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Radiosynthesis and first preclinical evaluation of an ^{18}F-radiolabelled ligand for cancer stem cells by non-invasive PET imaging

HELMHOLTZ ZENTRUM DRESDEN ROSSENDORF

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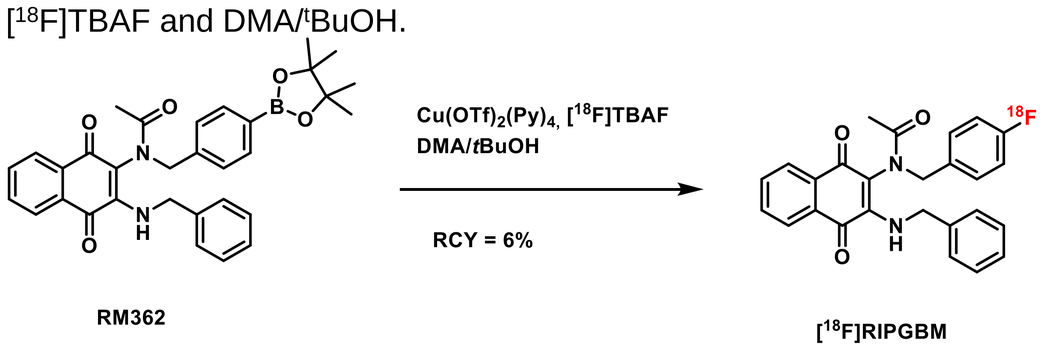
Background and Objectives

Cancer stem cells (CSC) are multipotent cells playing a critical role in tumor initiation, therapy resistance and recurrence. Therefore, their therapeutic targeting is of relevance for highly aggressive entities with poor prognosis such as glioblastoma (NCT02654964). To support the development of such targeted therapy we intended to develop a radiotracer enabling the non-invasive imaging of the CSCs population. Based on the work of Lucki *et al.** who discovered a promising prodrug termed RIPGBM selective of CSC, we aimed at developing an ^{18}F-radiolabelled RIPGBM, and to preliminary assess its potential as non-invasive imaging agent of a low-density population such as the CSC in a mouse model of human glioblastoma.

Methods

The reference compound *N*-(3-(benzylamino)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-*N*-(4-fluorobenzyl)acetamide (RIPGBM) and the corresponding boronic acid pinacol ester precursor for radiofluorination (RM361) were obtained by following the synthetic procedure reported by Lucki *et al.** The radiosynthesis of [^{18}F]**RIPGBM** was performed on an automated module in presence of $CU(OTf)_2(Py)_4$, [^{18}F]TBAF and DMA/^{t}BuOH.

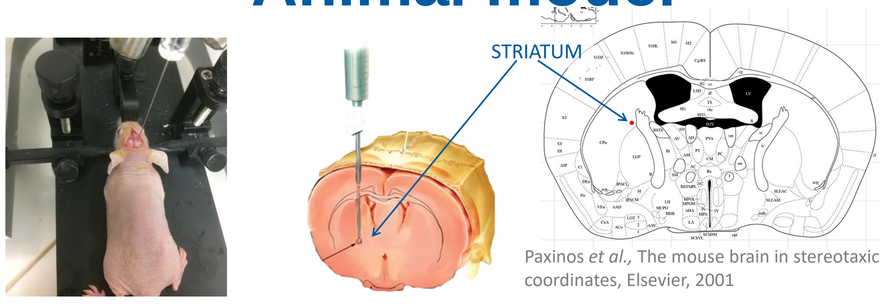


RM362 → [^{18}F]RIPGBM

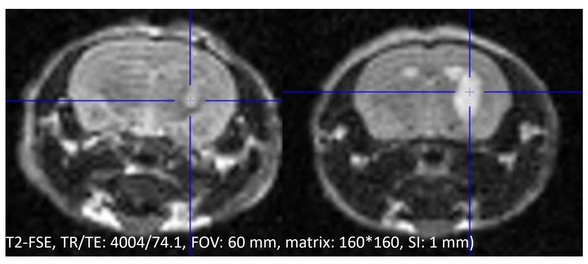
The radiosynthesis of [^{18}F]**RIPGBM** from the boronic acid pinacol ester RM362

*Lucki *et al*. PNAS 116, 6435–6440 (2019).

Animal model



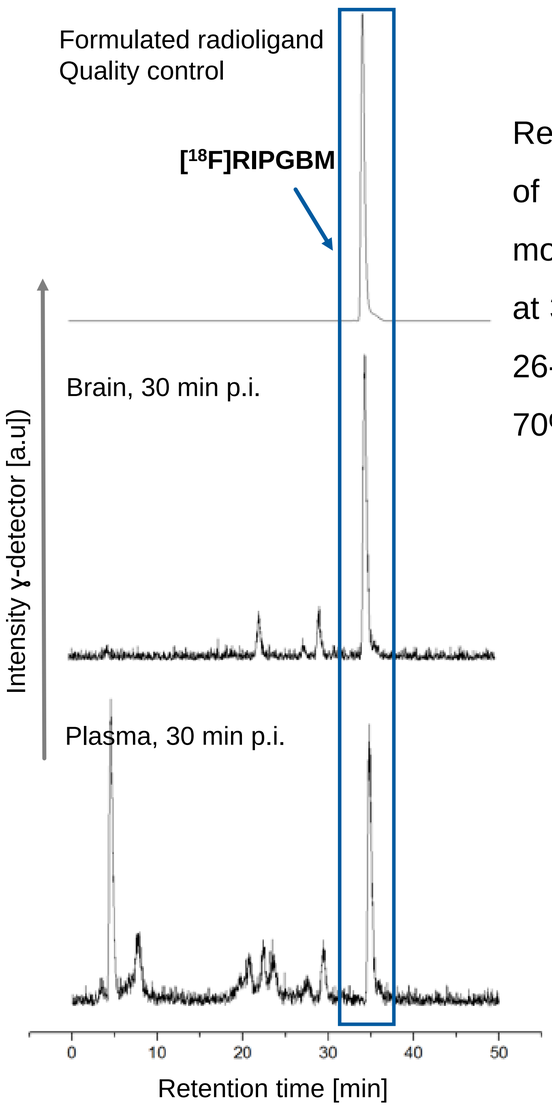
Stereotaxic injection of U87 cells (human glioblastoma, 50 000 cells/1µl) in the striatum (L: -2.0, AP: -0.5, DV: -3.0 mm) of nude mice.



Tumor monitoring by MRI (Mediso nanoScan®, PET/MRI 1T, Hungary) illustrated by coronal T2 weighted images of a nude mouse brain showing the growth of a U87 tumor 7 and 16 days post surgery.

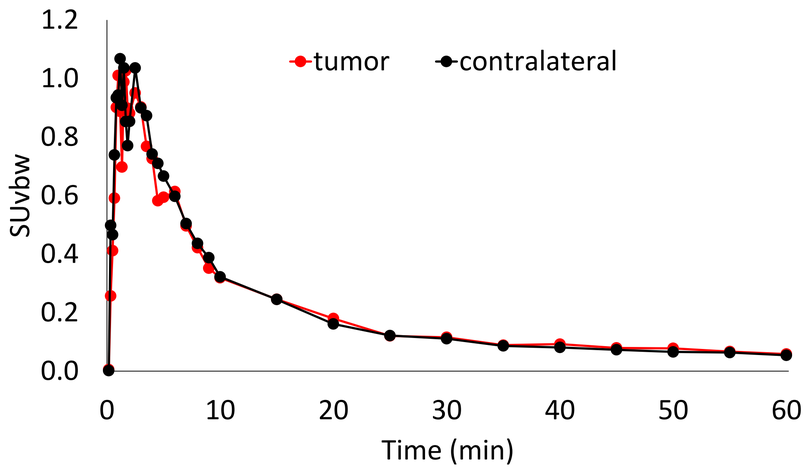
Results

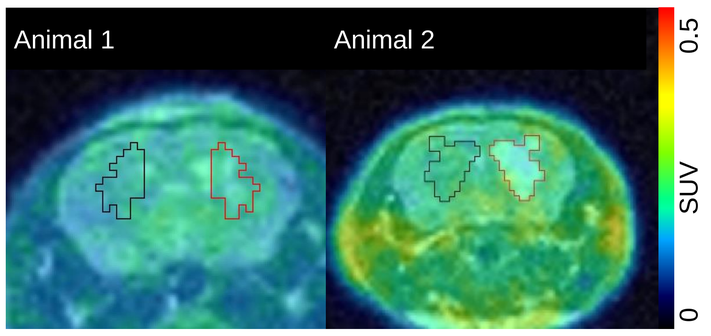
In vivo metabolism of [^{18}F]**RIPGBM** in mice



Representative radio-HPLC chromatograms of the formulated [^{18}F]**RIPGBM** and of the mouse brain and plasma samples obtained at 30 min p.i. (n=2) show a parent fraction of 26-30% in plasma, 73-74% in the brain and 70% in tumor hemisphere (data not shown).

Pharmacokinetic of [^{18}F]**RIPGBM** in mice





Time-activity curves (TAC) of the tumor and the contralateral regions (delineated from the T2wi) have an initial TAC peak value > 1.0 suggesting blood-brain penetration of [^{18}F]**RIPGBM** (n=2). Representative fused PET (0 - 60 min) / MR coronal images illustrate unspecific binding to the tumor.

Summary

- Successful development of a fully automated copper-mediated radiosynthetic procedure
- In vivo investigation reveals 30 % of radiometabolites in the brain/tumor region in mice
- PET imaging lacks specific retention in the target area presumably due to insufficient affinity of this radioligand

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