

DISEASE MODIFICATION IN NEURODEGENERATIVE DISORDERS – IS IT A VALID CONCEPT AND CAN IT BE STUDIED - YES

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The introduction of therapeutic approaches to neurodegenerative diseases is one of the challenges of translational research in the neurosciences. Since many attempts have failed in clinical studies, the goal of disease modification meets scepticism in the year 2013. However, we have no alternative other than finally approaching and meeting the goal.

In my view, recent evidence has demonstrated a number of bottlenecks and misconceptions in translational medicine on neurodegenerative diseases. This insight must be considered an advance in knowledge which finally must pay off. The most important are:

1. The step of in vitro to experimental in vivo studies and finally to humans has been underestimated. Major hurdles are a lack of mechanistic understanding of disease-related genes, uncritical approaches to animal models (toxic models, transgenic overexpression models) and methods of their study (biostatistics), and - in a number of studies - a lack of understanding of pharmacokinetics and dose-response relationships.
2. The problem which read-outs could be used for clinical studies. In some diseases – like ALS – natural read-outs like survival seem to appropriate whereas in other diseases such as Parkinson's and Alzheimer's disease functional measures (delayed onset design, neuropsychological instruments) have to be used preferentially. In other diseases like Frontotemporal Dementias ideas we still do not have read-outs which meet practical – and financial – expectations.
3. A lack of understanding on the natural, longitudinal history of the diseases. Since Heiko Braaks work we have a staging of AD and PD, we can distinguish between initiation and propagation of neurodegeneration, we have to anticipate preclinical periods which are longer than decades. But we have to answer more questions, among others: how long can the natural history be modified ? How different are the mechanisms of initiation and propagation ? Which factors are influenced by the known genetic factors ?

The etiology and pathogenesis of neurodegenerative diseases is more complex than previously thought. This was a painful experience of the previous two decades; however, this does not mean that we have to surrender, it rather means that we have to intensify our work. There is no alternative to disease-modifying strategies in neurodegenerative diseases – it remains a valid concept, but we to improve our insights and methods of study. The ultimate goal of disease modification remains prevention.