Non-conventional target approach for drug discovery against neurodegenerative diseases: Nrf2 upregulation

https://neurodegenerationresearch.eu/survey/non-conventional-target-approach-for-drug-discovery-against-neurodegenerative-diseases-nrf2-upregulation/

Name of Fellow
Institution
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Contact information of fellow
Country

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Non-conventional target approach for drug discovery against neurodegenerative diseases: Nrf2 upregulation

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Research Abstract

As a result of the aging population of the developed countries, neurodegenerative diseases (NDD) afflict an ever-increasing number of people. Alzheimer’s disease (AD) is the most prevalent NDD with more than 36 million people currently affected worldwide. Although AD has been studied for more than a hundred years, its “ultimate” trigger is not yet completely understood. Focus for over two decades on amyloid beta (A?) and tau protein, as targets to develop a neuroprotective medicine to delay Alzheimer’s disease (AD) progression, has so far failed. AD is developed as an extremely complex network of events, a fact that has led to the proposal of the “multifactorial hypothesis”. AD, to be defined, must be seen as interconnected processes, rather than independent pathways triggering the final consequences of the disease. In considering the genetic target-based approach, it should be taken into account that familial AD is less than 1%; thus, at least 99% of patients suffer a sporadic form of AD. It seems therefore reasonable to follow non-genetic approaches. For instance, the free radical theory implies progressive cell damage with age, leading to enhanced mitochondrial DNA mutations, futile mitochondrial Ca2+ cycling with excess ATP consumption, oxidative stress and ensuing mitochondrial dysfunction. Based on these observations, the objective in this proposal is the design of selective “multi-target drugs” able to modify two or more key steps in different AD related pathological pathways. By mixing several targets with tuneable properties in one molecule it will be possible to affect several pathways at once and therefore, affecting “redundancy” processes underlying AD. Non conventional selected target will be auto-defensive pathways (phase II gene expression) within the cell and the known targets that are known to be important in AD pathology. This multi-disciplinary approach will combine organic chemistry in order to develop novel structures with optimized properties.

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