Pharmacodynamics to Accelerate Antimicrobial Drug Development for AMR

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Therapeutics
Drug A, Dose A^1 versus Drug B, Dose B^1

Pharmacodynamics is the Bedrock of **ALL** Therapeutics…it sits here without being seen

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.

And, for AMR…

- It provides the necessary evidence to float the clinical development program when that evidence difficult/ impossible to obtain early on
- Consider current development pathways for BL/BLIs


DANGER
EXTREMELY
HIGH VOLTAGE

Why high voltage?

- We are the first to get a good view on whether a new compound could be a drug
- We preside over/ supervise/ advise on two critical steps
  - Step 1.
    - In vitro-to-in vivo transition
  - Step 2.
    - In vivo to early phase clinical studies

Relevant Documents

Antifungal Agents

J Antimicrob Chemother 2016; **71**: 3008–3019
doi:10.1093/jac/dkw298 Advance Access publication 5 August 2016

Journal of Antimicrobial Chemotherapy

Pharmacodynamics for antifungal drug development: an approach for acceleration, risk minimization and demonstration of causality

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From NIH/NIAID workshop June 2016

Generating robust and informative nonclinical *in vitro* and *in vivo* **bacterial** infection **model** efficacy **data** to support translation to humans.

Bulitta JB, Hope W, Eakin AE, Guina T, Tam VH, Louie A, Drusano GL, Hoover JL.

Antimicrob Agents Chemother. 2019 Mar 4. pii: AAC.02307-18. doi: 10.1128/AAC.02307-18. [Epub ahead of print]

Review.

PMID: 30833428 **Free Article**

Similar articles

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

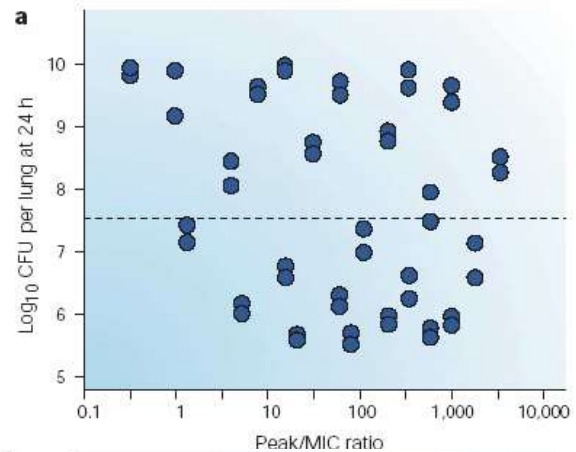
Central Role of PK-PD for Antimicrobial Drug Development

- *“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”*

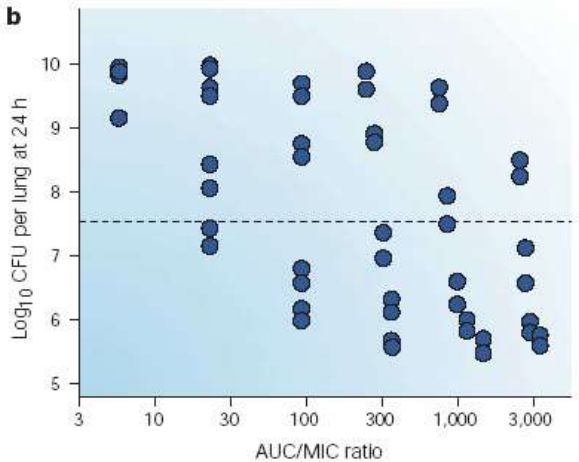
The First Big Task

Determination of the Relevant Pharmacodynamic Index

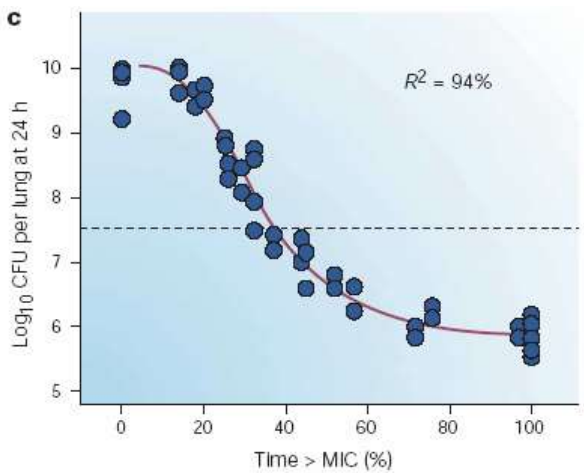
[Dose Fractionation Studies]



Peak:MIC



AUC:MIC



T>Threshold

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

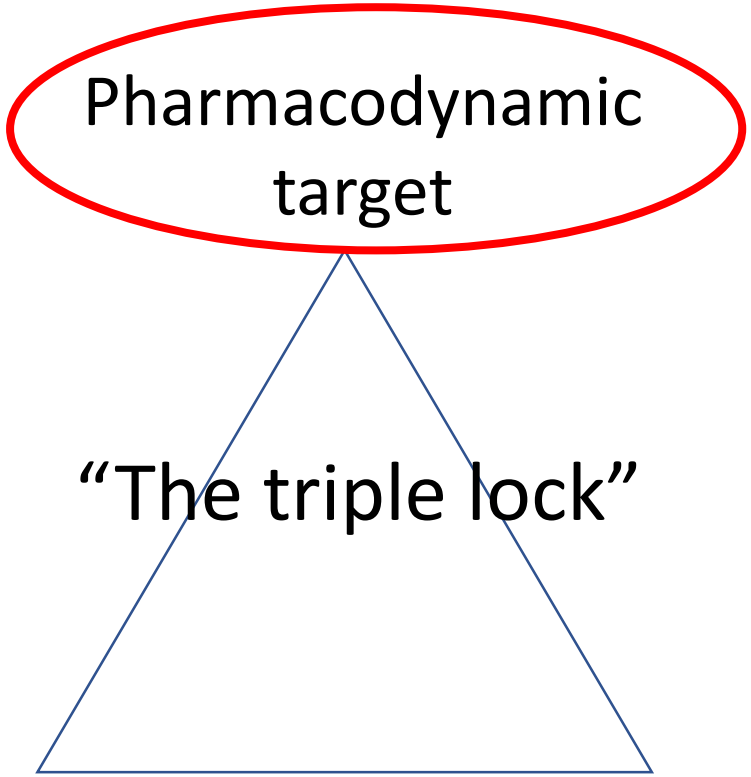
Next Steps

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



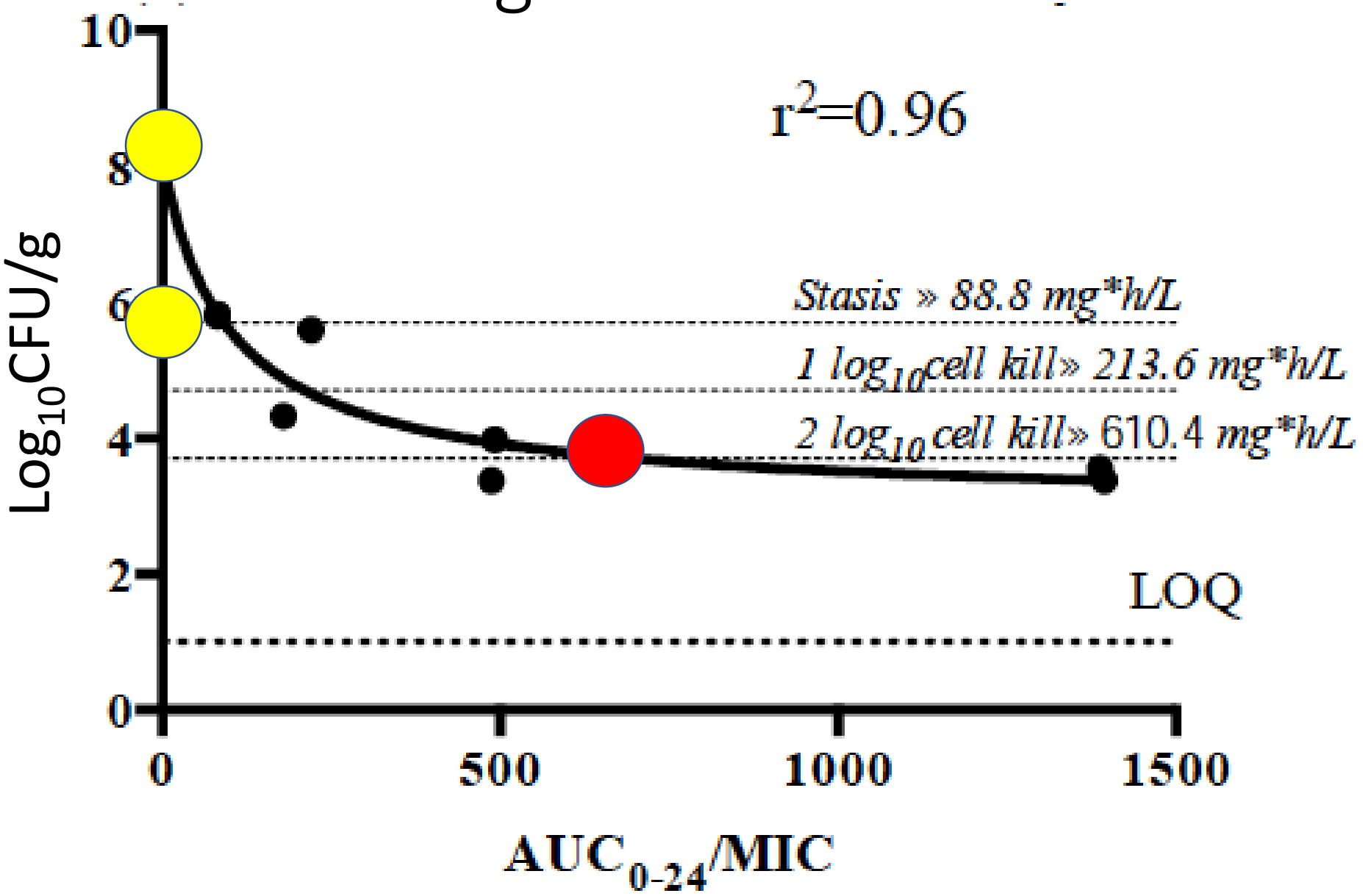
Clinical microbiology program for this part. Requires a definition of the wild type organisms

Phase I program, variability in PK, toxicity

Covering the wildtype

Clinical dose and schedule & limits on that dose

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 [cUTI]
  - Orders of logarithmic killing of more severe diseases [pneumonia]
- Capturing and quantifying the variability in the pharmacodynamics of wild-type organisms
  - Different strains, species and genera that are expected in the clinical program

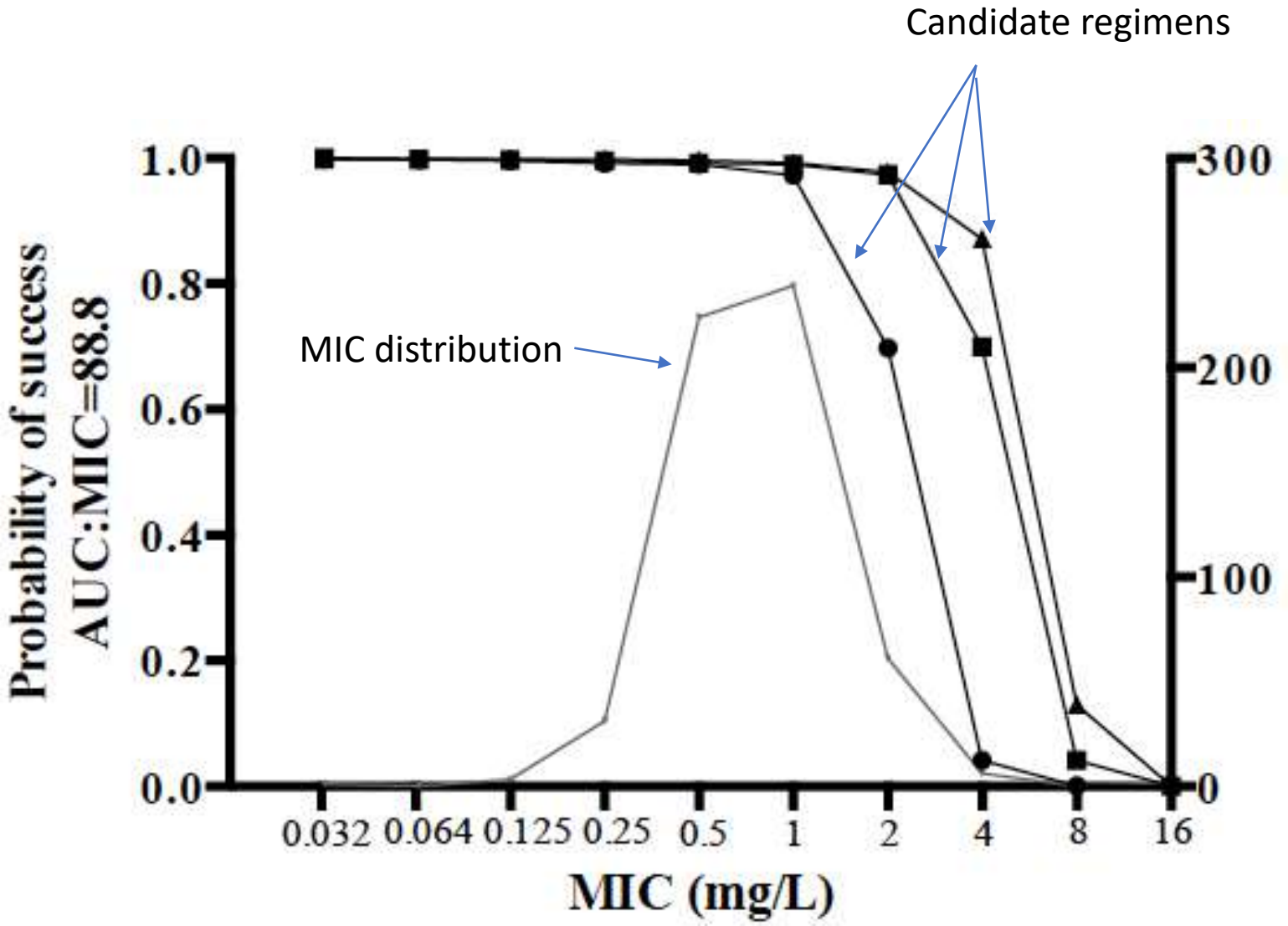
Pharmacodynamic Variability

- 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=4-12 [until you are sure]
- Which resistance mechanisms?
  - Two separate issues: see next few slides

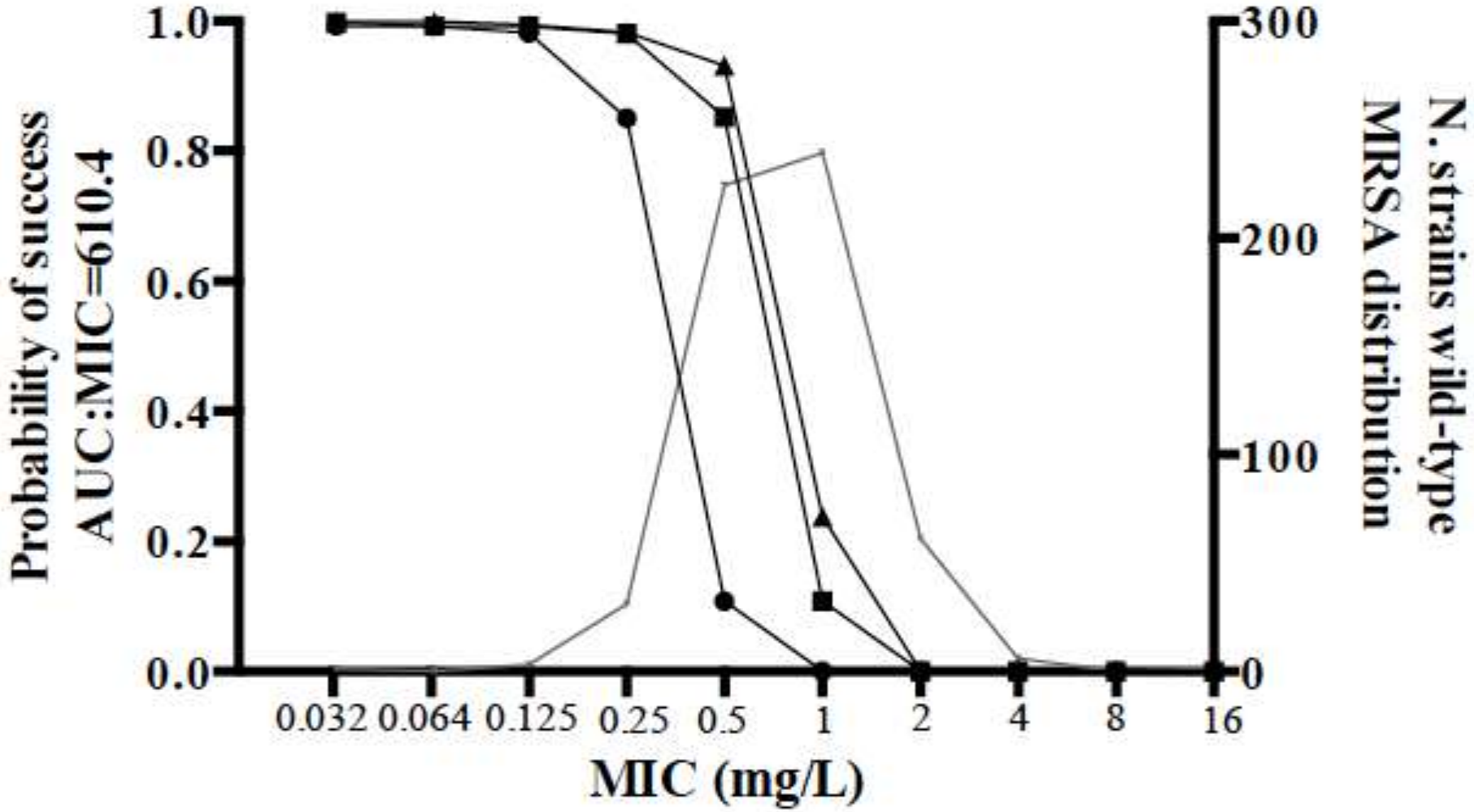
Strains with Different Resistance Mechanisms

- 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



Last Slide

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

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