Logistic PK PD equations explained

(ADC In-Vivo: Cytosol Effect: Cytotoxic)

2021-02-13 Created
2020-02-15 Fix 1st equation 5th term to include mass (W)
2021-03-22 Add unit conversions-table to first slide
2021-03-26 Add units-box below equations. Add W to 3rd eq. Remove K_P_dec terms from 1st, 6th and 8th eqs.
2021-04-18 Add protein binding terms to 3th equation
2021-04-27 Change protein binding terms for 3th equation and add new compartment
2021-09-30 Clarify ln(2)
2021-10-18 Change e_adc to e_drug in drug_ex_free
2021-10-15 Change N to tumor
2022-02-22 Add killing factor
2022-08-11 Change pinocytosis
2022-09-19 Add lysosome equation (DRUG_endo_lyso)
2023-02-20 add TMDD cell
2023-06-15 add antibody
2023-10-30 changed parameter naming and free Drug cellular metabolism was added
2023-11-15 added receptor shedding+ K_int of Ab changed to K_int of ADC + change of $Drug_f^{ex}$: ε^{ADC}
2023-11-23 $K_{pino}^{\mathrm{Ab},TMDDcell}$ changed to $K_{pino}^{ADC,TMDDcell}$ and $K_{pino}^{Ab,cell,lyso}$ to $K_{pino}^{ADC,cell,lyso}$

Logistic PK PD equations explained

(ADC In-Vivo: Cytosol Effect: Cytotoxic)

2023-12-13 Linear tumor growth

Parameter	Unit in UI	How?	Unit in Equations
CL_{ADC}	l/day/kg	/ 24	l/h/kg
CLD_{ADC}	l/day/kg	/ 24	l/h/kg
CL_{Drug}	l/day/kg	/ 24	l/h/kg
CLD_{Drug}	l/day/kg	/ 24	l/h/kg
K_{dec}^{P}	1/day	/ 24	1/h
P_{ADC}	um/day	/ 24	um/h
P_{Drug}	um/day	/ 24	um/h
D_{ADC}	cm^2/day	/ 24	cm^2/h
D_{Drug}	cm^2/day	/ 24	cm^2/h
$K_{on}^{Drug\ Target}$	1/nM/h	* SF / V^{Cell}	1/h
$Drug\ Target^{total}$	nM	* V^{Cell} / SF	1
τ	day	* 24	h
DT^{Tumor}	day	* 24	h

Amount of Antibody (nmol/kg) in central compartment

$$\frac{d(Ab_f^{C1})}{dt} = \underbrace{-\frac{CL_{Ab}}{V_{Ab}^{C1}} \times Ab_f^{C1}}_{\text{To clearance of Ab}} \underbrace{- \frac{CLD_{Ab}}{V_{Ab}^{C1}} \times Ab_f^{C1}}_{\text{To peripheral space}} \underbrace{+ \frac{CLD_{Ab}}{V_{Ab}^{C2}} \times Ab_f^{C2}}_{\text{From peripheral space}}$$

$$\underbrace{-\left(\frac{Ab_f^{C1}}{V_{Ab}^{C1}} - \frac{Ab_f^{ex}}{\varepsilon^{Ab}}\right) \times \frac{V^{tumor}}{BW} \times \left(\frac{2\times P_{Ab}\times R_{Cap}}{R_{Krogh}^2} + \frac{6\times D_{Ab}}{R_{Tumor}^2}\right)}_{\text{To tumor extracellular space}} \underbrace{-\left(K_{pino}^{ADC,TMDDcell} \times \left(\frac{NC^{TMDDcell}}{\mathrm{BW}\times V_{Ab}^{C1}}\right) \times Ab_f^{C1}\right)}_{\text{To pinocytosis into cells without effect}}$$

$$\underbrace{-K_{on}^{Ab,cell,ag} \times Ab_f^{C1} \times \left(Ag_t^{TMDDcell} - ADC_{b,ag}^{TMDDcell} - Ab_{b,ag}^{TMDDcell}\right) \times NC^{TMDDcell} \times \frac{SF}{\mathrm{BW}\times V_{Ab}^{C1}}}_{\text{To binding to receptor of cells without effect}}$$

$$\underbrace{+K_{off}^{Ab,cell,ag} \times Ab_{b,ag}^{TMDDcell} \times NC^{TMDDcell} \times \frac{SF}{\mathrm{BW}}}_{\text{From binding to receptor of cells without effect}} \underbrace{-K_{on}^{Ab,cell,ag} \times Ab_f^{C1} \times \frac{Ag_f^{C1}}{V_{Ab}^{C1}}}_{\text{To binding to shedded receptor}} \underbrace{+ K_{off}^{Ab,cell,ag} \times Ag_b^{C1}}_{\text{From unbinding of shedded receptor in C1}}$$

Units:

$$\frac{nmol}{kg\times h} = \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{kg} - \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg + \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg - \left(\frac{nmol/kg}{l/kg} - \frac{nmol/l}{1}\right) \times \frac{l}{kg} \times \left(\frac{\frac{um}{h}\times um}{um^2} + \frac{cm^2/h}{cm^2}\right)$$

$$- \frac{l}{h} \times \left(\frac{1}{l/kg\times kg}\right) \times \frac{nmol}{kg} - \frac{1}{\frac{nmol}{l}\times h} \times \frac{nmol}{kg} \times (1-1) \times 1 \times \frac{nmol}{kg\times\frac{l}{kg}} + \frac{1}{h} \times 1 \times 1 \times \frac{nmol}{kg} - \frac{1}{\frac{nmol}{l}\times h} \times \frac{nmol}{kg} \times \frac{nmol}{kg\times\frac{l}{kg}} + \frac{1}{h} \times \frac{nmol}{kg}$$

Amount of ADC (nmol/kg)
in central compartment

$$\frac{d(ADC_f^{C1})}{dt} = \underbrace{-\frac{CL_{ADC}}{V_{ADC}^{C1}} \times ADC_f^{C1}}_{\text{To clearance of ADC}} \underbrace{- \frac{CLD_{ADC}}{V_{ADC}^{C1}} \times ADC_f^{C1}}_{\text{To peripheral space}} \underbrace{+ \frac{CLD_{ADC}}{V_{ADC}^{C2}} \times ADC_f^{C2}}_{\text{From peripheral space}}$$

$$\underbrace{-\left(\frac{ADC_f^{C1}}{V_{ADC}^{C1}} - \frac{ADC_f^{ex}}{\varepsilon^{ADC}}\right) \times \frac{V^{tumor}}{BW} \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right)}_{\text{To tumor extracellular space}} \underbrace{- \left(K_{pino}^{ADC,TMDDcell} \times \left(\frac{NC^{TMDDcell}}{BW \times V_{ADC}^{C1}}\right) \times ADC_f^{C1}\right)}_{\text{To pinocytosis into cells without effect}}$$

$$\underbrace{-K_{on}^{ADC,cell,ag} \times ADC_f^{C1} \times \left(Ag_t^{TMDDcell} - ADC_{b,ag}^{TMDDcell} - Ab_{b,ag}^{TMDDcell}\right) \times NC^{TMDDcell} \times \frac{SF}{BW \times V_{ADC}^{C1}}}_{\text{To binding to receptor of cells without effect}}$$

$$\underbrace{+K_{off}^{ADC,cell,ag} \times ADC_{b,ag}^{TMDDcell} \times NC^{TMDDcell} \times \frac{SF}{BW}}_{\text{From binding to receptor of cells without effect}} \underbrace{-K_{on}^{ADC,cell,ag} \times ADC_f^{C1} \times \frac{Ag_f^{C1}}{V_{ADC}^{C1}}}_{\text{To binding to shedded receptor}} \underbrace{+ K_{off}^{ADC,cell,ag} \times Ag_b^{C1}}_{\text{From unbinding of shedded receptor in C1}}$$

Units: $\frac{nmol}{kg \times h} = \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{kg} - \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg + \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg - \left(\frac{nmol/kg}{l/kg} - \frac{nmol/l}{1}\right) \times \frac{l}{kg} \times \left(\frac{\frac{um}{h} \times um}{um^2} + \frac{cm^2/h}{cm^2}\right)$

$- \frac{l}{h} \times \left(\frac{1}{l/kg \times kg}\right) \times \frac{nmol}{kg} - \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol}{kg} \times (1 - 1 - 1) \times 1 \times \frac{nmol}{kg \times \frac{l}{kg}} + \frac{1}{h} \times 1 \times 1 \times \frac{nmol}{kg} - \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol}{kg} \times \frac{nmol}{kg \times \frac{l}{kg}} + \frac{1}{h} \times \frac{nmol}{kg}$

only info not for the code: $Ag_b^{C1} = Ab_{b,ag}^{C1} + ADC_{b,ag}^{C1}$

Amount of shedded receptor (nmol/kg) bound to ADC/mAb in central compartment

$$\frac{d(Ag_b^{C1})}{dt} = \underbrace{-\frac{CL_{Ag}}{V_{Ag}^{C1}} \times Ag_b^{C1}}_{\text{To clearance of bound shedded receptor}} \underbrace{-\left(\frac{Ag_b^{C1}}{V_{Ag}^{C1}} - \frac{Ag_b^{ex}}{\varepsilon^{Ag}}\right) \times \frac{V^{tumor}}{BW} \times \left(\frac{2 \times P_{Ag} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{Ag}}{R_{Tumor}^2}\right)}_{\text{To tumor extracellular space}}$$

$$\underbrace{+K_{on}^{Ab,cell,ag} \times Ab_f^{C1} \times \frac{Ag_f^{C1}}{V_{Ab}^{C1}}}_{\text{From binding to shedded receptor (Ab)}} \underbrace{- K_{off}^{Ab,cell,ag} \times Ag_b^{C1}}_{\text{To unbinding of shedded receptor (Ab)}} \underbrace{+ K_{on}^{ADC,cell,ag} \times ADC_f^{C1} \times \frac{Ag_f^{C1}}{V_{ADC}^{C1}}}_{\text{From binding to shedded receptor (ADC)}} \underbrace{- K_{off}^{ADC,cell,ag} \times Ag_b^{C1}}_{\text{To unbinding of shedded receptor (ADC)}}$$

$$\underbrace{+ K_{shed}^{Ag} \times \left(ADC_{b,ag}^{TMDDcell} + Ab_{b,ag}^{TMDDcell}\right) \times NC^{TMDDcell} \times \frac{SF}{BW}}_{\text{From shedding antigen bound to antibody and ADC of TMDD cell}}$$

Units: $\frac{nmol}{kg \times h} = \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{kg} - \left(\frac{nmol/kg}{l/kg} - \frac{nmol/l}{1}\right) \times \frac{l}{kg} \times \left(\frac{\frac{um}{h} \times um}{um^2} + \frac{cm^2/h}{cm^2}\right) + \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol}{kg} \times \frac{nmol}{kg \times \frac{l}{kg}} - \frac{1}{h} \times \frac{nmol}{kg} + \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol}{kg} \times \frac{nmol}{kg} \times \frac{nmol}{kg \times \frac{l}{kg}} - \frac{1}{h} \times \frac{nmol}{kg}$
$+ \frac{1}{h} \times (1 + 1) \times 1 \frac{nmol}{kg}$

Amount of shedded receptor (nmol/kg) free in central compartment

$$\frac{d(Ag_f^{C1})}{dt} = \underbrace{-\frac{CL_{Ag}}{V_{Ag}^{C1}} \times Ag_f^{C1}}_{\text{To clearance of free shedded antigen}} \underbrace{-\left(\frac{Ag_f^{C1}}{V_{Ag}^{C1}} - \frac{Ag_f^{ex}}{\varepsilon^{Ag}}\right) \times \frac{V^{tumor}}{BW} \times \left(\frac{2 \times P_{Ag} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{Ag}}{R_{Tumor}^2}\right)}_{\text{To tumor extracellular space}}$$

$$\underbrace{-K_{on}^{Ab,cell,ag} \times Ab_f^{C1} \times \frac{Ag_f^{C1}}{V_{Ab}^{C1}}}_{} \underbrace{+ K_{off}^{Ab,cell,ag} \times Ag_b^{C1}}_{\text{From unbinding of shedded receptor (Ab)}} \underbrace{- K_{on}^{ADC,cell,ag} \times ADC_f^{C1} \times \frac{Ag_f^{C1}}{V_{ADC}^{C1}}}_{\text{To binding to shedded receptor (ADC)}} \underbrace{+ K_{off}^{ADC,cell,ag} \times Ag_b^{C1}}_{\text{From unbinding of shedded receptor (ADC)}}$$

$$\underbrace{+K_{shed}^{Ag} \times \left(Ag_t^{TMDDcell} - ADC_{b,ag}^{TMDDcell} - Ab_{b,ag}^{TMDDcell}\right) \times NC^{TMDDcell} \times \frac{SF}{BW}}_{\text{From shedding free antigen of TMDD cell}}$$

Units: $\frac{nmol}{kg \times h} = \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{kg} - \left(\frac{nmol/kg}{l/kg} - \frac{nmol/l}{1}\right) \times \frac{l}{kg} \times \left(\frac{\frac{um}{h} \times um}{um^2} + \frac{cm^2/h}{cm^2}\right) - \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol}{kg} \times \frac{nmol}{kg \times \frac{l}{kg}} + \frac{1}{h} \times \frac{nmol}{kg} - \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol}{kg} \times \frac{nmol}{kg \times \frac{l}{kg}} + \frac{1}{h} \times \frac{nmol}{kg}$

$+\frac{1}{h} \times (1 - 1 - 1) \times 1 \frac{nmol}{kg}$

Concentration of drug (nM) in central compartment

$$
\frac{d(Drug_f^{C1})}{dt} = \underbrace{-\frac{CL_{Drug}}{V_{Drug}^{C1}} \times Drug_f^{C1}}_{\text{To clearance of drug}} \underbrace{-\frac{CLD_{Drug}}{V_{Drug}^{C1}} \times Drug_f^{C1}}_{\text{To peripheral space}} \underbrace{+\frac{CLD_{Drug}}{V_{Drug}^{C1}} \times Drug_f^{C2}}_{\text{From peripheral space}} \underbrace{+\frac{K_{dec}^{ADC} \times ADC_f^{C1} \times \overline{DAR}}{V_{Drug}^{C1}}}_{\text{From non-specific deconjugation of ADC}}
$$

$$
\underbrace{+\frac{CL_{ADC} \times \overline{DAR} \times \frac{ADC_f^{C1}}{V_{ADC}^{C1}}}{V_{Drug}^{C1}}}_{\text{From clearance of ADC}} \underbrace{-\left(Drug_f^{C1} - \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}}\right) \times \frac{V^{tumor}}{V_{Drug}^{C1} \times BW} \times \left(\frac{2 \times P_{Drug} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{Drug}}{R_{Tumor}^2}\right)}_{\text{To tumor extracellular space}}
$$

$$
\underbrace{-K_{on,off}^{Drug,ex,ntp} \times (1 - f_{ub}^{ex}) \times Drug_f^{C1} + K_{on,off}^{Drug,ex,ntp} \times f_{ub}^{ex} \times Drug_{b,ntp}^{C1}}_{\text{To and from protein binding}} \underbrace{+ Drug_f^{TMDDcell,cyto} \times K_{out}^{Drug,ex} \times \frac{NC^{TMDDcell} \times SF}{BW \times V_{Drug}^{C1}}}_{\text{From efflux from cells without effect}}
$$

$$
\underbrace{-K_{in}^{Drug,ex} \times \left(\frac{V^{TMDDcell} \times NC^{TMDDcell}}{BW \times V_{Drug}^{C1}}\right) \times Drug_f^{C1}}_{\text{To influx into cells without effect}}
$$

Units:

$$
\frac{nmol}{l \times h} = -\frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l} - \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l} + \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l} + \frac{\frac{1}{h} \times \frac{nmol}{kg} \times 1}{l/kg} + \frac{\frac{l}{h}/kg \times 1 \times \frac{nmol/kg}{l/kg}}{l/kg}
$$

$$
-\left(\frac{nmol}{l} - \frac{nmol}{l \times 1}\right) \times \frac{l}{l/kg \times kg} \times \left(\frac{\frac{um}{h} \times um}{um^2} + \frac{cm^2/h}{cm^2}\right) \frac{1}{h} \times \frac{nmol}{l} + \frac{1}{h} \times 1 \times \frac{nmol}{l} + \frac{1}{h} \times 1 \times \frac{1 \times nmol}{kg \times \frac{l}{kg}} - \frac{1}{h} \times \frac{l \times 1}{kg \times \frac{l}{kg}} \times \frac{nmol}{l}
$$

Concentration (nM) of drug bound to unspecific protein in central compartment/plasma

$$\frac{d(Drug_{b,ntp}^{C1})}{dt} = \underbrace{K_{on,off}^{Drug,ex,ntp} \times (1 - f_{ub}^{ex}) \times Drug_{f}^{C1}}_{\text{To unspecific protein binding}} - \underbrace{K_{on,off}^{Drug,ex,ntp} \times f_{ub}^{ex} \times Drug_{b,ntp}^{C1}}_{\text{To unspecific protein unbinding}}$$

Units: $\frac{nmol}{l \times h} = \frac{1}{h} \times 1 \times \frac{nmol}{l} - \frac{1}{h} \times 1 \times \frac{nmol}{l}$

Amount of Antibody (nmol/kg) in peripheral compartment

$$\frac{d\,(Ab_f^{C2})}{dt} = \underbrace{\frac{CLD_{Ab}}{V_{Ab}^{C1}} * Ab_f^{C1}}_{\text{From central space}} - \underbrace{\frac{CLD_{Ab}}{V_{Ab}^{C2}} * Ab_f^{C2}}_{\text{To central space}}$$

Units:

$$\frac{nmol}{kg \times h} = \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{kg} \qquad - \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg$$

Amount of ADC (nmol/kg) in peripheral compartment

$$\frac{d(ADC_f^{C2})}{dt} = \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C1}} \times ADC_f^{C1}}_{\text{From central space}} - \underbrace{\frac{CLD_{ADC}}{V_{ADC}^{C2}} \times ADC_f^{C2}}_{\text{To central space}}$$

Units:

$$\frac{nmol}{kg \times h} = \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{kg} - \frac{\frac{l}{h}/kg}{l/kg} \times nmol/kg$$

Concentration of drug (nM) in peripheral compartment

$$\frac{d(Drug_f^{C2})}{dt} = \underbrace{\frac{CLD_{Drug}}{V_{Drug}^{C2}} \times Drug_f^{C1}}_{\text{From central space}} - \underbrace{\frac{CLD_{Drug}}{V_{Drug}^{C2}} \times Drug_f^{C2}}_{\text{To central space}}$$

Units:

$$\frac{nmol}{l \times h} = \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l} \qquad - \frac{\frac{l}{h}/kg}{l/kg} \times \frac{nmol}{l}$$

Average drug-to-antibody ratio

$$\frac{d(\overline{DAR})}{dt} = \underbrace{-K_{dec}^{ADC} \times \overline{DAR}}_{\text{Due to non-specific deconjugation of ADC}}$$

Units:

$$\frac{1}{h} = \frac{1}{h} \times 1$$

Concentration (nM) of Antibody in media space

$$\frac{d(Ab_f^{ex})}{dt} = \underbrace{\left(\frac{Ab_f^{C1}}{V_{Ab}^{C1}} - \frac{Ab_f^{ex}}{\varepsilon^{Ab}}\right) \times \left(\frac{2 \times P_{Ab} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{Ab}}{R_{Tumor}^2}\right)}_{\text{From central space}}$$

$$\underbrace{+\left(-K_{on}^{Ab,cell,ag} \times \frac{Ab_f^{ex}}{\varepsilon^{Ab}} \times \left(Ag_t^{cell} - ADC_{b,ag}^{cell} - Ab_{b,ag}^{cell}\right) + K_{off}^{Ab,cell,ag} \times Ab_{b,ag}^{cell}\right) \times \frac{NC^{tumor} \times SF}{V^{tumor}}}_{\text{Binding and unbinding of Ab to receptors (Ag) on tumor cell}}$$

$$\underbrace{+\frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times Ab_{b,ag}^{cell} \times \frac{SF}{V^{tumor}}}_{\text{From intracellular content of dying cells}} \underbrace{- K_{pino}^{ADC,cell,lyso} \times \left(\frac{NCL^{tumor}}{\varepsilon^{Ab}}\right) \times Ab_f^{ex}}_{\text{To pinocytosis}}$$

$$\underbrace{-K_{on}^{Ab,cell,ag} \times \frac{Ab_f^{ex}}{\varepsilon^{Ab}} \times \frac{Ag_f^{ex}}{\varepsilon^{Ag}} + K_{off}^{Ab,cell,ag} \times \frac{Ag_b^{ex}}{\varepsilon^{Ag}}}_{\text{Binding and unbinding of Ab to shedded receptors}}$$

Units: $$\frac{nmol}{l \times h} = \left(\frac{nmol/kg}{l/kg} - \frac{nmol/l}{1}\right) \times \left(\frac{\frac{um}{h} \times um}{um^2} + \frac{cm^2/h}{cm^2}\right) + \left(-\frac{1}{\frac{nmol}{l} \times h} \times \frac{\frac{nmol}{l}}{1} \times (1-1) + \frac{1}{h} \times 1\right) \times \frac{1 \times nmol}{l}$$

$$+\frac{1}{h} \times mm^3 \times \frac{1}{mm^3} \times 1 \times \frac{nmol}{l} - \frac{l}{h} \times \left(\frac{1/l}{1}\right) \times \frac{nmol}{l} - \frac{1}{\frac{nmol}{l} \times h} \times \frac{\frac{nmol}{l}}{1} \times \frac{\frac{nmol}{l}}{1} + \frac{1}{h} \times \frac{\frac{nmol}{l}}{1}$$

Concentration (nM) of ADC in media space

$$\frac{d(ADC_f^{ex})}{dt} = \underbrace{\left(\frac{ADC_f^{C1}}{V_{ADC}^{C1}} - \frac{ADC_f^{ex}}{\varepsilon^{ADC}}\right) \times \left(\frac{2 \times P_{ADC} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{ADC}}{R_{Tumor}^2}\right)}_{\text{From central space}}$$

$$\underbrace{+\left(-K_{on}^{ADC,cell,ag} \times \frac{ADC_f^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - ADC_{b,ag}^{cell} - Ab_{b,ag}^{cell}\right) + K_{off}^{ADC,cell,ag} \times ADC_{b,ag}^{cell}\right) \times \frac{NC^{tumor} \times SF}{V^{tumor}}}_{\text{Binding and unbinding of ADC to receptors on tumor cell}}$$

$$\underbrace{+\frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(ADC_{b,ag}^{cell} + ADC_f^{cell,lyso}\right) \times \frac{SF}{V^{tumor}}}_{\text{From intracellular content of dying cells}} \underbrace{- K_{pino}^{ADC,cell,lyso} \times \left(\frac{NCL^{tumor}}{\varepsilon^{ADC}}\right) \times ADC_f^{ex}}_{\text{To pinocytosis}}$$

$$\underbrace{-K_{on}^{ADC,cell,ag} \times \frac{ADC_f^{ex}}{\varepsilon^{ADC}} \times \frac{Ag_f^{ex}}{\varepsilon^{Ag}} + K_{off}^{ADC,cell,ag} \times \frac{Ag_b^{ex}}{\varepsilon^{Ag}}}_{\text{Binding and unbinding of ADC to shedded receptor}}$$

Units: $\frac{nmol}{l \times h} = \left(\frac{nmol/kg}{l/kg} - \frac{nmol/l}{1}\right) \times \left(\frac{\frac{um}{h} \times um}{um^2} + \frac{cm^2/h}{cm^2}\right) + \left(-\frac{1}{\frac{nmol}{l} \times h} \times \frac{\frac{nmol}{l}}{1} \times (1 - 1 - 1) + \frac{1}{h} \times 1\right) \times \frac{1 \times nmol}{l}$

$+\frac{1}{h} \times mm^3 \times \frac{1}{mm^3} \times (1 + 1) \times \frac{nmol}{l} - \frac{l}{h} \times \left(\frac{1/l}{1}\right) \times \frac{nmol}{l} - \frac{1}{\frac{nmol}{l} \times h} \times \frac{\frac{nmol}{l}}{1} \times \frac{\frac{nmol}{l}}{1} + \frac{1}{h} \times \frac{\frac{nmol}{l}}{1}$

Amount (nmol) of drug in media space

$$\frac{d(Drug_f^{ex})}{dt} = \underbrace{\left(Drug_f^{C1} - \frac{Drug_f^{ex}}{V^{tumor} \times \varepsilon^{Drug}}\right) \times V^{tumor} \times \left(\frac{2 \times P_{Drug} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{Drug}}{R_{Tumor}^2}\right)}_{\text{From central space}} \underbrace{+ K_{dec}^{ADC} \times \frac{ADC_f^{ex}}{\varepsilon^{ADC}} \times \overline{DAR} \times V^{tumor}}_{\text{From non-specific deconjugation of ADC}}$$

$$\underbrace{+\left(\underbrace{K_{dec}^{ADC} \times ADC_{b,ag}^{cell} \times \overline{DAR}}_{\text{Non-specific deconj. of ADC}} \underbrace{+ K_{out}^{Drug,ex} \times Drug_f^{cell,cyto}\right) \times NC^{tumor} \times SF}_{\text{Efflux of drug from the cell}}}_{\text{From cells}}$$

$$\underbrace{-K_{in}^{Drug,ex} \times NC^{tumor} \times \left(\frac{V^{cell}}{V^{tumor} \times \varepsilon^{Drug}}\right) \times Drug_f^{ex}}_{\text{To influx into cells}} \underbrace{+ \frac{1}{\tau} \times V_{dyi,3,mm3}^{tumor} \times 10^5 \times \left(\mathrm{Drug}_f^{cell,cyto} + Drug_{b,dt}^{cell,cyto} + \mathrm{Drug}_f^{cell,lyso}\right) \times SF}_{\text{From intracellular content of dying cells}}$$

Units: $$\frac{nmol}{h} = \left(\frac{nmol}{l} - \frac{nmol}{l \times 1}\right) \times l \times \left(\frac{\frac{um}{h} \times um}{um^2} + \frac{cm^2/h}{cm^2}\right) + \frac{1}{h} \times \frac{nmol}{l} \times 1 \times l \quad + \left(\frac{1}{h} \times 1 \times 1 + \frac{1}{h} \times 1\right) \times 1 \times nmol$$
$$- \frac{1}{h} \times 1 \times \left(\frac{l}{l \times 1}\right) \times nmol + \frac{1}{h} \times mm^3 \times \frac{1}{mm^3} \times (1 + 1) \times nmol$$

Concentration (nM) of target molecules bound to ADC/mAb in media space

only info not for the code: $Ag_b^{ex} = Ab_{b,ag}^{ex} + ADC_{b,ag}^{ex}$

$$\frac{d(Ag_b^{ex})}{dt} = \underbrace{\left(\frac{Ag_b^{C1}}{V_{Ag}^{C1}} - \frac{Ag_b^{ex}}{\varepsilon^{Ag}}\right) \times \left(\frac{2 \times P_{Ag} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{Ag}}{R_{Tumor}^2}\right)}_{\text{From central space}} + \underbrace{K_{on}^{Ab,cell,ag} \times \frac{Ab_f^{ex}}{\varepsilon^{Ab}} \times \frac{Ag_f^{ex}}{\varepsilon^{Ag}}}_{\text{From binding to shedded receptor (Ab)}} - \underbrace{K_{off}^{Ab,cell,ag} \times \frac{Ag_b^{ex}}{\varepsilon^{Ag}}}_{\text{To unbinding of shedded receptor (Ab)}}$$

$$\underbrace{+K_{shed}^{Ag} \times \left(Ab_{b,ag}^{cell} + ADC_{b,ag}^{cell}\right) \times \frac{NC^{tumor} \times SF}{V^{tumor}}}_{\text{From shedded antigen bound to Ab and ADC}} \underbrace{+K_{on}^{ADC,cell,ag} \times \frac{ADC_f^{ex}}{\varepsilon^{ADC}} \times \frac{Ag_f^{ex}}{\varepsilon^{Ag}}}_{\text{From binding to shedded receptor (ADC)}} - \underbrace{K_{off}^{ADC,cell,ag} \times \frac{Ag_b^{ex}}{\varepsilon^{Ag}}}_{\text{To unbinding of shedded receptor (ADC)}}$$

Units: $$\frac{nmol}{l \times h} = \left(\frac{nmol/kg}{l/kg} - \frac{nmol/l}{1}\right) \times \left(\frac{\frac{um}{h} \times um}{um^2} + \frac{cm^2/h}{cm^2}\right) + \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol/l}{1} \times \frac{nmol}{l} - \frac{1}{h} \times \frac{nmol}{l} + \frac{1}{h} \times (1 + 1) \times \frac{1 \times nmol}{l} + \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol/l}{1} \times \frac{nmol}{l} - \frac{1}{h} \times \frac{nmol}{l}$$

Concentration (nM) of free target molecules in media space

$$\frac{d\left(Ag_f^{ex}\right)}{dt} = \underbrace{\left(\frac{Ag_f^{C1}}{V_{Ag}^{C1}} - \frac{Ag_f^{ex}}{\varepsilon^{Ag}}\right) \times \left(\frac{2 \times P_{Ag} \times R_{Cap}}{R_{Krogh}^2} + \frac{6 \times D_{Ag}}{R_{Tumor}^2}\right)}_{\text{From central space}} \underbrace{- K_{on}^{Ab,cell,ag} \times \frac{Ab_f^{ex}}{\varepsilon^{Ab}} \times \frac{Ag_f^{ex}}{\varepsilon^{Ag}}}_{\text{To binding to shedded receptor (Ab)}} \underbrace{+ K_{off}^{Ab,cell,ag} \times \frac{Ag_b^{ex}}{\varepsilon^{Ag}}}_{\text{From unbinding of shedded receptor (Ab)}}$$

$$\underbrace{-K_{on}^{ADC,cell,ag} \times \frac{ADC_f^{ex}}{\varepsilon^{ADC}} \times \frac{Ag_f^{ex}}{\varepsilon^{Ag}}}_{\text{To binding to shedded receptor (ADC)}} \underbrace{+ K_{off}^{ADC,cell,ag} \times \frac{Ag_b^{ex}}{\varepsilon^{Ag}}}_{\text{From unbinding of shedded receptor (ADC)}} \underbrace{+ K_{shed}^{Ag} \times \left(Ag_t^{cell} - ADC_{b,ag}^{cell} - Ab_{b,ag}^{cell}\right) \times \frac{NC^{tumor} \times SF}{V^{tumor}}}_{\text{From shedded free antigen}}$$

Units:

$$\frac{nmol}{l \times h} = \left(\frac{nmol/kg}{l/kg} - \frac{nmol/l}{1}\right) \times \left(\frac{\frac{um}{h} \times um}{um^2} + \frac{cm^2/h}{cm^2}\right) - \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol/l}{1} \times \frac{nmol}{l} + \frac{1}{h} \times \frac{nmol}{l}$$

$$- \frac{1}{\frac{nmol}{l} \times h} \times \frac{\frac{nmol}{l}}{1} \times \frac{nmol}{l} + \frac{1}{h} \times \frac{nmol}{l} + \frac{1}{h} \times (1 - 1 - 1) \times \frac{1 \times nmol}{l}$$

$K_{int}^{ADC,cell}$ *is used for both ADC and Ab*

Number of Antibody molecules bound to binding target on a single cell

$$\frac{d(Ab_{b,ag}^{cell})}{dt} = \underbrace{K_{on}^{Ab,cell,ag} \times \frac{Ab_f^{ex}}{\varepsilon^{Ab}} \times \left(Ag_t^{cell} - ADC_{b,ag}^{cell} - Ab_{b,ag}^{cell}\right)}_{\text{From binding to receptor from free ADC}} \underbrace{- K_{off}^{Ab,cell,ag} \times Ab_{b,ag}^{cell}}_{\text{To unbinding from receptor}} \underbrace{- K_{int}^{ADC,cell} \times Ab_{b,ag}^{cell}}_{\text{To internalization into cell}}$$

$$\underbrace{- \frac{\ln(2)}{DT^{tumor}} \times Ab_{b,ag}^{cell}}_{\text{To dilution as cells grow and divide}} \underbrace{- K_{shed}^{Ag} \times Ab_{b,ag}^{cell}}_{\text{Shedded Antigen bound to Ab}}$$

Units: $$\frac{1}{h} = \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol/l}{1} \times (1 - 1 - 1) - \frac{1}{h} \times 1 - \frac{1}{h} \times 1 - \frac{1}{h} \times 1 - \frac{1}{h} \times 1$$

Number of ADC molecules bound to binding target on a single cell

$$\frac{d(ADC_{b,ag}^{cell})}{dt} = \underbrace{K_{on}^{ADC,cell,ag} \times \frac{ADC_f^{ex}}{\varepsilon^{ADC}} \times \left(Ag_t^{cell} - ADC_{b,ag}^{cell} - Ab_{b,ag}^{cell}\right)}_{\text{From binding to receptor 1 from free ADC}} \underbrace{- K_{off}^{ADC,cell,ag} \times ADC_{b,ag}^{cell}}_{\text{To unbinding from receptor 1}} \underbrace{- K_{int}^{ADC,cell} \times ADC_{b,ag}^{cell}}_{\text{To internalization into cell}}$$

$$\underbrace{- \frac{\ln(2)}{DT^{tumor}} \times ADC_{b,ag}^{cell}}_{\text{To dilution as cells grow and divide}} \underbrace{- K_{shed}^{Ag} \times ADC_{b,ag}^{cell}}_{\text{Shedded Antigen bound to Ab}}$$

Units: $$\frac{1}{h} = \frac{1}{\frac{nmol}{l} \times h} \times \frac{nmol/l}{1} \times (1 - 1 - 1) - \frac{1}{h} \times 1 - \frac{1}{h} \times 1 - \frac{1}{h} \times 1 - \frac{1}{h} \times 1$$

$only\ info\ not\ for\ the\ code: Ag_f^{cell} = Ag_{cell}^t - \left(Ab_{b,ag}^{ex} + ADC_{b,ag}^{ex}\right)$ and $K_{int}^{ADC,cell}$ $is\ used\ for\ both\ ADC\ and\ Ab$

Number of receptor molecules on a single cell

$$\frac{d(Ag_t^{cell})}{dt} = \underbrace{-K_{int}^{ADC,cell} \times \left(ADC_{b,ag}^{cell} + Ab_{b,ag}^{cell}\right)}_{\text{To internalization of bound receptors (ADC + Ab)}} \underbrace{-K_{shed}^{Ag} \times \left(ADC_{b,ag}^{cell} + Ab_{b,ag}^{cell} + \left(Ag_t^{cell} - ADC_{b,ag}^{cell} - Ab_{b,ag}^{cell}\right)\right)}_{\text{Shedded of bound and free receptors}}$$

$$\underbrace{+K_{int}^{ADC,cell} \times \left(ADC_{b,ag}^{cell} + Ab_{b,ag}^{cell}\right) + K_{shed}^{Ag} \times \left(ADC_{b,ag}^{cell} + Ab_{b,ag}^{cell} + \left(Ag_t^{cell} - ADC_{b,ag}^{cell} - Ab_{b,ag}^{cell}\right)\right)}_{\text{Equal to synthesis rate}}$$

Units: $\frac{1}{h} = -\frac{1}{h} \times (1 + 1) - \frac{1}{h} \times (1 + 1 + (1 - 1 - 1)) + \frac{1}{h} \times (1 + 1) + \frac{1}{h} \times (1 + 1 + (1 - 1 - 1))$

Number of ADC molecules internalized in endosomal/lysosomal space on a single cell

$$\frac{d(ADC_f^{cell,lyso})}{dt} = \underbrace{K_{int}^{ADC,cell} \times ADC_{b,ag}^{cell}}_{\text{From internalization into cell}}$$

$$\underbrace{-K_{deg}^{ADC} \times ADC_f^{cell,lyso}}_{\text{To degradation}} \underbrace{+ K_{pino}^{ADC,cell,lyso} \times \frac{ADC_f^{ex}}{\varepsilon^{ADC} \times SF}}_{\text{From pinocytosis}} \underbrace{- \frac{\ln(2)}{DT^{tumor}} \times ADC_f^{cell,lyso}}_{\text{To dilution as cells grow and divide}}$$

Units: $\frac{1}{h} = \quad \frac{1}{h} \times 1 \quad - \frac{1}{h} \times 1 \quad + \frac{l}{h} \times \frac{nmol/l}{1 \times nmol} \quad - \frac{1}{h} \times 1$

Number of unbound drug molecules in endosomal/lysosomal space on a single cell

$$\frac{d(Drug_f^{cell,lyso})}{dt} = \underbrace{K_{deg}^{ADC} \times ADC_f^{cell,lyso} \times \overline{DAR}}_{\text{From degradation of ADC}} - \underbrace{K_{out}^{Drug,lyso} \times \left(\frac{V^{cell}}{V^{cell,lyso}}\right) \times Drug_f^{cell,lyso}}_{\text{To cytosol}}$$

$$\underbrace{+K_{in}^{Drug,lyso} \times Drug_f^{cell,cyto}}_{\text{From cytosol}} - \underbrace{\frac{\ln(2)}{DT^{tumor}} \times Drug_f^{cell,lyso}}_{\text{To dilution as cells grow and divide}}$$

Units:

$$\frac{1}{h} = \frac{1}{h} \times (1+1) \quad -\frac{1}{h} \times \left(\frac{l}{l}\right) \times 1 \quad +\frac{1}{h} \times 1 \quad -\frac{1}{h} \times 1$$

Free drug, number of molecules (1) per cell

$$\frac{d(Drug_f^{cell,cyto})}{dt} = \underbrace{+K_{out}^{Drug,lyso} \times \left(\frac{V^{cell}}{V^{cell,lyso}}\right) \times Drug_f^{cell,lyso} - K_{in}^{Drug,lyso} \times Drug_f^{cell,cyto}}_{\text{From and to lysosome}} \underbrace{- K_{out}^{Drug,ex} \times Drug_f^{cell,cyto}}_{\text{To efflux}}$$

$$\underbrace{-K_{on}^{Drug,cyto,dt} \times Drug_f^{cell,cyto} \times \left(DrugTarget_t^{cell,cyto} - Drug_{b,dt}^{cell,cyto}\right)}_{\text{To binding to drug target}} \underbrace{-K_{met}^{Drug} \times Drug_f^{cell,cyto}}_{\text{To metabolism}}$$

$$\underbrace{+K_{off}^{Drug,cyto,dt} \times Drug_{b,dt}^{cell,cyto}}_{\text{From unbinding from drug target}} \underbrace{+\ K_{in}^{Drug,ex} \times \left(\frac{V^{cell}}{V^{tumor} \times \varepsilon^{Drug}}\right) \times \frac{Drug_f^{ex}}{SF}}_{\text{From influx}} \underbrace{- \frac{\ln(2)}{DT^{tumor}} \times Drug_f^{cell,cyto}}_{\text{To dilution as cells grow and divide}}$$

Units: $\frac{1}{h} = \frac{1}{h} \times \left(\frac{l}{l}\right) \times 1 - \frac{1}{h} \times 1 - \frac{1}{h} \times 1 - \frac{1}{h} \times 1 \times (1 - 1) - \frac{1}{h} \times 1 + \frac{1}{h} \times 1 + \frac{1}{h} \times \left(\frac{l}{l \times 1}\right) \times \frac{nmol}{nmol} - \frac{1}{h} \times 1$

Bound drug, number of molecules (1) per cell

$$\frac{d(Drug_{b,dt}^{cell,cyto})}{dt} = \underbrace{K_{on}^{Drug,cyto,dt} \times Drug_{f}^{cell,cyto} \times \left(DrugTarget_{t}^{cell,cyto} - Drug_{b,dt}^{cell,cyto}\right)}_{\text{From binding to drug target}}$$

$$\underbrace{-K_{off}^{Drug,cyto,dt} \times Drug_{b,dt}^{cell,cyto}}_{\text{To unbinding from drug target}} \underbrace{- \frac{\ln(2)}{DT^{tumor}} \times Drug_{b,dt}^{cell,cyto}}_{\text{To dilution as cells grow and divide}}$$

Units: $\frac{1}{h} = \frac{1}{h} \times 1 \times (1 - 1) \quad -\frac{1}{h} \times 1 \quad -\frac{1}{h} \times 1$

Number of ADC molecules bound to binding target on a single cell without effect, in central compartment/plasma

$$\frac{d(ADC_{b,ag}^{TMDDcell})}{dt} = \underbrace{K_{on}^{ADC,cell,ag} \times \left(Ag_t^{TMDDcell} - ADC_{b,ag}^{TMDDcell} - Ab_{b,ag}^{TMDDcell}\right) \times \frac{ADC_f^{C1}}{V_{ADC}^{C1}}}_{\text{From binding to receptor}}$$

$$\underbrace{-K_{off}^{ADC,cell,ag} \times ADC_{b,ag}^{TMDDcell}}_{\text{To unbinding from receptor}} \underbrace{- K_{int}^{ADC,TMDDcell} \times ADC_{b,ag}^{TMDDcell}}_{\text{To Internalization into TMDD cell}} - \underbrace{K_{shed}^{Ag} \times ADC_{b,ag}^{TMDDcell}}_{\text{Shedded Antigen bound to Ab}}$$

Units:

$$\frac{1}{h} = \frac{1}{\frac{nmol}{l} \times h} \times (1 - 1 - 1) \times \frac{nmol/kg}{l/kg} - \frac{1}{h} \times 1 - \frac{1}{h} \times 1 - \frac{1}{h} \times 1$$

Number of Antibody molecules bound to binding target on a single cell without effect, in central compartment/plasma

$K_{int}^{ADC,TMDDcell}$ *is used for both ADC and Ab*

$$\frac{d(Ab_{b,ag}^{TMDDcell})}{dt} = \underbrace{K_{on}^{Ab,cell,ag} \times \left(Ag_t^{TMDDcell} - ADC_{b,ag}^{TMDDcell} - Ab_{b,ag}^{TMDDcell}\right) \times \frac{Ab_f^{C1}}{V_{Ab}^{C1}}}_{\text{From binding to receptor from free ADC}} \underbrace{- K_{off}^{Ab,cell,ag} \times Ab_{b,ag}^{TMDDcell}}_{\text{To unbinding from receptor}}$$

$$\underbrace{-K_{int}^{ADC,TMDDcell} \times Ab_{b,ag}^{TMDDcell}}_{\text{To internalization into cell}} \underbrace{- K_{shed}^{Ag} \times Ab_{b,ag}^{TMDDcell}}_{\text{Shedded Antigen bound to Ab}}$$

Units: $$\frac{1}{h} = \frac{1}{\frac{nmol}{l} \times h} \times (1 - 1 - 1) \times \frac{nmol/kg}{l/kg} - \frac{1}{h} \times 1 - \frac{1}{h} \times 1 - \frac{1}{h} \times 1 - \frac{1}{h} \times 1$$

Number of receptor molecules on a single cell without effect, in central compartment/plasma

$only\ info\ not\ for\ the\ code: Ag_f^{TMDDcell} = Ag_{cell}^{TMDDt} - \left(Ab_{b,ag}^{TMDDcell} + ADC_{b,ag}^{TMDDcell}\right)$ and $K_{int}^{ADC,TMDDcell}$ $is\ used\ for\ both\ ADC\ and\ Ab$

$$\frac{d(Ag_t^{TMDDcell})}{dt} = \underbrace{-K_{int}^{ADC,TMDDcell} \times \left(ADC_{b,ag}^{TMDDcell} + Ab_{b,ag}^{TMDDcell}\right)}_{\text{To internalization of bound receptors (ADC +Ab)}} \underbrace{-K_{shed}^{Ag} \times \left(ADC_{b,ag}^{TMDDcell} + Ab_{b,ag}^{TMDDcell} + \left(Ag_t^{TMDDcell} - ADC_{b,ag}^{TMDDcell} - Ab_{b,ag}^{TMDDcell}\right)\right)}_{\text{Shedding of bound and free receptors}}$$

$$\underbrace{+K_{int}^{ADC,TMDDcell} \times \left(ADC_{b,ag}^{TMDDcell} + Ab_{b,ag}^{TMDDcell}\right) + K_{shed}^{Ag} \times \left(ADC_{b,ag}^{TMDDcell} + Ab_{b,ag}^{TMDDcell} + \left(Ag_t^{TMDDcell} - ADC_{b,ag}^{TMDDcell} - Ab_{b,ag}^{\mathrm{TMDD}cell}\right)\right)}_{\text{Equal to synthesis rate}}$$

Units: $\frac{1}{h} = -\frac{1}{h} \times (1 + 1) - \frac{1}{h} \times (1 + 1 + (1 - 1 - 1)) + \frac{1}{h} \times (1 + 1) + \frac{1}{h} \times (1 + 1 + (1 - 1 - 1))$

Number of ADC molecules in lysosomal space of non-effect (TMDD) cells

$$\frac{d(ADC_f^{TMDDcell,lyso})}{dt} = \underbrace{K_{int}^{ADC,TMDDcell} \times ADC_{b,ag}^{TMDDcell}}_{\text{From internalization into cell without effect}} - \underbrace{K_{deg}^{ADC,TMDDcell} \times ADC_f^{TMDDcell,lyso}}_{\text{To degradation}} + \underbrace{K_{pino}^{ADC,TMDDcell} \times \frac{ADC_f^{C1}}{SF \times V_{ADC}^{C1}}}_{\text{From pinocytosis}}$$

Units: $\frac{1}{h} = \frac{1}{h} \times 1 - \frac{1}{h} \times 1 + \frac{l}{h} \times \frac{\frac{nmol}{kg}}{nmol \times \frac{l}{kg}}$

Number of unbound Drug molecules in lysosomal space on a single cell without effect

$$\frac{d(Drug_f^{TMDDcell,lyso})}{dt} = \underbrace{-K_{out}^{Drug,lyso} \times \left(\frac{V^{TMDDcell}}{V^{TMDDcell,lyso}}\right) \times Drug_f^{TMDDcell,lyso}}_{\text{To cytosol}}$$

$$\underbrace{+K_{in}^{Drug,lyso} \times Drug_f^{TMDDcell,cyto}}_{\text{From cytosol}} \underbrace{+ K_{deg}^{ADC,TMDDcell} \times ADC_f^{TMDDcell,lyso} \times \overline{DAR}}_{\text{From degradation of ADC}}$$

Units: $\frac{1}{h} = -\frac{1}{h} \times \left(\frac{l}{l}\right) \times 1 + \frac{1}{h} \times 1 + \frac{1}{h} \times 1 \times 1$

Number of unbound drug molecules in cytosol on a single cell without effect

$$\frac{d(Drug_f^{TMDDcell,cyto})}{dt} = \underbrace{K_{in}^{Drug,ex} \times V^{TMDDcell} \times \frac{Drug_f^{C1}}{SF}}_{\text{From influx into cell}} \underbrace{- K_{out}^{Drug,ex} \times Drug_f^{TMDDcell,cyto}}_{\text{To efflux from cell}}$$

$$\underbrace{+K_{out}^{Drug,lyso} \times \left(\frac{V^{TMDDcell}}{V^{TMDDcell,lyso}}\right) \times Drug_f^{TMDDcell,lyso}}_{\text{From lysosomal compartment}} \underbrace{- K_{in}^{Drug,lyso} \times Drug_f^{TMDDcell,cyto}}_{\text{To lysosomal compartment}} \underbrace{-K_{met}^{Drug} \times Drug_f^{TMDDcell,cyto}}_{\text{To metabolism}}$$

Units: $\frac{1}{h} = \frac{1}{h} \times l \times \frac{\frac{nmol}{l}}{nmol} - \frac{1}{h} \times 1 + \frac{1}{h} \times \left(\frac{l}{l}\right) \times 1 - \frac{1}{h} \times 1 - \frac{1}{h} \times 1$

Tumor volume

$$V_{mm3}^{tumor} = V_{pro,mm3}^{tumor} + V_{dyi,1,mm3}^{tumor} + V_{dyi,2,mm3}^{tumor} + V_{dyi,3,mm3}^{tumor}$$

$$\frac{\mathrm{d}(V_{pro,mm3}^{tumor})}{\mathrm{dt}} = \left(\frac{\frac{\ln(2)}{\mathrm{DT}^{tumor}} \times \left(1 - \frac{V_{pro,mm3}^{tumor}}{V_{max}^{tumor}}\right)}{\left(1 + \left(\frac{\ln(2)}{\mathrm{DT}^{tumor}} \times \frac{V_{pro,mm3}^{tumor}}{k_{lin}}\right)^{\psi}\right)^{\frac{1}{\psi}}} - \mathrm{R_{Kill}} \right) \cdot V_{pro,mm3}^{tumor}$$

$$\frac{\mathrm{d}(V_{dyi,1,mm3}^{tumor})}{\mathrm{dt}} = \mathrm{R_{Kill}} \cdot V_{pro,mm3}^{tumor} - \frac{1}{\tau} \cdot V_{dyi,1,mm3}^{tumor}$$

$$\frac{\mathrm{d}(V_{dyi,2,mm3}^{tumor})}{\mathrm{dt}} = \frac{1}{\tau} \cdot (V_{dyi,1,mm3}^{tumor} - V_{dyi,2,mm3}^{tumor})$$

$$\frac{\mathrm{d}(V_{dyi,3,mm3}^{tumor})}{\mathrm{dt}} = \frac{1}{\tau} \cdot (V_{dyi,2,mm3}^{tumor} - V_{dyi,3,mm3}^{tumor})$$

Logistic (Thomas Rysiok)

$$t_l = \ln\left(\frac{Drug_f^{cell,cyto} \times SF}{V^{cell}}\right) - \ln(EC_{50})$$

$$LOGI = \frac{k_g}{1 + (\frac{k_g}{k_z} - 1) \times e^{-k_r \times k_g \times t_l}}$$

$$R_{kill} = k_{kill,\,max} \times \left(\frac{\ln(2)}{\mathrm{DT}^{tumor}}\right)^{f\_DT\_kill} \times LOGI$$