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

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NIH (NINDS)

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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 a-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 a-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 a-synuclein aggregation and 3) determine the effects of O-GlcNAcylation on the cellular toxicity of a-synuclein. These studies are significant, as the effects of O-GlcNAcylation are almost completely unknown. Additionally, blocking a-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:

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Investments > €500k

Member States:
United States of America

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Parkinson's disease & PD-related disorders

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N/A

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