Leveraging Ubiquitin-Proteasome System Genetic Vulnerabilities to Target Pathological Tau Conformers in Alzheimer's Disease

Minzhi Huang *

College of Professional Studies, Northeastern University, Boston, United States of America

* Corresponding Author Email: huang.minzh@northeastern.edu

Abstract. Alzheimer's disease (AD) affects over 55 million people worldwide and is marked by progressive cognitive decline, behavioral changes, and substantial socioeconomic burden. Beyond amyloid-β plaques, increasing evidence implicates tau pathology, particularly hyperphosphorylated and misfolded conformers, as a more robust predictor of disease severity. However, the limited success of tau-directed immunotherapies is partly due to impaired intracellular clearance mechanisms, especially the ubiquitin-proteasome system (UPS). Genome-wide association studies have identified key genetic vulnerabilities in UPS-related genes like the PARK2, UBQLN1, and CUL1, which impair tau ubiquitination and proteasomal degradation. This exploratory review seeks to illustrate a newly emerging therapeutic strategy that enhances tau immunotherapy by leveraging residual UPS activity in genetically at-risk individuals. Monoclonal antibodies and active vaccines targeting conformationally pathogenic tau species, such as cis-pT231 and tau oligomers, can be engineered to function as molecular chaperones to direct misfolded tau toward the UPS for degradation. Integrating cryogenic electron microscopy (cryo-EM)-guided antibody design, induced pluripotent stem cell (iPSC)-derived neuronal models, and FcRn-mediated brain delivery, this strategy offers a genetically informed, mechanistically effectiveness, and translationally feasible path toward precision treatment of AD.

Keywords: Alzheimer's disease (AD), ubiquitin-proteasome system (UPS), *PARK2*, *UBQLN1*, *CUL1*.

1. Introduction

AD is the most common type of dementia causing over 55 million people worldwide to be diagnosed and its prevalence are expected to grow with aging population [1]. AD is characterized by progressive memory loss, cognitive decline, and changes in behavior. There is a profound emotional and economic burden on individuals, families, and healthcare systems. Neuropathologically, AD is marked by two major proteinopathies: extracellular amyloid-beta (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein. While Aβ pathology has long dominated therapeutic research, that increasing clinical and molecular evidence suggests that tau pathology correlates more strongly with the severity and progression of cognitive impairment. Tau aggregation spreads between brain regions following a stereotypical pattern, and its accumulation closely aligns with neuronal loss and cognitive impairments in AD, making tau as a critical therapeutic target.

The key to the clearance of aggregated proteins like pathological tau is the UPS, which is an intracellular machinery that is responsible for maintaining protein homeostasis. The UPS operates through cascade enzymes like ubiquitin-activating enzymes (E1), conjugating enzymes (E2), and ligases (E3) that tag damaged proteins with ubiquitin chains. These enzymes would be targeting them for degradation by the 26S proteasome. However, with the grow in age, the system would become increasingly impaired, which is a major risk factor for AD. Also, genetic mutations in UPS components could further impair the UPS function and promote the accumulation of neurotoxic proteins including tau. This age- or mutation-related decline in UPS activity exacerbates the pathological burden in neurodegenerative diseases.

Recently, genome-wide association studies (GWAS) found several UPS-related genes, such as *PARK2*, *UBQLN1*, and *CUL1*, to be risk loci associated with AD. Functional analyses show that

mutations in these genes disrupt key processes in tau clearance. Specifically, *PARK2* loss of function reduces the ubiquitination of misfolded tau, that allowing toxic aggregates to accumulate. *UBQLN1* mutations would interfere with the chaperone-mediated trafficking of ubiquitinated tau to the proteasome, while *CUL1* variants would directly impair E3 ligase scaffolding. In general, these studies have shown that there is a clear genetic and mechanistic link between impaired UPS function and tau pathology, but it is always possible for providing innovative therapeutic approaches.

One possible strategy to be explored is the development of UPS-enhancing immunotherapies which can selectively target pathological tau conformers. Monoclonal antibodies (mAbs) and active vaccines are all being designed to recognize disease-associated epitopes, such as cis-pT231 or oligomeric tau, and not only to neutralize toxicity but also to direct tau towards proteasomal degradation. In this context, these antibodies may mimic molecular chaperones, that compensating for genetic impairments in the UPS by facilitating tau tagging and transport. Such approaches could synergize with residual UPS activity in genetically predisposed neurons, so that it would enhance intracellular clearance and reducing neurotoxicity. The goal of this review is to systematically review recent advances in UPS-enhancing tau immunotherapy, with a particular focus on how genetic vulnerabilities in the UPS influence therapeutic efficacy. By integrating the research findings from different disciplines like molecular biology, genetics, and immunology, it is proposed to have a framework for precision-targeted interventions that leverages on UPS function to eliminate pathological tau in AD and offers effective directions for better and personalized treatment.

2. Molecular Characteristics and Pathological Conformations of Tau

The nexus for targeting pathological tau conformers via UPS-enhancing immunotherapy is strongly supported by converging lines of empirical and theoretical evidence. Firstly, tau has emerged as a leading therapeutic target. Longitudinal clinicopathological studies show that tau burden as measured by tau-PET correlates better in terms of space and time with cognitive decline than Aβ [2]. Genetically, APOEε4 is the prime AD risk allele. However, GWAS increasingly implicate loci involved in tau biology and proteostasis (e.g., MAPT, BIN1) as major risk modifiers [3].

Secondly, clinical proof-of-concept for tau-directed immunotherapy has been demonstrated, validating the general approach. Passive immunotherapies like semorinemab (anti-tau mAb) significantly reduced plasma NfL and CSF p-tau181 in Phase 2 trials, albeit with varied results in cognitive measures, whereas active vaccines such as ACI-35 (against pS396/pS404 tau) elicited a robust antibody response alongside a good safety profile [4, 5]. These studies hence confirm that tau antibodies enter the CNS and bind the epitope of interest.

3. Mechanisms and Dysfunction of UPS

UPS is important for protein quality control and cellular homeostasis. It has made up with a tightly regulated enzymatic cascade that involving E1 ubiquitin-activating enzymes, E2 conjugating enzymes, and E3 ligases, which coordinate the attachment of polyubiquitin chains to misfolded or damaged proteins. Once tagged, these proteins are recognized and degraded by the 26S proteasome. Molecular chaperones, such as Hsp70 and CHIP (C-terminus of Hsc70-interacting protein), help in recognizing substrate and delivering, especially for proteins with abnormal conformations like misfolded tau.

With the aging brain and under the cellular stress, the efficiency of the UPS would decline. This results in impaired clearance of aggregation-prone proteins, including tau, so that it further leads to their toxic accumulation. Experimental studies show that tau is a direct UPS substrate, and that inhibition or dysfunction of UPS components would result in increased tau aggregation and neurotoxicity. This shows that the UPS not only as a clearance mechanism but also as a critical node of therapeutic intervention in AD. The genetic and functional susceptibility of the UPS in AD offers the mechanistic basis for therapeutic upregulation. Landmark GWAS analyses consistently associate

AD risk with variants in UPS genes (PARK2, UBQLN1, CUL1), with functional studies confirming their role in tau clearance [6, 7].

4. UPS Genetic Susceptibility and Impact on Tau Clearance

PARK2 (Parkin) haploinsufficiency in human neurons hinders the ubiquitination of misfolded tau, causing its accumulation [6]. *UBQLN1* mutations cause a failure of chaperone-mediated delivery of ubiquitinated tau to the proteasome. These results align with the ubiquitin-proteasome neurodegeneration theory which postulates that the decline of UPS activity due to aging or mutations causes the accumulation of toxic proteins [8].

GWAS indicate that genetic variants in UPS-related genes increase the chances of developing AD. For instance, *PARK2* (Parkin), *UBQLN1*, and *CUL1* have been repeatedly implicated in studies that looking at mechanisms of tau clearance. Parkin is an E3 ubiquitin ligase that tags misfolded tau for degradation. Mutations or haploinsufficiency of *PARK2* impair this function, which results in tau accumulation. *UBQLN1* is a factor that's responsible for trafficking ubiquitinated proteins, and its dysfunction would lead to the failure of tau trafficking to the proteasome. *CUL1* is part of the SCF E3 ligase complex scaffold and which it facilitates the recognition of substrate and ubiquitination.

The implications of these mutations are backed by data from both in vitro and in vivo studies. Neurons from iPSC mutation carriers have shown reduced proteasome-mediated tau degradation, which indicates an accumulation of tau protein in the form of aberrant aggregates. In addition, transgenic mice studies where the UPS components are missing show worsened tau pathology. Therefore, these studies demonstrate a mechanistic pathway linking UPS genetic risk factors and tau deposition, thus providing a basis to develop targeted therapies toward genetically defined AD cohorts.

5. UPS-Enhanced Tau Immunotherapy Strategies

Tau-targeted immunotherapies have recently become an attractive option to alter disease progression. Passive immunotherapies like mAbs are being developed to bind to pathological tau epitopes, including phosphorylated and conformational epitopes, such as cis-pT231. Many of these antibodies are now moving into clinical trials, and some antibodies such as semorinemab and gosuranemab have shown reductions in tau biomarkers, although any cognitive benefit has been minimal.

Active immunotherapies such as vaccines aim to activate endogenous antibody responses against pathological tau. ACI-35, which targets phosphorylated tau epitopes pS396/pS404 showed a good safety and immunogenicity signal in earlier phase trials. These findings demonstrate the feasibility of tau-targeted immunotherapy, while also underscoring persistent challenges of delivery, target engagement, and downstream clearing.

To enhance efficacy, UPS-enhancing immunotherapy has been proposed. In this scenario, the antibody would neutralize toxic tau and provide recognition of tau to the UPS by acting as a molecular chaperone. This is based on the premise that some UPS function could remain, which might accommodate patients with a partial loss-offunction mutation. Fc domain engineering, and FcRn-mediated transcytosis are the vehicles to effectively transport an antibody across the BBB, which could also be the key bottleneck to drug development in the CNS. The development of immunotherapy in parallel with small molecules, like PROTACs or molecular glues, which could facilitate proximity between tau and E3 ligases might synergize clearance pathways, although significant limitations regarding brain penetration still exist.

6. Technological Platforms and Future Prospects

Advancing UPS-enhancing immunotherapy against pathological tau conformers requires access to, and continual refinement of, specialized technical platforms. Cryo-EM resolves disease-specific

tau folds, thereby supporting the design of rational antibodies, exemplified by the generation of mAbs targeting tau oligomers [9, 10]. Functional UPS assay, such as measurements of ubiquitination, proteasome activity and tau turnover can be performed in iPSC-derived neurons from *PARK2* or *UBQLN1* variant carriers [11]. Transgenic mice that express human tau with UPS gene knockouts (e.g., Park2^−/−; 3xTg-AD) provide a platform to evaluate therapeutic synergy and mechanism [12].

The UPS-enhancing immunotherapy against pathological tau conformers discussed below is strongly justified on the established foundations of AD pathophysiology. AD is primarily a neurodegenerative disorder that progresses by the overwhelming aggregation of misfolded proteins, primarily amyloid-beta (Aβ) plaques and neurofibrillary tangles of hyperphosphorylated tau. What's important is that, in fact, the spatiotemporal propagation of tau pathology correlates better with cognitive decline than that of Aβ, collectively solidifying tau as the more primary therapeutic target. Maintaining proteostasis, the quality state of proteins, is an overarching cellular goal, for which the UPS targets damaged and misfolded proteins for degradation. Supporting genetic evidence, such as the GWAS implicating *PARK2, UBQLN1, CUL1*, and functional evidence make a sound argument that impairment of the UPS is a central mechanism of AD pathogenesis, especially in relation to clearing tau from its toxic accumulation. Therefore, harnessing residual UPS function is an approach entirely justified by its mechanistic rationale. Thus, the proposal here is to rely on this understanding of AD as a tau-centric pathology with a vulnerable UPS, that integrates enhanced immunotherapy interventions that leverage the role of engineered antibodies as a molecular chaperone to move pathological tau conformers to the impaired UPS for enhanced degradation.

As Aβ-targeting therapies continue to show limited success in late-stage trials, a much-needed emphasis on other pathological hallmark features and targeted measures of intervention for AD must be emphasized. In particular, the primary consideration has been given to the pathological tau aggregation as it is more strongly correlated with cognitive decline. At the same time, there have been have several active and passive immunotherapies has been proposed against tau, albeit with all limited success in humans, partly because of the inability to get proper targeting of the most neurotoxic conformers and activate endogenous clearance pathways. This proposal seeks to facilitate tau immunotherapy and attempt to take advantage of specific genetic vulnerabilities associated with brain intrinsic protein quality control machinery, in particular the UPS.

GWAS show polymorphisms in significant components of the UPS, such as *PARK2, UBQLN1, CUL1,* that hold great risk for individual susceptibility to AD. This strongly suggests that its ubiquitin-mediated protein arrest may be part of the pathology. Nevertheless, these genetic changes have typically created haploinsufficiencies or some impairment for E3 ubiquitin ligases and chaperones to recognize, ubiquitinate, and target misfolded proteins like tau for degradation. The hypothesis is that monoclonal antibodies (mAbs) or active vaccine epitopes, designed rationally to bind unique disease-associated conformational epitopes on pathological tau species (e.g., cis-pT231 tau, oligomeric tau), will neutralize the toxicity conferred by the expression of these epitopes and may even act as molecular chaperones directing pathological tau away from the compromised, although partially functional UPS in genetically at-risk neurons. Tagging pathologic tau by antibody Fc domains or vaccine-induced opsonins could mitigate low E3 ligases or related clearance mechanisms (e.g., autophagy) and therefore override the genetic deficits in clearance of misfolded proteins toward proteasomal degradation. This approach identifies deep genetic substrates for conformational immunotherapy beyond simply bulk clearance of antigen toward targeting mechanism to endogenously use proteostasis pathways with increased therapeutic relevance in stratified AD populations defined by genetic risk profiles within the UPS. In this sense, UPS could enable the personalization of tau immunotherapies, and the validated targets and clinically viable modalities potentially derived from a mechanistic understanding of proteostasis rescue best situate these strategies for clinical translation.

7. Conclusion

This review has reflected on the mechanistic interplay of pathological tau conformers and the UPS in the context of AD, which identifying how the convergence of both pathologies provides an opportunity for targeted immunotherapeutic interventions. The tau pathology, particularly in hyperphosphorylated, misfolded, and conformationally toxic species, such as cis-pT231 and tau oligomers, plays a significant role in driving neurodegeneration. The UPS is capable of maintaining proteostasis through selective degradation of proteins, becomes impaired due to age-related decline and genetic disruptions. The functional collapse allows the pathological tau species to accumulate, spread, and exert their toxicity. Dual pathology represents an interesting therapeutic window, as it can target pathological tau conformers while either improving or complementing UPS function. Genetic studies have also provided valuable insight into this link. Variants in UPS-related genes like *PARK2*, *UBQLN1*, and *CUL1*, that have emerged from genome-wide association studies as significant AD risk factors. These mutations affect ubiquitin ligase activity, substrate trafficking, and proteasomal degradation capacity, each of them contributes to the impaired clearance of pathological tau. The identification of the mutations offers not only mechanistic insights, but also practical value for therapeutic stratification. Patients with these variants represent a genetically defined subpopulation who may particularly benefit from UPS-enhancing immunotherapies, which clearly shows the way for precision medicine approaches in AD.

Monoclonal antibodies and active vaccines offer a promising modality for targeting tau pathology. When engineered with conformation-specificity, these immunotherapies should bind selectively to neurotoxic tau conformers, either neutralizing their seeding capacity, and promoting tau clearance. The advantages of these antibodies are they could be molecular chaperones, directing tau toward the UPS even when its function is partially compromised. Active vaccines, like ACI-35, that induce a sustained endogenous immune response and have demonstrated favorable safety profiles in early clinical trials. Collectively, these strategies hold promise for mitigating tau accumulation while leveraging innate protein degradation systems. Nonetheless, several challenges still exist. Efficient delivery across the BBB is still a bottleneck, although strategies like FcRn-mediated transcytosis offer solutions. Immunogenicity still needs optimization to prevent adverse immune responses while maintaining therapeutic efficacy. Another, clinical trial design must account for genetic heterogeneity, stage of disease progression, and biomarker-guided patient selection. Looking ahead, the integration of genetic profiling, tau-specific immunotherapy, and UPS modulation, suggests the possibility of personalized AD treatment. Combination strategies perhaps incorporating antibody therapy with proteolysis-targeting chimeras (PROTACs) or autophagy inducers, or gene editing approaches could yield synergistic therapeutic effects. Ultimately, therapeutic strategies that are informed by the patient’s molecular and genetic profiles will be better positioned to halt or even reserve the pathological cascade of tau in AD.

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