

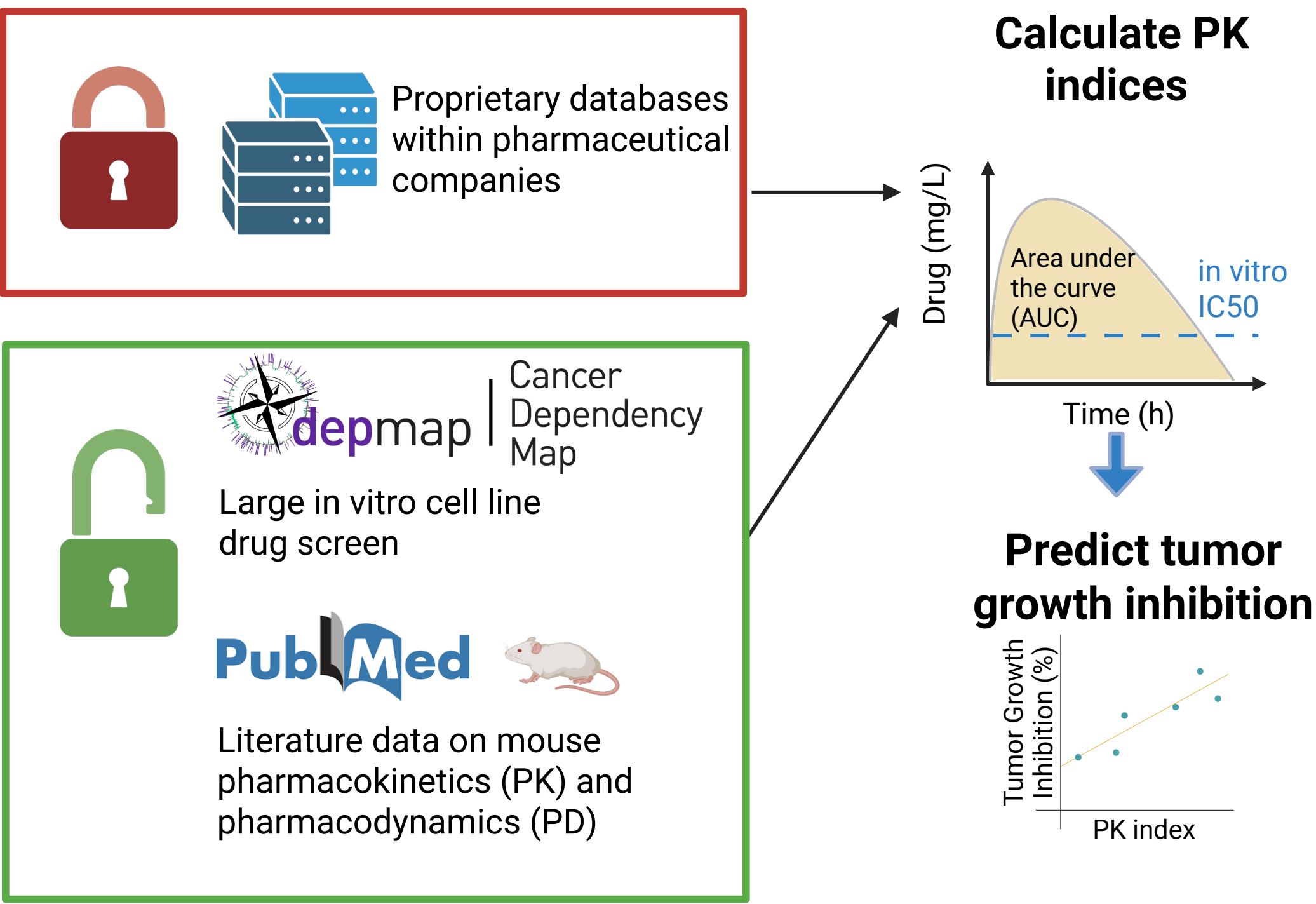
An in vitro to in vivo translational framework for the prediction of drug efficacy in preclinical cell line derived xenografts



Junqi Chen¹, Grigory Nesvijevski¹, **Janice Goh¹**
¹ Bioinformatics Institute (BII), Agency for Science, Technology and Research (A*STAR), 30 Biopolis Street, #07-01 Matrix, Singapore 138671, Republic of Singapore

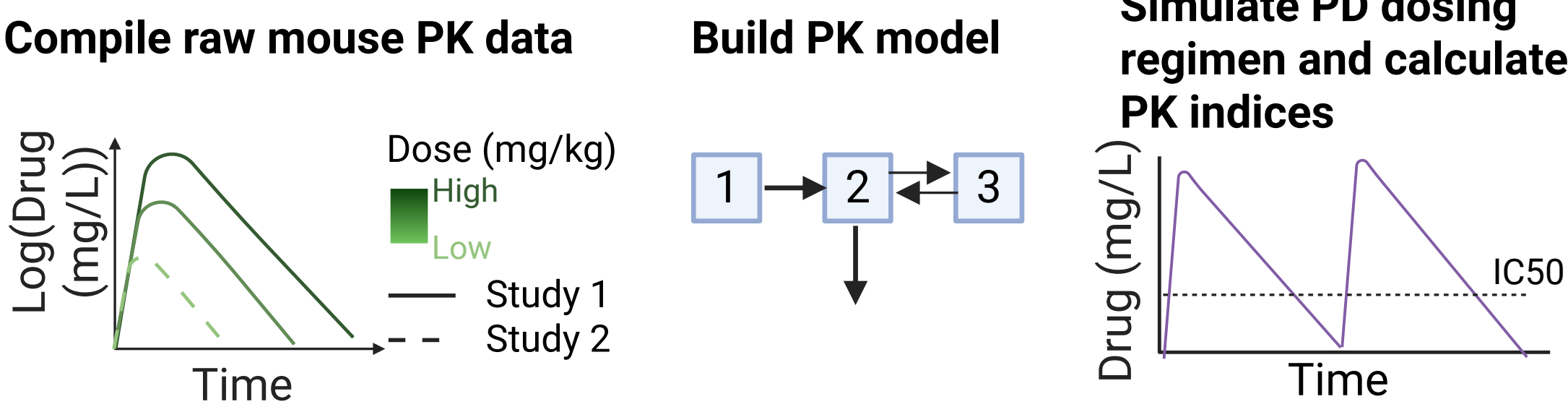
INTRODUCTION

Can we integrate public data across diverse projects to improve drug development?



Drug development is expensive. In oncology, recent publications show that C_{ss}/IC_{50} is a useful metric for the prediction of tumor growth inhibition in mice experiments. However, such predictions often rely on the need for a large amount of both in vitro cell line efficacy data, as well as mouse PK data. Many of these databases are not open access however, making it hard for smaller labs to develop similar pipelines. Capitalizing on the large amount of publicly available data from DepMap¹ and literature via mouse cell line derived xenograft (CDX) studies, we thus aim to develop a similar pipeline, allowing us to make in vitro to in vivo efficacy predictions without the need of conducting large scale experiments to build up our database.

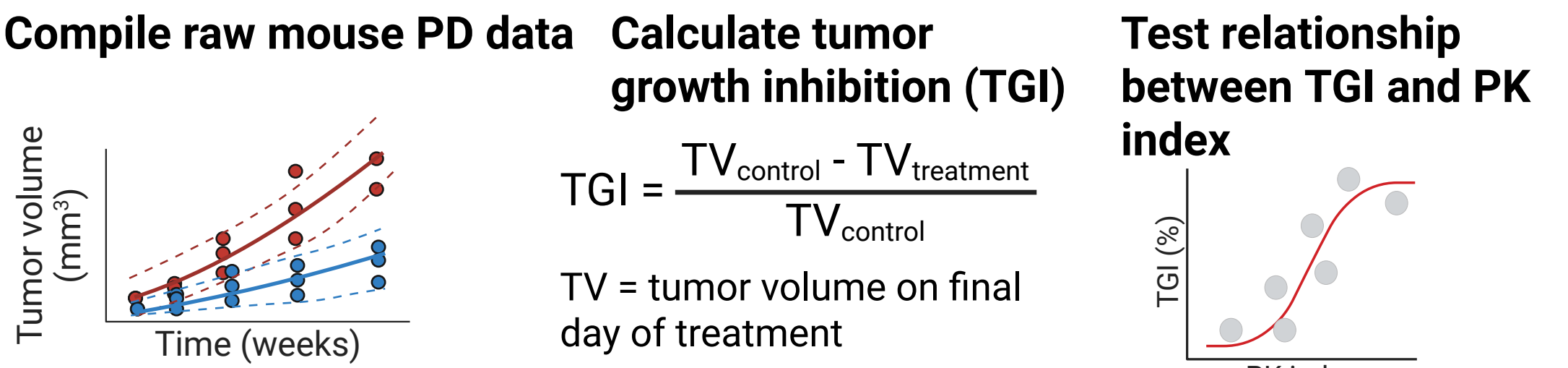
METHODS



- Selection criteria for PK data**
- LC-MS/MS quantification
 - Drug vehicle matches PD experiment

- PK model development**
- Test 1-, 2- and 3-compartment models, linear clearance, saturated clearance and transit compartment models for absorption for best fit

- PK indices calculation**
- Area under the curve (AUC) as a ratio to IC50 (AUC/IC_{50}), AUC above IC50 ($AUC > IC_{50}$), Area under the effect curve ($AUEC$)² and average drug concentration over the whole experimental duration (C_{avg}/IC_{50}) were calculated



- Selection criteria for PD data**
- Cell line derived model with matching in vitro drug potency data from DepMap for non small cell lung cancer, triple negative breast cancer and other cancers when the studies tested more than 1 cancer type
 - Tumor implantation via subcutaneous injection into mouse flank
- Testing TGI vs PK index relationship**
- Both linear regression and 4-parameter logistic function were tested

CONCLUSION & FUTURE WORK

Using public datasets, we were able to derive PK indices and test their predictivity against observed tumor growth inhibition values from preclinical CDX models. We found that C_{ss}/IC_{50} gave the best predictiveness following other similar findings in literature³. This demonstrates that data integration of a diverse set of studies can similarly be useful in developing a database for translational efficacy predictions. This in vitro to in vivo prediction pipeline is promising in helping us to better prioritize novel drugs and appropriate doses for testing in animals, thereby accelerating drug discovery and saving resources. Future work includes expanding this dataset to query all cell lines and treatments in DepMap, allowing us to test a diverse set of chemical structures and compounds, creating a pipeline that allows for robust prediction even among new drug classes.

RESULTS

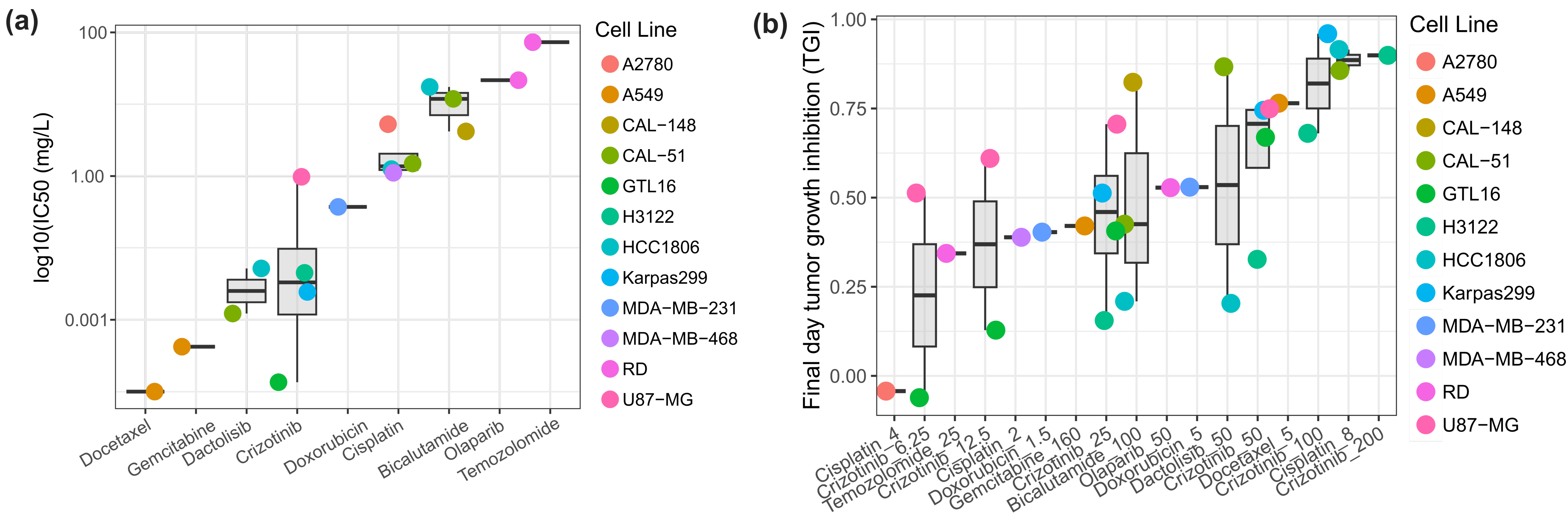


Fig 1. Compiled PD data from literature shows multiple CDX studies can be obtained and integrated with in vitro and PK data
(a) Compiled IC50 data from DepMap with accompanying PK model (b) Compiled tumor growth inhibition data

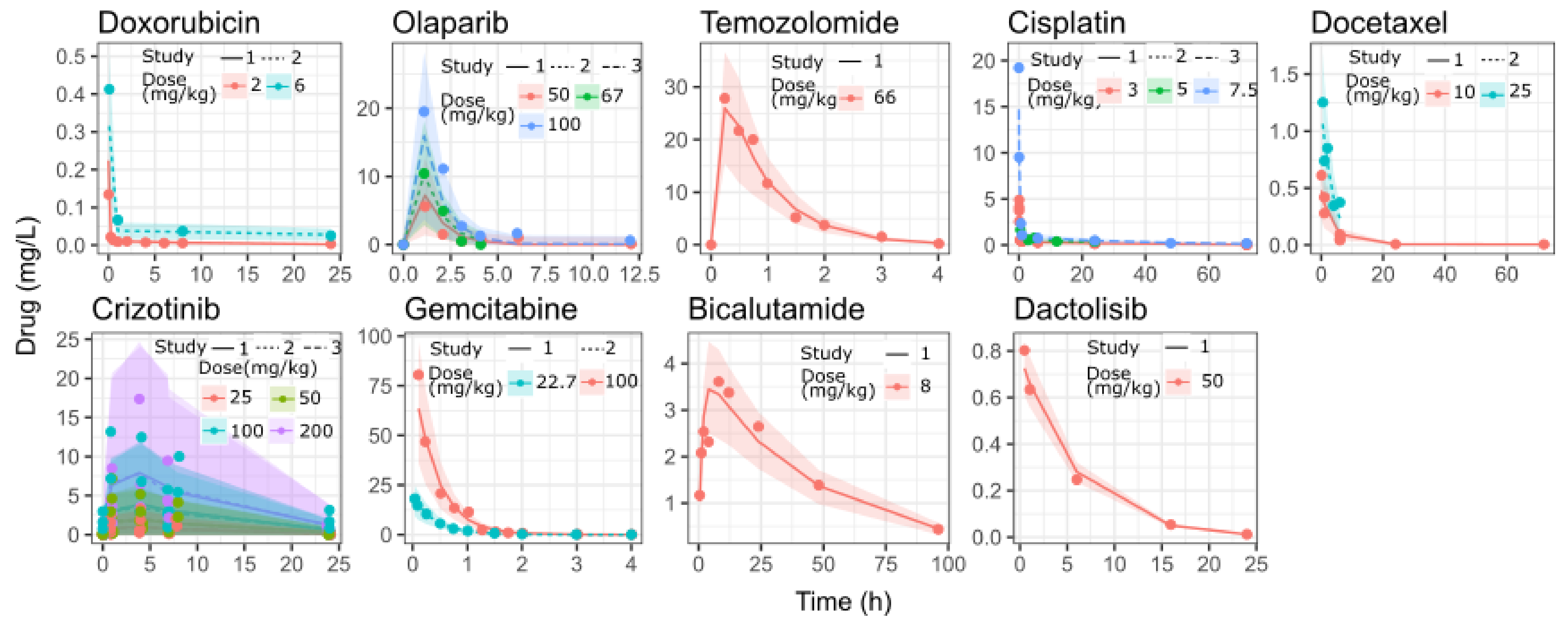


Fig 2. Mouse PK data with visual predictive check shows that mouse PK data can be compiled across studies regardless of mouse strain as long as quantification was done using LC-MS/MS and drug vehicle matches between studies.

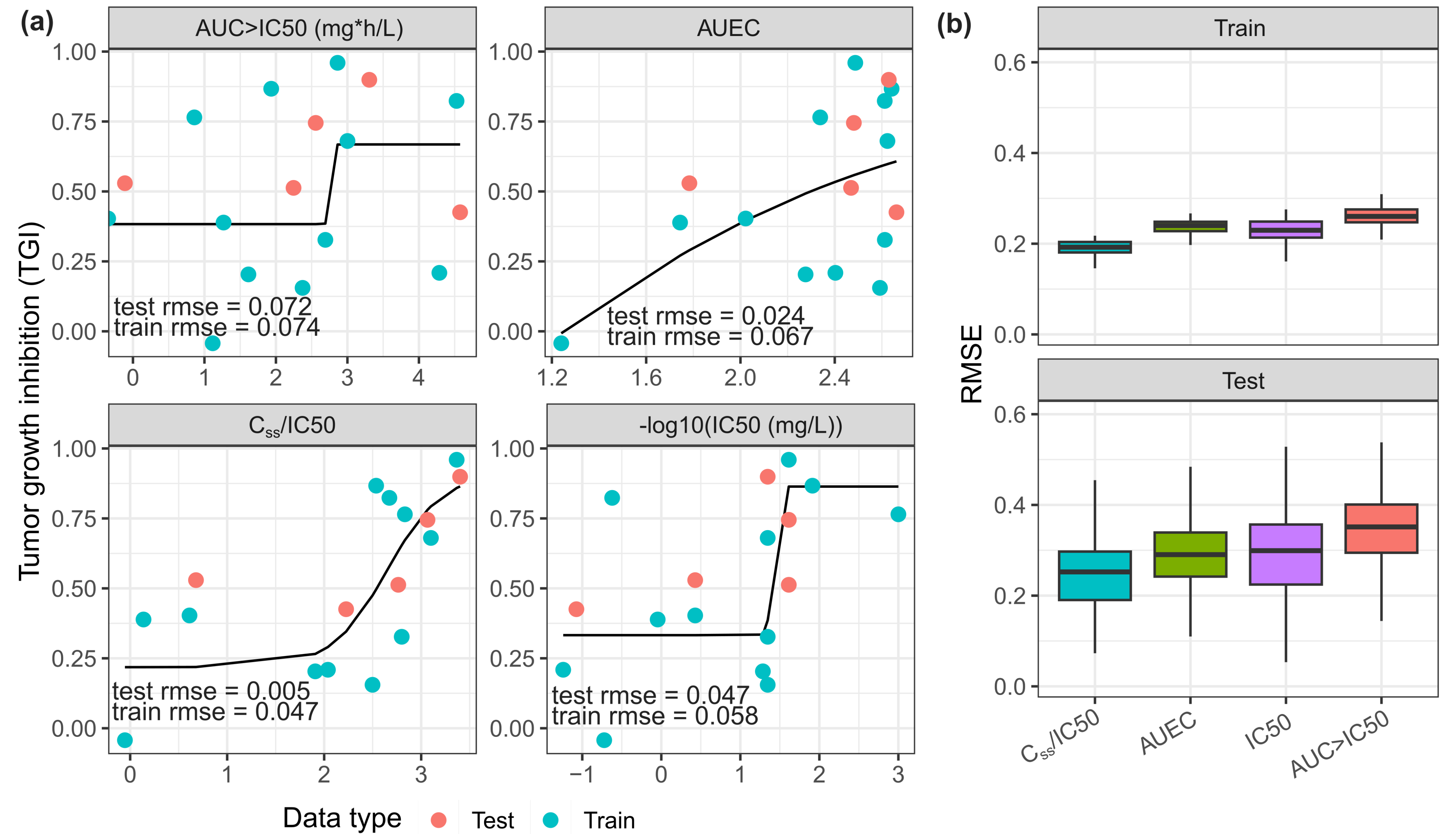


Fig 3. C_{ss}/IC_{50} is the best PK index for predicting tumor growth inhibition (a) Example model fit with training and testing datasets across all PK indices. (b) Bootstrap of 1000 model fits using root mean squared error (RMSE) shows C_{ss}/IC_{50} consistently produces the best results.

References
1. Yang, W. et al. Genomics of Drug Sensitivity in Cancer (GDSC): a resource for therapeutic biomarker discovery in cancer cells. *Nucleic Acids Res* **41**, D955–D961 (2013).
2. Chen, C., Lavezzi, S. M. & Iavarone, L. The area under the effect curve as an efficacy determinant for anti-infectives. *CPT Pharmacometrics Syst Pharmacol* **11**, 1029–1044 (2022).
3. Huber, H.J., Misty, H.B. Explaining in-vitro to in-vivo efficacy correlations in oncology pre-clinical development via a semi-mechanistic mathematical model. *J Pharmacokinet Pharmacodyn*. 2024 Apr;51(2):169-185. doi: 10.1007/s10928-023-09891-7. Epub 2023 Nov 6. PMID: 37930506; PMCID: PMC10982099.