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Kinetic modeling of novel radiotracers for the GABA Transporter-1 in nonhuman primates

Paul Gravel[1], Chao Wang[1], Daniel Holden[1], Krista Fowles[1], MingQiang Zheng[1], Jean-Dominique Gallezot[1], Edilio Borroni[2], Michael Honer[2], Luca Gobbi[2], Gilles Tamagnan[3], Henry Huang[1], Richard E. Carson[1]

[1]PET Center, Department of Radiology and Biomedical Imaging, Yale University, New Haven, CT, USA
[2]Pharma Research and Early Development, F. Hoffmann-La Roche Ltd., Basel, Switzerland
[3]Department of Psychiatry, Yale University, New Haven, CT, USA

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Roche

Introduction

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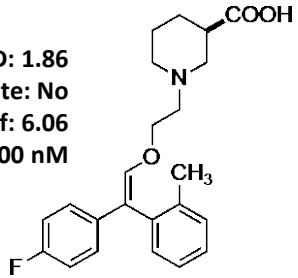
- GABA transporter 1 (GAT-1), the principal GABA transporter in the brain, is an important target to study due to its potential role in a number of neuropsychiatric disorders.
- Although PET radiotracers exist for the GABA receptors, none have been successful for GAT-1.
- The focus of this work is to evaluate the kinetic behavior of two novel F-18 PET radiotracers ([^{18}F]GATT-34 and [^{18}F]GATT-44) for imaging the GAT-1 transporter.

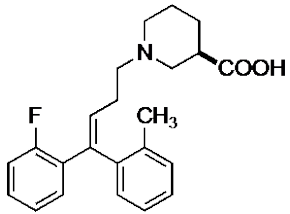
GATT-34

LogD: 1.86
PgP substrate: No
PAMPA Peff: 6.06
IC_{50} < 100 nM



GATT-44

LogD: 1.49
PgP substrate: No
PAMPA Peff: 6.19
IC_{50} < 100 nM



For more information on the radiochemistry refer to Abstract:
Development of Novel Brain-Penetrant Radioligands for PET Imaging of GABA Transporter-1
C. Wang et al., Radiopharmaceutical Young Investigator Award Session

Methods

- Two anesthetized non-human primates (NHP) each underwent a baseline and a blocking scan
  - NHPs scanned on Focus-220 small animal PET scanner
  - [^{18}F]GATT-34 (181±6 MBq) as well as [^{18}F]GATT 44 (182±5 MBq)
  - tiagabine (*aka* Gabitril: antiepilepsy, dose: 0.5 mg/kg, administered over 10 min at ~10 min prior to tracer injection)
  - arterial blood was collected for measurement of the input function

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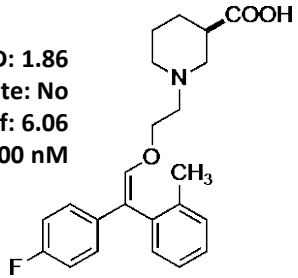
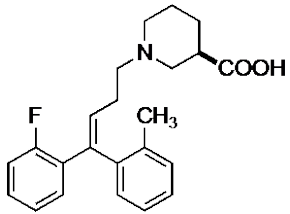


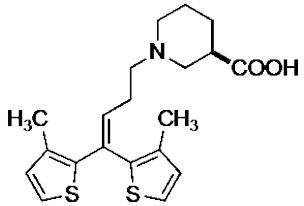
GATT-44

LogD: 1.49
PgP substrate: No
PAMPA Peff: 6.19
IC_{50} < 100 nM



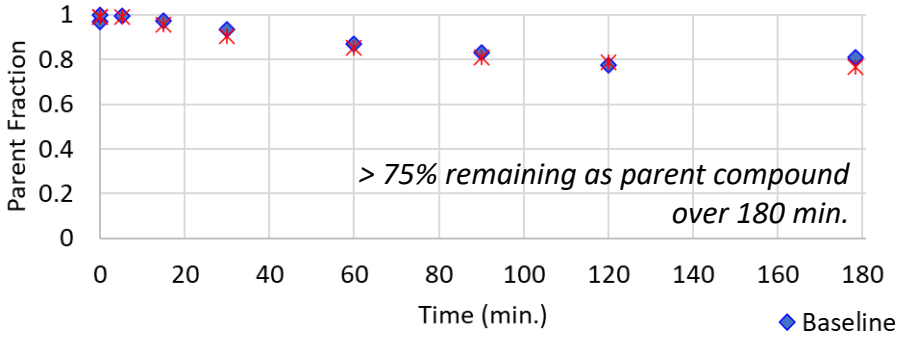
Tiagabine

LogD: 1.43
PgP substrate: low
PAMPA Peff: 7.80
IC_{50}: 0.07 nM

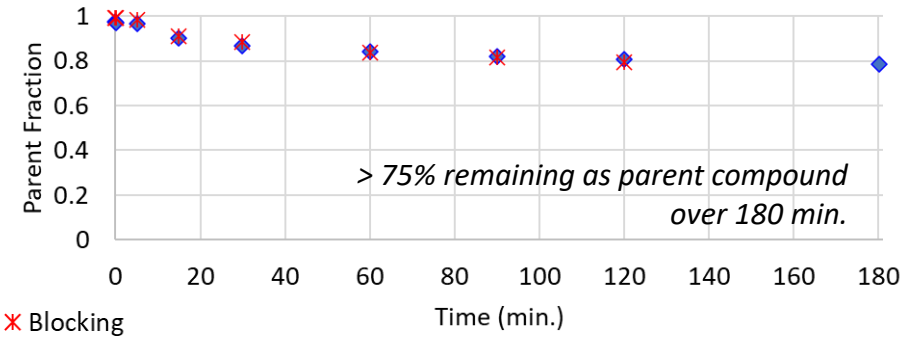


Parent Fraction and Arterial Input Functions (AIFs)

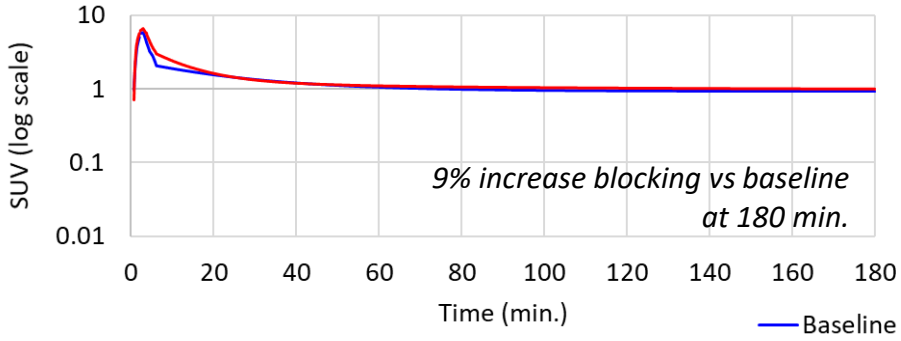
[^{18}F]GATT-34 Parent Fraction: Baseline and Blocking



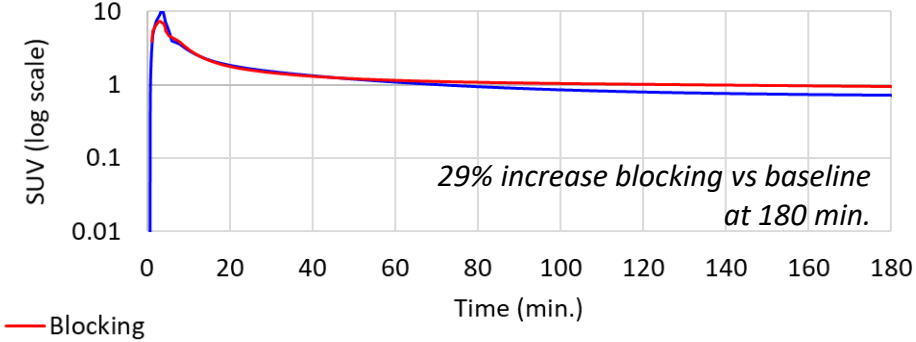
[^{18}F]GATT-44 Parent Fraction: Baseline and Blocking



[^{18}F]GATT-34 SUV AIF: Baseline and Blocking



[^{18}F]GATT-44 SUV AIF: Baseline and Blocking



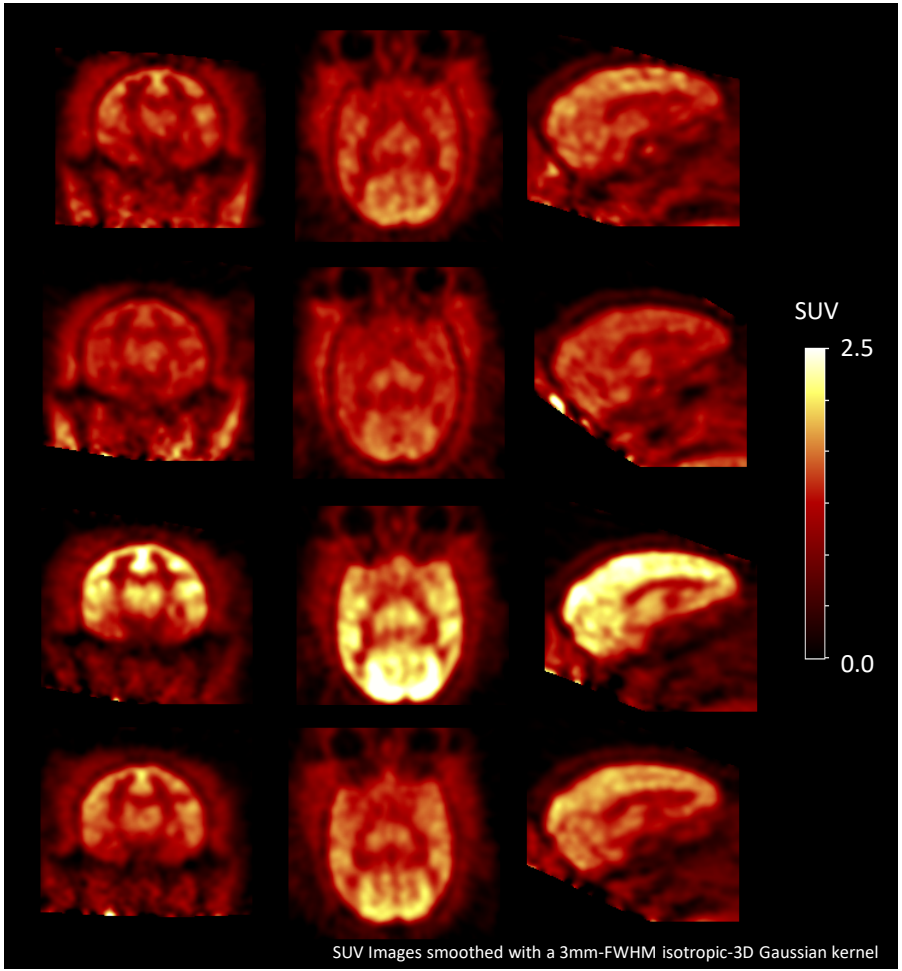
SUV Images (90-120 min.) and SUV TACs

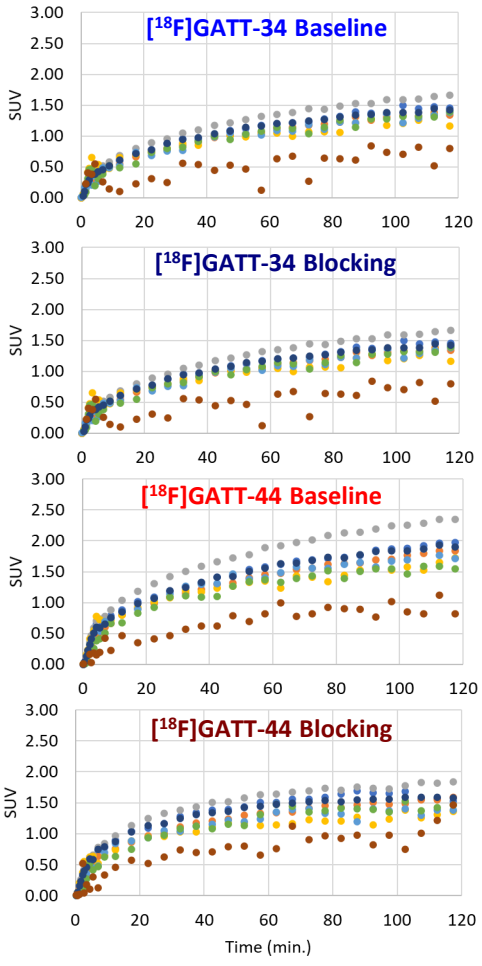
[^{18}F]GATT-34 Baseline

[^{18}F]GATT-34 Blocking

[^{18}F]GATT-44 Baseline

[^{18}F]GATT-44 Blocking



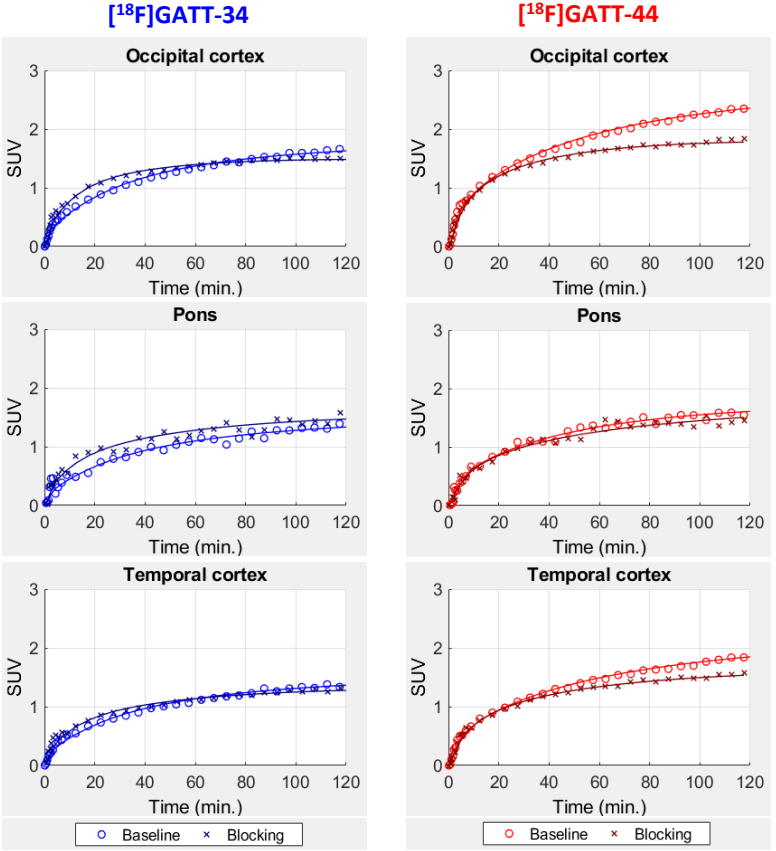


Volume of distribution (V_T) values*

ROI Name	GATT-34 V_T Baseline (mL/cm³)	GATT-34 V_T Blocking (mL/cm³)	GATT-44 V_T Baseline (mL/cm³)	GATT-44 V_T Blocking (mL/cm³)
Caudate	1.37	1.25	1.98	1.20
Cerebellum	1.70	1.37	3.24	1.60
Cingulate cortex	2.17	1.50	3.82	1.92
Frontal cortex	1.82	1.42	3.43	1.70
Hippocampus	1.33	1.20	2.18	1.10
Insula	2.01	1.45	4.12	1.89
Occipital cortex	2.01	1.46	4.25	1.86
Pons	1.71	1.57	2.68	1.87
Putamen	1.62	1.37	2.63	1.43
Temporal cortex	1.72	1.32	3.65	1.75
Thalamus	1.41	1.20	1.84	1.10
Average	1.71	1.37	3.08	1.58
SD	0.28	0.12	0.86	0.32
Range	[1.33 - 2.17]	[0.20 - 1.57]	[1.84 - 4.25]	[1.10 - 1.92]

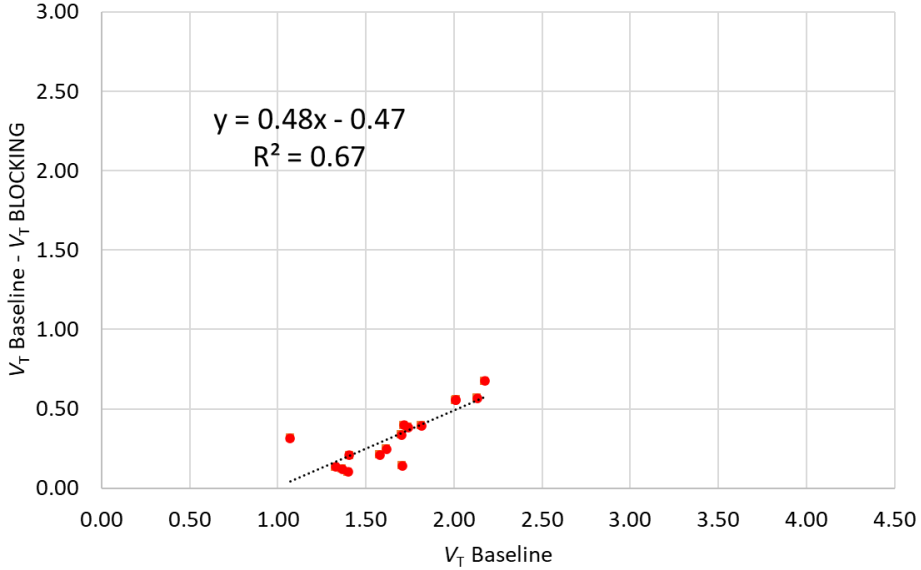
K_1 values were similar between tracers and conditions, and were very low: 0.015 (mL/min/cm³) on average

** The 1-TCM without a blood volume component (V_b = 0) delivered an overall reliable performance with standard error (SE< 10% on average) for ROIs investigated.*

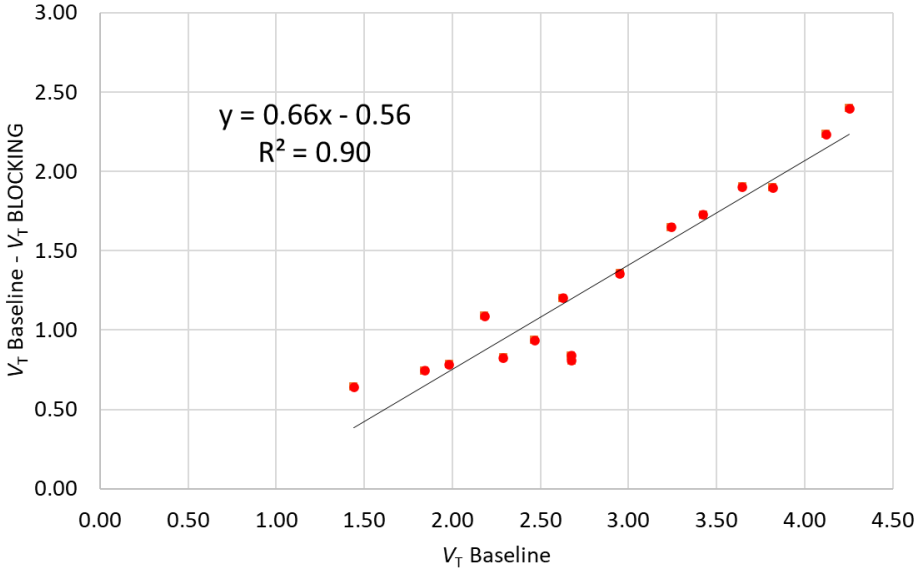


Lassen Plots

[^{18}F]GATT-34 Lassen Plot



[^{18}F]GATT-44 Lassen Plot



[^{18}F]GATT-34
About 48% of binding sites are blocked.
V_{ND} = 0.98 mL/cm^3

[^{18}F]GATT-44
About 66% of binding sites are blocked.
V_{ND} = 0.85 mL/cm^3

Baseline V_T and BP_{ND} values

ROI Name	GATT-34 V_T Baseline (mL/cm^3)	*GATT-34 BP_{ND} Baseline (unitless)	GATT-44 V_T Baseline (mL/cm^3)	*GATT-44 BP_{ND} Baseline (unitless)
Caudate	1.37	0.40	1.98	1.32
Cerebellum	1.70	0.74	3.24	2.79
Cingulate cortex	2.17	1.22	3.82	3.47
Frontal cortex	1.82	0.86	3.43	3.01
Hippocampus	1.33	0.36	2.18	1.56
Insula	2.01	1.06	4.12	3.82
Occipital cortex	2.01	1.05	4.25	3.98
Pons	1.71	0.75	2.68	2.13
Putamen	1.62	0.65	2.63	2.08
Temporal cortex	1.72	0.76	3.65	3.27
Thalamus	1.41	0.44	1.84	1.16
Average	1.71	0.75	3.08	2.60
SD	0.28	0.28	0.86	1.01
Range	[1.33 - 2.17]	[0.36 - 1.22]	[1.84 - 4.25]	[1.16 - 3.98]

* $BP_{ND} = V_T/V_{ND} - 1$

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- [^{18}F]GATT-34 and [^{18}F]GATT-44 are specific to the GAT-1 transporter
  - [^{18}F]GATT-34: tiagabine blocked 48% of specific binding with a V_{ND} of 0.98 mL/cm^3 and average BP_{ND} = 0.75
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- [^{18}F]GATT-44 appears to be superior due to its higher brain uptake and higher binding potential
- Evaluation of two additional ligands is underway with plans to progress the best ligand to humans

Acknowledgments

We acknowledge the Yale PET Center staff for their contribution to this project.

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and is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.