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rEVOLUTIONary BIOTHERAPEUTICS

Alternative antimicrobials: live biotherapeutics for lung infections

Jeanette Mucha, Cofounder and CEO

November 20, 2019

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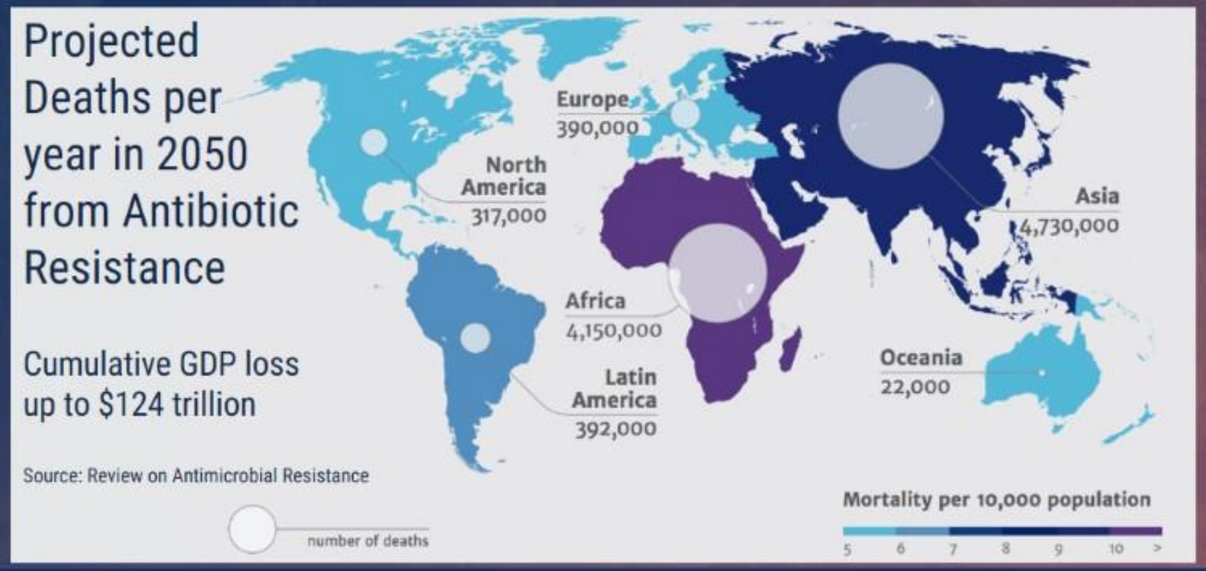
What are our options against antibiotic resistance?



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Approach	Limitations
New Antibiotics	Low margins and use, cannot be responsibly used for prevention, many have wide spectrum activity causing dysbiosis in gut
Phage	Must be used in cocktails because they are too specific for strains, resistance forms easily, biofilm barriers prevent entry
Peptides	Easily lose activity, difficult to deliver
Antibodies	Expensive to produce, similar specificity and entry problems as phage
Vaccines	Lengthy development time, difficult for bacterial mucosal infections
Microbiome Consortia	Mechanism is typically undefined or unknown, based on correlation data

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Live Biotherapeutics as Drug Delivery Vehicles

In situ drug production

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Better Bugs as Drugs – Live Microbes with Multiple Mechanisms

Using our MERGE technology

Our patented MERGE (Microbial Enhanced Recombinants Generated by Evolution) platform allows us to transfer useful traits from one species of yeast or bacteria to another

STEP 1

Screen library of unique microbes for Host/ Donor

STEP 2

Environmental pressure can transfer or create new traits

STEP 3

Selection of assays & screening

MERGE naturally moves mechanisms of action into second generation probiotics to be used directly as live therapeutics (Beneficial Bugs as Drugs), eradicating antibiotic resistant superbugs

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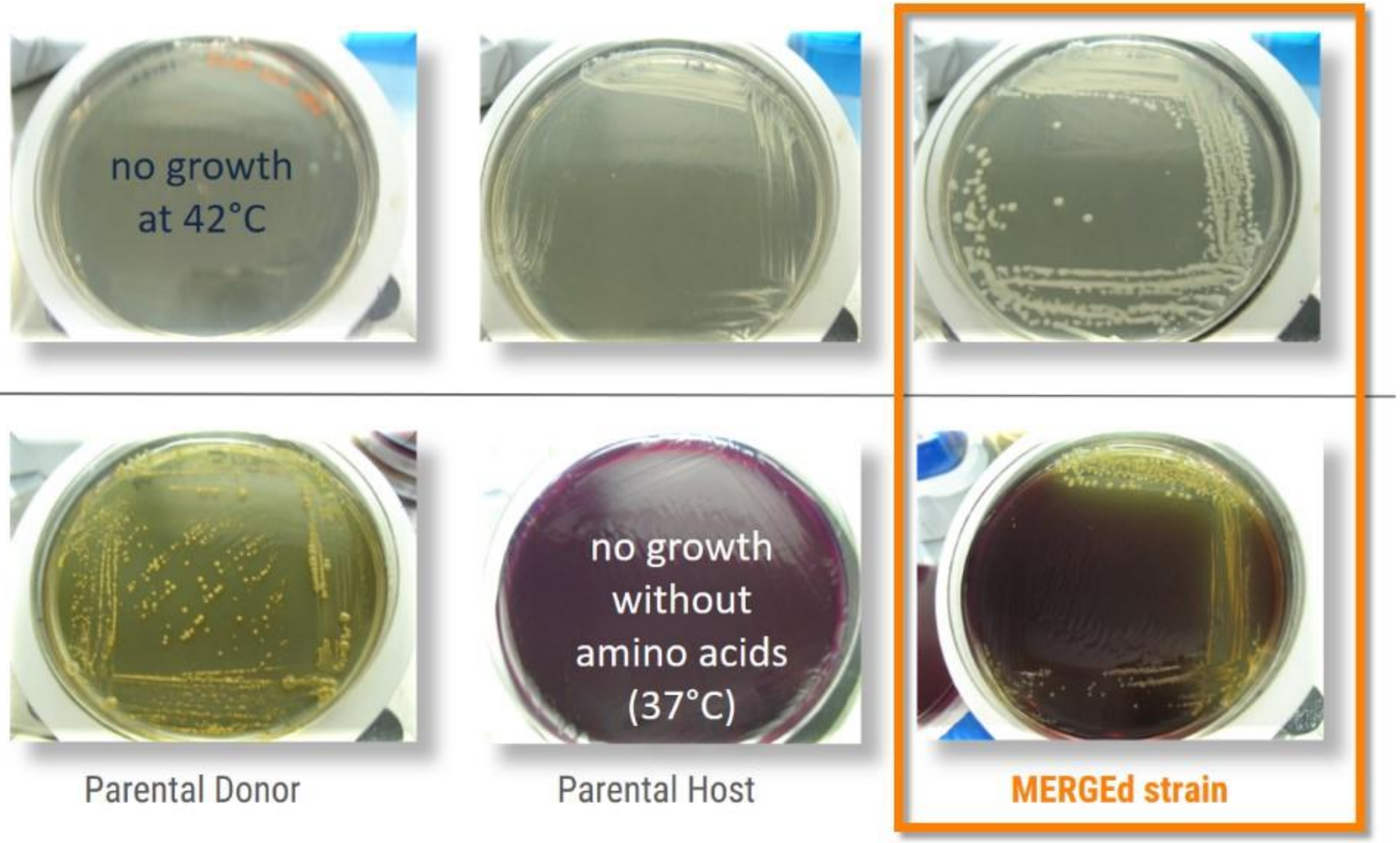
How MERGE Works



Like a Meyer lemon that has a sweet rind from a mandarin orange and acidic flesh from a traditional lemon; our MERGEd strains retain the best traits from both species

In this example, our MERGEd strain both survives a fever and can make its own essential amino acids

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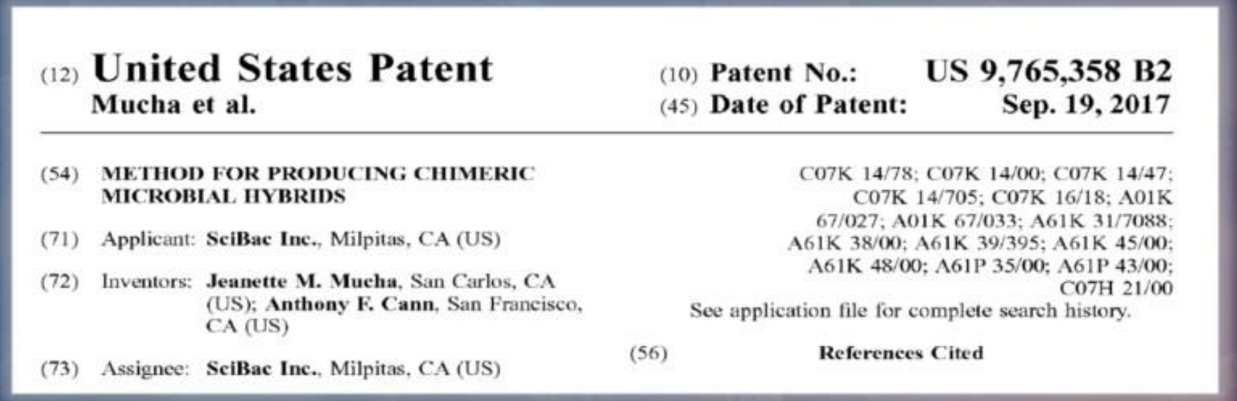
Patented Technology



(12) **United States Patent**
Mucha et al.

(10) **Patent No.: US 9,765,358 B2**
(45) **Date of Patent: Sep. 19, 2017**

(54) **METHOD FOR PRODUCING CHIMERIC MICROBIAL HYBRIDS**

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(73) Assignee: **SciBac Inc.**, Milpitas, CA (US)

C07K 14/78; C07K 14/00; C07K 14/47; C07K 14/705; C07K 16/18; A01K 67/027; A01K 67/033; A61K 31/7088; A61K 38/00; A61K 39/395; A61K 45/00; A61K 48/00; A61P 35/00; A61P 43/00; C07H 21/00

See application file for complete search history.

(56) **References Cited**

- Platform method patent pending in EU, India, China, Japan, Australia, and Canada
- Provisional use patents for gastrointestinal biotherapeutics (filed Sept 2018), and lung biotherapeutics (filed Oct 2018 – converting Oct 2019)
- Plans for:
  - Formulation and/or use patents for anti-microbial novel small molecules
  - Method for optimal lung delivery

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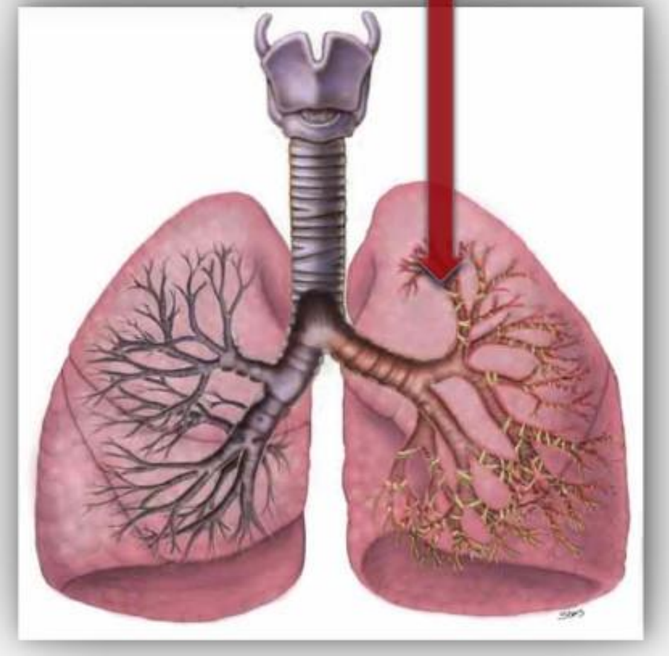
Cystic Fibrosis (CF)

- Fatal, autosomal recessive disorder
- About 30,000 cases in the USA, up to 100,000 globally
- Pathogenesis in respiratory tract
  - Thick, sticky mucus
  - Chronic infection
  - Airway obstruction
  - Progressive lung destruction



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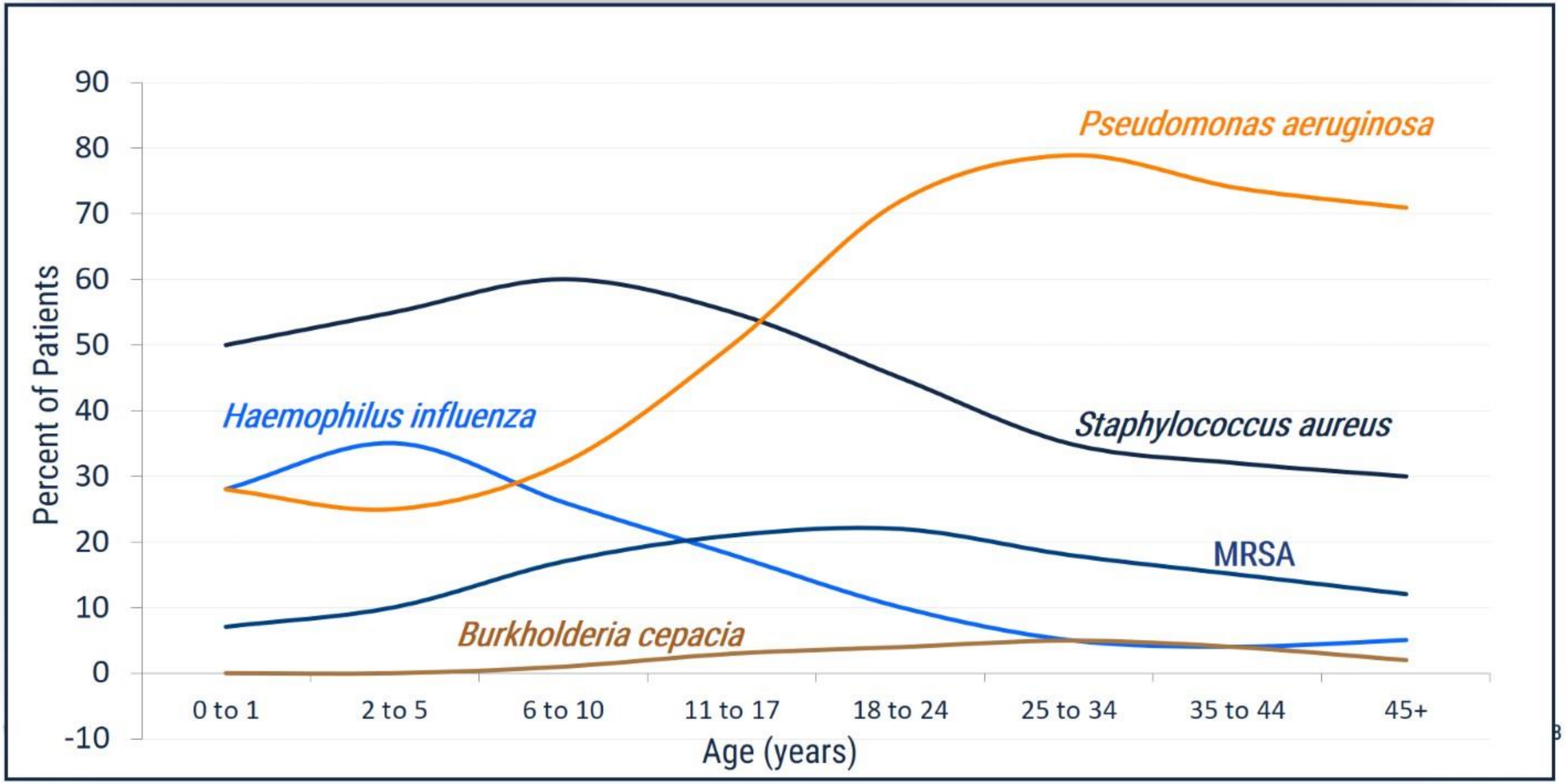
Chronic Infections in Cystic Fibrosis



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Psuedomonas aeruginosa – Nature of Antibiotic Resistance

Chronic Infections Hide in Anaerobic Biofilm

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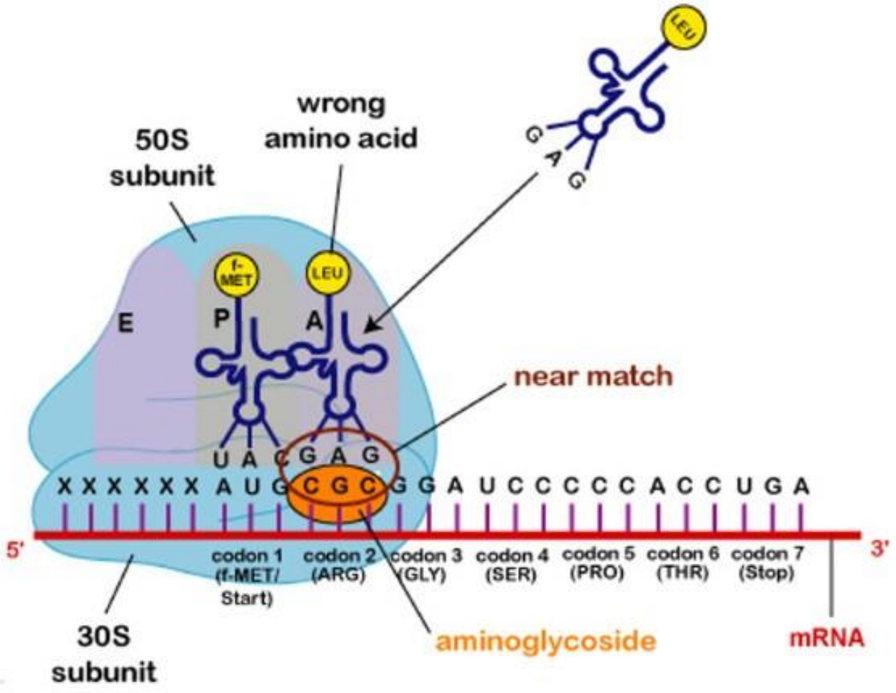
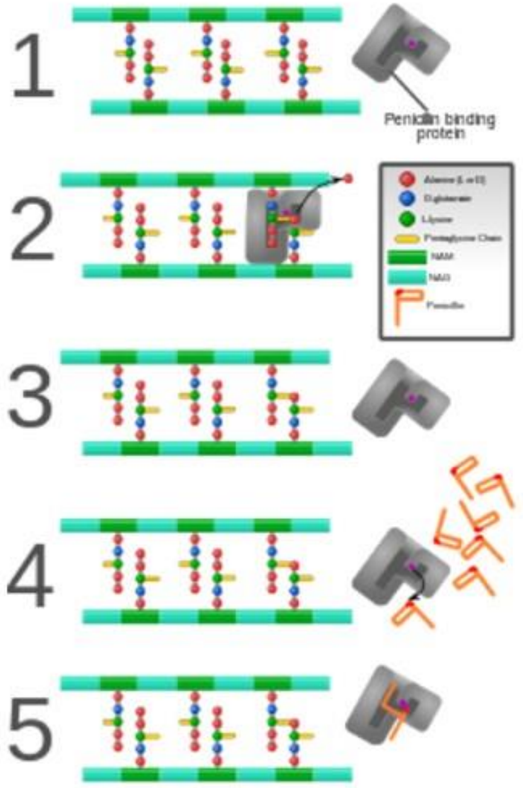
Tobramycin: prevents translation



Aztreonam: prevents peptidoglycan formation



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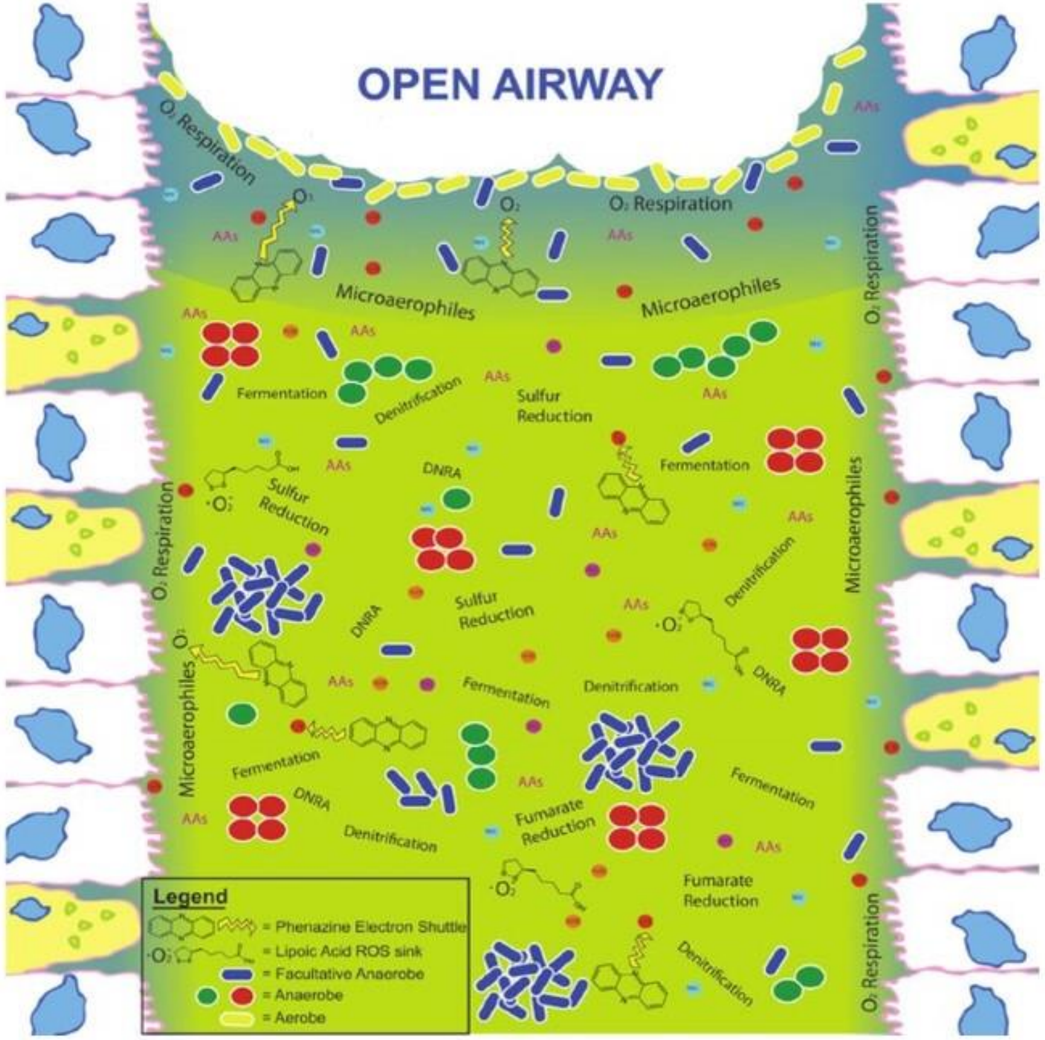
Chronic Infections Hide in Anaerobic Biofilms within CF Mucus



Quinn RA, Mbio 5:2, 2014

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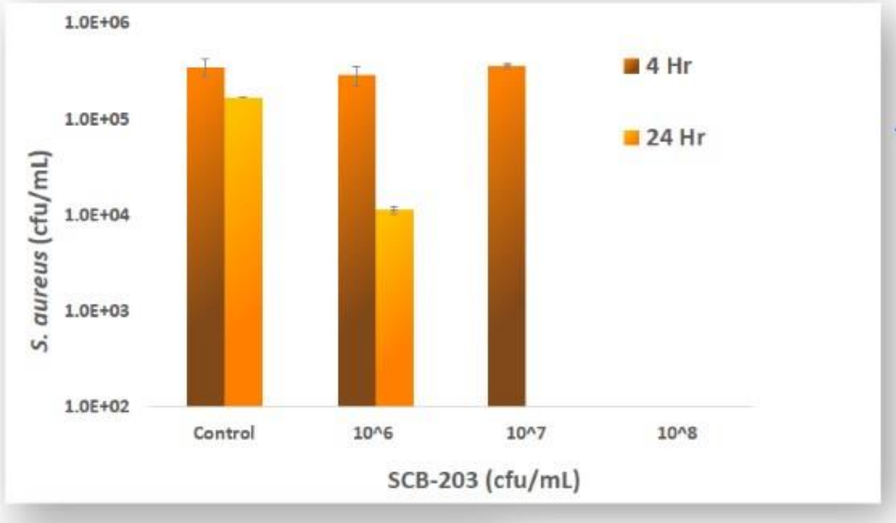
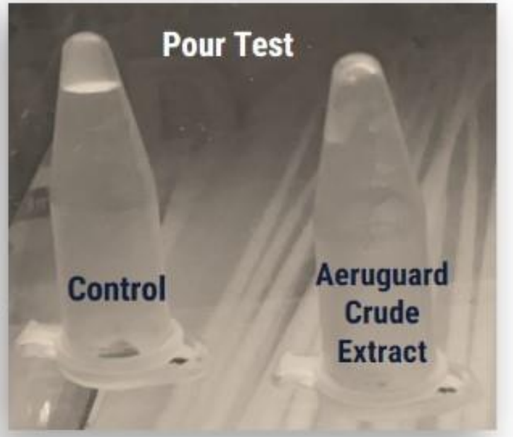
Aeruguard (SCB-203)

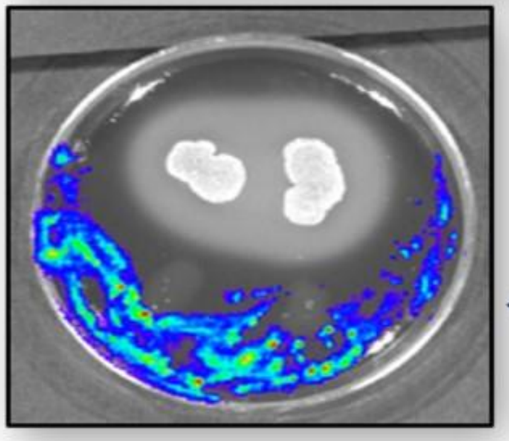
The only cystic fibrosis treatment that targets chronic infections



01 kills *S. aureus*

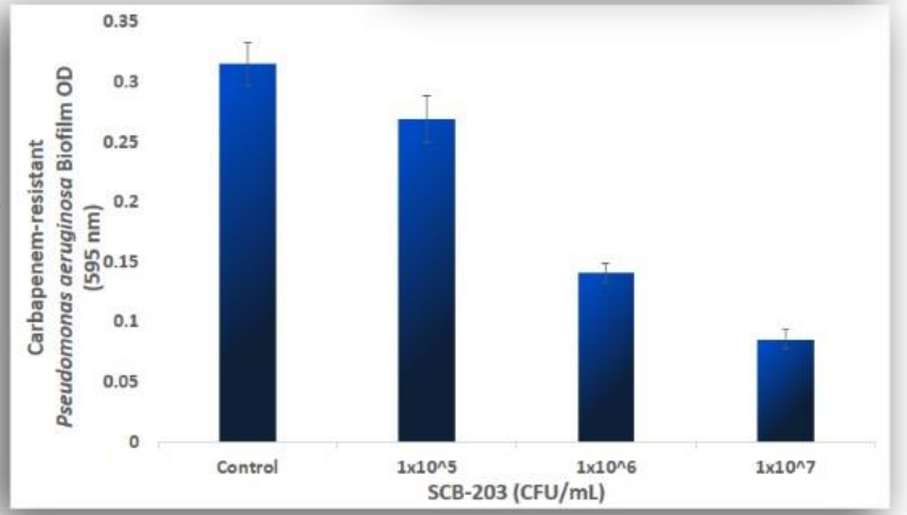
02 mucolytic





03 kills *P. aeruginosa*

04 removes biofilm



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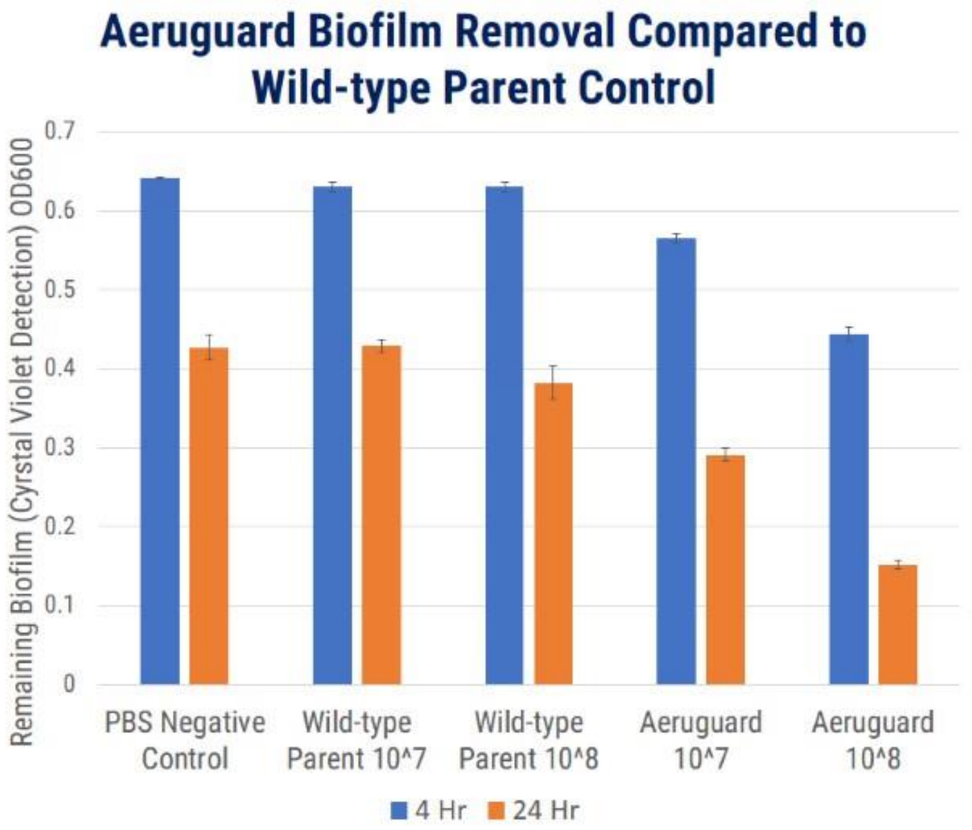
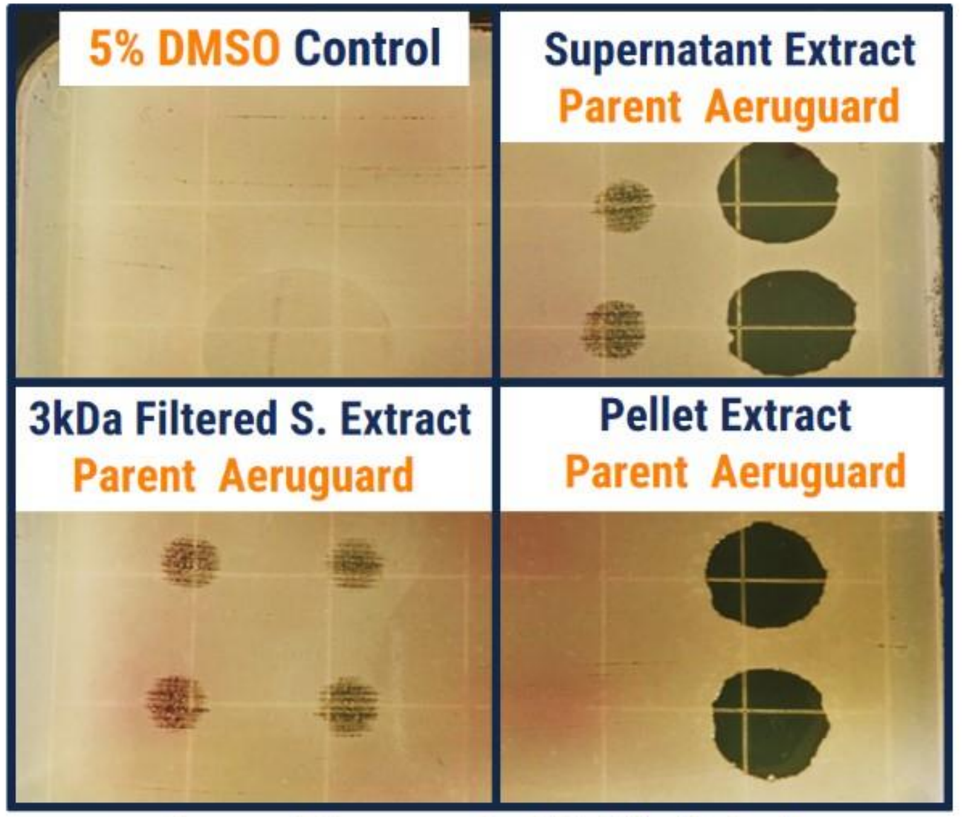
MERGE Strain Improvements

Aeruguard (SCB-203) was selected for its ability to eat protein AND:

Pseudomonas Biofilm Removal

Staphylococcus Direct Killing





Agar plate spread with CF clinical *Staphylococcus aureus* isolate

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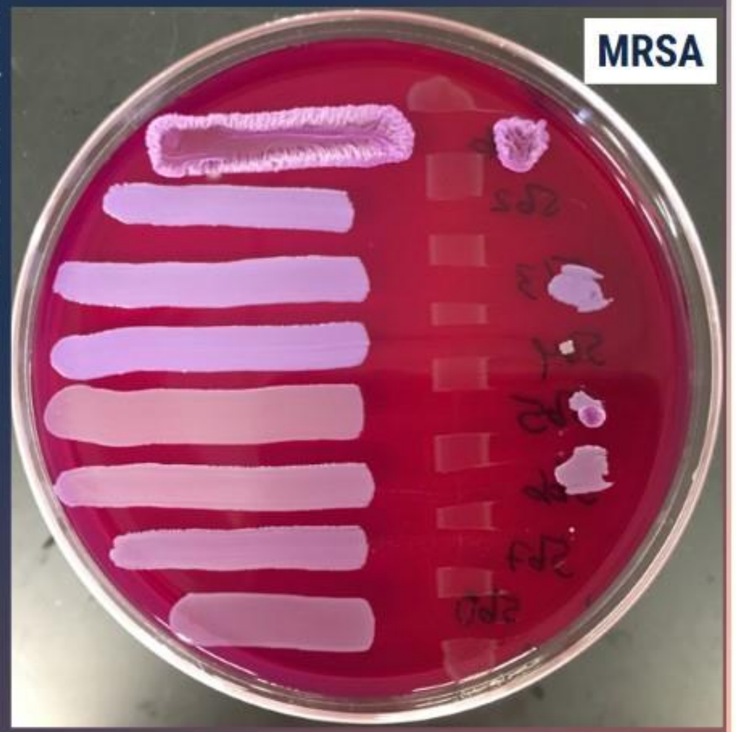
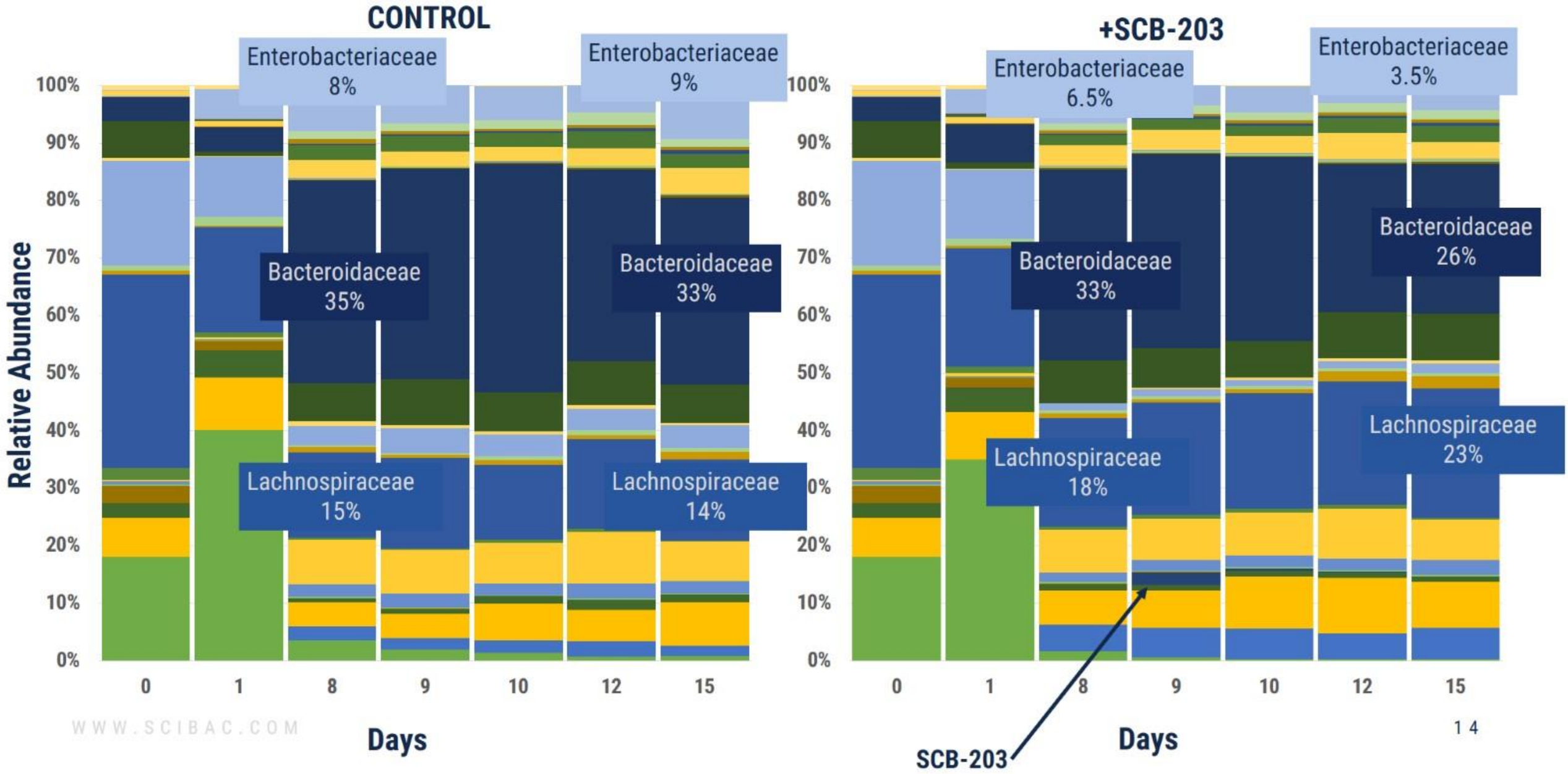
SCB-203 Has Broad Antibacterial Activity in Cystic Fibrosis and Beyond



Antibiotic Resistant Bacteria (n)	Median Inhibition by LH1 (mm)	Range (mm)
Pseudomonas aeruginosa (43)*	7	4 - 9
Staphylococcus aureus (24)*	10	8 - 22
Burkholderia cenocepatia (2)*	8	4.5 - 12
B. multivorans (2)*	13	11.5 - 14
B. gladioli (2)*	12	11 - 12
Stenotrophomonas maltophilia (1)*	12	12
Achromobacter xylosoxidans (1)*	13	13
A. dolans (1)*	12	12
A. ruhlandii (1)*	11	11
Acinetobacter baumannii (29)*	13	10 - 19
Escherichia coli (15)*	10	4.5 - 15
Klebsiella pneumoniae (14)*	7	4 - 12
E. faecium (6)*	6	4.5 – 8.5
Enterobacter aerogenes (3)*	11	9 – 11.5
Enterobacter cloacae (2)	11	10 - 12
Serratia marcescens (1)	12.5	12.5
Klebsiella oxytoca (1)	11	11
Enterococcus avium (1)	6.5	6.5

*includes clinical isolates

Healthy Gut Exposure – WGS Metagenomic Data (Family)



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ANTIBIOTIC	SUSCEPTIBLE TO (µg/ml)	RESISTANT TO (µg/ml)
Clarithromycin	0.16	
Aztreonam (AT)	2.0	
Rifampicin	0.125	
Amoxicillin/Clavulanic Acid	0.125	
Piperacillan	0.19	
Linezolid	0.5	
Tetracycline	0.5	
Erythromycin	0.023	
Imipenem	0.094	
Vancomycin	1.5	
Ciprofloxacin		32
Amikacin		48
Levofloxacin		12
Trimethoprim/Sulfamethoxazole		32
Tobramycin (TM)		512

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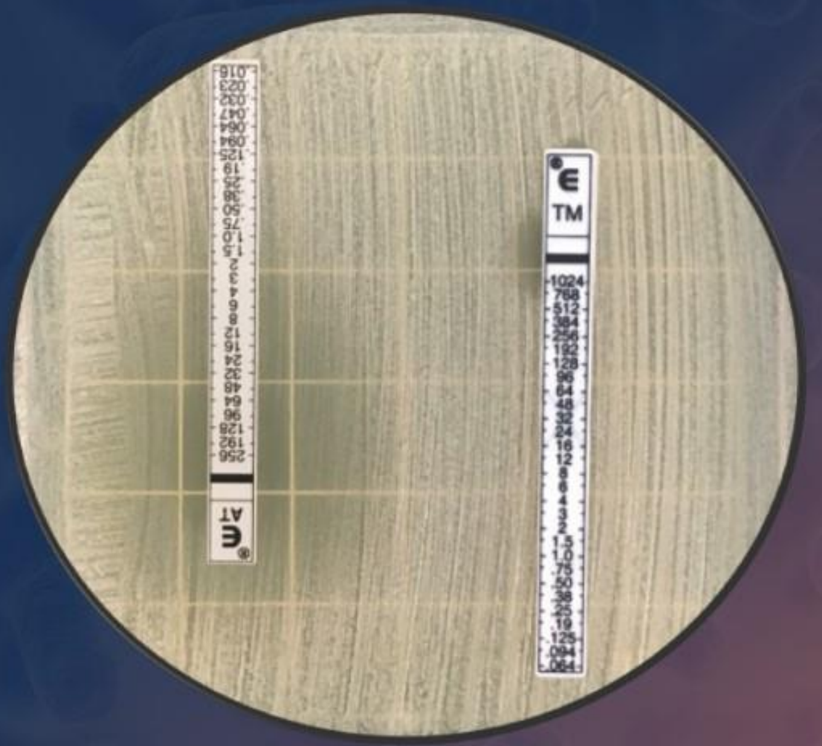
Antibiotic Panel: Aeruguard (SCB-203)



Aeruguard with Etests for AT and TM

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Aeruguard Clinical Trials Plan for CF Patients

Plan B:
Aeruguard + Tobramycin (TM)

- Patients maintain current antibiotic cycle:
  - Tobramycin (TM) for 28 days
  - Aztreonam (AT) for 28 days
- Aeruguard delivered through nebulizer
- Aeruguard administered during TM cycle:
  - Naturally resistant to TM, not AT
  - Will be removed during AT cycle

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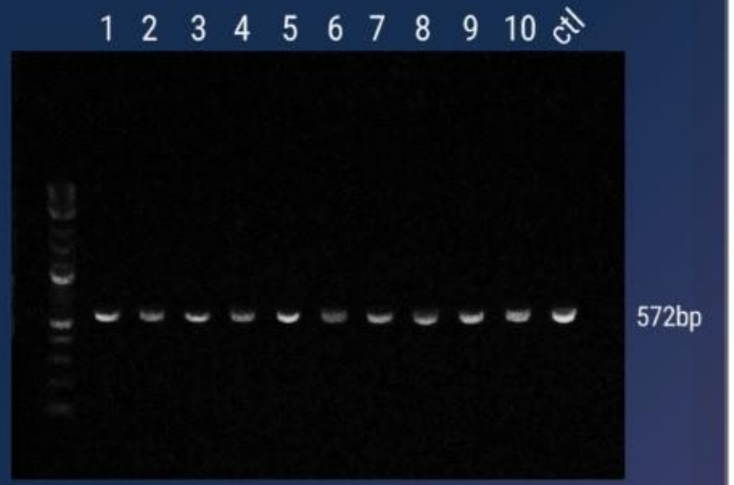

PCR shows new gene for antimicrobial activity is stable

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Stability of New Antimicrobial

- Working glycerol stock of SCB-203
  - PCR Anti-microbial gene from individual colonies and sequence
  - 9 of 9 colonies have mutation
- Doublings Experiment
  - Pick colony, dilute to low density and then let grow to stationary phase (2x)
  - Colony counts indicate 61 doublings took place
  - Analysis of antimicrobial gene from 10 individual colonies found:
  - 10 of 10 colonies have mutation
- Conclusion: The gene for the new antimicrobial is stable and trackable during manufacturing through PCR

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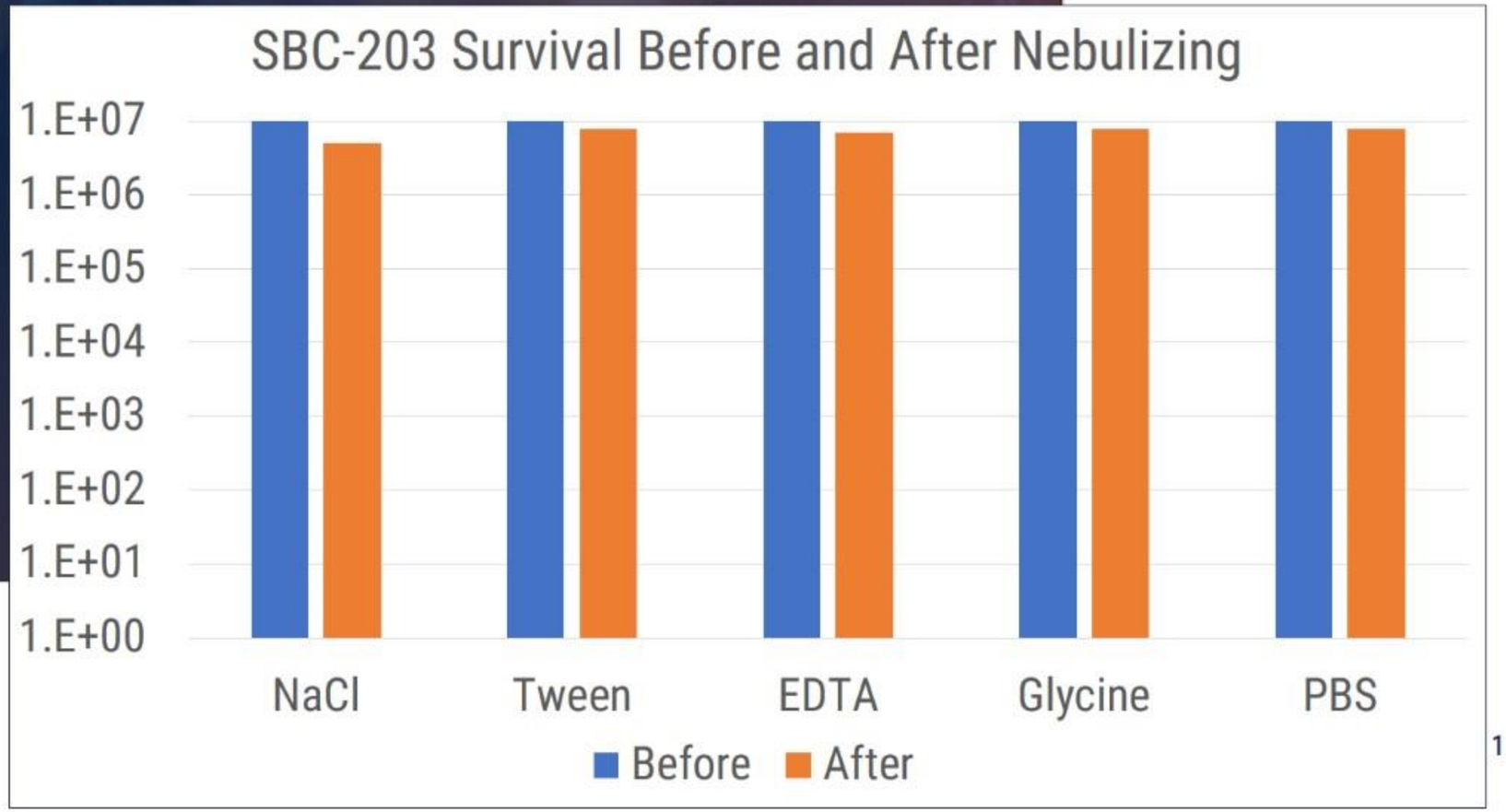
Survival through a Pari ProNeb Ultra Nebulizer

- overnight SCB-203 cultures
- reconstituted in FDA approved lung excipients
- nebulized for ten minutes
- plated for (CFU) survival



Cystic Fibrosis Pseudomonas Anti-Infectives Competition

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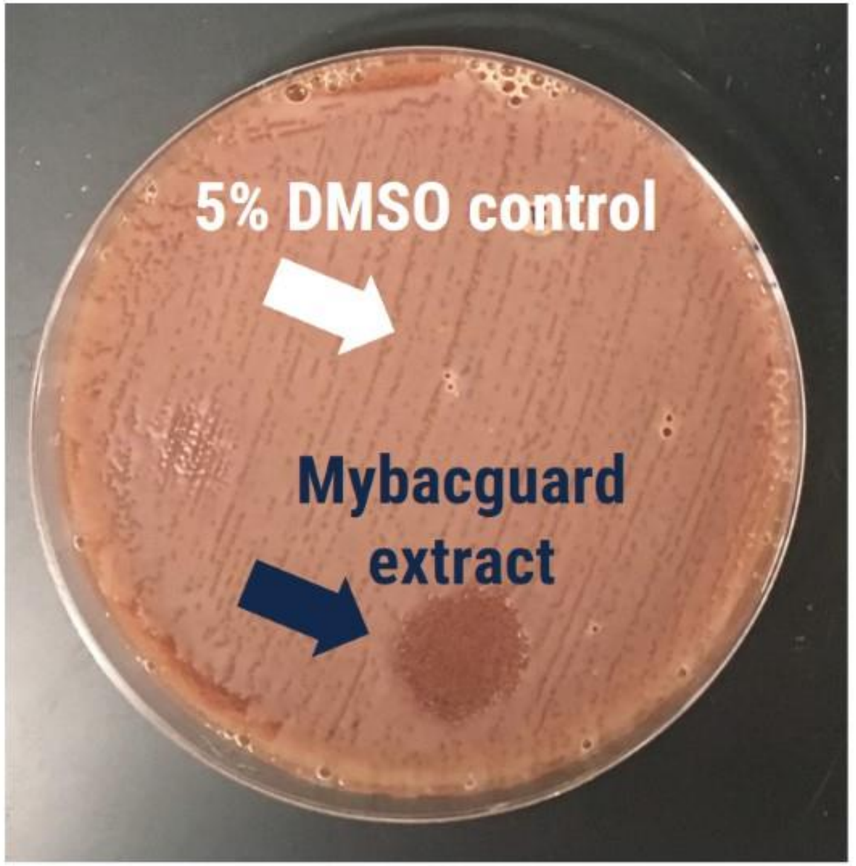
Anti Non-tuberculous Mycobacteria (NTM) Activity



Mycobacteroides abscessus
ATCC Strain 19977 spread on an agar plate

- A second lung therapeutic, Mybacguard, will treat CF chronic NTM infections found in 10% of CF patients
- Development underway with an SBIR grant using National Jewish Health in vitro and animal models
- Currently Insmed's Arikayce is the only on-label drug and is only 20% more effective in *M. avium* cases over the control group; must be taken with other off-label antibiotics.
- There are NO other drugs approved or in the clinic for *M. abscessus* infections

NTM lung infections are an UNMET NEED in 10% of CF patients and rising

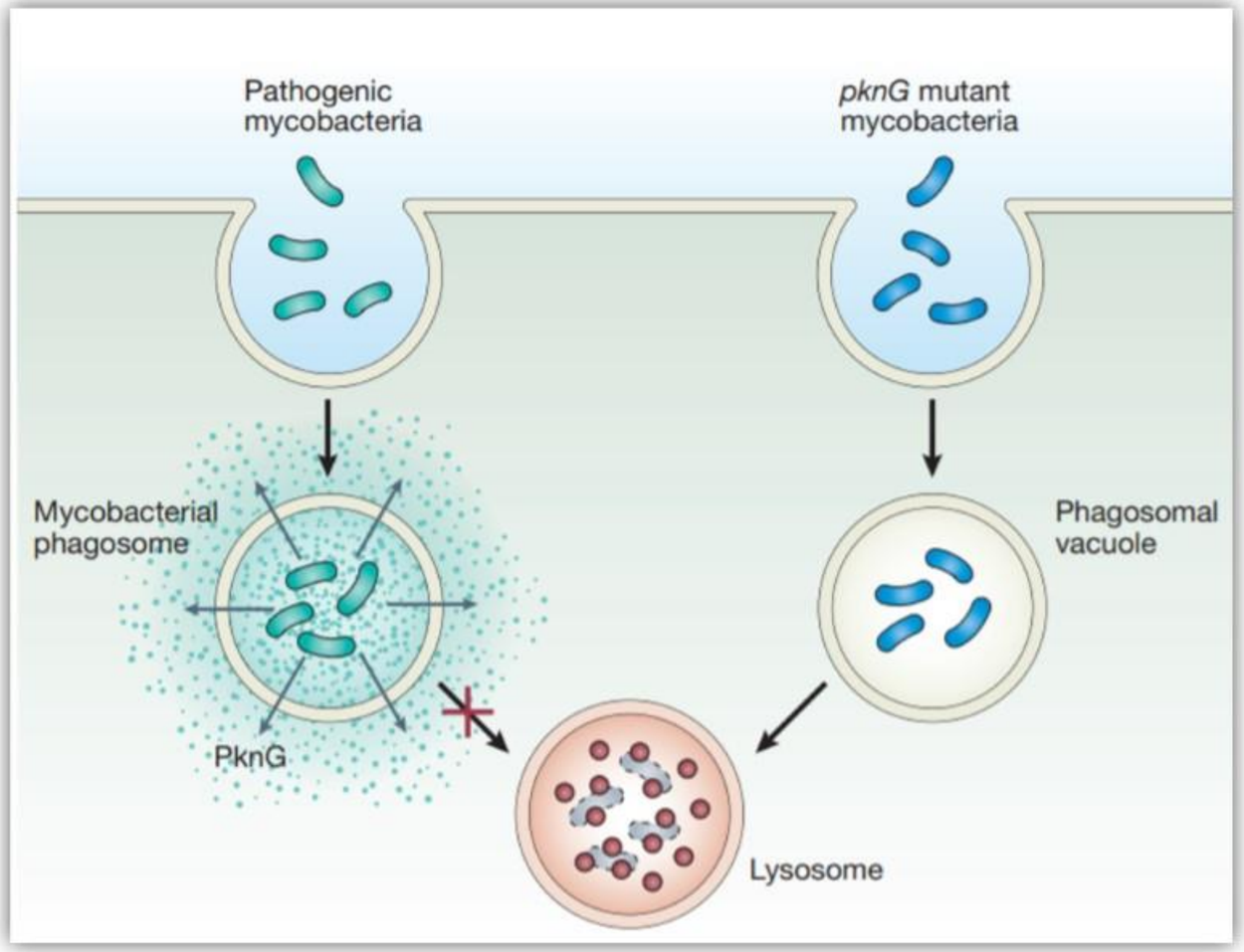
Non-Tuberculous Mycobacteria (NTM) Pathology

- Mycobacteria are hydrophobic & easily aerosolized
- Infections from gardening, or simply showering – NTM found in tap water

Shown is tuberculosis (TB) pathology inside a macrophage

NTM differences in pathogenesis:

- Large amounts of nitric oxide in phagosomes surprisingly promotes survival
- Survival found to pH 5.5 where TB is 6.0
- Capsase 7/8/9 induced to cause macrophage apoptosis and spread NTM



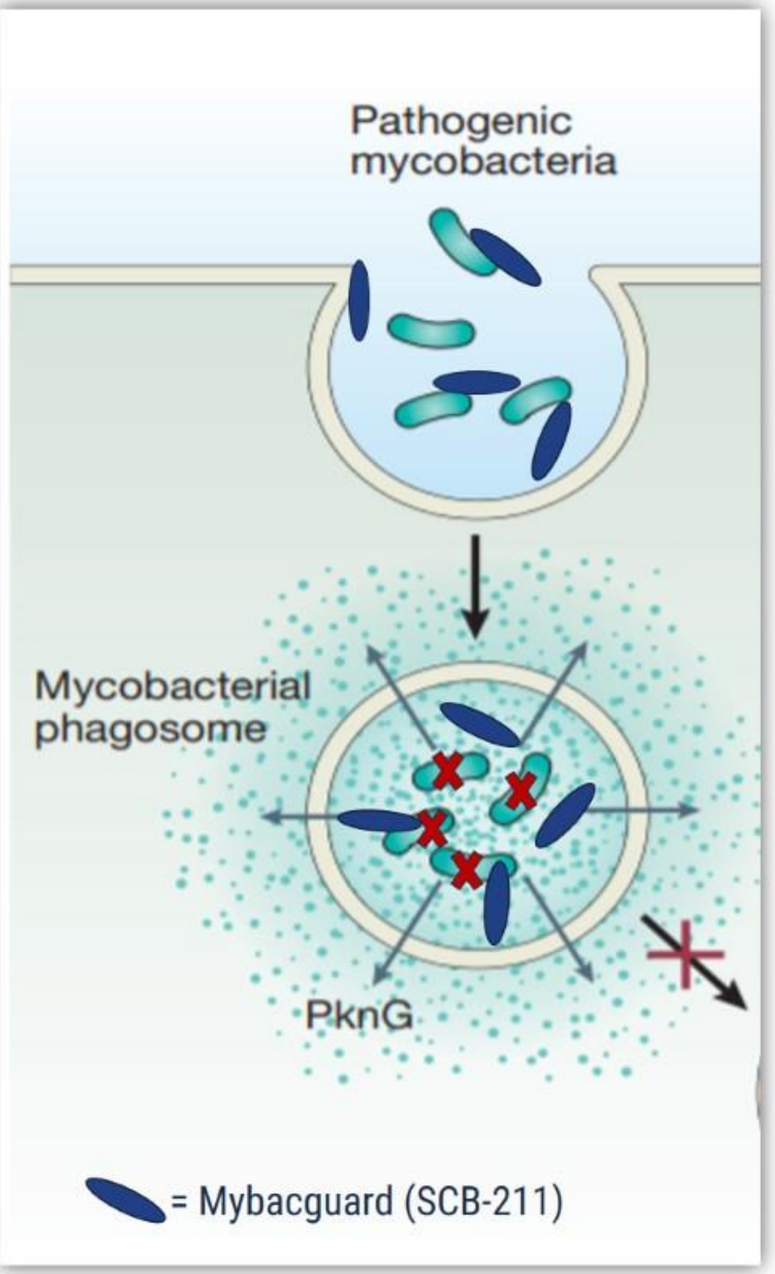
Warner, D. F., & Mizrahi, V. (2007). *The survival kit of Mycobacterium tuberculosis. Nature Medicine, 13(3), 282–284.* doi:10.1038/nm0307-282

Sousa, Sara et al. (2019) *Nontuberculous Mycobacteria Persistence in a Cell Model Mimicking Alveolar Macrophages. Microorganisms* vol. 7,5 113. doi:10.3390/microorganisms7050113

Trojan Horse Design

Mybacguard (SCB-211) features:

- Motile – can swim to macrophages
- Expected to be engulfed by macrophages
- Secretes bacteriocin to kill NTM
- Survives low pH in phagosomes
- Removes biofilm
- Mucolytic



Warner, D. F., & Mizrahi, V. (2007). *The survival kit of Mycobacterium tuberculosis. Nature Medicine, 13(3), 282–284.* doi:10.1038/nm0307-282

Cystic Fibrosis NTM Anti-Infectives Competition

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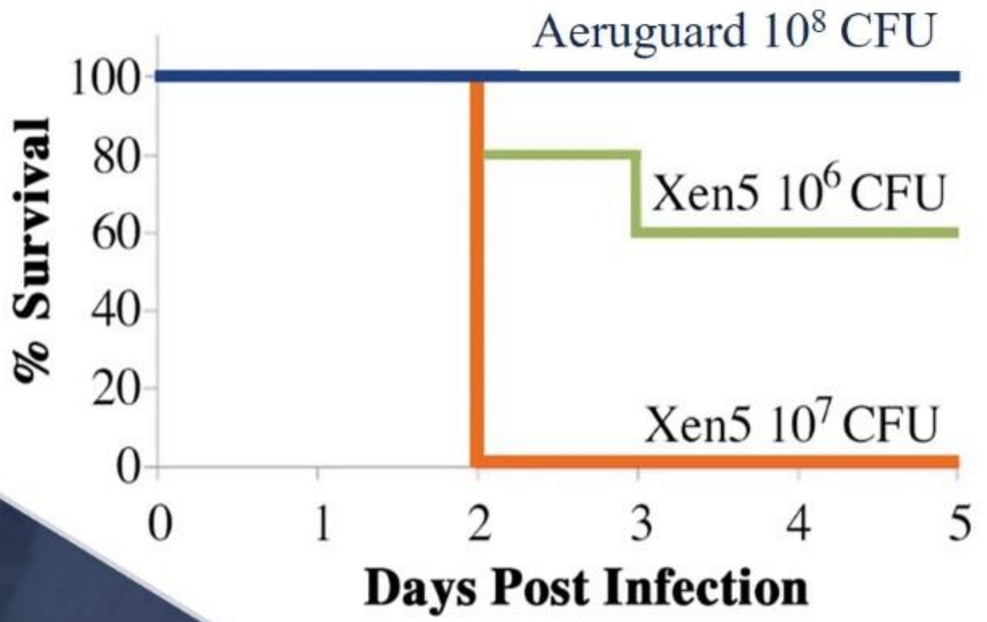
Preliminary *in vivo* Safety Tests



- Administered SCB-201 to healthy BALB/c mice at high concentrations to test for signs of illness compared to Pseudomonas
- *P. aeruginosa* at 10^6 and 10^7 compared to SCB-201 at 10^8, given intranasally
- No signs of illness or death were observed

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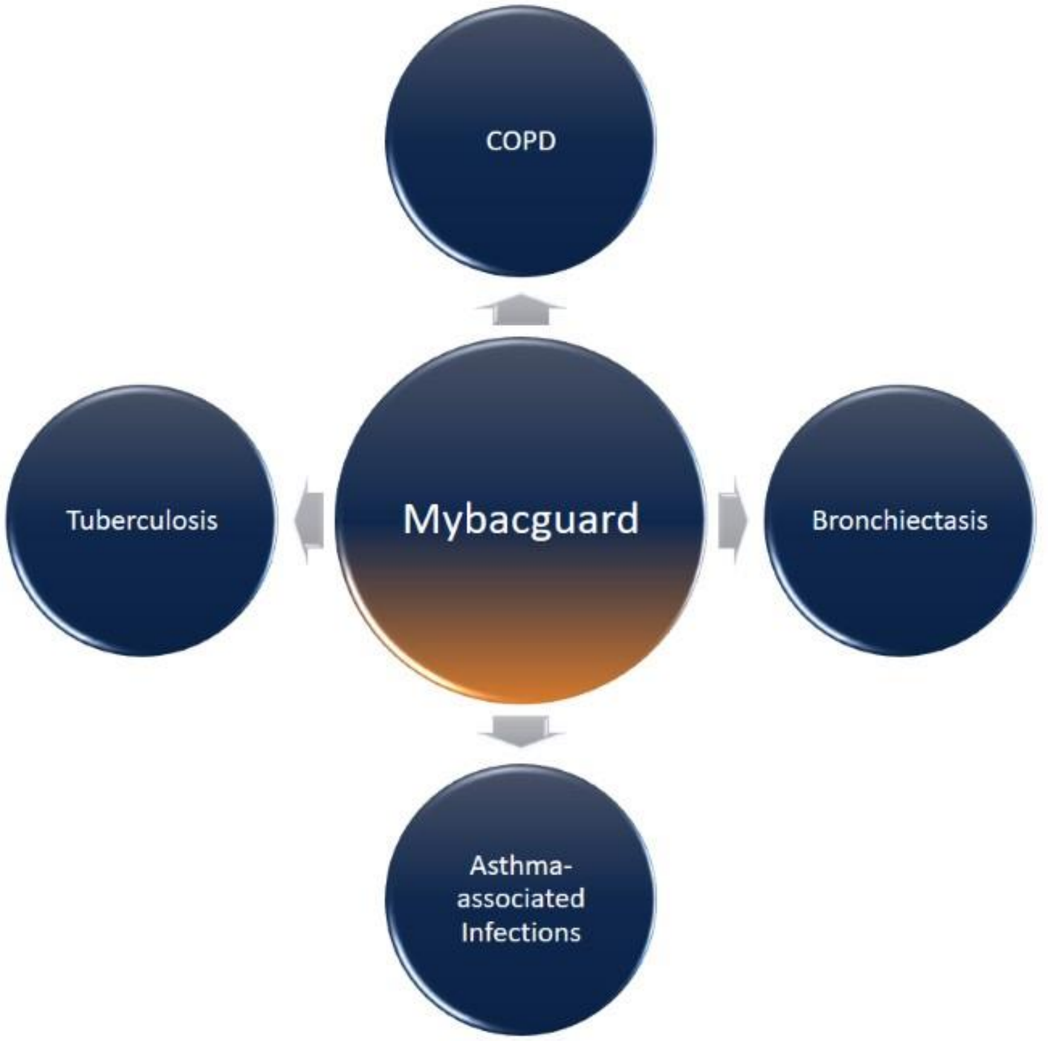
Indications Beyond Cystic Fibrosis Lung Infections



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