1. THE OBJECTIVE OF THE PROJECT

Alzheimer's Disease (**AD**) is a progressive and irreversible neurodegenerative disorder, which leads to death. It represents the major cause of dementia in the elderly population, with a great socio-economic impact in the worldwide community. AD currently affects approximately 44 million people worldwide and is predicted to triple by 2050. Nearly 10% of people over the age of 65 is estimated to be affected by AD. With an estimated global cost of over $600 billion, new therapeutic approaches are sorely needed. In contrast to the familial form of AD that has an early onset, the sporadic form of AD has a late onset at about age 65 and accounts for over 95% of all the cases. AD is accompanied by a dysregulation of the estrogen receptor (**ER**) signaling which is essential system for neuroprotection. ER signaling involves a nuclear (classical) signaling that governs the vast majority of hormonal effects in peripheral tissues, and a non-nuclear (membrane, extra-nuclear) signaling that enables acute regulation of estrogenic signaling throughout the brain. Interestingly, over recent years, membrane non-nuclear ERs emerged as potential therapeutic targets to induce neuroprotection, avoiding detrimental hormonal side effects elicited by the activation of classical nuclear ERs. Current basic study proposes a novel therapeutic approach for sporadic AD that relies on a selective activation of non-nuclear ERs with a newly designed **Pa**thway **P**referential **E**strogen-**1** (**PaPE-1**). Importantly, it is anticipated that PaPE-1 will selectively up-regulate non-nuclear ER signaling without evoking adverse hormone effects via nuclear ERs. The basic research hypothesis assumes that: **A.** A selective activator of non-nuclear ERs i.e., PaPE-1, possesses neuroprotective potential and causes neuroprotection in mouse and human models of sporadic AD. **B.** The mechanism of neuroprotection is associated with up-regulation of non-nuclear ER signaling that is accompanied by an inhibition of neurotoxicity and neuroinflammation, as well as by normalization of epigenetic statuses of neuronal cells and restoration of memory and cognitive deficits.

2. THE RESEARCH TO BE CARRIED OUT

Neuroprotective capacity of PaPE-1 will be estimated in the mouse and human models of sporadic AD *in vitro* and/or *in vivo*. To take into account clinical aspects, the compound will be administered after the initial damage. Effects of PaPE-1 will be determined in context of neurotoxicity, neuroinflammation, PaPE-1-dependent signaling pathways, epigenetic modifications, and/or memory and cognitive deficits.

3. REASONS FOR CHOOSING THE RESEARCH TOPIC

A report of World Health Organization (WHO) and Alzheimer's Disease International (ADI) calls for governments and policymakers to make dementia a global public health priority. The number of people living with dementia worldwide, estimated at 35.6 million in 2010, is set to nearly double every 20 years, reaching 65.7 million in 2030 and 115.4 million in 2050. There is no current cure to stop progression of AD. Novel therapies against AD are urgently needed. Despite the elevated economic costs, it is still not fully understood how AD is progressing and new approaches to treat this pathology are required. Transcriptome meta-analysis revealed a central role for sex steroids deficiency in the degeneration of hippocampal neurons in AD. However, the application of estrogens as neuroprotectants in humans presents numerous limitations, such as increased risk of breast cancer and thromboembolism. Recently, it became evident that the membrane-associated non-nuclear ERs, which govern numerous cell processes in the brain, have abilities to share the neuroprotection attributed to estradiol and phytoestrogens as well as to exert beneficial effects in peripheral tissues. A newly designed PaPE-1 activates specifically the membrane non-nuclear ERs and has a safe pharmacological profile, but no attempts have been made to utilize PaPE-1 to protect neuronal cells and the entire brain from AD-induced damage. A signal cross-talk between non-nuclear ERs and AD development has not yet been shown.

4. THE MOST IMPORTANT EXPECTED EFFECTS

The foundational nature of proposed research would rely on the demonstration that selective activation of non-nuclear ERs leads to neuroprotection in mouse and human models of sporadic AD. The breakthrough technological contribution of this project relies on the therapy that selectively targets signaling pathways which are essential for neuroprotection, but does not cause serious adverse effects. The unique properties of PaPE-1 account for high selectivity and a safe pharmacological profile that gives perspectives for successful therapeutic use of the compound against AD pathology. Hence, investigating the molecular mechanisms by which PaPE-1 regulates AD-related processes would provide necessary pre-clinical validations and lead to the development of a novel multifactorial therapy that targets the membrane-associated non-nuclear ERs and opens up new therapeutic perspectives for AD.