

**Stony Brook University  
The Graduate School**

Doctoral Defense Announcement

**Abstract**

**Synthesis and Positron Emission Tomography Studies of Radioligands Targeting  $\alpha 7$   
Nicotinic Acetylcholine Receptors in the Central Nervous System**

By

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The pharmacological effects the action of nicotine on nicotinic acetylcholine receptors (nAChR) have been implicated in many diseases such as Alzheimer's disease, schizophrenia, and tobacco dependence. Brain imaging using positron emission tomography (PET) for each nAChR subtype allows us biological information on subtype-specific function and pathological change. While  $\alpha 4\beta 2$  nAChR PET tracers have been developed, the development of PET for  $\alpha 7$  nAChR has been hampered due to the lack of suitable radioligands. It is, therefore, important to develop  $\alpha 7$  nAChR-selective PET tracers for *in vivo* imaging studies to better understand the role of  $\alpha 7$  nAChR in specific CNS disorders. Furthermore, PET imaging of drug targeting  $\alpha 7$  nAChR can also contribute to drug development by providing information on drug distribution *in vivo*.

In this work, we first investigated the drug pharmacokinetics of GTS-21, a partial  $\alpha 7$  nAChR agonist drug, using PET in the baboon and rat. C-11 labeled GTS-21 at different position and their corresponding two major demethylated metabolites which have been considered as contributing to the therapeutic effects of GTS-21, were synthesized. PET study revealed that extremely rapid uptake and clearance of [2-methoxy- $^{11}\text{C}$ ]GTS-21 from the brain, and significant brain uptake of 2-OH-GTS-21, suggesting that it might contribute to the therapeutic effects of GTS-21. Second, C-11 labeled Norethyl-N-methyl-methyllycaconitine and nicotine were synthesized and PET study in the baboon was performed. We also designed putative quinuclidine-based  $\alpha 7$  nAChR ligands based on our quantitative structure-activity relationship and synthesized ligand candidates through cross-coupling reactions of heteroaryl bromides and heteroaryl carboxylic acid.

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