West Virginia University

Anti-LPS Bactericidal Monoclonal Antibodies Protect Against *Pseudomonas aeruginosa* Challenge in Mice

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Our approach to combatting AMR

Treatment **Prevention**

Antibodies as drugs

- Pathogen-specific antibodies

- Immediate immunity
- Can confer protection regardless of the immune status of the infected host

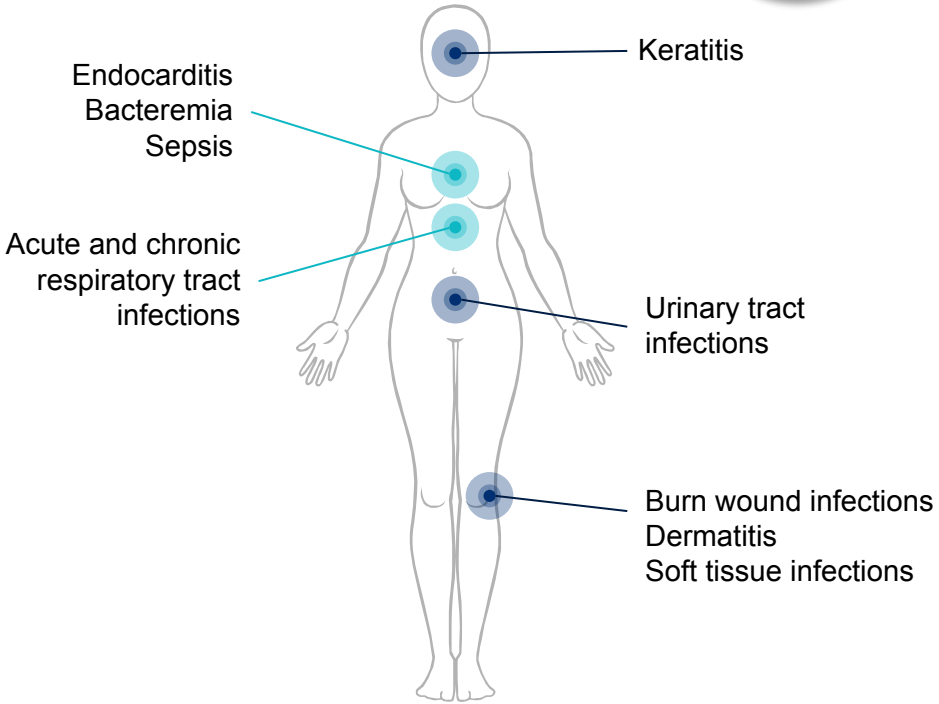
Applications of therapeutic antibodies

Pseudomonas aeruginosa

- Opportunistic Gram-negative bacterium
- Highly antimicrobial resistant
- No vaccine available

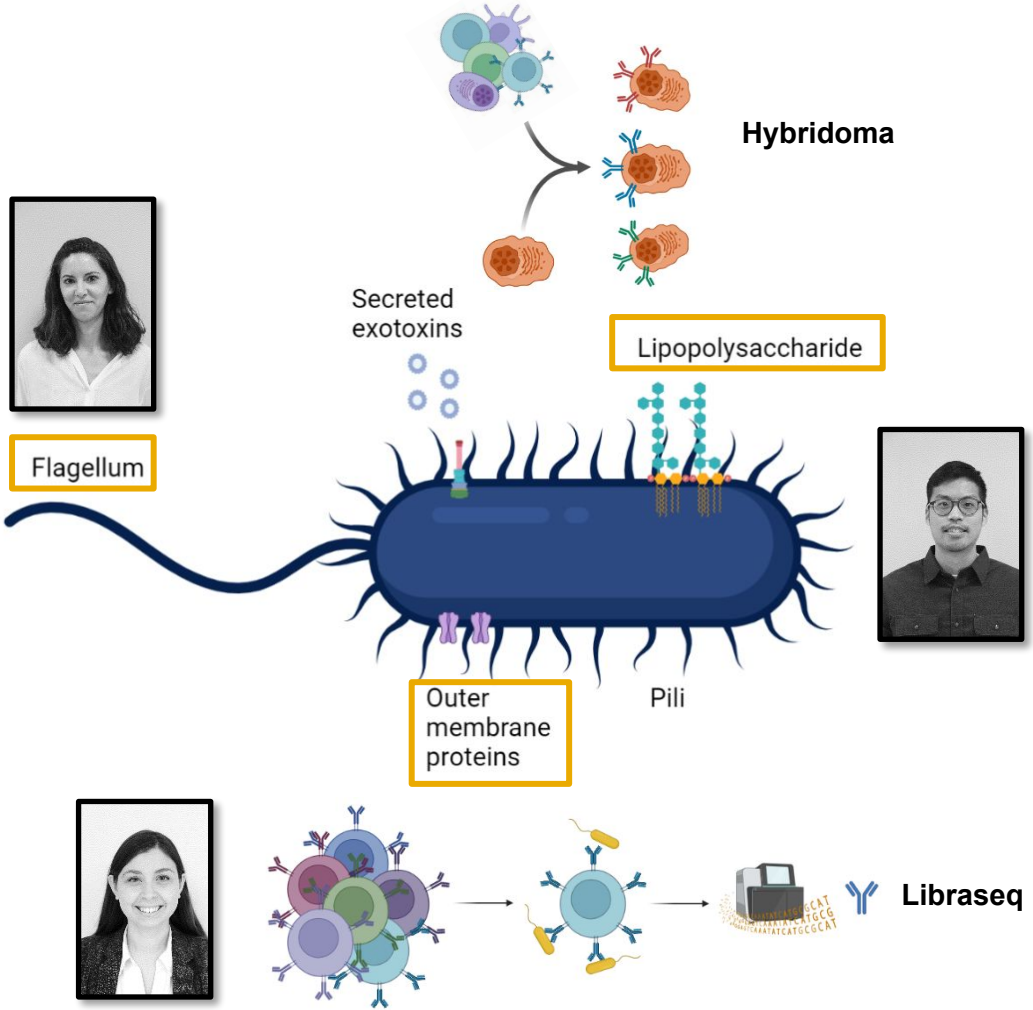
Applications:

- Sepsis
- (Pneumonia)
- (Topical – wound)

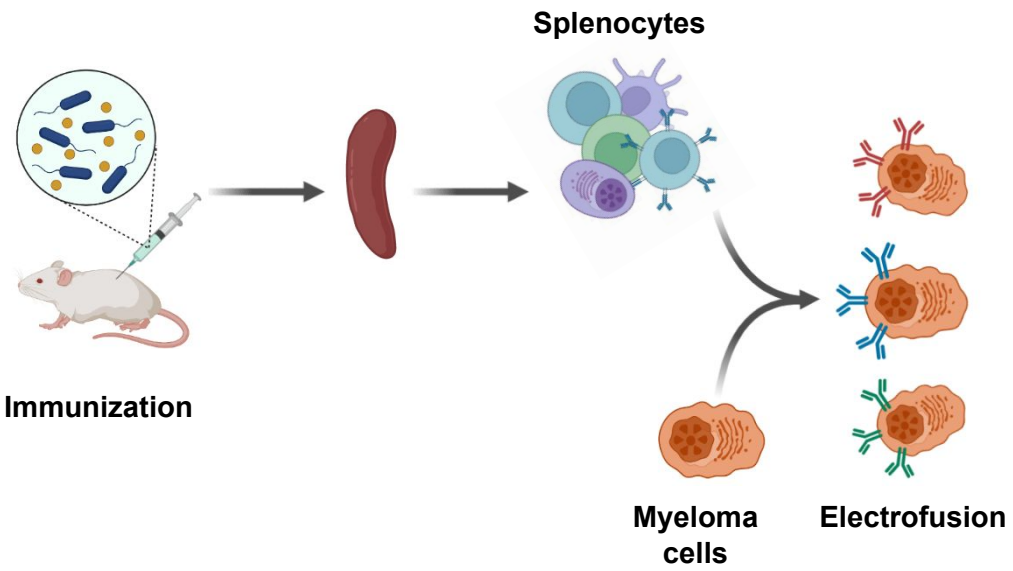


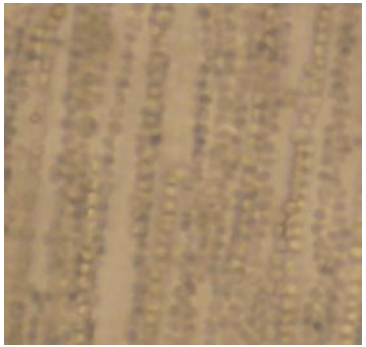
Antibody targets

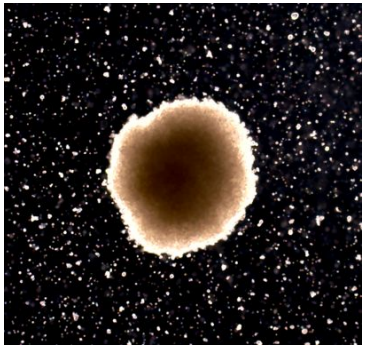
- Immunogenic
- Surface-exposed
- Conserved



How therapeutic antibodies are made







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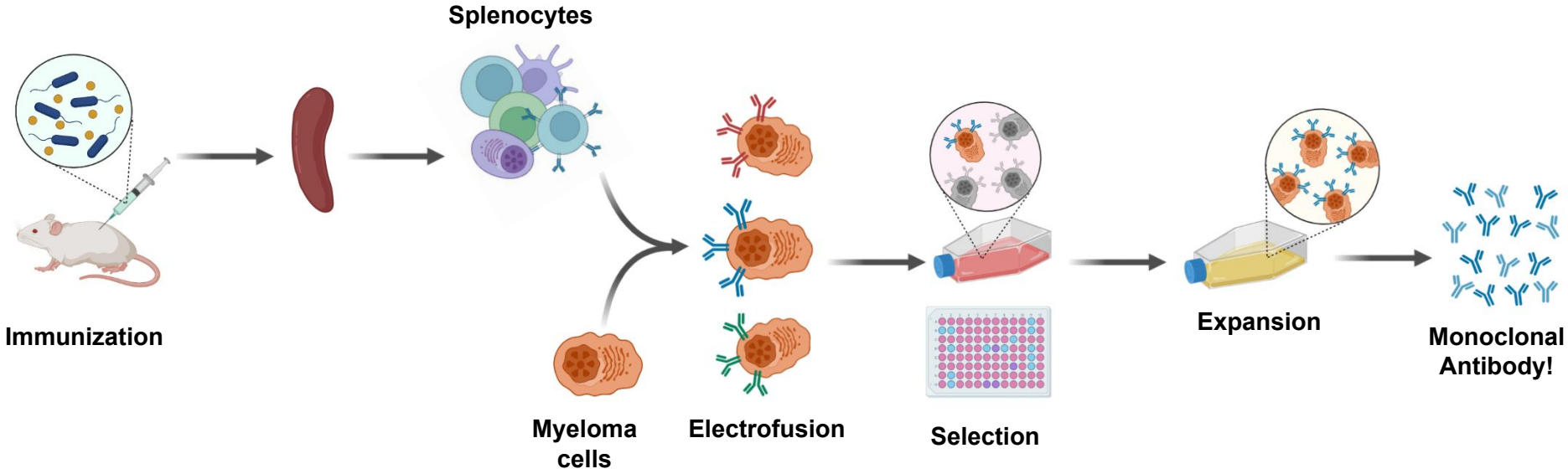
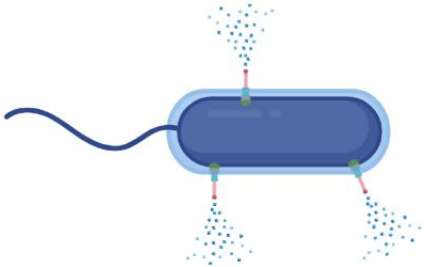


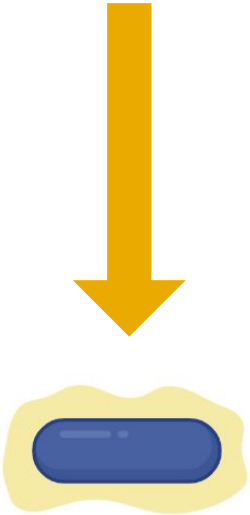
Antibody targets

- Immunogenic
- Surface-exposed
- Conserved
- Relevant during infection



P. aeruginosa strains from acute infections

Pseudomonas **Isolation Agar**



P. aeruginosa strains from chronic infections

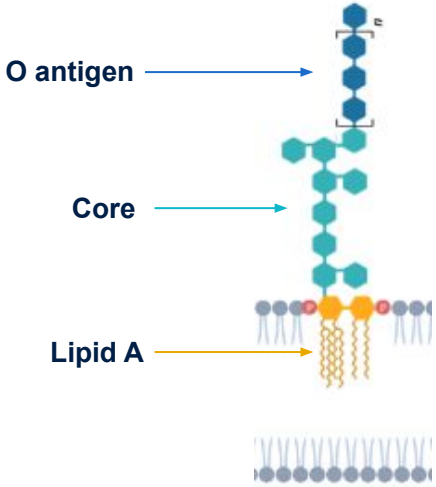
Pseudomonas **Isolation Agar + Ammonium Metavanadate**

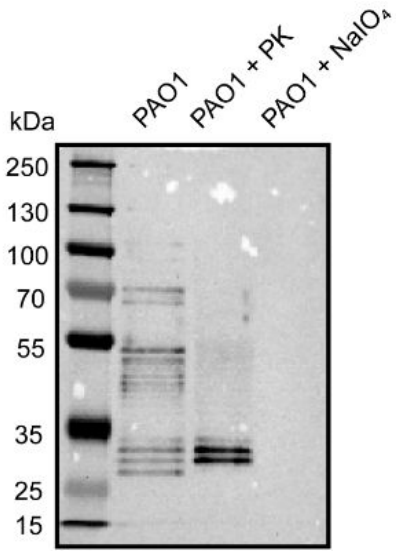
Source: Damron et al, Mol. Micro 2013

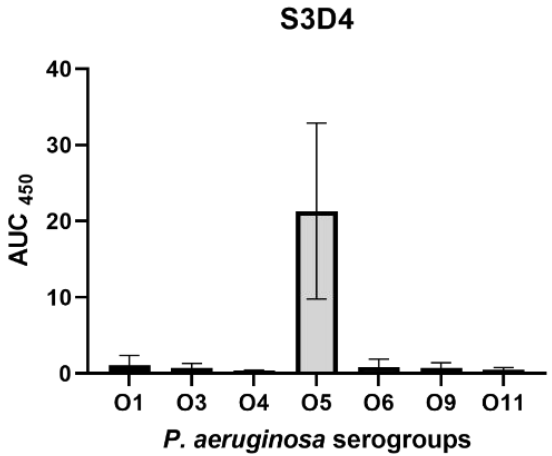
Antibodies against lipopolysaccharide

Jason Kang, MD

Lipopolysaccharide (LPS) structure

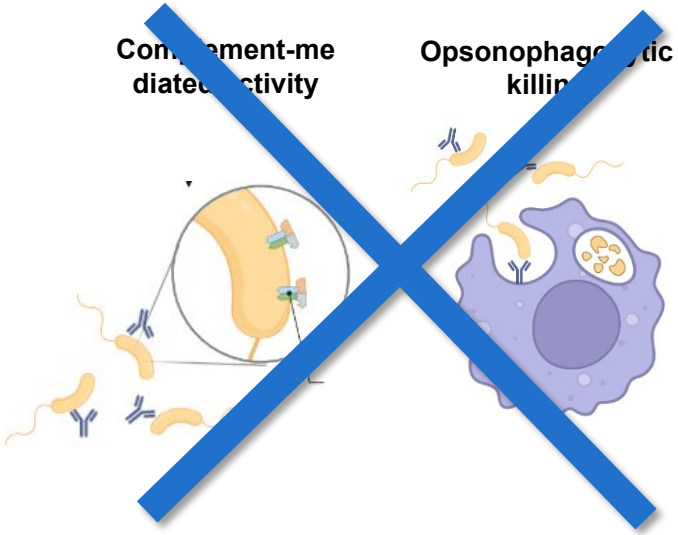


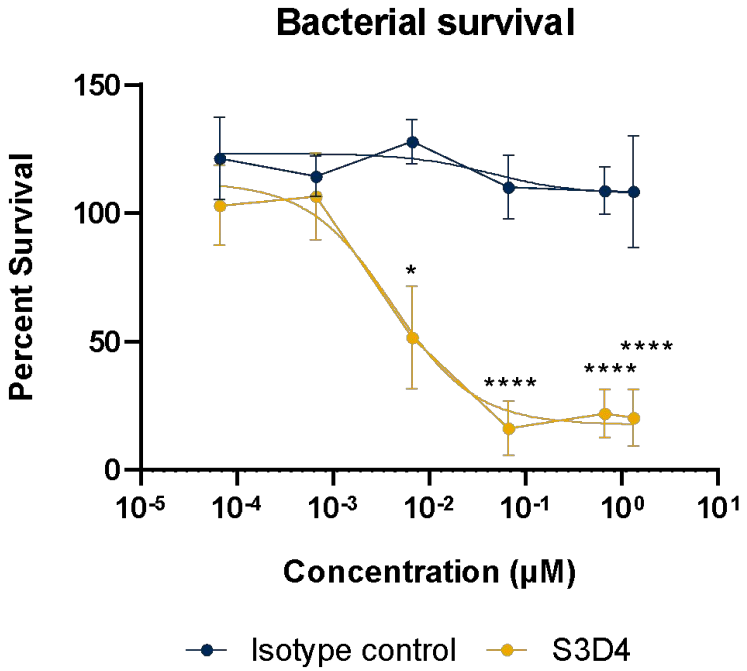




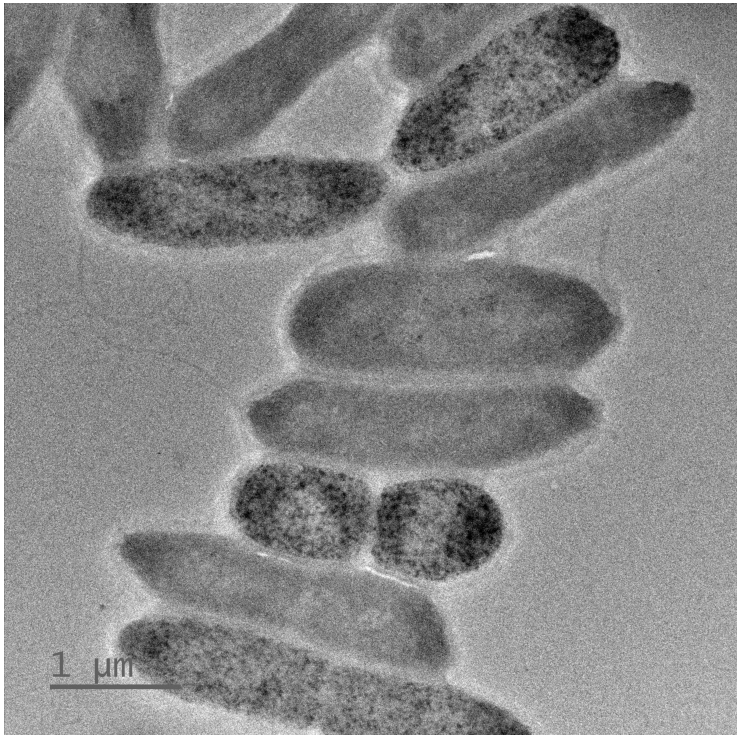
PK = Proteinase K

Novel antibody function?





Effect of S3D4 on the cell



Hypothesis: **loss of membrane integrity and permeabilization?**

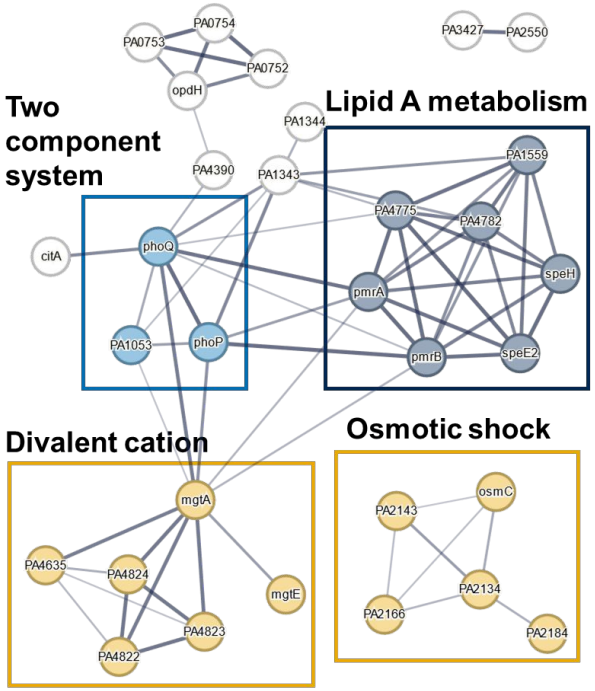
Effect of S3D4 on the cell

Exposure of PAO1 to the IC_{50} of S3D4
RNA sequencing at 15min, 1h, and 2h post exposure

Future experiments:

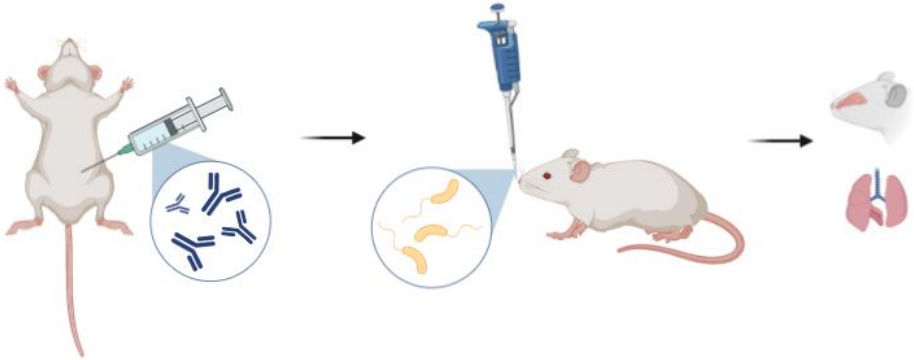
- Membrane permeability assays
- Atomic force microscopy

…



Antibody functionality *in vivo*

Pneumonia model

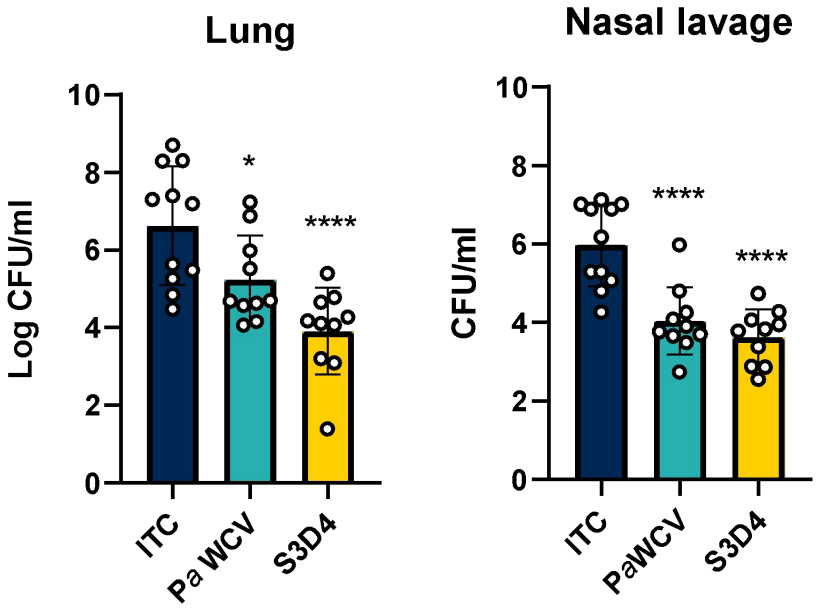


Passive immunization

Intranasal infection

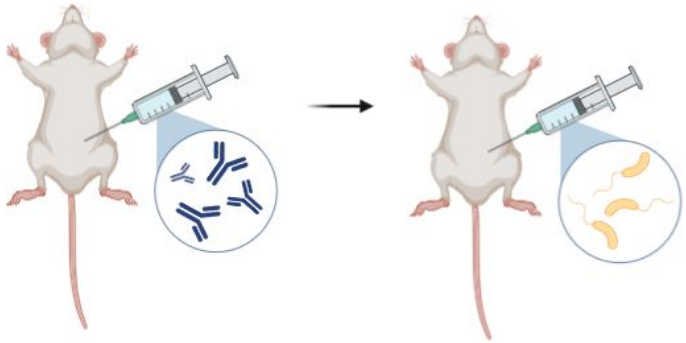
Quantification of bacteria in tissue

Antibody functionality *in vivo* - Pneumonia



Antibody functionality *in vivo*

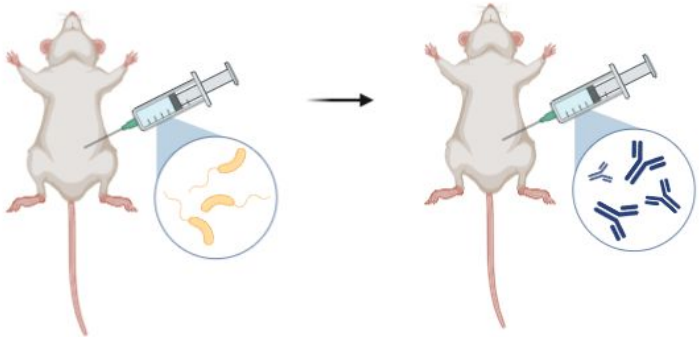
Prophylaxis sepsis model



Passive immunization

Intraperitoneal Infection +8 hrs

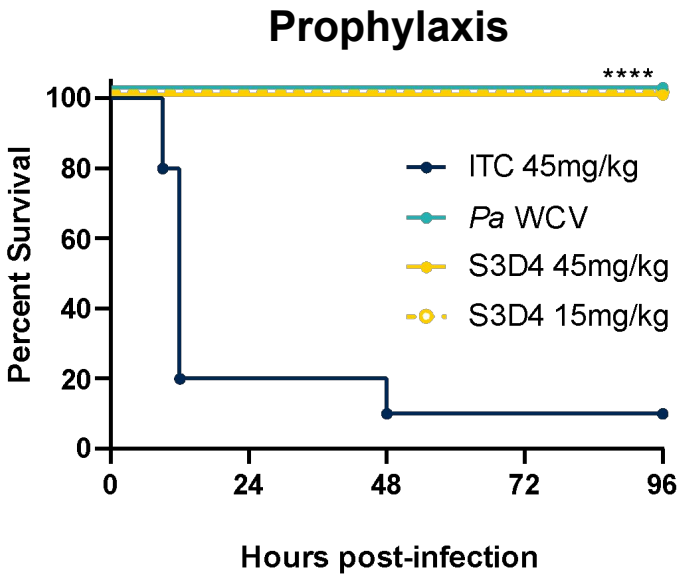
Treatment sepsis model

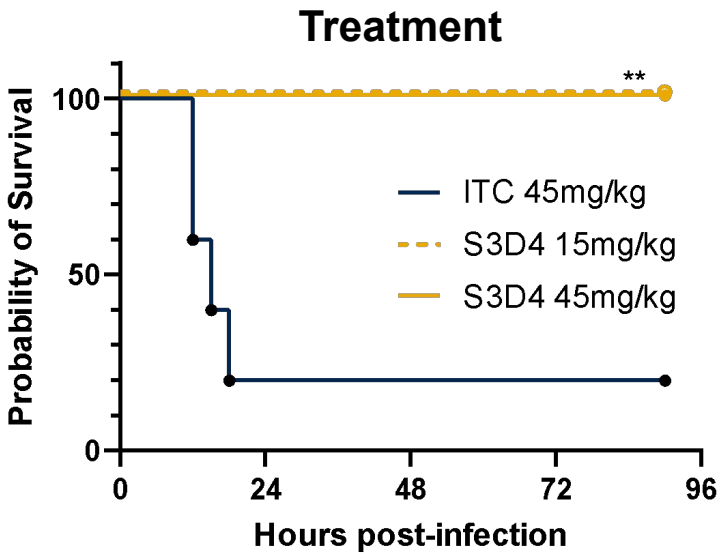


Intraperitoneal infection

Passive Immunization +2 hrs

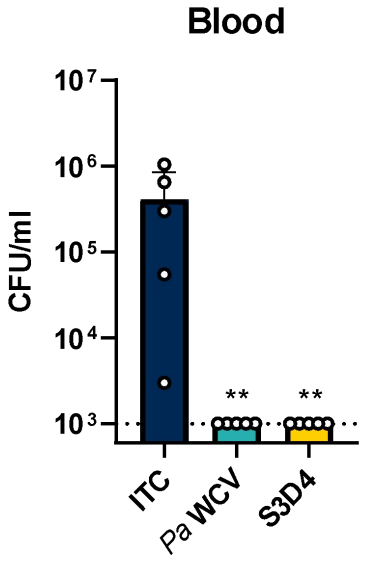
Antibody functionality *in vivo* - Sepsis



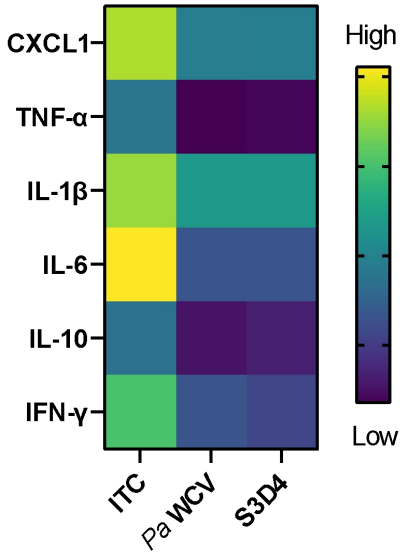


Pa WCV = serum from *P. aeruginosa* whole cell vaccinated mice

Antibody functionality *in vivo*

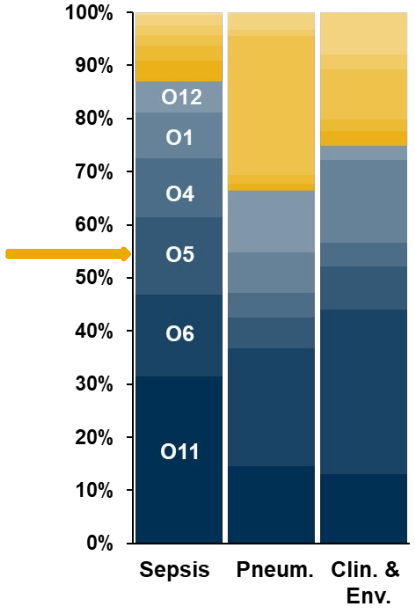


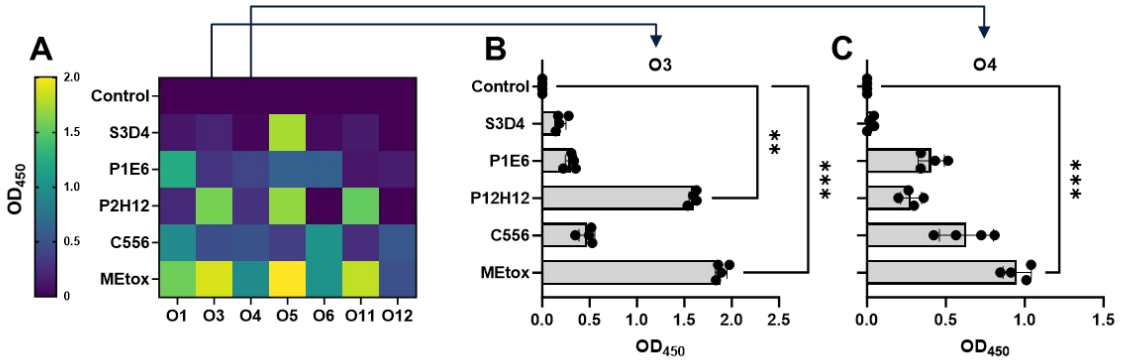
S3D4 clears circulating bacteria in less than 6h!



No cytokine storm!

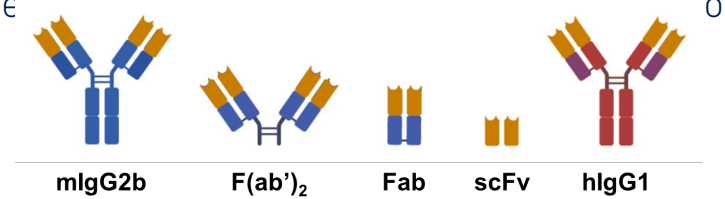
Future directions – Can we make cocktails?

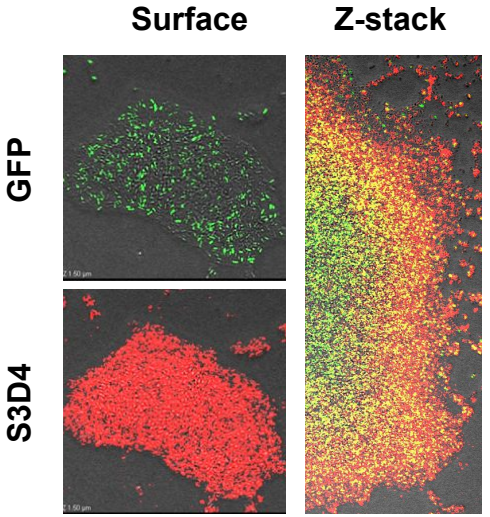




Important questions moving forward:

- What part of S3D4 mediates function?
  - Can we use [illegible] ofilms?



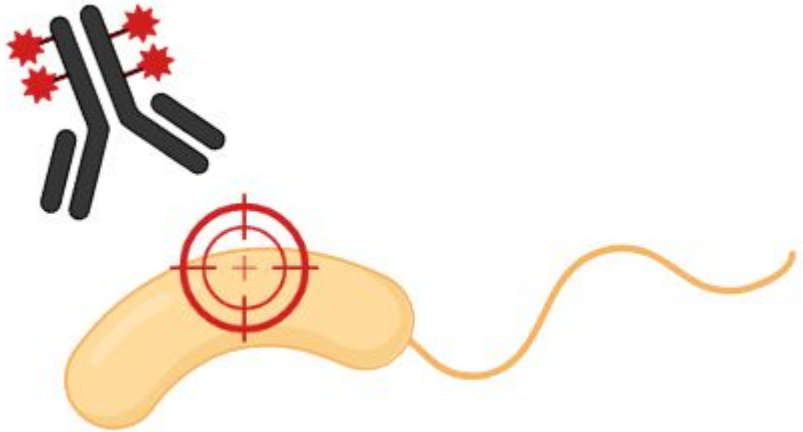


- Can we make more with similar functions?
- Can bacteria become resistant to them?
- Do they work in combination with antibiotics?

Next generation immunotherapies

Antibody-drug conjugates (ADC)!

- Delivery of antibiotic at the site of infection
- Smaller doses used to achieve efficacy
- Combination with antibody-mediated clearance

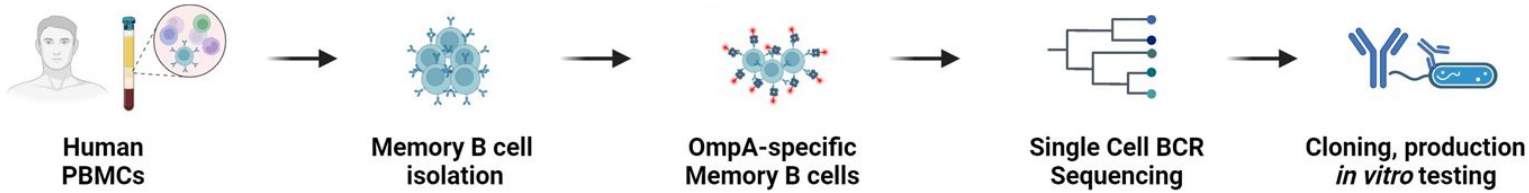


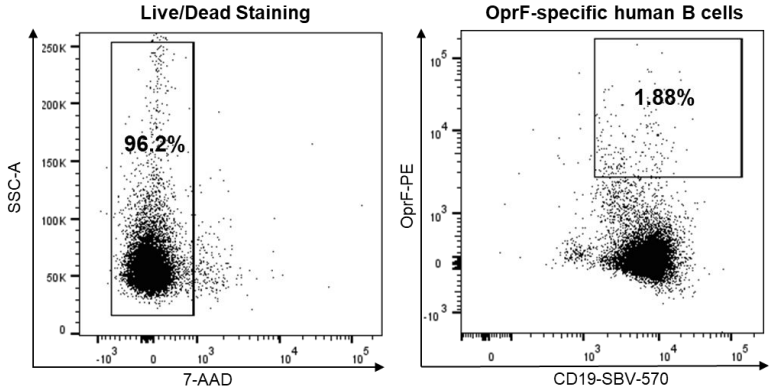
Current problems

Mice are not humans…

… and murine mAbs are not humans mAbs.

Novel approach in the lab: Libra-seq





Isolated 844 cells from $5x10^6$ PBMCs isolated from intermittently infected CF patient

Acknowledgements

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- Sarah Jo Miller
- Spencer Dublin

Collaborators

- Damron lab
- Lukomski lab
- Robinson lab
- Lewis lab
- Wilks lab
- Barzilay lab

MIT CSAIL

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Partners

VACCINE DEVELOPMENT CENTER

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merlin BIOTECH
The Cure is in the Message

THANK YOU!