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A CELLULAR MODEL FOR THE SCREENING OF MOLECULES AFFECTING TDP-43 AGGREGATION

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Summary: the present invention refers to the field of biotechnology for drug development in the area of neurodegenerative disorders. In particular, it refers to a novel, cell-based model for the study of pathological protein aggregation occurring during neurodegeneration and its use for the screening of therapeutically active molecules. More in particular, it refers to a cellular model for the screening of drugs for the treatment of neurodegenerative diseases due to TDP-43 protein aggregation, including Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Lobar Degeneration (FTLD).

Background of the invention: many neurodegenerative diseases are characterized by abnormal protein aggregates that accumulate in the nerve cells and are found in the patients' brains. The formation of these abnormal aggregates is both a hallmark of these diseases and an essential pathogenic event. In particular, this is the case of the aggregates formed by modified variants of cellular TDP-43 (TAR DNA-binding protein 43); two examples of TDP-43 proteinopathies are Amyotrophic Lateral Sclerosis (ALS) and FrontoTemporal Lobar Degeneration (FTLD). Currently, no specific treatment for these diseases is available.

Description of the invention: the aim of the present invention is to provide a stable, cell-based assay to monitor the formation of TDP-43 aggregates, to be used for the screening of novel drugs aimed at preventing protein aggregation. The inventors found that the introduction, into cells, of a number *n* of tandem repeats (where *n* is equal to or greater than 2) of a sequence of the C-terminal, Q/N-rich region of TDP-43 can trigger the formation of phosphorylated and ubiquitinated aggregates in a way that is similar to those observed in the patients. In this manner, the inventors have developed a highly reproducible, cell-based, TDP-43 aggregation model that successfully mimics the formation of pathological aggregates.

Applications/Suggested use: the developed cellular model mimics pathological TDP-43 aggregation and is thus useful for the screening of molecules (chemical drugs, peptides, nucleic acids and others) potentially able to interfere with the formation of these aggregates, acting either directly or indirectly through the modulation of cell function (e.g. cell stress, aging, etc.). Since pathological TDP-43 aggregation is essentially involved in neurodegeneration and disease development, the compounds identified through this invention might find eventual clinical application in the treatment of the TDP-43 proteinopathies.

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