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”

- 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

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

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

Model Development
ADC schematic, *in vivo*

Model components

Plasma PK

Tumor Penetration

Tumor Model

Peripheral space

Plasma

Extracellular Matrix

Target Tumor Cell

ADC
mAb
linker
drug/payload
Target
Surface exchange
Vascular exchange
payload target (e.g., tubulin, DNA,...)
Tumor penetration was modeled as a combination of surface exchange and vascular exchange.
Surface exchange and vascular exchange for ADC/drug penetration in solid tumors

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

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

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 $P$

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

(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.

ADC plasma PK was modeled using a two-compartment model.
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)
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

\[
\begin{align*}
\frac{d \ C_{1Drug}}{dt} &= -\frac{CL_{Drug}}{V1_{Drug}} \cdot C_{1Drug} - \frac{CLD_{Drug}}{V1_{Drug}} \cdot C_{1Drug} \\
&\quad + \frac{CLD_{Drug}}{V1_{Drug}} \cdot C_{2Drug} \\
&\quad - \frac{2 \cdot P_{Drug} \cdot R_{Cap} \cdot (C_{1Drug} \cdot \varepsilon_{Drug} - Drug^{ex})}{R_{Krogh}^2} \\
&\quad - \frac{6 \cdot D_{Drug} \cdot (C_{1Drug} \cdot \varepsilon_{Drug} - Drug^{ex})}{R_{Tumor}^2} \\
&\quad + \frac{X_{1ADC} \cdot DAR \cdot k_{dec,plasma}^{ADC}}{V1_{Drug}} + \frac{CL_{ADC} \cdot DAR \cdot X_{1ADC}}{V1_{Drug}}
\end{align*}
\]
DAR (Drug-antibody ratio: #payload(s)/antibody)

\[ \frac{d \text{DAR}}{dt} = -k_{\text{dec,plasma}} \cdot \text{DAR} \]
Tumor model
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?

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

\[
\begin{align*}
\text{flux}_{\text{ADC,antigen, binding}} &= k_{\text{on}}^{\text{ADC}} \cdot \text{ADC}_{\text{free}}^{\text{ex}} \cdot \frac{A_{\text{total}} - \text{ADC}_{\text{bound}}^{\text{ex}}}{\epsilon_{\text{ADC}}} \\
\text{flux}_{\text{ADC,antigen, unbinding}} &= k_{\text{off}}^{\text{ADC}} \cdot \text{ADC}_{\text{bound}}^{\text{ex}} \\
\text{flux}_{\text{free,ADC, dec}} &= k_{\text{dec}}^{\text{ADC}} \cdot \text{ADC}_{\text{free}}^{\text{ex}} \\
\frac{d}{dt} \text{ADC}_{\text{free}}^{\text{ex}} &= \frac{2 \cdot P_{\text{ADC}} \cdot R_{\text{Cap}}}{R_{\text{Krogh}}^2} \cdot \left(\frac{X1_{\text{ADC}}}{V1_{\text{ADC}}} \cdot \epsilon_{\text{ADC}} - \text{ADC}_{\text{free}}^{\text{ex}}\right) + \frac{6 \cdot D_{\text{ADC}}}{R_{\text{Tumor}}^2} \cdot \left(\frac{X1_{\text{ADC}}}{V1_{\text{ADC}}} \cdot \epsilon_{\text{ADC}} - \text{ADC}_{\text{free}}^{\text{ex}}\right) - \text{flux}_{\text{ADC,antigen, binding}} + \text{flux}_{\text{ADC,antigen, unbinding}} - \text{flux}_{\text{free,ADC, dec}}
\end{align*}
\]
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\textsubscript{on} and k\textsubscript{off}) informed by:
  - Target affinity assays
  - SPR/Biacore affinity
  - Cell-based binding assay
- ADC bound to antigen can internalize (k\textsubscript{int}) into tumor cell or deconjugate (k\textsubscript{dec}) to release payload in the extracellular space
Exercise 1: Derive the equation for ADC-antigen complex \( C_{ADC_b \_ex \_nM} \)

\[
\begin{align*}
\text{flux}_\text{ADC\_antigen\_binding} &= k_{on}^{ADC} \cdot AD_{free}^{ex} \cdot \frac{Ag_{total} - AD_{bound}^{ex}}{e_{ADC}} \\
\text{flux}_\text{ADC\_antigen\_unbinding} &= k_{off}^{ADC} \cdot AD_{bound}^{ex} \\
\text{flux}_\text{bound\_ADC\_dec} &= k_{dec}^{ADC} \cdot AD_{bound}^{ex} \\
\text{flux}_\text{bound\_ADC\_internalization} &= k_{int}^{ADC} \cdot AD_{bound}^{ex} \\
\frac{d}{dt} AD_{bound}^{ex} &= \text{flux}_\text{ADC\_antigen\_binding} - \text{flux}_\text{ADC\_antigen\_unbinding} - \text{flux}_\text{bound\_ADC\_dec} - \text{flux}_\text{bound\_ADC\_internalization}
\end{align*}
\]
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 ($k_{\text{int}}$) into the tumor cell
- **Internalization rate** ($k_{\text{int}}$) informed by:
  - Internalization assays, turnover assays
- After internalization of ADC, ADC can be degraded ($k_{\text{deg}}$) to release drug in the cytoplasm
- **Degradation rate** ($k_{\text{deg}}$) is informed by:
  - Receptor expression (immunofluorescence)
  - Receptor shedding

\[
\frac{d C_{ADC\_endolyso}}{dt} = k_{\text{int}} \cdot C_{ADC\_bound} - k_{\text{deg}} \cdot C_{ADC\_endolyso}
\]
Exercise 2: Derive the dynamics for the endosomal/lysosomal ADC (C_ADC_endolyso_cell_nM)

\[
\text{flux}_{\text{bound ADC internalization}} = k_{\text{int}}^{\text{ADC}} \cdot A\text{DC}_{\text{ex}}^{\text{cell}}
\]

\[
\text{flux}_{\text{end ADC deg}} = k_{\text{deg}}^{\text{ADC}} \cdot A\text{DC}_{\text{cell}}^{\text{endo/lyso}}
\]

\[
\frac{d}{dt} A\text{DC}_{\text{cell}}^{\text{endo/lyso}} = \text{flux}_{\text{bound ADC internalization}} - \text{flux}_{\text{end ADC deg}}
\]
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 ($k_{\text{diff}}$).

- Bidirectional diffusion rate ($k_{\text{diff}}$) informed by:
  - Linker design and drug properties.

\[
\frac{d \text{Drug}_{\text{free}}}{dt} = k_{\text{ADC}} \cdot \text{DAR} \cdot \text{ADC}_{\text{endo/lyso}} - k_{\text{on}} \cdot \text{Drug}_{\text{free}} \cdot (\text{Tub}_{\text{total}} - \text{Drug}_{\text{cell bound}}) + k_{\text{Tub}} \cdot \text{Drug}_{\text{cell bound}} - k_{\text{off}} \cdot \text{Drug}_{\text{bound}} - k_{\text{out}} \cdot \text{Drug}_{\text{free}} + k_{\text{diff}} \cdot (\text{Drug}_{\text{free}} - \text{Drug}_{\text{free}})
\]
Unconjugated intracellular tubulin-bound payload

- Free drug reversibly binds to the target in the cytoplasm, causing cell death
- Binding constants ($k_{\text{on}}$ and $k_{\text{off}}$) 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 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.

\[
\frac{d\text{ Drug}_{\text{free}}^{\text{ex}}}{dt} = \frac{2 \cdot P_{\text{Drug}} \cdot R_{\text{Cap}}}{R_{\text{Krogh}}^2} \cdot (C_{1_{\text{Drug}}} \cdot \varepsilon_{\text{Drug}} - \text{Drug}_{\text{free}}^{\text{ex}}) \\
+ \frac{6 \cdot D_{\text{Drug}}}{R_{\text{Tumor}}^2} \cdot (C_{1_{\text{Drug}}} \cdot \varepsilon_{\text{Drug}} - \text{Drug}_{\text{free}}^{\text{ex}}) \\
+ k_{\text{out}}^{\text{Drug}} \cdot \text{Drug}_{\text{cell}}^{\text{ex}} + k_{\text{dec}}^{\text{ADC}} \cdot \text{DAR} \cdot (\text{ADC}_{\text{free}}^{\text{ex}} + \text{ADC}_{\text{bound}}^{\text{ex}}) \\
- k_{\text{diff}}^{\text{Drug}} \cdot (\text{Drug}_{\text{free}}^{\text{ex}} - \text{Drug}_{\text{free}}^{\text{cell}})
\]
Modeling the PD effect of the ADC through drug induced killing

Tumor killing driven by:
- intracellular unconjugated drug concentration
- maximal killing rate
- $\text{KC}_{50}$ (or $\text{IC}_{50}$)

Tumor growth model describes exponential growth followed by linear growth.

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

Tumor Volume determined by

$$\frac{d}{dt} TV = (\text{Growth}(TV) - K_{\text{Kill}}(\text{Drug}_{\text{free}}^{\text{cell}} + \text{Drug}_{\text{bound}}^{\text{cell}})) \cdot TV$$

Tumor growth model based on the following resources:
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

Model predictions of tumor growth inhibition driven by intracellular concentration of payload in tumor cell
Modeling Activity: Local Sensitivity Analysis
Results for $k_{off}$, binding affinity of drug DM-1 for tubulin

Local Sensitivity Analysis 3.6 mg/kg Q3W, parameter=$k_{off}$, Tub

% Tubulin Occupancy, parameter=$k_{off}$, Tub

Percent Tubulin Occupancy $= \frac{Drug_{bound}}{Tub_{total}} \cdot 100$
Results for P_ADC: permeability of ADC across the tumor blood vessels

Local Sensitivity Analysis 3.6 mg/kg Q3W, parameter=P_ADC

% Tubulin Occupancy, parameter=P_ADC

Tumor Diameter (cm)

% Tubulin Occupancy

0 10 20 30 40 50 60

0 25 50 75 100

0 10 20 30 40 50 60

0 1x 10x 0.1x

0 1x 10x 0.1x
ADC Modeling Extensions
Bystander effect

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.
Tumor penetration model with PDEs


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


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