Characterization of Tau vaccines identifies diverse antibody binding and efficacy profiles.

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KEY TAKEAWAY: ***Specific forms of Tau can be targeted by vaccines with subsequent functional impact.***

BACKGROUND

The accumulation of misfolded Tau in the brain correlates with clinical decline in Alzheimer's Disease (AD) but manifests decades earlier than cognitive symptoms[1].

Targeting pathological Tau prior to the clinical onset of AD could help prevent disease and/or progression[2].

Vaccine-based immunotherapy is a tractable approach for the prevention of Alzheimer's Disease.

We present preclinical characterization of Tau vaccines based upon Vaxxinity's platform.

METHODS

Vaccination: Leads were formulated in Adju-Phos CpG1 at 100 ug/mL + 300 ug / 0.25 mL peptide. Guinea pigs were given 5 intramuscular shots 3 weeks apart, with the terminal bleed collected at 15 wpi.

Immunogenicity: Antibodies against the T helper peptide, adjuvant components, and Tau were quantified by ELISA in serial dilution.

Antibody Characterization: Antibody binding was characterized against recombinant and brain-derived Tau preps by Western blot, dot blot, and biolayer interferometry (BLI). Assessments of in vitro function were made via Tau FRET-aggregation and pHrodo uptake assay in HEK293 and B103 cells.

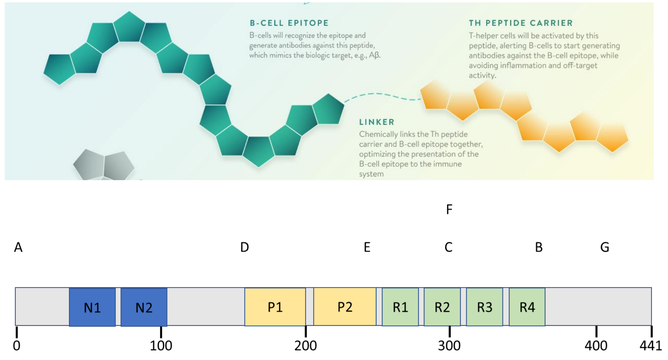
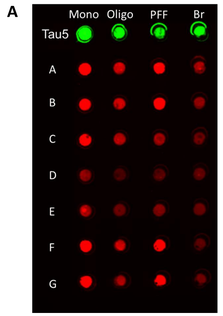


Figure 1: Vaxxinity Platform targeting Tau. Schematic diagram of the platform, Th peptide carrier linked to the target-specific B-cell epitope (Top) . Tau primary structure with functional domains and targeting peptides annotated (Bottom).

Table 1: Immunogenicity of Tau candidates

Lead	UbITh1	CpG1	Antigen	Mono	PFF
A	10	107	396	504	17,400
B	10	221	1,490	3,512	2,060
C	10	199	2,827	5,732	745
D	17	18	10,086	574	601
E	10	15	5,216	554	498
F	10	39	97	2,782	4,050
G	10	59	4,003	3,299	4,556

Ec50 values generated via 12-point dilution curve ELISAs probing against the T helper peptide, CpG, Tau lead-specific peptides, full length monomeric Tau (Mono) and Tau preformed fibrils (PFF) using the terminal bleed sera (15 weeks) from vaccinated male Hartley guinea pigs.



PFF				
Rank	Ab	KD (M)	Ab	Koff (1/s)
1	Bep	1.32E-09	A	3.22E-04
2	A	8.03E-09	B	5.25E-04
3	E	1.09E-08	G	5.53E-04
4	F	1.31E-08	Bep	6.88E-04
5	B	1.32E-08	F	7.02E-04
6	G	1.34E-08	E	7.26E-04
7	C	1.50E-08	C	8.47E-04
8	D	2.81E-08	D	1.19E-03

Figure 2: Antibody binding characterization. The binding potency of vaccine-derived antibodies against three forms of recombinant Tau (monomeric, oligomeric, and PFF) and a sarkosyl extract from postmortem brain tissue (Br) were characterized via dotblot (A). Diverse binding profiles were observed against the different forms of Tau. BLI results show antibody binding to Tau forms for Leads with Kd in nM range, with three Leads having slower off rates than Bepranemab (B). Representative binding curves of Bep and Lead A to PFF are presented.

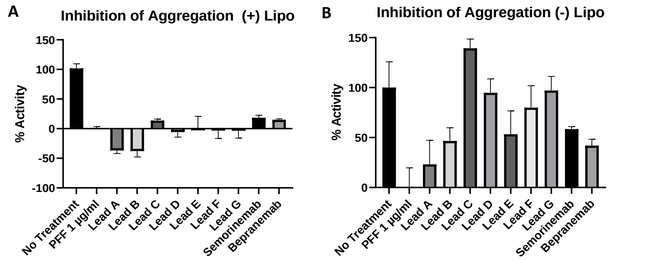


Figure 3: Aggregation assay using Tau biosensor line. Tau biosensor lines[3] were used to assess the functional inhibition of vaccine derived antibodies compared to anti-Tau mAbs, Semorinemab and Bepranemab. Assay conditions included the addition of lipofectamine (A) and without lipofectamine (B). Only the condition without lipofectamine resulted in Abs inhibiting aggregation.

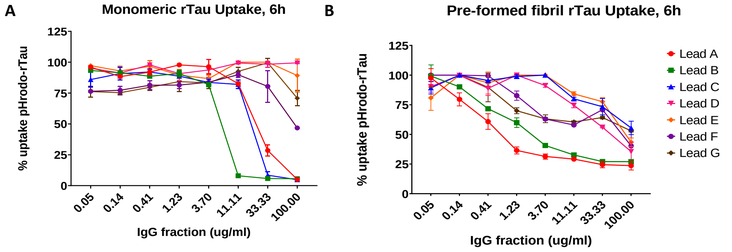


Figure 4: Tau uptake assay. B103 cells were exposed to pHrodo labeled Tau preparations for 6h. Upon uptake, pHrodo-Tau fluoresces, which enabled quantification using the IncuCyte live cell imager. Leads A, B, C and F inhibit the uptake of monomeric Tau in dose response (A). All Leads resulted in a dose-dependent reduction of PFF uptake (B) . Leads vary in potency; however, all exhibited stronger inhibition of PFF than monomeric Tau uptake.

CONCLUSIONS

The antibodies from Vaxxinity's leading Tau candidates display diverse binding profiles against different forms of Tau. No significant immunogenicity was observed against the UbITh1 peptide or CpG1.
Functional assays illustrate that binding antibodies prevent aggregation by inhibiting uptake.

REFERENCES

1. Congdon and Sigurdsson. *Nat. Rev. Neurol.* 2018
2. Makin. *Nature*. 2018
3. Frost et al. *J. Biol. Chem*. 2009