CIC biomaGUNE is developing image biomarkers to study new treatments for Alzheimer's disease

CIC biomaGUNE is exploring new tools for researching the pathophysiology of the second leading cause of death among those aged 70 years and over

It has developed a PET tracer for the *in vivo* detection and longitudinal monitoring of the evolution of the butyrylcholinesterase enzyme in the brains of mice with Alzheimer's disease

Donostia-San Sebastián, 26 May, 2021. Alzheimer's disease is the most common cause of dementia. It is one of the principal causes of death worldwide and the second most common one among the over 70s, affecting 13 million people all over the planet. Currently, there is no effective treatment for Alzheimer's available on the market, nor is there any reliable option for the early diagnosis of the disease. The diagnosis is therefore mainly based on clinical symptoms, which occur at later stages of the disease, when it is much too late for successful medical intervention. There is therefore an urgent need to identify new disease biomarkers to enable longitudinal and non-invasive monitoring of disease progression as the first step towards designing new treatment, diagnostic and theragnostic strategies based on the study of the pathophysiology of the disease and the mechanisms involved in its progression. The aim is also to develop new tools for assessing treatment response.

A series of processes characteristic of the disease have been described. Many of these processes begin decades before the onset of clinical symptoms, constituting a unique opportunity for the early diagnosis of the disease and the eventual evaluation of response to treatment. For example, increased activity of butyrylcholinesterase has been observed in the brains of patients with Alzheimer's and in animal models of the disease, suggesting that this enzyme may be a potential biomarker. 'When the brain starts to deteriorate as a result of the disease, butyrylcholinesterase levels increase in comparison with healthy brains, indicating that this enzyme may be a biomarker for the progression of the disease', explains Jordi Llop, a researcher working at CIC biomaGUNE.

One of the strategic areas identified by CIC biomaGUNE's Radiochemistry and Nuclear Imaging Laboratory is the development of new image biomarkers for Alzheimer's disease. The researchers working on the project have managed to label a potent selective inhibitor of butyrylcholinesterase using carbon-11, enabling them to monitor the biodistribution and longitudinal evolution of the abundance of this enzyme in the brains of mouse models for Alzheimer's disease, using positron emission tomography (PET), a technique which is highly sensitive with good spatiotemporal resolution. 'This is the first time a PET tracer has been developed to detect, *in vivo*, the presence or over-expression of this enzyme in a diseased brain. The fact that we have been able to demonstrate its effectiveness in a longitudinal study is also

important, since it traces the evolution of the changes that occur in this enzyme level throughout the course of the animal's life' states Llop, the director of the laboratory.

A tool for continued exploration

According to Llop, it is possible that this tool may not end up being used for the purposes of early detection, since 'it is a compound labelled with carbon-11, an isotope with a very short half-life that is not particularly useful in the healthcare environment. However, merely having a tool that enables us to determine the amount of this enzyme in the brain of animal models over time will enable better characterisations and allow us to pinpoint the exact moment at which it starts to over-express, so we can then continue searching for the reason why'.

Llop views the results as a tool for characterising models or developing new drugs: 'it may, for example, help us develop therapies focused on inhibiting butyrylcholinesterase, in order to study, from a longitudinal perspective, whether or not the treatment is effective. Another possible field of application may be pathophysiological research into what happens during the development of the disease'.

Other studies are currently being carried out with other animal models: 'being able to demonstrate that the technique works in other models would be a significant step forward in terms of being able to use it in clinical practice–not in patient care, but possibly within the framework of a clinical trial'. Nevertheless, Llop warns that studies related to neurodegenerative disorders take a long time to complete, since they cover the entire development of the disease. The team does not therefore expect to find further results for around two years. Llop also highlights the importance of studying how butyrylcholinesterase levels evolve over time in Alzheimer's patients. He remarks that it is necessary to test possible therapies and claims that, even though the results of his team's study are promising, there is still much work to be done.

The study was carried out in collaboration with the University of Ljubljana, the Achucarro Basque Centre for Neuroscience and the Department of Nuclear Medicine at the University Hospital of Araba, among others. 'We have made the most of the knowledge and strengths of various Basque institutions to conduct a very ambitious and multidisciplinary project' concludes Llop.

About CIC biomaGUNE

The Cooperative Biomaterials Research Centre, CIC biomaGUNE, is a member of the Basque Research and Technology Alliance (BRTA) and carries out cutting-edge research on the interface between Chemistry, Biology and Physics, with special focus on the study of the properties of biological nanostructures at a molecular scale, and their biomedical applications. In 2018 it was officially designated a 'María de Maeztu' Unit of Excellence for complying with certain requisites denoting outstanding quality in the field of research at a worldwide level, coupled with a high level of impact and a high degree of competitiveness.

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