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Development of a Dual Aβ/Tau Vaccine for the Treatment and Prevention of Alzheimer's Disease

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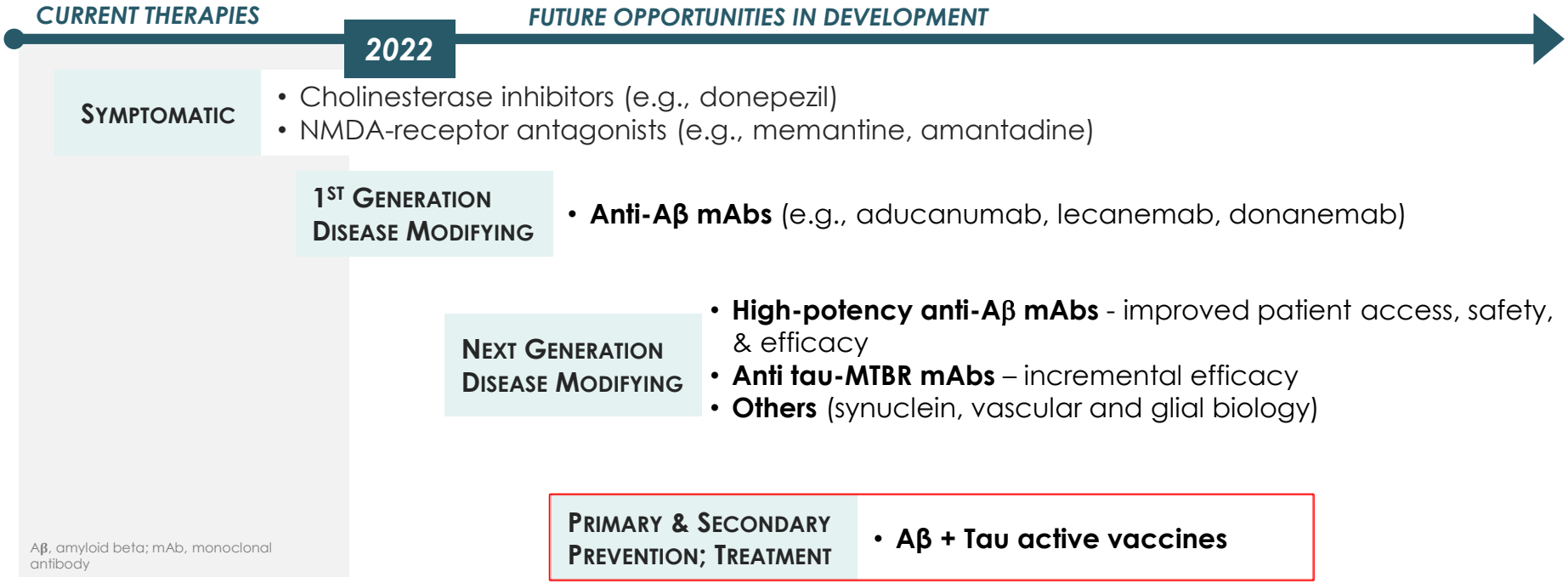
W. Zago is an employee of Prothena Biosciences Inc, South San Francisco, USA; has stock options in Prothena Corporation plc; and is an inventor on patent applications.

Incremental Innovation in Alzheimer's Disease Therapeutics
From Treatment to Disease Prevention



Aβ, amyloid beta; mAb, monoclonal antibody

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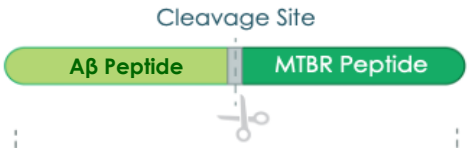
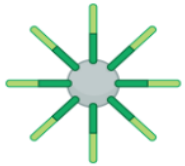
Dual Aβ/Tau Vaccine – Design and Attributes





Desirable Attributes	Design	Desirable Output
• Single construct vaccine able to induce meaningful and balanced tau and Aβ response in older adults	✓ Linear peptide, cleavable linkers ✓ Optimal carriers, immunization schedule, adjuvant	✓ Optimal antigen presentation with persistent immune response ✓ Overcomes immunodominance and immunosenescence
• Induces antibodies that clear plaques and neutralize soluble Aβ and tau	✓ Validated tau and Aβ epitopes ✓ Elements for Induction of mature Th-response	✓ Antibodies bind relevant epitopes on pathogenic proteins ✓ IgG switch and affinity maturation
• No cytotoxic T-cell response associated with meningoencephalitis	✓ Short epitopes ✓ Peptides with no anticipated off-target binding	✓ No cytotoxic T-cell responses ✓ Specific antibodies

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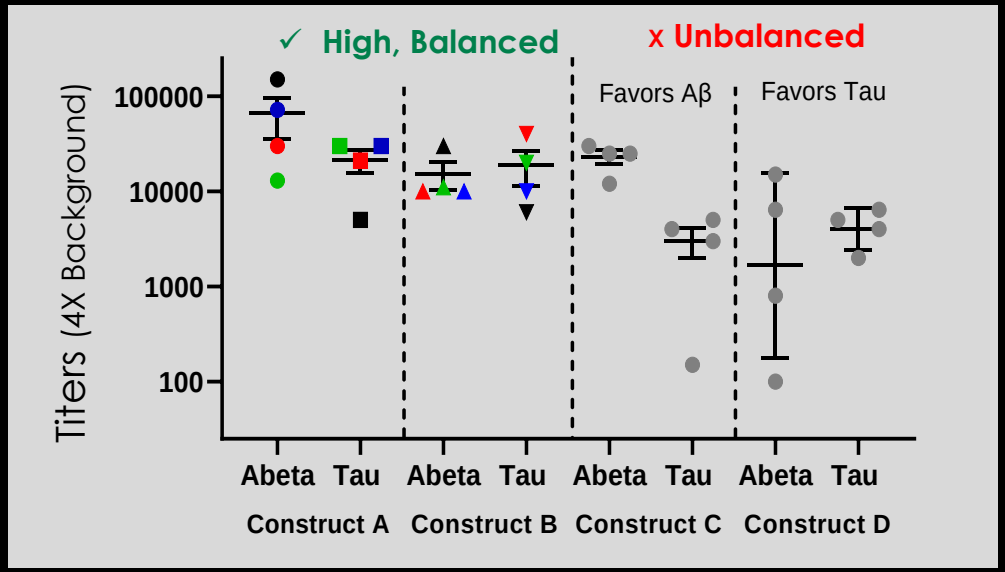
Quantity

Dual Aβ/Tau vaccines generate appropriate magnitude of immune response



✓ **High**
✓ **Balanced**
✓ **Consistent**

Mouse titer analysis on bleeds performed by ELISA against recombinant tau and $A\beta_{42}$
N=4 mice/group; mean +/- SEM

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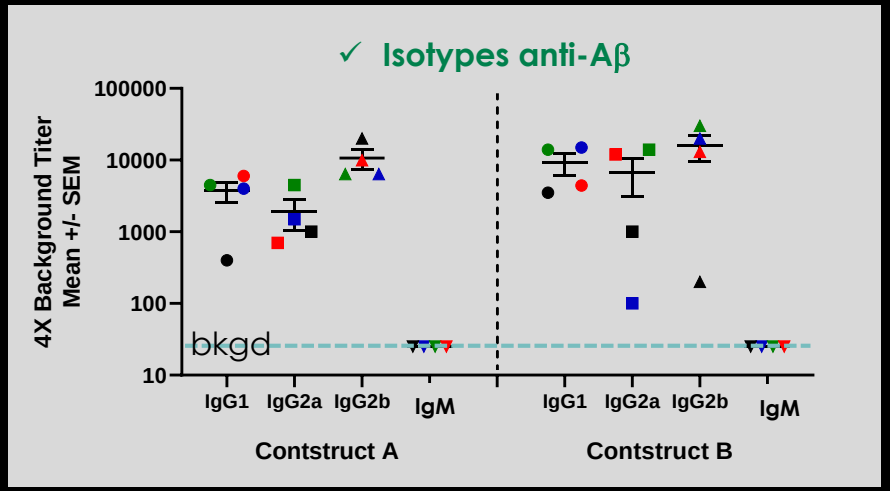
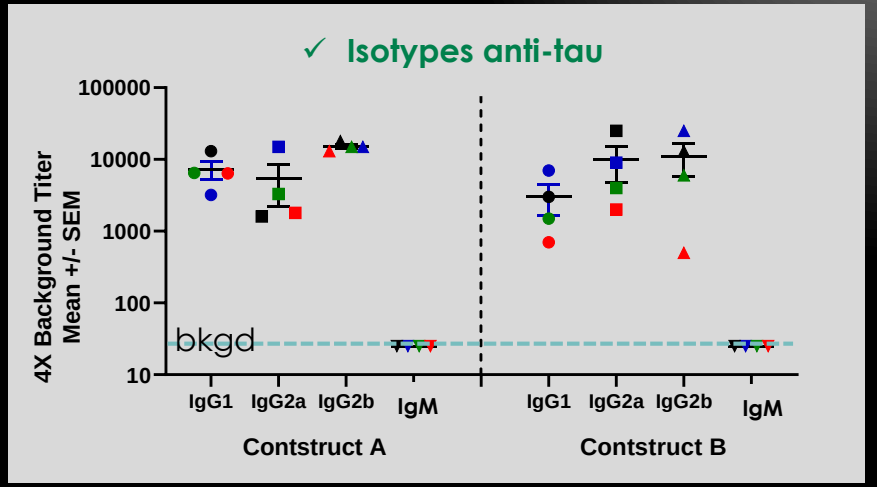
Quality

Dual Aβ/Tau vaccines generate appropriate antibody isotypes





✓ High levels of IgG's; low/undetectable IgM's

Mouse titer analysis on bleeds performed by ELISA against recombinant tau and Aβ
N=4 mice/group; mean +/- SEM

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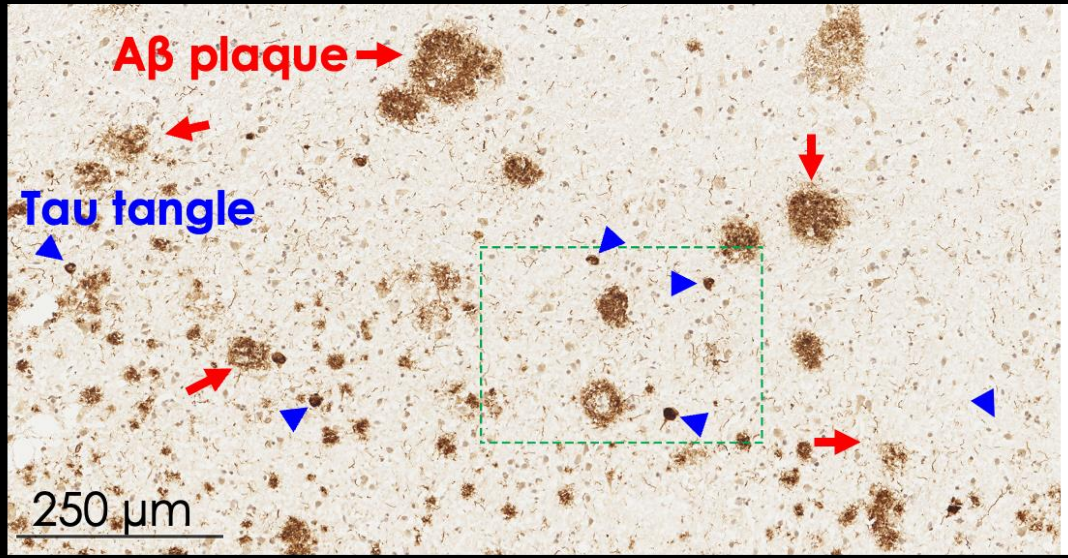
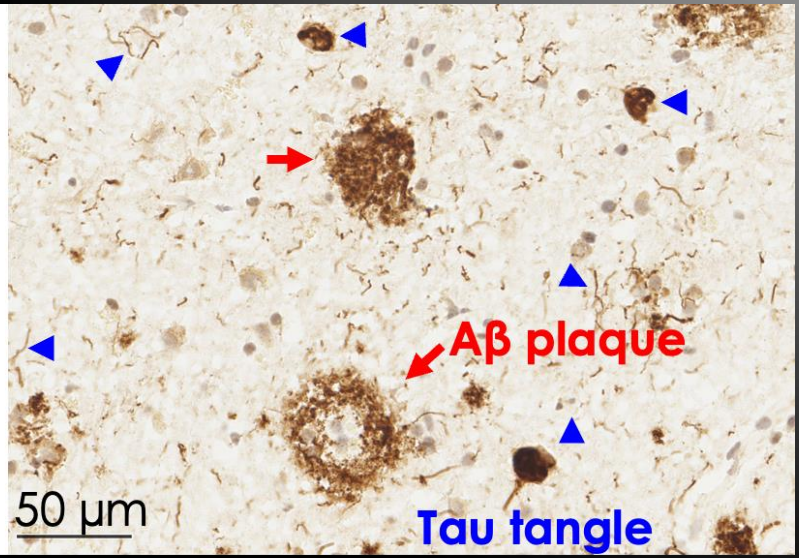
Quality

Dual Aβ/tau vaccines generate antibodies that bind Aβ and tau pathology





Immunoreactivity of immunized guinea pig serum (1:300 dilution) to brain from patient with AD

✓**Strong immunoreactivity to tau and Aβ pathology in AD brain**
✓**…at relevant dilutions for CNS exposures (0.3%)**

Red arrows = Aβ pathology (plaques)
Blue arrow heads = Tau pathology (cell bodies and neurites)

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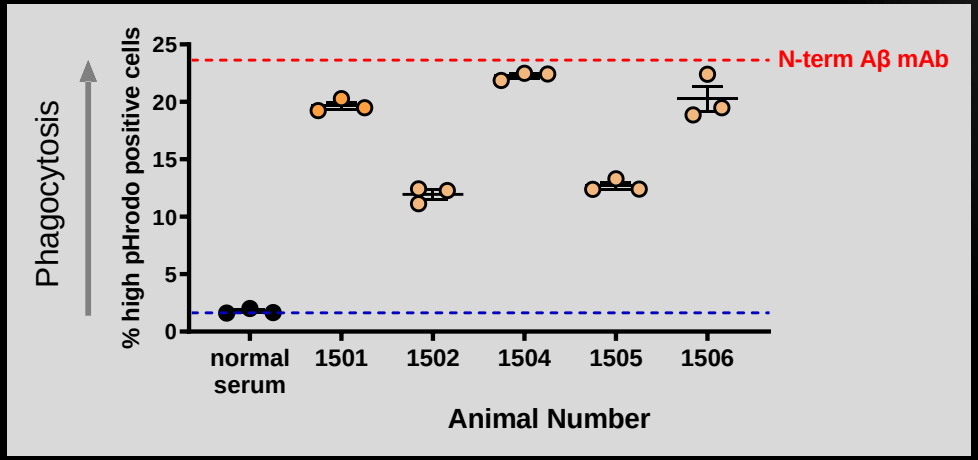
Quality

Dual Aβ/Tau vaccines generate antibodies with proper attributes for amyloid plaque clearance

Insoluble Aβ Phagocytosis



✓ **Antibodies capable of inducing phagocytosis of fibrillar Aβ**

- pHrodo™-conjugated, synthetic $A\beta_{1-42}$ fibrils with immunized guinea pigs IgG's (10μg/ml total IgG; ~1:1000 of sera concentration) in the presence of human phagocyte cell line
- Positive control: 0.1 μg/ml of picomolar affinity N-terminal Aβ antibody

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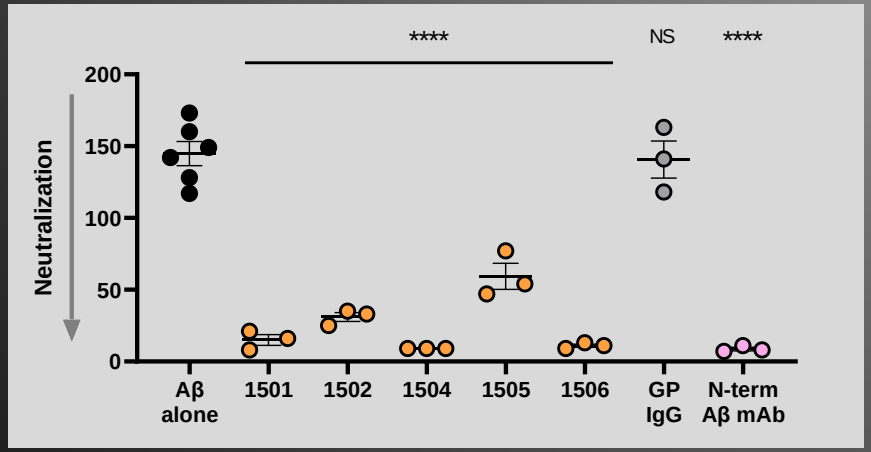
Quality

Dual Aβ/Tau vaccines generate antibodies that neutralize soluble Aβ

- ✓ **Antibodies capable of blocking soluble Aβ from binding to synapses**



N=3-6 samples/guinea pig; mean +/- SEM

- 500nM Aβ soluble aggregates incubated immunized guinea pigs IgG (500nM total IgG) and added to primary hippocampal neurons
- Positive control: 500nM of picomolar affinity N-terminal Aβ antibody

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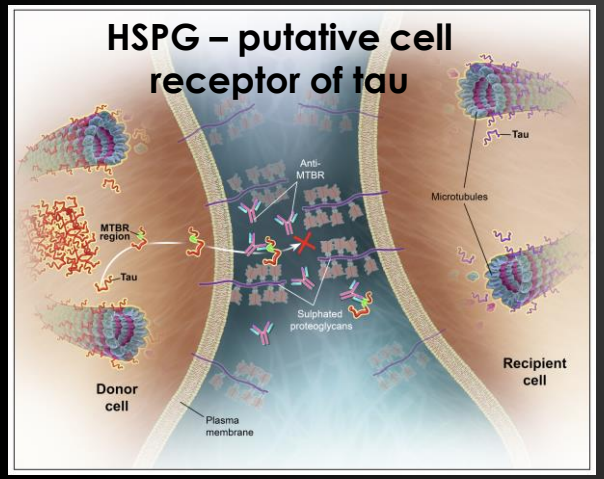
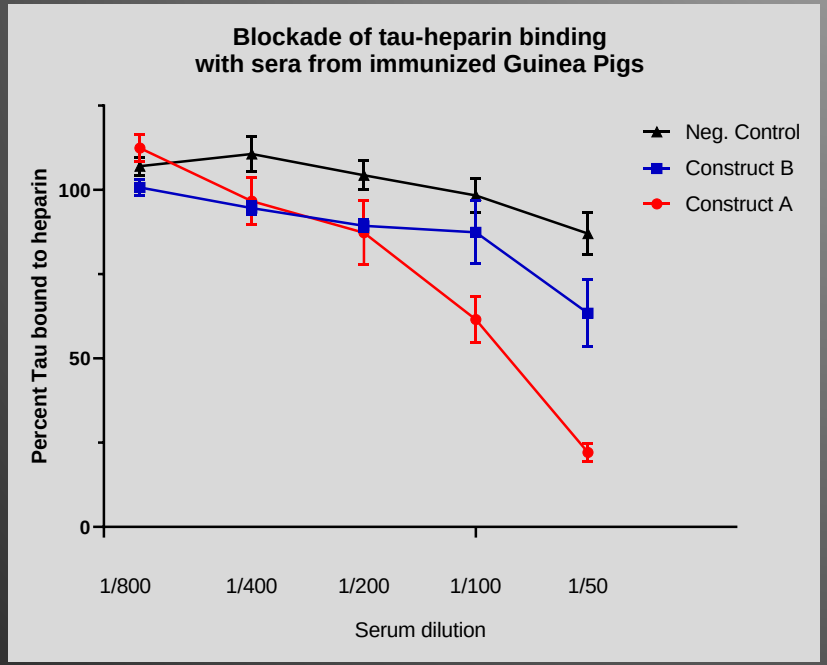
Quality

Dual Aβ/tau vaccines generate antibodies that neutralize tau





✓ **Antibodies capable of blocking soluble tau from binding to a HSPG-analog (heparin)**

Blockade of tau (100ng/ml) binding to heparin in the presence of sera from immunized guinea pigs was determined by ELISA;
N=4 guinea pigs/group; data represents mean +/- SEM

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Safety

Dual Aβ/Tau vaccines avoid cytotoxic T-cell responses in non-human primates

T-cell response following two chronic immunization schedules

	Monkey Number	T-cell Response to Aβ	T-cell Response to tau	Response to PHA (Positive Control)
Four Immunizations	1001	No	No	Yes
	1002	No	No	Yes
	1003	No	No	Yes
	1501	No	No	Yes
Three Immunizations	2001	No	No	Yes
	2003	No	No	Yes
	2501	No	No	Yes
	2102	No	No	Yes

✓ **Unable to induce measurable cytotoxic T-cell activity in monkeys**

Isolated peripheral blood mononuclear cells (PBMCs) from immunized monkeys for 6 months were analyzed for cellular immune response by ELISpot assay; N=4 cynomolgus monkeys/group

PHA = phytohemagglutinin

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Dual Aβ/Tau Vaccine
Discussion

- ✓We designed novel linear, dual Aβ/tau vaccine constructs that properly drive generation of antibodies against Aβ and tau in multiple preclinical species, including non-human primates

- ✓Dual Aβ/Tau vaccines generated titers with quantity (levels, balanced Aβ/tau response), quality (epitopes, isotypes, apparent affinity, and anti-tau and Aβ activity), and apparent safety (no cytotoxic T-cell response in primates)

- ✓These preclinical data support clinical development of this dual-immunogen vaccine for the potential treatment and/or prevention of Alzheimer's disease