OGA inhibition as a novel therapeutic approach for tauopathies

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PSP Neuroscience Hub

O-GlcNAcylation is a post-translational modification (PTM) of proteins that recently has emerged as a potential regulator of diverse cellular functions

Post-translational modifications (PTMs) on tau have long been recognized as affecting protein function and contributing to neurodegeneration. These modifications are usually catalyzed by enzymes and involve the addition of chemical groups, sugars, or proteins to specific residues of the targeted protein.[1]

O-GlcNAcylation refers to the glycosylation of serine and threonine residues with O-GlcNAc monosaccharide (G) and it is exclusively regulated by 2 enzymes: OGA and OGT[2]. *(Figure 1)*

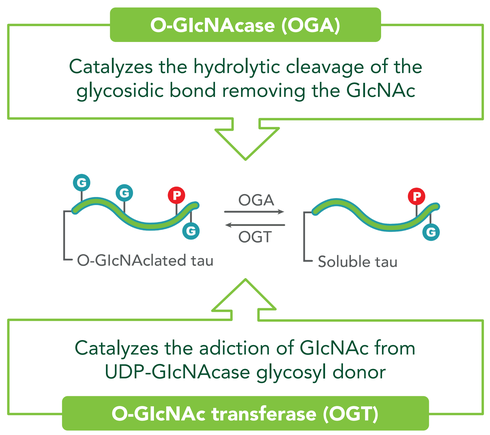


Figure 1. The balance of OGA and OGT in tau protein O-GlcNAcylation

O-GlcNAcylation may act as a protective layer against phosphorylation of different proteins like tau[3]

Under normal conditions, there is an equilibrium between O-GlcNAcylation and phosphorylation which maintains physiological nature of tau. *(Figure 2)*

O-GlcNAcylation and phosphorylation can happen in the same residues, suggesting a complex antagonistic crosstalk between these PTMs.

Additionally, O-GlcNAcylation of tau proteins at Serine 400 has been shown to directly inhibit aggregation[4].

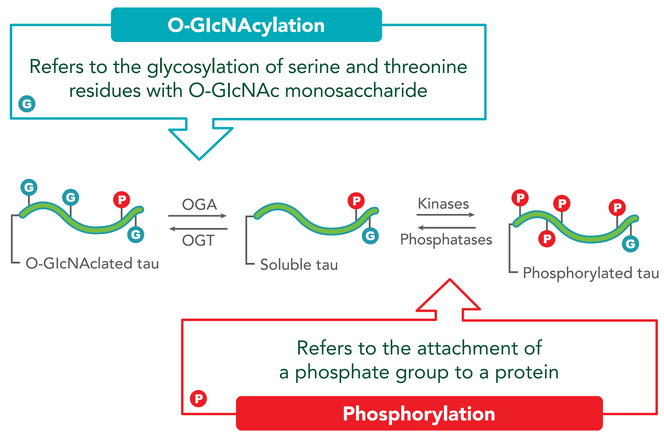
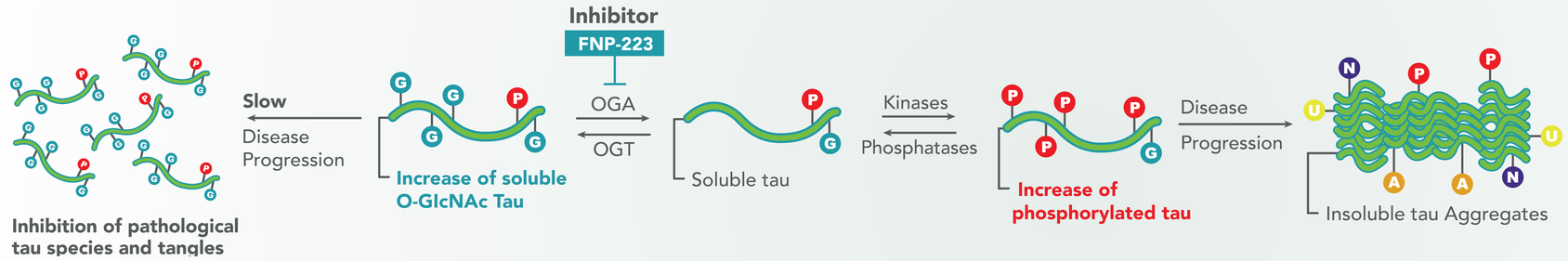


Figure 2. Functional interplay of O-GlcNAcylation and phosphorylation in

A new promising therapeutic approach for tauopathies such as Progressive Supranuclear Palsy (PSP) is OGA inhibition

OGA-OGT imbalance leds to tauopathy progression



An imbalance towards tau hyperphosphorylation disrupts tau functions. In pathological conditions, when **hyperphosphorylation** is promoted, **tau tends to detach from microtubules and self-aggregate into neurofibrillary tangles**[4]. These aggregates are a common **feature of tauopathies like PSP**.

OGA inhibition as disease-modifying treatment

Pharmacological blockade of OGA would result in a shift in tau towards the soluble non-toxic form, inhibiting both oligomer formation and pathological tangle formation. Decreasing pathogenic tau and tau aggregates in the brainstem also decreases neuronal cell loss.[5]

Figure 3. FNP-223 Mechanism of Action (MoA)

FNP-223 is a new chemical compound that functions as a reversible and substrate-competitive inhibitor of the OGA. Inhibiting OGA prevents the access of the substrate to the catalytic pocket, impeding the removal of O-GlcNAc modifications (G) from tau protein.

Inhibiting OGA is expected to cause a rapid increase of glycosylated tau protein. O-GlcNAc (G) when attached to tau prevents the deleterious aggregation of tau without disturbing the conformational properties and normal physiological function of tau monomers.[6] *(Figure 3)*

Video MoA avaliable in the PSP Hub!

FNP-223 a novel OGA inhibitor positioned as a potential disease-modifying treatment for PSP

OGA inhibition has already proved therapeutic potential in different preclinical models providing a strong rationale for the development of OGA inhibitors as disease-modifying agents in tauopathies[6]. **FNP-223, a new oral selective OGA inhibitor, has demonstrated safety and efficacy in reducing tau aggregates in preclinical models**[7]. Acute and chronic treatment with FNP-223 in animal models has demonstrated to increase glycosylated tau protein while decreasing tau aggregates, as well as improving survival and motor function. **It has also demonstrated favorable safety, PK and brain penetration in clinical phase I studies and was well tolerated with no dose-limiting toxicities or serious adverse events**[8].

Conclusions

Targeting the O-GlcNAcylation pathway through **selective OGA inhibition**, such as **with FNP-223, offers a compelling disease-modifying strategy for PSP**, supported by strong preclinical evidence and early clinical safety and efficacy data.

Based on these results and following its commitment to developing transformative products for diseases with unmet needs, Ferrer is developing a RDBPC **Phase 2 study to assess the clinical efficacy, safety and PK of FNP-223 to slow the progression of PSP**: The PROSPER Study[9].

Study PROSPER
PROGRESSIVE SUPRANUCLEAR PALSY

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