

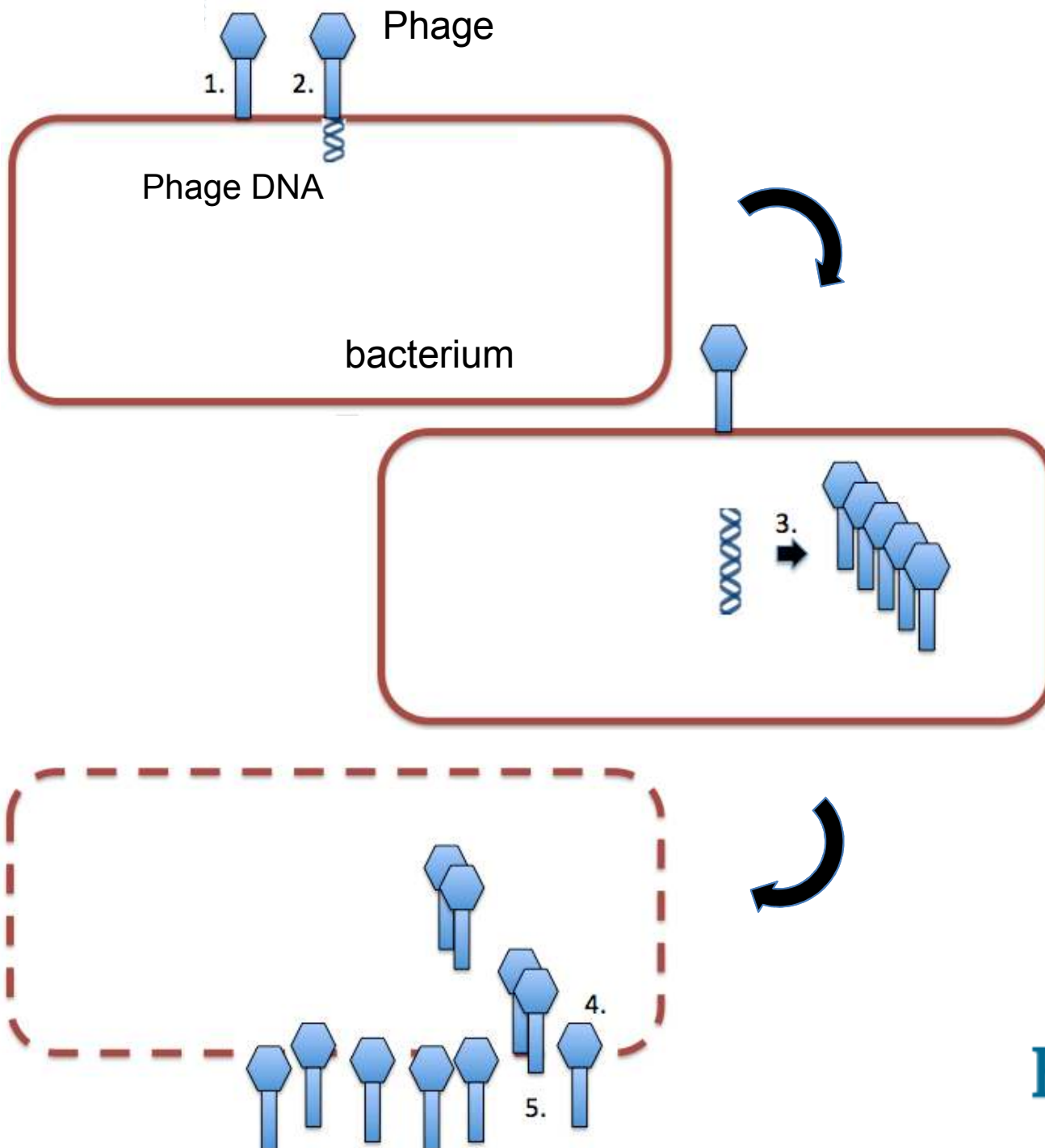
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“A simple solution for the resistance problem”

“Dutch physicians are missing chances...”

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Phage = virus

1. Phage attaches
2. Phage injects DNA
3. Phage replicates
4. Phage lyses bacterium
5. Daughter-phages are released

Bacteriophages

- Are abundant in nature
- Are specific for (sub)species
- Lytic phage produces endolysins
- Endolysins lyse bacterial cell walls
- Therapy: whole phage or endolysine



Successes of phage therapy

- 100 years of solitude -

- **In typhoid fever** (Beckfrich and Hauduroy 1922; Smith 1924; Hauduroy 1925, Knauf et al 1946 Desranleau et al 1948, 1949)
- **In cholera** (d'Herelle 1931)
- **In *S. aureus* bacteraemia** (d'Herelle 1931, Sauve 1936, MacNeal and Frisbee 1936, Chanishvili 2012)

S. aureus trials in Moscow & Tblisi (Chanishvili, 2012*)

653 adults (1980 – 1985)

Treatment	# patients	'Complete cure'
Antibiotics alone	308	31.8%
Phage therapy iv	130	43.8%
Phage therapy iv + antibiotics	215	71.2%

* Cited by Speck et al 2015

Nina Chanishvili*

Eliava Inst of Bacteriophage, Tblisi

- No proper design of studies:
 - No placebo
 - No proper coding
 - No balance between patients & controls
 - Sometimes no controls/ historical controls
 - Pretreatment with antibiotics
 - Phage titres not given

“Nevertheless, past experience indicates some effectiveness of phage therapy and prophylaxis”.

**Adv Virus Res 2012;83:3-40*

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Antimicrobial Agents
and Chemotherapy®

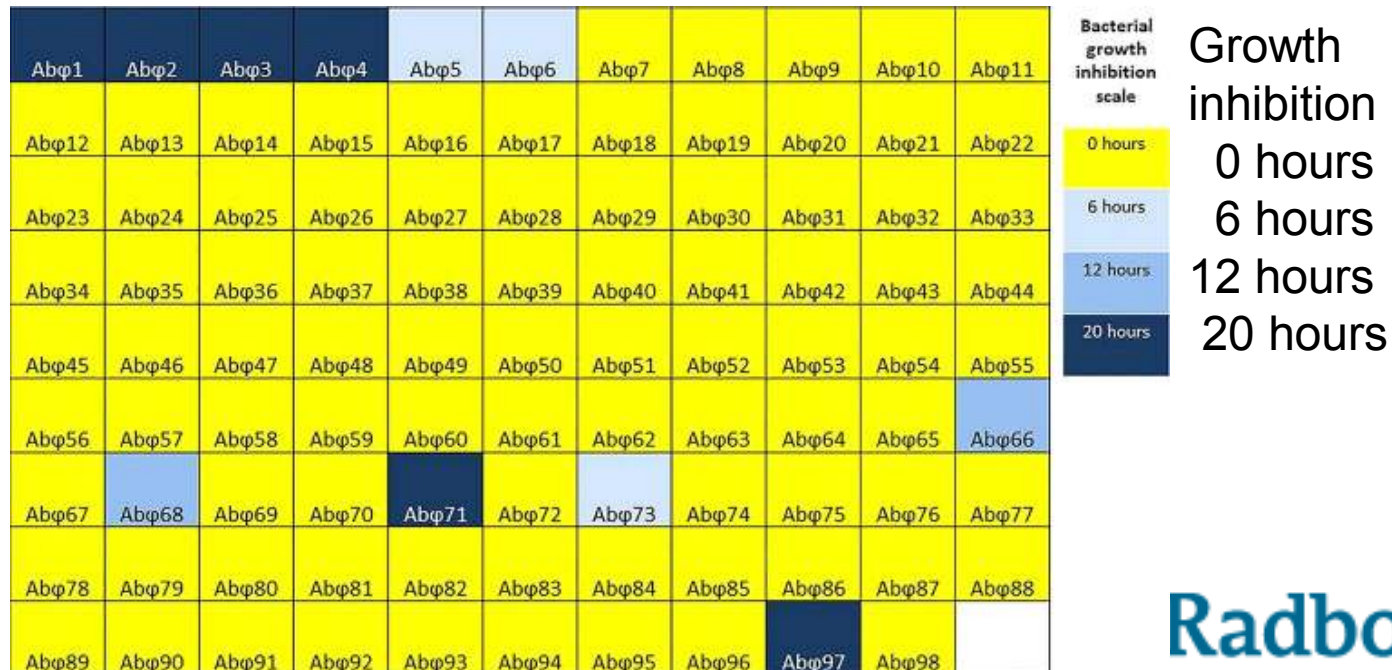
Development and Use of Personalized Bacteriophage-Based Therapeutic Cocktails To Treat a Patient with a Disseminated Resistant *Acinetobacter baumannii* Infection

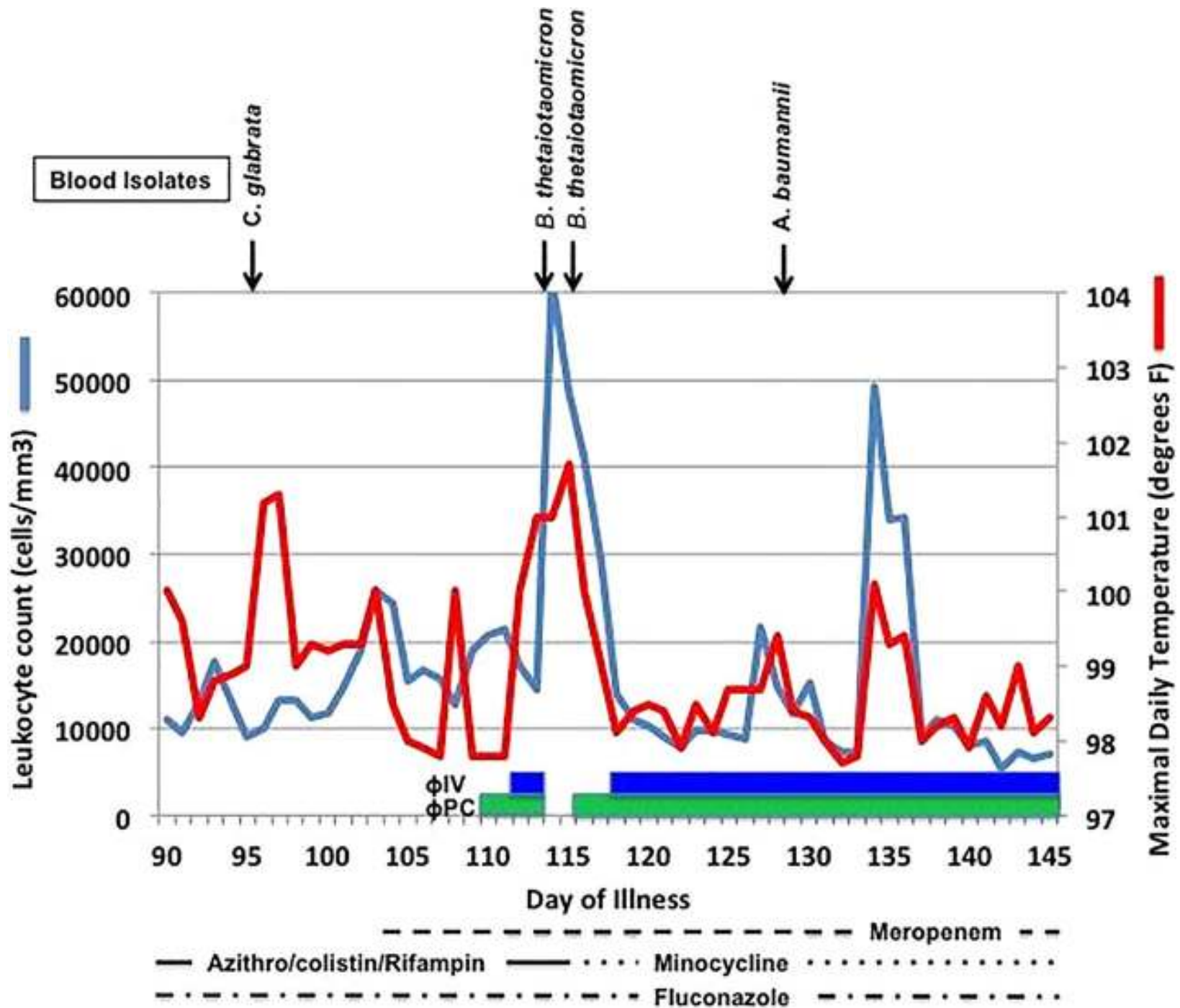
Robert T. Schooley,^a Biswajit Biswas,^{b,c} Jason J. Gill,^{d,e}
Adriana Hernandez-Morales,^f Jacob Lancaster,^g Lauren Lessor,^e Jeremy J. Barr,^{g,o}
Sharon L. Reed,^{a,h} Forest Rohwer,^g Sean Benler,^g Anca M. Segall,^g Randy Taplitz,^a
Davey M. Smith,^a Kim Kerr,^a Monika Kumaraswamy,^a Victor Nizet,^{i,j} Leo Lin,ⁱ
Melanie D. McCauley,^a Steffanie A. Strathdee,^a Constance A. Benson,^a
Robert K. Pope,^k Brian M. Leroux,^k Andrew C. Picel,^l Alfred J. Mateczun,^b
Katherine E. Cilwa,ⁿ James M. Regeimbal,^b Luis A. Estrella,^b David M. Wolfe,^b
Matthew S. Henry,^{b,c} Javier Quinones,^{b,c} Scott Salka,^m Kimberly A. Bishop-Lilly,^{b,c}
Ry Young,^{e,f} Theron Hamilton^b

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Male 68 years

- Diabetes, necrotising pancreatitis
- MDR *Acinetobacter baumannii* pancreatic pseudocyst





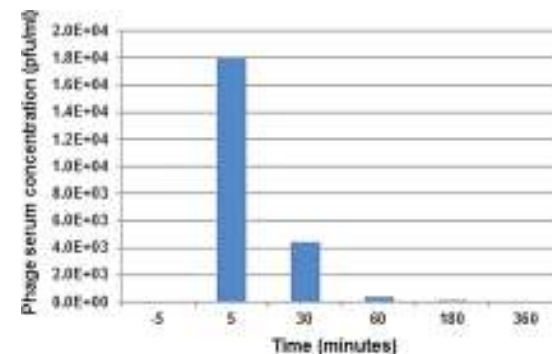
Problems with Phage therapy

- Selection of virulent, rapidly proliferating, rapidly lysing phages directed against the causative bacterium
- Purification of the phage (Pirnay et al Pharm Res 2015)
- 1 phage or cocktail? (antagonism? resistance?)

NB: Schooley et al: mix of 8 phages, < 8 days resistance!

Pharmacokinetics of phage therapy

- Administration local, oral, intravenously, intracavitary
- Resorption?
- Uptake by macrophages in liver and spleen?
- Which fraction reaches the infection?
- Replication in vivo?
- Clearance:

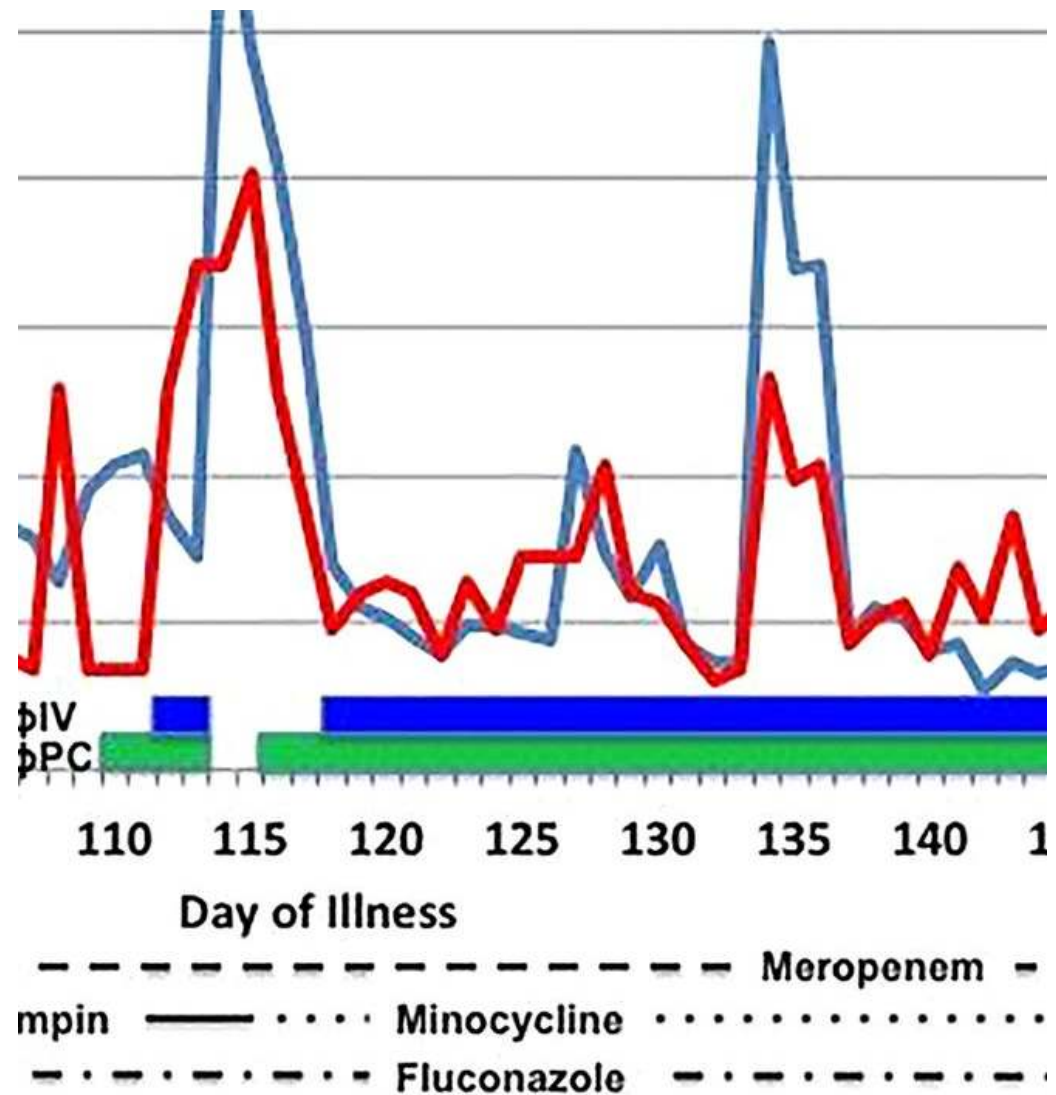


Which dose?

- phage diameter > 60 nm
- > 10^{13} /ml too viscous for injection
- Schooley et al: 5×10^9 intracavitary en 5×10^9 intravenously

Effectivity?



- Schooley et al:
Effect?
 - minocyclin!
 - iv & ic



Side effects phage therapy

- In the twenties: fever and shock
- Although one would expect otherwise: side effects are reported as minimal...
- Endotoxin release?

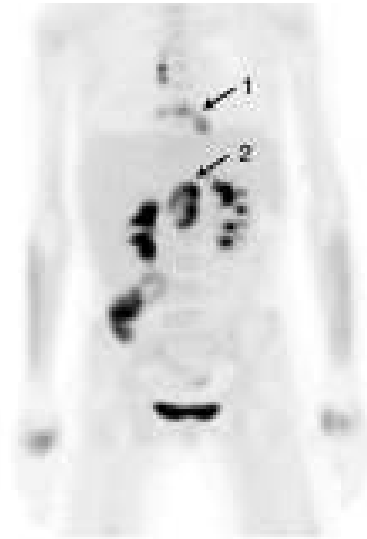
Engineered bacteriophages for treatment of a patient with a disseminated drug-resistant *Mycobacterium abscessus*

Rebekah M. Dedrick^{1,4}, Carlos A. Guerrero-Bustamante^{1,4}, Rebecca A. Garland¹, Daniel A. Russell¹, Katrina Ford², Kathryn Harris², Kimberly C. Gilmour², James Soothill², Deborah Jacobs-Sera¹, Robert T. Schooley³, Graham F. Hatfull ^{1*} and Helen Spencer ^{2*}

- ❖ 15-yr-old female with CF and recent lung transplant
- 8 years of *M. abscessus* (*massiliense*) infection

15-yr-old CF patient

- Post-transplant after cessation of antibiotics (← side effects):
 - Redness at sternotomy & pulmonary consolidation; *M. abscessus* from sputum.
 - PET-CT



- EBV viremia → Rituximab

15-yr-old CF patient

- 7 mo post-transplant
 - Skin lesions (2 → 20)
granulomatous
 - Destructive granulomatous
at sternotomy scar
 - *M. abscessus*

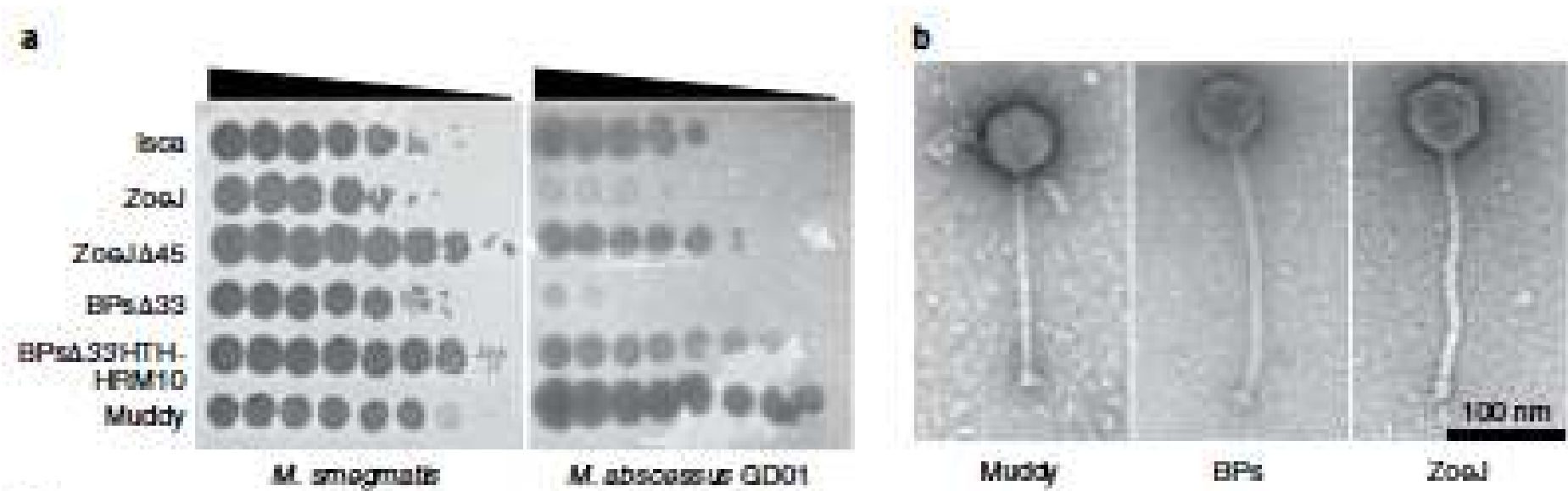


Phage selection

Screening >10 000 phages

(Science Education Alliance Advancing Genomics and Evolutionary Sciences)

- 3 phages selected (1 engineered)



Phage therapy*

- Preparation 10^9 /ml
- Cocktail of the 3 phages
- No bacterial survival after in-vitro exposure
- Test dose of 10^9 in sternal wound
- Thereafter 10^9 iv every 12 hours for each phage for 32 weeks
- Also topical daily for sternal wound and skin lesions

* Concomitant R/ amikacin, bedaquiline, clofazimine



Before treatment

Post treatment

- Healing of lesions
- No resistance to phages
- Persistence of Mycobacteria in skin lesions up to 5 months!

Additional findings

- Phages detectable in serum, sputum (10^{10} /ml), faeces, wound swabs.
- Apparently phage replication
- Persistent Mycobacteria remained susceptible to phages
- Minimal side effects
- Minimal cytokine response

Local therapy

Efficacy and tolerability of a cocktail of bacteriophages to treat burn wounds infected by *Pseudomonas aeruginosa* (PhagoBurn): a randomised, controlled, double-blind phase 1/2 trial

Patrick Jault, Thomas Leclerc, Serge Jennes, Jean Paul Pirnay, Yok-Ai Que, Gregory Resch, Anne Françoise Rousseau, François Ravat, Hervé Carsin, Ronan Le Floch, Jean Vivien Schaal, Charles Soler, Cindy Fevre, Isabelle Arnaud, Laurent Bretaudeau, Jérôme Gabard

Conclusions Phage therapy

- Conceptually attractive:
 - Great specificity (no effect on colonising microflora)
 - No cross resistance with antibiotics
- Very laborious, great technical challenges
- Clinical effect is difficult to assess
- Need for proof-of-concept studies!

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endolysins



NB Freely available on Internet (not licensed as a drug!)

MAAS TRIAL (Atopic eczema) Trials, 2017

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