A QSP model to understand clinical cytokine dynamics following bispecific dosing in solid tumors

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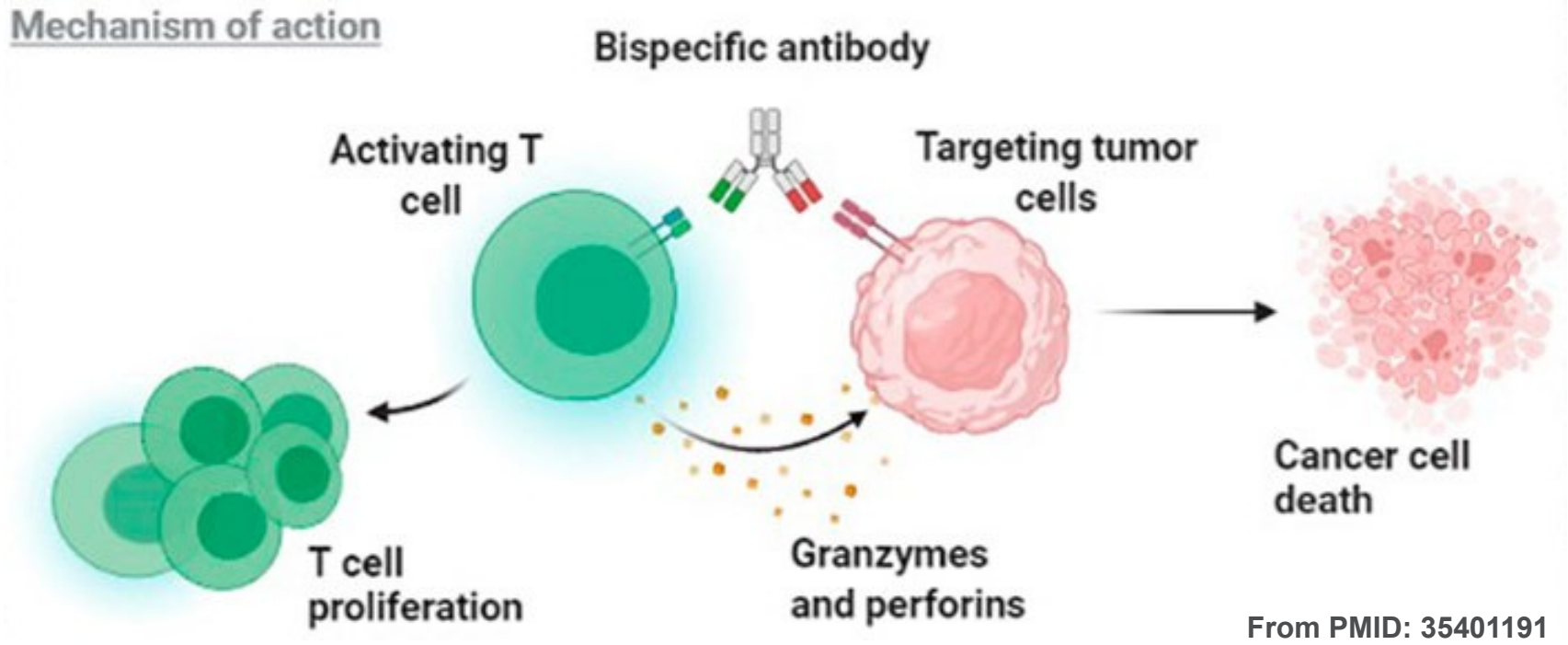
Bispecific antibodies are a promising class of therapeutics



From PMID: 35401191

R/R multiple myeloma (fifth line) – % ORR from BCMA targeting therapies

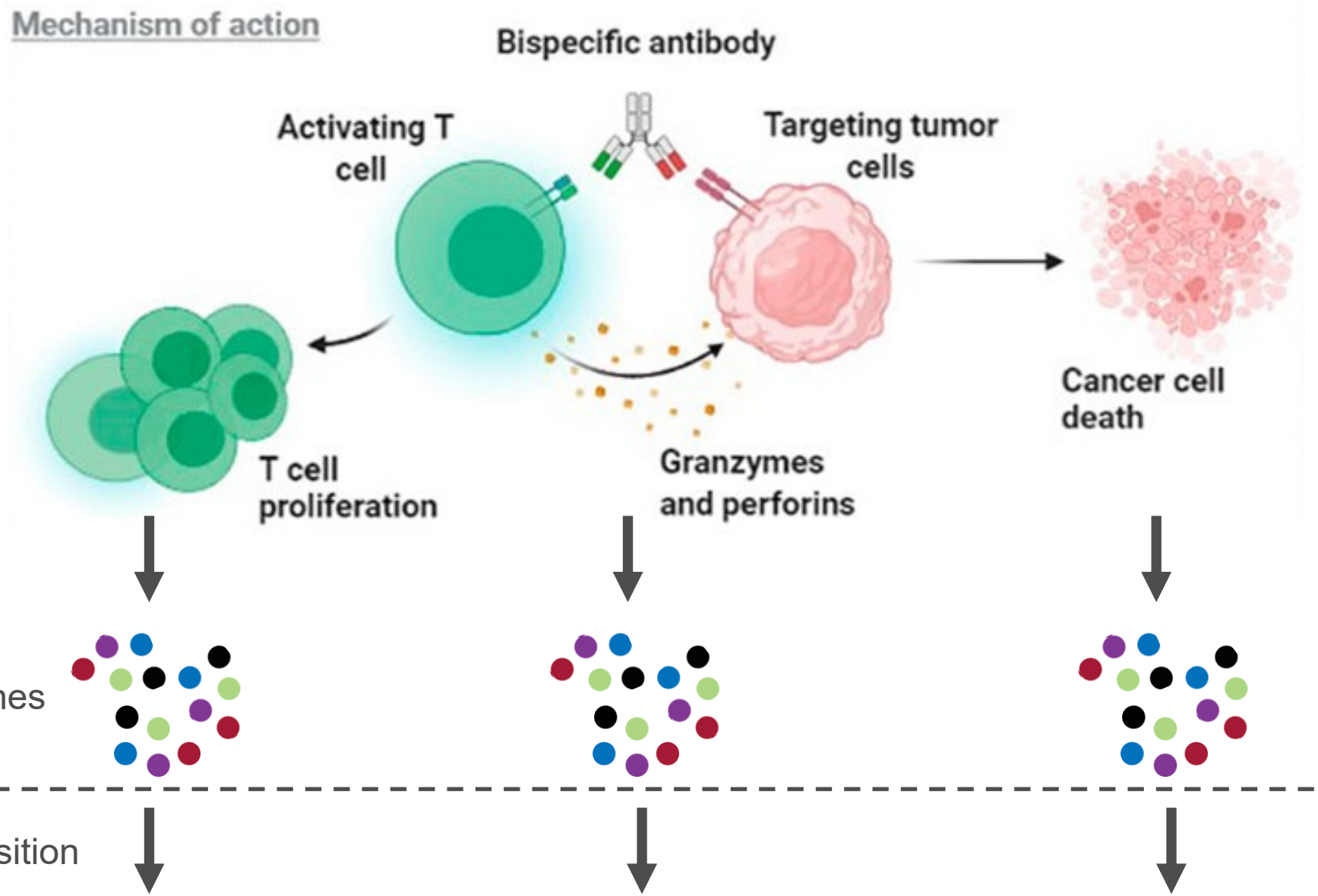
Blenrep (ADC) – 31%

Abecma (CAR T) – 73%

Carvykti (CAR T) – 98%

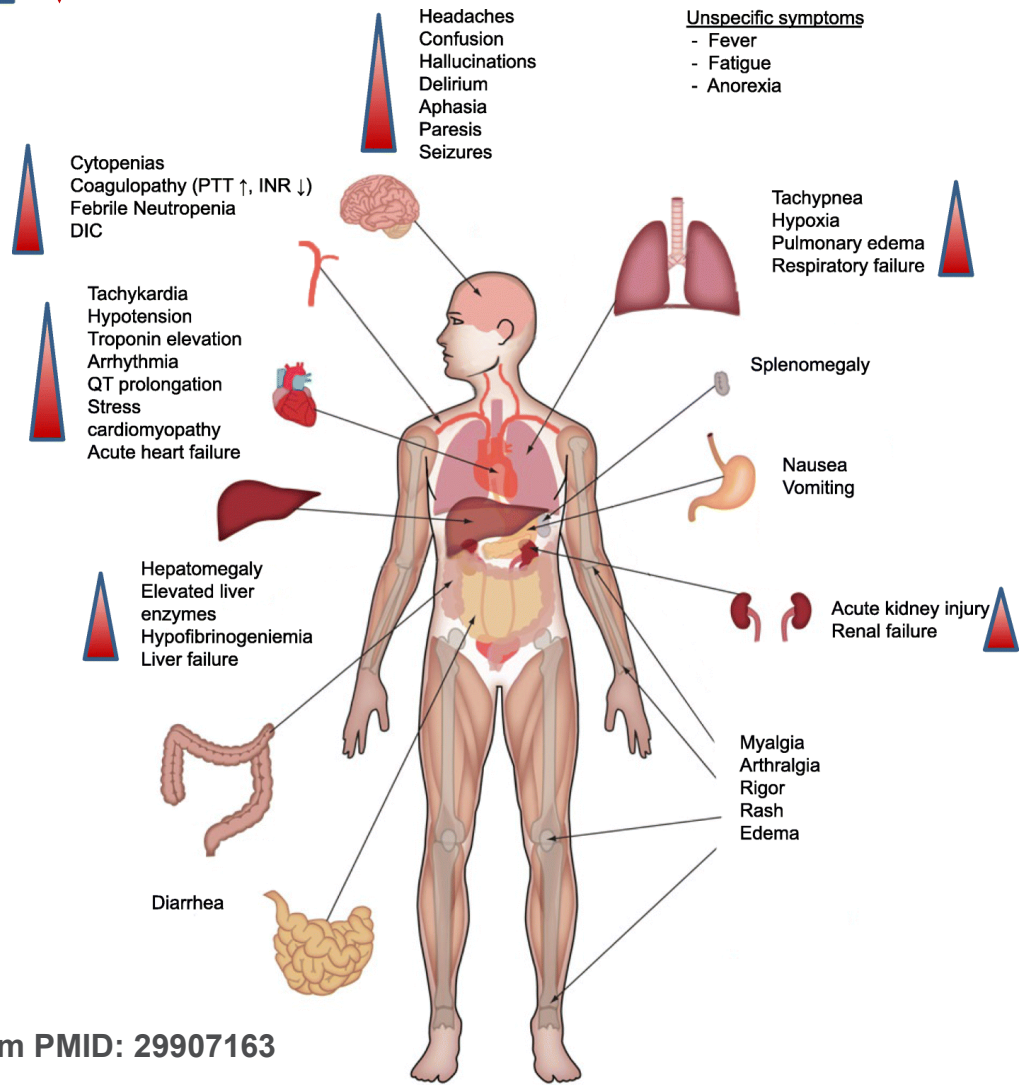
Tecvayli (Bispecific) – 68%

Cytokine release occurs as a part of bispecific therapy mechanism of action



Cytokine release syndrome (CRS) is a dose limiting toxicity for bispecific therapies

Increased cytokines = increased toxicity



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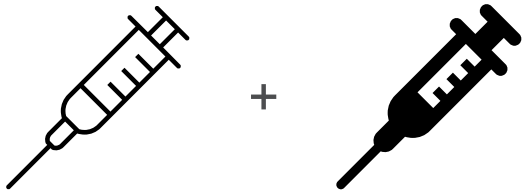
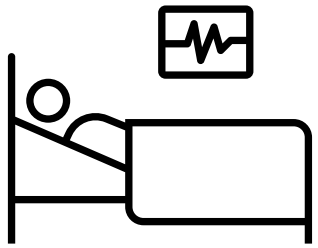
Clinical management

Stopping or reducing bispecific therapy



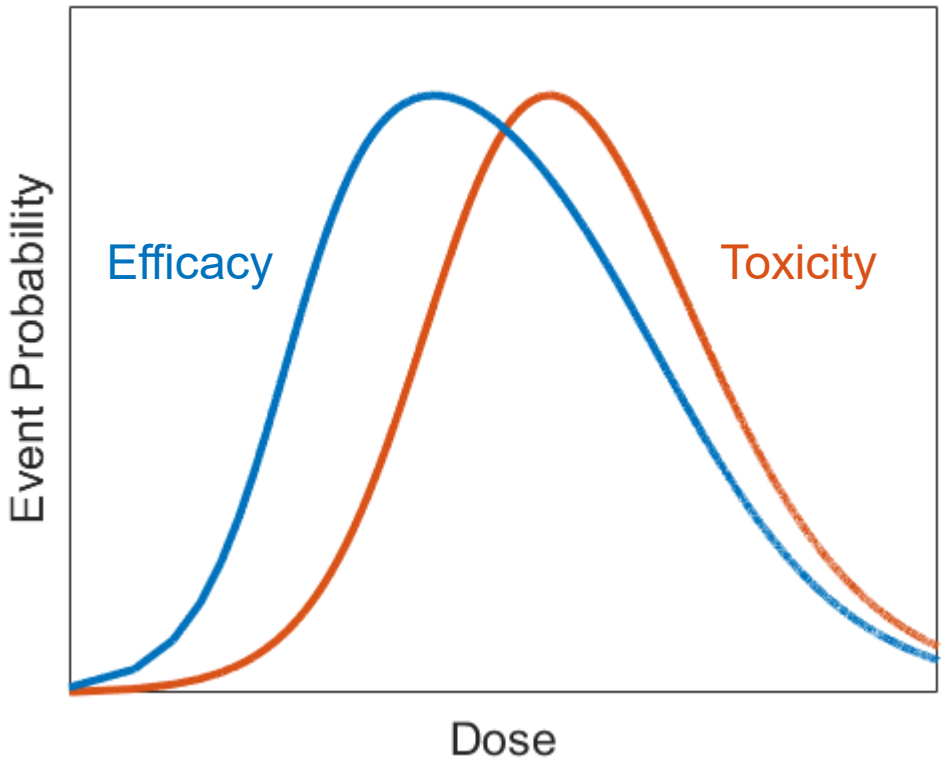
Starting CRS therapy



Hospitalization

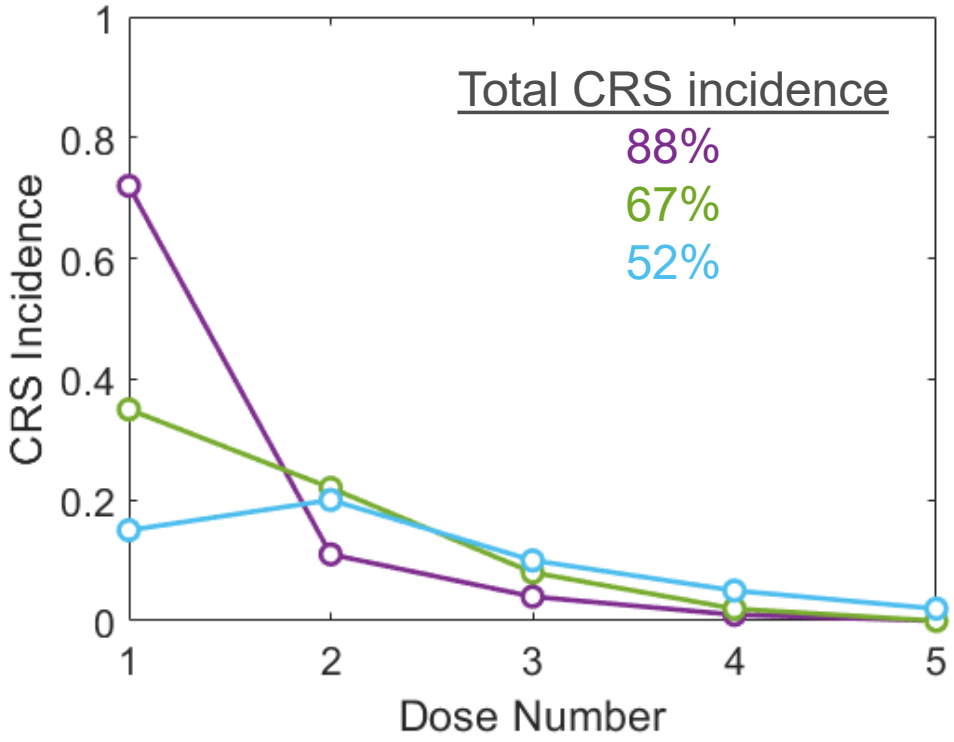
Dose selection is complex but critical for bispecific therapy clinical trials

Prozone effect



Step-up dosing

Number of step-ups	Regimen
0	50 mg QW
1	D1: 25 mg, D8: 50 mg QW
2	D1: 10 mg, D8: 25 mg, D15: 50 mg QW



Approved CD3-based bispecifics have complex dosing regimens and high CRS incidence

Drug	Indication	Dose Regimen	CRS Incidence
Blinatumomab	R/R acute lymphocytic leukemia	Cycle Day 1-28: 28 µg/day infusion Cycle Day 29-42: Treatment-free	14%
Mosunetuzumab	R/R follicular Lymphoma	Day 1: 1 mg Day 2: 2 mg Day 15: 60 mg Day 21: 60 mg Day 42: 30 mg QW	44%
Tebentafusp-tebn	Metastatic uveal melanoma	D1: 20 µg D8: 30 µg D15: 68 µg QW	89%
Teclistamab	R/R multiple myeloma	D1: 0.06 mg/kg SC D3 - 5: 0.3 mg/kg SC D5 - 9: 1.5 mg/kg QW SC	72%

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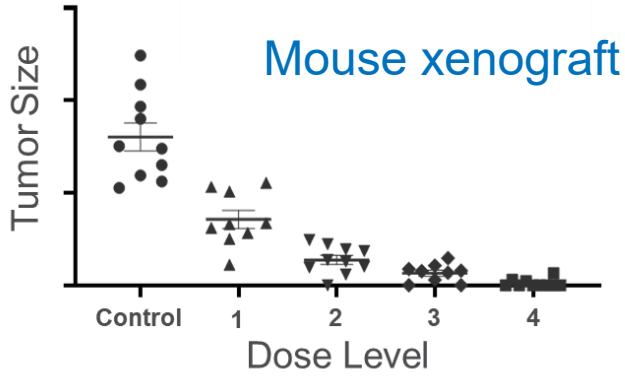
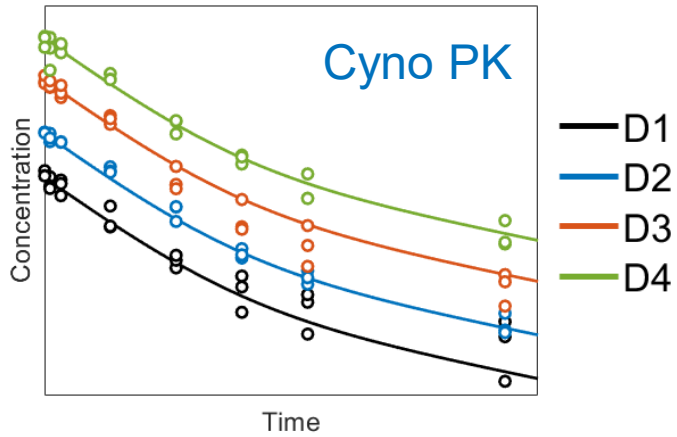
How do we select a bispecific FIH dose regimen?

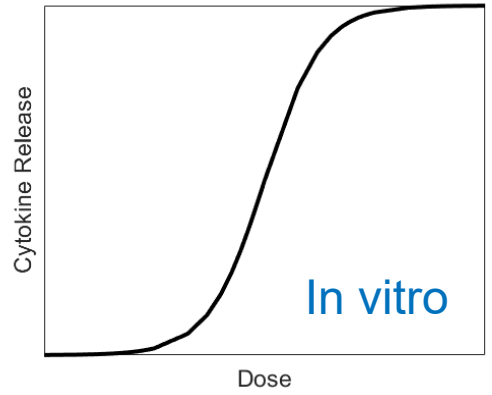
Efficacy (tumor growth inhibition)

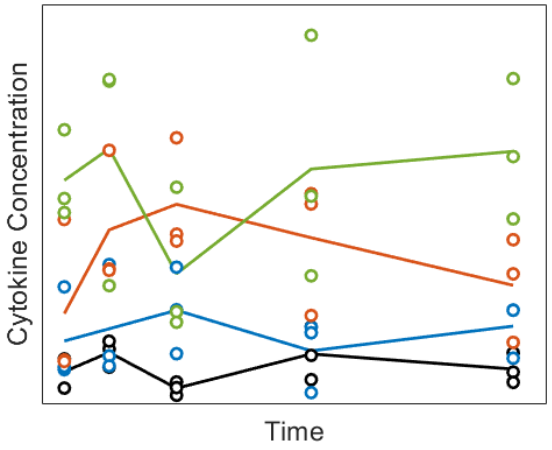




Predict human MABEL

Safety (CRS)





Mouse/Cyno PD

Not readily translatable to human

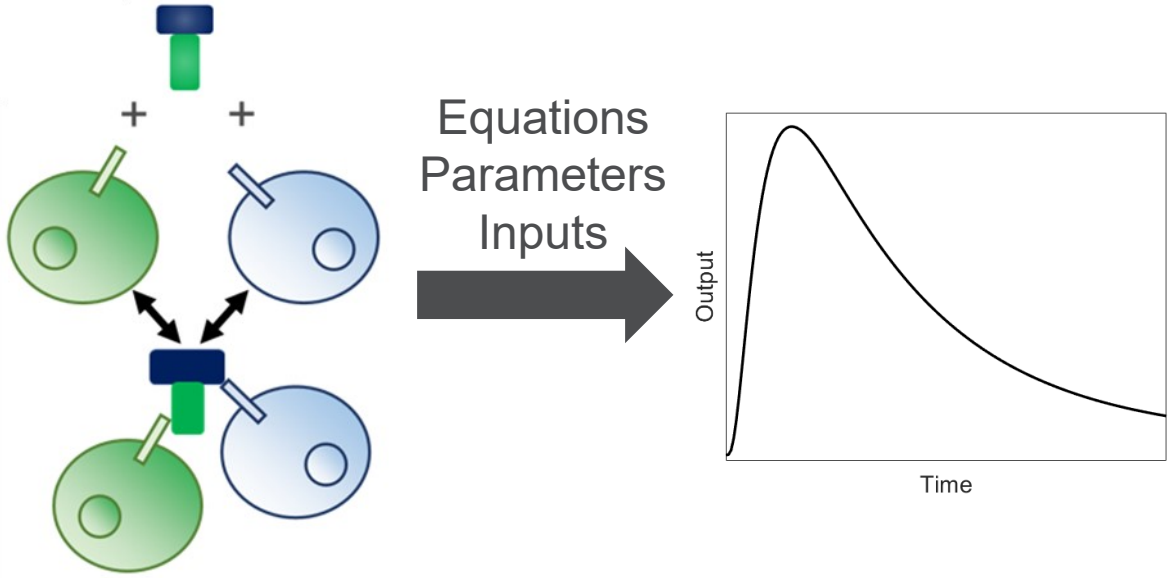
***Goal**: Can we predict clinical cytokine dynamics to support dose selection?*

Quantitative systems pharmacology (QSP) modeling to support safety prediction

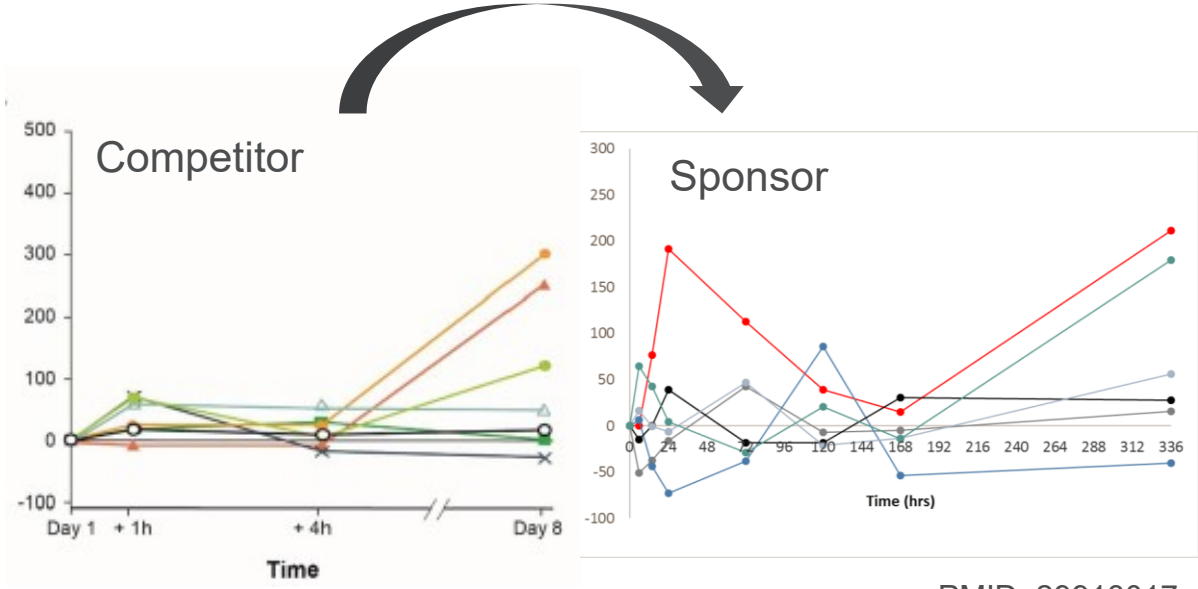
QSP: Mechanistic representations of pharmacology encompassing relevant disease pathology, drug disposition, and drug-disease interactions to provide a holistic quantitative understanding of disease biology and anticipated treatment effects

2 nice features of QSP modeling

1. Data of interest is not necessary



2. Ability to translate similar data



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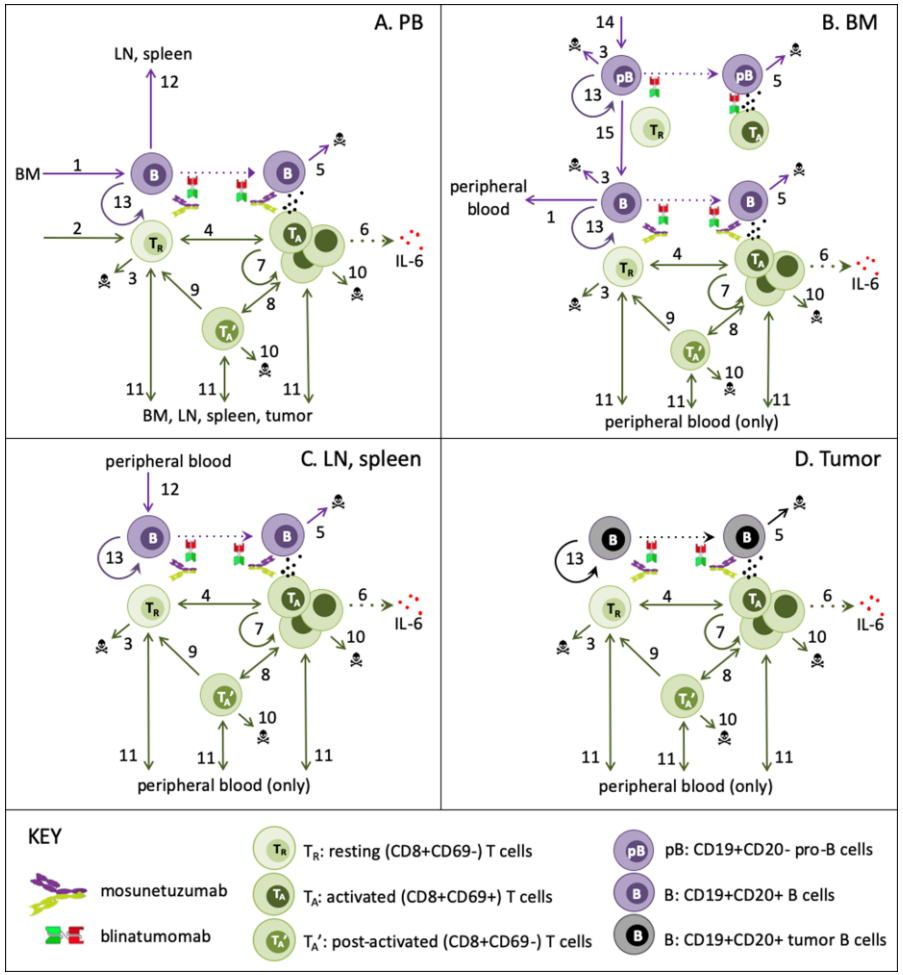
Survey of publicly available QSP models finds none that are readily applicable for this program goals

Goal: Predict clinical peripheral cytokine dynamics from bispecific dosing in solid tumor



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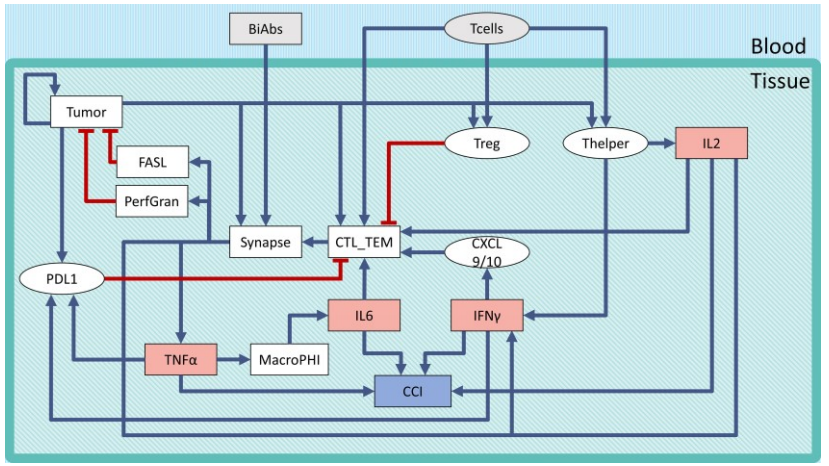

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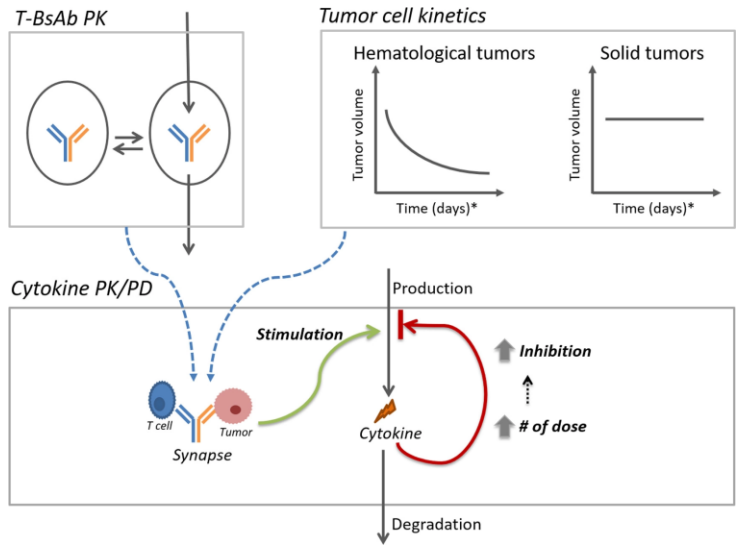

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Tebentafusp clinical data was chosen for translation to predict clinical cytokine dynamics for our bispecifics of interest

Tebentafusp clinical data

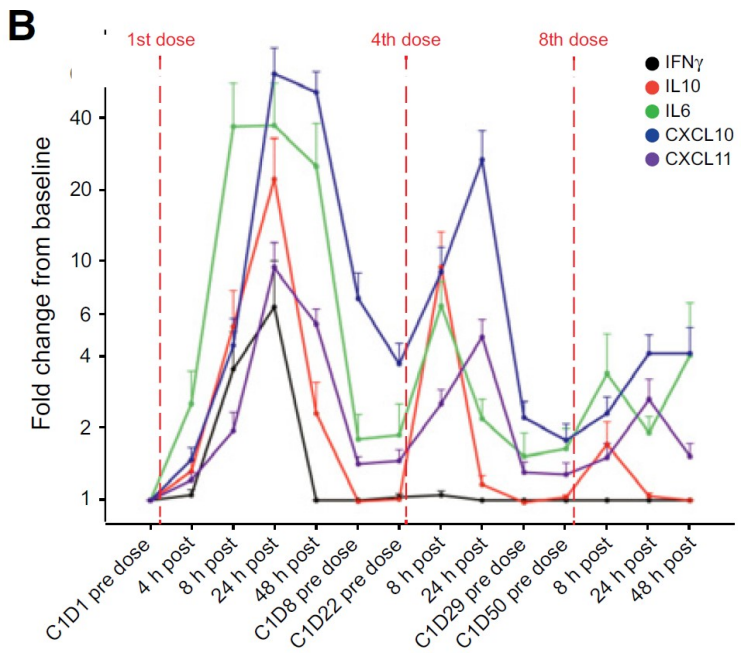

Table 6: Population Pharmacokinetic Parameter

Parameter	Units	Estimate
CL	L/day	4.33
V_1	L	5.25
Q	L/day	11.4
V_2	L	470

Develop and calibrate model to published clinical data (Tebentafusp)

↓

Translate to bispecific of interest

↓

Predict dose-response

↓

Validate/update with clinical data

↺

Parameters updated

- Dosing
- PK
- CD3 affinity
- Tumor antigen affinity/expression
- Tumor baseline size
- Tumor immune cell content
- Etc…

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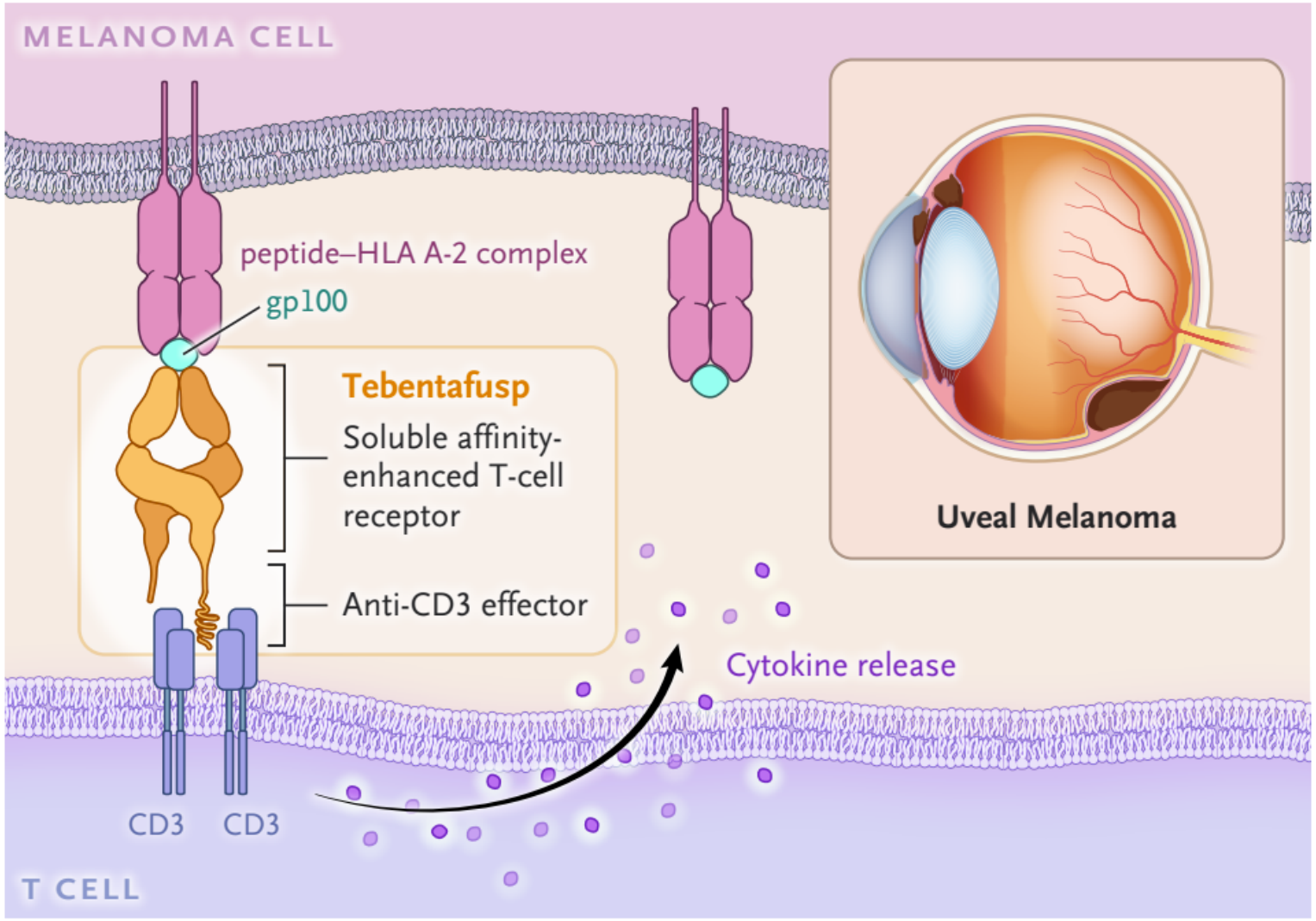
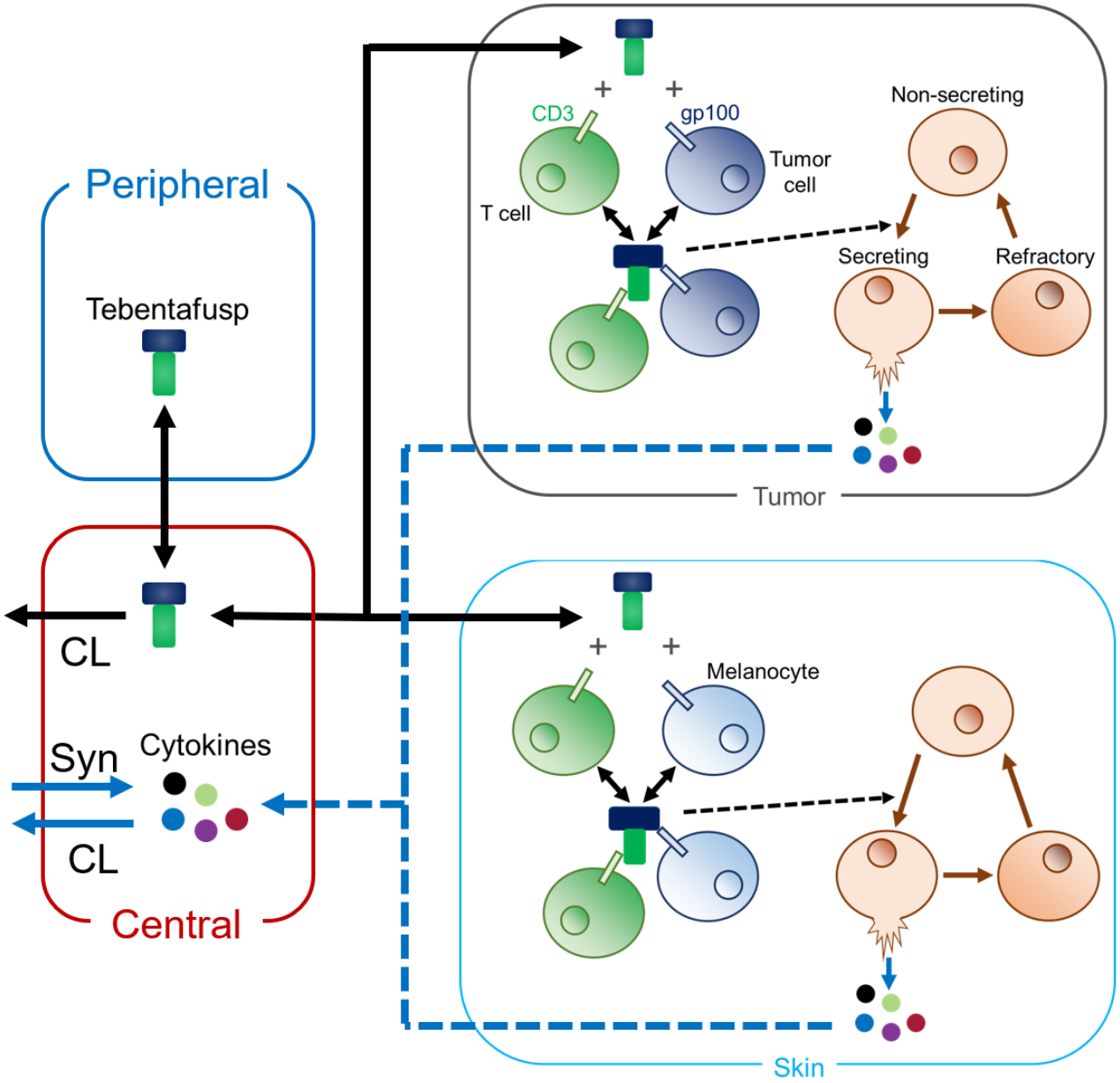
Tebentafusp – FDA approved CD3-based bispecific



- FDA approved for unresectable or metastatic uveal melanoma on January 25th 2022
- Currently the only CD3 bispecific approved for solid tumors
- Analogous clinical data of interest available publicly (PK, cytokine dynamics)

PMID: 34551229

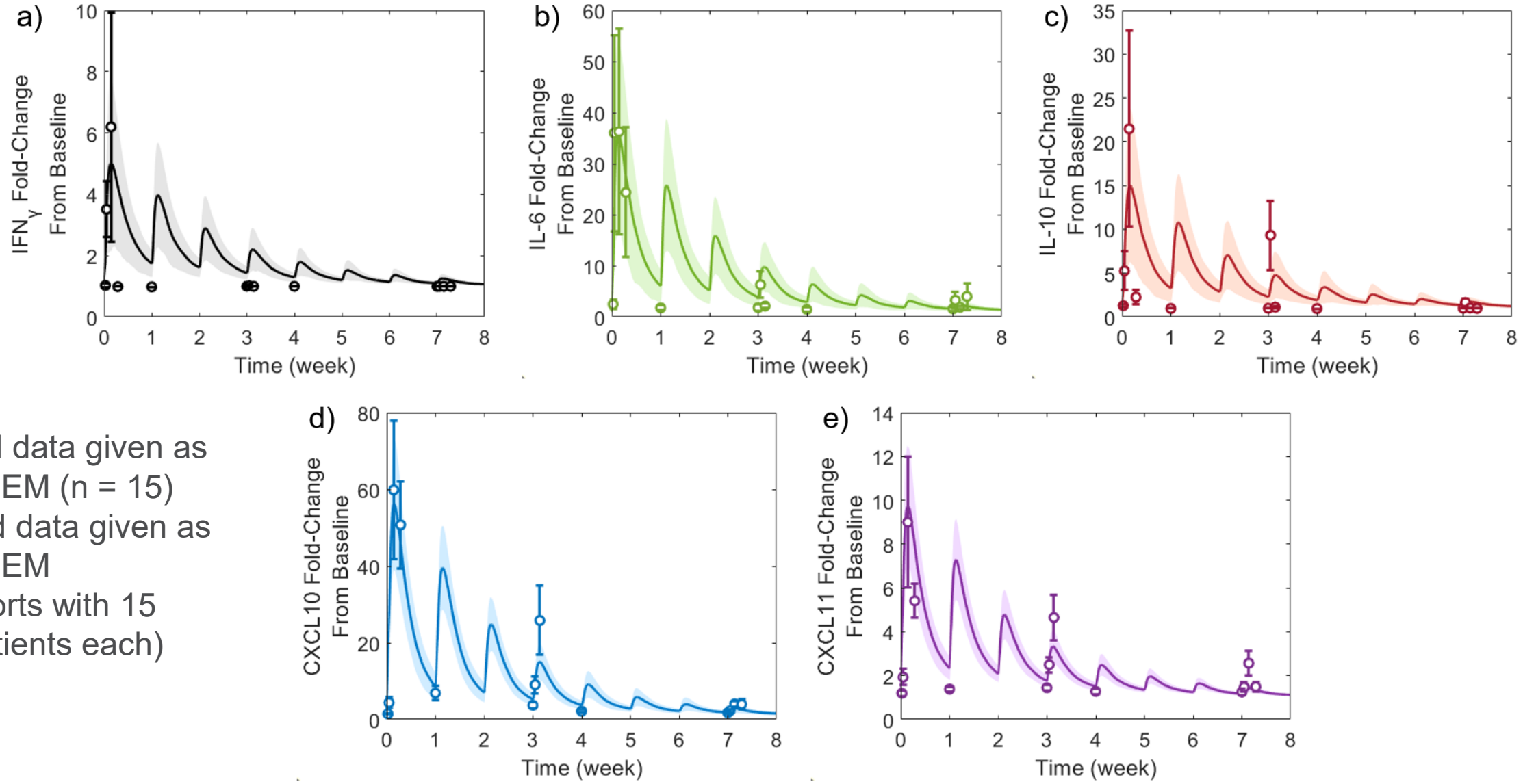
QSP model to capture tebentafusp clinical cytokine dynamics



Key MOA assumptions

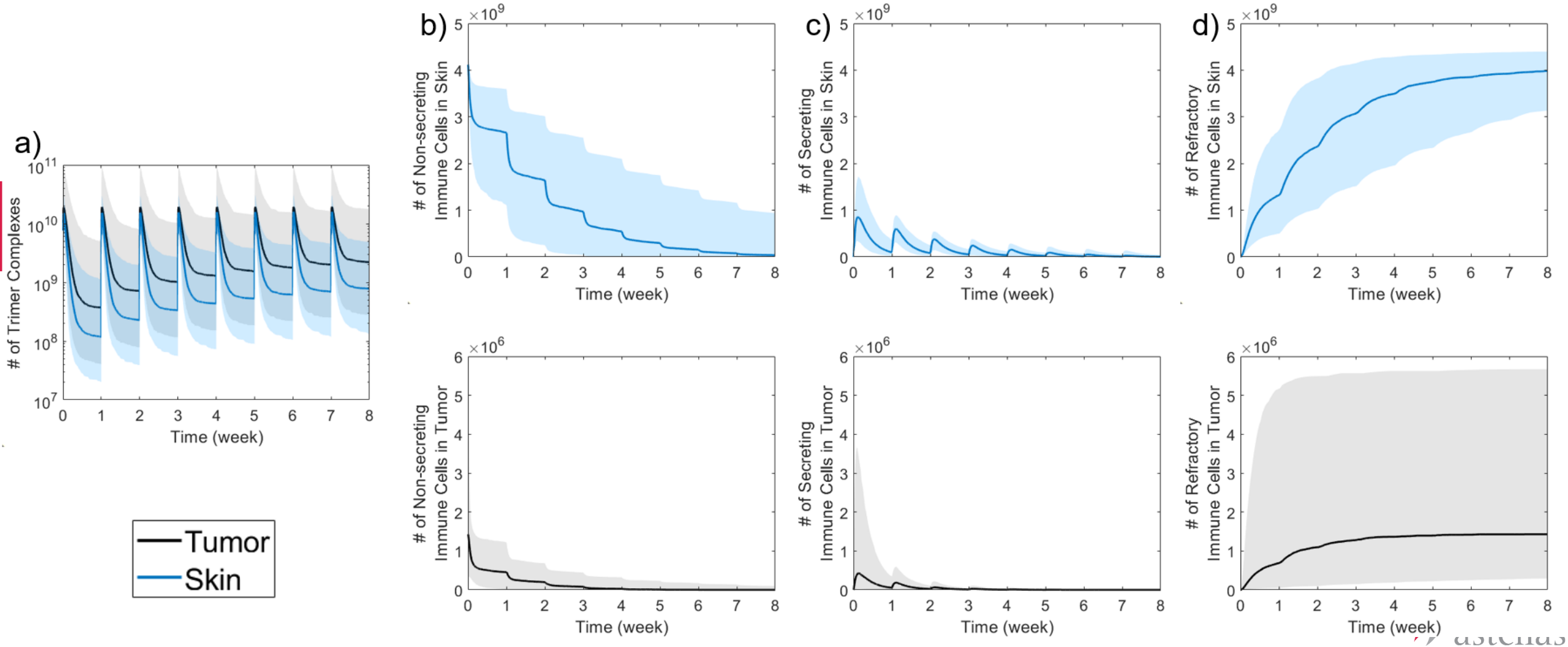
- Trimer formation triggers cytokine secretion by immune cells
- Immune cells become cytokine secretion refractory (trigger insensitive) over time
- There is a long refractory period before immune cells become trigger sensitive again

Model captures Tebentafusp cytokine dynamics



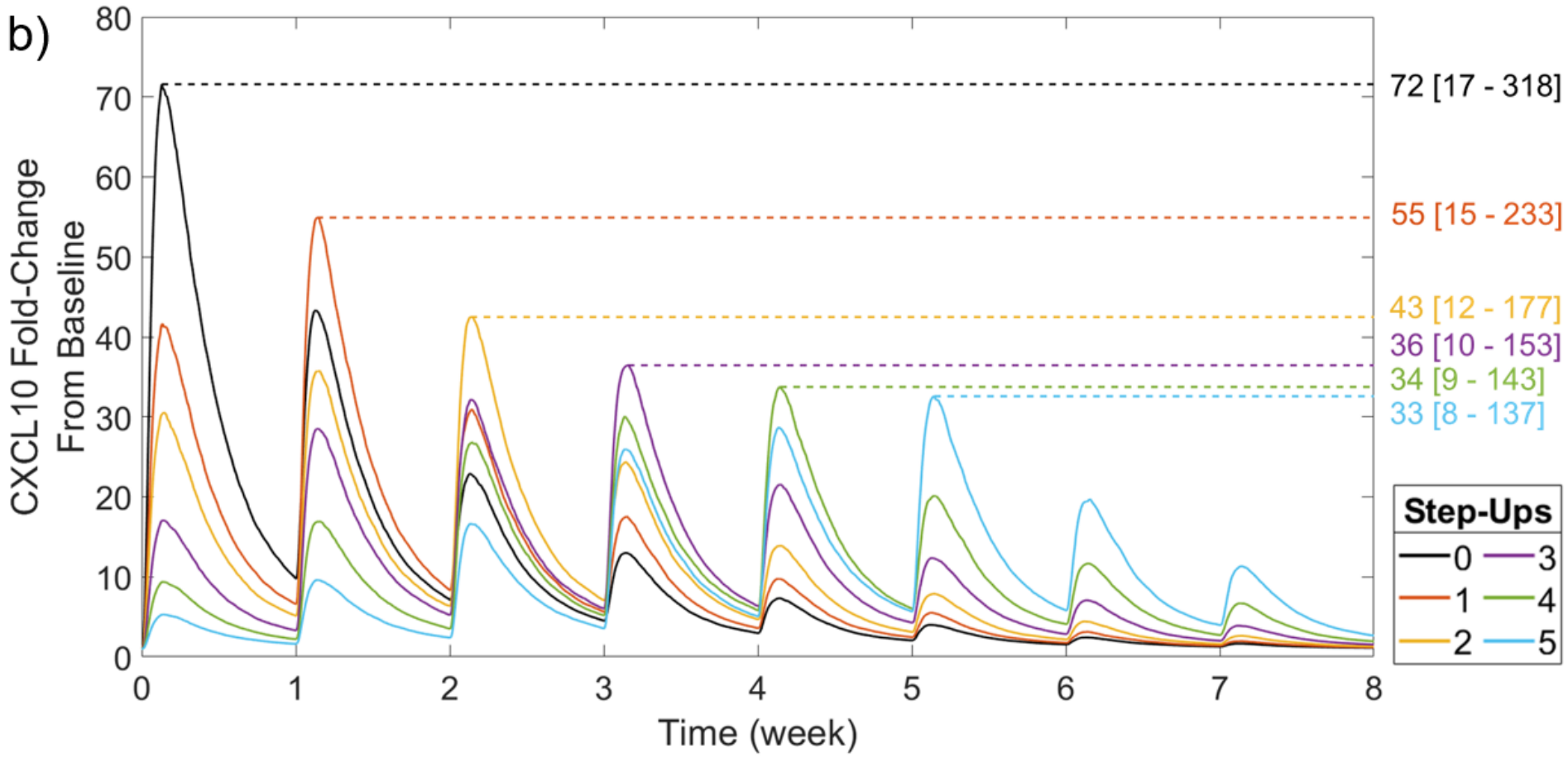
Observed data given as mean ± SEM (n = 15)
Simulated data given as mean ± SEM
(100 cohorts with 15 virtual patients each)

Model predicts on-target off-tumor interaction is the primary driver of peripheral cytokines

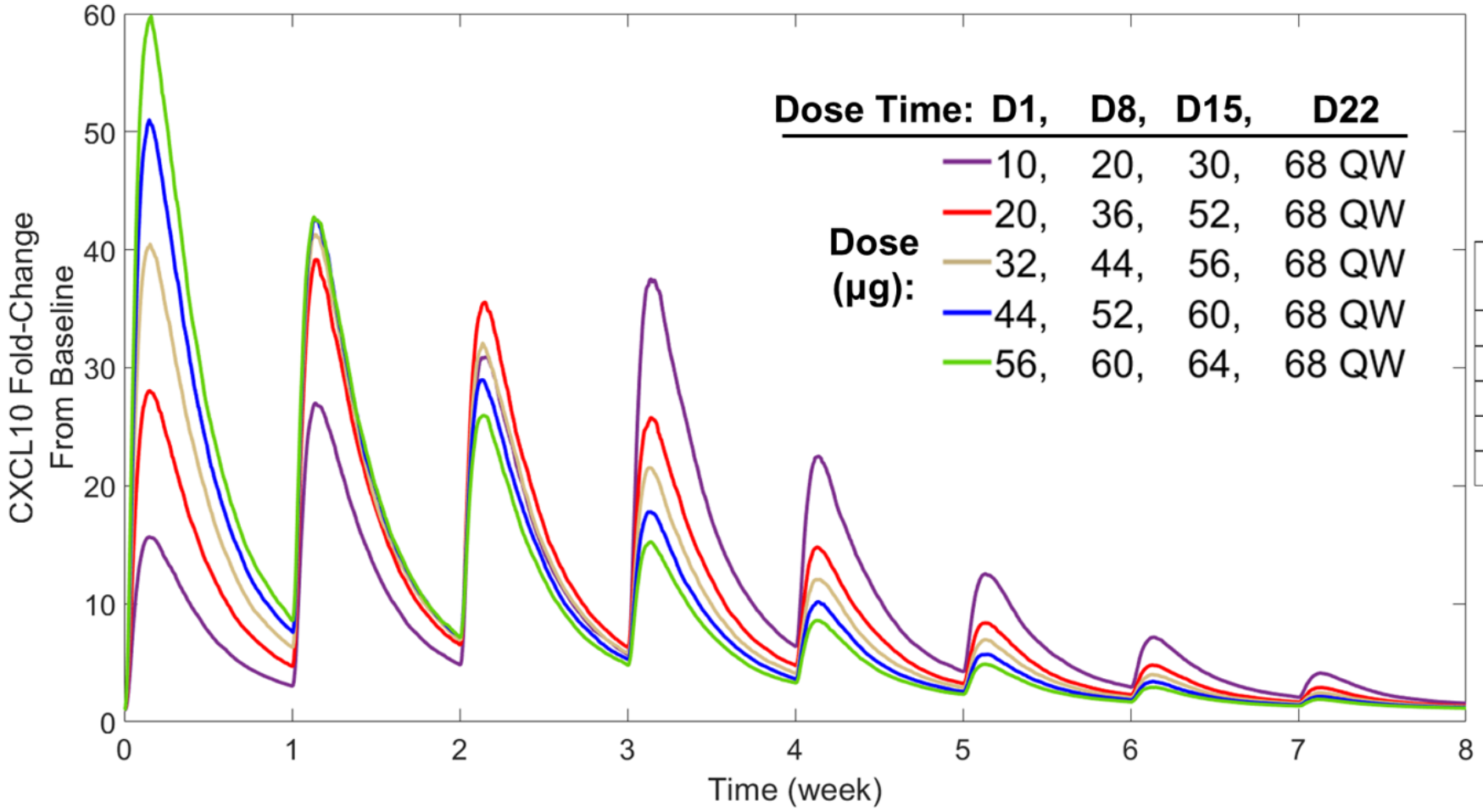


2 step-up doses is optimal for reducing cytokine release

Number of step-up doses	Dosing regimen
0	D1: 68 µg QW
1	D1: 30 µg D8: 68 µg QW
2	D1: 20 µg D8: 30 µg D15: 68 µg QW
3	D1: 10 µg D8: 20 µg D15: 30 µg D22: 68 µg QW
4	D1: 5 µg D8: 10 µg D15: 20 µg D22: 30 µg D29: 68 µg QW
5	D1: 2.5 µg D8: 5 µg D15: 10 µg D22: 20 µg D29: 30 µg D36: 68 µg QW



The dose range applied during step-up affects CRS



First Dose (µg)	T_{max} (day)	C_{max} (Fold-Change from Baseline)
10	22	36
20	8	39
32	8	41
44	1	51
56	1	60

Step-up dosing is not expected to effect bispecific efficacy

a)

Number of step-up doses	Dosing regimen
0	D1: 68 µg QW
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2	D1: 20 µg D8: 30 µg D15: 68 µg QW
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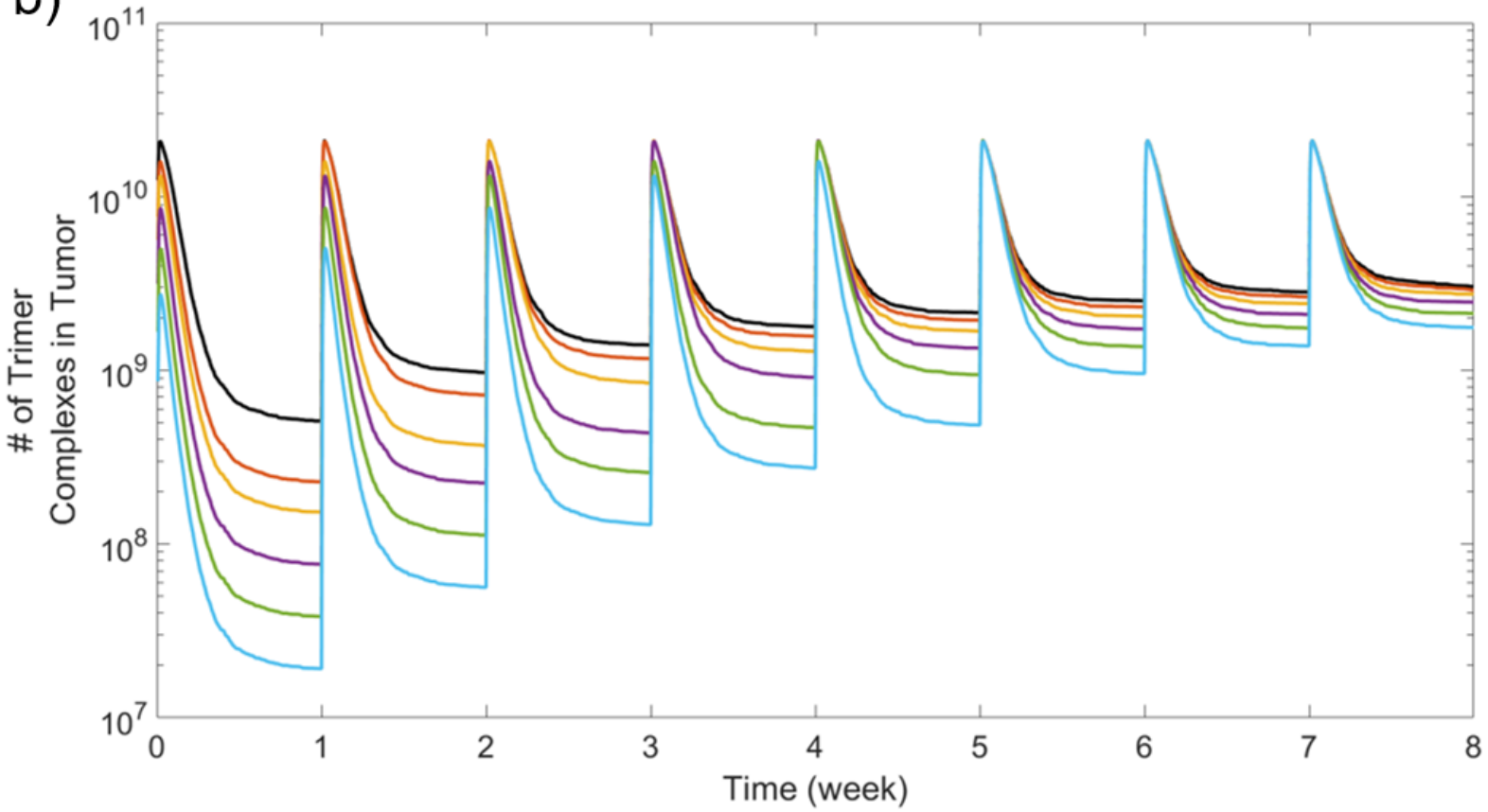
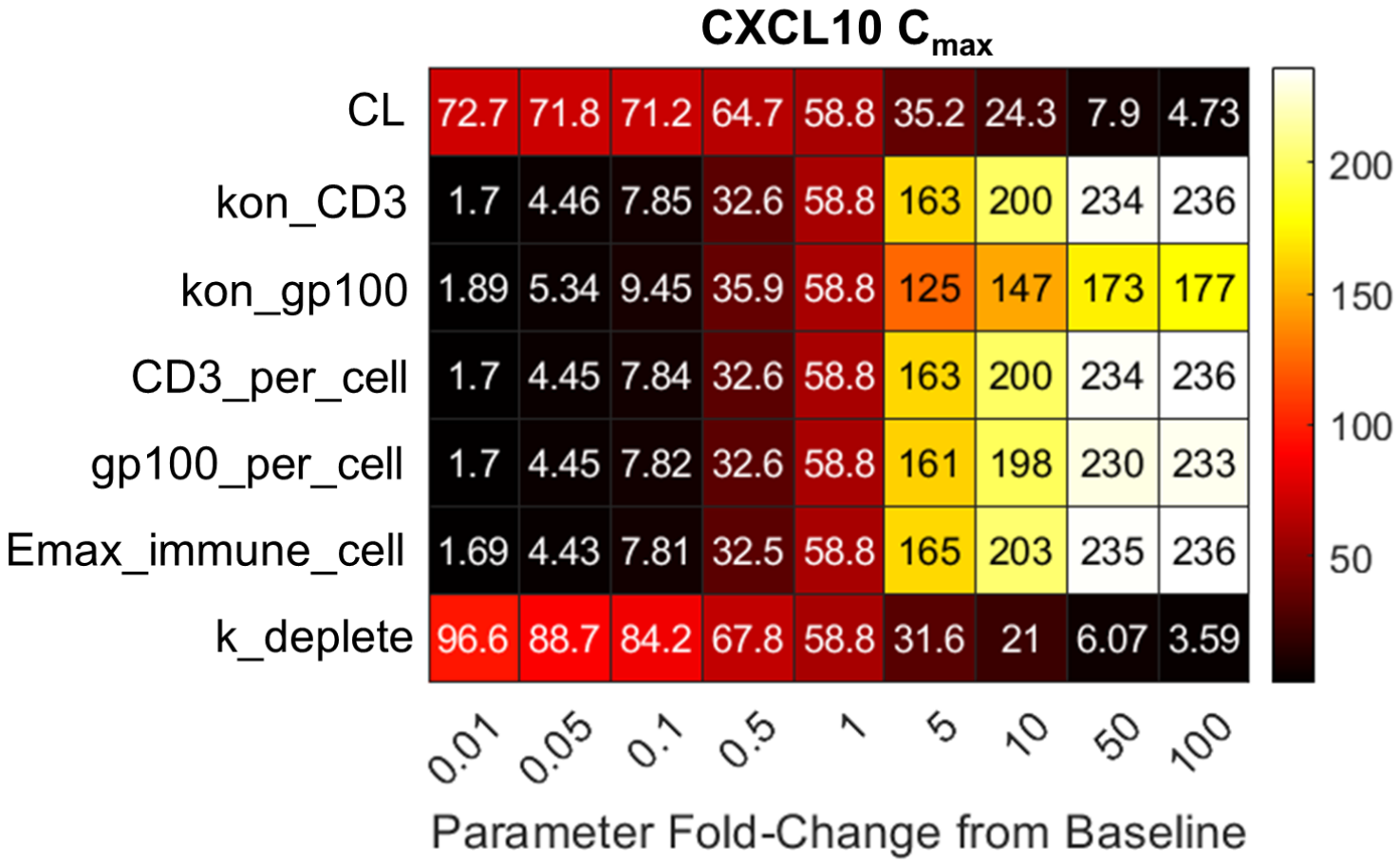
b)



c)

# step-ups	0	1	2	3	4	5
$AUC_{0\text{-}1week}$	3.1 [0.5 – 21]	1.9 [0.3 – 13]	1.4 [0.3 – 10]	0.8 [0.1 – 5.5]	0.5 [0.08 – 3.1]	0.3 [0.04 – 1.6]
$AUC_{7\text{-}8week}$	5.5 [1.0 – 34]	5.4 [0.9 – 33]	5.2 [0.9 – 33]	4.9 [0.9 – 31]	4.6 [0.8 – 29]	4.3 [0.8 – 27]

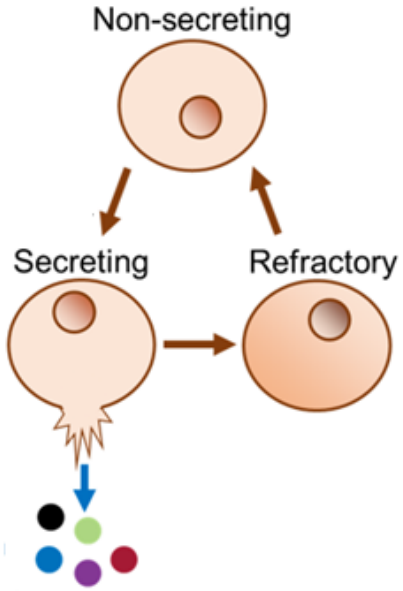
Utilizing QSP modeling to investigate strategies to mitigate CRS



Sensitivity analysis quantifies cytokine release with respect to selectable bispecific or tumor parameters

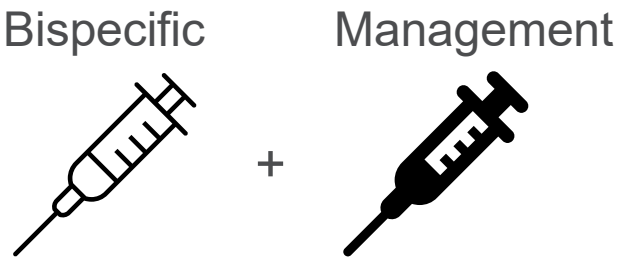
Future QSP model directions and applications

Extend model scope



- Immune cells (dendritic, NK, etc.)
- Tumor growth inhibition
- Linking cytokines to CRS

Add CRS management



- CRS management therapy (tocilizumab, siltuximab, etc.)
- Optimize management time
- Optimize management criteria

Apply to other bispecifics

NCT	Phase	Indications
NCT01723475	1	Metastatic castration-resistant prostate cancer
NCT03792841	1	Metastatic castration-resistant prostate cancer
NCT03296696	1	R/R Glioblastoma

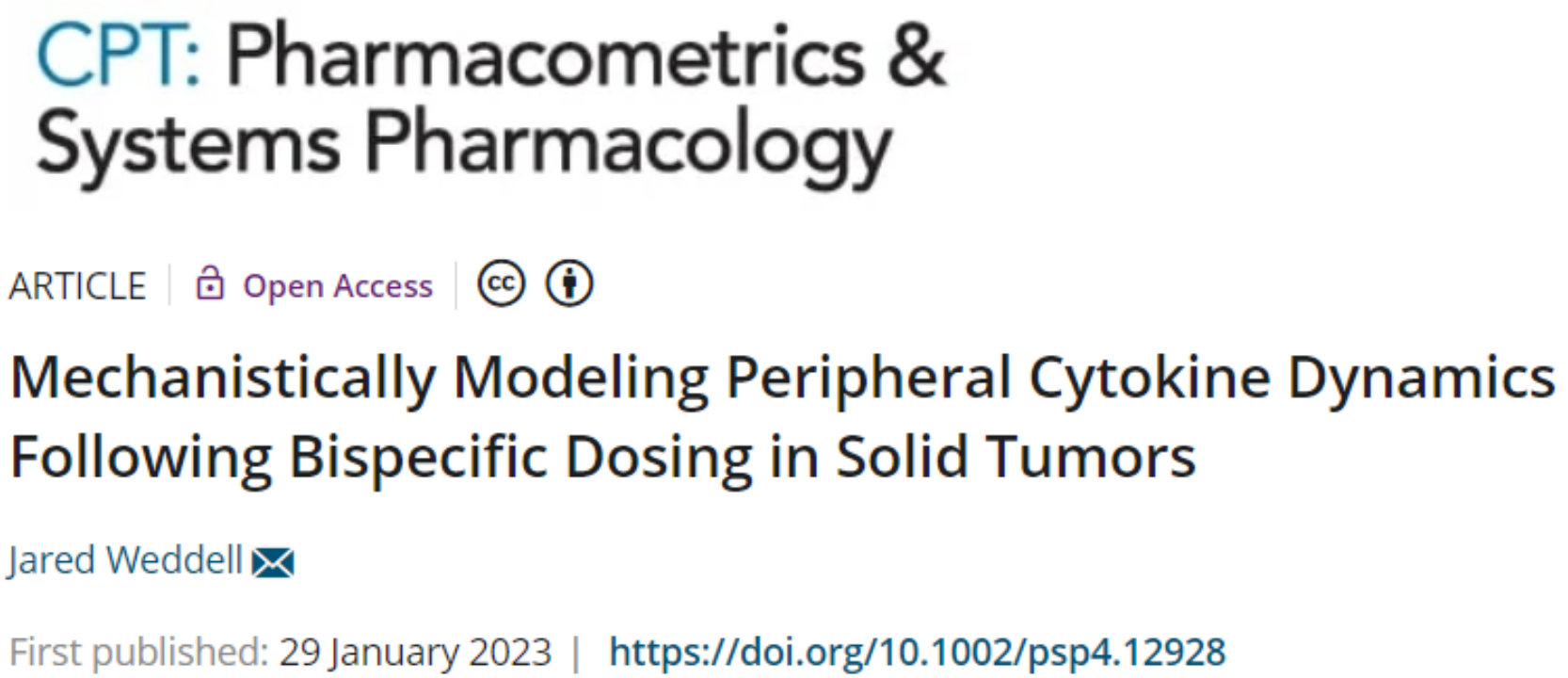
PMID: 34039409

- > 50 CD3-bispecifics in clinical development currently
- Non-CD3 bispecifics (CD137, dual TAAs, etc.)

Summary

- The QSP model provides mechanistic insights into:

1) cytokine attenuation by immune cell desensitization
2) toxicity from on-target off-tumor effects
3) safety (cytokine) and efficacy (tumor trimer) versus step-up dose regimen



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Acknowledgements

Astellas PKMS-US

Astellas bispecific project teams