Sabirnetug Shows Superior Selectivity for Aβ Oligomers Over Monomers Compared to Recombinant Lecanemab and Aducanumab

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Introduction

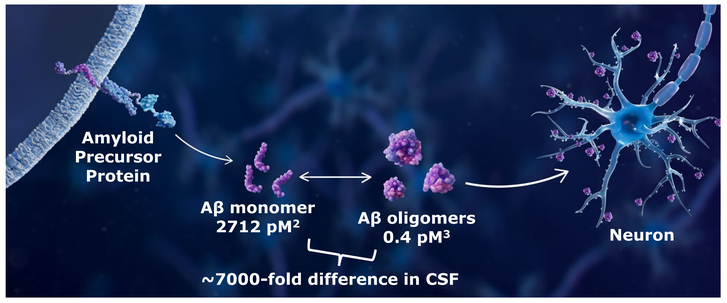


Figure 1. Soluble amyloid β oligomers (AβOs) are early persistent drivers of Alzheimer's disease pathogenesis. In the brain, Aβ monomers are cleaved from the membrane-bound amyloid precursor protein (APP) and then aggregate into soluble AβOs as well as soluble protofibrils and insoluble fibrils (not shown). In Alzheimer's disease (AD), soluble aggregates such as AβOs can bind neuronal synapses and induce synaptic toxicity leading to cognitive decline[1]. This makes AβOs an attractive therapeutic target. CSF concentrations of Aβ monomers & AβOs are presented here as an example since ISF concentrations are less well characterized.

- In biofluids, Aβ monomers are orders-of-magnitude more abundant than AβOs (e.g., ~7,000-fold for $Aβ_{1-40}$ monomer over AβOs in CSF)[2,3]. Such differences in abundance must be overcome in any biofluid through which an AβO-targeted immunotherapy passes to reach AβOs in the brain.
- AβO-targeted immunotherapies without sufficient selectivity may be sequestered by monomers, limiting their ability to engage synaptotoxic AβOs and ultimately their therapeutic efficacy.
- Sabirnetug (ACU193) is a monoclonal antibody designed to selectively target toxic soluble AβOs. In the INTERCEPT-AD[4] phase 1 study, sabirnetug's ability to engage AβOs in the AD central nervous system (i.e., CSF) was confirmed. Synaptic biomarkers also trended away from AD progression following sabirnetug treatment,[5] consistent with the hypothesis that AβO targeting may protect synaptic integrity. Sabirnetug's efficacy in mild cognitive impairment and early Alzheimer's disease is currently being investigated in the ALTITUDE-AD phase 2 study (NCT06335173).
- Here, we compare sabirnetug's binding affinities for AβOs and Aβ monomer with the binding affinities of recombinant versions of other Aβ-targeting antibodies: lecanemab, aducanumab, and the murine precursor to donanemab.

Methods

Overall approach: capture the test conformer by a coupled antibody and conduct surface plasmon resonance (SPR) interaction analysis with the antibody of interest

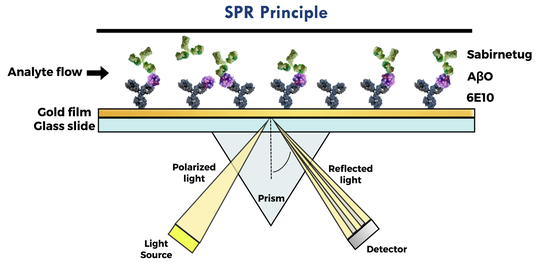


Figure 2. Binding kinetics of each antibody to Aβ conformers was determined by surface plasmon resonance (SPR). SPR exploits physical properties of light to measure binding interaction between two molecules.

- Analyzing **Aβ monomers:** the **test antibody** (sabirnetug or other Aβ-targeting antibody, see Table 1) was immobilized onto an IgG capture sensor chip and the interaction was monitored by injections of increasing peptide concentrations in a **Multi Cycle Kinetic (MCK)** assay setup (Figure 3, left panel).
- Analyzing **Aβ oligomers:** the capture antibody (**6E10**) was coupled onto HCA sensor chip, followed by the immobilization of **Aβ oligomers** and washing out unbound species (Figure 2). The interaction between the **Aβ oligomers** and the **test antibody** was monitored by sequential injections of increasing test antibody concentrations in a **Titration Cycle Kinetic (TCK)** assay setup (Figure 3, right panel).
- The **dissociation constant (K_D)** was calculated at steady-state for fast kinetics by the Langmuir Steady-State model or based on kinetic evaluation for slower kinetics by the 1:1 Langmuir Binding model or the TCK model, respectively, depending on the used assay setup.

Table 1. Aβ-targeting antibodies tested

Antibody	Isotype	Manufacturing method
r-lecanemab	human IgG1	Recombinant transient expression in HEK 293 FreeStyle™ cells, purified by affinity and size exclusion chromatography
r-aducanumab	human IgG1	
murine r-donanemab (mE8)	mouse IgG2a	Recombinant expression in stably transfected HEK 293 FreeStyle™ cells, purified by affinity chromatography

r = recombinant

Table 2. Aβ conformers tested

Structure	Preparation	Manufacturer
monomer	$Aβ_{1-28}$	peptides&elephants
	$Aβ_{1-40}$, $Aβ_{1-42}$	Fraunhofer IZI-MWT
AβO	Amyloid β-derived diffusible ligands (ADDLs)[6]	Northwestern University
	Stabilized $Aβ_{1-42}$ oligomers	GBS Leiden

Aβ conformer-specific SPR assay formats: Multi Cycle Kinetic approach for monomeric species and Titration Cycle Kinetic approach for multimeric species (AβOs)

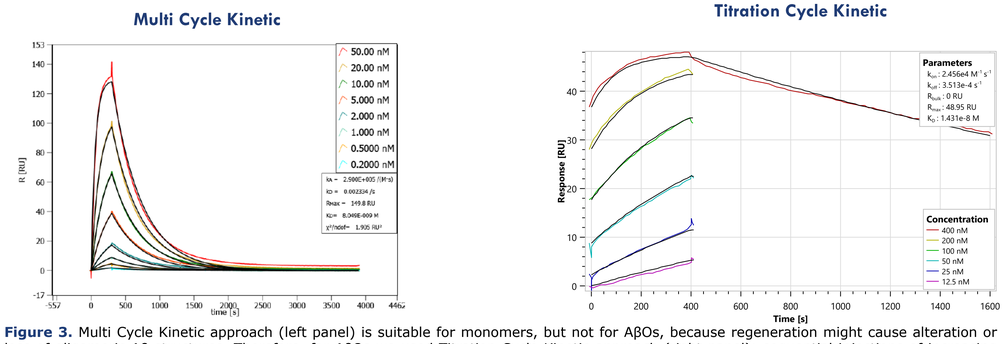


Figure 3. Multi Cycle Kinetic approach (left panel) is suitable for monomers, but not for AβOs, because regeneration might cause alteration or loss of oligomeric Aβ structures. Therefore, for AβOs we used Titration Cycle Kinetic approach (right panel): sequential injections of increasing concentrations of the analyte (antibody of interest) over the ligand (AβO) without dissociation or regeneration between each sample concentration.

Results

Sabirnetug shows the highest binding affinity among the tested antibodies to the two tested AβO preparations

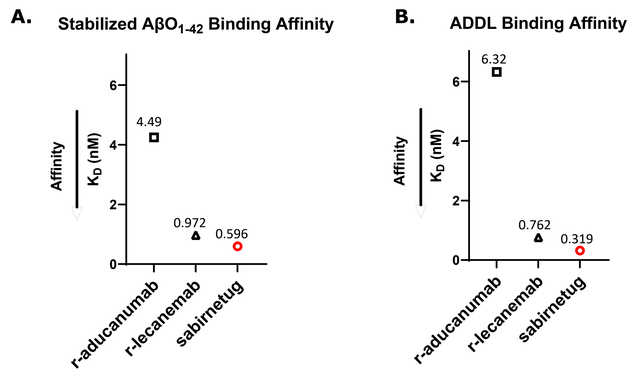


Figure 4. Binding affinity to different preparations of AβOs for sabirnetug, r-aducanumab, and r-lecanemab A) Stabilized $Aβ_{1-42}$ oligomers and B) ADDLs. r=recombinant.

- Sabirnetug showed the highest binding affinities to the AβO preparations (lowest K_D); similar for both stabilized $AβO_{1-42}$ and ADDLs.
- r-lecanemab had the next highest binding affinities, which were also similar between stabilized $AβO_{1-42}$ and ADDLs.
- Murine r-donanemab had a non-quantifiable signal for both AβO preparations (not shown).
- Relative trend in affinity for each AβO preparation is similar among the antibodies tested.

Sabirnetug shows low µM binding affinity to the two tested monomeric proteoforms

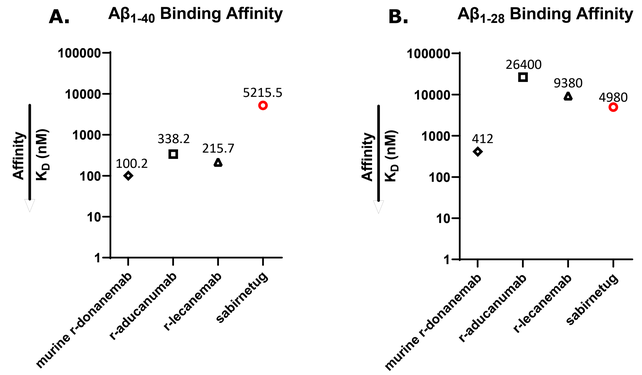


Figure 5. Binding affinities to different monomeric peptides A) $Aβ_{1-40}$ and B) $Aβ_{1-28}$. Affinity to $Aβ_{1-42}$ peptide, attempted for use as a monomeric peptide, is not shown due to oligomerization during the experiment time frame. Note the log 10 scale.

- Effort was made to keep each peptide monomeric. However, oligomerization was observed for $Aβ_{1-42}$ (not shown).
- Minimal oligomerization was observed for $Aβ_{1-40}$ during the limited time of the experiment.
- $Aβ_{1-28}$ remained entirely monomeric for the duration of the measurements.
- Differences in relative affinity trends for $Aβ_{1-40}$ and $Aβ_{1-28}$ among the tested antibodies could be due to epitope availability or conformational changes of Aβ proteoforms.

Sabirnetug shows the highest selectivity for AβOs over $Aβ_{1-40}$ monomer

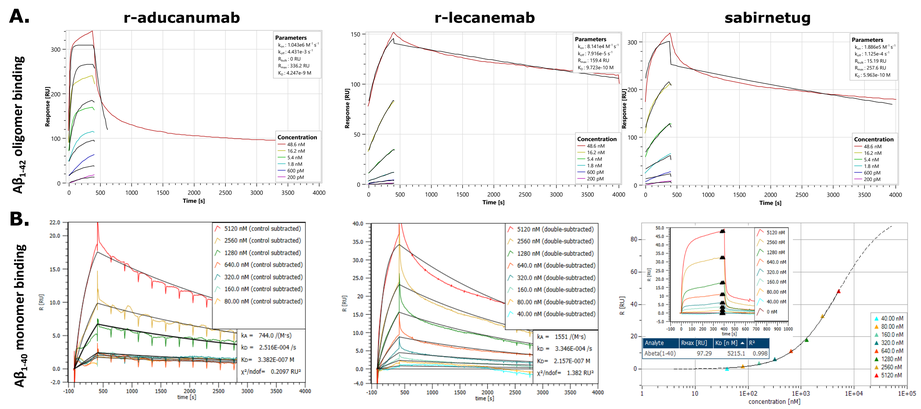
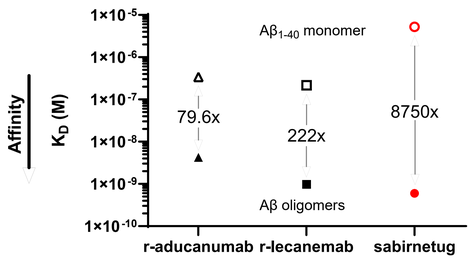


Figure 6. Sensorgrams obtained in kinetic analyses of antibody binding to oligomeric and monomeric standards. A) Kinetic data obtained for binding of test antibodies to stabilized $Aβ_{1-42}$ oligomers, using TCK method. Note different y-axis ranges. B) Kinetic data obtained for $Aβ_{1-40}$ monomer binding to test antibodies, using MCK method. To determine K_D for slow kinetics the 1:1 Langmuir binding model was used (r-aducanumab & r-lecanemab); for fast kinetics the Langmuir Steady-State model was used (sabirnetug). C) Summary of binding affinity data (K_D) stabilized $Aβ_{1-42}$ oligomers and $Aβ_{1-40}$ monomer for sabirnetug, r-lecanemab, and r-aducanumab.

C. Selectivity for AβOs over $Aβ_{1-40}$ monomer



- **Sabirnetug** is **8,750-fold more selective** for stabilized $Aβ_{1-42}$ oligomers vs $Aβ_{1-40}$ monomer.
- **r-lecanemab** is **222-fold more selective** for stabilized $AβO_{1-42}$ vs $Aβ_{1-40}$ monomer.
- **r-aducanumab** is **79.6-fold more selective** for stabilized $AβO_{1-42}$ vs $Aβ_{1-40}$ monomer.

Sabirnetug shows the highest selectivity for AβOs over $Aβ_{1-40}$ monomer & comparable to r-lecanemab selectivity for AβOs over $Aβ_{1-28}$ monomer

Fold-selectivity for:	ADDLs/ $Aβ_{1-28}$	ADDLs/ $Aβ_{1-40}$	Stabilized $AβO_{1-42}$/ $Aβ_{1-28}$	Stabilized $AβO_{1-42}$ / $Aβ_{1-40}$
r-aducanumab	4177	53.5	6220	79.6
r-lecanemab	12300	283	9650	222
sabirnetug	15600	16300	8360	8750

Table 3. Fold-selectivity for each given oligomer preparation over each given monomer species was calculated as K_D for monomer binding divided by K_D for oligomer binding.

RESEARCH HIGHLIGHTS

- Careful selection of SPR technique is needed to measure oligomer affinity of antibodies.
- Sabirnetug showed the highest selectivity for AβOs over monomeric $Aβ_{1-40}$ compared to the recombinant Aβ monoclonal antibody therapeutics tested.
- Sabirnetug's observed high level of selectivity makes it well positioned to target AβOs in AD tissues and biofluids.

1. Cline, et al., J Alzheimers Dis, 2018; 61(s1): S567-S610. 2. Willemse, et al., 2021. Alzheimers Dement. 13(1): e12182. 3. Ostrowitzki, et al., JAMA Neurol, 2022; 79(11): 1113-1121. 4. Siemers, et al., J Prev Alzheimers Dis, 2025;12(1):100005. 5. Siemers, et al., J Prev Alzheimers Dis, 12(4):100082. 6. Lambert, et al., J Neurochem 2001; 79 (3):595-605