

Table S2: Model parameters

Category	Parameter	Definition	Unit	Value (Mouse)	Ref.	Value (Human)	Ref.
Therapeutic protein PK	N_A	Avogadro's constant	mol^{-1}	6.02×10^{23}	N/A	6.02×10^{23}	N/A
	$k_{a,Ag}$	absorption rate constant from injection site to plasma	Day^{-1}	Ag-specific	N/A	Ag-specific	N/A
	k_{el}	elimination rate	Day^{-1}	Ag-specific	N/A	Ag-specific	N/A
	k_{12}	distribution rate constant from plasma to extra central compartment	Day^{-1}	Ag-specific	N/A	Ag-specific	N/A
	k_{21}	distribution rate constant for antigenic protein, from extra central compartment to plasma	Day^{-1}	Ag-specific	N/A	Ag-specific	N/A
	k_{13}	distribution rate constant for antigenic protein, from plasma to peripheral tissues	Day^{-1}	Ag-specific	N/A	Ag-specific	N/A
	k_{31}	distribution rate constant for antigenic protein, from peripheral tissues to plasma	Day^{-1}	Ag-specific	N/A	Ag-specific	N/A
	V_p	Plasma volume	L	1.46×10^{-3}	N/A	2.75	N/A
	V_{ec}	Extra volume (other than plasma) in the central compartment	L	Ag-specific	N/A	Ag-specific	N/A
	T-epitope characteristics of therapeutic proteins	N	Number of T-epitopes	dimensionless	Ag-specific	N/A	Ag-specific
k_{on}		On rate for T-epitope-MHC-II binding	$\text{pM}^{-1}\text{day}^{-1}$	8.64×10^{-3}	(1)	8.64×10^{-3}	(1)
k_{off}		Off rate for T-epitope-MHC-II binding	day^{-1}	Ag-specific	N/A	Ag-specific	N/A
β_{MS}		Elimination rate for maturation signal (LPS)	Day^{-1}	1.8480	(2)	0.3696	(3)
Dendritic cells	β_{ID}	Death rate for immature DCs	Day^{-1}	0.0924	(4)	0.0924	(4)
	δ_{ID}	Maximum activation rate for immature DCs	Day^{-1}	1.5	(5)	1.5	(5)
	K_{MS}	LPS concentration at which immature DC activation rate is 50% maximum.	ng/L	9.852×10^3	(6)	9.852×10^3	(6)
	β_{MD}	Death rate for mature DCs	Day^{-1}	0.2310	(7)	0.2310	(7)
	cp_0	amount of endogenous competing protein in the plasma	pmole	3.025×10^8	(8)	3.025×10^8	(8)
Antigen presentation	$k_{on,c}$	On rate for competing peptide-MHC-II binding	$\text{pM}^{-1}\text{day}^{-1}$	8.64×10^{-3}	(1)	8.64×10^{-3}	(1)
	$k_{off,c}$	Off rate for competing peptide-MHC-II binding	day^{-1}	34560	(8)	34560	(8)
	α_{Ag^E}	Internalization rate for antigenic protein (Ag^E) into endosome	Day^{-1}	14.4	(8)	14.4	(8)
	β_{Ag^E}	Degradation rate for Ag^E in endosome	Day^{-1}	17.28	(8)	17.28	(8)
	β_p	Degradation rate for epitope peptide	Day^{-1}	144	(8)	144	(8)
	β_M	Degradation rate for MHC-II	Day^{-1}	1.663	(9)	1.663	(9)
	β_{PM}	Degradation rate for MHC-peptide	Day^{-1}	0.1663	(9)	0.1663	(9)

	k_{ext}	exocytosis rate for MHC-peptide complex in endosomes	Day ⁻¹	28.8	(8)	28.8	(8)
	k_{in}	internalization rate for MHC-peptide complex on DC membrane, and for antigen-bound BCR complex	Day ⁻¹	14.4	(8)	14.4	(8)
	$K_{\text{pM,N}}$	number of T-epitope-MHC-II to achieve 50% activation rate of naïve helper T cells	dimensionless	400	(10)	400	(10)
	$K_{\text{pM,M}}$	number of T-epitope-MHC-II to achieve 50% activation rate of memory helper T cells	dimensionless	40	(10)	40	(10)
	V_{D}	Volume of a dendritic cell	L	2.54×10^{-12}	(8)	2.54×10^{-12}	(8)
	V_{E}	Volume of endosomes in a dendritic cell	L	4×10^{-16}	(8)	4×10^{-16}	(8)
	β_{NT}	Death rate of naïve helper T cells	Day ⁻¹	0.0056	(11)	0.0029	(12)
	δ_{NT}	Maximum activation rate of naïve helper T cells	Day ⁻¹	1.5	(5)	1.5	(5)
	ρ_{AT}	maximum proliferation rate for AT	Day ⁻¹	2.3998	(13, 14)	0.5973	(14, 15)
T helper cells	β_{AT}	Death rate of activated helper T cells	Day ⁻¹	0.18	(16)	0.18	(16)
	δ_{MT}	Maximum activation rate of memory helper T cells	Day ⁻¹	1.5	(5)	1.5	(5)
	β_{MT}	Death rate of memory helper T cells	Day ⁻¹	0.0012	(16)	2.7397×10^{-4}	(17)
	β_{FT}	Death rate of functional helper T cells	Day ⁻¹	0.18	(5)	0.18	(5)
	f_1	Percentage for ATs to differentiate to MTs	dimensionless	0.5	(18)	0.5	(18)
	J	Number of B cell subclones	dimensionless	17	(18)	17	(18)
	K_a^I	Association rate constant for Ag-BCR/Ab binding ^I	pM ⁻¹	$3.91 \times 10^{-9} - 2.56 \times 10^{-4}$	(18)	$3.91 \times 10^{-9} - 2.56 \times 10^{-4}$	(18)
	BRN	BCR number on each B cell	dimensionless	1.2×10^5	(19)	75000	(20)
	K_{R}	occupied BCR number to achieve 50% activation rate of naïve B cells	dimensionless	1	(18)	1	(18)
	δ_{NB}	Maximum activation rate of naïve B cells	Day ⁻¹	3	(5)	3	(5)
B cells	CC_{N}	the carrying capacity for 1 FT cell to stimulate the activation and proliferation of target NBs	dimensionless	10	Data fitting	10	Data fitting
	CC_{M}	the carrying capacity for 1 FT cell to stimulate the activation and proliferation of target MBs	dimensionless	100	(21)	100	(21)
	$\rho_{\text{AB}_\text{N}}$	Maximum proliferation rate for activated B cells from naïve B cells	Day ⁻¹	1.3	(5, 22)	0.3333	(22, 23)
	$\rho_{\text{AB}_\text{M}}$	Maximum proliferation rate for activated B cells from memory B cells	Day ⁻¹	2.6	(5, 22)	0.7273	(22, 23)
	β_{AB}	Death rate of activated B cells	Day ⁻¹	0.9	(5)	0.2518	(5, 23)

Ab and immune complex	g_1	Percentage for ABs to differentiate to MBs	dimensionless	0.5	(18)	0.5	(18)	
	g_2	Percentage for ABs to differentiate to SPs	dimensionless	0.4	Data fitting	0.4	Data fitting	
	δ_{MB}	Maximum activation rate of memory B cells	Day ⁻¹	3	(5)	3	(5)	
	β_{MB}	Death rate of memory B cells	Day ⁻¹	0.005	(24)	7.83×10^{-5}	(25)	
	β_{SP}	Death rate of short-lived plasma cells	Day ⁻¹	0.2310	(26)	0.2310	(26)	
	β_{LP}	Death rate of long-lived plasma cells	Day ⁻¹	0.0050	(27)	0.0050	(27)	
	α_A	Secretion rate of antibody by plasma cells	Day ⁻¹	1.68×10^8	(18)	8.64×10^8	(28, 29)	
	β_A	Elimination rate for Ab	Day ⁻¹	0.099	(30)	0.0301	(26)	
	β_C	Elimination rate for Ag-Ab complex	Day ⁻¹	Ag-specific	N/A	Ag-specific	N/A	
	$AgIS_0$	Initial amount of Ag in the injection site	pmole	Ag-specific	N/A	Ag-specific	N/A	
	Ag_0	Initial amount of Ag in the plasma	pmole	Ag-specific	N/A	Ag-specific	N/A	
	$Agec_0$	initial amount of Ag in the extra central compartment	pmole	0	N/A	0	N/A	
	Agp_0	initial amount of Ag in the peripheral tissues	pmole	0	N/A	0	N/A	
	MS_0	Initial amount of maturation signal (LPS)	ng	Ag-specific	N/A	Ag-specific	N/A	
	ID_0	Initial immature DC number	cells	8000	N/A	5×10^7	(26)	
	MD_0	Initial mature DC number	cells	0	N/A	0	N/A	
	cp^E_0	Initial amount of endogenous competing protein in endosome	pmole	0	N/A	0	N/A	
	cpt^E_0	Initial amount of endogenous competing peptide in endosome	pmole	0	N/A	0	N/A	
	Initial conditions	$cptM^E_0$	Initial amount of endogenous competing peptide-MHC complex in endosome	pmole	0	N/A	0	N/A
		$cptM_0$	Initial amount of endogenous competing peptide-MHC complex on dendritic cell membrane	pmole	0	N/A	0	N/A
Ag^E_0		Initial amount of Ag in endosome	pmole	0	N/A	0	N/A	
p^E_0		Initial amount of T-epitope peptides from Ag digestion in endosome	pmole	0	N/A	0	N/A	
M^E_0		Initial amount of MHC-II molecule in a single mature dendritic cell	pmole	0	N/A	0	N/A	
pM^E_0		Initial amount of T-epitope-MHC-II complex in endosome	pmole	0	N/A	0	N/A	
pM_0		Initial amount of T-epitope-MHC-II complex on dendritic cell membrane	pmole	0	N/A	0	N/A	
M_0		Free MHC-II molecule on dendritic cell membrane	pmole	0	N/A	0	N/A	
NT_0		Initial naïve T cell number	cells	16	(31)	1.445×10^3	(26, 32)	

AT_N ₀	Initial number for activated T cells derived from naïve T cells	cells	0	N/A	0	N/A
AT_M ₀	Initial number for activated T cells derived from memory T cells	cells	0	N/A	0	N/A
MT ₀	Initial memory T cell number	cells	0	N/A	0	N/A
FT ₀	Initial functional T cell number	cells	0	N/A	0	N/A
NB ₀ ²	Initial naïve B cell number (total number of 17 clones)	cells	760	(33)	5200	(26, 33)
AB_N ₀	Initial number for activated B cells derived from naïve B cells	cells	0	N/A	0	N/A
AB_M ₀	Initial number for activated B cells derived from memory B cells	cells	0	N/A	0	N/A
SP ₀	Initial number of short-lived plasma cells	cells	0	N/A	0	N/A
LP ₀	Initial number of long-lived plasma cells	cells	0	N/A	0	N/A
MB ₀	Initial memory B cell number	cells	0	N/A	0	N/A
A ₀	Initial amount of antibody	pmole	0	N/A	0	N/A

1. The initial binding affinity (K_a) of BCR and ADA to antigenic protein. It is assumed that the 17 sub-groups have binding affinities that are 2 fold different in adjacent groups.

$$K_{a,i} = 1 \times 10^{-6} \times 2^{\lfloor J - \frac{17+1}{2} \rfloor}, J = 1, 2, \dots, 17$$

By setting up the binding affinities by this equation, the K_a for the middle group is $1 \cdot 10^{-6} \text{ pM}^{-1}$, and the affinities span a physiologically plausible range (18).

2. Initial naïve B cell number (NB₀). B cells and ADA are assumed to be heterogeneous and contain 17 sub-groups (18). It is assumed that the naïve B cell number distributes normally among the 17 clones.

Note: Parameters that are listed as "Ag-specific" will have specific values depending on the antigenic proteins. These parameters include PK parameters (e.g., k_a, A_g, k_{el}), antigen properties (e.g., N (number of T-epitope), k_{off} (MHC binding affinity of T-epitope)), and immune challenge conditions (e.g., A_{g0} (amount of injected antigen)).

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