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Thursday

Optimization of PET tracers for TDP-43 proteinopathies

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State of the art: TDP-43 proteinopathy is common in patients with frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) and is present as co-pathology in other neurodegenerative diseases further complicating the diagnosis. Selective and sensitive biomarkers of TDP-43 pathology are currently not available. Direct detection of TDP-43 aggregates by positron emission tomography (PET) holds promise for better diagnosis, patient stratification and assessment of therapeutic efficacy in clinical trials.
Methodology: Binding affinities of small molecules from AC Immune's proprietary MorphomerTM library were evaluated on TDP-43 aggregates enriched from FTLD-TDP brain samples. Target engagement was further assessed by autoradiography on sections from brains with different types of FTLD-TDP pathology. Binding selectivity over other aggregation-prone proteins was evaluated. Brain pharmacokinetic (PK) profile was established in mice, and selected 18F-radiolabeled compounds were also profiled by PET PK in non-human primates (NHP).
Results: Screening of >700 compounds led to identification of 3 distinct chemical series that bound with nanomolar affinity to pathological TDP-43 derived from FTLD-TDP brain samples. Selectivity over amyloid beta, alpha-synuclein and Tau was established for selected compounds. Target engagement on FTLD-TDP Type A and C inclusions was shown by high resolution autoradiography. For some compounds, PK properties suitable for first-in-human PET tracer evaluation were established in NHP.
Conclusions: We identified for the first time compounds from distinct chemical series displaying target engagement on FTLD-TDP Type A and C pathology. Medicinal chemistry optimization is ongoing to further improve the affinity to pathological TDP-43 aggregates and brain PK profile for development as PET tracer.

Conflicts of interest

All authors are employees of AC Immune entitled to stock options