Radiofluorinated PET Imaging based on the PARP1 inhibitor Olaparib

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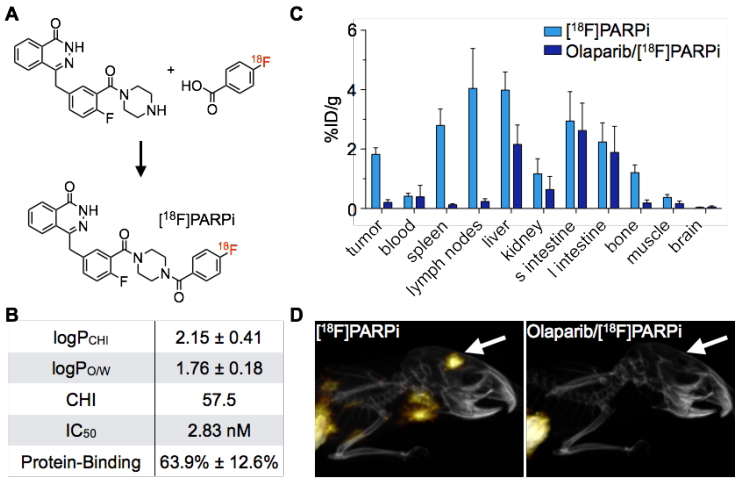
Introduction: PARP1 inhibitors have played an important role in pharmaceutical research, and PARP1-targeted imaging analogs have generated new opportunities to visualize tumor growth and monitor interventions. Capitalizing on the development of PARP1-targeted fluorescent probes for glioblastoma imaging[1,2], we sought to develop an ^{18}F-based PET imaging agent for PARP1 expression.

Methods: The ^{18}F-labeled PARP1 inhibitor [^{18}F]PARPi was generated by conjugating a PARP1-targeting 2H-phthalazin-1-one scaffold to 4-[^{18}F]fluorobenzoic acid in the presence of the coupling reagent HBTU. Biochemical binding assays, optical *in vivo* competition, and pharmacokinetic and biodistribution studies, together with PET/CT and PET/MRI studies of the cold and radiolabeled small molecule, were performed in U251 MG xenograft mouse models of glioblastoma.

Results: The PARP1 tracer was determined to have suitable pharmacokinetic properties for brain tumor imaging (IC_{50} = 2.8 nM; $logP_{CHI}$ = 2.15 ± 0.41; plasma-free fraction = 63.9% ± 12.6%), and was shown to occupy PARP1 expressed in the nuclei of tumor cells. The imaging agent accumulates selectively in orthotopic brain tumor tissue, and its uptake can be reduced by 87% when binding sites are saturated with 500-fold olaparib Accumulation in subcutaneous brain tumors was measured to be 1.82 ± 0.21 %ID/g, whereas in healthy brain, the uptake was only 0.04 ± 0.01 %ID/g.

Conclusion: We have developed [^{18}F]PARPi, an imaging agent with high affinity for PARP1, and confirmed its selectivity as a non-invasive whole body PARP1 imaging agent. In xenograft mouse models of glioblastoma, and that tumors can be delineated with high precision and good signal/noise ratios. We have shown that the uptake is specific to PARP1 expression, and our results indicate that this imaging agent might be of use as a tool for non-invasive imaging of PARP1 expression in glioblastoma.



$logP_{CHI}$	2.15 ± 0.41
$logP_{O/W}$	1.76 ± 0.18
CHI	57.5
IC_{50}	2.83 nM
Protein-Binding	63.9% ± 12.6%

Figure 1. (A) Olaparib based PARP1 targeting 2H-phthalazin-1-one scaffold was conjugated to [^{18}F] 4-fluorobenzoic acid in the presence of the coupling reagent HBTU to yield the final [18F]PARPi. (B) Key pharmacokinetic properties. (C) Biodistribution study in selected tissues. After injection of [^{18}F]PARPi into tumor xenograft mice, mice were euthanized and radioactivity in organs was counted (n= 12). (D) Representative 3D PET/CT scan of orthotopic U251 bearing-mouse after injection of [^{18}F]PARPi (left, unblocked) or after injection of blocking agent olaparib and [^{18}F]PARPi (right, blocked) at 2 hours p.i.

References:

1. Irwin CP, Portorreal Y, Brand C et al. *Neoplasia*. 2014.
2. Carlucci G, Carney B, Brand C et al. *Mol Imaging Biol*. 2015.