A Lytic Bacteriophage Bank and Host-Range Matching Platform for Burkholderia cepacia Complex Infection in Cystic Fibrosis

Project Summary / Abstract

Burkholderia cepacia complex (Bcc) infection is among the most feared complications in cystic fibrosis (CF): these intrinsically multidrug-resistant Gram-negative bacteria can drive a rapid clinical decline, and chronic Bcc infection is a contraindication to lung transplantation at many centers. Antibiotic options are few and frequently fail. Lytic bacteriophages are an attractive precision alternative because they kill through a mechanism orthogonal to antibiotic resistance and can be matched to a patient's specific Burkholderia strain; some Bcc phages additionally encode depolymerases that strip the protective exopolysaccharide, potentially re-sensitizing the organism to host immunity and antibiotics. The central obstacle is supply: well-characterized, strictly lytic Burkholderia phages are far scarcer than for Pseudomonas or Staphylococcus, and the genus is genetically diverse, so rapid host-range matching and a curated bank are prerequisites for any clinical use. We will (1) assemble and genomically vet a lytic Bcc phage bank against a panel of contemporary CF Bcc isolates and define a rapid host-range matching assay; (2) establish preclinical efficacy, depolymerase activity, and phage-antibiotic synergy in infection models; and (3) build an expanded-access / emergency-IND-ready framework so matched phage can reach the patients with the fewest options. All key biological resources will be authenticated. The expected outcome is the first systematic, clinically actionable Bcc phage-matching platform — turning a transplant contraindication into a potentially manageable infection.

Specific Aims

Bcc infection in CF combines intrinsic multidrug resistance, the risk of rapid clinical deterioration, and frequent disqualification from lung transplantation, yet there is no reliable antibiotic salvage. Lytic phages offer a strain-matched, resistance-orthogonal option, but their clinical use is gated by the scarcity of characterized lytic Burkholderia phages and the absence of a rapid matching pipeline. We will close that gap.

Aim 1. Assemble and genomically vet a lytic Bcc phage bank and a rapid host-range matching assay. From environmental and clinical sources we will isolate strictly lytic phages against a panel of contemporary CF Bcc isolates (spanning the major species, including B. cenocepacia and B. multivorans), whole-genome sequence each to exclude integrase/lysogeny, toxin, and antimicrobial-resistance genes, and define a same-week host-range/match assay. *Go/no-go:* a banked cocktail covering ≥60% of the isolate panel with strictly lytic, genomically clean phages. [ILLUSTRATIVE coverage target]

Aim 2. Establish preclinical efficacy, depolymerase activity, and phage-antibiotic synergy. We will quantify killing and biofilm activity of matched phages and cocktails, characterize depolymerase-mediated capsule stripping and antibiotic re-sensitization, and test efficacy in Galleria and murine respiratory infection models with and without standard antibiotics.

Aim 3. Build an expanded-access / emergency-IND-ready clinical framework. We will define release criteria, a matching turnaround standard, and a correlative protocol so that, under an FDA emergency/expanded-access IND with IRB oversight, matched phage can be offered to Bcc-infected CF patients who have exhausted options, linking match quality and depolymerase activity to microbiologic and clinical readouts.

Impact. A curated, genomically vetted Bcc phage bank with rapid matching would give the most desperate CF patients a precision option where antibiotics offer almost none — and could remove chronic Bcc infection as an absolute barrier to life-saving transplantation.

Significance

Bcc infection is a low-incidence but high-consequence problem in CF: it disproportionately drives morbidity, can precipitate steep decline, and is a transplant contraindication at many centers precisely because no dependable therapy exists. The organisms are intrinsically resistant to most antibiotics, and combination regimens are often suppressive at best. This is exactly the niche where a resistance-orthogonal, strain-matched modality is most valuable, and where the inability to treat has the steepest human cost. Aligning with NHLBI's mission to preserve lung function in chronic pulmonary disease — and with the Cystic Fibrosis Foundation as a natural non-federal partner — this work targets a population with few or no alternatives. The principal scientific barrier is not whether phages can kill Bcc (multiple groups have shown lytic Bcc phages and efficacy in infection models) but whether a clinically usable supply and matching pipeline can be built for a genetically diverse genus. Solving that supply-and-matching problem is the rate-limiting step for translation.

Innovation

This proposal is innovative in three ways. First, it treats the scarcity of lytic Burkholderia phages as the central, addressable problem — building a genomically vetted bank and a same-week matching assay rather than assuming phage availability. Second, it foregrounds depolymerase-armed phages as a mechanism to strip the Bcc exopolysaccharide and re-sensitize the organism, an angle underexploited in Bcc. Third, it pairs bank construction with a pre-specified expanded-access/eIND framework, so that the deliverable is not just isolated phages but a clinically actionable pathway for a population that currently has none.

Approach

Aim 1 — Bank construction & rapid matching

Rationale. Clinical use requires a curated, strictly lytic, genomically clean bank plus a fast match. **Experimental design.** Isolate phages against a banked CF Bcc panel; sequence and annotate each (exclude lysogeny/toxin/AMR genes); define host range; build a same-week plaque/turbidity match assay. **Expected outcomes.** A defined multi-phage cocktail with documented coverage and safety screens. **Pitfalls & alternatives.** If lytic coverage is low for a species, pursue engineered-lytic derivatives and depolymerase-only constructs; expand environmental sampling.

Aim 2 — Preclinical efficacy, depolymerase & synergy

Rationale. Matching must translate to killing in vivo and ideally to antibiotic re-sensitization. **Experimental design.** Quantify lysis, biofilm activity, capsule stripping, and phage-antibiotic synergy in vitro; test efficacy in Galleria and murine respiratory models ± antibiotics; monitor resistance and fitness cost of escape. **Expected outcomes.** Cocktail and pairing rules that maximize killing and suppress resistance. **Pitfalls & alternatives.** If resistance emerges, use multi-receptor cocktails and steer toward capsule-loss trade-offs.

Aim 3 — eIND-ready clinical framework

Rationale. The deliverable must be usable for real patients. **Experimental design.** Define GMP-aligned release/quality criteria, a matching turnaround standard, and a correlative protocol; engage FDA on the emergency/expanded-access IND pathway; pre-specify microbiologic and clinical endpoints and consent for a vulnerable population. **Expected outcomes.** A ready framework to offer matched phage under eIND with IRB oversight. **Pitfalls & alternatives.** If matching fails for a patient's isolate, the bank's diversity and engineered derivatives provide fallbacks; absent a match, the framework documents the gap rather than proceeding.

Timeline

Year 1: isolate banking, sequencing, match-assay development [ILLUSTRATIVE]. Year 2: preclinical efficacy, depolymerase and synergy studies [ILLUSTRATIVE]. Year 3: quality/release criteria, eIND package, first correlative expanded-access cases [ILLUSTRATIVE].

Budget Justification

Modular R21-scale budget [ILLUSTRATIVE]: personnel (PI, phage scientist, bioinformatician, CF clinical collaborator), phage isolation/sequencing, model systems, and regulatory preparation. All figures [ILLUSTRATIVE], to be set with the institution.

Vertebrate Animals

Galleria (invertebrate) and murine respiratory infection models are proposed in Aim 2; murine work will follow IACUC-approved protocols with humane endpoints and the minimum animals required for statistical power [ILLUSTRATIVE].

Human Subjects / Clinical Trial

Aim 3 prepares — but this exploratory award does not execute — an expanded-access pathway. Any clinical administration of investigational phage would proceed under an FDA emergency/expanded-access IND (eIND) with IRB oversight and informed consent; see the regulatory pathway for context.

Team & Environment

Template roles to fill: PI (phage biology/CF microbiology); CF pulmonary/infectious-disease physician; bacteriophage genomicist/bioinformatician; GMP/quality advisor; regulatory/bioethics lead. Environment: an academic phage-isolation and CF clinical program with biobanking capacity.

References

- Lauman P, Dennis JJ. Advances in Phage Therapy: Targeting the Burkholderia cepacia Complex. Viruses. 2021;13(7):1331. https://doi.org/10.3390/v13071331