PHAGE-FUSO: A Strictly Lytic, Clade-Resolved Bacteriophage Cocktail Targeting Tumor-Resident *Fusobacterium nucleatum* (Fna C2) to Restore Chemotherapy and Checkpoint-Inhibitor Sensitivity in Colorectal Cancer

Funding mechanism: NCI · R01 (Research Project Grant)

> *Note on figures: all durations, dollar amounts, animal numbers, and effort percentages are placeholders marked* **[ILLUSTRATIVE]** *and must be replaced with institution-specific values, a biostatistician's power analysis, and sponsored-programs quotes before submission. The proposal cites only verified primary literature; every citation should be re-confirmed against the source of record.*

Project Summary / Abstract

Colorectal cancer (CRC) is the second-leading cause of cancer death worldwide, and a biologically defined subset is driven and worsened by *Fusobacterium nucleatum* (Fn) — a Gram-negative oral anaerobe that selectively colonizes tumor tissue, promotes proliferation and epithelial–mesenchymal transition (EMT), recruits immunosuppressive myeloid-derived suppressor cells (MDSCs), and confers resistance to both chemotherapy and immune checkpoint blockade. This reframes Fn-positive CRC, in part, as a treatable bacterial infection layered on top of a tumor. The standard tool for bacterial depletion — broad-spectrum antibiotics — is the wrong instrument: it lowers Fn burden only at the cost of gut dysbiosis and resistance selection, eroding the very commensal community that supports anticancer immunity.

Bacteriophages offer a precision alternative: they are host-specific and self-amplify at the site of infection, allowing an anti-Fn phage to deplete the tumor-promoting bacterium while sparing commensals. Preclinical proof-of-concept is now substantial and convergent. Phage-guided irinotecan nanoparticles depleted Fn and augmented first-line chemotherapy in CRC mice, with negligible

toxicity in piglets (Zheng et al., 2019). A silver-armed M13 hybrid (M13@Ag) scavenged gut Fn, reduced MDSC accumulation, remodeled the tumor-immune microenvironment, and — combined with anti–PD-1 or FOLFIRI — significantly prolonged survival over phage monotherapy (Dong et al., 2020). A naturally **lytic** Fn phage, ØTCUFN3, suppressed Fn-induced CRC-cell proliferation and EMT *in vitro* and shrank Fn-induced xenografts *in vivo* (Lam et al., 2025). Gut-phageome profiling shows Fn-phage signatures track CRC across multinational cohorts (Shen et al., 2021).

Yet no registered human trial evaluates anti-Fn phage therapy for CRC, and the field lacks (i) a strictly lytic, sequence-defined phage bank, (ii) validated delivery to tumor-resident, biofilm-associated Fn, and (iii) clade-resolved host-range data against the oncogenic **Fna C2** lineage. **Central hypothesis:** a host-range-matched, strictly lytic anti-Fn cocktail, delivered to tumor-resident Fna C2, will selectively deplete Fn while sparing commensals and thereby restore responsiveness to FOLFIRI and anti–PD-1. Three aims test this with pre-registered go/no-go criteria: **(1)** build and characterize a strictly lytic anti-Fn cocktail with defined Fna C2 activity; **(2)** quantify delivery and Fn-depletion pharmacodynamics at the tumor in orthotopic and *Apc*-mutant models, benchmarked against an antibiotic comparator; and **(3)** test whether phage-mediated Fn depletion sensitizes tumors to chemotherapy and checkpoint blockade, with Fn-negative arms as the causal control. The deliverable is a characterized, IND-enabling cocktail and a delivery/pharmacodynamic framework positioning anti-Fn phages as a commensal-sparing microbiome adjuvant to standard oncology care.

Specific Aims

Fn-positive CRC behaves, in part, as a treatable bacterial infection layered on top of cancer: the organism is causally linked to tumor proliferation, EMT, an immunosuppressive myeloid milieu, and resistance to both chemotherapy and checkpoint blockade. Removing it should **restore, not replace,** the efficacy of standard regimens. Existing antibacterials are too broad and damage the protective microbiome. Bacteriophages — host-specific and self-amplifying — are the natural precision tool, and three independent groups have now shown anti-Fn phage constructs deplete Fn and improve chemo-/immunotherapy responses in CRC models (Zheng et al., 2019; Dong et al., 2020; Lam et al., 2025).

Central hypothesis. A strictly lytic, host-range-matched bacteriophage cocktail, delivered to tumor-resident *F. nucleatum* of the oncogenic Fna C2 clade, will selectively deplete Fn while preserving commensal diversity, and thereby convert chemotherapy- and checkpoint-resistant CRC toward responsiveness.

Aim 1 — Build and characterize a strictly lytic anti-Fn phage cocktail with defined activity

against Fna C2. Anchoring on the published lytic phage ØTCUFN3 (Lam et al., 2025) plus newly isolated phages, we will determine host range and efficiency-of-plating (EOP) across a clinical-isolate library enriched for Fna C2; whole-genome sequence and annotate every phage to exclude integrase, toxin, and antibiotic-resistance genes; map receptors and quantify resistance-emergence frequencies for single phages versus cocktails; and confirm retained anti-oncogenic activity (suppression of Fn-induced CRC-cell proliferation and EMT markers). *Go/no-go (locked before Aim 2):* a sequenced, strictly lytic 2–4-phage cocktail meeting pre-specified coverage, safety, manufacturability, and resistance-suppression thresholds (Table 1).

Aim 2 — Quantify delivery to, and depletion of, tumor-resident Fn in CRC models. In orthotopic and *Apc*-mutant CRC models colonized with defined Fna C2, we will measure phage biodistribution, intratumoral phage titer and Fn killing, biofilm penetration, off-target microbiome composition, and the MDSC compartment, across a dosing range and against vehicle and **antibiotic comparators**. *Outcome:* dose–exposure–effect relationships establishing whether luminal/oral phage reaches and depletes biofilm-associated tumoral Fn while sparing commensals — the niche where antibiotics fail.

Aim 3 — Test phage-enabled sensitization to chemotherapy and checkpoint blockade. In Fn-colonized orthotopic CRC, we will combine the cocktail with FOLFIRI and with anti–PD-1 in randomized, adequately powered, blinded-readout studies, with **Fn-negative arms as the causal control**. Endpoints: tumor growth, survival, intratumoral Fn burden, and immune remodeling (MDSCs, antigen-presenting-cell activation, effector T-cell infiltration). *Outcome:* a pre-specified go/no-go efficacy package quantifying whether Fn depletion restores chemo- and checkpoint responsiveness in an Fn-dependent manner.

Impact. Success would deliver the first IND-enabling, strictly lytic, clade-resolved anti-Fn phage cocktail and a rigorous delivery/pharmacodynamic framework, reframing Fn-positive CRC as a microbially targetable disease and providing a precision, commensal-sparing adjuvant to standard chemo- and immunotherapy.

Significance

Burden and unmet need. CRC is the second-leading cause of cancer death worldwide, and outcomes for the Fn-associated subset are disproportionately poor. *F. nucleatum* is not a bystander. It selectively colonizes tumor tissue, drives epithelial proliferation and EMT, recruits immunosuppressive myeloid cells, and actively undermines therapy — blunting chemotherapy and contributing to checkpoint-inhibitor resistance. Fn is therefore a mechanistically validated target whose removal is hypothesized to restore the efficacy of regimens patients already receive.

Why current approaches fail. The conventional means of depleting Fn — broad-spectrum antibiotics — is poorly suited to this problem. It lowers Fn burden while collapsing commensal diversity and selecting for resistance, eroding the microbial community that supports anticancer immunity and, in the case of checkpoint blockade, the very ecology associated with response. A precision antibacterial that removes Fn while leaving the microbiome intact is therefore highly desirable.

Why phage, why now. Bacteriophages are the only antibacterial modality that is simultaneously **host-specific** (capable of clearing Fn while sparing commensals), **self-amplifying** on target (so dose tracks pathogen load), and **non-antibiotic** (avoiding cross-resistance with the chemotherapeutics and antibiotics this population already receives). Three independent groups have converted this principle into CRC-relevant proof-of-concept: phage-guided chemotherapy delivery (Zheng et al., 2019), an immune-remodeling phage hybrid that synergizes with anti–PD-1 and FOLFIRI (Dong et al., 2020), and a naturally lytic Fn phage with direct anti-oncogenic activity (Lam et al., 2025). Gut-phageome data further show that Fn-phage signatures classify CRC across multinational cohorts, supporting both a biomarker-defined target population and the biological centrality of Fn–phage interactions (Shen et al., 2021).

What changes if we succeed. This program is squarely aligned with NCI's tumor-microbiome priorities: it targets a defined bacterial driver of an NCI-relevant cancer using a precision modality with established phage-guided-delivery precedent in CRC. By focusing on the oncogenic **Fna C2** clade and on **tumor-resident, biofilm-associated** Fn — the exact reservoir most relevant to therapeutic resistance and the compartment where antibiotics fail — the work targets the niche that matters most. A positive program would shift Fn-positive CRC from "inflammation/tumor to be suppressed" toward "a specific bacterial driver to be selectively removed," giving oncologists a commensal-sparing adjuvant that *rescues* standard chemo- and immunotherapy rather than adding antibiotic collateral damage.

Innovation

Four features distinguish this proposal.

- **From homing device to drug-like lytic therapeutic.** The published Fn-targeting constructs use the phage chiefly as a *vehicle* — azide-modified phage conjugated to irinotecan-loaded nanoparticles (Zheng et al., 2019) and silver-coated M13 (M13@Ag; Dong et al., 2020). The recent isolation of the naturally lytic ØTCUFN3, which directly inhibits Fn-induced proliferation and EMT and shrinks Fn-induced xenografts (Lam et al., 2025), opens a path to a **self-amplifying, strictly lytic** therapeutic. We extend this from a single phage to a host-range-matched cocktail to suppress resistance.

- **Clade-resolved, not monolithic.** Rather than treating "Fn" as a single entity, we build and validate activity against the oncogenic **Fna C2** isolates implicated in CRC, leveraging the recognition from gut-phageome profiling that Fn-phage signatures track CRC (Shen et al., 2021).
- **Tumor-resident, biofilm-associated delivery as a primary scientific problem.** We quantify biodistribution and biofilm penetration rather than *assuming* that luminal dosing reaches tumor Fn — directly addressing the niche where antibiotics fail.
- **A built-in causal control.** Fn-negative arms in Aim 3 make the efficacy test a true mechanism test: benefit must be Fn-dependent. Combined with an antibiotic comparator in Aim 2 (precision vs. collateral disruption) and pre-registered go/no-go tables, the program is designed to yield decision-grade, falsifiable results rather than a descriptive efficacy screen.

Conceptually, the innovation is to frame anti-Fn phages not as standalone cures but as **sensitizers** — a commensal-sparing microbiome adjuvant that restores chemotherapy and checkpoint-inhibitor efficacy.

Approach

Overview & experimental logic

The program advances along a de-risking staircase. **Aim 1** makes and characterizes the right strictly lytic cocktail against the right (Fna C2) strains and *locks* its composition against pre-registered criteria. **Aim 2** establishes that the cocktail reaches and depletes tumor-resident, biofilm-associated Fn while sparing commensals, with an antibiotic comparator to quantify precision and PK/PD to anchor dose. **Aim 3** tests whether that depletion restores chemo- and checkpoint responsiveness, with Fn-negative arms pinning any benefit to Fn. Strain-resolved Fn quantification and microbiome sequencing are the connective tissue across all three aims.

Aim 1 — Build and characterize a strictly lytic anti-Fn phage cocktail with defined activity against Fna C2

Rationale. A clinically credible cocktail must be lytic (not temperate), free of toxin/AMR/integrase genes, and active across the Fna C2 isolates that colonize human tumors. ØTCUFN3 provides a validated lytic starting point — it produced clear lytic plaques and achieved complete *in vitro* inhibition of Fn at MOI 10–100 within 24 h (Lam et al., 2025) — and a multi-phage, multi-receptor cocktail reduces emergence of phage-resistant Fn.

Experimental design.

1. **Isolate library.** Assemble a clinical-isolate library emphasizing **Fna C2**, alongside non-C2 *F. nucleatum* and representative gut commensals for off-target screening. Whole-genome sequence and clade-assign each isolate.
2. **Phage sourcing & sequencing.** Starting from ØTCUFN3 and phages newly isolated by enrichment against Fna C2 (oral/wastewater/clinical sources), whole-genome sequence and annotate each phage; **exclude any carrying integrase, known virulence, or AMR genes**; retain strictly lytic genomes.
3. **Host-range matrix.** Determine host range and EOP for every phage × isolate pair; build a coverage model mapping candidate cocktails to fraction of Fna C2 strains covered.
4. **Receptors & resistance.** Map surface receptors via resistant-mutant sequencing; quantify *in vitro* resistance-emergence frequencies for single phages versus cocktails; prefer complementary-receptor combinations.
5. **Functional confirmation.** Confirm retained anti-oncogenic activity using the Lam et al. (2025) readouts — suppression of Fn-induced CRC-cell proliferation (e.g., HCT116) and reversal of EMT markers (↓N-cadherin/Snail/Vimentin, ↑E-cadherin).
6. **Lock.** Select a 2–4-phage cocktail meeting Table 1 criteria and freeze composition before Aim 2.

Table 1. Pre-specified cocktail release criteria (go/no-go). *Thresholds are* **[ILLUSTRATIVE]** *and to be finalized with CMC/biostatistics input.*

Criterion	Threshold [ILLUSTRATIVE]
Coverage of circulating Fna C2 isolates	≥90% at EOP ≥ 0.1
Resistant-mutant suppression (combined cocktail)	No outgrowth over 48 h in time-kill at target MOI
Genome safety	Strictly lytic; no integrase / AMR / toxin genes

Criterion	Threshold [ILLUSTRATIVE]
Retained anti-oncogenic activity	Significant ↓ proliferation and EMT-marker reversal vs. Fn-only control
Off-target sparing	No lysis of tested commensal panel
Manufacturability	Reaches $\geq 10^{10}$ PFU/mL; endotoxin removable to clinical spec

Expected outcomes. A sequenced, strictly lytic 2–4-phage cocktail with a documented Fna C2 host-range map, defined receptors, lower resistance emergence than any single component, and retained anti-proliferative/anti-EMT activity.

Potential pitfalls & alternatives.

- *Narrow Fn host range limits Fna C2 coverage.* → Broaden environmental/clinical sourcing; if natural diversity is insufficient, host-range adaptation by serial passage on diverse Fna C2 isolates; permit a 4-phage rather than 2-phage formulation.
- *Strict-anaerobe culture is demanding.* → Standardize anaerobic propagation, titering, and QC SOPs early.
- *Engineered/CRISPR-armed phages* are deliberately **out of scope** to keep the lead product drug-like and IND-tractable; noted only as a long-term option.

Aim 2 — Quantify delivery to, and depletion of, tumor-resident Fn in CRC models

Rationale. Therapeutic benefit requires phage to reach biofilm-associated Fn on tumors — the niche where antibiotics fail. Prior work showed phage-guided constructs reach Fn-colonized tumors and that M13@Ag depletes gut Fn and reduces MDSC accumulation (Zheng et al., 2019; Dong et al., 2020), but delivery pharmacodynamics for a *strictly lytic cocktail* to tumor-resident Fn remain undefined.

Experimental design. In orthotopic CRC and *Apc*-mutant models colonized with defined Fna C2, administer the cocktail by clinically plausible luminal/oral routes and quantify, over time:

- **Phage biodistribution** and **intratumoral phage titer** (does the cocktail amplify where Fn is?);

- **Intratumoral Fn burden** by strain-resolved qPCR/metagenomics;
- **Biofilm penetration** (co-imaging of phage and Fn within tumor biofilm);
- **Off-target microbiome composition** by sequencing;
- **MDSC compartment** by flow cytometry.

Comparators & dosing. Vehicle and **antibiotic comparator** arms benchmark precision (selective Fn depletion vs. broad microbiome disruption). A dose-ranging sub-study defines exposure–effect relationships and the dose carried into Aim 3.

Rigor. Sex included as a biological variable; randomized allocation; blinded image/burden scoring; ARRIVE-compliant reporting; biostatistician-set group sizes.

Expected outcomes. Quantitative dose–exposure–effect relationships demonstrating selective intratumoral Fn depletion with preserved commensal diversity (vs. antibiotic-induced collapse), evidence on tumor-biofilm penetration, and an MDSC reduction mirroring that reported for M13@Ag.

Potential pitfalls & alternatives.

- *Oral phage inactivated in transit / fails to reach tumor.* → Protective/encapsulated, acid-buffered formulation; redosing; confirm gut viability ex vivo. As a delivery-chassis fallback, the validated phage-guided nanoparticle strategy (Zheng et al., 2019) can carry lytic phage to Fn-colonized tumors.
- *Biofilm tolerance blunts killing.* → Prioritize depolymerase-active phages; evaluate combination with the nanoparticle approach.
- *Low/variable colonization.* → Standardize Fna C2 inoculation and confirm engraftment before dosing.

Aim 3 — Test phage-enabled sensitization to chemotherapy and checkpoint blockade

Rationale. Fn drives chemoresistance and contributes to checkpoint resistance; depleting it should restore sensitivity. M13@Ag combined with anti–PD-1 or FOLFIRI significantly prolonged survival over phage monotherapy in CRC mice (Dong et al., 2020), and phage-guided irinotecan augmented first-line chemotherapy (Zheng et al., 2019) — supporting a sensitizer mechanism for a strictly lytic cocktail.

Experimental design. In Fn-colonized orthotopic CRC, test the cocktail **alone** and **combined** with

(a) FOLFIRI and (b) anti–PD-1, in randomized, adequately powered, blinded-readout studies.

- **Endpoints:** tumor growth; survival; intratumoral Fn burden; immune remodeling — MDSC accumulation, antigen-presenting-cell maturation, and effector T-cell infiltration.
- **Causal control: Fn-negative arms** receiving the identical cocktail/therapy test whether benefit is Fn-dependent. If the cocktail confers benefit *only* in Fn-colonized tumors, the effect is mechanistically attributable to Fn depletion rather than to nonspecific phage immunomodulation.
- **Decision rule:** pre-specified go/no-go criteria (e.g., a defined survival/tumor-growth advantage in combination arms that is absent in Fn-negative arms) gate IND-enabling development.

Rigor. Sex as a biological variable; randomization; blinded scoring; power analysis at 80% power, two-sided α 0.05 (group sizes biostatistician-set) **[ILLUSTRATIVE]**; ARRIVE-compliant reporting.

Expected outcomes. Demonstration that Fn depletion restores chemo- and checkpoint responsiveness — survival benefit in combination arms and immune remodeling consistent with reversal of Fn-driven suppression — that is **absent in Fn-negative controls**.

Potential pitfalls & alternatives.

- *Phage immunogenicity/neutralization limits repeat dosing.* → Monitor anti-phage responses; adjust schedule/composition; the UV/Fn-negative arms also control for nonspecific particle immunomodulation.
- *Single-agent depletion insufficient.* → Combination arms and the nanoparticle-delivery fallback (Zheng et al., 2019) provide alternatives.
- *Benefit confined to Fn-high tumors.* → Refines rather than negates the indication and supports a biomarker-defined population (Shen et al., 2021).

Timeline

All durations are **[ILLUSTRATIVE]**.

- **Year 1:** Aim 1 — isolate library, phage isolation, sequencing, host-range mapping.
- **Years 1–2:** cocktail assembly, receptor/resistance characterization, functional confirmation; **cocktail lock** by end of Y2.
- **Years 2–3:** Aim 2 — delivery, biofilm-penetration, and pharmacodynamic studies vs. antibiotic comparator; dose selection.

- **Years 3–4:** Aim 3 — monotherapy and FOLFIRI/anti–PD-1 combination efficacy with Fn-negative controls.
- **Year 5:** confirmatory combination studies, go/no-go review, and IND-enabling characterization/CMC groundwork.

Budget Justification (modular R01-style sketch)

Figures are **[ILLUSTRATIVE]** *modular estimates; replace with sponsored-programs numbers.*
Direct costs: $250,000/year [ILLUSTRATIVE] over **5 years [ILLUSTRATIVE]**.

- **Personnel:** PI (microbiology/phage biology; effort **[ILLUSTRATIVE]**); Co-I (GI/immuno-oncology; effort **[ILLUSTRATIVE]**); one postdoctoral fellow and one technician **[ILLUSTRATIVE]**; biostatistics support **[ILLUSTRATIVE]**.
- **Other:** anaerobic culture and phage production/QC; whole-genome sequencing and microbiome profiling; mouse-model colonies, orthotopic surgery, and imaging; FOLFIRI and anti–PD-1 reagents; per-isolate characterization consumables.
- **CMC/GMP:** scale-up beyond research-grade banks is anticipated as a later-phase cost **[ILLUSTRATIVE]** and is scoped here only at the groundwork level needed to position an IND.

All endpoints — the Fna C2 host range, tumor-resident delivery, MDSC remodeling, and chemo-/checkpoint sensitization — are NCI-relevant oncology outcomes; the microbiology in Aim 1 exists to enable them and is budgeted as integral to the oncology aims rather than as a separable program.

Vertebrate Animals

Animal work is proposed in Aims 2 and 3. Models include orthotopic CRC and *Apc*-mutant tumor models with defined *F. nucleatum* (Fna C2) colonization, used for delivery/pharmacodynamics (Aim 2) and efficacy (Aim 3), consistent with the published Fn–CRC models in which anti-Fn phage constructs were validated (Zheng et al., 2019; Dong et al., 2020; Lam et al., 2025).

- **Justification for vertebrate use.** *In vitro* systems cannot recapitulate tumor-resident biofilm Fn, phage biodistribution/amplification *in vivo*, or immune remodeling (MDSC accumulation, T-cell infiltration); these are the decision-grade endpoints of the program.
- **Numbers & rigor.** Group sizes minimized via *a priori* power analysis **[ILLUSTRATIVE]**;

randomized allocation, blinded outcome scoring, sex included as a biological variable, ARRIVE-compliant reporting.
- **Optional toxicology.** A piglet safety readout may be incorporated as a dedicated toxicology assessment (not a CRC-efficacy model), following the negligible-toxicity precedent for orally administered phage-guided constructs in piglets (Zheng et al., 2019).
- **Welfare.** Humane tumor-burden endpoints, analgesia per veterinary guidance, early-removal criteria; all procedures undergo institutional IACUC review per PHS policy.

Human Subjects / Clinical Trial

No human-subjects research is proposed in this R01; the work is preclinical and IND-enabling, matching the current entirely-preclinical status of the field (no registered human trial of anti-Fn phage therapy for CRC). For completeness, the translational path: first-in-human use of an investigational phage cocktail would proceed under FDA oversight, with early individual-patient access feasible via the **emergency/expanded-access IND (eIND)** route before a formal multi-patient IND and trial. Any future clinical protocol would require **IRB** approval, informed consent, and a biomarker strategy to identify Fn/Fna C2-positive candidate patients (Shen et al., 2021). These activities are future directions and are not part of the proposed budget period.

Investigators & Environment

Template roles to be filled with real names/institutions and NIH biosketches.

- **Contact PI — [NAME, INSTITUTION]:** bacteriophage biology, anaerobe microbiology, and phage manufacturing/QC — de-risks Aim 1 (strictly lytic cocktail assembly, host-range/resistance characterization) and the CMC groundwork.
- **Co-Investigator — [NAME, INSTITUTION]:** GI/immuno-oncology with CRC mouse-model, checkpoint, and FOLFIRI expertise — de-risks Aims 2–3 (orthotopic/*Apc* models, immune monitoring, combination pharmacology).
- **Co-Investigator — [NAME, INSTITUTION]:** tumor-microbiome and gut-phageome analysis — supports clade resolution and the biomarker logic linking Fna C2 to CRC (Shen et al., 2021).
- **Consultants:** regulatory/CMC advisor for phage IND strategy; biostatistician for power analysis and pre-registered decision rules.

The published programs in this space — phage-guided nanoparticles and M13@Ag (Zhang group; Zheng et al., 2019; Dong et al., 2020) and the lytic ØTCUFN3 (Lam/Chang group; Lam et al., 2025) — define the field's expertise base and are natural scientific reference points and potential collaborators.

Environment. The host institution will provide BSL-2/anaerobic microbiology, a sequencing/bioinformatics core, an AAALAC-accredited animal facility with orthotopic surgery and imaging, and immune-monitoring capabilities.

Authentication of key biological resources. Phage identity and strictly lytic status will be confirmed by whole-genome sequencing each working bank; *F. nucleatum* isolates will be clade-typed (Fna C2 vs. non-C2) and authenticated by sequencing; mouse strains and tumor lines will be authenticated and mycoplasma-screened per institutional policy.

References

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