Co-crystallization strategies to supplement the structure of tau protein filaments by X-ray crystallography

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Alzheimer's disease (AD) is a neurodegenerative disorder, which represents the most common type of dementia. The main hallmark of AD is the accumulation of aggregated tau protein filaments in the cerebral cortex. The first atomic structures of AD filaments were solved by cryo-electron microscopy in 2017 and 2018, showing residues G304-E380 (Fig. 1) [1,2]. However, it is known that the PHF core is longer and consists of residues I297-E391 [3], so, there are still unresolved parts in the structure of the core. In our work, we aim to solve these missing parts by X-ray crystallography, using specific recombinant antibodies. The monoclonal antibodies MN423 and DC11 recognize a conformational epitope on the PHF core (Fig. 1A) [4,5]. The idea of crystallizing antibody-tau complexes is based on the hypothesis that the specific antibody could induce folding of the tau protein to mimic the folding in pathology [6]. In our work, conformational antibodies MN423 and DC11 and other two helper antibodies DC8E8 and DC25 were used to co-crystallize with recombinant tau and form binary and ternary antibody-tau complexes. So far, we have crystallized eight different complexes, obtained crystals from six of them and diffraction data collected at the synchrotron sources of the X-ray radiation (DESY, Hamburg and PSI, Villigen). The crystals diffracted to 1.5-3 Å resolution.

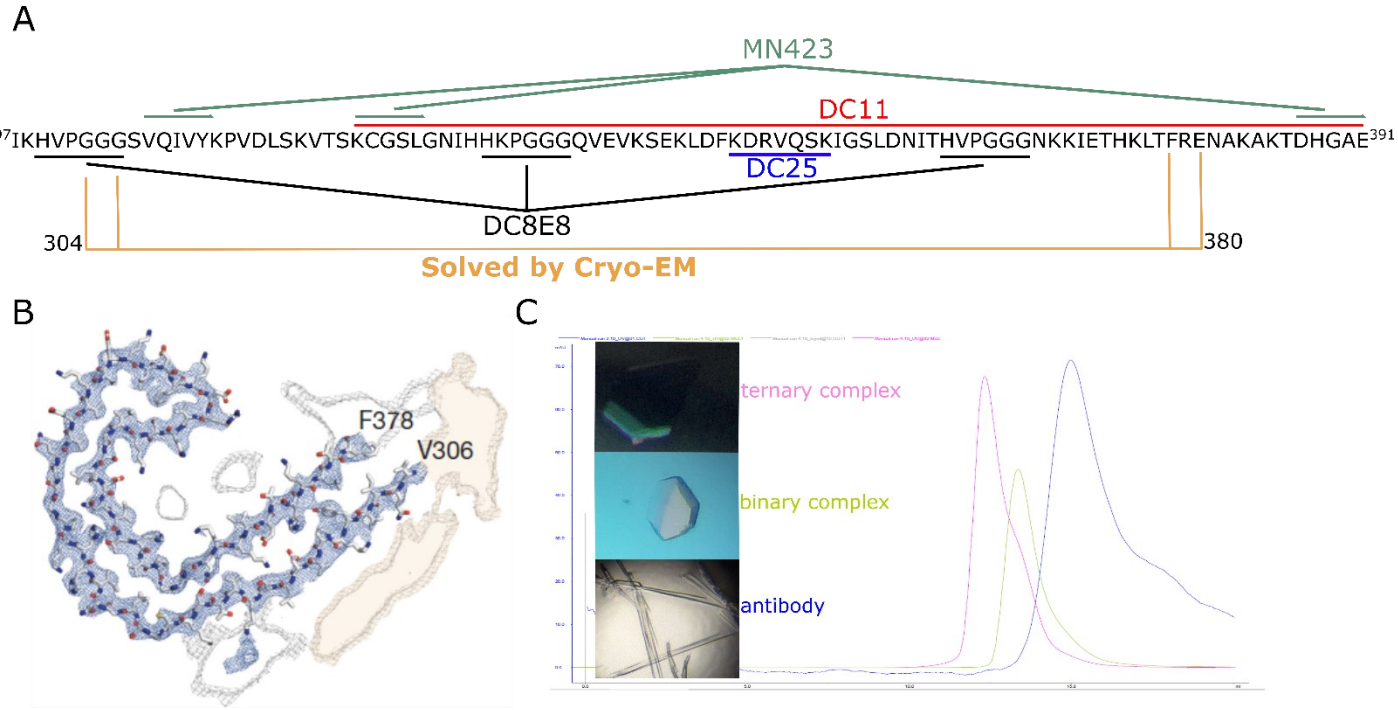

Figure 1. (A) Epitopes of the specific antibodies used for the co-crystallization with recombinant tau fragments. (B) AD protofilament solved by Cryo-EM [1]. (C) Purification of antibody-tau complexes and example of obtained crystals.

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