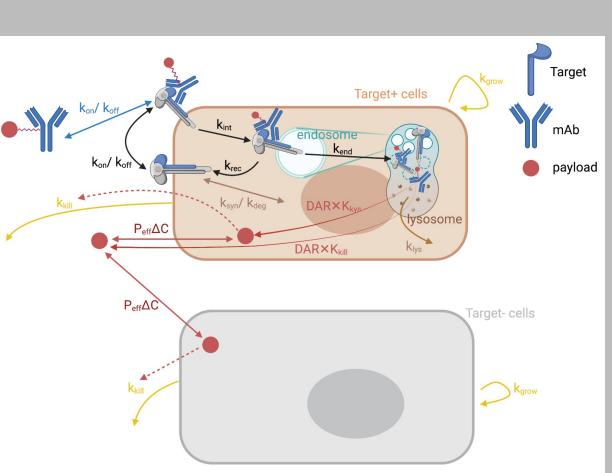


# Hands-on Case Studies Session: A Step-by-Step Guide to Building a QSP Model (Using ADC in Oncology)

24-Sept-2022

Matthew Riggs, Ph.D.  
Chief Science Officer, MetrumRG



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# Conflict of Interest Statement

Matthew Riggs is employed by Metrum Research Group (MetrumRG). MetrumRG is a contract research organization. The *Hands On Case Studies* used in this section of the workshop are taken from literature examples published by authors not affiliated with MetrumRG. There are therefore no understood conflicts of interest to declare.



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# Matthew Riggs, PhD, FISoP

- BS Pharmacy; Ph.D. Pharmaceutical Sciences – University of Connecticut School of Pharmacy
- Experienced and passionate developer of therapeutics for rare and metabolic diseases.
- 20+ years of experience applying modeling and simulation methods to clinical and drug development decision support
- 4.5 years in Clinical Pharmacology at Pfizer Global R&D
- 17 years at Metrum Research Group
- Founded MetrumRG's Systems Pharmacology group
- As CSO, works closely with our PKPD, Systems Pharmacology, Statistics, Data Science, and HPC (Metworx<sup>TM</sup>) teams to continually advance our quantitative decision support



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# Acknowledgments

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  - Kiersten Utsey, PhD
  - Yuezhe Li, PhD
- MetrumRG Pharmacokinetics Pharmacodynamics (PKPD) Group
  - John Mondick, PhD (VP, PKPD)



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# Outline

Introduction		Define the Needs		QSP Model Development and Application	
Logging into Metworx	A tool to develop the model (open-source: mrgsolve in R)	Understanding the system: can you draw it?	Understanding the data: can (did) you collect it?	Inputs Assumptions Design Considerations Outputs	minimum, optimal criteria for candidate, dose, tumor target
Today's example: Antibody Drug Conjugates	Evaluating ADC Candidates	Understand the question: what does model need to predict (reliably)?	Prediction outcome: e.g., tumor dynamic response	VVUQ Rubrics Risk based evaluation of sensitivity to assumptions, uncertainty	Extensions to consider: extending to <i>in vivo</i> and clinical cases
Evaluating Targetable Tumor Types	Factors to Consider: Drug load (DAR), target expression level	Other Considerations: e.g., impact of bystander effect			



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# Metworx Log In: Scalable HPC Cluster Creation

Step 1: go to <https://demo.metworx.com/>

Step 2: Enter Fingerprint: **f45f126836**

The screenshot shows the Metworx login interface. At the top is the Metworx logo. Below it is a text instruction: "Enter your organization's fingerprint. If you don't have a fingerprint, select 'No Fingerprint'." A red arrow points to the input field where the fingerprint "f45f126836" is entered. Below the input field is a red circle containing a diagonal slash over the "NO FINGERPRINT" button.

metworx

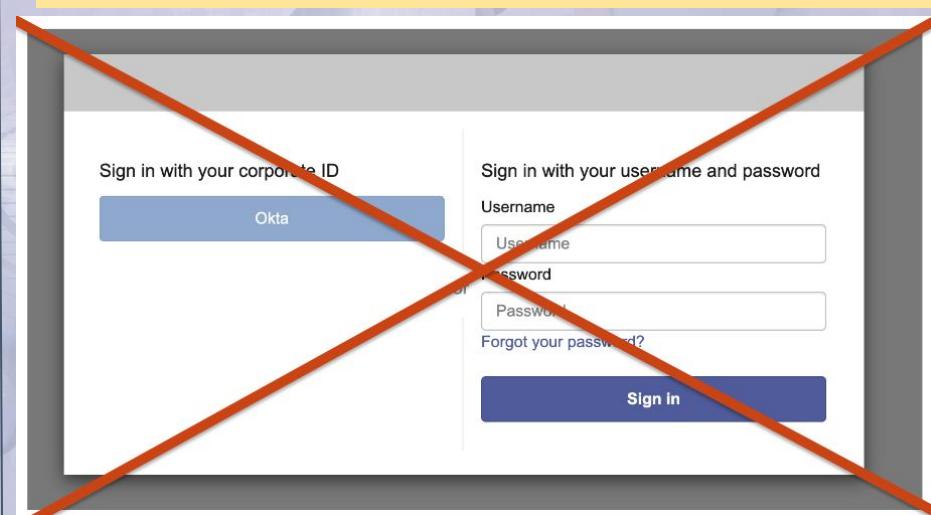
Enter your organization's fingerprint. If you don't have a fingerprint, select "No Fingerprint".

f45f126836

NO FINGERPRINT SUBMIT

If you do not enter fingerprint correctly you will see the below menu and must take the following :

- Close your browser
- Open an Incognito Browser
- Repeat steps 1 and 2



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# Metworx Log In: Scalable HPC Cluster Creation

Step 1: go to **demo.metworx.com**

Step 2: Enter Fingerprint: **f45f126836**



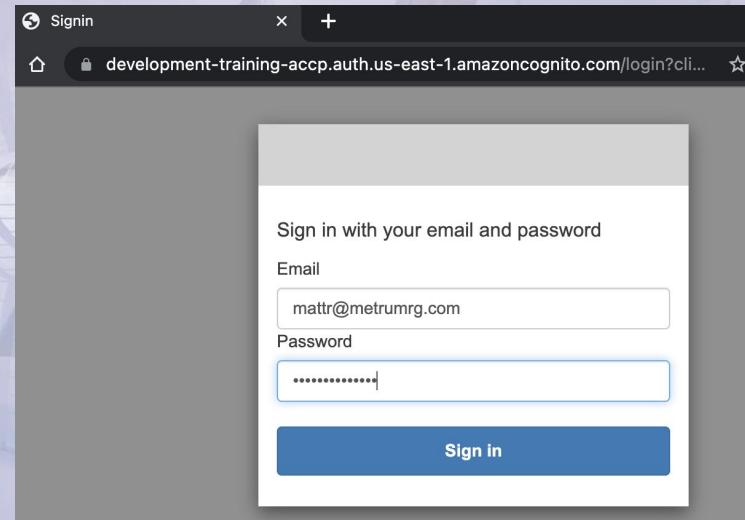
Enter your organization's fingerprint. If you don't have a fingerprint, select "No Fingerprint".

→

NO FINGERPRINT ← SUBMIT

If you did your enter fingerprint correctly you will see the below menu :

- Use your email address as username
- Use the password supplied to you by email



Sign in with your email and password

Email

Password

Sign in



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# Metworx Log In: Scalable HPC Cluster Creation

The screenshot shows the Metworx web application interface. At the top, there is a navigation bar with icons for back, forward, refresh, and home, followed by the URL "demo.metworx.com". To the right of the URL are icons for star, square, and "Incognito", and a three-dot menu. Below the navigation bar is the Metworx logo. On the left side, there is a section titled "My Active Workflows" with a sub-section "0 of 3 Active". Below this, it says "No active workflows". On the right side, there is a section titled "Start a New Workflow" with a dropdown menu showing "metworx-22.08" and a "LAUNCH" button. A red arrow points to the "LAUNCH" button. Below this, there is a section titled "Workflow Info" with a detailed description of the software pre-installed on the workflow.

metworx

Dashboard My Info Sign Out Support Contact

My Active Workflows 0 of 3 Active

No active workflows

Start a New Workflow

metworx-22.08 ? LAUNCH

Workflow Info

All Workflows are launched with the following software pre-installed: RStudio Workbench, RStudio Connect, RStudio Desktop, R, NONMEM, PsN, Python, Pirana, Monolix Suite, Matlab, Git, Apache Subversion, pkgr, GNU Fortran, TexLive (LaTex), Ubuntu (OS), NginX, and Sun Grid Engine



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My Active Workflows 0 of 3

Launch metworx-22.08

Workflow Information

Enter information for your workflow

Workflow Name \* **MRaccp**

Must start with a letter, be at least 4 characters, can contain letters or numbers (no spaces)

Username \* mattt

Workflow username can not be changed after creation. If you need assistance, contact support.

Password \* **\*\*\*\*\***

Confirm Password \* **\*\*\*\*\***

Enter password must be a minimum of 6 characters

Type in password again

Head Node \* 2 vCPU / 8 GB RAM (~\$0.12/hr)

Select the size of your head node

Compute Node \* 2 vCPU / 4 GB RAM (~\$0.09/hr)

Select the size of your compute node

Show advanced settings

Disk Information

Complete one of the following disk selections

New Disk \* **ACCPworkshop**

Pick a name for disk

Size (GB) \* **110**

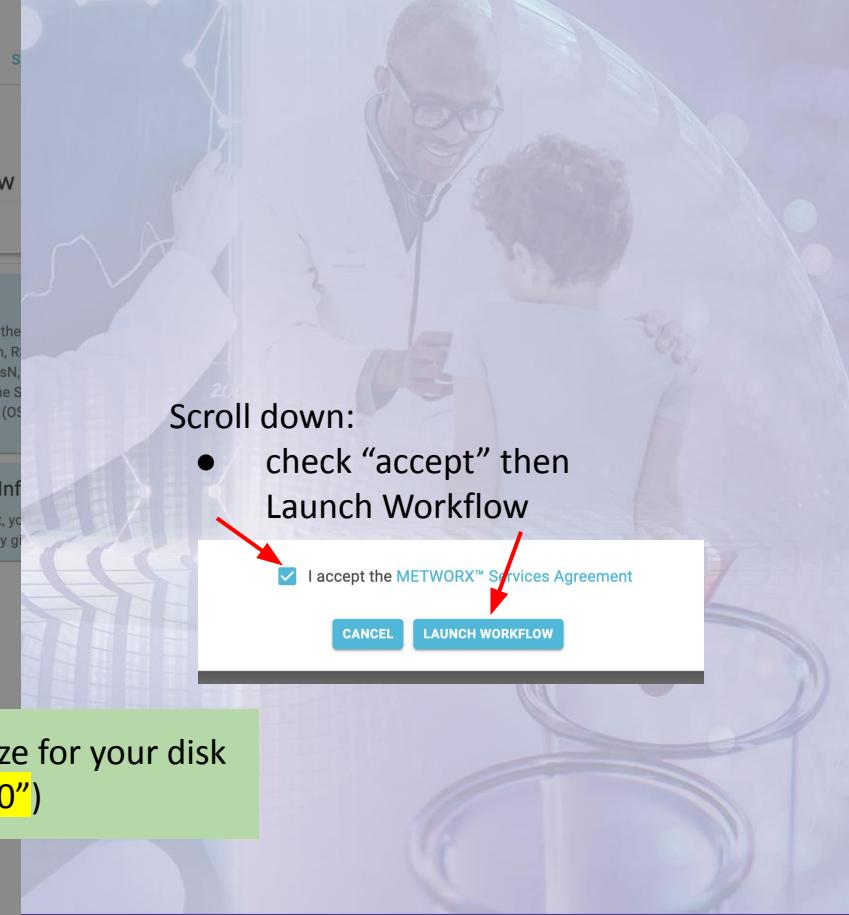
Between 5 to 16384 GB

1. Name your workflow

2. Enter a password (remember it!!)

3. Name your disk

4. Pick a size for your disk (enter "110")



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# Metworx Dashboard – Workflow is Launching

## My Active Workflows 1 of 3 Active



MRaccp i

- ⌚ Created: 1 minute ago
- 🕒 Blueprint: metworx-22.08
- 💽 Disk: ACCPworkshop
- 📅 Status: Creating...

UPDATE

SHUT DOWN

RSTUDIO

RSCONNECT

GUACAMOLE

Head Node

2 vCPU / 8 GB RAM (~\$0.12/hr)

110 GB

PERFORMANCE

Cluster Nodes

2 vCPU / 4 GB RAM (~\$0.09/hr)

0 nodes (of 3)

0 pending jobs



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# Metworx Dashboard – Workflow has Launched

## My Active Workflows

1 of 3 Active



MRaccp

- Created: 20 minutes ago
- Blueprint: metworx-22.08
- Disk: ACCPworkshop
- Status: Running

UPDATE

SHUT DOWN

RSTUDIO

RSCONNECT

GUACAMOLE

Head Node

2 vCPU / 8 GB RAM (~\$0.12/hr)

110 GB

PERFORMANCE

Cluster Nodes

2 vCPU / 4 GB RAM (~\$0.09/hr)

0 nodes (of 3)

0 pending jobs

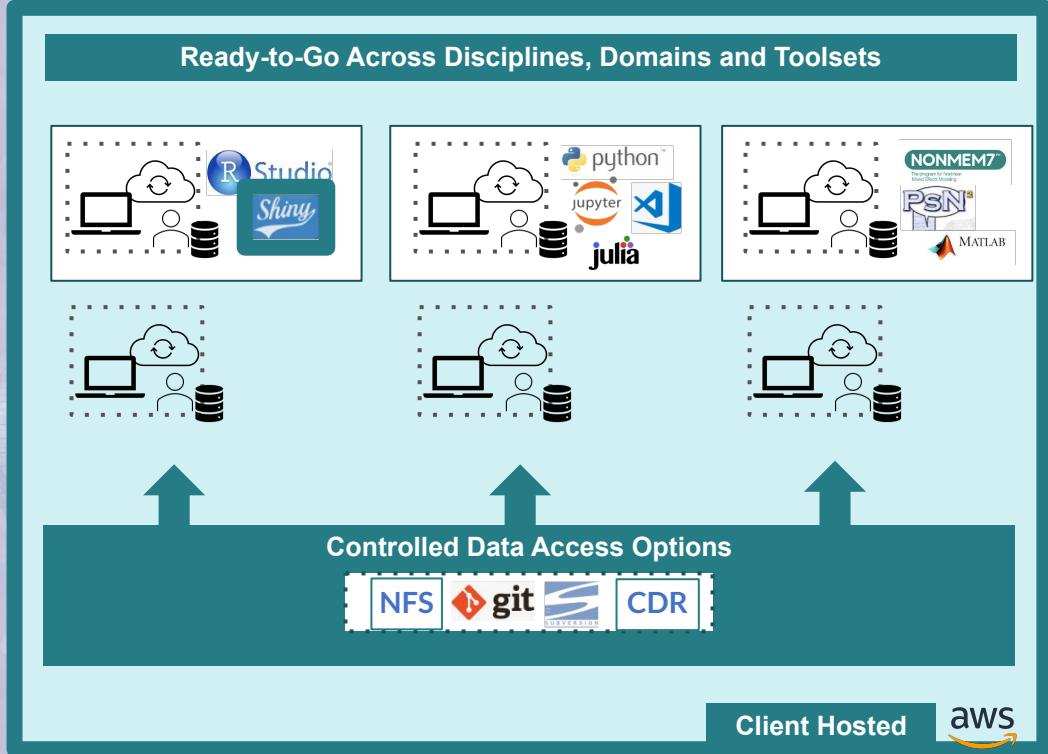
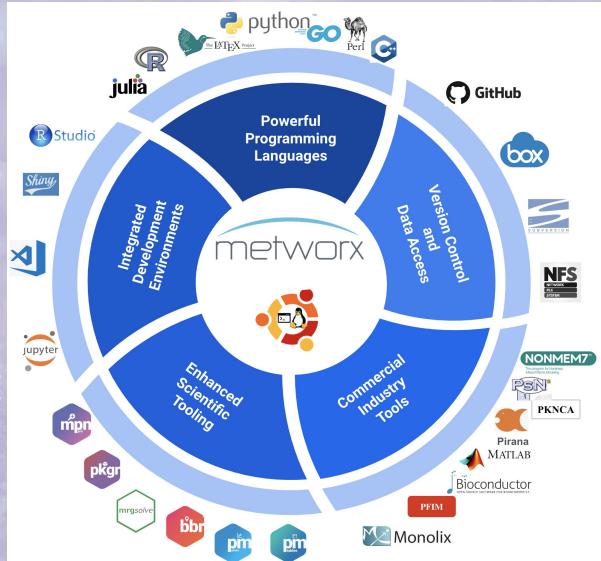


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# Metworx Workflows



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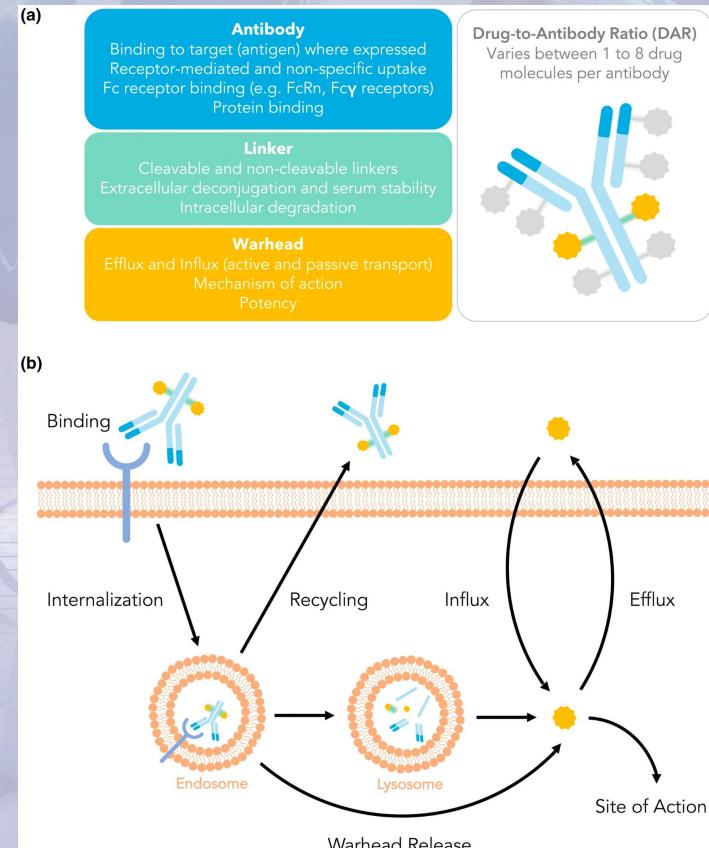
# Key ADC properties and mechanisms for QSP modeling

(a) The antibody, linker, and warhead components of ADCs each have different design properties that must be considered during modeling. Another key characteristic is the drug-to-antibody ratio (DAR), which typically varies between one and eight.

(b) Key mechanisms of action of the ADC include binding to the target antigen, internalization into the cell, trafficking and recycling of the ADC, endosomal cleavage of the linker or lysosomal degradation of the ADC for warhead release, influx and efflux of the warhead, and cell killing effects at the site of action.

ADC, antibody-drug conjugate; QSP, quantitative systems pharmacology.

From: Figure 1 of 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>

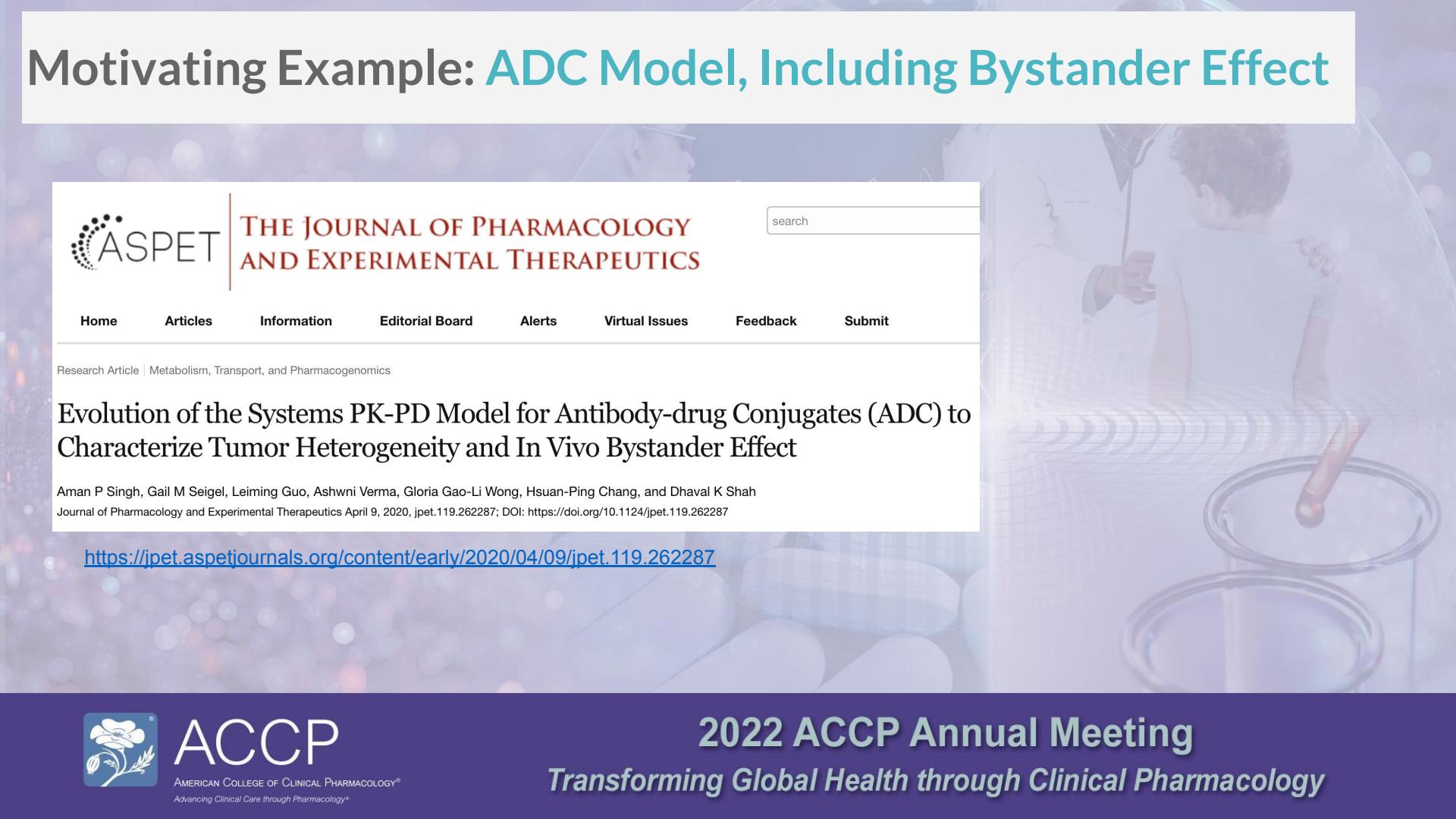


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# Motivating Example: ADC Model, Including Bystander Effect



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Research Article | Metabolism, Transport, and Pharmacogenomics

## Evolution of the Systems PK-PD Model for Antibody-drug Conjugates (ADC) to Characterize Tumor Heterogeneity and In Vivo Bystander Effect

Aman P Singh, Gail M Seigel, Leiming Guo, Ashwni Verma, Gloria Gao-Li Wong, Hsuan-Ping Chang, and Dhaval K Shah  
Journal of Pharmacology and Experimental Therapeutics April 9, 2020, jpet.119.262287; DOI: <https://doi.org/10.1124/jpet.119.262287>

<https://jpet.aspetjournals.org/content/early/2020/04/09/jpet.119.262287>



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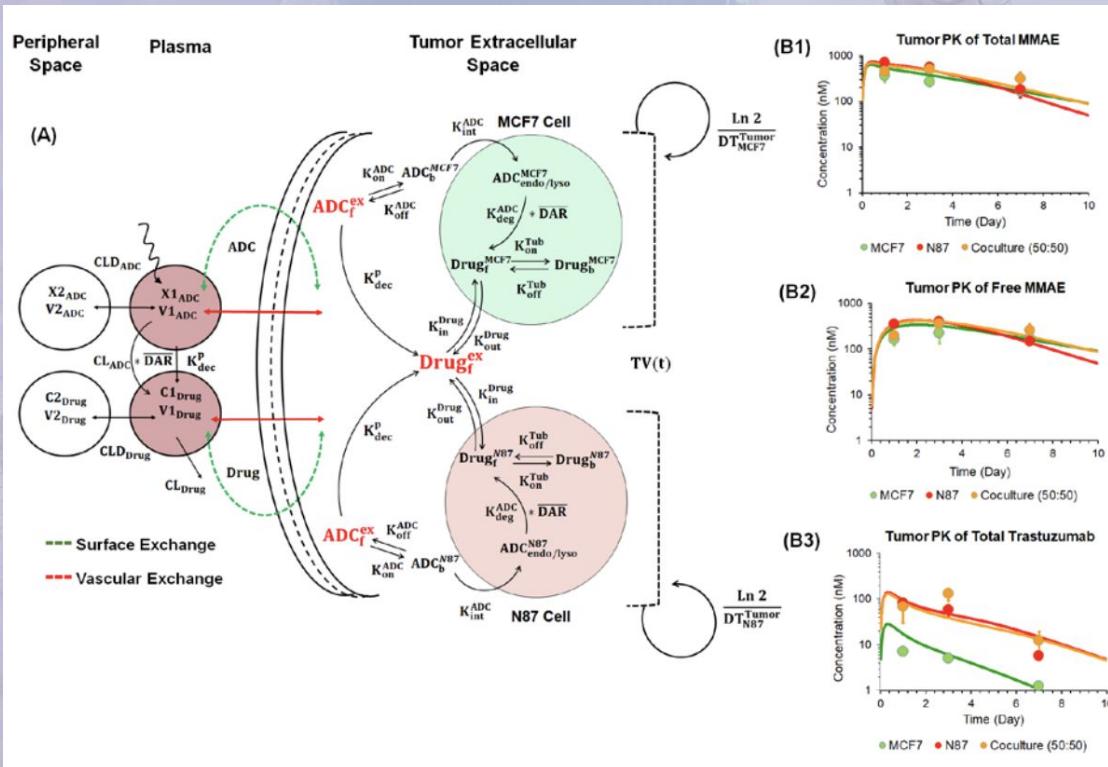
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# Motivating Example: Draw it, Develop it, Deploy it

A schematic diagram of a systems pharmacokinetic model developed to characterize T-vc-MMAE PK in a heterogeneous tumor containing N87 and GFP-MCF7 cells

Figure 3 of Singh, A. P., Seigel, G. M., Guo, L., Verma, A., Wong, G. G.-L., Cheng, H.-P., & Shah, D. K. (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.

<https://jpet.aspetjournals.org/content/early/2020/04/09/jpet.119.262287>



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# But First, We Need a Tool

## Getting Started with R and mrgsolve:

Citation: CPT Pharmacometrics Syst. Pharmacol. (2019) 8, 883–893; doi:10.1002/psp4.12467

### TUTORIAL

#### Quantitative Systems Pharmacology and Physiologically-Based Pharmacokinetic Modeling With mrgsolve: A Hands-On Tutorial

Ahmed Elmokadem<sup>1</sup>, Matthew M. Riggs<sup>1</sup> and Kyle T. Baron<sup>1,\*</sup>

mrgsolve is an open-source R package available on the Comprehensive R Archive Network. It combines R and C++ coding for simulation from hierarchical, ordinary differential equation-based models. Its efficient simulation engine and integration into a parallelizable, R-based workflow makes mrgsolve a convenient tool both for simple and complex models and thus is ideal for physiologically-based pharmacokinetic (PBPK) and quantitative systems pharmacology (QSP) model. This tutorial will first introduce the basics of the mrgsolve simulation workflow, including model specification, the introduction of interventions (dosing events) into the simulation, and simulated results postprocessing. An applied simulation example is then presented using a PBPK model for voriconazole, including a model validation step against adult and pediatric data sets. A final simulation example is then presented using a previously published QSP model for mitogen-activated protein kinase signaling in colorectal cancer, illustrating population simulation of different combination therapies.

Elmokadem, A., Riggs, M. M., & Baron, K. T. (2019). Quantitative Systems Pharmacology and Physiologically-Based Pharmacokinetic Modeling With mrgsolve: A Hands-On Tutorial. *CPT: Pharmacometrics & Systems Pharmacology*, 8(12), 883–893.

<https://doi.org/10.1002/psp4.12467>

## Additional resources:

### Introduction to mrgsolve

- <https://mrgsolve.org>
- <https://mrgsolve.org/basics>

### Repository with course example:

- <https://github.com/metrumresearchgroup/cptpsp-tutorial-2019>

bamlanivimab PBPK paper (Chigutsa et al. Vol 111(3) 2022, p. 595-604):

- <https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.2459>
- <https://github.com/metrumresearchgroup/bioPBPK>



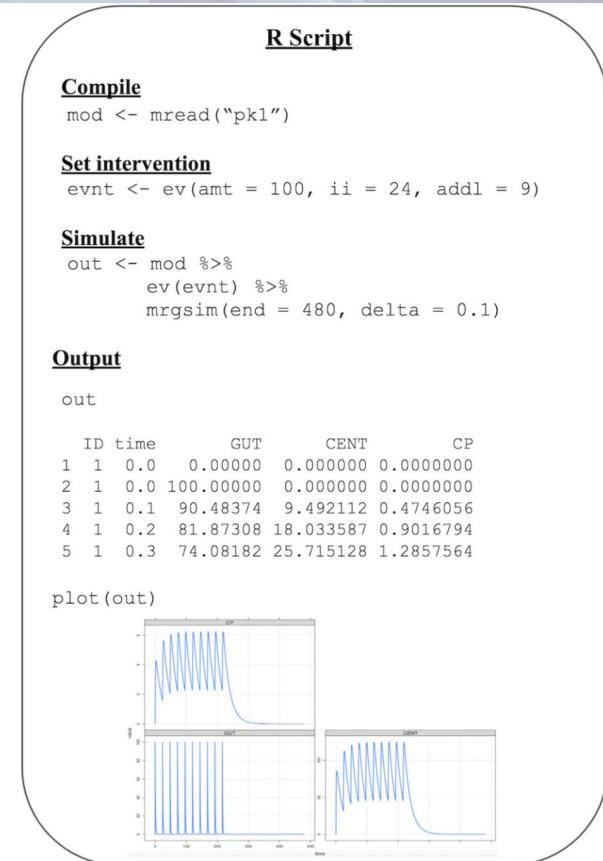
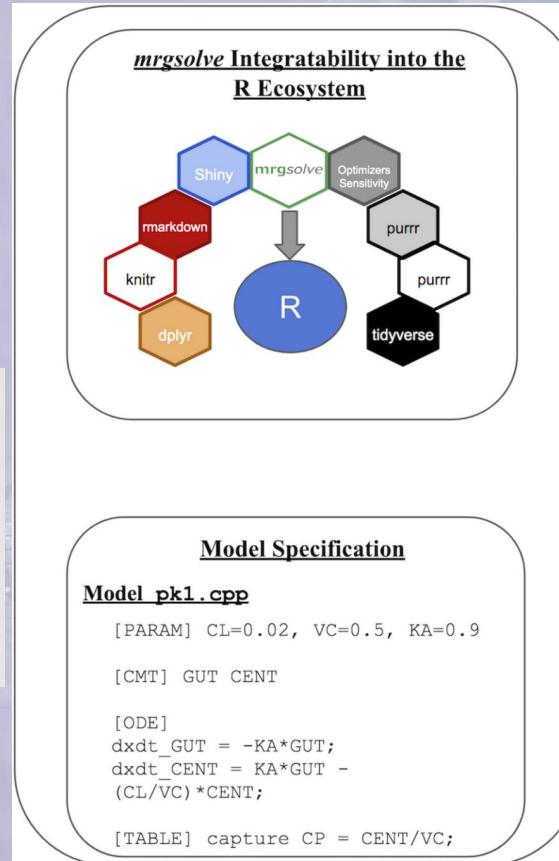
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# Getting Started with R and mrgsolve:

In Metworx / Rstudio:  
/model/pk1.cpp  
/script/pk1.R



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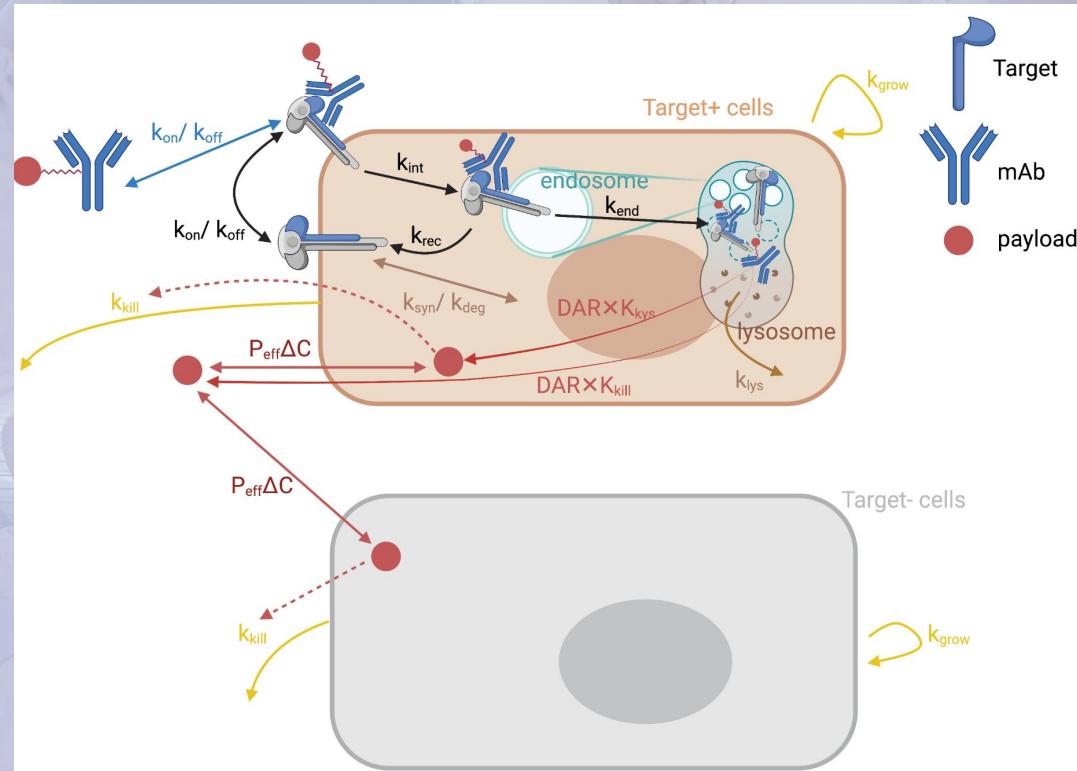
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# Simplified Case example: ADC schematic, *in vitro* only

## Step 1

- Understanding the System: Draw it



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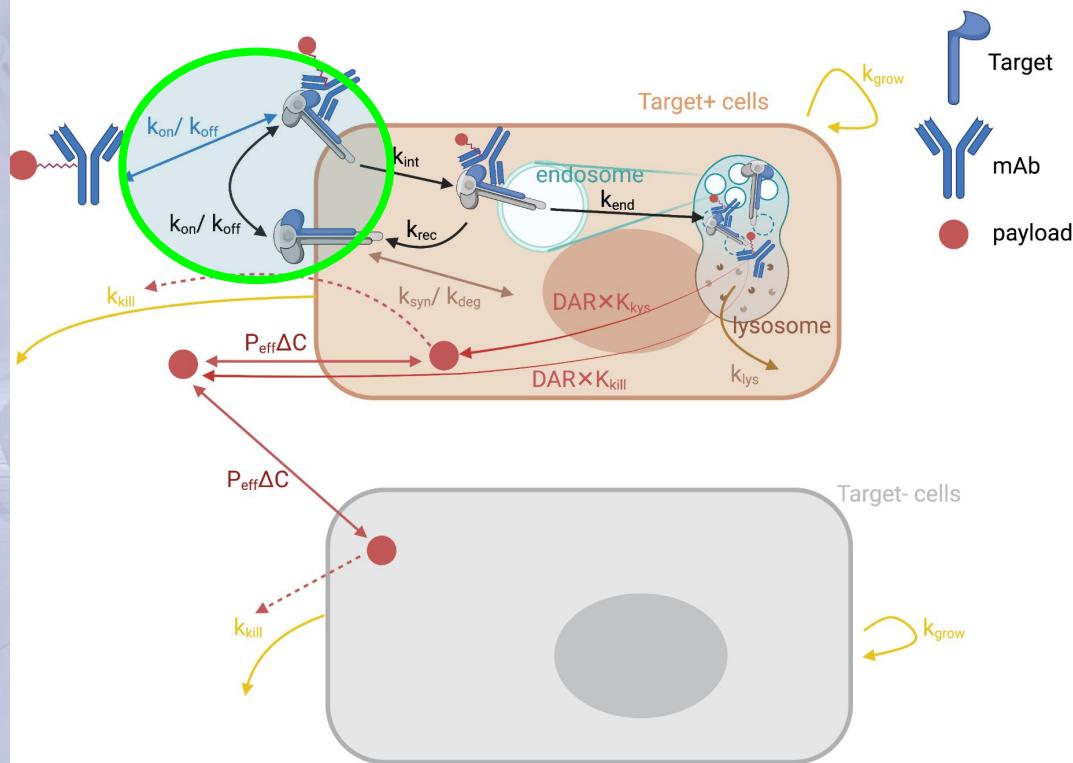
# Understanding the data: how can you collect it?

## Target Binding

### Kon/Koff informed by:

- Target affinity assays
  - SPR/Biacore affinity
  - Cell-based binding assay
  - Any considerations about multiple epitopes, avidity, bivalent binding?

## *in vitro* ADC Modeling



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# Model Code Target Binding

```
[PARAM]
// Compartment volumes and surface areas
Vm = 5e-4 // Media volume

// Rate constants
Kon = 0.0 // ADC/receptor on rate constant
Kd = 0.3 // ADC/receptor dissociation rate

// Get Koff from Kd and Kon
double Koff = Kd*Kon*6.022e23/1e9 ; // Convert back to nM

[CMT]
// Media
A_m // ADC in media

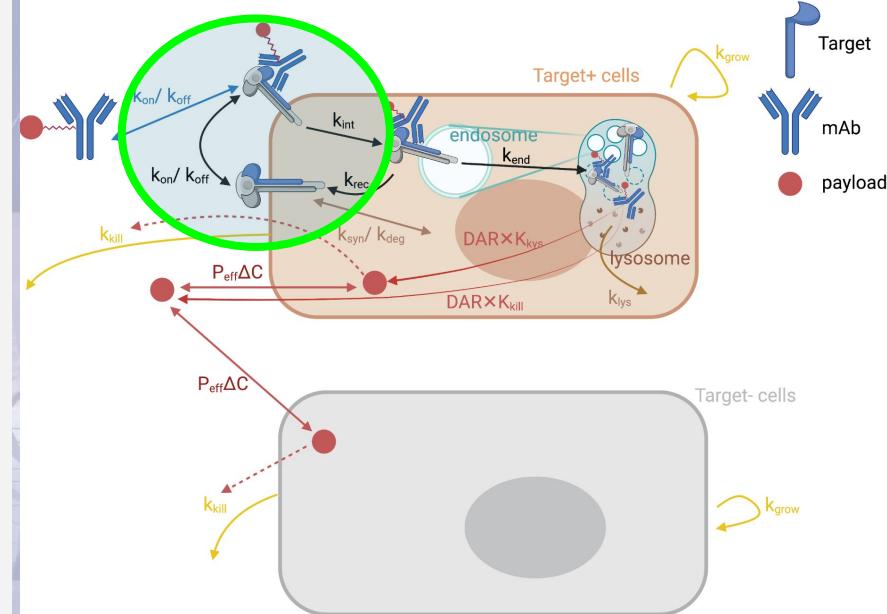
// Cell surface
R_s // Cell surface receptors
AR_s // Surface-bound ADC/receptor complex

[ODE]
// ADC in media binding to surface receptor
double flux_AR_s_binding = A_m/Vm*R_s*Kon;

// Surface ADC/receptor unbinding
double flux_AR_s_unbinding = AR_s*Koff;

// ADCs in media
// Flux = unbinding - binding
dxdt_A_m = flux_AR_s_unbinding*Ntot - flux_AR_s_binding*Ntot;
```

# in vitro ADC Modeling



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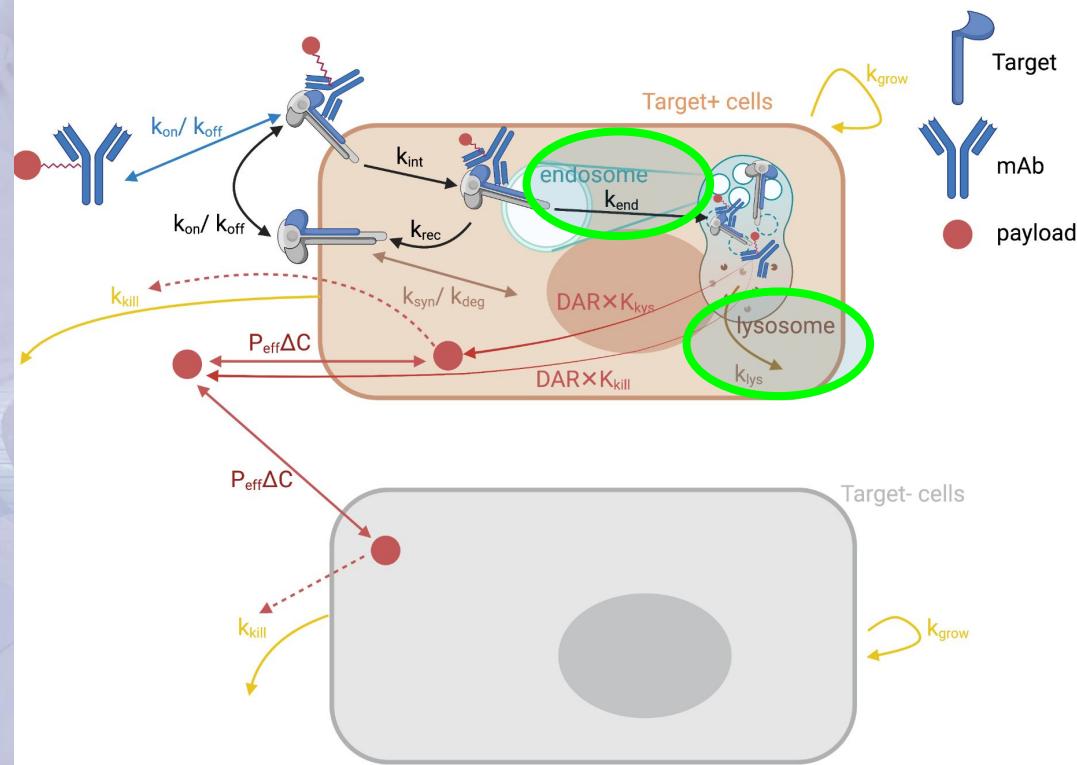
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# Understanding the data: how can you collect it? Lysosomal Degradation

Lysosomal degradation rate  
( $K_{lys}$ ) informed by:

- Lysosomal degradation rate
- Approximated by linker kinetics

## *in vitro* ADC Modeling



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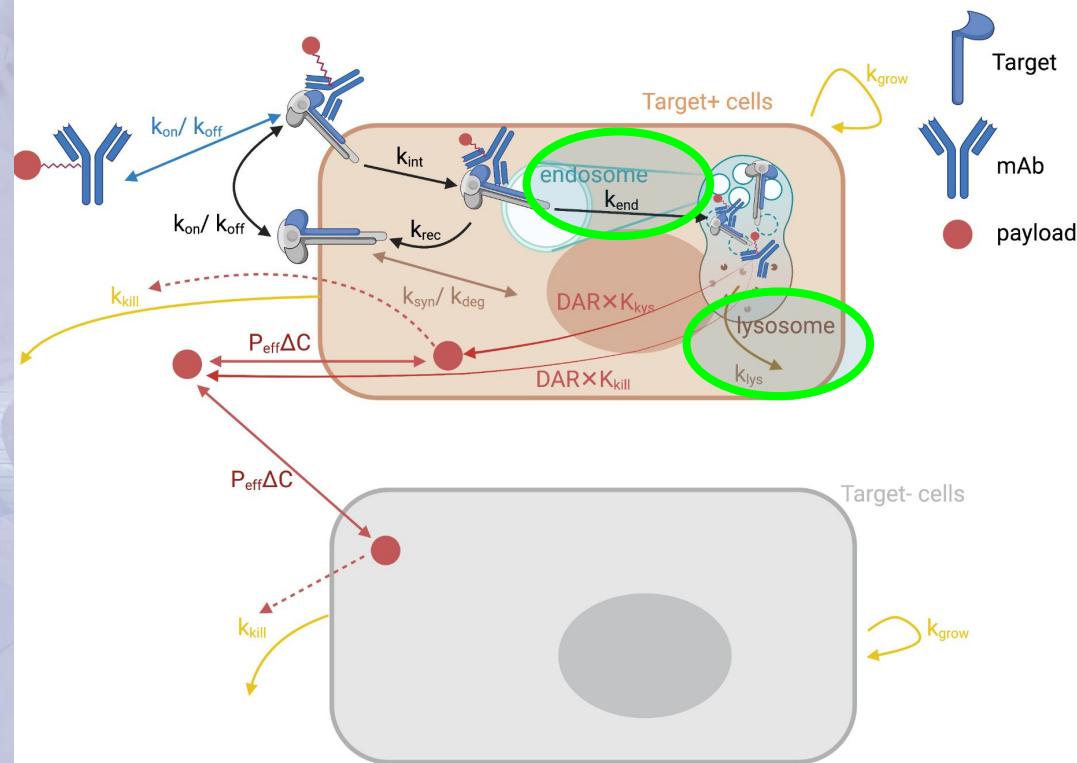
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# Understanding the data: how can you collect it? Endocytosis

Endocytosis rate ( $K_{end}$ ) informed  
by combination of:

- Degradation rate in lysosome
- IC<sub>50</sub> for payload
- Permeability
- Concentration of payload in the media
- DAR

## *in vitro* ADC Modeling



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# Model Code Lysosomal degradation in vitro ADC Modeling

```
[PARAM]
// Rate constants
Klys = 0.0 // Lysosomal deg rate const int ADC/receptor
Kend = 0.0 // Endosomal sorting rate for int ADC/receptor

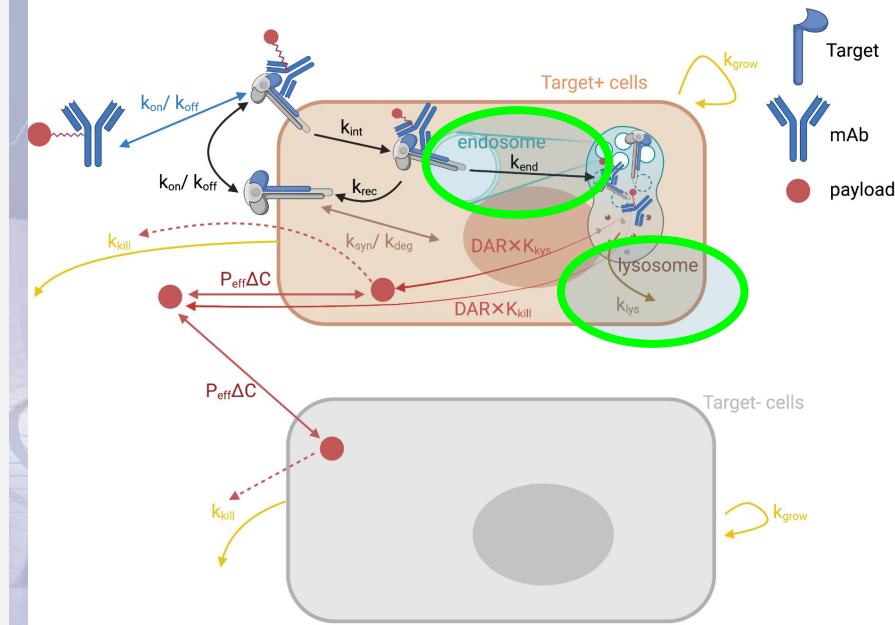
[CMT]
// Endosome
AR_e // Endosomal ADC/receptor complex

// Lysosome
AR_l // Lysosomal ADC/receptor complex

[ODE]
// Endosomal ADC/receptor complex transport to lysosome
double flux_AR_e_to_AR_l = AR_e*Kend;
// Lysosomal ADC/receptor complex catabolized
double flux_AR_l_cat = AR_l*Klys;
// Endosomal ADC/receptor unbinding
double flux_AR_e_unbinding = AR_e*Koff;

// ADC/receptor complex in endosome
// Flux = internalization - unbinding - transport to lysosome - recycling
dxdt_AR_e = flux_AR_s_int - flux_AR_e_unbinding - flux_AR_e_to_AR_l - flux_AR_e_recycle;

// ADC/receptor complex in lysosome
// Flux = transport from endosome - catabolism
dxdt_AR_l = flux_AR_e_to_AR_l - flux_AR_l_cat;
```

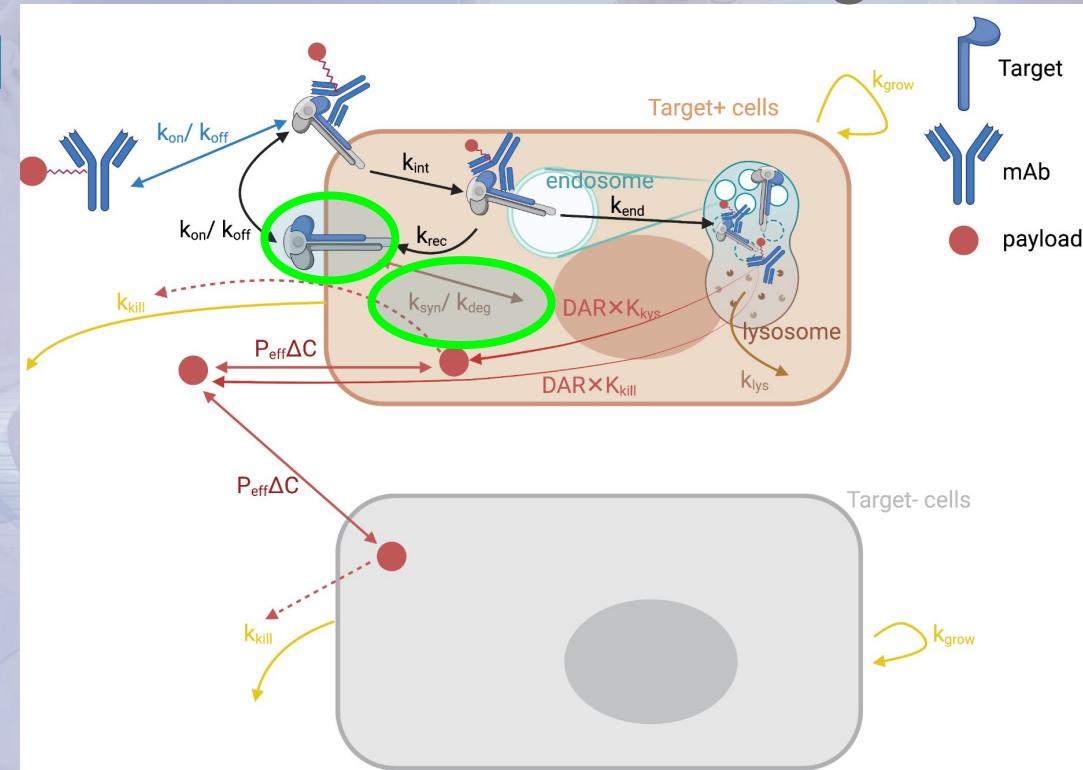


# Understanding the data: how can you collect it? **Receptor Expression and Dynamics**

## Receptor Expression and Dynamics informed by:

- Receptor expression (immunofluorescence)
- Receptor shedding
- Competition with ligand
- Feedback upregulation/ downregulation
- Effects of receptor dimerization, phosphorylation, signaling

## *in vitro* ADC Modeling



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# Model Code Receptor Expression and Dynamics

```

[MAIN]
R_s_0 = Nr; // Initial cell surface receptor expression

// Initial number of cells in well
Nc_1_0 = Nc0; // All cells are healthy
...
Nc_4_0 = 0.0;

// Calculate Ksyn
double Ksyn = Nr * Kdeg;

// Calculate initial number of free receptor in endosomes
R_e_0 = Ksyn/Kend;

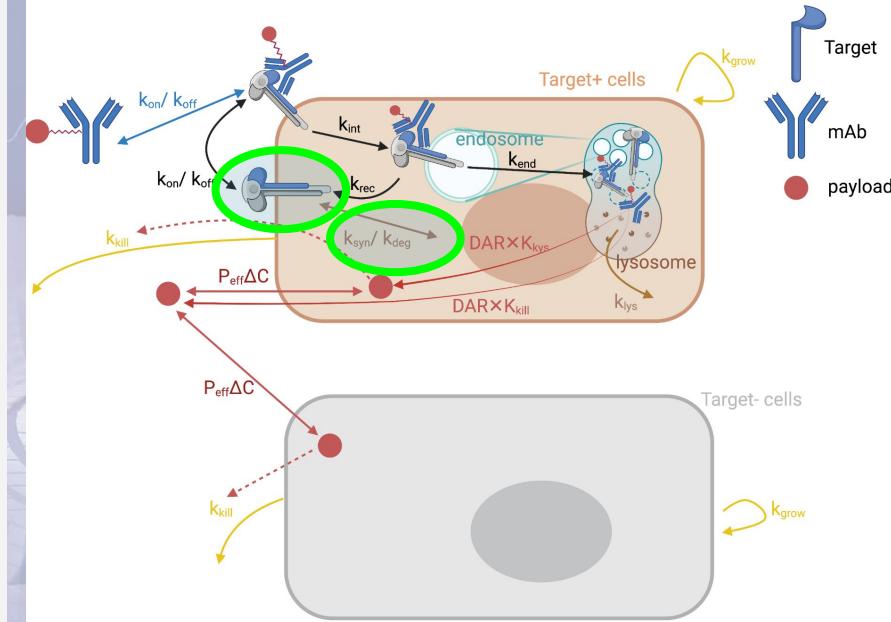
[PARAM]
Krec = 0.0 // Rate for receptors recycling to surface
Krec_AR = 0.0 // Rate of AR complex recycling to surface
Nr = 20e3 // Surface receptor expression (receptors/cell)
Kdeg = 1.0 // Surface-bound receptor degradation rate

[CMT]
//

[ODE]
// Surface receptor synthesis and feedback
double flux_R_s_syn = Ksyn;
// Endosomal receptor recycles to surface
double flux_R_e_recycle = R_e*Krec;

```

# in vitro ADC Modeling



```

// Free receptors on surface
// Flux = synthesis + unbinding +
//        recycling - binding - degradation
dxdt_R_s = flux_R_s_syn + flux_AR_s_unbinding +
           flux_R_e_recycle - flux_A_R_s_binding -
           flux_R_s_degrade;

```

# Understanding the data: how can you collect it? **Internalization and Recycling**

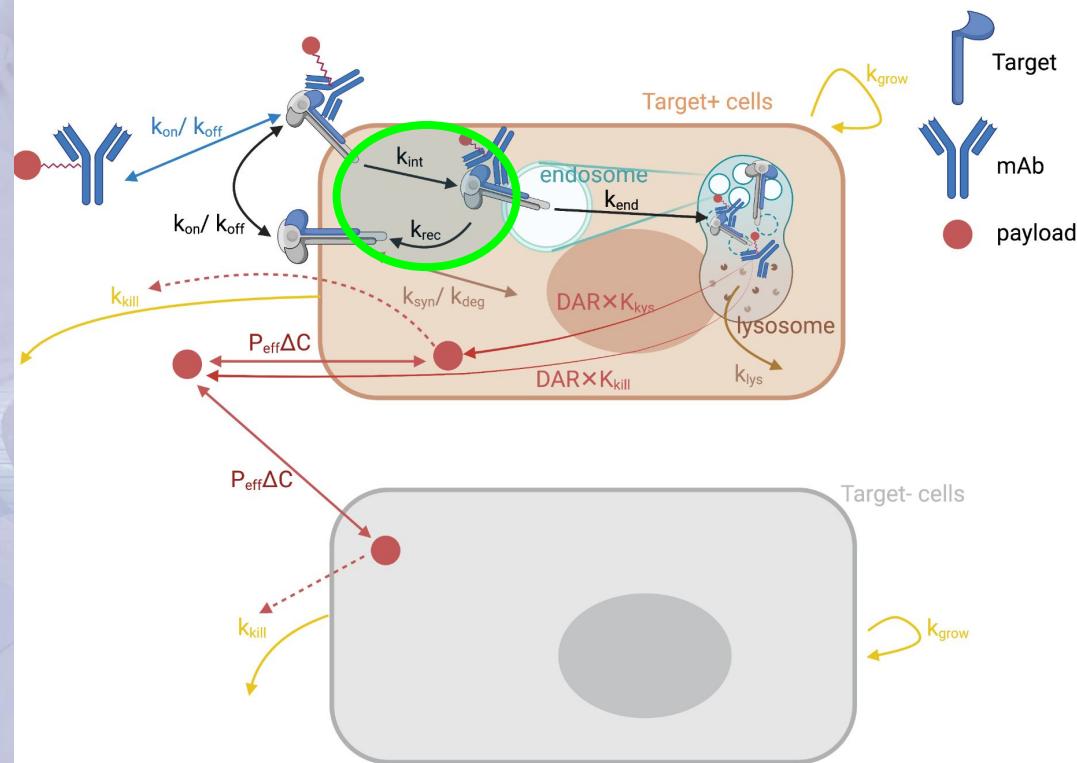
**Internalization rate (Kint)  
informed by:**

- Internalization assays, turnover assays

**Recycling rates (Krec) informed by:**

- receptor-alone and complex recycling rates (CHX)
- turnover assays

## *in vitro ADC Modeling*



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# Model Code Internalization and Recycling

# in vitro ADC Modeling

```
[PARAM]
Kint = 0.0 // ADC/receptor complex int rate constant

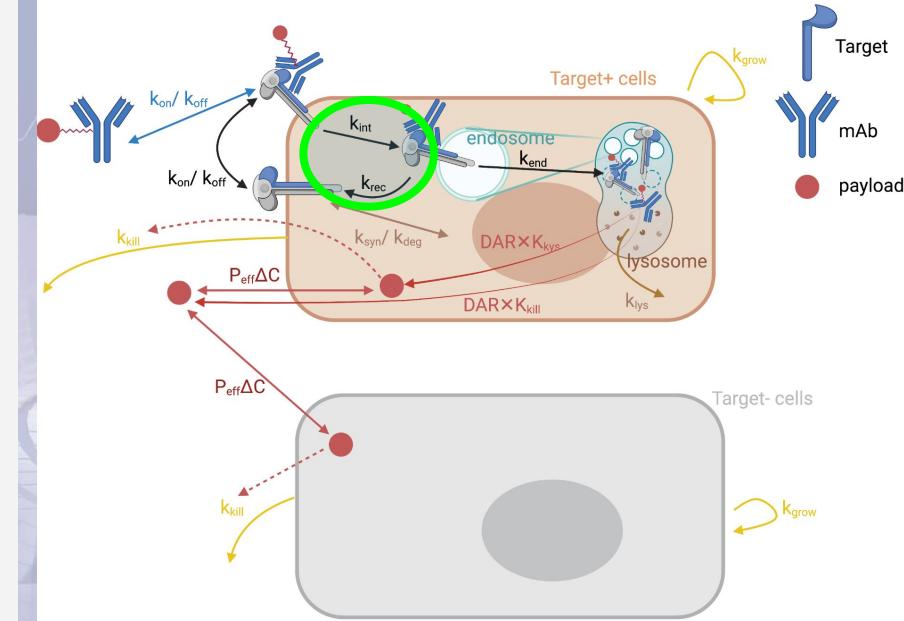
[CMT]
// Cell surface
R_s // Cell surface receptors
AR_s // Surface-bound ADC/receptor complex

[ODE]
// Receptor occupancies (using baseline receptor abundance)
double RO = AR_s/R_s_0;

// ADC/receptor complex internalizing to endosome
double flux_AR_s_int = AR_s*Kint;

// Endosomal ADC/receptor recycles to surface
double flux_AR_e_recycle = AR_e*Krec_AR;

// ADCs bound to cell surface
// Flux = binding - unbinding - internalization + recycling
dxdt_AR_s = flux_A_R_s_binding - flux_AR_s_unbinding - flux_AR_s_int + flux_AR_e_recycle;
```



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# Understanding the data: how can you collect it? **Payload Release and Distribution**

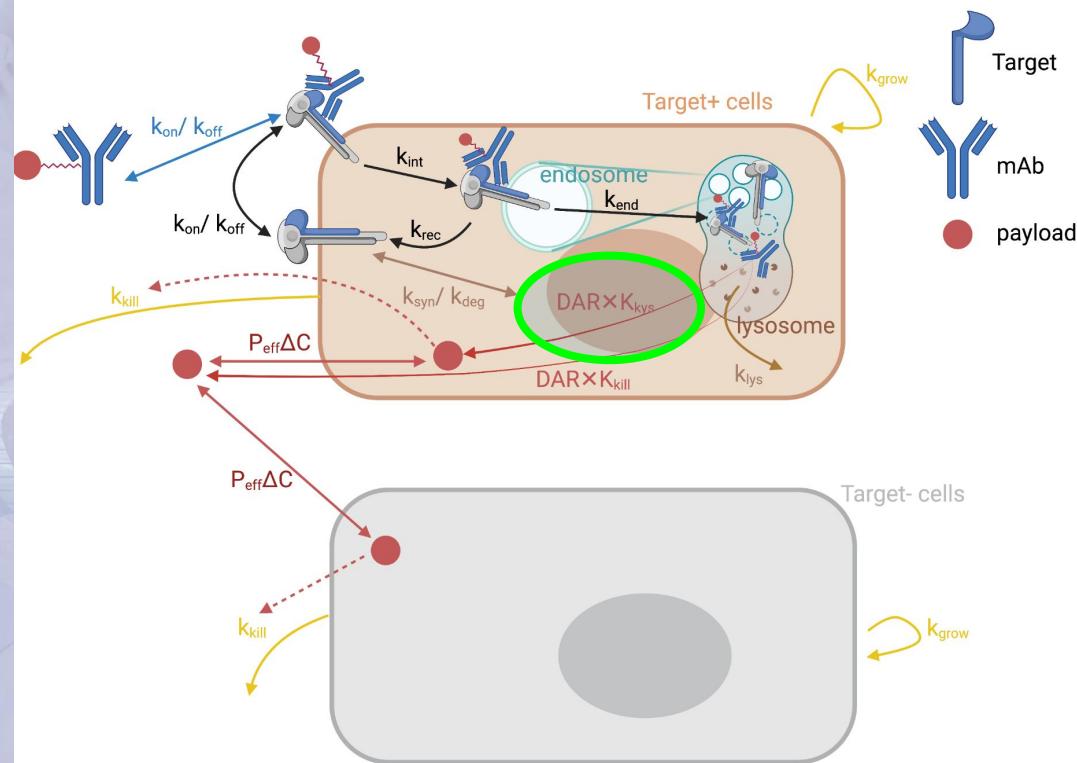
## Payload release informed by:

- Linker stability
- pH-dependent linker cleavage?
- Protease linker cleavage?
- Intracellular environment?

## Payload distribution informed by payload:

- Physchem, protein binding, cellular permeability, diffusivity, etc.

# *in vitro* ADC Modeling



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# Model Code Payload Release & Distribution *in vitro* ADC Modeling

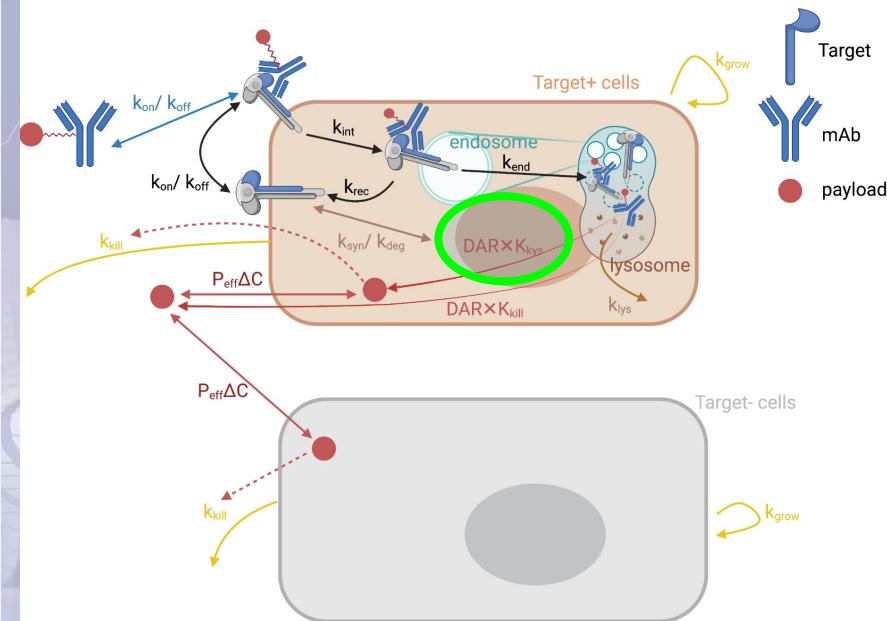
```
[PARAM]
Klys = 0.0 // Lysosomal deg rate constant int ADC/receptor

[CMT]
// Lysosome
AR_1 // Lysosomal ADC/receptor complex
A_1 // Lysosomal free ADC

[ODE]
// Lysosomal ADC/receptor complex catabolized
double flux_AR_1_cat = AR_1*Klys;

// Lysosomal antibody catabolized
double flux_A_1_cat = A_1*Klys;

// ADC/receptor complex in lysosome
// Flux = transport from endosome - catabolism
dxdt_AR_1 = flux_AR_e_to_AR_1 - flux_AR_1_cat;
```



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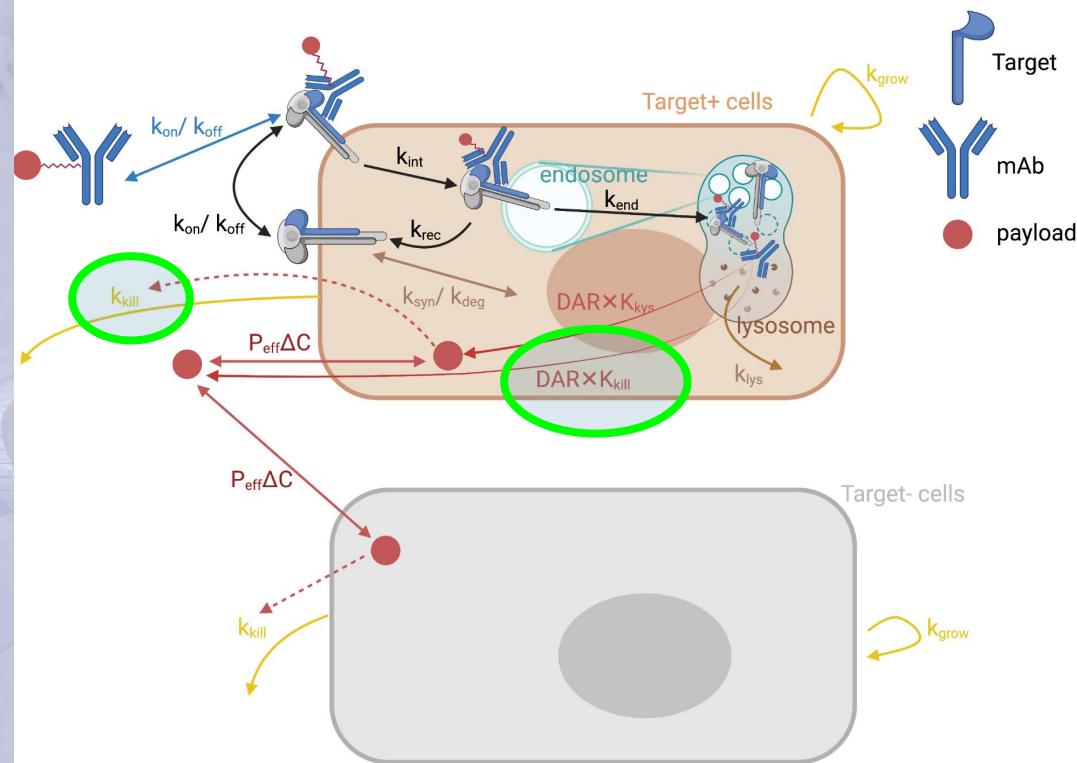
# Understanding the data: how can you collect it? Cell Killing

Cell killing effect ( $K_{kill}$ ) depends on mechanism of action, but generally informed by:

- Payload Release
- IC50s
- Cell half lives

Cell cycle-dependent payload sensitivity data/information is also considered

## *in vitro* ADC Modeling



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# Model Code Cell Killing

```
[PARAM]
Kkill = 0.0 // Baseline cell killing/death rate
// Killing effect model
EC50_Payload = 1.0 // Killing due to payload
Emax_Payload = 0.0

EC50_ADCC = 1.0 // Killing due to ADCC
Emax_ADCC = 0.0

[ODE]
// Unconjugated payload in cytoplasm
// Flux = payload escape from lysosome - diffusion from cytoplasm to media
dxdt_P_c = flux_P_l_to_P_c - flux_P_c_to_P_m;

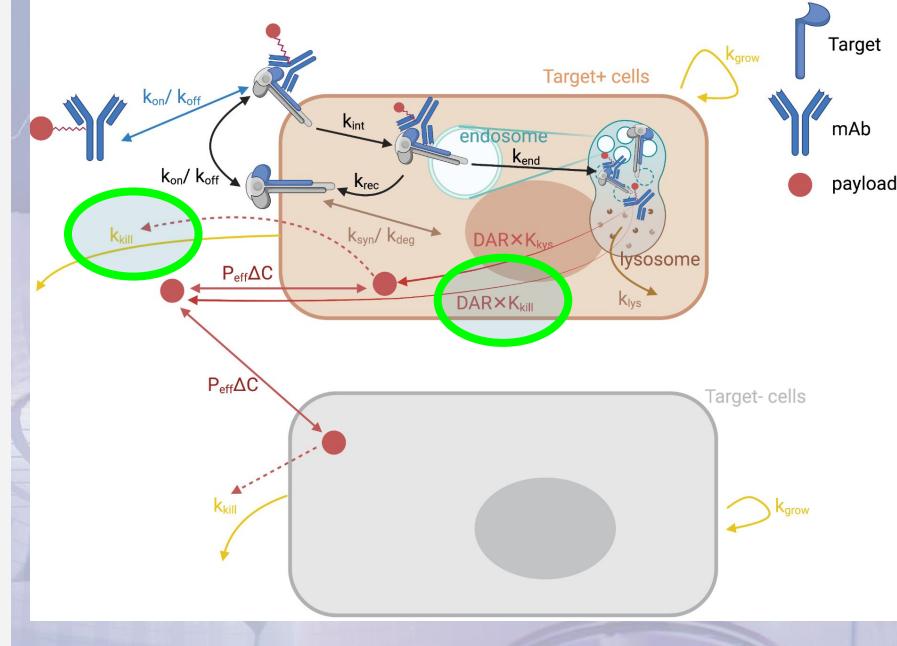
// Overall cell growth/death
dxdt_Nc_1 = Kgrow_eff*Nc_1 - Kkill_eff*Nc_1;

// Transit compartments (non-growing) for cells in process of being killed
dxdt_Nc_2 = Kkill_eff*Nc_1 - Nc_2/tau;
dxdt_Nc_3 = (Nc_2 - Nc_3)/tau;
dxdt_Nc_4 = (Nc_3 - Nc_4)/tau;

// Total number of cells in well
double Ntot = Nc_1 + Nc_2 + Nc_3 + Nc_4;

// Effective kill rate = baseline death rate + payload killing rate + ADCC killing rate
// ADCC is assumed to be negligible, here.
double Kkill_eff = Kkill + Emax_Payload * (P_c/Vc/6.022e23*1e9)/(EC50_Payload + (P_c/Vc/6.022e23*1e9)) + Emax_ADCC*RO/(EC50_ADCC + RO);
```

# *in vitro* ADC Modeling



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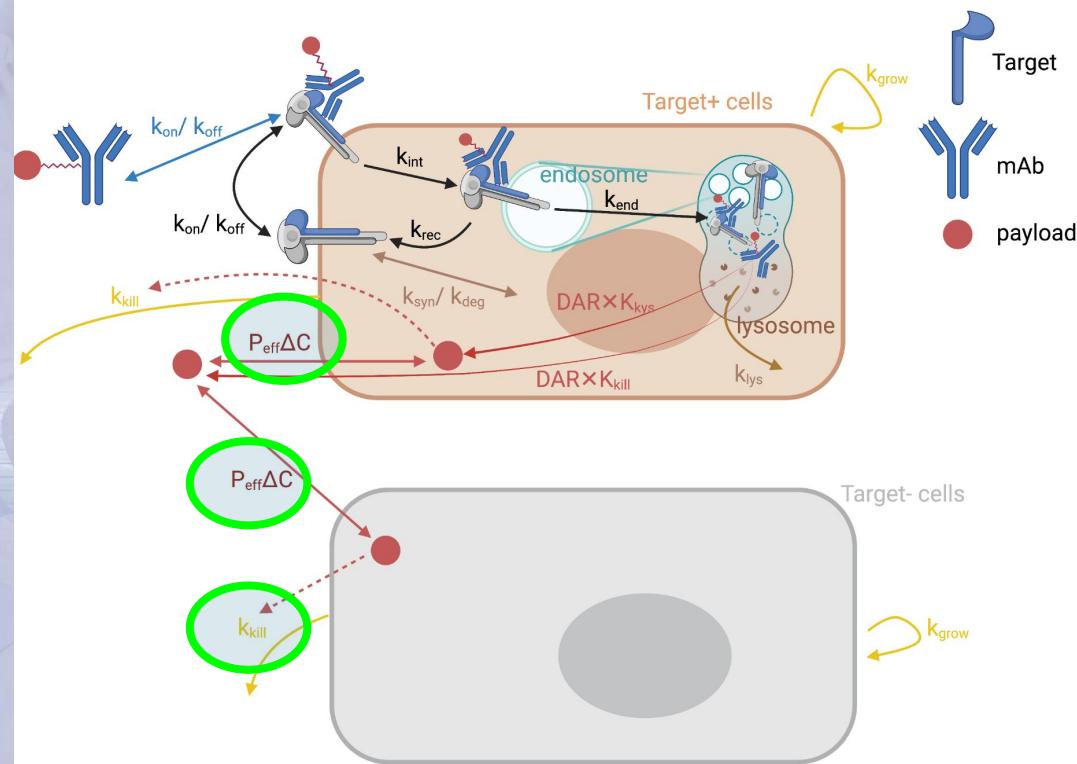
# Understanding the data: how can you collect it? **Bystander Killing**

Various forms of bystander effect  
influence data package required

**Bystander killing informed by:**

- Knowledge of mechanism
- Co-culture data
- Cell half lives
- Membrane permeability
- Diffusivity
- IC50

## *in vitro ADC Modeling*



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# Model Code Bystander Killing

# in vitro ADC Modeling

```
[MAIN]
// Initial number of target negative cells in well
NcNeg_1_0 = Nc0; // All cells are healthy
...
NcNeg_4_0 = 0.0;

[ODE]
// Unconjugated payload in media
// Flux = diffusion from cytoplasm to media
dxdt_P_m = flux_P_c_to_P_m*Ntot + DAR*Kkill_eff*Nc_1*(A_e + A_l + AR_e +
AR_s)/Nc_1;

[develop expression for diffusion into and conc in target; then create
(modify from below) a Kkill_eff specific for target neg cells

e.g.,
// Overall cell growth/death FOR TARGET NEGATIVE CELLS
dxdt_NcNeg_1 = Kgrow_eff*Nc_1Neg - Kkill_eff*NcNeg_1;

// Transit compartments (non-growing) for target neg cells in process of
being killed
dxdt_NcNeg_2 = Kkill_eff*NcNeg_1 - NcNeg_2/tau;
dxdt_NcNeg_3 = (NcNeg_2 - NcNeg_3)/tau;
dxdt_NcNeg_4 = (NcNeg_3 - NcNeg_4)/tau;

// MAKE A NEW ONE OF THESE Effective kill rate = baseline death rate + payload killing rate + ADCC killing rate
// ADCC is assumed to be negligible, here.
double Kkill_eff = Kkill + Emax_Payload * (P_c/Vc/6.022e23*1e9)/(EC50_Payload + (P_c/Vc/6.022e23*1e9)) + Emax_ADCC*RO/(EC50_ADCC + RO);
```



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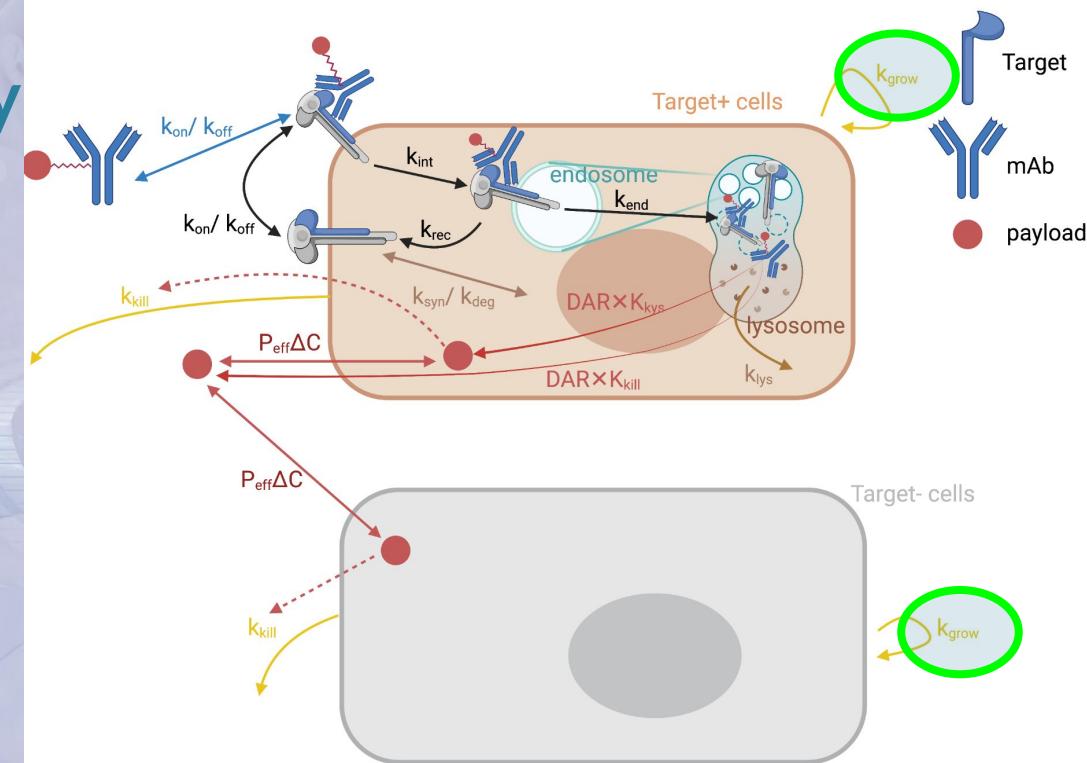
# Understanding the data: how can you collect it? Cell Growth and Viability

Cellular growth rates ( $k_{grow}$ )  
informed by :

- Seeding ratios if coculture
- Cell doubling times (or estimate from control)
- Confluence conditions

// Effective growth rate = rate from cell multiplication limited to confluence number  
`double Kgrow_eff = Kgrow*(1 - Ntot/Nmax);`

## *in vitro ADC Modeling*



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# QSP 101 Points to Consider Beyond This Intro



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# Considering QSP for Regulatory Interactions

FROM  
MOLECULE TO  
PATIENT

<https://www.ascpt.org/Portals/28/docs/Annual%20Meetings/2019%20Annual%20Meeting/Speaker%20Presentations/Wednesday/QSP%20Precon%20%20Zineh%20Presentation.pdf?ver=2019-04-01-105241-317>

- Quantitative Systems Pharmacology at the US FDA:  
From Aspiration to Translation

Issam Zineh, PharmD, MPH

Office of Clinical Pharmacology | Office of Translational Sciences  
US Food and Drug Administration | March 13, 2019

## Issue-Based Approach to Engagement

- 
- What is the intended purpose and context for the given quantitative approach?
    - Is the modeling (with or without accompanying simulation) intended to be mechanistically explanatory of an observed phenomenon?
    - Is the exercise intended to be used for clinical trial planning?
    - Is the output intended to stand in for a clinical trial?
  - Very different situations that would necessitate different conversations:
    - Some may not necessitate a conversation at all
    - Others would require dialogue around model credibility, decision risk, and resulting evidentiary requirements.

FROM  
MOLECULE TO  
PATIENT



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# Considering QSP for Regulatory Interactions

FROM  
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- Quantitative Systems Pharmacology at the US FDA:  
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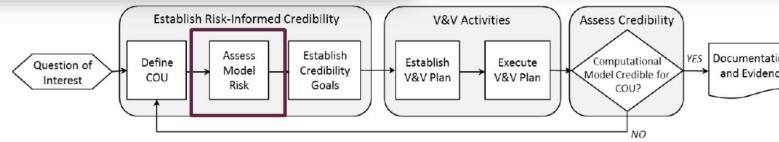
<https://www.ascpt.org/Portals/28/docs/Annual%20Meetings/2019%20Annual%20Meeting/Speaker%20Presentations/Wednesday/QSP%20Precon%20%20Zineh%20Presentation.pdf?ver=2019-04-01-105241-317>



## Risk-Informed Credibility Framework

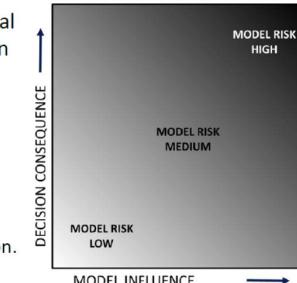
In order to more fully leverage computational modeling and simulations for medical products and clinical care, we need a methodology to ensure appropriate credibility.

**Credibility:** the trust, through the collection of evidence, in the predictive capability of a computational model for a context of use



**Model risk** is the possibility that the computational model leads to an incorrect decision that results in patient harm and/or other undesirable impacts.

- Model influence** is the contribution of the computational model relative to other available evidence in making a decision.
- Decision consequence** is the significance of an adverse outcome resulting from an incorrect decision.



Courtesy T. Morrison, CDRH | ASME V&V40 Subcommittee

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# Considering QSP for Regulatory Interactions

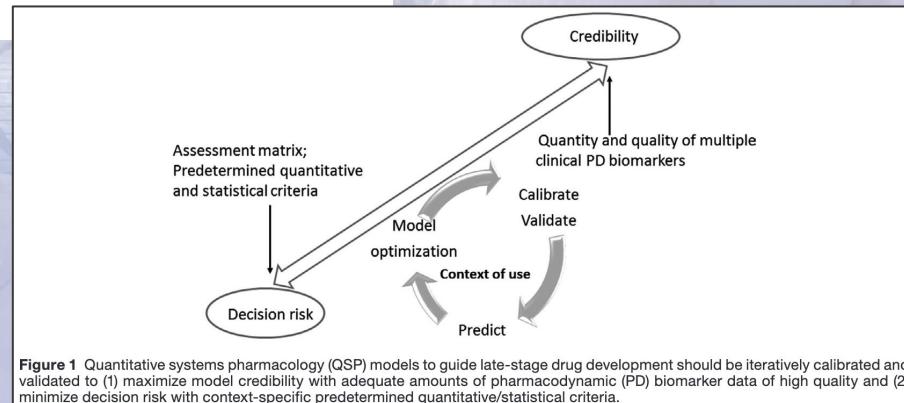
Citation: CPT Pharmacometrics Syst. Pharmacol (2020) 9, 675–677; doi:10.1002/psp4.12567

## PERSPECTIVE

### A Perspective on Quantitative Systems Pharmacology Applications to Clinical Drug Development

<https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/psp4.12567>

Jane P. F. Bai<sup>1,\*</sup>, Justin C. Earp<sup>1</sup>, David G. Strauss<sup>1</sup> and Hao Zhu<sup>1</sup>



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# Considering QSP for Regulatory Interactions

Citation: CPT Pharmacometrics Syst. Pharmacol. (2020) 9, 21–28; doi:10.1002/psp4.12479

## WHITE PAPER

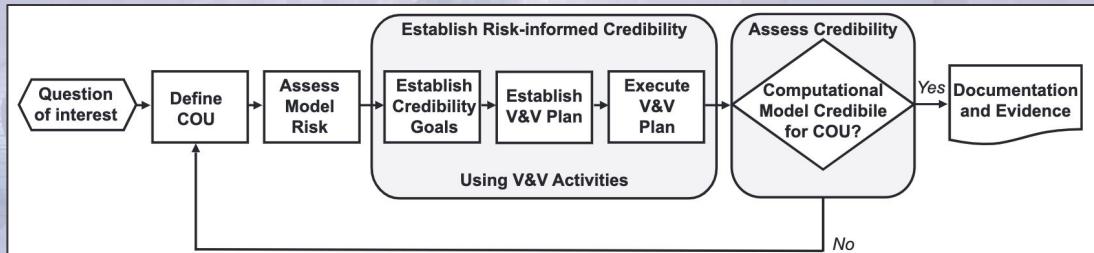
### Consideration of a Credibility Assessment Framework in Model-Informed Drug Development: Potential Application to Physiologically-Based Pharmacokinetic Modeling and Simulation

Colleen Kuemmel<sup>1,\*</sup>, Yuching Yang<sup>1</sup>, Xinyuan Zhang<sup>1</sup>, Jeffry Florian<sup>1</sup>, Hao Zhu<sup>1</sup>, Million Tegenge<sup>2</sup>, Shiew-Mei Huang<sup>1</sup>, Yaning Wang<sup>1</sup>, Tina Morrison<sup>3</sup> and Issam Zineh<sup>1</sup>

The use of computational models in drug development has grown during the past decade. These model-informed drug development (MIDD) approaches can inform a variety of drug development and regulatory decisions. When used for regulatory decision making, it is important to establish that the model is credible for its intended use. Currently, there is no consensus on how to establish and assess model credibility, including the selection of appropriate verification and validation activities. In this article, we apply a risk-informed credibility assessment framework to physiologically-based pharmacokinetic modeling and simulation and hypothesize this evidentiary framework may also be useful for evaluating other MIDD approaches. We seek to stimulate a scientific discussion around this framework as a potential starting point for uniform assessment of model credibility across MIDD. Ultimately, an overarching framework may help to standardize regulatory evaluation across therapeutic products (i.e., drugs and medical devices).

<https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/psp4.12479>

The Kuemmel et al 2020 paper provides rubrics, e.g., for establishing an assessment of model risk.



**Figure 1** Overview of the ASME V&V 40 risk-informed credibility assessment framework. Modified from ASME V&V 40-2018, by permission of the ASME.<sup>13</sup> All rights reserved. ASME, American Society of Mechanical Engineers; COU, context of use; V&V, verification and validation.



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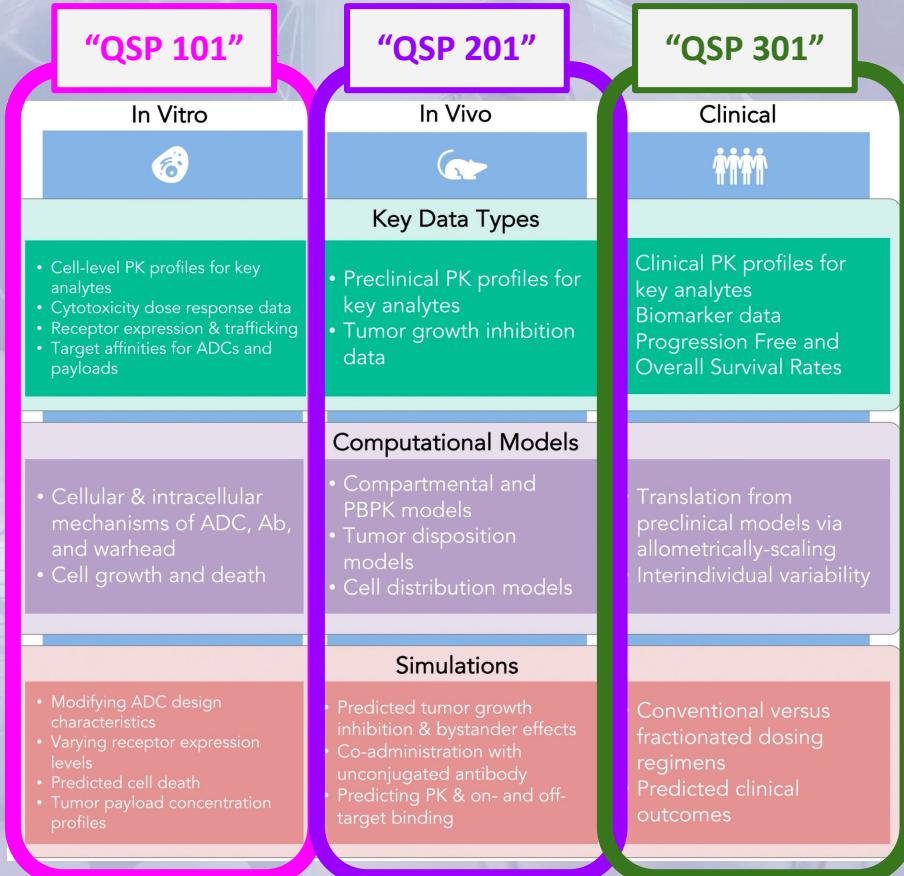
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# Structure and key considerations for QSP modeling of ADCs

During QSP modeling of ADCs, the relevant data types may vary between different biological scales, as do the structures of the computational models themselves. Subsequently, the resulting simulations enable the exploration of different phenomena at the in vitro, in vivo, and clinical scales.

Ab, antibody; ADC, antibody-drug conjugate; PBPK, physiologically-based pharmacokinetic; PK, pharmacokinetic.

From: Figure 2 of 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>



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# Structure and key considerations for QSP “201” and “301”

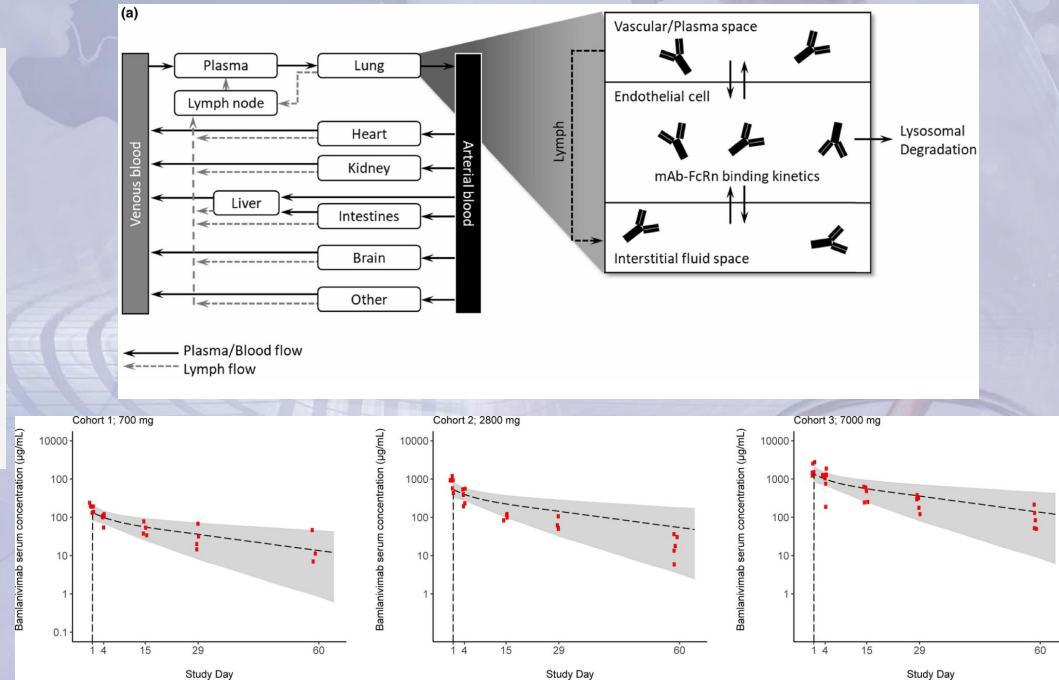
Integrating in vitro information, including the PK, e.g., using PBPK. Open-source example of mAb PBPK here:

<https://github.com/metrumresearchgroup/bioPBPK>

Example of PK prediction from PBPK model developed with *in vivo* data only compared to clinical results:

<https://ascpt.onlinelibrary.wiley.com/doi/10.1002/cpt.2459>

Chigutsa, E., Jordie, E., Riggs, M., Nirula, A., Elmokadem, A., Knab, T., & Chien, J. Y. (2022). A Quantitative Modeling and Simulation Framework to Support Candidate and Dose Selection of Anti-SARS-CoV-2 Monoclonal Antibodies to Advance Bamlanivimab Into a First-in-Human Clinical Trial. *Clin Pharmacol Therapeutics*, 111(3), 595–604.



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# Questions: QSP Models Hands On Case Studies



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an innovation by  
**METRUM**  
RESEARCH GROUP

Reproducible. Traceable. Controlled. Scalable.

# What is Metworx



## MetrumRG Expertise

- Technology and service backed by our scientists
- Reflects the evolving needs across the industry
- Meets most modeling and simulation needs and built to tackle some of the hardest challenges out of the box



## Scalability

- Resources are dedicated and not shared
- Multiple levels of parallelization; no fixed grids
- Customize high performance computing needs



## Reproducibility

- Reproducible team based collaboration framework
- Supports optional git or svn version-control repositories
- Shared, transparent & fully reproducible models



## Future Vision

- Enables future vision for MIDD
- Innovating to improve drug development decisions
- Not limited to current practice



## Traceability

- Easily traceable computational platform
- Traceability supported through various options from software level to tooling and package dependencies



## Security

- Security and data isolation by private AWS accounts
- Client controlled security credentials
- Encrypted data in-transit and at-rest

*"This solution has disrupted the way we approach model informed drug development, allowing scientists to tackle problems in new and previously impractical ways."*

~ Marc R. Gastonguay, PhD  
CEO and Founder

## Fast FAQs - MetrumRG on Metworx

Project hours				100s of thousands
Filings				thousands
Clients				hundreds
Platform users				hundreds
Sponsor audits		dozens		

### Typical client profile:

Our clients include many of the largest pharmaceutical companies in the world, rapid growth startups, and many of the pioneers in biomedical modeling and simulation.

# Introduction to the Ecosystem

Metworx creates libraries of **BLUEPRINTS**, which are made available to users so they can launch consistent instances of compute environments running to known specifications everytime. An actively running instance of a blueprint is called a

