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Biomarkers in AD drug development: can't live without 'em

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Our growing dependence on biomarkers in Alzheimer's disease (AD) therapeutic research is most unfortunate. The prospects for rapid advance would be better without them. That is, if we could directly observe AD in individuals at all stages of disease (as we can observe a rash or synovitis), drug evaluation could be based on reliable direct observation with minimal chance of error. If we could indirectly observe the disease using reliable measures (as we can track renal diseases with blood and urine tests), our situation would be nearly as good. But to our frustration, the available indirect measures of AD, such as cognitive performance tests, are highly error-prone. Spaghetti plots of the ADAScog- the cognitive assessment tool most widely used in AD therapeutic research (in mild cognitive impairment [MCI] and AD) are discouragingly messy (Figure 1a); to overcome the noise, we need either potent efficacy (not yet seen in this field), or large and costly trials (1). The low signal-to-noise issue is even more problematic for the development of disease-modifying interventions that aim to slow progression in the long-term rather than improve symptoms in the short-term. As shown in Figures 1 and 2, neuroimaging biomarkers such as hippocampal volume can show obvious advantages that translate into greater power to track disease progression.

A bigger problem still is that the optimal time for disease-modifying intervention may be in the pre-symptomatic stage of AD, when none of our cognitive or clinical measures are useful. It seems reasonable to expect that agents that target the underlying pathobiology of AD will have greater impact on disease progression before there is substantial irreversible functional loss. Biomarkers that track disease at very early stages, such as FDG-PET (2) and volumetric MRI (3), are essential, and we must work toward validation.

So biomarkers are indispensable in AD drug development. We had better understand them better; our history with AD biomarkers has not been particularly encouraging. More than once, we have been led astray by biomarker signals that failed to predict clinical response (4, 5). On the other hand, recent advances in the utilization of biomarkers to elucidate central nervous system pharmacodynamics seem very promising (6, 7).

Some biomarkers have particularly strong "face validity" as indicators of disease state potentially useful in drug development. As noted by Cummings, MRI volumes correlate with neuronal loss and tangle formation, and they track closely with disease progression, and are influenced by amyloid deposition even in the pre-symptomatic stage. FDG-PET shows metabolic activity that correlates with cognitive function, and is more efficient than cognitive measures as an indicator of disease progression. Despite the early difficulties with MRI as an outcome (eg discordant results with AN-1792 (8) and bapineuzumab (9)),

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improvement in acquisition and analysis methods, and movement to earlier disease stages, may increase the likelihood of eventual validation.

One aspect not touched on in Cummings' excellent review is the use of biomarkers in the analysis of noisy data. The problem displayed by the mess of spaghetti in figure one can be mitigated, at least a bit, by analysis plans that utilize biomarkers to reduce unexplained variance in the observed data. For example, incorporating a measure of disease stage, such as hippocampal volume, into analyses of cognitive data can improve power and decrease sample sizes by 10% (10).

Perhaps the most exciting recent development in AD biomarker research was the report that amyloid PIB-PET imaging can demonstrate a reduction in fibrillar amyloid with monoclonal antibody treatment in AD (11). This may be quite valuable in showing target engagement with small studies. Whether such activity is eventually shown to predict clinical benefit, or how big a signal is necessary to predict clinical benefit at different disease stages, of course remains to be established.

It is timely and valuable to have Cummings' authoritative review of biomarkers in AD drug development, covering definitions, roles in all stages of drug development and regulatory issues. The latter are particularly worrisome as we move toward studies in very early disease with biomarker outcomes. Fortunately, regulatory agencies such as the FDA and EMA are cognizant of the enormous clinical need for such studies, and the regulatory bar has a reasonable height. If investigators in the field can establish a "reasonable likelihood" that impact of a drug on an unvalidated biomarker will predict eventual clinical benefit, and will design and conduct reasonable post-marketing studies to confirm such benefit, biomarkers may be considered as surrogate endpoints. Conceivably, even if clinical benefit in AD dementia is weak, if such benefit is associated with a change in a biomarker, this may be cited in support of considering effect on that biomarker at a very early stage to be reasonably likely to predict later clinical benefit. Clinical methodology and a regulatory pathway allowing the development of disease-modifying treatments at the early asymptomatic stage of disease may be the past chance of blunting the enormous impact of the AD epidemic.

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Figure 1a.

Figure 1b.

Figure 1.

Figure 1a. Spaghetti plots of ADAScog13 in MCI. Rise in scores over two years is disorderly, with low signal to noise ratio. Figure 1b. In contrast, change in hippocampal volume is more linear and parallel.

Figure 2a.

Figure 2b.

Figure 2.

Figure 2a, Longitudinal change in ADAScog13 score in MCI. Figure 2b, longitudinal change in hippocampal volume in MCI, showing better signal (magnitude of change over time) to noise (size of error bars) ratio. All figures generated by Michael Donohue using data from the Alzheimer's Disease Neuroimaging Initiative (10), downloaded on May 28, 2010.