Linking Clinical Tumour Response to Preclinical Tumour Models

Data & Clarity

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DDIP, 29 Nov 2018

About me

Mathematical and statistical modelling, Bioinformatics

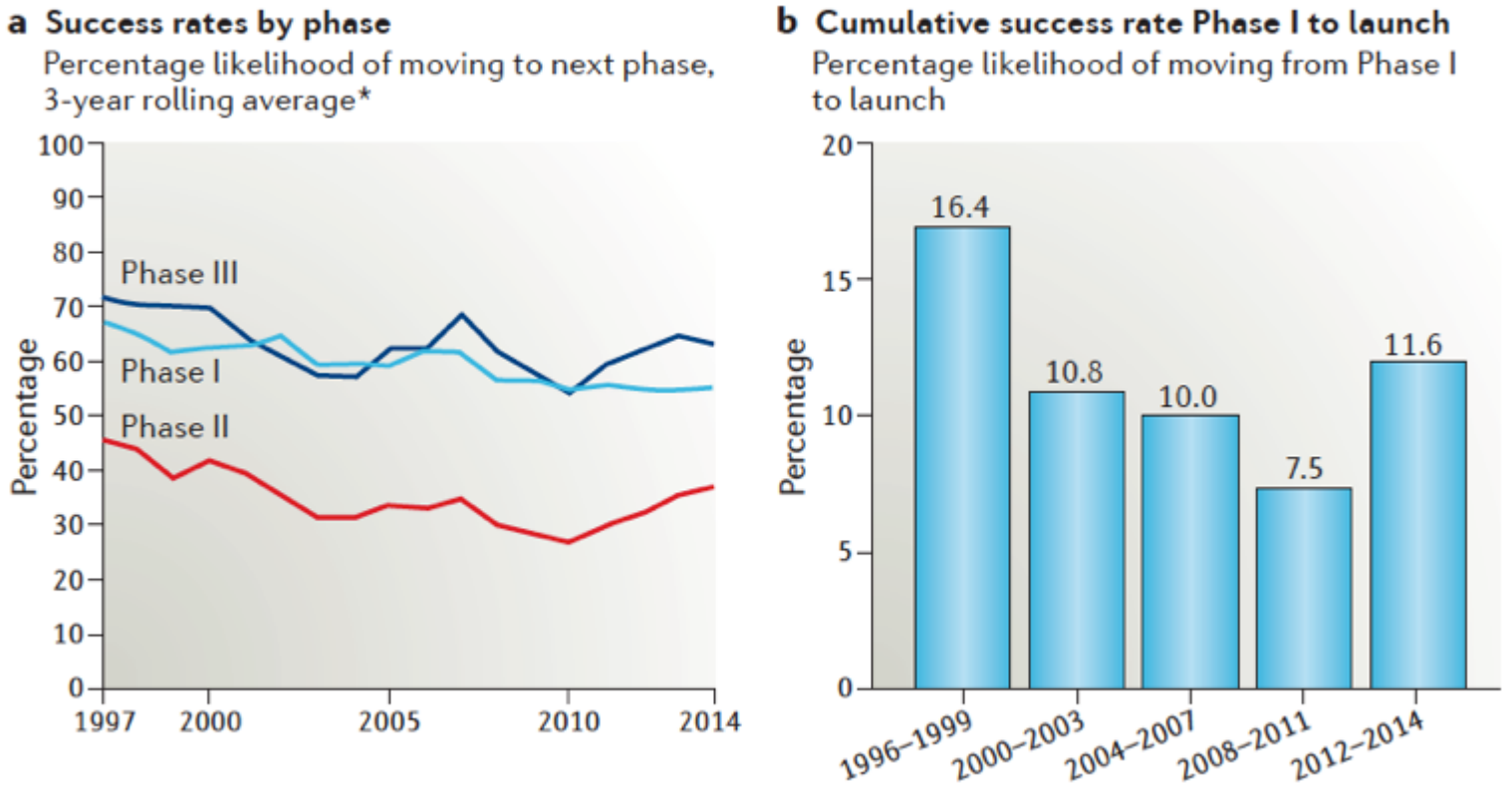
- Chemical Engineering, BE, 1998-2002
- Biological and Chemical Engineering, MSc, 2002-2003 — Singapore–MIT Alliance
- Cancer Bioinformatics, 2003-2005 — NUS National University of Singapore
- Systems Biology, PhD, 2005-2009 — University of Aberdeen
- Systems Biology, Postdoc, 2009-2011 — CRISP
- Physiological Modeller & PK/PD Modeller, 2011-2015 — AstraZeneca
- PK/PD Modelling Lab Head, 2016-2018 — Boehringer Ingelheim
- PK/PD Modeller & Data Scientist, Aug 2018 - now

Aims

- **Review** the pain points in drug R&D
- **Understand PK/PD rationales** that are relevant to different types of biomarker data
- **Evaluate** preclinical tumour models and **forecast** clinical efficacy
- **The Open Project (TOP)**

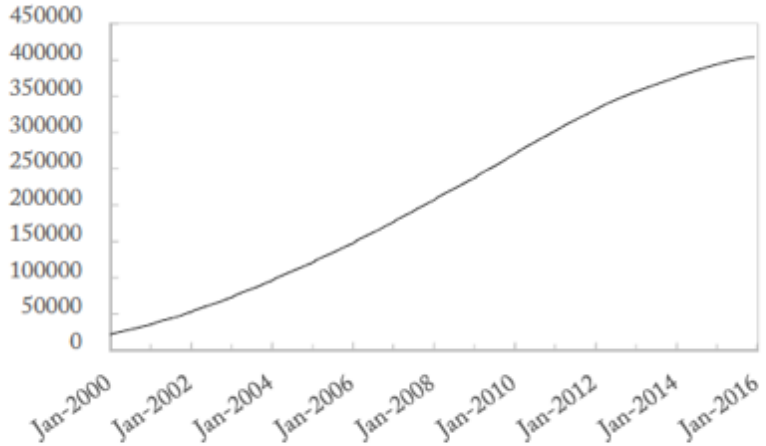
1. THE REASON WHY?

Probability of Success: Phase-by-phase

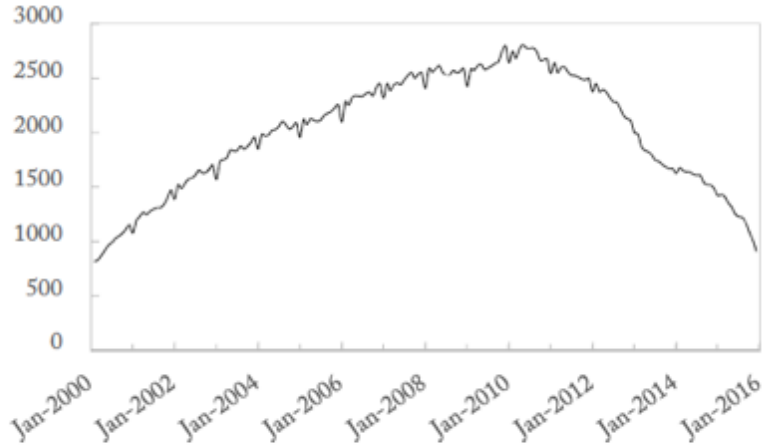


Smietana *et al*. (2016) Trends in clinical success rates. *Nat Rev Drug Disc*. 15: 379-380

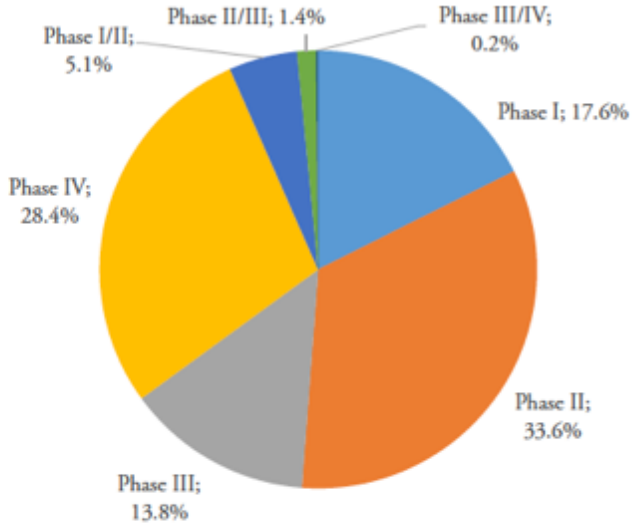
Clinical trials 2000-2015



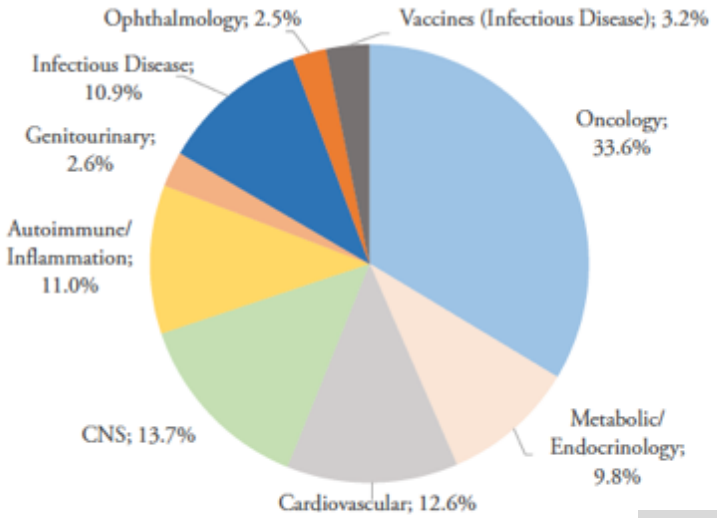
(a) Cumulative number of trials over time



(b) Increase in the number of trials over time



(c) Proportion of trials by phases

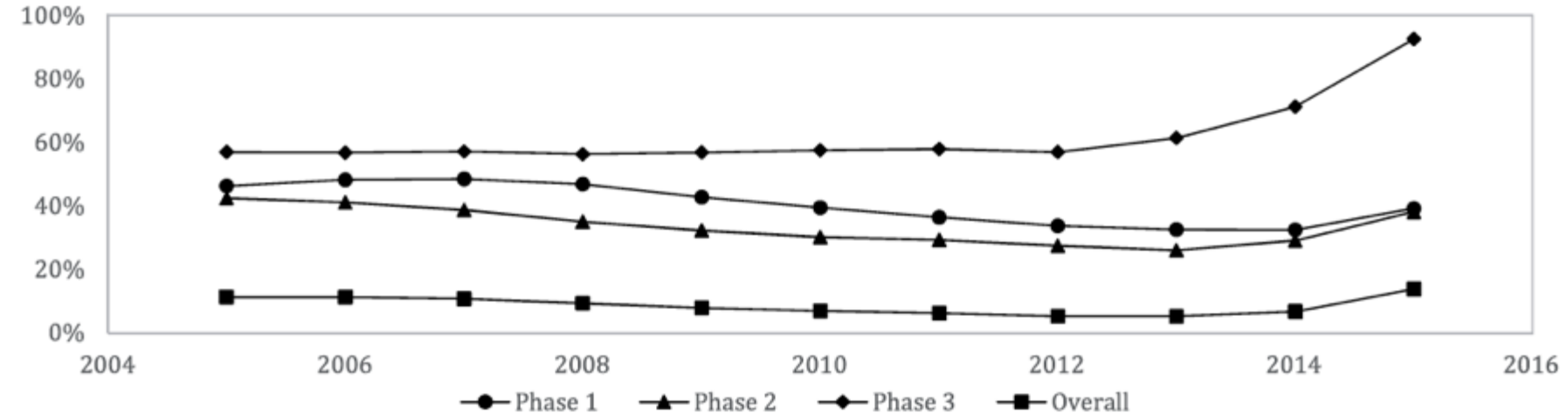


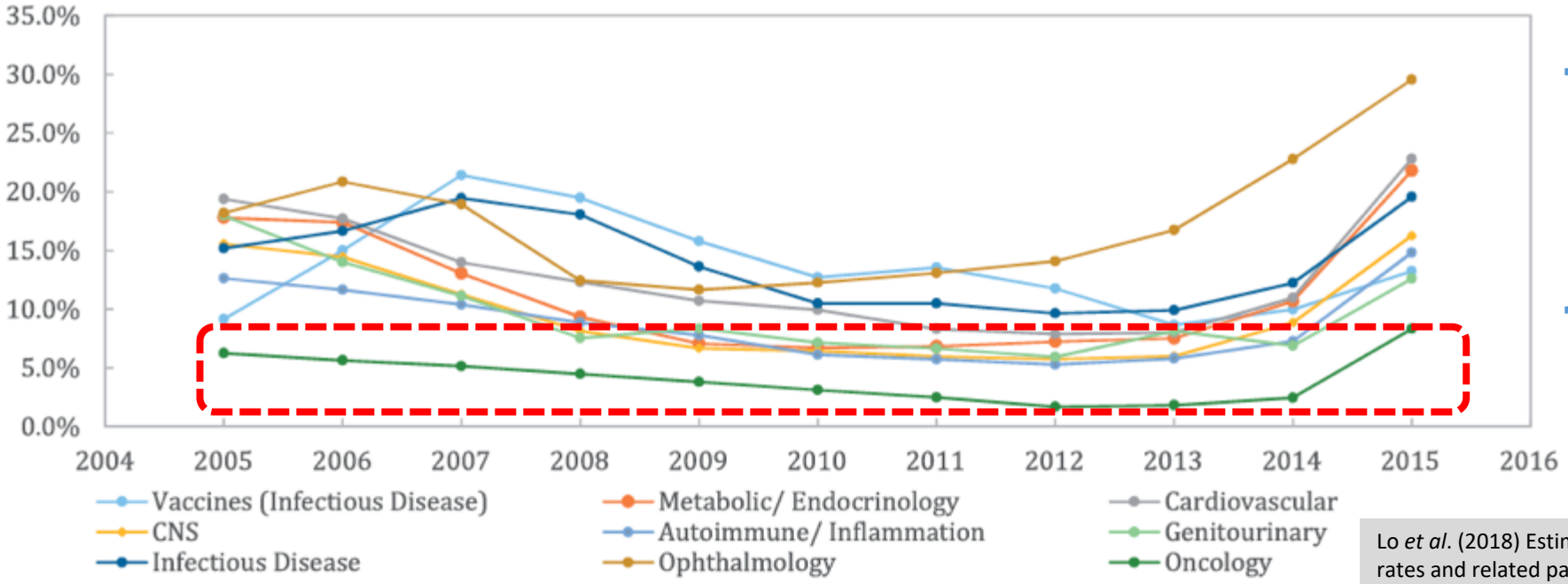
(d) Proportion of trials by therapeutic groups

~186,000 trials in total

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

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

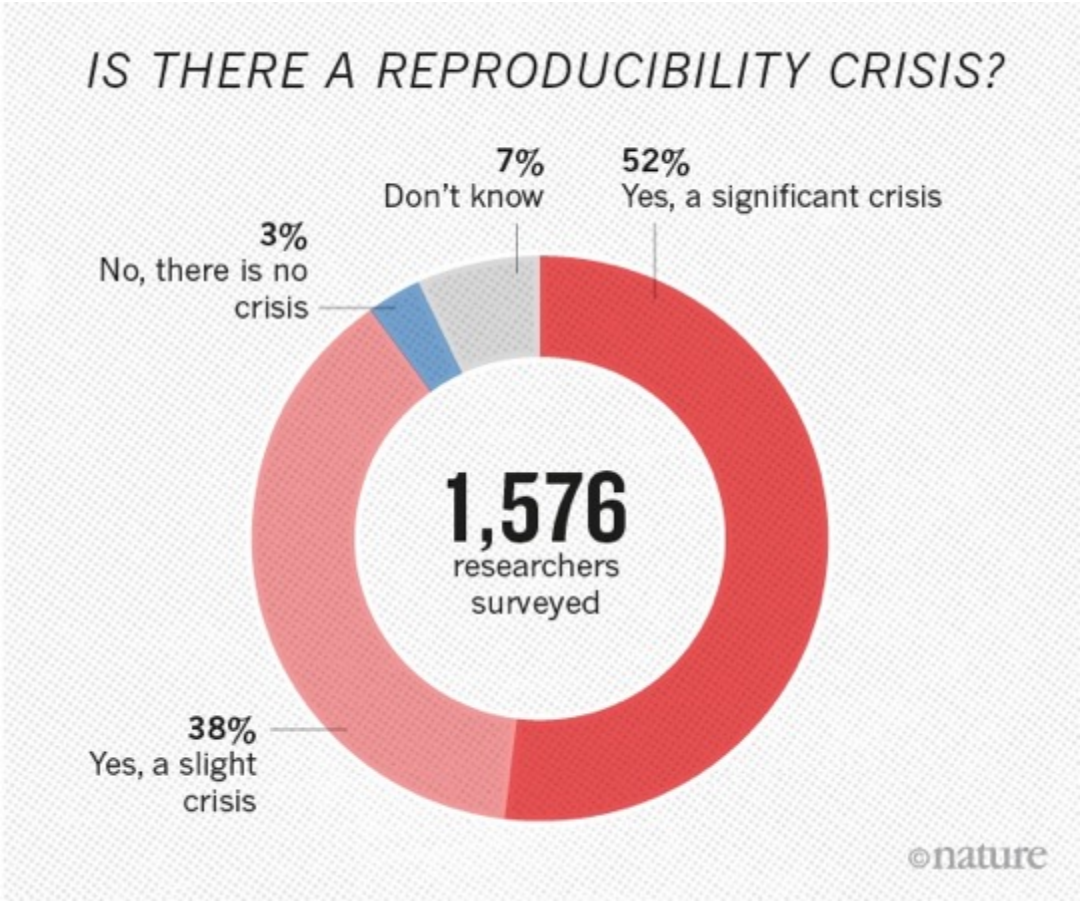
Cancer drug: Phase 2 is key

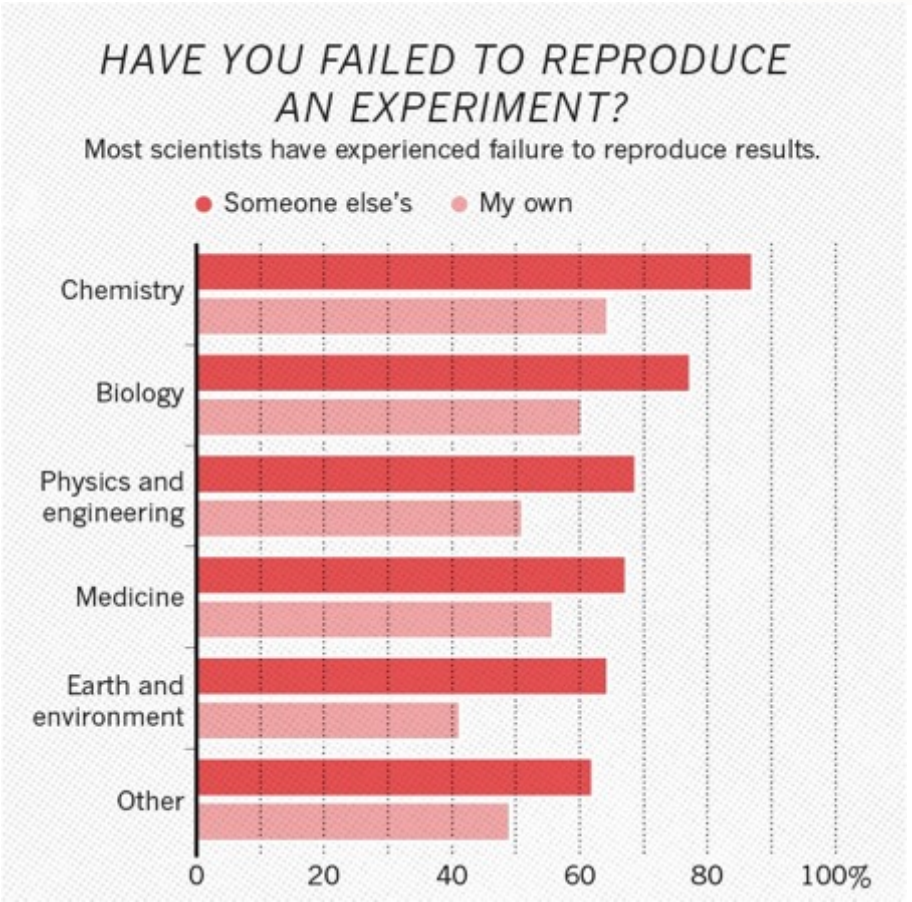
All indications (industry)

	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

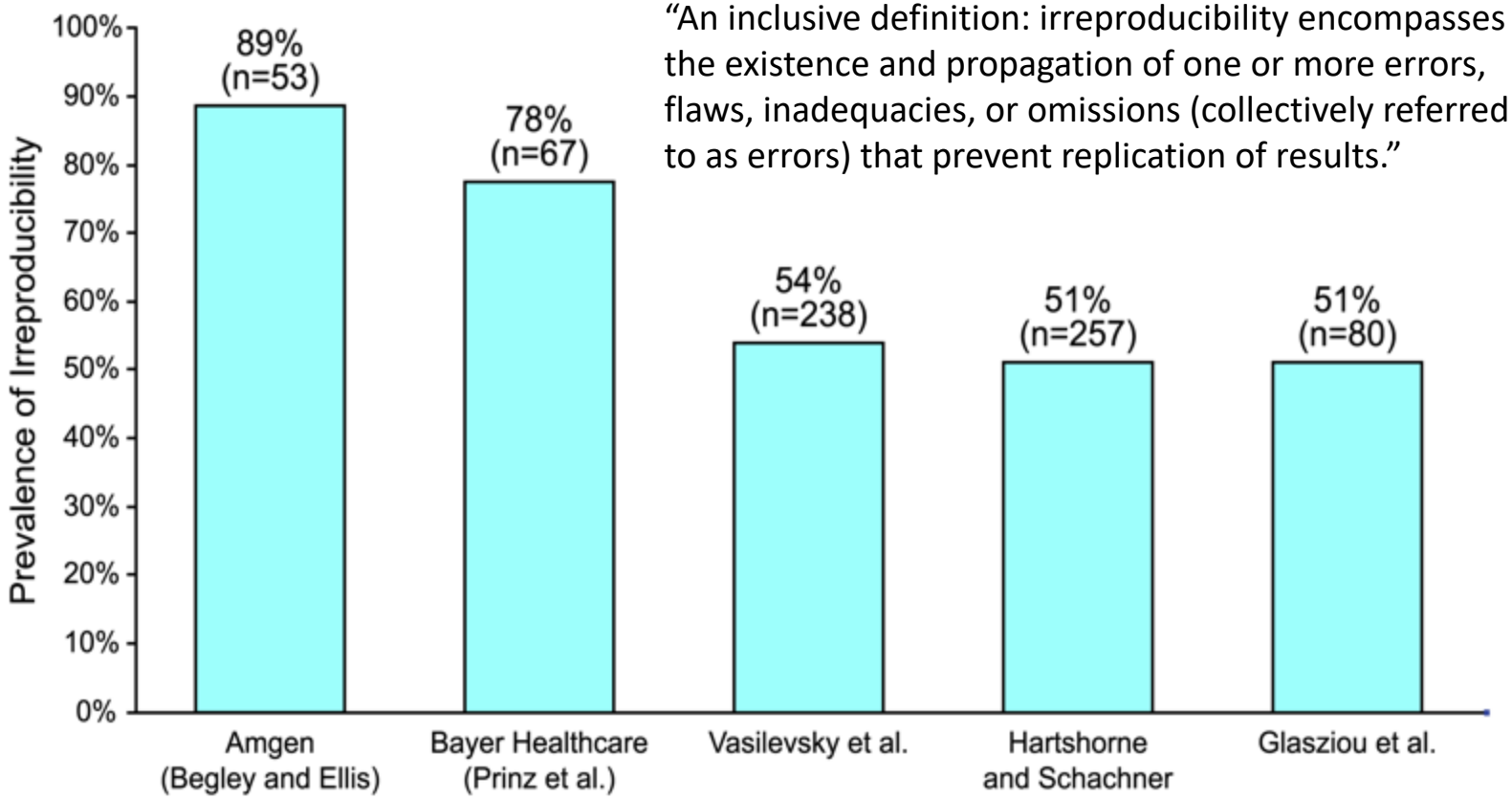
Data irreproducibility crisis





1,500 scientists lift the lid on reproducibility
Survey sheds light on the 'crisis' rocking research.
Monya Baker 25 May 2016 Corrected: 28 July 2016
http://www.nature.com/news/1-500-scientists-lift-the-lid-on-reproducibility-1.19970

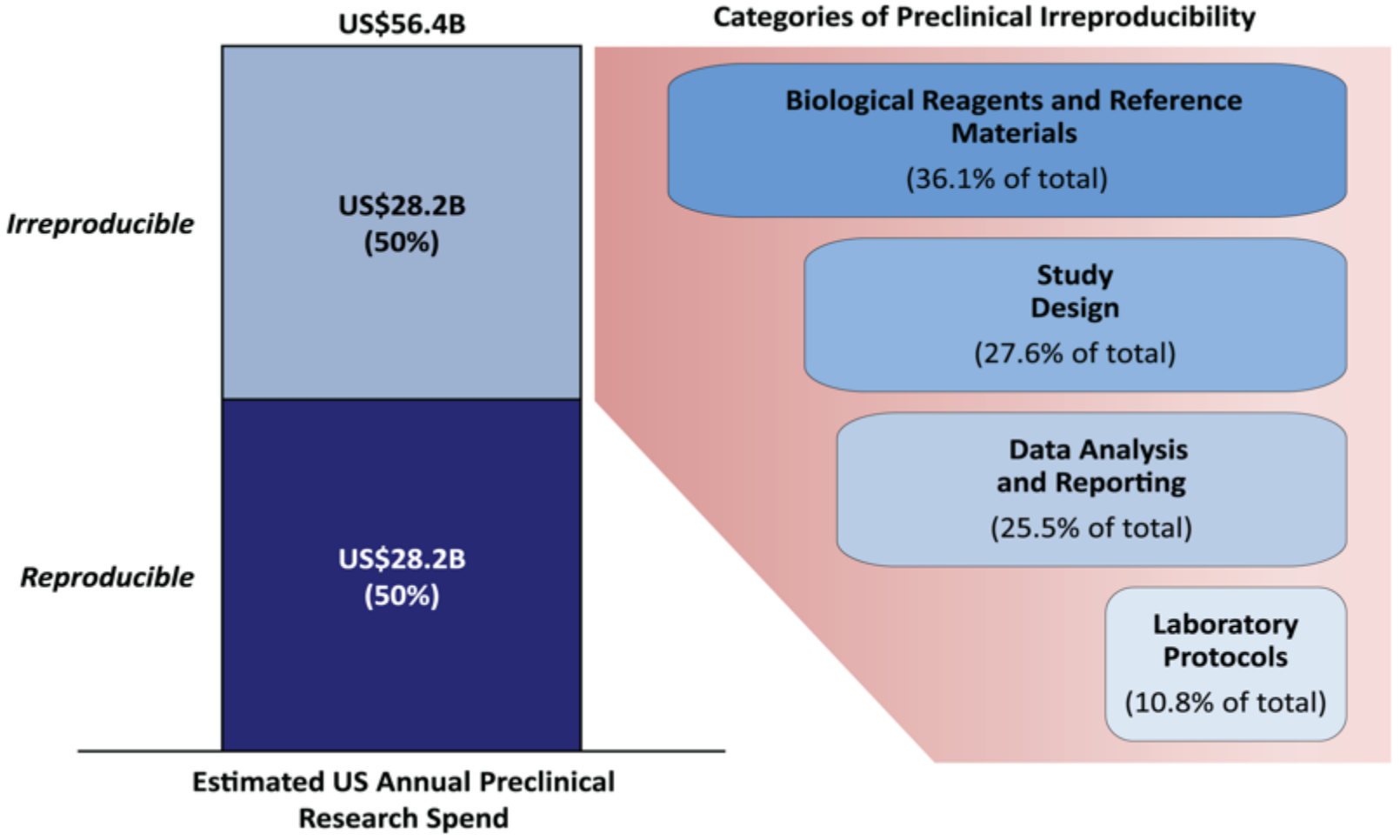
Data irreproducibility is extensive



"An inclusive definition: irreproducibility encompasses the existence and propagation of one or more errors, flaws, inadequacies, or omissions (collectively referred to as errors) that prevent replication of results."

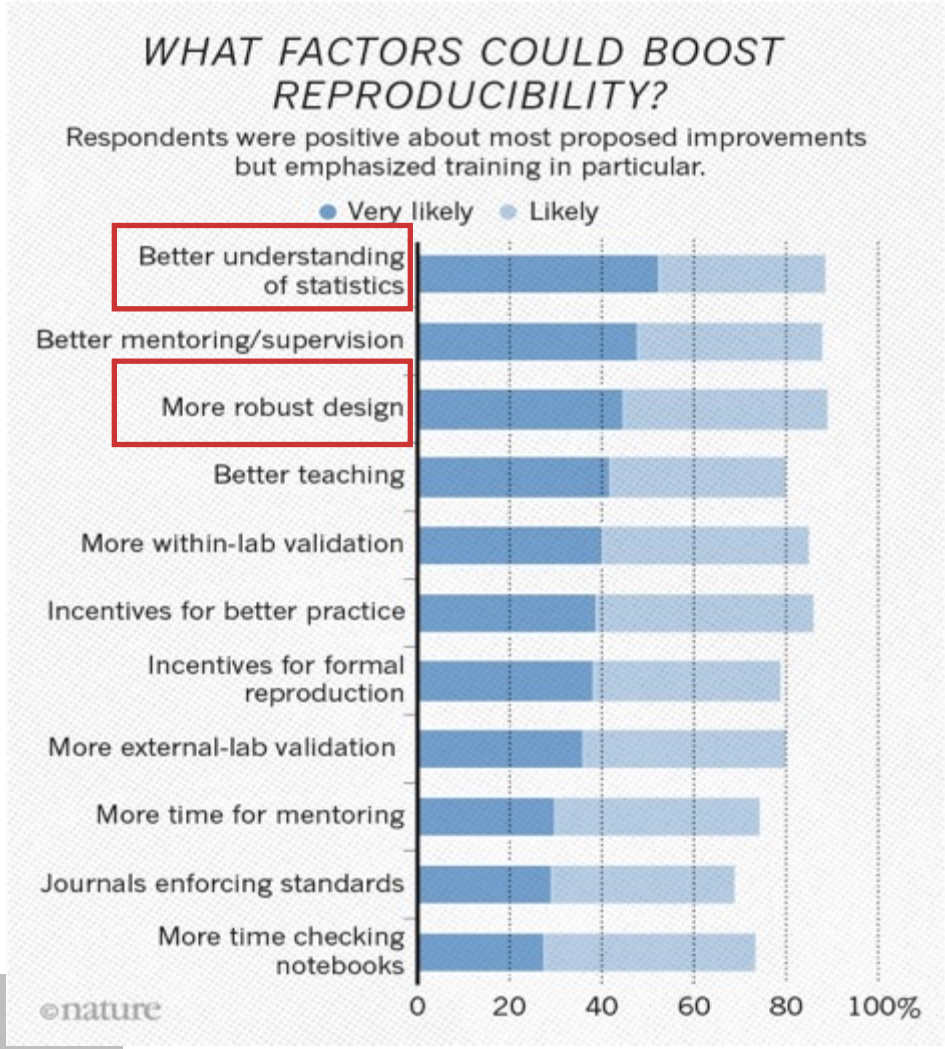
Freedman LP, Cockburn IM, Simcoe TS (2015) The Economics of Reproducibility in Preclinical Research. PLoS Biol 13(6): e1002165. doi:10.1371/journal.pbio.1002165

Data irreproducibility is expensive



Freedman LP, Cockburn IM, Simcoe TS (2015) The Economics of Reproducibility in Preclinical Research. PLoS Biol 13(6): e1002165. doi:10.1371/journal.pbio.1002165

How to boost reproducibility?



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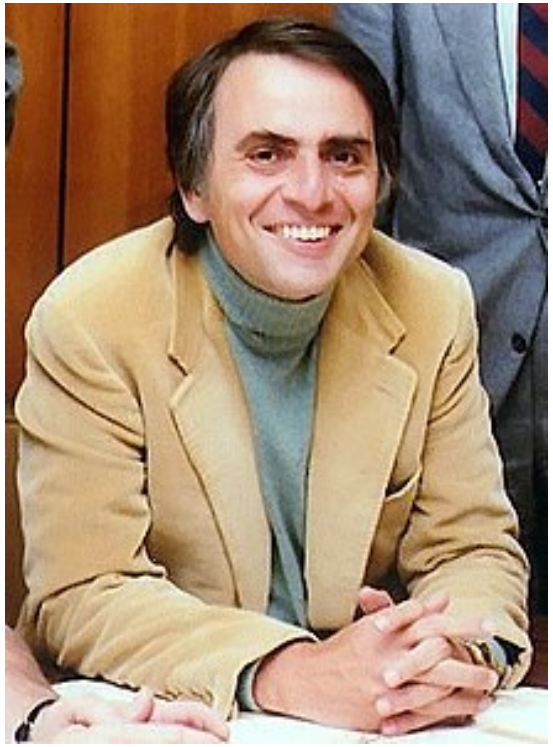
The spirit



"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)

2. TRANSLATIONAL ONCOLOGY MODELLING BASICS

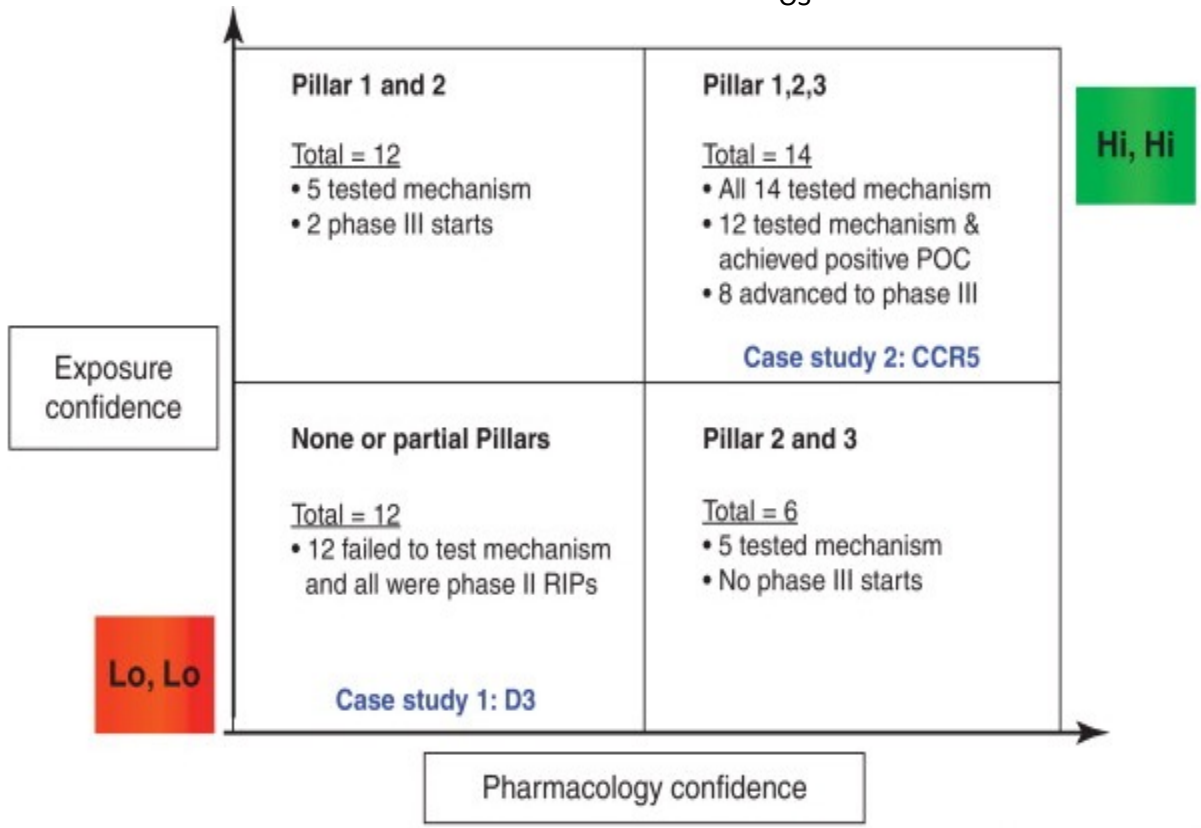
Efficacy data in drug discovery & development

Exposure	Direct Target Engagement	Indirect Target Engagement	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

Pfizer 3 pillars (2012)

Exposure	Direct Target Engagement	Indirect Target Engagement	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

- "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 Engagement	Physiological Response	Disease Modulation	Outcome/ Endpoints
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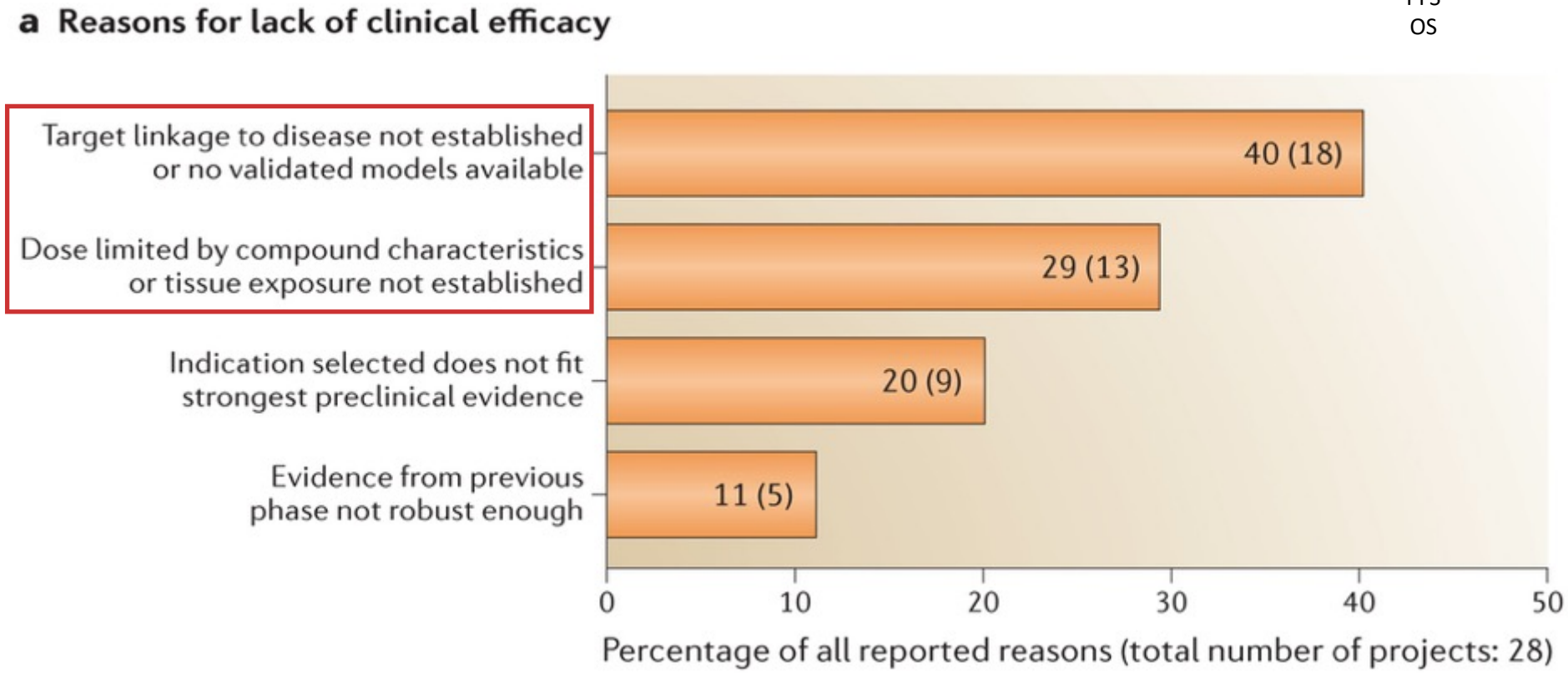
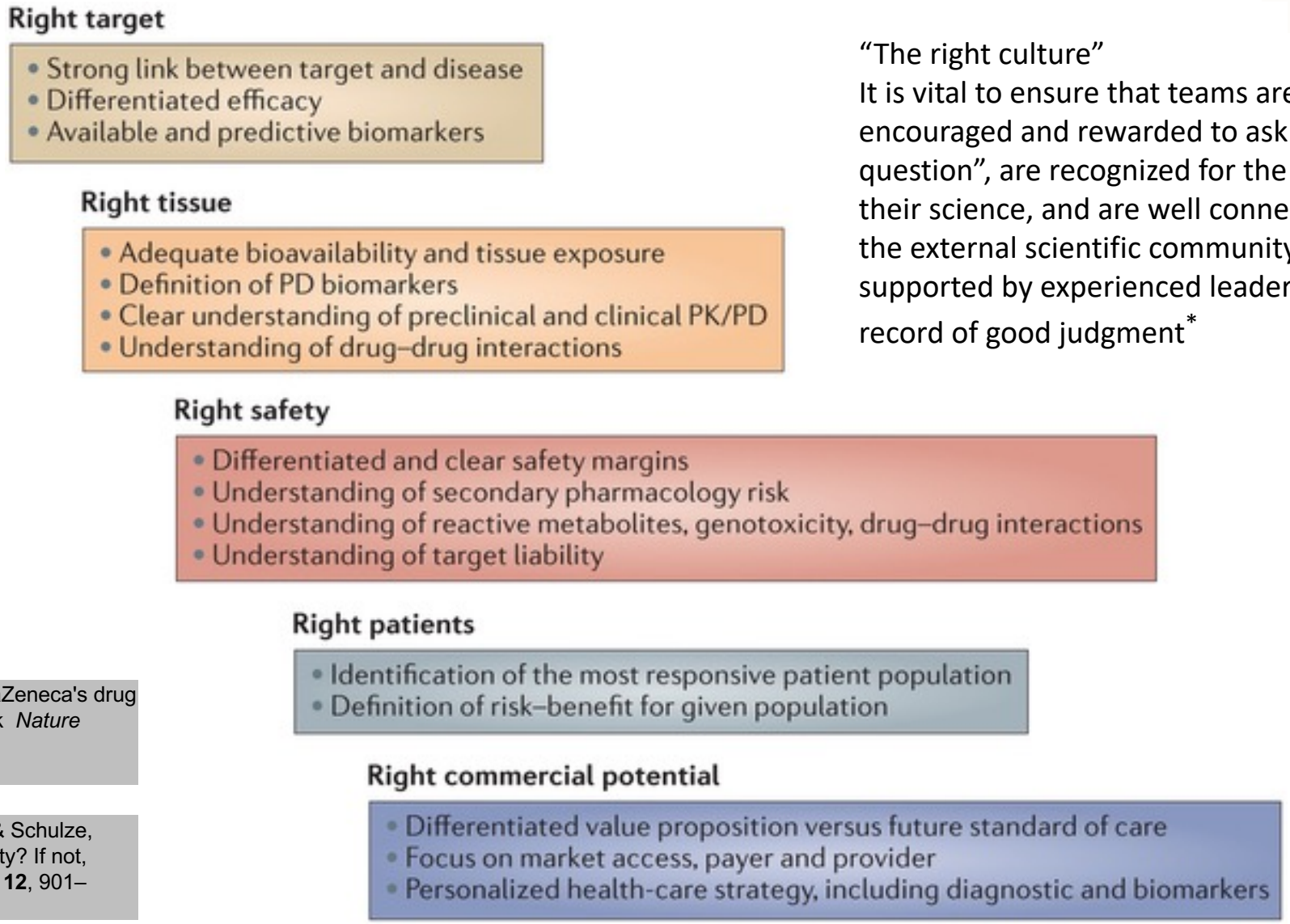


Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework
Nature Reviews Drug Discovery **13**, 419–431 (2014) doi:10.1038/nrd4309

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*

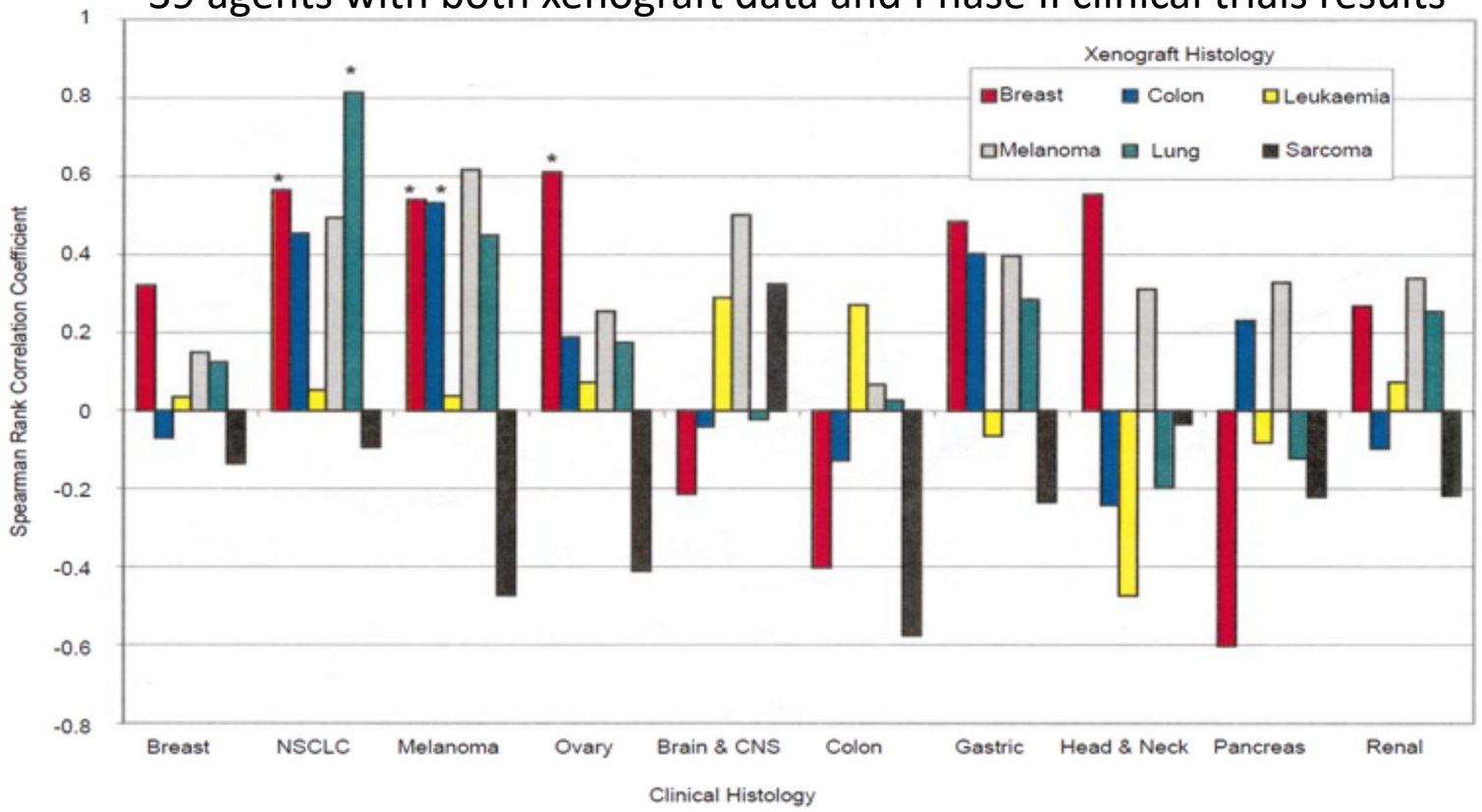
Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework *Nature Reviews Drug Discovery* 13, 419–431 (2014) doi:10.1038/nrd4309

* 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).

How reliable are xenograft tumour models?

- **2001** Method: **Mouse MTD efficacy** was compared with clinical response
- **2001** perspectives: for compounds with *in vivo* activity in **>1/3** xenograft models, there was activity in **>1** Phase II trials.

"39 agents with both xenograft data and Phase II clinical trials results"



Johnson et al, British Journal of Cancer (2001) 84(10), 1424–1431

Should mouse xenograft models be abandoned?

Mouse MTD efficacy was only **moderately** predictive of clinical response

Next question: What is the problem?

- Tumour biology difference (growth rates, immune competence, stromal content, orthotopic location)?
- Exposure differences?

Is mouse MTD efficacy relevant?

- The ratio R=(AUC-mouse-MTD)/(AUC-humans) was computed for 9 compounds
- Results: R<1 was a necessary, but not sufficient condition for success

Drug	Clinical Result	Calculated Ratio: (Mouse MTD AUC) /(Human clin. AUC)	Calculation details
Carzelesin	**Failure**	40	Table 2 (80/2)
DMP840	**Failure**	7	Table 2 (17.5/2.5)
MGI-114	**Failure**	7	p839, col2 text (214/33)
9-AC	**Failure**	4	Kirstein et al., Clin. Canc. Res., 7, 358 (2001)
Sulophenur	**Failure**	3	Table 2 (8/3)
Topotecan	**Success**	0.3	Table 2 (10/3)
Melphalan	**Success**	0.3	Table 2 (1/3.5)
EPO906	**Failure**	0.3	*See Backups*
Irinotecan	**Success**	0.2	Table 2 (16/100)

Peterson and Houghton, Eur. J. Canc., 40, 837 (2004)

Exposure difference is relevant

Looks like exposure difference is relevant

Next question: By correcting the difference, can we find any consistency between preclinical models and clinical data?

- Case study: 10 successful chemotherapy drugs

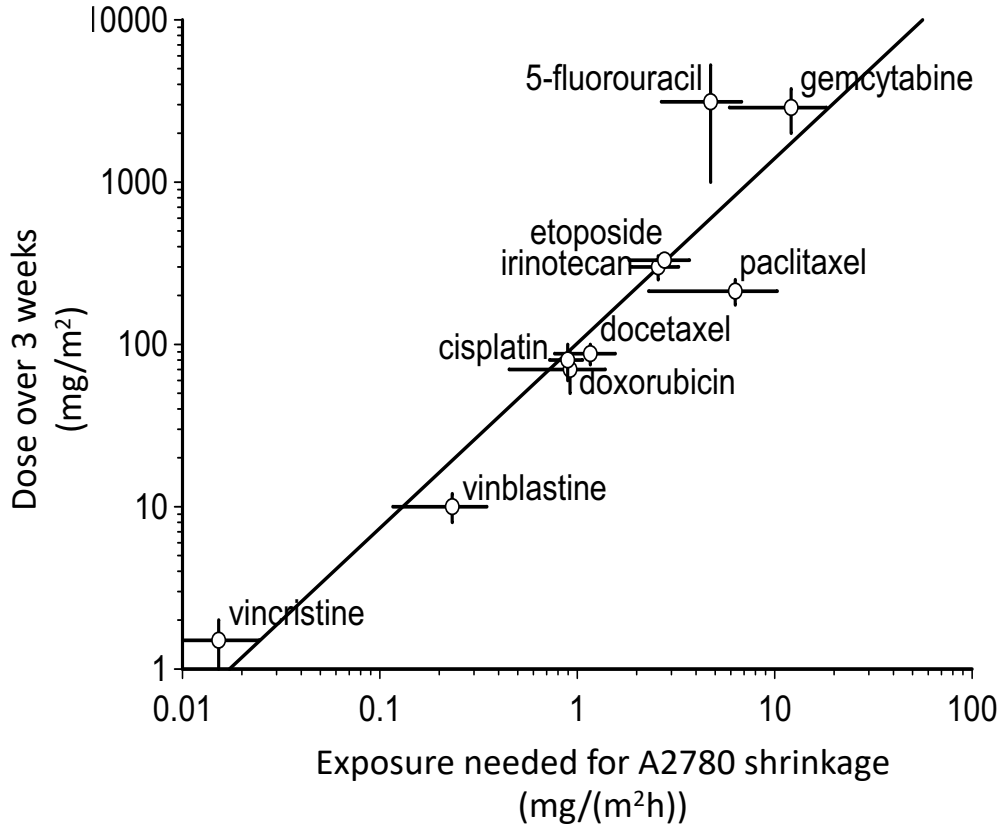
Can we learn from successful chemotherapies?

Methods

- 10 chemotherapy drugs were tested on mouse A2780 ovarian carcinoma xenografts.
- PK/PD models were constructed to estimate the exposures needed for preclinical tumor shrinkage.

Results

- Strong correlations (R = 0.94) was observed between preclinical exposures needed for tumor shrinkage and the exposures achieved in the clinic under standard treatment.



Rocchetti et al., Eur. J. Canc., 43, 1862 (2007)

Exposure difference is relevant

Looks like exposure is relevant to a large extent to clinical success!

Next question: Can we predict clinical failure?

- Case study: 8 chemo/targeted treatments for 10 indications with known clinical outcomes

Compelling preclinical evidence requires…

- What is the minimum preclinical efficacy required for clinical success?
  - Can we establish a robust translational criteria?

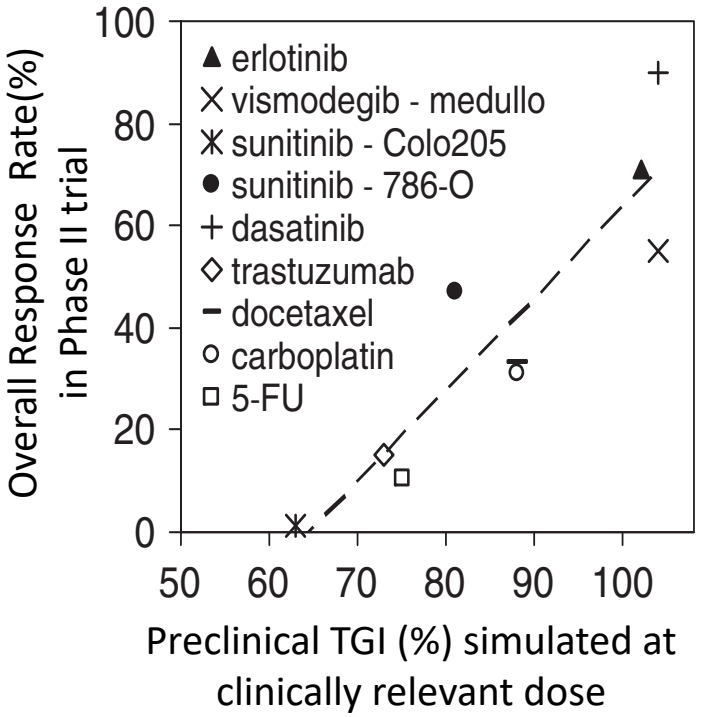
Method

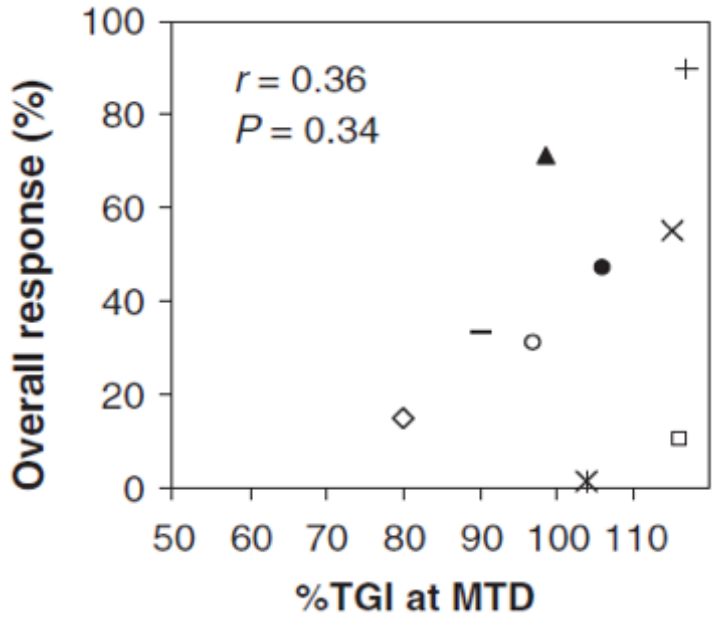
A model-based method to predict *clinical efficacy* based on *preclinical xenograft* based studies for both chemotherapies and targeted therapies

A minimum clinical efficacious exposure can be predicted for *tumor cell-directed therapy*.

Main Limitations

Attaining this minimum clinical exposure is a necessary but not sufficient condition.





Wong *et al.*, *Clin. Canc. Res.*, 18, 3846, (2012)

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. TRANSLATIONAL PK/PD MODELLING

- Can *in vivo* tumour models forecast clinical tumour responses?

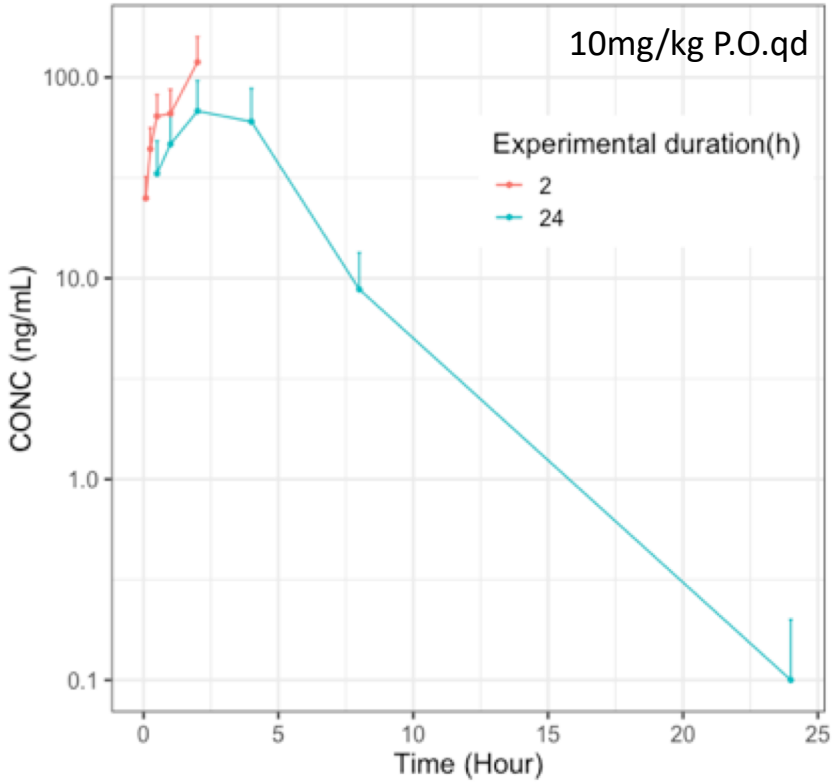
Afatinib: *In vivo* <-> clinical efficacy

- Situation
  - Afatinib (an EGFRi) has been studied in PC-9 xenograft and in NSCLC patients
  - Need to evaluate different EGFR inhibitors
- Task
  - What is the minimum PC-9 efficacy required to see clinical response?
- Action
  - Construct afatinib preclinical PK/PD model for PC-9 data
  - Simulate PC-9 response under the clinical exposure
  - Compare the simulated tumour growth with clinical responses
- Result
  - PC-9 gave similar but different responses with clinical tumours

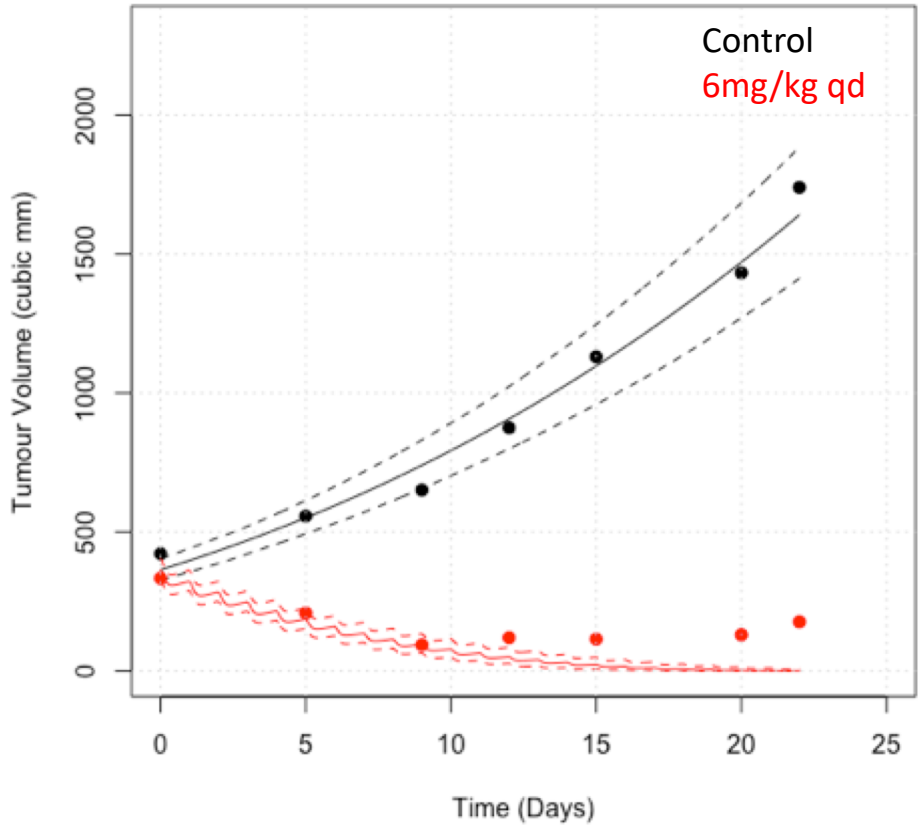
Afatinib Preclinical Modelling

- Afatinib Preclinical PK/PD – PC9
- Exposure-response model was constructed
- Limited data: Consider only the first 9 days in the treatment arm

Exposure (van Hoppe 2017)

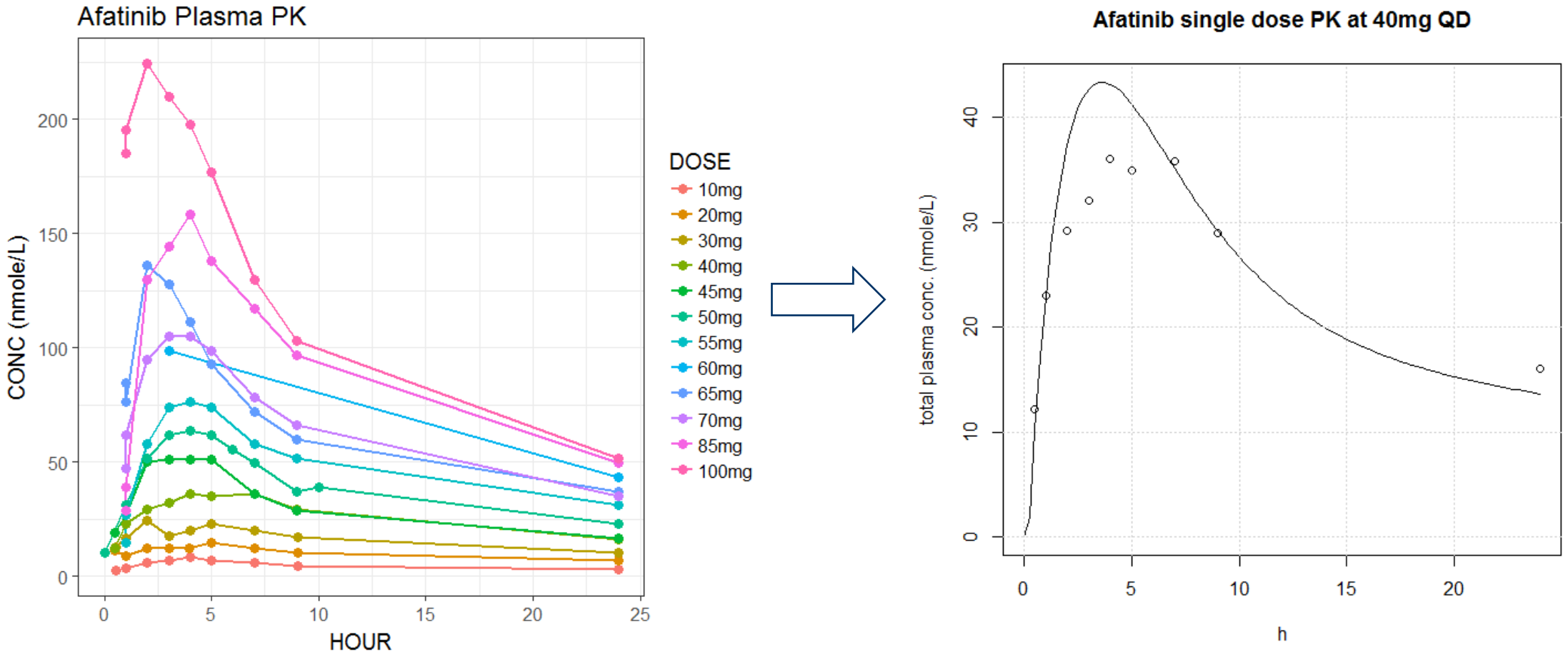


Efficacy (Yamaoka 2017)



Afatinib Clinical PopPK

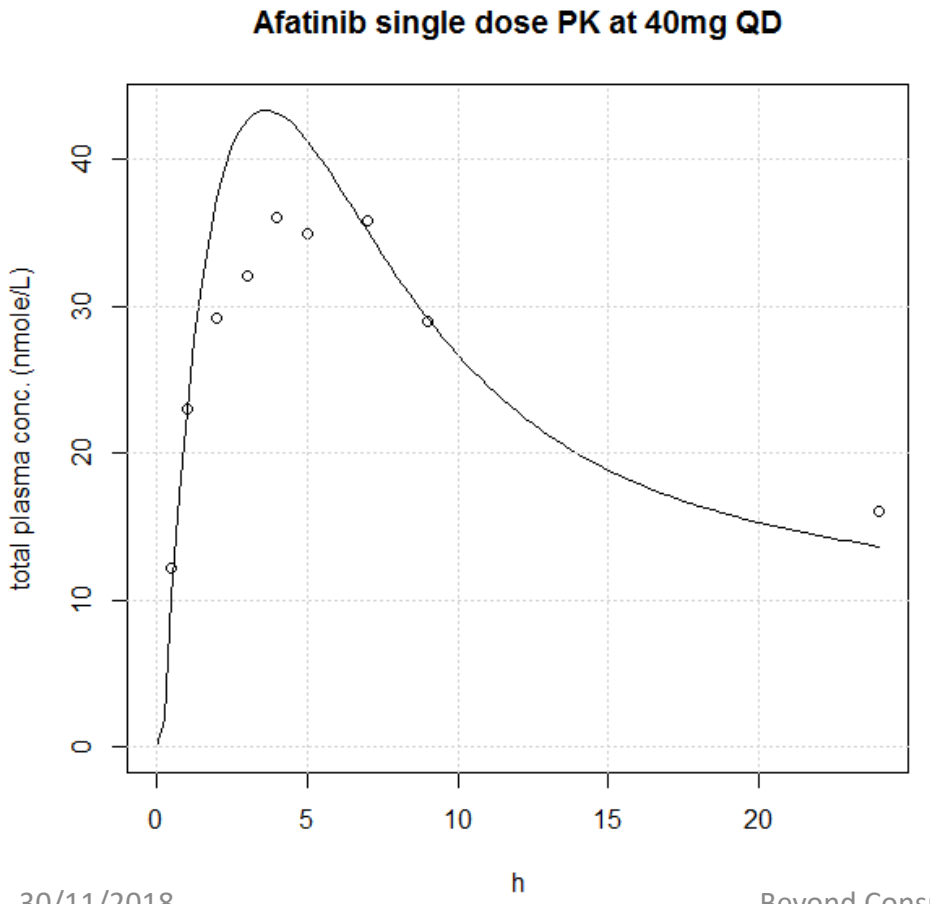
- PopPK data and modelling reproduced in nmole/L

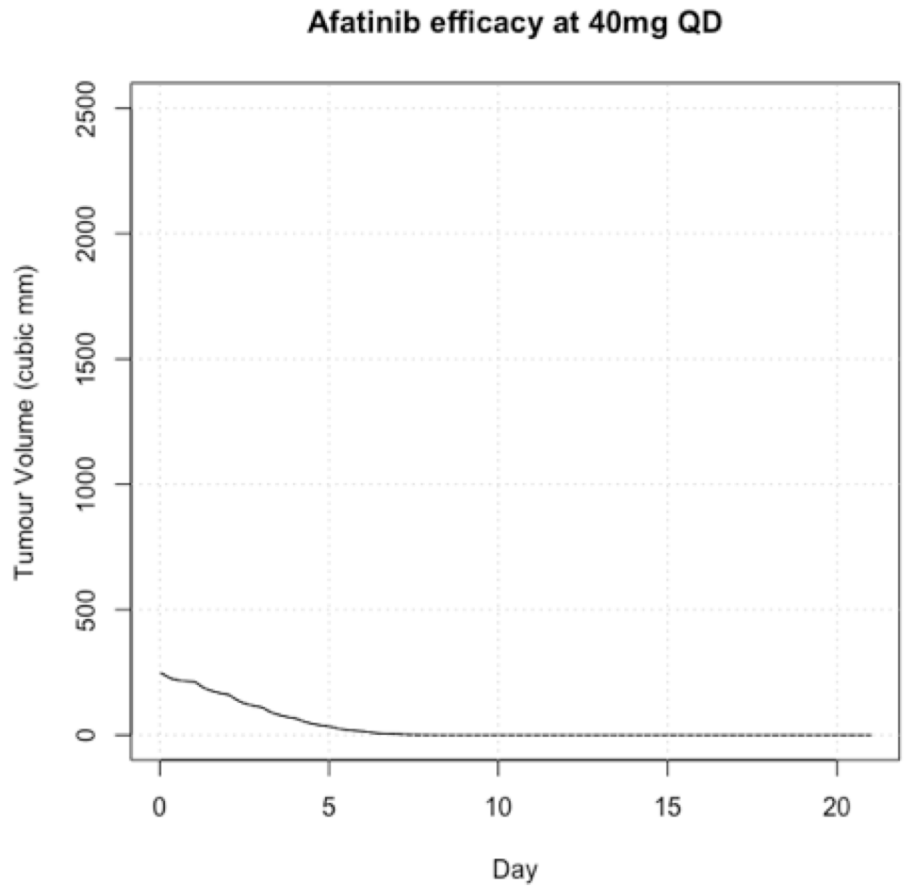


Wind et al. Clin Pharmacokinet (2013) 52:1101–1109

PC9 response under clinical Afatinib exposure

- Simulate PC-9 response under mean clinical exposure
- Corrected for plasma protein binding
- Predicted tumour regression based on limited PC-9 efficacy data





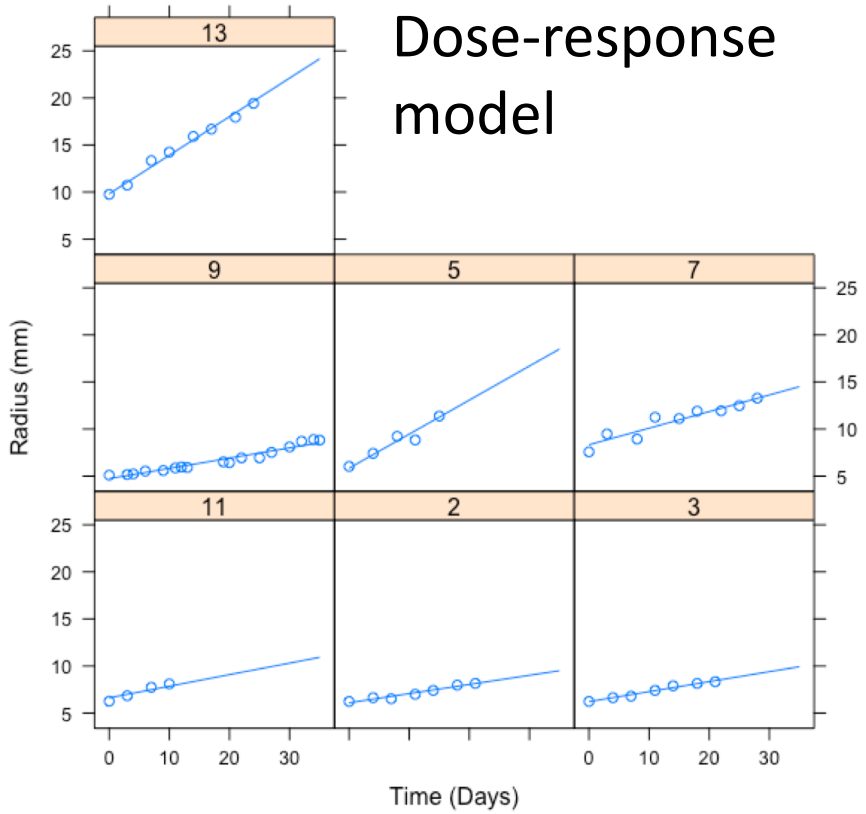
In vivo -> clinical efficacy

- Situation:
  - Mia PaCa2 is an often-used pancreatic cancer model
- Task:
  - Is Mia PaCa2 predictive of clinical efficacy?
- Action:
  - Infer Mia PaCa2 *in vivo* dose-efficacy relationship
  - Simulate Mia PaCa2 tumour growth under the clinical dose
  - Compare the simulated tumour growth with clinical responses
- Result:
  - Simulated Mia PaCa2 tumour growth under the clinical dose was slightly less sensitive than clinical tumours
  - This reassures the validity of Mia PaCa2 as a model for gemcitabine

Gemcitabine dose-response in Mia PaCa2

- Gemcitabine in Mia PaCa2 model
  - Drug is metabolised intracellularly
- Linear mixed effects model constructed
  - Suggests a weak dose-response relationship

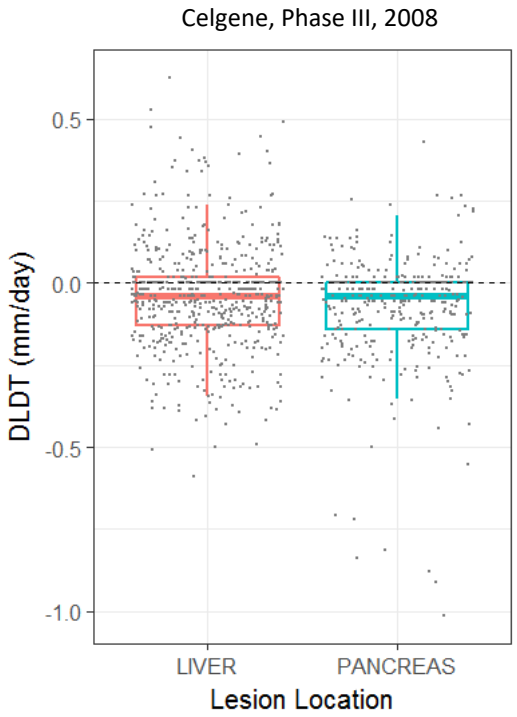
References
Yoon 2012
Yoon 2012
Azzariti 2011
Campbell 2010
Yeo 2014
Engelke 2013
Yada 2008

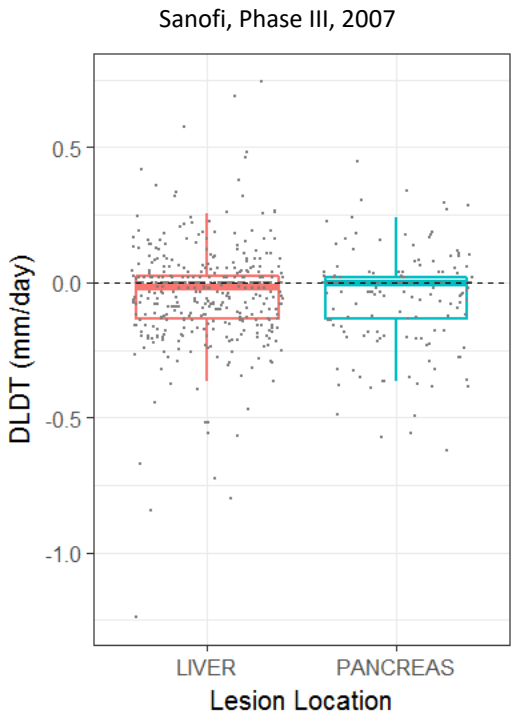


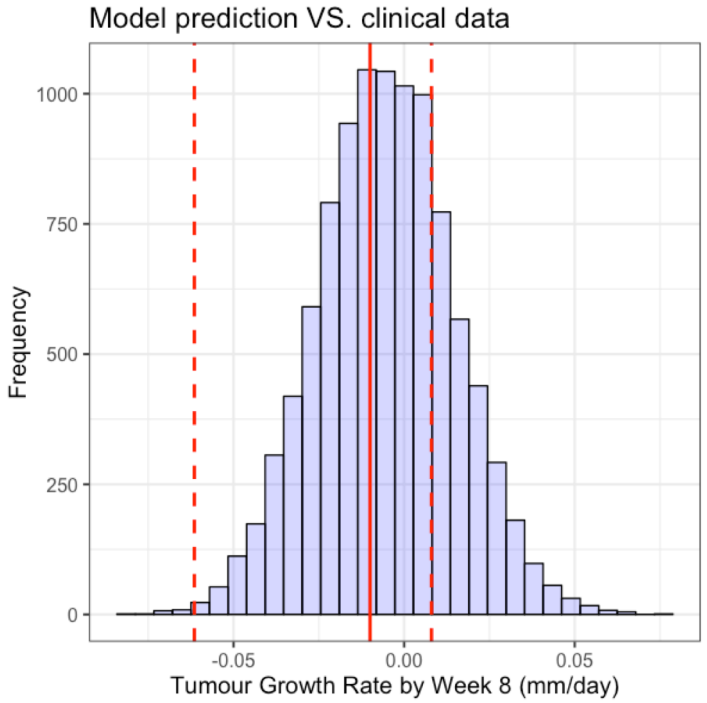
Dose-response model

Translation

- Tumour shrinkage rate distribution
  - Red solid: median
  - Red dashed: IQR
  - Blue solid: mean
- Mia PaCa2 moderately under-estimates clinical responses







THE OPEN PROJECT

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

- Participation
  - 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 need to demonstrate understanding of the code, rules, and culture of the project before being invited to join

Goals

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

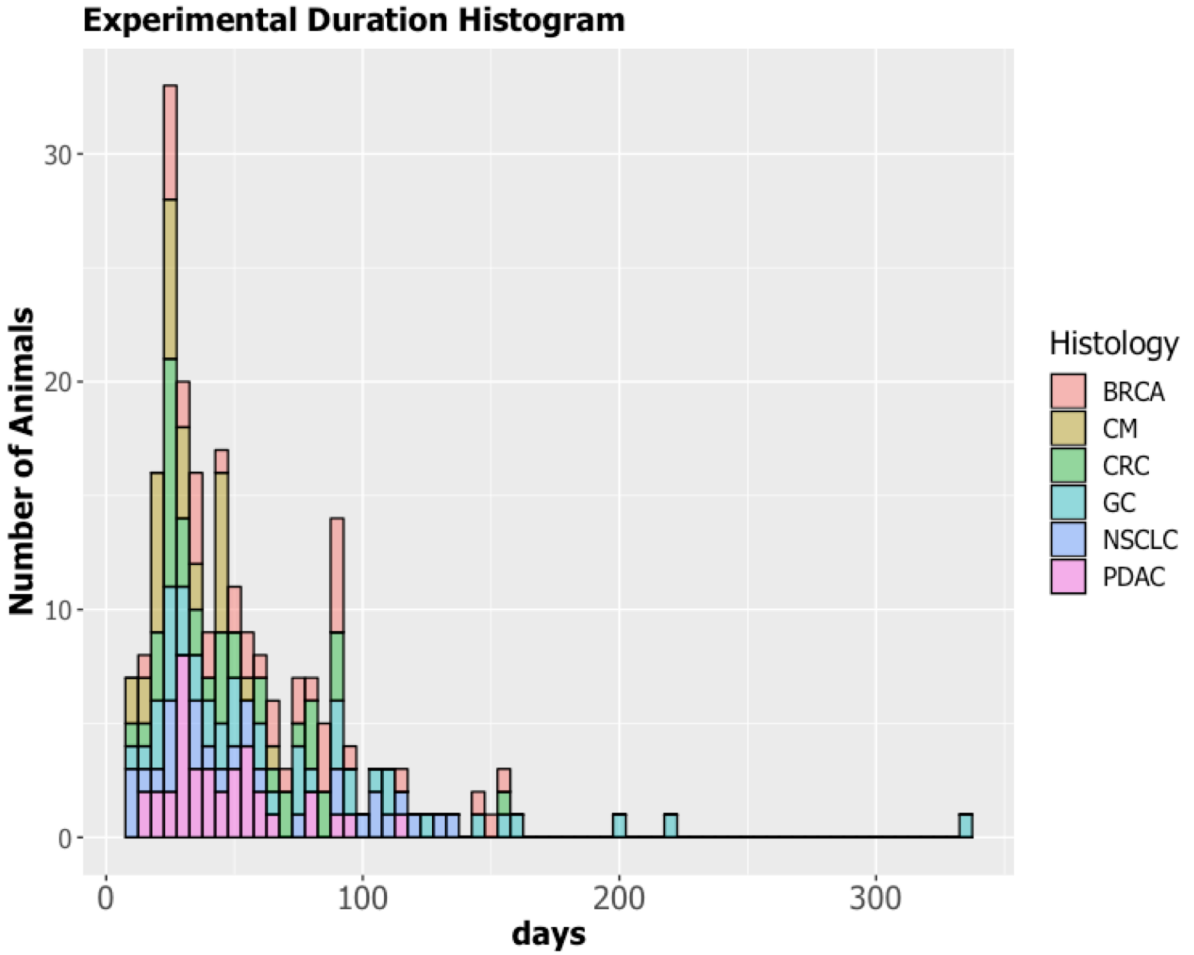
- Which rate laws accurately predict tumour growth?
  - Extrapolation: future tumour growth
  - Good inference is necessary but not sufficient for good prediction
  - Uncertainty in model structure

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



Gao et al, Nature Medicine (2015) 21(11), 1318–1425

Main points

- **Drug R&D**
  - Lack of efficacy, irreproducibility, data modelling, good culture
- **PK/PD rationales**
  - Dose-….-response relationship is key to success
  - How much details depend on data, feasibility, the purpose
- **Evaluate** preclinical tumour models and **Forecast** clinical efficacy
  - Preclinical models need assessments
  - Provides basis for experimental design and data interpretation
  - Translational modelling should be done before project starts
  - Industrial standards
- **The Open Project (TOP)**
  - Translational oncology
  - Openness, transparency, meritocracy

DATA ≠ SUCCESS

DATA + MODEL = SUCCESS

Acknowledgement

Conception of project idea and discussions

Hitesh Mistry
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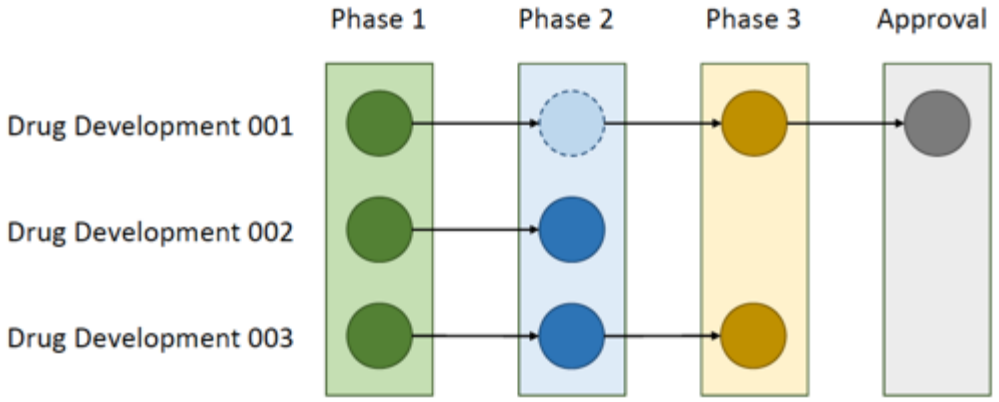
https://github.com/TheOpenProject/

- Why should I care?
- Who should contribute to TOP?
- Why contribute to The Open Project (TOP)?
- Vision & mission of TOP
- What is TOP doing?
- Ways to contribute to TOP
- Who contributes to TOP?
- The spirit of TOP

YOU?

Supporting slides

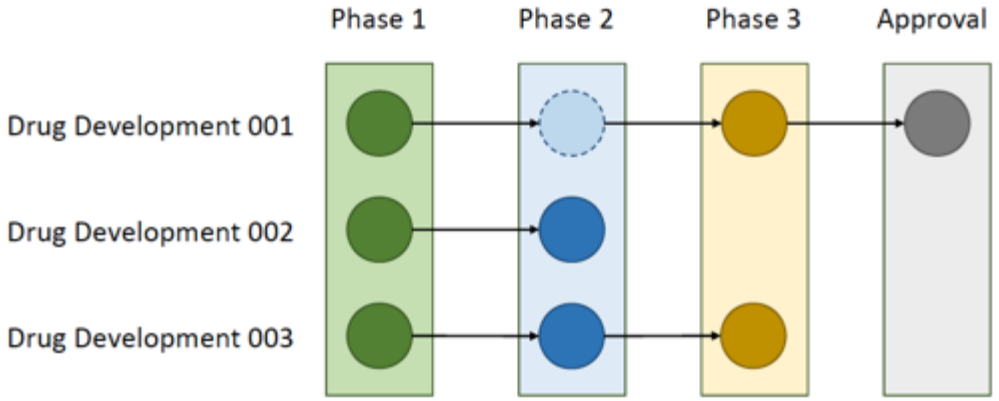
Probability of Success (POS)



- 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

Path-by-path formal definition

- Trial status

$$s = \begin{cases} ip, & \text{if all the trials are in progress} \\ t, & \text{if the program failed to proceed to phase } i+1 \text{ (i.e., terminated)} \\ m, & \text{if the phase transition can be inferred to be missing} \end{cases}$$

- Conservation law

Total trials in phase j

Observable trials in phase j

$$n^{j+1} = n^j + n_m^j - n_{ip}^j - n_t^j \qquad \forall j = 1, 2, 3$$

Total active trials in phase j

Probability of success (Ph j to j+1)

$$\mathrm{POS}_{j,j+1}(\text{Path-by-Path}) = \frac{n^{j+1}}{n^j + n_m^j - n_{ip}^j}$$

Observable trials in phase j+1

Total active trials in phase j

Probability of success (Ph 1 to registration)

$$\mathrm{POS}_{1,\mathrm{APP}}(\text{Path-by-Path}) = \frac{n^{\mathrm{Approval}}}{n^1 + n_m^1 - n_{ip}^1 - n_{ip}^2 - n_{ip}^3}$$

Phase-by-phase formal definition

- Trial status

$$s = \begin{cases} ip, & \text{if all the trials are in progress} \\ t, & \text{if the program failed to proceed to phase } i+1 \text{ (i.e., terminated)} \\ m, & \text{if the phase transition can be inferred to be missing} \end{cases}$$

- Conservation law

Total trials in phase j

Observable trials in phase j

$$n^{j+1} = n^j + n_m^j - n_{ip}^j - n_t^j \qquad \forall j = 1, 2, 3$$

Total active trials in phase j

$$\mathrm{POS}_{j,j+1}^p = \frac{n^{j+1} - n_m^j}{n^j - n_{ip}^j}$$

Observed transitions to phase j

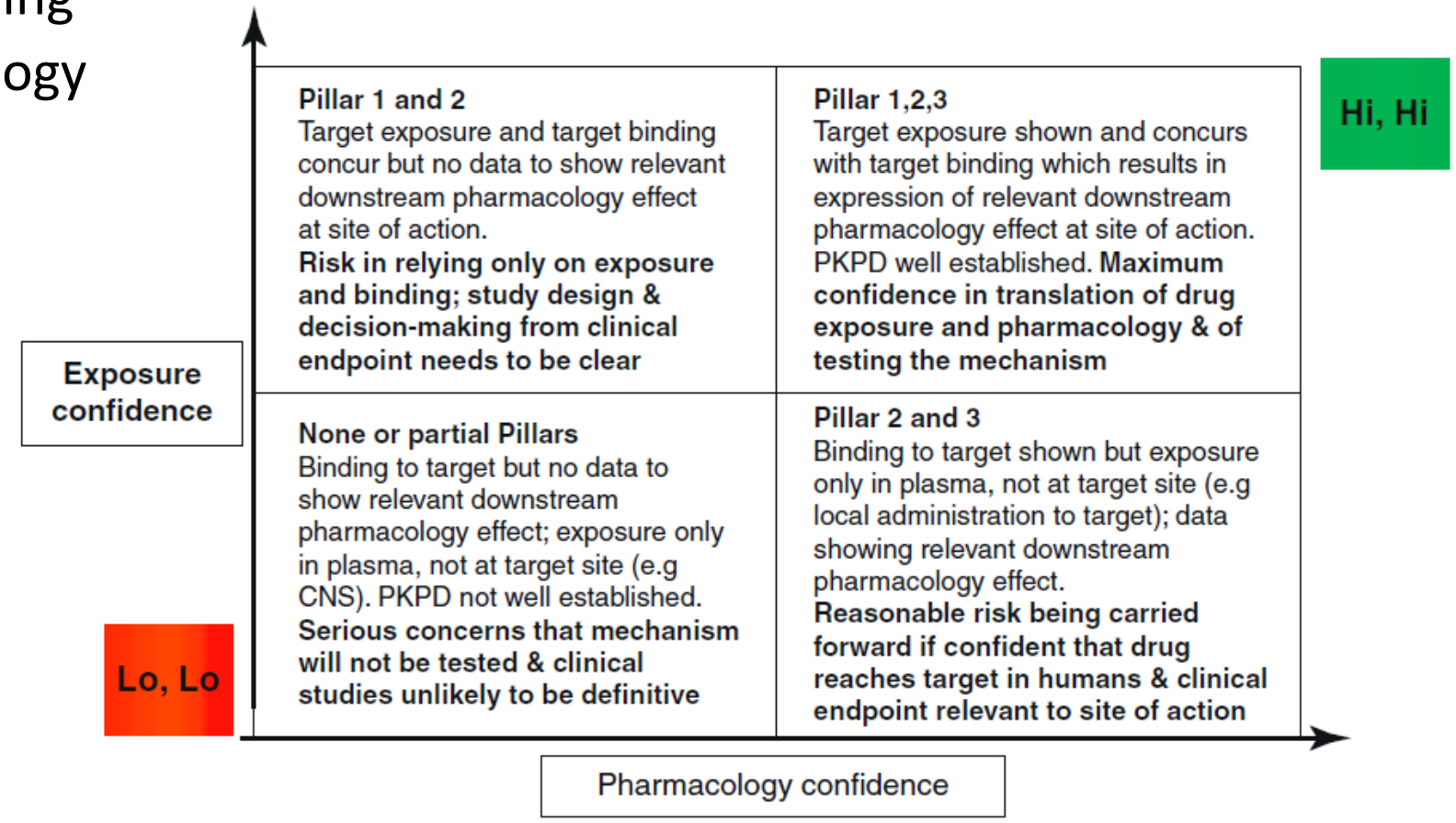
Observed active trials in phase j

$$\mathrm{POS}_{1,\mathrm{APP}}^p = \prod_{j \in \{1,2,3\}} \mathrm{POS}_{j,j+1}^p$$

- If no missing trials, the two models are identical

Pfizer 3 pillars

- "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)

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 to demonstrate 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

2. Clinical data -> *In vivo* mono 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

2

Information required

- Competitor 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

- Competitor compounds
  - Preclinical PK/PD models
  - Clinical popPK model
  - Translational efficacy modelling
- Own compound
  - Preclinical PK/PD model of efficacy data
  - Forecasted clinical PK
  - Forecasted clinical results (ORR)

2. Clinical data -> *In vivo* mono 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

Triggering question

- What *in vivo* efficacy is needed to be better than (direct and indirect) competitors?
- What potency is needed to be better than (direct and indirect) competitors?
- What is the desired PK profile of our candidate compound?

2. Clinical data -> *In vivo* combi 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

2

Information required

- Combination partner
  - PK/PD information of tumour models
  - Clinical popPK
- Own compound
  - Preclinical PK/PD/Efficacy data
  - Forecast clinical PK

Objective: Identify combination partner to deliver the best clinical efficacy

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 dosages for the combination treatments
- Identify the best dosing schedule

2. Clinical data -> *In vivo* combi 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

Triggering question

- What *in vivo* efficacy is needed to be better than (direct and indirect) competitors?
- What potency is needed to be better than (direct and indirect) competitors?
- What is the desired PK profile of your candidate compound?
- How would you predict efficacy (e.g. ORR) for your drug combination in the clinics?

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

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)

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