ASCPT

FROM MOLECULE TO PATIENT

ASCPT 2019 ANNUAL MEETING

FROM MOLECULE TO PATIENT

Identifying biological signals differentiating responders and non-responders to MPDL3280A (Anti-PDL1) in NSCLC using QSP modeling of immune checkpoints

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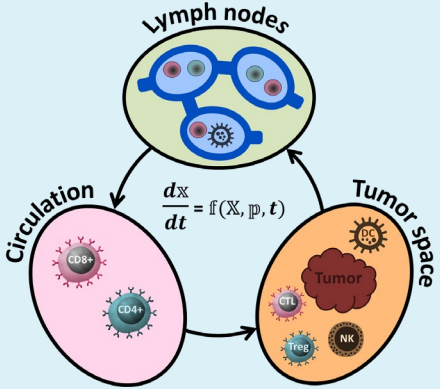
Modeling platform goals

1. Help prioritizing combinations of immune checkpoint inhibitors
2. Address project-specific questions related to the clinical development of ongoing CIT programs

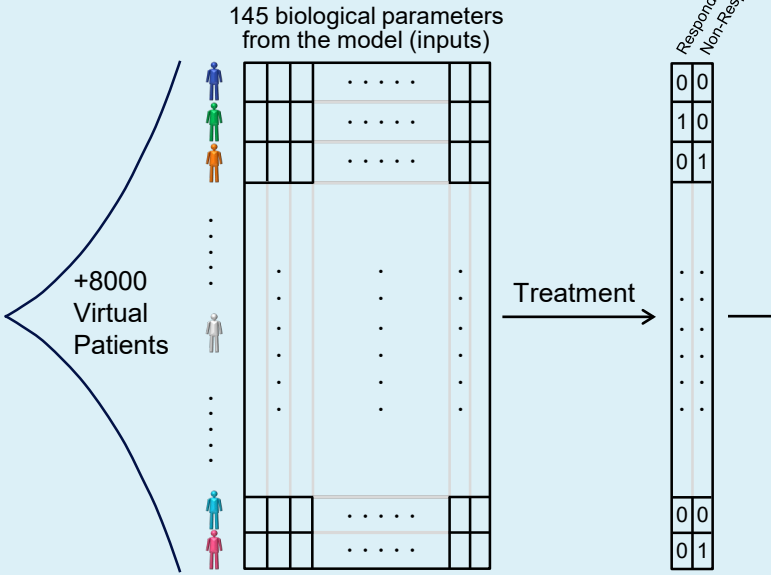
E.g.
- Clarify complex dose-response relationships
- Identify signals of response (biomarkers)
- Assess synergy in combination treatments
- Optimization of dose scheduling
- Assessment of treatment duration
- Evaluation of combination sequencing effects
- Patient stratification (responder vs. non-responder)

Overview of the approach

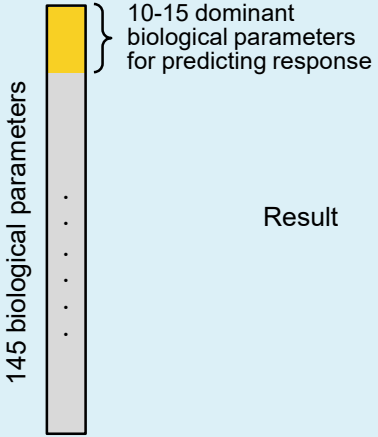
QSP Model



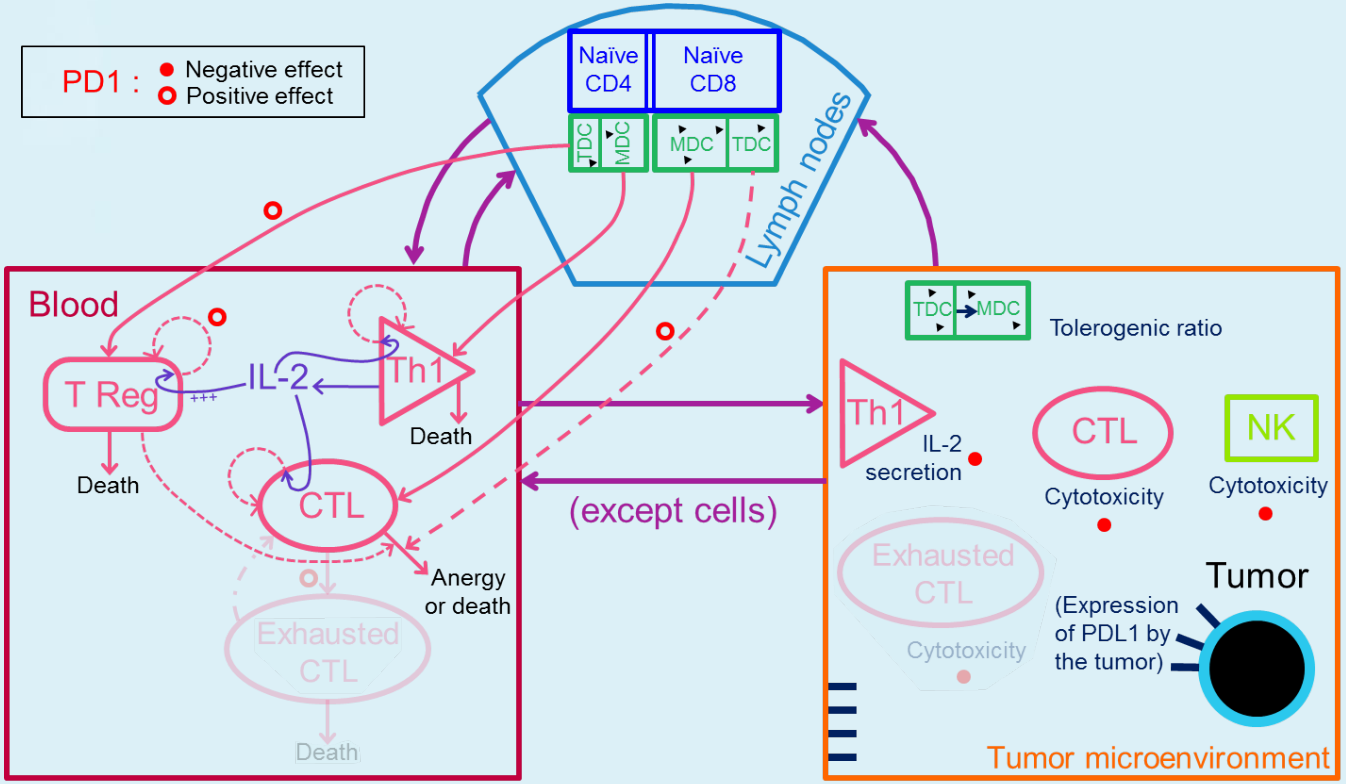
Virtual Population



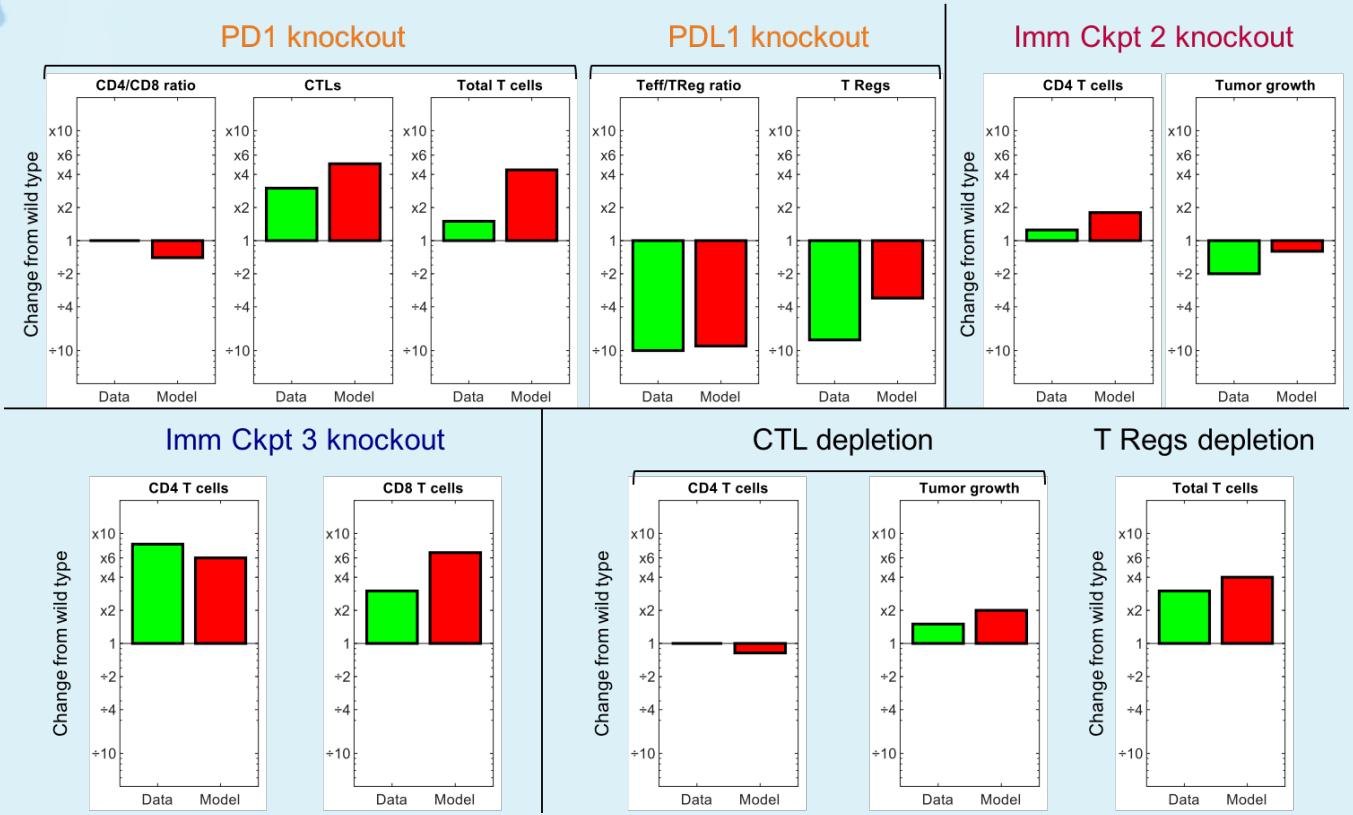
Machine Learning Analysis



Overview of the biology in the model

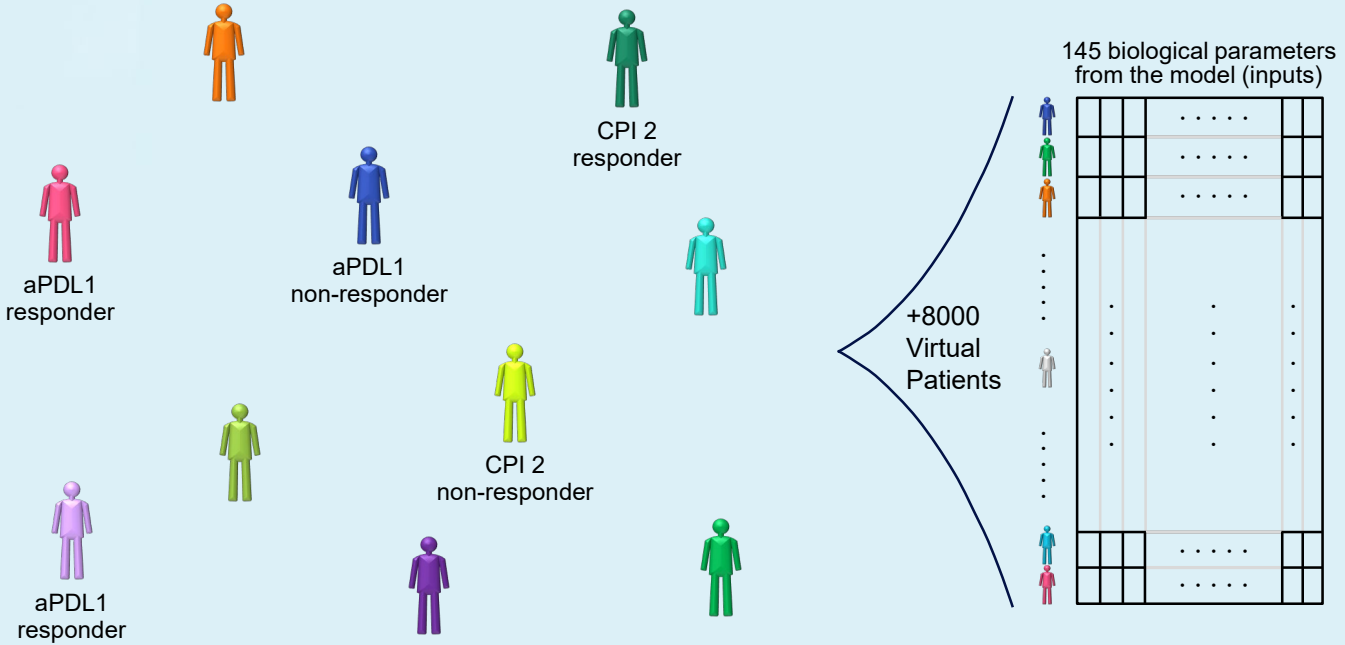


Virtual patients must satisfy basic biology



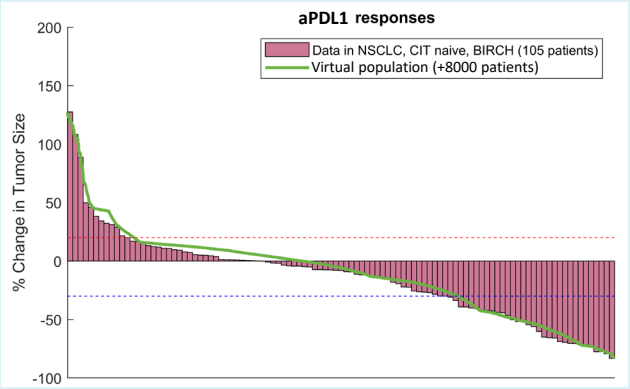
* Imm Ckpt ≡ Immune Checkpoint

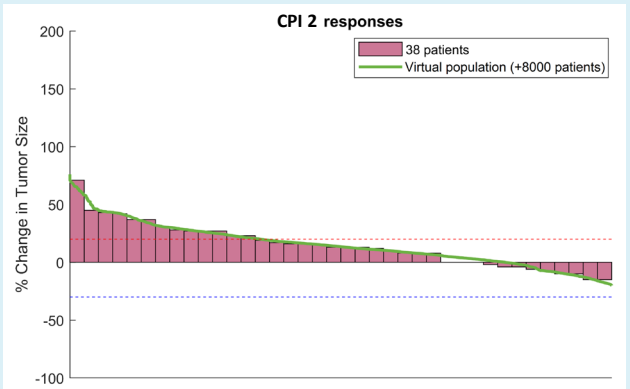
Virtual population with high diversity in biology

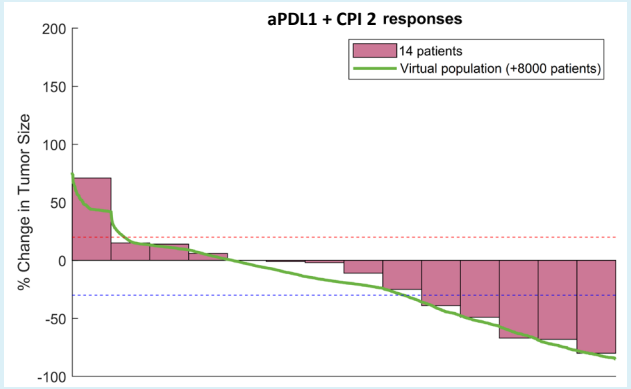


* CPI = CheckPoint Inhibitor

Calibration of the virtual population to match clinical response data





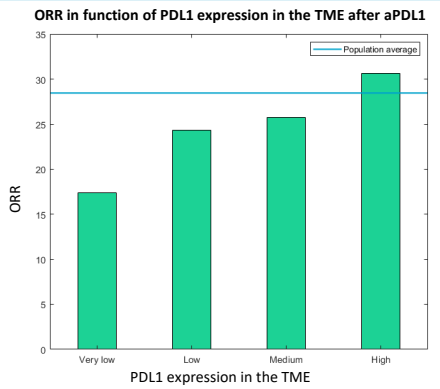


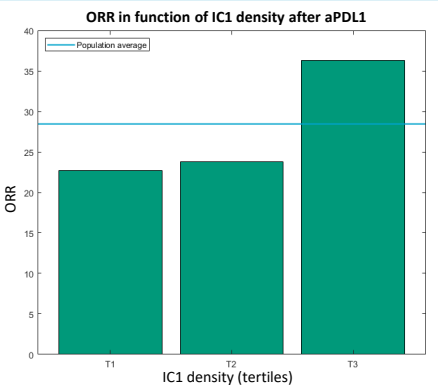
* CPI = CheckPoint Inhibitor

Pieces of model and virtual population validation

FROM MOLECULE TO PATIENT

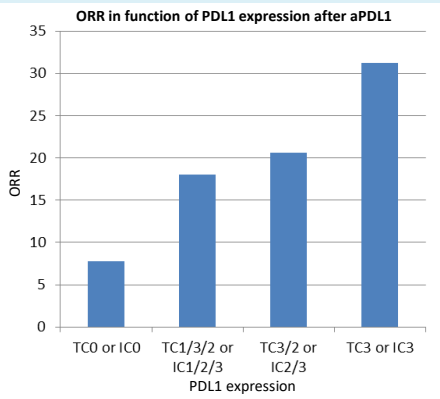
Model

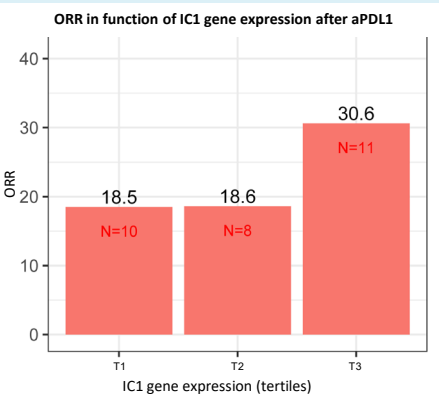




Model

Data





Data

* IC1 = Some Immune Cell

Machine learning approach & results

Identify differences in biology which separate aPDL1 responders and non-responders

Using the Machine Learning algorithms:

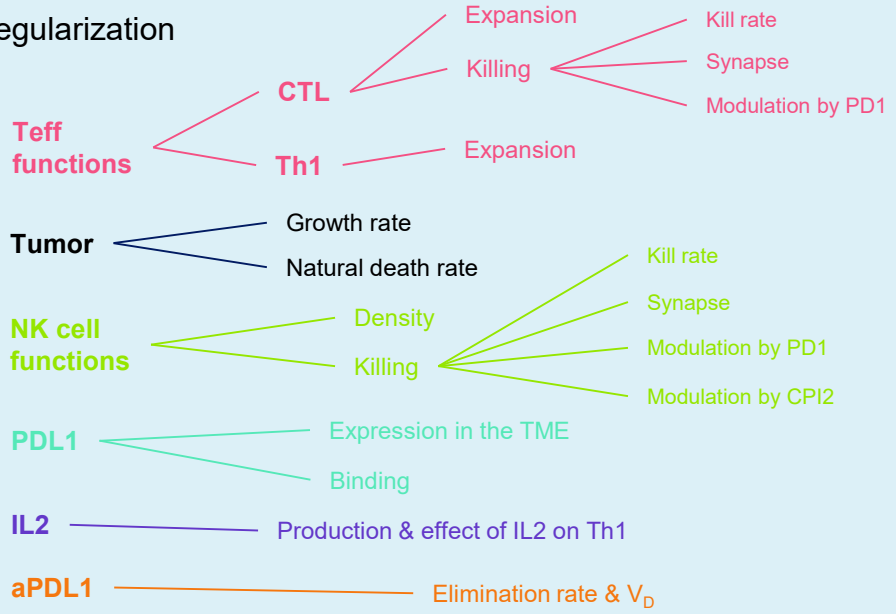
- Multivariate linear regression with LASSO regularization
- Support Vector Machine (SVM)

LASSO:

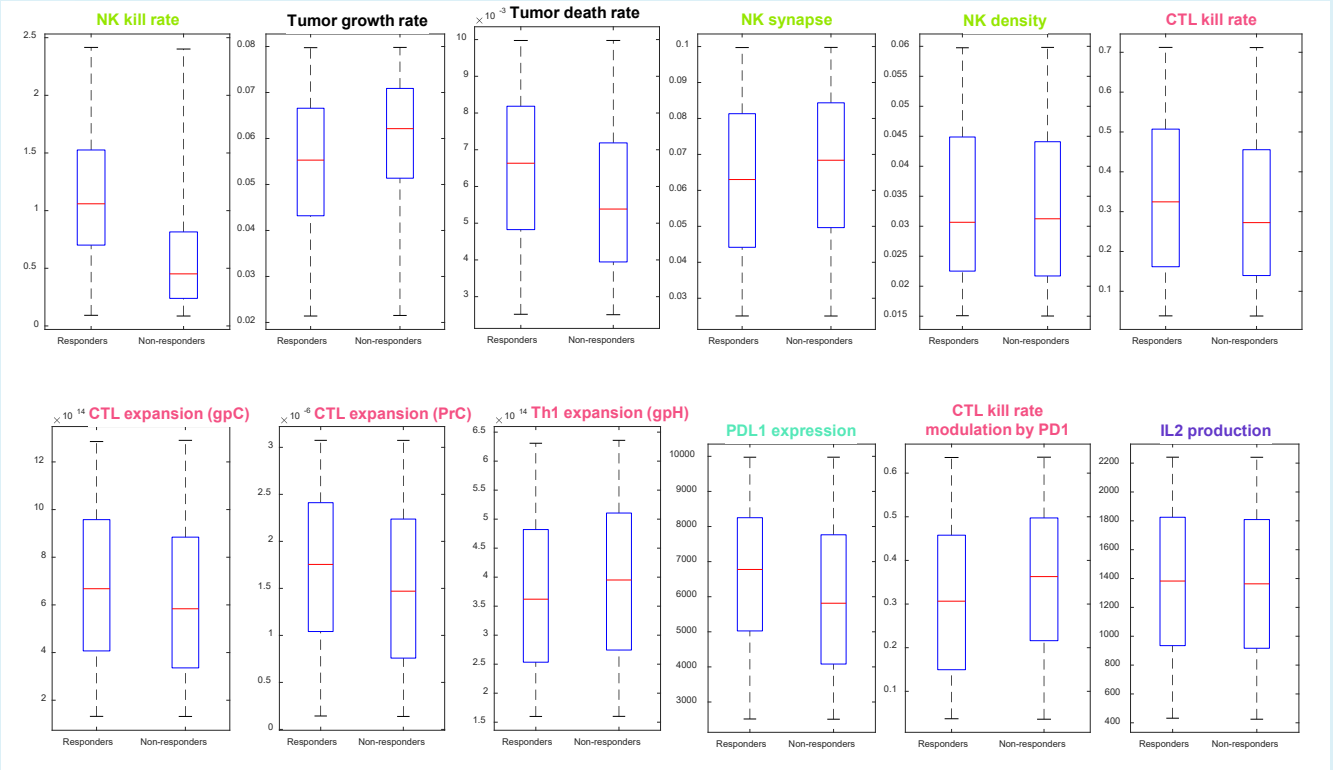
Parameters	Coefficients
kk	-0.566
beta	0.387
kapop	-0.299
KDK	0.183
Pi50pkPD1	0.181
K	-0.178
kc	-0.149
gpC	-0.122
PrC	-0.105
gpH	0.0677
KDPD1	0.0622
Pi50pcPD1	0.0458
PrH	0.0437
KDC	0.0383
PDL1tO	-0.0338
gpI	-0.0334
keaPDL1	-0.0227

SVM:

Parameters	Coefficients
kk	-1.92
beta	1.73
kapop	-1.35
Pi50pkPD1	1.28
gpC	-0.73
KDK	0.646
PrC	-0.611
KDPD1	0.501
gpH	0.485
PDL1tO	-0.476
kc	-0.415
Pi50pkCPI2	-0.361
kkCPI2	-0.341
kcCPI2	-0.326
Pi50pcPD1	0.297
K	-0.231
ErI	-0.189



Biological signals need to be considered together for prediction



Collaboration & partnership with biomarker scientists

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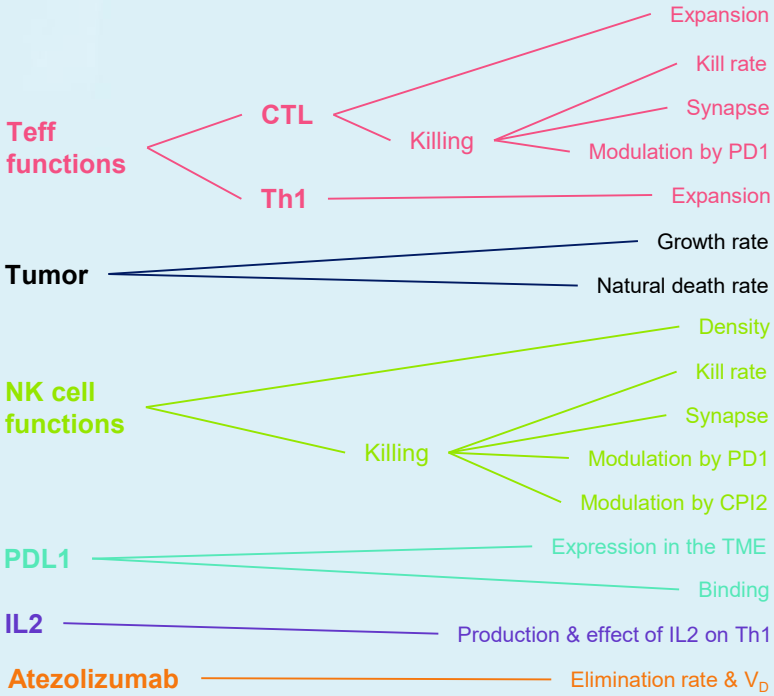

Translate into

A clinically measurable panel of biomarkers

Acknowledgements

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