Getting from lab bench to clinic: CMC and practical considerations for phage products

Susan Lehman, PhD
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• Identify the gap between phage biology and phage therapeutic products

• Commonly acknowledged challenges in developing phages as medicines

• The biggest challenge for phage therapy may be bridging R&D expertise and CMC expertise
  • Getting the right R&D data
  • Leveraging R&D data to enable manufacturing
  • Practical product considerations
  • Assembling regulatory package
Bridging the Gap to Phage Therapy

Tons of Great Phage Knowledge!

- Genome sequences
- Lifestyle
- Transduction potential
- Host range
- Complementation
- Frequency of resistance
- Genetic engineering

Tons of Great Antimicrobial Development Knowledge!

- Drug discovery
- PK/PD
- Toxicology
- Manufacturing
- Regulatory
- Clinical trial design

penicillin
AmpliPhi Product Development Overview

Traditional Drug Development Programs:
- nonclinical data, GMP manufacturing, clinical trials, regulatory engagement

<table>
<thead>
<tr>
<th>Indication</th>
<th>Collaborator</th>
<th>Discovery</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AB-SA01 (cocktail targeting <em>Staphylococcus aureus</em>)</strong></td>
<td></td>
<td></td>
<td></td>
<td>Can proceed in US with existing data</td>
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</tr>
<tr>
<td>Chronic Rhinosinusitis (CRS)</td>
<td>THE UNIVERSITY of ADELAIDE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wounds / implant-associated infections</td>
<td>USAMRIID U.S. ARMY</td>
<td></td>
<td></td>
<td>Open IND</td>
<td></td>
</tr>
<tr>
<td><strong>AB-PA01 (cocktail targeting <em>Pseudomonas aeruginosa</em>)</strong></td>
<td></td>
<td></td>
<td></td>
<td>Successful MHRA consultation</td>
<td></td>
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<tr>
<td>Cystic Fibrosis (CF)</td>
<td>Royal Brompton &amp; Harefield</td>
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</tr>
<tr>
<td>Chronic Rhinosinusitis (CRS)</td>
<td>THE UNIVERSITY of ADELAIDE</td>
<td></td>
<td></td>
<td>Modeled on AB-SA01</td>
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</table>

In response to urgent unmet clinical needs, AmpliPhi has also collaborated with clinicians, as requested, under expanded access schemes.
Commonly Discussed Challenges

Challenges Developing Early Data
- Phages have different mechanism of action than small molecules
- Standard methods for assessing anti-infectives sometimes don’t work the same way for phages, and need new ways to address the question
  - e.g. Phage-Antibiotic Synergy
  - PK/PD
  - Preclinical efficacy models

Clinical Challenges
- Growing enthusiasm among clinicians, but also doubt
- Clinical trial design

Regulatory Challenges
- Phages can fit into traditional drug approval pathway
- How can cocktails be adapted to suit changing bacterial populations?
Getting from Lab Bench to Clinic

- Library of phages
- Broad and complementary host ranges
- WGS, RFLP, TEM, etc
- Preclinical in vivo testing
- Two-tier banks for manufacturing
- R&D, GMP/GLP/GCP
- Storage & stability
- Formulation & drug delivery
- Toxicology
- Clinical trial design & execution
- QA/Quality systems
- Qualified QC methods
- Regulatory approval
- Process development & validation
Manufacturing:
Make the Same Thing Every Time

- Ensure process consistency, use well-characterized parent stocks, limit serial passage
- Example for a 4-phage product:

AmpliPhi products aseptically prepared per EU GMP Annex 1 Manufacture of Sterile Medicinal Products
Manufacturing:
Demonstrate you Made the Same Thing Every Time

Analytical Methods:
- Demonstrate product consistent to *yourself and others* by testing defined characteristics against established criteria
- Develop from your phage characterization and process development data

Characteristics of a good research assay:
- Does it measure what you think it does? If measurement is indirect, are you confident in the inference?
- Reasonable controls (positive, negative, standard curves)
- General repeatability (run the experiment more than once)

Extra considerations when transitioning to GMP manufacturing:
- More in-depth knowledge of linearity, accuracy, precision, range & limit of detection
- Standardize process-related losses
- Objective outcomes with unambiguous interpretation, reasonable speed
- Quantify assay consistency: individual operators, between operators, among labs
- Are ultimate assay tolerances tight enough (or too tight) to be useful?
## Assay Development:
### Transitioning from R&D to Manufacturing

- Staged development, with assays and their validation level maturing over time
- In-process assays and release assays
- Assays may be industry standard and product-specific

<table>
<thead>
<tr>
<th>Features of Interest</th>
<th>Considerations</th>
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<tbody>
<tr>
<td><strong>Phage Concentration</strong></td>
<td>Monitor yield/losses at various stages of process</td>
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<tr>
<td></td>
<td>What host?</td>
</tr>
<tr>
<td></td>
<td>Testing single phage vs cocktail?</td>
</tr>
<tr>
<td><strong>Identity &amp; Purity of Phage(s)</strong></td>
<td>Speed?</td>
</tr>
<tr>
<td></td>
<td>Potential ambiguity?</td>
</tr>
<tr>
<td></td>
<td>Informative? (e.g. differentiate phages, detect problems)</td>
</tr>
<tr>
<td></td>
<td>Testing single phage vs cocktail?</td>
</tr>
<tr>
<td><strong>Removing Impurities</strong></td>
<td>General vs specific?</td>
</tr>
<tr>
<td>(Host Cell Protein, DNA, endotoxin)</td>
<td>Quantitative?</td>
</tr>
<tr>
<td></td>
<td>What is appropriate for the intended use?</td>
</tr>
<tr>
<td><strong>Contamination</strong></td>
<td>What are main concerns at various stages of process?</td>
</tr>
<tr>
<td></td>
<td>What are possible sources?</td>
</tr>
<tr>
<td></td>
<td>Is final product sterile?</td>
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# Practical Considerations

<table>
<thead>
<tr>
<th>Issue</th>
<th>Examples</th>
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<tbody>
<tr>
<td><strong>Formulation &amp; Drug Delivery</strong></td>
<td></td>
</tr>
<tr>
<td>Route of administration</td>
<td>IV, inhaled, sinus rinse, wound packing</td>
</tr>
<tr>
<td>Delivery device</td>
<td>Nebulizer, metered dose device</td>
</tr>
<tr>
<td>Compatibility with current clinical</td>
<td>Methods for use, other SOC drugs</td>
</tr>
<tr>
<td>practices</td>
<td></td>
</tr>
<tr>
<td>Formulation matrix</td>
<td>Liquid, gel, lyophilized</td>
</tr>
<tr>
<td><strong>Storage &amp; Stability</strong></td>
<td></td>
</tr>
<tr>
<td>Storage conditions</td>
<td>Temperature, production stage, container, redundancy</td>
</tr>
<tr>
<td>Minimum requirements</td>
<td>Fit into usage plans, meet guidelines</td>
</tr>
<tr>
<td><strong>Toxicology</strong></td>
<td></td>
</tr>
<tr>
<td>Based on device &amp; formulation</td>
<td>Adapt device-mediated exposure to test animal</td>
</tr>
<tr>
<td>Match to clinical strategy</td>
<td>Anticipated durations of treatment</td>
</tr>
</tbody>
</table>
Clinical Development Considerations

Clinical Indication
• Identify good infection target (phage biology + unmet clinical need)
• Plan clinical trial progression
• Sufficient patient population to enroll planned trials

Endpoints
• What to measure to get meaningful, interpretable safety and clinical efficacy data?
• Need new assays?
• Duration of treatment and follow-up
• Phage products introduce new questions

Infrastructure
• Clinical microbiology labs may not be equipped for phage-specific assays
• Are current microbiology methods appropriate for phage susceptibility assessment?
• Consider centralized testing for multi-center study?
Regulatory Package Components to Support Clinical Trial

Integrated Product Development Plan

Investigator’s Brochure

Nonclinical Data
  e.g. phage characterization, pharmacology, toxicology

Quality Information
  e.g. details of product composition (DS, DP, excipients); manufacturing processes and controls; manufacturing facility; container closure; stability data, reference standards

Clinical
  e.g. trial protocol, investigator & site details, informed consent

For more details: ICH and FDA websites
Getting from Lab Bench to Clinic

library of Phages

broad and complementary host ranges

WGS, RFLP, TEM, etc

preclinical in vivo Testing

two-tier banks for manufacturing

production & process validation

R&D

GMP/GLP/GCP

storage & stability

formulation & drug Delivery

QA/Quality systems
qualified QC methods

clinical trial design & execution

toxicology

regulatory approval

clinical trial design & execution
Expanded Access

Commitment to Quality

- Using GMP products when possible
- Non-GMP material should still meet high standards.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>GMP Product</th>
<th>Non-GMP Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phage Characterization</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Detailed Production Records</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Purification Appropriate for Human Use</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Microbiological Testing</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Defined Storage &amp; Handling Conditions</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Commitment to Patient Safety

- Help physicians collect data at baseline, during, and after treatment:
  - data relevant to patient safety
  - data to understand impact of phages on clinical progress
Summary

• Challenge for phage therapy is the integration of phage community’s expertise with drug development community’s expertise → they are compatible!

• GMP phage production is possible; regulatory agency approval to conduct clinical trials is possible

• We can realize the benefits of phage therapy while maintaining commitment to high quality products and processes

• Lots to learn as we all move forward
Thank You