Paci-PHI

Evolution-proof therapy against MDR bacterial pathogens

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**EXPERT TEAM**

Paul TURNER, PhD  
*Dean of Science, Professor of Microbiology and Ecology & Evolutionary Biology*  
*Yale University*  
*Yale School of Medicine*  

Paul TURNER is a world renowned expert in bacteriophage biology and microbial evolution.

Benjamin CHAN, PhD  
*Associate Research Scientist*  
*Yale University*  

Benjamin CHAN has 10 years of industry and academic experience developing and using therapeutic phage.

Deepak NARAYAN, MD  
*Professor, Chief of Surgery*  
*Yale-New Haven Hospital*  
*West Haven VA Hospital*  

Deepak NARAYAN is a highly accomplished and respected physician.
PROBLEM: Antibiotic resistance crisis

- Global problem: Increasing proportion of bacteria show resistance to antibiotics.
- Pace of antibiotic discovery has not kept up with evolution of bacterial resistance.
ALTERNATIVE: Phage therapy

- Phages are viruses that specifically kill only certain bacteria.
- Phages are self-amplifying ‘drugs’, designated GRAS (generally regarded as safe) by FDA.

Lytic phage reproduction
ALTERNATIVE: Phage therapy is SAFE

- SAFE: Example phage products designated as GRAS:
  
  - *Listshield* (2006), Intralytix, USA
  - *PhageGuard Listex* (2008), Micreos, Netherlands
  - *PhageGuard Salmoonelex* (2010), Micreos, Netherlands

- NON-IMMUNOGENIC: Immune response to phages is minimal (if at all).

- INEXPENSIVE: Phages can be cheaply produced in large volumes.

*Accelerated approval for Phase II trials is possibility.*
• HOWEVER, bacteria can evolve phage resistance, similar to antibiotic problem:
SOLUTION: Force evolutionary trade-offs in target bacteria

- INNOVATION: Use phages to select for antibiotic re-sensitivity and reduced virulence in pathogenic bacteria

Re-sensitizing bacteria to antibiotics therefore extends the lifetime and improves the effectiveness of current antibiotics.
**PROOF:** *In vitro* and *in vivo* data targeting MDR *P. aeruginosa*

- *Pseudomonas aeruginosa* is priority pathogen (World Health Organization, 2017).

- Hospital infections on rise; high mortality in cystic fibrosis, severe burn, immunocompromised patients.

Phage OMKO1 broadly selects for antibiotic re-sensitivity in clinical, environmental, and model strains, because **OprM** binding target highly genetically conserved.
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CAZ = ceftazidime
CIP = ciprofloxacin
PROOF: *In vitro* and *in vivo* data targeting MDR *P. aeruginosa*

- *In vivo* data show phage-antibiotic synergy that rescues mice from lethal pneumonia

**Mouse pneumonia model**

**Controls:**

**Phage rescue mice at all drug doses:**
PROOF: Emergency phage treatment in 2 patients

- Jan 2016 – complete resolution of MDR *P. aeruginosa* biofilm infection of indwelling prosthesis (aortic arch graft) in elderly man;

![CT image showing infected collection and site of targeted aspiration during therapy](image1)

Treated patient in 2017 with Drs. Turner and Chan

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STAT Online News: In the Lab

*A virus, fished out of a lake, may have saved a man’s life — and advanced science*

*By Carl Zimmer*

December 7, 2016

Chan et al. 2018 *Evolution, Medicine & Public Health*

See also: NPR Science Friday, 2016, 2018
PROOF: Emergency phage treatment in 2 patients

- Dec 2017 – complete re-sensitization to antibiotics in Pan-Drug Resistant *P. aeruginosa*-infected lungs of 22-year-old woman with cystic fibrosis.

<table>
<thead>
<tr>
<th>Change in <em>P. aeruginosa</em> pre vs. post treatment</th>
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<td><strong>Aminoglycoside</strong></td>
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<td><strong>Fluoroquinolone</strong></td>
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<td><strong>Cephalosporin</strong></td>
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<td><strong>Beta lactam</strong></td>
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• ‘Phage composition forcing trade-off between phage resistance and antibiotic sensitivity’ – international patent filed by Yale (2016)

• Seeking U.S. FDA approval (and funding) for phase I/II clinical trials:
  - Acute (including hospital acquired) pneumonia
  - Cystic fibrosis associated pulmonary infections
  - Urinary tract infections (including catheter-associated)
  - Burn/wound infections
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• Held FDA type B meeting in 2017
  - No call for toxicology or pharmacokinetic/pharmacodynamics studies
  - With secured funding, will apply for IND to perform phase I/II trials
  - Hospital in NC with prepared IRB and identified patients; active discussions with YNHH and TX hospital
Our library contains 100s of phages, with abundant candidates that force similar trade-offs in clinically relevant bacteria, aside from *Pseudomonas aeruginosa*:

- *Salmonella*
- *Shigella spp.*
- *Klebsiella pneumoniae*
- *Vibrio cholerae*
- Pathogenic *E. coli*

Isolation and characterization of new therapeutic candidates.

Scale up, QC/QA, GMP, CMC

Phase I/II clinical trial performed at three sites in the USA

BLAVATNIK FUNDING REQUEST

We request $300K for scale-up and production, in developing our most promising phage-therapy candidate against MDR P. aeruginosa.
COST BREAKDOWN

Funding used to:
• Establish master bank
• Scale-up production
• Conduct sterility/stability testing of materials for clinical trial (50 patients, phase I/II)

All in approved GMP facility: Adaptive Phage Therapeutics; Gaithersburg, MD
Total cost: $560K

We negotiated one-time reduced cost as research outcome would be mutually beneficial.
Actual cost: $300K