Research Project Proposal

The ac-K174 Tau as a biomarker for the early-diagnosis of Alzheimer Disease and a *device* for its detection

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INTRODUCTION

The Alzheimer's Disease (AD) is the most common form of dementia, characterized by memory loss, cognitive decline and neurodegeneration. It is caused principally by the accumulation of amyloid beta (Aß) peptide and Tau protein. Affecting over 35 million people worldwide, it is of an increased need the development of an early diagnostic based on the discovery of early, affordable and available non-invasive biomarkers (1). Recent evidence has demonstrated that the acetylation on the lysine 174 of Tau is an early critical pathological change to soluble Tau realized at the early stages in AD brains (Braak I-II), which leads to Tau accumulation and toxicity (2). However, the use of technologies with high sensibility will be required for its detection as this biomarker is expected to appear in low concentrations. For this reason, the current research project aims to validate the ac-K174 Tau as an early-diagnosis biomarker and to demonstrate its detection with a *device* proposal, as it could serve as a reliable biomarker for the detection of AD during early stages.

HYPOTHESIS

Can the acetylation of the lysine residue 174 of Tau protein be a biomarker for the early diagnosis of Alzheimer's Disease?

OBJECTIVES

Validation of ac-K174 Tau as an early-diagnosis AD biomarker.

- To establish the detectability of the ac-K174 Tau biomarker.
- Temporal diagnostic of AD development for determining ac-K174 Tau appearance in AD.
- Determination of normal and pathologic levels of the ac-K174 Tau.

Device design proposal for ac-K174 Tau detection.

PROJECT TIMELINE

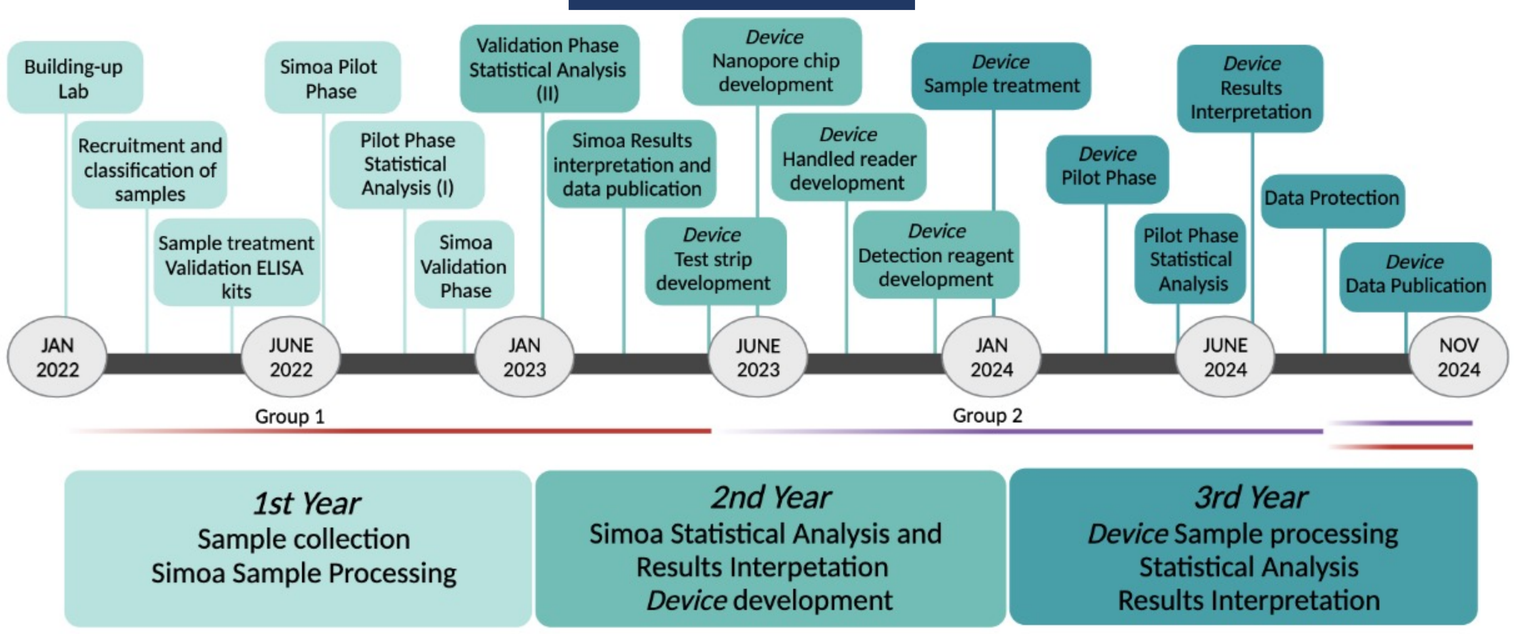

Figure 1: Representative scheme of the three-year ac-K174 Tau project workflow. The technical staff involved is divided in two groups: Group 1 (Simoa tasks) and Group 2 (*Device* development tasks).

ac-K174 SIMOA VALIDATION AND DETECTION

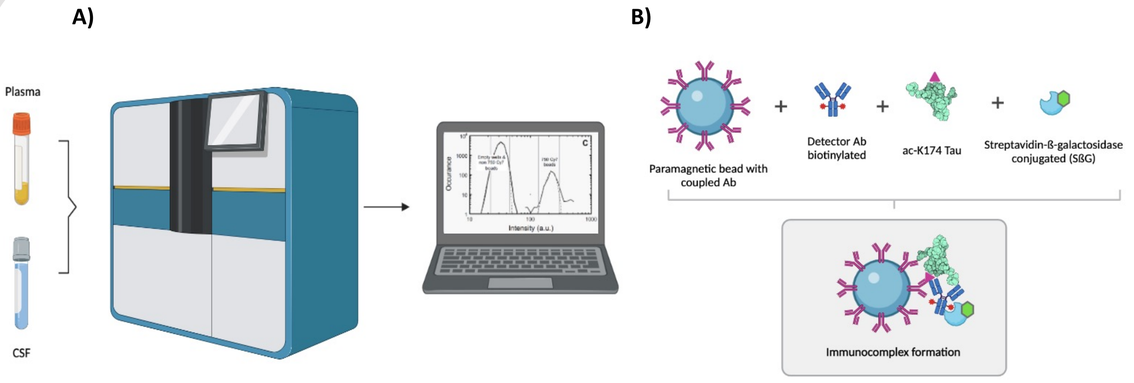

Figure 2: A) Schematical representation of the procedure for the detection of ac-K174 in plasma and cerebrospinal fluid (CSF) during the pilot and validation phase. The results recorded by Simoa HD-1 analyzer will shown in an intensity histogram (3) and later be analyzed with *GraphPad Prism* and *R software*. B) ELISA ac-K174 Tau kit.

DEVICE PROPOSAL

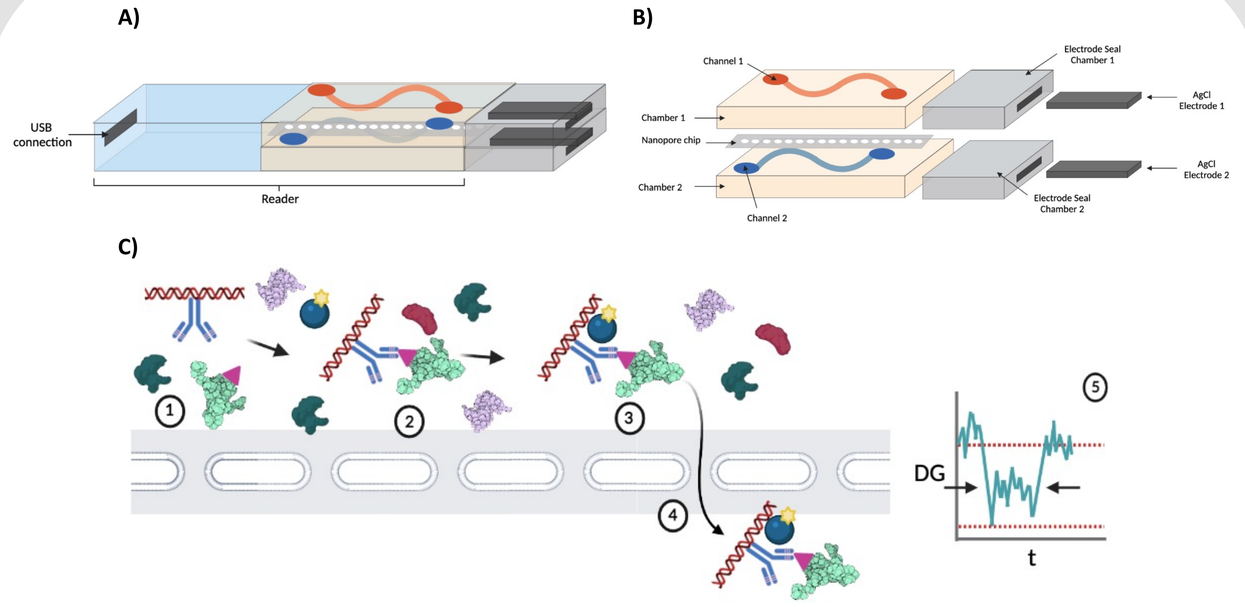

Figure 3: Schematics of the assembled test strip A) and exploded with the reader B) *device* drawings. C) *Device* channel 1; dsDNA scaffold, AC312 Ab, ac-K174 Tau floating on the plasma, 2; Specifical binding to ac-K174, 3; Paramagnetic bead union and immunocomplex formation, 4; Voltage supply and immunocomplex driving through nanopore into the opposing chamber, 5; Temporary shift in the ionic current recorded as a detectable signal.

EXPECTED RESULTS

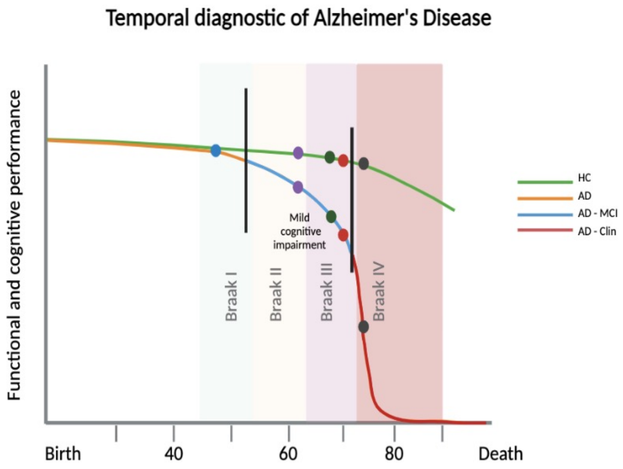

Figure 4: Graphical representation of the expected biomarker profile during healthy conditions and AD progression. Green line (Healthy control), Orange line (AD pathology), Blue line (MCI stage), Red line (AD clinically diagnosed). Blue circle (ac-K174), Purple circles (Aß40/Aß42), Green circles (Tau), Red circles ($pTau_{181}$) and Brown circles (Nfl).

CONCLUSIONS

The establishment of the ac-K174 Tau biomarker as a non-invasive early-stage AD biomarker and the *device* could assist in the routine clinical practice:

- Improving the AD diagnosis at early stages facilitating the implementation of available or potential treatments.
- Allowing the affected individuals to decide about important matters before becoming demented.
- Providing time before the symptoms develop and identifying which individuals should be evaluated for initiation of treatment in a more rapid and cheaper way than with current technologies.

3-YEAR RESEARCH PROJECT FINAL BUDGET

427,938 $

DISSEMINATION PLAN

2 *Open Access* Publications

2 Conferences & Congresses: 2023 AAIC and 2024 AP/DP

Achievements and Knowledge Donatives: Alzheimer's Association

REFERENCES

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2. Min SW, Chen X, Tracy TE, Li Y, Zhou Y, Wang C, et al. Critical role of acetylation in tau-mediated neurodegeneration and cognitive deficits. Nat Med [Internet]. 2015 Oct 1 [cited 2021 Apr 24];21(10):1154–62. Available from: https://www.nature.com/articles/nm.3951
3. Morin TJ, McKenna WL, Shropshire TD, Wride DA, Deschamps JD, Liu X, et al. A handheld platform for target protein detection and quantification using disposable nanopore strips. Sci Rep [Internet]. 2018 Oct 4 [cited 2021 Apr 24];8(1):1–12. Available from: https://www.nature.com/articles/s41598-018-33086-7