

“Real World” Challenges in performing Clinical Trials for Drug Resistant Diseases

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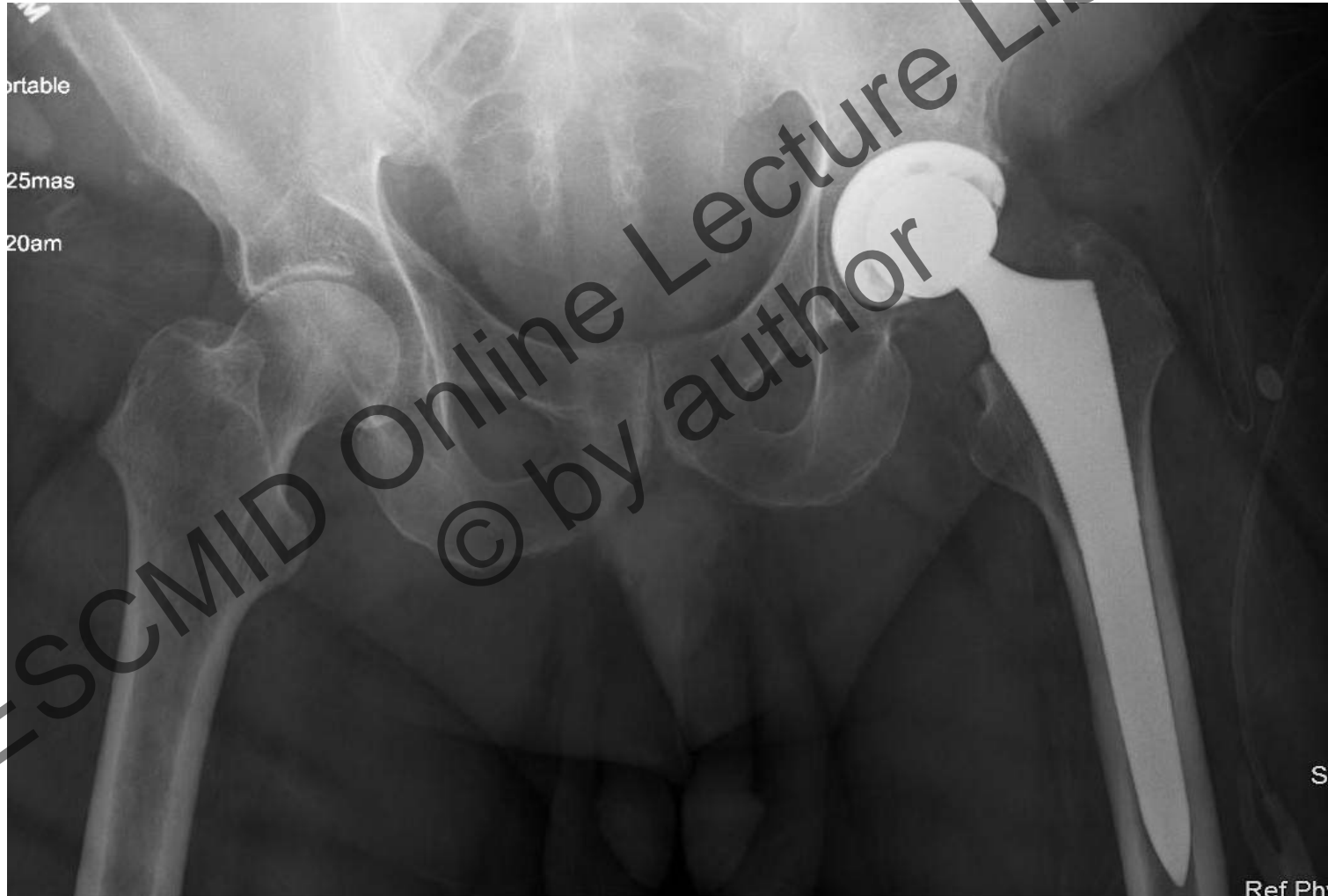


Acknowledgements – the short list

- Frank Talley
 - The lessons of daptomycin
- John Powers
 - Sometimes an adversary, always a friend
- Fernando Baquero
 - Beware the hype over AMR
- John Rex
 - The power of persistence
- Hasan Jafri
 - Constructive collaboration
- Mark Esser
 - Always thinking!



Special thanks to Stephen Cummings, MD



3 And feel free to ask me about biofilms and antibiotic resistance later



MedImmune

Yes I do believe in infection control!

**Nasal swab checking for
For MRSA (negative!)**

Prevention is righteous!!



Something I learned at this meeting

While it is true that children are not small adults it is also true that some adults are large children

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A case in point



Understanding Resistance

- IMHO Conventional Wisdom is misleading
 - **If not just plain wrong**

“The laws of natural selection dictate that bacteria will eventually develop resistance to practically any antibiotic. Selective pressure exerted by widespread antimicrobial use is a driving force in the development of antibiotic resistance.”

S. Levy

“It ain’t necessarily so.” Sportin Life in *Porgy & Bess*



What came first? Therapeutic use or Resistance?

“An Enzyme from Bacteria Able to Destroy Penicillin”

Dec. 28, 1940 E.P. Abraham & E. Chain Nature 146:837

First successful therapeutic use of penicillin: March 1942

Anne Sheafe Miller was treated for and cured of a streptococcal infection (Mrs. Miller died May 27, 1999 at the age of 90)

(Oh and by the way we are **still** waiting for penicillin resistance to emerge in the group A strep)

And if we don't really understand resistance how are we going to beat it?



A “new” paradigm for multidrug resistance defines our antibacterial strategy

- The propensity for organisms to become multiply resistant appears to be a function of genome size
 - Better environmental adaptability?
 - Plasticity of the genome and expression patterns?
- Examples:
 - *Pseudomonas aeruginosa* 6.3 Mb (can be and often is “pan resistant”)
 - *E. coli* (and other enterobacteriaceae) 4.0-5.6 Mb (bad news strains exist)
 - *Mycobacterium tuberculosis* 4.4 Mb (can run out of therapeutic options)
 - *Staphylococcus aureus* 2.8 Mb (same as *S. epi*)
 - *Staphylococcus epidermidis* 2.6 Mb (MDR strains are common)

 - *Neisseria meningitidis* 2.2 Mb (a lot like the pneumococcus)
 - *Streptococcus pneumoniae* 2.1 Mb (MDR-lite)
 - *Streptococcus pyogenes* 1.9 Mb (some resistance but no beta-lactam resistance)
 - *Treponema pallidum* 1.1 Mb (almost no resistance)

Projan Antimicrobial Agents & Chemotherapy April 2007



“The Andersen Hypothesis” (as stated by many)

See: Andersson DI. Persistence of antibiotic resistant bacteria. *Current Opinion in Microbiology*. 6:452-6, 2003

- Resistance (either via mutation or acquisition) imposes a fitness burden on the bacterium
- Over time compensatory mutations are selected for restoring the fitness of the bacterium
- The compensatory mutations, therefore “stabilize” the resistance phenotype and lock in the resistance genotype
- This explains the persistence of resistant strains in the face of antibiotic cycling



Clinical Trials do not represent the “Real World”

- Non-inferiority trials
 - **Confession: I have a non-inferiority complex**
 - Is there such a thing as “bio-creep”*?
 - Not if you choose the right comparator
- But what exactly is “standard of care”?
 - May vary from physician to physician
- And how do you define a “resistant strain”?

*Everson-Stewart, Emerson. Bio-creep in non-inferiority clinical trials. Stat Meds 2010 29:2769



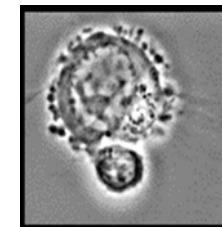
However Hubris is a Deadly Sin

- Double blind, placebo controlled studies are not a guarantee of clinical and regulatory success (perhaps more so the opposite)
- Sometimes you have to believe the data, even if it is not your own (maybe especially if it is not your own data)

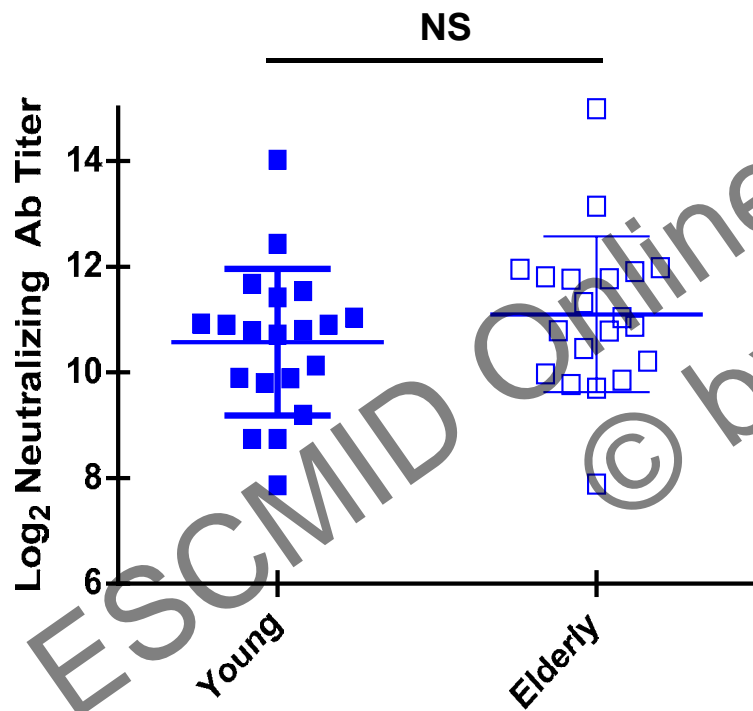
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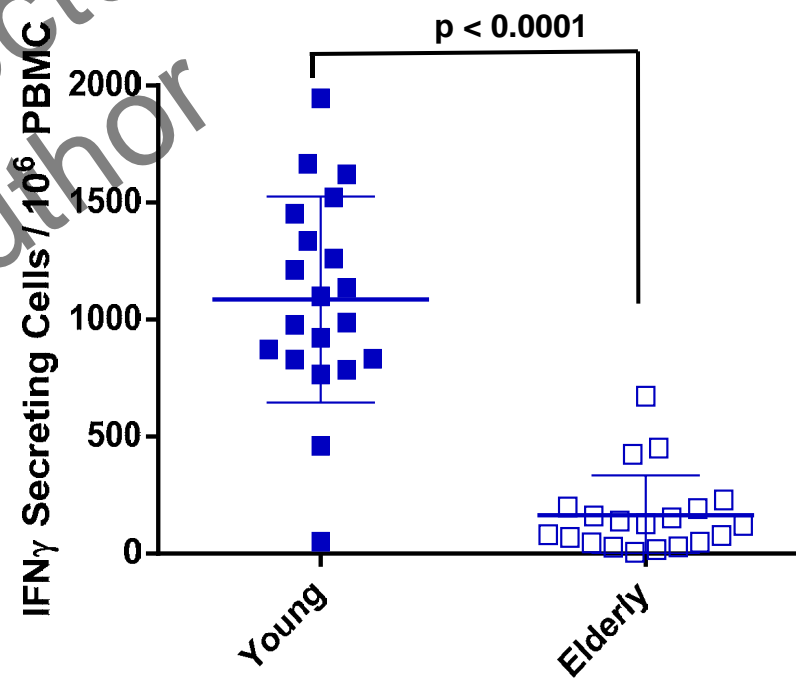
Immune Profile of Young Versus Elderly



A. RSV Neutralizing Antibodies



B. RSV F-Specific IFN-γ T Cells



Cherukuri A, Patton K, Gasser RA Jr, Zuo F, Woo J, Esser MT, Tang RS. Adults 65 years old and older have reduced numbers of functional memory T cells to RSV fusion protein. Clin Vaccine Immunol. 2013;239-47.



A revised paradigm for infectious disease research

- Drug discovery is hard
- Drug development is harder
- And the economics are impossible (today)

What is NPV and why is it killing my research? Fighting the battle of **opportunity cost** and the lesson of Alzheimer's Disease R&D



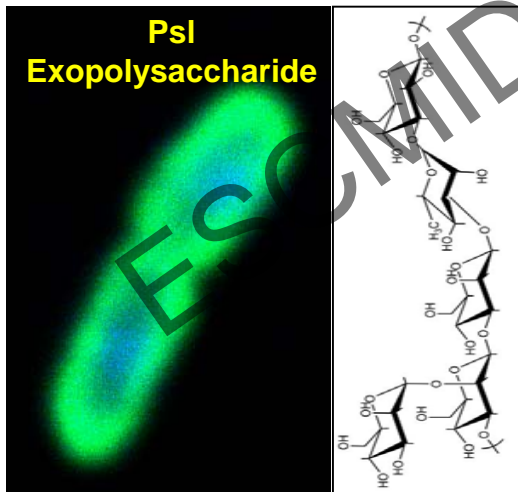
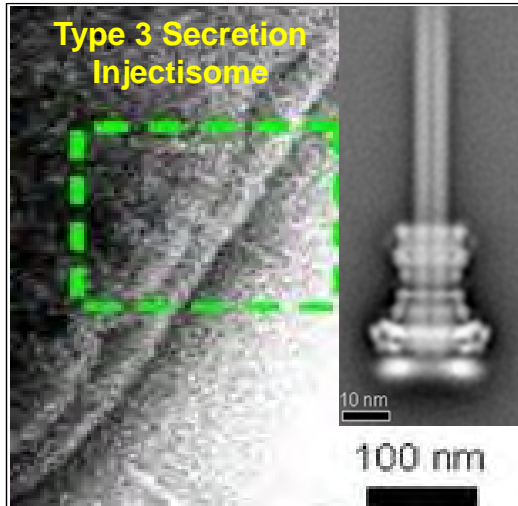
**And now for the poster child for
“development is harder”**

MEDI3902, a bispecific mAb for the prevention, treatment and or preemption of *Pseudomonas aeruginosa* infections

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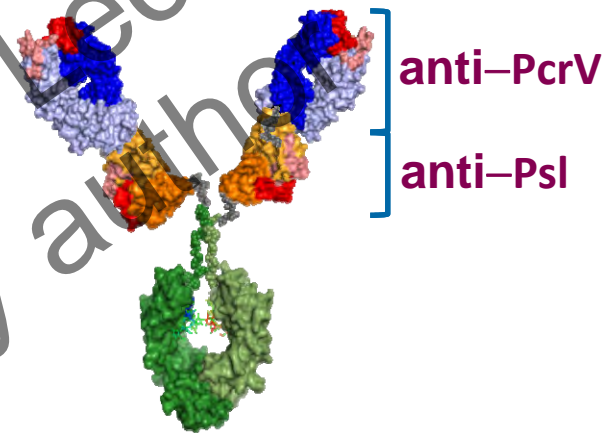


MEDI3902: Multi-Mechanistic BiSpecific mAb



Target 1: PcrV - Virulence

- MOA: Prevents toxin injection into host cells
- Dramatically reduces bacterial virulence
- High affinity mAb to low density target



MEDI3902

Target 2: Psl: Colonization-Persistence

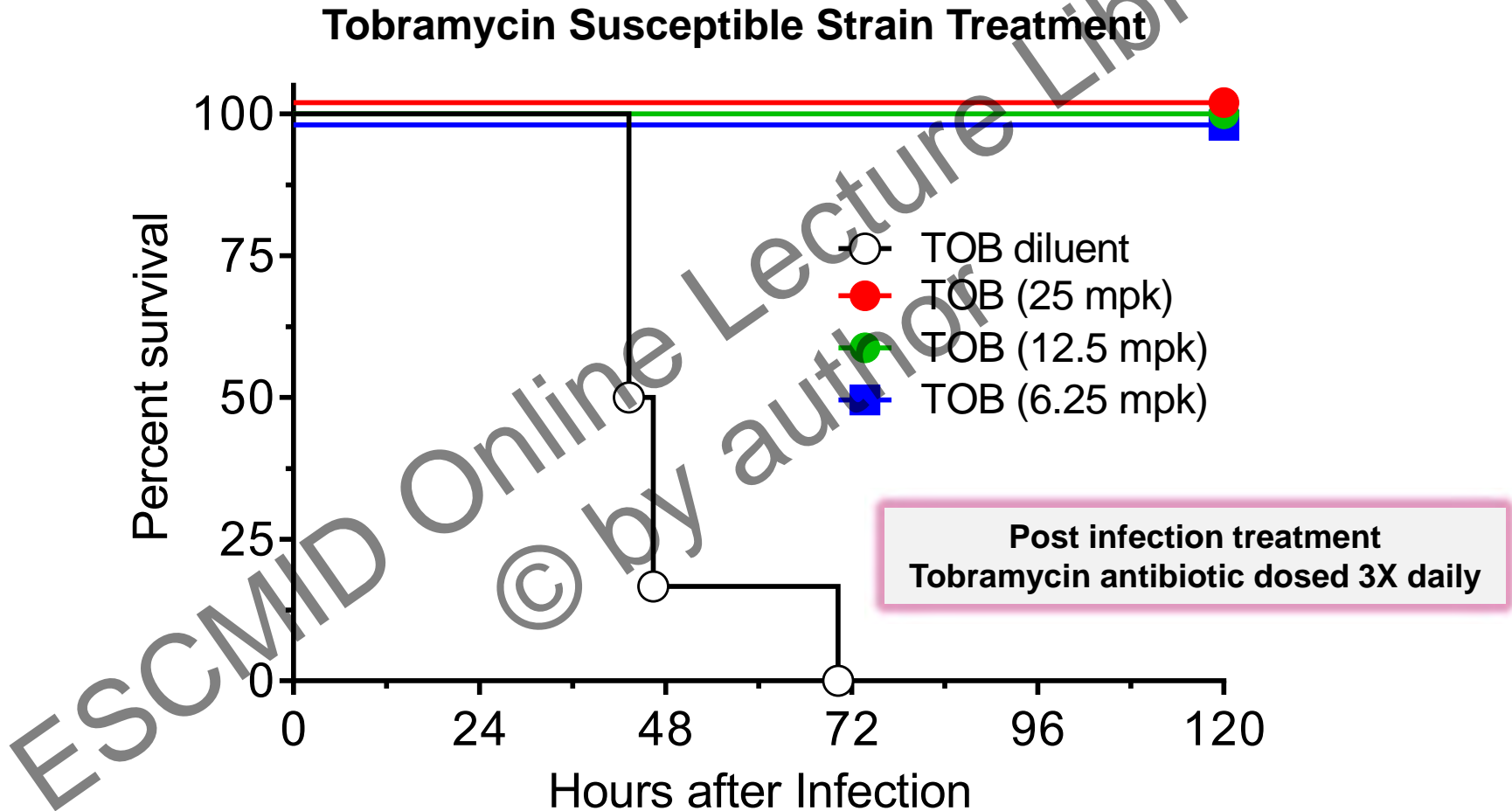
- Dual MOA: Clearance and blocks cell adherence
- Lower affinity mAb to high density target
- Psl binding enhances avidity-targeting of MEDI3902

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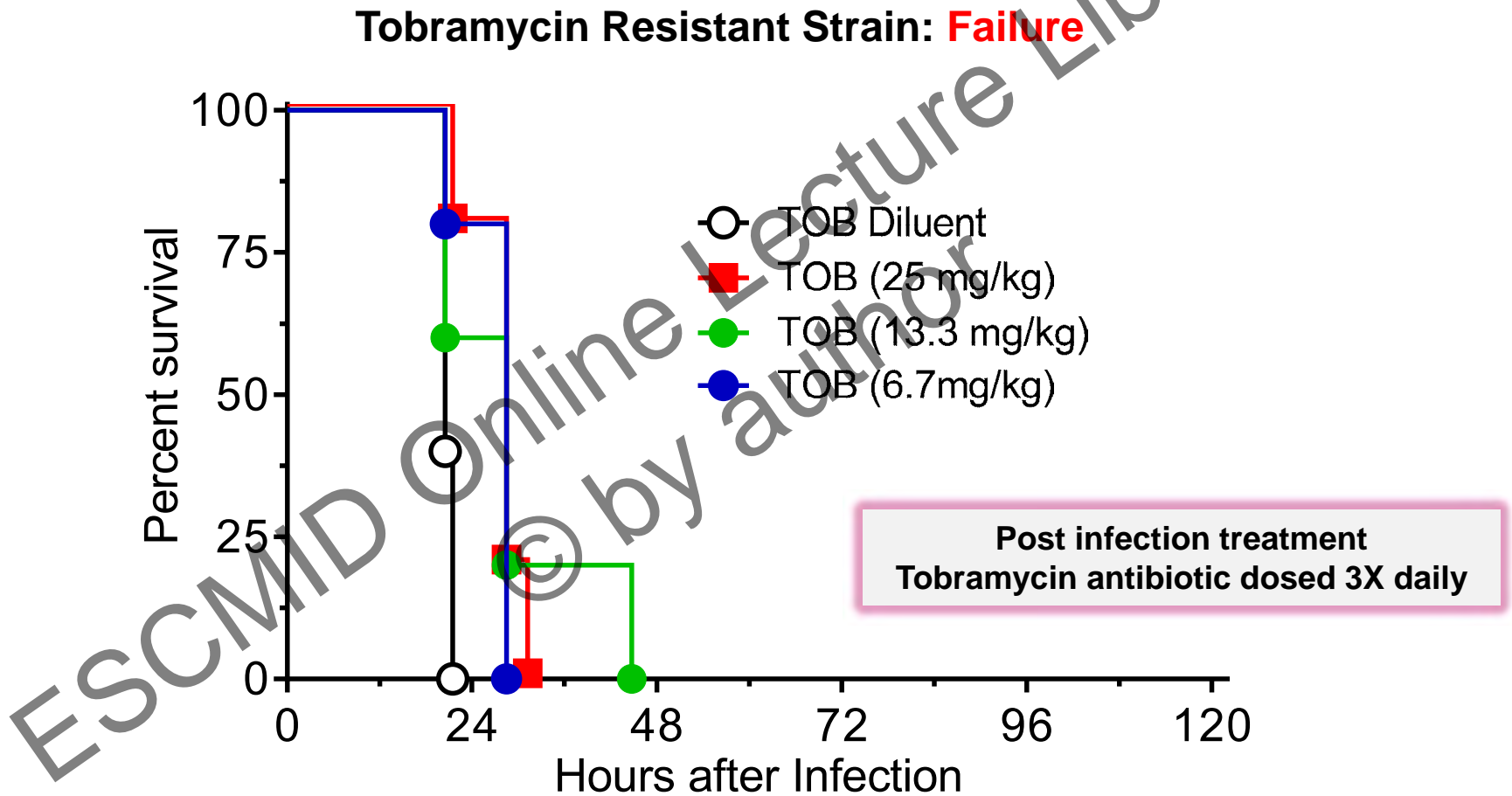
mAb + Antibiotic Adjunctive Therapy?



MEDI3902 + Antibiotic Synergy vs Drug Resistant Strain

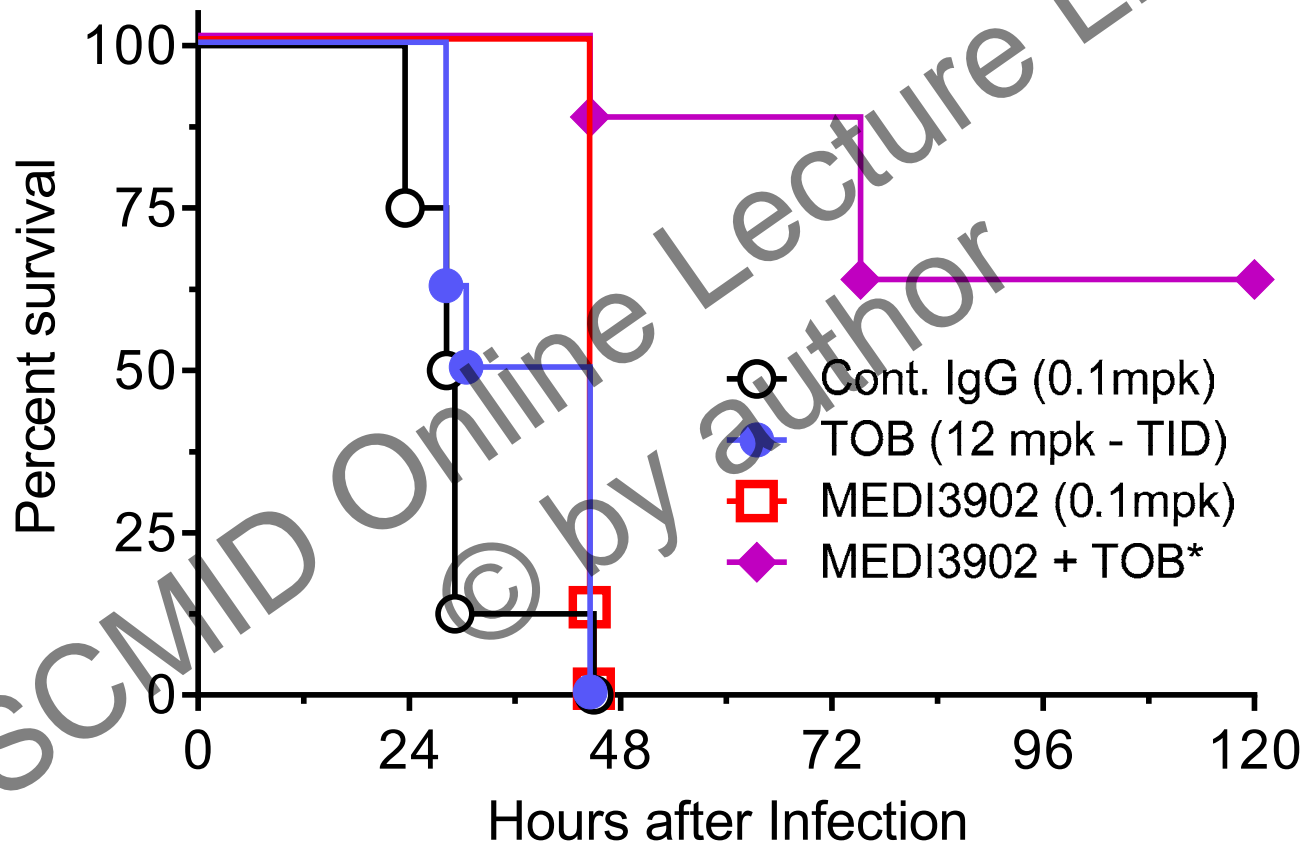


MEDI3902 + Antibiotic Synergy vs Drug Resistant Strain



MEDI3902 + Antibiotic Synergy vs Drug Resistant Strain

MEDI3902 + Tobramycin: **Adjunctive Therapy**

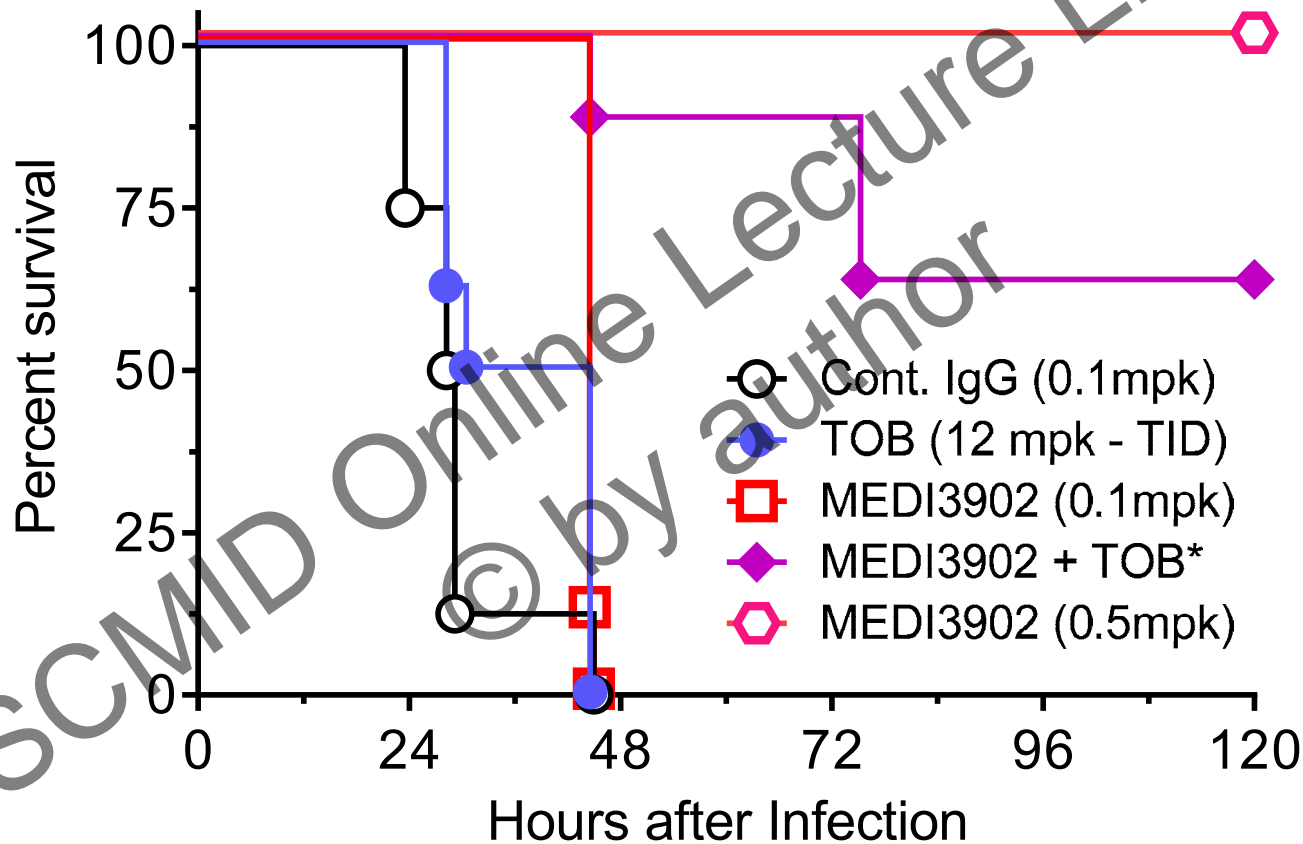


MEDI3902 + antibiotic adjunctive therapy is synergistic even against a highly drug-resistant *P. aeruginosa* isolate



MEDI3902 + Antibiotic Synergy vs Drug Resistant Strain

MEDI3902 + Tobramycin: **Adjunctive Therapy**



MEDI3902 + antibiotic adjunctive therapy is synergistic even against a highly drug-resistant *P. aeruginosa* isolate



Tolerability vs. Safety

- How informative are (PK and safety) studies in healthy volunteers?
- Daptomycin studies were halted (by Lilly) mainly because of elevated CPK
 - Yet that turned out to be a red herring



The biggest confounding factor in comparator-based trials?

- IMHO it is dosing with an effective antibiotic for 24 hours before beginning the test article (study drug)
 - Another (this time negative) lesson from daptomycin

Silverman et al Inhibition of Daptomycin by Pulmonary Surfactant: In Vitro Modeling and Clinical Impact
J Inf Dis (2005) 191: 2149-2152



Know thy PK/PD – get the dosing right

- In antibacterial research we have the distinct advantage of predictive animal models
 - The pharmacokinetics and pharmacodynamics that were effective in animal models usually scale well to humans (my favorite model is the neutropenic mouse thigh model)
- Often we get the human dose wrong (on the low side)
 - Robert Arbeit, M.D. when asked if he was worried about a drug's tolerability: "Yes. But I would push the dose"



If you build it will they come?

- Every time a new agent is developed a network of clinical investigators must be assembled de novo
 - This takes time and money and often has significant learning curve
- Is there a better way? Does John Rex have the answer? And can we afford the infrastructure??
- Hey what about open label, adaptive trials in Phase 2a? Should the network we build cut their teeth on this type of trial?



For some light reading...

See the August 15, 2016 supplement to *Clinical Infectious Diseases* Facilitating Antibacterial Drug Development in a Time of Great Need (available on line and free of charge)

McDonnell et al. Efficient Delivery of Investigational Antibacterial Agents via Sustainable Clinical Trial Networks

François et al. The SAATELLITE and EVADE Clinical Studies Within the COMBACTE Consortium: A Public–Private Collaborative Effort in Designing and Performing Clinical Trials for Novel Antibacterial Drugs to Prevent Nosocomial Pneumonia



And now for the biggest challenge.... how are we going to pay for it?

The GAIN Act won't work, "bounties" for novel drugs that get approved neither, in fact no back end solution will solve the "opportunity cost" dilemma. What might? something:

- **S**traightforward (i.e. uncomplicated)
- **I**ncentivizing (data sharing)
- **M**anageable (no additional bureaucracy)
- **P**olitically palatable (not a "giveaway")
- **L**egitimate (no sunset or cap provisions)
- **E**conomical (a true "win-win")



Some Background

“The **Research & Experimentation Tax Credit** or R&D Tax Credit is a general business tax credit under Internal Revenue Code section 41 for companies that incur research and development (R&D) costs in the United States. The R&D Tax Credit was originally introduced in the Economic Recovery Tax Act of 1981 sponsored by U.S. Representative Jack Kemp and U.S. Senator William Roth. Since the credit's original expiration date of December 31, 1985, the credit has expired eight times and has been extended fifteen times. The last extension expired on December 31, 2014. In 2015, Congress made permanent the research and development tax credit in a measure of the government spending bill.” Quoted from Wikipedia



The “SIMPLE” Concept

Companies that perform R&D in AMR (and related areas of BioPreparedness) would receive a 2X R&D Tax credit.

This differs from models where companies only get compensation for delivering a drug or a diagnostic or stockpiling contracts.

It will deliver value to (profitable) companies on an ongoing (and immediate) basis and free up public funding for SMEs which are often more innovative.



Thanks for your attention!

Beware of false dichotomies:

“When you come to fork in the road, take it.”

Lawrence Peter (Yogi) Berra

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