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Therapeutic development for Alzheimer's disease at Eli Lilly and Company

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Alzheimer's disease (AD) is the most common form of dementia, which is estimated to affect more than 46 million people worldwide[1]. This number is expected to double every 20 years, reaching 131.5 million by the middle of the century. As a result, in the absence of effective disease-modifying therapies, AD is projected to have an increasing impact on patients, carers and on society, with massive costs incurred by health systems throughout the world.

In its earliest clinical stages, AD is typically associated with a progressive loss of memory and other cognitive domains. Subsequently, this leads to functional deficits in activities of daily living, neuropsychiatric symptoms in some patients and ultimately death[2]. Strong genetic and biochemical evidence highlights a central role for the amyloid pathway in the pathogenesis of AD[3]. The central theme of the 'amyloid hypothesis' is that protein mis-folding of the amyloid-β (Aβ) peptide leads to the extracellular accumulation of toxic Aβ aggregates, including β-amyloid plaques, which are the causative factor for the initiation of the neurodegenerative cascade that includes inflammation, gliosis, neuronal damage and synaptic loss. Furthermore, the injury caused by extracellular Aβ aggregates is thought to trigger the spread of neurofibrillary tangle (NFT) pathology in the form of misfolded, aggregated tau proteins beyond the medial temporal lobe[4] — a key step in the onset of clinical symptoms. The combined insults lead to synapse loss, neuronal cell death and tissue atrophy. Importantly, although significant progress has been made over the past two decades, many mechanistic unknowns remain, including what is the exact neurotoxic moiety of Aβ (soluble oligomer or fibril), what is the nature of the interaction between extracellular β-amyloid/Aβ and intracellular tau, what is the role of inflammation in the neurodegenerative cascade and what ultimately drives neuronal death[3]?

In vitro experiments and current *in vivo* models are not adequate to fully address this multitude of complex questions and inform on the likelihood of therapeutic success; the ultimate test of a hypothesis, therefore, comes from large-scale clinical trials. However, therapeutic development, from initial hypothesis to non-clinical compound development and phase 1, 2 and 3 clinical trials, can take up to 15 years and cost in excess of a billion dollars[5]. This expensive and lengthy development process limits the number of potential therapies that can be tested and partly explains why, despite considerable investment in the academic and pharmaceutical sectors, there is currently no disease-modifying therapy that can slow or halt disease progression. The symptomatic treatments that are available, cholinesterase inhibitors and memantine (an NMDA receptor antagonist), provide only modest cognitive benefits and these are rapidly overwhelmed as the disease progresses[2].

Given the increasing prevalence of AD, addressing this unmet medical need is of primary importance. Lilly is committed to improving treatment options for AD and has been working towards this goal for 28 years. Here, we outline our extensive pipeline of potential therapeutics and molecular diagnostics that reflect this longstanding investment.

Lilly's Alzheimer's disease therapeutic portfolio

Lilly's AD programme is focused on developing disease-modifying therapies that slow or halt clinical progression by targeting the underlying causes of the disease. We have prioritized targets and pathways that are validated by human genetics. This has led to our current emphasis on Aβ/β-amyloid and tau. In addition, although our main focus is on disease modification, we continue to look for improved treatments for both the

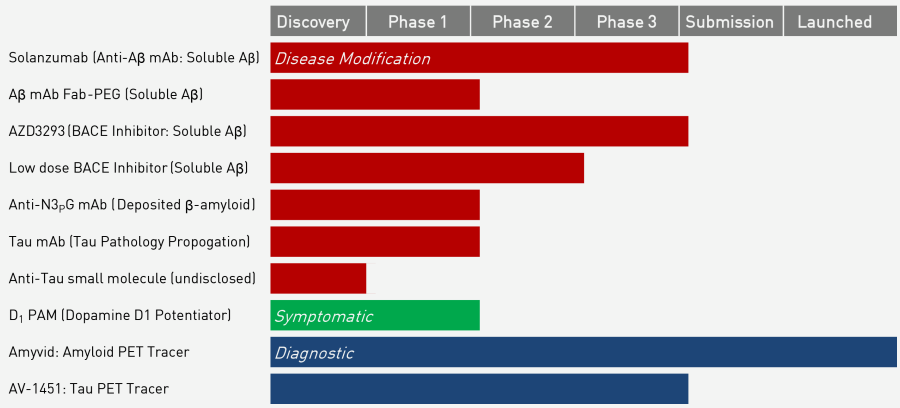

Figure 1 | Lilly's Alzheimer's disease portfolio. Therapeutics and diagnostics in clinical and late preclinical development are shown. The names of individual assets are listed with molecular targets shown in parentheses. The development stage of each asset is indicated in the bar chart. Aβ, amyloid-β peptide; BACE, β-secretase; mAb, monoclonal antibody; $N3_pG$ Aβ; amyloid-β peptide with pyroglutamate modification at position 3; D_1 PAM, D_1 dopamine receptor positive allosteric modulator.

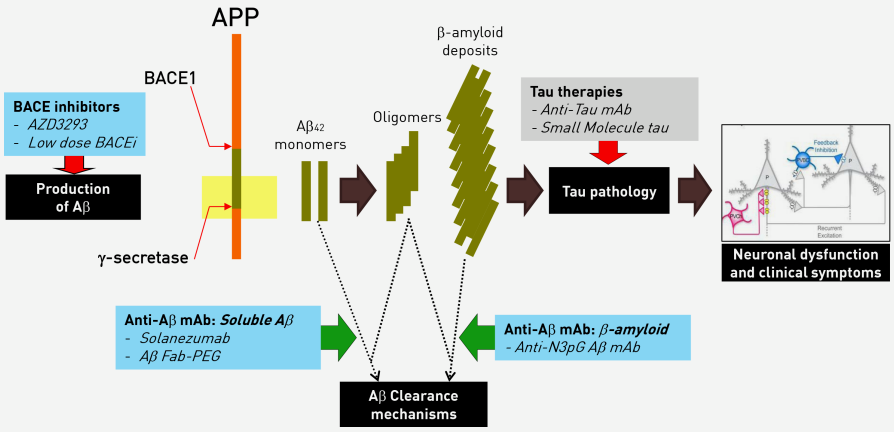

Figure 2 | Targeting multiple stages in the amyloid cascade for disease modification. Schematic representation of the amyloid cascade with Lilly's current disease-modification programmes shown at the pathogenic stages they impact. Targeting multiple stages in the disease cascade as shown also enables the development of rational combinations that are expected to have enhanced efficacy compared with individual monotherapies. APP, amyloid precursor protein; Aβ, amyloid-β peptide; BACE, β-secretase; mAb, monoclonal antibody; AZ BACEi, AZD3293 BACE inhibitor; $N3_pG$ Aβ; amyloid-β peptide with a pyroglutamate modification at position 3.

cognitive and psychiatric symptoms of AD. We recognize that even after disease-modifying treatments become available there will be a continued, or even increased, need for effective symptomatic therapies.

At present Lilly's AD therapeutic portfolio includes seven assets that are in clinical development (Fig. 1). These include six potential disease-modifying therapies and a novel approach to improving cognitive function. The current portfolio also includes two molecular diagnostics: Amyvid (florbetapir), a β-amyloid PET tracer and flortaucipir, a tau PET tracer in phase 3 trials (Figs 1 and 3).

The disease-modifying programmes are intended to target different points in the hypothesized pathogenic cascade with a major focus on Aβ production, Aβ/β-amyloid clearance and tau pathology (Fig. 2). The rationale behind targeting the disease at multiple stages is that, first, as with other chronic diseases, we anticipate that multiple therapies will be required to achieve optimal disease modification across the full range of people with AD, reflecting the different disease stages and other variables in this population. Moreover, despite recent increases in our knowledge, there is considerable uncertainty about which species of amyloid and tau are most important for synaptic- and neurodegeneration, and by extension which are most important to target for effective treatment. Second, by targeting different points in the pathogenic process we have the opportunity to develop rational combinations that have the potential for enhanced efficacy compared with individual monotherapies.

Aβ/β-amyloid therapeutics

Most of Lilly's disease-modifying programmes in clinical development target Aβ/β-amyloid (Fig. 2). This emphasis on Aβ/β-amyloid reflects the robust genetic and pathological evidence that supports an early and causative role for Aβ (especially the longer form $Aβ_{42}$) in the development of AD[3]. In addition, recent evidence from clinical trials of experimental Aβ/β-amyloid therapies has provided further support for this approach[3]. The current portfolio of programmes target Aβ production and Aβ/β-amyloid clearance with a mixture of small molecules and monoclonal antibodies.

To target Aβ production, Lilly has two BACE1 inhibitors in clinical development. These molecules inhibit β-secretase, which is one of two enzymes responsible for the generation of Aβ from the amyloid precursor protein (APP) (Fig. 2). The more advanced of these molecules (AZD3293) is being developed in partnership with Astra Zeneca and is now in phase 3 trials, having successfully passed an interim phase 2 safety assessment in early 2016. This molecule has previously been shown to reduce Aβ levels in cerebrospinal fluid (CSF) by more than 70% at a dose of 50mg per day in healthy volunteers. The current phase 3 trial of AZD3293 (AMARANTH, NCT02245737) is being conducted in patients who have prodromal and mild amyloid-PET positive AD. A second phase 3 trial (DAYBREAK-ALZ, NCT02783573) is being conducted in patients with mild-AD only. The second BACE1 inhibitor (LY3202626) is a highly potent molecule that entered phase 2 trials in 2016 (NAVIGATE-AD, NCT02791191). LY3202626 has been shown to reduce CSF Aβ levels by more than 90% at a dose of 26mg per day (for 14 days) in healthy volunteers. This BACE inhibitor freely penetrates the brain, which, combined with its high potency, means that low doses will produce substantial reductions in CNS Aβ levels. This reduces

the risk of peripheral off-target effects, including those mediated by BACE2 inhibition. Other BACE inhibitors currently in clinical development are not selective for BACE1 over BACE2. LY3202626 can also be used to explore higher levels of central Aβ reduction (>90%) than has been previously possible.

To enhance Aβ/β-amyloid clearance, Lilly is developing two types of monoclonal antibody (mAb) therapy (Fig. 2). The first type of antibody binds selectively to monomeric Aβ and does not bind to aggregated β-amyloid deposits. The most advanced example of this type of antibody is solanezumab, which is in phase 3 clinical testing[6]. Solanezumab binds to monomeric Aβ with high affinity, primarily in the periphery and as a consequence is thought to reduce the pool of free monomer in the central nervous system (CNS). In turn, this leads to a shift in CNS Aβ equilibria to favour the dissolution of β-amyloid deposits as well as smaller oligomeric assemblies, which may represent the most toxic Aβ species. In two previous phase 3 trials (EXPEDITION 1 and 2) in mild-moderate AD, solanezumab missed its primary endpoints. However, in a pre-specified secondary analysis, solanezumab treatment was associated with a 34% slowing in the rate of cognitive decline (measured using ADAS-Cog$_{14}$) in patients with mild AD from the two trials[6]. As a result, a further phase 3 trial was initiated (EXPEDITION 3, NCT01900665) that included only patients with mild AD with β-amyloid pathology, as evidenced by amyloid PET scans or CSF analyses. Initial findings from EXPEDITION 3 are expected to be announced at the end of 2016. A second immunotherapy in the portfolio, which targets monomeric Aβ is Aβ antibody Fab-PEG, which like solanezumab is expected to shift Aβ equilibria in favour of dissolution of Aβ aggregates in the CNS. However, this asset, in contrast to solanezumab, is the antigen-binding fragment (Fab) of a mAb that targets soluble monomeric Aβ linked to a polyethylene glycol molecule. Aβ antibody Fab–PEG is optimized for subcutaneous dosing, and more rapid clearance of antibody–Aβ complexes than solanezumab. It also has an extremely high affinity for monomeric Aβ (around 50-fold greater than solanezumab), which may enhance the pharmacodynamic impact on Aβ clearance. Aβ antibody Fab–PEG is currently in phase 1 trials.

The second class of anti-amyloid mAb in the Lilly portfolio binds exclusively to β-amyloid deposits and is thought to remove pre-existing β-amyloid through microglial-mediated phagocytosis. The most advanced antibody of this type, currently in phase 1 trials, is a humanized immunoglobulin (IgG) 1 (LY3002813) directed at an Aβ epitope that is present only in β-amyloid plaques (Aβ modified with a pyro-glutamate residue, N3$_p$G). The murine surrogate of this anti-N3$_p$G Aβ antibody has previously been shown to robustly clear pre-existing β-amyloid deposits in a transgenic model (PDAPP line)[7]. Importantly, β-amyloid clearance occurred in the absence of microhaemorrhage, suggesting that this antibody may be able to remove β-amyloid in patients without causing vasogenic oedema — a common safety concern observed in human studies with previous therapeutic antibodies with a similar mechanism[7,8]. Recent phase 1 clinical data with the anti-N3$_p$G Aβ antibody have indicated that 3 to 5 doses of LY3002813 10mg kg^{-1} intravenously can reduce amyloid deposits (amyloid PET) in patients with AD by a mean of 40–50% over 7 months, without evidence of vasogenic oedema[9]. Although antibody treatment was complicated by immunogenicity, these initial observations suggest that preclinical findings with the anti-N3$_p$G Aβ antibody will translate to patients with AD. In addition, when the N3$_p$G murine surrogate antibody was used in combination with a BACE inhibitor, a synergistic and near complete removal of pre-existing β-amyloid was observed in our preclinical models, indicating the therapeutic potential of this combination.

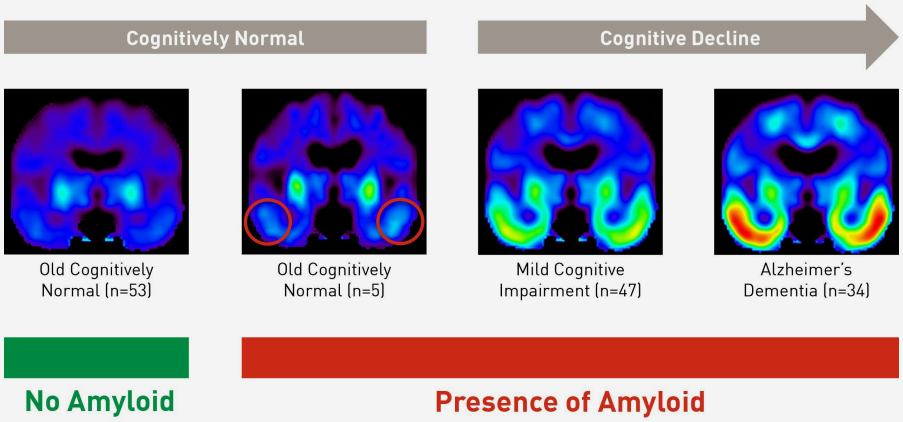

Figure 3 | Imaging tau pathology in patients with ^{18}F-flortaucipir. Summary of the images collected from baseline scans in a phase 2 study of ^{18}F-flortaucipir (adapted from ref 10). Each brain PET scan was normalized by the activity in the cerebellum, averaged across the patients in each diagnostic group and displayed as a coronal slice. Cognitively normal subjects without amyloid positivity (^{18}F-florbetapir) show minimal retention of tracer in the cortex, but there is evidence of early tau signals on the amyloid-positive cognitively normal subjects in the inferior temporal lobes. In both these groups, the overall tau signal across the cortex is low. By contrast, in subjects with cognitive impairment and amyloid positivity, there is increased signal in the temporal lobes, and in the presence of dementia tau signals in multiple lobes of the brain. These data suggest that ^{18}F-flortaucipir PET is able to provide important information on the spread of neurofibrillary tangles (NFT) with Alzheimer's disease progression.

Tau pathology therapeutics

The accumulation and trans-neuronal spreading of aggregated tau is the second area of focus for Lilly's disease-modifying therapeutic portfolio. Neurofibrillary tau pathology has been shown to correlate closely with clinical progression both through classical neuropathological studies and in patients using Lilly's tau PET tracer flortaucipir[10]. Moreover, genetic evidence from related human tauopathies has demonstrated that tau dysfunction is sufficient to cause neurodegeneration, further supporting the hypothesis that the development and spread of tau pathology is crucial for disease progression in AD[11]. It seems increasingly likely that Aβ/β-amyloid accumulation predisposes the spread of tau pathology beyond the medial temporal lobe into connected neocortical regions (Fig. 3)[4,10]. The precise mechanism of tau-pathology spread remains unclear, but attention has increasingly focused on the trans-neuronal transmission of aggregated tau seeds that are capable of templating their structure onto endogenous tau within connected neurons[12].

This 'prion-like' transmission of tau pathology is the basis of Lilly's leading tau therapeutic (Figs 1 and 2) — a humanized mAb (tau mAb) designed to bind and neutralize extracellular tau seeds, preventing their transmission to other synaptically connected neurons. The murine surrogate of the therapeutic tau mAb has previously been shown to efficiently inhibit tau pathogenesis in multiple transgenic models of human tauopathy. This tau mAb is currently in phase 1 trials and is Lilly's first tau therapeutic to enter clinical development. A second small-molecule tau therapy, designed to block the intra-neuronal formation of tau aggregates, is currently in late preclinical development (Figs 1 and 2).

Improved therapies for symptom relief

The major focus of Lilly's AD programme is the development of disease-modifying therapies, however, we are also committed to the delivery of improved treatments for the relief of both the cognitive and neuropsychiatric symptoms of AD. This recognizes that improved symptomatic treatments will still be needed even after disease-modifying therapies become available. The most advanced symptomatic treatment within the Lilly portfolio is a D_1 receptor positive allosteric modulator (D_1 PAM), which is mainly a treatment for cognitive decline in Alzheimer's and Parkinson's disease (Fig. 1). Dopamine's action on D_1 receptors in the prefrontal cortex has long been shown to be crucial for memory and central executive function in both primates and humans[13]. D_1 PAMs, therefore, offer the potential to alleviate cognitive dysfunction by restoring dynamic dopaminergic modulation in prefrontal cortex impaired by neurodegenerative disease. Lilly's leading D_1 PAM is currently in a phase 1 trial.

Clinical development strategy for disease-modifying therapies

Current models of AD pathogenesis and its relationship to clinical symptoms are based on neuropathology, basic science, clinical research and biomarkers[14]. An asymptomatic preclinical stage (clinical dementia rating (CDR) of 0) is defined by amyloid accumulation throughout the cortex, beginning years before clinical symptoms. Amyloid deposition predisposes people to NFT pathology and neurodegenerative changes in vulnerable brain regions. The initial symptoms of mild cognitive impairment (prodromal AD; CDR 0.5) develop when a threshold level of neurodegeneration occurs in the hippocampus and entorhinal cortex. Further deterioration to dementia (CDR 1–3) is associated with NFT pathology spread, progressive synaptic loss and neuronal loss on a background of peak amyloid deposition. Based on this formulation, AD pathophysiology occurs in the hippocampus, entorhinal cortex and neocortex at different times and rates, accounting for the clinical features of the disease.

Accordingly, the greatest impact of disease-modifying therapeutics is likely to be earlier in the disease, prior to irreversible neuronal loss. However, the disease process is slow and variable, especially in preclinical and prodromal stages, so that clinical trials require large sample sizes and a long duration to identify treatment effects (in the current absence of a surrogate biomarker). The Lilly clinical development programmes for solanezumab and two BACE inhibitors (AZD3292 and LY3202626) highlight several approaches to address these challenges: initiating treatment earlier in the disease, enriching for AD pathology based on confirmation of amyloid status, and incorporation of biomarkers of neurodegeneration as potential surrogate markers of progression and treatment effect.

The original solanezumab EXPEDITION 1 and 2 phase 3 clinical trials involved people with mild-moderate AD without confirmation of amyloid status. Treatment benefit in cognition and function was observed in patients with mild AD pooled from the two studies, but a significant proportion of patients in the study were found to be amyloid negative[15]. To replicate and expand on the EXPEDITION 1 and 2 results, subsequent solanezumab studies are focusing on earlier stages of disease, including mild AD (EXPEDITION 3, NCT01900665); prodromal AD (ExpeditionPRO, NCT02760602); preclinical AD (A4, NCT02008357); and presymptomatic AD in autosomal dominant AD mutation carriers (DIAN, NCT01760005). These studies, as well as the clinical trials of BACE inhibitors AZD3293 (AMARANTH (NCT02245737), DAYBREAK–ALZ (NCT02783573) and LY3202626 (NAVIGATE–AD (NCT02791191)) require confirmation of amyloid status by CSF $A\beta_{42}$ or amyloid PET imaging. The solanezumab, AZD3293 and LY3202626 clinical trials also have sub-studies assessing effects of treatment on imaging markers of neurodegeneration such as tau PET and volumetric MRI. By incorporating a range of biomarkers across multiple clinical trials in preclinical and early AD, we aim to identify potential surrogate markers of progression and treatment effects.

Molecular diagnostics: an established amyloid PET tracer and the advent of tau imaging

In addition, to delivering therapeutics, Lilly is committed to the development of innovative molecular diagnostics, exemplified by amyloid and tau PET tracers that are being used to identify patients with AD pathology, track progression and demonstrate treatment response. Lilly's amyloid PET tracer, ^{18}F-florbetapir, has been extensively investigated, including the first study to compare PET images to histopathology at autopsy. This led to ^{18}F-florbetapir being the first imaging agent to gain regulatory approval to estimate β-amyloid neuritic plaque density[16]. In addition to the potential clinical utility, multiple applications of ^{18}F-florbetapir as a biomarker for the presence and progression of amyloid plaques in AD research have been explored. One recent focus, has been on the use of amyloid imaging to provide early detection of AD pathology, prior to symptoms. This is being tested by using ^{18}F-florbetapir PET to screen for preclinical AD in the first major therapeutic trial for an at-risk, but asymptomatic population[17].

In contrast to amyloid plaque tracers, the discovery of tracers for the visualization of neurofibrillary tau pathology has been very recent. Lilly's most advanced tau tracer, ^{18}F-flortaucipir (previously AV1451 and T807) was described in 2013 (ref. 18) as having a high affinity for filamentous tau lesions and selectivity compared with other β-pleated pathological deposits. The first in-human study of healthy control subjects and subjects diagnosed with AD demonstrated good brain uptake and, in those with AD, subsequent cortical retention of tracer in areas consistent with the pathological distribution of neurofibrillary tau[19]. As neurofibrillary tau pathology tracks with neurodegeneration and the clinical progression of the disease[4], ^{18}F-flortaucipir is being developed as a potential biomarker of neurodegeneration. To this end, Lilly has made ^{18}F-flortaucipir widely available for academic research, and there are currently more than 40 studies underway using this imaging tool. Recent human data have demonstrated that PET imaging with ^{18}F-flortaucipir can reproduce the Braak staging of neurofibrillary tangles in patients and have provided insights into the role of β-amyloid in driving the spread of tau

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pathology[10] (Fig. 3). It is therefore hoped that tau imaging can shed new light on AD pathobiology and, potentially, accelerate the development of new therapeutics.

Concluding remarks

AD and other forms of dementia represent one of the most significant health-care crises affecting modern society. The projected increase in the number of patients over the next 50 years, if not addressed, will have an enormous impact on the lives of patients, carers and worldwide healthcare systems[1]. As a result the development of disease-modifying therapies that can slow the progression, or delay the onset, of dementia is becoming increasingly important. It is estimated that a treatment that delays the onset of dementia by just 5 years would reduce the number of patients in the United States alone by 5.5 million by 2050 (ref. 20). Lilly is working to meet this challenge by delivering a comprehensive portfolio of disease-modifying therapeutics and diagnostics that are designed to increase our ability to successfully identify, treat and prevent AD.

It is important, however, to recognize that the development of effective disease-modifying treatments will be just the start of the process to address the developing AD crisis. Currently, health-care systems are designed for the symptomatic treatment paradigm and change is necessary to reach the patients that will benefit most from disease-modifying therapies. In particular, health-care systems will need to adapt their approach to detection and diagnosis. At present, most patients either never receive a diagnosis or are diagnosed at a relatively late stage of the disease (US data[20]). But to have greatest benefit, disease-modifying treatments need to be given early in the course — ideally before symptoms occur — when there is the greatest opportunity to preserve brain function. Solving this problem will involve patient and doctor education, in particular removing the stigma associated with the disease, which delays many people seeking help. It will also require increased access to molecular diagnostics that can identify the patients who will respond to these therapies early in their disease.

At Lilly, we recognize that one company alone cannot be successful. Therefore, in addition to the development of new medicines, Lilly is committed to working with health-care systems around the world and, where appropriate, to have a role in ensuring that the right patients, get the right drug, at the right time.

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