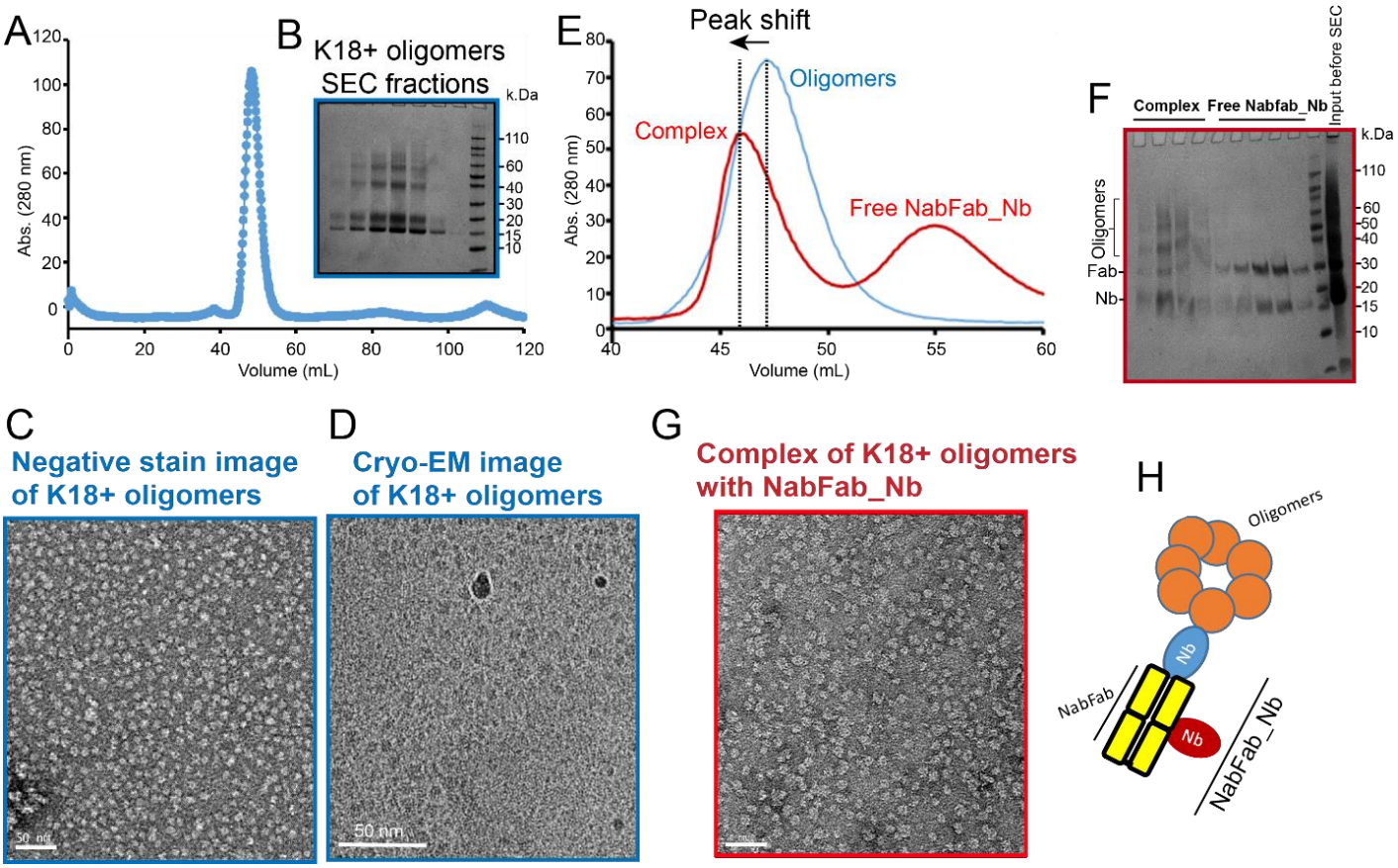

Figure 1. Tau-K18+ oligomers formed using synthetic brain lipids. **(A)** Separation of tau-K18+ oligomer after 3 days of incubation with synthetic brain lipids, by SEC. **(B)** *SDS PAGE* analysis of tau-K18+ oligomer fractions from the SEC peaks. Under denaturation conditions, the oligomers dissociate to monomers and high molecular weight species ranging in size from 40 to 80 k.da. **(C)** EM image of tau-K18+ oligomers. Electron micrographs of the oligomer peak fraction reveals spherical particles that are ~10 nm in diameter. **(D)** Raw cryo-EM image of tau-K18+ oligomers. The scale bar is 50 nm. The cryo-EM images were recorded by FEI Tecnai TF20 electron microscope. **(E)** Purification the complex of tau-K18+ oligomers and NabFab_Nb antibody after SEC. **(F)** *SDS PAGE* analysis of tau-K18+oligomer-NabFab_Nb complex fractions from the SEC peaks. Under denaturation conditions, the complex dissociated to 15 k.da band corresponding to the nanobody size, 28 k,da band corresponding to Fab size and high molecular weights corresponding to the oligomer molecular size species. **(H)** Proposed cryo-EM model for tau oligomers stabilized by a nanobody. We used a Fab that bind to a nanobody as a fiducial and size enhancer (50 kDa) for cryo-Em imaging.

References

1. Cova I, *et al.* (2017) Worldwide trends in the prevalence of dementia. *J Neurol Sci* 379:259-260.
2. Cardenas-Aguayo Mdel C, Gomez-Virgilio L, DeRosa S, & Meraz-Rios MA (2014) The role of tau oligomers in the onset of Alzheimer's disease neuropathology. *ACS Chem Neurosci* 5(12):1178-1191.
3. Abskharon R, *et al.* (2020) Crystal structure of a conformational antibody that binds tau oligomers and inhibits pathological seeding by extracts from donors with Alzheimer's disease. *J Biol Chem* 295(31):10662-10676.
4. Bloch JS, *et al.* (2021) Development of a universal nanobody-binding Fab module for fiducial-assisted cryo-EM studies of membrane proteins. *Proc Natl Acad Sci U S A* 118(47).
5. Tsuchida T, *et al.* (2020) Crystal structure of the human tau PHF core domain VQIINK complexed with the Fab domain of monoclonal antibody Tau2r3. *FEBS Lett*.
6. Ait-Bouziad N, *et al.* (2017) Discovery and characterization of stable and toxic Tau/phospholipid oligomeric complexes. *Nat Commun* 8(1):1678.
7. Cao Q, Boyer DR, Sawaya MR, Ge P, & Eisenberg DS (2019) Cryo-EM structures of four polymorphic TDP-43 amyloid cores. *Nat Struct Mol Biol* 26(7):619-627.
8. Abskharon R, *et al.* (2022) Cryo-EM structure of RNA-induced tau fibrils reveals a small C-terminal core that may nucleate fibril formation. *Proc Natl Acad Sci U S A* 119(15):e2119952119.
9. Jiang YX, *et al.* (2022) Amyloid fibrils in FTLD-TDP are composed of TMEM106B and not TDP-43. *Nature* 605(7909):304-309.