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Anti-tau nanobodies for targeting intracellular aggregates in tauopathies

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The diversity of tauopathies probably involves distinct pathological mechanisms, nevertheless, they are all characterized by intracellular deposits of Tau, as neurofibrillary tangles. However, Tau is found either inside or outside the cell and there is a real debate in the community on which Tau species should be targeted. The extracellular Tau protein would belong to the prion-like Tau propagation hypothesis and be a good target for Alzheimer's disease (AD). The intracellular Tau target would be the aggregating Tau species found in all tauopathies. More difficult to decrease, these intracellular species may nevertheless be therapeutic targets in rare forms of tauopathies such as fronto-temporal lobar degeneration and progressive supranuclear palsy. The specificities of these rare pathologies, which do not follow the typical spatial and temporal stages observed in AD, are insufficiently considered by the current strategies in early clinical development stages.
Fragments of the IgG, such as nanobodies, are interesting for intracellular targets because they can be delivered following a gene therapy approach. We developed anti-tau nanobodies which have been optimized to be intracellular. These nanobodies were validated sing lentiviral vectors and experimental models of tauopathy.
Our results has shown, thanks to lentiviral vectors, that Tau-specific nanobodies, binding in the region at the core of Tau filaments, prevent Tau self-association inside the cells and limit the seeding process throughout the brain in mouse models.
This approach is pertinent given what is known on pathological and clinical data regarding rare tauopathies such as fronto-temporal lobar degeneration (FTLD-tau) and progressive supranuclear palsy.

Conflicts of interest

Nanobodies described in this study have been patented