging revealed significant tumor-specific tracer accumulation
- *Ex vivo* biodistribution analysis confirmed EGFR-targeted vector biodistribution, as well as tumor-selective NIS-mediated iodide uptake
- In conclusion, our preclinical data confirm the enormous potential of EGFR-targeted synthetic polymers for systemic NIS gene delivery in an advanced orthotopic tumor model and open the exciting prospect of NIS-mediated radionuclide therapy in advanced disease

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