Identification and Evaluation of [^{18}F] PIPE-497, the First CNS-Penetrant PET Tracer for the Imaging of Lysophosphatidic Acid Receptor 1 in the Clinic

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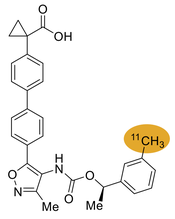
Introduction and Rationale

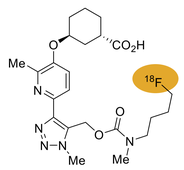
Antagonism of lysophosphatidic acid receptor subtype 1 (LPAR1) represents a promising therapeutic approach for mitigating aberrant LPA-mediated signaling associated with neuroinflammation. **PIPE-791**, a potent and CNS-penetrant LPAR1 antagonist with slow tight-binding characteristics, has been identified and advanced into clinical development for the potential treatment of neuropathic pain, multiple sclerosis, and IPF. To accurately and noninvasively quantify the LPAR1 occupancy achieved in the brain for a given dose of PIPE-791, a CNS-penetrant positron emission tomography (PET) tracer for the selective imaging of LPAR1 was needed.

Earlier Generations of LPAR1 PET Tracers



[^{11}C] BMT-136088

- First generation LPAR1 PET tracer
- ✓ Excellent potency; LPAR1 IC_{50} = 8.8 nM
- ○ High non-specific binding; rodent $f_{u,\ plasma}$ < 0.01
- ○ Poor stability; < 25% remaining in NHP hepatocyte incubation @ 30 min
- ○ Low brain-to-plasma ratio; K_p < 0.01



[^{18}F] BMS-986327

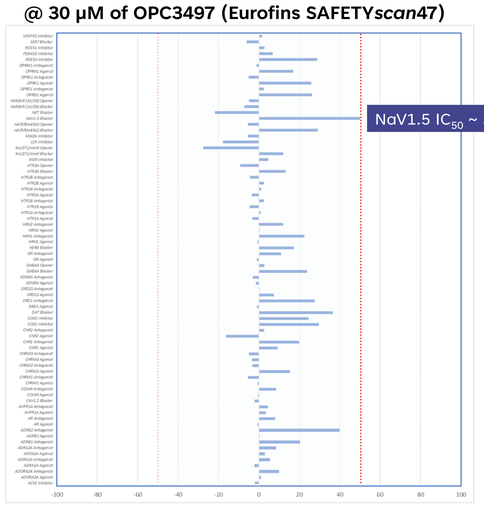
- Second generation LPAR1 PET tracer
- ✓ Good potency; LPAR1 IC_{50} = 24.5 nM
- ✓ Low non-specific binding; rodent $f_{u,\ plasma}$ > 0.1
- ✓ Excellent stability; > 80% remaining in NHP hepatocyte incubation @ 30 min
- ○ Low brain-to-plasma ratio; K_p = 0.05

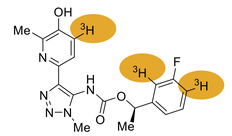
While **[^{18}F] BMS-986327** was determined to be a suitable PET tracer for quantifying LPAR1 expression in the lungs of IPF patients (NCT04069143) and had been fully integrated into the Ph II therapeutic trial of admilparant (NCT04308681, to assess lung LPAR1 occupancy), the tracer was not CNS penetrant.

Profile of OPC3497

Key Parameters	Human	Cyno	Rat
PPB (% free, % remaining @ 6 h)	16, 98	14, 97	14, 77
BTB (% free, % remaining @ 6 h)	-	-	7.8, 100
Hep Cl_{int} (mL/min/kg)	167	489	2500
PK			
CL_u (mL/min/kg)	-	250	400
Vd (L/kg)	-	2.1	11.6
$T_{1/2}$ (h)	-	1.0	7.3
Brain-to-Plasma $K_{p,uu}$	-	-	0.44

% Functional Activity vs. Control Ligand @ 30 µM of OPC3497 (Eurofins SAFETY*scan*47)

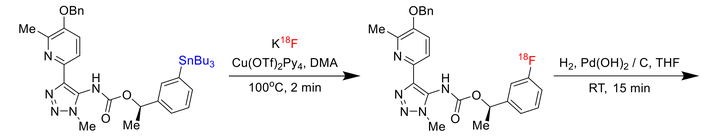


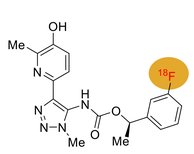


[^{3}H] OPC3497

Regions of Interest	Binding K_d (nM)
Hu LPAR1	2.8
Hu White Matter	4.4
Hu Corpus Callosum	2.6
Hu Striatum	1.6
Hu Putamen	1.6
Hu Internal Capsule	2.6
Cyno Corpus Callosum	4.7
Cyno Striatum	3.8
Cyno Cortex	7.5
Rat Corpus Callosum	1.5
Rat Striatum	1.7

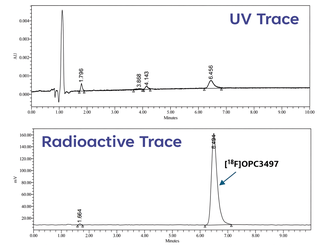
Radiosynthesis of PET Tracer





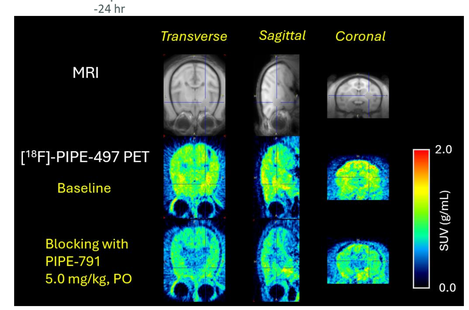
[^{18}F] PIPE-497

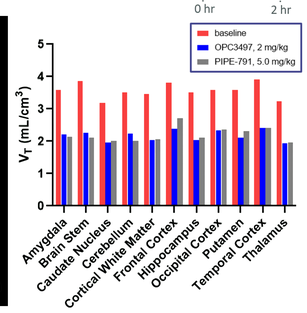
2.8% radiochemical yield
> 168 GBq/µmol @ EOS



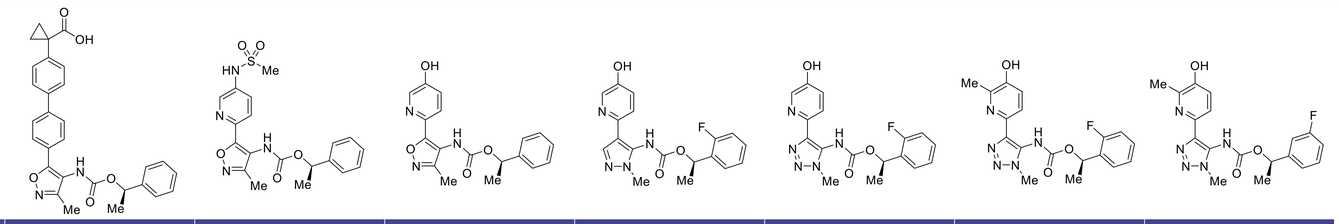
NHP PET Imaging and Analysis

Study Design:



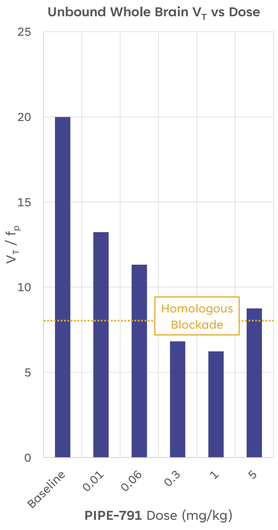


Structure Activity Relationship



Key Parameters	Compound 1	Compound 2	Compound 3	Compound 4	Compound 5	Compound 6	OPC3497
LPAR1 IC_{50} < 25 nM							
Rodent $f_{u,\ plasma}$ > 0.1?							
Rodent $f_{u,\ brain}$ > 0.1?							
Stable in rat plasma @ 6 h?							
Rat CL_u < 400 mL/min/kg?							
Brain-to-Plasma $K_{p,uu}$ > 0.3?							

- ➢ Substitution of the phenyl cyclopropyl carboxylic warhead (in **BMT-136088**) with an OH was tolerated for LPAR1 potency and led to a significant decrease in non-specific binding.
- ➢ Substitution of an isoxazole with a triazole (in **BMS-986327**) and addition of a methyl group *ortho* to OH improved metabolic stability.
- ➢ Incorporation of a *meta*-fluorine allowed for the installation of the ^{18}F nuclei and was less labile towards carbamate cleavage in plasma versus *ortho*-fluorine.



- ➢ One male cynomolgus macaque completed eight **[^{18}F] PIPE-497** scans: baseline, test-retest, and after competition with **OPC3497** (2 mpk, IV) and **PIPE-791** (0.01, 0.06, 0.3, 1, & 5 mpk, PO).
- ➢ Scans were processed in PMOD v3.802.
- ➢ Logan graphical analysis (t^* = 35 min) was used to estimate V_T with blood volume correction (0.05).
- ➢ Baseline V_T of **[^{18}F] PIPE-497** was determined to be 2.40 mL/cm^3 in the brain.
- ➢ Test-retest variability was found to be 25%.
- ➢ Homologous blockade with **OPC3497** reduced V_T by 43%, demonstrating good specific binding and a displaceable signal.
- ➢ Heterologous blockade with increasing oral doses of **PIPE-791** administered 24 h prior to the IV bolus administration of **[^{18}F] PIPE-497** led to dose-dependent reductions in whole brain V_T, with an unbound plasma EC_{50} of ≤ 0.10 nM.
- ➢ **[^{18}F] PIPE-497** has been used to evaluate brain LPAR1 occupancy of **PIPE-791** in HV and prMS patients (NCT.06683612)

Disclosure Statement: Austin Chen, Chris Baccei, Thomas Schrader, Jeff Roppe, Lino Valdez, Alex Broadhead, Kymmy Lorrain, Didier Bagnol, Karin Stebbins, Mike Poon, and Dan Lorrain are/were employees of Contineum Therapeutics and hold/held equity in the company. Contineum Therapeutics has filed patent applications related to PIPE-791.

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