BioClotAD

Development of a neuroimaging biomarker to identify the pro-coagulant state in Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia with hallmarks such as amyloid plaques, tau tangles, inflammation, neurodegeneration, cerebral atrophy and vascular pathology. Therapeutic approaches to treat AD are failing and this is partially due to the fact that AD is a multifactorial disease. Efforts must be focused on the development of multidrug personalized therapies targeting the different mechanisms contributing to an individual's pathology instead of the "one target, one treatment" approach that has not been successful thus far. The success of such a combinatorial therapeutic approach relies on the development of proper diagnostic tools to identify the different factors contributing to disease development.

Part of the vascular component present in AD is a profound cerebral hypoperfusion that, interestingly, is also present during mild cognitive impairment and even in cognitively normal individuals at high-risk for AD. This decrease in cerebral blood flow is partially due to the chronic dysregulation of hemostasis present in AD. Increasing evidence shows that a pro-thrombotic milieu is present in AD favoring the formation and persistence of fibrin clots and contributing to disease onset and progression. Interestingly, long-term treatment with the direct thrombin inhibitor dabigatran inhibits the deposition of cerebral fibrin and preserves cognition, cerebral perfusion, and blood brain barrier function (BBB), and ameliorates neuroinflammation and amyloid deposition in AD mice. These results open an exciting field for future investigation on whether the use of already approved direct oral anticoagulants might be of therapeutic value in AD. However, as part of the multifactoriality of this disorder, this pro-coagulant state is not present in 100% of the AD patients and therefore those AD patients that would benefit from this type of treatment need to be carefully identified.

The present joint proposal aims at developing a novel non-invasive imaging biomarker to identify this pro-coagulant state in AD. For that purpose, the research Consortium gathered to carry out this project comprises experts in neuroscience, biochemistry, preclinical imaging, radiochemistry and translational approaches, and all groups work at cutting-edge European institutions. We will use molecular biology approaches in combination with molecular imaging tools to develop a suitable imaging probe to detect the fibrin clots in the vessels but also inside the AD brain parenchyma. Such a probe will be an instrumental biomarker to 1) better pre-select those AD patients with a pro-coagulant state that will be suitable for clinical trials/treatment with anti-thrombotics; and 2) avoid the exposure of AD patients with no pro-thrombotic state to anticoagulants. Although dabigatran is one of the oral direct anticoagulants with low risk of intracranial bleeding, the risk is still present and should not be entirely neglected. Hence, oral anticoagulation should be carefully evaluated on an individual basis to ensure its use outweighs any bleeding risk.

AD is a multifactorial disease. This stresses the importance of developing individualized diagnostic and therapeutic strategies to target the different mechanisms contributing to pathology. One of the mechanisms worth diagnosing and treating in AD is the pro-coagulant state.

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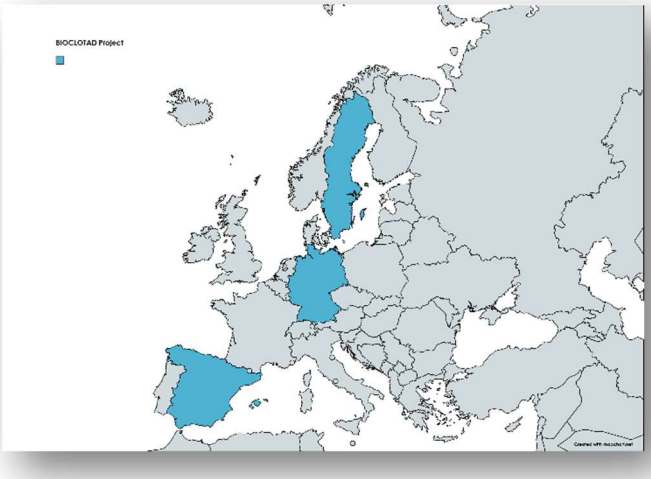

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