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AC Immune clears first hurdle for α-synuclein PET tracer

With AD/PD 2022 readout, AC Immune achieves non-invasive imaging of α-synuclein in human brains with selective PET tracer

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With early proof of concept that its α-synuclein PET tracer can selectively detect toxic plaques in multisystem atrophy patients, AC Immune brings the field a step closer to non-invasively diagnosing diseases involving α-synuclein, and developing disease-modifying therapies.

At the AD/PD 2022 International Conference on Friday, AC Immune S.A. (NASDAQ:ACIU) reported that AC-12589, a PET tracer the company designed to selectively bind the toxic α-synuclein that aggregates in the brains of patients with certain neurodegenerative diseases, could be used to identify patients with the rare neurodegenerative disease multisystem atrophy (MSA).

In a study of 25 participants, the PET tracer differentiated patients with MSA from healthy controls and from patients with Parkinson's disease and dementia with Lewy bodies (DLB) — other diseases that involve α-synuclein but have different patterns of synuclein α-aggregation in the brain.

The data are the first example of non-invasive imaging of α-synuclein in the human brain — an advance that could lead to the kinds of improvements in diagnosis, progression monitoring and drug development that β-amyloid PET tracers are bringing to Alzheimer's disease.

MSA, Parkinson's disease and other α-synucleinopathies are now diagnosed and monitored with blood and cerebrospinal fluid assays, both of which measure the soluble form of the protein and not the toxic form that aggregates in the brain. It isn't clear how well levels of soluble α-synuclein correlate with brain aggregates. The other problem with the blood test is that it measures α-synuclein from other tissues, not just the brain.

A selective imaging agent would solve the problems, but designing one has been challenging. There's a low abundance of α-synuclein in the brain, and its aggregates are similar in structure to the more abundant β-amyloid and tau aggregates, meaning tracers need to have particularly high affinity and selectivity.

AC Immune has cleared the first hurdles with AC-12589, showing it can detect α-synucleinin the brain, but it isn't yet clear whether this agent will be able to definitively diagnose Parkinson's disease.

AC Immune told BioCentury in a statement that accumulation of α-synuclein was most distinctive in MSA patients, where levels of pathological α-synuclein are highest.

"While PD and LBD patients were differentiated from normal volunteers, it is not yet clear if we can use ACI-12589 to positively differentiate them. The question is the focus of ongoing investigations," the company said.

And while the company had expected to see a clear signal in MSA because of the high level of pathological protein, it's also possible that alternative protein conformations across the diseases could contribute to the lower signal in Parkinson's and LBD.

For MSA, the company's next steps include human dosimetry studies and manufacturing activities to support larger longitudinal studies.

"We expect that as we develop ACI-12598 for MSA, we will gain valuable learnings that may allow for future applications in PD or LBD, either with ACI-12589 or with next-generation a-syn PET tracers," the company said.

AC Immune, which has a pipeline of vaccine, antibody and small molecule clinical candidates for Alzheimer's disease, also has α-synuclein vaccine ACI-7104 in Phase II development for Parkinson's disease and other α-synucleinopathies.

At least 12 other companies have therapies targeting α-synuclein in clinical development, any of which could benefit from an α-synuclein PET tracer.