**Development of radiotracers for TSPO polymorphisms**

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**Introduction:** The translocator protein (TSPO) is a key PET imaging target for visualizing neuroinflammation across a broad range of CNS diseases. The clinical utility of TSPO-PET has been hindered by genotype-dependent radiotracer binding discrepancies related to the rs6971 polymorphism (A147T). These binding variations compromise radiotracer reliability across patient populations.

**Aims**: To develop a pan-TSPO radiotracer that enables specific, accurate imaging of microglial-mediated neuroinflammation.

**Methods**: We employed a validated HEK293T cellular model overexpressing either wild-type or A147T variant TSPO to screen compounds. These candidates were assessed for high-affinity, genotype-independent binding using a competition radioligand binding assay. Our lead candidate was radiolabelled and progressed to small animal pharmacokinetic studies, as well as *in situ* autoradiography on diseased human brain tissue from patients homozygous for wild type or A147T TSPO as well as heterozygous patients.

**Results:** Structure-affinity relationships identified a lead radiotracer candidate with robust, genotype-insensitive binding. Our lead tracer was able to image all genotypes of TSPO tissue in the *ex vivo* study, in contrast to another TSPO radiotracer widely used in human studies, which loses affinity at the A147T TSPO polymorphism.

**Discussion.** Current radiotracers are limited by genotype-dependent variability. Our work addresses the barrier of genotype-dependent variability seen in past TSPO PET tracers which have held back the field. By identifying a genotype-independent candidate TSPO-PET ligand, this work advances a new generation of TSPO PET tracers suitable for broader clinical application.

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