Stiftung zur Förderung der Erforschung von Ersatz- und Ergänzungsmethoden zur Einschränkung von Tierversuchen

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Project

Establishment of in vitro models for neuroprotection with molecular connotations to human neurodegenerative diseases

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Stiftung zur Förderung der Erforschung von Ersatz- und Ergänzungsmethoden zur Einschränkung von Tierversuchen

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General background: Neural derivatives of human and murine embryonic stem cells (hESC and mESC) as potential replacement of animal models for stroke, Alzheimer, multiple sclerosis and ALS.

The aim of this project is the characterization of endpoints from murine and human stem cell models for the quantification of neuroprotective effects of therapeutic compounds. Previous work with these models has so far aimed at a precise molecular and functional description of neurotoxic conditions (protein biomarker signatures for neuronal stress). Based on established protocols for neural differentiation in both models, it is planned to further examine various stages of neuronal maturation with regard to neurotransmitters, known marker proteins and pharmacologic properties, and subsequently to define appropriately correlated endpoints for both species.
Functional endpoints of this type would then be differently screened for surrogate markers by advanced Proteomics technologies. Previous work of the team conducting this study has shown that the approach adequately represents molecular events and processes underlying certain human diseases of the central nervous system and can be successfully used for the quantification of compound effects [1, 2, 3]. Briefly, neuronal stress is induced by three different conditions, representing human pathomechanisms, namely ischemia, excitotoxicity and toxicity induced by amyloidogenic peptides. Functional and molecular events observed so far in the murine ESC and other models [4, 5, 6] encourage us to extend these studies to human ESC models, with the ultimate aim to develop a human in vitro system representing crucial aspects of human neurodegenerative diseases, which thus could at least partially replace corresponding animal models like e.g. MCAO-models for stroke, transgenic mouse models for Alzheimer's disease and ALS, or the extremely irksome models for multiple sclerosis (MOG-EAE) [7]. First results of the project have been accepted for publication [8].

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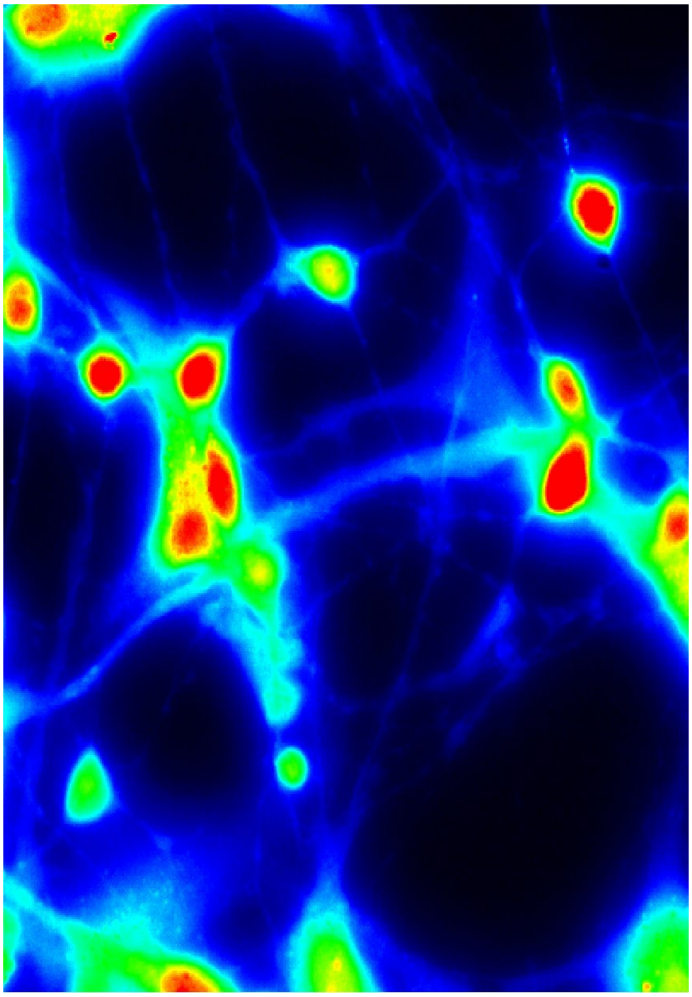

Fluorescence measurements on neurons derived from human stem cells: The uptake of calcium ions (shown in yellow and red) into the cells is induced by neuronal stress. This calcium influx mechanistically relates to stroke, therefore this method also allows for substance screening.

Literature

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