Investigation of Heat shock Factor 1 as a Therapeutic Target for Huntington’s Disease

https://www.neurodegenerationresearch.eu/survey/title-of-piinvestigation-of-heat-shock-factor-1-as-a-therapeutic-target-for-huntingtons-disease/

Title of project or programme

Title of PI Investigation of Heat shock Factor 1 as a Therapeutic Target for Huntington’s Disease

Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
Professor	Gillian	Bates	King’s College London	UK

Address of institution of lead PI

Institution	Kings College London
Street Address	Guys Hospital, Great Maze Pond
City	London
Postcode	SE1 9RT

Country

- United Kingdom

Source of funding information

Medical Research Council

Total sum awarded (Euro)

1796764.8

Start date of award

01-03-2009

Total duration of award in months

48

The project/programme is most relevant to

- Huntington’s disease
- Neurodegenerative disease in general

Keywords

Research abstract in English

Within the aging populations of the developed world the health, social and economic burden of neurodegenerative disease is already substantial and expected to increase. The occurrence of the most common neurodegenerative disorders: Alzheimer’s disease (AD), Parkinson’s disease (PD) and

amyotrophic lateral sclerosis (ALS) is largely sporadic, however, rare familial cases of these diseases, together with inherited monogenic disorders such as Huntington’s disease (HD) have provided clues to their aetiology. In AD, PD, ALS and HD, mutations result in the propensity of disease-associated proteins to misfold, form a-sheet structures and become ‘aggregation-prone’ properties for which they have been named ‘protein-folding’ diseases. In all cases, disease-modifying therapies do not exist.

All cells maintain protein-folding homeostasis through integrated protein-folding and clearance networks and pathways. Molecular chaperones direct the folding of newly synthesised and damaged proteins and those that cannot be successfully folded into their native conformation are degraded through the ubiquitin proteasome system (UPS) or cleared by lysosome-mediated autophagy. In the presence of an aggregation-prone protein, the mechanisms that maintain protein folding homeostasis become overwhelmed resulting in misfolding and aggregation. The capacity to maintain protein folding homeostasis diminishes with age, resulting in an increasing susceptibility to protein folding disease in the elderly.

Strategies that might decrease the propensity of an aggregation-prone protein to misfold include increasing either the protein folding or protein degradation capacity of the cell. One possible approach is to induce the cellular stress response. Conditions of cellular stress including elevated temperature and oxidative damage activate the heat shock response which results in the immediate induction of heat shock proteins that encode molecular chaperones and other proteins important for the recovery from stress induced protein damage. Heat shock factor 1 (HSF1) is the master regulator of the heat shock response and can be activated pharmacologically by inhibition of Hsp90. We shall use complimentary approaches: exposure to elevated temperature, administration of a brain penetrant Hsp90 inhibitor and the generation of mice expressing an inducible form of activated HSF1 to define the neuronal heat shock response in vivo and to determine whether activation of HSF1 can alleviate disease-related phenotypes in a mouse model of HD. Thereby, we shall validate whether HSF1 activation is a rational therapeutic target for HD, and by extension, other protein-folding neurodegenerative disorders.

Lay summary
In which category does this research fall?

- Basic research