Geerts et al. [2023] and Lin et al. [2022] Parameters

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1 Introduction

This document compiles and compares the rate constants, binding affinities, and kinetic parameters from the Geerts et al. [2023] PBPK / QSP model and the Lin et al. [2022] model for amyloid-beta dynamics and antibody interactions.

2 Geerts et al. [2023] Model Parameters

2.1 Antibody Affinities

Table S0 from Geerts et al. [2023] shows the binding affinities for various antibodies against different amyloid-beta species:

Binding Affinities (nM)

Antibody	Monomer	Oligomers	Protofibrils	Plaques	Reference
Lecanemab	2290*	67.3	0.16*	1.79*	Lord et al. [2009]; Söderberg et al. [2023]
Aducanumab	7350*	2.23*	1.5	2.5*	Arndt et al. [2018]; Söderberg et al. [2023]
Donanemab	50	50	50	0.14	Demattos et al. [2012]

*Note: All units are in nanomolar (nM). Values marked with * are from Söderberg et al. [2023] kinetic measurements. Donanemab values taken from Geerts et al. [2024]*

Kinetic Parameters from Soderberg et al. (2022)

Aβ Species / Antibody	k_a ($M^{-1}s^{-1}$)	k_d (s^{-1})	K_D (nM)
Aβ Monomer			
Lecanemab	$8.1 \pm 6.9 \times 10^4$	$1.6 \pm 1.0 \times 10^{-1}$	$2300 \pm 910*$
Aducanumab	$2.0 \pm 0.36 \times 10^4$	$1.5 \pm 0.11 \times 10^{-1}$	$7300 \pm 990*$
Small Aβ Protofibril			
Lecanemab	$5.3 \pm 1.1 \times 10^5$	$4.5 \pm 1.7 \times 10^{-4}$	0.97 ± 0.66
Aducanumab	$2.5 \pm 0.53 \times 10^7$	$5.2 \pm 1.7 \times 10^{-2}$	$2.2 \pm 1.0*$
Large Aβ Protofibril			
Lecanemab	$7.6 \pm 2.1 \times 10^5$	$1.1 \pm 0.36 \times 10^{-4}$	$0.16 \pm 0.07*$
Aducanumab	$3.8 \pm 0.56 \times 10^7$	$3.0 \pm 0.56 \times 10^{-2}$	$0.79 \pm 0.10*$
Aβ Fibril			
Lecanemab	$1.5 \pm 0.47 \times 10^5$	$2.5 \pm 0.91 \times 10^{-4}$	$1.8 \pm 0.93*$
Aducanumab	$2.1 \pm 1.3 \times 10^6$	$6.2 \pm 3.9 \times 10^{-3}$	$3.3 \pm 2.2*$

*Note: Values marked with * are likely used in Geerts et al. [2023]*

2.2 Lin et al. [2022] Binding Parameters for Aducanumab

Aducanumab Binding Parameters in Lin et al. [2022]

Target	$k_{\mathbf{on}}$ **($\mathbf{nM^{-1}s^{-1}}$)**	$k_{\mathbf{mAb}}$ **($\mathbf{s^{-1}}$)**	K_D **(nM)**	**Reference**
Aβ Monomer	1.00×10^{-3}	1.00	1000	Ferrero et al. [2016]
Aβ Oligomer	1.00×10^{-3}	2.00×10^{-2}	20	Assumed equal to plaque
Aβ Plaque	1.00×10^{-3}	2.00×10^{-2}	20	Sevigny et al. [2016]

Note: All association rate constants (k_{on}) are set to a typical protein–protein binding rate of

1.00×10^{-3} *$nM^{-1}s^{-1}$, based on Schlosshauer and Baker [2004].*
The monomer dissociation rate (k_{mAb}) was fit to plasma Aβ data from Ferrero et al. [2016], while the plaque dissociation rate was fit to SUVR data from Sevigny et al. [2016].

Note Kd values are adjusted in Lin et al. [2022] from in virtro measurements according to this description:

"The value of Kd measuring the binding affinity between aducanumab and aggregated Aβ was an important parameter that was initially set to be the same as in vitro measurement 0.2 nM8. However, it was adjusted to 20 nM to capture SUVR data with the rationale as follows: The drug concentration in CSF is estimated to be 0.5% of the concentration in plasma which was measured directly in clinical studies. The drug concentration in the brain ISF was comparable to CSF concentration. If the binding affinity between drug and plaque was 0.2 nM, it would saturate the ADCP process at a low dose (ADCP is affected by both the binding affinity and the drug-induced clearance rate as the plaque concentration is high), which contradicts with the observed SUVR data. The SUVR data suggests increasing the dose of aducanumab from 1 to 10 mg/kg Q4W leads to faster plaque reduction, namely, ADCP process is not saturated within the dose range tested. Since the measurements from in vitro settings might not translate to in vivo, the clinical data justify the use of a different value of Kd in the model."

2.3 Fitted Parameters in Lin et al. [2022] Model

The following parameters from Lin et al. [2022] were fitted to match the CSF antibody and plaque concentration data from Geerts et al. [2023] in last week's presentation. The parameters are grouped by how tightly they are constrained during optimization. I allowed 10% variation to well-determined parameters such as volumes binding affinities, but 10X variation in other parameters. The values presented are the initial values in Lin et al. [2022] for Aducanumab. When fitting to data for Lecanemab or Donanemab, we will change the $k_{\mathbf{mAb}}$ initial value to those from our Kd refrences.

Strongly Constrained Parameters ($\pm$10%) from Lin et al. [2022]

Parameter	**Value (Initial)**	**Parameter description**	**Reference / Comments**
V_{plasma}	3 L	Plasma volume	Pearson et al. [1995]
$V_{\text{peripheral}}$	3 L	Peripheral volume	Assumed to be same as plasma
V_{csf}	0.139 L	CSF volume	Nau et al. [2010]
$V_{\text{brain\_isf}}$	0.261 L	Brain ISF volume	Shah and Betts [2012]
$k_{\mathbf{mAb0}}$	1.00 $\text{nM}^{-1}\text{s}^{-1}$	Association rate constant between drug and Aβ monomer	Ferrero et al. [2016]
$k_{\mathbf{mAb1}}$	2.00×10^{-2} $\text{nM}^{-1}\text{s}^{-1}$	Association rate constant between drug and Aβ oligomer	Assumed equal to plaque
$k_{\mathbf{mAb2}}$	2.00×10^{-2} $\text{nM}^{-1}\text{s}^{-1}$	Association rate constant between drug and Aβ plaque	Sevigny et al. [2016]

Parameters Being Fitted from Lin et al. [2022]

Parameter	Value (Initial)	Parameter description	Reference / Comments
Less Constrained (0.1x – 10x)			
k_{clearFcR}	1.9254×10^{-4} s^{-1}	Degradation rate of FcR on macrophages	Typical receptor turnover rate Mellman [1983]
k_{clearmAb}	1.4586×10^{-6} s^{-1}	1st order elimination rate in plasma	Fitted to aducanumab PK data Ferrero et al. [2016]
k_{12mAb}	2.50×10^{-6} s^{-1}	Distribution rate from plasma to peripheral	
k_{21mAb}	1.00×10^{-6} s^{-1}	Distribution rate from peripheral to plasma	
k_{13mAb}	1.7222×10^{-9} s^{-1}	Transport rate from plasma to CSF	Liu et al. [2013],Roberts et al. [2014],Zhou et al. [2007]
k_{31mAb}	4.1667×10^{-5} s^{-1}	Transport rate from CSF to plasma	
k_{13mix}	1.7222×10^{-9} s^{-1}	Transport rate from plasma to CSF	Assumed to have the same transport rate as A oligomer
k_{31mix}	4.1667×10^{-5} s^{-1}	Transport rate from CSF to plasma	Assumed to have the same transport rate as A oligomer
k_{14mAb}	1.6045×10^{-6} s^{-1}	Transport rate from plasma to ISF	Fitted to CSF aducanumab data (internal)
k_{41mAb}	3.20×10^{-3} s^{-1}	Transport rate from ISF to plasma	Same as above
k_{14mix}	1.6045×10^{-6} s^{-1}	Transport rate from plasma to ISF	Assumed to have the same transport rate as A oligomer
k_{41mix}	1.4811×10^{-8} s^{-1}	Transport rate from ISF to plasma	Same as above
k_{43mAb}	1.5509×10^{-5} s^{-1}	Transport rate from ISF to CSF	Fitted to CSF aducanumab data (internal)
k_{43mix}	2.3264×10^{-8} s^{-1}	Transport rate from ISF to CSF	Assumed to have the same transport rate as Aβ oligomer
k_{offPF}	10 s^{-1}	Dissociation rate between drug-oligomer or drug-plaque complex and FcR	Assumed ADCP to be in linear range for all the dose tested
k_{catADCP}	0.0036 s^{-1}	Catalytic rate constant	Fitted to SUVR data Sevigny et al. [2016]

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