PharmaCog

Advancing science and treatment of Alzheimer's Disease

June 2015

1. Executive summary – Year 5

1.1. Project rationale and overall objectives of the project

Following the failure of several late stage clinical studies in Alzheimer's disease (AD), there is now a critical need to predict the value of clinical assets early in development. To reduce the attrition rate early in clinical development and maintain future investment, a consensus regarding the predictive value of behavioural, neuroimaging, electrophysiological, cerebral spinal fluid (CSF) and blood markers is urgently required. The PharmaCog consortium is a unique opportunity for the pharmaceutical industry and academia to combine their collective knowledge, expertise and data in a pre-competitive partnership to deliver a unique translatable platform for drug development in AD. The immediate benefits of such an interaction include the harmonisation of best-practice protocols, the integration of latest technologies and the definition and translation of novel endpoints from preclinical to clinical, thereby increasing the successful development of new medicines for AD.

1.2. Overall deliverables of the project

Considering the huge financial investment required to progress drug candidates in AD, there is an urgent need for a consensus on the best possible design of Phase II studies to inform the decision to transition to Phase III. PharmaCog has made good progress on the main tenet of the project, i.e. the development of an innovative multidimensional matrix that combines advanced statistical methodology with systems biology, pharmacology, neuroanatomy, neurophysiology (EEG), biochemistry, functional imaging and neuropsychology. Parallel studies are being performed in animals, healthy volunteers and selected patient cohorts and are structured around three central themes: 1) development of translational and reversible 'challenge' models in support of efficacy studies; 2) development and validation of pharmacodynamic markers suitable to support the determination of efficacious exposure of drug; 3) development of predictive markers sensitive to early disease progression and development in humans and in animal models. The Pharmacog consortium will deliver a unique database on the effect of AD drugs on a matrix of biomarkers.

1.3. Summary of progress versus plan since last period

During Year 5, the project completed outstanding pre-clinical studies and either achieved the original goals or made good progress to an agreed endpoint despite significant changes in personnel within the consortium. The clinical studies will now terminate at the end of 2015 and have also progressed well. Important data is now beginning to emerge which will be communicated to both the scientific community and European public during 2015. In particular, the measured EEG in

challenge models and in AD patients is very encouraging and discussions with regulators will be scheduled to assess its impact on the future of drug discovery in AD.
Good progress has been made in advancing the pre-clinical and clinical cognitive challenge models within WP1 and WP2. EEG data analyses on the clinical SD study (WP1) has previously demonstrated an increase of current density values in widespread delta and theta sources and a decrease of current density values of posterior alpha 1 and alpha 2 sources in healthy volunteers who experienced a condition of resting state eyes closed (EEG data recorded by Marseille and Toulouse units). As such, the effects of the SD "challenge" on these cortical sources are reminiscent of those repeatedly reported in AD patients in the same conditions (Babiloni et al., Curr Alzheimer Res. 2014) and in subjects with mild cognitive impairment (MCI) and positivity to ABeta-42 of WP5. During 2014, this deterioration of cortical sources of resting state EEG rhythms is postulated to be only partially recovered by chronic administration of donepezil or memantine and by single administration of modafinil before SD. Since Donepezil and Memantine have moderate effects on patients' cognitive symptoms, it is not unexpected that they only partially recovery the effect of SD challenge on EEG biomarkers. This suggests that this model could be used as an experimental medicine model for evaluating drugs that modify neuronal networks prior to conducting studies in AD patients. Experimental models developed in WP2 are of interest for fundamental research and drug development but equally important are the consensus and data that have been generated in 2014. It highlighted some of the intrinsic issues such as variability and signal window with some of the challenge models. Whilst these issues may prevent their routine use in drug development, it is important data to ensure future proposals for such translational models consider these hurdles.

Conventional analyses of Event-Related Potentials in WP3 study (the multicentric clinical trial to identify a biomarker MATRIX sensitive to the pharmacodynamic effects in response to the administration of AChEI (donepezil) in healthy volunteers (WP3-001)) has shown that characteristics of the P300 component (amplitude, latency, area) are not influenced by donepezil. However, analyses of the induced activity of the EEG signal from oddball tasks (CSD-ERSPs and -ITCs) showed dynamic changes related to the effect of donepezil. A higher neuronal synchronization in the frontal regions was observed for rare stimuli, in auditory and visual tasks, suggesting an increase in the efficiency of attention processes, update information and in maintainance of working memory. Nevertheless, after 500 mg, administration of donepezil was associated with a reduction of neuronal synchronization in frontal and occipital regions, that could be related to loss of memory and attention efficiency and explain a limitation in the clinical effect of donepezil. WP4 has performed 2-deoxy-glucose uptake in rats using a compound with a different mechanism of action than the 4 gold standard compounds. While target engagement can be concluded, a pharmacodynamic read-out is more difficult to interpret.

WP5 has continued the assessments of follow-up: all T06 and T12 visits have been completed using a broad range of translational endpoints (MRI based on ADNI, EEG, cognition, biological samples, and novel biomarkers characterized by PharmaCog SMEs). The assessments of the later time-points have also started and T18 visits have almost been completed for the whole group. Following the approval earlier this year of a non-funded 12-month time extension for the clinical workpackages within the project we expect successful completion of the study. One of the partners, IHD, has recently decided to leave the Consortium due to financial constraints. The impact on WP5 is minimal since their assay to detect a combination of PKC/Abeta measurements, which was shown to discriminate AD

transgenic mice vs littermates, was not able to discriminate Abeta high/low MCI patients in WP5. Within WP6, the EEG group finished characterising the three lines of genetically engineered mice and showed translational EEG markers that reflect aging and/or amyloid pathology, i.e. there is a slowing down of EEG in all of the lines. This provides complementary data to changes in EEG seen in MCI patients that negatively correlate with CSF Abeta levels (WP5). The profiling of the mouse lemur during aging was completed. Whilst age-dependent behavioural changes were found, the best predictor of cognitive impairment was an increase of fasting glycaemia without modification of glucose tolerance. This very interesting finding is consistent with the increased risk of cognitive impairment and risk of Alzheimer' disease in diabetes in humans. The drug studies using amyloid lowering agents produced unexpected data regarding their effects on the functional consequences of lowering beta amyloid but nonetheless important data to consider when moving these agents forward to the clinic.

To enable the storage and the analysis of all results (neuropsychological assessment, EEG, imaging), we have developed a Pharmacog-Matrix based on X-NAT, that is an open-source informatics software platform. The primary functionality of XNAT is to provide a tool to build a place to store and control access to neuroimaging data but it also offers the following advantages: (1) user control, search and retrieval, and archiving capabilities; (2) research-based processing pipelines; (3) capability to link up with supercomputer processing power to shorten image processing time

PharmaCog has continued to make use of the existing dissemination channels provided by Alzheimer Europe. Building on the previous newsletters, events and publications have been updated on the website and it is now kept up to date by AlzEurope (who produce around 3500 magazines three times a year). In addition, AlzEurope will produce a 16-20 page colour publication dedicated to the PharmaCog project in the latter half of 2015. The aim of the report, which will be written in lay English, is to provide an overview of the "active" work packages and the main achievements and conclusions of the project. AE will use the bulk of its remaining funding from the project to produce and distribute the report. The report will be distributed to the same recipients of the Dementia in Europe magazine, whose circulation varies between 3,000 and 3,500. It will be sent to all the Members of the European Parliament and many high-level decision makers in the European Commission. PharmaCog has continued to develop effective external collaborations eg. with the IMI EMIF project and continued to engage with the EMA regarding biomarkers in AD.
PharmaCog has successfully articulated the main achievements through 13 oral presentations to international conferences, 6 scientific publications (including 4 original articles and 2 reviews) and 10 posters to the major neuroscience meetings including AAIC and SFN conferences.