EDITORIAL FOREWORD

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'Alzheimer' Review Series

Still debating a cause and diagnostic criteria for Alzheimer's disease

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Guest Editor

We have all heard of Alzheimer's disease (AD) and of suffering from the burden of dementia, although the main cause of this illness described over a century ago remains hotly debated. There is no doubt that in the last decades a lot of progress has been achieved in understanding the pathogenic mechanisms of AD but no unifying theory was able to entirely explain the occurrence of neuropathological lesions and the progression of the disease yet [1]. Even though the AD classical hallmarks are the senile plaques and the neurofibrillary tangles, the amyloid cascade and the tau hyperphosphorylation theories have to be integrated with other research views in order to obtain a more complete pathogenic scenario. Inflammation and interleukins [2–4], metals [5], mitochondria-related oxidation processes [6], cholesterol rafts [7] and vascular factors [8–9] are only few such complementary directions of research. Moreover, in the core of the canonical theories of AD big switches happen from time to time. To pick one example, once believed to be only extracellular, β-amyloid has now convincingly been shown to accumulate intraneuronally as well [10]. Furthermore, new hypotheses about β-amyloid toxicity gained some experimental proof, for instance the one regarding the ion channel function [11]. Papers, at least on some of these subjects, were published in Journal of Cellular and Molecular Medicine in the last few years [12–14].

Development of transgenic mouse models in the past decade allowed researchers to answer specific questions about the disease development, but no model recapitulates the evolution and pathology of AD with fidelity. A fight for better models still goes on. Since the identification of first AD families and dis-covery of presenilins, genetics has made a big prom-ise to AD research. Characterization of the γ-secre-tase complex, which executes the final proteolytic cut of the precursor to yield the amyloid, is probably one important pay-off. Clinical trials using γ-secretase inhibitors will probably give answers to two questions. The amyloid cascade theory ultimate question comes first: is it enough to inhibit β-amyloid production to stop AD? The second question is linked to the physiological γ-secretase function [15]: will the inhibitors be safe enough?

Despite all diverging theoretical considerations, some symptomatic treatment has become available for AD. However, unlike Parkinson's disease, the neurotransmission failure theory did not give rise to drugs able to fully compensate the patient status, since acetylcholine esterase inhibitors were found to have significant but only modest and transitory effects [16]. Therefore, like in all other neurodegenerative diseases, the search for early biomarkers and disease modifying therapies is going on in AD as well [17–18]. From all therapeutic attempts, immunotherapy seems to be the closest to become applicable,

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since it effectively clears the pathology from the brains [2].

Apart from all debates in the field of AD pathogenesis, it is to be noted a recent paper from an important group of clinical AD researchers, claiming the need to change the AD diagnostic criteria, which should be based more on initial discreet symptoms and on already available biomarkers, like structural magnetic resonance imaging, molecular PET neuroimaging and cere-brospinal fluid analyses [19]. Even though pros and cons will continue on this crucial issue, a majority of experts in the field agrees with the requirement of an earlier diagnosis, which would theoretically allow a more efficient therapeutic intervention [20].

Considering all these recent and massive developments in the AD field, the Journal of Cellular and Molecular Medicine decided to initiate an *AD review series*, based on the integration of existing theories, on new emerging data in the field and on translation and validation of the currently existing knowledge. In this issue, A. Cedazo-Minguez from Karolinska Institute (Stockholm, Sweden) reviews recent data accumulated in the field of apolipoprotein E, the main lipid transporter in the central nervous system and the best established risk factor for sporadic AD [21]. In the future issues, the tau pathology in dementia [22] and the relationship between the β-amyloid excess and tau hyperphosphorylation [10] will be dis-cussed. By this series we would also like to create a fertile discussion about the impact of basic and pre-clinical research on clinical progress in diagnosing and treating AD.

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