Discovery and development of diagnostics and therapeutics for TDP-43 proteinopathies
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• TDP-43 therapeutic antibody project is the exclusive property of AC Immune.
• TDP-43 PET imaging project is non-exclusively partnered with Biogen.
Introduction
TDP-43, a therapeutic and biomarker target

- TDP-43 is a RNA/DNA binding protein expressed primarily in the nucleus where it functions as a regulator of gene transcription and RNA metabolism

- Pathological aggregation of TDP-43 is found in multiple neurodegenerative diseases
  - 97% of cases of ALS
  - 45% of cases FTD
  - 50% of cases of AD

- TDP-43 spreading and seeding contributes to disease pathogenesis

Therapeutic target – mAb program
Diagnostic tool: patient stratification and longitudinal measurements of disease progression and treatment efficacy – PET ligand program
The SupraAntigen™ platform
Immunotherapy against conformation-specific targets

- Synthetic peptide of 8-60 aa as antigen
- Anchor to induce and stabilize conformation
- Liposome to carry peptide and adjuvant
- Adjuvant to enhance immunogenicity

Key features of platform derived molecules
- Mimic pathological conformation
- Are highly immunogenic
- Have favorable safety

(1) Monophospholipid A

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Generation of therapeutic antibodies

Antibody generation

- Use the SupraAntigen™ platform to generate mAbs specifically targeting disease-associated TDP-43 species
- Different antigen conjugation chemistries to control peptide/protein conformation on the liposome

Aim: to generate a panel of conformation-specific antibodies against TDP-43
TDP-43 mAb target engagement
IHC on frozen brain sections

pTDP-43
(CosmoBio TIP-PTD-p02)
pan TDP-43
(Proteintech 10782-2-AP)
misfolded TDP-43
(ACI mAb Clone A)

mAb Clone A detects TDP-43 aggregates in cytoplasm (arrows) in FTD brain tissues and does not bind to physiological, nuclear TDP-43

Ref: AC Immune unpublished data
TDP-43 mAb target engagement
IHC on paraffin-embedded brain sections

- In collaboration with Prof. Manuela Neumann

mAb Clone B detects TDP-43 aggregates in cytoplasm (arrows) in FTD brain tissues and does not bind to physiological, nuclear TDP-43

Ref: AC Immune unpublished data
TDP-43 mAb binding properties

Binding by Surface Plasmon Resonance (SPR)

Preferential binding to aggregated TDP-43 was observed. Characterization in functional assays is ongoing.

EM data provided by Senthil Kumar Thangaraj (Prof. Lashuel lab)

Ref: AC Immune unpublished data
TDP-43 PET tracer development

Challenges

- Sparse pathology - high affinity ligand needed for PET imaging
- Mixed pathologies - high selectivity over other aggregated proteins
- Specifically target cytoplasmic aggregates over monomeric TDP-43 located in the nucleus
- Screening and validation on FTD/ALS donor brain samples
- No tool compound available for assay development and benchmarking
Selectivity by radiobinding assays on AD brain homogenates

Confirm on 3 patient samples QC + analog testing

In vitro ADME and mouse PK

Radiolabeling and 18F-PK studies

Direct fluorescent staining on ALS/FTD brain section

> 660 cpds tested on human ALS/FTD brain sections by direct staining

Four hit series validated

Three $^3$H-radioligands for assay development

Three compounds profiled in mouse PK

Two $^{18}$F-radioligand profiled in mouse-PK
Confirmed hits
Hit Series I, II and IV

Compound A (Series I) on type A/C pathology

Compound B (Series II) on type A pathology

Compound C (Series IV) on type A pathology

Ref: AC Immune unpublished data
Radiobinding Assay

3H-Cpd-D binding to FTD-derived aggregated TDP-43 and AD brain

- Affinity measurements (Kd and Ki) for binding of Cpd-D on FTD brain-derived TDP-43 aggregates
- No specific binding measured for 3H-Cpd-D on AD brain homogenate
- Screening of compounds in Ki determination using 3H-Cpd-D is ongoing

Kd determination

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Kd = 131.5 nM
R² = 0.93

Ki determination

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Ki = 237.2 nM
R² = 0.95

3H-Cpd-D selectivity over Aβ in AD brain homogenate

- 3H-Cpd-D
  - 2% AD Brain insoluble
  - 1% AD Brain insoluble (Kd = 9.1 nM)

- 3H-Ref-AD
  - 1% AD Brain insoluble

Affinity measurements (Kd and Ki) for binding of Cpd-D on FTD brain-derived TDP-43 aggregates

No specific binding measured for 3H-Cpd-D on AD brain homogenate

Screening of compounds in Ki determination using 3H-Cpd-D is ongoing

Ref: AC Immune unpublished data
Cpd-D shows a promising cold PK profile with at least 1.45% of brain uptake, Tmax ≤ 2 min but no complete washout from the brain.

18F-Cpd-D pharmacokinetic experiments confirm a fast brain uptake (≤ 2 @4%ID), as well as a good but not complete washout from the brain.
Conclusion and perspectives

TDP-43 therapeutic antibody program

- Using SupraAntigen technology we generated antibodies selective for misfolded TDP-43
- These mAbs will be used for:
  - Identification of TDP-43 species linked to disease stage or disease severity
  - Characterization in functional assays in vitro
  - PoC efficacy studies in animal models with TDP-43 pathology

TDP-43 PET imaging program

- Following our screening cascade we identified four hit series with distinct chemical scaffolds interacting with pathological TDP-43 aggregates
- We have radiolabeled with tritium four tool compounds; our lead molecule binds to FTD patient brain homogenates with an affinity of 134 nM
- Our compound showed promising 18F-PK properties for a PET imaging agent: quick and high brain uptake and fast but not complete washout from the brain
- A screening campaign using radiobinding assays is ongoing in order to identify compounds with higher affinity and improved pharmacokinetic profiles

Ref: AC Immune unpublished data
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Contact:
tamara.seredenina@acimmune.com