8th CONFERENCE
Clinical Trials on Alzheimer's Disease

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CTAD Congress secretariat

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EMERGING INTEREST IN NEUROINFLAMMATION AS A TREATMENT TARGET FOR ALZHEIMER'S DISEASE

Barcelona, Spain, November 6, 2015. Renewed interest in the role of neuroinflammation as a driver of Alzheimer's disease (AD), and its potential as a therapeutic target, took center stage at the 8th International Conference on Clinical Trials for Alzheimer's Disease (CTAD) today. According to Richard Margolin, M.D., of CereSpir, Inc., while neuroinflammation has long been suspected as an important player in the pathogenesis of AD, a number of negative studies of anti-inflammatory treatments in the early 2000s dampened enthusiasm.

"The field languished for at least a decade, until three years ago when intriguing findings about genetic risks for Alzheimer's disease clustering around the innate immune system began to emerge, pointing to defects driving pathology," said Margolin. Now, he said, "the study of neuroinflammation in AD is expanding by leaps and bounds." A detailed understanding of the innate immune system and its role in the disease is still evolving, but we now know that the phenotypes of the two key cells comprising the system –astrocytes and microglia – change in the course of the disease. This is dramatic for microglia, which are both factories for producing the chemical component of inflammation – cytokines – and machines designed to engulf injured or dead cells, debris and toxins through phagocytosis. In health, microglia are neuroprotective, demonstrating a robust phagocytic capacity. As AD progresses, however, they begin to spew large amounts of tissue-destructive cytokines and lose their ability to phagocytose dangerous substances such as amyloid fibrils.

Researchers in both academia and industry are investigating the reasons why the earlier trials failed. For example, were the molecular targets wrong, were the trial designs inappropriate, or were the drugs given too early or too late in the disease process?

At the same time the exciting findings about the innate immune system are beginning to be translated into treatment strategies. A handful of companies such as CereSpir are pursuing various appproaches. "One strategy is to reduce cytokine production," Margolin said, "but our approach is to pair that with enhancement of phagocytosis, because we think both are important and the combination could be synergistic.Preclinical studies showed beneficial effects for our drug CSP-1103 on both properties, and cytokine reductions were also seen in healthy volunteers and patients with mild cognitive impairment."

Designing optimal trials for the new generation of anti-inflammatory drugs will also be critical to their evaluation. "We'll need appropriate biomarkers and a good understanding of the link between proposed pharmacological mechanisms and clinical effects," said Margolin. "For trials, this means information about the population most likely to benefit, the appropriate treatment duration, and the best readouts." For example, some evidence suggests that the cellular and molecular features of neuroinflammation differ at different stages of disease, which may impact the timing when a neuroinflammation intervention is most likely to be effective.

Margolin said CereSpir is trying to learn from the older antiinflammatory trials in planning its first late-stage trial of CSP-1103, which the company will conduct in patients with mild cognitive impairment due to AD. "Our trial will use an adaptive design because that approach enables a certain degree of flexibility, for example, in determining the final sample size for a trial," he said. "Regulatorily acceptable adaptive designs are attractive in late-stage development because they can potentially help accelerate the process, which is very important, given the long treatment periods required at this time for disease-modifying AD drugs."

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