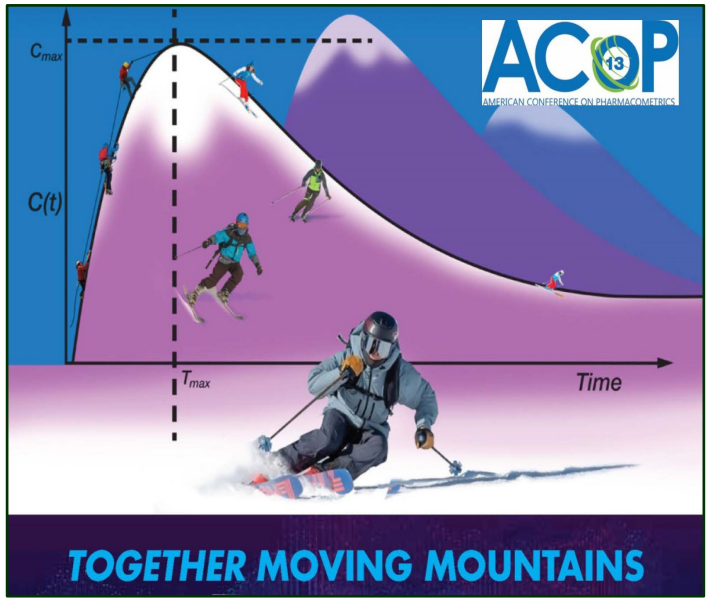



**Session 1a: Modeling and Simulation in Support of New Modalities in Oncology Drug Development**

# The application of PK/PD modelling in the clinical development of BT5528 - a novel toxin delivery platform

**Hongmei Xu, Russ Wada, Helen Kastrissios, Johanna Lahdenranta, Gavin Bennett, Zixu Wang, Phil Jeffrey**

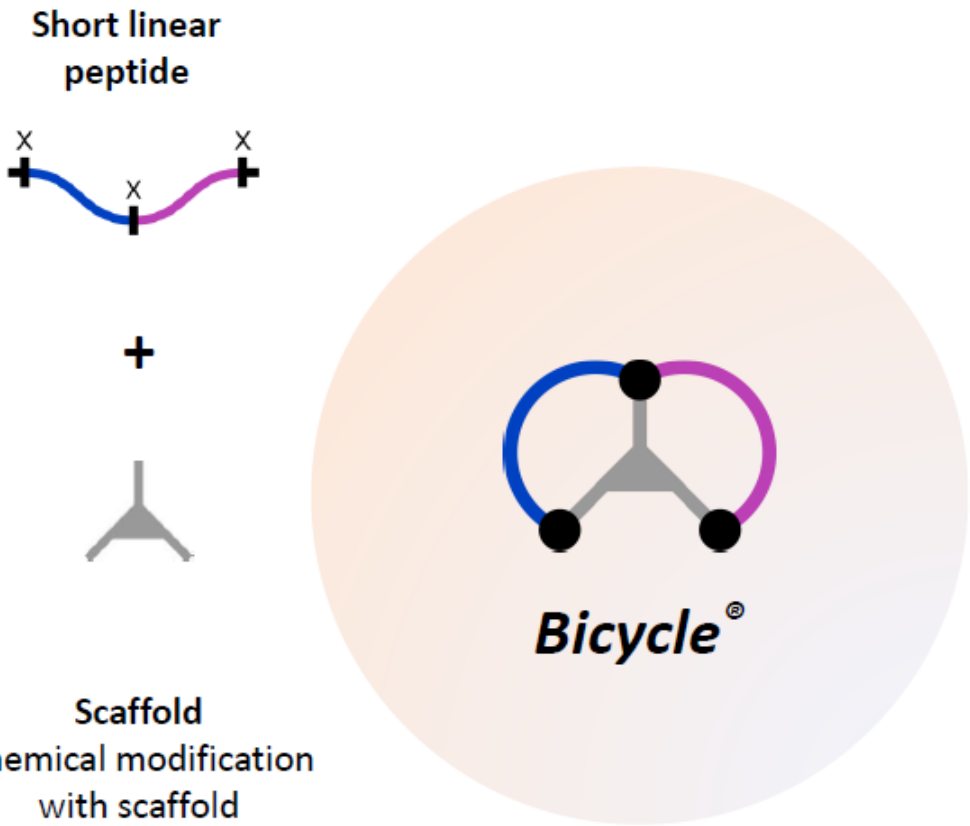
Bicycle®

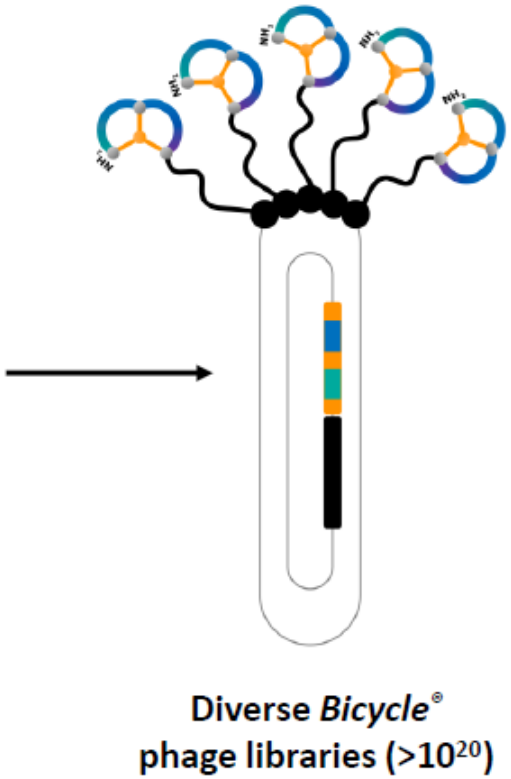
# Forward-looking statements

This presentation may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements may be identified by words such as “aims,” “anticipates,” “believes,” “could,” “estimates,” “expects,” “forecasts”, “goal,” “intends,” “may” “plans,” “possible,” “potential,” “seeks,” “will,” and variations of these words or similar expressions that are intended to identify forward-looking statements. All statements other than statements of historical facts contained in this presentation are forward-looking statements, including statements regarding: our future plans; our current and prospective product candidates, planned clinical trials and preclinical activities; the potential of the Bicycle platform; the goals of the company’s modeling activities with respect to plasma and tumor concentrations of BT5528 and MMAE; and, predictions regarding clinical concentrations of BT5528 and MMAE in tumor and in plasma respectively.

Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on our current beliefs, expectations and assumptions regarding future plans and strategies, our development plans, our preclinical and clinical results, our plans to initiate clinical trials and the designs of the planned trials and other future conditions, and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, risks related to the ongoing COVID-19 pandemic, the risk that any one or more of our product candidates will not be successfully developed or commercialized, the risk of cessation or delay of any ongoing or planned clinical trials, the risk that we may not realize the intended benefits of our technology, including that we may not identify and develop additional product candidates for our pipeline, the risk that our predictions based on modelling activities will not prove to be accurate, the risk that our product candidates or procedures in connection with the administration thereof will not have the safety or efficacy profile that we anticipate, the risk that prior results will not be replicated or will not continue in ongoing or future studies or trials, the risk that we will be unable to obtain and maintain regulatory approval for our product candidates, and risks associated with our dependence on third-parties. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled “Risk Factors” in our Quarterly Report on Form 10-Q, filed with the Securities and Exchange Commission on August 4, 2022, as well as in other filings we may make with the SEC in the future, as well as discussions of potential risks, uncertainties and other important factors in our subsequent filings with the Securities and Exchange Commission. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

# *Bicycles* are a new therapeutic modality – bicyclic peptides




**Powerful/versatile platform**

- Immense combinatorial potential
- Combines advantages of both small molecules and antibodies

**Multi-formats**

- Monomeric Bicycles
- Bicycle Toxin Conjugates® (BTCs)
- Tumor-targeted immune cell agonists (*Bicycle* TICAs)

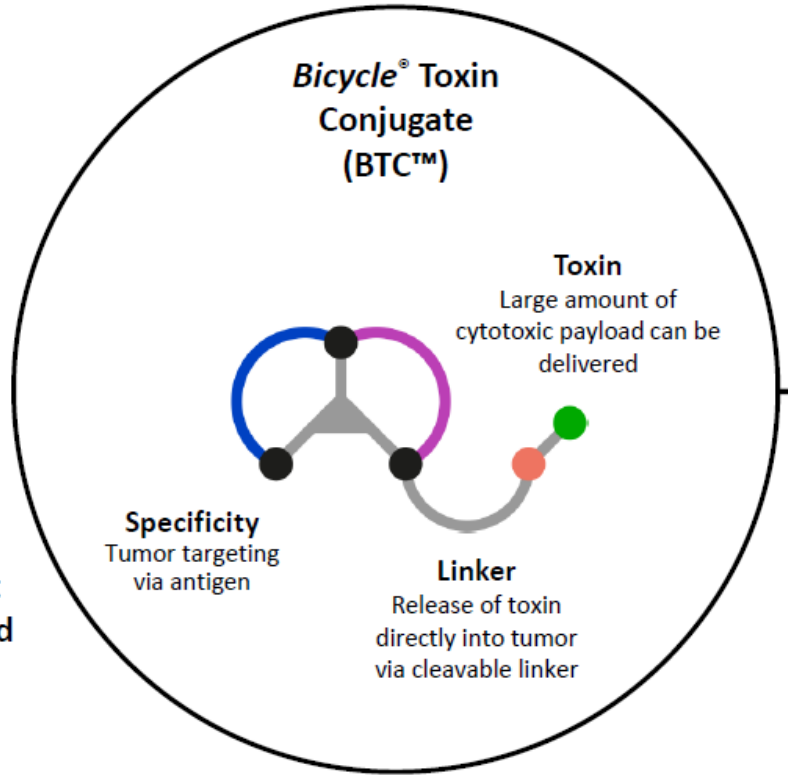
**Robust patent protection**
with 121 patent families*

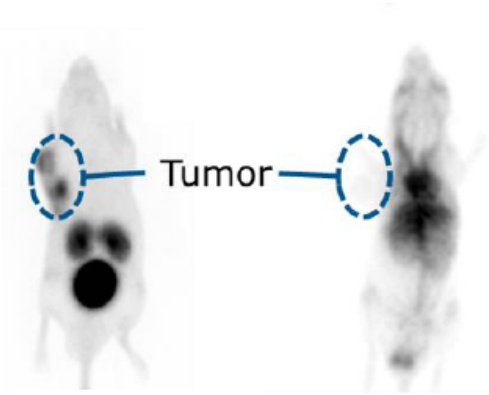
*As of June 30, 2022

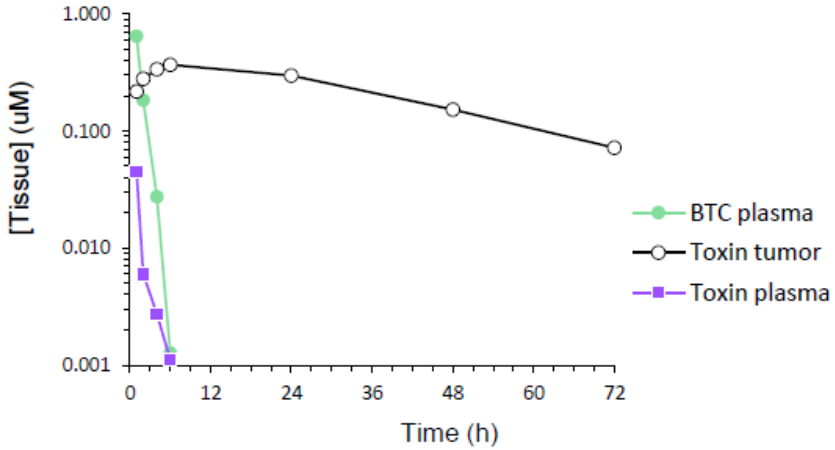
# Bicycle Toxin Conjugates (BTCs) – preclinical data indicate high potency with high specificity

- MW of 1.5-2kDa
- 50-100x smaller than antibodies

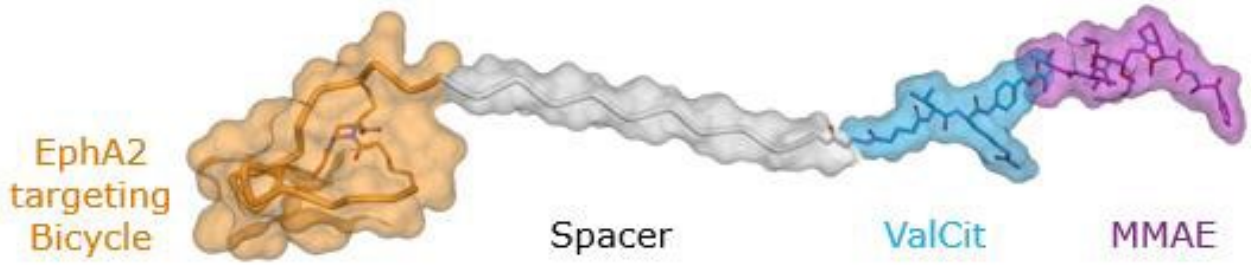
- High selectivity
- Allows more potent toxin to be delivered directly to tumor



# BT5528 is a first-in-class BTC-targeting EphA2




- BT5528 is a novel BTC that binds to tumor cells expressing cell surface EphA2
  - High expression across wide range of solid tumors
  - Toxin is released and retained in tumor cells resulting in tumor cell death and bystander killing
- BT5528 is small and hydrophilic, allowing:
  - Rapid penetration into solid tumors
  - Short systemic exposure, renally excreted

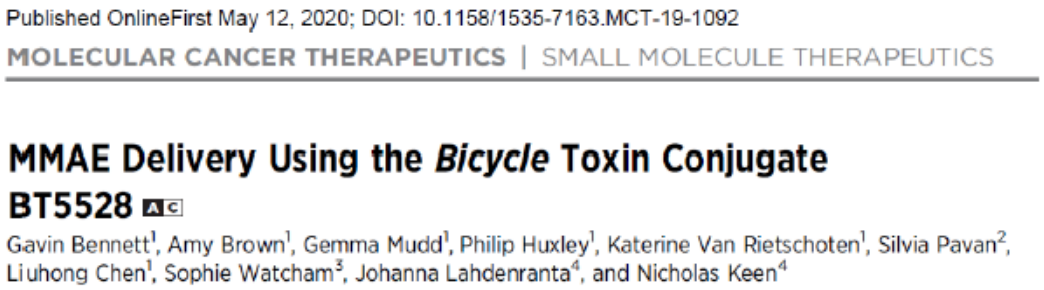

Journal of Medicinal Chemistry

pubs.acs.org/jmc Article

Identification and Optimization of EphA2-Selective Bicycles for the Delivery of Cytotoxic Payloads

Gemma E. Mudd,* Amy Brown, Liuhong Chen, Katerine van Rietschoten, Sophie Watcham, Daniel P. Teufel, Silvia Pavan, Rachid Lani, Philip Huxley, and Gavin S. Bennett

Cite This: https://dx.doi.org/10.1021/acs.jmedchem.9b02129 Read Online


Published OnlineFirst May 12, 2020; DOI: 10.1158/1535-7163.MCT-19-1092

MOLECULAR CANCER THERAPEUTICS | SMALL MOLECULE THERAPEUTICS

MMAE Delivery Using the *Bicycle* Toxin Conjugate BT5528

Gavin Bennett[1], Amy Brown[1], Gemma Mudd[1], Philip Huxley[1], Katerine Van Rietschoten[1], Silvia Pavan[2], Liuhong Chen[1], Sophie Watcham[3], Johanna Lahdenranta[4], and Nicholas Keen[4]

# BT5528 development status

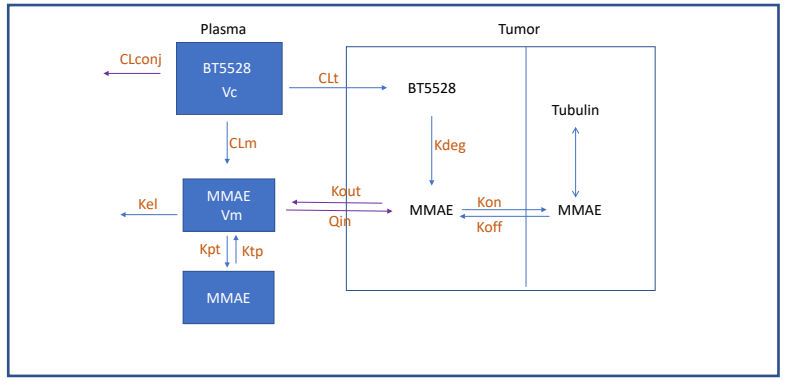
- BT5528 is being investigated in patients with advanced solid tumors historically known for expression of EphA2
- The goals of this modeling activity are to:
  - Develop an integrated model of plasma and tumor concentrations of BT5528 and MMAE in mice and in humans
  - Link tumor concentrations of MMAE to tumor regression in mice and in humans
  - Provide a framework to support RP2D decision-making for BT5528 and for other bicyclic peptides

# Summary of data

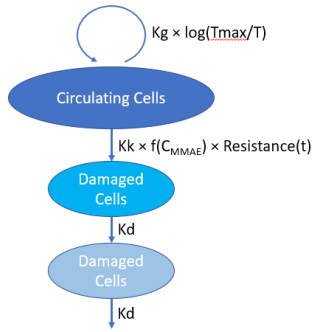
| Study | Species | Doses | N | BT5528 PK samples | MMAE PK samples | Tumor size data |
|---|---|---|---|---|---|---|
| Study 01 | Mouse | 0, 0.167, 0.5, 1.5 mg/kg | 24 | 0 | 0 | 364 |
| Study 02 | Mouse | 0.167, 0.5, 1.5 mg/kg | 63 | 0 | 15 plasma<br>63 tumor | 0 |
| Study 03 | Mouse | 1.5 mg/kg | 22 | 61 plasma<br>8 tumor | 87 plasma<br>16 tumor | 0 |
| BT5528-100 | Human | 2.2, 4.4, 6.5, 8.5, 10 $mg/m^2$ | 64 | 1609 plasma | 1605 plasma<br>5 tumor | 155 |

# Modeling schematic

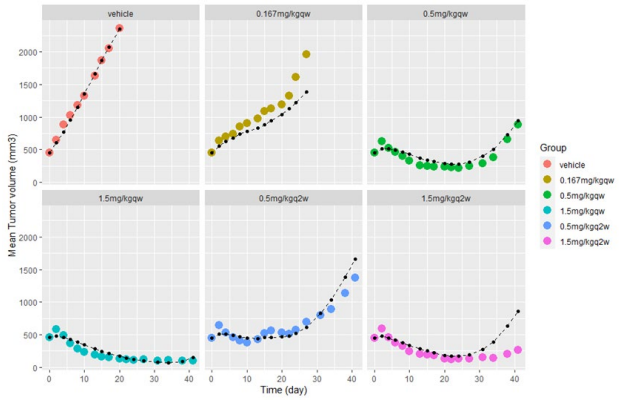
## Mouse PBPK Model



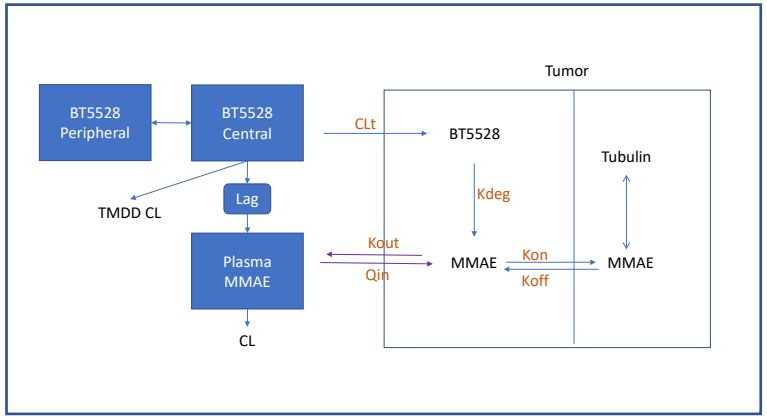

## Mouse Tumor Model



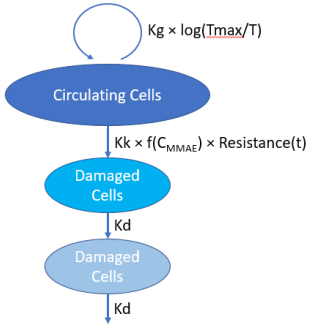

## Mouse Tumor Size Fits




## Human PopPK + Scaled Human PBPK Model

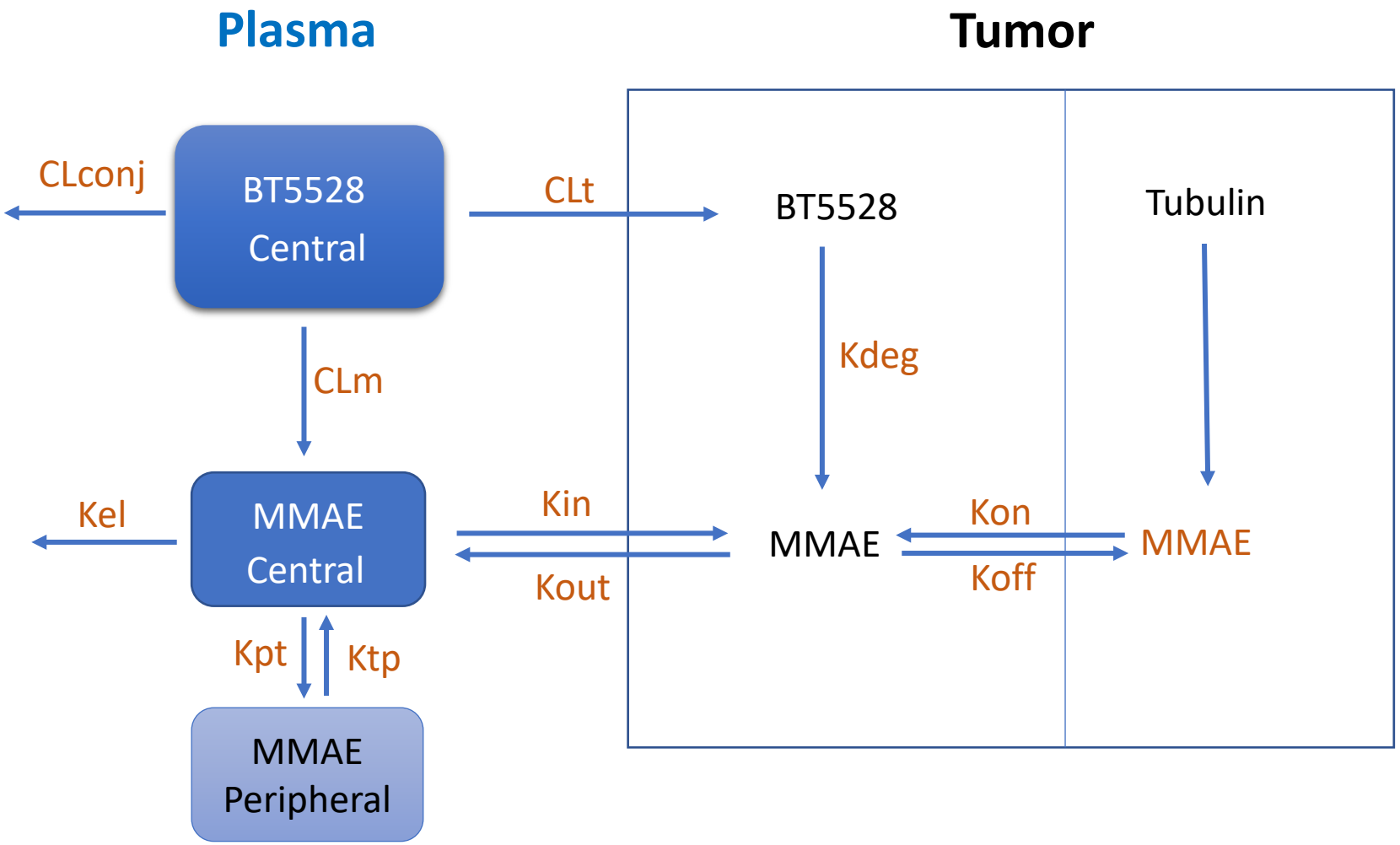



## Scaled Human Tumor Model



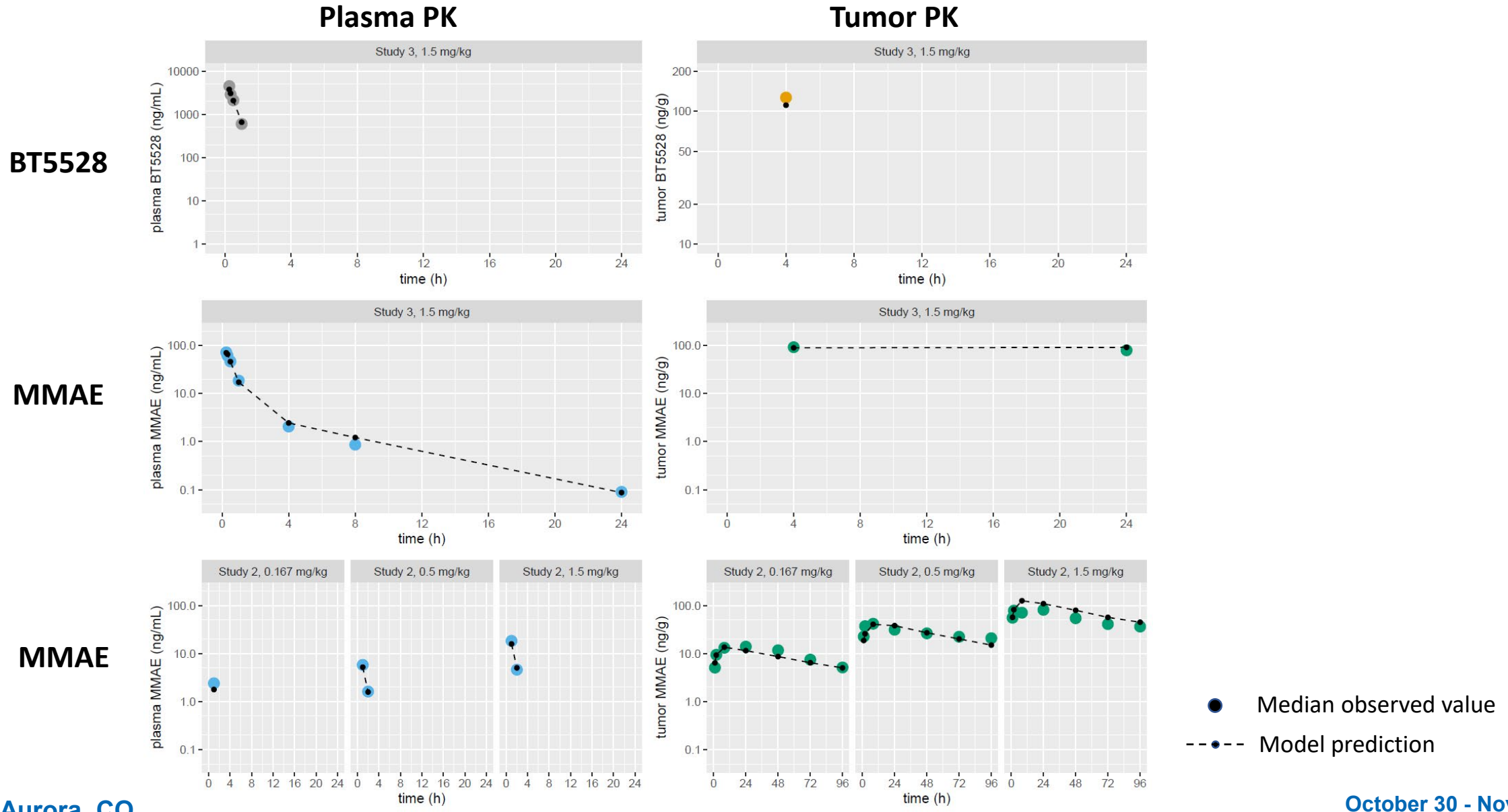

PopPK: population PK
PBPK: physiologically based PK

# Mouse PBPK-based model

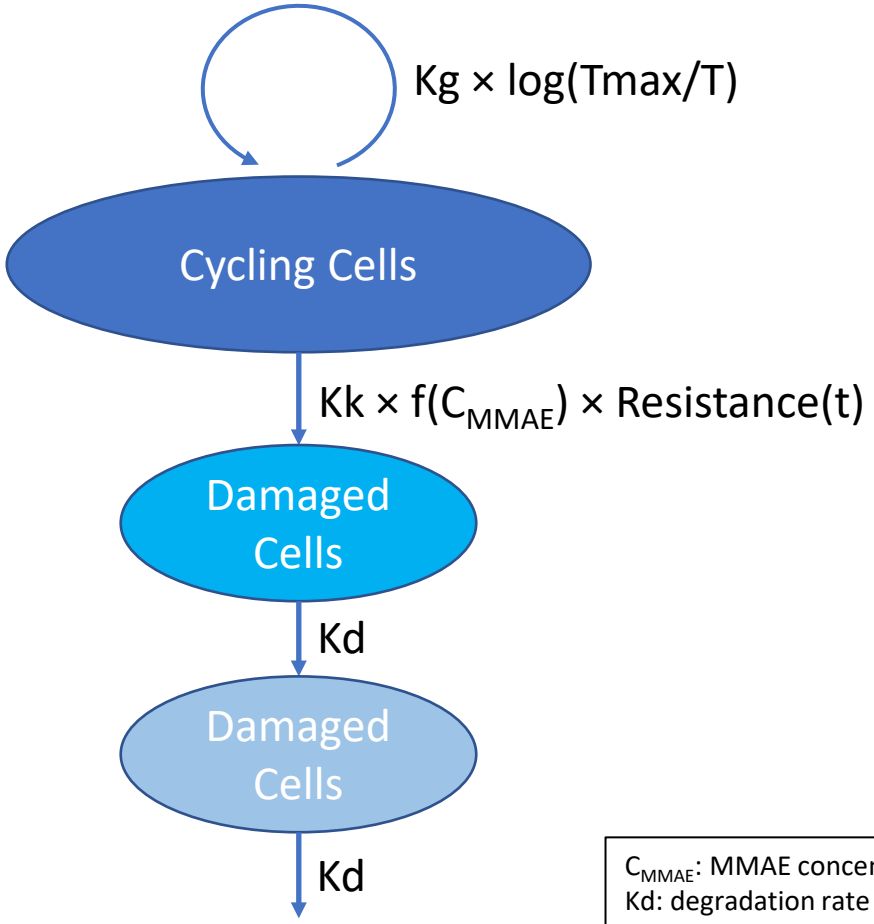



CL: clearance
Kdeg: degradation rate constant
Kel: rate of elimination
Kin: rate constant from plasma to tumor
Koff: dissociation rate constant
Kon: association rate constant
Kout: rate constant from tumor to plasma
Kpt: rate of plasma to tissue
Ktp: rate of tissue to plasma

# Mouse PBPK model described plasma and tumor PK data well



# Mouse tumor model

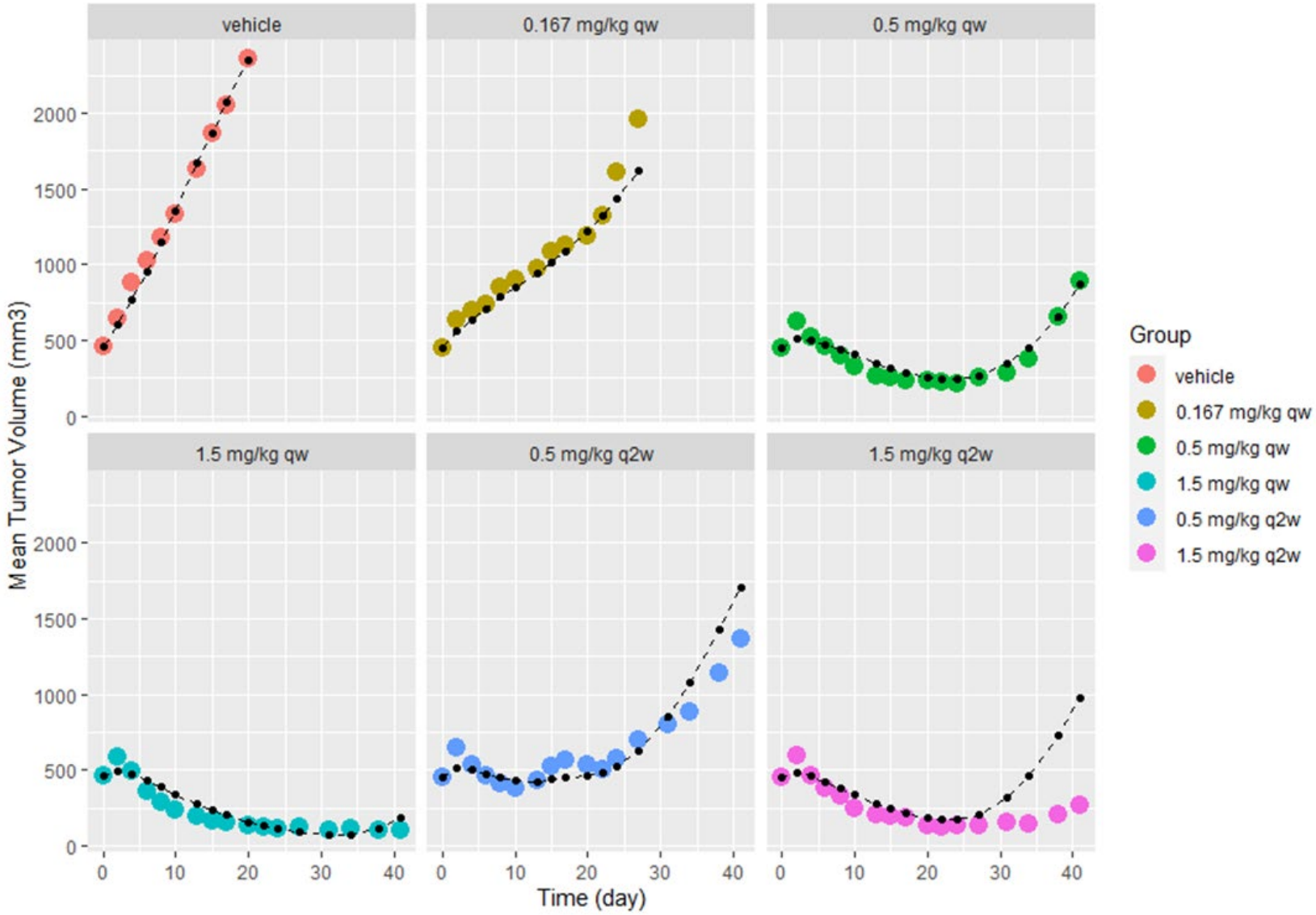



$C_{MMAE}$: MMAE concentration
Kd: degradation rate constant
Kg: growth rate
Kk: killing rate

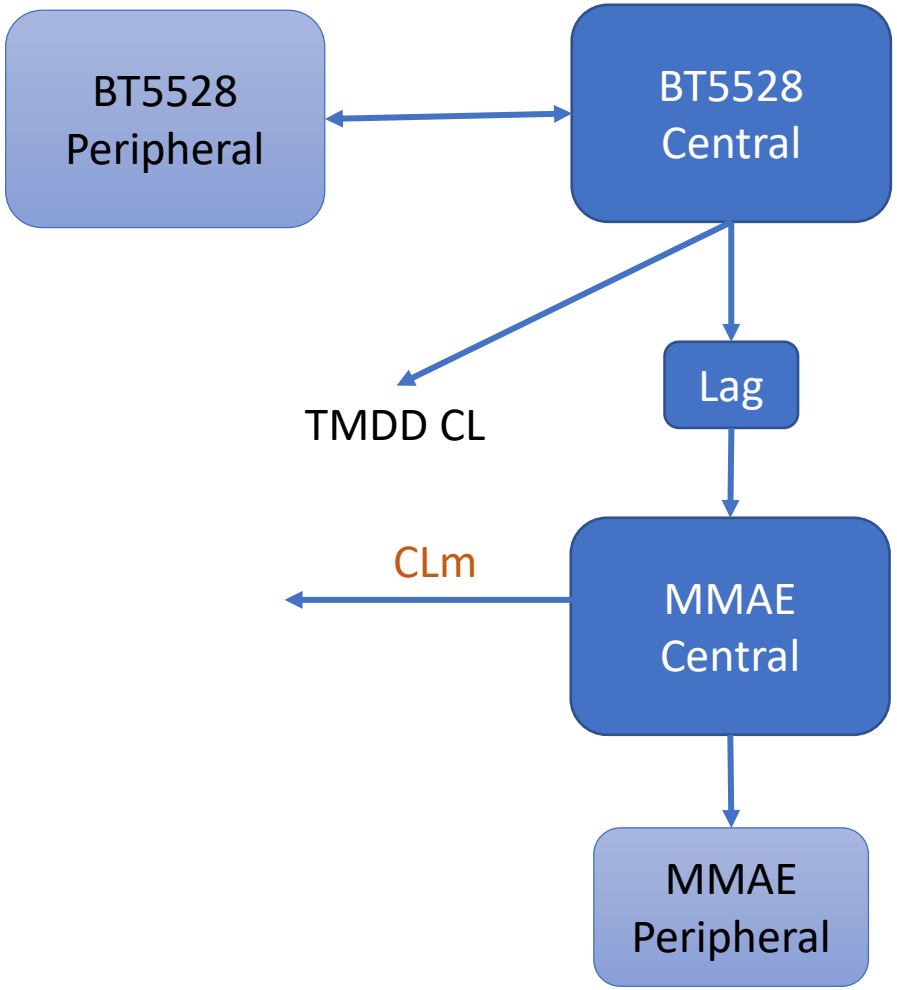
- Substantial tumor suppression was seen from 0.5 mg/kg, however rebound was observed after treatment discontinuation
- Complete suppression was observed at 1.5 mg/kg dose

Simeoni, M. *et al. Cancer Res.* 64, 1094–1101 (2004)
Claret, L. *et al. J. Clin. Oncol.* 27, 4103–4108 (2009)

# Mouse tumor model describes the tumor volume data well

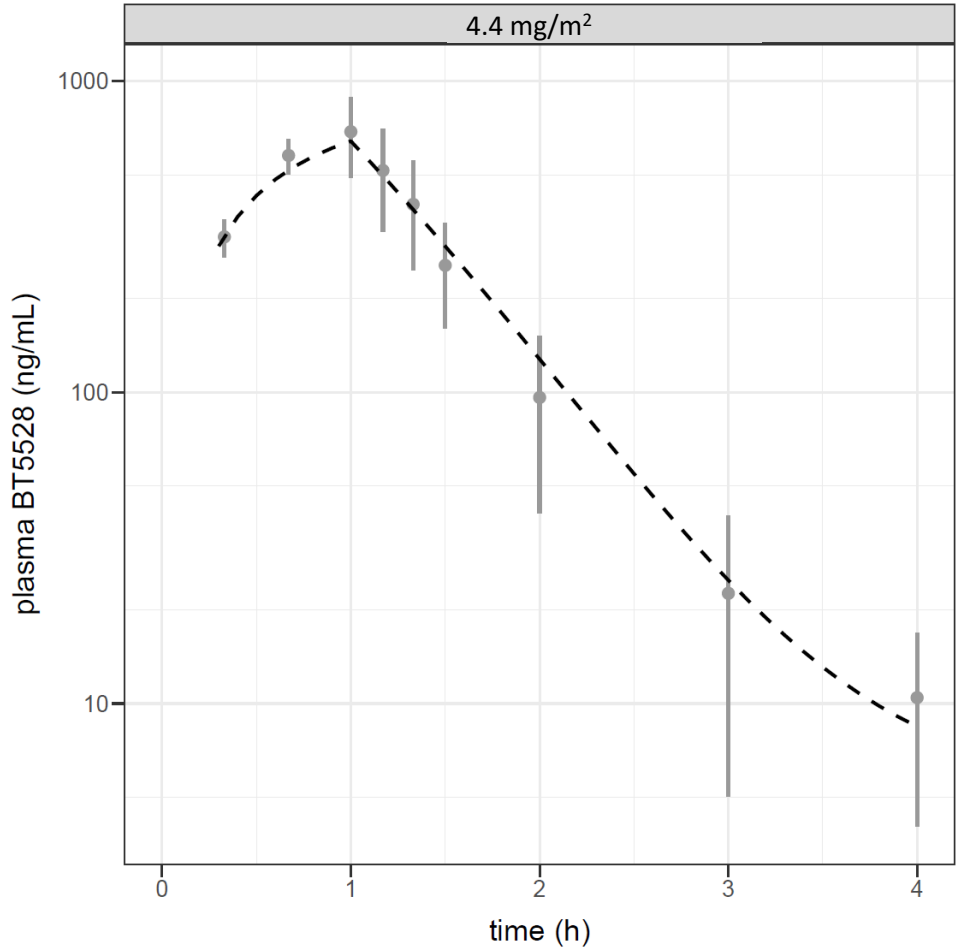


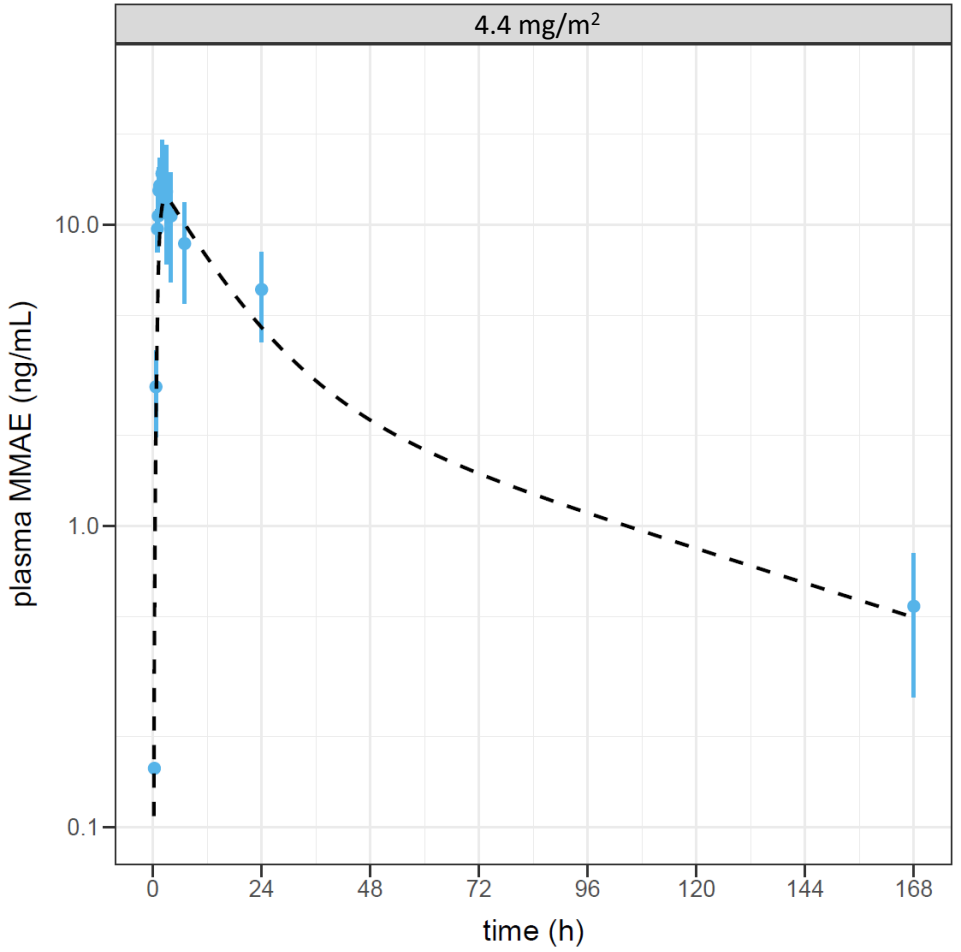
# Human PopPK Model




CLm: MMAE clearance
Lag: lag time

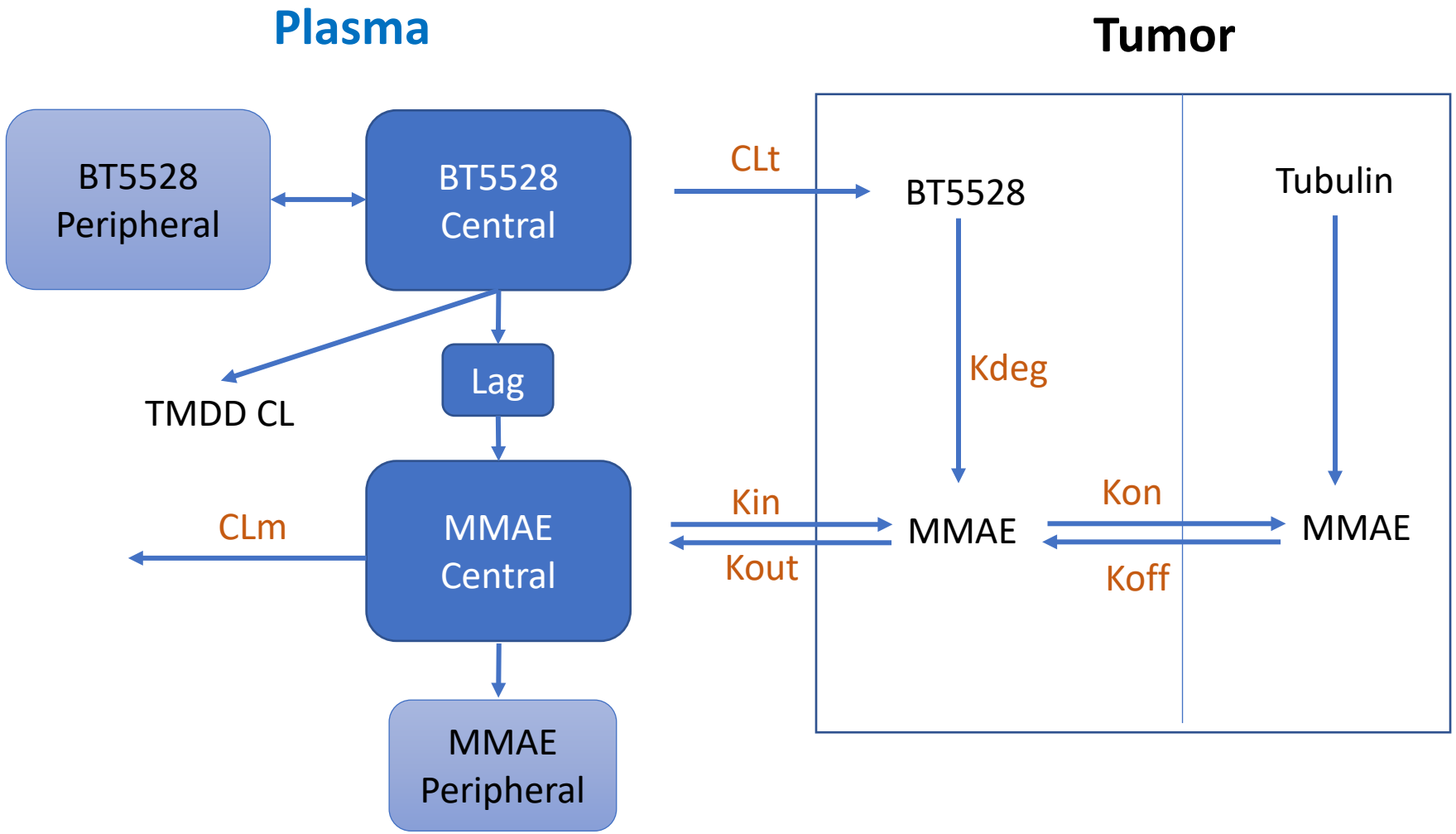
# The clinical PopPK model accurately describes the systemic concentrations of BT5528 and MMAE in cancer patients




Model prediction (dashed line) versus observed mean (±SD)

# Human PopPK-PBPK Model



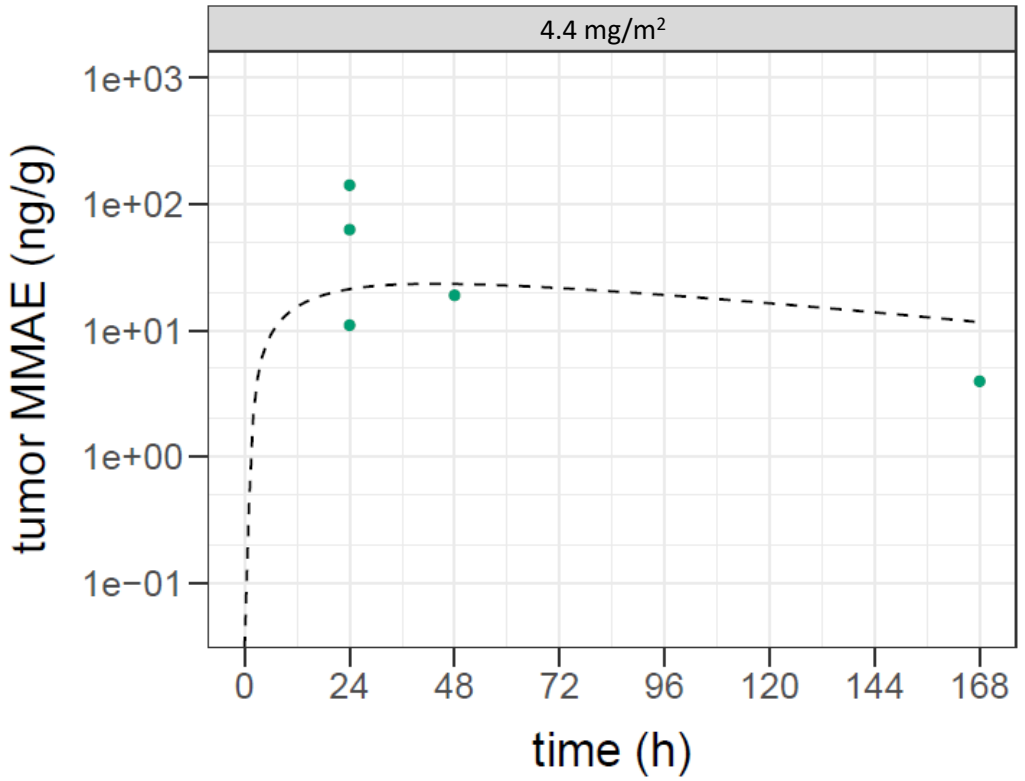

Assumptions

- Similar tubulin binding parameters (KD, Kon, Koff) across species.
- Tumor flux parameters ($Q_{5528}$ and $Q_{MMAE}$, ml/h/g) were scaled to humans using standard allometry (0.75 coefficient).

Note: CLt and Kin scaled allometrically by weight (coefficient of 0.75)

CL: clearance
Kdeg: degradation rate constant
Kel: rate of elimination
Kin: rate constant from plasma to tumor
Koff: dissociation rate constant
Kon: association rate constant
Kout: rate constant from tumor to plasma
Kpt: rate of plasma to tissue
Ktp: rate of tissue to plasma
TMDD: target mediated drug disposition
Vc: central volume of distribution for BT5528
Vm: central volume of distribution for MMAE

# The linked PopPK-PBPK model also describes the clinical tumor concentrations of MMAE well

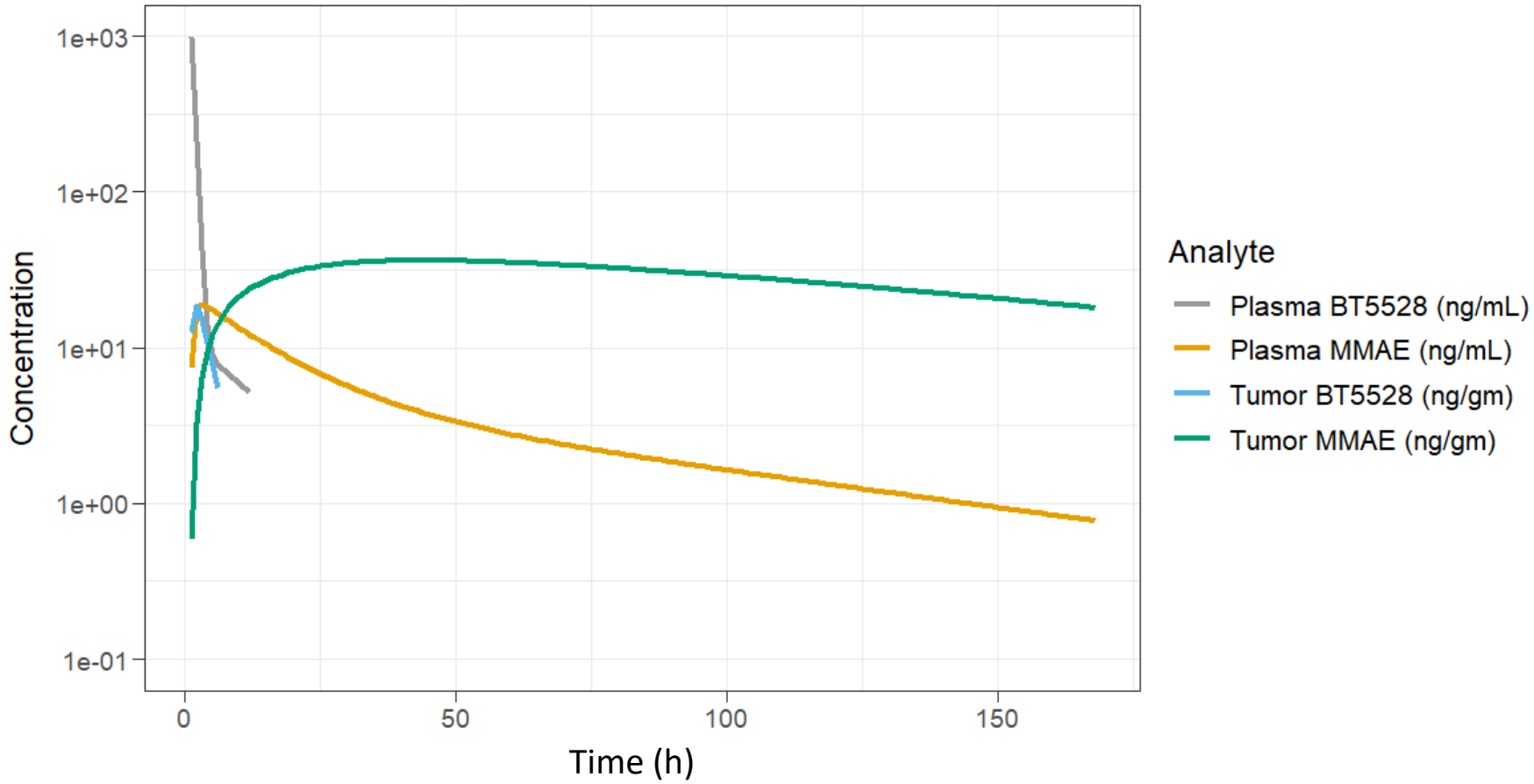



observed concentrations from different dose cohorts; median dose of 4.4 (2.2 to 8.5) mg/m$^2$

model prediction from 4.4 mg/m$^2$

# Concentrations of MMAE in tumor are predicted to exceed concentrations of MMAE in plasma

Predicted clinical plasma concentrations of BT5528 and MMAE and tumor concentrations of MMAE following a single dose BT5528 at 6.5 mg/m$^2$



# Key findings of the PopPK-PBPK modeling

- BT5528 has a short terminal plasma half-life
- MMAE has rapid penetration into the tumor and is retained in the tumor through binding to tubulin
- Plasma concentrations of MMAE are a good surrogate for tumor concentrations of MMAE
  - validation based on extensive preclinical mouse data
  - emerging clinical data supports clinical translation

# Conclusions

- This preclinical and clinical PBPK-PopPK-tumor size modeling paradigm has enabled a prediction of tumor payload profiles for new BTCs
- This paradigm also supports dose selection and dose optimization that fully leverages both preclinical and clinical data, which is aligned with Project Optimus

# Acknowledgement


- Patients, their families and carers
- Investigators and clinical staff

QuanTx Consulting

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Bicycle Therapeutics team, especially…

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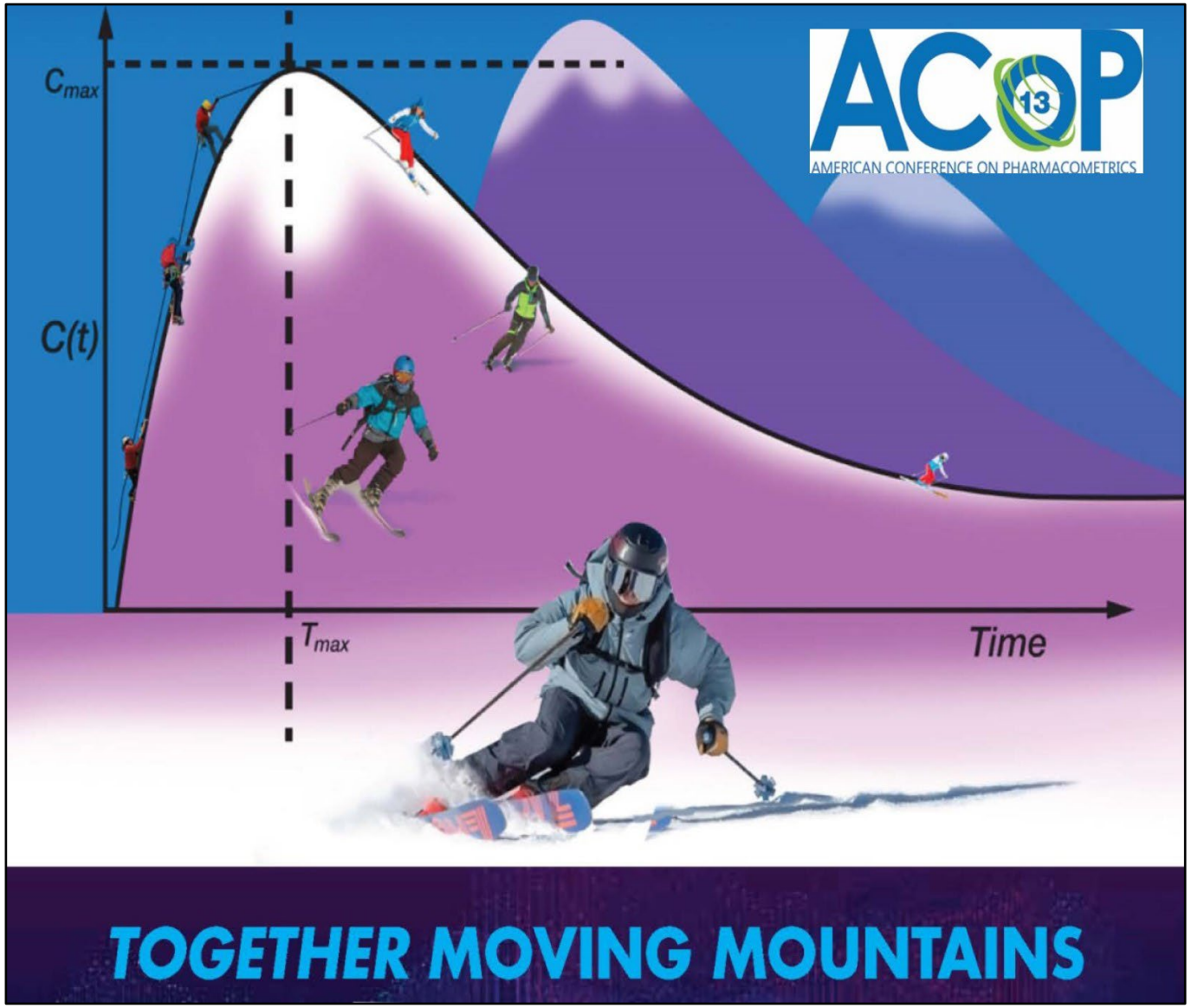
- Nicholas Keen
- Sebastien Hazard
- Johanna Lahdenranta
- Gavin Bennett
- Zixu Wang
- Punit Upadhyaya
- Joseph Tweed
- Adriana Domingo

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