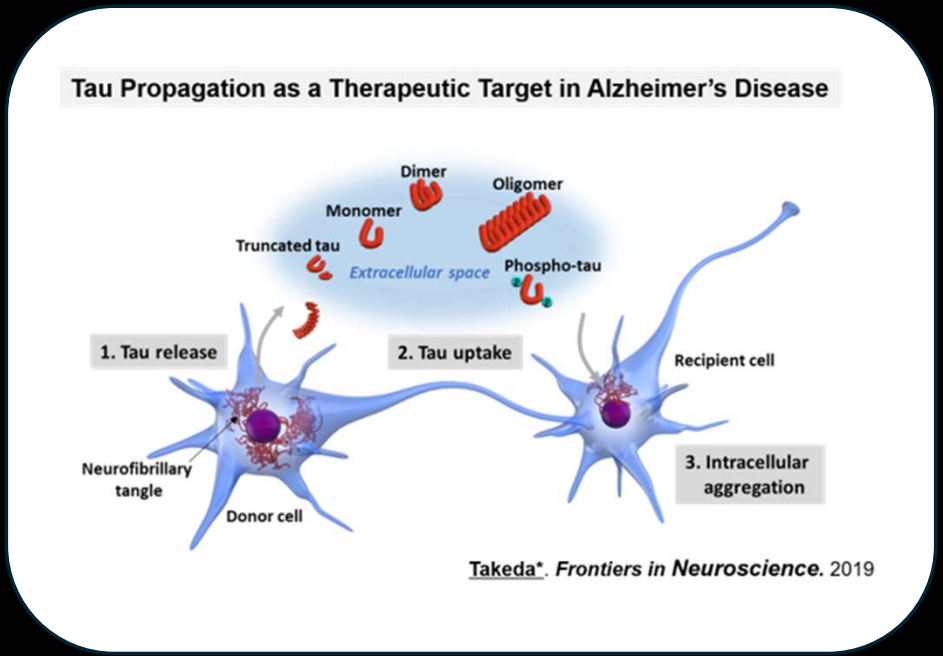
ペプチド
医薬品

アルツハイマー病の
タウ伝播リン酸化部位をターゲットする
ペプチドワクチン治療



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B-166

Development of an anti-phospho-tau vaccine as a disease-modifying therapy for Alzheimer's disease

アルツハイマー病に対する新たな疾患修飾薬としてのタウワクチン療法の開発

The University of Osaka Graduate School of Medicine

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Executive Summary

Objective:

To develop a breakthrough disease-modifying therapy for Alzheimer's disease (AD) by specifically neutralizing and clearing pathological tau, thereby arresting the progression of dementia and cognitive decline.

Target Disease & Modality:

Target Disease: Alzheimer's disease (covering patients from Mild Cognitive Impairment [MCI] to dementia).
Potential expansion to other tauopathies (e.g., Progressive Supranuclear Palsy, Corticobasal Degeneration).

Modality: Peptide-based vaccine (Antibody-Inducing Peptide) targeting highly optimized pathologically phosphorylated tau epitopes.

Mechanism of Action:

Blocks intercellular "tau propagation" by inducing specific antibodies that neutralize extracellular high-molecular-weight (HMW) seed-competent phosphorylated tau species before they are taken up by neighboring neurons.

Current Development Stage:

Confirmed POC with strong efficacy in vivo model supported by the AMED Translational Research Program (preF, FY2026–FY2027).
Under optimization of vaccine formulations and preparation for PMDA consultations.

Competitive Advantages:

Direct Pathological Correlation: Unlike amyloid-beta (Aβ), tau accumulation directly correlates with neuronal loss and cognitive decline, offering potentially higher therapeutic efficacy even after symptom onset.

Economic & Social Value:

Exceptionally lower manufacturing costs compared to monoclonal antibodies; less frequent administration (booster regimen) reduces the burden on patients and caregivers.

Proposed Partnership Scheme

Seeking pharmaceutical partners for co-development, formulation optimization, non-clinical safety/toxicology studies, and clinical trials.
Aiming to license out the program to an industry partner upon achieving early clinical POC.

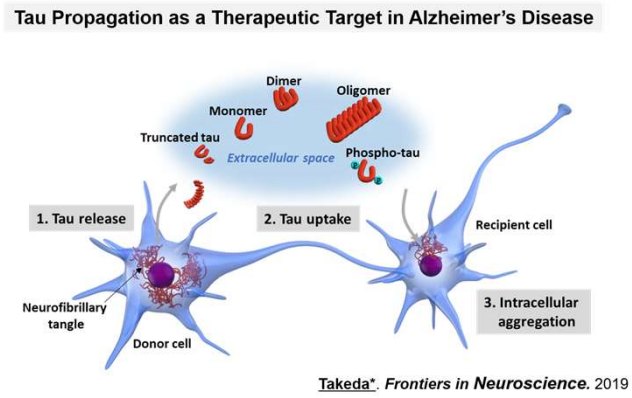
Backgrounds

Global Burden & New Target

- The global dementia population is projected to reach 153 million by 2050, making the development of disease-modifying therapies an urgent global priority.
- While tau is a highly promising therapeutic target, effective methods to specifically remove pathological tau have not yet been established.

Key Challenges & Unmet Needs

- Limited Efficacy: Current anti-Aβ antibody therapies for Alzheimer's disease offer only limited therapeutic efficacy.
- Demand for Low-Cost Care: Rapid patient increases in developing countries and the slowly progressive nature of the disease demand highly cost-effective treatment options.



Targeted Goal; Developing an affordable, highly-targeted tau vaccine to fundamentally halt Alzheimer's disease.

Objective & Target Disease

- Target: Mild Cognitive Impairment (MCI) and Alzheimer's disease (AD).
- Goal: Specifically remove extracellular "seed-competent" propagating tau species to halt dementia progression.

Clinical Positioning

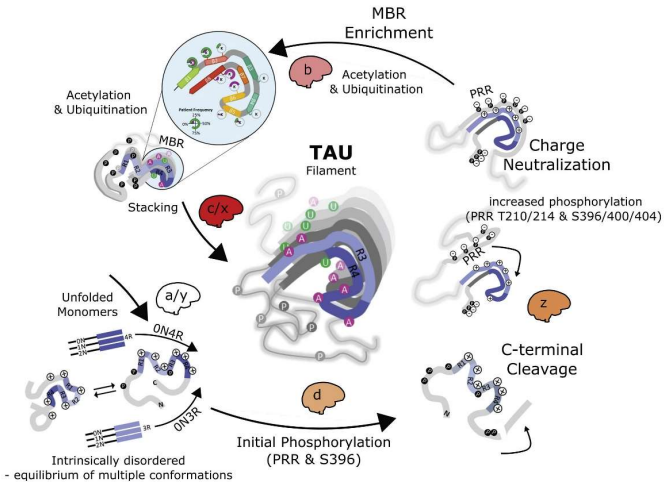
- Wider Treatment Window: Effective even after symptom onset, as tau accumulation directly correlates with cognitive decline (unlike Aβ).
- Favorable Safety: Designed as a short peptide that avoids cellular immune responses to mitigate brain inflammation.
- Low Burden: Significantly lowers manufacturing costs and reduces patient/caregiver burden via an infrequent booster dosing regimen.

Market Opportunity

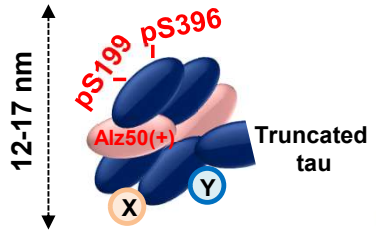
- Target Population: ~68.4 million patients globally (including MCI).
- Market Size: Global AD drug market is projected to exceed 500 billion JPY by 2030 (immunotherapies accounting for >50%).
- Exit Strategy: Establish early exploratory clinical POC, followed by high-value licensing out to global pharmaceutical partners.

Key Data

High-molecular-weight p-tau as a therapeutic target for Alzheimer's disease



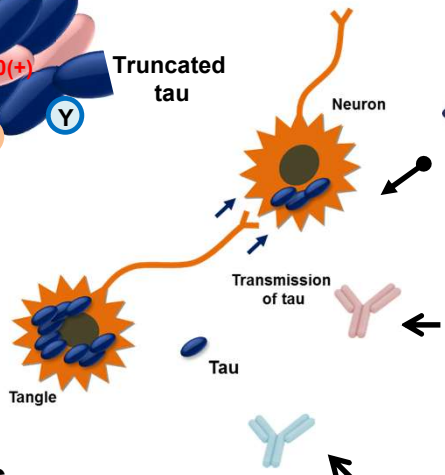
Wesseling, **Takeda**, et al. ***Cell*** 2020



Comprehensive profiling of post–translational modification

Mass-spec analysis

Takeda* et al. ***Nature Communications*** 2015
Takeda* et al. ***Annals of Neurology*** 2016
Takeda*. ***Frontiers in Neuroscience*** 2019



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Phospho-tau Vacccine

Patent No. 7687699 (Nakagami, Takeda)

← **Tau antibody therapy**(N-term)

Takeda* et al. ***Am J Pathol.*** 2017

↖ **Tau antibody therapy**(C-term)

Nicholls, **Takeda**, et al. ***PlosOne*** 2017

We have identified a distinct "propagating tau" species that drives Alzheimer's disease progression, comprehensively characterized its biochemical properties, and demonstrated its potential as a promising immunotherapeutic target.

Other Data

Other available non-confidential data

- Key Publications & Patents: Fundamental papers on tau propagation (Nature Commun. 2015, Cell 2020) and the granted patent (Patent No. 7687699).

After execution of Non-Disclosure Agreement

- In vivo Proof of Concept: Summary data of vaccine treatment in Tau-Tg mice showing up to an 80% reduction in brain tau accumulation and behavioral improvement.
- Epitope Sequence Details: The specific amino acid sequence of the selected target phosphorylated tau epitope.
- Formulation & Adjuvants: Specific adjuvant names and combination ratios with DDS (LNP) technologies.
- Advanced in vivo Data: Individual animal quantitative data comparing pre-onset vs. post-onset efficacy in Tau-Tg mice.
- Detailed MoA Data: Specific assays on synaptic tau reduction and preservation of synaptic function (Tau-biosensor cell data).
- Surrogate Marker Candidates: Specific tau phosphorylation patterns identified via brain proteomics to monitor treatment efficacy.

Reference（Patents / Key Papers）

Patent:

- Title: Immunogenic composition targeting phosphorylated tau protein.
- Patent No.: Patent No. 7687699 (issued on May 26, 2025)
- Application No.: PCT/JP2021/032847 (Filing Date: September 7, 2021)
- Applicant: The University of Osaka
- Inventors: Hironori Nakagami, Shuko Takeda, et al.

Selected Key Publications:

- **Takeda S**, et al. Neuronal uptake and propagation of a rare phosphorylated high-molecular-weight tau species derived from tau-transgenic mouse and human AD brain. Nat Commun, 6:8490, 2015.
- Yoshida S, **Nakagami H (Corresponding author),** ..., Tomioka H, et al. The CD153 vaccine is a senotherapeutic option for preventing the accumulation of senescent T cells in mice. Nat Commun, 11(1):2482, 2020.
- Wesseling H, **Takeda S (Co-author),** et al. Tau PTM Profiles Identify Patient Heterogeneity and Stages of Alzheimer's Disease. Cell, 183(6):1699-1713, 2020.
- **Takeda S**, et al. Seed-competent HMW tau species accumulates in the cerebrospinal fluid of AD mouse model and human patients. Ann Neurol, 80(3):355-367, 2016.
- Nobuhara CK, ..., **Takeda S (Last author).** Tau Antibody Targeting Pathological Species Blocks Neuronal Uptake and Interneuron Propagation of Tau in Vitro. Am J Pathol, 187(6):1399-1412, 2017.

Competitive Advantage;

Specifically neutralizing "seed-competent" propagating tau with a safe, low-cost peptide vaccine to fundamentally halt Alzheimer's disease.

Novelty & Improvements

- **Specific Epitope Targeting**: Targets precise phosphorylation sites critical for intercellular tau propagation.
- **10x Higher Neutralization**: Induced antibodies exhibit up to 10-fold higher neutralization efficiency against propagating tau than existing antibodies.

Differentiation (vs. Anti-Aβ Monoclonal Antibodies)

- Efficacy: Tau pathology directly correlates with neuronal loss, enabling clinical efficacy even after symptom onset.
- Safety: Short peptide design avoids HLA-binding and cellular immune responses, eliminating brain inflammation risks.
- Convenience: Infrequent booster injections replace frequent, long-term intravenous infusions, reducing patient/caregiver burden.
- Economy & Business Value: Significantly lower manufacturing costs compared with monoclonal antibodies, driving greater production efficiency, improved margins, and broader market access.

Research & Development Load Map

Pre-clinical & CMC Milestones:

- FY2026–2027: Establish non-clinical Proof of Concept (POC) in AD mouse models and optimize formulation.
- FY2027–2028: Finalize drug specifications and establish GMP manufacturing systems.
- FY2028–2029: Complete non-clinical safety/toxicology studies and submit IND (Investigational New Drug).

Clinical Development Stage:

- FY2030+: Initiate Phase I/IIa exploratory clinical trials led by the University of Osaka & FunPep.

Exit & Partnering Milestone:

- Timing: Immediately after establishing early clinical POC (completion of Phase IIa).
- Strategy: Out-license the program to a global pharmaceutical partner for pivotal Phase IIb/III trials and commercialization.

Our Team

An established, cross-functional R&D alliance integrating clinical medicine, basic science, and industrial peptide expertise.

Project Leader / Principal Investigator (PI)

Associate Professor Shuko Takeda, M.D., Ph.D.
Department of Clinical Gene Therapy, Osaka University Graduate School of Medicine
Role: Overall project management, in vivo efficacy evaluation, and surrogate biomarker development.

Co-Investigator

Professor Hironori Nakagami, M.D., Ph.D.
Department of Health Development and Medicine, Osaka University Graduate School of Medicine
Role: Vaccine formulation development, adjuvant/DDS optimization, and pre-clinical study design.

Industrial Partner

Hideki Tomioka, Ph.D. (CSO & Director of R&D)
FunPep Co., Ltd. (Osaka University-launched biotech venture)
Role: GMP-compliant manufacturing process development, formulation optimization, and CMC strategy.

Proposed Partnership Scheme;

Expected Roles for the University of Osaka & FunPep

- IND Preparation: Optimize vaccine formulation (adjuvants/DDS) and complete non-clinical safety/toxicology studies.
- Early-stage Clinical Trials: Drive Phase I/IIa exploratory clinical trials to establish early Proof of Concept (POC).
- Biomarker Discovery: Identify translatable surrogate biomarkers (CSF phosphorylated tau patterns) to monitor treatment efficacy.

Roles Requested for Corporate Partners

- Late-stage Clinical Trials: Design, fund, and execute global Phase IIb/III pivotal clinical trials.
- Regulatory & Commercialization: Manage global regulatory filings, industrial GMP scale-up, and commercial marketing/distribution.

Collaborative Research Initiatives

- Patient Stratification: Co-develop patient screening tools (using CSF biomarkers or tau-PET) to identify high-responder populations.
- Indication Expansion: Co-evaluate therapeutic efficacy for other orphan tauopathies (e.g., Progressive Supranuclear Palsy [PSP], Corticobasal Degeneration [CBD]).