A study evaluating phage therapy in cystic fibrosis subjects with *Pseudomonas aeruginosa* infection

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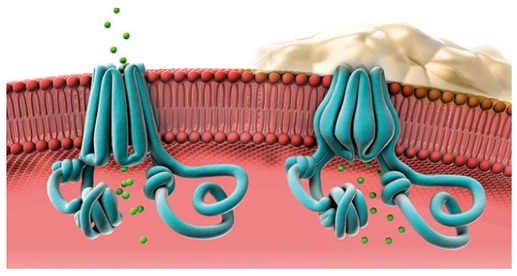
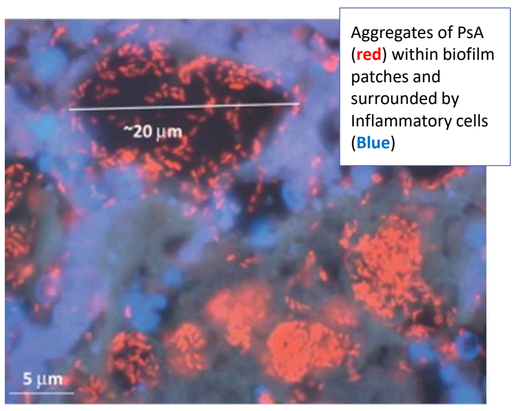
Cystic Fibrosis (CF)

- The CFTR protein is present on epithelial cells throughout the body. In CF lungs, mutations in CFTR cause thick and sticky mucus that provides an environment for bacteria to infect and propagate.
- Pseudomonas aeruginosa (PsA) is a main pathogen that colonizes the lungs of adult CF patients.
- The disease causes severe damage to the lungs, digestive system and other organs with > 80% of deaths from respiratory failure
- 105K individuals are estimated to live with CF worldwide, with 33k in the US alone



Normal (left) and abnormal CFTR proteins (right)

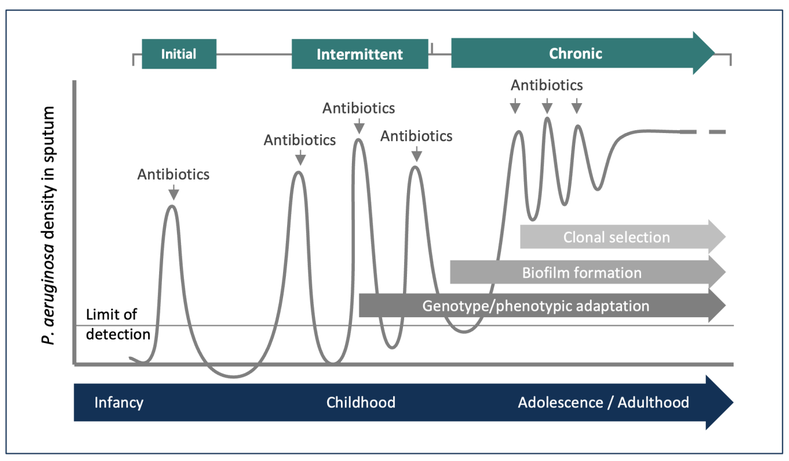


Aggregates of PsA (**red**) within biofilm patches and surrounded by Inflammatory cells (**Blue**)

PsA bacteria lead to persistent inflammation causing tissue damage and eventually necrosis of lung tissue

Bacterial infection and antibiotic resistance

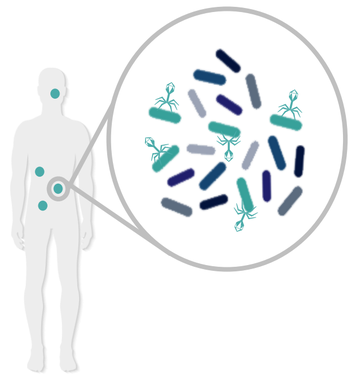
Over the last 2 decades, with the rise of antibiotic resistance, benefits of inhaled antibiotics have diminished. After prolonged and repeated antibiotic courses, increased resistance to antibiotics has lowered efficacy, creating a large unmet need for CF patients suffering from Chronic *PsA*.



Phage therapy

1. SPECIFIC

Each phage binds only to specific bacterial strains



2. KILLING MECHANISM ORTHOGONAL TO ANTIBIOTICS

Lysin proteins burst bacterial cell wall from within

3. BREAKDOWN BIOFILM

Phage can breakdown biofilm (a polysaccharide mesh secreted by bacteria)

4. AMPLIFY

Phage components multiply and assemble within bacterial cell

5. SAFETY PROFILE

100s of compassionate use cases with no significant side effects to date

Key challenges in developing phage therapies

- **Host range –** Infecting a narrow range of bacterial strains
- **Resistance -** Bacterial defense systems (e.g., CRISPR)
- **Biofilm –** Bacteria producing mucoid layer that is hard to penetrate

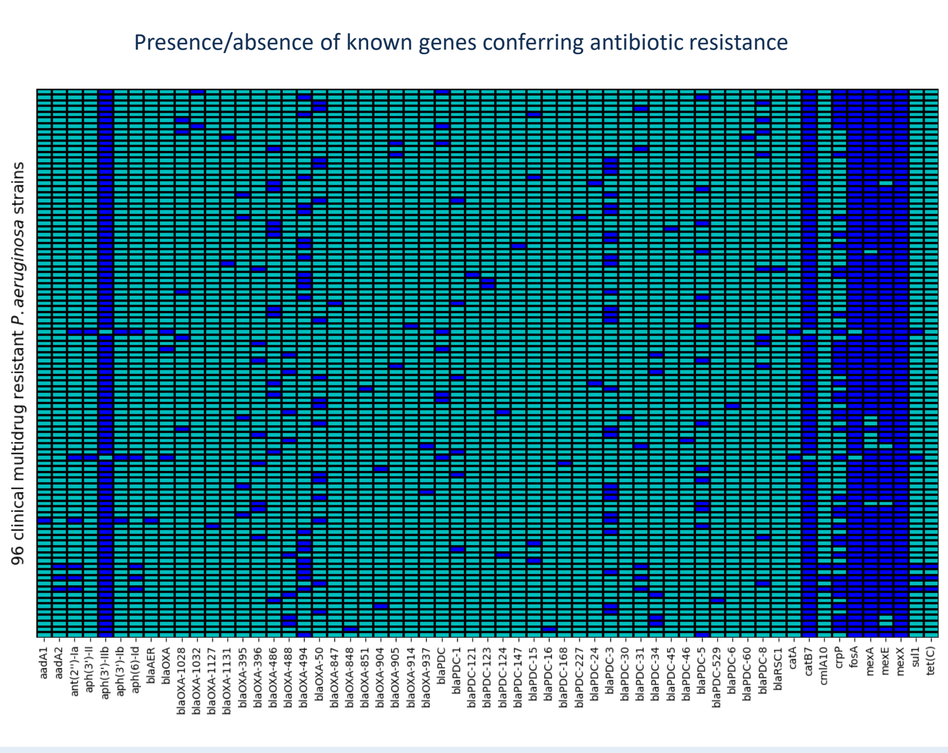
BX004

- **Product** – Proprietary phage cocktail targeting *PsA*
- **Patient population** – CF patients with chronic *PsA* lung infections
- **Delivery** – Inhalation
- **Key features** – Potentially effective on antibiotic resistant strains, enables breakdown of biofilm

Phage cocktail design

BX004 on antibiotic resistant strains

BX004 was active in killing all 96 strains described below displaying multiple antibiotic resistant genes



Clinical study design

Phase 1b/2a – Part 1 (actual n=9)

Objectives

- Safety, PK and microbiologic/clinical activity

9 Subjects

- 7 received nebulized BX004 phage therapy
- 2 received nebulized placebo
- 7 days duration (3 ascending, 4 multiple dosing)

Phase 1b/2a – Part 2 (planned n=24)

Objectives

- Safety and efficacy

At least 24 subjects

- 16 receive nebulized BX004 phage therapy
- 8 receive nebulized placebo
- 10 days duration of treatment

Endpoints

- Safety and tolerability
- Decrease in *PsA* burden
- Sputum pharmacokinetics
- FEV1 (forced expiratory volume)

Study Population

- CF patients with chronic *PsA* infection

Phase 1b/2a – Part 1 results

Mean *P. aeruginosa* CFU reduction at Day 15 (compared to Baseline):

-1.42 log_{10} CFU/g (BX004) **compared to -0.28 log_{10} CFU/g** (placebo) on top of standard of care inhaled antibiotics