PK-PD in Support of Accelerated Programs: How Much is Enough?

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The Title Belongs to the Superfamily of Rhetorical Questions

- For example
  - How many technical replicates are appropriate?
  - How many experiments should be done?
  - How do I know when an experiment is “right”?
- My answer to all of these questions is
  - Until you are sure!
- Which begs the next question what do you mean by “sure”
  - I would be prepared to be the first person to administer a new compound to a patient

The Role of Pharmacokinetics-Pharmacodynamics

- Provides of supportive evidence for causality - i.e. evidence that
  - The observed effects are a result of the drug*
  - The drug exerts a known and predictable biological effect that can be harnessed for therapeutic benefit*
- Is an alternative to other ways causality can be established
  - Multiple comparative clinical trials

*These ideas from Peck CC, Rubin DB, Sheiner LB. Hypothesis: a single clinical trial plus causal evidence of effectiveness is sufficient for drug approval. Clin Pharmacol Ther 2003; 73: 481–90.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2016
EMA/CHMP/594085/2015
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products

Central Role of PK-PD for Antimicrobial Drug Development

- *"For reasons of lack of feasibility and/or as part of abbreviated clinical development programs…for unmet need…essential there are very robust PK-PD analyses to support the likely adequacy of regimens…"*
- *"Minimise or replace dose-finding studies"*
- *"Central role in regimen selection"*
- *"Selection of regimens for special populations"*
- *"Selection of regimens for minimization of selection of resistance"*

EMA/CHMP/594085/2015 Also Says…

- Not a detailed guidance on methodology for modelling and simulation
- Allows for alternative strategies (but suggests discussion with EU Competent Authorities)
- Acknowledges the field is mature and fit-for-purpose, but is also developing quickly

Some Additional Observations Before We Start [1/2]

- There is no PK-PD recipe book, grand plan, road map, text or mantra
  - Plans change after the first experiment
  - There is no “right” way to construct a package
- Programs take very good communication, trust and cooperative working between sponsors and PD labs
  - Nothing can happen without that
- It’s not easy, it’s not cheap, but it is generally fun

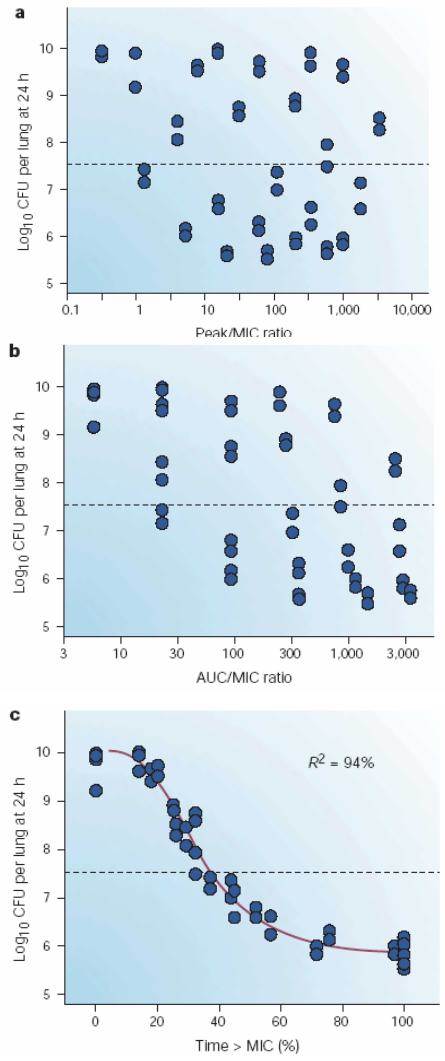
Some Additional Observations Before We Start [2/2]

- It is dangerous to make too many assumptions about the PD of a drug
- Our own approach is to do the experiment and see what we get
- We are primarily guided by the pharmacodynamics
  - Make the observation, then figure out why
  - (not the other way around)

The First Big Task

Determination of the Relevant Pharmacodynamic Index

[Dose Fractionation Studies]



Peak:MIC

AUC:MIC

T>Threshold

Dose Fractionation Studies

- Dose fractionation studies are hard, hard, hard!! [see next few slides]
- These studies serve two purposes:
  - For the general narrative expected by many
    - A drug is Cmax:MIC, AUC:MIC, T>MIC
    - Complex biology shoe-horned into one of three measures even if it doesn't fit well
  - For the investigator where the nuances provide an opportunity to achieve a deep understanding of pharmacodynamics
    - Hysteresis, effect site concentrations, drug-receptor interactions, protein binding, immune effects, emergence of resistant clones, tissue-specific effects, driver switching, use of alternative PD indices all arise here
    - A narrative is imperative

EMA: "in vitro and in vivo models have strengths & weaknesses and may be regarded as complementary"

- Advantages of fractionation in laboratory animal models
  - Biological barriers
  - Immune effectors
  - Not confounded by resistance
  - Effect site PK
- Thigh and lung can be used
  - Less variance with thigh
  - More effect with lung

- Advantages of fractionation using *in vitro* models
  - [not easier, not cheaper, not faster]
  - The ability to examine the pharmacodynamics of resistance
  - The ability to escape from limitations of lab animal PK
  - Ability to more easily perturb the regimen to uncover relevant biology

More Notes on Dose-Fractionation Studies

- These are difficult for the following reasons
  - Uncommon to get the experiments properly centered the first time
  - Distinguishing real biology from noise
  - Deep understanding of the PK-PD & design principles important
    - Schedules crowd too closely around the t1/2, everything pushed to AUC
    - If schedules stretch too far beyond t1/2 everything pushed to time>MIC
    - Fractionating at minimal & maximal effect can only ever return AUC

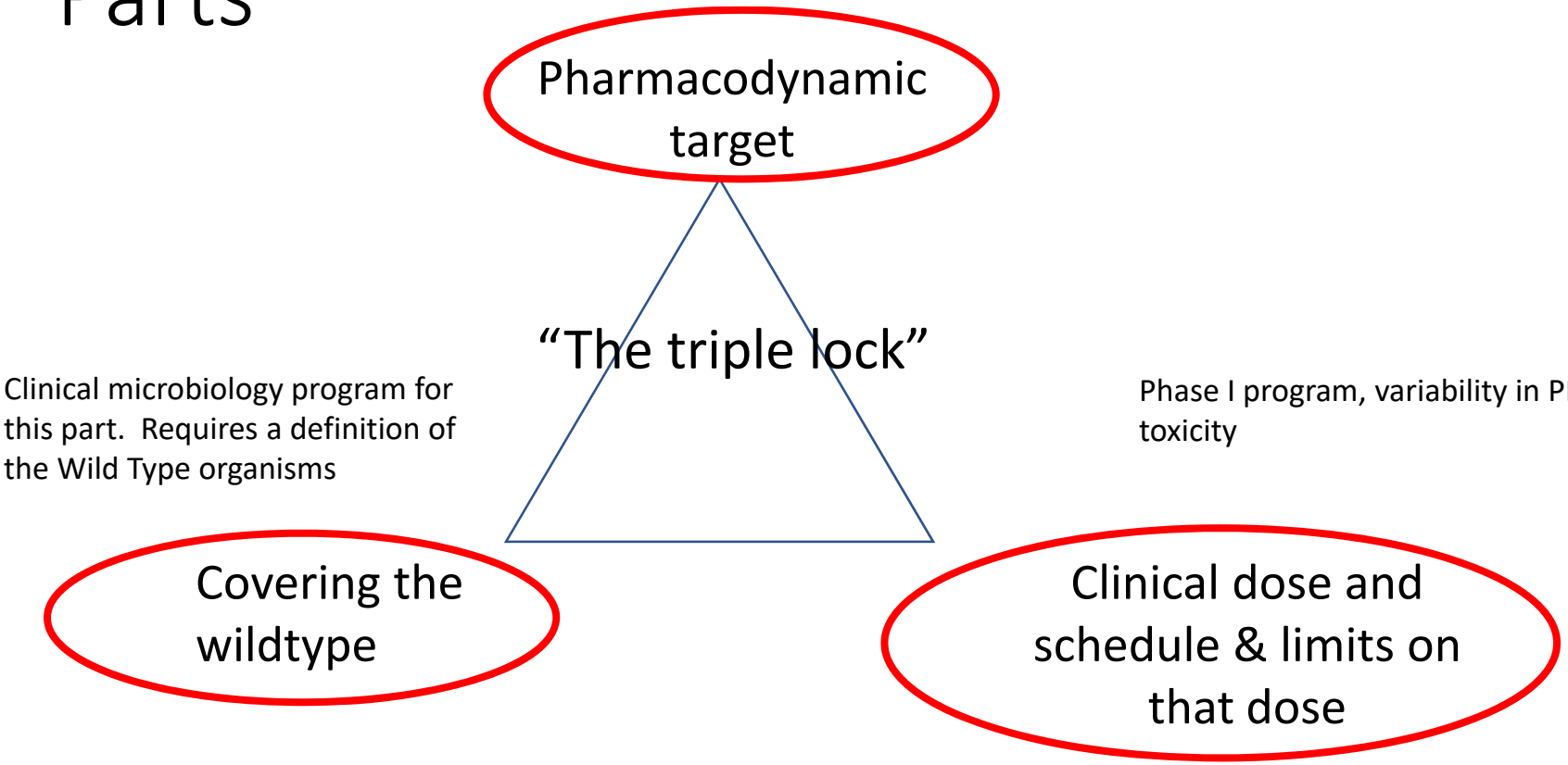
Next Steps

The magnitude of the PDI

[Do I have a drug?]

The Triple Lock… Three Interlocking Parts

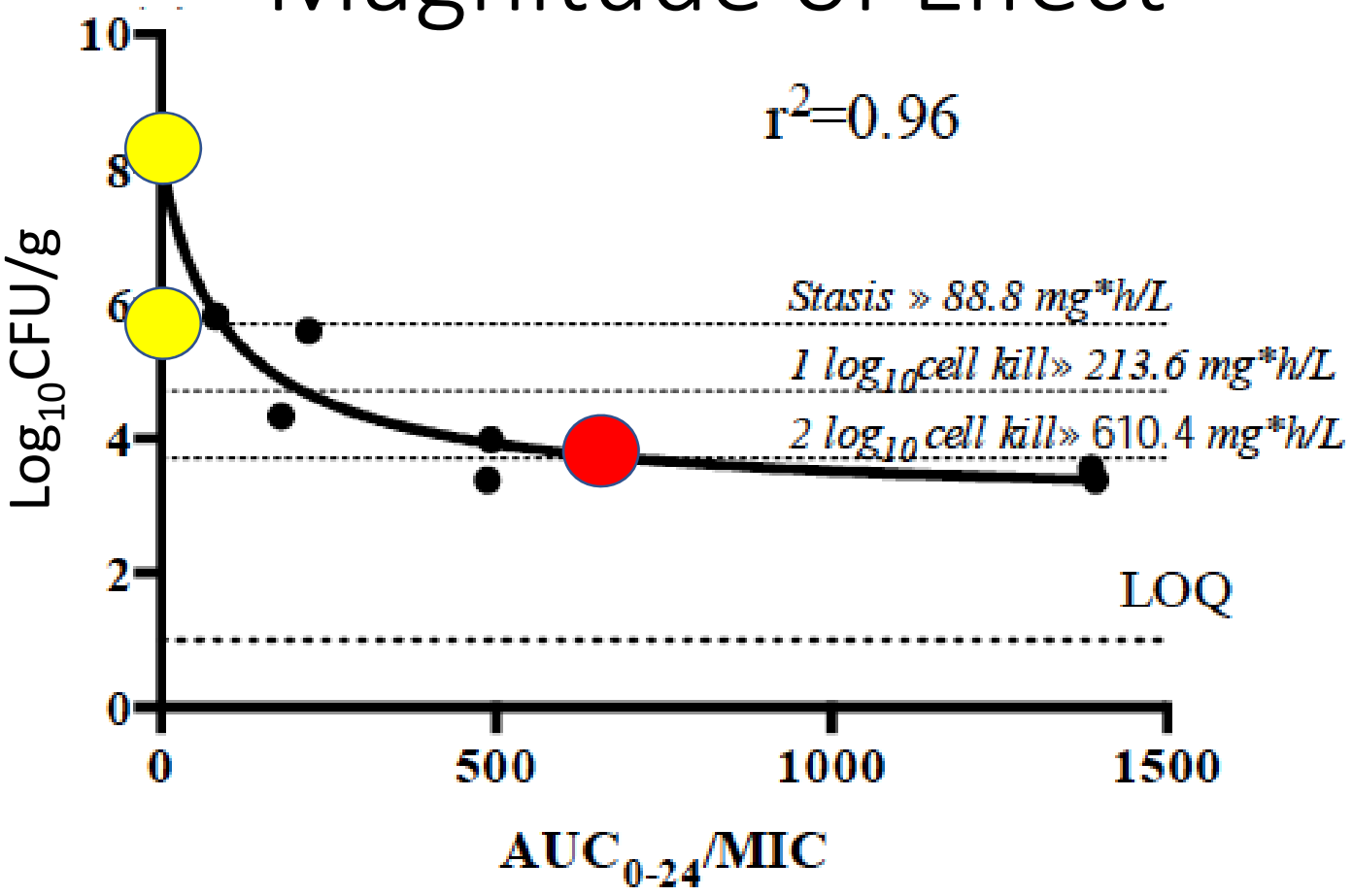
Magnitude of the Pharmacodynamic Index associated with stasis, 1-log, 2 log drops etc. from *in vivo* and *in vitro* studies



Clinical microbiology program for this part. Requires a definition of the Wild Type organisms

Phase I program, variability in PK, toxicity

Magnitude of Effect



What is Required to [Accurately] Determine the Magnitude of the Pharmacodynamic Index?

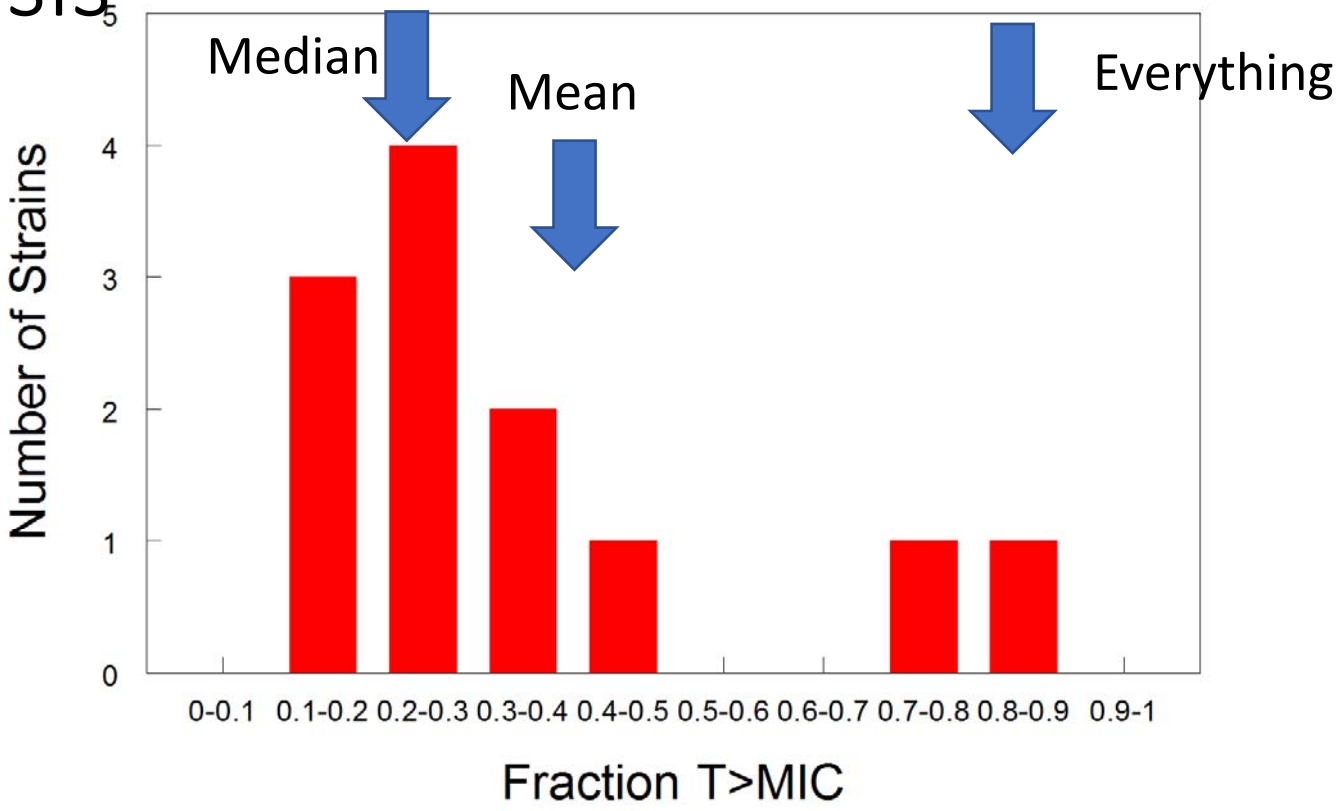
Key Ideas

- Linking different PD targets in experimental systems with clinical indications
  - Stasis for less severe clinical indications
  - Orders of logarithmic killing of more severe diseases
- Capturing and quantifying the variability in the pharmacodynamics of wild-type organisms
  - Different strains, species and genera that are expected in the clinical program

Pharmacodynamic Variability

- How many species?
  - Certainly leading pathogens are important
  - (e.g. *E. coli*, *Klebsiella pneumoniae*, but not every member of Enterobacteriaceae)
- How many strains of each species?
  - n=4-10 [until you are sure]
- Which resistance mechanisms?
  - Two separate issues: see next few slides

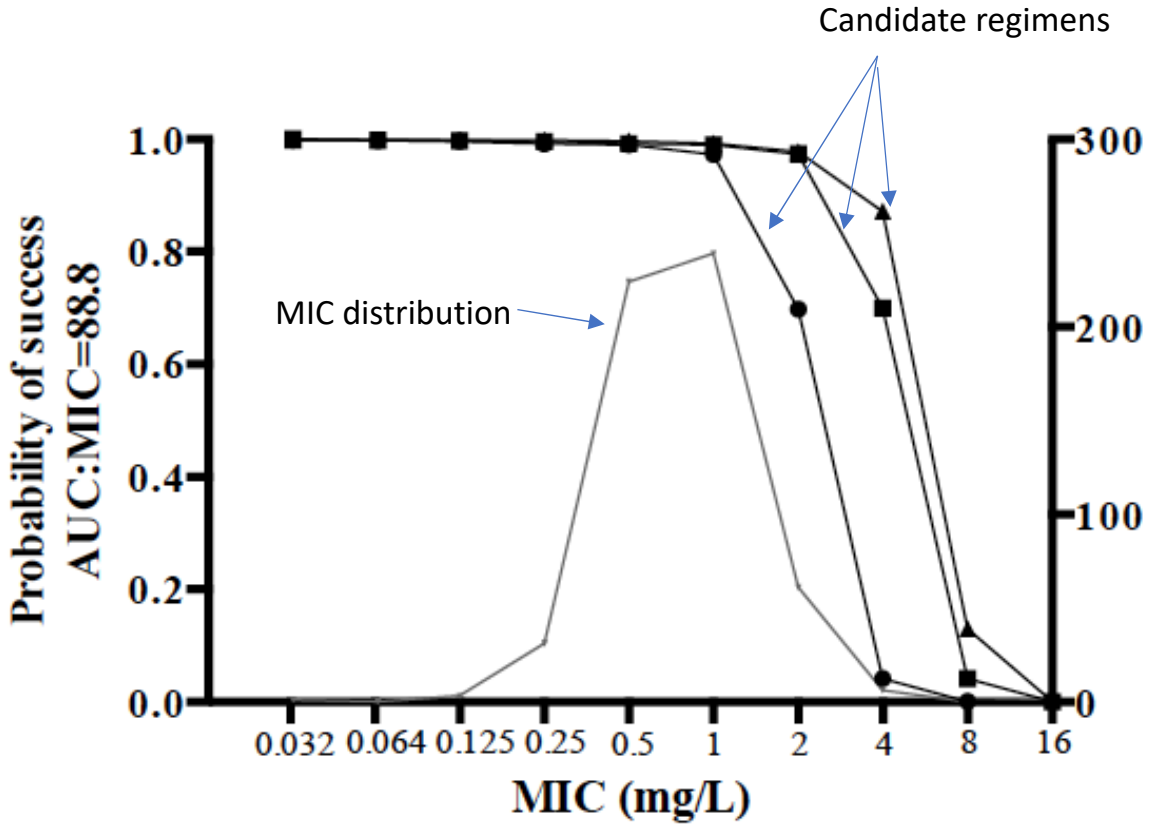
Pharmacodynamic Index Producing Stasis



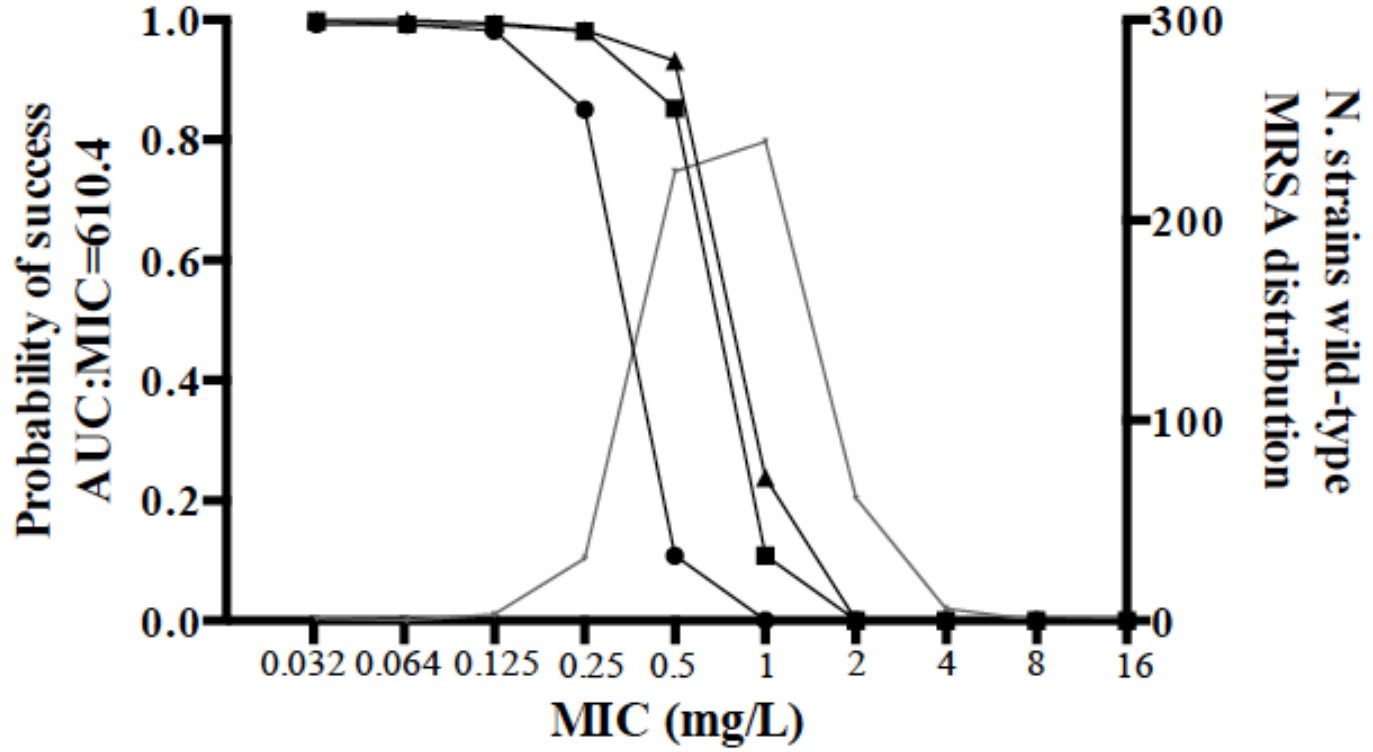
Strains with Different Resistance Mechanisms

- Selecting strains with a range of MICs
  - Provides evidence the MIC is transmitting biologically relevant information
  - MICs within the WT and beyond the WT
  - ***Building evidence that the MIC is helpful***
- Demonstrating activity against resistance mechanisms expected in the clinical program
  - The PD of the new drug should be the same as WT
  - e.g. a new carbapenem should be pharmacodynamically naïve to presence of an ESBL
  - ***Explicit demonstration of the lack of cross resistance***

Probability of Success with Stasis Target



Probability of Success with 2-log Target



The allure of rigor, certainty and absolutism

- The following combination is lethal for pretty much any drug
  - A very rigorous endpoint (e.g. orders of logarithmic killing + suppression of resistance)

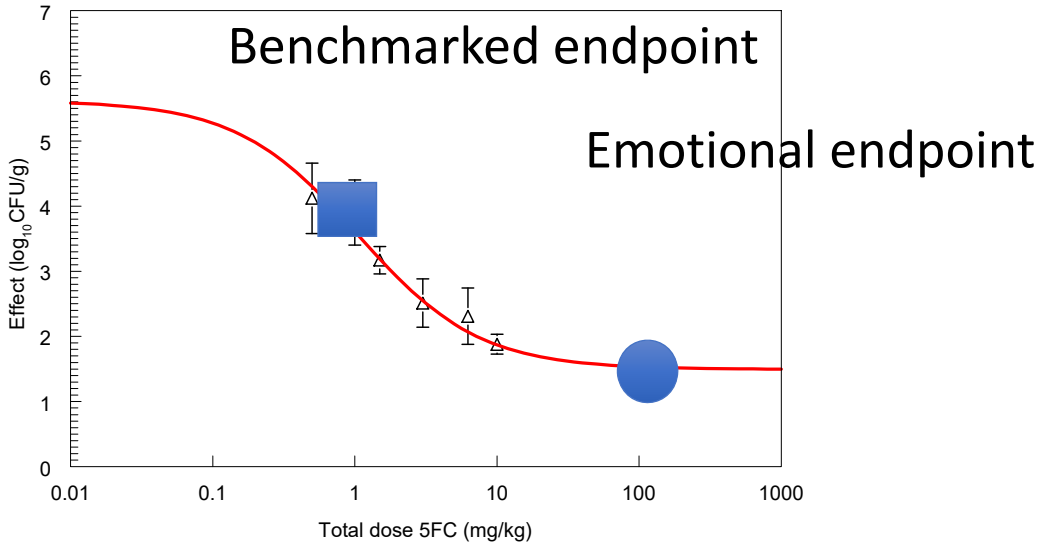
  +

  - Strains with the highest pharmacodynamic index are covered

  +

  - 90% Probability of target attainment at the upper edge of the wild-type

Endpoints & Benchmarking



And lastly, from Tom Parr

…if we can tell about the PDI, we will get “the dose” and all will go forward. But if we can tell the story in more than one way, and it seems to hang together by so to speak triangulation of the stories, it is even better, and more likely correct and useful.

All good

Strategy for The “Triangulation of Stories”

- Orthogonal reasoning [John Rex]
- Exercise (or stress) model systems [Alan Forrest]
- Use more than one model system
  - Another laboratory animal model
  - Hollow fibre model
  - *Actively manage and seek explanation for discordant results*
- Use more than one PD lab
- Use more than one study readout
  - Log_{10}CFUs, biomarkers are the primary endpoints
  - Survival, histopathology, inflammatory markers, radiology, bioluminescence are secondary
- Use multiple strains
  - Geographically disperse, well-characterised, established provenance
  - Using strains with resistance mechanisms likely to be encountered in clinical trials

Last Slide

- Thank you
- We are at www.liverpool.ac.uk/apt
- @APTlivuni

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