ELF data (Study Designs, Interpretation, Role in Dose Selection)

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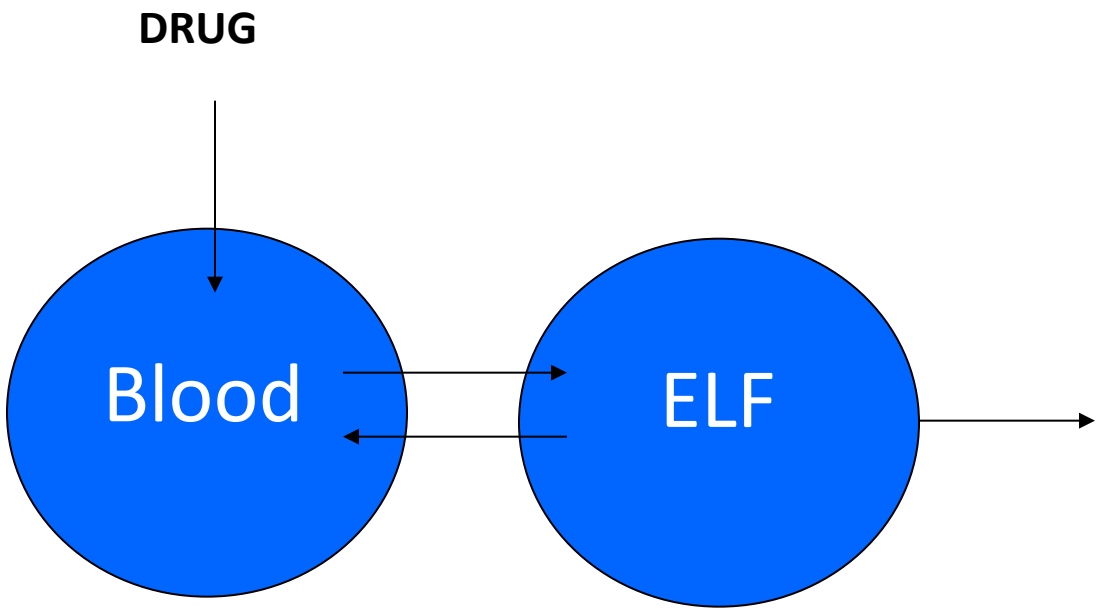
What is this talk really about?

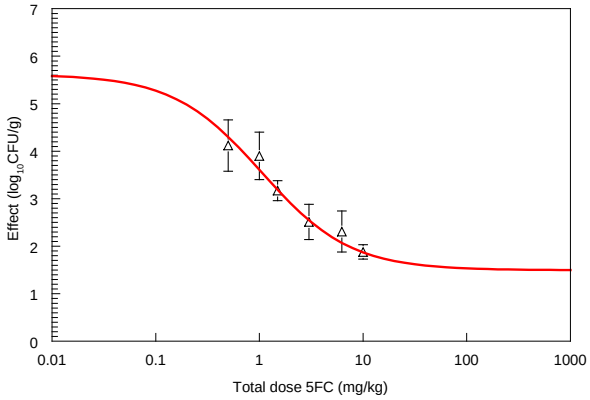
It is my intention to provide a conceptual framework for studies of ELF for pneumonia

Not a blow by blow description of every ELF study

Does the antibiotic-time profile in ELF provide a more complete understanding of the antimicrobial effect in pneumonia?



Antimicrobial effect



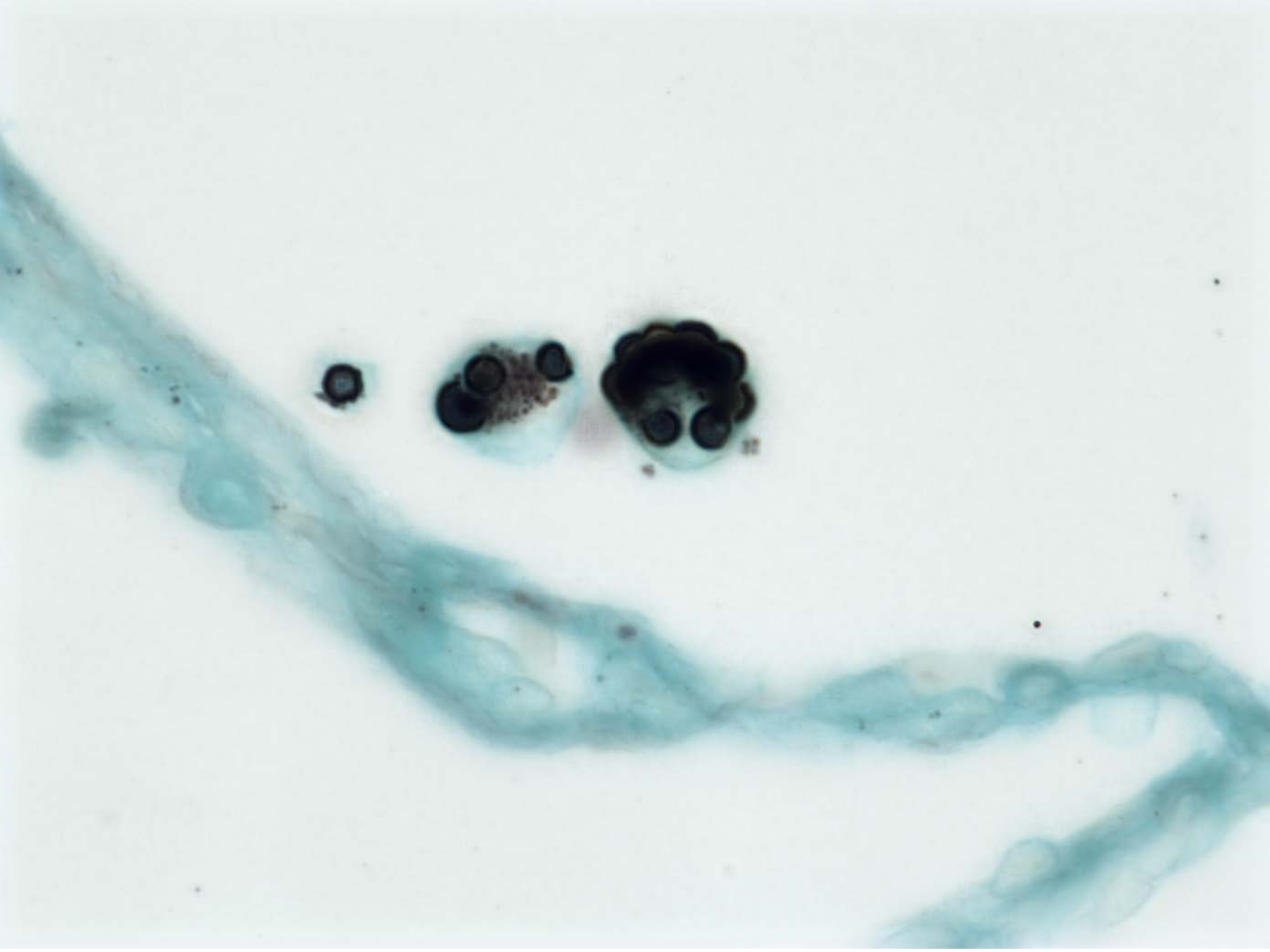
Three critical junctures involving ELF for developing drugs for pneumonia

- Preclinical-to-Phase I
  - Major Issues
    - Relevance of ELF for the pathogen/ pathogenesis in question
    - Estimate of ELF penetration in laboratory animal models & patients
- Phase I-to-Phase II/III
  - Major Issues
    - Estimate of ELF penetration in patients
    - Variance structure of data
    - Design of clinical studies in critically ill patients
- Phase I-II back to Preclinical (the virtuous circle)
  - Major Issues
    - Resistance studies in hollow fibre to make sure regimen is right for further study in Phase II-III

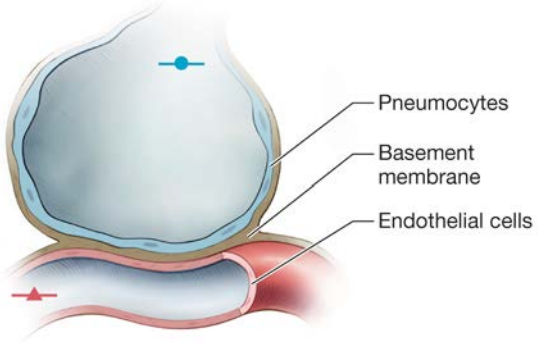
The lung is a “sanctuary site”

- It has its own rules of engagement
- Appears very difficult to predict ELF penetration on basis of physicochemical properties
  - Cephalosporins have significantly different penetration ratios
    - Ceftobiprole (19%)[1]
    - Cefepime (100%)[2]
    - Ceftazidime (20-30%)[3,4]
- More than one subcompartment
  - PAMs
  - Alveolar epithelium, endothelium, interstitial space
- Movement of cells (macrophages & neutrophils) into and out of the lung

[1]Rodvold et al AAC 2009, [2]Boselli et al Crit Care Med 2003, [3]Nicolau et al JAC 2015, [4]Boselli et al Intensive Care Med 2004



Two meanings of ELF

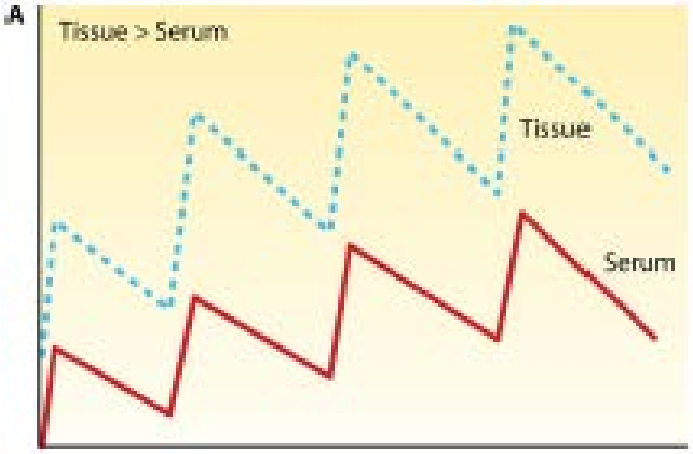


<u>It's a real thing</u>

- A compartment that is fully mixed (probably not)
- A compartment devoid of protein (probably not)
- A compartment that is directly linked with the site of infection (well, yes, but only in part)

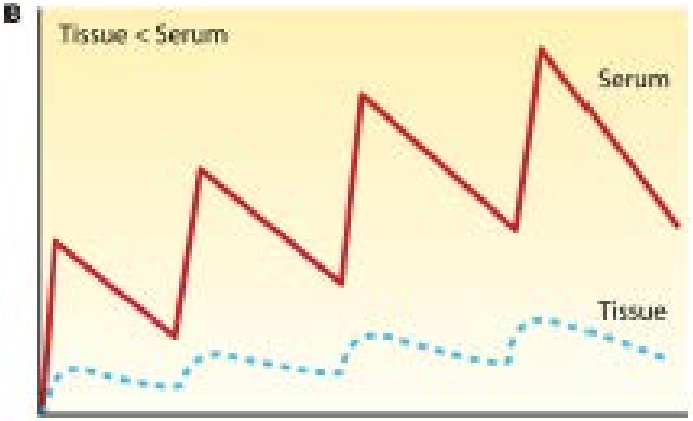
<u>It's a useful construct</u>

- A measurable compartment that is closer to the "real action"
- A <u>better</u> predictor of drug activity than serum



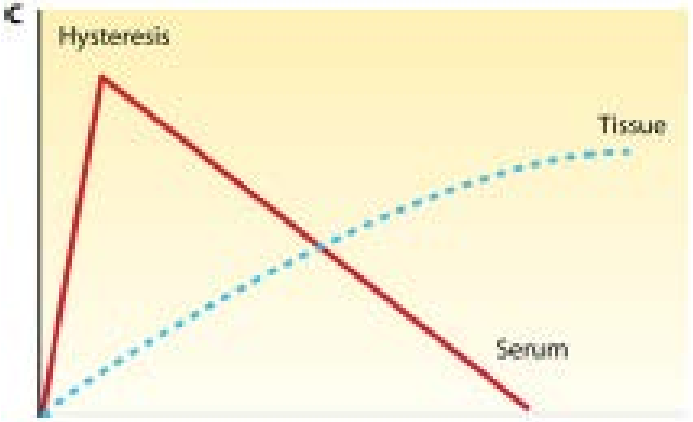
ELF > Serum

- Macrolides
- Oxazolidinones



Serum > ELF

- Beta lactams
- Aminoglycosides



Serum ≈ ELF, but hysteresis

Juncture #1

Preclinical-to Early Clinical Phase

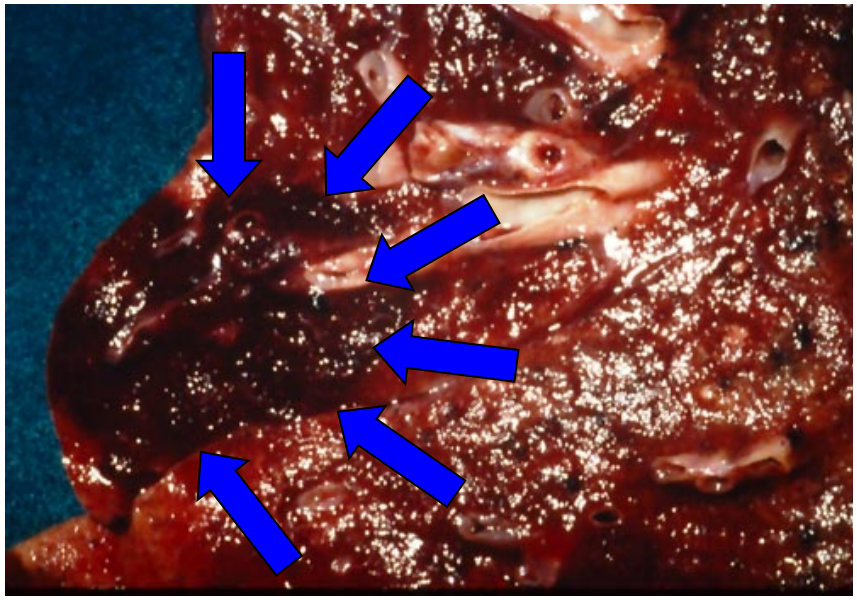
Preclinical to Early Phase Clinical Bridging: Assumptions re. ELF

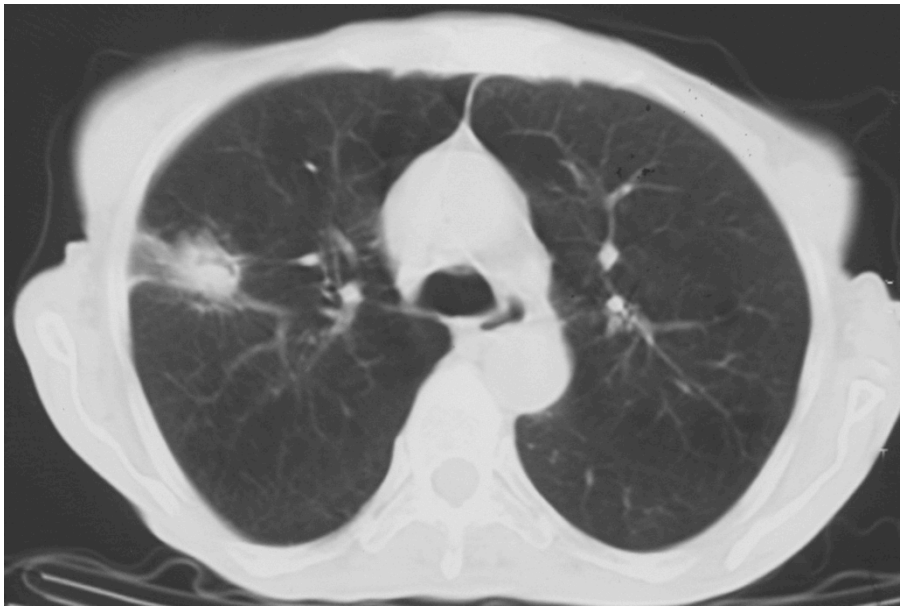
- **ASSUMPTION 1.**
  - If ELF is not measured there is a fundamental assumption that the trafficking of drug to and from the effect site is the same in the experimental model and in the patient
  - This assumption is EVERYWHERE in the PK-PD literature
  - And, is often not acknowledged as a potential limitation
- **ASSUMPTION 2.**
  - The ELF compartment is relevant for both the experimental model (where drug is being directly measured and predictions made) and for the patient
  - Could measure ELF in the mouse and patient, but it is the "wrong" compartment for both
    - i.e. true and true and unrelated
    - Perhaps this applies to fungal pneumonia or lung abscess?

Preclinical to Early Phase Clinical Bridging: Assumptions

- **Assumption 3.**
  - The standard PK-PD model applies
  - The activity of a drug can be best explained in terms of the T>MIC, AUC:MIC, peak:MIC
  - Probably OK for early uncomplicated disease, but not for
    - Antimicrobial resistance
    - Chronic infection
    - Destructive pneumonia
    - Intracellular pathogens

e.g., ELF is unlikely to provide useful information for more advanced pathological changes in pneumonia, fungal pneumonia, lung abscess etc. etc.





Additional issues for estimating ELF penetration in preclinical studies

- A BAL from a mouse isn't the easiest procedure
- There are multiple sources of error that are likely multiplicative (not additive)
  - Experimental error
  - Bad experimental design
  - Measurement (assay) error (e.g. urea in serum, urea in BAL and the drug)
- All of which compounds substantial inherent biological/ pharmacological variability that is already there
  - e.g. median penetration ceftobiprole is 68.8% and the interquartile range is 25.1-187.3%!![1]

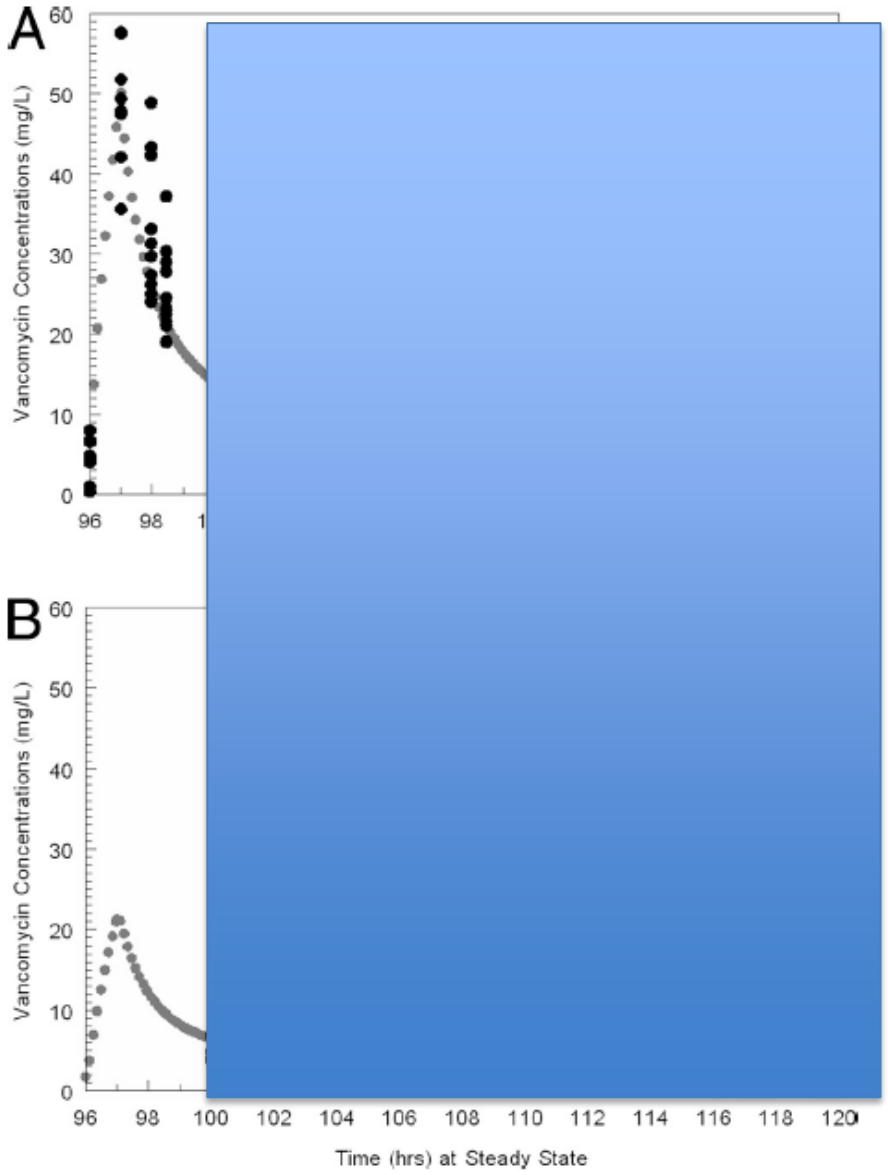
[1]Rodvold et al AAC 2009 53(8) 3294-301

Other issues of importance

- A mistake is to assume targets for blood also apply to ELF
  - e.g. an AUC:MIC of 400 for vancomycin applies to both blood and ELF
  - T>30-40% for the beta lactams applies to both sites
  - ELF targets must be specifically determined
- There is also the issue of protein binding in ELF
  - Frequent assumption is that this is negligible
  - Anyone that has lavaged anything knows this isn't likely to be true
  - If it does not have protein at the start, it does at the end!

ELF Penetration in Healthy Volunteers: A Summary

- An ever-increasing number of studies
- Population PK models fitted to serum and ELF PK circumvents the problem of a single ELF measurement from a patient
- Urea dilution as a correction factor for dilution appears well accepted
- Penetration ratio expressed as free serum drug exposure: (total drug) ELF drug exposure
- Monte Carlo simulation to demonstrate the extent of variability even in Phase I patients is standard



Design Issues in Phase I Clinical Trials

Lodise et al AAC 2011 55(12) 5507-11

Real World: My view and for discussion

- Seems as if ELF estimation has become standard
  - It's nice to know drug is at the site of infection
- If the mouse and the Phase I patients line up "well" then that's probably OK
  - (whatever "well" means)
- The question is what to do if they are (substantially) different?
  - Will now take time and money to sort…the consequences of having this wrong are large
  - Cannot simply ignore the result
  - Consider a repeat study in a second laboratory
  - Consider a second laboratory animal species
  - Consider humanised PK in the mouse
  - If it is real, need to consider how to bridge the results safely and properly

Juncture #2

Early Clinical Phase- to-Sick Patients

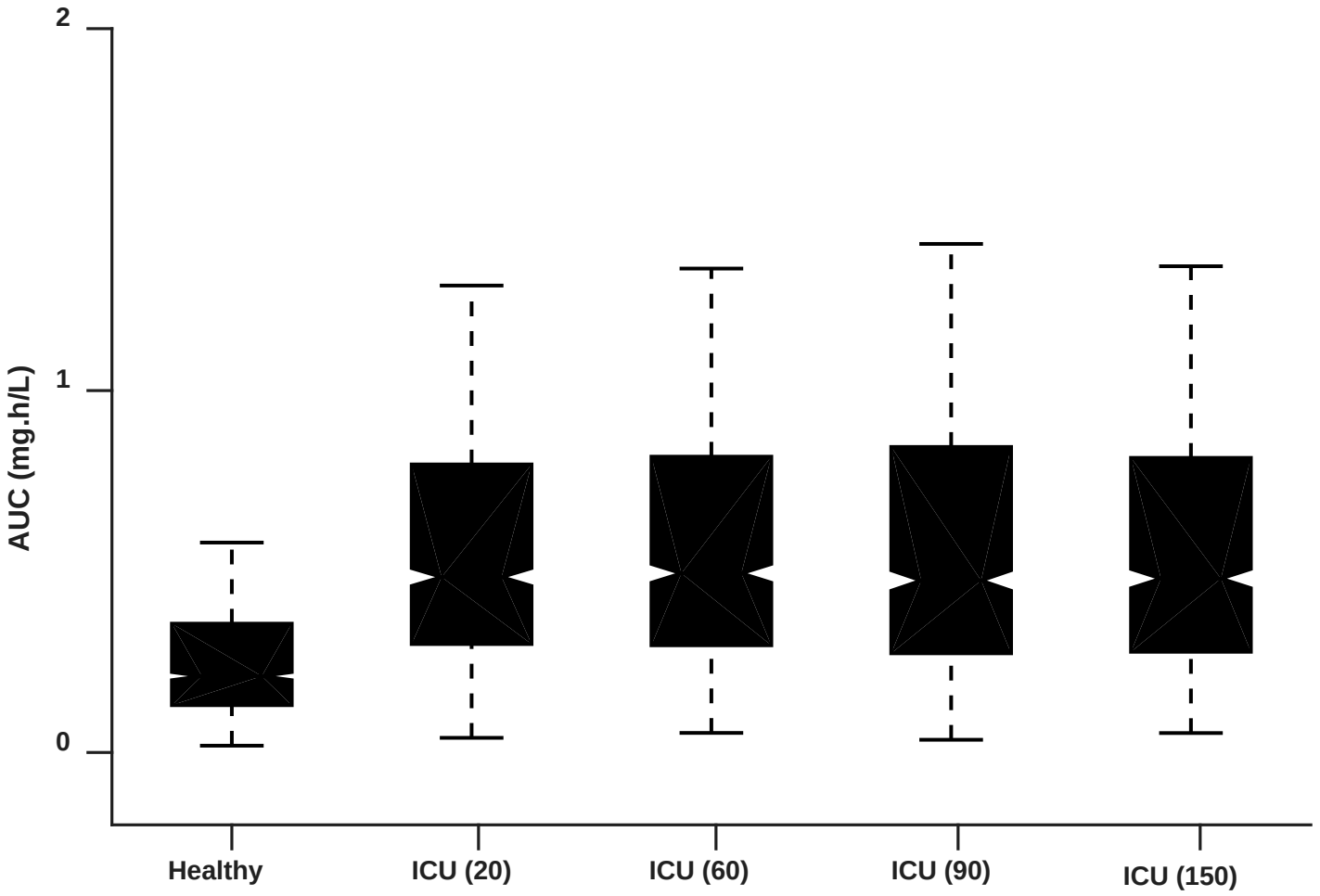
Design Issues in Phase II/III

- Decide whether the drug is being given for PK or effect
  - For PK: administer on a standard backbone (issues of DDI need to be addressed)
  - Efficacy: potential ethical challenges amongst others
- One BAL often possible because establishing a microbiological diagnosis is standard of care
  - But a second may be challenging

Two fundamental questions at this stage

- Are the point estimates for ELF penetration in volunteers and patients comparable?
  - How many patients are required to get a robust estimate of central tendency?
    - (when variability in patients is not known *a priori*)
  - May require more than one study
- What extent of variability is present in patients?
  - How many patients are required to get a robust estimate of variability?
    - (when variability in patients is not known *a priori*)
- Not much information on how Phase I patients predict drug behavior in sick patients
  - They can be discordant in either direction

Simulations - AUC Ratio (ELF/Plasma) piperacillin/tazobactam 4000 mg Q8h, AUC_{16-24}



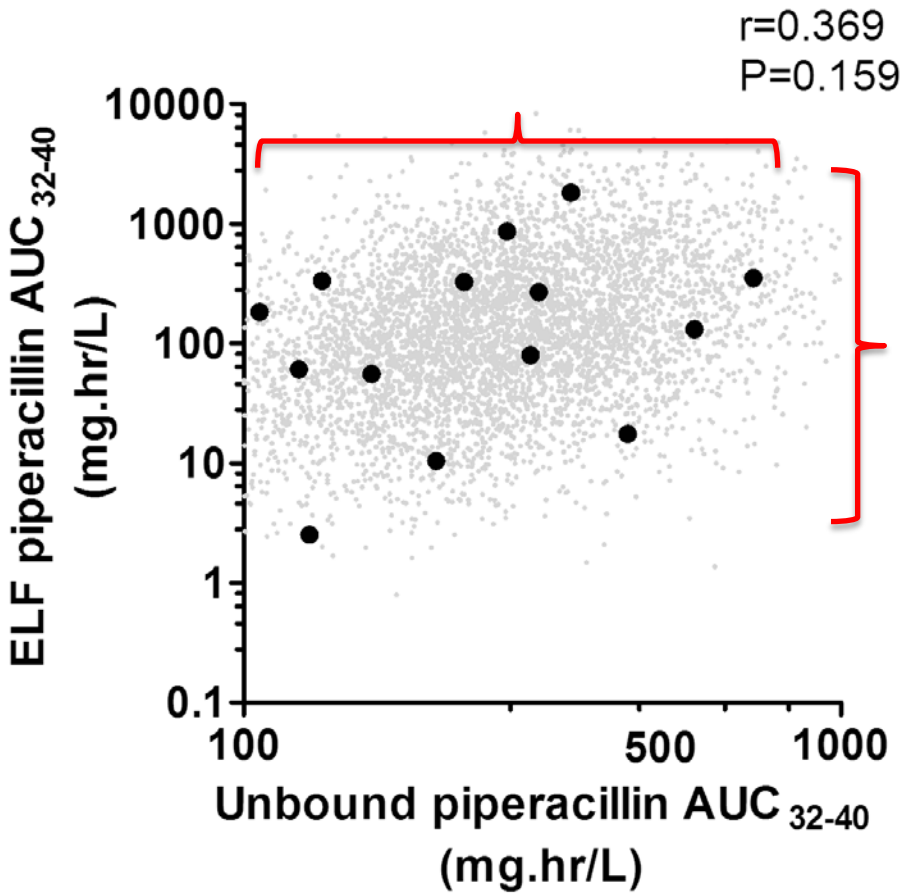
Variability is key

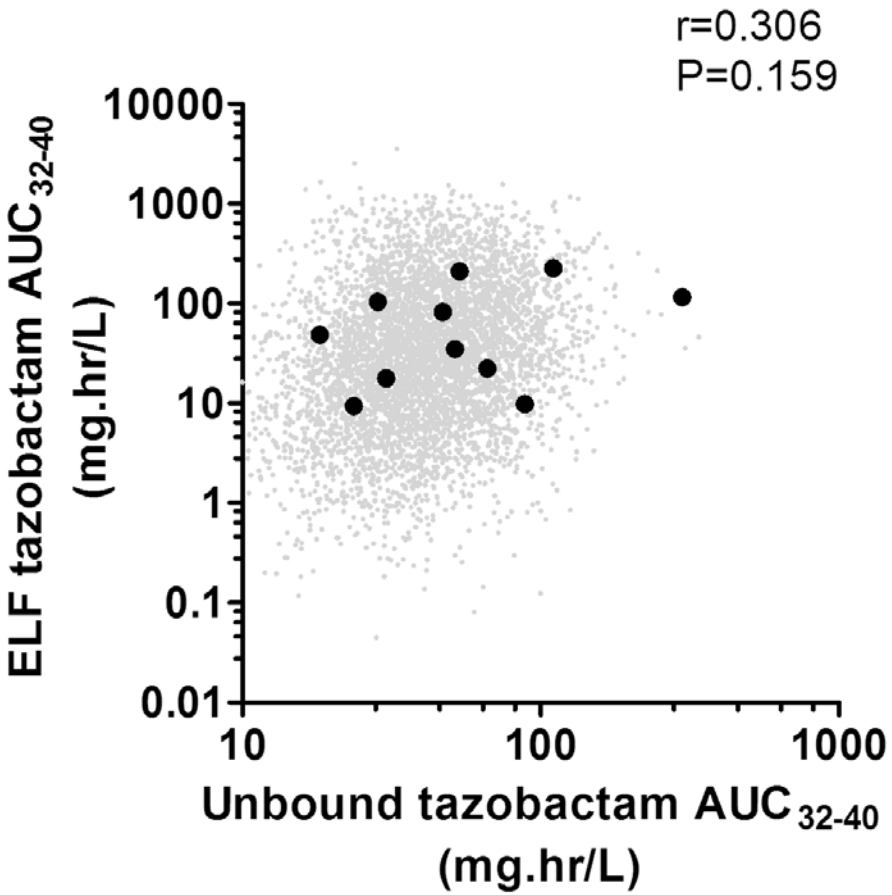
- Meropenem

Parameter	AUC_{plasma} (mg · h/liter)	AUC_{ELF} (m · h/liter)	Penetration ratio (%)
Mean	150.8	82.30	81.6
Median	130.9	35.00	25.42
SD	87.40	140.1	223.0

Lodise et al AAC 2011 55(4) 1606-10

Poor correlation between plasma and ELF for pip/taz





Felton et al Clin Pharm Ther 2014 96(4) 438-48

Three steps to solve ELF PK quickly in sick patients

- Penetration ratio at steady state
  - Can be solved quickly by infusion
  - Allow both serum and ELF compartments to come to steady state before sampling
  - See approach by Boselli et al for many drugs
- Then examine if there is hysteresis
  - Drug administered intermittently
- Then examine the extent of variability

Juncture #3

From Sick Patients back to the lab

The virtuous cycle

- Increasing information related to the relationship between drug exposure and the emergence of resistance
- Deep understanding required to satisfy everyone emergence of resistance will not quickly render the agent defunct
- Requires going back to a preclinical model when deep into the clinical development program

HFIM

- ELF concentrations can be simulated in a HFIM
- Animal models of pneumonia difficult for resistance studies
  - Too short (generally need >24 hours)
  - Too severe (mortality in 24 hours)
  - Too variable (emergence of resistance stochastic)

HFIM and ELF

- Can only do the relevant HFIM study to mimic ELF concentrations when the ELF concentrations are in hand
  - Some measure of central tendency
  - Some idea about dispersion
- Has not been usual to loop back to the lab at this late stage, but is the only way to be really clear about resistance

In summary

- ELF is the best we have, but there are clearly gaps in knowledge
- The whole problem feels slightly “underdone”
  - Laboratory animals may not link well to patients
  - Volunteers may not link well to sick patients
  - We are matching means/ medians in systems that are highly variable rather than using all the distribution
- Enough uncertainty to remain critical, not be too dogmatic, and encourage further research/ dialogue
- Clearly more research required to build better prediction tools and pathways

Last slide

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

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