DUAL ACTION AGAINST ALZHEIMER'S IN ALZSTATIN

STOCKHOLM, Sweden (Nyhetsbyrån Direkt) The research company Alzecure Pharma, which are focusing on projects in Alzheimer's disease, sees the Alzstatin platform as having the potential to counteract Alzheimer's disease in two different ways. Firstly, by reducing the production of a harmful protein, and secondly by changing the ratio of certain specific amyloid beta (Aβ) peptides in the brain.

"By having this dual effect, you can reduce the production of the harmful protein while increasing the amount of the protective protein", says Martin Jönsson to Nyhetsbyrån Direkt.

In preclinical studies, Alzecure has seen evidence that the company's drug candidates within the Alzstatin platform can change the ratio of amyloid beta (Aβ) peptides in the brain.

The peptide Aβ42 is said to be an essential part of the build-up of increasingly larger structures in the brain that over time form amyloid plaques, which according to the amyloid hypothesis, is a cause of the development of Alzheimer's disease.

While the drug candidates in the Alzstatin platform reduce the amount of the harmful Aβ42, they also increase the protective forms of amyloid beta, namely Aβ37 and Aβ38. The numbers at the end indicate how many amino acids the specific amyloid beta peptide contains. Thus, the disease-causing Aβ42 is a 42 amino acid long variant.

The Alzstatin platform currently consists of two drug candidates - ACD679 and ACD680. Both of them belong to the gamma secretase modulator class of drugs, which affect the cleavage of the harmful Aβ42 into shorter forms.

Unlike the disease-modifying drugs Leqembi (lecanemab) from Bioarctic, with its partner Eisai, and donanemab from Eli Lilly, the drug candidates ACD679 and ACD680 are small molecules. Another difference concerns the mechanism of action between Leqembi and donanemab compared to the Alzstatin compounds. While Leqembi and donanemab target protofibrils and plaques, structures that arise later in the process of plaque formation in the brain, the Alzstatin projects target the actual building block of the plaques, namely Aβ42, occurring much earlier in the chain of events. In addition to this mechanism, an altered ratio of Aβ37, Aβ38 to Aβ42 may also reduce the ability of Aβ42 to aggregate into increasingly larger structures.

Several scientific papers published in recent years support the use of gamma secretase modulators in Alzheimer's disease and the findings on the role of Aβ42, Aβ37 and Aβ38 in the disease.

An article published in the scientific journal Neurology in 2022, with Professor Oskar Hansson at the University of Lund as one of the co-authors, demonstrates a connection between higher levels of Aβ38 from spinal fluid samples and a lower risk of changes linked to Alzheimer's disease. The findings of the study suggest that gamma secretase modulators may be an effective option in the treatment of Alzheimer's disease.

Another article published in the scientific journal Alzheimer's & Dementia in November 2021 describes the relationship between the peptides Aβ37/42 as a biomarker for Alzheimer's disease.

Another article in Chemical Science in 2022 highlights how three Aβ peptides individually and in combination prevent the aggregation of Aβ42, which is said to be responsible for the build-up of plaques in the brain. The co-author of this article is a well-known name in the field of Alzheimer's disease, namely Professor Henrik Zetterberg, but also Professor Sara Linse at the University of Lund. The article focuses on variants Aβ 37, 38 and 40. The results show that the three shorter variants of amyloid-beta, individually and in combination, prevent the build-up of Aβ42.

Larger molecules targeting the protein tau, known as tau antibodies, must not only cross the blood-brain barrier but also enter the cell membrane, which according to Martin Jönsson "can be a challenge". Since tau spreads later in the course of Alzheimer's disease, one way of treating the disease in the future may be to enter an earlier phase of the disease. This is Alzecure Pharma's plan for the Alzstatin platform.

Among the advantages of small molecules, Alzecure's management sees them as more cost-effective than larger biologics. In addition, small molecules are suitable for tablet formulations that could be taken at home.

Another positive aspect is that, unlike antibodies, the Alzstatin platform is not expected to come with side effects in the form of brain swelling (oedema) and brain microbleeds (ARIA). In order to avoid experiencing the above-mentioned side effects with the new disease-modifying therapies coming to the market (Leqembi and donanemab), brain imaging tests such as MRI and PET scans are used. However, the Alzstatin platform is not expected to involve such costly examinations.

Alzecure sees several ways forward with the Alzstatin platform. On the one hand, the company's drug candidates could be used as maintenance treatment after disease-modifying drugs such as Leqembi (lecanemab) and donanemab have cleared existing plaques. There would also be an opportunity to develop a combination therapy with a so-called monoclonal antibody for the treatment of early Alzheimer's disease. A third area of use could be preventive treatment of the disease based on, for example, genetic risk factors such as ApoE4 or based on biomarkers. Preventive treatments could also be evaluated in familial forms of the disease and in people with Down’s syndrome.

According to Martin Jönsson, there are few known gamma secretase modulator programs available. Swiss pharmaceutical giant Roche is expected to present phase 1 results for its drug candidate RG6289, which belongs to the gamma secretase modulator class of drugs, at the CTAD Alzheimer's scientific congress, which will take place between October 24 and 27, 2023. This presentation will be thoroughly followed by Alzecure's management, who hope that Roche may pave the way with its project.

Given positive results in phase 1 with RG6289, Roche would enter phase 2 for the first time with the second generation gamma secretase modulators.

Alzecure also conducts research within another platform for Alzheimer's, namely Neurorestore. The platform includes the drug candidates ACD856 and ACD 857. Together with the Alzstatin platform, Martin Jönsson believes that Alzecure covers the treatment from early to late stages of Alzheimer's disease.

Within an hour, another presentation of interest to Alzecure will be held during the Alzheimer's Congress CTAD in October 2023. The second presentation is about the Japanese company Eisai's drug candidate E2511, which will be of interest to the Neurorestore platform.

The study that Eisai will present is a phase 1 study with a compound in the TrkA-PAM class of drugs, which has demonstrated disease-modifying properties in neurodegenerative diseases. Eisai's drug candidate targets the TrkA receptor and affects nerve growth factors (NGF), which are small proteins. According to research referred to by Eisai, activation of NGF signalling via TrkA has the potential to be a disease-modifying treatment. This is because it is expected to restore the function and connectivity of certain nerve cells in certain neurodegenerative diseases such as Alzheimer's disease.

Alzecure's drug candidate ACD856 targets not only NGF signalling via the TrkA receptor, but also the TrkB receptor and the signalling protein BDNF (Brain-derived neurotrophic factor). BDNF has been shown to influence neuronal health and lower levels of BDNF have been associated with faster cognitive decline and disease progression in Alzheimer's disease. By potentially being able to affect both cognition and nerve cell function and survival via two receptors instead of Eisai's drug candidate E2511, which only targets one receptor, Alzecure believes that they have a clear differentiation with their compound.

During the CTAD congress, Alzecure will present preclinical results for the drug candidate ACD856, from the Neurorestore platform, which will demonstrate the drug candidate's potential disease-modifying effect.

"It can potentially display additional disease-modifying properties", says Martin Jönsson, stating that the study shows why it is an advantage to target both TrkA and TrkB receptors.

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