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In Search of Therapeutic Solutions for Alzheimer's Disease

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1. Introduction

Alzheimer's Disease (AD) is the most frequent cause of dementia in the elderly. Prevalence is about 10% in populations of 65 years and older and it increases rapidly as life expectancy increases. Estimates indicate that there are around 36 million cases around the world, while associated costs are higher than US\$ 600 billion (Wimo & Prince, 2010). The histopathological characteristics of AD are represented by two main lesions: senile plaques and neurofibrillary tangles (NFTs). The formers main component is the amyloid beta peptide (A β peptide) adopting β -sheet structures, while the latter have the hyperphosphorylated tau protein and pathological forms of tau as a major component (Maccioni et al., 2001). AD has triggered a plethora of hypotheses to explain its pathogenesis, possibly strengthened by the fact that no cure has yet been found for this devastating disease since its first description by Alois Alzheimer in 1907. Although, significant advances have been made in neuroscience in the last few decades, the data has not provided effective therapeutic solutions for AD.

1.1 Many hypotheses, one disease, no cure

Many hypotheses have been postulated on the physiopathology of AD (Maccioni and Perry, 2009). During the last two decades, the central paradigm was the **amyloid hypothesis**, based on events triggered by the A β cascade: as the unique driving force in neurodegeneration. The hypothesis proposes that accumulation of A β in the brain primarily influences pathogenesis of the disease and the rest of the processes in AD are results of the imbalance between production and degradation of A β (Hardy & Selkoe, 2002). Nevertheless, recent clinical trials based on this hypothesis have been inconclusive. In fact, the amyloid cascade hypothesis has resulted in misleading approaches to find therapeutic alternatives until

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recently (Hardy, 2009). These targets include A β vaccines, antibodies against β -amyloid, γ -secretase inhibitors and drugs that block direct A β aggregation (Extance, 2010; Gandy, 2010; Rinne et al., 2010).

In this context, new paradigms have been proposed that consider all the implications of the disease and valid therapeutic targets are now emerging. AD is a complex illness involving many risk factors. In fact, during its progress, oxidative stress as well as innate immune system activation appears to play a role. Considering AD as a result of multifactorial events, it is plausible that a concatenated series of damage signals affect brain cells, mainly microglial cells, thus triggering an abnormal response in neuro-immunomodulation with consequent effects on neurons. A common molecular feature of these anomalous signals leads to tau self-aggregation into oligomers as a final event (Maccioni et al., 2010).

1.2 The neuroimmunomodulation hypothesis of AD

During the past few years, increasing sets of evidence support the major role of deregulation of interaction patterns between glial cells and neurons in the pathway toward neuronal degeneration. Neurons and glial cells, together with brain vessels, constitute an integrated system for brain function. Inflammation is a process intimately related to the onset of several neurodegenerative disorders, including Alzheimer's disease (AD). Several hypotheses have been postulated to explain the pathogenesis of AD, but none provide insight into the early events that trigger metabolic and cellular alterations in neuronal degeneration (Rojo et al., 2008).

A study of the factors resulting in AD, has led us to postulate the **neuroimmunomodulation hypothesis**, which focus on pathological events in the neuron-glia cross-talks. Data suggests an important role of the immune system in regulating the progression of the brain aging and neurodegenerative diseases, where the crosstalk between these systems determines the progression of pathological event (Lucin & Wyss-Coray, 2009). In this context, the microglia, the resident macrophages of the CNS, are key factors in the regulation of local cellular environment relative to inflammation. The persistence of activated microglia long after acute injury and in chronic disease suggests that these cells have an innate immune memory of tissue injury and degeneration. Microglial phenotype is also modified by systemic infections or inflammation. Systemic inflammation is associated with a decline in function in patients with chronic neurodegenerative disease, both acutely and in the long term (Perry et al., 2010).

The idea that alterations in the brain immunomodulation are critical for AD pathogenesis provides the most integrative view on this cognitive disorder, considering that converging research lines have revealed the involvement of inflammatory processes in AD. Studies on microglia and neuronal cultures, together with experiments in animal models, and the clinical evidence, suggest that a series of endogenous damaged signals that include, among other factors, A β oligomers, oxygen free radicals, iron overload, cholesterol levels in neuronal rafts, folate deficiency, head injury, LDL species and homocysteine trigger the activation of microglial cells. Inflammatory cytokines play a dual role: either promoting neurodegeneration or neuroprotection. This equilibrium is shifted toward the neurodegenerative phenotype upon the action of several risk factors that trigger innate damage signals and activate microglia and then release of inflammatory cytokines (Figure 1) (Fernandez et al., 2008; Maccioni et al., 2009).

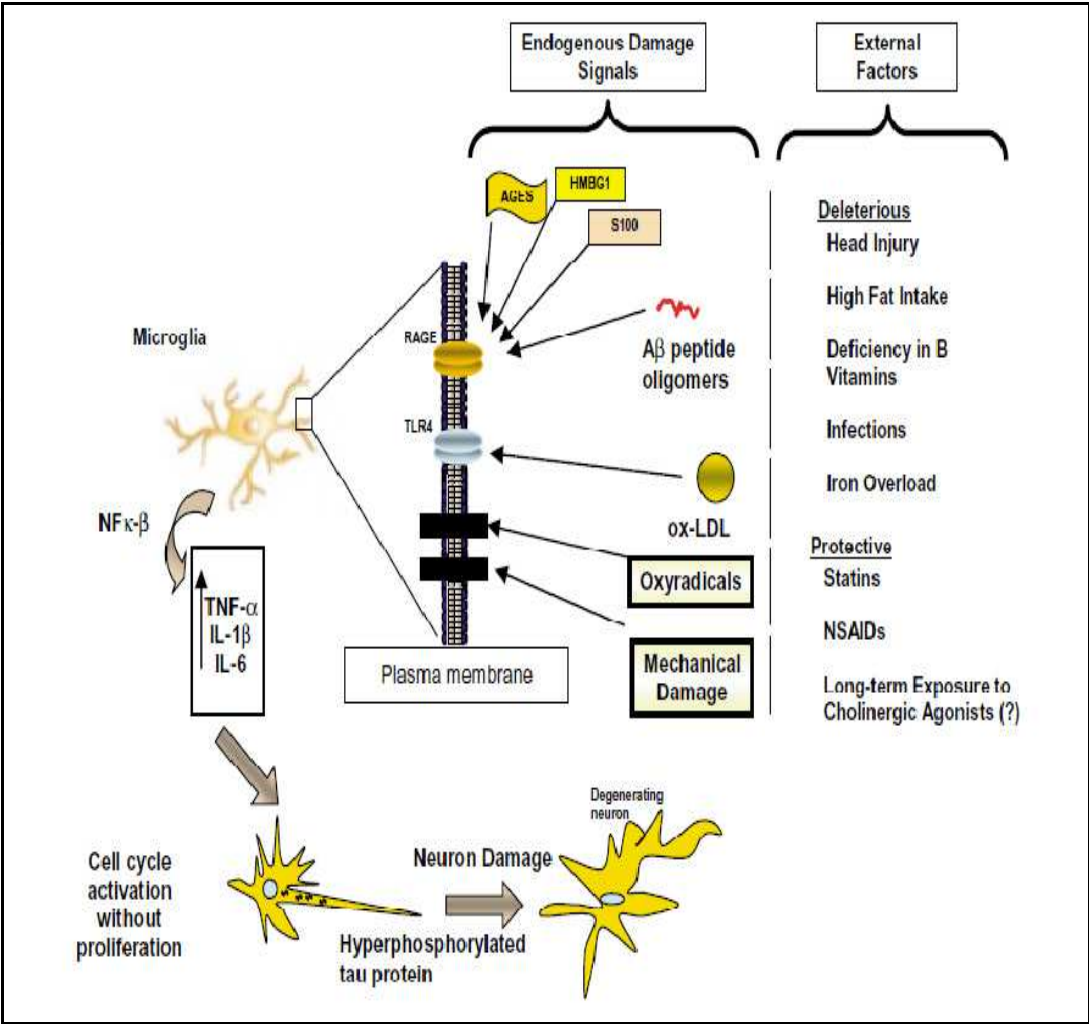


Fig. 1. **Neuroinflammation Hypothesis in the pathogenesis of AD.** Schematic representation of the hypothetical roles of endogenous danger/alarms signals built into the innate immune system in the early stages of the pathogenesis of AD. Consequentially, (as it may apply to different individuals), danger signals can trigger innate immune system alarm mechanisms resulting in the production of tumor necrosis factor alpha (TNF- α), interleukin-1 β (IL-1 β) and interleukin-6 (IL-6). These signals would then mediate neuronal damage, reflected in alterations such as tau hyperphosphorylation and paired helical filaments formation.

The progression of AD, encompasses increased damage in brain parenchyma preceding the onset of symptoms. Suggesting that tissue distress triggers damage signals and drives neuroinflammation. These signals via toll-like receptors, or receptors for highly glycosylated end products, or other glial receptors activate sensors of the native immune system, inducing the anomalous release of cytokines and promoting the neurodegenerative cascade, a hallmark of brain damage that correlates with cognitive decline. We show that this activation induces NFκ-β expression with the consequent release of cytokine mediators such as TNF- α , IL-6 and IL-1 β . An over expression of these mediators may trigger signaling cascades in neurons leading to activation of protein GSK3 β , cdk5 kinases, along with inhibition of phosphatases such as PP1, resulting in hyperphosphorylation and self-aggregation of tau protein into neurotoxic oligomeric species. The aggregation of tau protein

is the final pathway and key event in the Alzheimer's pathogenesis (Morales et al., 2010, Farias et al., 2011).

The evidence correlating inflammation and tau phosphorylation has been provided by neuropathology markers and mouse transgenic models with Alzheimer disease. Activated microglia has been found in the postmortem brain tissues of various human tauopathies including Alzheimer's disease (AD) and frontotemporal dementia (FTD) (Gebicke-Haerter, 2001). The administration of LPS, in order to generate systemic inflammation, significantly induced tau hyperphosphorylation in the triple transgenic mouse model of AD (3xTg) and rTg4510 mice. In line with this evidence, microglial activation also preceded tangle formation in a murine model of tau pathology (Yoshiyama et al., 2007). Also immunosuppression of young P301S Tg mice with FK506 attenuated tau pathology and increased lifespan, thereby linking neuroinflammation to early progression of tauopathies (Yoshiyama et al., 2007, Lee et al., 2010; Kitazawa et al., 2005). In addition, the neurodegenerative lesions caused by human truncated tau promote inflammatory response manifested by upregulation of immune-molecules (CD11a,b, CD18, CD4, CD45 and CD68), the morphological activation of microglial cells and leukocyte infiltration in a rat model of tauopathy (Zilka et al., 2009).

On the other hand, it has been demonstrated that proinflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6, and nitric oxide, released from astrocytes can accelerate tau phosphorylation and formation of neurofibrillary tangles (NFTs) in vitro (Li et al., 2003, Quintanilla et al., 2004, Saez et al., 2004). Likewise, the activation of microglia and the microglial-derived proinflammatory cytokine TNF α can induce accumulation of aggregation-prone tau molecules in neurites via reactive oxygen species (Gorlovoy et al., 2009). Recently, it has been identified the fractalkine receptor (CX3CR1) as a key microglial pathway in protecting against AD-related cognitive deficits that are associated with aberrant microglial activation and elevated inflammatory cytokines. In vitro experiments demonstrated that microglial activation elevates the level of active p38 MAPK and enhances tau hyperphosphorylation within neurons which can be blocked by administration of an interleukin-1 receptor antagonist and a specific p38 MAPK inhibitor. This finding suggests that CX3CR1 and IL-1/p38 MAPK pathway may serve as novel therapeutic target for human tauopathies (Bhaskar et al., 2010, Cho et al., 2011).

Other sources of evidence to support neuroimmunomodulation theory are epidemiological data that show individuals consuming nonsteroidal anti-inflammatory drugs (NSAIDs) have a lower risk of AD (McGeer et al, 2006). In fact, patients receiving systemic NSAIDs developed significantly less AD manifestations, suggesting that ameliorating inflammation in the brain helps to prevent or slow down the onset of AD (McGeer et al., 1996). However, controlled randomized clinical trials with common NSAIDs have not shown a positive effect in the decline of AD (Rojo et al, 2008).

Genetic and epidemiological evidence has implicated increased TNF α production as a risk factor for AD. In fact, excess TNF is present in the CSF of individuals with Alzheimer's disease (AD). Recently, Tobinick and colleagues have demonstrated that perispinal administration of etanercept, a potent anti-TNF fusion protein, produced sustained clinical improvement in a 6-month, open-label pilot study in patients with AD ranging from mild to severe. Subsequent

case studies have documented rapid clinical improvement following perispinal etanercept in both AD and primary progressive aphasia, providing evidence of rapidly reversible, TNF-dependent, pathophysiological mechanisms in AD and related disorders. Although, some researchers undermine results by their methodologies, perispinal etanercept for AD needs further studies to be validated and gives us new perspectives to support the critical role of immune system in AD (Tobinick & Gross, 2008a, 2008b; Tobinick, 2009).

1.3 Integrated efforts toward prevention, diagnosis and treatment of AD

In the field of prevention of AD, studies have indicated that dietary factors, antioxidants, exercise along with healthy styles of life contribute to diminish risk factors for AD. In addition, the search for dietary supplements, phytocomplexes, and nutraceuticals from natural sources have suggested novel preventive alternatives against AD, based on preclinical and clinical trials outcomes. These include molecular complexes with either anti-inflammatory, antioxidant or anti-amyloidogenic properties. The extraordinary properties of polyphenolic extracts may help as coadjuvant in the AD therapy. Investigations are directed to design powerful nutraceuticals, which derive from distinct sources and could be consumed by the high-risk population. This provides data on the action of *Shilajit* and other nutraceuticals as a new tools for prevention.

Innovative approaches are critical in order to improve early detection of AD, which in turn is critical to find therapeutic solutions, and for monitoring new drugs developments against the disease. Our laboratory has developed an integrated strategy to establish reliable diagnosis tools with a high efficacy. We found that different benzimidazoles that tag aggregates of tau protein, serve as specific markers for PET neuroimaging, in order to monitor advances of the disease. Clinical studies are underway to validate PET images that differentiate stages of AD and controls. As a complementary approach, we have studied tau in cerebrospinal fluid (CSF) and also in peripheral blood platelets, providing promising biological non-invasive markers for AD (Maccioni et al, 2006; Neumann et al, 2011).

Until now there are no drugs available as an efficient therapy of AD. Current therapeutic targets focus on avoiding formation of tau aggregates in neurons, modulation of the innate immune system, chelating heavy metals and diminishing the burden of the amyloidogenic molecular variants. On one hand, clinical trials include: tau aggregation inhibitors (like methylene blue with promising results in phase II trials), tau kinase inhibitors, microtubule stabilizers and unfolded protein response modulators. As mentioned earlier, it has been demonstrated that the relationship between anti-inflammatory molecules (NSAIDs) and the prevalence of AD in longitudinal studies. Unfortunately, no specific drug has a positive effect in the treatment of the disease in controlled double-blind trials. It could be hypothesized that we still do not understand enough about the specific molecules and its receptors involved in the immune system's cross-talk between neuron and glial cells. We believe that the next generation of drugs should focus on these specific targets.

2. New tools for AD diagnosis

More than a century has passed since Dr. Alois Alzheimer described the case of Auguste D, a 51 years old patient with a history of progressive cognitive impairment. Histopathology of brain tissue demonstrated the presence of senile plaques, neurofibrillary tangles (NFTs) and

arteriosclerotic changes (Alzheimer, 1907). Today, despite the importance of AD (the world's primary cause of neurodegenerative dementia) the advances in knowledge of clinical and pathophysiological aspects, and the definitive diagnosis of AD still depends mainly on histopathological analysis.

In contrast, the reliability of standard clinical evaluation is limited, and in most cases allow us only to diagnose the disease as "possible" or "probable" AD (McKhann et al., 1984). This shortcoming of standard clinical methods is specially relevant in early and unusual presentations of AD and has driven the interest to develop both biochemical and imaging tests to support the diagnosis (Dubois et al., 2007; Wiltfang et al., 2007). In this regard the 2011 diagnostic criteria (McKhann et al., 2011) considered the contribution of markers for the pathophysiological process of AD. These criteria divided biomarkers of AD in two classes: a) Biomarkers of brain A β deposition -i.e. CSF A β 1-42 levels and brain Positron Emission Tomography (PET) amyloid imaging - and b) biomarkers of downstream neuronal degeneration or injury -i.e. CSF total and phosphorylated forms of tau; 18 fluorodeoxyglucose (FDG) PET imaging of temporo - parietal cortex; and atrophy on Nuclear Magnetic Resonance (NMR) imaging in medial, basal, and lateral temporal lobe, and medial parietal cortex. The contribution of AD biomarkers has made possible to raise the concept of **preclinical AD** as a diagnostic category based on AD biomarkers modifications without definite cognitive decline (Sperling et al., 2011).

2.1 Role of biomarkers in AD

A biomarker corresponds to an indicator of the presence or extent of disease, which is directly associated with the clinical features and prognosis of the disease. Biomarkers for cognitive impairment and dementia have been proposed by several research groups in recent years (Maccioni et al., 2004). The consensus report of "The Ronald and Nancy Reagan Research Institute of the Alzheimer's Association" and the "National Institute on Aging working group" on "Molecular and Biochemical Markers of Alzheimer's Disease" (The Ronald and Nancy Reagan Research Institute of the Alzheimer's and Association National Institute on Aging Working Group, 1998) listed the specific criteria and features for an ideal biomarker of AD. It "should detect a fundamental feature of neuropathology and be validated in neuropathologically-confirmed cases: it should have a sensitivity >80% for detecting AD and a specificity of >80% for distinguishing other dementias: it should be reliable, reproducible non-invasive, simple to perform, and inexpensive". Based on these criteria, scientists have been able to discard many substances that are unsuitable as biomarkers and do not contribute or improve AD diagnosis (Mulder et al., 2000).

Biochemical markers for AD have been extensively sought in bodily fluids, and key proteins of AD neuropathology -A β , tau and hyperphosphorylated tau isoforms- have been evaluated as potential markers for AD diagnosis and for follow up in clinical trials.

2.1.1 Biomarkers in CSF

As CSF is in close contact with nerve tissue, it is not surprising that CSF has been considered a reliable indicator of brain tissue environment. Most published literature described two main types of CSF-based biomarkers :

- **Amyloid beta (A β) levels:** in AD CSF the concentration of A β , fraction 1-42 (A β 1-42) is regularly reduced to less than 50% of its normal value and has been considered a reliable marker of AD, with a sensitivity of 78% and 81-83% specificity (Wiltfang et al., 2007). Low levels of A β 1-42 can also predict the onset of cognitive decline in older women without dementia (Gustafson et al., 2007). Meanwhile, since the fraction A β 1-40 is the major constituent of total CSF A β , A β 1-42 / A β 1-40 ratio has also been evaluated and has been proposed as a better marker than isolated A β 1-42 levels (Wiltfang et al., 2007).
- **Tau and phosphorylated tau:** Tau protein is aggregated in paired heliocidal filaments (PHFs) and neurofibrillary tangles (NFTs) of AD brains and has been proposed as a pathogenic protein in the disease (Maccioni, 2011). Tau levels are also increased in CSF of AD patients, so they have been studied as suitable biomarkers. In patients with mild cognitive impairment -that in many cases will progress to dementia- CSF tau levels can differentiate those that correspond to depressive syndromes from those that will effectively progress to AD (Schönknecht et al., 2007).

Under pathogenic conditions tau undergoes several modifications that include phosphorylation, truncation, glycation, etc. (Farías et al., 2011), so these forms of modified tau have also been evaluated as biological markers. Tau phosphorylated at threonine 181 (p-tau 181) demonstrates to be useful for differentiating control and AD subjects from subjects with dementia with Lewy Bodies, being a better marker of AD than A β 1-42 and total tau (Vanderstichele et al., 2006). Hyperphosphorylated tau increases in AD subjects, as well as in those with mild cognitive impairment that will progress to AD (Andersson et al., 2007; Maccioni et al., 2006).

A β 1-42, total tau and p-tau may serve as useful markers to predict progression from mild cognitive impairment to AD (Diniz et al., 2008). CSF p-tau levels also may have a role monitoring response to treatment (Degerman et al., 2007). However, the real value of CSF markers to predict progression of cognitive decline is disputed and may be less robust than cognitive assessment to predict conversion from mild cognitive impairment to AD (Gomar et al., 2011). Apolipoprotein E (Apo E) ϵ 4 genotype may be related to levels of biomarkers in CSF, since increased levels of total tau and p-tau and decreased A β 1-42 have been described in CSF of patients with severe involvement of episodic memory and Apo E- ϵ 4 (+) (Andersson et al., 2007).

Although A β and tau levels in CSF are the most studied and validated biological markers of AD with enough stability, (Slats et al., 2011); the mayor pitfall of CSF biological markers is the necessity of invasive techniques such as lumbar puncture to obtain samples. Adverse effects are present at 11.7% of subjects, being with clinically significant at 3.97%, including post lumbar puncture headache 0.98% - 5% (Maccioni et al., 2006; Peskind et al., 2005). As a way to face problems of CSF analyses, new and non-invasive biomarkers available in blood, saliva and urine are currently under investigation.

2.1.2 Peripheral biomarkers

Levels of A β have been studied in plasma of AD patients. However, A β 1-40 levels are not specific for AD and in fact are affected by age (Luchsinger et al., 2007). On the other hand, plasma A β 1-42 may be altered early in the disease, but since this marker is not reliable

enough, correlation with neuroimages or other biological markers is needed (Blasko et al. 2008). Other metabolic and nutritional markers have also been studied, including levels of folic acid and vitamin B12 but results are conflicting so far (Irizarry et al. 2005; Isobe et al. 2005; Köseoglu & Karaman 2007; Serot et al. 2005; Seshadri et al. 2002).

2.1.3 Apo E polymorphisms

Apo E is a plasma protein involved in cholesterol transport. In the CNS, Apo E is also involved in growth and repair of the nervous system during development and after injury. The Apo E gene has 3 alleles: $\epsilon 2$, $\epsilon 3$, $\epsilon 4$. The $\epsilon 4$ allele is associated with an increased risk of AD (Rojo et al., 2006), $\epsilon 4$ allele is present among 40 to 50% AD subjects (Farrer et al., 1997). Actually Apo E- $\epsilon 4$ is considered as a risk factor of AD (Mayeux et al., 1998).

2.1.4 Inflammatory markers

Proinflammatory molecules have been studied as potential peripheral markers of AD. As stated in preceding paragraphs, in the context of neuroimmunomodulation hypothesis, there is consistent evidence that inflammatory mechanisms play an important role in AD pathophysiology. However, results are inconsistent. In patients with AD elevated levels of plasma soluble CD-40 and a decrease in TGF- $\beta 1$ have been described, while assessments of IL-1, IL-2, IL-6 and TNF- α have yielded conflicting results (Rojo et al, 2008).

2.1.5 Altered p53

Alterations in the tertiary folding of p53 protein can be recognized in fibroblasts from patients with AD (Uberti et al., 2006). This altered protein is also present in blood mononuclear cells of AD patients. Measurements of these p53 variants by cytofluorometry and immunoprecipitation techniques may serve as AD biomarker with high sensitivity and specificity (90% and 77% respectively) (Lanni et al, 2008; Uberti et al., 2008).

2.1.6 Platelets Amyloid Precursor Peptide (APP)

APP is a transmembrane protein that, by proteolytic cleavage, generates A β , the major component of senile plaques. Therefore, APP could be a useful biomarker in AD. Platelets carry more than 95% of circulating APP, containing all the necessary machinery for APP metabolism, so there has been postulated that changes in platelets metabolism that include, but are not limited to APP processing, may correlate to brain pathophysiological processes of AD (Hochstrasser et al., 2011; Neumann et al., 2011; Zainaghi et al., 2007).

Several APP fractions can be resolved by electrophoresis and immunoblot techniques of platelets extracts. Analyses have found a reduction in 130 kDa APP isoforms in relation to 110 kDa APP in AD patients. These alterations in platelets APP ratio are related to severity and progression of the disease (Borroni et al., 2006) High sensitivity and specificity -around 80 to 95%- have been described for this technique (Borroni et al., 2006; Padovani et al., 2002). Platelets APP ratio may be altered early in AD and can be used to detect the conversion of mild cognitive impairment to AD (Borroni et al., 2003; Borroni et al., 2006) and also to monitor treatment responses (Borroni et al., 2001; Liu et al., 2005). However this method is not quantitative and there are important differences in reported data between different studies; this is likely due to differences in multiple steps of sample management and processing.

2.1.7 Platelets tau

Our group has recently demonstrated that platelets also contain tau protein. High molecular weight forms of tau that probably correspond to oligomeric protein can be resolved by electrophoresis and immunoblot with tau specific antibodies. The ratio of high molecular weight tau to normal weight tau in platelets is increased in AD patients so this kind of analysis may represent a novel biomarker for AD (Neumann et al., 2011).

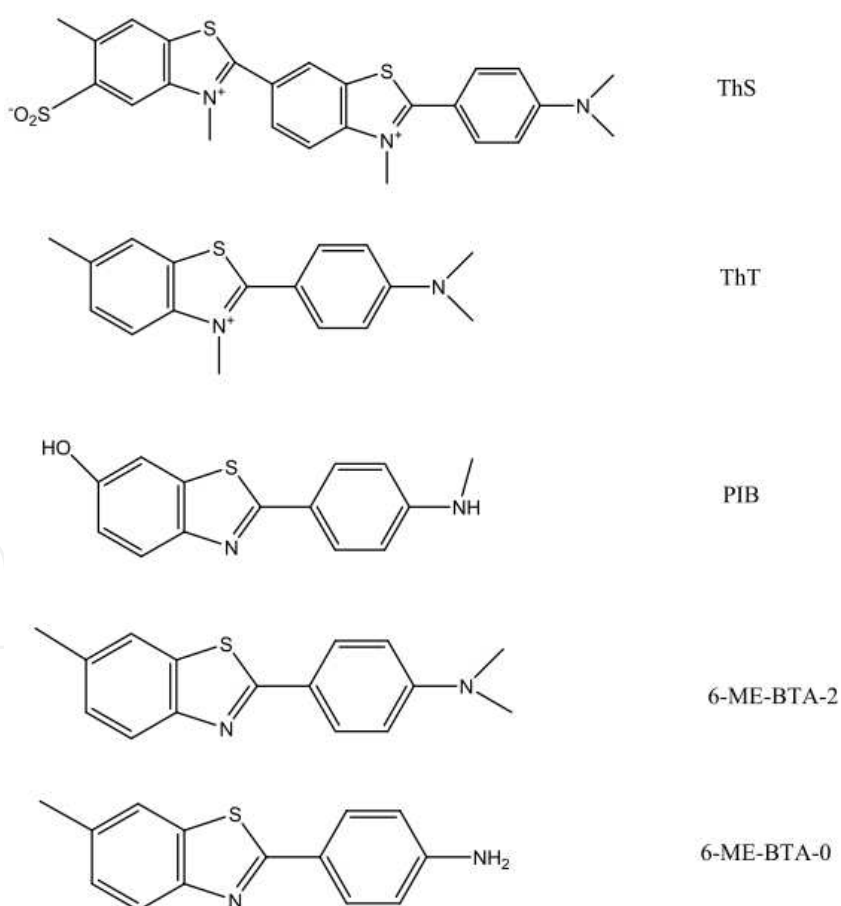
2.2 Disease specific radiotracers: New avenues to pathology-specific imaging technologies

The development of new NMR and PET imaging technologies has become a topic of major interest for both clinical and fundamental neuroscientists over the past few years, as it presents the unparalleled possibility of visualizing pathological processes in the brain parenchyma in a non-invasive and real time manner. Major progresses have been achieved in this field in the past decade mainly due to the use of functional NMR technologies and innovative PET tracers. However, although these current neuroimaging technologies provide precise information on structural and functional aspects of the brain, they have failed to provide information on the specific pathological processes and structural alterations occurred in different neurodegenerative diseases, including Alzheimer. Therefore, the development of new pathology-specific imaging technologies is still an urgent need. This would allow us to make a more accurate diagnose of brain disorders and also to efficiently monitor a number of experimental therapies currently under investigation.

Regarding AD-specific PET tomography, researchers have focused their attention mainly on obtaining maps of the proposed hallmark lesions of this disease, i.e., the senile plaques (SP) and the neurofibrillary tangles (NFT's) formed by hyperphosphorylated tau. After the publication of Klunk et al. (Klunk et al., 2004) reporting the potential application of Pittsburgh Compound-B as a specific radiotracer for the amyloid deposits in the human brain, a new era in the development of *in vivo* AD neuroimaging seems to have started. Almost at the same time Verhoeff et al. (Verhoeff et al., 2004) published a similar study with another PET radiotracer. None of these studies proved to be applicable for diagnosis of early stages of AD. However they helped us to understand the clinical significance of visualizing cerebral amyloid burden in AD diagnosis. Not long after reports on amyloid-specific PET tracers were published, several groups including ours pointed out the relevance of addressing this challenge from a seemingly more relevant and perhaps more efficient perspective, which is visualizing aggregated forms of tau protein. (Rojo et al., 2007a, 2007b). Recently we reported the potential of benzimidazoles derivatives as pathology-specific PET tracers (Rojo et al., 2010). This work led us to discover that FDA-approved drugs, such as **Lansoprazole and Astemizole** (Rojo et al., 2010), were promising candidates for AD-specific radiotracers (Figures 2 and 3).

The existence of a pathology-specific neuroimaging technology of AD would also allow a rational evaluation of the biological effects of a number of experimental pharmacological therapies available presently, as well as other promising tools to treat AD patients, and methods for clinical trial of anti-tau therapeutic approaches (Rojo et al., 2011).

Molecular structure of these ligands varies from large proteins and peptides such as the A peptide and radio-active monoclonal antibodies to small molecules derived from Congo red, Chrisamina-G, tioflavine-T, and acridine orange (Figure 2). Recent studies have demonstrated that is possible to obtain images of plaques and NFTs *in vivo* whether separately or simultaneously. So far, the most successful molecules have been those with a relatively low molecular weight (Figure 2) (Mathis et al., 2005). It has been shown that some benzimidazole and quinoline derivatives tag aggregated forms of tau *in vitro* and in the context of human brain (Mathis et al., 2005; Okamura et al., 2004; Okamura et al., 2005; Rojo et al., 2007a). This could serve as the milestone for developing neuroimaging technologies to visualize NFTs in the brain of AD patients and those affected with mild cognitive impairments (MCI). We believe that in the future, significant progress will be achieved in this area due to the recent discovery of different benzimidazoles and benzothiazoles with high affinity for brain aggregates of tau protein (Rojo et al., 2007b). Another important step in this area is the search of FDA-approved drug with similar structural features to those of Thioflavine T and other benzothiazole compounds. This implies the possibility of skipping expensive, cumbersome and time-consuming safety studies in humans for their approval in AD diagnosis *in vivo* (Rojo et al, 2010, 2011).



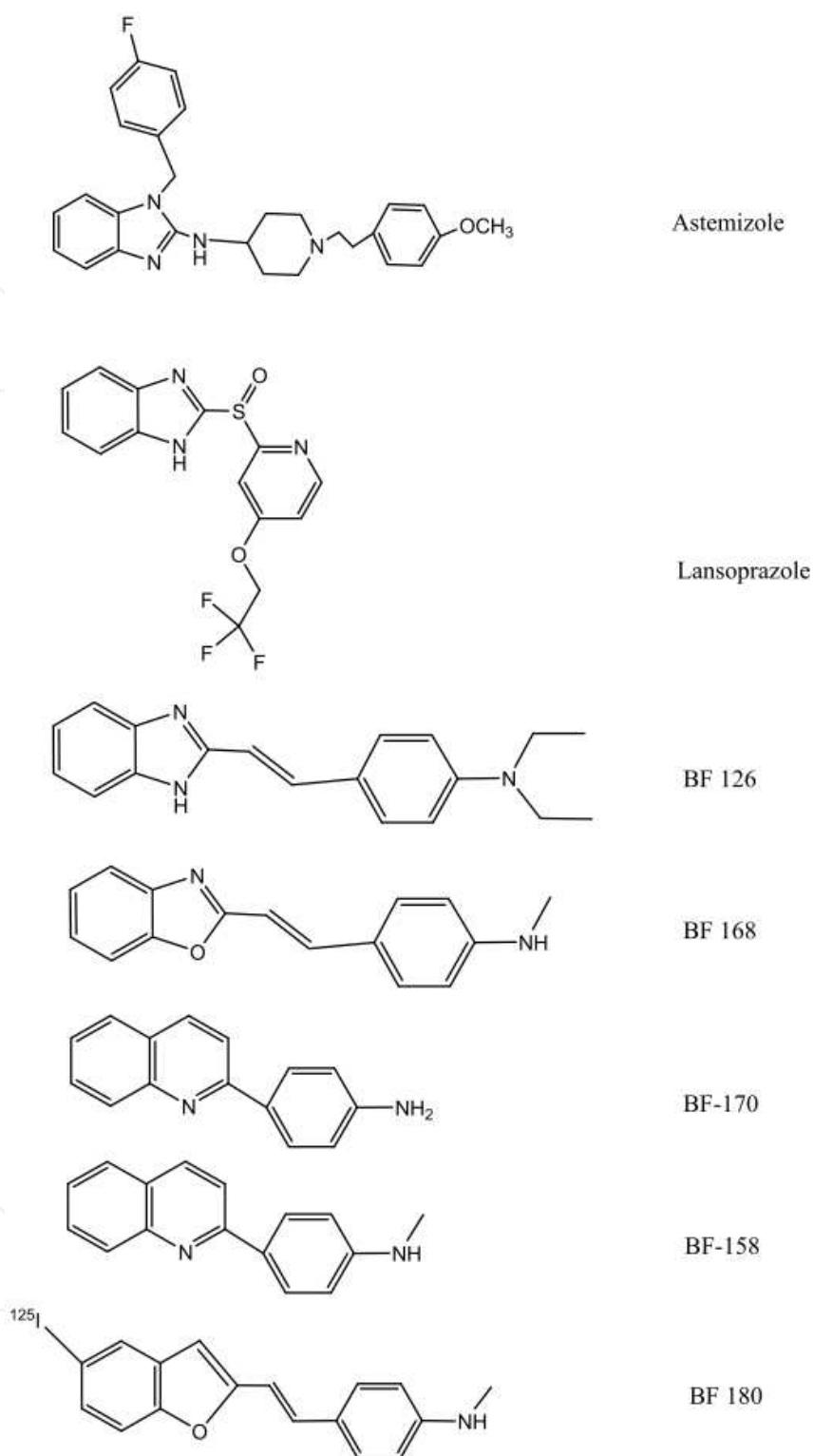


Fig. 2. **Benzimidazole and benzothiazole derivatives proposed as potential biomarkers for PET imaging in AD.** Several small molecules have been proposed as PET tracers for both amyloid and tau aggregates. In this figure ThS shows the proposed structures for Thioflavine S (ThS); Thioflavine T (ThT); Pittsburgh compound (PIB), and other amyloid specific radiotracers such as 6-ME-BTA 2 and 6ME-BTA-0. Also here the figure shows the NFTs-specific proposed PET tracers Astemizole, Lansoprazole, BF-126, BF 170, and BF-158.

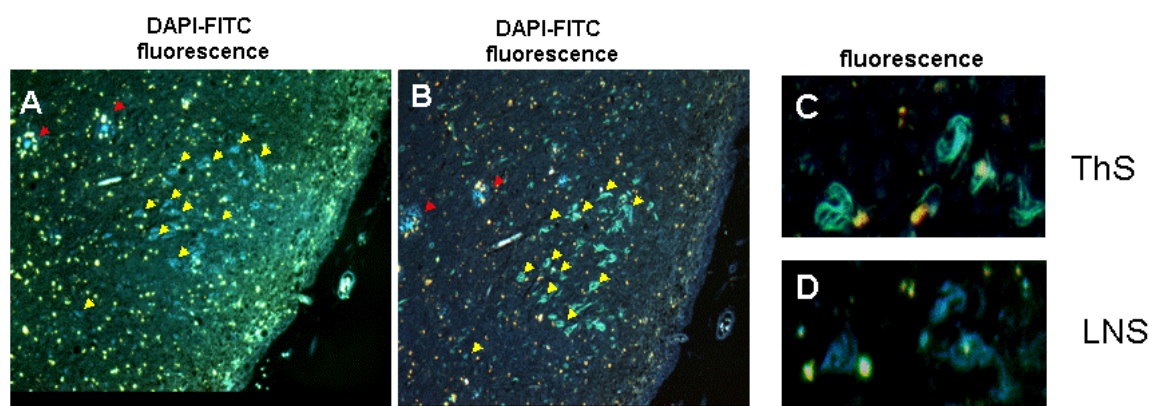


Fig. 3. Neuropathological staining of brain sections from the entorhinal cortex of AD patients. Senile plaques (red arrowheads) and NTFs (yellow arrowheads) can be clearly tagged by Thioflavine-S (B, C). Lansoprazole (A,D) tagged NTFs and neurite-like structures in the core of senile plaques.

3. Novel approaches toward prevention and treatment of Alzheimer's Disease (AD)

AD is the most common type of dementia characterized by the formation of two main protein aggregates in the brain: senile plaques (SP) consisting of the amyloid- β peptide and neurofibrillary tangles (NFT's), consisting of the microtubule-associated protein tau. Tau accumulates in a hyperphosphorylated state forming intracellular deposits named to as paired helical filaments which generate the NFT's (Maccioni et al., 2010). Formally approved during the past two decades, pharmacological treatments for AD are mainly based on restoring the levels of acetylcholine transmission in the brain being essentially symptomatic therapies. The anticholinesterase (anti-ChE) agents currently used such as rivastigmine, donepezil and galantamine failed in providing a substantial improvement in the mental health condition of AD patients (Aizenstein, 2008). Cholinesterase inhibitors appear to increase phosphorylated tau in AD (Chalmers et al., 2009). Anti-ChE drugs are being used for symptomatic treatment of mild to moderate AD. Tacrine was the first anti-ChE which showed positive clinical results, however, it is not in use any more due to severe hepatotoxicity. Through the progress of AD, brain cholinergic neurotransmission becomes significantly diminished, thus limiting clinical efficacy of the above mentioned anti-ChE agents. A new drug is being used CerebrolysinTM, based on a combination of peptides and administered intravenously, has shown discrete results. On the other hand the drug memantine, which modulates NMDA-related pathways in brain, has shown moderate results in cases of mild to advanced stages of AD. Moreover, nonsteroidal anti-inflammatory drugs (NSAIDs) appears as promising treatments according to epidemiological studies are able to reduce the risk of developing AD. A 2006 pilot study showed small but significant improvements in various cognitive rating scales in patients with AD after treatment with etanercept (Tobinick et al. 2008a,b; Navarrete et al., 2011). A further study, administering to a single AD patient via perispinal infusion, showed rapid and significant improvement of Alzheimer's symptoms. Nowadays over 300 compounds are being tested for AD at different stages of development, 175 of them are being evaluated at the level of clinical trials. However, the finalized studies have shown only negative results, creating great concern among the medical community who is still expecting an efficacious therapy for AD.

Another compound is huperzine A, an acetylcholinesterase inhibitor that occurs naturally in a species of moss that has been used in China for centuries for the treatment of blood disorders (Wang et al., 2011). The herb has been used to treat AD in China since the late 1990's and is sold in the US as a dietary supplement to help maintain memory (Rafii et al., 2011). The first synthetic approach to produce huperzine A, was recently published aiming to replace the only natural source of huperzine A, the plant *Huperzia serrata*, which produces small amounts of huperzine A. Another drug, memantine directed to NMDA receptors, shows only moderate actions in advanced cases of the disease (Raina et al., 2008). On the other hand, recent anti-amyloid strategies, have failed in their efficacy or safety on their last development phases (Holmes et al., 2008). Statins appear to reduce the burden of NFTs, but clinical studies are not conclusive (Rojo et al., 2006; Boimel et al., 2009). In the whole context, tau based therapies represent a potential therapeutic target, specifically those that diminish its aggregation, or alter its hyperphosphorylation (Alvarez et al., 2001). To those agents, several anti-tau miscellaneous strategies such as normal microtubule-stabilizing agents can be added to the new search for anti-AD drugs (Maccioni, 2011; Navarrete et al., 2011). Thus, a combination of molecules such as anti-tau agents will be determinant for a substantial control of AD in the future.

3.1 Searching for innovative tau aggregation inhibitors

Physiologically tau stabilizes the microtubule structure, but in the neurons of patients with AD the microtubule system is believed to be disrupted, with the concomitant axonal transport deficits and degeneration (Farias et al., 2011). Several lines of evidence have shown that tau aggregation is the main event involved in the neurodegenerative process, due to the conversion of either soluble tau or oligomers into insoluble filaments. This process correlates with the clinical progression of AD and cognitive impairment (Maccioni and Perry, 2009). The identification of mutations in the tau gene in hereditary frontotemporal dementia revealed that tau dysfunction is central to neurodegeneration (Nakashima et al., 2005). Thus, improvement in the cognition of a transgenic model displaying both NFT's and SP depends on blockage of tau filaments formation (Zhang et al., 2005). Cellular models where tau is overexpressed evidence the cytotoxicity of formed intracellular aggregates. In the search of new molecules for the treatment of AD, many drugs focused on A β aggregation have failed in stopping the progression of the disease (Navarrete et al., 2011). The immunization against A β was effective in reducing amyloid plaque load, but it had little effect on improving cognitive functions. A recent study shows the failure of a phase III clinical trial with a γ -secretase inhibitor (Carlson et al., 2011; Lleo and Saura, 2011). Therefore it seems timely to consider alternative drug discovery strategies for AD based on approaches directed at reducing misfolded tau and compensating for the loss of normal tau function.

3.2 Tau hypothesis in the context of the AD clinic

Nowadays AD etiopathogenesis is not yet established, despite different and numerous hypotheses (Maccioni and Perry, 2009). Nevertheless, there is agreement about its early onset, as a result of the convergence of a set of genetic and/ or environmental factors, which vary on time among patients and increase along with age (Glatz et al., 2006; Maccioni et al., 2010). At different stages of the process, a cascade of pathological events is triggered, where factors such as A β oligomers, iron overload or oxygen free radicals modify microglial cells

thus inducing anomalous signaling to neuronal cells (Fernandez et al., 2008; Maccioni et al., 2009; Morales et al., 2010). These events finally result in alterations of cellular signposting and biochemical abnormalities that lead to cellular dysfunction, the lack of neurotransmission, cellular death and clinical expression of dementia.

For years, the dominant hypothesis was that of the amyloid cascade, which sets the amyloid precursor protein (APP) metabolism dysfunction on the central nervous system, as the responsible agent for extraneuronal formation of SP (Hardy & Selkoe, 2002; Hardy, 2009). The major problem of this postulate is that a significant number of cognitively healthy elderly people, also exhibit abundant amyloid plaques, without a cognitive function impairment. Besides, diverse clinical assays carried out with different anti-amyloid molecules, despite consistent effects on preclinical stages, have not shown cognitive and/or functional benefits in treated patients at advance stages of AD (Aizenstein et al., 2008; Panza et al., 2011). In this context, as the amyloid cascade hypothesis does not allow to explain the integrity of AD pathogenesis, the interest on tau hypothesis and neurofibrillary tangles, that sets tau protein abnormal phosphorylation as the possible responsible for these tangles formation, and the consequent neuronal death, has increased (Navarrete et al., 2011). On the other hand, recent data suggest an eventual connection between APP and tau protein, even though they have been treated as different contexts to physiopathologically explain AD (Alvarez et al., 2001; Otth et al., 2003; Czapski et al., 2011; Fuentes and Catalan, 2011).

Studies in APP mice crossed to mutant tau mice, injection of A β into the brain of these tau mutant mice and studies on neuronal cells, support the notion that A β aggregates can drive neurofibrillary pathology (Otth et al., 2003; Hernandez et al., 2009; Kocherhans et al., 2010). Such investigations bear out the notion that although AD may be considered a primary A β amyloidosis and a secondary tauopathy, tau pathology is the major factor that contributes to neurodegeneration (Maccioni et al., 2010).

Moreover, FDA approved drugs over last decades are seemingly drugs which only reinforce cholinergic neurotransmission, as donepezil, galantamine and rivastigmine, or that moderates glutamate/NMDA receptor memantine are approved. After several years of clinical experience on drugs use, it can be concluded that AD treatment with cholinesterase inhibitors and memantine, is essentially symptomatic (Raina et al., 2008). Even though it may result in a moderate improvement, lacks of a real clinical output relative to cognition measurements and global evaluation of dementia. Recent *in vitro* and *in vivo* data suggest that cholinergic drugs may even have negative impact on amyloid- β -peptide and tau behavior. According to recent studies, patients treated with ChEIs had accumulated significantly more phospho-tau in their cerebral cortex compared to untreated patients. This data suggests the possibility that increased tau phosphorylation may influence long-term clinical responsiveness to ChEIs (Chalmers et al., 2009; Fuentes and Catalan, 2011).

Efforts to develop drugs more focused on AD underlying pathology, have considered different agents, called disease modifiers, and linked to diverse etiopathogenic hypotheses. Anti-amyloid strategies, such as active or passive immunization, or secretase inhibitors, have been predominant, nevertheless they have failed on the efficacy or security on their last development phases (Lleo and Saura, 2011). Actually, molecules that could restrict tau aggregates and the consequent formation of neurofibrillary tangles, have already begun to be explored on clinical trials, having the consideration that the last mentioned lesions, are

the responsible for most of the AD cognitive impairments. However, the only anti-tau therapies that have reached the human clinical trial stage are lithium, methylene blue and NAP (Nakashima et al., 2005; Medina et al., 2011; Navarrete et al., 2011).

3.3 Anti-tau miscellaneous strategies

A variety of intracellular proteins have been implicated in regulating both tau aggregation and folding, or potentially mediate clearance of the misfolded and aggregated tau protein. In this context, the ubiquitin ligase C-terminus of heat shock cognate70-interacting protein (CHIP) can polyubiquitinate tau and may play a crucial role in preventing accumulation of phospho-tau and NFTs (Staff et al., 2008). Studies suggest that modulation of CHIP and the ubiquitin proteasome system could alter tau pathology. Finally, heat shock proteins have been suggested as possible modifiers of tau pathology. HSP90 inhibitors that induce a heat shock response reduce tau phosphorylation at certain sites and are currently being tested in humans as anti-cancer agents (Dickey, 2007, reviewed in Fuentes and Catalan, 2011). Thus, on the basis of information that sequestration of tau results in loss of the normal microtubule-stabilizing function, normal microtubule-stabilizing agents have been tested in several tau mouse models. Paclitaxel administered to the tau mouse model, in a micellar formulation increased microtubule stability and rendered these polymers less dynamics. After three-months of paclitaxel treatment, transgenic mice showed rise on fast axonal transport and of the microtubules bundles in neuronal cells (Zhang et al., 2005). Authors also showed motor function improvement in comparison to the not-treated mice. Considering that paclitaxel does not cross hematoencephalic barrier, its action would be mediated through retrograde transport to spinal motoneurons among other possible explanations.

Moreover, there is another compound named to as NAP, a derivative octapeptide of a natural neurotrophic protein, which cross the blood brain barrier, and has shown to promote microtubules assembly (Matsuoka et al., 2008). Nasal administration for several months to elderly mice that had developed tau aggregations and A β deposition, resulted in reduction on tau phosphorylation and A β levels, with a cognitive function improvement (Matsuoka et al., 2008). A similar approach has also been employed in an animal model of tauopathy, anti-tau pathologically phosphorylated immunotherapy, where a diminished charge of NFT's was observed, and the presence of serum antibodies, without evidence of clinical deficits or encephalitis.

3.4 AD prevention: The emergence of natural products in the control of tau pathology

The development of small-molecules that inhibit the aggregation of tau appears as a valid therapeutic target for treatment of AD and as a consequence of the failure on drugs directed against the amyloid and the cumulative evidence in favor of tau hypothesis, current therapeutic strategies are aimed at searching for compounds that can either inhibit the formation of pathological tau filaments or disaggregate them. This hypothesis has been favored by current findings on the compound *methylthioninium chloride* (known as methylene blue), a previously described inhibitor of tau aggregation. A recent study with this compound in phase II clinical trial shows an 81% reduction of cognitive decline with the use of the compound as compared to placebo (Wischnik et al., 1996; Medina et al., 2011).

Compounds described for their anti-aggregating capacity in the formation of amyloid aggregates are the polyphenols. In this context, synthetic polyphenols have proved effectiveness in the inhibition of heparin-induced tau aggregation. Following this approach, the current therapeutic strategies are aimed to look for natural phytochemicals and polyphenolic extracts that can be able to either inhibit or disaggregate tau filament formation (Bastianetto et al., 2008; Kim et al., 2010; Cornejo et al., 2011). It has been suggested that naturally occurring phytochemicals have the potential to prevent AD based on their anti-amyloidogenic, anti-oxidative and anti-inflammatory properties. Despite this, there are few phytocomplexes emerging in order to prevent tau aggregation. Only a cinnamon extract and a grape seed polyphenolic extract have been described for this purpose (Peterson et al., 2009). Fulvic acid is one of the most interesting phytocomplex molecules (Goshal et al., 1990). This is a mixture of polyphenolic acid compounds resulting from the long-term microbial degradation of lignin, among other sources. It has several nutraceutical properties, and is one of the most interesting naturally-occurring phytochemicals for their extremely high antioxidant properties and apparent neuroprotective effect. For instance, the interaction of prion protein with fulvic acid and its inhibitory effect on the content of β -sheet structure and the formation of protein aggregates has been described in detail. Only a few polyphenolic molecules have emerged to prevent tau aggregation, and natural drugs targeting against tau have not been approved yet (Peterson et al., 2009; Cornejo et al., 2011). Fulvic acid, a humic substance, has several nutraceutical properties with potential activity to protect cognitive impairment. In this work we provide evidence to show that aggregation process of tau protein, forming paired helical filaments (PHFs) *in vitro*, is inhibited by fulvic acid affecting the length of fibrils and their morphology (Cornejo et al., 2011; Carrasco et al., unpublished results). In addition, we investigated whether fulvic acid is capable of disassembling preformed PHFs. We showed by mean of analysis of aggregation, atomic force microscopy (AFM) and electron microscopy that the fulvic acid is an active compound against pre formed fibrils affecting the whole structure by diminishing length of PHFs and probably acting at the hydrophobic level, as we observed by mean of atomic force techniques. Thus, fulvic acid is likely to provide a new insight to develop potential treatments for AD based on natural products. These observations allowed us to conclude that fulvic acid inhibits heparin-induced tau aggregation *in vitro*. On the other hand, fulvic acid promotes the disassembling of tau preformed fibrils. Thus, fulvic acid could provide a new insight for developing treatments based on natural products for AD (Cornejo et al., 2011; Farias et al, unpublished observations).

4. Conclusion

A major hallmark of AD is the presence of NFT's containing tau protein. The neuroimmunomodulation theory of AD together with the revitalized tau hypothesis on Alzheimer's pathogenesis provided a fundamental paradigm to understand this disease. This is very important considering that the slow progress in therapeutic approaches has been the result of a lack of a solid paradigm on this devastating disease. In this context, beside the anticholinesterases, most researchers have focused on drugs that affect the production of β -amyloid or disassembly of senile plaques, with very limited results. Therefore, tau became a major target for future therapeutic approaches. As tau clearly presents a potential therapeutic target in AD, there is a high rise on new drugs investigation

that would early interfere with the cascade that leads to tangles formation, and that might contribute to control neuronal degeneration and cognitive impairment. A critical step in the design of potential strategies to control AD is to find reliable biomarkers for its early diagnosis. Despite many efforts in this direction no markers to detect AD at the pre-symptomatic level are available. After the acceptance of tau/amyloid biomarker in the CSF, research is directed to establish a non-invasive marker technology. Innovative studies point to an *in vivo* PET technology based on neuroimaging of NFT's and tau filaments by using lansoprazole as a radiotracer, and blood biomarkers based on altered tau and amyloid variants in platelets.

Considering the scenario in which new synthesized drugs and novel therapeutic approaches have failed in their clinical trials, new hopes come from the search of natural products and phytocomplexes. Polyphenols have been described for their anti-aggregating capacity in the formation of amyloid aggregates. Most recently, synthetic polyphenols have proved effectiveness in the inhibition of heparin-induced tau aggregation. Following this approach, the current therapeutic strategies are aimed at looking for natural phytochemicals and polyphenolic extracts able to either inhibit or disaggregate tau filament formation. In addition, it has been suggested that naturally occurring phytocomplexes have the potential to prevent AD based on their neuroprotective, anti-oxidative and anti-inflammatory properties. Despite this, there are few natural complexes emerging in order to prevent tau aggregation. These include cinnamon and grape extracts, the anti-oxidant resveratrol, and recently fulvic acid. The combination of vitamins essential for brain health such as folic acid, vitamins B6 and B12 with natural compounds such as natural extracts from plants, flavones, flavonoids and the natural product *shilajit* offer an interesting approach toward the therapy of Alzheimer's disease.

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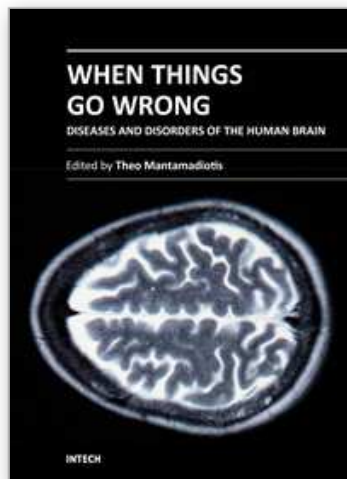
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In this book we have experts writing on various neuroscience topics ranging from mental illness, syndromes, compulsive disorders, brain cancer and advances in therapies and imaging techniques. Although diverse, the topics provide an overview of an array of diseases and their underlying causes, as well as advances in the treatment of these ailments. This book includes three chapters dedicated to neurodegenerative diseases, undoubtedly a group of diseases of huge socio-economic importance due to the number of people currently suffering from this type of disease but also the prediction of a huge increase in the number of people becoming afflicted. The book also includes a chapter on the molecular and cellular aspects of brain cancer, a disease which is still amongst the least treatable of cancers.

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