Alzheimer's Disease Autoantibodies, Vaccines and Therapeutic Antibodies Pipeline, 2011

Description:
This report presents a comprehensive review of autoantibodies, and pipeline vaccines and therapeutic antibodies, in Alzheimer's disease (AD). Currently, drug treatments for AD are dominated by cholinesterase inhibitors and an NMDA receptor antagonist. While these treatments give benefits to some patients, there is an urgent need for disease-modifying therapies. New drug classes are in the pipeline – however, significant growth in this field is in the development of vaccines and therapeutic antibodies.

Autoantibodies

Autoantibodies are antibodies that target an individual's own proteins. In some cases, the immune system may respond aberrantly to normal proteins, as seen in autoimmune diseases. The immune system may also respond to proteins that are changed (for example, by disease), resulting in them being recognised as 'non-self'. Autoantibodies are now attracting significant interest in the AD field, with more than twenty types identified and studied, notably relating to Abeta.

The presence of autoantibodies in AD patients is highly relevant to the current immunotherapeutic pipeline (vaccines and therapeutic antibodies) being developed to target this disease. As well as their diagnostic significance, autoantibodies may also give insights into new treatment strategies. The immune system is able to respond to antigens that are present at only very low levels in the body – therefore, the characterisation of AD-related antigens and their respective antibodies may allow detection of changes that occur early in the development of AD. New technologies, such as the peptoid combinatorial platform being developed by OPKO Health, offer new and more rapid advances in this field. This report discusses findings on AD-related autoantibodies in relation to the current pipeline of vaccines and therapeutic antibodies.

Immunotherapies

Immunotherapeutic drugs divide broadly into two groups: vaccines that elicit an active immune response (generating antibodies that target the disease), and therapeutic antibodies that bypass the immune system and directly target the disease (so-called passive immune treatment).

This report identifies 35 candidate immunotherapy treatments for AD in the development pipeline: 17 vaccines and 18 therapeutic antibodies. Overall, these include eight candidates (22%) in early research, nine (26%) in pre-clinical research, 10 (29%) at Phase I, five (14%) at Phase II and three (9%) at Phase III. Of the 35 vaccines and therapeutic antibodies, 18 (51%) are in clinical development (Phase I-III). These developments involve 30 companies: 22 primary developers and eight commercial partners (international pharmaceutical companies). Of these 30 companies, 16 are SMEs (small to medium sized enterprises) and 14 are major international companies.

The first vaccine candidate for AD was AN1792, developed by Elan. This vaccine molecule, which entered Phase I in 1999, was based on a synthetic form of Abeta1–42. This trial was soon followed by a Phase II study, involving 372 patients with mild-to-moderate AD. However, this trial was terminated in January 2002 when it found that ~6% of patients developed meningoencephalitis and leukoencephalopathy.

Significant efforts have been made to understand why AN1792 produced an adverse response in some patients, and to study other requirements such as the need to elicit an adequate immune response (i.e. antibody titre). Since 2002, research has identified other factors relevant to the development of AD-targeting immunotherapies. These include strategies to avoid the inflammatory T-Cell mediated immune response (Th1, linked to the adverse reactions seen in the case of AN1792) and, instead, to elicit an antibody-producing anti-inflammatory B-Cell response (Th2). Other areas include the targeting or avoidance of epitopes associated with the Th1 and Th2 response; different mechanistic approaches to the targeting of Abeta (e.g. soluble Abeta, conformationally modified forms, Abeta fibrils, plaque); the selective targeting of the N-terminal or C-terminal ends of Abeta; and delivery and transport across the blood brain barrier. This research, together with innovation in the discovery, development and early testing of new molecules, has resulted in the development of 35 candidate immunotherapies seen in the current pipeline, most of which are differentiated by design, production or underlying Abeta targeting characteristics.
This report gives a comprehensive overview of developments in this field and, as part of this analysis, provides a summary of the research background to each developmental candidate and associated companies. Alongside the commercial pipeline, this report reviews current AD-targeted research (by academic research groups) relevant to vaccines and antibodies. These advances provide a source of new opportunities to address primary developmental challenges in this field.

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Three vaccines, Phases I, I and III
Vaccine, Research stage; Antibody, Research stage
Two vaccines, both Preclinical stage
Antibody, Research stage
Antibody, Phase III
Vaccine, Phase II
Antibody, Preclinical stage
Two antibodies, Phase III and Preclinical stage; vaccine, Phase II
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