THE OPEN PROJECT

beyond
a cut above

Translational PK/PD Modelling

Data & Clarity

Tao You, PhD

About me

Mathematical and statistical modelling, Bioinformatics

- Chemical Engineering, BE, 1998-2002
- Biological and Chemical Engineering, MSc, 2002-2003
- Cancer Bioinformatics, 2003-2005
- Systems Biology, PhD, 2005-2009
- Systems Biology, Postdoc, 2009-2011
- Physiological Modeller & PK/PD Modeller, 2011-2015
- PK/PD Modelling Lab Head, 2016-2018
- PK/PD Modeller & Data Scientist, Aug 2018 - now

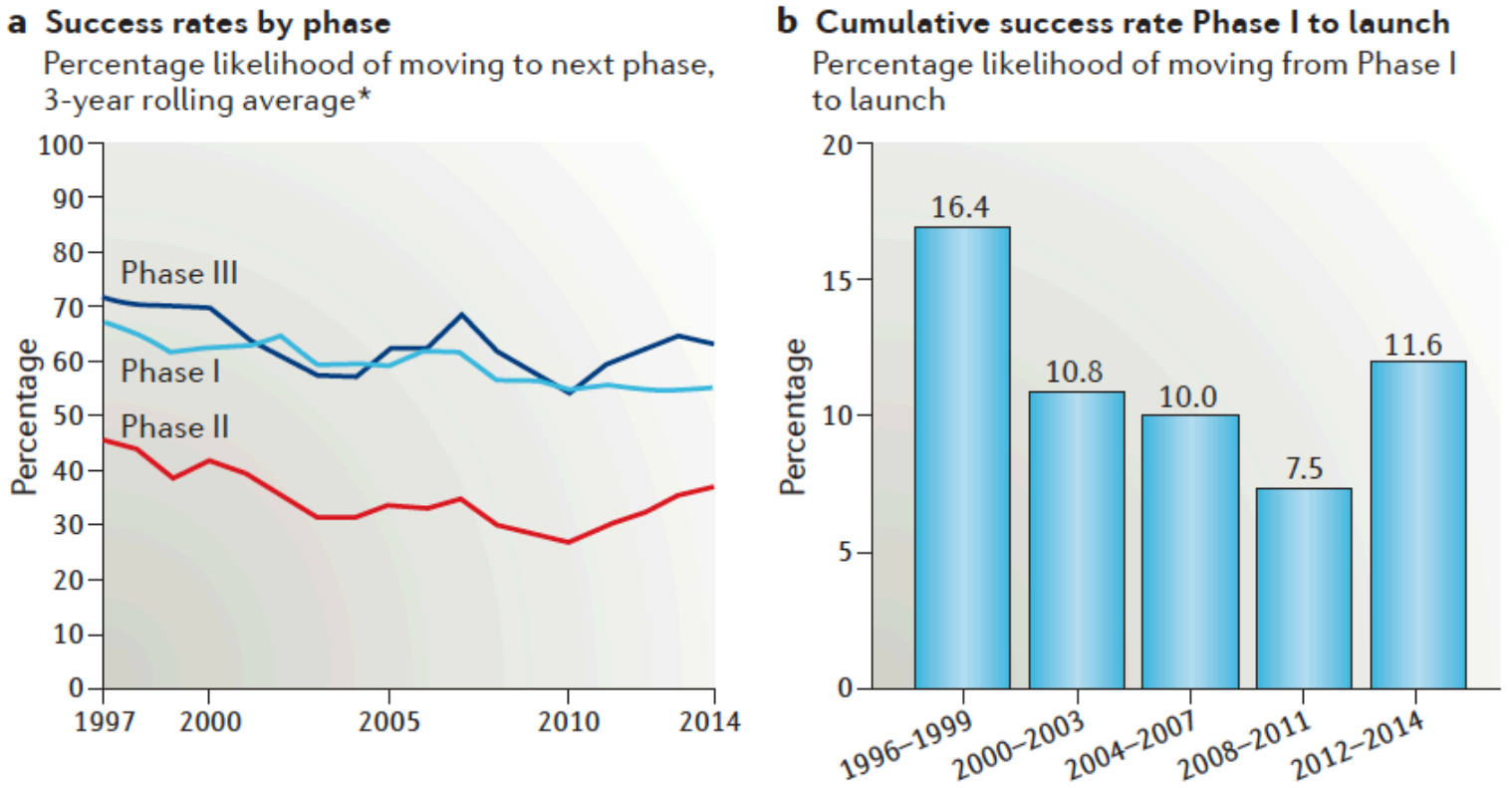
Singapore–MIT Alliance

Aims

- **Review** the pain points in drug R&D
- **Evaluate** the growth of *in vivo* tumour models
- **Translational** PK/PD modelling: Value proposition, examples
- **Gene signature** for tumour growth

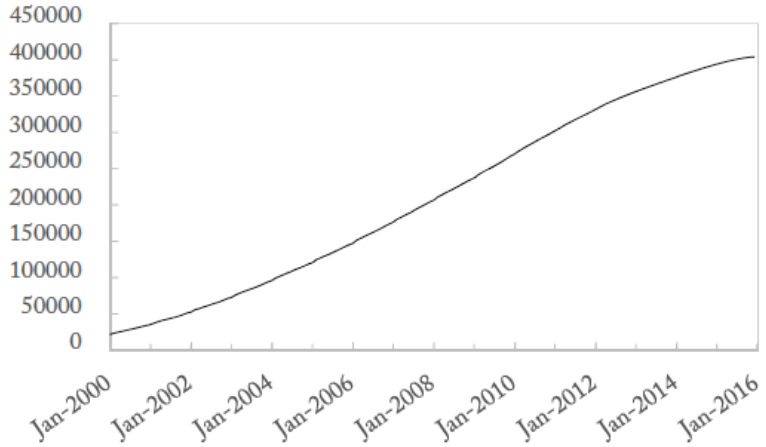
1. THE REASON WHY?

Probability of Success: Phase-by-phase

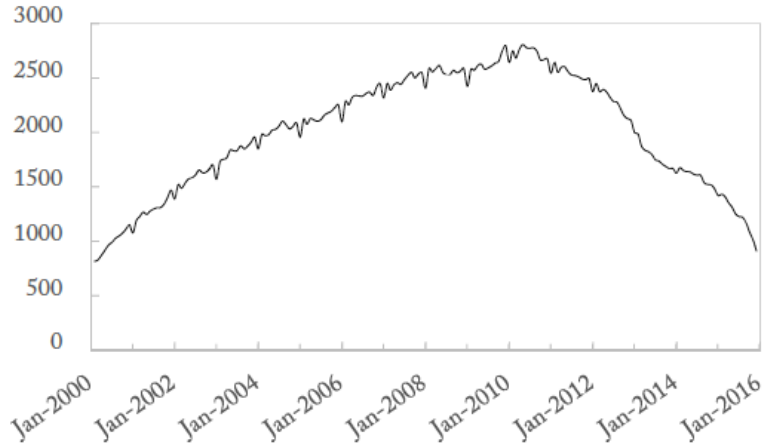


Smietana *et al*. (2016) Trends in clinical success rates. *Nat Rev Drug Disc*. 15: 379-380

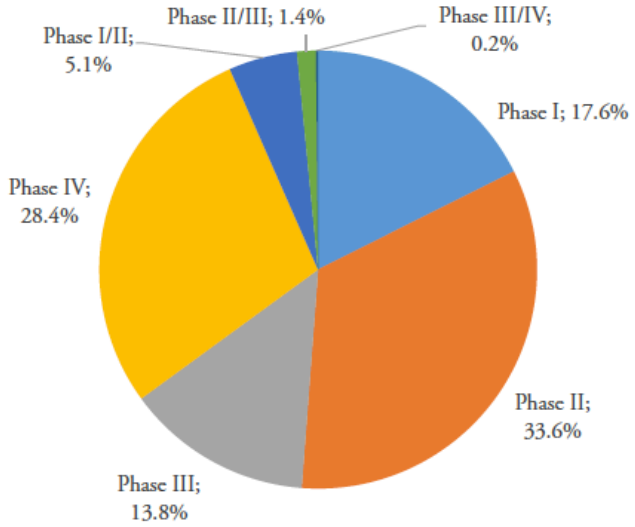
Clinical trials 2000-2015



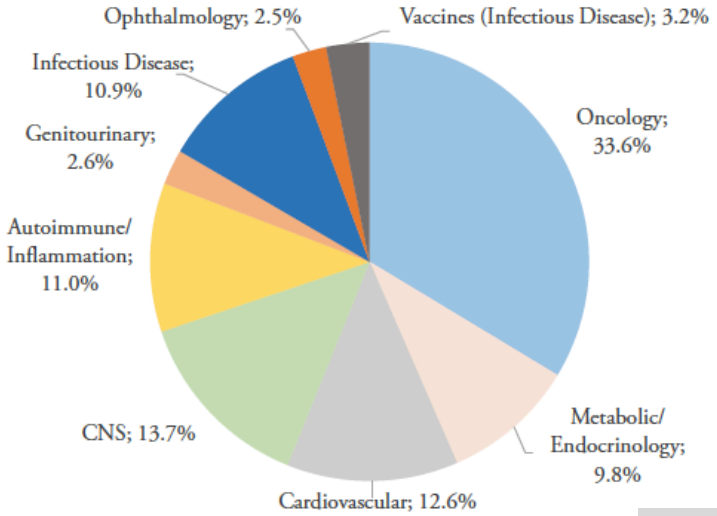
(a) Cumulative number of trials over time



(b) Increase in the number of trials over time



(c) Proportion of trials by phases

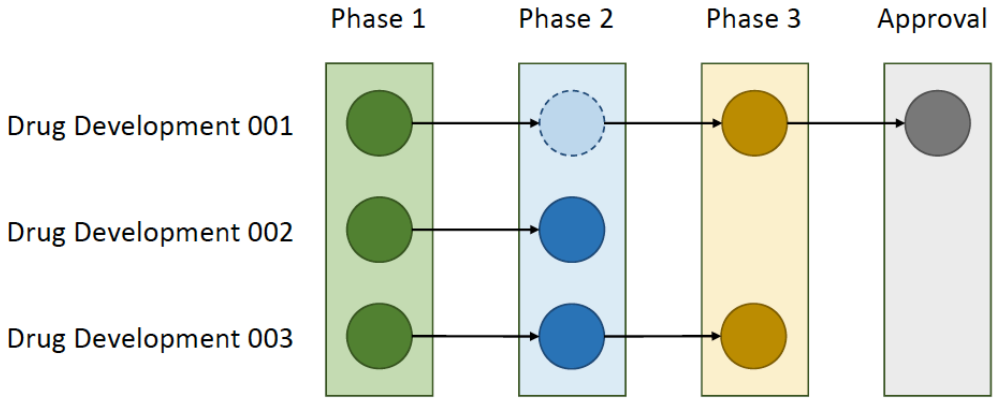


(d) Proportion of trials by therapeutic groups

~186,000 trials in total

Lo *et al*. (2018) Estimation of clinical trial success rates and related parameters. *Biostatistics*. p 1–14

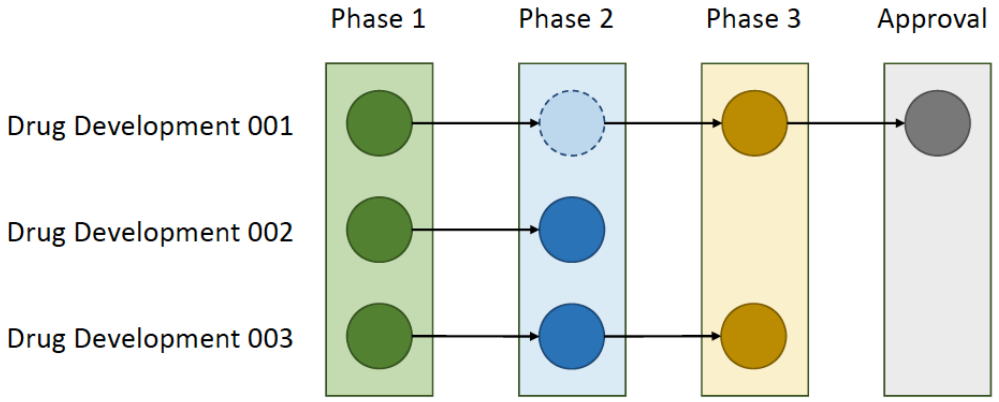
Probability of Success (POS)



- Phase-by-phase counting
  - $POS_{1,2} = 1$
  - $POS_{2,3} = \frac{1}{2}$
  - $POS_{3,App} = \frac{1}{2}$
  - $POS_{1,App} = 1x \frac{1}{2} x \frac{1}{2} = \frac{1}{4}$
  - Widely used in the past
  - Ignore missing trials

Lo *et al*. (2018) Estimation of clinical trial success rates and related parameters. *Biostatistics*. p 1–14

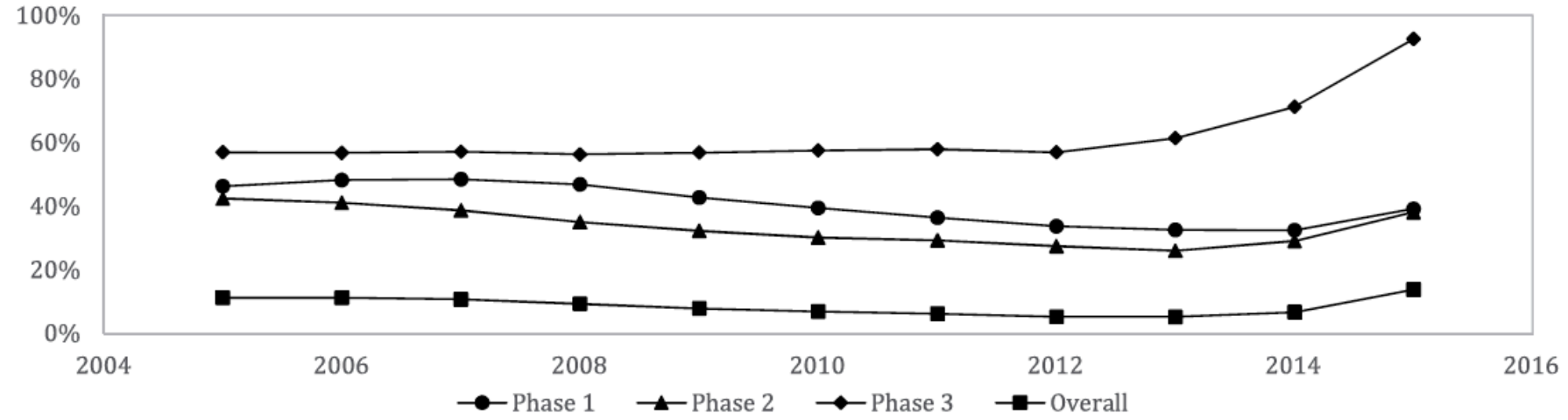
Probability of Success (POS)

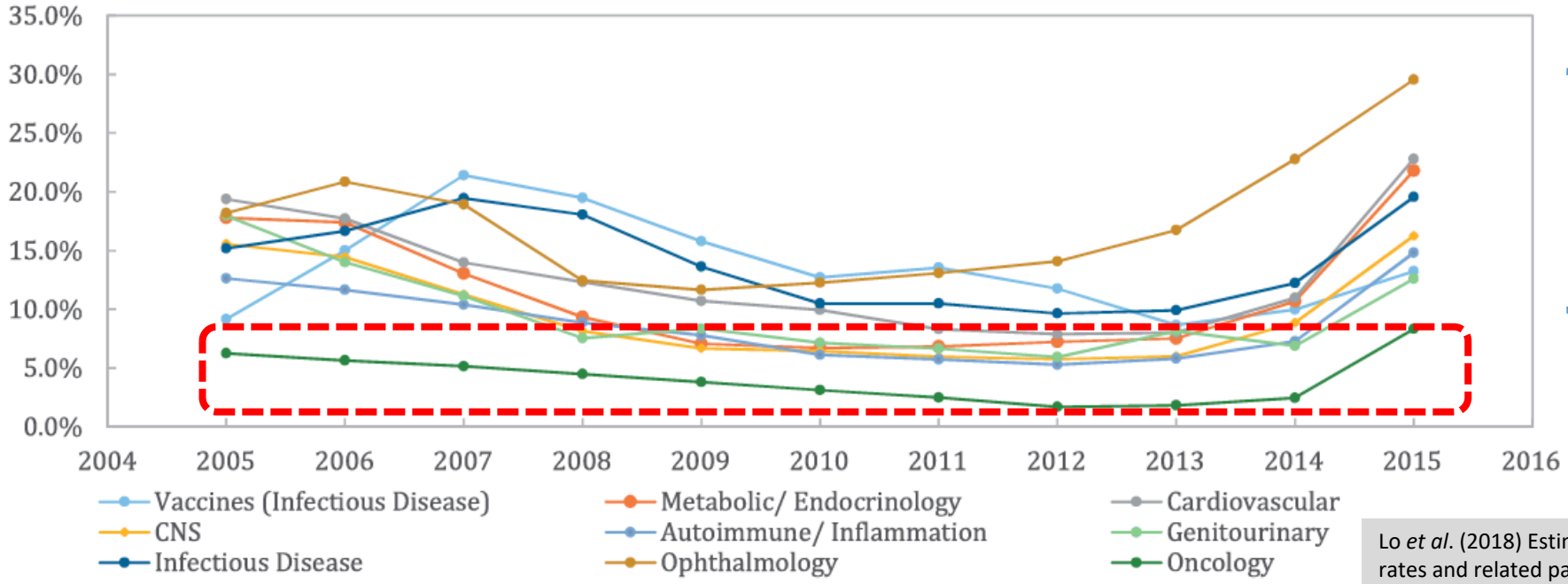


- Path-by-path counting
  - Missing Phase 2 is inferred
  - $POS_{1,2} = 1$
  - $POS_{2,3} = \frac{2}{3}$
  - $POS_{3,App} = \frac{1}{2}$
  - $POS_{1,App} = 1x \frac{2}{3} x \frac{1}{2} = \frac{1}{3}$
  - Used by Lo *et al*
  - Considers missing, in progress and terminated trials
  - More accurate description than phase-by-phase

Lo *et al*. (2018) Estimation of clinical trial success rates and related parameters. *Biostatistics*. p 1–14

Cancer drug programmes are more risky (on average) than previously thought





$POS_{1,App}$

20.9%

3.4%

Lo *et al*. (2018) Estimation of clinical trial success rates and related parameters. *Biostatistics*. p 1–14

Cancer drug: Phase 2 is key

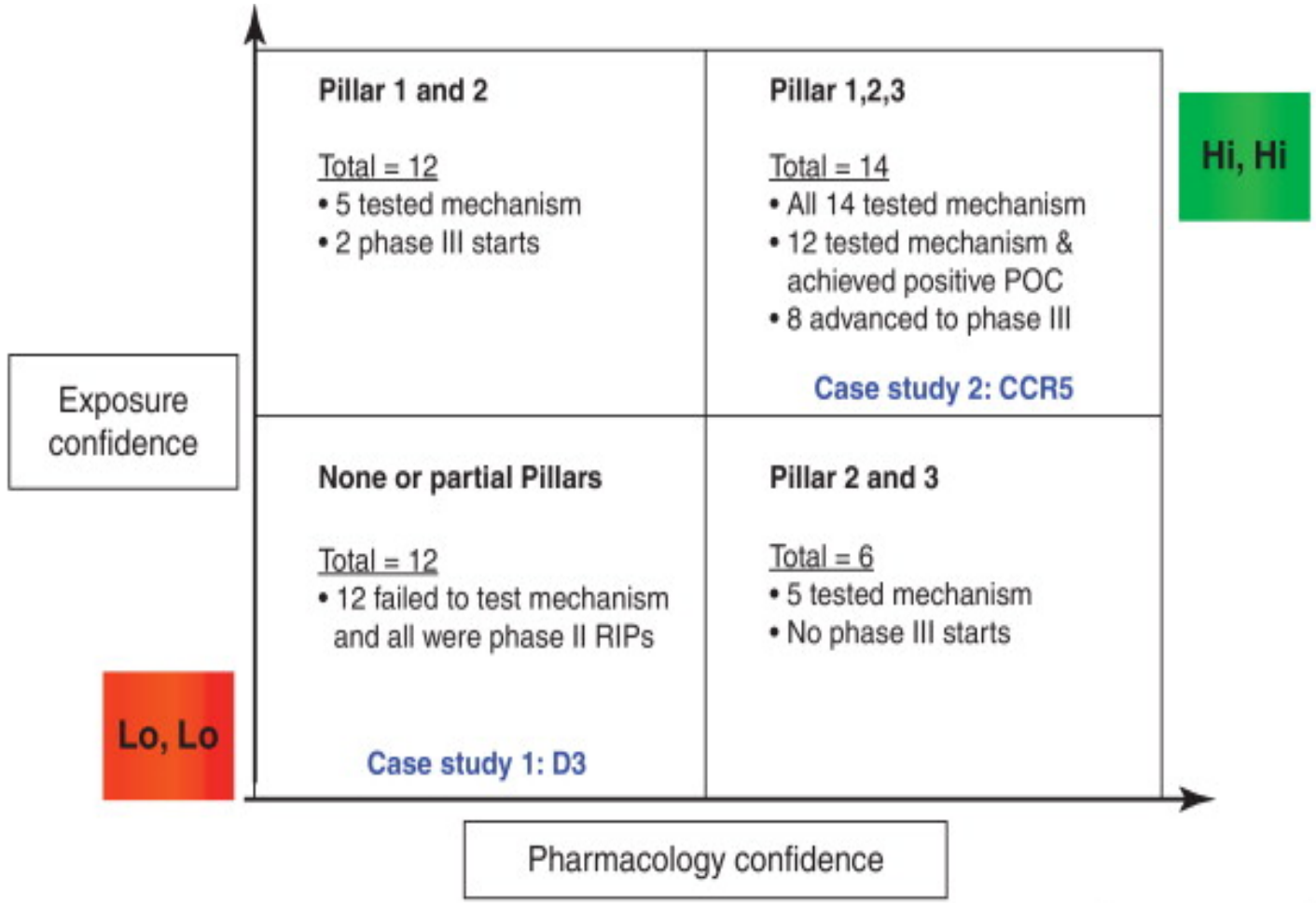
All indications (industry)

	Phase 1 to Phase 2		Phase 2 to Phase 3			Phase 3 to Approval		Overall
Therapeutic group	Total paths	$POS_{1,2}$, % (SE, %)	Total paths	$POS_{2,3}$, % (SE, %)	$POS_{2,APP}$, % (SE, %)	Total paths	$POS_{3,APP}$, % (SE, %)	POS, % (SE, %)
Oncology	17 368	57.6 (0.4)	6533	32.7 (0.6)	6.7 (0.3)	1236	35.5 (1.4)	3.4 (0.2)
Metabolic/ Endocrinology	3589	76.2 (0.7)	2357	59.7 (1.0)	24.1 (0.9)	1101	51.6 (1.5)	19.6 (0.7)
Cardiovascular	2810	73.3 (0.8)	1858	65.7 (1.1)	32.3 (1.1)	964	62.2 (1.6)	25.5 (0.9)
CNS	4924	73.2 (0.6)	3037	51.9 (0.9)	19.5 (0.7)	1156	51.1 (1.5)	15.0 (0.6)
Autoimmune/ Inflammation	5086	69.8 (0.6)	2910	45.7 (0.9)	21.2 (0.8)	969	63.7 (1.5)	15.1 (0.6)
Genitourinary	757	68.7 (1.7)	475	57.1 (2.3)	29.7 (2.1)	212	66.5 (3.2)	21.6 (1.6)
Infectious disease	3963	70.1 (0.7)	2314	58.3 (1.0)	35.1 (1.0)	1078	75.3 (1.3)	25.2 (0.8)
Ophthalmology	674	87.1 (1.3)	461	60.7 (2.3)	33.6 (2.2)	207	74.9 (3.0)	32.6 (2.2)
Vaccines (Infectious Disease)	1869	76.8 (1.0)	1235	58.2 (1.4)	42.1 (1.4)	609	85.4 (1.4)	33.4 (1.2)
Overall	41 040	66.4 (0.2)	21 180	58.3 (2.3)	35.1 (2.2)	7532	59.0 (0.6)	13.8 (0.2)

Lo *et al*. (2018) Estimation of clinical trial success rates and related parameters. *Biostatistics*. p 1–14

Pfizer 3 pillars (2012)

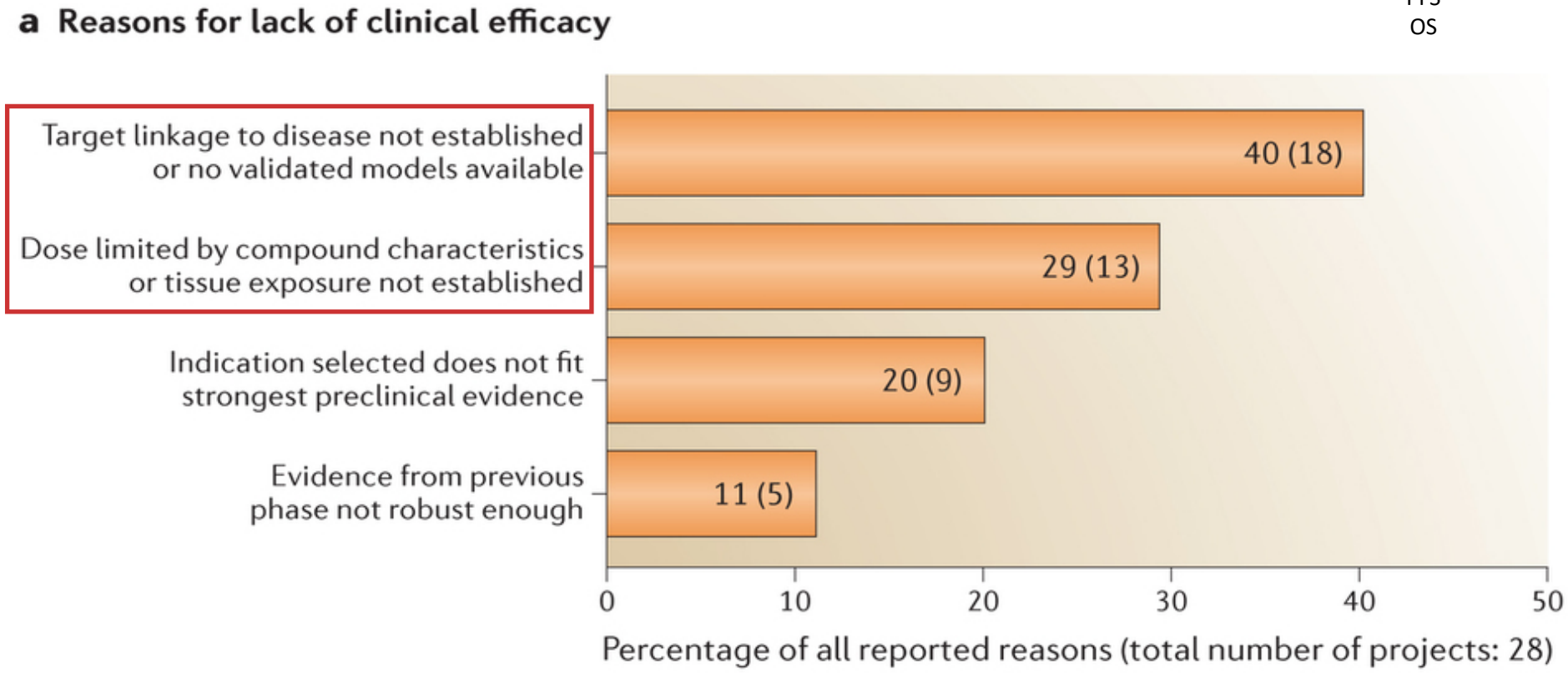
- "Pfizer 3 pillars"
  1. Suitable exposure (site of action, duration)
  2. Sufficient target binding
  3. Adequate pharmacology



Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival *Drug Discovery Today.* 17, 419–424 (2012)

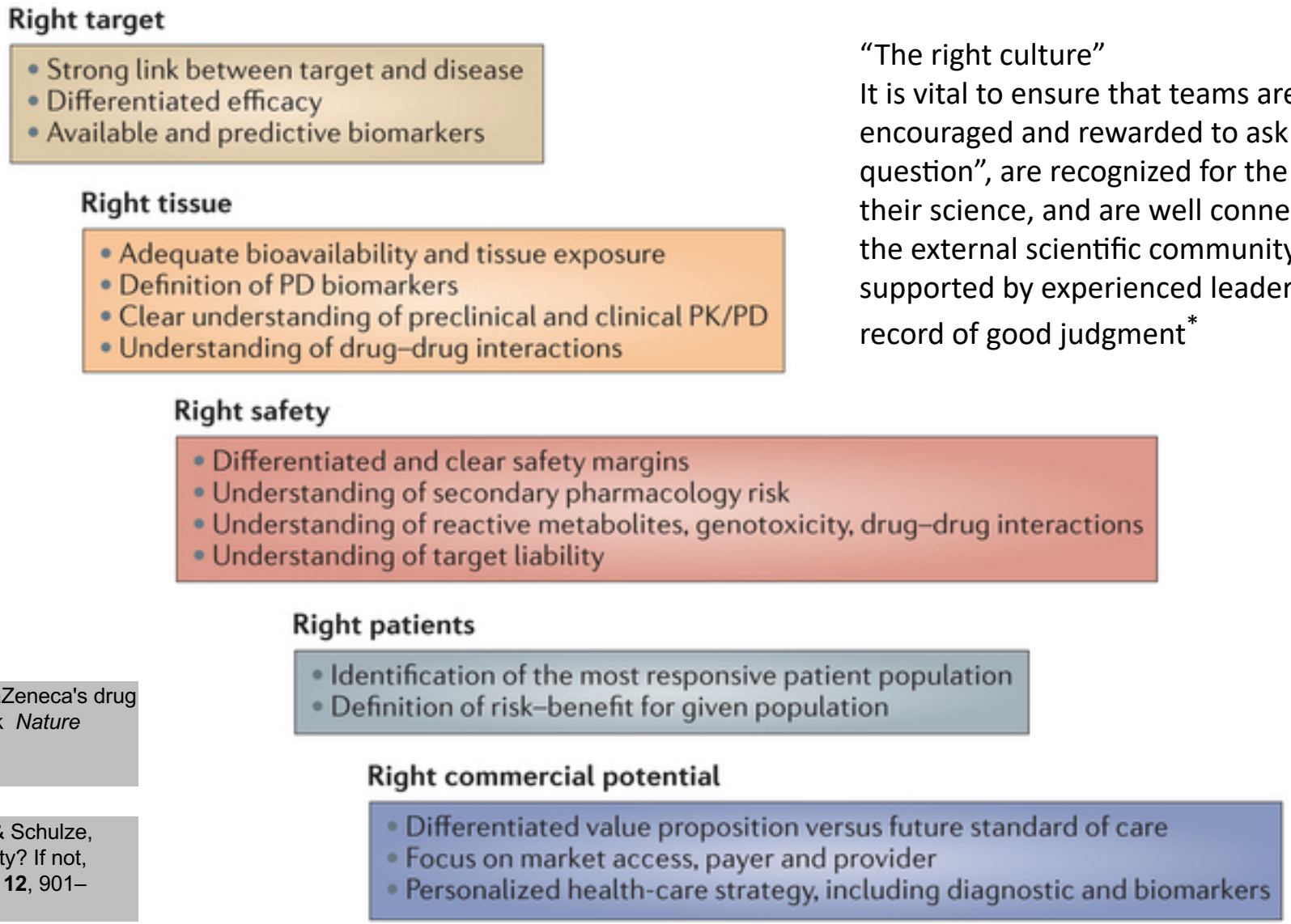
AstraZeneca: Lack of clinical efficacy (2014)

Exposure	Direct Target Engagement	Indirect Target	Physiological Response	Disease Modulation	Outcome/ Endpoints
	target itself "immediate" target	"downstream" signalling	tumour perfusion blood glucose	cell cycle arrest proliferation apoptosis	cellular growth inhibition tumour growth inhibition ORR PFS OS



Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework
Nature Reviews Drug Discovery **13**, 419–431 (2014) doi:10.1038/nrd4309

AstraZeneca 5R's framework

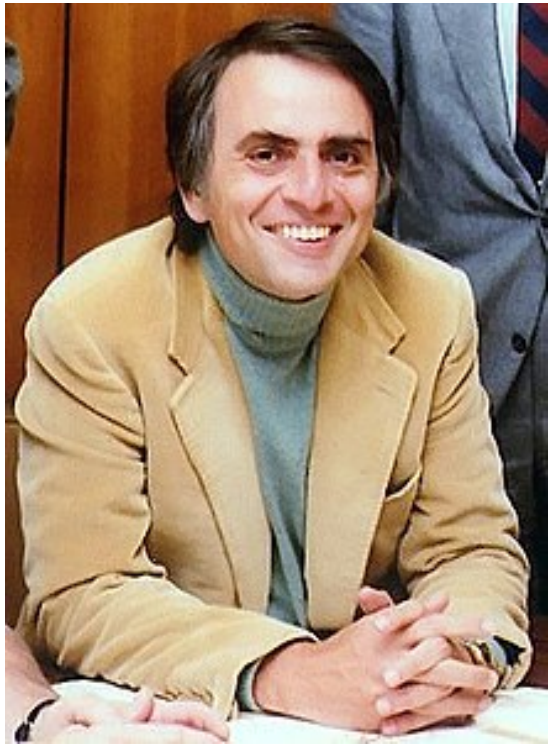


"The right culture"
It is vital to ensure that teams are encouraged and rewarded to ask the "killer question", are recognized for the quality of their science, and are well connected to the external scientific community and supported by experienced leaders with a record of good judgment*

Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework *Nature Reviews Drug Discovery* 13, 419–431 (2014) doi:10.1038/nrd4309

* Ringel, M., Tollman, P., Hersch, G. & Schulze, U. Does size matter in R&D productivity? If not, what does? *Nature Rev. Drug Discov.* **12**, 901–902 (2013).

The spirit



“We can judge our progress by the courage of our questions and the depth of our answers, our willingness to embrace what is true rather than what feels good.”

— Carl Sagan (1934-1996)

THE OPEN PROJECT (TOP)

- Vision

  Affordable and effective novel therapies discovered and developed based on all accessible, relevant data in a timely manner

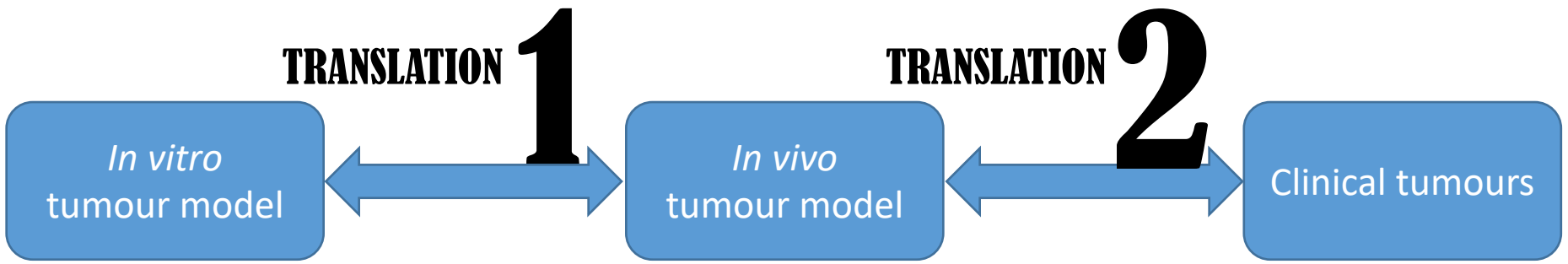
- Mission

  Pioneer in translational modelling to develop, validate and improve quantitative methods and tools for accurate experimental design to enable robust decision making in drug discovery and development

THE OPEN PROJECT (TOP)

- Participants
  - Open: Any one can join for free to share data, models, codes and ideas
  - Transparent: All results are properly documented to help the community
  - Meritocracy: Participants are required to demonstrate understanding of the code, rules, and culture of the project before being invited to join

Translational Oncology Modelling Goals



Challenges

Translation 1. *in vitro* efficacy <-> *in vivo* efficacy

- How do *in vitro* tumour models grow?

- How do *in vivo* tumour models grow?
  - Which rate law accurately recapitulates tumour growth?
  - Which rate law accurately predicts tumour growth?
- Can *in vivo* gene expression predict *in vivo* tumour growth?

Growth: Exchangeable with "response to treatments"

1. *In vitro data -> In vivo* design

	Exposure		Target Engagement		Disease Modulation		Outcome
In vitro	Medium	⟷	Direct / Indirect	⟷	DM	⟷	Efficacy
In vivo	Plasma Tissue	⟷	Direct / Indirect	⟷	DM	⟷	Efficacy
Clinical	Plasma		Direct / Indirect		DM		Efficacy

1

Objective: Define the necessary compound profile to fulfill PoM criterion

Value

- Project direction: A valid target compound profile to support PoM study
- Time saving: Shorter path to an *in vivo* experiment that demonstrates understanding of efficacy

Deliverables

- Target compound profile criteria
- Design of an *in vivo* experiment to demonstrate *in vivo* efficacy

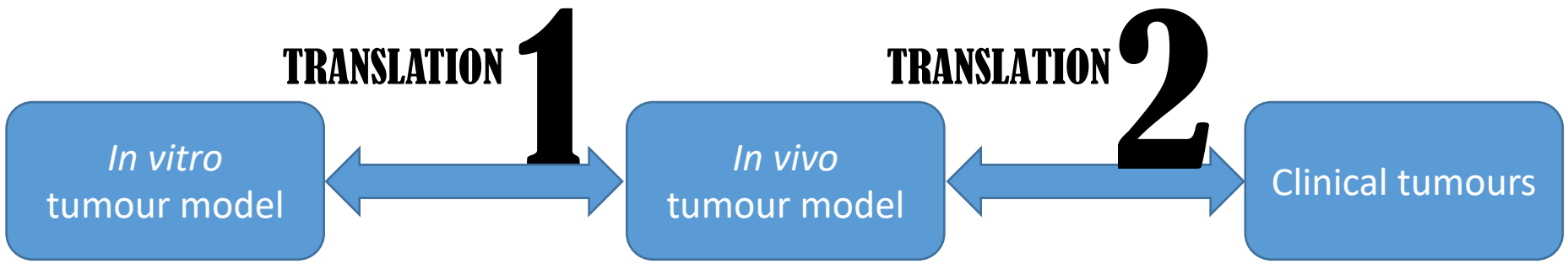
Triggering questions

- How would you forecast *in vivo* efficacy based on IC_{50} (*in vitro* potency)?
- Do your data confirm the therapeutic concept?

Information required

- *In vitro* Target Engagement markers
- *In vitro* Disease Modulation marker
- Modelling that predicts *in vivo* efficacy based on *in vitro* efficacy

Translational Oncology Modelling Goals



Challenges

Translation 2. *in vivo* efficacy <-> clinical efficacy

- How do clinical tumours respond?
- Can *in vivo* tumour models forecast clinical tumour responses?

2. Clinical data -> *In vivo* design

	Exposure	Target Engagement	Disease Modulation	Outcome
In vitro	Medium	Direct / Indirect	DM	Efficacy
In vivo	Plasma Tissue	Direct / Indirect	DM	Efficacy
Clinical	Plasma	Direct / Indirect	DM	Efficacy

Information required

- Competitor/combination compounds
  - PK/PD information of tumour models
  - Clinical popPK
- Own compound
  - Preclinical PK/PD/Efficacy data
  - Forecasted clinical PK

Objective: Define and support PoC strategy (phases 1-2)

Value

- Project direction: A valid target compound profile supported by clinical evidence
- Time saving: Shorter path to an *in vivo* experiment supporting clinical feasibility

Deliverables

- Identify clinical efficacious doses and optimal dosing schedule for the (combination) treatment
- Identify the best clinical combination partner

3. *In vivo* data -> Clinical design

	Exposure	Target Engagement	Disease Modulation	Outcome
In vitro	Medium	Direct / Indirect	DM	Efficacy
In vivo	Plasma Tissue	Direct / Indirect	DM	Efficacy
Clinical	Plasma	Direct / Indirect	DM	Efficacy

1

2

3

Information required

- *In vitro* and *in vivo* Target Engagement marker
- *In vitro* and *in vivo* Disease Modulation marker
- Preclinical TGI data
- Clinical tumour imaging data (RECIST criteria)
- Forecast clinical PK

Objectives: Define PoP criterion (phase 1)

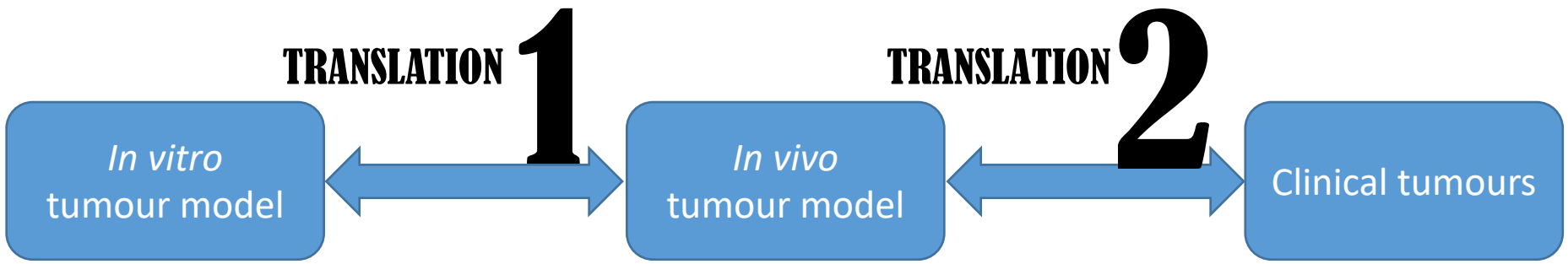
Benefit

- Project direction: A valid clinical biomarker experiment design supported by preclinical science
- Time saving: The right experiment indicating signs of clinical efficacy at the first time

Deliverables

- Forecast clinical PK
- Target clinical modulation of TE (i.e. minimum TE that is needed to modulate disease)
- Recommended timing of biopsy to assess TE

Translational Oncology Modelling Goals



Challenges we tackle here

- How do *in vivo* tumour models grow?
  - Which rate law accurately recapitulates tumour growth?
  - Which rate law accurately predicts tumour growth?
- Can *in vivo* gene expression predict *in vivo* tumour growth?

2. *IN VIVO* TUMOUR GROWTH RATE LAWS

- Which rate law accurately recapitulates tumour growth?
- Which rate law accurately predicts tumour growth?

THE BACKGROUND

Tumour Growth Rate Laws

- Linear
  - Tumour radius expands linearly
  - TV is used for fitting for consistent error model: $TV = \frac{4}{3}\pi(r_0 + g * t)^3$
- Exponential
  - $TV = TV_0 e^{at}$
- Exponential-linear: incompatible with tumour that shrinks
  - $\frac{dV}{dt} = a_0 V, t \leq \tau; \frac{dV}{dt} = a_1, t > \tau$. V is smooth: $\tau = \frac{1}{a_0} log\left(\frac{a_1}{a_0 V_0}\right)$
- Logistic
  - $\frac{dV}{dt} = aV\left(1 - \frac{V}{K}\right)$ a: growth rate (/day); K: carrying capacity (mm^3)
- Gompertz
  - $\frac{dV}{dt} = \alpha e^{-\beta t} V$ α: growth rate (/day); β: decay rate (/day)

Linear (actually cubic) growth

- Tumour radius expands linearly: $TV = \frac{4}{3}\pi(r_0 + g * t)^3$
- First proposed by Mayneord in 1932
- Assumption: Solid tumour growth is limited to a thin surface layer of cells (competition for space, not nutrients)
- Notable data that "support" the model:
  - Jensen's rat sarcoma: n=8
  - Walker rat tumour: n=5
  - *In vitro* cell colonies with proliferating rim: n=15
  - Cell line derived xenografts: n=16
  - Clinical untreated low-grade gliomas: n=27

Mayneord, W.V. (1932) On a law of growth of Jensen's rat sarcoma. Am. J. Cancer 16, 841–846

Schrek, R. (1935) A quantitative study of the growth of the Walker rat tumor and the Flexner–Jobling rat carcinoma. *Am. J. Cancer* 24, 807–822

Brú, A. *et al.* (2003) The universal dynamics of tumor growth. Biophys. J. 85, 2948–2961

Mandonnet, E. *et al*. (2003) Continuous growth of mean tumor diameter in a subset of grade II gliomas. Ann. Neurol. 53, 524–528

Exponential growth

- $TV = TV_0 e^{at}$ with doubling time $\ln(2)/a$
- First proposed by Collins in 1956
- Assumption: Tumour cell doubling time is constant
- Notable clinical data that "support" the model:
  - Soft tumour: L1210 leukemia in 1970
  - Solid tumours (sometime restricted to the initial period):
    - Untreated breast cancer: n=12
    - Primary pulmonary malignancies: n=41
    - Pulmonary metastases from various primary tumours: n=118
    - Pulmonary metastases from mesenchymal malignancies: n=16
    - Renal cell carcinomas: n=16

Collins, V.P. *et al*. (1956) Observations on growth rates of human tumors. Am. J. Roentgenol. *Radium Ther. Nucl. Med.* 76, 988–1000

Shackney, S.E. (1970) A computer model for tumor growth and chemotherapy, and its application to l1210 leukemia treated with cytosine arabinoside (nsc-63878). *Cancer Chemother. Rep.* 54, 399–429

Friberg, S. and Mattson, S. (1997) On the growth rates of human malignant tumors: implications for medical decision making. *J. Surg. Oncol*. 65, 284–297

Exponential-linear

- Exponential-linear: incompatible with tumour that shrinks
  - $\frac{dV}{dt} = a_0 V, t \leq \tau; \frac{dV}{dt} = a_1, t > \tau$. V is smooth: $\tau = \frac{1}{a_0} log\left(\frac{a_1}{a_0 V_0}\right)$
  - Simeoni model approximates the original model

$$\frac{dw(t)}{dt} = \frac{\lambda_0 \cdot w(t)}{\left[1 + \left(\frac{\lambda_0}{\lambda_1} \cdot w(t)\right)^{\Psi}\right]^{1/\Psi}}$$

$$w(0) = w_0$$

$$\Psi = 20$$

  - Popular among PK/PD community
- Notable data that "support" the model:
  - Various types of CDX tumour: n=30

Simeoni, M *et al*. (2004) Pharmacokinetic-Pharmacodynamic Modeling of Tumor Growth Kinetics in Xenograft Models after Administration of Anticancer Agents. *Cancer Research*. 64, 1094 – 1101

Logistic growth

- $\frac{dV}{dt} = aV\left(1 - \frac{V}{K}\right)$ a: growth rate (/day); K: carrying capacity (mm^3)
- First proposed by Robertson in 1923
- Assumption: Solid tumour growth is limited to a finite size
- Notable data that "support" the model:
  - Breast cancer: n=433

Robertson, T.B. (1923) The Chemical Basis of Growth and Senescence. J.B. Lippincott & Co.

Gompertz growth

- $\frac{dV}{dt} = \alpha e^{-\beta t} V$ α: growth rate (/day); β: decay rate (/day)
- First proposed by Casey in 1934
- Assumption: Diffusion and competition for nutrients / tumour self-seeding
- Notable data that "support" the model:
  - *In vivo* animal tumours: n=19
  - B-16 melanoma: n=8; 13762 carcinoma: n=10
  - Breast cancer patients: n=250

Klein, G. and Revesz, L. (1953) Quantitative studies on the multiplication of neoplastic cells in vivo. I. growth curves of the Ehrlich and mc1m ascites tumors. J. Natl. Cancer Inst. 14, 229–277

Norton L *et al*. (1976) Predicting the course of Gompertzian growth. *Nature* **264:** 542–545

Norton, L. (1988) A Gompertzian model of human breast cancer growth. Cancer Res. 48, 7067–7071

Exceptions

- Spontaneous regression
- No growth
- Irregular growth rates
- Accelerations of growth

Friberg, S. and Mattson, S. (1997) On the growth rates of human malignant tumors: implications for medical decision making. *J. Surg. Oncol*. 65, 284–297

Goals

- Which rate laws accurately recapitulate tumour growth?
  - Parametric inference: DATA + MODEL STRUCTURE → PARAMETRIC DISTRIBUTION
  - Interpolation: Models are often used to make interpolated predictions

- Which rate laws accurately predict tumour growth?
  - Extrapolation: future tumour growth
  - Good inference is necessary but not sufficient for good prediction
  - Uncertainty in model structure

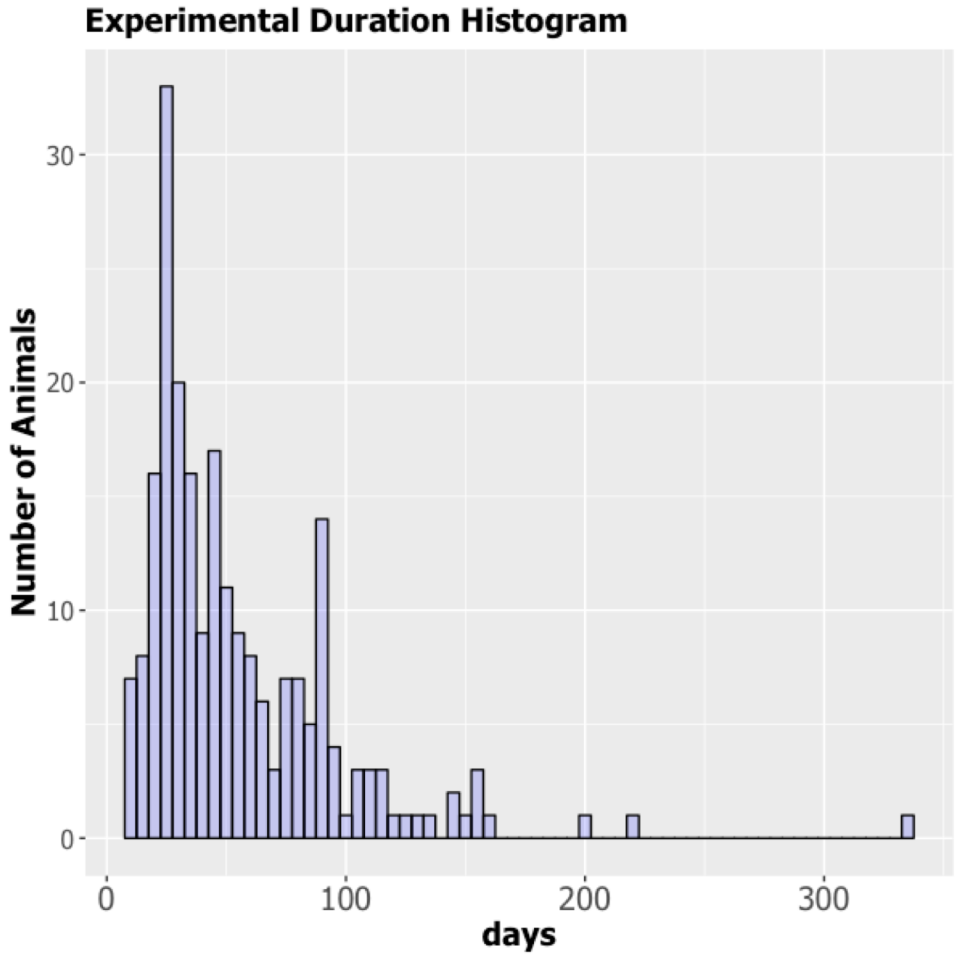
beyond
a cut above

THE DATA

Novartis Mouse Clinical Trial

PDX control experiment overview

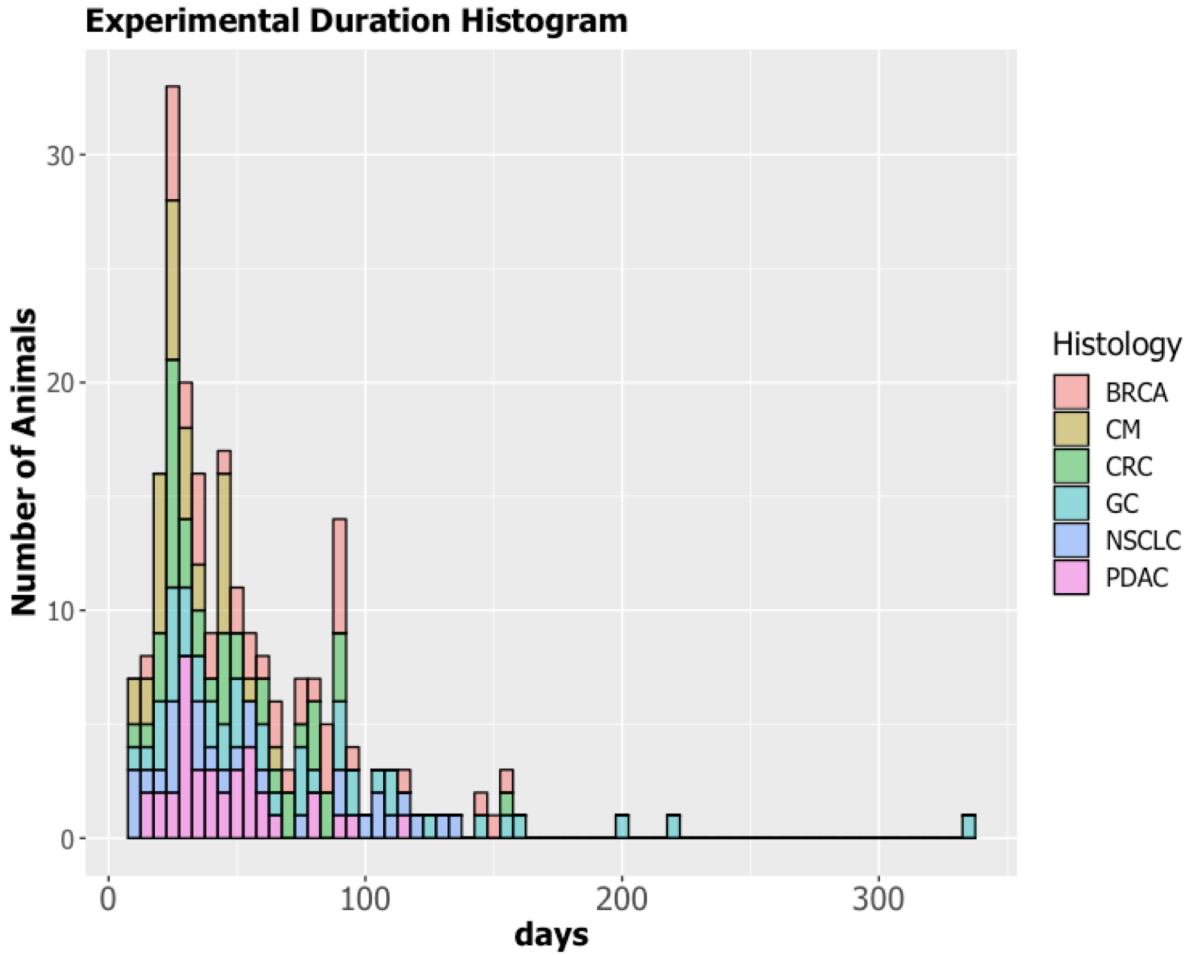
- 224 PDX's in total
- Most control experiments are less than 100 days
- First peak: 15-20 days
- Second peak: 85-90 days



Novartis Mouse Clinical Trial

PDX control experiment by histology

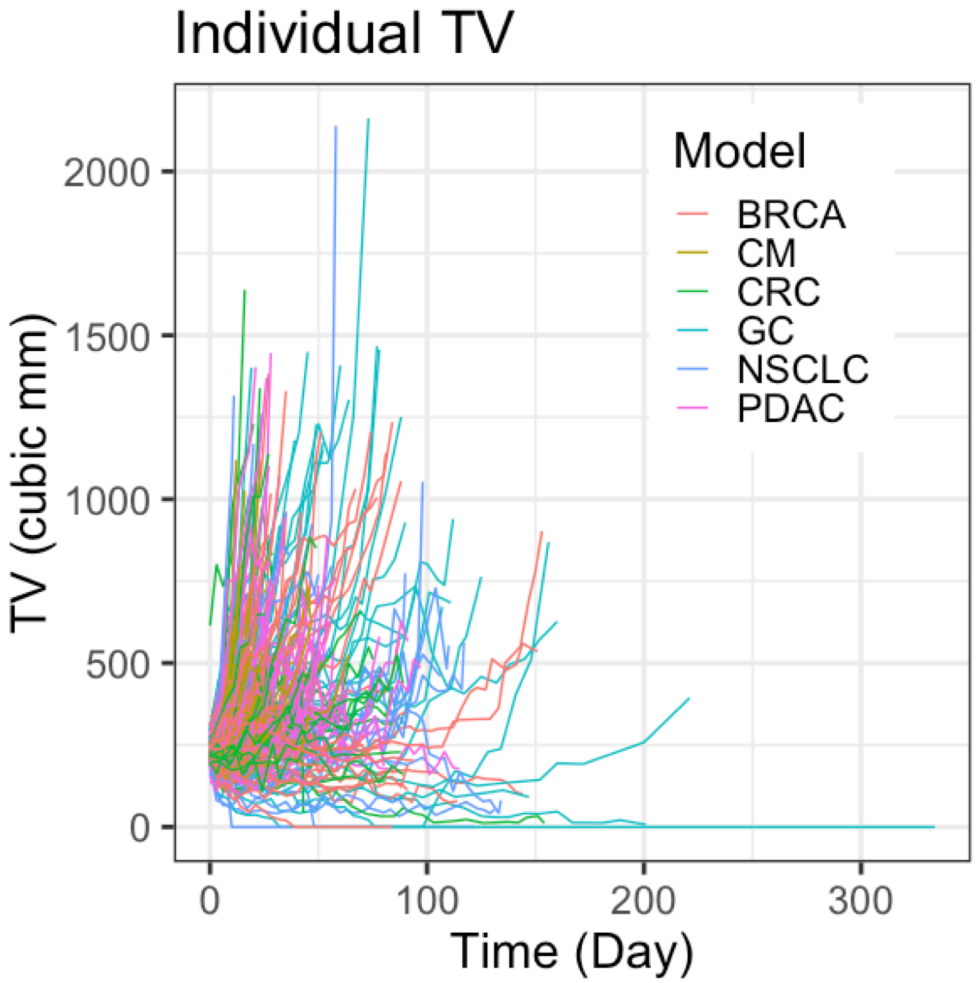
- Histology
  - GC (gastric) 44
  - CRC (colorectal) 42
  - BRCA (breast) 39
  - NSCLC (non-small cell lung) 29
  - PDAC (panc duct adeno) 37
  - CM (cutaneous melanoma) 33
- Experimental duration distribution
  - Similar across histology
- Second peak (85-90 days):
  - BRCA
  - CRC
  - GC
- All CM experiments ≤ 64 days



Novartis Mouse Clinical Trial

PDX control experiment overview

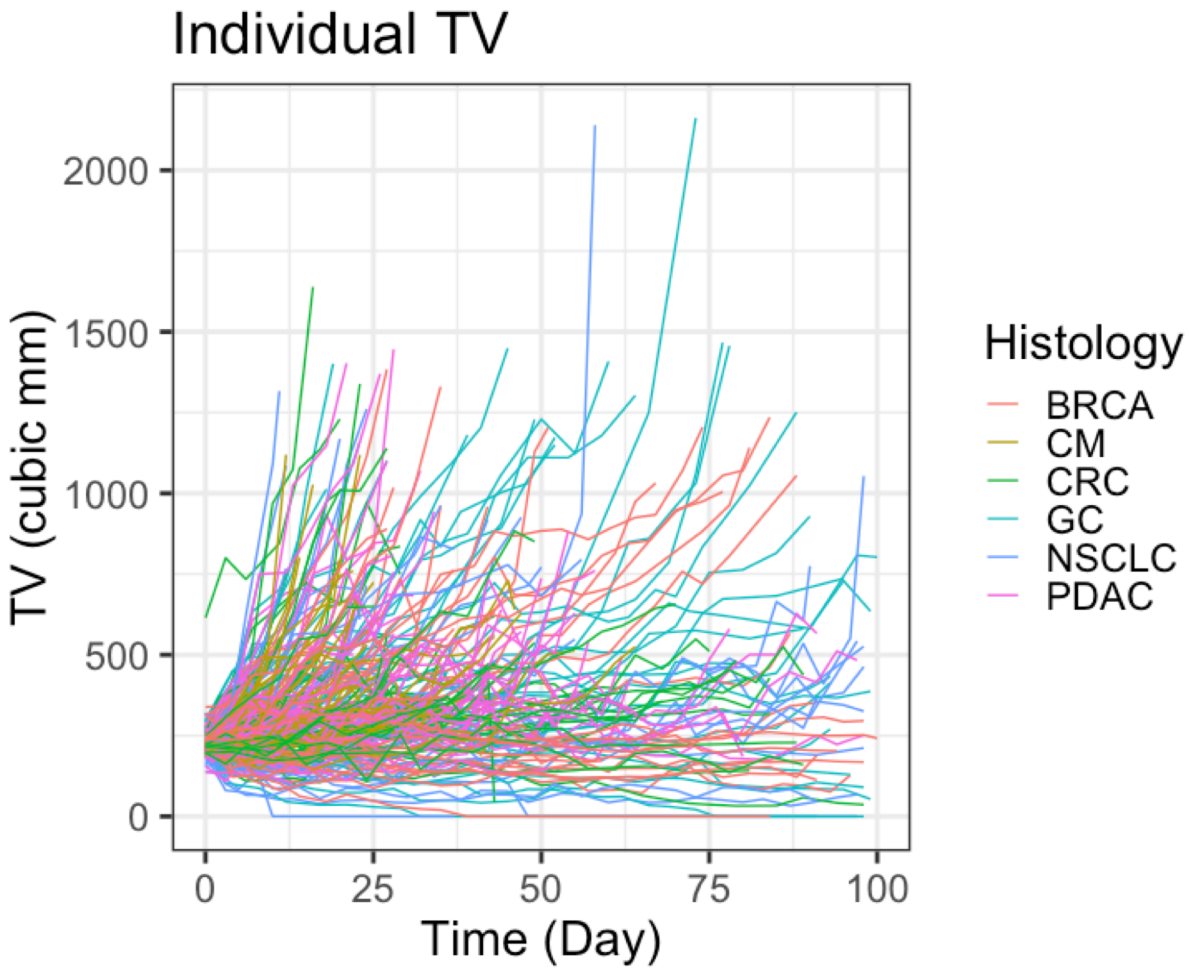
- Starting volume
  - 100~300mm^3
- Exceptions
  - Spontaneous regression: Yes
  - No growth: Yes
  - Irregular growth rates: Maybe
  - Accelerations of growth: Morphological or genetic adaptation?



Novartis Mouse Clinical Trial

PDX control experiment overview

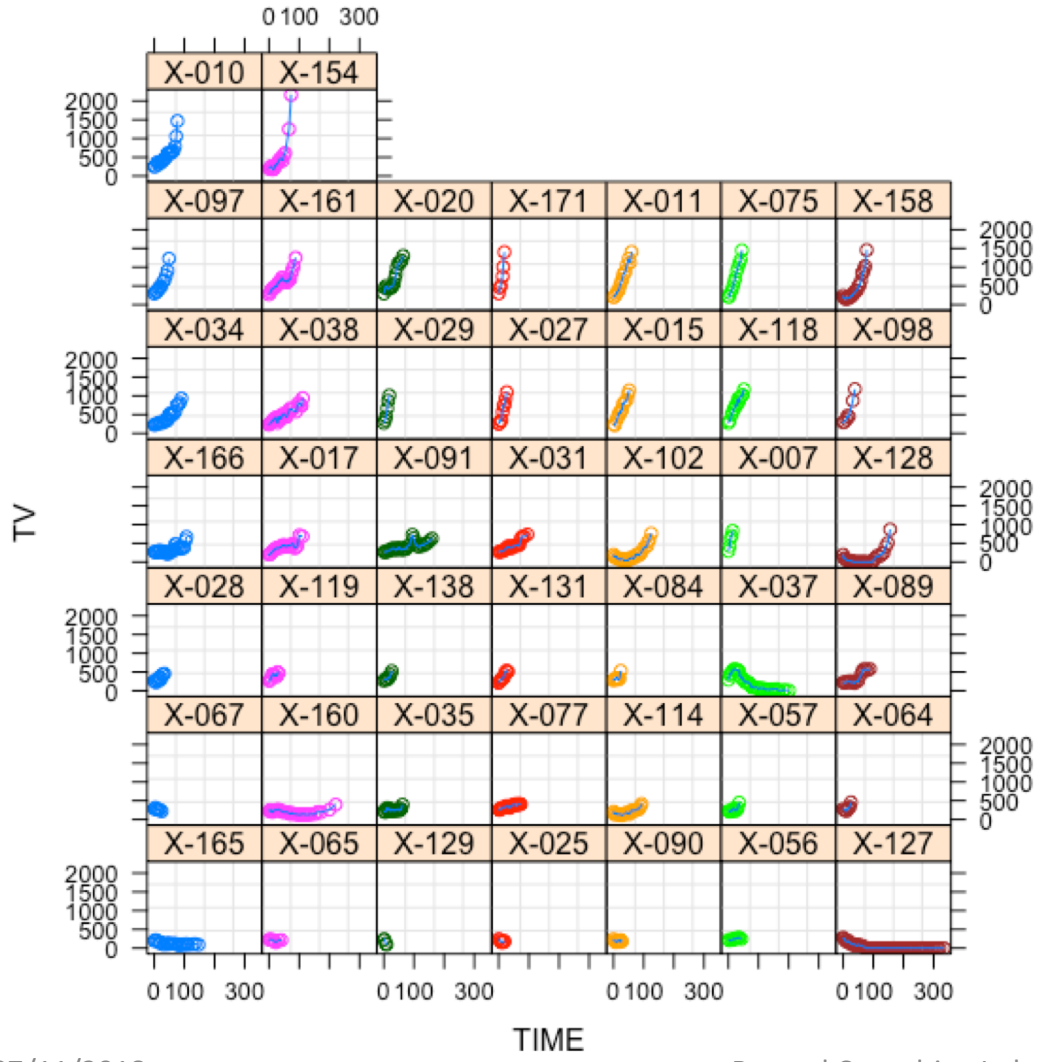
- Growth (day 0~100)
  - Tumour growth varies by histology?
  - Hard to tell from this plot
  - See each histology next



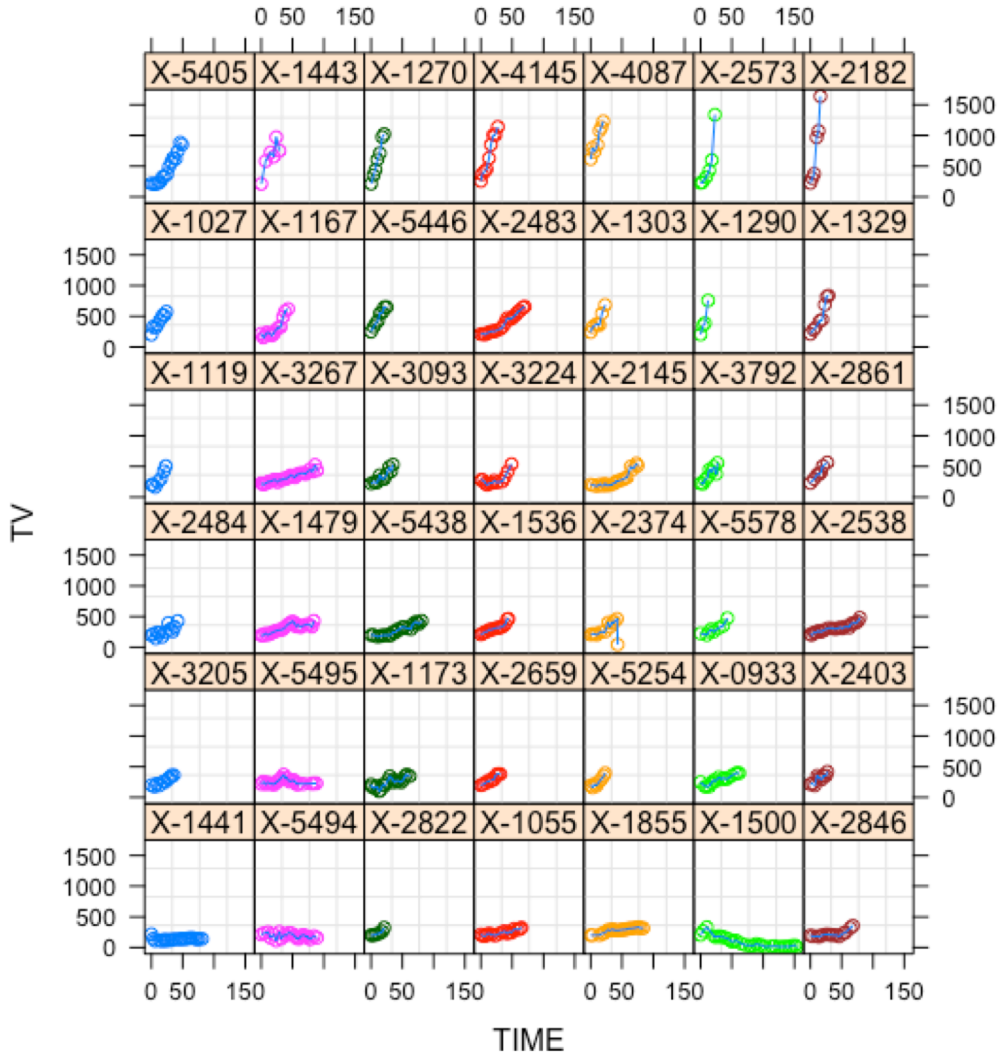
PDX control experiments

X: PDX number

GC



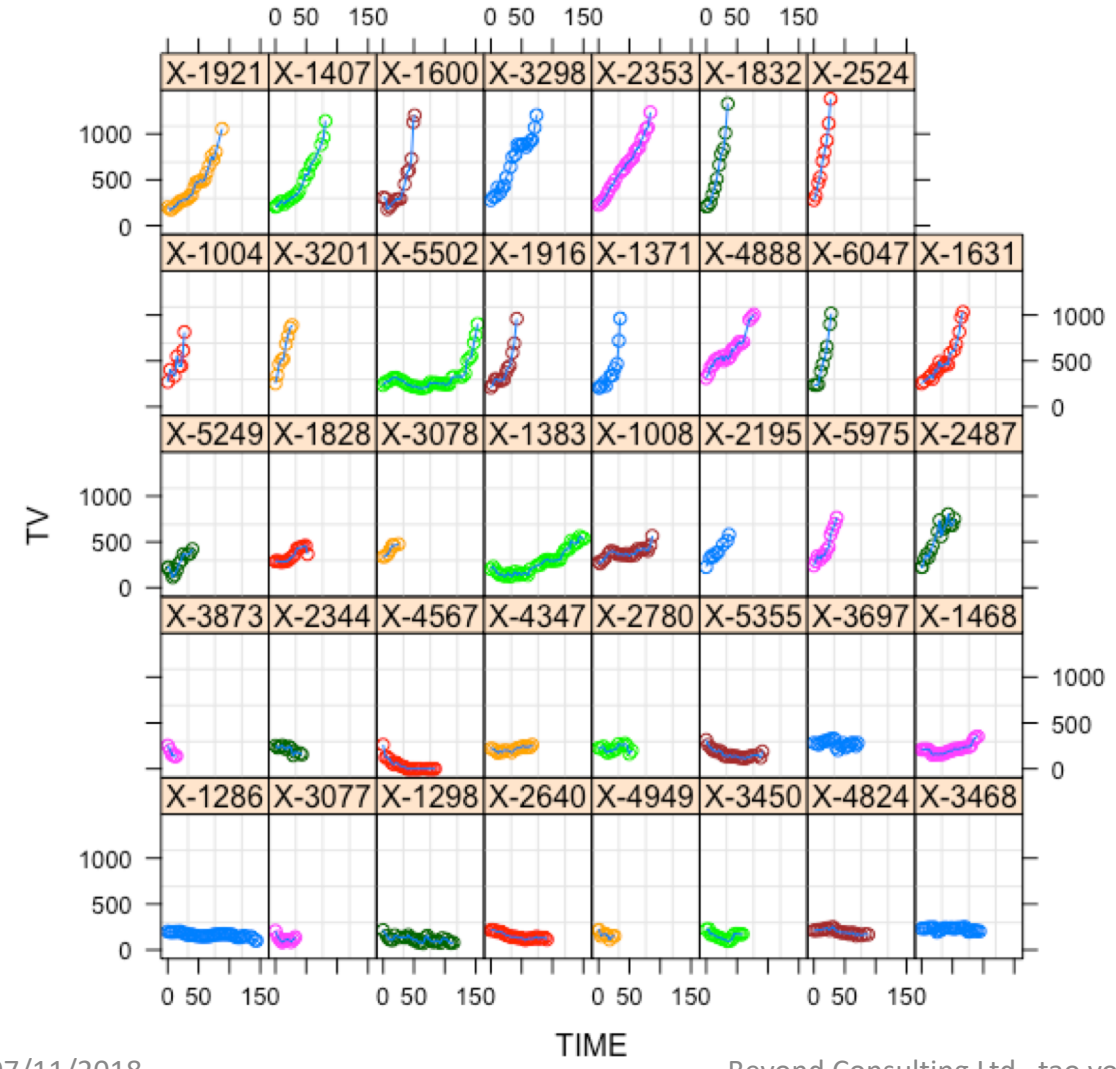
CRC



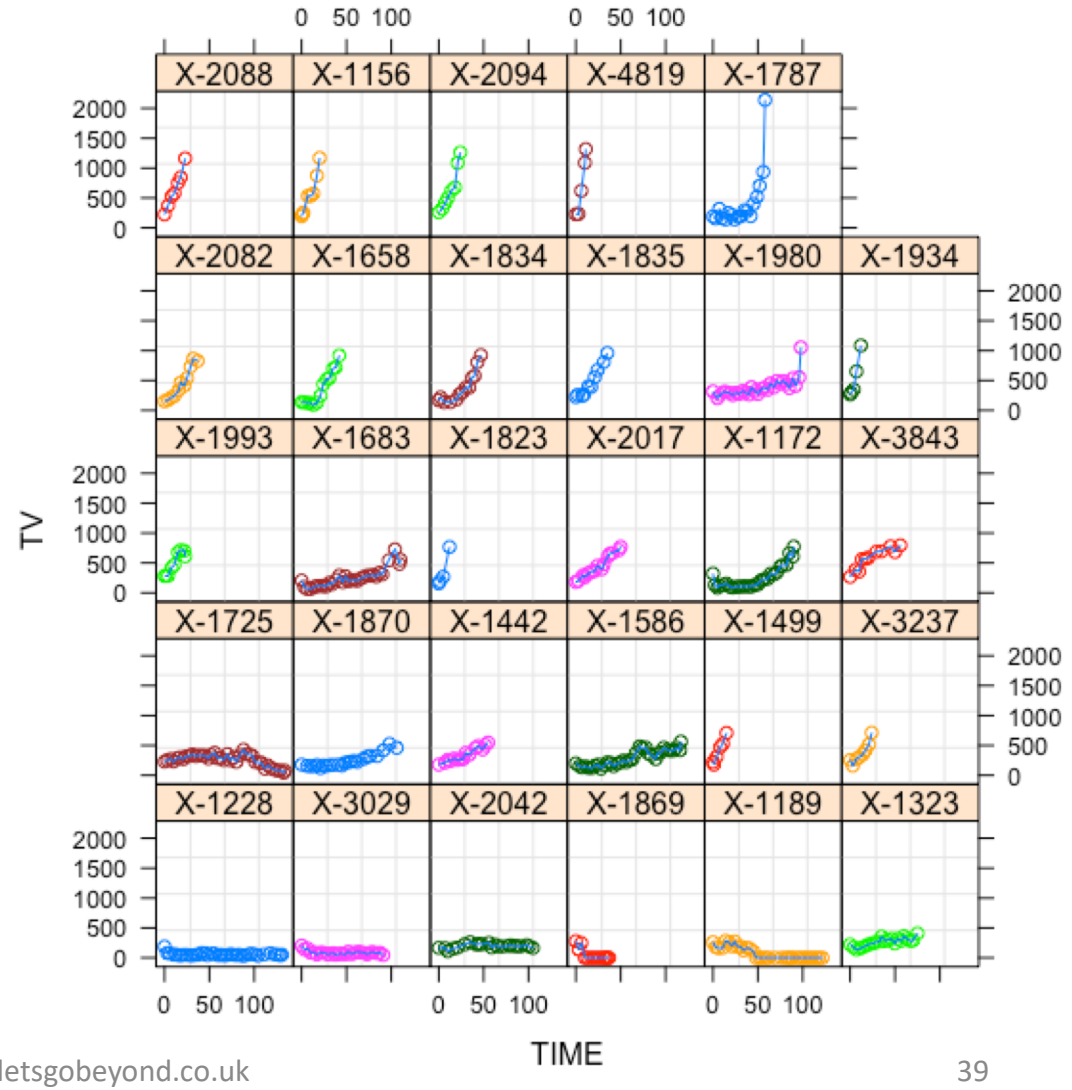
PDX control experiments

X: PDX number

BRCA



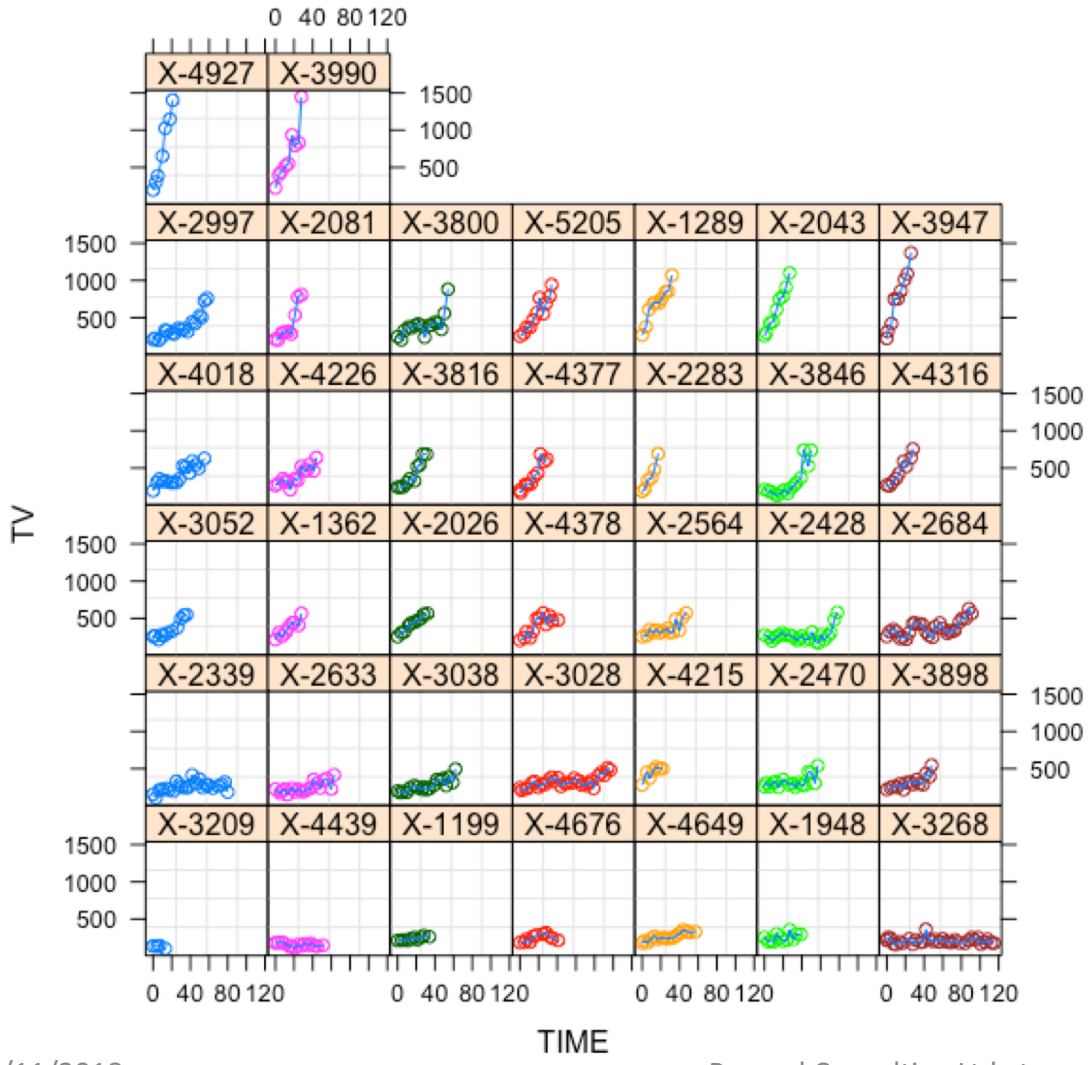
NSCLC



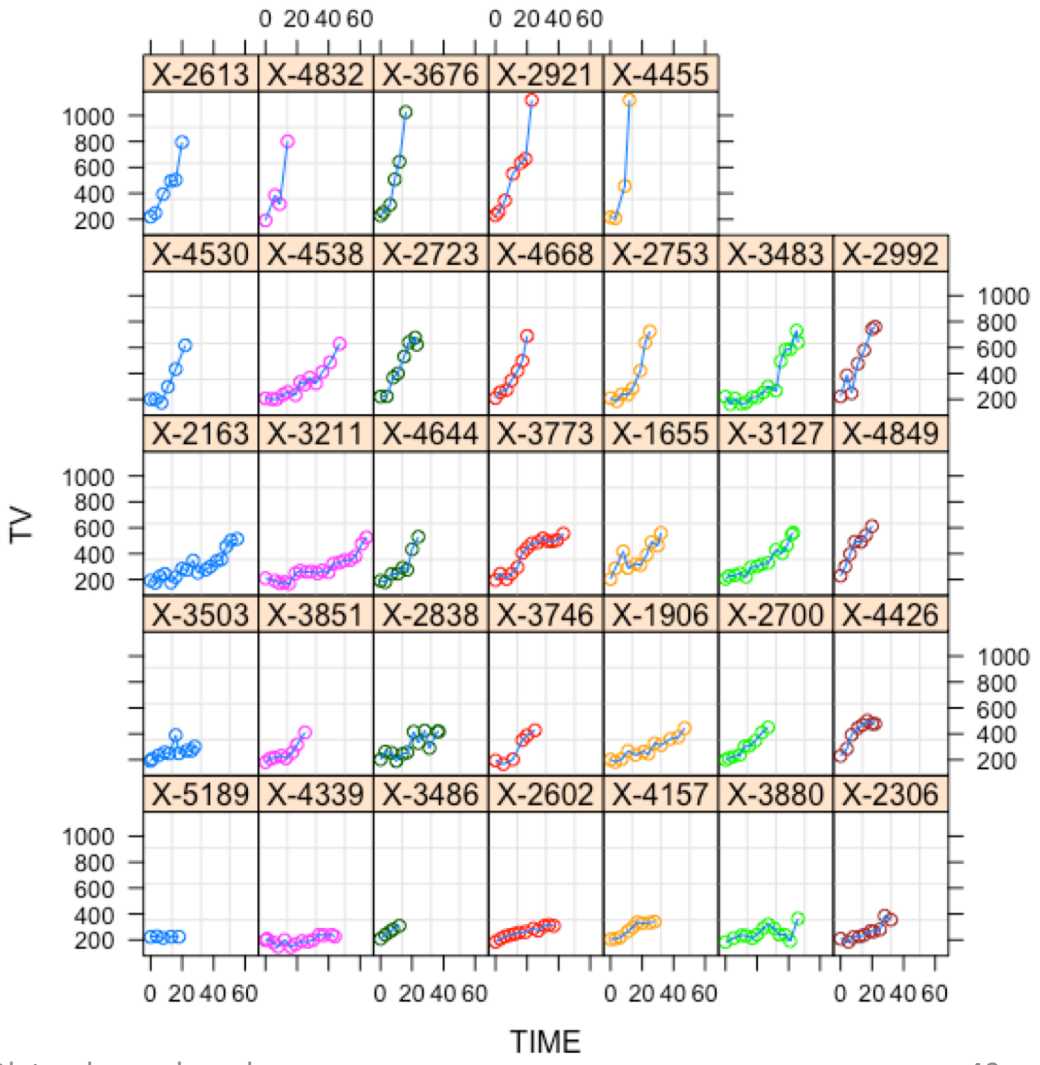
PDX control experiments

X: PDX number

PDAC



CM



WHICH RATE LAW ACCURATELY RECAPITULATES TUMOUR GROWTH?

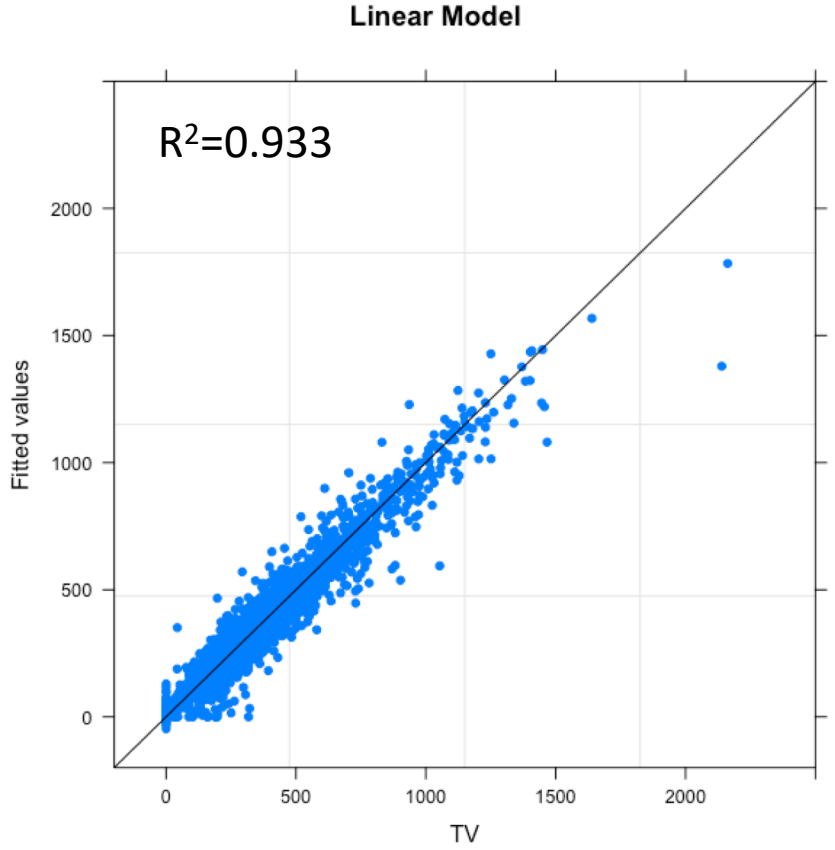
Linear model fits well

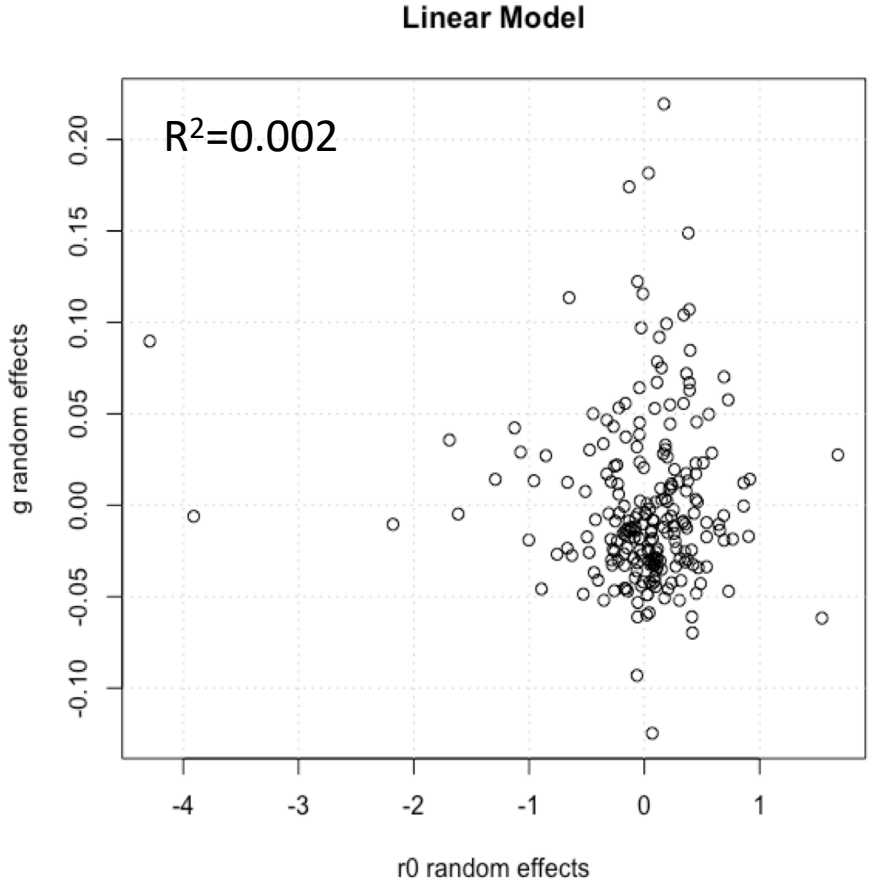
- Fixed: r_0, g; Random: diag(r_0, g)

	Value	Std. Error	DoF	t-value	P-value
r_0	3.6	0.043	3160	84	0
g	0.041	0.0032	3160	13	0

$$TV = \frac{4}{3}\pi(r_0 + g * t)^3$$

Fitting by NLME in R:
TV_0 = 200 mm^3
g = 0.041 mm/day





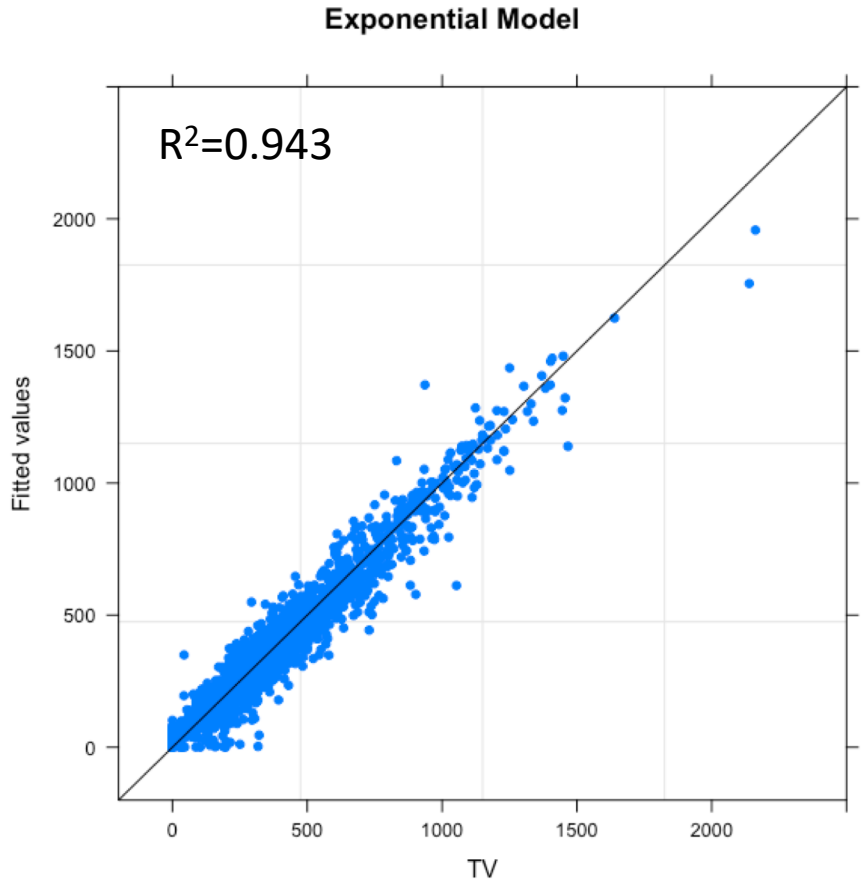
Exponential model fits well

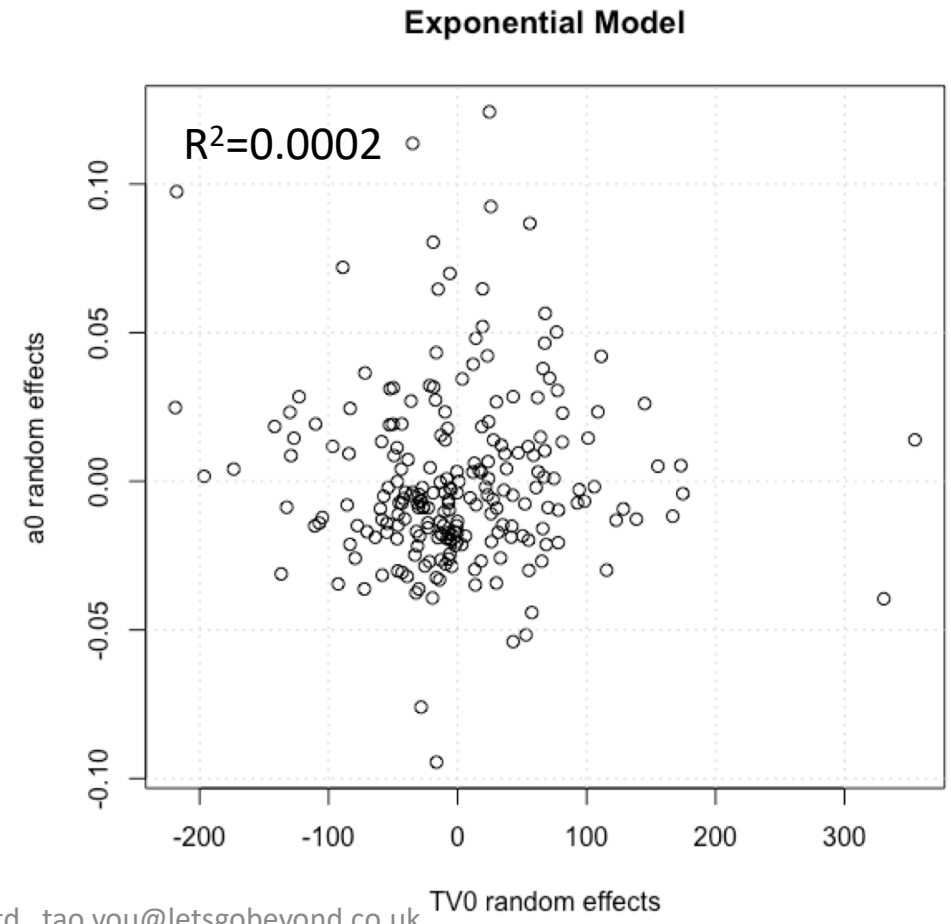
- Fixed: TV_0, a; Random: diag(TV_0, a)

$$TV = TV_0 e^{at}$$

	Value	Std. Error	DoF	t-value	P-value
TV_0	220	5.4	3160	41	0
a	0.026	0.0020	3160	13	0

Fitting by NLME in R:
TV_0 = 220 mm^3
a = 0.026





Exponential-linear model was actually just exponential

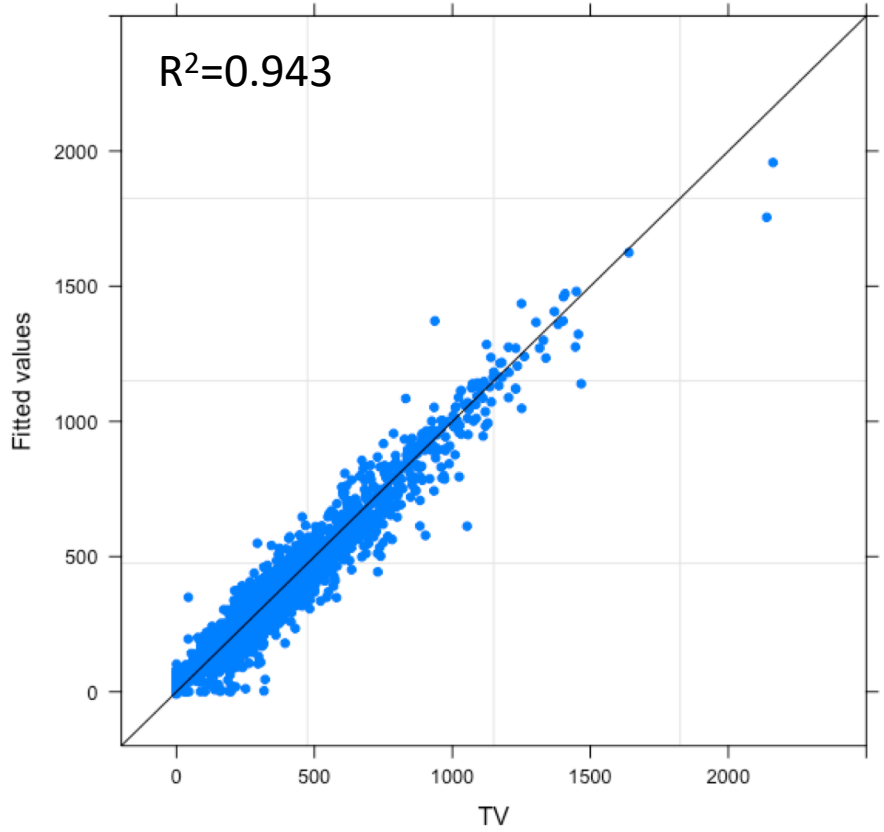
- Fixed: TV_0, a_0, $\boldsymbol{\tau}$; Random: diag(TV_0, a_0)

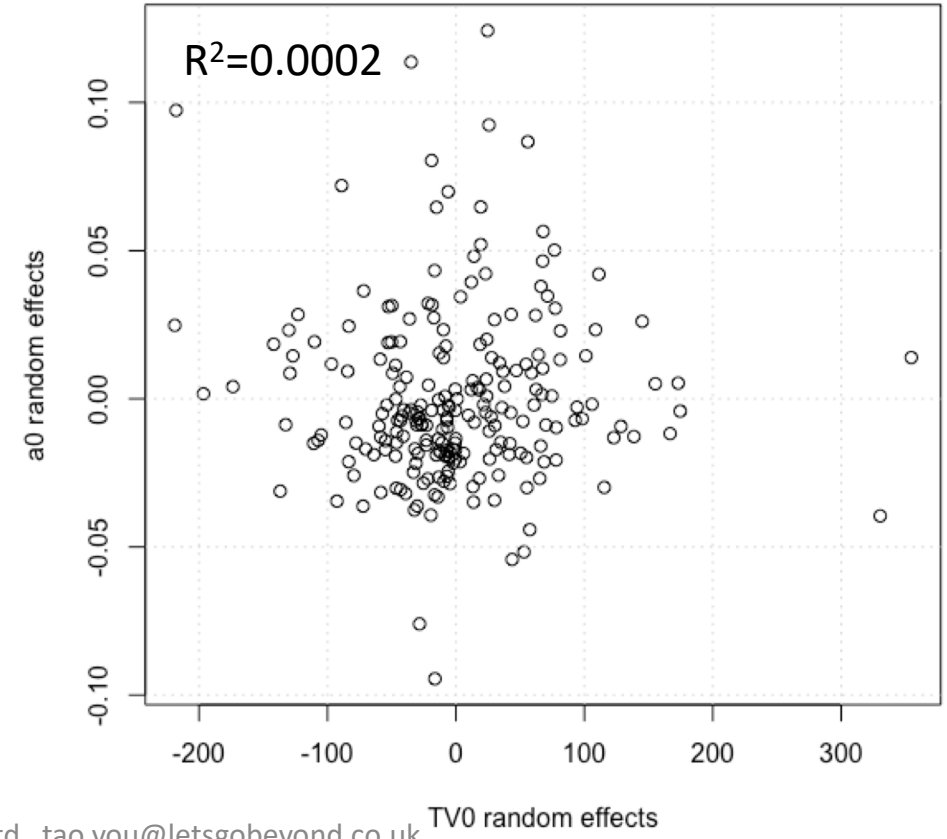
	Value	Std. Error	DoF	t-value	P-value
TV_0	220	5.4	3159	41	0
a_0	0.026	0.0020	3159	13	0
$\boldsymbol{\tau}$	280	8600	3159	0.032	0.97

$\frac{dV}{dt} = a_0 V, t \leq \tau; \frac{dV}{dt} = a_1, t > \tau$. V is smooth: $\tau = \frac{1}{a_0} log\left(\frac{a_1}{a_0 V_0}\right)$

Fitting by NLME in R :
TV_0 = 220 mm^3
a = 0.026
$\boldsymbol{\tau}$: Not sure

This fitting is based on all tumours. Looking at each histology may lead to different results.





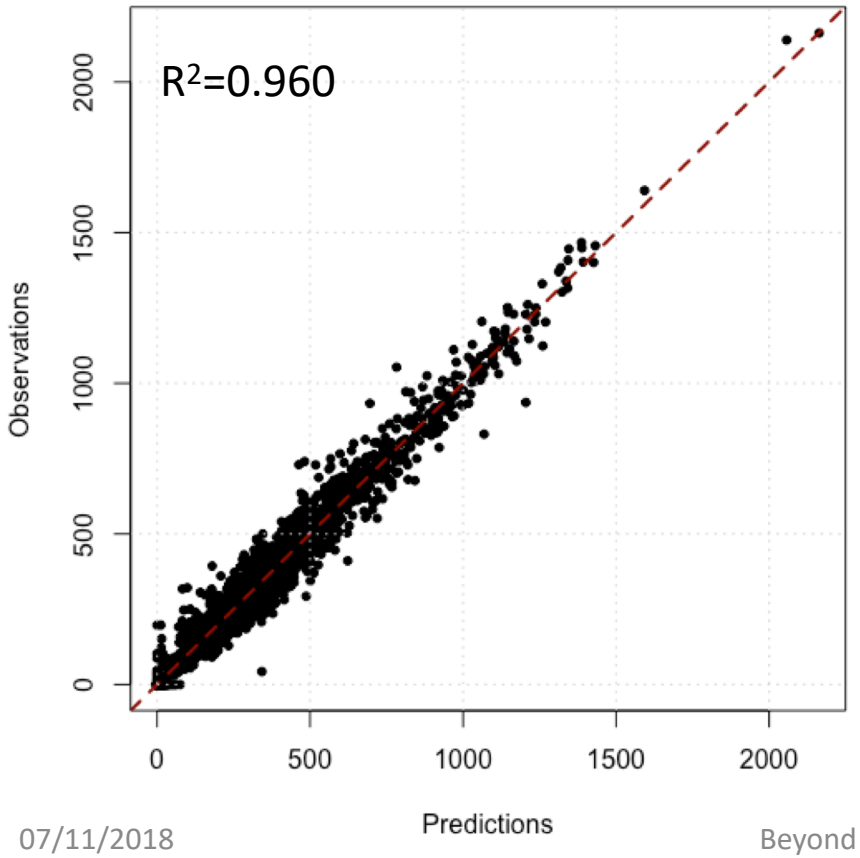
Logistic model fits well using SAEMIX

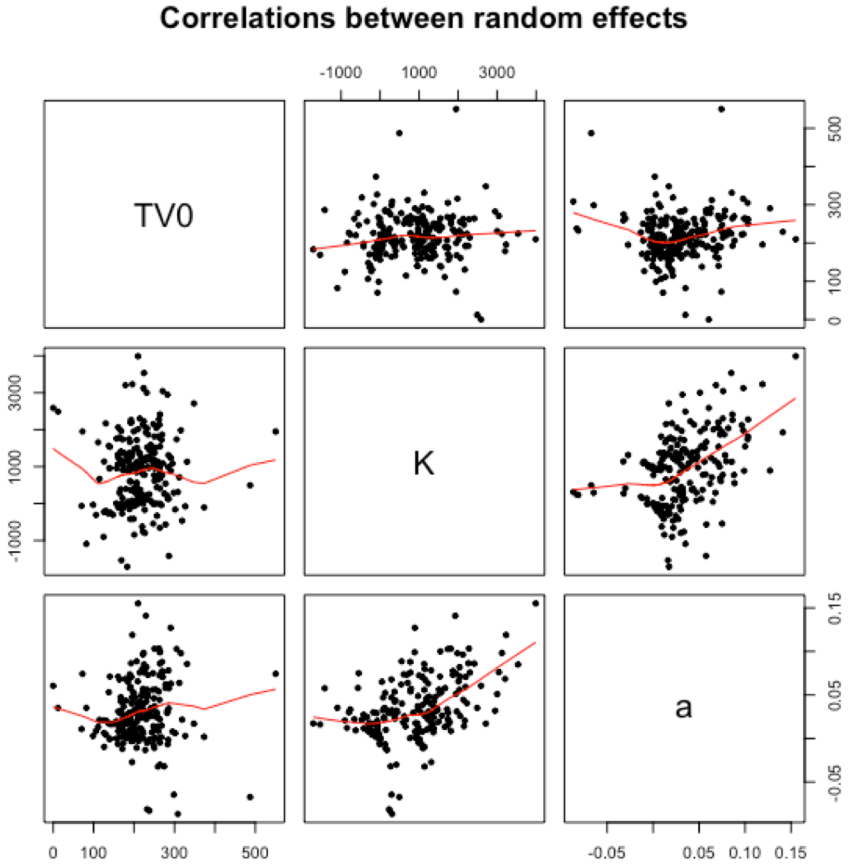
- Fixed: TV_0, K, a; Random: diag(TV_0 , K, a)

$$\frac{dV}{dt} = aV\left(1 - \frac{V}{K}\right)$$ a: growth rate (/day); K: carrying capacity (mm^3)

	Value	Std. Error	CV(%)
TV_0	220	4.7	2.2
K	950	160	16
a	0.032	0.0029	9.0

Fitting looks OK. Random effects not correlated
Logistic model can recapitulate all PDX's





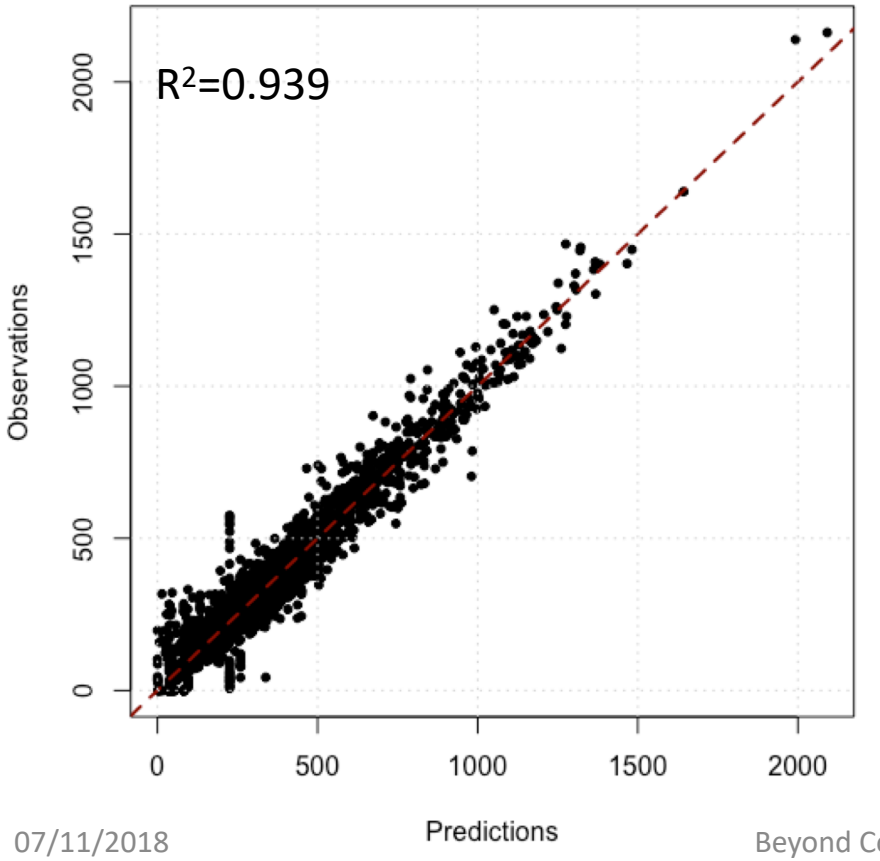
Gompertz model was actually just exponential

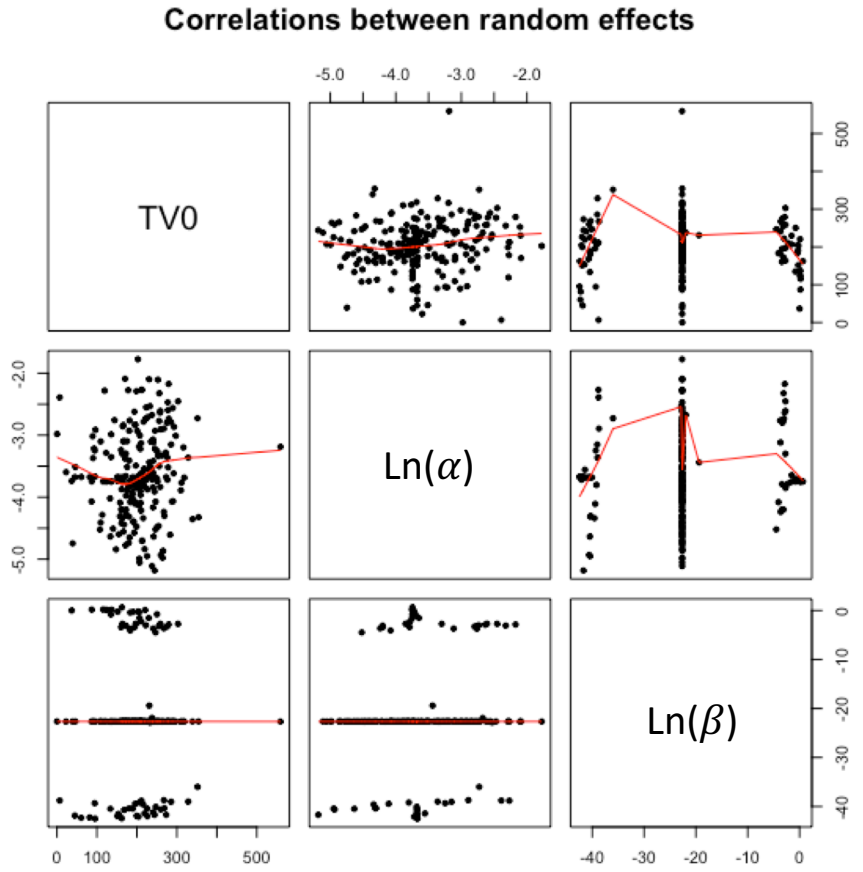
- Fixed: TV_0, α, β; Random: diag(TV_0+α+β)

$\frac{dV}{dt} = \alpha e^{-\beta t} V$ α: growth rate (/day); β: decay rate (/day)

	Value	Std. Error	CV(%)
TV_0	210	5.0	2.4
Ln(α)	-3.7	0.059	1.6
Ln(β)	-22.7	2.8	12

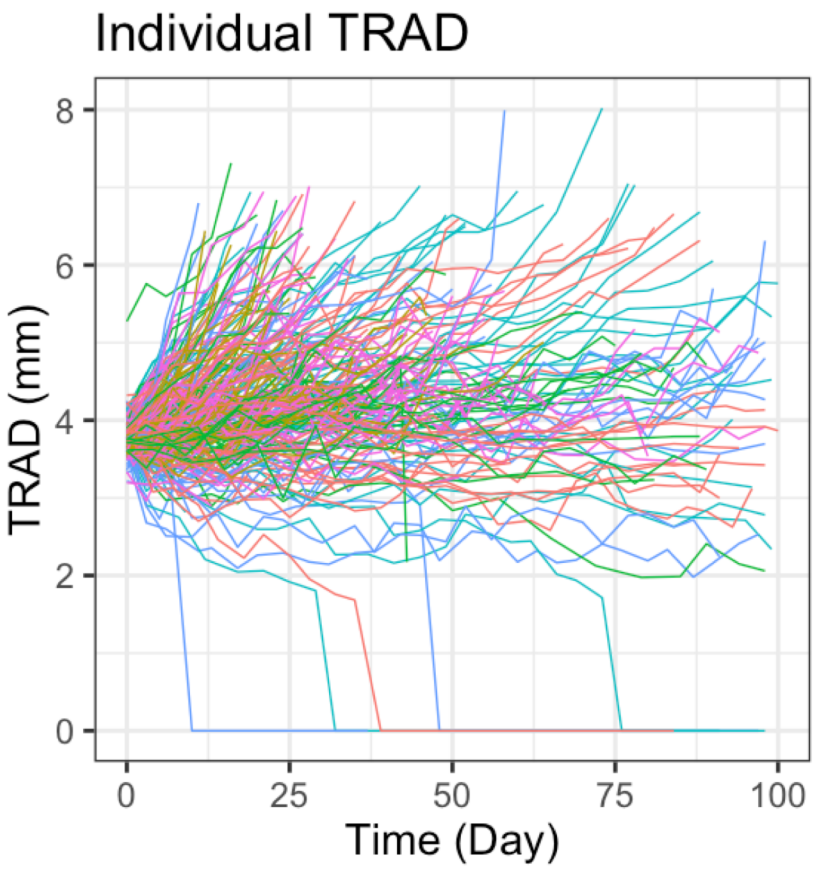
Fitting by SAEMIX: β is close to zero. Random effects not correlated. Gompertz reduced to exponential.

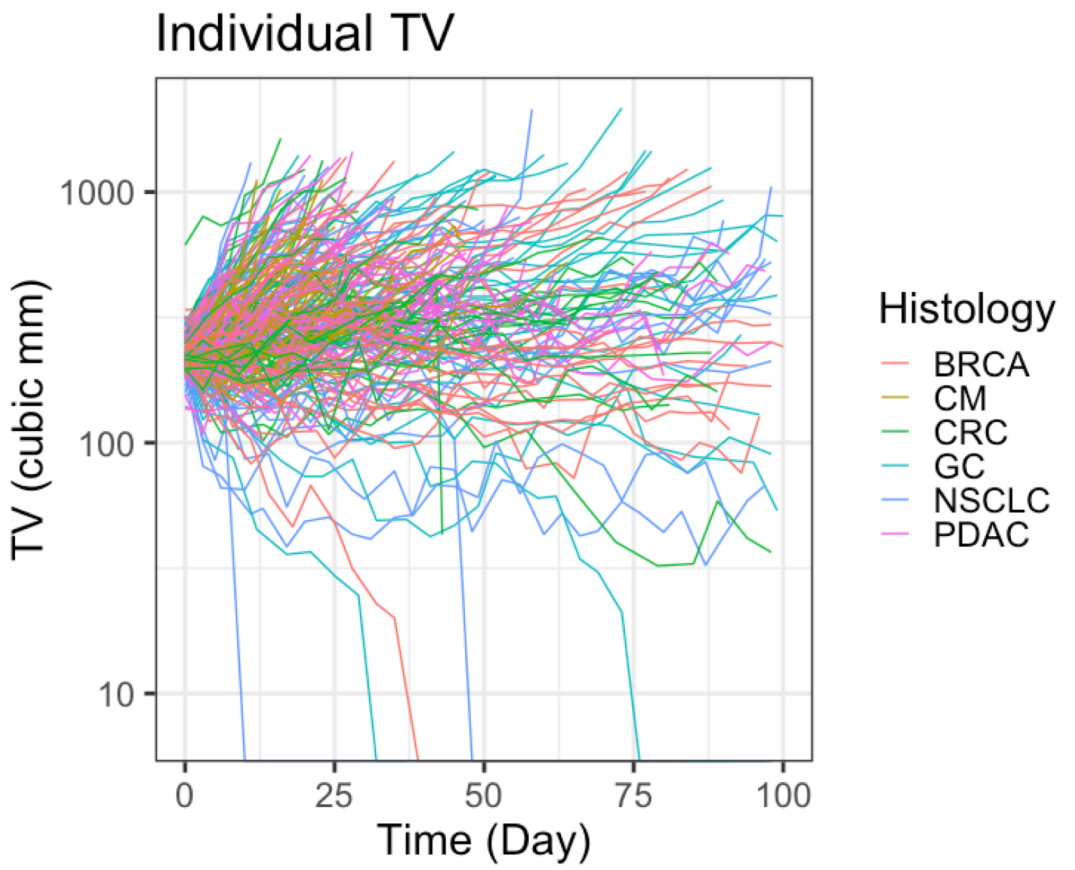




All rate laws accurately recapitulate control PDX growth

- Parametric inferences were successful
- Exponential-linear, logistic and Gompertz reduced to exponential model
- Essentially only two types of dynamics: linear and exponential



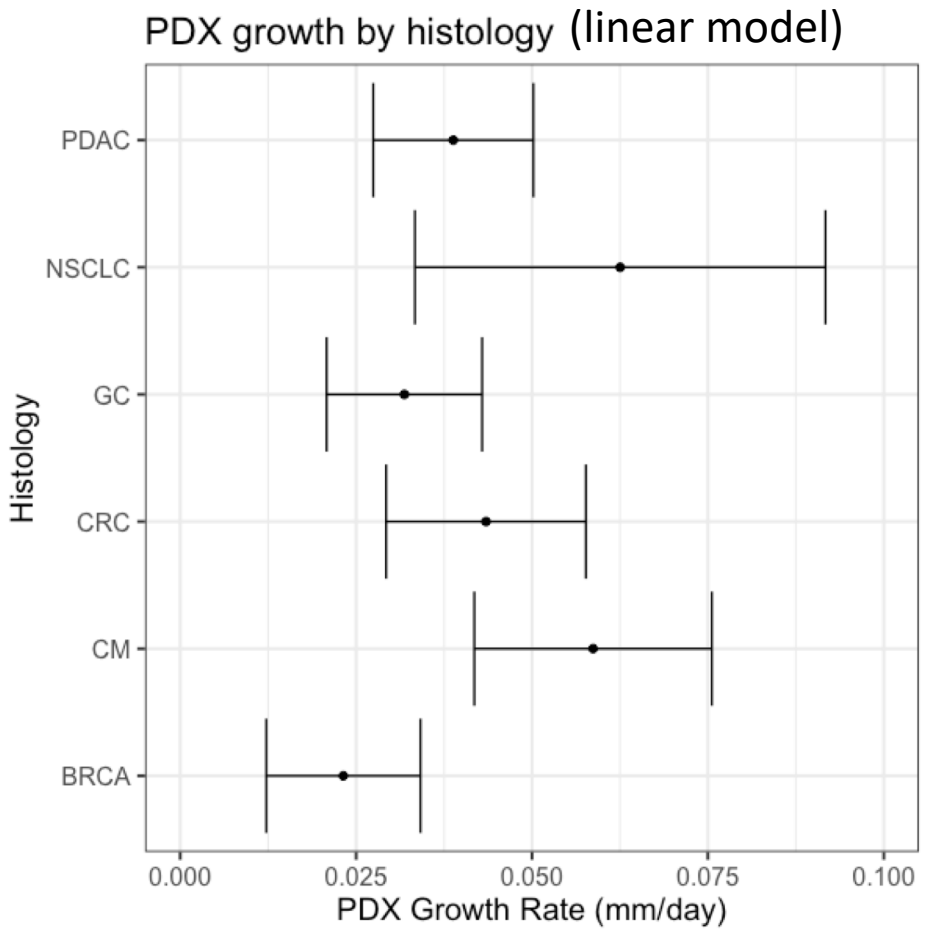


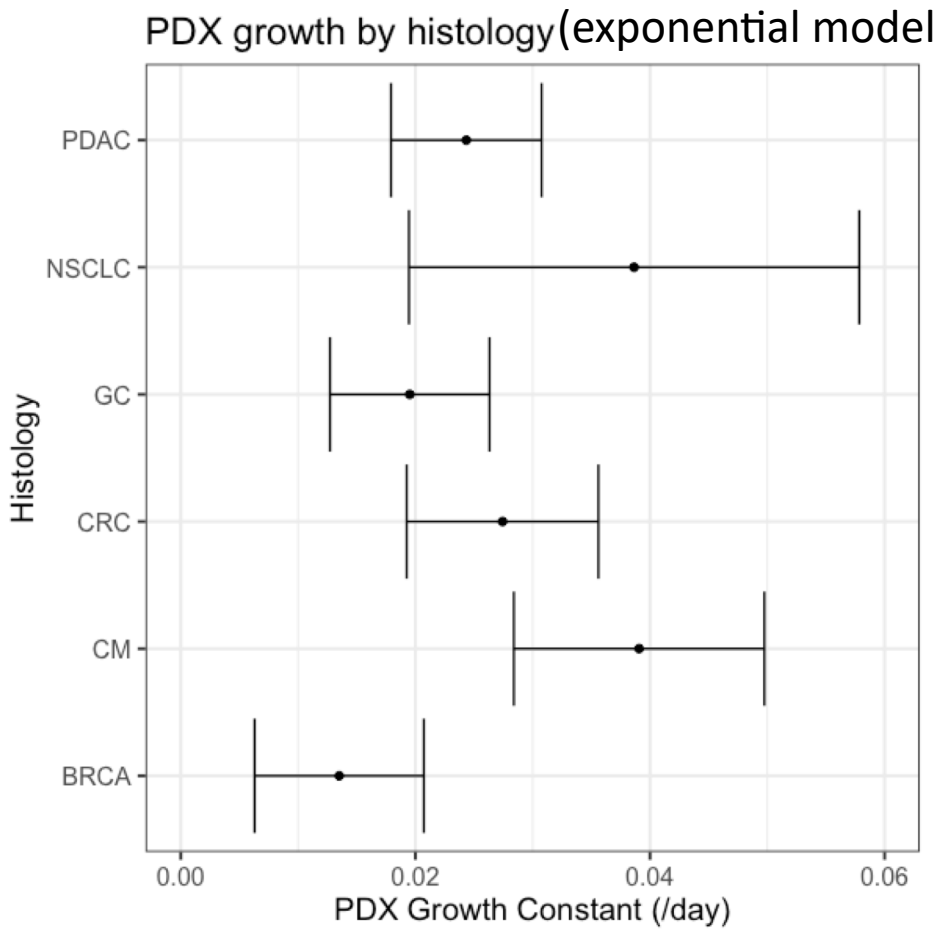
All rate laws accurately recapitulate control PDX growth

- Parametric inferences were successful
- Exponential-linear, logistic and Gompertz reduced to exponential model
- Essentially only two types of dynamics: linear and exponential
- Does growth rate vary by histology?
  - Inference using linear and exponential models
  - Are inference results consistent?

Growth rate varies by histology

- Inferences by both models are largely consistent
  - Linear: NSCLC and CM grow significantly faster than BRCA
  - Exponential: PDAC, NSCLC, CM grow significantly faster than BRCA





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