hGTS13: a promising halogenated theranostic for high-grade glioma and Non-Small Cell Lung Cancer

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Introduction: System x_c^- is an amino acid antiporter playing a key role in cellular redox homeostasis. It is overexpressed in multiple cancers such as glioma and Non-Small Cell Lung Cancer (NSCLC) and is associated with cancer cell proliferation, invasion, metastasis, development of chemo-resistance and poor survival.[1,2] Consequently, system x_c^- is a promising target for targeted radionuclide therapy (TRT). [^{18}F]FSPG (Fig. 1A) is the most widely studied radiotracer targeting system x_c^-. However, it is limited by its high uptake in inflammation, and elevated kidney and pancreas uptake. [^{18}F]hGTS13 (Fig.1A) is a second-generation radiotracer targeting x_c^- showing an improved tumor uptake in NSCLC rat models, and lower pancreas and kidney retention but higher liver uptake compared to [^{18}F]FSPG.[3] We report here the evaluation of [^{18}F]hGTS13 in rat model of high-grade glioma and the effect of the replacement of ^{18}F by the natural isotope of a therapeutic halogen (^{Natural}X) on the celluar uptake of the hGTS13 scaffold in NSCLC cells.

Methods: First, we evaluated [^{18}F]hGTS13 tumor uptake in rat models of glioma. Sprague-Dawley rats (n=5) were orthotopically implanted with C6 glioma cells into the right entorhinal cortex and tumor growth monitored by contrast-enhanced T1-weighted MRI. 3-weeks after implantation, rats were administered ~25 MBq [^{18}F]hGTS13 and imaged for 60min. Next, we realized a competition assay using NSCLC cells H460. Cells were plated 24h prior to the experiment. The next day, media was replaced by HBSS for the control (n=4) and 0.5M of [^{Natural}X]hGTS13 in HBSS for the tests (n=4) and cells were incubated 10-min at 37°C. Then, 0.185 MBq [^{18}F]hGTS13 were added and the cells incubated for 60-min. Media was removed, cells washed then lysed and the activity counted.

Results: Dynamic PET/CT imaging of C6-glioma bearing rats with [^{18}F]hGTS13 revealed high and sustained uptake within the intracranial gliomas (Fig. 1B). Tumor uptake peaked within the first few minutes post-injection (4.8 ± 0.8%ID/g) and remained steady throughout the scanning with a tumor-to-background ratio of 18.1 ± 4.8 at the 60-min timepoint. The competition assay in NSCLC cells showed a strong inhibition of [^{18}F]hGTS13 uptake by co-incubation with [^{Natural}X]hGTS13 as the uptake decreased from 90.9 ± 10.1% uptake/mg protein to 3 ± 0.6% (Fig1.C).

Conclusions: Our imaging results prove that [^{18}F]hGTS13 has a high and sustained glioma uptake in rats. Our NSCLC cell study demonstrates that hGTS13 maintains a good binding affinity for x_c^- after the replacement of ^{18}F by the natural isotope of a therapeutic halogen. We expect similar results when using the therapeutic radionuclide. Hence, [^{18}F/X]-hGTS-13 is a promising small molecule theranostic pair for high-grade glioma and NSCLC.

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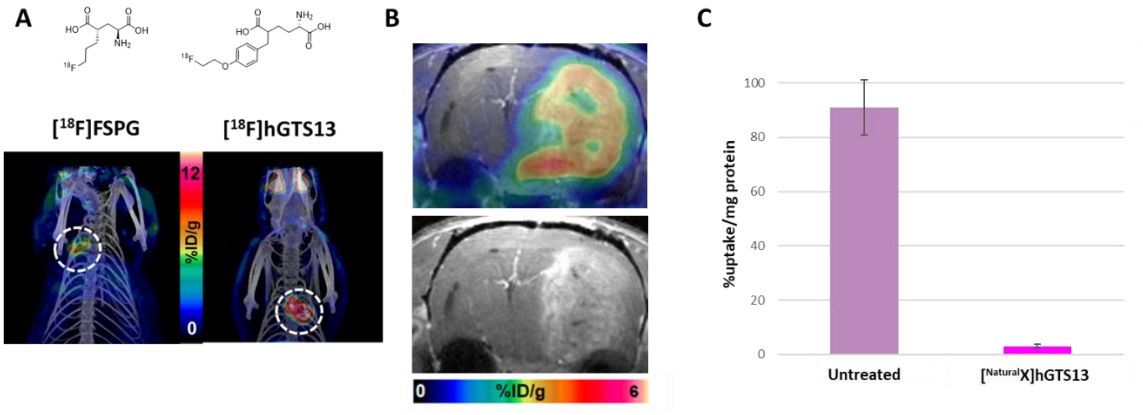

Figure 1. A. Structures of the radiotracers [^{18}F]FSPG and [^{18}F]hGTS13 and their comparative tumor uptake in NSCLC rat models. Images are all shown 60-70 min post-injection. **B**. Representative ^{18}F-hGTS13 PET/MRI image of a rat bearing an orthotopic C6 glioma, image is summed 30-60min post-injection. **C**. Competition study of [^{18}F]hGTS13 with the natural halogenated therapeutic counterpart in H460 cells at 60 min post-addition of radioactivity.

References:

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