In Vivo evaluations of microtubule-based PET radiotracer, [^{11}C]MPC-6827 in murine models of Alzheimer's Disease

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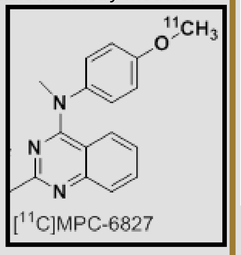
INTRODUCTION

- In healthy neurons, tau binds to microtubules (MTs) to regulate its stability. In Alzheimer's disease (AD) brain, tau is detached from MTs and phosphorylated at multiple sites.
- There is a critical need for early AD biomarkers that capture changes in neuronal integrity and stability, especially in the context of Aβ and tau pathology.
- MT PET imaging agent could be an ideal bridge between classical biomarkers and molecular imaging tools, providing a solid platform to image brain functions (early on) in AD.
- We have recently reported the radiochemical synthesis of the first brain-penetrating MT PET ligand, [^{11}C]MPC-6827 and it's *in vivo* PET imaging in normal mice.[1,2]
- In this presentation, we report the *in vivo* evaluations of [^{11}C]MPC-6827 in amyloid β (Aβ)-over expressing (APP-PS1, 5xFAD) and tau-over expressing (P301S) transgenic and wild-type AD mice.

METHODS

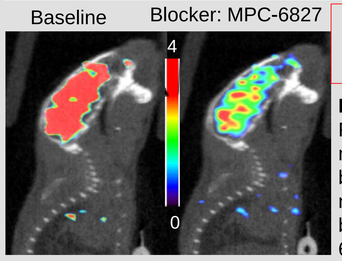
- Radiochemical synthesis of [^{11}C]MPC-6827 was achieved by alkylating the corresponding desmethyl-precursor with [^{11}C]MeI in DMF using NaOH in a GE-FX2MeI/FX2M radiochemistry module.
  RCY = 45 ± 5 %, RP = 95 ± 3 %,
  SA = 2.9 ± 0.6 Ci/mmol,
  n >20, decay corrected to EOS. [1,2]
- Aβ staining was performed in all APP-PS1 and P301S mice.
- Dynamic PET imaging was performed in both transgenic (TG) and wild-type (WT) (n=3/group) APP-PS1 at 22 months), 5xFAD (at 15 months) and P301S mice (at 8 months) by injecting 120 ± 20 µCi of [^{11}C]MPC-6827



- *Ex vivo* post-PET biodistribution studies were performed in both TG and WT APP/PS1 and 5xFAD mice (n=3/group).
- Post-PET blocking biodistribution studies were performed in transgenic 5xFAD mice (n=6) by injecting the non-radioactive MPC-6827 (5 mg/kg), 45 min before the radiotracer injection.

RESULTS

1. PET/CT imaging in normal mice



First brain penetrating MT PET radiotracers

Figure 1: Representative mPET/CT 0-60 min brain images in normal mice at baseline and MPC-6827 blockade

2. Aβ staining

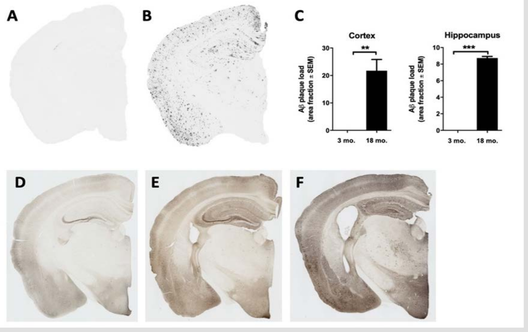


Figure 2: Aβ staining in the APPswe/PSEN1dE9 mouse at (**A**) 3 and (**B**)18 months of age. No plaque deposition is observed in the young, 3 months old mice. In contrast, significant plaque pathology is observed in the cortex and hippocampus of 18 months old mice (**C**) AT8 staining for phosphorylated tau in the P301S mouse at (**D**) 6, (**E**) 9 and (**F**) 11 months of age.

3. PET/CT imaging in APP-PS1 mice

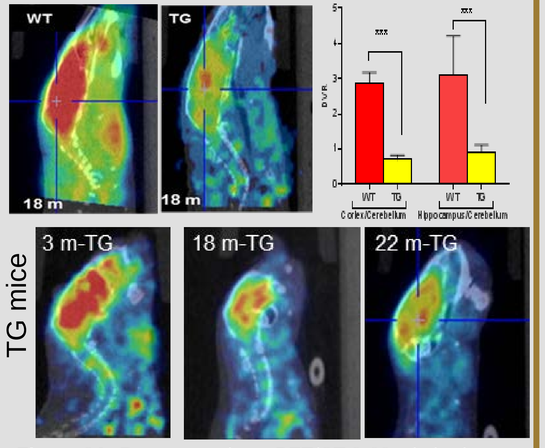


Figure 3A: Representative mPET/CT 0-60 min brain images in APP/PS1 mice (**A**) Wild type (WT) at 18 months, (**B1**) Transgenic mice (TG) at 18 months and #B. TG mice at 3, 18 and 22 months.

5. PET/CT imaging in P301S mice

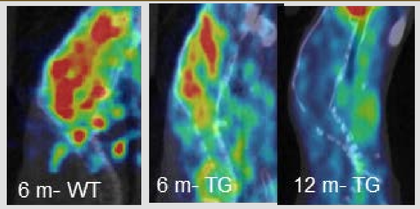


Figure 5: Representative mPET/CT 0-60 summed brain images in (**A**) wild-type at 6 months and (**B**) transgenic P301S mice at 6 and 12 months

6. Biodistribution studies in APP-PS1 mice

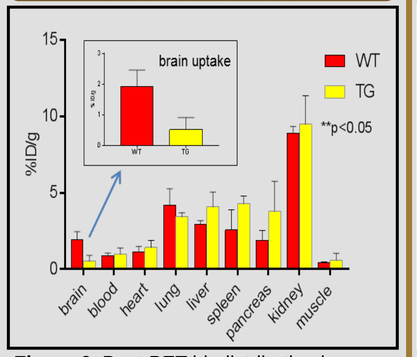


Figure 6: Post-PET biodistribution in APP/PS1 wild-type and transgenic mice, with brain uptake in the inset

7. Biodistribution studies in P301S mice

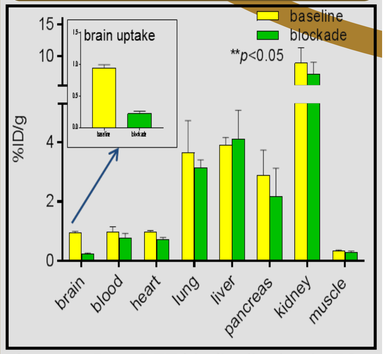


Figure 7: Post-PET biodistribution in TG P301S mice at baseline and blockade conditions with brain uptake in the inset

CONCLUSIONS

- [^{11}C]MPC-6827 showed significant lower radioactive uptake in the transgenic APP-PS1, 5xFAD and P301S mice over their corresponding wild-type control mice.
- Post-PET biodistribution results in brain corroborated well with the microPET/CT analysis.
- [[^{11}C]MPC-6827 -potential early PET imaging biomarker of AD related diseases
- Next steps:
  Correlating [11C]MPC-6827 uptake with tau pathologies
  PET imaging in NHP model of AD

References and Support

1.. Kumar JSD and Kiran Kumar SS et al. *J Med Chem*, 61(5), 2118-2123, 2018;
2. Kiran Kumar SS et al. *ACS Med Chem Lett*, 9 (5), 452-456, 2018

WFSM- CTSA: UL1TR001420, WFSM ADRC P30AG049638, WFSM startup