How much is enough?

- 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

- PK-PD provides 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*
- PK-PD 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.

EMA guidance on PK-PD

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"

Additional observations before we start [2/2]

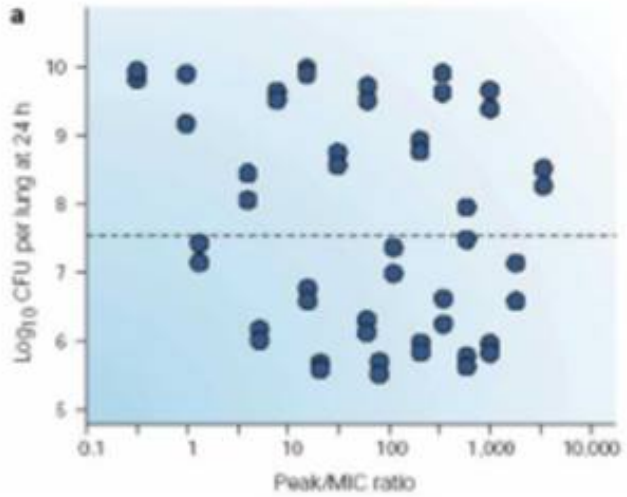
- It is dangerous to make too many assumptions about the PD of a drug
- Our own approach is to do the experiment and see what we get
- We are primarily guided by the pharmacodynamics
  - Make the observation, then figure out why
  - (not the other way around)

The first big task

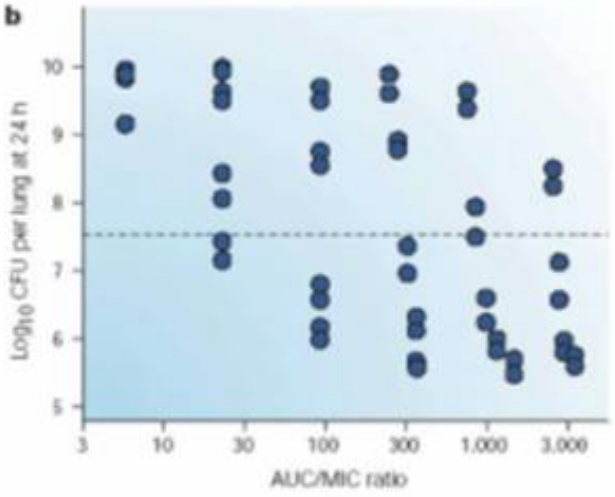
Determination of the Relevant Pharmacodynamic Index

(Dose Fractionation Studies):

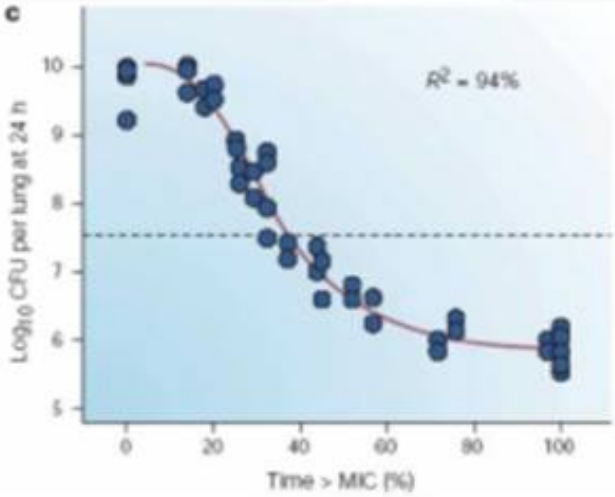
Peak:MIC



AUC:MIC



T>Threshold



MIC – Minimal inhibitory concentration
AUC – Area under the curve

CARB-X

ECCMID

GARDP
Global Antibiotic Research & Development Partnership

In vitro vs. in vivo experimental models

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

- 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

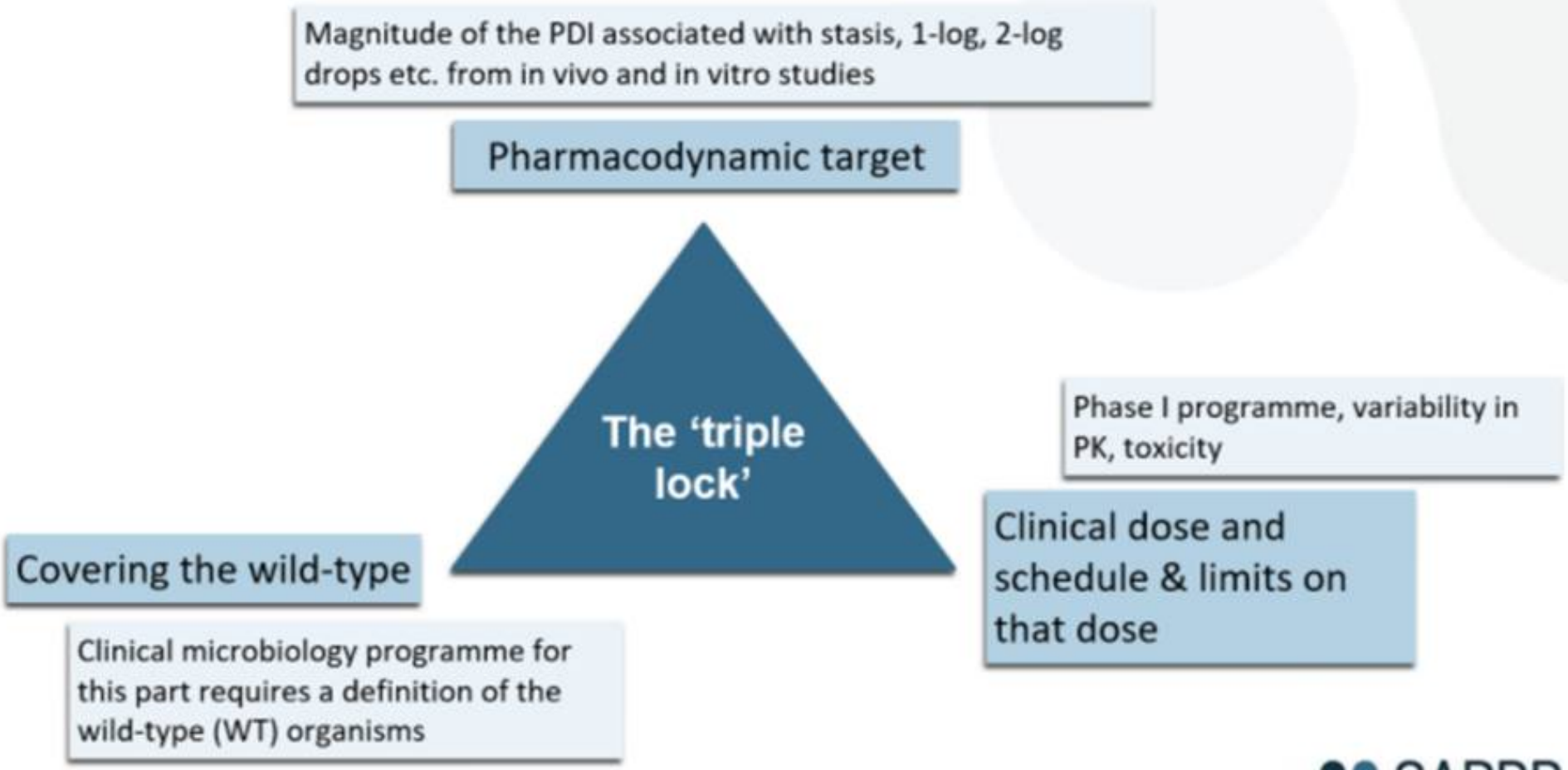
In vitro models are not easier, not cheaper, not faster

Difficulties of dose-fractionation studies

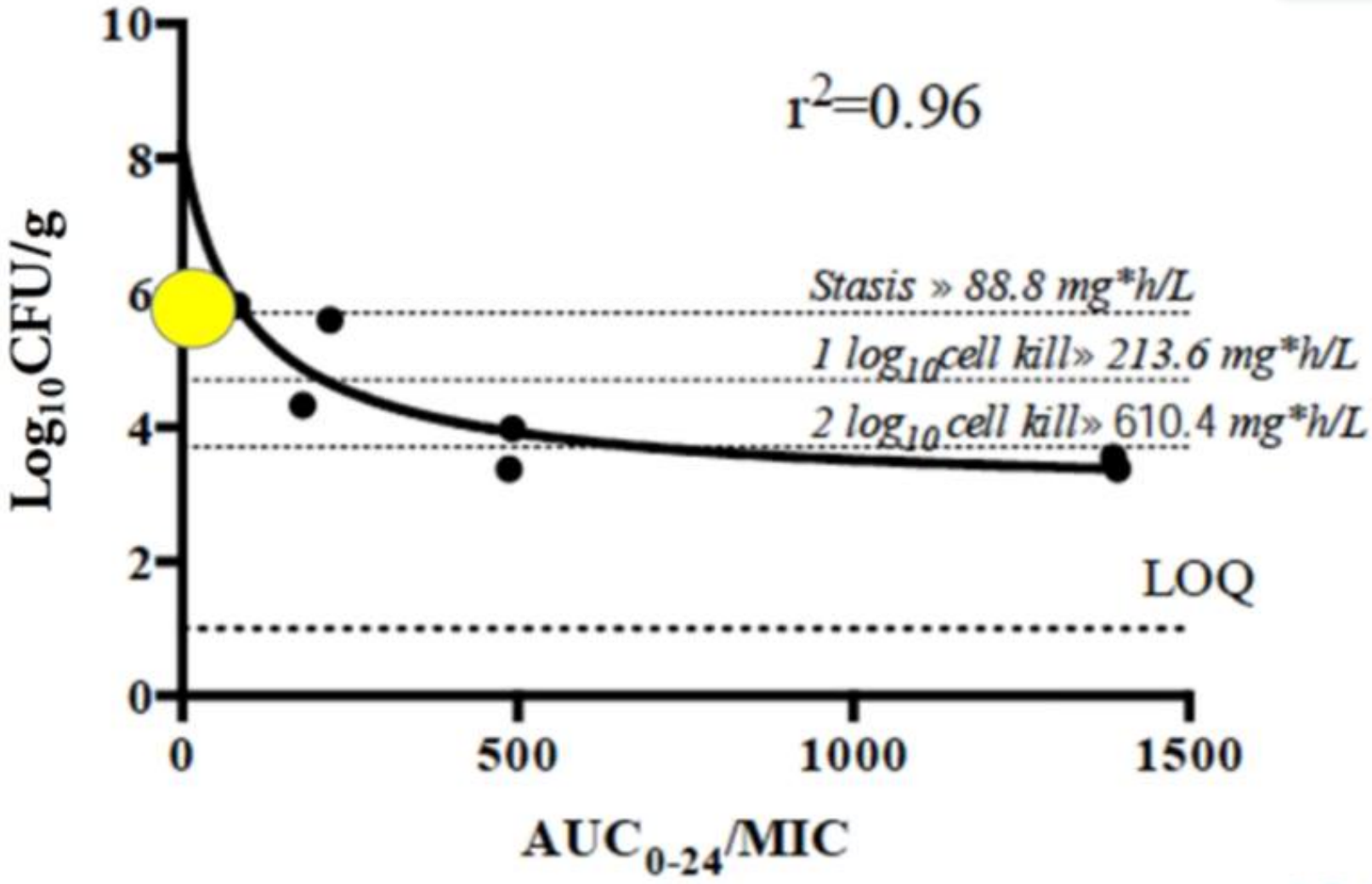
- Uncommon to get the experiments properly centred the first time
- Distinguishing real biology from noise
- Deep understanding of the PK-PD & design principles important
  - Schedules crowd too closely around the t1/2, everything pushed to AUC
  - If schedules stretch too far beyond t1/2 everything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

Next steps

The magnitude of the pharmacodynamic index (PDI) – Do I have a drug?



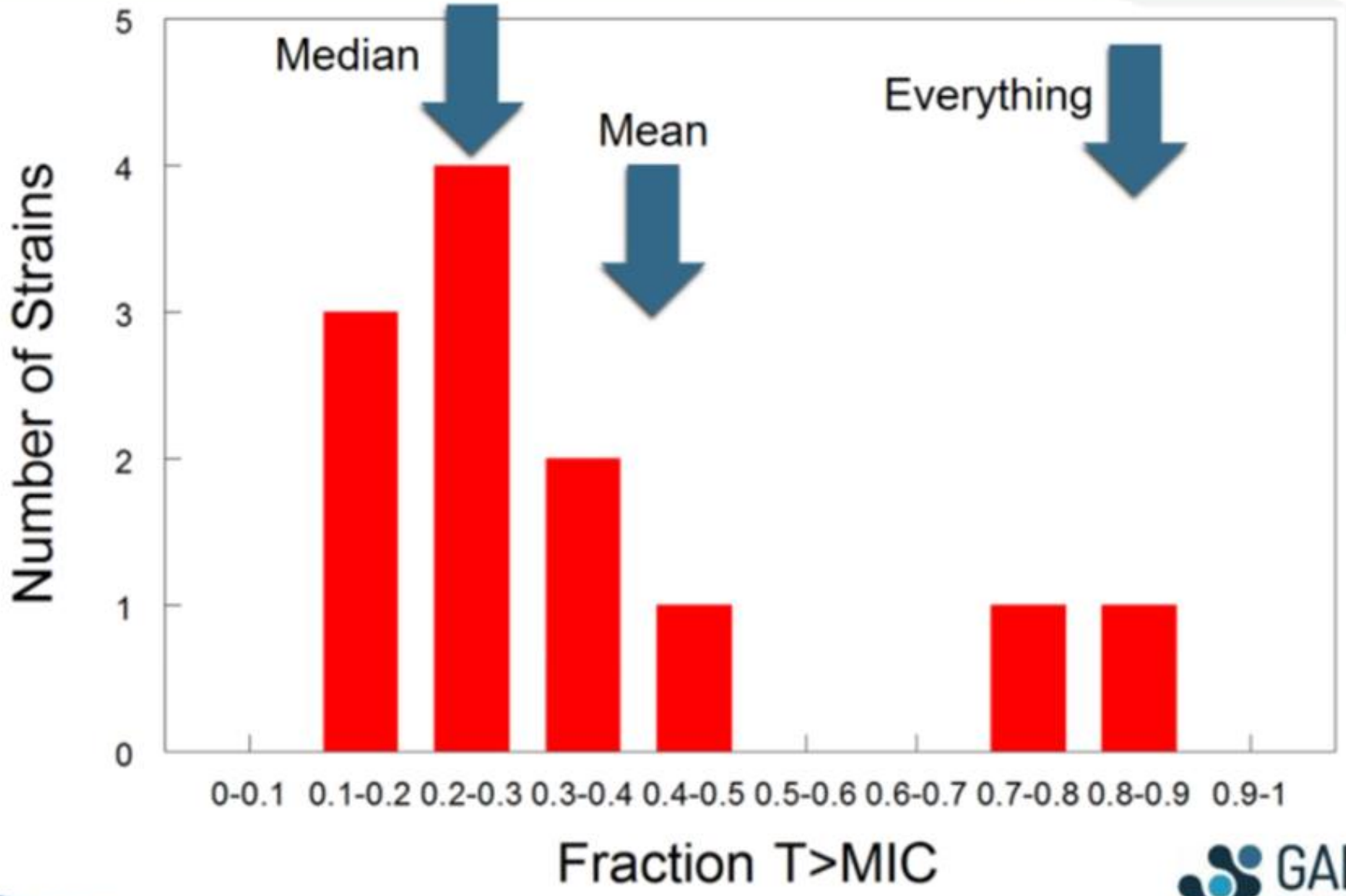
Magnitude of effect



Pharmacodynamic variability

- How many species?
  - Certainly leading pathogens are important
  - (e.g. *Escherichia 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

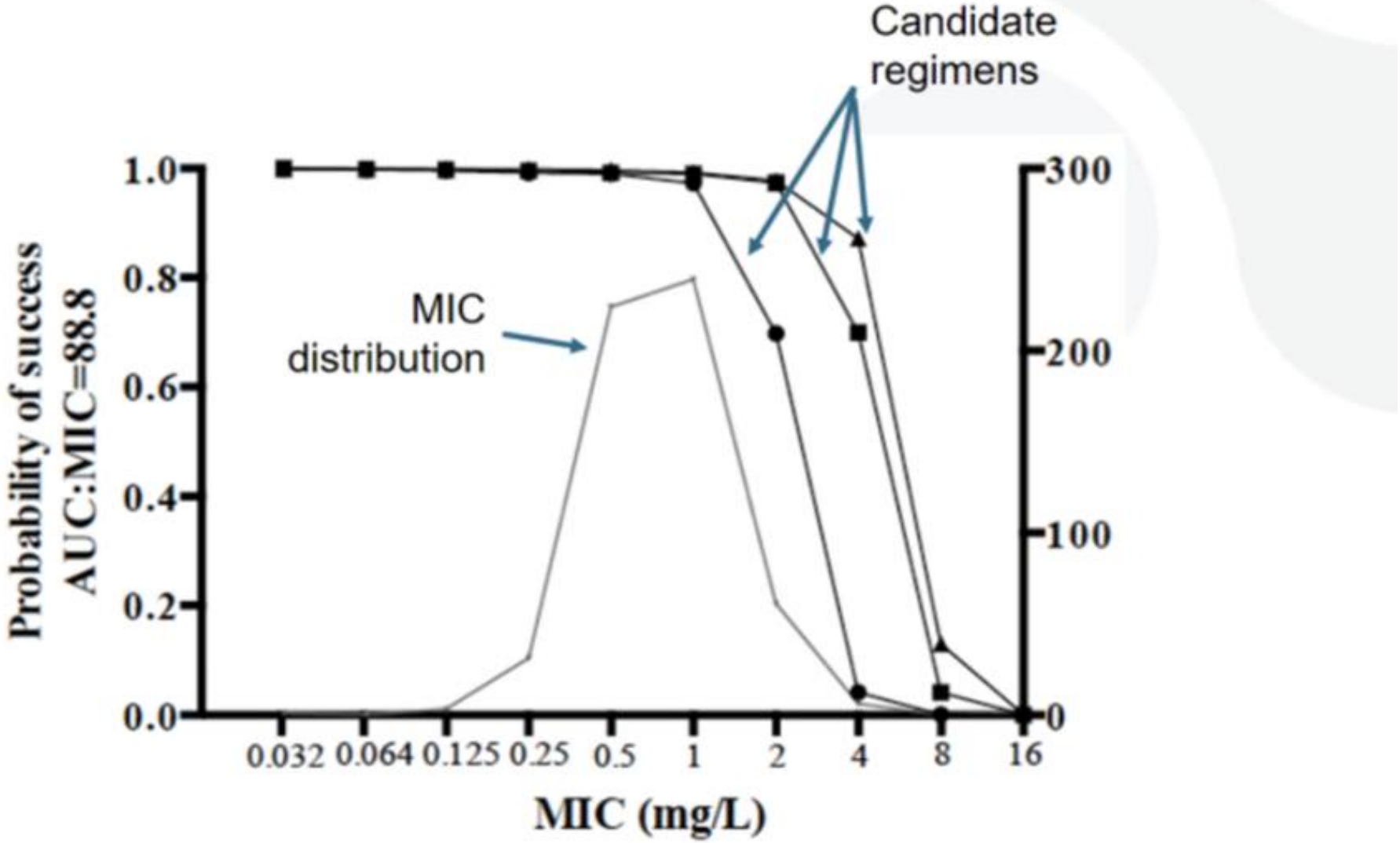


GARDP
Global Antibiotic Research

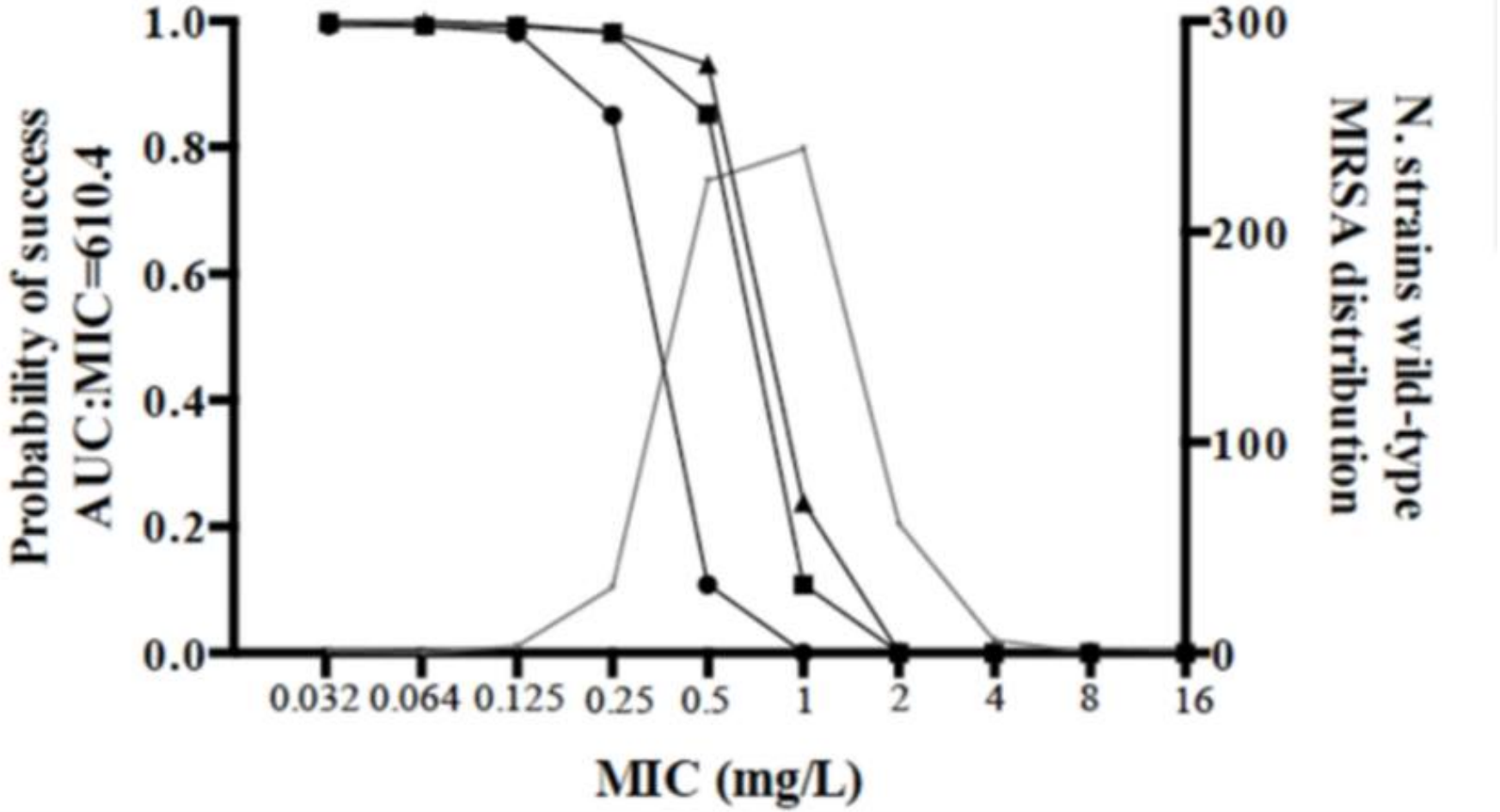
Strains with different resistance mechanisms

- 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 programme
  - 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

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 fiber 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-characterized, established provenance
  - Using strains with resistance mechanisms likely to be encountered in clinical trials

Endpoints & benchmarking