Phage therapy from product concept to late-stage clinical development



How do phage fit into our armamentarium?
How do they differ from traditional products?
Why is reproducibility the key focus of this symposium?

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Slides happily shared

1

Disclosures (2023-2026)



- During the period 2022-2025, I am / have been
  - Chief Medical Officer, F2G, Ltd.
  - Editor-in-Chief, AMR.Solutions
  - Chair, AMR Action Fund SAB
  - Operating Partner & Consultant, Advent Life Sciences
  - Adjunct Professor of Medicine, McGovern Medical School, Houston, TX
- I have received grant support from Wellcome Trust.
- I sit on the scientific advisory board of the AMR Action Fund (AMRAF)
- I am currently a shareholder in AstraZeneca Pharmaceuticals, F2G, Ltd., and Advent Life Sciences
- The opinions expressed are my own and do not necessarily reflect the opinion of any of the groups with which I work

2

Overview of this session



- **We accept the idea that phage can kill bacteria!**
  - This is obvious! But, this is not enough to make phage into a medicine!
- Key organizing question for this symposium
  - **How much standardization must phage accept to be dose-able, trial-ready, and licensable — without losing the personalization that makes it work?**
  - Stated differently: **How do we license something that is designed to vary?**
- We have organized 4 talks on this theme:
  - This talk: An overview
  - Gauri Rao: How do you apply PK-PD to phage?
  - Frank Smreckar: How do you create a manufacturing platform for phage?
  - Radu Botgros: Regulatory perspective

3

Why phage? Why now?



- Antimicrobial resistance continues to progress
  - The pipeline is fragile[1]
  - Few novel mechanisms
  - Rising resistance.
- Phage offer a narrow-spectrum and microbiome-sparing option
  - Their (narrow) spectrum is a feature, not a bug
  - Their (narrow) spectrum shapes everything downstream
- They are self-amplifying at the site of infection
  - This is fundamentally different pharmacology!

[1]See https://amr.solutions/pathogens-and-pipelines/ for recent pipeline reviews

4

How are phage different from a classical small molecule?



- Phage are
  - Living, replicating biological agents — not fixed chemical entities
  - Host-specific (often strain-level), so coverage is narrow and must be engineered
- Phage co-evolve with the target
  - Bacteria develop resistance
  - Phage can be adapted
- Manufacturing is different!
  - Grown on a bacterial host
  - Intrinsically variable to manufacture
  - **And this variability is key to their utility**

5

Consequences of these features



- A single phage covers only a narrow slice of a species
  - Any given phage is likely insufficient as a stand-alone medicine
- Achieving adequate coverage demands a strategy
  - Phage cocktails, phage banks, or patient-specific matching
- So “develop a phage” really means design a programme to deliver
  - “the right phage(s)
  - “at the right dose”
  - “to the right patient
  - “reproducibly.”
- Call those the 4 R’s of phage:
  - **R**ight phage, **R**ight dose, **R**ight patient, **R**eproducible

6

Development models for phage: Trade-offs!



- There are 3 ways to proceed:
  - **Fixed cocktail**
    - Defined, manufacturable, licensable
    - But: Potentially a resistance risk due to limited/inflexible coverage
  - **Phage bank / platform**
    - Flexible coverage from a characterised library
    - But: Harder to define as a single product
  - **Personalised / magistral**
    - Best match to the patient's isolate
    - But: Doesn't scale, no standard product, only a limited evidence base
- Most programs are something of a hybrid

7

The central paradox



- Personalised, real-world phage therapy works
  - Large observational series report positive outcomes
- Pirnay 2024[a]
  - 100 consecutive cases
  - Clinical improvement in 77.2%
  - Target-pathogen eradication in 61.3%
  - Eradication was 70% less likely without concomitant antibiotics
- Yet, most other randomised controlled trials of non-personalised products have yielded inconsistent results
- Why the gap?
  - Problems arise from (lack of) matching, (wrong) dose, and (lack of) reproducibility
  - **Not whether phage "work" in principle**

[a]Pirnay, JP, Djebara, S, Steurs, G *et al.* Personalized bacteriophage therapy outcomes for 100 consecutive cases: a multicentre, multinational, retrospective observational study. *Nat Microbiol* **9**, 1434–1453 (2024). https://doi.org/10.1038/s41564-024-01705-x

8

2025: The year of cautious optimism



- Locus: LBP-EC01 / ELIMINATE[1]
  - **Engineered phage cocktail** for drug-resistant *E. coli* UTI; PK-guided dosing, then randomized phage + antibiotic vs antibiotic alone
  - **Key**: A **defined product** delivering the **right phage** at the **right dose**
- BiomX: BX211[2]
  - Randomized Phase 2 in *S. aureus* diabetic foot osteomyelitis; banked phages were matched to each patient's isolate, with encouraging healing signals
  - **Key:** A scalable model for the **right phage** for the **right patient**
- Armata: AP-SA02 / diSArm[3]
  - In complicated *S. aureus* bacteremia, adjunctive IV phage increased Day 12 response from 58% to 88% (p=0.047)
  - **Key:** Randomized signal that the **right defined phage** product can show **reproducible efficacy**

[1]ELIMINATE trial, ClinicalTrials.gov: NCT05488340. [2]Lipsky BA, et al. BX211 Phase 2 diabetic foot osteomyelitis study. *Open Forum Infect Dis*. 2026. [3]Miller LG, et al. AP-SA02 Phase 2a complicated *S. aureus* bacteremia study. *Open Forum Infect Dis*. 2026.

9

9

Reproducibility: The key concern



- If composition, titre or host-range shift batch-to-batch or patient-to-patient, what exactly is being dosed, trialled, and approved?
- Reproducibility links every downstream problem:
  - PK-PD
  - Manufacturing specs
  - Regulatory classification
  - Trial endpoints
- The field's task is to
  - **Bound variability** enough **to be a medicine**
  - **Without flattening the matching** that makes phage effective

2026-09-24 - JH Rex - GAMRIC - Phage therapy symposium - Opening 10

10

Our roadmap for today



- What are we solving for? Three talks:
  - Dose and exposure for a self-replicating agent (Dr. Rao)
  - Consistent, characterised supply despite the inherent biological variability of phage (Dr. Smreckar)
  - A regulatory route that fits a variable product (Dr. Botgros)
- Goal: Develop products/processes that solve for “the 4 Rs”
  - **R**ight phage, **R**ight dose, **R**ight patient, **R**eproducible
- Parked for later:
  - Trial design
  - Funding

11

In summary



- Phage are narrow-spectrum, self-replicating, variable
  - Thus, the product is a program, and
  - Reproducibility is the constraint
- So, on to the next talk
  - If the product can vary, can the dose also vary?
  - Dr. Rao, you’re up!

12