

# Functional Analysis of O-GlcNAc Modifications Using Synthetic Protein Chemistry

<https://www.neurodegenerationresearch.eu/survey/functional-analysis-of-o-glcnac-modifications-using-synthetic-protein-chemistry/>

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### Country

USA

## Title of project or programme

Functional Analysis of O-GlcNAc Modifications Using Synthetic Protein Chemistry

## Source of funding information

NIH (NINDS)

## Total sum awarded (Euro)

€ 1,494,839.45

## Start date of award

01/08/2015

## Total duration of award in years

4

## The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

## Keywords

synthetic protein, Protein Chemistry, alpha synuclein, Son, parkin gene

## Research Abstract

? DESCRIPTION (provided by applicant): "Functional Analysis of O-GlcNAc Modifications using Synthetic Protein Chemistry" O-GlcNAc modification (O-GlcNAcylation) is a dynamic protein-modification that is absolutely required for embryonic development in mammals, and is misregulated in diseases, including diabetes, neurodegeneration and cancer. Although approximately 1000 potential proteins are modified by O-GlcNAc, the effects of the vast majority of these modifications on protein function are completely unknown. This critical lack of knowledge exists in-part because traditional methods are deficient for the study of site-specific O-GlcNAcylation events. The long-term goal of our research program is to understand the consequences of O-GlcNAcylation on proteins that are key to human disease. The objectives of this application are to develop protein engineering strategies that uniquely enable the generation of proteins with site-specific O-GlcNAc modifications and to apply these methods to understand the effects of O-GlcNAcylation on the protein  $\alpha$ -synuclein, the aggregation-prone protein in Parkinson's disease. Our preliminary studies demonstrate that homogeneously O-GlcNAcylated proteins can be prepared using synthetic chemistry. Furthermore, we have used synthetic protein chemistry to demonstrate that O-GlcNAcylation blocks  $\alpha$ -synuclein aggregation. Guided by these preliminary studies, we will: 1) continue to develop general synthetic-strategies for the preparation of O-GlcNAcylated proteins, 2) investigate the molecular mechanism by which O-GlcNAcylation blocks  $\alpha$ -synuclein aggregation and 3) determine the effects of O-GlcNAcylation on the cellular toxicity of  $\alpha$ -synuclein. These studies are significant, as the effects of O-GlcNAcylation are almost completely unknown. Additionally, blocking  $\alpha$ -synuclein aggregation is a key potential therapeutic strategy in Parkinson's disease. Our approach is also innovative as it enables the effects of O-GlcNAcylation to be directly tested in a site-specific fashion and can be applied to other critical proteins in the future.

### Lay Summary

**PUBLIC HEALTH RELEVANCE:** "Functional Analysis of O-GlcNAc Modifications using Synthetic Protein Chemistry" This proposal is aimed at developing and applying strategies to understand the site-specific effects of O-GlcNAc modification on protein function. These studies will enable the study of the consequences of O-GlcNAc modification on proteins that are critical in human diseases including neurodegeneration, cancer and diabetes. This is a key prerequisite to targeting O-GlcNAc as a therapeutic strategy.

### Further information available at:

#### Types:

Investments > €500k

#### Member States:

United States of America

#### Diseases:

Parkinson's disease & PD-related disorders

#### Years:

2016

#### Database Categories:

N/A

**Database Tags:**

N/A