OPTIMIZATION OF PET TRACERS FOR TDP-43 PROTEINOPATHIES

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AC Immune

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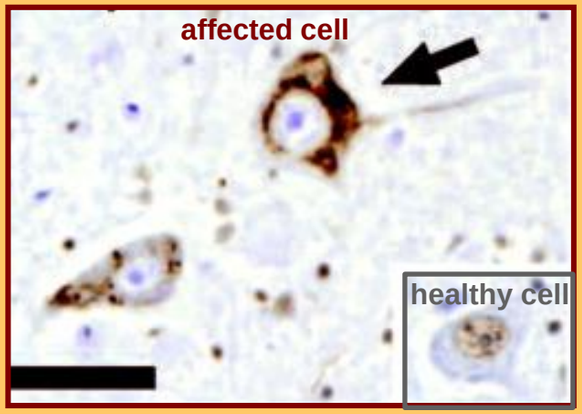
Conflict of interest disclosure

Tamara Seredenina is an employee of AC Immune entitled to stock options

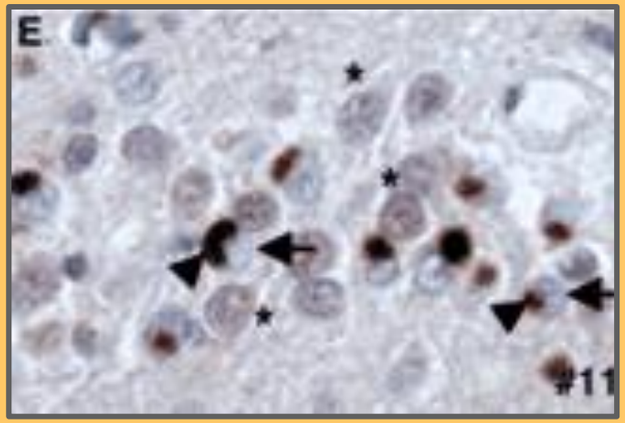
TDP-43, a biomarker for TDP-43 proteinopathies

Amyotrophic lateral sclerosis (ALS)



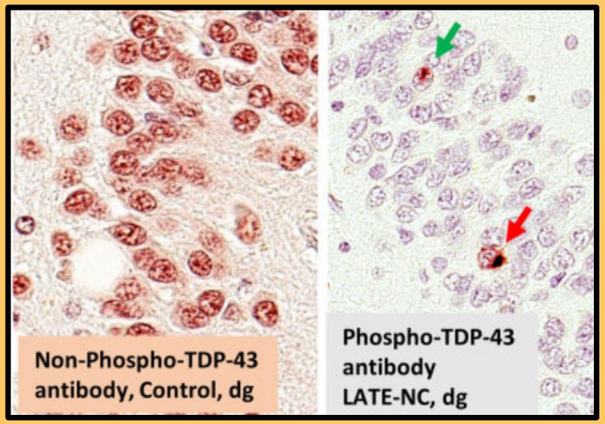
Igaz et al., Am J Path., 2008

Frontotemporal dementia (FTD)



Neumann et al., Science, 2006

Control **Limbic-predominant age-related TDP-43 encephalopathy (LATE)**



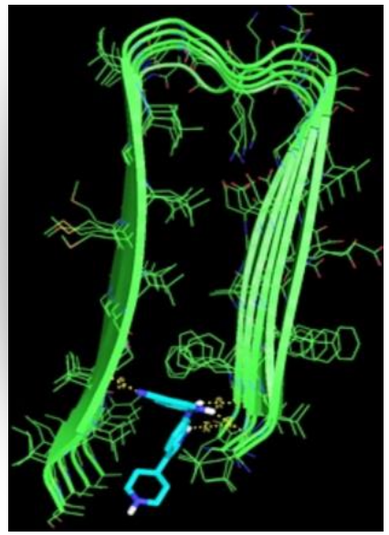
Nelson et al., Brain, 2019

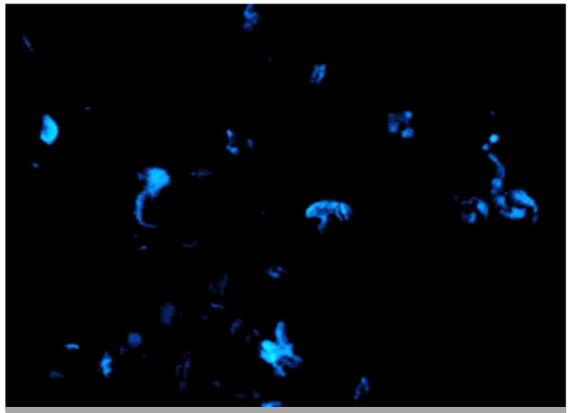
- TDP-43 pathology is found in multiple neurodegenerative disorders including ALS, FTD and AD
- The development of therapeutics for TDP-43 proteinopathies requires specific and sensitive biomarkers
- ACIU uses its Morphomer® platform to identify potential PET tracer binding to aggregated TDP-43
- ACIU uses its SuprAntigen® library of antibodies to enable detection of TDP-43 species relevant to CNS pathology in CSF and blood

- TDP-43 biomarkers will increase the probability of success of therapeutic trials in TDP-43 proteinopathies allowing the recruitment of a more homogenous patient population and longitudinal assessment

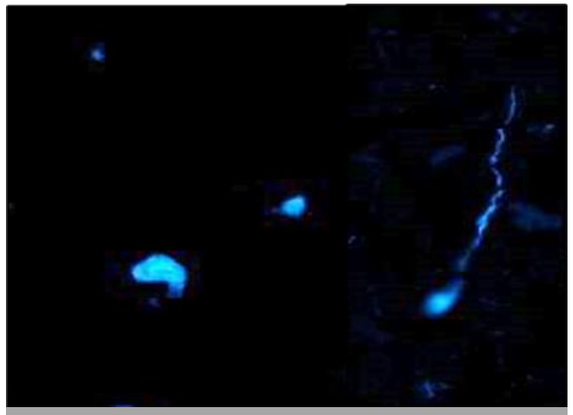
Development of PET tracers for neurodegeneration

Morphomer® platform

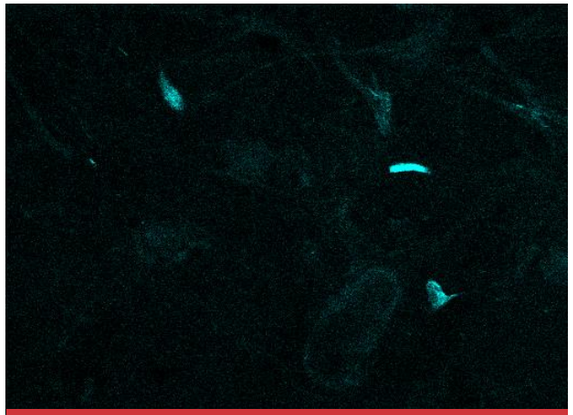




Tau neurofibrillary tangles



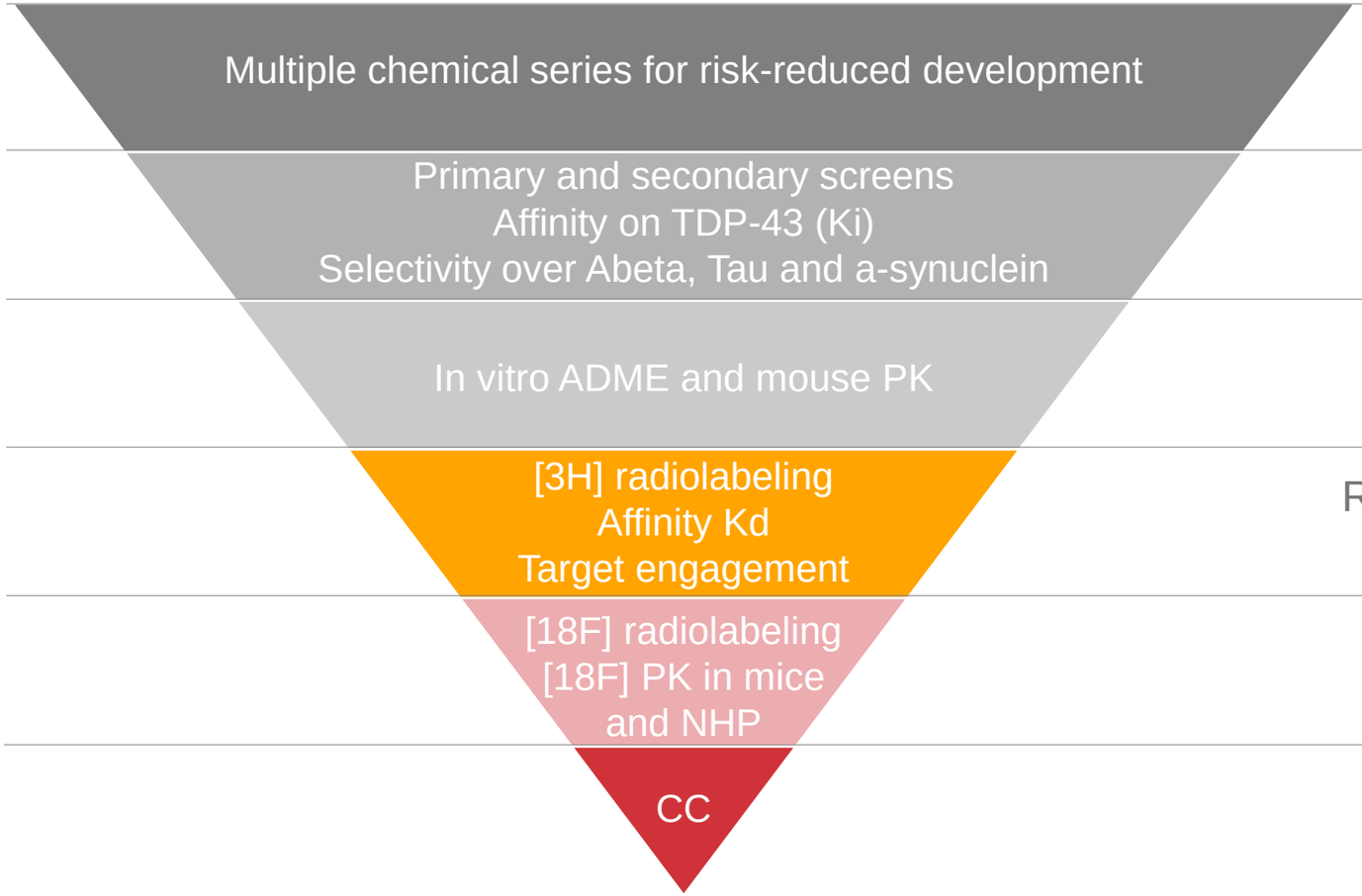
a-synuclein Lewy bodies and neurites



TDP-43 inclusions

- AC Immune's PET tracers: Tau tracer PI-2620 in Phase 2 and a-syn tracer ACI-12589 in FiH studies
- Robust library of conformation-specific, non-peptidic small molecules with desirable CNS properties constructed and continually refined and expanded over many years
- Rely only on patient-derived brain samples for target engagement
- Comprehensive screening, rational design and early validation processes rapidly generate highly specific hit compounds

Screening strategy for PET tracer development



Morphomer library, scaffold hopping, rational design, focused screening

Radiobinding assay on insoluble fractions from FTLD-TDP, AD and PD brains

Solubility, permeability, microsomal stability, chemical stability, neuroPK

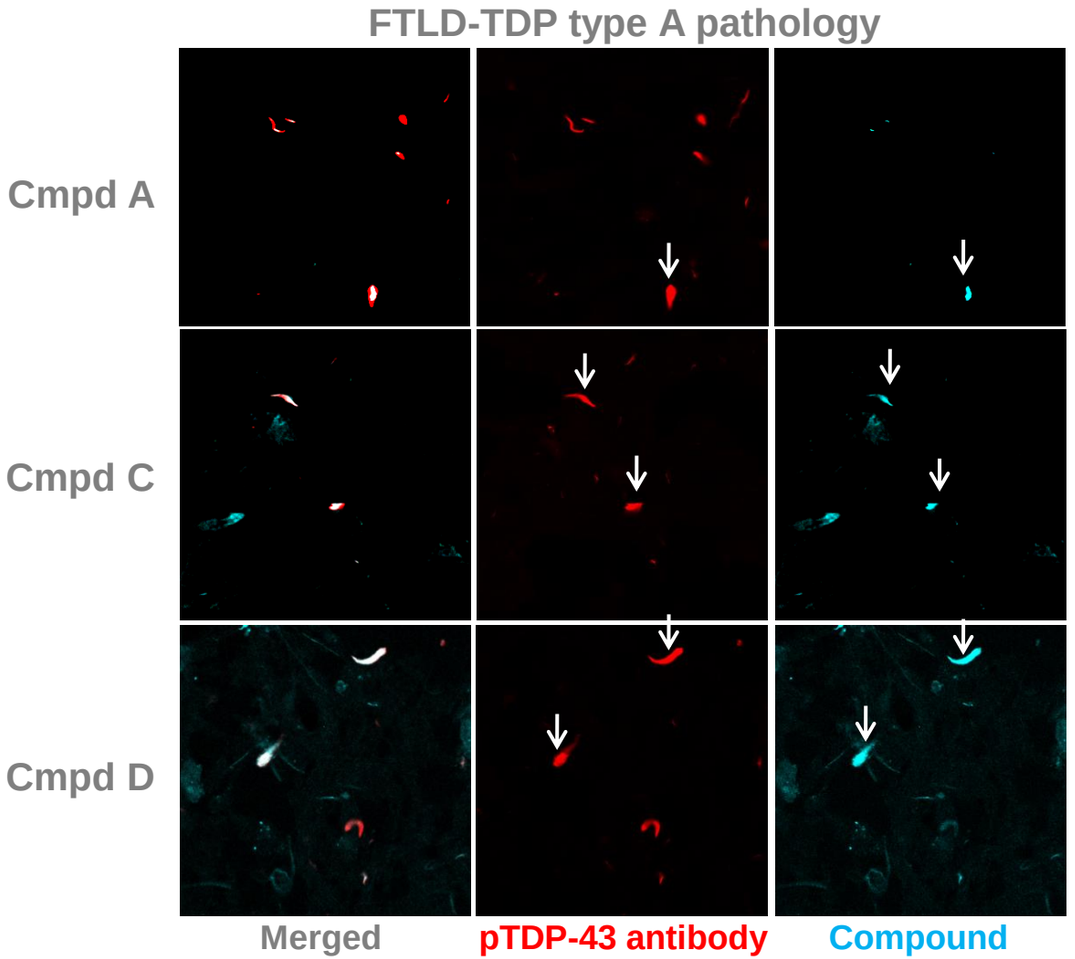
Radiobinding assay and autoradiography on brains with FTLD-TDP

Assessment of properties for CNS PET-tracer

Clinical candidate
IND-enabling studies

- Lead candidates selected based on affinity to TDP-43 aggregates, selectivity over Abeta and Tau and PK profile optimal for CNS PET tracer

Identification of a reference compound

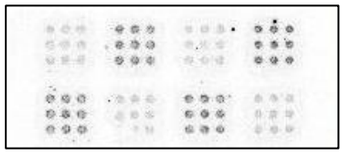


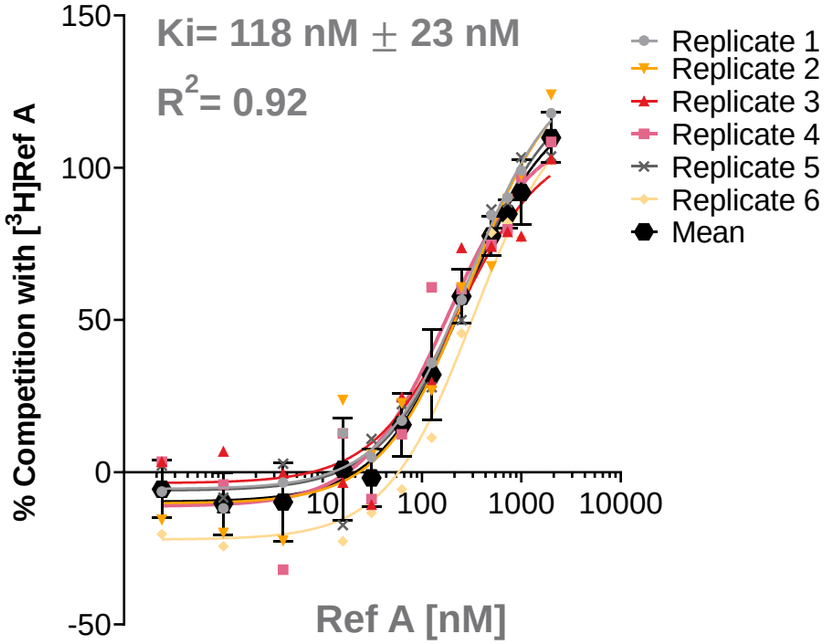
- 660 compounds screened from the Morphomer® library by direct fluorescent staining
- Two reference compounds identified

Binding to TDP-43 aggregates from human brain

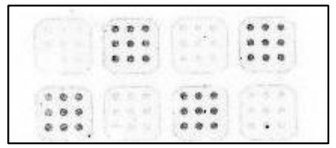
Competition binding experiments to determine Ki

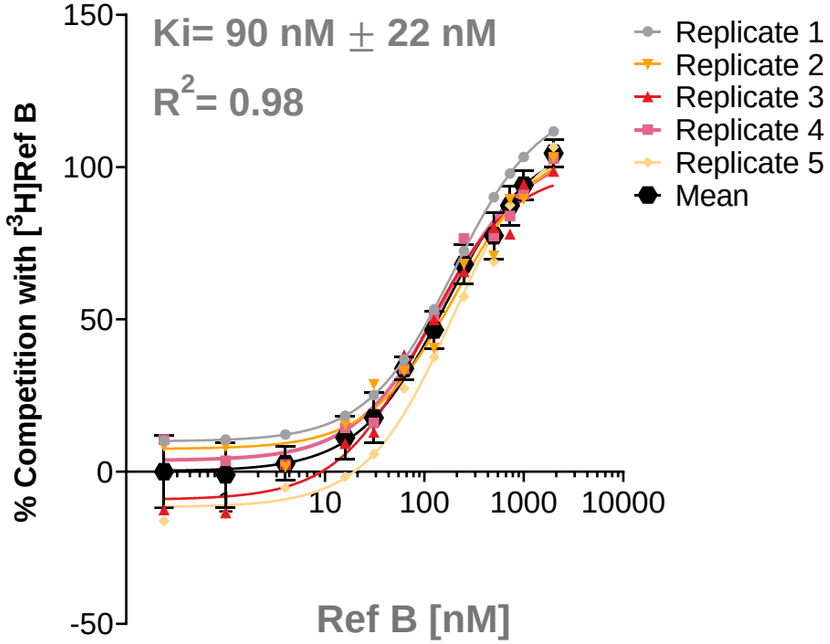
Ref A (2 µM)	DMSO	Ref A (2 µM)	DMSO
DMSO	Ref A (2 µM)	DMSO	Ref A (2 µM)





Ref B (2 µM)	DMSO	Ref B (2 µM)	DMSO
DMSO	Ref B (2 µM)	DMSO	Ref B (2 µM)



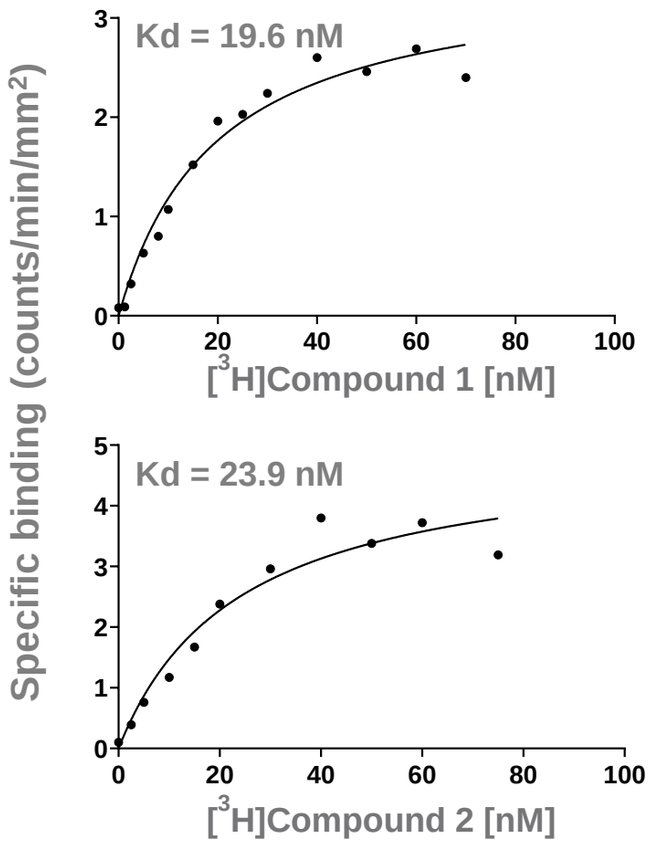


- Micro-radiobinding assay using automated spotting of sarkosyl-insoluble fractions from human brain with FTLD-TDP pathology is used for compound screening (Ki)
- Robust and reproducible signal using reference compounds [^{3}H]Ref A and [^{3}H]Ref B

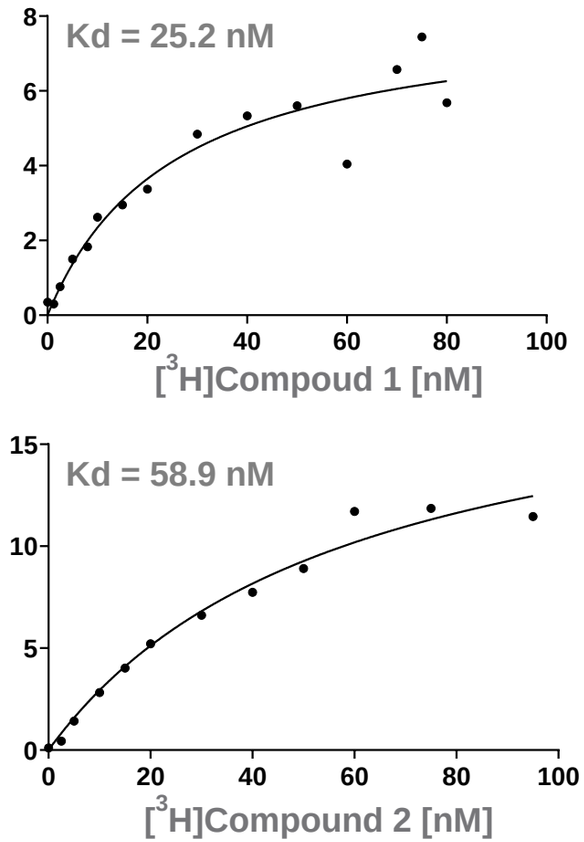
Binding to TDP-43 aggregates from human brain

Saturation binding experiments to determine binding affinity (Kd)

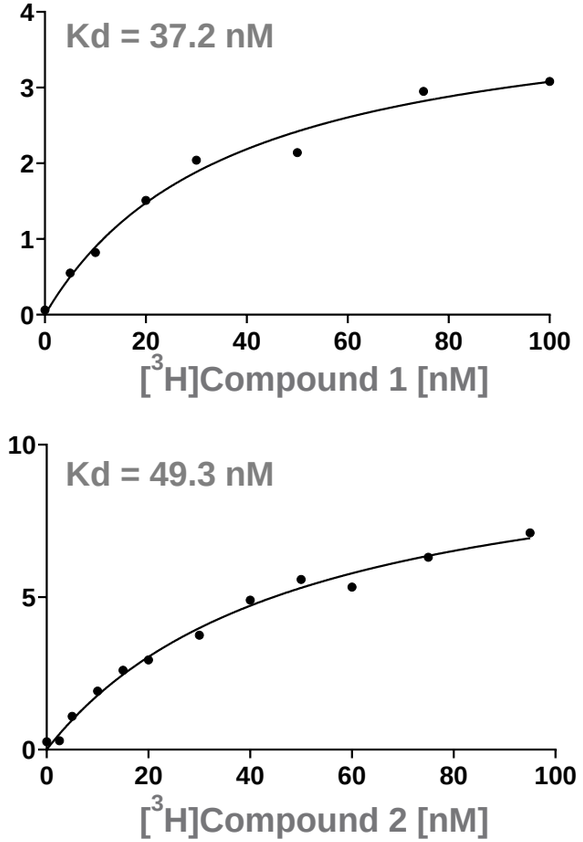
FTLD-TDP Type A



FTLD-TDP Type B



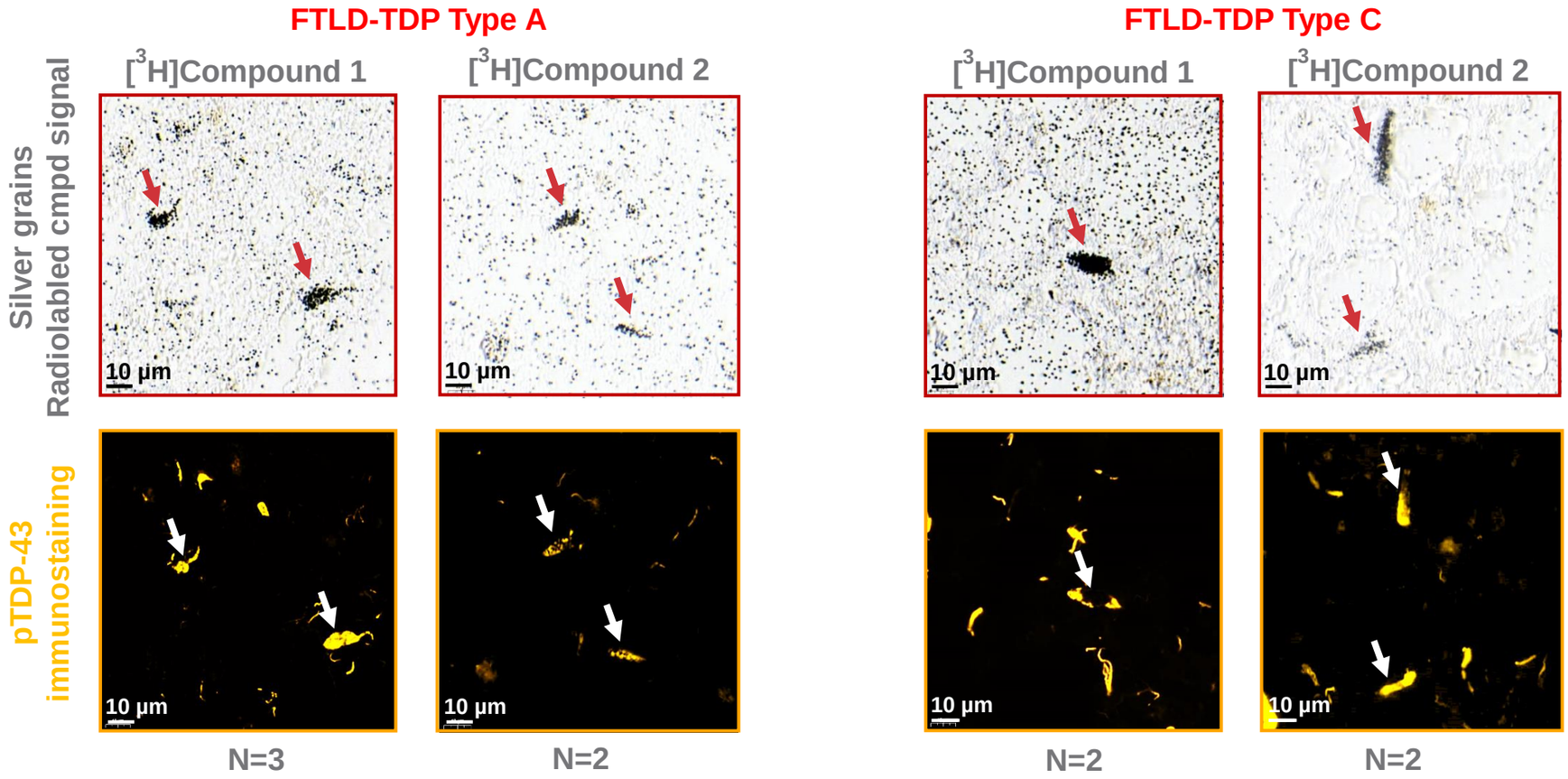
FTLD-TDP Type C



- Identification of novel compounds with low nanomolar affinity to sarkosyl-insoluble fractions from patient brain with different types of FTLD-TDP pathology

Target engagement on FTLD-TDP brain sections

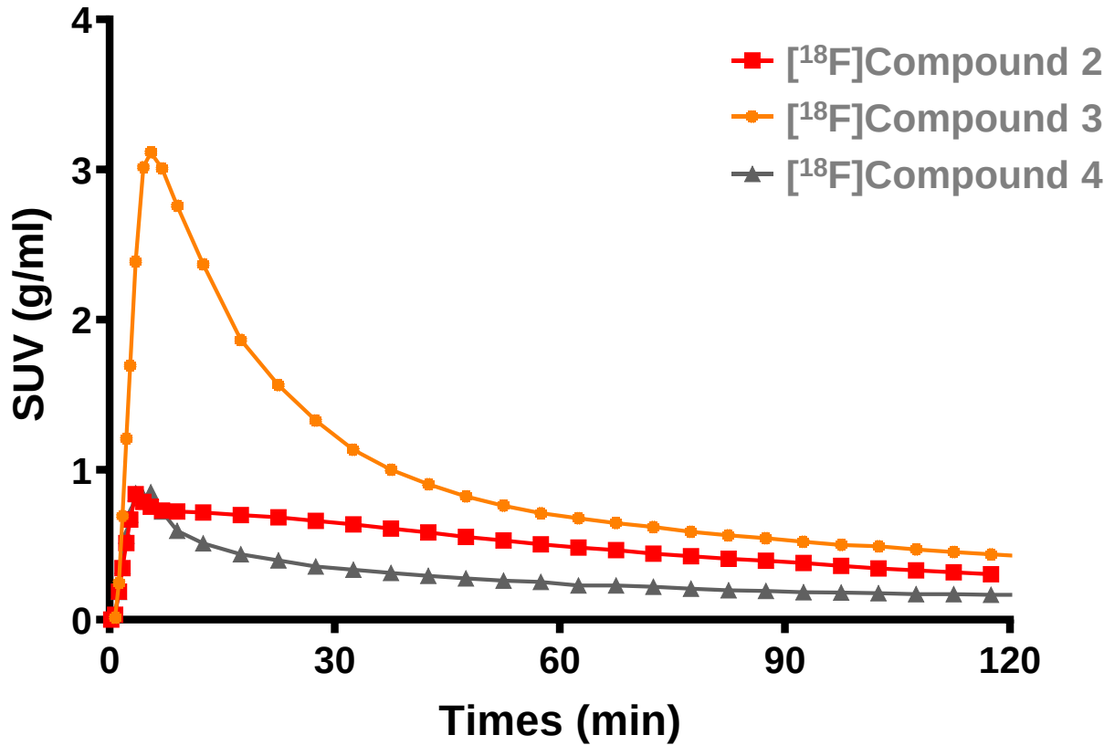
High resolution autoradiography



- First proof of target engagement on brain samples with FTLD-TDP type A and C pathology, showing compound co-localization with pTDP-43 antibody labeling

Pharmacokinetic profile

PK profile in brain after intravenous administration in non-human primates



- [18F]Compound 2 shows fast brain uptake (1.4% injected dose) and steady but incomplete washout
- Structurally similar analogs show improved PK profile with higher brain uptake and faster washout
- Optimization ongoing to further improve the brain uptake and washout

Summary

TDP-43 PET imaging program

1	▪ Multiple unique assays developed to assess binding to human brain homogenates and target engagement on human brain tissue
2	▪ Novel, highly valuable reference compounds binding to TDP-43 aggregates from patient brain identified
3	▪ Building on our expertise in TDP-43 biology and extensive experience with developing CNS PET tracers, novel hit series with low nanomolar affinity and target engagement on FTLD-TDP brains identified ▪ Proven fast brain uptake in non-human primates
4	▪ Optimization ongoing to explore structure-activity relationship and further improve affinity, selectivity over other aggregation-prone proteins, and pharmacokinetic properties suitable for CNS PET

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AC Immune TDP-43 PET team

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AC Immune

We continue to shape the future of neurodegeneration by discovering and developing breakthrough therapies through pioneering science and precision medicine

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