2023 ACoP14 Workshop: ADC Example

04-November 2023

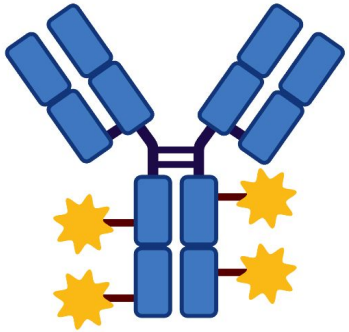
Agenda

- ADC background
- ADC model development (in vivo)
- Julia simulation

Antibody Drug Conjugates (ADCs) Background

Antibody Drug Conjugates (ADCs)

"Maximizing efficacy while minimizing systemic toxicity"



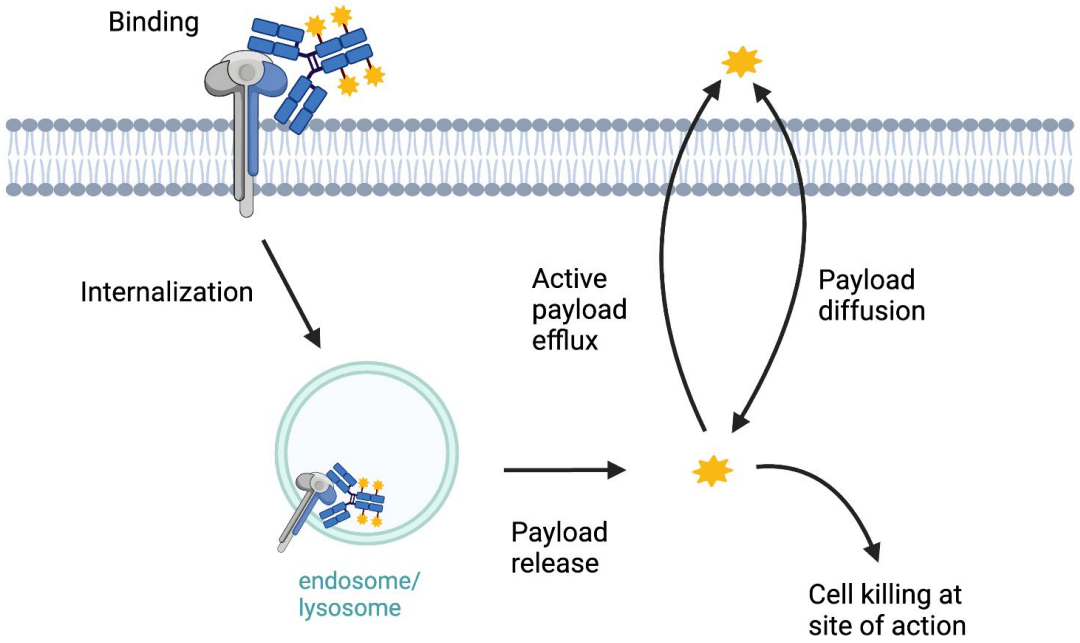
Monoclonal Antibody (mAb)
selective to specific antigen of the surface of cancer cell

Chemical Linker
cleavable or non-cleavable
affects stability, efficiency, and bioavailability of ADC

Payload (Drug)
cytotoxic compound with high potency

- ADCS are composed of three main components with different design properties:
  - The **mAb** targets antigen that are preferentially expressed in cancer cells with limited expression in normal tissues
  - The **linker** is typically stable in circulation but can be degraded under certain conditions
  - The **payload** is highly toxic and may diffuse across the cell membrane
- A key characteristic of ADC is the **drug-to-antibody ratio (DAR)**, which typically varies between 1 and 8

Key ADC mechanisms of action for QSP modeling



Key mechanisms of action (MoA)

- ADC-antigen binding
- Internalization
- ADC degradation & payload release
- Payload diffusion/ active efflux
- Cell-killing effect

Lam, I., Pilla Reddy, V., Ball, K., Arends, R. H., & Mac Gabhann, F. (2022). Development of and insights from systems pharmacology models of antibody-drug conjugates. CPT: Pharmacometrics & Systems Pharmacology, 11(8), 967–990. https://doi.org/10.1002/psp4.12833

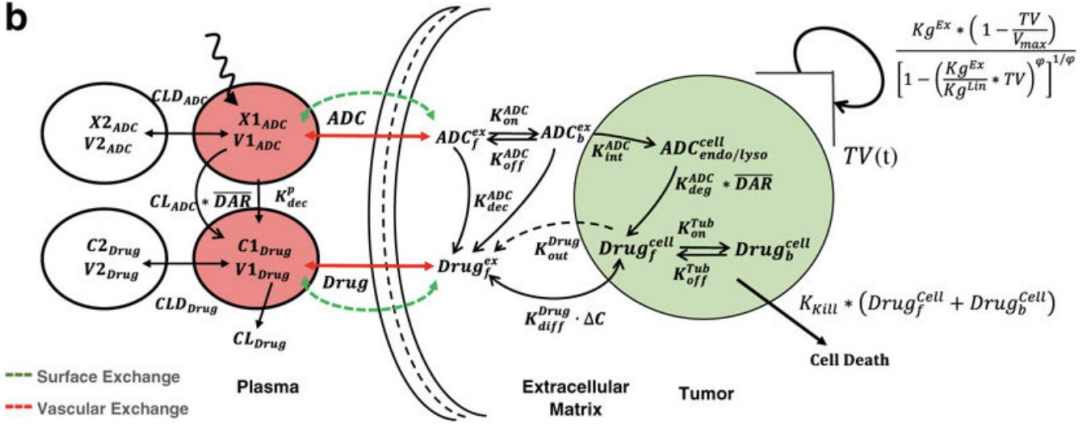
Published QSP Model for anti-HER2 ADC Trastuzumab Emtansine (T-DM1)

The AAPS journal
Author Manuscript
HHS Public Access

Application of a PK-PD Modeling and Simulation-Based Strategy for Clinical Translation of Antibody-Drug Conjugates: a Case Study with Trastuzumab Emtansine (T-DM1)

Aman P. Singh and Dhaval K. Shah

- T-DM1 (mAb trastuzumab linked with cytotoxic payload DM1) was approved in 2013
- Singh and Shah published a multi-scale PK-PD model characterizing the tumor distribution of T-DM1 and DM1 catabolites and ADC-induced tumor growth killing



From Figure 1 of Singh, A. P., & Shah, D. K. (2017). Application of a PK-PD Modeling and Simulation-Based Strategy for Clinical Translation of Antibody-Drug Conjugates: a Case Study with Trastuzumab Emtansine (T-DM1). *The AAPS journal*, *19*(4), 1054–1070. https://doi.org/10.1208/s12248-017-0071-y

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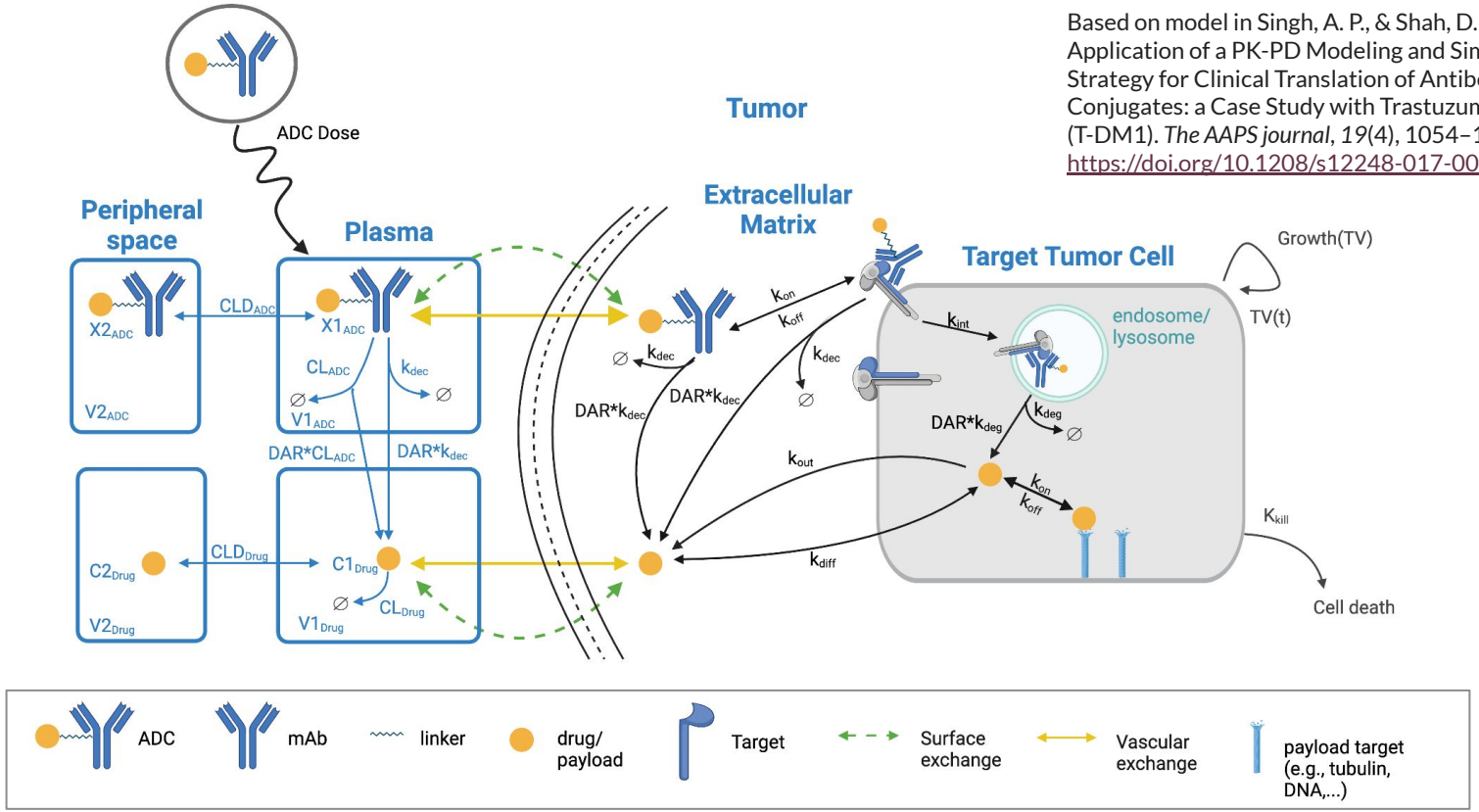
Model Development

ADC schematic, *in vivo*

Based on model in Singh, A. P., & Shah, D. K. (2017). Application of a PK-PD Modeling and Simulation-Based Strategy for Clinical Translation of Antibody-Drug Conjugates: a Case Study with Trastuzumab Emtansine (T-DM1). *The AAPS journal*, *19*(4), 1054–1070. https://doi.org/10.1208/s12248-017-0071-y



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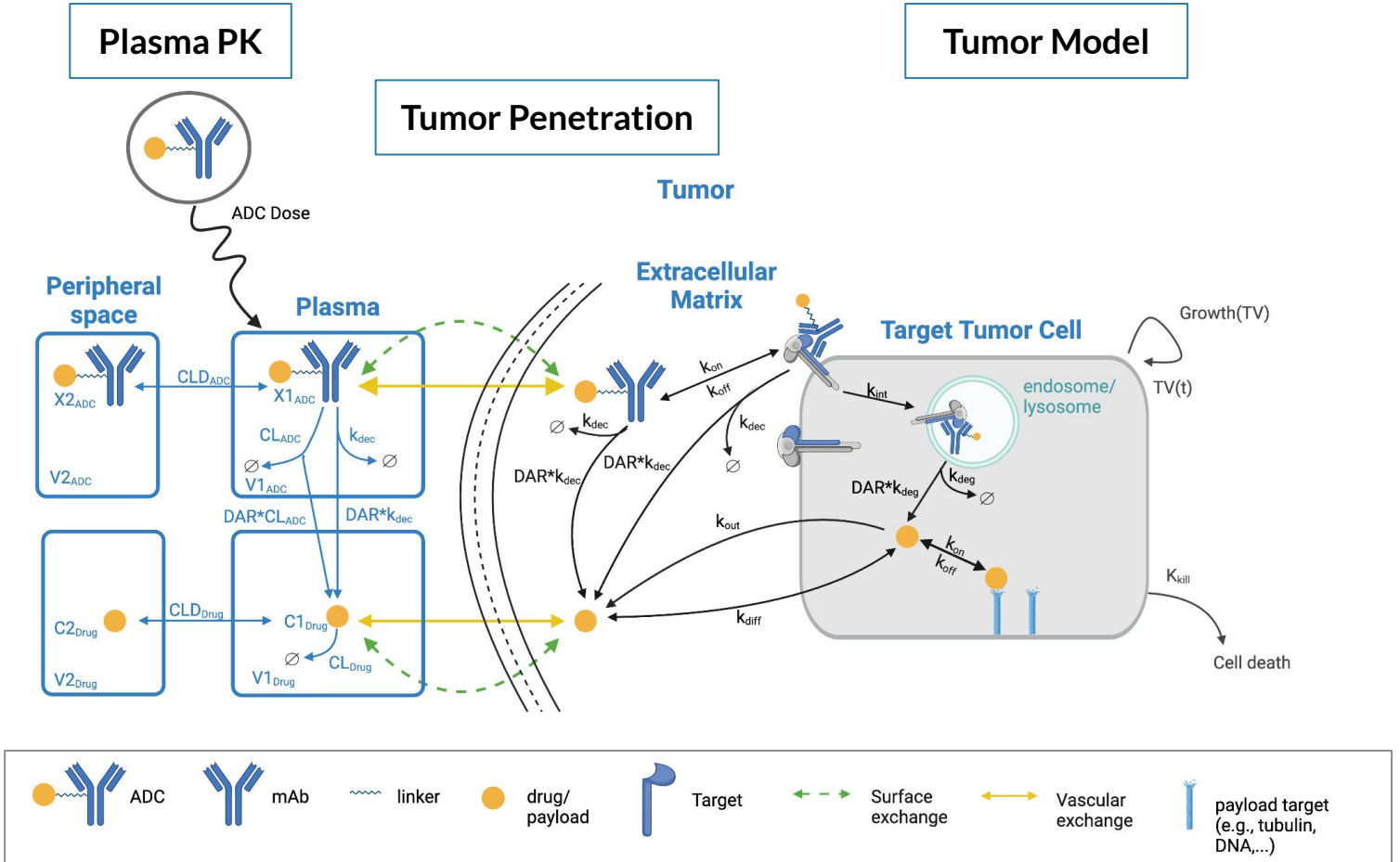
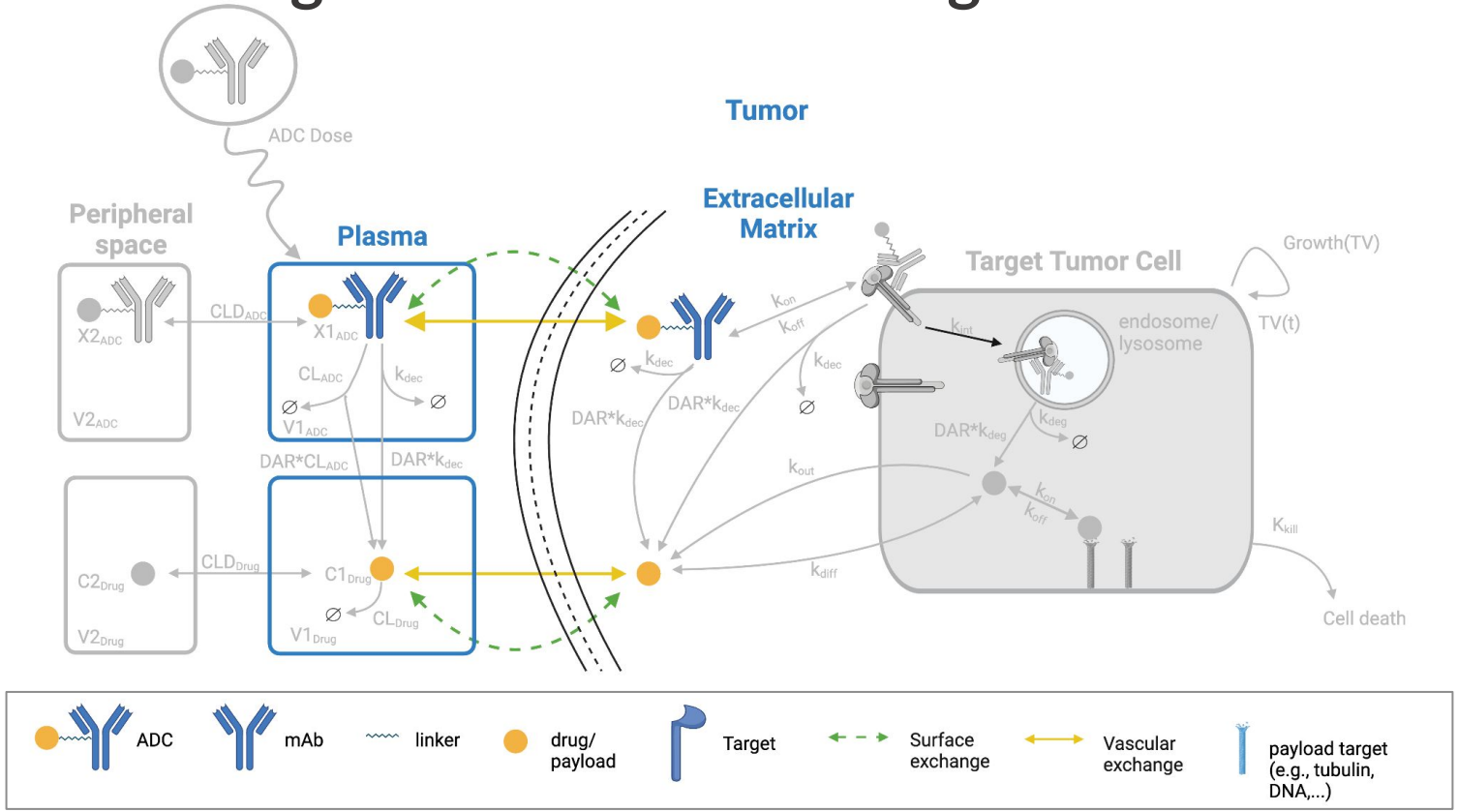
Model components



Tumor penetration was modeled as a combination of surface exchange and vascular exchange



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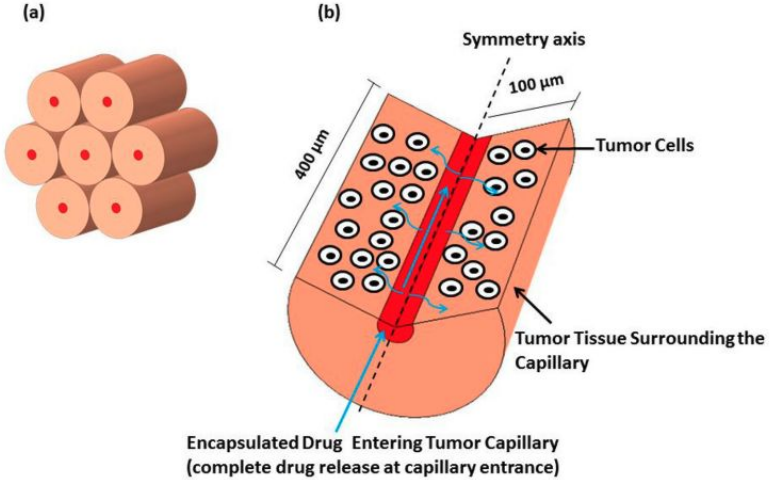
Surface exchange and vascular exchange for ADC/ drug penetration in solid tumors



(a) Tumor tissue is assumed to consist of identical Krogh cylinders.
(b) An individual Krogh cylinder is shown in a cross-section with tumor capillary and surrounding tissue.

From: Figure 1 of Ramajayam, K. K., Newton, D. A., & Haemmerich, D. (2022). Selecting ideal drugs for encapsulation in thermosensitive liposomes and other triggered nanoparticles. *International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group*, *39*(1), 998–1009. https://doi.org/10.1080/02656736.2022.2086303

When tumor is large, ADC and drug distribution in tumor is driven by **vascular exchange** (described by Krogh cylinder model) which is a function of permeability rate P

$$\text{Vascular Exchange} = \frac{2 \cdot P \cdot R_{Cap}}{R^2_{Krogh}}$$

R_{Cap} ← Capillary Radius

R_{Krogh} ← Distance between 2 capillaries

When tumor is small, ADC and drug distribution in tumor is driven by **surface exchange** which is a function of diffusion rate D

$$\text{Surface Exchange} = \frac{6 \cdot D}{R^2_{Tumor}}$$

R_{Tumor} ← Tumor Radius

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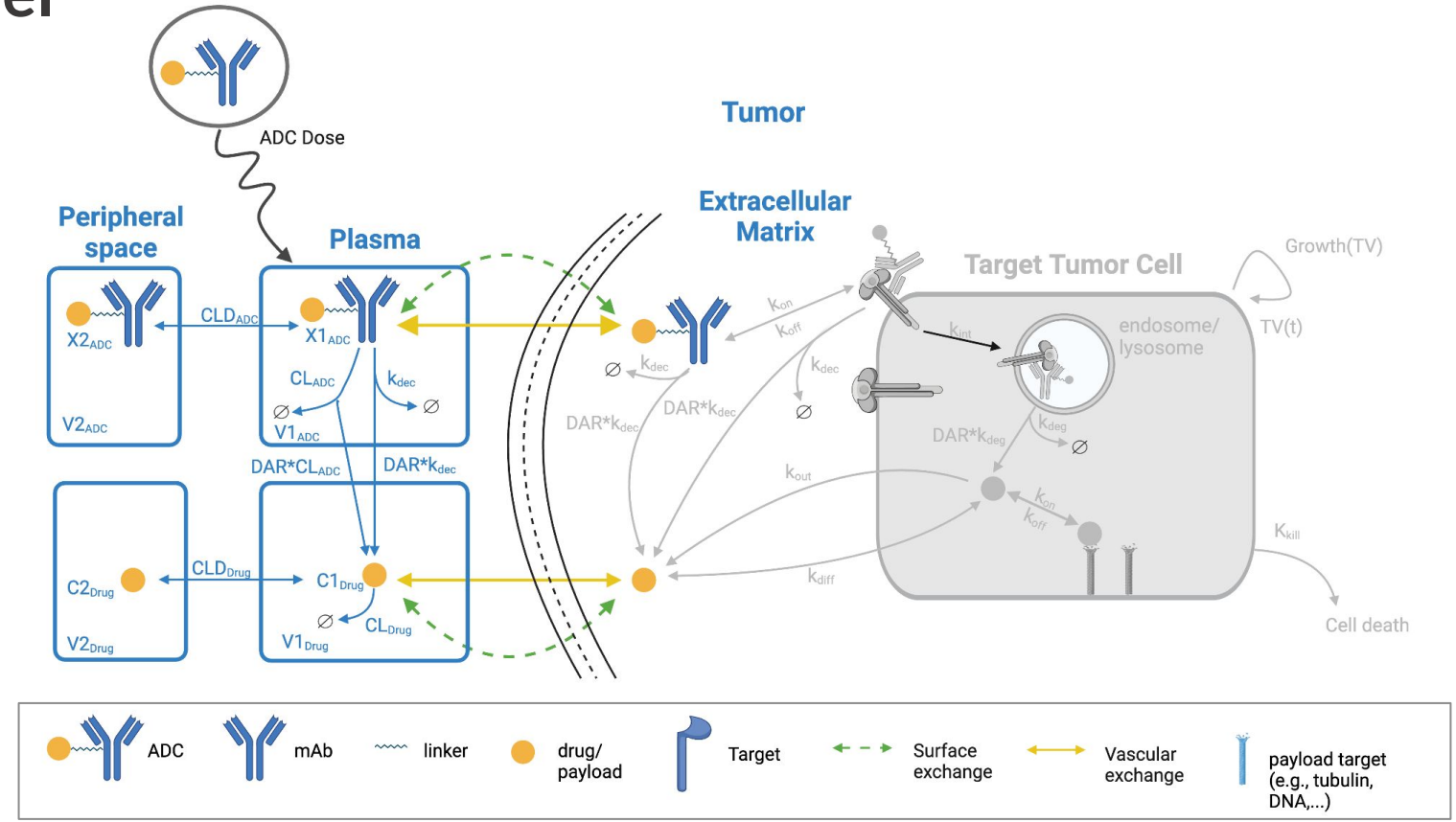
ADC plasma PK was modeled using a two-compartment model



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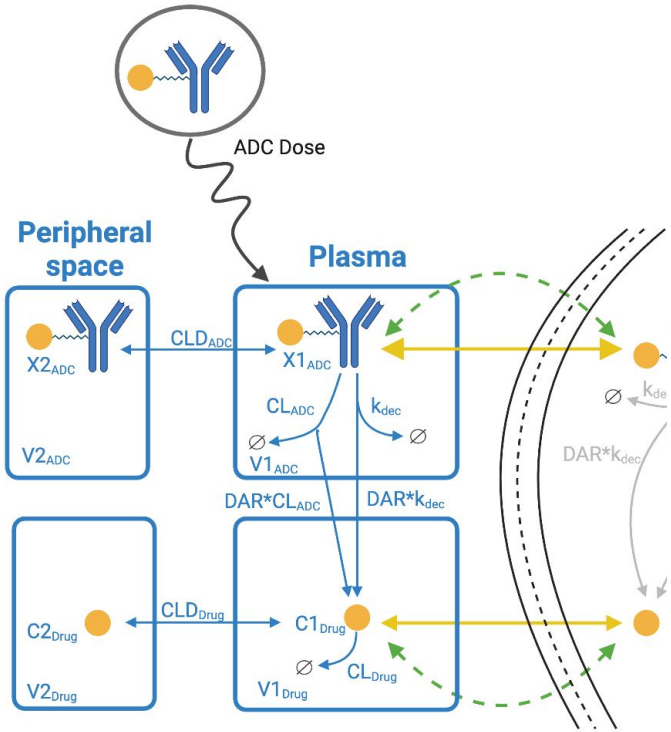
ADC in the plasma



- PK of ADC in plasma updated to include penetration of ADC in tumor with vascular and surface exchange terms as a function of tumor volume (TV)
- Tumor void fraction (ε) specific for ADC and drug (based on respective molecular weight)

Central and distributional clearance & non-specific deconjugation

$$\frac{d\,X1_{ADC}}{dt} = \boxed{\begin{aligned} &- \frac{CL_{ADC}}{V1_{ADC}} \cdot X1_{ADC} - \frac{CLD_{ADC}}{V1_{ADC}} \cdot X1_{ADC} \\ &+ \frac{CLD_{ADC}}{V2_{ADC}} \cdot X2_{ADC} - k^{ADC}_{dec,plasma} \cdot X1_{ADC} \end{aligned}}$$

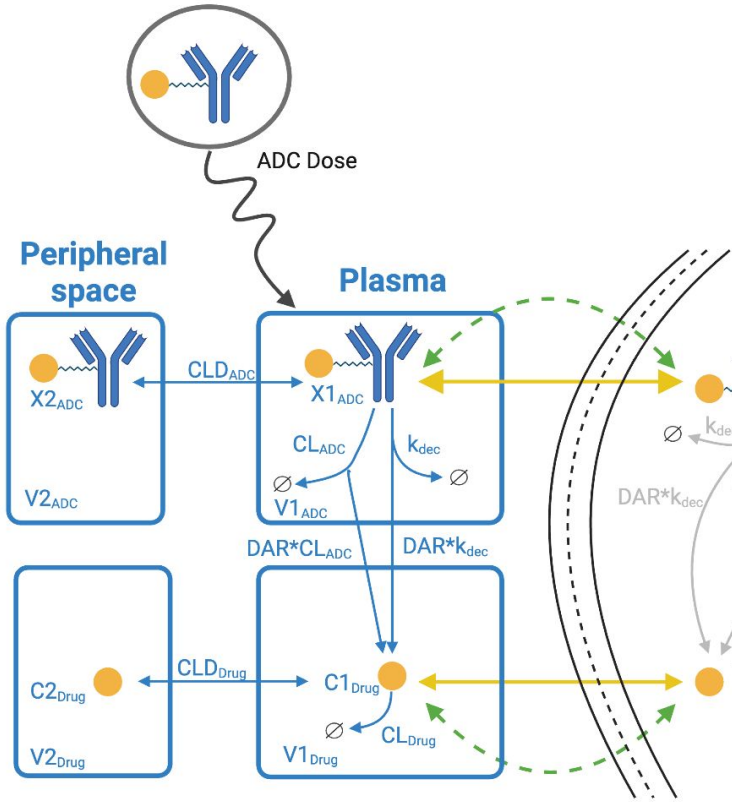
Vascular exchange

$$- \frac{2 \cdot P_{ADC} \cdot R_{Cap}}{R^2_{Krogh}} \cdot \left(\frac{X1_{ADC}}{V1_{ADC}} \cdot \varepsilon_{ADC} - ADC^{ex}_{free} \right) \cdot TV$$

Surface exchange

$$- \frac{6 \cdot D_{ADC}}{R^2_{Tumor}} \cdot \left(\frac{X1_{ADC}}{V1_{ADC}} \cdot \varepsilon_{ADC} - ADC^{ex}_{free} \right) \cdot TV$$

Drug (Payload) in the plasma



- PK of drug in plasma and peripheral compartment also described by simple two compartment model
- Drug PK includes **DAR-dependent deconjugation and degradation** of ADC

Central and distributional clearance

$$\frac{d\,C1_{Drug}}{dt} = \boxed{-\frac{CL_{Drug}}{V1_{Drug}}\cdot C1_{Drug} - \frac{CLD_{Drug}}{V1_{Drug}}\cdot C1_{Drug} + \frac{CLD_{Drug}}{V1_{Drug}}\cdot C2_{Drug}}$$

Vascular exchange

$$- \frac{2\cdot P_{Drug}\cdot R_{Cap}}{R_{Krogh}^2}\cdot (C1_{Drug}\cdot \varepsilon_{Drug} - Drug_{free}^{ex})$$

Surface exchange

$$- \frac{6\cdot D_{Drug}}{R_{Tumor}^2}\cdot (C1_{Drug}\cdot \varepsilon_{Drug} - Drug_{free}^{ex}) + \frac{X1_{ADC}\cdot DAR\cdot k_{dec,plasma}^{ADC}}{V1_{Drug}} + \frac{CL_{ADC}\cdot DAR\cdot \frac{X1_{ADC}}{V1_{ADC}}}{V1_{Drug}}$$

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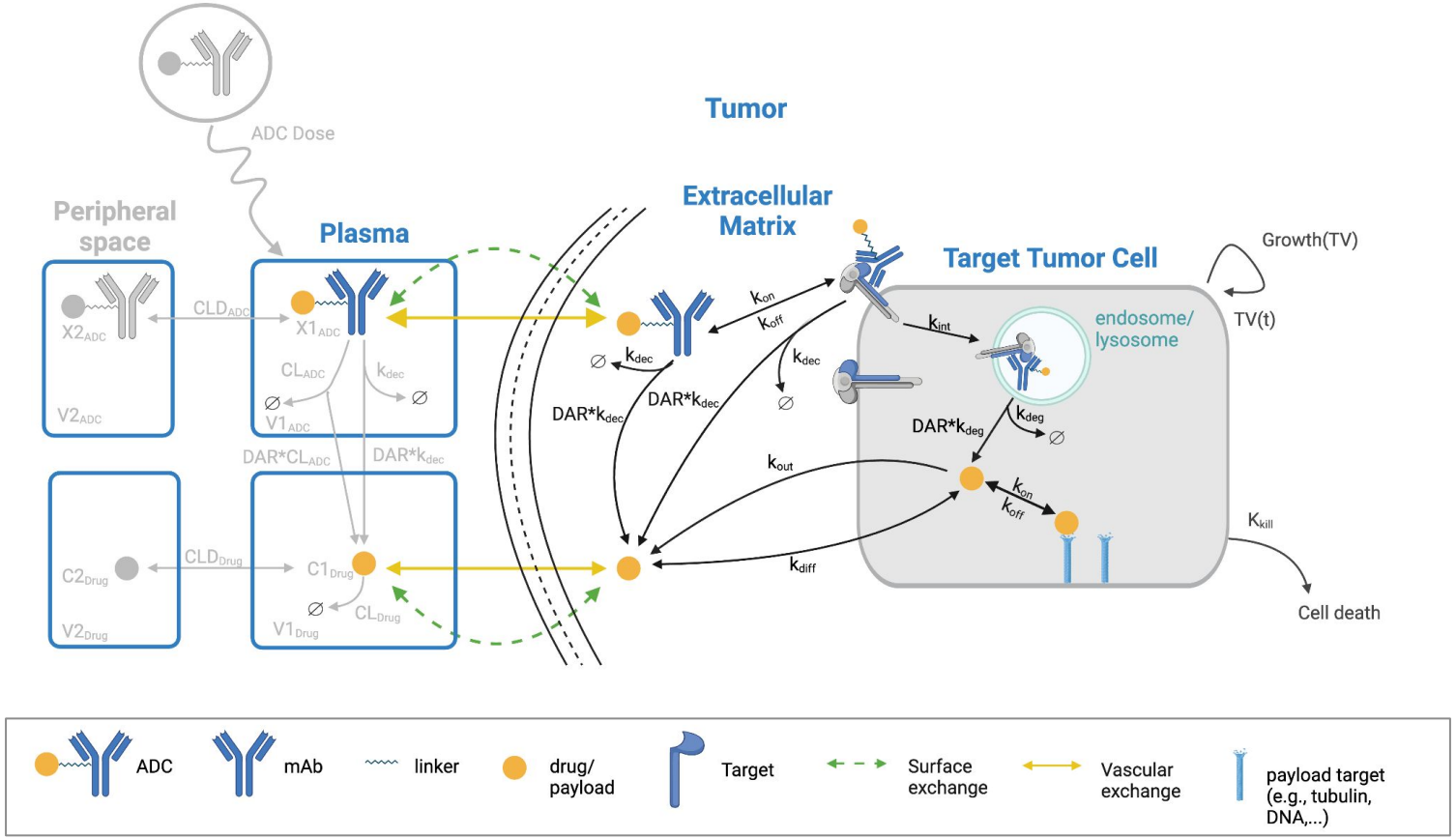
DAR (Drug-antibody ratio: #payload(s)/antibody)

$$\frac{d\ DAR}{dt} = -k^{ADC}_{dec,plasma} \cdot DAR$$

Tumor model



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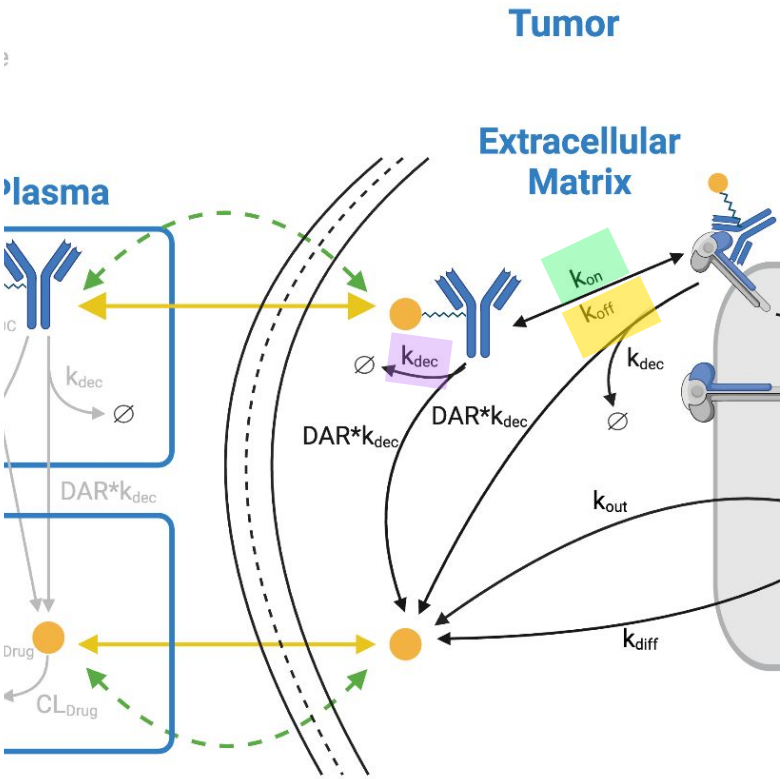
Free ADC in tumor extracellular space

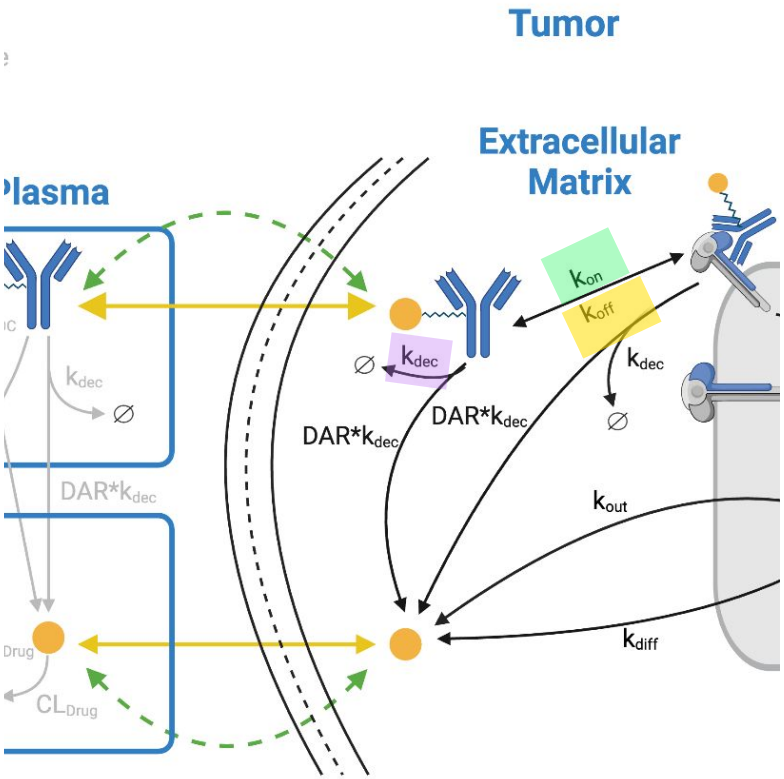


- ADC can distribute to the tumor via surface and vascular exchange processes
- ADC in the extracellular space can bind (k_{on} and k_{off}) to free antigen or deconjugate (k_{dec}) releasing drug
- **Deconjugation rate (k_{dec})** informed by:
  - Linker stability
  - pH-dependent linker cleavage?
  - Protease linker cleavage?

$$\frac{d\,ADC_{free}^{ex}}{dt} = \frac{2 \cdot P_{ADC} \cdot R_{Cap}}{R_{Krogh}^2} \cdot \left(\frac{X1_{ADC}}{V1_{ADC}} \cdot \varepsilon_{ADC} - ADC_{free}^{ex} \right) + \frac{6 \cdot D_{ADC}}{R_{Tumor}^2} \cdot \left(\frac{X1_{ADC}}{V1_{ADC}} \cdot \varepsilon_{ADC} - ADC_{free}^{ex} \right) - k_{on}^{ADC} \cdot ADC_{free}^{ex} \frac{(Ag_{total} - ADC_{bound}^{ex})}{\varepsilon_{ADC}} + k_{off}^{ADC} \cdot ADC_{bound}^{ex} - k_{dec}^{ADC} \cdot ADC_{free}^{ex}$$

Free Antigen

Free ADC in tumor extracellular space



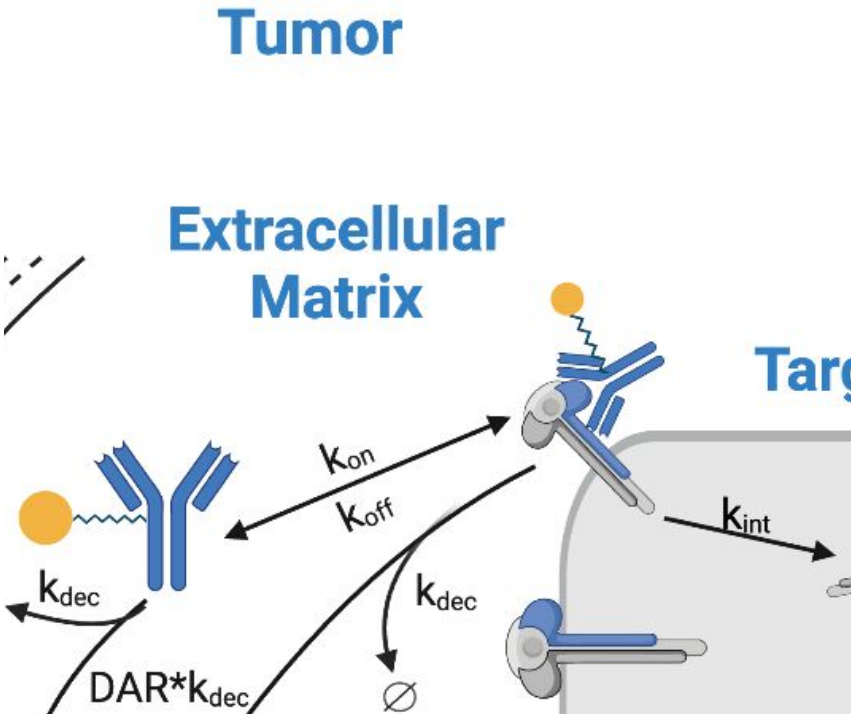
$$\text{flux\_ADC\_antigen\_binding} = k_{on}^{ADC} \cdot ADC_{free}^{ex} \cdot \frac{Ag_{total} - ADC_{bound}^{ex}}{\epsilon_{ADC}}$$

$$\text{flux\_ADC\_antigen\_unbinding} = k_{off}^{ADC} \cdot ADC_{bound}^{ex}$$

$$\text{flux\_free\_ADC\_dec} = k_{dec}^{ADC} \cdot ADC_{free}^{ex}$$

$$\frac{d}{dt} ADC_{free}^{ex} = \frac{2 \cdot P_{ADC} \cdot R_{Cap}}{R_{Krogh}^2} \cdot \left(\frac{X1_{ADC}}{V1_{ADC}} \cdot \epsilon_{ADC} - ADC_{free}^{ex}\right) + \frac{6 \cdot D_{ADC}}{R_{Tumor}^2} \cdot \left(\frac{X1_{ADC}}{V1_{ADC}} \cdot \epsilon_{ADC} - ADC_{free}^{ex}\right) - \text{flux\_ADC\_antigen\_binding} + \text{flux\_ADC\_antigen\_unbinding} - \text{flux\_free\_ADC\_dec}$$

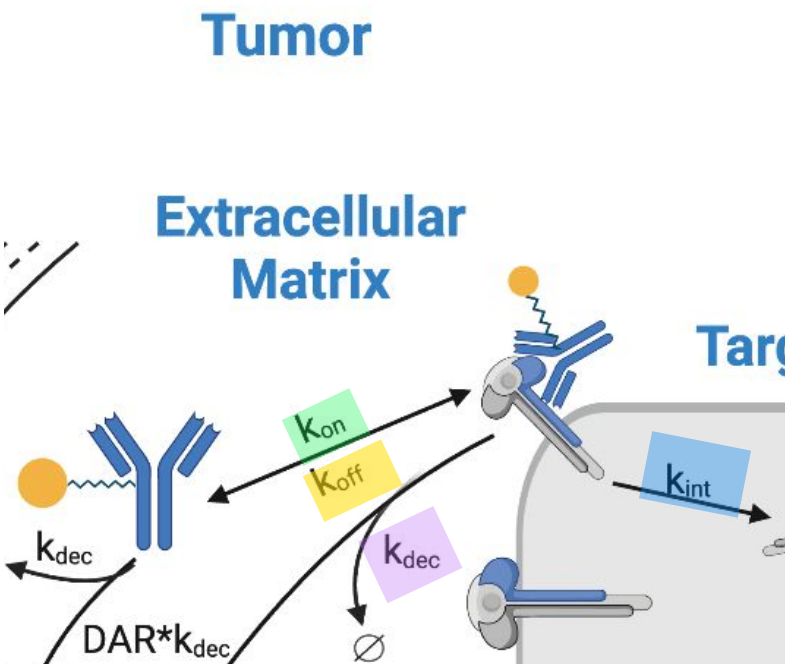
Exercise 1: Derive the equation for ADC-antigen complex (C_ADC_b_ex_nM)



Questions to consider:

- What are the key mechanisms of action taking place?
- What parameters are involved in these processes?

Exercise 1: Derive the equation for ADC-antigen complex (C_ADC_b_ex_nM)



- ADC in extracellular space can bind to free antigen on tumor cell
- **Binding constants (k_{on} and k_{off})** informed by:
  - Target affinity assays
  - SPR/Biacore affinity
  - Cell-based binding assay
- ADC bound to antigen can internalize (k_{int})into tumor cell or deconjugate (k_{dec})to release payload in the extracellular space

Free Antigen

$$\frac{d\,ADC^{ex}_{bound}}{dt} = k^{ADC}_{on} \cdot ADC^{ex}_{free} \cdot \frac{(Ag_{total} - ADC^{ex}_{bound})}{\varepsilon_{ADC}} - \left(k^{ADC}_{off} + k^{ADC}_{int} + k^{ADC}_{dec}\right) \cdot ADC^{ex}_{bound}$$

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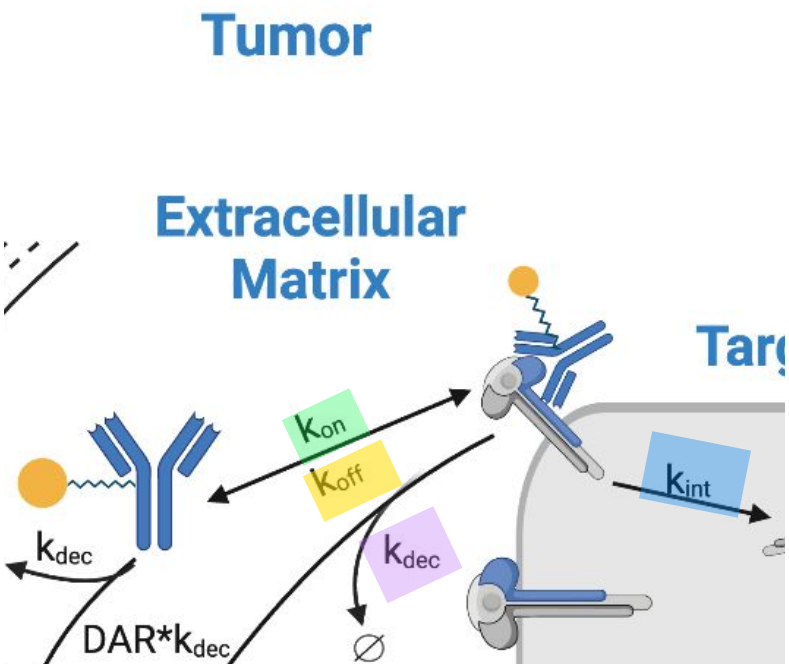
Exercise 1: Derive the equation for ADC-antigen complex (C_ADC_b_ex_nM)



$$\text{flux\_ADC\_antigen\_binding} = k_{on}^{ADC} \cdot ADC_{free}^{ex} \cdot \frac{Ag_{total} - ADC_{bound}^{ex}}{\epsilon_{ADC}}$$

$$\text{flux\_ADC\_antigen\_unbinding} = k_{off}^{ADC} \cdot ADC_{bound}^{ex}$$

$$\text{flux\_bound\_ADC\_dec} = k_{dec}^{ADC} \cdot ADC_{bound}^{ex}$$

$$\text{flux\_bound\_ADC\_internalization} = k_{int}^{ADC} \cdot ADC_{bound}^{ex}$$

$$\frac{d}{dt} ADC_{bound}^{ex} = \text{flux\_ADC\_antigen\_binding} - \text{flux\_ADC\_antigen\_unbinding} - \text{flux\_bound\_ADC\_dec} - \text{flux\_bound\_ADC\_internalization}$$

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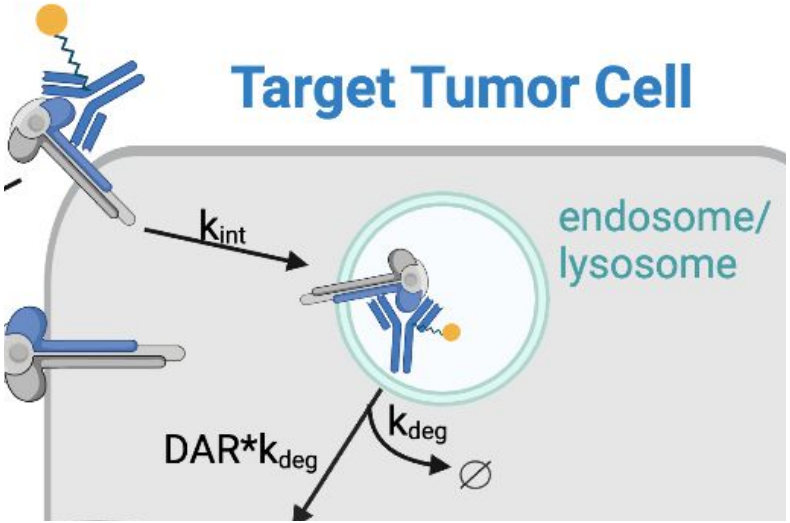
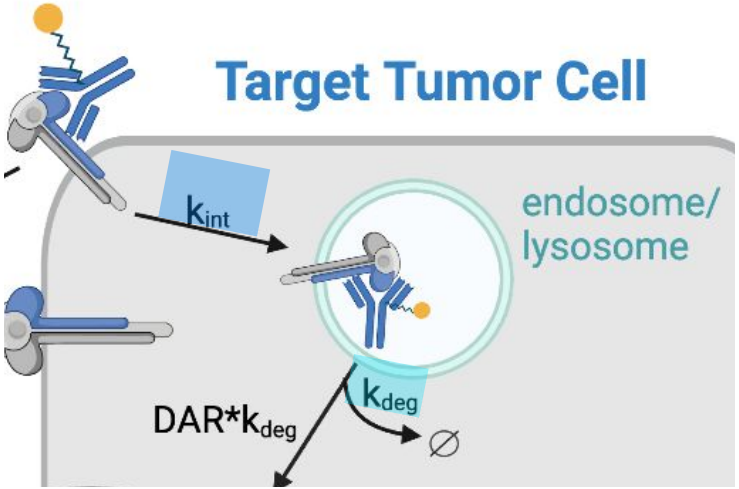
Exercise 2: Derive the dynamics for the endosomal/ lysosomal ADC (C_ADC_endolyso_cell_nM)



Questions to consider:

- What are the key mechanisms of action taking place?
- What parameters are involved in these processes?

Exercise 2: Derive the dynamics for the endosomal/ lysosomal ADC (C_ADC_endolyso_cell_nM)



- ADC bound to antigen is internalized (k_{int}) into the tumor cell
- **Internalization rate (k_{int})** informed by:
  - Internalization assays, turnover assays
- After internalization of ADC, ADC can be degraded (k_{deg}) to release drug in the cytoplasm
- **Degradation rate (k_{deg})** is informed by:
  - Receptor expression (immunofluoresence)
  - Receptor shedding

$$\frac{d\ ADC_{endo/lyso}^{cell}}{dt} = k_{int}^{ADC} \cdot ADC_{bound}^{ex} - k_{deg}^{ADC} \cdot ADC_{endo/lyso}^{cell}$$

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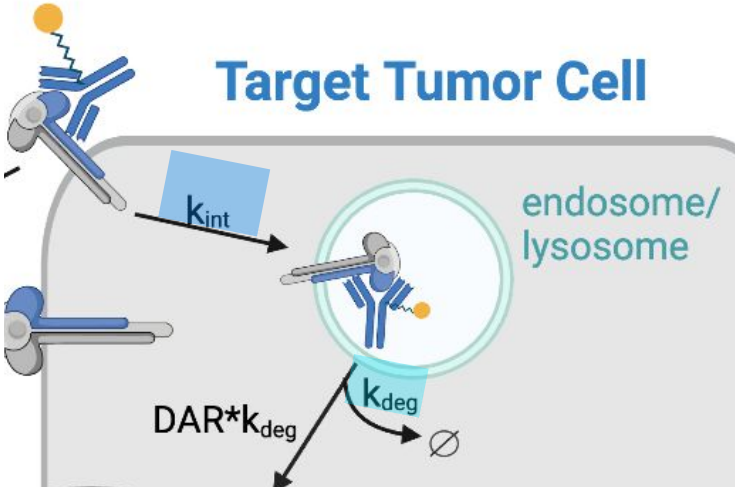
Exercise 2: Derive the dynamics for the endosomal/ lysosomal ADC (C_ADC_endolyso_cell_nM)

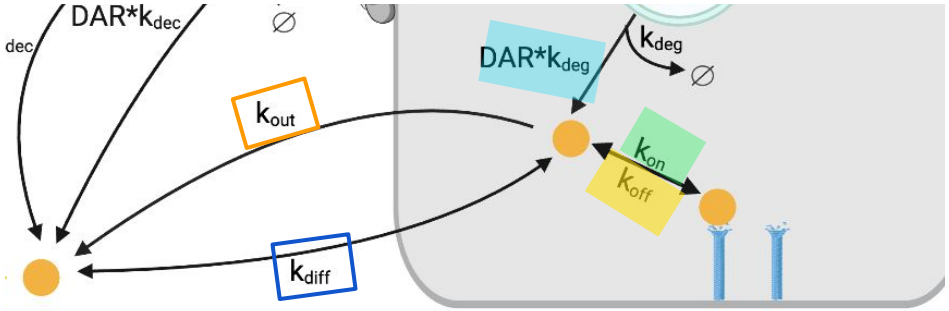


$$\text{flux\_bound\_ADC\_internalization} = k_{int}^{ADC} \cdot ADC_{bound}^{ex}$$

$$\text{flux\_end\_ADC\_deg} = k_{deg}^{ADC} \cdot ADC_{endo/lyso}^{cell}$$

$$\frac{d}{dt} ADC_{endo/lyso}^{cell} = \text{flux\_bound\_ADC\_internalization} - \text{flux\_end\_ADC\_deg}$$

Unconjugated intracellular free payload



- DAR-dependent degradation of ADC along with release of drug from the target results in free drug in the intracellular space
- Free drug can diffuse in and out of the cytoplasm via bidirectional diffusion process (k_{diff})
- **Bidirectional diffusion rate (k_{diff})** informed by:
  - Linker design and drug properties

Free Payload Target

$$\frac{d\,Drug_{free}^{cell}}{dt} = k_{deg}^{ADC} \cdot DAR \cdot ADC_{endo/lyso}^{cell} - k_{on}^{Tub} \cdot Drug_{free}^{cell} \cdot (Tub_{total} - Drug_{bound}^{cell})$$
$$+ k_{off}^{Tub} \cdot Drug_{bound}^{cell} - k_{out}^{Drug} \cdot Drug_{free}^{cell} + k_{diff}^{Drug} \cdot (Drug_{free}^{ex} - Drug_{free}^{cell})$$

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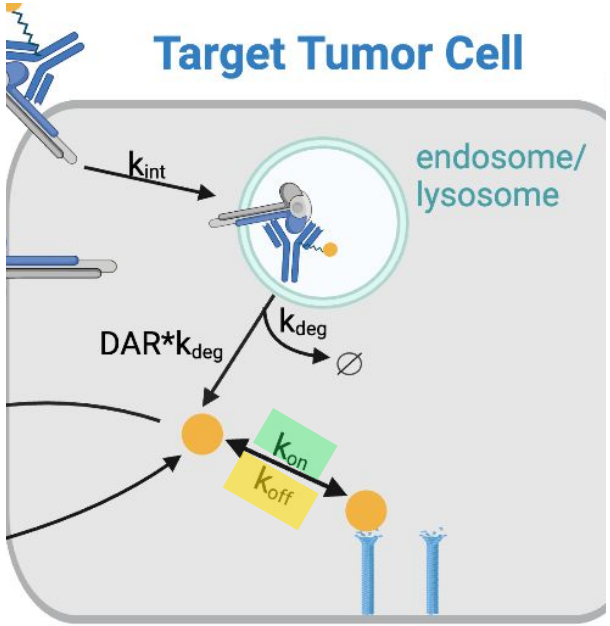
Unconjugated intracellular tubulin-bound payload

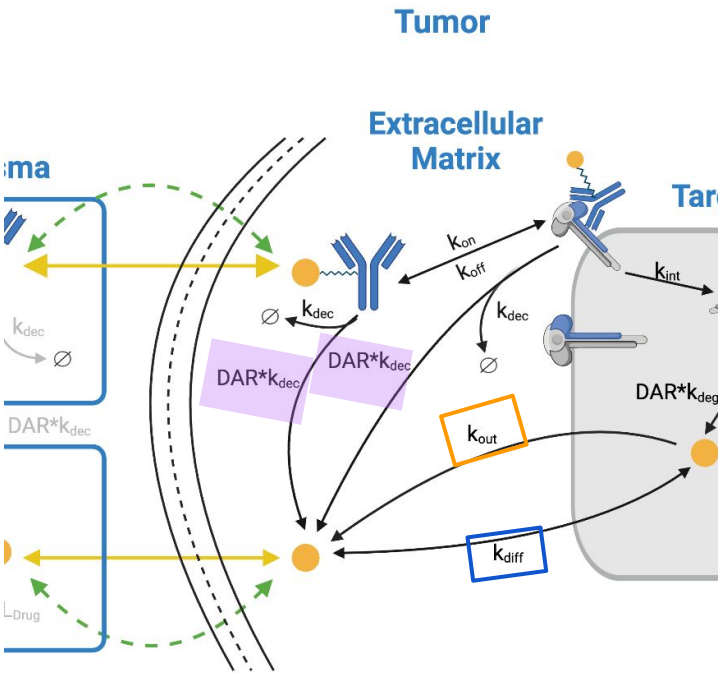


- Free drug reversibly binds to the target in the cytoplasm, causing cell death
- **Binding constants (k_{on} and k_{off})** informed by:
  - Target affinity assays
  - SPR/Biacore affinity
  - Cell-based binding assay
- Drug can cause death via:
  - Microtubule disruption
  - DNA damage
  - Topoisomerase inhibition

Free Payload Target

$$\frac{d\ Drug_{bound}^{cell}}{dt} = k_{on}^{Tub} \cdot Drug_{free}^{cell} \cdot \left(Tub_{total} - Drug_{bound}^{cell}\right) - k_{off}^{Tub} \cdot Drug_{bound}^{cell}$$

Free payload in the tumor extracellular space



- Free drug can enter the tumor via vascular and surface exchange characterized by drug-specific permeability and diffusion rates
- DAR-dependent deconjugation of free ADC and antigen-bound ADC can result in free drug in the extracellular space
- Outward active efflux (k_{out}) can transport free drug out of the tumor cell for some drugs

$$\frac{d\,Drug_{free}^{ex}}{dt} = \frac{2 \cdot P_{Drug} \cdot R_{Cap}}{R_{Krogh}^2} \cdot (C1_{Drug} \cdot \varepsilon_{Drug} - Drug_{free}^{ex}) + \frac{6 \cdot D_{Drug}}{R_{Tumor}^2} \cdot (C1_{Drug} \cdot \varepsilon_{Drug} - Drug_{free}^{ex}) + k_{out}^{Drug} \cdot Drug_{free}^{cell} + k_{dec}^{ADC} \cdot DAR \cdot (ADC_{free}^{ex} + ADC_{bound}^{ex}) - k_{diff}^{Drug} \cdot (Drug_{free}^{ex} - Drug_{free}^{cell})$$

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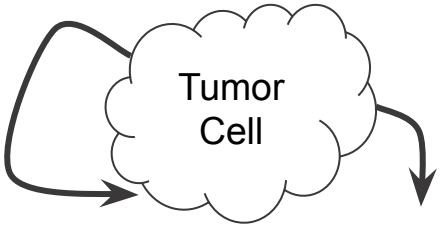
Modeling the PD effect of the ADC through drug induced killing

$$\text{Growth}(TV) = \frac{k_{\text{growth}}^{\text{exponential}}}{\left(1+\left(\frac{k_{\text{growth}}^{\text{exponential}}}{k_{\text{growth}}^{\text{linear}}} \times TV\right)^{\Psi}\right)^{\frac{1}{\Psi}}}\left(1-\frac{TV}{V_{\max}}\right)$$

Tumor growth model describes exponential growth followed by linear growth.



Tumor killing driven by:

- intracellular unconjugated drug concentration
- maximal killing rate
- KC_{50} (or IC_{50})

$$K_{Kill}(Drug_{free}^{cell} + Drug_{bound}^{cell}) = \frac{k_{kill}^{max} \cdot (Drug_{free}^{cell} + Drug_{bound}^{cell})}{KC_{50} + Drug_{free}^{cell} + Drug_{bound}^{cell}}$$

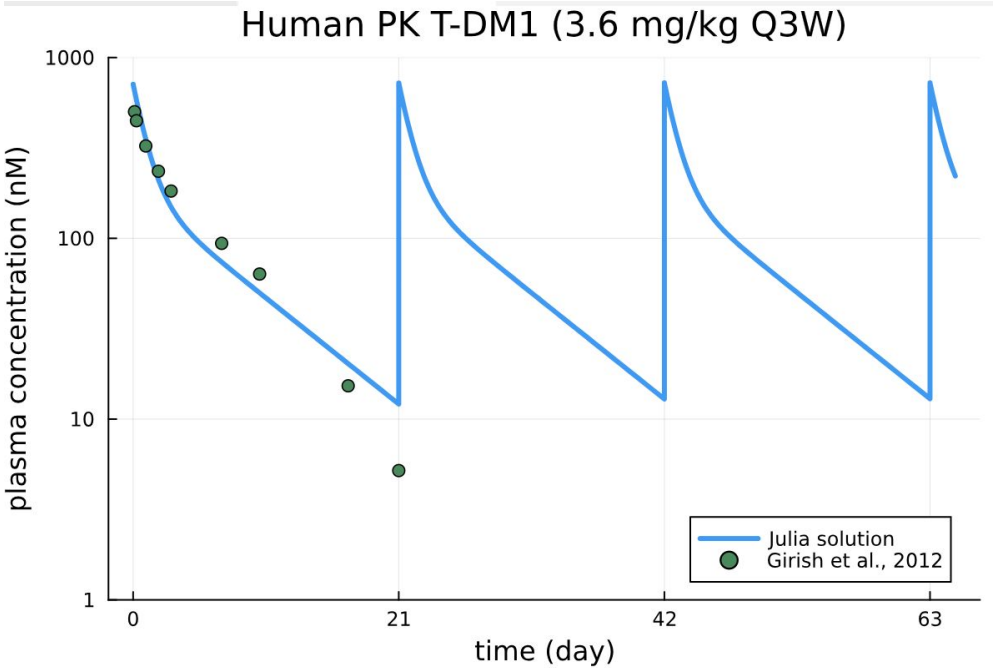
Tumor Volume determined by $\frac{d\ TV}{dt} = (Growth(TV) - K_{Kill}(Drug_{free}^{cell} + Drug_{bound}^{cell})) \cdot TV$

Tumor growth model based on the following resources:

- Haddish-Berhane, N., Shah, D. K., Ma, D., Leal, M., Gerber, H. P., Sapra, P., Barton, H. A., & Betts, A. M. (2013). On translation of antibody drug conjugates efficacy from mouse experimental tumors to the clinic: a PK/PD approach. *Journal of pharmacokinetics and pharmacodynamics*, *40*(5), 557–571. https://doi.org/10.1007/s10928-013-9329-x
- Simeoni, M., Magni, P., Cammia, C., De Nicolao, G., Croci, V., Pesenti, E., Germani, M., Poggesi, I., & Rocchetti, M. (2004). Predictive pharmacokinetic-pharmacodynamic modeling of tumor growth kinetics in xenograft models after administration of anticancer agents. *Cancer research*, *64*(3), 1094–1101. https://doi.org/10.1158/0008-5472.can-03-2524

Model implementation in Julia

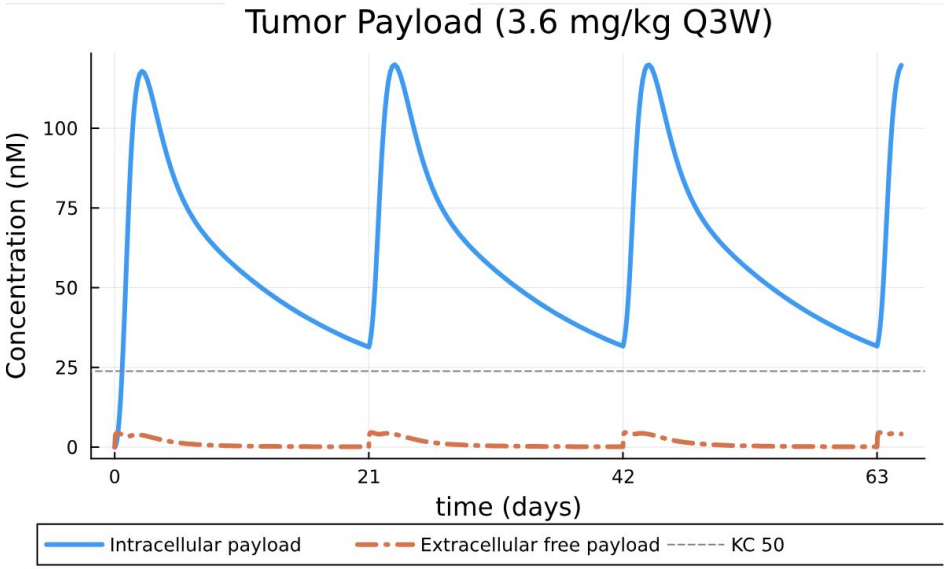
Model predicted T-DM1 PK matches clinical observations

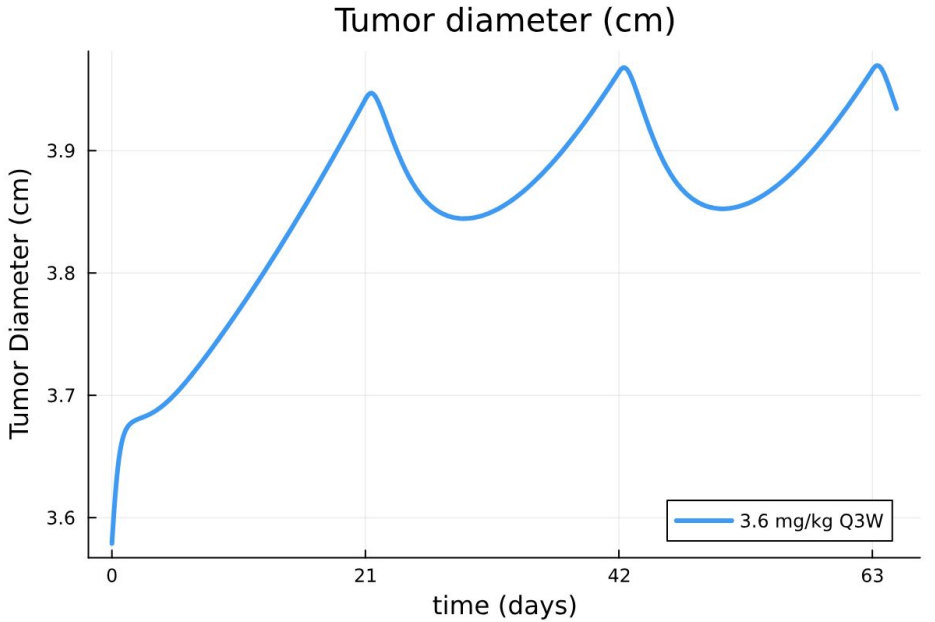


- T-DM1 DAR: 3.5
- Dose: 3.6 mg/kg Q3W
- Body weight: 70kg
- Model simulated for 65 days

Data from Girish, S., Gupta, M., Wang, B., Lu, D., Krop, I. E., Vogel, C. L., Burris Iii, H. A., LoRusso, P. M., Yi, J. H., Saad, O., Tong, B., Chu, Y. W., Holden, S., & Joshi, A. (2012). Clinical pharmacology of trastuzumab emtansine (T-DM1): an antibody-drug conjugate in development for the treatment of HER2-positive cancer. *Cancer chemotherapy and pharmacology*, *69*(5), 1229–1240. https://doi.org/10.1007/s00280-011-1817-3

Model predictions of tumor growth inhibition driven by intracellular concentration of payload in tumor cell





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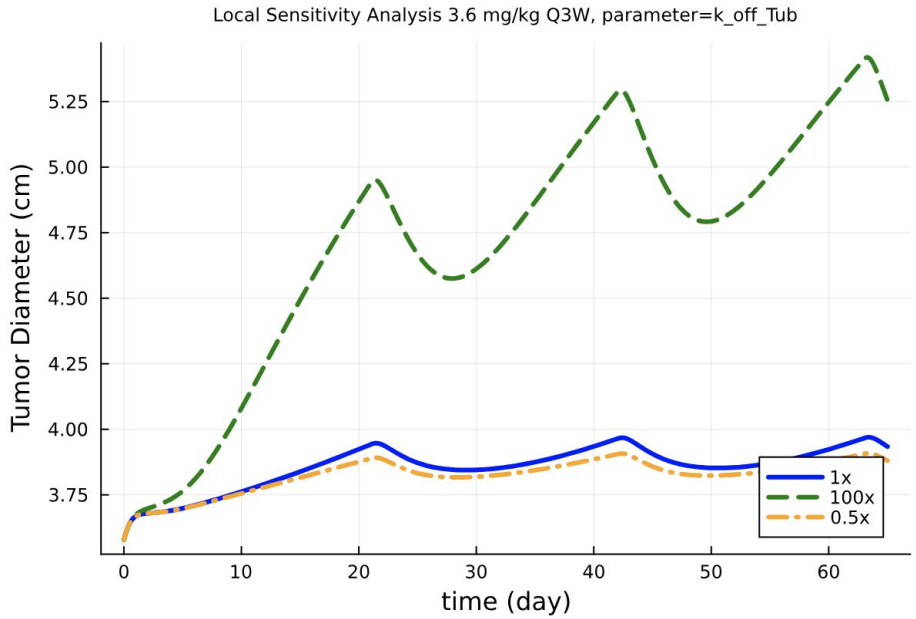
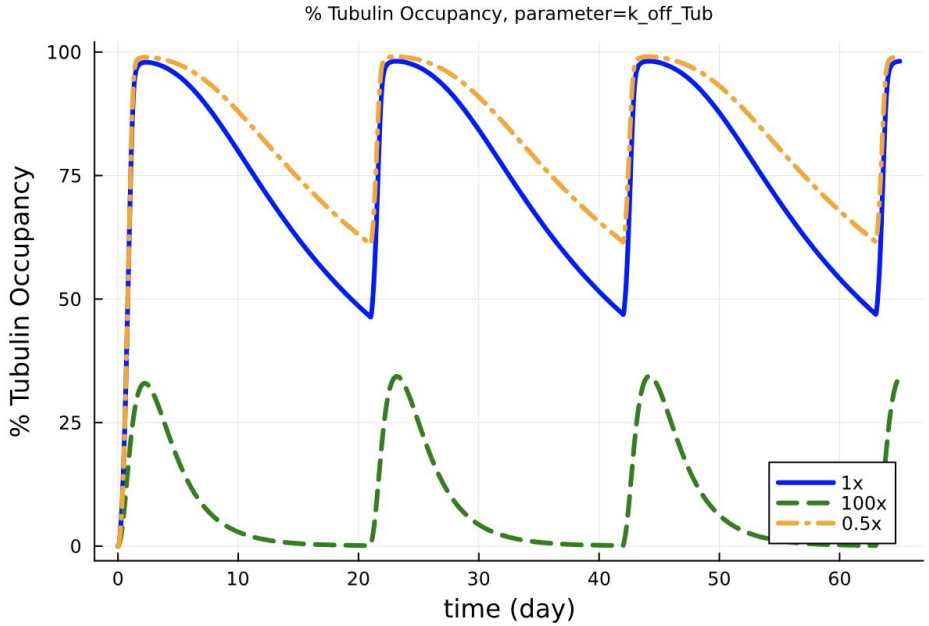
Modeling Activity: Local Sensitivity Analysis

Results for k_off_Tub: binding affinity of drug DM-1 for tubulin





$$\text{Percent Tubulin Occupancy} = \frac{Drug_{bound}^{cell}}{Tub_{total}} \cdot 100$$

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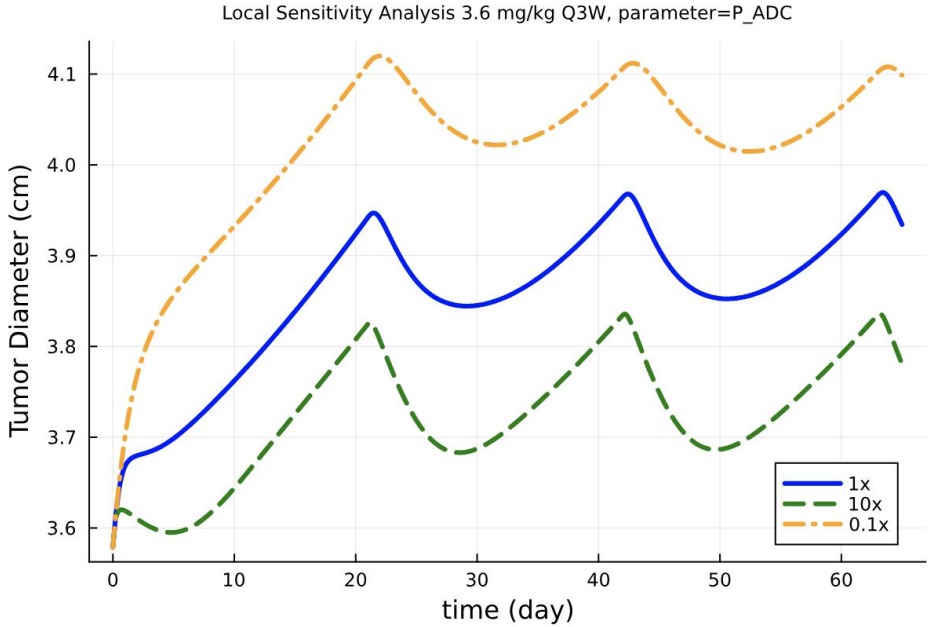
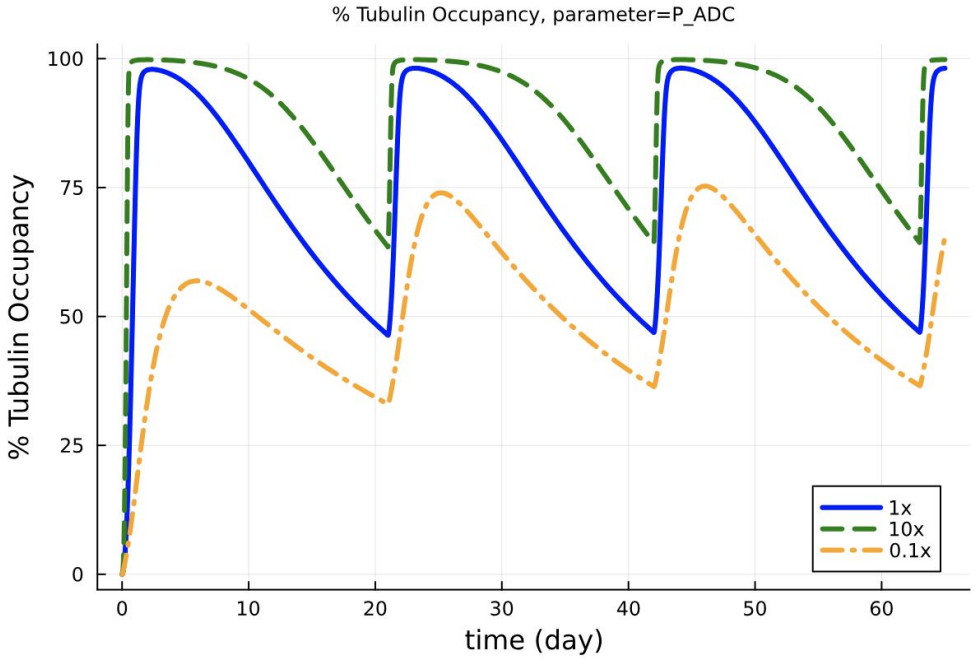
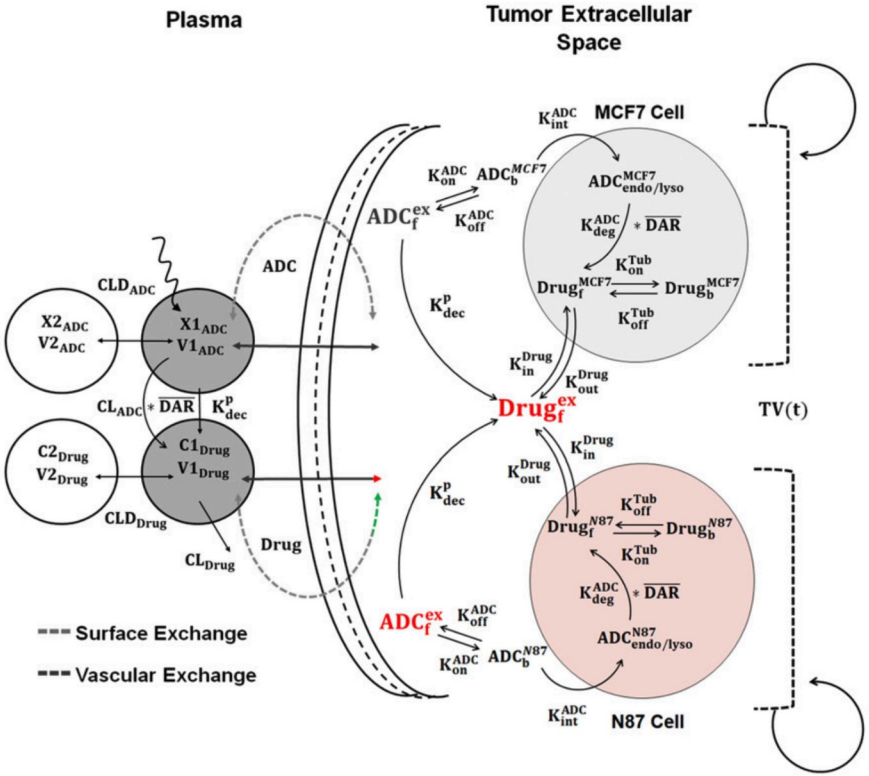
Results for P_ADC: permeability of ADC across the tumor blood vessels





ADC Modeling Extensions

Bystander effect



Receptor-positive tumor cells

Receptor-negative tumor cells

Figure adapted from Singh, et al.,. (2020). Evolution of the Systems Pharmacokinetics-Pharmacodynamics Model for Antibody-Drug Conjugates to Characterize Tumor Heterogeneity and In Vivo Bystander Effect. The Journal of pharmacology and experimental therapeutics, 374(1), 184–199.

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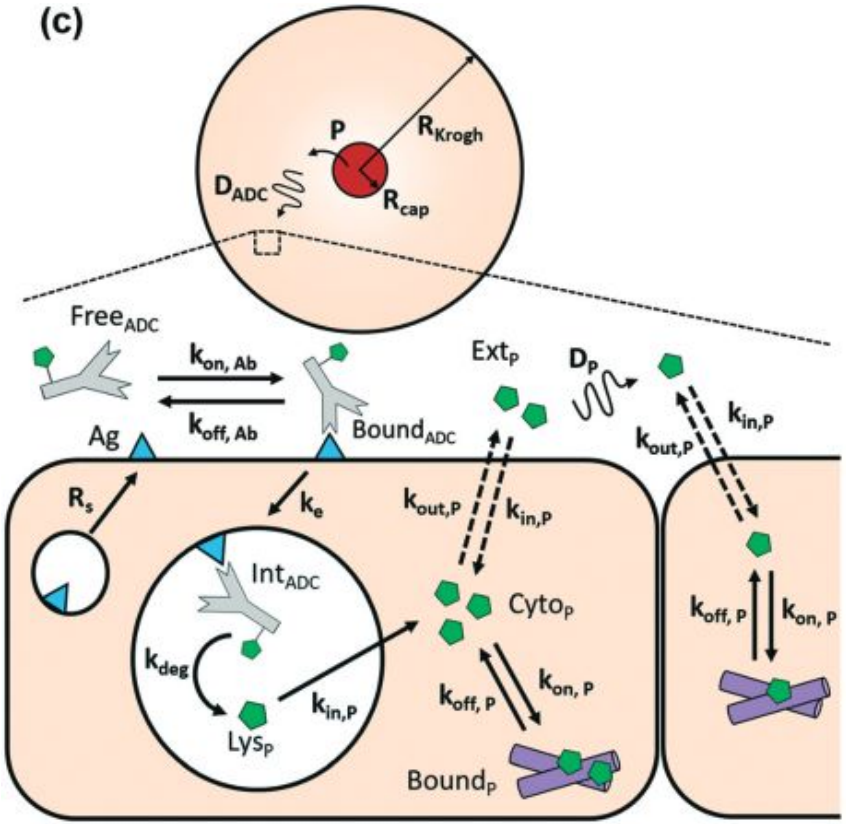
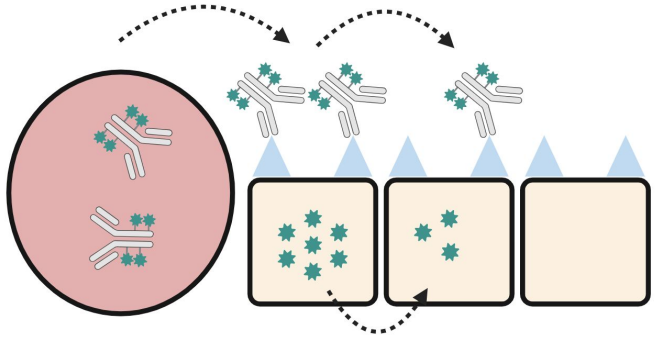
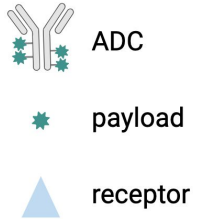
Tumor penetration model with PDEs







(c) Graphical depiction of Krogh cylinder model (top) incorporating bystander effects of payload at the cellular level (bottom)

From Figure 1 of Khera, E., Cilliers, C., Bhatnagar, S. & Thurber G.M. (2018). Computational transport analysis of antibody-drug conjugate bystander effects and payload tumoral distribution: implications for therapy. *Molecular Systems Design & Engineering*, *3*(1), 73 - 88. https://doi.org/10.1039/c7me00093f

PBPK

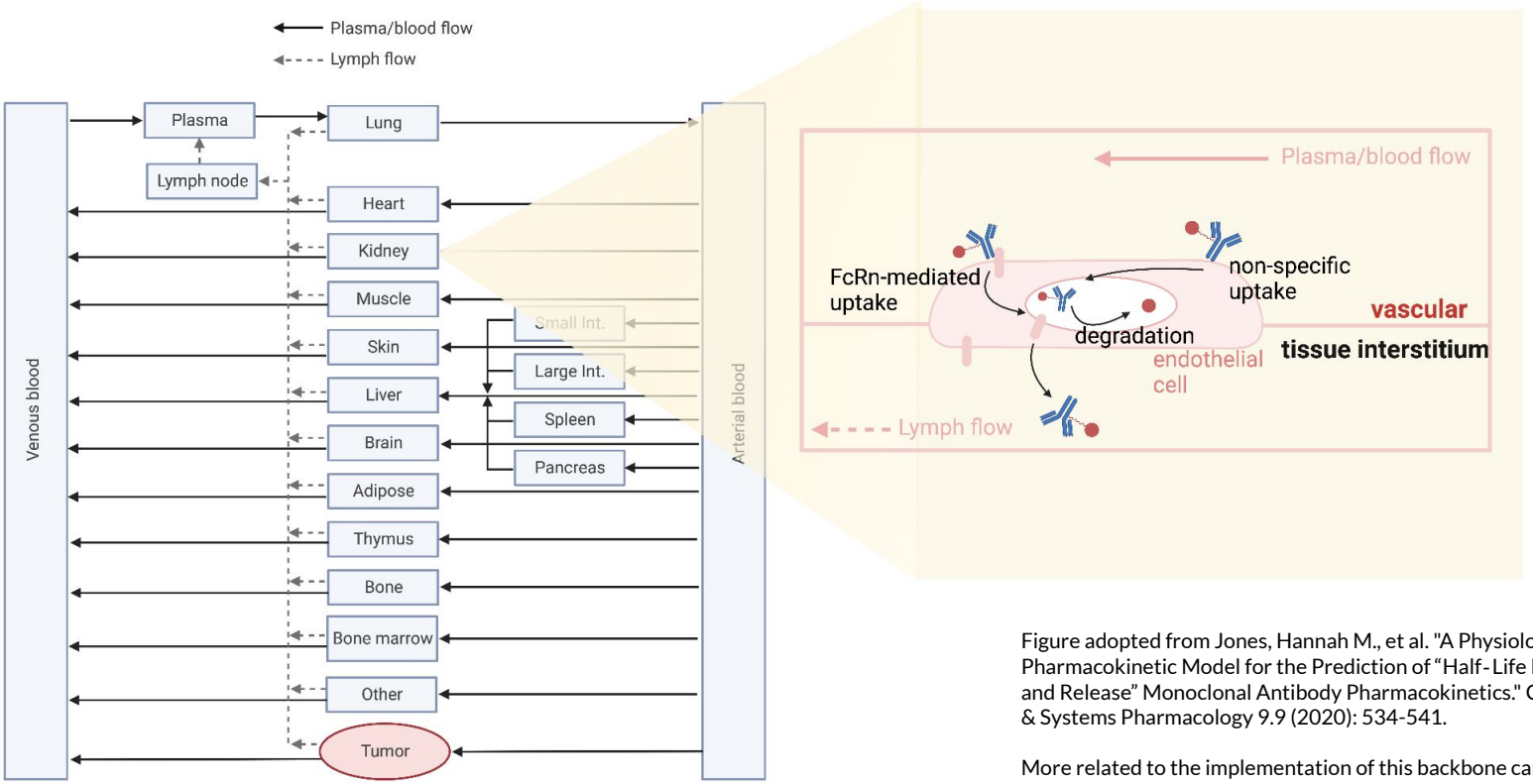


Figure adopted from Jones, Hannah M., et al. "A Physiologically-Based Pharmacokinetic Model for the Prediction of "Half-Life Extension" and "Catch and Release" Monoclonal Antibody Pharmacokinetics." CPT: Pharmacometrics & Systems Pharmacology 9.9 (2020): 534-541.

More related to the implementation of this backbone can be found in this Metrum GitHub repo.

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