IN ALZHEIMER MICE WE TRUST? – OR IS CLINICAL BIOMARKER TRIALS NEEDED FOR DRUG DEVELOPMENT?"

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Early diagnosis of AD will be of utmost importance if disease-arresting drugs, such as Aβ immunotherapy or secretase inhibitors, prove to be effective. Diagnostic tools would be especially valuable to allow a diagnosis of AD very early in the disease process, to enable the initiation of treatment before neurodegeneration is too severe and widespread. Intense research efforts have resulted in several promising biomarkers, including MRI measurements of atrophy, PET imaging of glucose metabolism and Aβ deposits, and CSF biomarkers.

Three CSF biomarkers have been developed that reflect the central pathogenic processes in AD, including the neuronal degeneration (total tau, T-tau), the deposition of Aβ in plaques (the 42 amino acid form of Aβ, Aβ42), and the phosphorylation of tau with formation of tangles (phospho tau, P-tau). These biomarkers have been evaluated in numerous studies, and have consistently been found to have high diagnostic accuracy for AD and for MCI cases that will progress to AD with dementia (i.e. have incipient AD).

Recently, standardized assays have also been developed to cover other aspects of the AD pathogenesis, including APP isoforms (sAPPα and sAPPβ) and BACE1 activity. These biomarkers are now being evaluated by several research groups.

There is also an ongoing search for new CSF biomarkers for AD using proteomics techniques. Using a combination of immunoprecipitation (IP) and mass spectrometry (MALDI-TOF-MS and FT-ICR-MS) to identify novel Aβ isoforms in human CSF, we found a series of shorter isoforms, including Aβ1-15, Aβ1-16 and Aβ1-17. In the first clinical study showed an increase in Aβ1-16, apart from the expected decrease in Aβ1-42. Further experiments show that these shorter Aβ isoforms are not formed by proteolytic degradation of longer Aβ isoforms, but instead represent a novel pathway for APP processing.

CSF biomarkers may also be valuable to identify and monitor the biochemical effect of new Aβ modulatory drug candidates directly in living AD patients in clinical trials. In drug development, genetically engineered (transgenic) mice that harbor mutated human *APP* or *presenilin* genes are commonly used to assess new drug candidates. A reduced Aβ burden (number of Aβ plaques) is taken as an indication of a positive treatment response. In a recent review (Blennow et al, Lancet 2006;368:387-403) we presented a table showing that as many as 46 different treatment strategies result in a substantial (50–90%) reduction in Aβ burden in these mice, a number which is now up to more than 100. Although some of these are promising drug candidates which now are in different stages of clinical trials, it is unlikely that all these 100 molecules can be used to treat patients with sporadic AD, and several have been found to lack an effect in large clinical trials. These data show that AD transgenic mice have a low predictive power for treatment efficacy in patients with sporadic AD, and calls for caution when translating data from mice to man.

To bridge the gap between animal studies and large clinical trials, and to help selecting the most promising drug candidates, short-term pilot studies using biomarker information to detect desired biochemical drug effects may be a valuable approach. Further, in a slowly progressive disorder like AD, evaluation of the clinical effect of a drug using rating scales requires large patient materials and extended treatment periods. This is particularly true for trials on drugs with the potential to slow down the degenerative process, but without any direct symptomatic effect.

As a proof of concept, studies on CSF acetylcholinesterase (AChE) during long-term treatment with the AChE inhibitors donepezil and galantamine show marked increase in CSF AChE, which differs between drugs depending on their mechanisms of action, show dose-dependency, and also correlate to the clinical outcome. These data show that CSF biomarker may be valuable tools in clinical trials.

At present, there are few studies on CSF biomarkers in treatment trials with amyloid-targeting drugs in man. Preliminary data show that acute administration of γ-secretase inhibitors result in the expected reduction in the primary biomarker CSF Aβ. Data from the interrupted phase IIa AN1792 Aβ immunotherapy trial show a reduction in the secondary biomarker CSF tau. A recently published study also shows a dose-dependent decrease in CSF Aβ42 in a trial on the anti-amyloid agent PBT2.

In trials with anti-amyloid drugs, a primary (or “specific”) biomarker is designed to monitor the central biochemical effect (such as Aβ42 and β-sAPP) of an Aβ modulatory drug, while a secondary (or “downstream”) biomarker (such as T-tau) monitor downstream effects such the neuronal degeneration. The intra-individual variation of these CSF biomarkers is remarkably low both during 6 and 24 months. This means that even minor changes in these biomarkers can be identified, which paves the way for their use in clinical trials.