Exploring antivirulence strategies for treating severe infections

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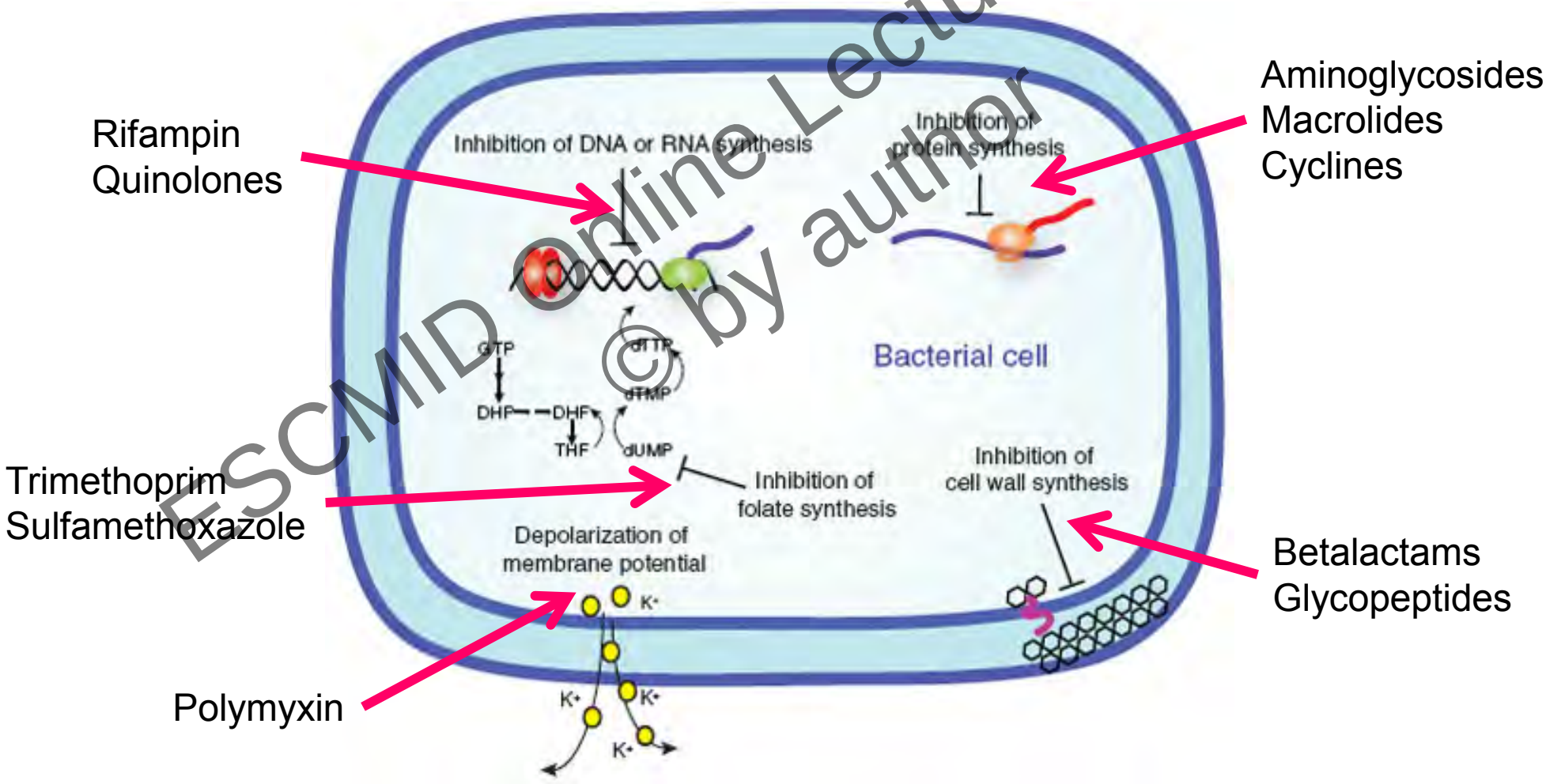
Conflicts of interest: Consulting or Lecture fees:

- KaloBios-sanofi, Kenta-Aridis, Medimmune, Nektar-Bayer, Pfizer, Trius, Janssen-Cilag, Cubist, Astellas

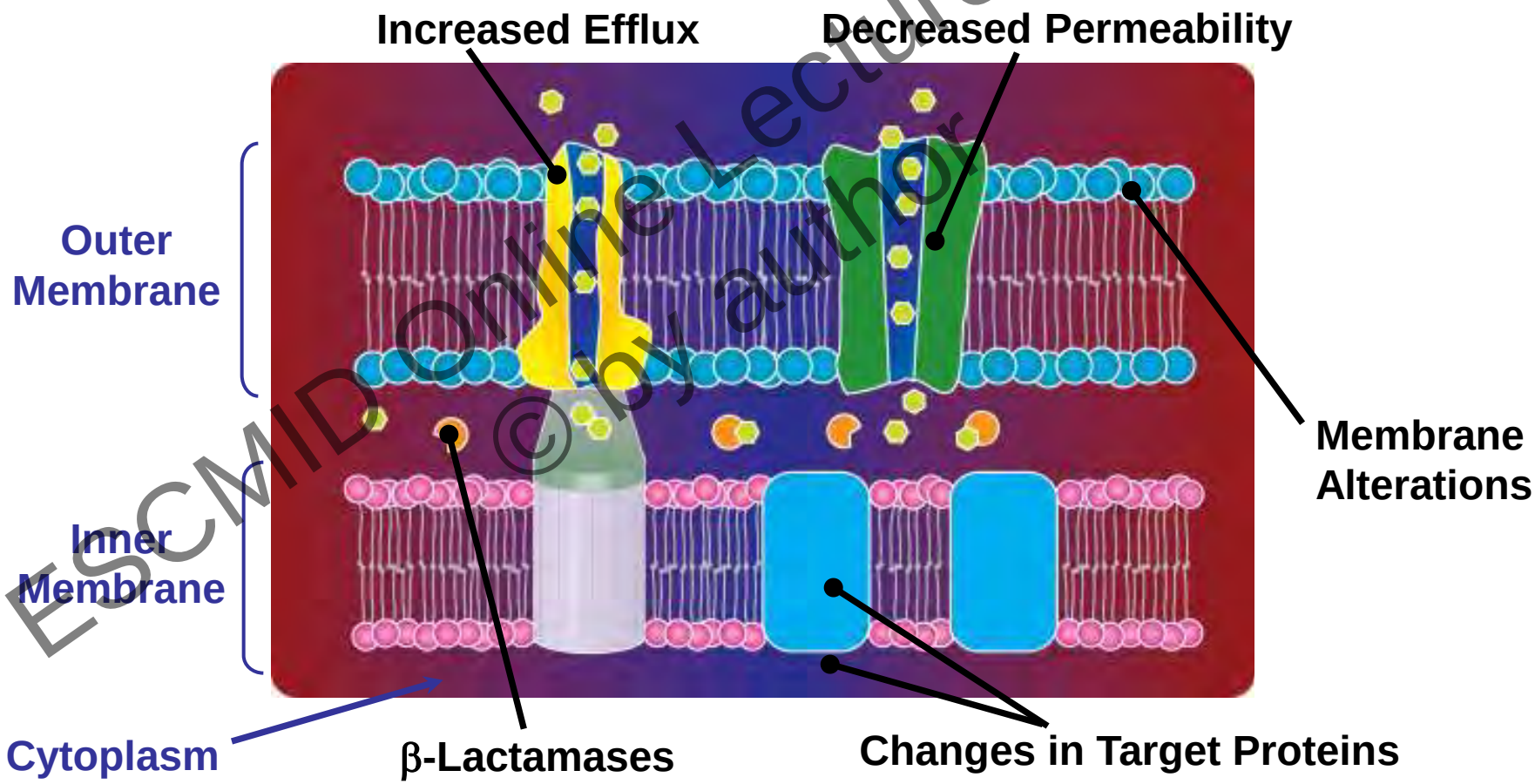
The “Usual” Paradigm

Conventional Therapeutics, such as Antibiotics, Target Pathogen Viability

Clatworthy AE, et al. Nat Chem Biol. 2007;9:541-8

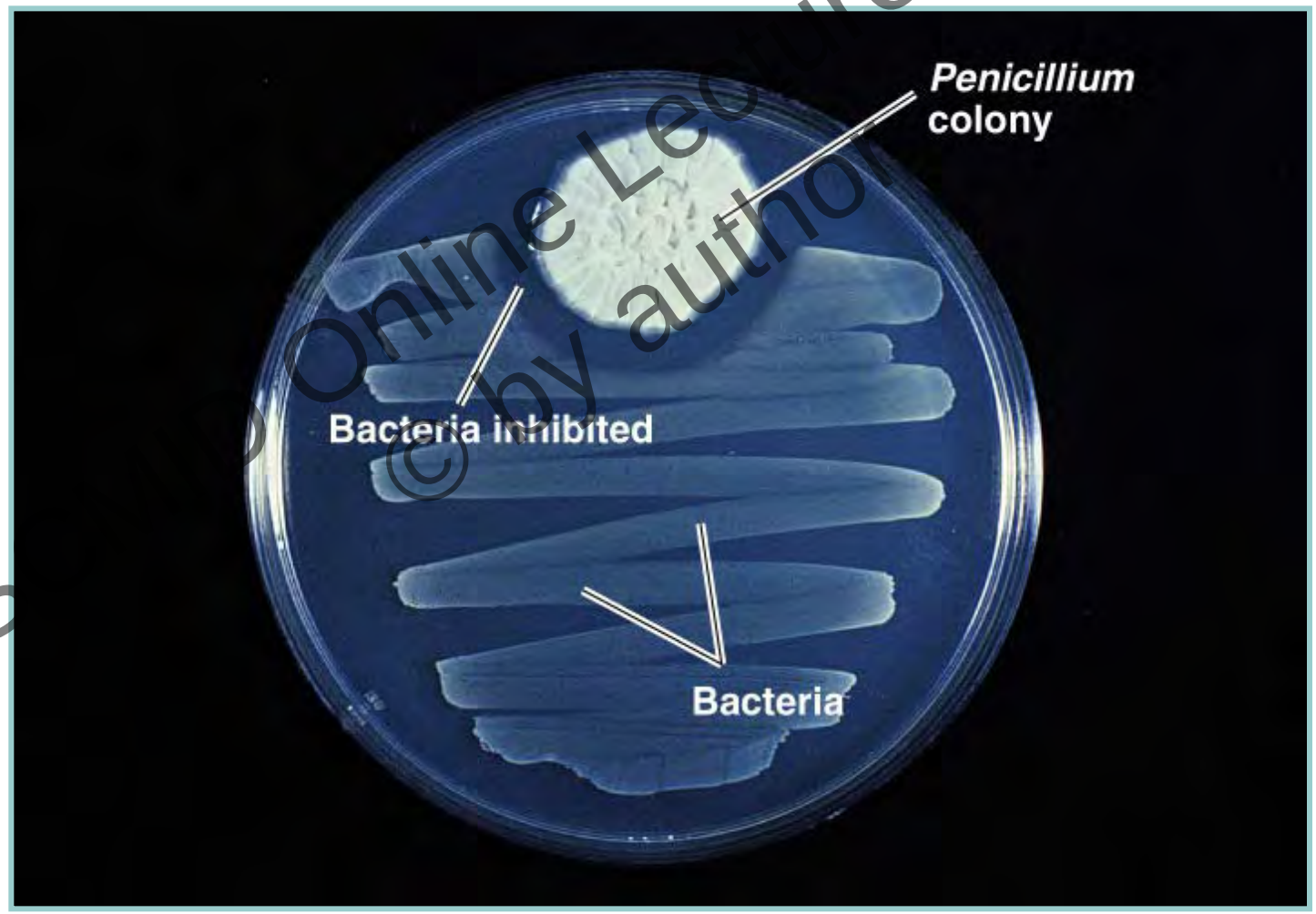


Potential Mechanisms of Resistance in GNB



Nicolau DP Expert Opin Pharmacother 2008;9:23-37

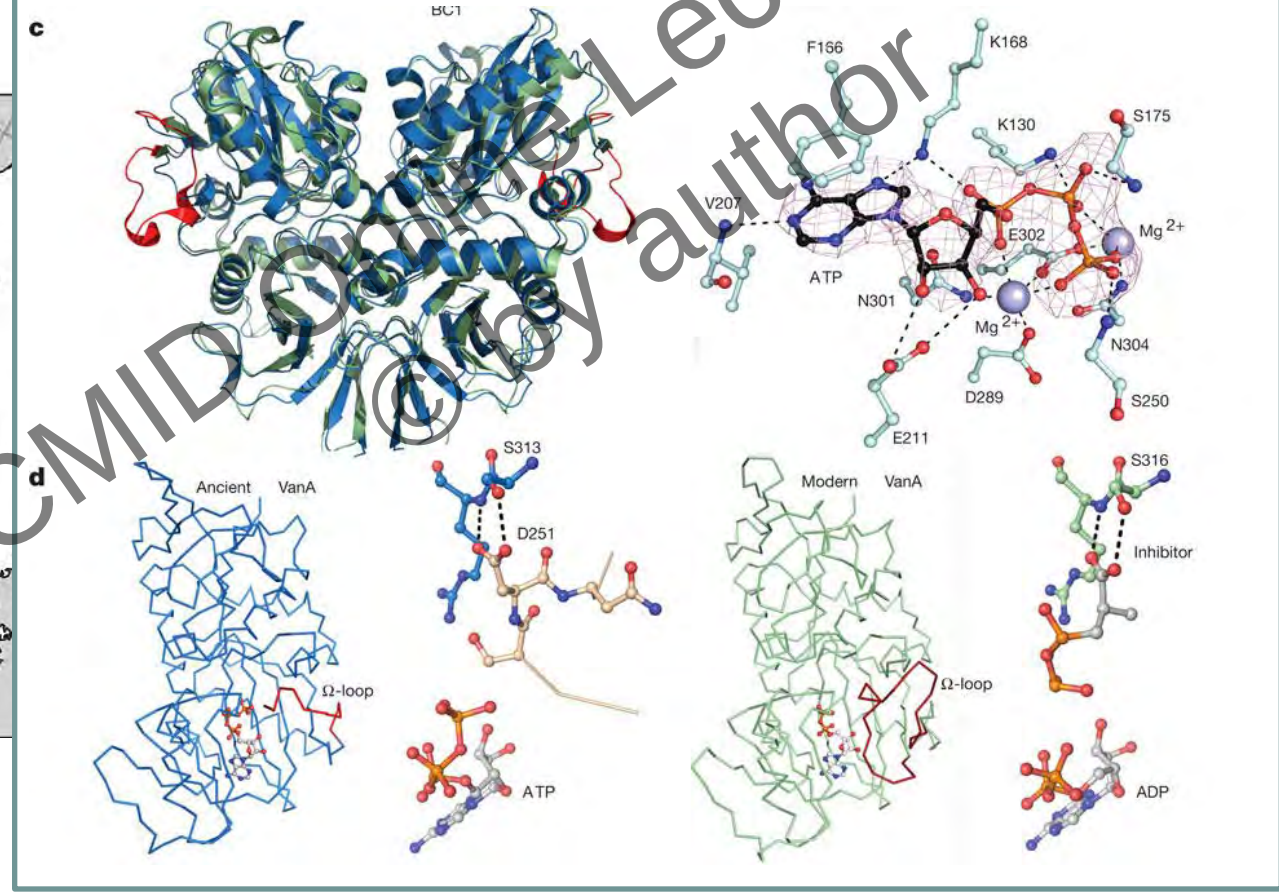
Most antimicrobial agents we are using for killing bacteria were in fact “invented” by microorganisms to defend their “territory”

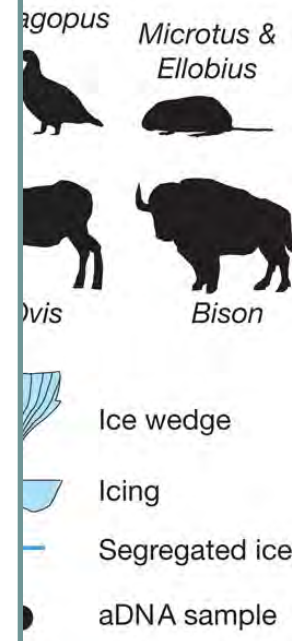


Antibiotic resistance is ancient as demonstrated by metagenomic analyses of ancient DNA from 30,000-year-old permafrost se

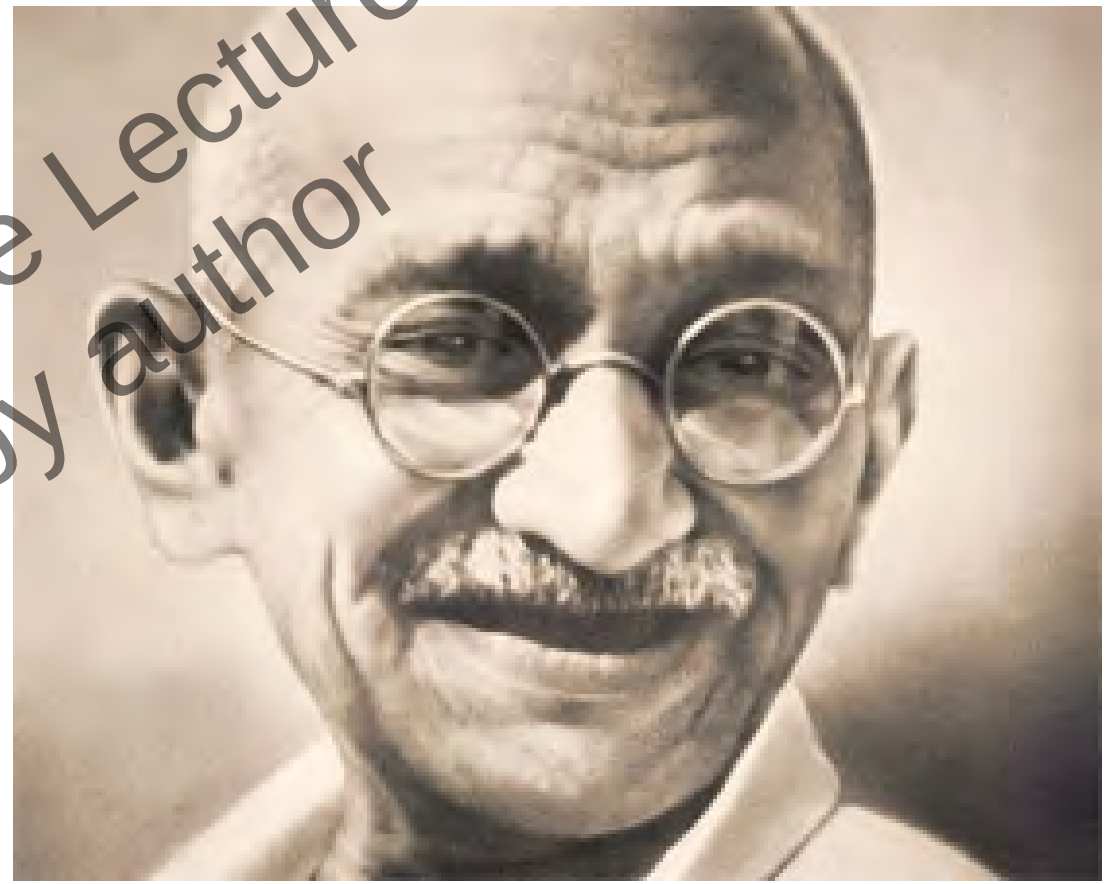
77(7365):457-61

Structure and function studies on the complete vancomycin resistance element VanA confirmed its similarity to modern variants



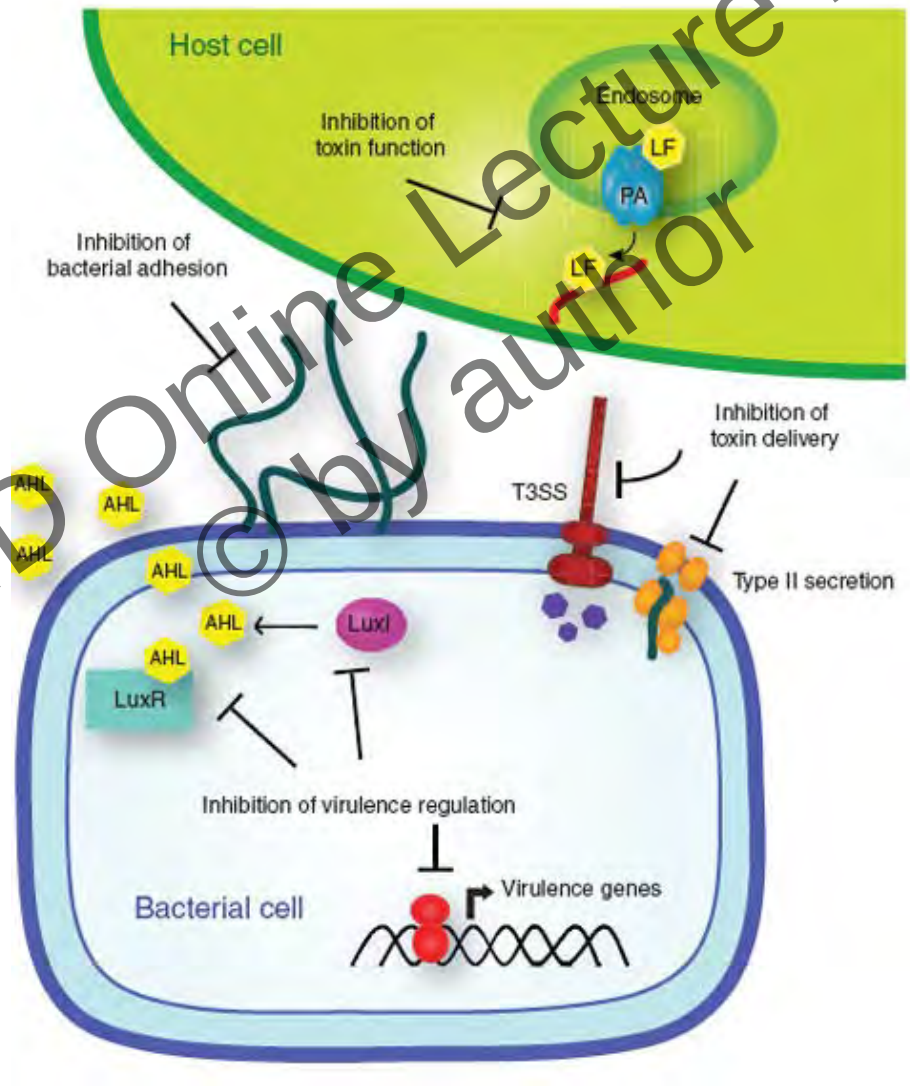


A “New” Paradigm



Alternative Approaches Designed to Target Virulence Factors

Clatworthy AE, et al. Nat Chem Biol. 2007;9:541-8



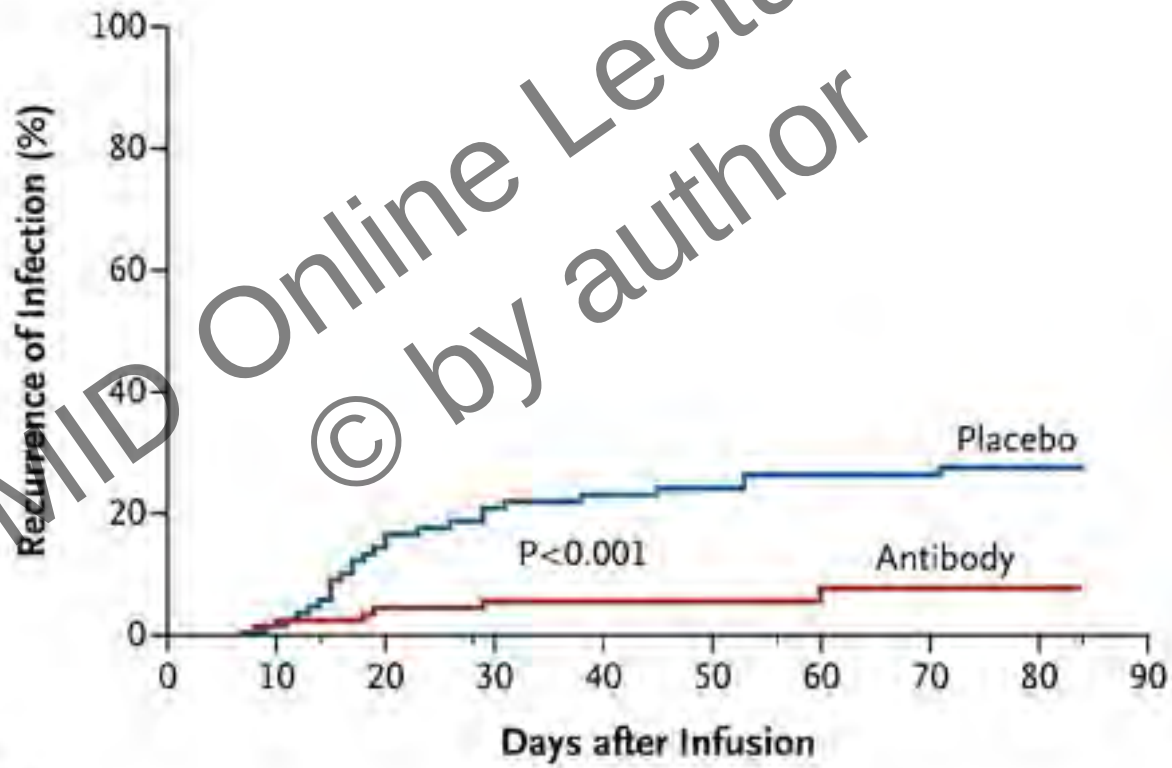
Alternative Approaches Targeting Microorganisms Virulence Factors

Clatworthy AE, et al. Nat Chem Biol. 2007;9:541-8

- These approaches have several potential advantages:
  - They expand the repertoire of bacterial targets.
  - They preserve the host endogenous microbiome.
  - They exert less selective pressure for the development of antibiotic resistance relative to current antibiotics.

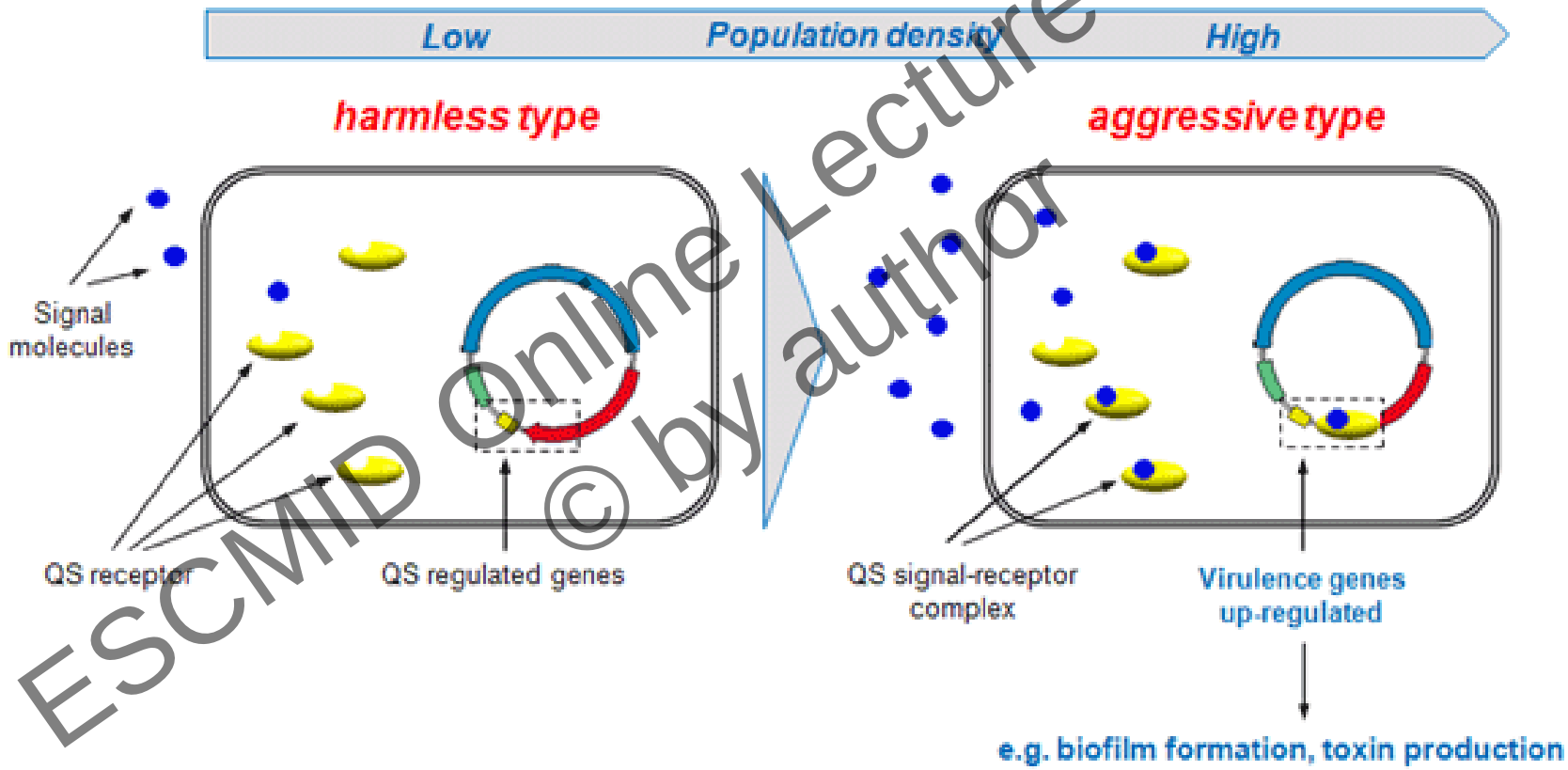
Time to Recurrence of *Clostridium difficile* Infection

Lowy I et al. N Engl J Med 2010;362:197-205



No. at Risk				
Antibody	101	93	89	85
Placebo	99	77	66	62

The “Quorum Sensing” system



Signal molecules, such as N-acyl-L-homoserine lactones (AHLs), are utilized by bacteria to monitor their own population densities and to activate virulent genes

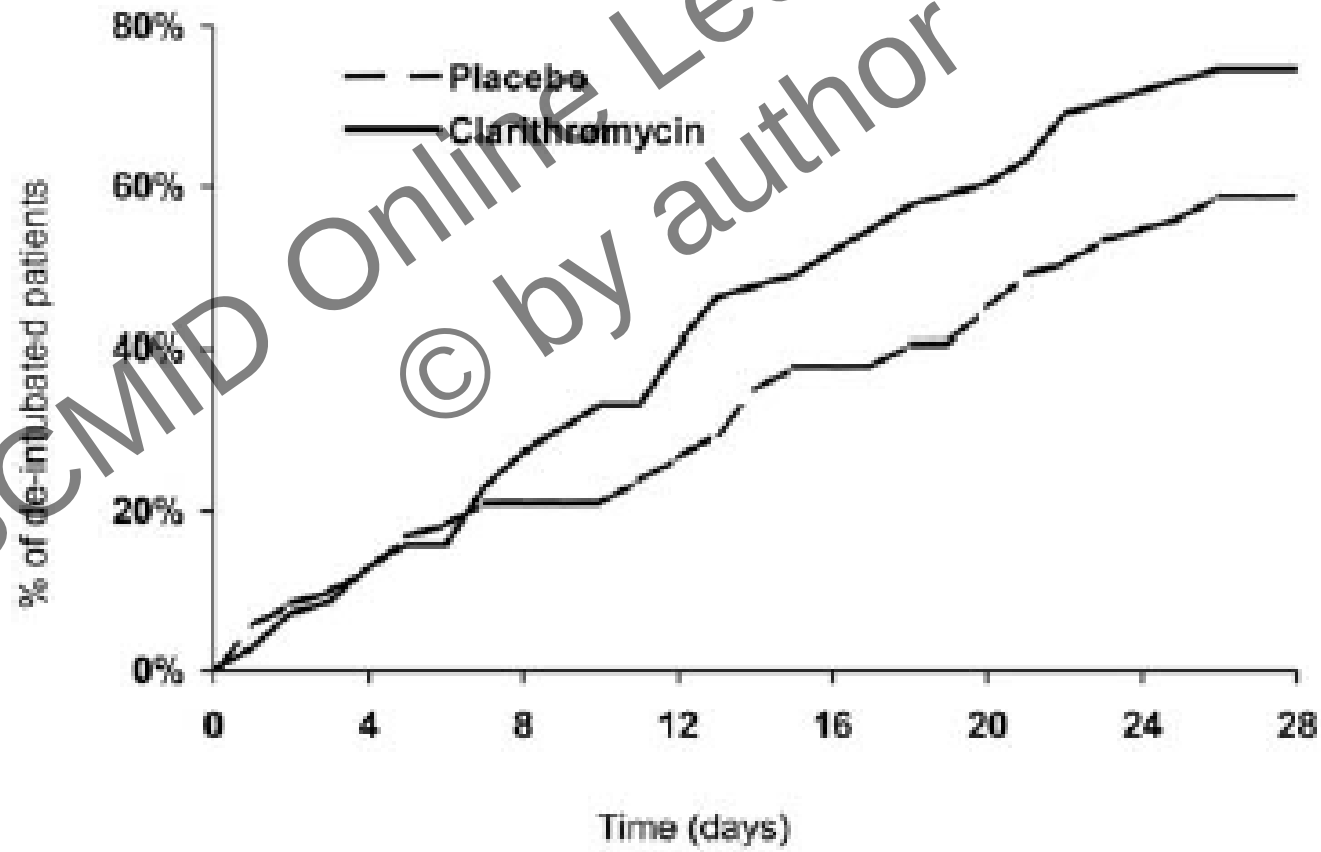
Effect of Clarithromycin in Patients with Sepsis and VAP

Giamarellos-Bourboulis EJ, et al. CID 2008;46:1157–64

- **200 patients with sepsis and VAP** were enrolled in a **double-blind**, randomized, multicenter trial in Greece
- **Clarithromycin** (1 g) was administered IV once daily for **3 consecutive days** in 100 patients; another 100 patients were treated with placebo
- **Main outcomes** were **resolution of VAP, duration of MV, and sepsis-related mortality within 28 days**

Cumulative time to weaning from ventilation among placebo-treated and clarithromycin-treated patients

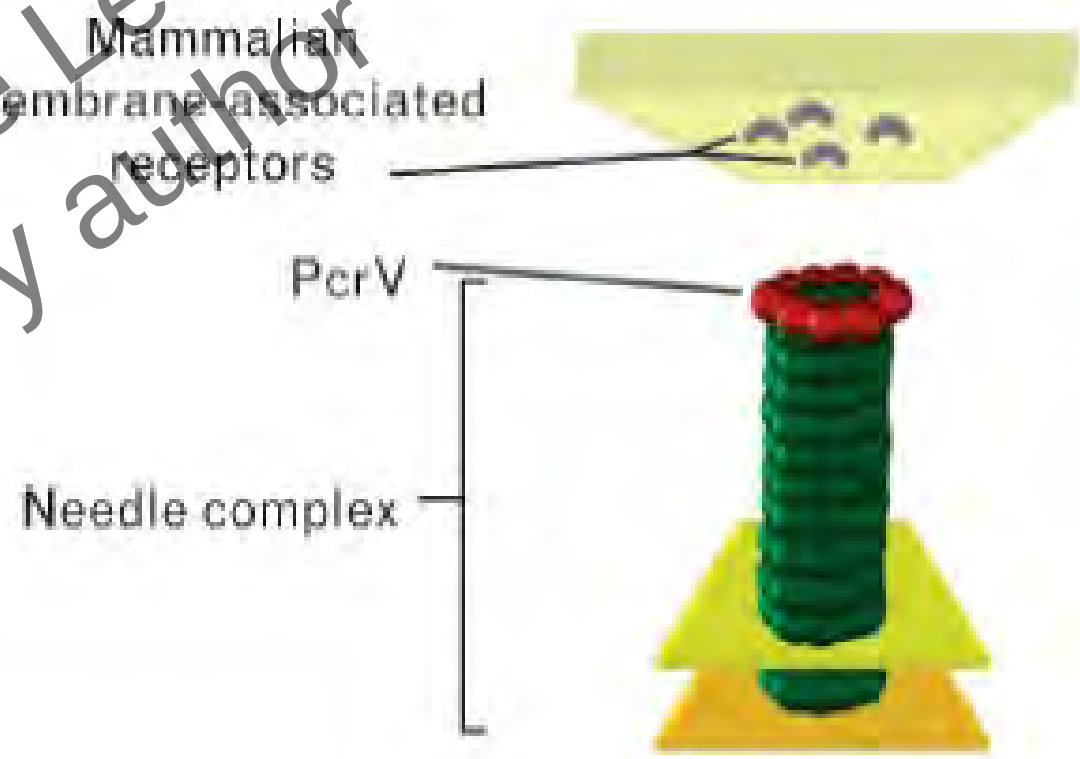
Giamarellos-Bourboulis EJ, et al. CID 2008;46:1157–64



Type III Secretion System and Antibody-based Blockage of this Virulence System

Kubori et al. Science 1998

- The type III secretion system involves a needle-like complex that traverses the bacterial bi-layer, crowned by PcrV proteins at the distal tip.



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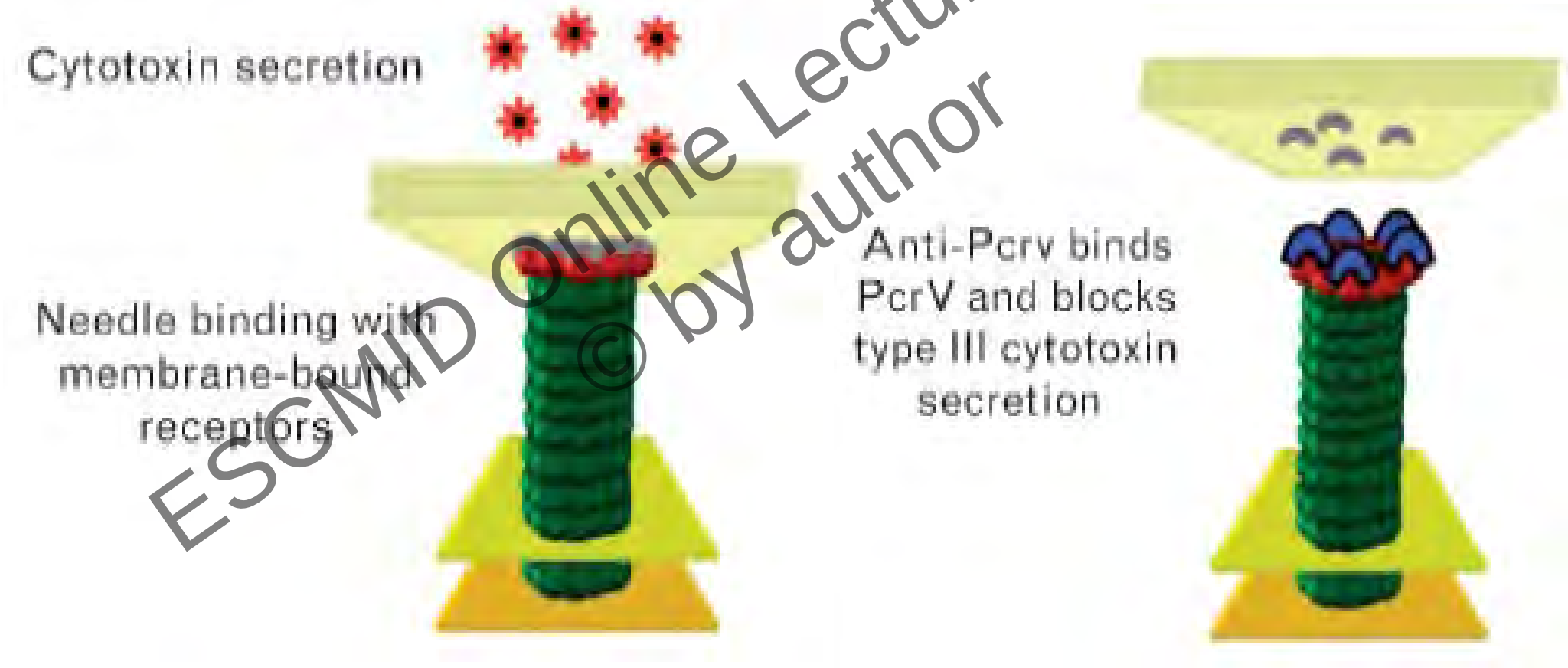
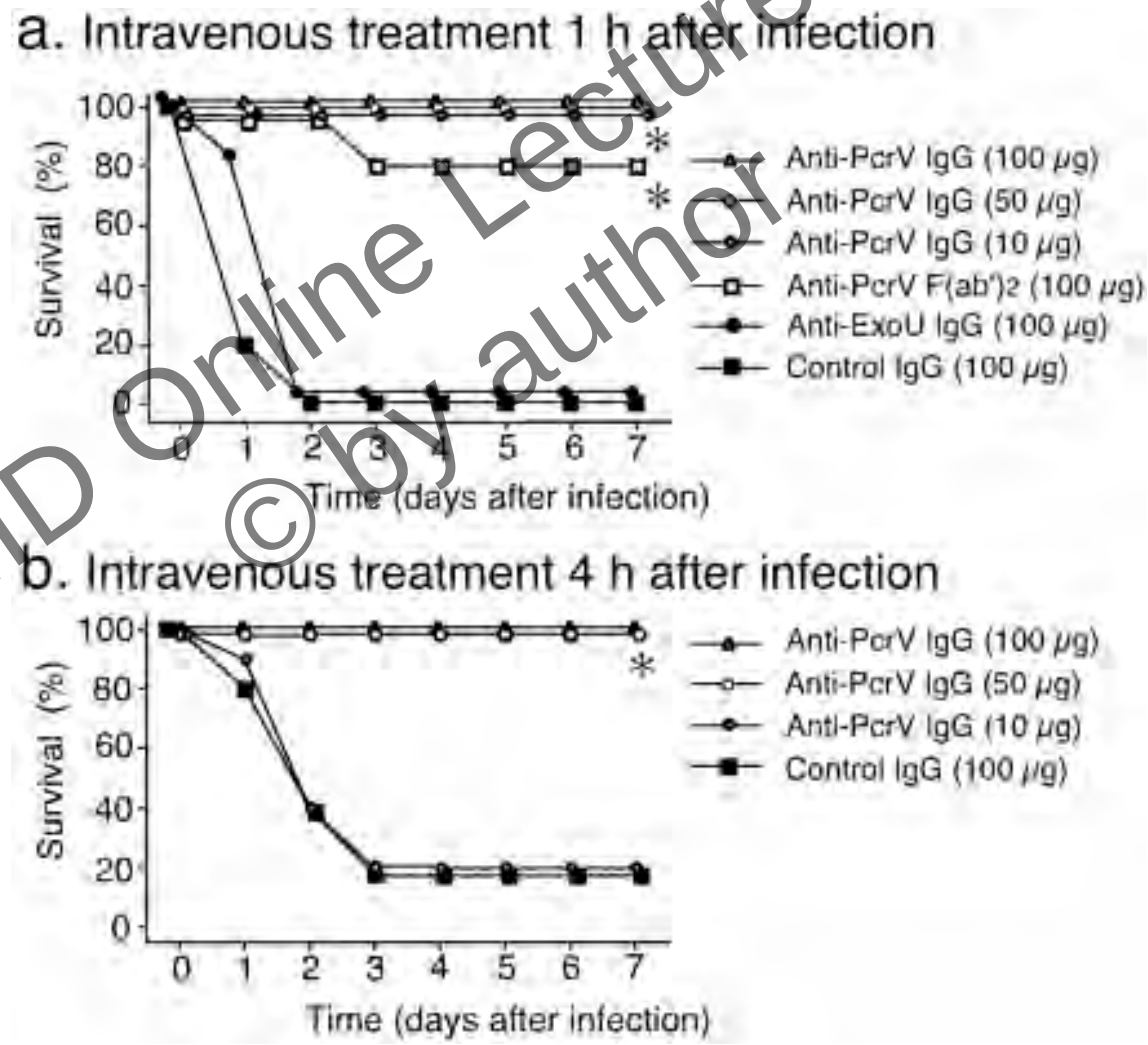


Anti-PcrV Antibodies Protect Mice Against *Pa*-mediated Lethality

Shime et al, J Immunol 2001;167:5880-6



Safety and pharmacokinetics of an anti-PcrV monoclonal antibody in ventilated patients colonized with *P. aeruginosa*: A randomized, double-blind, placebo-controlled trial

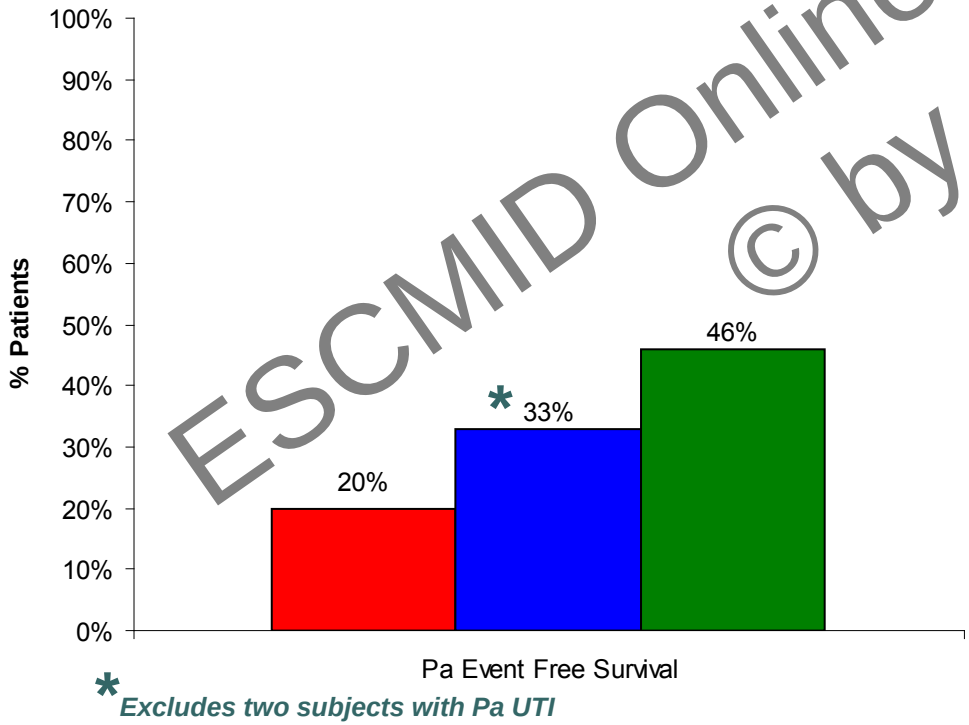
François B., et al. Crit Care Med 2012;40(8):2320-6

- Inclusion criteria
  - On MV and expected to remain ventilated for ≥3 days
  - Documented pulmonary *Pa* colonization
  - ≥ 10^3 CFU/mL by ETA or ≥ 10^2 CFU/mL by BAL culture
- Exclusion criteria
  - patients with cystic fibrosis
  - Currently diagnosed with *Pa* VAP
  - Change in systemic antibiotic therapy active against *Pa* within 72 hours prior to culture used for documenting pulmonary *Pa* colonization for study entry

KB001 MVP Trial:
Day 28 Clinical Outcomes
Evaluable Population

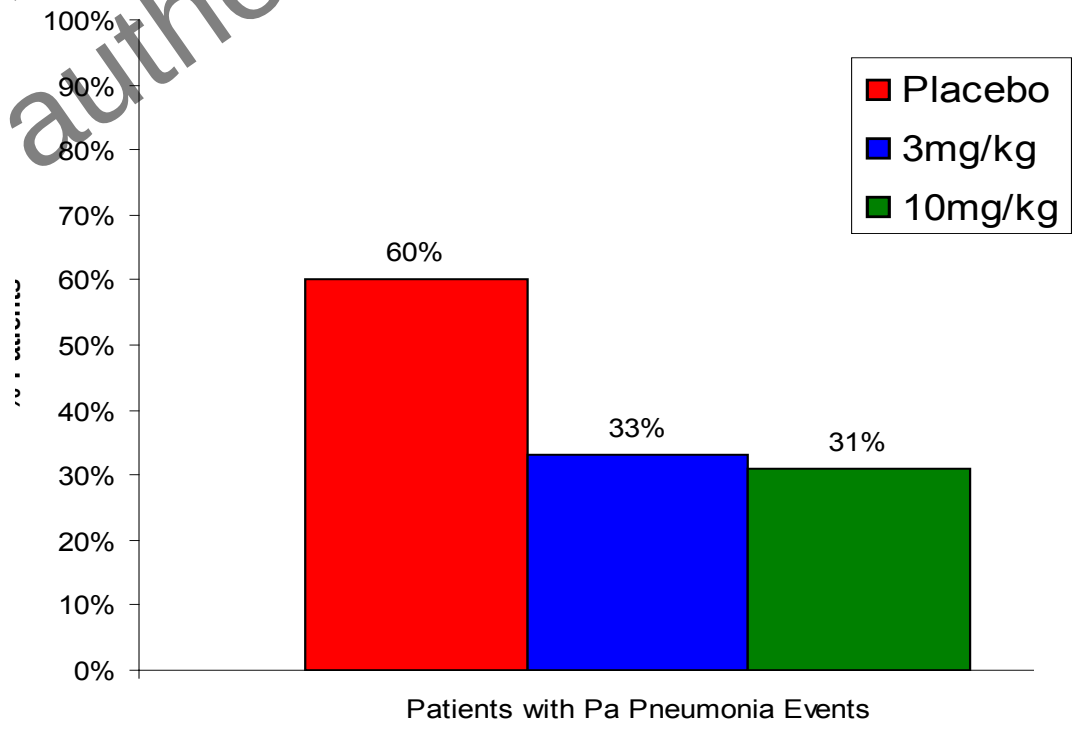
François B., et al. Crit Care Med 2012;40(8):2320-6

Increased *Pa* Event Free Survival

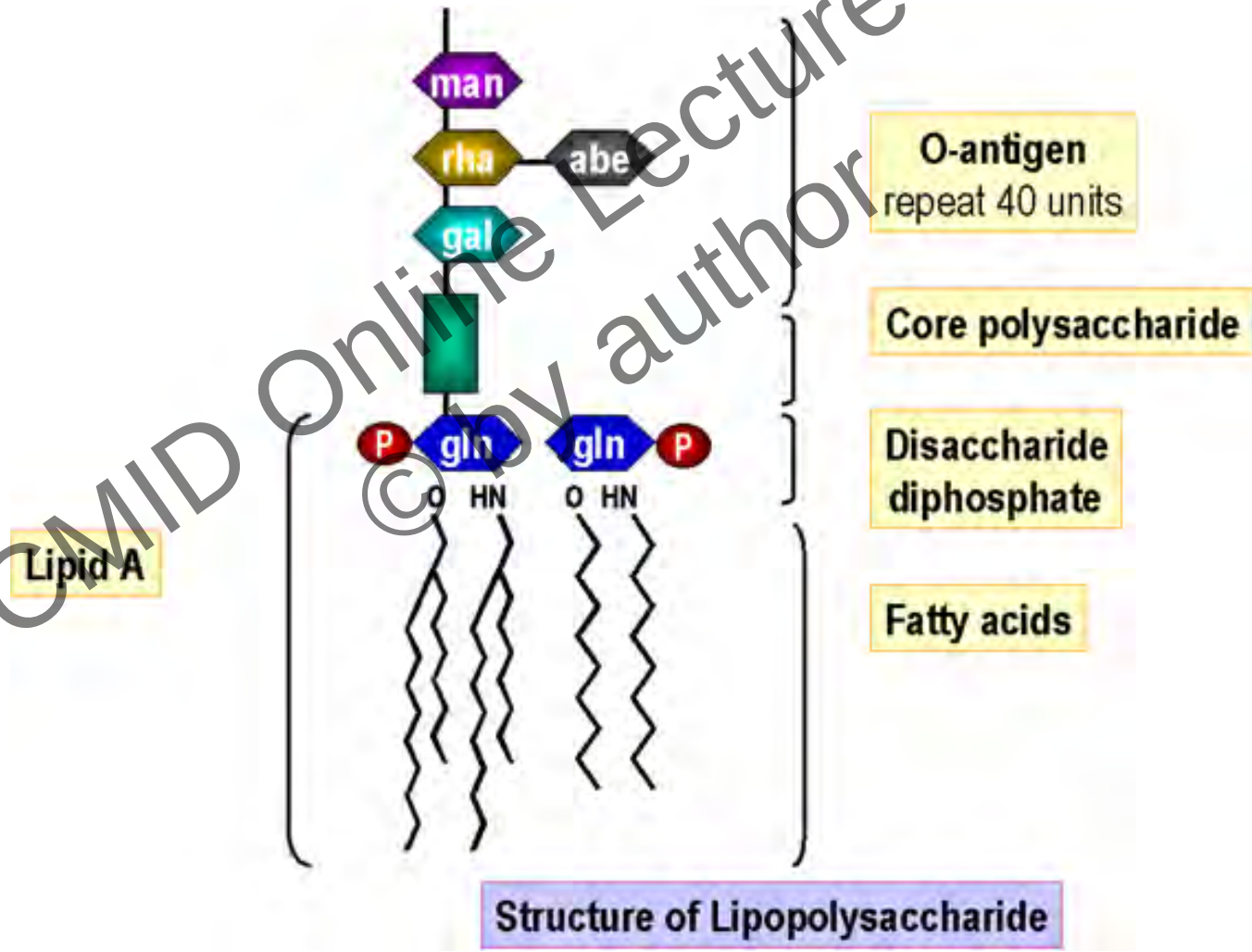


* *Excludes two subjects with Pa UTI*

Decreased *Pa* VAP events



Adjunctive Immunotherapy Targeting *P. aeruginosa* LPS



Specific adjunctive immunotherapy with panobacumab in patients with *P. aeruginosa* O11 pneumonia

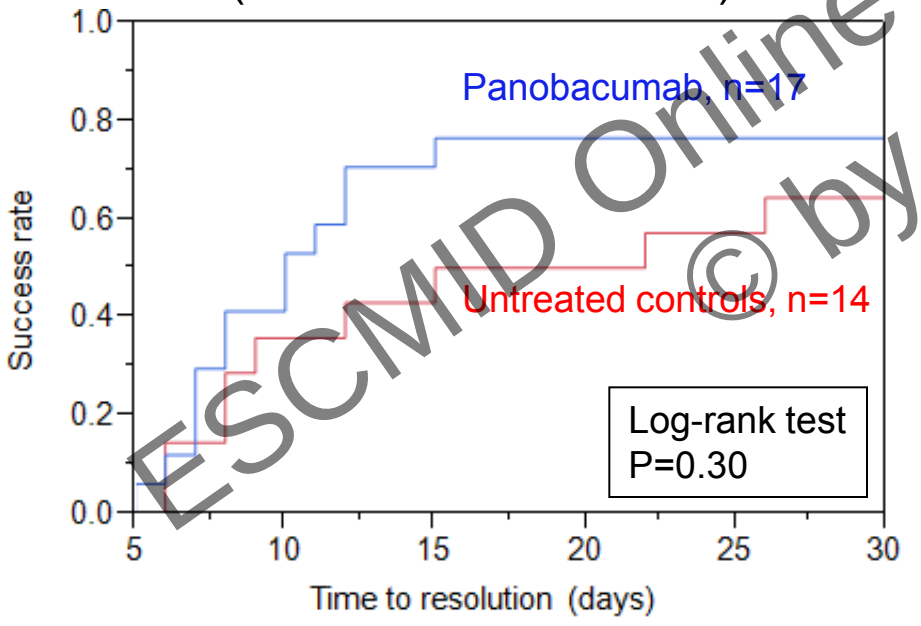
Lu Q, et al. J A C 2011;66(5):1110-6

- Multicentre, open pilot Phase 2a clinical trial of 3 doses of 1.2 mg/kg **panobacumab, a fully human monoclonal anti-lipopolysaccharide IgM**, given every 72 h in **17 patients developing nosocomial *P. aeruginosa* (serotype O11) pneumonia**

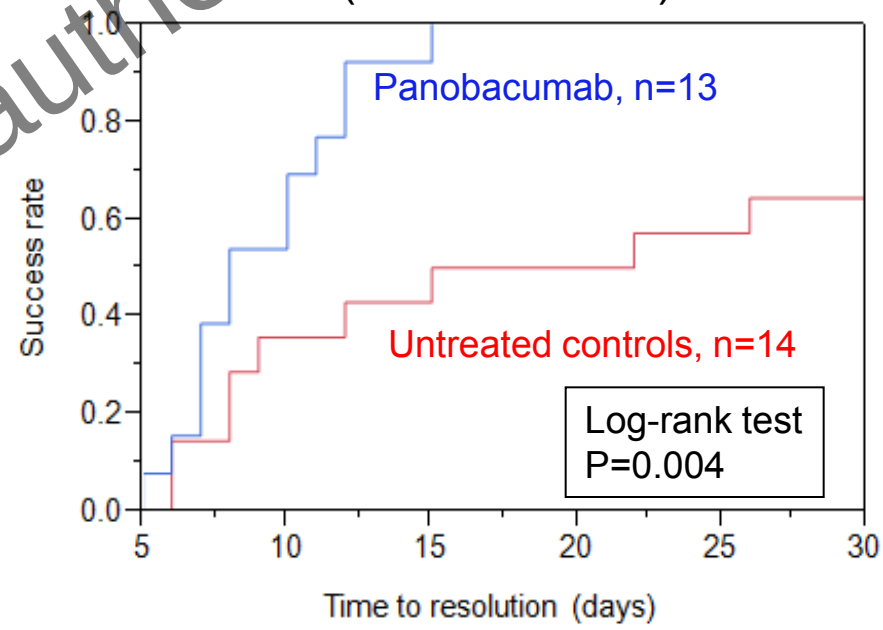
Specific adjunctive immunotherapy with panobacumab in patients with *P. aeruginosa* O11 pneumonia

Que YA, et al. Eur J Clin Microbiol Infect Dis. 2014 ;33:1861-7

ITT Population
(at least one dose mab)

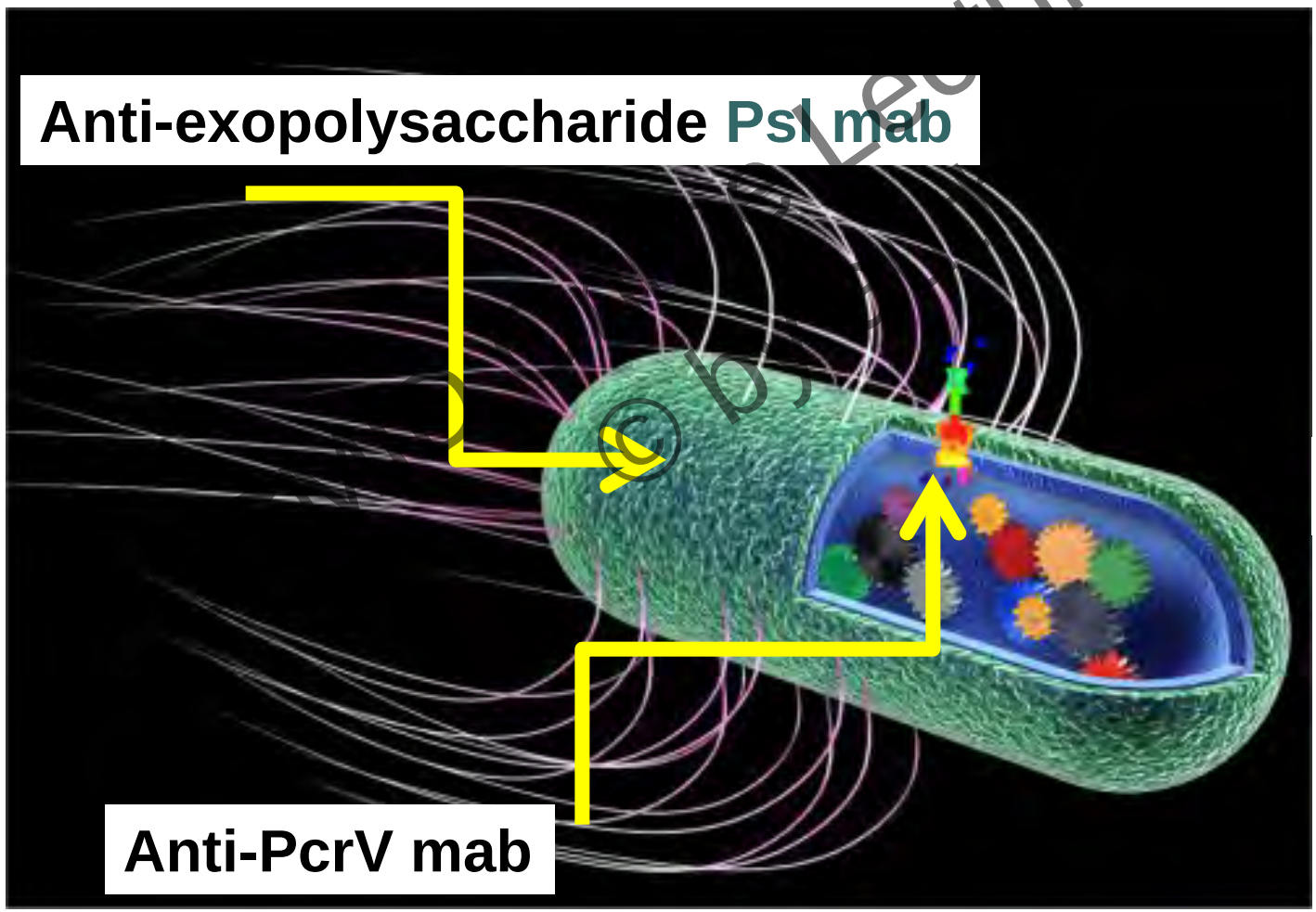


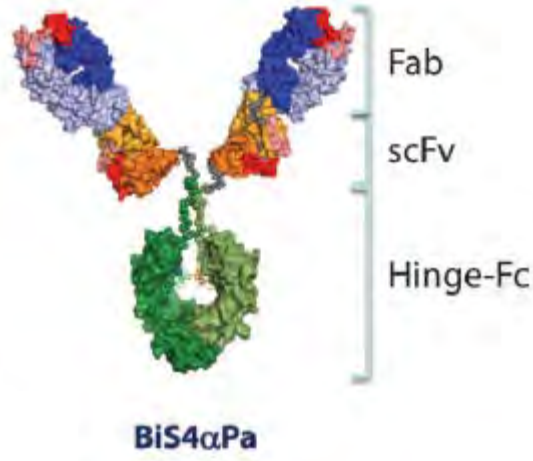
Per Protocol Population
(≥3 doses mab)



A multifunctional bispecific antibody against *P. aeruginosa*

DiGiandomenico A, et al. Science Translational Medicine 2014





A multifunctional bispecific antibody protects against *P. aeruginosa*

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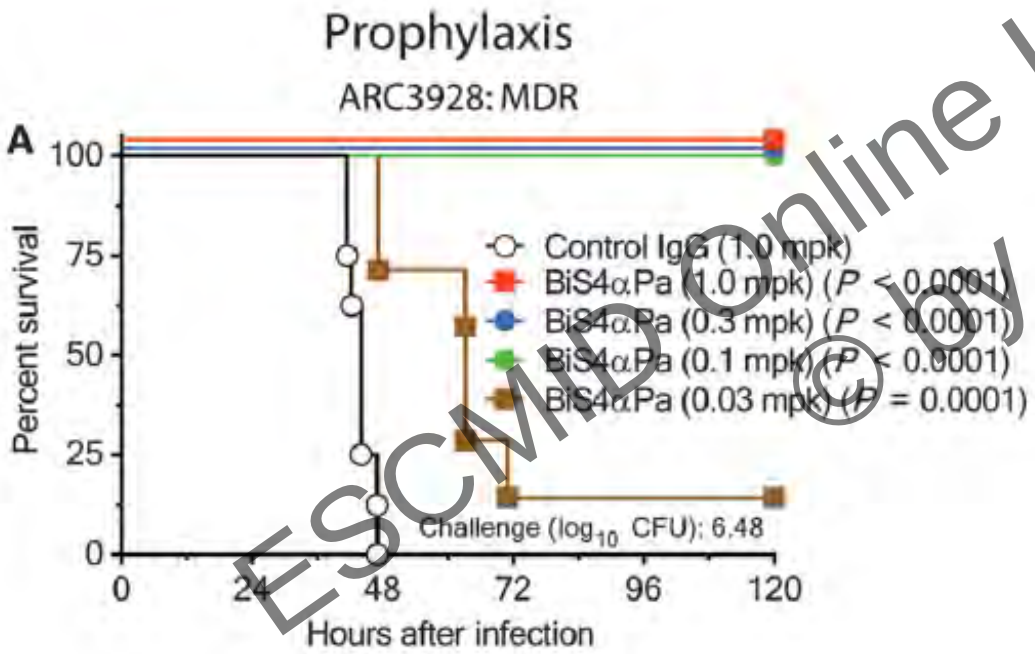

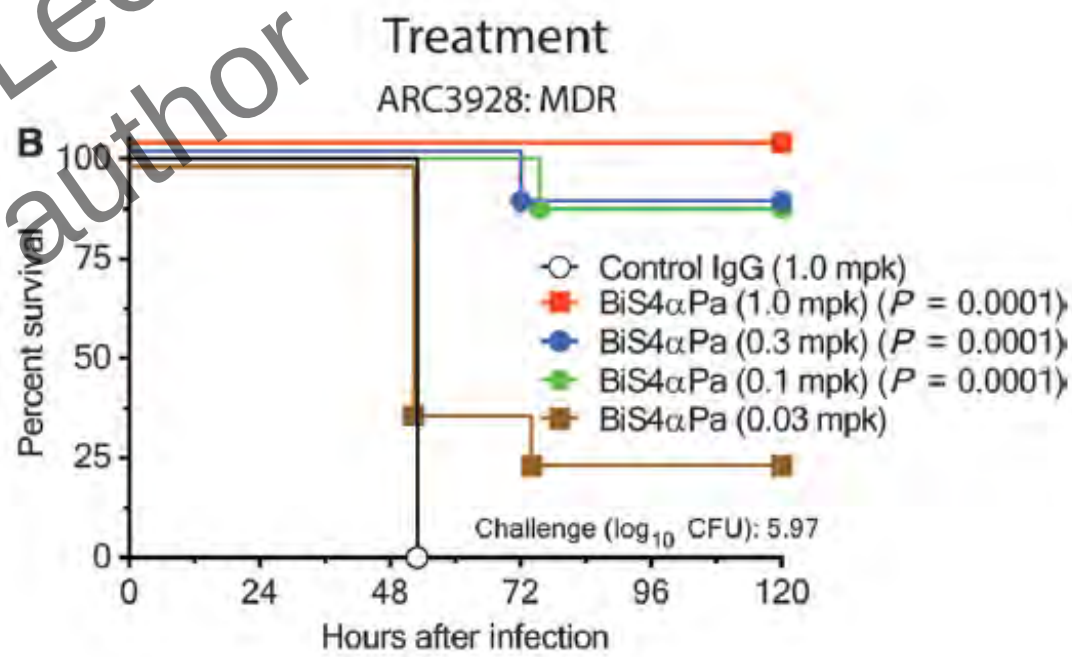

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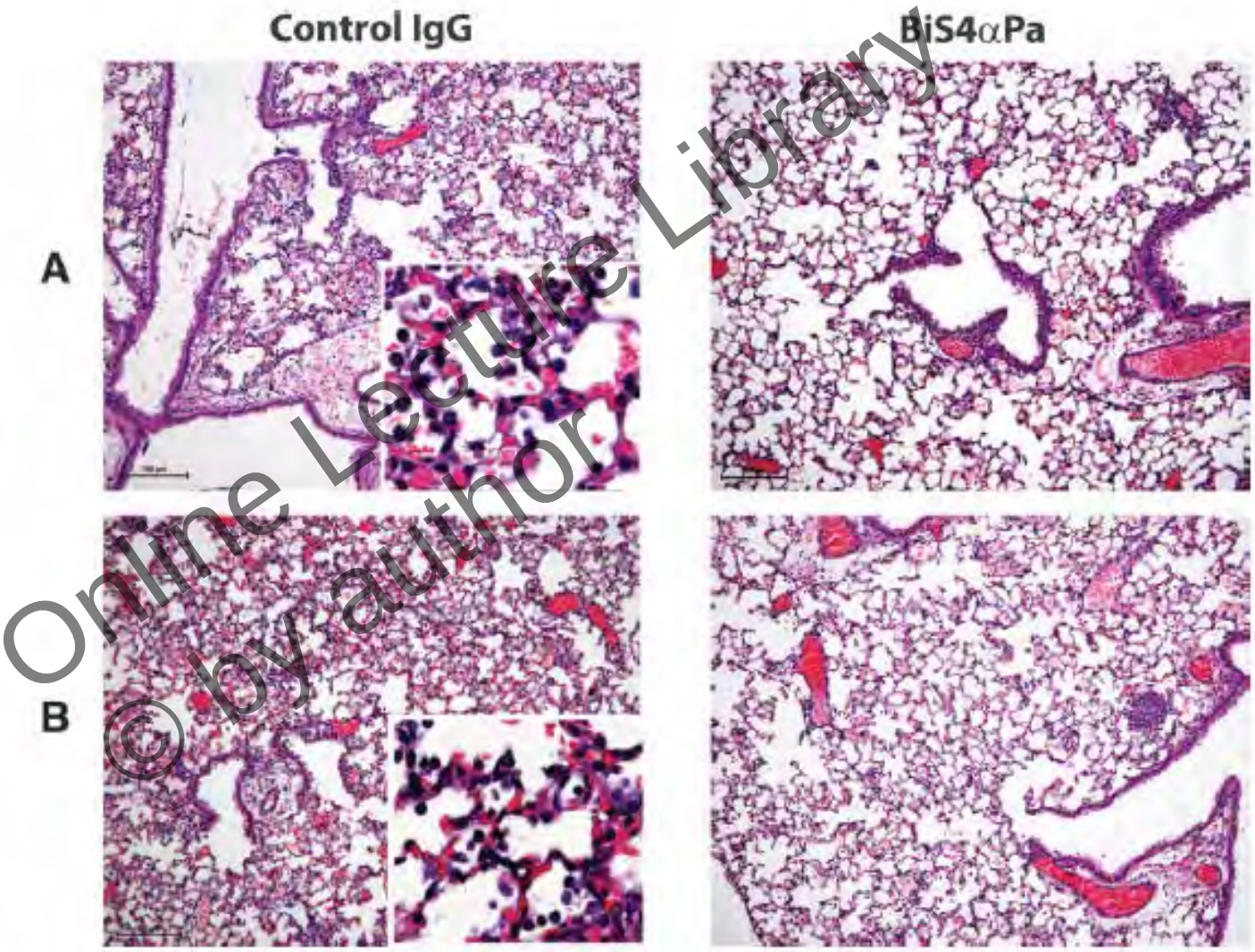
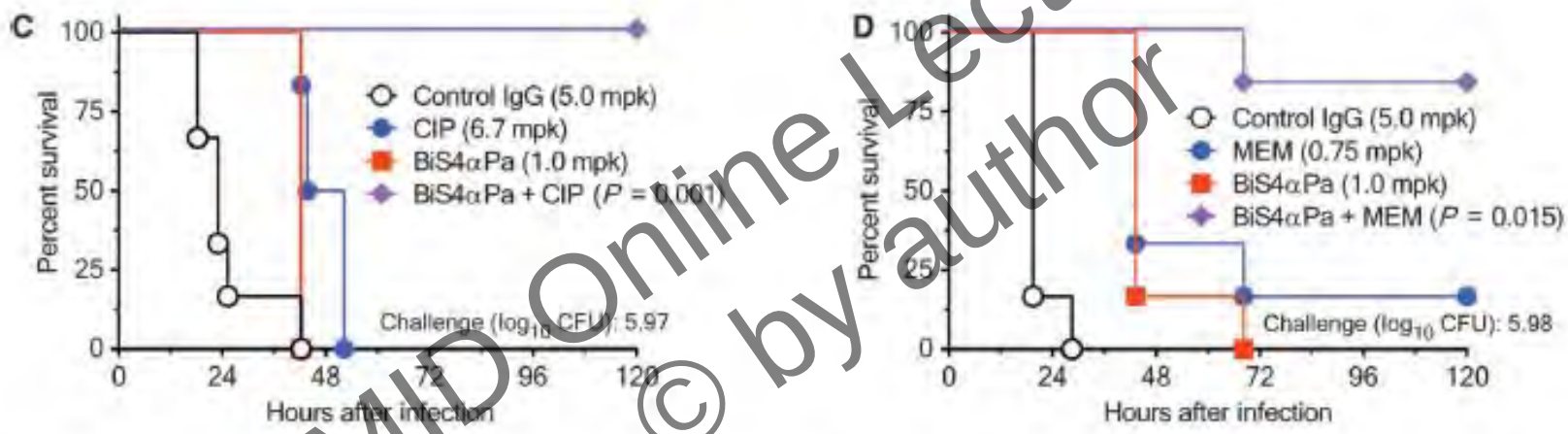
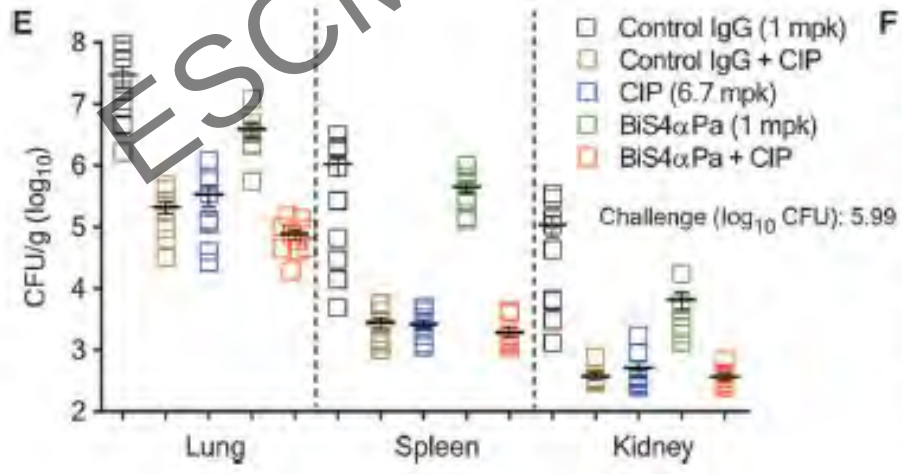


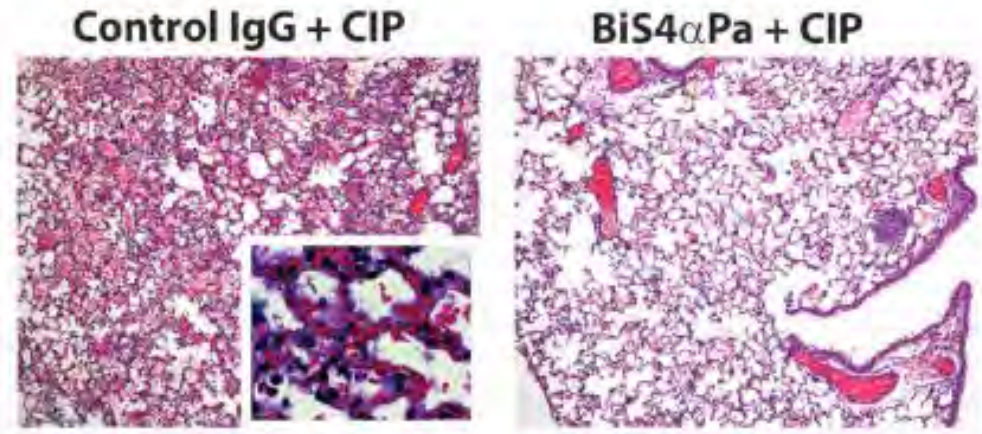
Fig. 3. BiS4αPa-mediated reduction in pneumonia lung pathology in mice. (**A** and **B**) Mice received IgG control or BiS4αPa prophylactically ($n = 3$ for each, respectively) (A) or as a single-agent treatment at 4 hours after infection with *P. aeruginosa* strain 6077 ($n = 3$ for each, respectively) (B).

A multifunctional bispecific antibody protects against *P. aeruginosa*

DiGiandomenico A, et al. Science Translational Medicine 2014

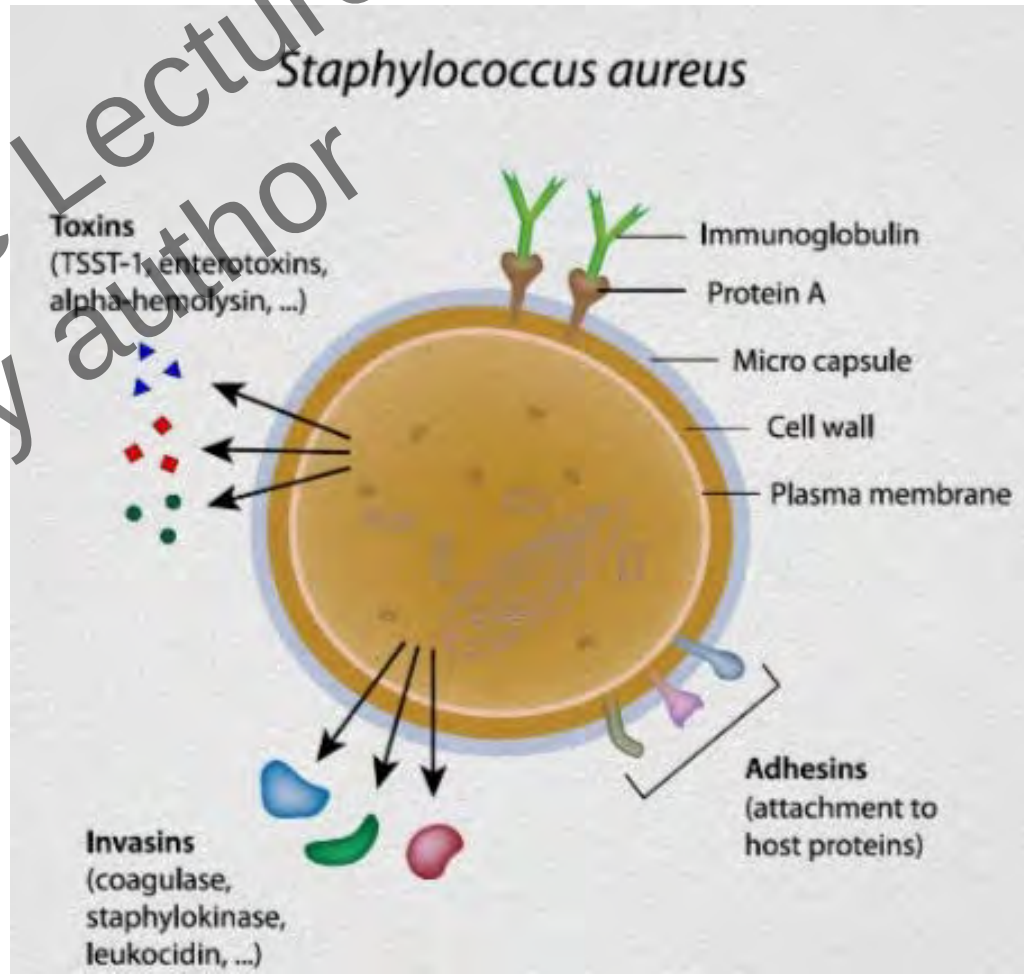






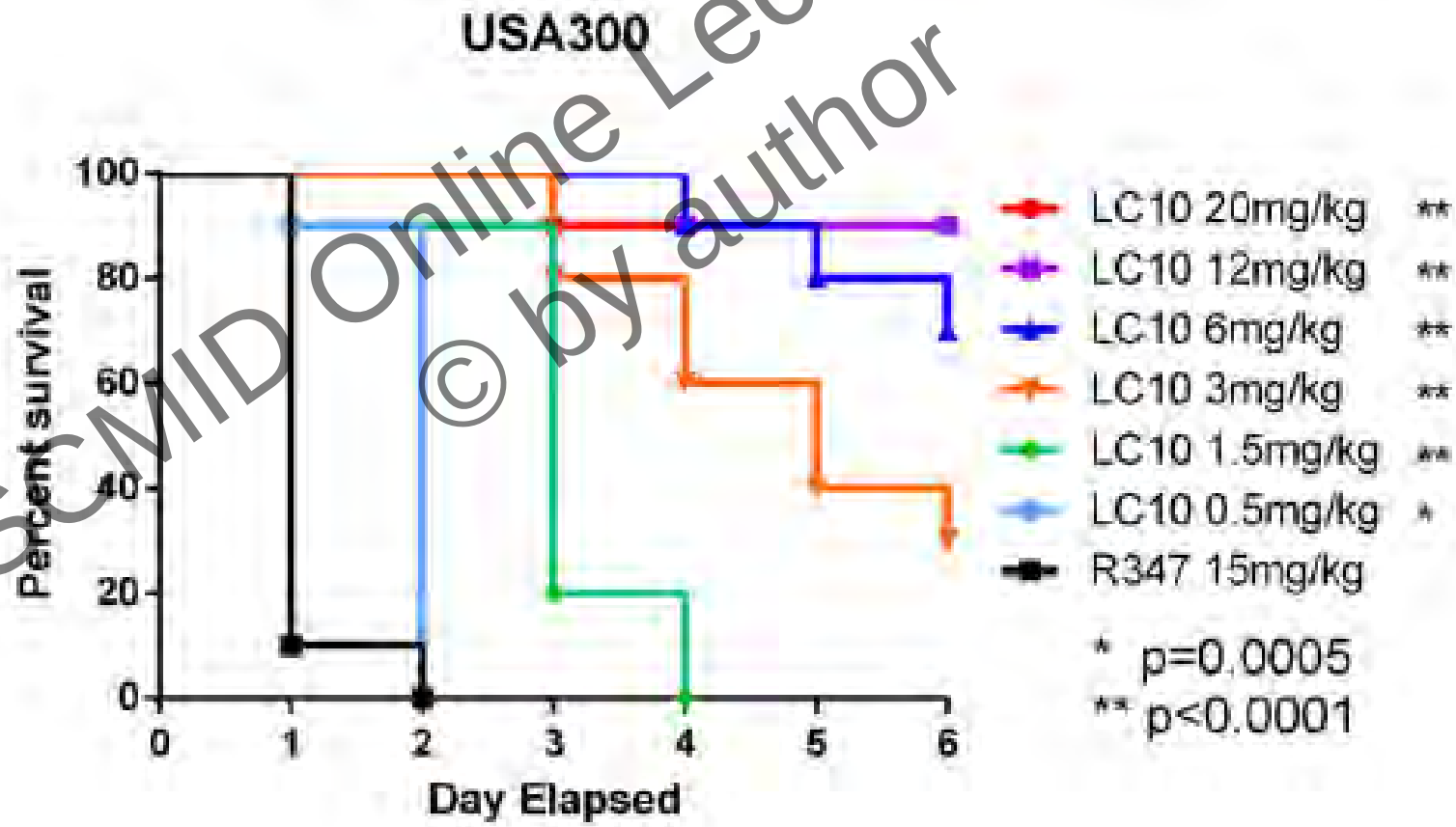
Adjunctive Immunotherapy Targeting *S. aureus* Alpha-Toxin

Alpha-toxin is one of **the major cytotoxic agent** released by ***S. aureus*** and the first identified member of the **pore forming beta-barrel toxin family**



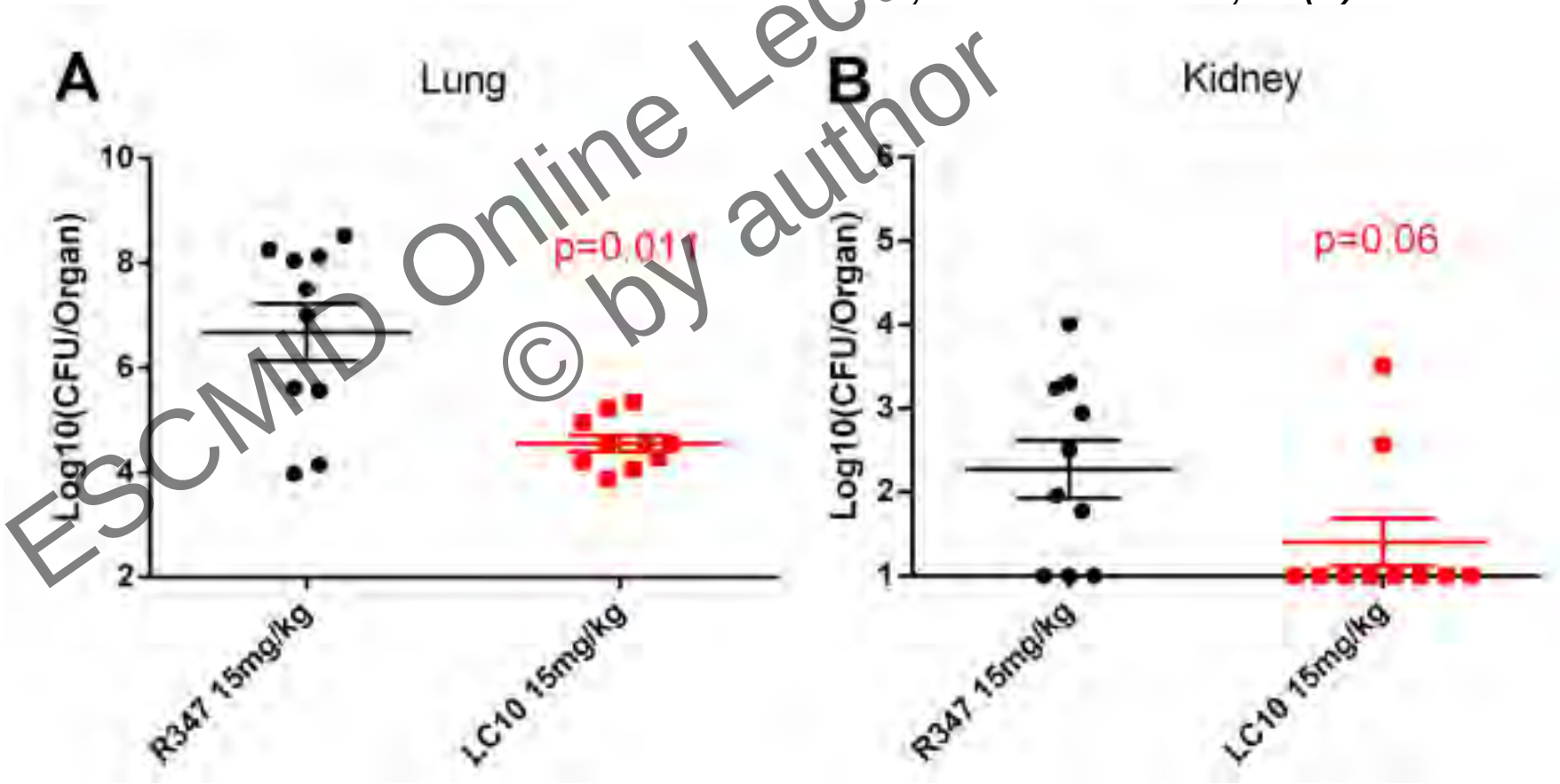
Treatment with monoclonal antibody targeting alpha-toxin, a pore-forming toxin, increased survival of infected mice with *S. aureus*

Hua L., et al. AAC 2014, 58(2):1108-17



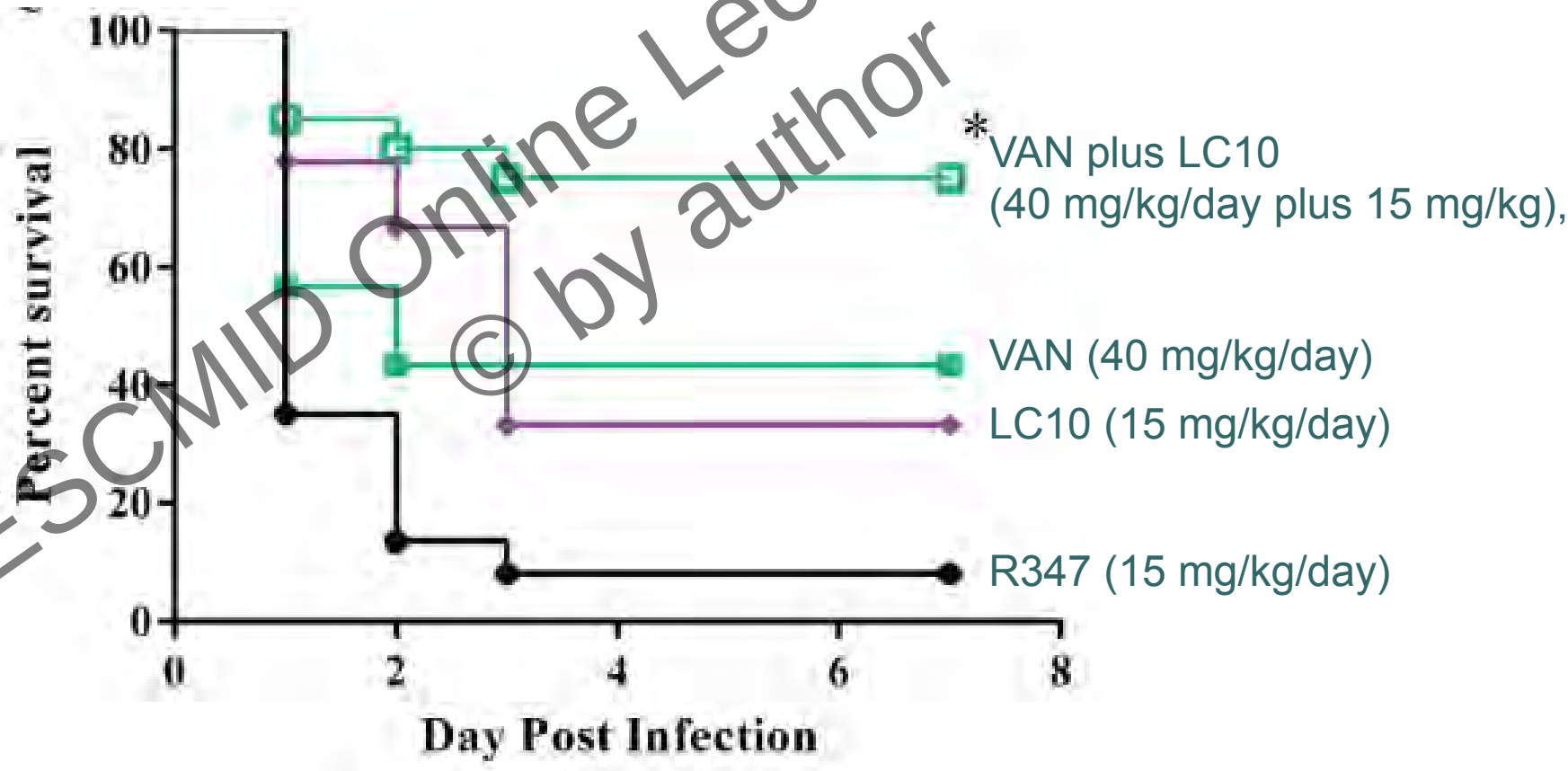
Treatment with a mab targeting the alpha-toxin, a pore-forming toxin, reduced bacterial numbers in the lungs and kidneys of infected mice with *S. aureus*

Hua L., et al. AAC 2014, 58(2):1108-17



Treatment with a combination of mab and vancomycin resulted in a significant increase in survival relative to monotherapies

Hua L., et al. AAC 2014, 58(2):1108-17



Non-antibiotic approaches for treating severe infections

- **Better understanding of the factors that influence the virulence of bacteria, as well as innovative strategies** has rendered possible to envision **non-antibiotic approaches** for preventing or treating severe infection.
- However, and even if recent experimental studies are very encouraging, convincing **clinical data are still lacking to support their routine use**.