Development of inhibitors of protein phosphatases involved in neurodegenerative diseases and investigation of their effects in animal models

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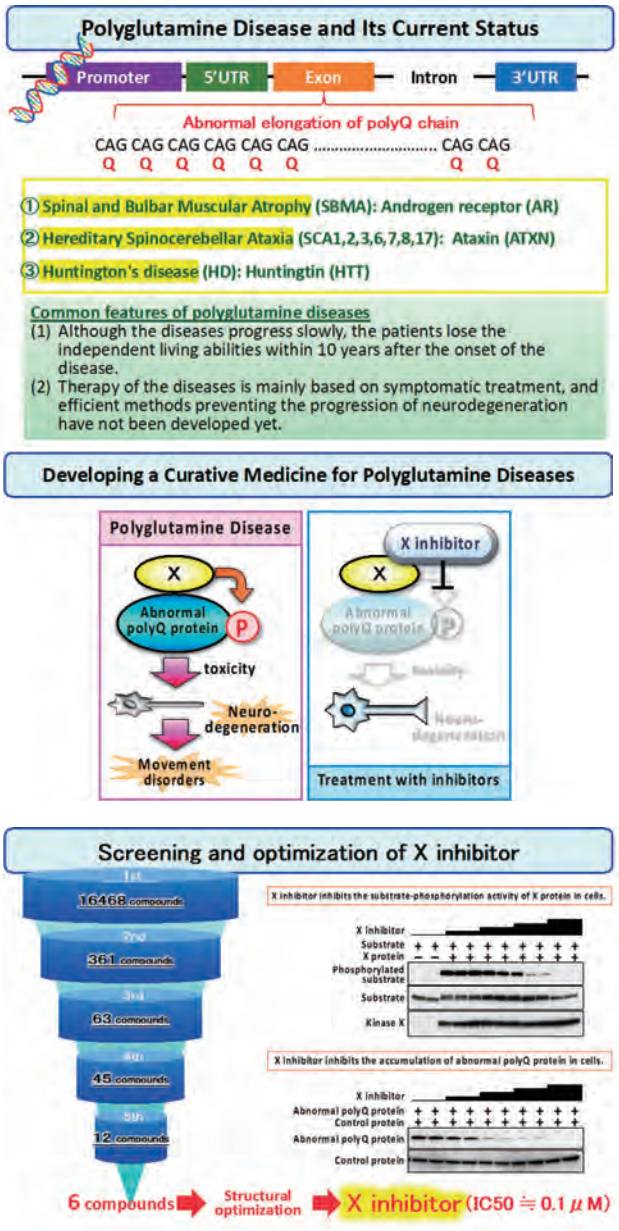
Project Outline

Polyglutamine disease is an inherited neurodegenerative disorder including SBMA (Spinal and Bulbar Muscular Atrophy), Sca (Spinocerebellar ataxia), and Huntington's disease. In polyglutamine diseases, the number of repeats of the CAG sequence encoding glutamine is abnormally increased in the genes responsible for each disease, resulting in the expression of proteins with abnormally long polyglutamine sequences, which accumulate in neurons along aging and lead to degeneration. All types of polyglutamine disease cause severe disability, and independent living becomes impossible within 10 years after onset. However, current treatment of polyglutamine disease generally consists of symptomatic therapies such as improvement of motor and neurological symptoms with antipsychotic drugs, improvement of ataxic symptoms with drugs that activate the nervous system, exercise therapy, lifestyle guidance, and treatment of complications. On the other hand, the development of effective therapies targeting neurodegeneration itself has not progressed and remains as an urgent issue. In recent years, the mechanism by which abnormal polyglutamine proteins lead to neurodegeneration has been partially clarified, and the development of therapeutic methods based on these findings is gradually progressing both in Japan and overseas. Evaluation of some of these methods have already been initiated, but sufficient therapeutic effects have not been confirmed at this time.

In this project, we will focus on protein kinase X, which phosphorylates abnormal polyglutamine proteins and promotes its cytotoxicity, and create a drug that prevents neurodegeneration through inhibition of its activity. Because kinase X "directly" regulates abnormal polyglutamine proteins, our approach is expected to broaden the range of therapeutic strategies.

Through our extensive screening and structural modification, we have succeeded in creating a potent and selective X inhibitor. The X inhibitor inhibited the substrate-phosphorylation activity of X protein and inhibited the accumulation of abnormal polyglutamine proteins in the cell. This indicates that the X inhibitor has the potential to be a fundamental therapeutic agent for polyglutamine disease.

We are currently testing the therapeutic efficacy of the X inhibitor in mouse models of polyglutamine diseases and further modifying its structure to improve its properties as a drug. We hope that this project will lead to the development of definitive therapies for polyglutamine disease.



Target disease: Polyglutamine disease
Patent information: Under planning
Characteristics of the Technology: Development of a curative medicine for polyglutamine diseases
Marketability and challenges in development: Polyglutamine disease is a genetic disorder, for which only symptomatic treatment currently exists. Therefore, it is expected to develop a curative medicine that prevents the onset of the disease or suppresses the progression of symptoms.