Alzheimer’s disease (AD) is the most common type of senile dementia. It affects predominantly people over 65 years of age, with the less prevalent early-onset AD commencing much earlier. As of September 2010, there were 35.6 million AD patients worldwide. This number is rapidly increasing and is predicted to reach 65.7 million by 2030 and 115.4 million by 2050. The prevalence (5% of people over 65 years-old and 20% of those over 80 years of age), duration and severity of AD pose both social and economic burden (70% of beds in hospitals, long stays) in all industrialized countries [1] where AD has become a major public health problem [2]. It is now largely recognized that AD begins decades before it can be currently diagnosed [3]. Diagnosis of AD is still ascertainable relatively late in the course of the disease, after significant neurodegeneration [4]. Identifying earlier and easily accessible markers of AD remains though of critical importance to disease management. The Alzheimer’s Association (USA) has recently highlighted the fact that “disclosing the diagnosis early in the disease process allows the individual to maximize quality of life and play an active role in planning for the future.” Disclosing the diagnosis after the dementia has advanced, in turn, “may no longer be meaningful to the affected individual.” (http://www.alz.org/professionals_and_researchers_diagnostic_disclosure.asp). The purpose of the present Special Issue “Bridging the Therapeutic Gap in Alzheimer’s Disease: Diagnose Early, Treat Effectively” in “Current Alzheimer’s Research” is to shed light on new candidates for the earlier diagnostic tools and therapeutic targets.

The current AD diagnosis is primarily based on the neuropsychological testing. Early clinical symptom is memory loss, manifested initially as minor distractions. This initial stage is designated as Subjective Cognitive Decline (SCD) and concerns the individuals who, in contrast to those with Mild Cognitive Impairment (MCI), display unimpaired performance on cognitive tests [5]. MCI, prodromal phase of AD which is now recognized as the clinically expressed, symptomatic AD [6], is the earliest stage at which the AD diagnosis can currently be established. In addition to evidence of hippocampal-type amnestic syndrome from cognitive testing, clinical diagnosis of AD requires additional support from neuroimaging methods and detection of biomarkers. The latter include monitoring concentrations of amyloid-beta peptides (notably of the Aβ42 / Aβ40 ratio ) as well as of total (T-Tau) and hyperphosphorylated tau (P-tau Thr181 & Thr231) proteins in the cerebrospinal fluid (CSF) [7]. Amyloid oligomers and plaques accumulation can also be imaged by 1 florbetapir F-18 (or alternative C-11 Pittsburgh compound B, PiB ligand) Positron Emission Tomography (PET) but nonlinear association between Aβ content in CSF and PET scan remains of concern [8]. Moreover, CSF sampling is relatively invasive and is not always well tolerated or feasible in a number of elderly patients. Non-invasive imaging methods such as Fluoro-2-deoxy-D-glucose (FDG)-PET, which gives insights into the brain metabolism [9], are of great clinical utility. Indeed, altered cerebral metabolism (both hyper- and hypo-metabolism) has been associated with different stages of AD [10]. Magnetic resonance imaging (MRI) at increasing field strength and resolution is another helpful, non-invasive approach for identification of the functional abnormalities. This powerful technology allows for local and global estimations of brain atrophy [11], used to complement PET-detected hippocampal and cortical neurodegeneration in the medial temporal lobe. Taken together, these recently achieved technological and conceptual achievements yielded a considerably improved certainty of AD diagnosis. These achievements have been translated into the the six gold-standard (“core feasible”) biomarkers. Half of them are CSF biomarkers such as: 1) Aβ42 / Aβ40 ratio; 2) T-Tau and 3) P-tau Thr181 & Thr231. The other half are neuroimaging measures: 4) hippocampal atrophy; 5) florbetapir F-18 or C-11 PiB retention; 6) (FDG)-PET as a functional measure of neurodegeneration. Combined use of these biomarkers allows for the first time to detect the pathophysiological abnormalities during the prodromal / MCI stage, though before overt clinical symptoms. Moreover, for the first time, these gold-standard criteria allow for differential diagnosis between AD and other types of dementia or cognitive impairment not only at the late- (i.e. AD-related dementia), but also at the much earlier stages of disease.
such as MCI due to AD, prodromal AD and preclinical AD [12].

Once AD is diagnosed, the therapeutic choice concerns the treatments that are only disease-modifying and offer relatively limited benefit. These issues have been largely discussed in a number of excellent recent reviews, including in this Journal and will be only overviewsed here to provide the current therapeutic framework. Three (rivastigmine, galantamine and donepezil) out of the four available drugs for the treatment of AD target the cholinergic system. The fourth drug, memantine, targets the glutamatergic system by blocking NMDA receptors. However, all of these therapeutic targets appear secondary and neither of them is currently thought to be causally involved in the development of AD.

In order to target closer the primary causes of AD, the focus has shifted to the amyloid cascade hypothesis of AD [13] and a number of clinical trials have been performed targeting amyloid. One strategy to combat amyloid-beta production was to inhibit γ-secretase, the second cleavage step in the processing of Amyloid Precursor Protein (APP) to Aβ. Initial γ-secretase inhibitors (GSIs) failed in clinical trials due to the worsening of cognitive performance and an increased incidence of skin cancer [14, 15]. Since γ-secretase has many substrates besides APP, including the notch receptor, a second generation of γ-secretase-targeting drugs was developed that spared notch signaling, called γ-secretase modulators (GSMs). Although initial GSIs failed in clinical trials, studies are ongoing to test new GSIs [15]. Targeting β-secretase is another strategy being studied to attenuate production of Aβ. A number of BACE1 inhibitors have failed in clinical trials due to safety concerns. One compound, MK-8931, has made it to phase 3, which is currently underway [15]. Notably, both GSIs and BACE1 inhibitors target the production of Aβ. However, it has been hypothesized that the sporadic form of AD may be caused by reduced clearance of Aβ [16]. In order to target clearance, antibodies against Aβ are thought to be a possible strategy to treat AD. Both active and passive immunization approaches have been considered to decrease the brain Aβ content and tested in clinical trials with some studies still ongoing [16, 17]. An early active immunization trial with the compound AN-1792 had to be terminated due to an increased risk of meningoencephalitis. However, post-mortem studies revealed a reduced number of amyloid plaques as well as a decrease in plaque-associated dystrophic neurites in the absence of documented cognitive improvement [17, 18]. Additional immunization protocols are currently being tested and a number have moved on to phase 2 and 3 clinical trials.

One possible reason for the failure of these trials is that they were started at a stage when the disease was already too far along and the neurodegeneration far too advanced for cognitive function to be rescued. Therapeutic strategies aimed at earlier intervention to prevent the development of the full-blown pathology may therefore stand a better chance at success. The focus has though been to shift from neuroprotection to studying earlier stages of AD to intervene as early as possible. Based on the encouraging observations from DIAN (Dominantly Inherited Alzheimer’s Network)- Therapeutic Trials Unit from testing solanezumab and gantenerumab, humanized monoclonal Aβ antibodies in individuals with mild-to-moderate AD [19], a secondary prevention trial has been initiated in presymptomatic carriers of autosomal dominant AD mutations [20]. The border has been moved a bit further with the ongoing trial using solanezumab in clinically asymptomatic older subjects with PET scans positive for brain Aβ deposits [20].

However, still only 20-50% of dementia cases are recognized and treated in the context of primary care and this proportion is certainly much greater in low- and middle-income countries. This “treatment gap” is due to the long latency between the beginning of AD pathology and the manifestation of the clinical symptoms, while disease remains undiagnosed and consequently untreated. Earlier diagnosis and timely intervention are critical to bridge the therapeutic gap in AD. However, bridging the AD therapeutic gap is no small feat. It requires an understanding of the fundamental mechanisms of memory formation and storage and a significant improvement of our diagnostic methods and treatment strategies. In parallel, a new point of view is emerging regarding the possibility that the long latency of AD may represent a window of opportunity to take action by applying non-medical intervention strategies (e.g. physical activity, cognitive exercises, social interactions, improved sleep and a healthy diet) to prevent or decelerate dementia. The practical consideration is what can be done with the current knowledge, right now, to improve the quality of life for AD patients and their caregivers. Can we already recommend pragmatic strategies that could be utilized until the advancement of science yields better therapeutics?

Our goal in this Special Issue is two-fold. We will first provide new insights into the selected candidates for biomarkers of the earliest stages of AD pathogenesis, namely those involved in synaptic function and the balance between excitatory and inhibitory neurotransmission. Although there are dozens of plausible candidates that may be involved in the earliest synaptic dysfunctions during the initial stages of AD, we will focus on those that have garnered widespread attention. Among the most promising targets for clinical translation are the inhibitory gamma aminobutyric acid (GABA)ergic neurotransmission and related neuronal circuit synchronization. Secondly, we will illustrate a few therapeutic strategies applicable during the asymptomatic stage of AD. In the latter context, we will discuss how early therapeutic interventions may not only slow down the disease progression but also reduce the current therapeutic gap.

Previous non-invasive electrophysiological in vivo exploration by electroretinogram (ERG) in patients at the advanced stages of AD has indicated impaired communication between the groups of retinal neurons [21] which likely reflects impaired neurotransmission. Synaptic dysfunctions yielding excitation/inhibition disbalance towards neuronal hyperexcitability is amongst the first detectable, AD-related functional alterations, at least in the vulnerable brain region such as hippocampus [22]. Reed and colleagues (Centre de Recherche des Cordeliers, France) therefore propose to shift towards the earlier stages of AD and explore retina by ERG during the asymptomatic period [23]. They suggest that, because retina is a part of the brain, the eye can provide a window to the brain and serve as the source of the earliest AD biomarkers [23]. Retina and brain have the common devel-
opment of the AD candidate, Canada), illustrates how physical activity and management of the neuronal networks synchronization, memory formation and storage of memory [27] are spared. This is a primordial observation since it provides the rationale for the deep brain stimulation (DBS) of projection circuits as a putative therapeutic approach towards rescuing the neuronal networks synchronization, memory formation, transfer and storage [30]. Mondragon-Rodriguez and colleagues (Universidad Nacional Autónoma de México Querétaro, México) discuss additional evidence in favor of using DBS as a therapeutic strategy for AD [31] on the basis of the recently reported increase in bilateral hippocampal volume in two AD patients after DBS application to fornix. They moreover propose that DBS maybe an interesting avenue to explore for an earlier treatment of AD since a significant amelioration has been observed in DBS-treated MCI patients [32]. Finally, based on their previous work demonstrating the tau-dependent impairment of synaptic activity, Mondragon-Rodriguez and colleagues stress the importance of considering the new therapeutic strategies targeting tau (in addition to Aβ) and briefly summarize the state of the art in this research domain [31]. The last contribution, by Maliszewska-Cyna and colleagues (Sunnybrook Research Institute, Canada), illustrates how physical activity and management glucose metabolism may normalize the AD-related neurotransmission impairments and subsequently improve brain function and cognitive performance [33]. More specifically, these authors discuss the beneficial effects on, not only GABAergic, but also glutamatergic, cholinergic, serotonin and opioid AD-associated impairments of neurotransmission [33]. The robust preventive and protective effects of physical activity on reducing the risk to develop AD or convert from MCI to AD, especially when applied prior to or during the early stages of AD, are also reviewed. These effects appear associated with a decrease of amyloid-related pathology which is particularly important when physical exercise, combined with low glucose consumption, are initiated at the early stages of AD pathogenesis. The authors conclude that such multimodal approach represents a simple, safe and cost-effective approach that can definitively be proposed during the asymptomatic stage to any individual at risk to develop AD, even before the clinical diagnosis.

In conclusion, bridging the therapeutic gap in AD requires identifying novel hypothesis-driven, as well as exploratory biochemical and electrophysiological targets that may serve both as earlier diagnostic biomarkers and targets to develop new, earlier applicable treatments. Bridging this gap is a major healthcare challenge and its success will have significant impact at two main levels. Globally, it will reduce the burden of AD in aging societies world-wide, given that aging remains the major risk factor to develop AD. Individually, bridging the therapeutic gap will improve the quality of life for each patient and their caregivers. In addition, a secondary benefit from discovering earlier diagnostic AD biomarkers is that it will offer the possibility to apply earlier even the existing treatments and thus likely improve their efficacy.

We therefore hope that this Special Issue will inspire and motivate others to engage and collaborate so as to identify early diagnostic markers and therapeutic interventions for AD, which will allow for treatment of AD at early, possibly asymptomatic, stages of the disease to achieve better treatment efficacy.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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