

# Molecular mechanisms of huntingtin misfolding

<https://neurodegenerationresearch.eu/survey/molecular-mechanisms-of-huntingtin-misfolding/>

## Principal Investigators

LANGEN, RALF

## Institution

UNIVERSITY OF SOUTHERN CALIFORNIA

## Contact information of lead PI

### Country

USA

## Title of project or programme

Molecular mechanisms of huntingtin misfolding

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NIH (NINDS)

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4

## The project/programme is most relevant to:

Huntington's disease

## Keywords

Huntington gene, polyglutamine, solid state nuclear magnetic resonance, Huntington Disease, Spin Labels

## Research Abstract

? DESCRIPTION (provided by applicant): Huntington's disease (HD), the most common of all polyglutamine (polyQ) diseases, is characterized by the misfolding and aggregation of huntingtin

(htt). Of particular importance to the etiology of HD is the N- terminal htt exon 1 (HDx1) region, which becomes progressively more prone to aggregation and misfolding as the length of its polyQ tract increases. Elevated numbers of glutamines (typically >40) cause the formation of various cytotoxic amyloid structures including fibrils, protofibrils and smaller oligomeric structures (Fig. 1). Cell and animal studies suggest that inhibition of misfolding is a promising avenue for preventing HD. However, the lack of structural information on these species has prevented a clear understanding of the mechanisms of HDx1 misfolding and hampered efforts to modulate this misfolding process as an avenue for therapeutic treatment. This proposal exploits two recent biochemical and methodological advances made by the Langen group. First, it became possible to generate clean preparations of various misfolded forms of HDx1 containing 46Q. These include two different fibril types, one that is toxic and one that is only weakly toxic, as well as a protofibrillar form of highly toxic HDx1. Second, together with Professors Siemer and Chiu, the Langen group has begun to apply a powerful and synergistic combination of structural methods that include site-directed spin labeling (SDSL) together with EPR, solid state NMR (ssNMR) and cryo-EM for studying HDx1 misfolding. The preliminary results have revealed exciting potential for this novel approach. The first aim seeks to compare and contrast the structures of toxic and weakly toxic HDx1 fibrils using SDSL, ssNMR and cryo-EM. This comparison will provide insights into the structural features that distinguish toxic from non-toxic forms of HDx1. Such information is likely to facilitate future efforts aimed at preventing the formation of toxic species. In Specific Aim 2, we will investigate the structures of highly toxic, A11 positive protofibrils, which form early during the misfolding process. Such early misfolding intermediates have been suggested to be the primary toxic pathogens in many amyloid diseases, but their structures remain poorly understood. Specific Aim 3 follows up on preliminary data that show that negatively charged membranes, especially those mimicking mitochondrial membranes, potentially accelerate misfolding and promote the formation of toxic, A11 positive structures. This aim will study how membranes accelerate HDx1 misfolding and how this interaction, in turn, may disrupt membrane integrity. The proposed studies might explain how interaction of Hdx1 with cellular membranes can promote toxicity and why mitochondrial function is so disrupted in HD patients. Phosphorylation at positions 13 and 16 has been shown to protect from toxicity. In order to understand how this modification might be protective, we will test how it affects the formation of fibrils, toxic protofibrils and membrane-mediated misfolding.

### **Lay Summary**

**PUBLIC HEALTH RELEVANCE:** Huntington's disease is a debilitating neurodegenerative disease caused by an unusually long stretch of glutamine residues (typically more than 40) in the huntingtin protein. Such polyglutamine expansions, which are also present in a number of other disease-forming proteins, make proteins alter their structures into toxic forms. In order to understand how to prevent the misfolding of polyglutamine-containing proteins, we will determine how huntingtin changes its structure into toxic forms and how some cellular membranes can speed up this process.

**Further information available at:**

### **Types:**

Investments > €500k

### **Member States:**

United States of America

**Diseases:**

Huntington's disease

**Years:**

2016

**Database Categories:**

N/A

**Database Tags:**

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