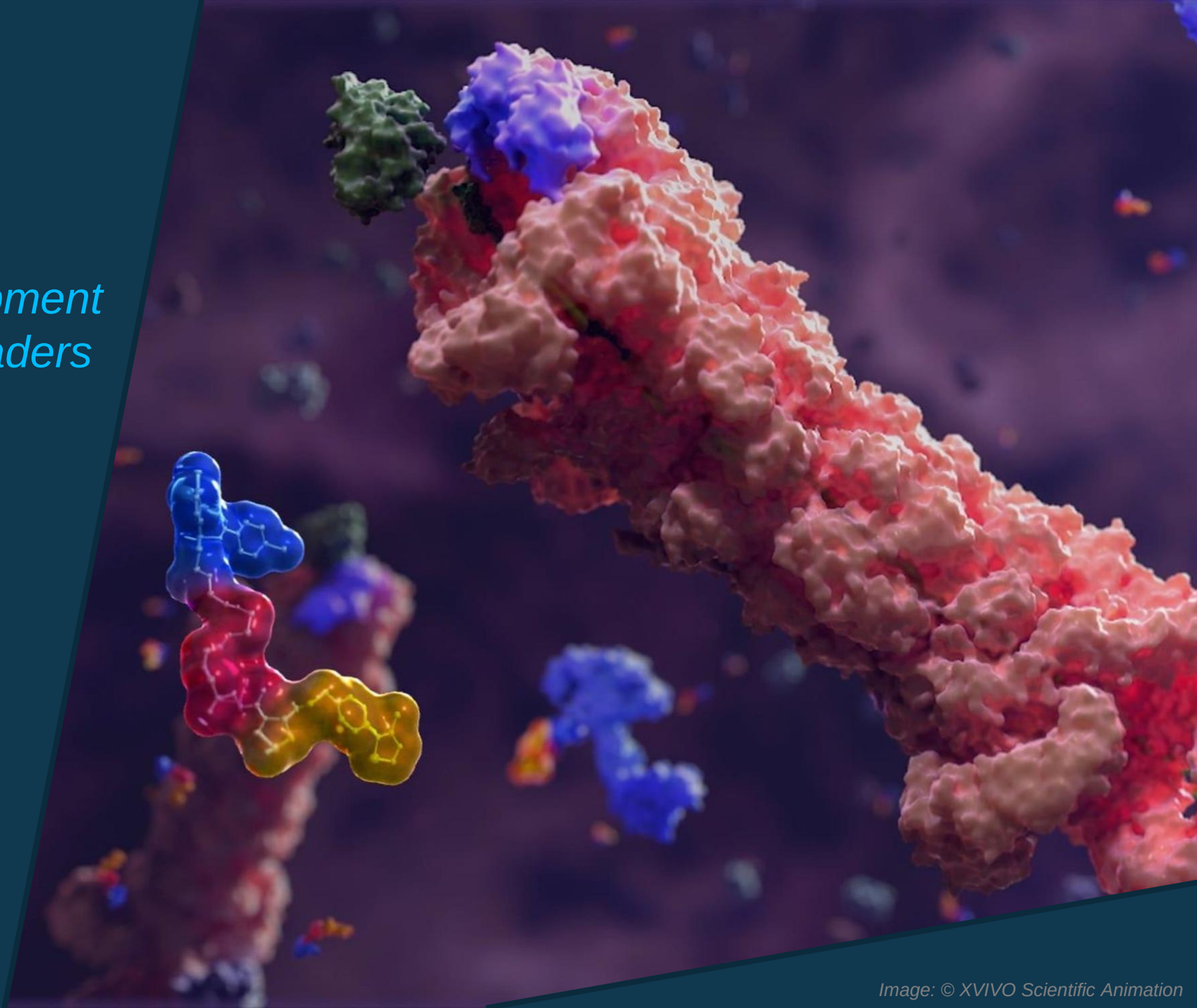
Transforming the Development of Targeted Protein Degraders

The Translational Power of PK/PD Modeling beyond the Human Dose Projection

Robin T. U. Haid [1,2]

[1] *ETH Zurich – Institute of Pharmaceutical Sciences*
[2] *Bayer AG – Preclinical Modeling & Simulation*

Rosa's Worldwide Webinar, San Diego, CA
March 12, 2025



Introduction

Thalidomide turned out to be the first (unintended) protein degrader

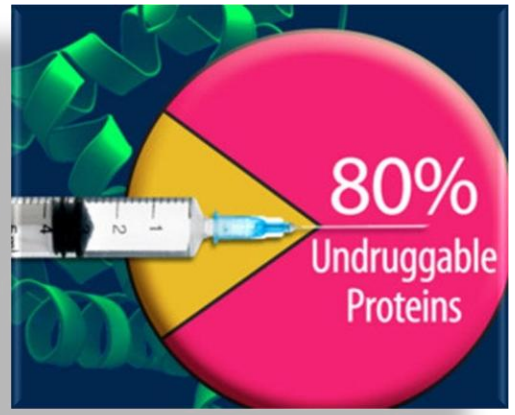
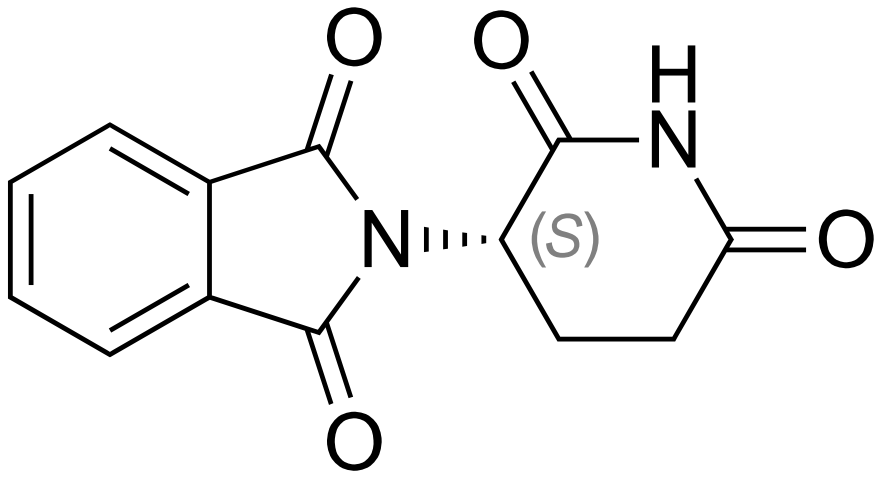


Image: © Michael Helfenbein

Thalidomide (Contergan®)



Images: © Thomann (2007) Dtsch. Arztebl.,104 A-2778–2782

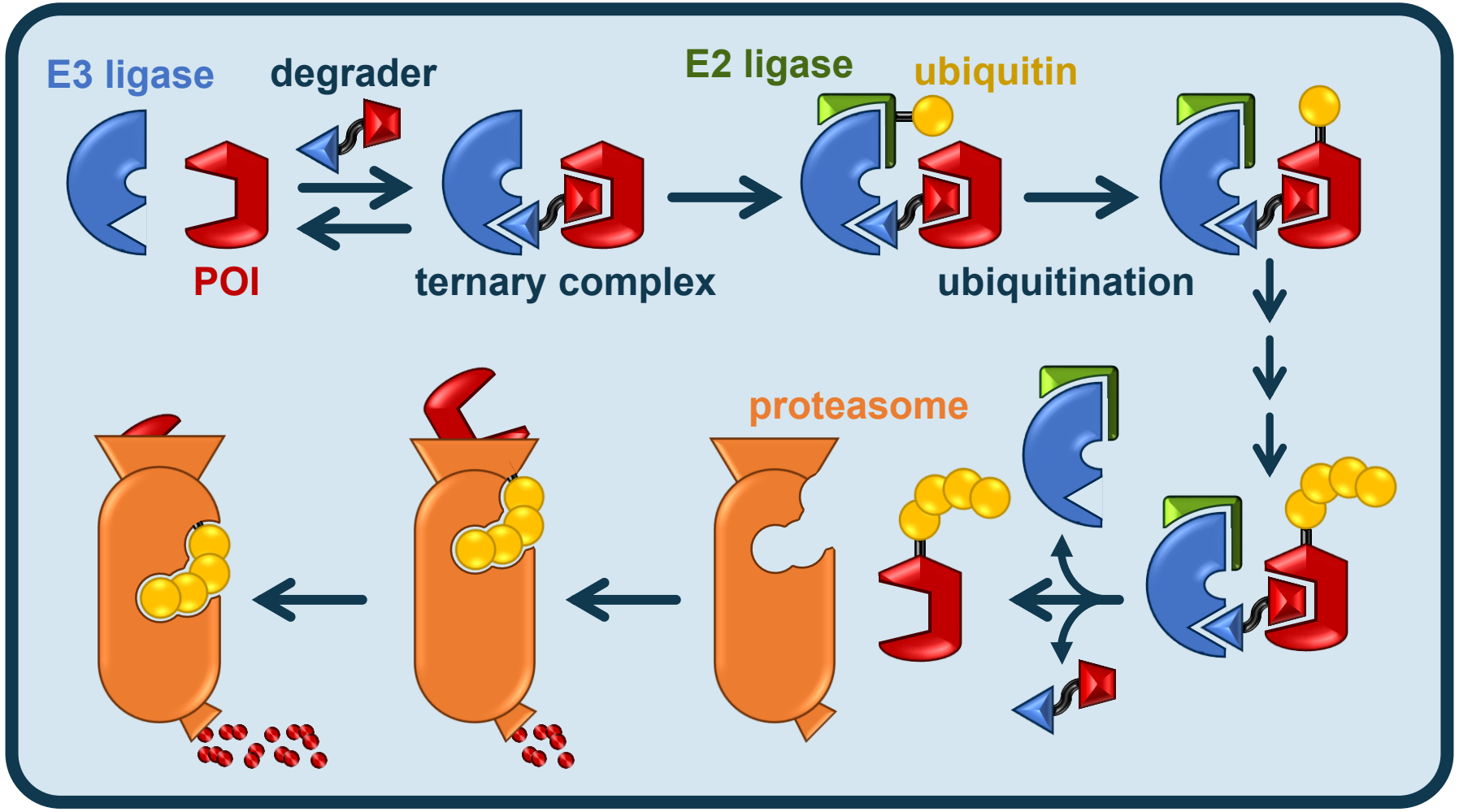
Image: © New Zealand Truth

Teratogenicity caused by **degradation** of SALL4, a transcription factor [1,2]

[1] *Matyskiela et al. (2018) Nat. Chem. Biol.* DOI: 10.1038/s41589-018-0129-x
[2] *Ichikawa et al. (2022) Nature* DOI: 10.1038/s41586-022-05333-5

Mechanism of Action

Targeted protein degraders employ the cell's intrinsic protein recycling system [3,4]

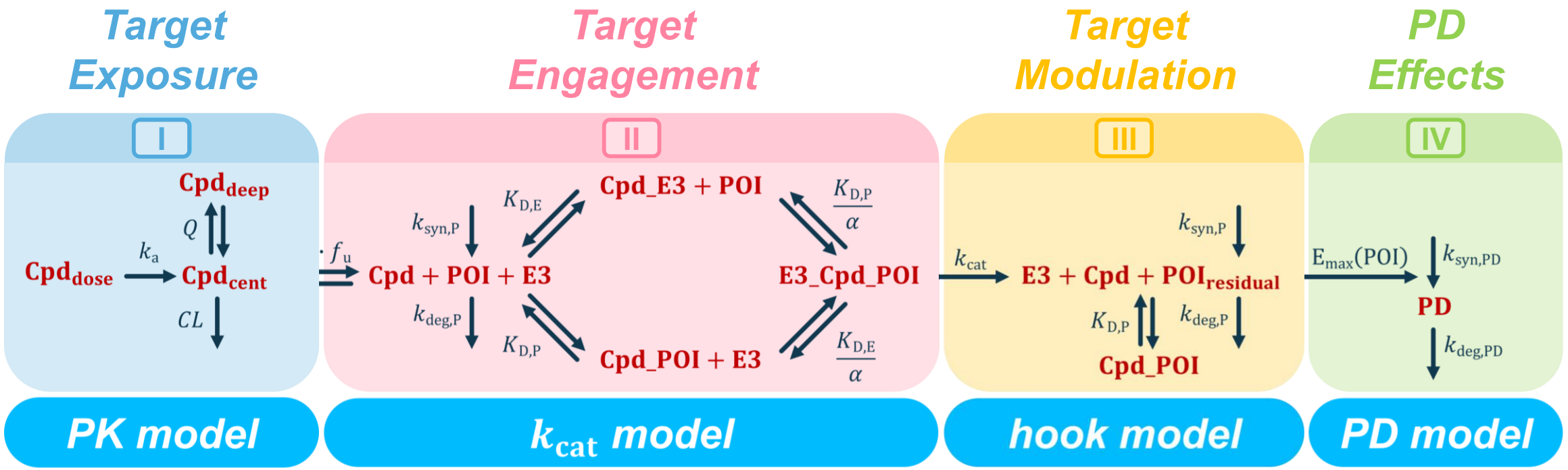


POI ... Protein Of Interest (i.e., target)

[3] *Sakamoto et al. (2001) Proc. Natl. Acad. Sci. USA* DOI: 10.1073/pnas.141230798
[4] *Lu et al. (2015) Chem. Biol.* DOI: 10.1016/j.chembiol.2015.05.009

Modeling Approach

Bring the four pillars concept to degraders [5,6,7]



POI ... Protein Of Interest (i.e., target)

Structure of **mechanistic modeling** framework for degrader **prioritization** and **optimization**

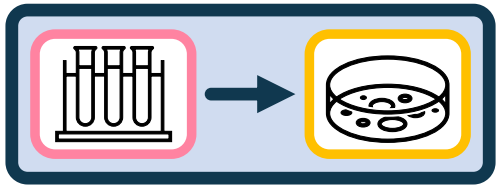
[5] *Nowak & Jones (2021) SLAS Discov.* DOI: 10.1177/2472555220979584
[6] *Haid & Reichel (2023) Pharmaceutics* DOI: 10.3390/pharmaceutics15010195
[7] *Haid & Reichel (2024) Clin. Pharmacol. Ther.* DOI: 10.1002/cpt.3273

Purpose

Predictive PK/PD modeling makes an impact at three crucial translational steps

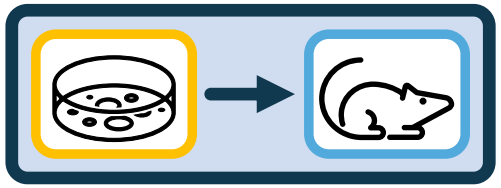
1) Translation from biochemical to cellular level

   - How to increase degradation potency?



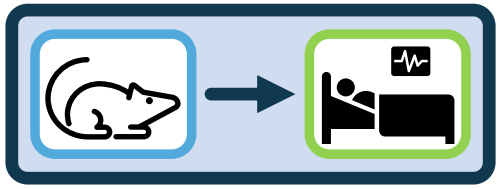
2) Translation from cellular level to animal model

   - Which compounds to take in vivo?



3) Translation from animal model to clinical readout

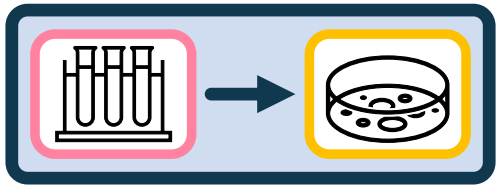
   - At what dose do we get a therapeutic effect?



Purpose

Predictive PK/PD modeling makes an impact at three crucial translational steps

1) Translation from biochemical to cellular level



- How to increase degradation potency?

2) Translation from cellular level to animal model

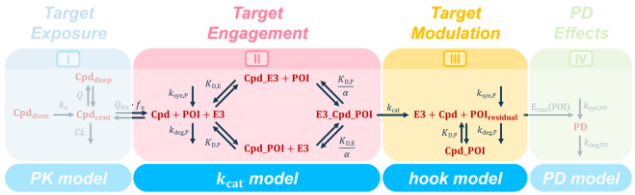
- Which compounds to take *in vivo*?

3) Translation from animal model to clinical readout

- At what dose do we get a therapeutic effect?

I) *Model-Informed Optimization of TPDs*

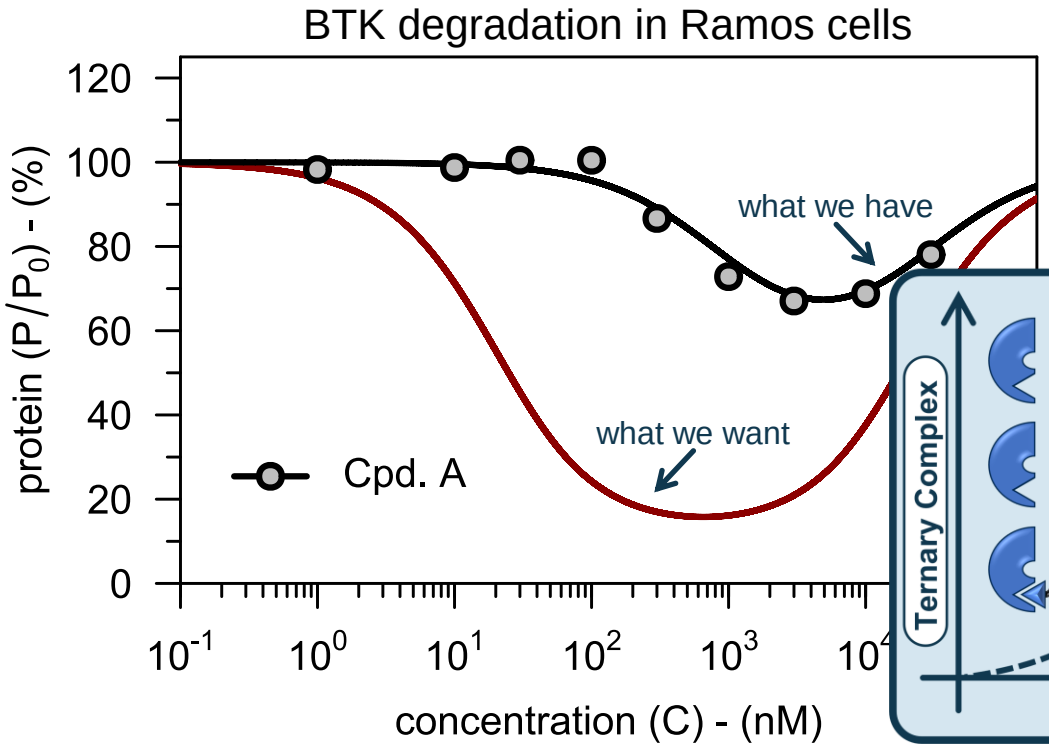
Predict binding affinities that will result in desired degradation [8,9]



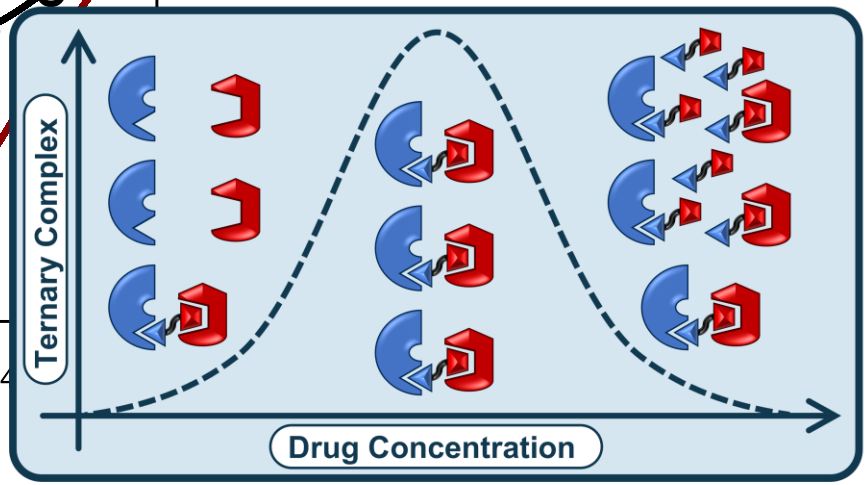
	Cpd. A
$K_{D,P}$ (nM)	1,535
$K_{D,E}$ (nM)	15,700
α (1)	0.89

- three binding partners, thus three affinity constants

$K_{D,P}$ … affinity for target protein (POI)
$K_{D,E}$ … affinity for E3 ligase (enzyme)
α … interaction of POI and E3 ligase



1) the binding affinities [8] are used to fit the observed degradation data

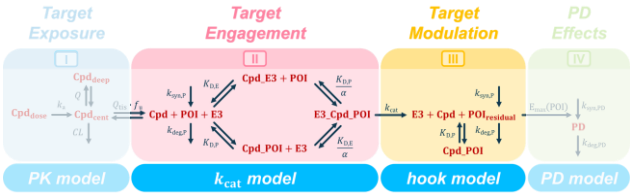


The first step to **improving** a poor degrader is **identifying** its shortcomings

[8] data: *Zorba et al. (2018) Proc. Natl. Acad. Sci. USA* DOI: 10.1073/pnas.1803662115
[9] data: *Bradshaw et al. (2015) Nat. Chem. Biol.* DOI: 10.1038/nchembio.1817

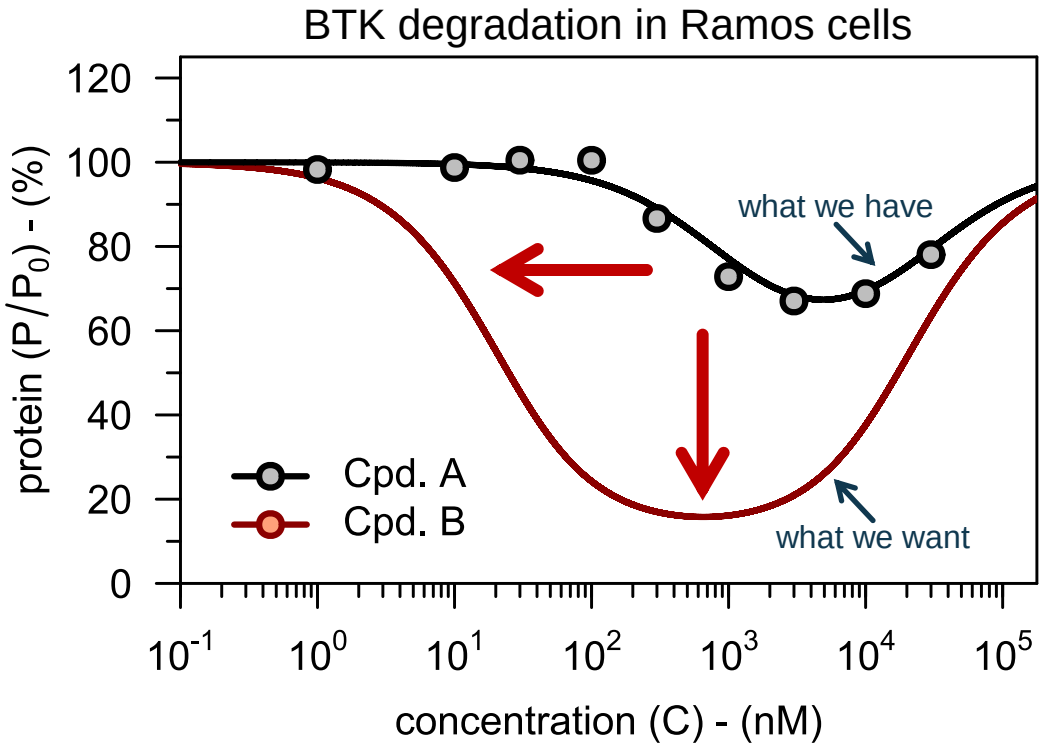
I) *Model-Informed Optimization of TPDs*

Predict binding affinities that will result in desired degradation [8,9]



	Cpd. A	Cpd. B
$K_{D,P}$ (nM)	1,535 →	×10
$K_{D,E}$ (nM)	15,700 →	×5
α (1)	0.89 →	×1.5

- higher affinities needed for desired degradation



1) the binding affinities [8] are used to fit the observed degradation data

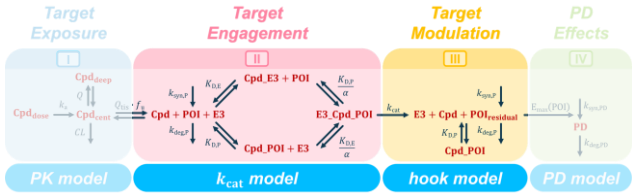
2) the resulting model tells us how binding affinities have to be improved

Due to its **multiparametric** nature (three binding affinities), degrader optimization is often **non-intuitive**

[8] data: *Zorba et al. (2018) Proc. Natl. Acad. Sci. USA* DOI: 10.1073/pnas.1803662115
[9] data: *Bradshaw et al. (2015) Nat. Chem. Biol.* DOI: 10.1038/nchembio.1817

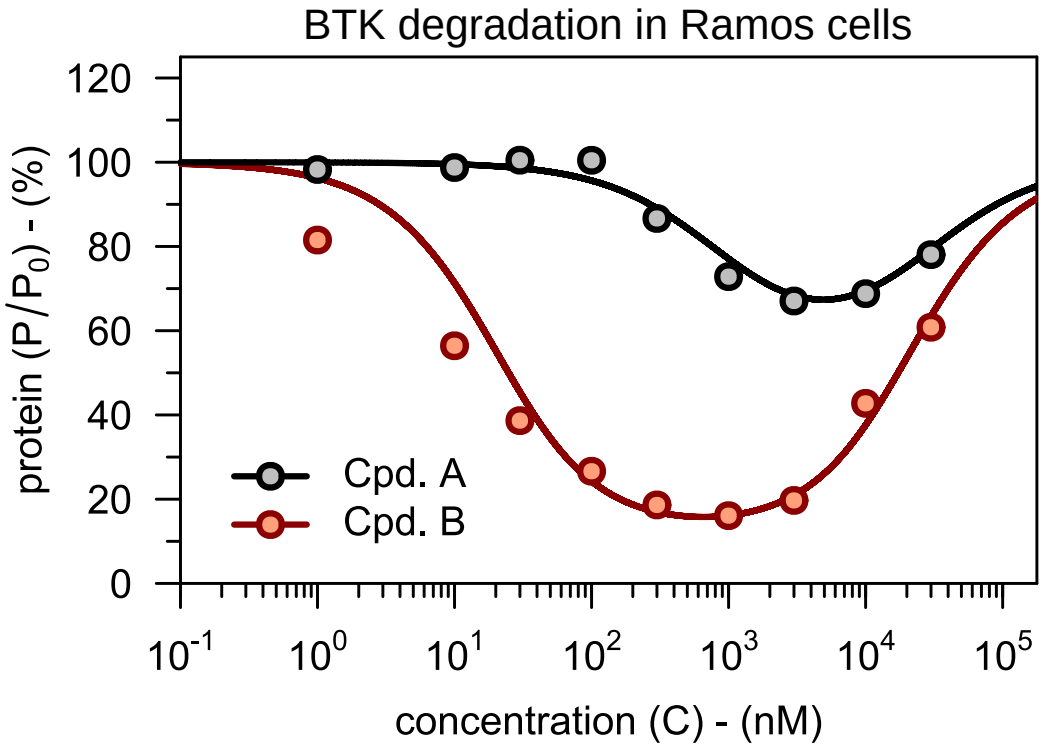
I) *Model-Informed Optimization of TPDs*

Predict binding affinities that will result in desired degradation [8,9]



	Cpd. A	Cpd. B
$K_{D,P}$ (nM)	1,535	138
$K_{D,E}$ (nM)	15,700	3,100
α (1)	0.89	1.34

- all three binding affinities need to be considered



1) the binding affinities [8] are used to fit the observed degradation data
2) the resulting model tells us how binding affinities have to be improved
3) the prediction is validated with experimental data from a real degrader (i.e., Cpd. B)

The k_{cat} *model* [6] **guides** medicinal **chemistry** during compound **optimization**

[6] *Haid & Reichel (2023) Pharmaceutics* DOI: 10.3390/pharmaceutics15010195
[8] data: *Zorba et al. (2018) Proc. Natl. Acad. Sci. USA* DOI: 10.1073/pnas.1803662115
[9] data: *Bradshaw et al. (2015) Nat. Chem. Biol.* DOI: 10.1038/nchembio.1817

Purpose

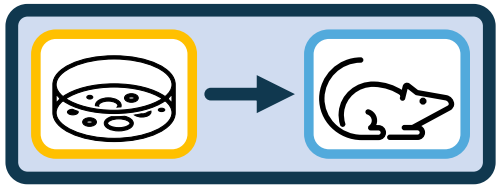
Predictive PK/PD modeling makes an impact at three crucial translational steps

1) Translation from biochemical to cellular level

✓ How to increase degradation potency?

2) Translation from cellular level to animal model

➢ Which compounds to take in vivo?

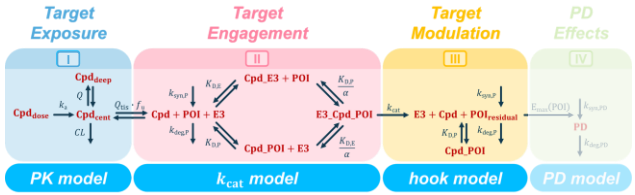


3) Translation from animal model to clinical readout

➢ At what dose do we get a therapeutic effect?

II) *Designing Animal Efficacy Studies*

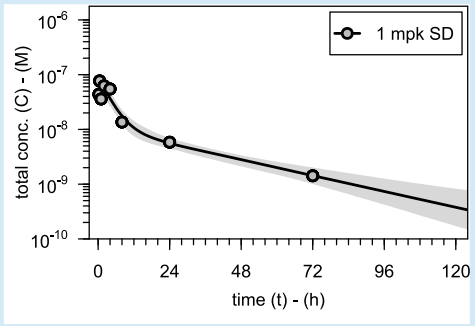
Integrate plasma conc. with assay data to predict outcome [10,11]



Input

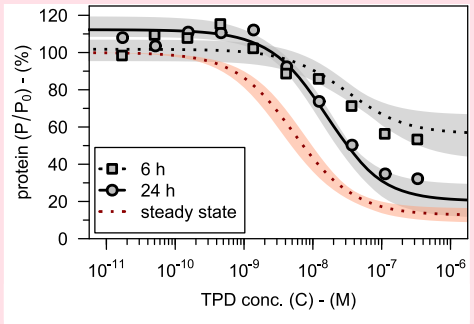
In Vivo PK

$CL = 1.08$ L/kg/h
$V_{ss} = 21.6$ L/kg
$F = 78\%$



In Vitro PD

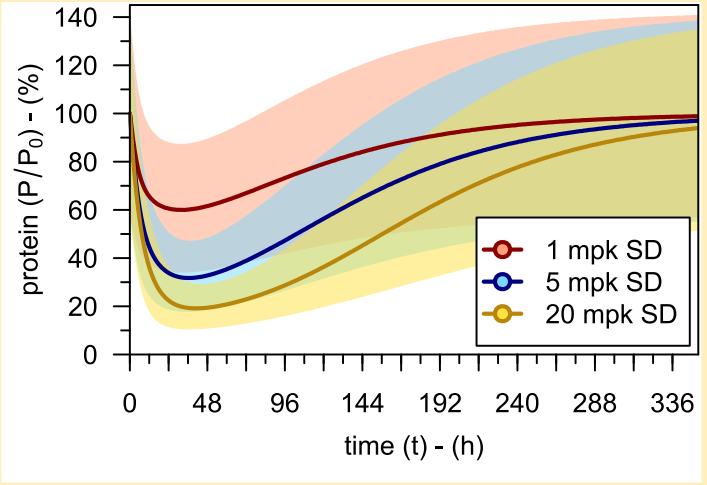
$D_{max} = 87\%$
$DC_{50} = 5.3$ nM
$t_{½,P} = 47$ h
$f_{u,rel} = 100\%$



Model [7]

Output

In Silico Simulated PK/PD Study



RIPK2 (POI) levels in rat PBMCs ($n = 5$)

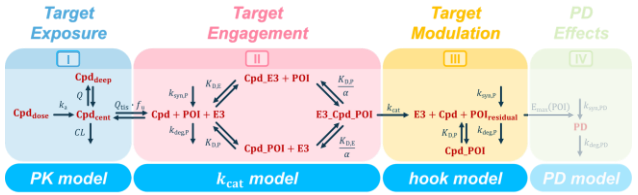
- time-course of protein degradation for different doses incl. uncertainty*

* uncertainty informed from experimental variability (vehicle group)

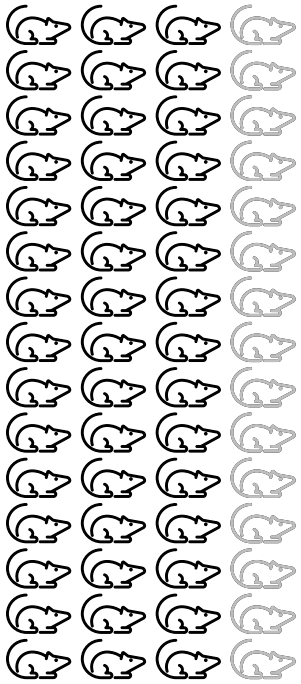
[7] *Haid & Reichel (2024) Clin. Pharmacol. Ther.* DOI: 10.1002/cpt.3273
[10] data: *Mares et al. (2020) Commun. Biol.* DOI: 10.1038/s42003-020-0868-6
[11] data: *Mathieson et al. (2018) Nat. Commun.* DOI: 10.1038/s41467-018-03106-1

II) *Designing Animal Efficacy Studies*

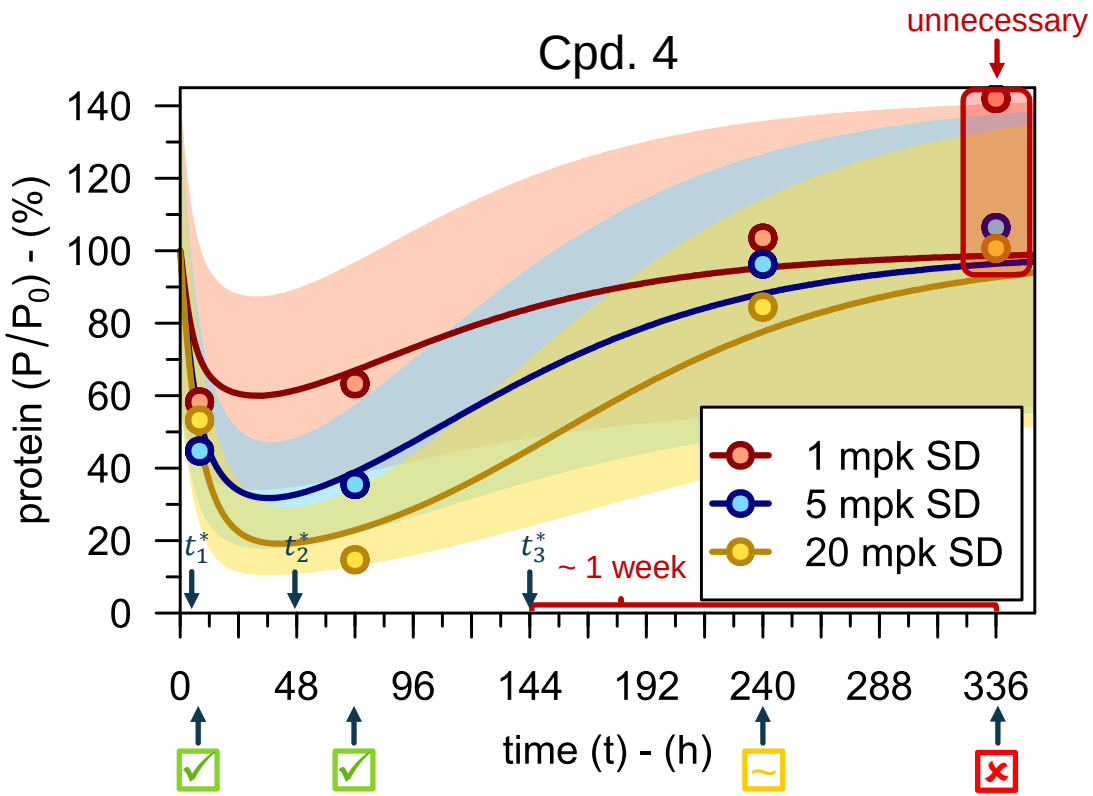
A priori predictions are used to optimize study protocols [10,11]



Cpd. 4 (n=60)



➢ 25% fewer rats



1 mpk SD sufficient?

strong or weak effect?

first & last time point?

when max. degradation?

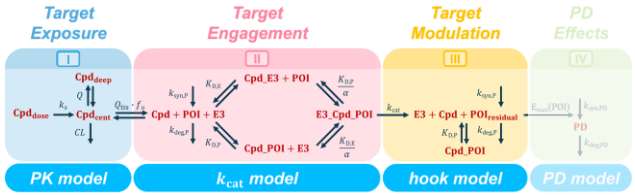
If a compound seems promising, **predictions** are **confirmed** experimentally to **validate** the model

[10] data: *Mares et al. (2020) Commun. Biol.* DOI: 10.1038/s42003-020-0868-6

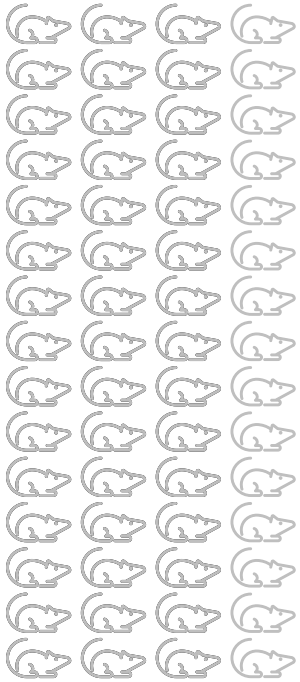
[11] data: *Mathieson et al. (2018) Nat. Commun.* DOI: 10.1038/s41467-018-03106-1

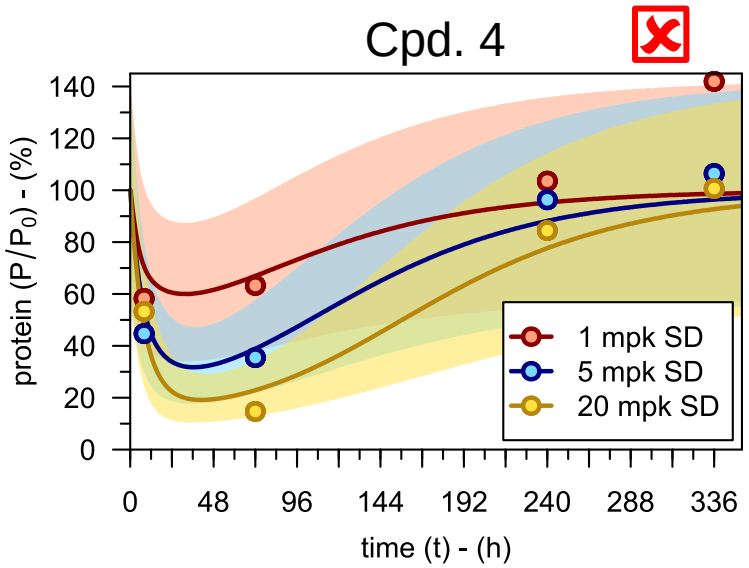
II) *Designing Animal Efficacy Studies*

In silico screening is faster, cheaper, and more ethical [10,11]



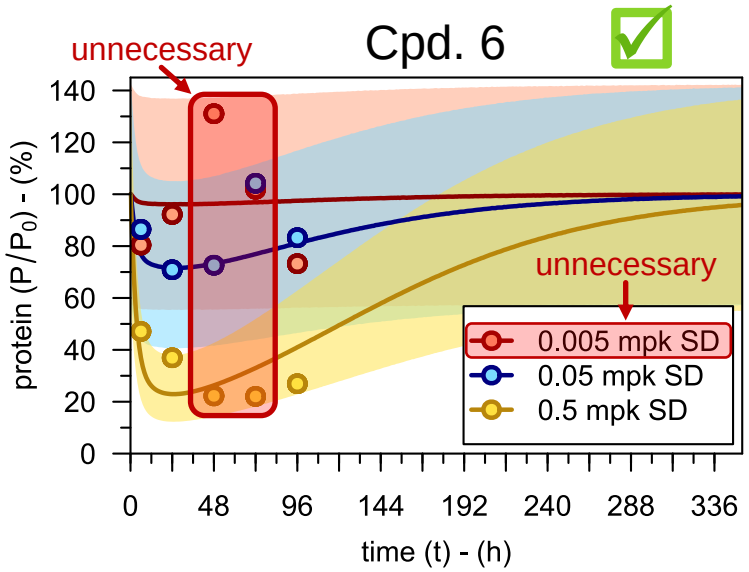
Cpd. 4 (n=60)





➢ 100% fewer rats

Cpd. 6 (n=75)



➢ 60% fewer rats

Modeling enhances the value of studies,
while **reducing** the number of **animals**

[10] data: *Mares et al. (2020) Commun. Biol.* DOI: 10.1038/s42003-020-0868-6
[11] data: *Mathieson et al. (2018) Nat. Commun.* DOI: 10.1038/s41467-018-03106-1

Purpose

Predictive PK/PD modeling makes an impact at three crucial translational steps

1) Translation from biochemical to cellular level

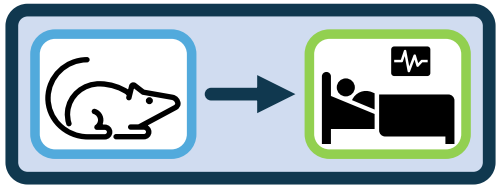
✓ How to increase degradation potency?

2) Translation from cellular level to animal model

✓ Which compounds to take in vivo?

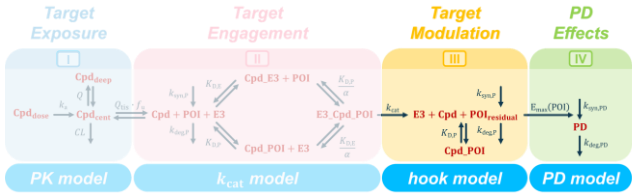
3) Translation from animal model to clinical readout

➢ At what dose do we get a therapeutic effect?

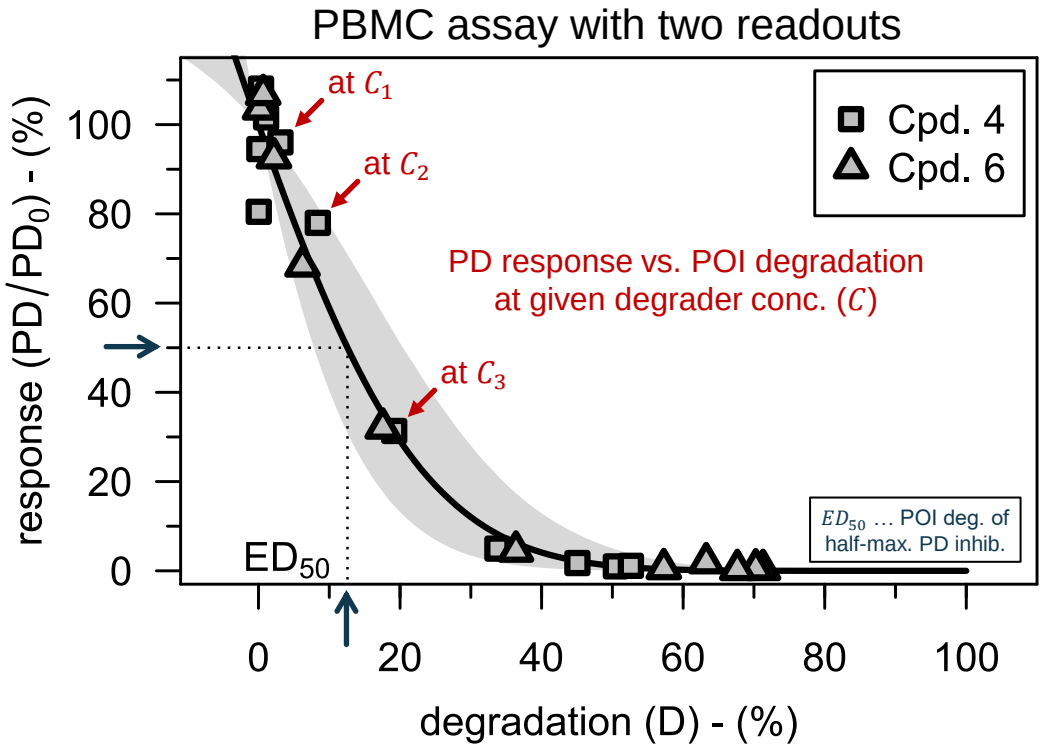


III) *Turning Data into Relevant Information*

Link protein degradation to a meaningful biomarker response [10,11]



1) incubate cells in the presence of various degrader conc. in vitro
2) determine the extent of deg. & PD response at those conc.
3) relate observed PD response to observed POI deg. (see plot)



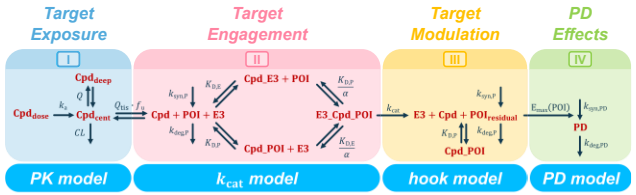
- degradation of RIPK2 (POI) reduces downstream TNF-α (PD) response
- as little as 13% of RIPK2 deg. reduces TNF-α response by 50% ($ED_{50} = 13\%$)
- this relationship is independent of the cpd. used to achieve such degradation

Establish **how much degradation** you need to get the desired pharmacodynamic **effect**

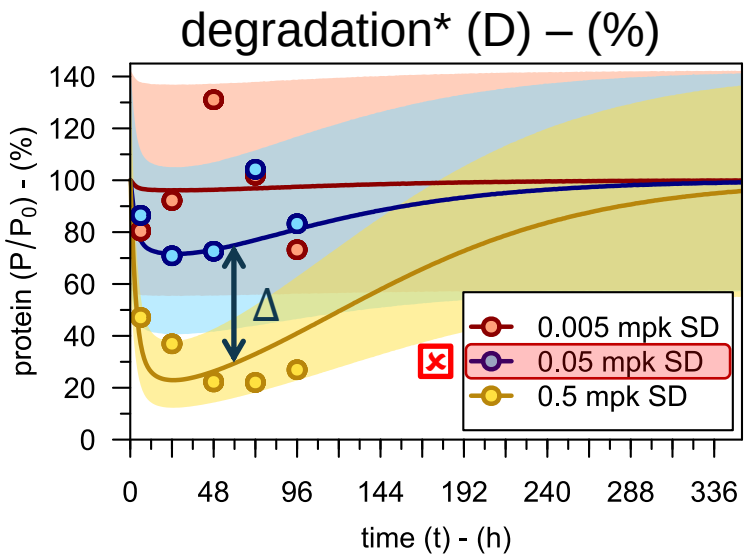
[10] data: *Mares et al. (2020) Commun. Biol.* DOI: 10.1038/s42003-020-0868-6
[11] data: *Mathieson et al. (2018) Nat. Commun.* DOI: 10.1038/s41467-018-03106-1

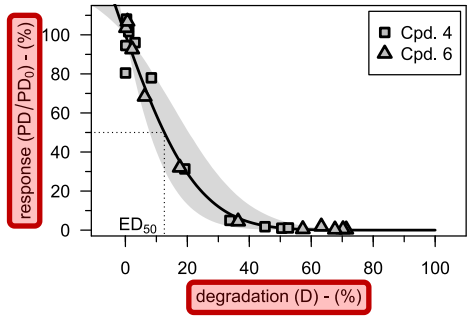
III) *Turning Data into Relevant Information*

Extend predictions beyond protein degradation for greater impact [10,11]



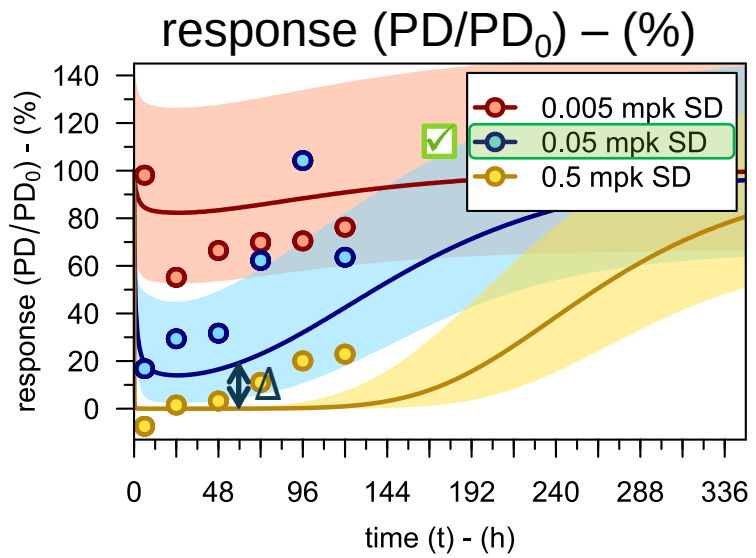
Cpd. 6





Model [7]

* inhibition by degrader is also being included (here: only minor effect)

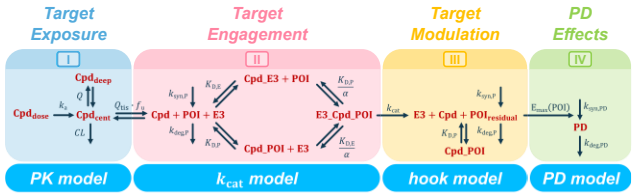


Limited degradation is already sufficient
to achieve a **substantial PD** response

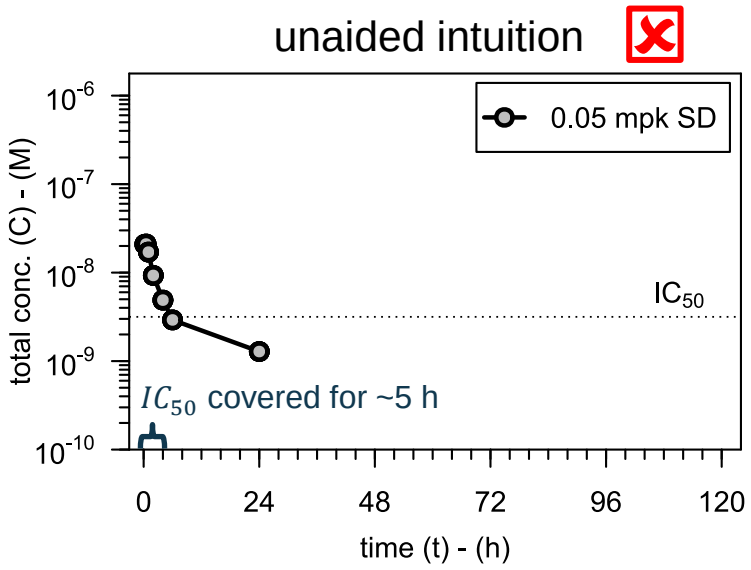
[7] *Haid & Reichel (2024) Clin. Pharmacol. Ther.* DOI: 10.1002/cpt.3273
[10] data: *Mares et al. (2020) Commun. Biol.* DOI: 10.1038/s42003-020-0868-6
[11] data: *Mathieson et al. (2018) Nat. Commun.* DOI: 10.1038/s41467-018-03106-1

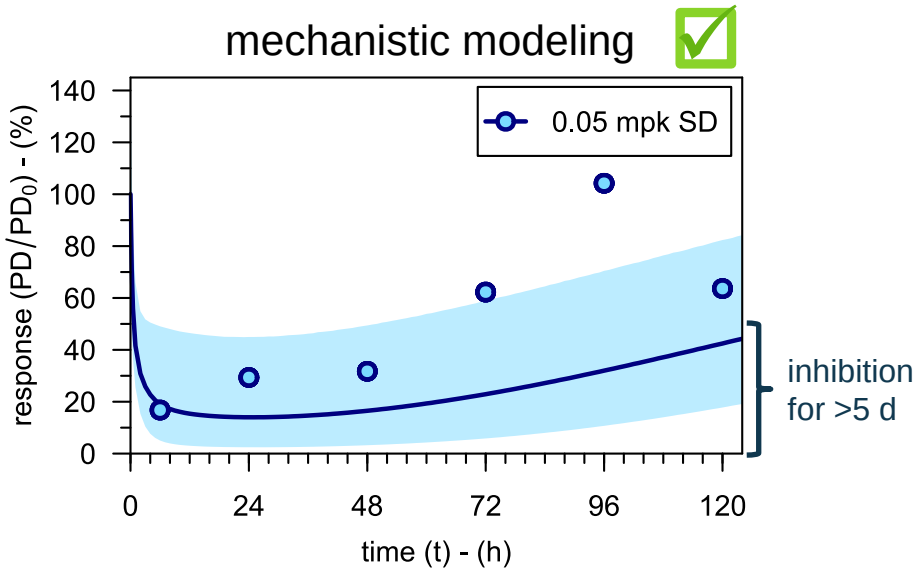
III) *Turning Data into Relevant Information*

Modeling keeps you going, even where intuition might fail you [10,11]



Cpd. 6



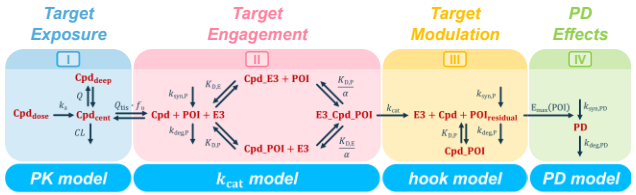


Degrader **pharmacology** is often non-trivial
and thus calls for **mechanistic modeling**

[10] data: *Mares et al. (2020) Commun. Biol.* DOI: 10.1038/s42003-020-0868-6
[11] data: *Mathieson et al. (2018) Nat. Commun.* DOI: 10.1038/s41467-018-03106-1

III) *Turning Data into Relevant Information*

Validate the model with animal data from preclinical PK/PD studies [7]



already implemented

Discovery

learn

In Vitro Assay

degradation

PD effect

predict

Measured PK

drug conc.

PK/PD Study

Cpd. 3

Study Design

Cpd. 1

Cpd. 2

Cpd. 3

confirm

Purpose of Modeling:

1) guide LO efforts

2) check assumptions

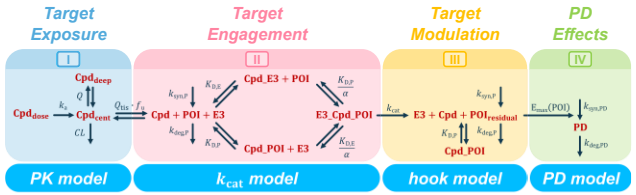
3) validate assays

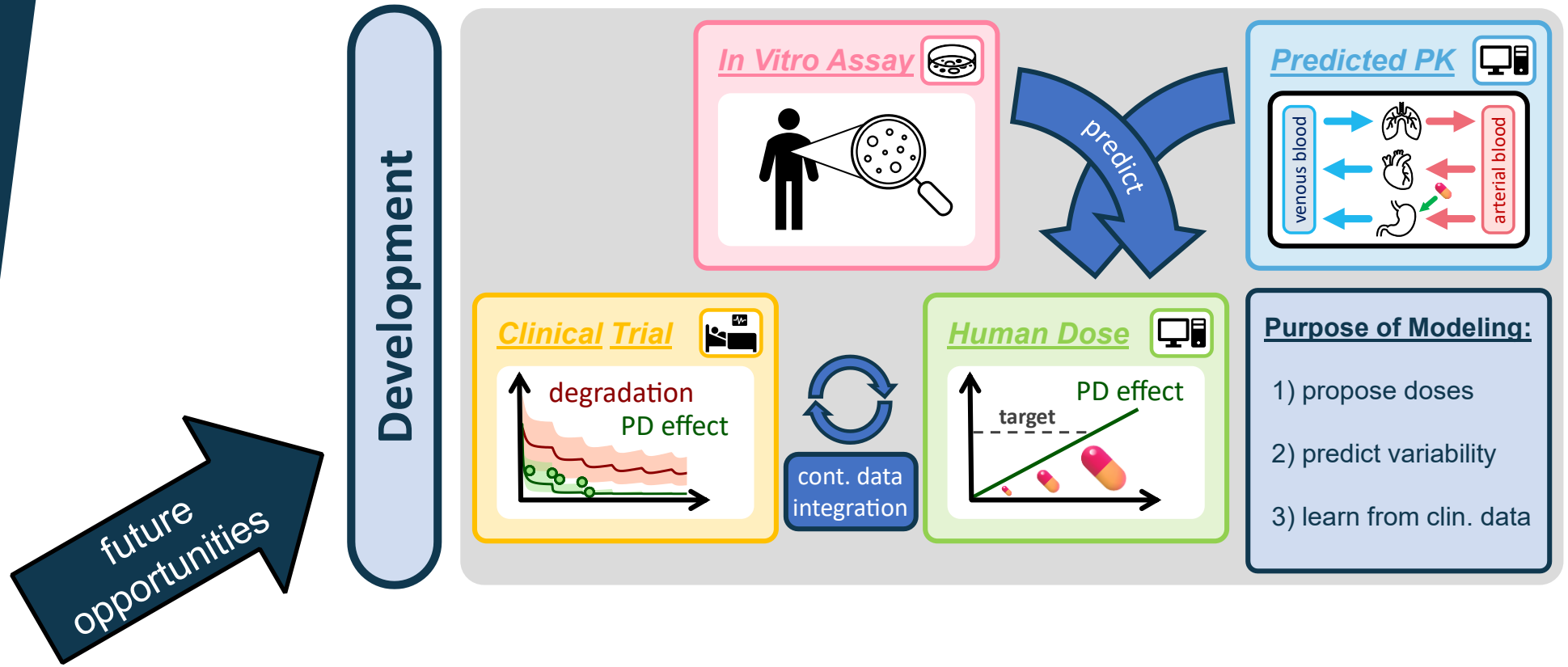
4) build trust in model

[7] *Haid & Reichel (2024) Clin. Pharmacol. Ther.* DOI: 10.1002/cpt.3273

III) *Turning Data into Relevant Information*

Apply PK/PD modeling to predict efficacious dose in clinical trials [7]





Use the **same model** and the **same assays**
but apply them to **human material**

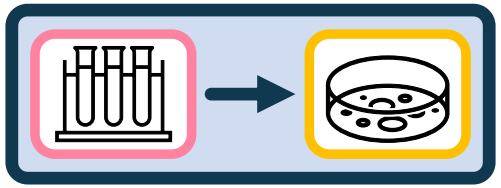
[7] *Haid & Reichel (2024) Clin. Pharmacol. Ther.* DOI: 10.1002/cpt.3273

Impact

Predictive PK/PD modeling transforms degrader drug development in three ways

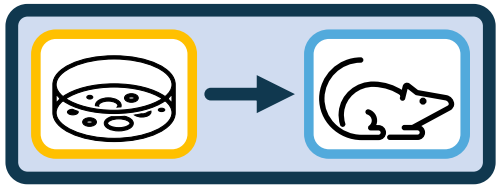
1) Translation from biochemical to cellular level

   - Modeling informs the optimization of degradation potency



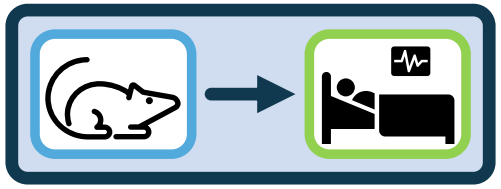
2) Translation from cellular level to animal model

   - Model-informed design makes studies more efficient



3) Translation from animal model to clinical readout

   - Modeling drastically increases the value of preclinical data



Case Study

LO phase oncology

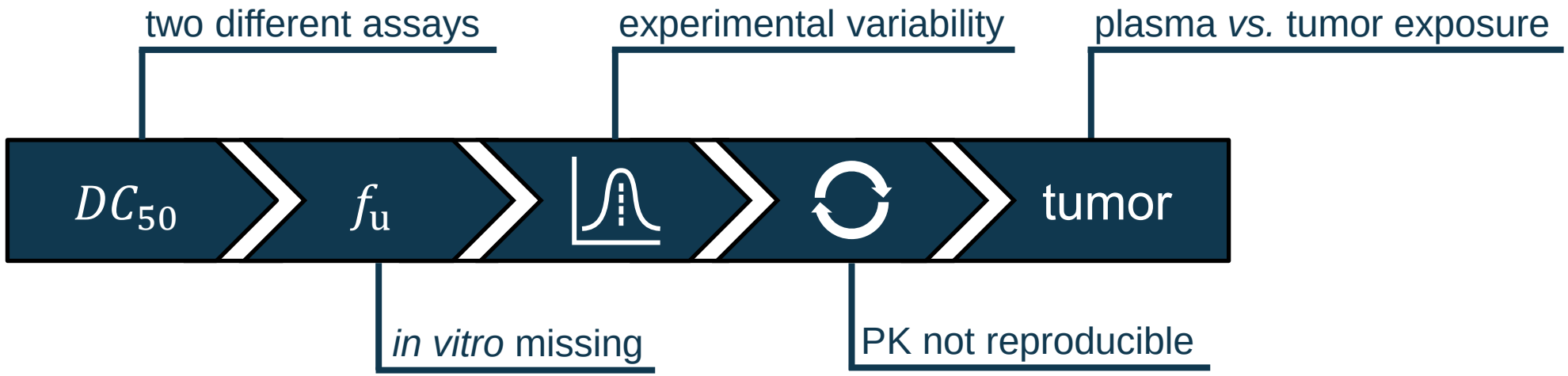
- Status:
  - degradation assays & exposure studies done
  - no PK/PD studies have been performed yet

- Questions:
  - which cpds. to put in mouse xenograft model?
  - what does a suitable study design look like?

- Approach:
  - predict *in vivo* drug effects from *in vitro* data
  - perform modeling for many cpds. in parallel

Translational PK/PD Modeling

Trials and tribulations of real-life LO projects



Contradictory Data

Which assays can we trust?

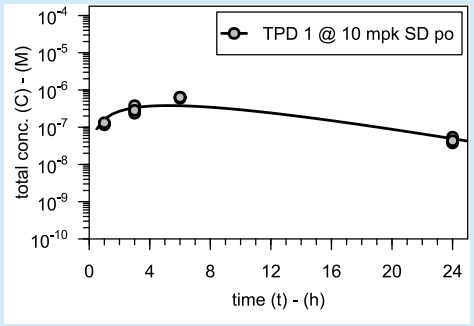
DC_{50}

Input

In Vivo PK

$AUC_{\text{norm}} = 0.6$

$t_{½,\text{TPD}} = 5.0\ \text{h}$



In Vitro PD

$t_{½,\text{POI}} = 2\ \text{d}$

$D_{\text{max}} = 100\%$

$f_{\text{u,mouse}} = 6\%$

$DC_{50,\text{u},90\%\text{huPl}} = 8.9\ \text{nM}$

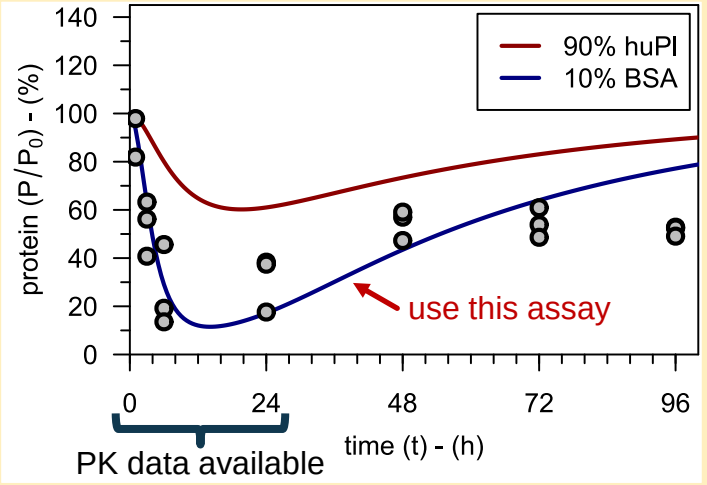
$DC_{50,\text{u},10\%\text{BSA}} = 1.6\ \text{nM}$

} same assay, different media

Model [7]

Output

In Silico Simulated PK/PD Study



POI levels in tumor xenograft mice ($n = 3$)

- time-course of protein degradation using different potency assays as input

[7] *Haid & Reichel (2024) Clin. Pharmacol. Ther.* DOI: 10.1002/cpt.3273

Missing Data

Imputation of input

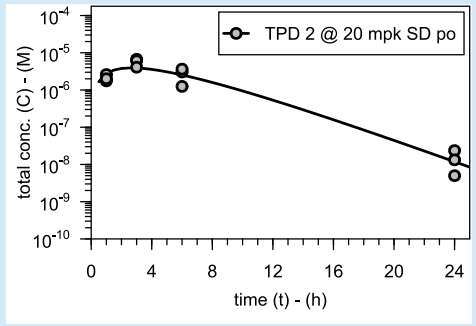
DC_{50} → f_u

Input

In Vivo PK

$AUC_{norm} = 1.1$

$t_{½,TPD} = 2.4$ h



In Vitro PD

$t_{½,POI} = 2$ d

$D_{max} = 100\%$

$DC_{50,10\%BSA} = 0.7$ nM

$f_{u,mouse} = 0.2\%$

predicted by dilution method

$\hat{f}_{u,media} = 24\%$

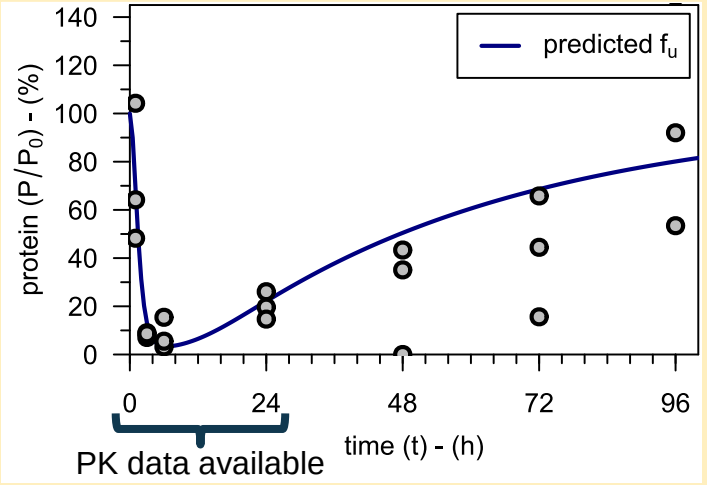
measured later

$f_{u,media} = 24\%$

Model [7]

Output

In Silico Simulated PK/PD Study



POI levels in tumor xenograft mice ($n = 3$)

- time-course of protein degradation using predicted unbound fraction

[7] *Haid & Reichel (2024) Clin. Pharmacol. Ther.* DOI: 10.1002/cpt.3273

Messy Data

Signal or noise?

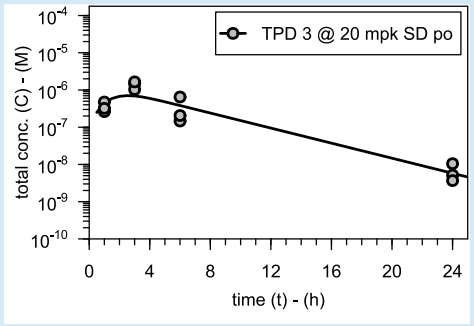
DC_{50} → f_u → 

Input

In Vivo PK

$AUC_{norm} = 0.2$

$t_{½,TPD} = 2.9$ h



In Vitro PD

$t_{½,POI} = 2$ d

$D_{max} = 100\%$

$DC_{50,u,fit} = 0.047$ nM

$DC_{50,u,10\%BSA} = 1.3$ nM

poor identifiability

$f_{u,mouse} = 1.3\%$

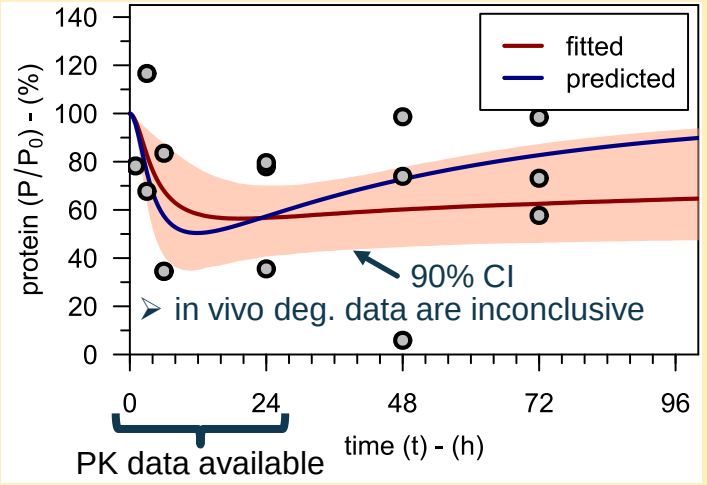
$D_{max,fit} = 100\%$

$t_{½,POI,fit} = 18$ d

Model [7]

Output

In Silico Simulated PK/PD Study



POI levels in tumor xenograft mice ($n = 3$)

- time-course of protein degradation using measured vs. fitted parameters

[7] *Haid & Reichel (2024) Clin. Pharmacol. Ther.* DOI: 10.1002/cpt.3273

Irreproducible Data

The role of the unpredictable

DC_{50} → f_u →  → 

Input

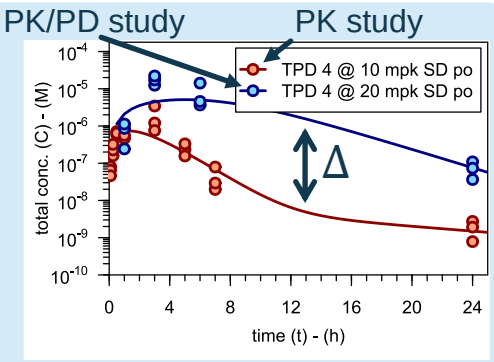
In Vivo PK

$AUC_{\text{norm,PK}} = 0.3$

$AUC_{\text{norm,PKPD}} = 2.9$

$t_{½,\text{TPD,PK}} = 0.8\ \text{h}$

$t_{½,\text{TPD,PKPD}} = 2.7\ \text{h}$



Model [7]

In Vitro PD

$t_{½,\text{POI}} = 2\ \text{d}$

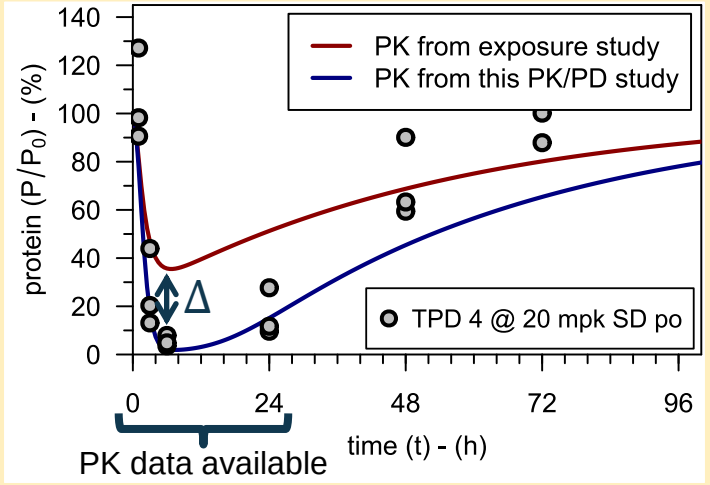
$D_{\max} = 100\%$

$f_{\text{u,mouse}} = 0.6\%$

$DC_{50,\text{u,10\%BSA}} = 0.48\ \text{nM}$

Output

In Silico Simulated PK/PD Study



POI levels in tumor xenograft mice ($n = 3$)

- time-course of protein degradation using expected vs. observed PK profile

[7] Haid & Reichel (2024) Clin. Pharmacol. Ther. DOI: 10.1002/cpt.3273

Surprising Data

Filling knowledge gaps

DC_{50} → f_u → tumor

Input

In Vivo PK

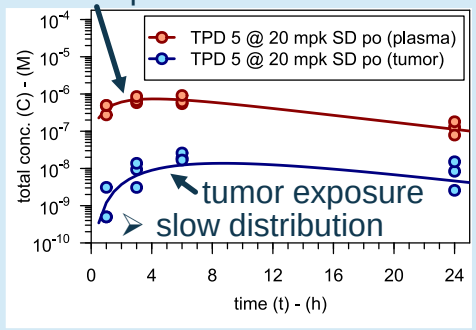
$AUC_{norm,pla} = 0.4$

$AUC_{norm,tum} = 0.01$

$t_{½,TPD,pla} = 6.3$ h

$t_{½,TPD,tum} = 12$ h

plasma exposure



Model [7]

In Vitro PD

$t_{½,POI} = 2$ d (fitted to tumor PD)

$D_{max} = 100\%$

$DC_{50,u,10\%BSA} = 0.07$ nM

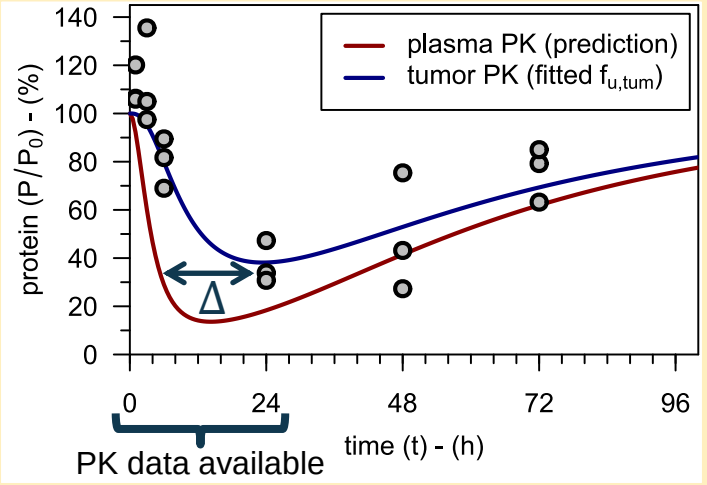
measured in plasma: $f_{u,mouse} = 0.1\%$

$f_{u,tum,fit} = 2.2\%$

validation from orthogonal method: $\hat{f}_{u,tum} = 5.3\%$ (similar)

Output

In Silico Simulated PK/PD Study



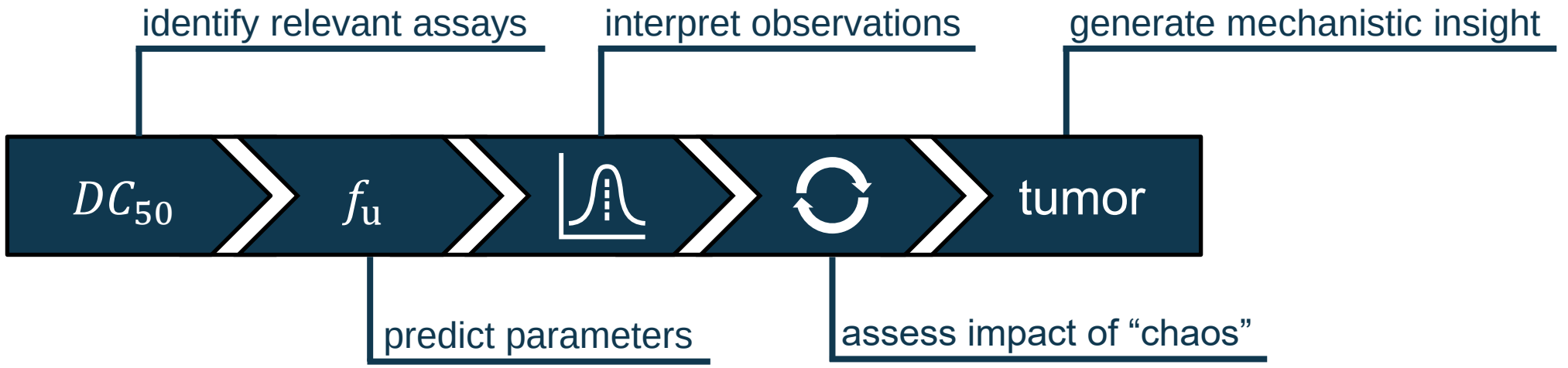
POI levels in tumor xenograft mice ($n = 3$)

- time-course of protein degradation using plasma vs. tumor PK profile

[7] *Haid & Reichel (2024) Clin. Pharmacol. Ther.* DOI: 10.1002/cpt.3273

Impact of Modeling

Supporting LO phase project



Acknowledgements

I thank the following collaborators for valuable discussions and inspiration

❖ **Bayer AG**

- Supervision
  -) Andreas Reichel
- DMPK
  -) Stephan Menz
  -) Christoph P. Hethey
  -) Stefanie Zimmermann
  -) Katrin Georgi
  -) Philip Lienau
- Pharmacology
  -) Clara Lemos
- Lead Discovery
  -) Laura Luh
- Medicinal Chemistry
  -) Philipp M. Cromm

❖ **ETH zürich**

- Institute of Pharmaceutical Sciences (IPW)
  -) Prof. Stefanie-Dorothea Krämer

❖ **PharMetrX**

- University of Potsdam
  -) Prof. Wilhelm Huisinga
- Freie Universität Berlin
  -) Prof. Charlotte Kloft

Discussion

Any questions?

Haid & Reichel (2023)
Pharmaceutics

Haid & Reichel (2025)
Drug Discov. Today

Haid & Reichel (2024)
Clin. Pharmacol. Ther.