



**National Jewish
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NTM
Lecture Series
for Patients and Families

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Novel Therapies for NTM



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Disclosures

Consultant: Genentech, Pfizer

Advisory Board Member: AN2, Hyfe, Insmmed, MannKind, Matinas BioPharma Holdings, Inc., Nob Hill, Paratek Pharmaceuticals, Spero Therapeutics, Zambon

Data Monitoring Committee: Ostuka Pharmaceutical, Bill and Melinda Gates Foundation

Contracted Research: AN2 Therapeutics, Bugworks, Insmmed, Juvabis, Paratek Pharmaceuticals

Novel Treatments for NTM

Repurposed Drugs	<ul style="list-style-type: none">• Dual beta-lactams ± beta-lactamase inhibitors• Cycline derivatives• Rifabutin (for <i>M. abscessus</i>)• Apramycin
New Drugs	<ul style="list-style-type: none">• Epetraborole• SPR720
New Formulations	<ul style="list-style-type: none">• Inhaled tigecycline• Inhaled clofazimine
Non-antimicrobial Agents	<ul style="list-style-type: none">• Inhaled NO• Inhaled GM-CSF• Gallium• Bacteriophage

Clinical Pipeline for NTM Drugs

Phase 1

Gallium
Apramycin

Phase 2

Bedaquiline
Clofazimine
Epetraborole
IL-7
Inhaled GM-CSF
Inhaled nitric oxide
Omadacycline
SPR720

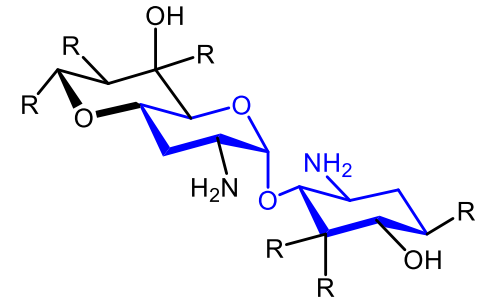
Phase 3

Amikacin liposome
inhalation suspension (ALIS)
Azithromycin vs clarithromycin
Clarithromycin vs moxifloxacin
2 vs 3 drugs for MAC

Green – recruiting
Blue – not yet recruiting
Red – completed
Black – on hold

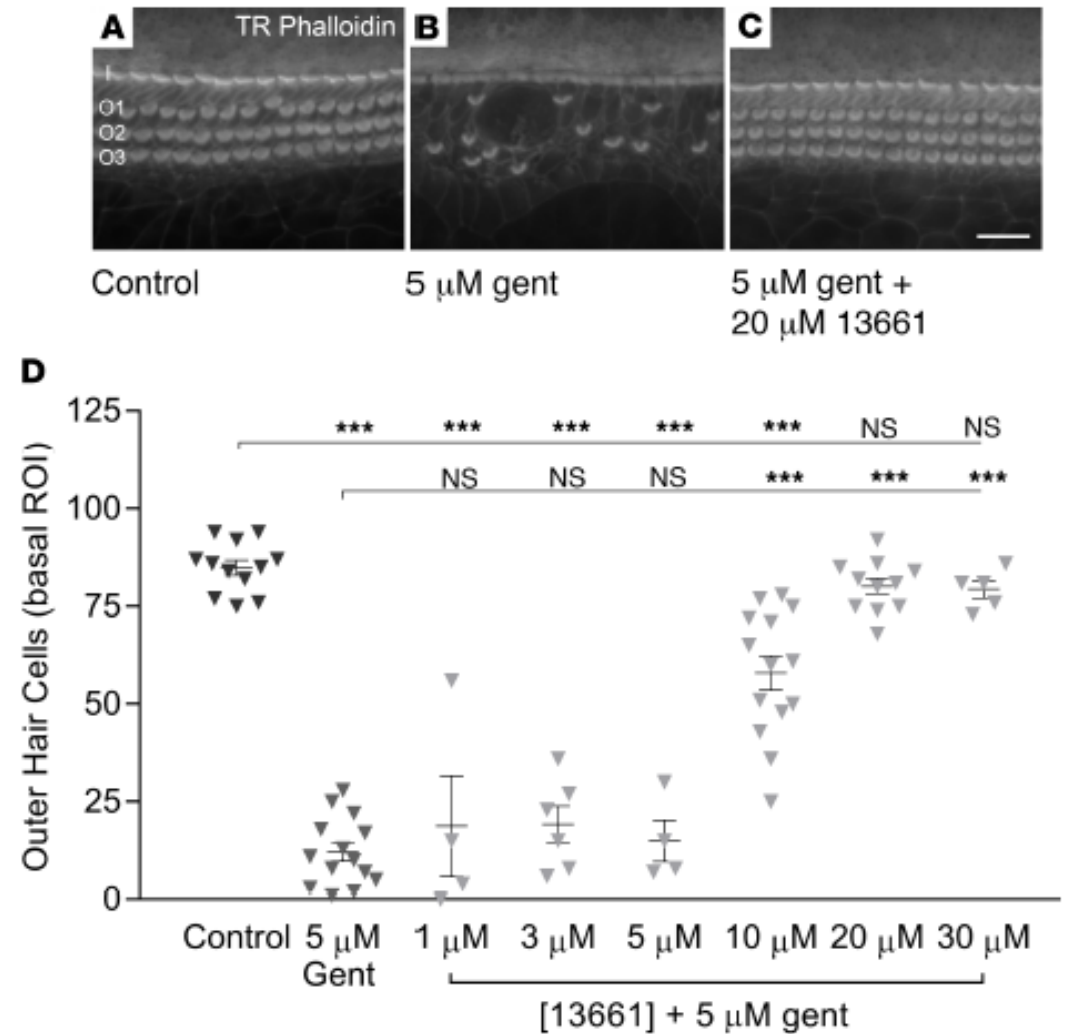
Apramycin

- New aminoglycoside subclass
- Less toxic than comparator aminoglycosides
- Evades almost all aminoglycoside resistances
- High lung penetration following parenteral administration
- Potent in-vivo efficacy in CF mice, both subcutaneous & inhaled



ORC-13661- Protects mouse sensory hair cells from aminoglycoside ototoxicity

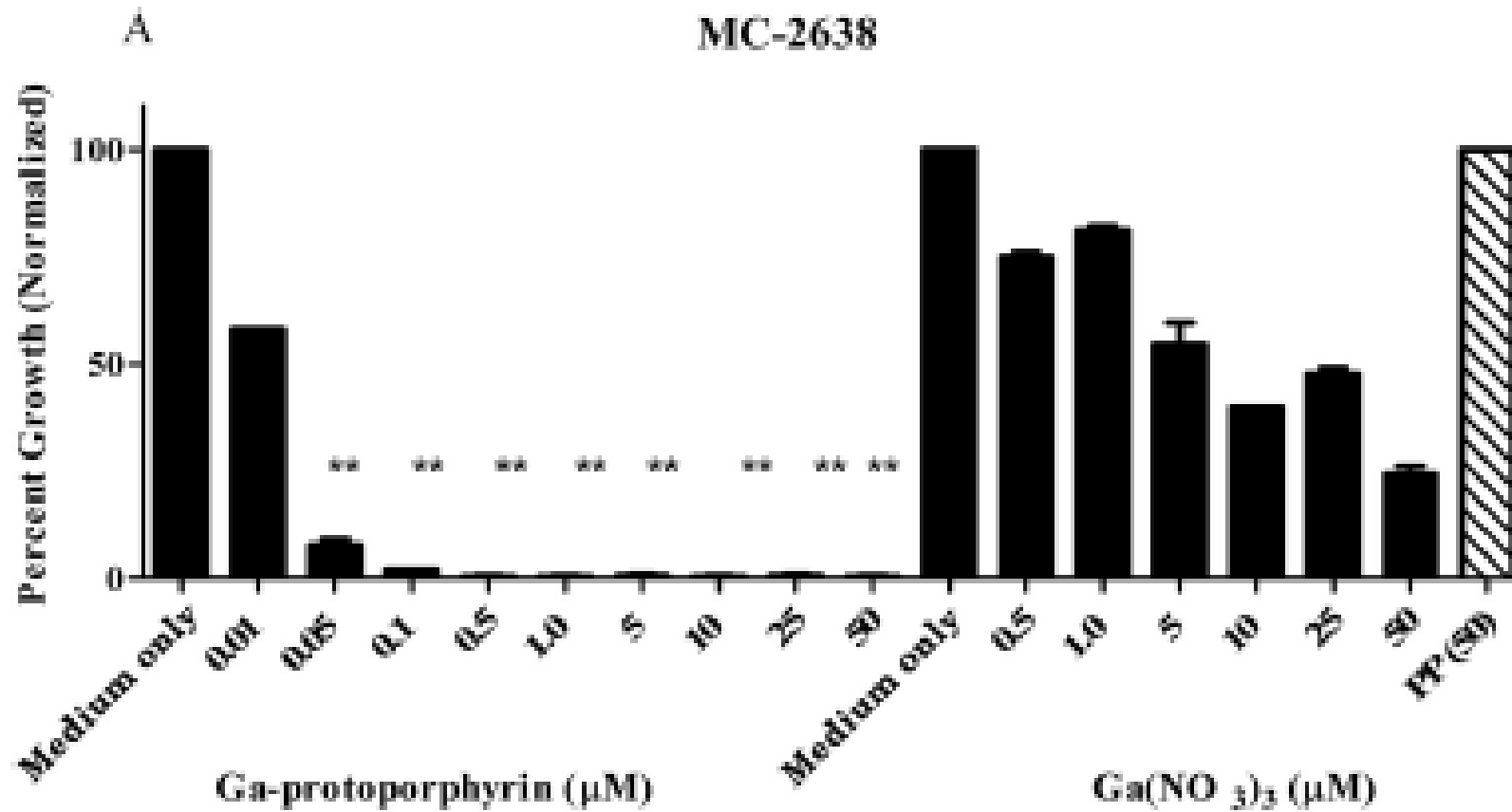
- Aminoglycosides damage the sensory hair cells in the inner ear
- ORC-13661 is thought to prevent entry of aminoglycosides into the hair cell



Gallium

- Iron is essential for the growth of mycobacteria
 - Iron is important in DNA synthesis, metabolism, and oxidative stress responses
- Control of availability or interference with Fe uptake inhibits growth of *M. tuberculosis* and virulence is increased with greater availability
- Gallium can compete with Fe and inhibit Fe-dependent enzymes in mycobacteria
- Ga (NO₃)₃ [gallium nitrate] is FDA approved for hypercalcemia of malignancy

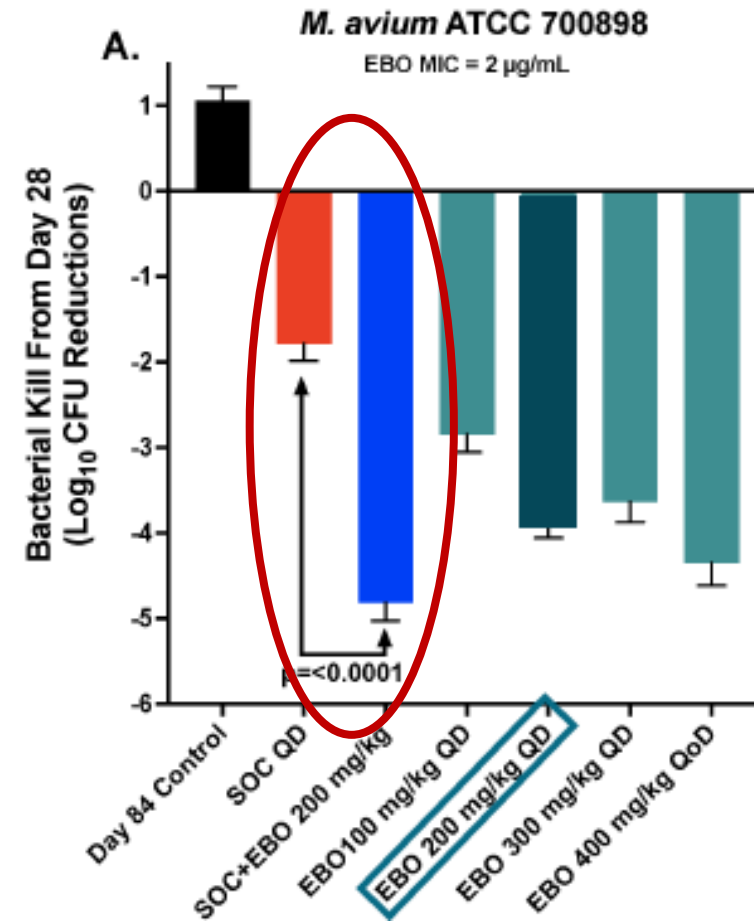
Gallium: Inhibition of *M. abscessus*



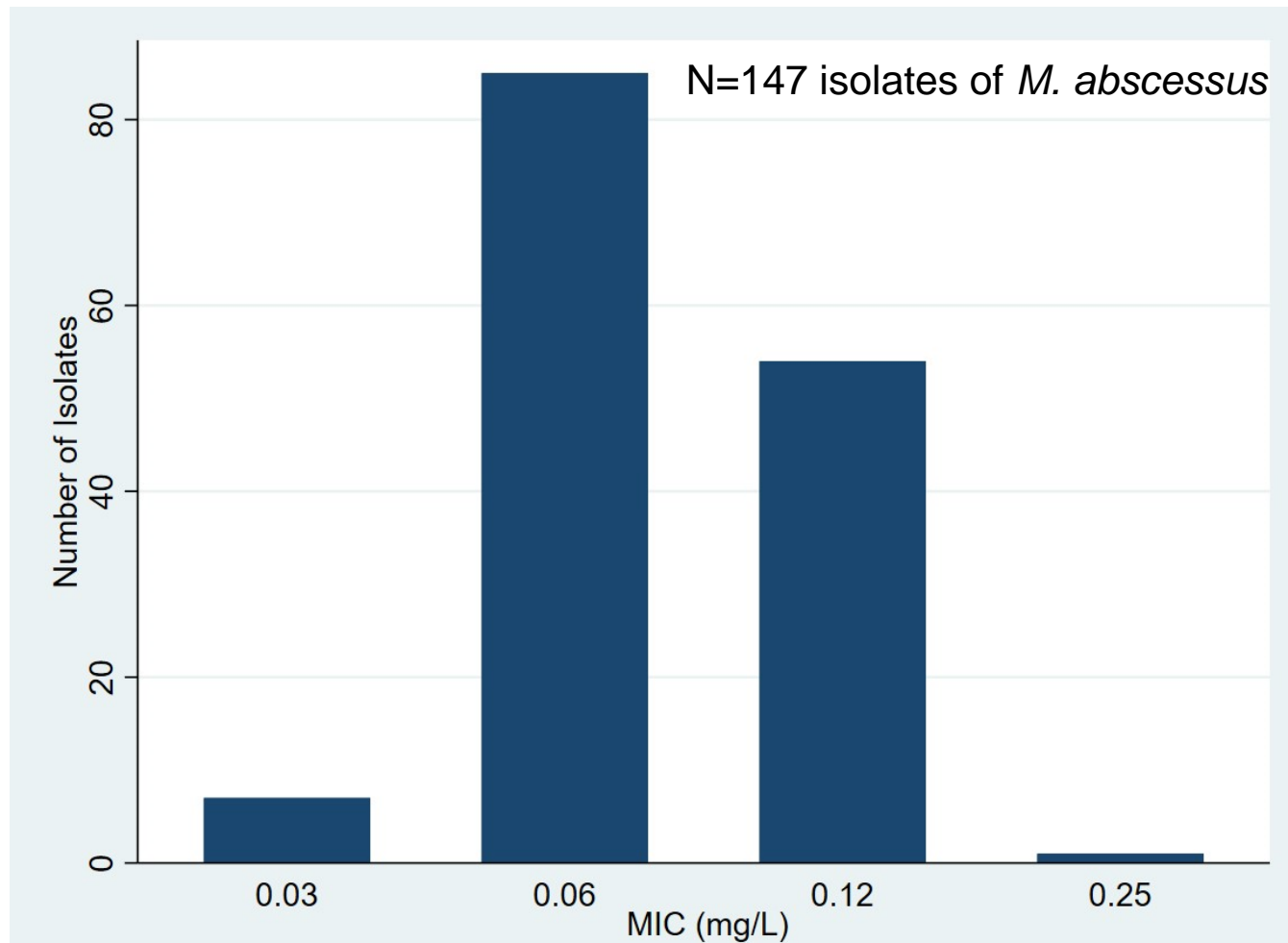
* P < 0.001

Epetraborole

- Epetraborole is a novel boron-containing molecule that inhibits protein synthesis in mycobacteria
- It is active against MAC and *M. abscessus*



Distribution of Epetraborole Minimal Inhibitory Concentrations Against *Mycobacterium abscessus*



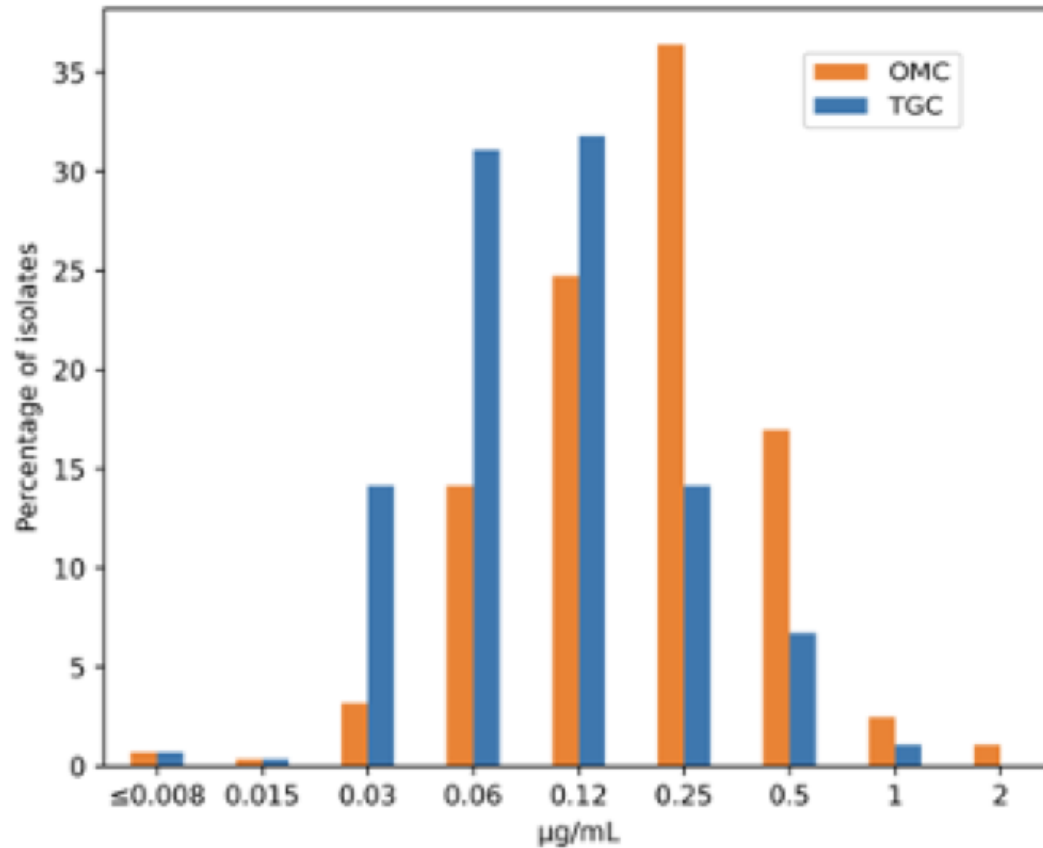
Epetraborole is very active against *M. abscessus*

Cycline Derivatives

- Tigecycline has good activity against *M. abscessus* but is associated with high rates of nausea/vomiting (30-50%)
- Omadacycline is a newer cycline that comes in both oral and IV preparations
 - approved by the US FDA for treatment of community-acquired bacterial pneumonia and skin infections in 2018
- Compared with tigecycline, nausea/vomiting are less frequent
 - nausea/vomiting occurred in 15%/8% of patients with the IV form and 25%/12% with oral dose

Omadacycline and Tigecycline MIC ($\mu\text{g}/\text{mL}$) Distributions for *M. abscessus* isolates"

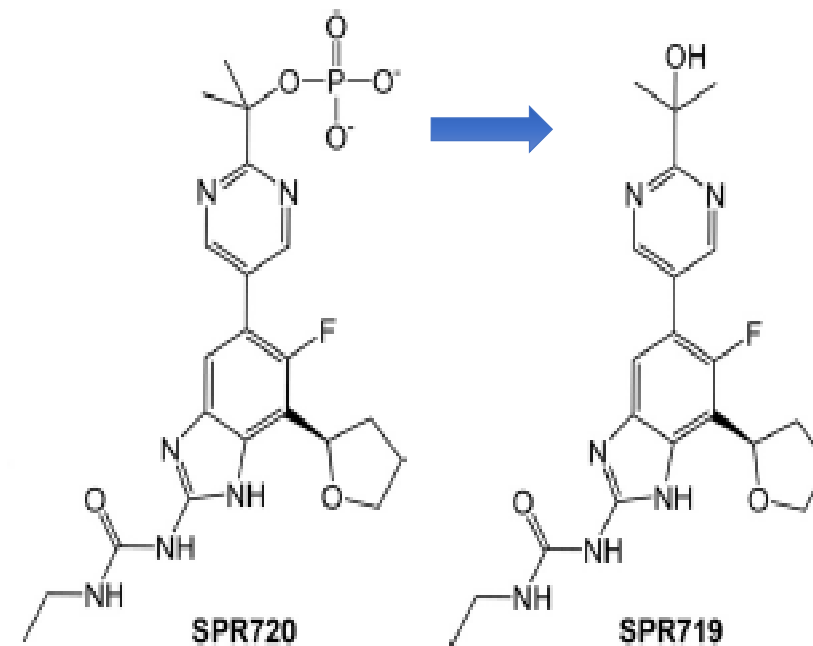
MAB (n=283)



Omadacycline is very active against *M. abscessus*

SPR720/SPR719

- SPR720 is a non-fluoroquinolone gyrase B inhibitor that is converted to SPR719 which is the active agent
- In vitro (laboratory), mouse model, and hollow fiber models have demonstrated activity against slowly growing NTM like MAC and *M. kansasii*
- The drug is formulated for oral administration



In vitro (laboratory) Activity of SPR719

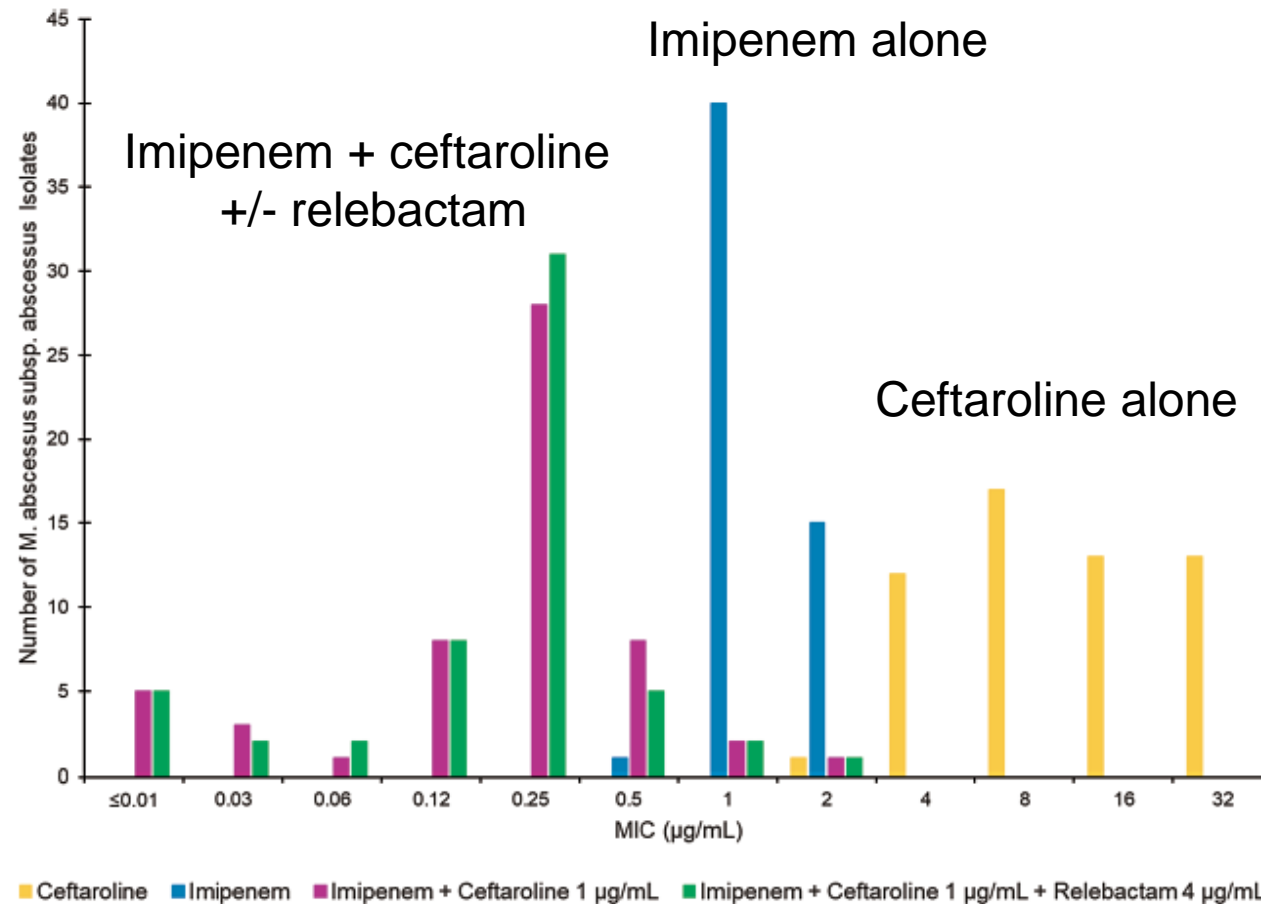
NTM species	N ¹	MIC range	MIC50	MIC90
MAC	73	0.06-4	1	2
<i>M. kansasii</i>	21	<0.03-0.25	<0.03	0.125
<i>M. simiae</i>	4	2-8	NA	NA
<i>M. malmoense</i>	3	0.06-0.5	NA	NA
<i>M. xenopi</i>	5	0.06-0.5	NA	NA

MAC- *M. avium* complex; NA – not applicable

Beta-lactam Antibiotics

- Beta-lactam antibiotics include penicillins, cephalosporins and carbapenems
- The class of antibiotics can be inhibited by enzymes in mycobacteria
- *Mycobacterium abscessus* produces a broad spectrum β -lactamase enzyme (Bla_{Mab})
- Inhibition of Bla_{Mab} by drugs (avibactam) improves the efficacy of imipenem against *M. abscessus in vitro*, in macrophages and zebrafish embryos
- Combinations of beta-lactams have shown synergistic activity against *M. abscessus* in vitro and in mouse models

In vitro Activity Imipenem, Ceftaroline and Combination



Two beta-lactam antibiotics show synergistic activity against *M. abscessus*

79 year old woman with remote history of pulmonary TB with right upper lobe ant. and post. segmentectomies. Now with *M. abscessus*

5/19 – started on treatment

Amikacin (IV) 500 mg MWF

Imipenem (IV) 500 mg twice daily

Clofazimine 100 mg daily

7/19 – changed to inhaled amikacin and clofazimine

10/19 – restarted on treatment

12/19 - Ceftaroline 600 mg twice daily was added to the regimen

6/20 - Gained 5 kg, normalized CRP and albumin and converted cultures to negative. Has remained negative for ~ 4 years



5/19



12/19



6/20

Summary of In Vitro Synergy Between β -lactams and β -lactamase Inhibitors

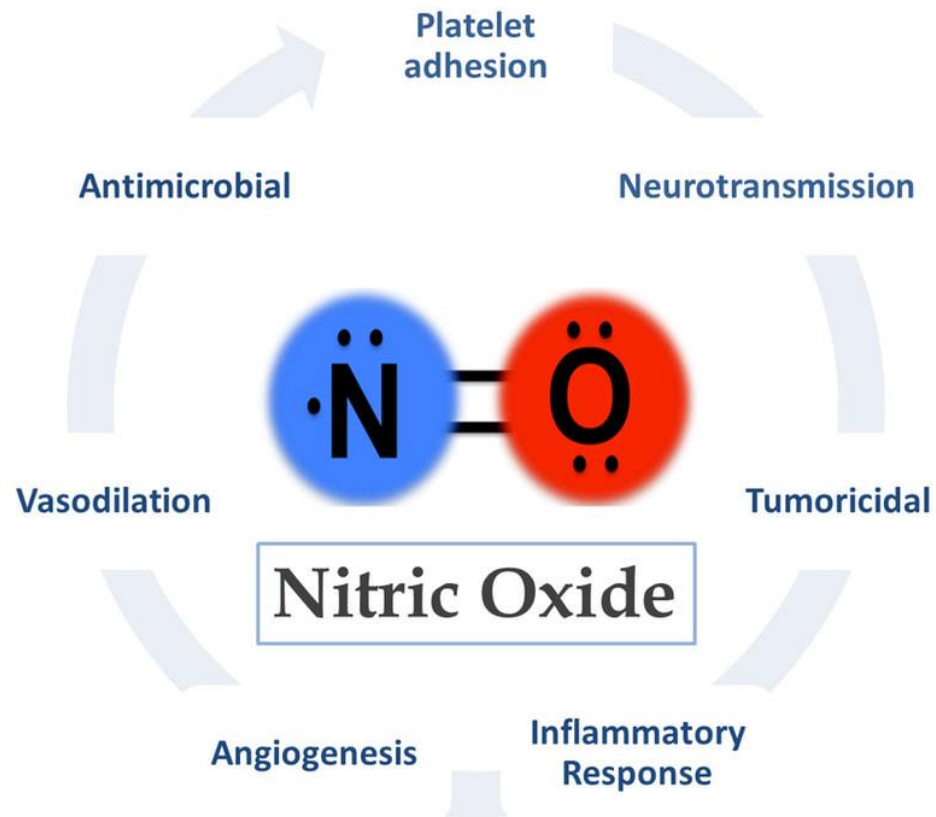
Imipenem	X							
Faropenem	✓	X						
Tebipenem			X					
Ceftazidim	✓			X				
Ceftaroline	✓			✓	X			
Cefuroxime	✓					X		
Cefoxitin	✓						X	
Amoxicillin								X
Avibactam			✓	✓	✓	✓		✓
Relebactam			✓			✓		✓
Nacubactam		✓	✓		✓			✓
Zidebactam			✓					
	Imipenem	Faropenem	Tebipenem	Ceftazidim	Ceftaroline	Cefuroxime	Cefoxitin	Amoxicillin

Green = synergy observed

Orange = additive

Color intensity represents the number of studies

Nitric Oxide (NO)



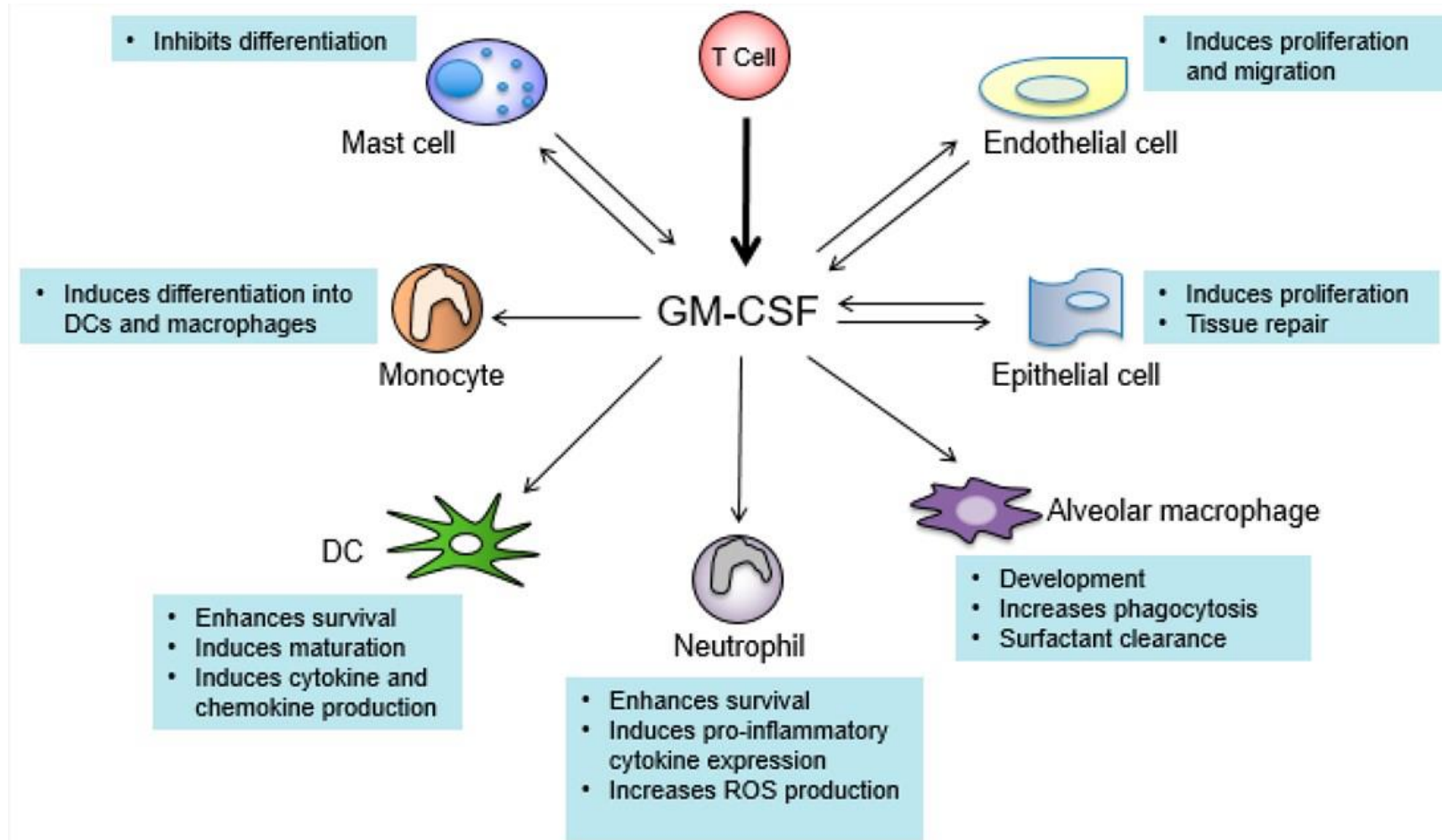
Nitric oxide (NO) is produced by macrophages and plays a key role in immunity against mycobacteria and other pathogens

NO also exist as a colorless gas which can be administered via inhalation

Inhaled NO in Adults with NTM Pulmonary Disease

- Patients with NTM lung disease who had persistently positive cultures
 - 10 patients (9 were on long term antimicrobial therapy)
- Treated with nitric oxide gas (gNO) for 50 minutes three times daily, five days a week for three weeks (total-15 treatment days)
- Results:
 - 4 (40%) patients had negative cultures after 3 weeks of therapy
 - Following treatment cessation, 3 became culture positive again
 - Treatment was well tolerated with no discontinuations

Granulocyte-macrophage colony-stimulating factor (GM-CSF)



Inhaled GM-CSF in Treatment Refractory NTM

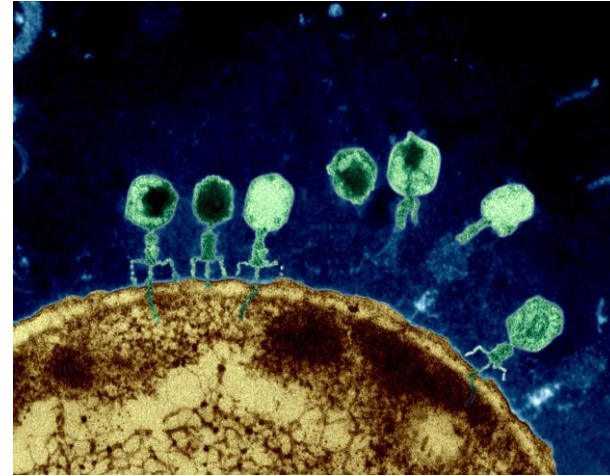
- 32 patients with chronic, culture positive NTM (24 MAC, 8 MAB)
 - 16 on guideline-based therapy
 - 16 not on guideline-based therapy
- Inhaled GM-CSF (molgramostim) 300 µg/day over 48 weeks
- Results:
 - 8 patients (25%) achieved culture conversion (durable in 4)
 - 7 with MAC, 1 with MAB
 - Among 24 with MAC, additional 4 converted smears to negative
 - Clinical endpoints did not improve
 - SAEs were generally due to pulmonary exacerbations or worsening NTM infection

Inhaled GM-CSF in Treatment Refractory NTM in People with Cystic Fibrosis

- 14 people with CF enrolled (28 screened)
 - Group 1 - 7 on guideline-based therapy for at least 9 months and still culture positive
 - Group 2 - 3 not on guideline-based therapy and still culture positive for at least 28 days
 - Group 3 – 4 culture positive but did not meet ATS criteria for disease
- Inhaled GM-CSF 300 µg/day over 48 weeks
- Results:
 - 7 patients (50.0%) achieved culture conversion (durable in 3)
 - Conversion varied among the 3 cohorts: Group 1 (43%) , Group 2 (33%), Group 3 (75%)
 - SAEs in 25%-33% and were generally due to pulmonary exacerbations

Bacteriophage

- Bacteriophage - Virus that infect bacteria
- Phages are the most abundant organisms in the biosphere - 10^{31} phage with entire population turning over every few days
- Genomically, small, old and diverse
- Anecdotal reports of successful treatment for resistant microbes



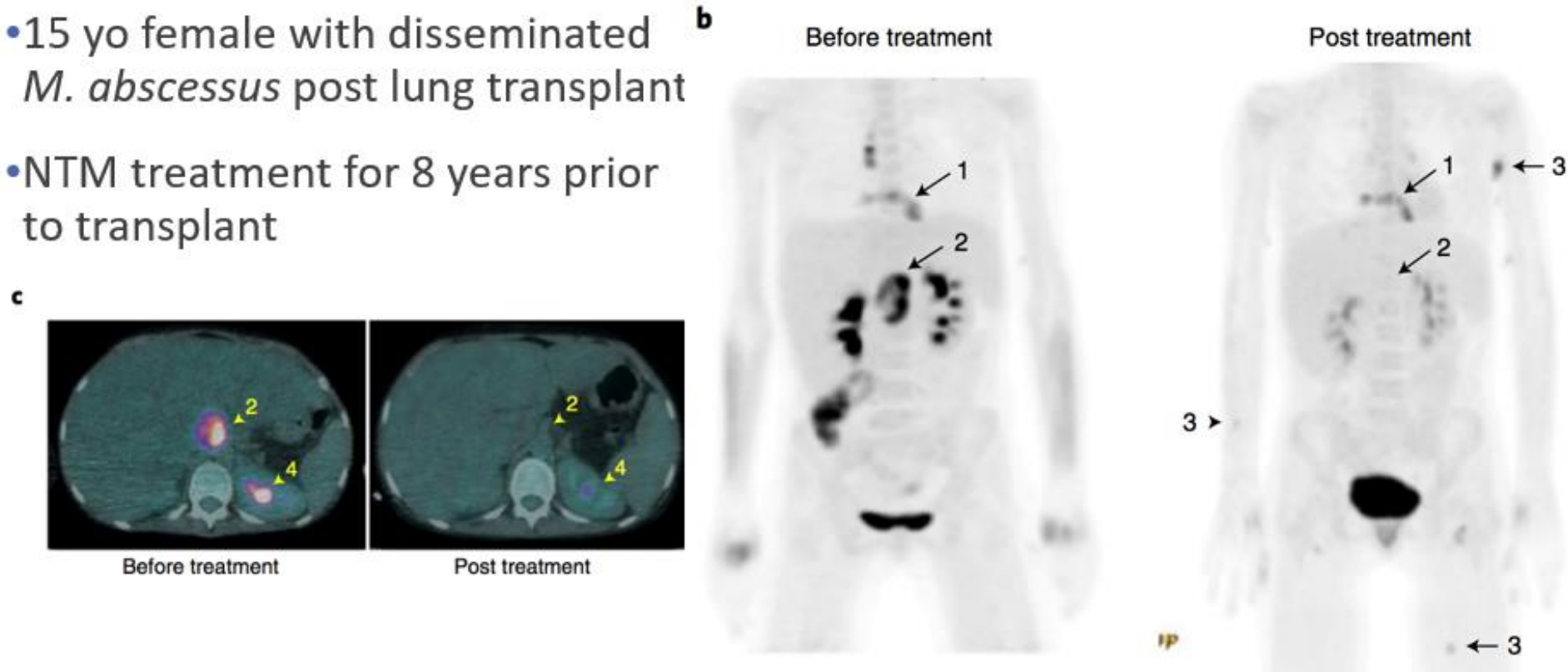
Antimicrobial Agents
and Chemotherapy®

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,^h Jeremy J. Barr,^g Sharon L. Reed,^{h,i} Forest Rohwer,^g Sean Benler,^g Anca M. Segall,^g Randy Taplitz,^g Davey M. Smith,^g Kim Kerr,^g Monika Kumaraswamy,^g Victor Nizet,^g Leo Lin,^g Melanie D. McCauley,^g Steffanie A. Strathdee,^g Constance A. Benson,^g Robert K. Pope,^g Brian M. Leroux,^g Andrew C. Picel,^g Alfred J. Mateczun,^g Katherine E. Cilia,^g James M. Regembal,^g Luis A. Estrella,^g David M. Wolfe,^g Matthew S. Henry,^g Javier Quinones,^g Scott Salka,^g Kimberly A. Bishop-Lilly,^g Ry Young,^g Theron Hamilton^g

Mycobacteriophage therapy

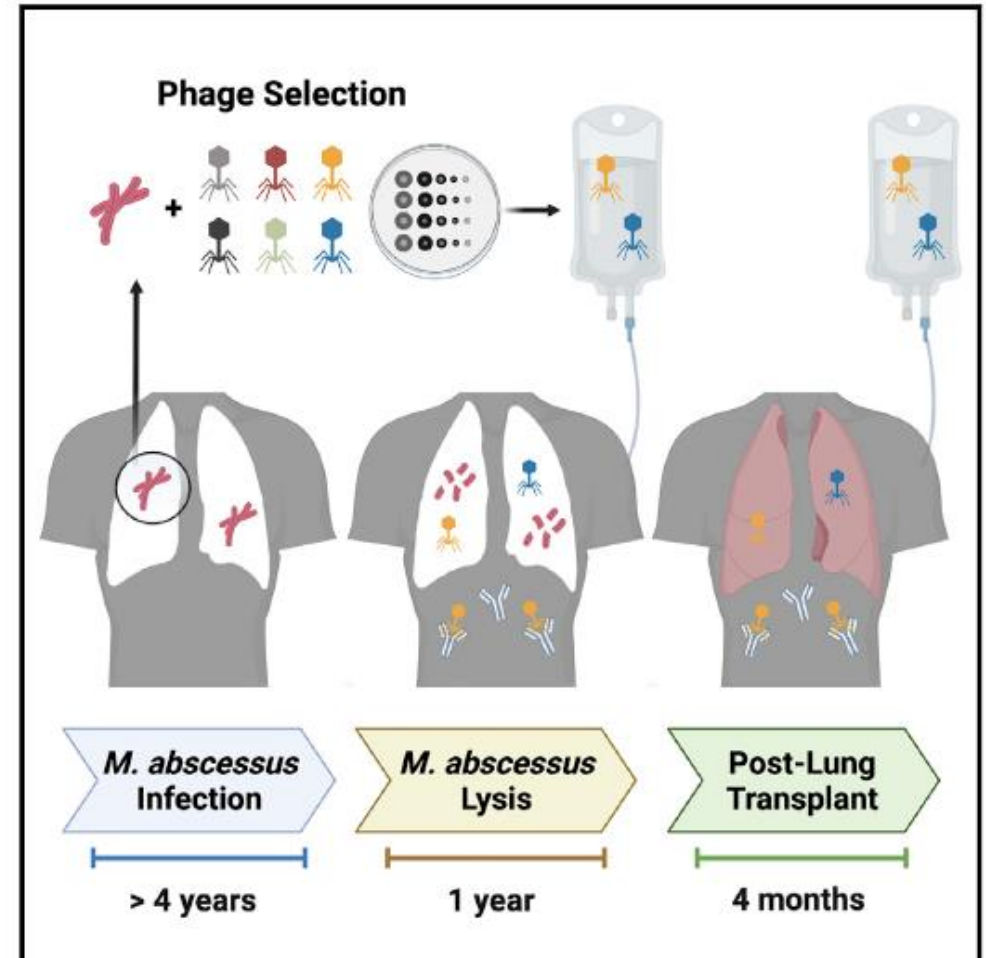
- 15 yo female with disseminated *M. abscessus* post lung transplant
- NTM treatment for 8 years prior to transplant



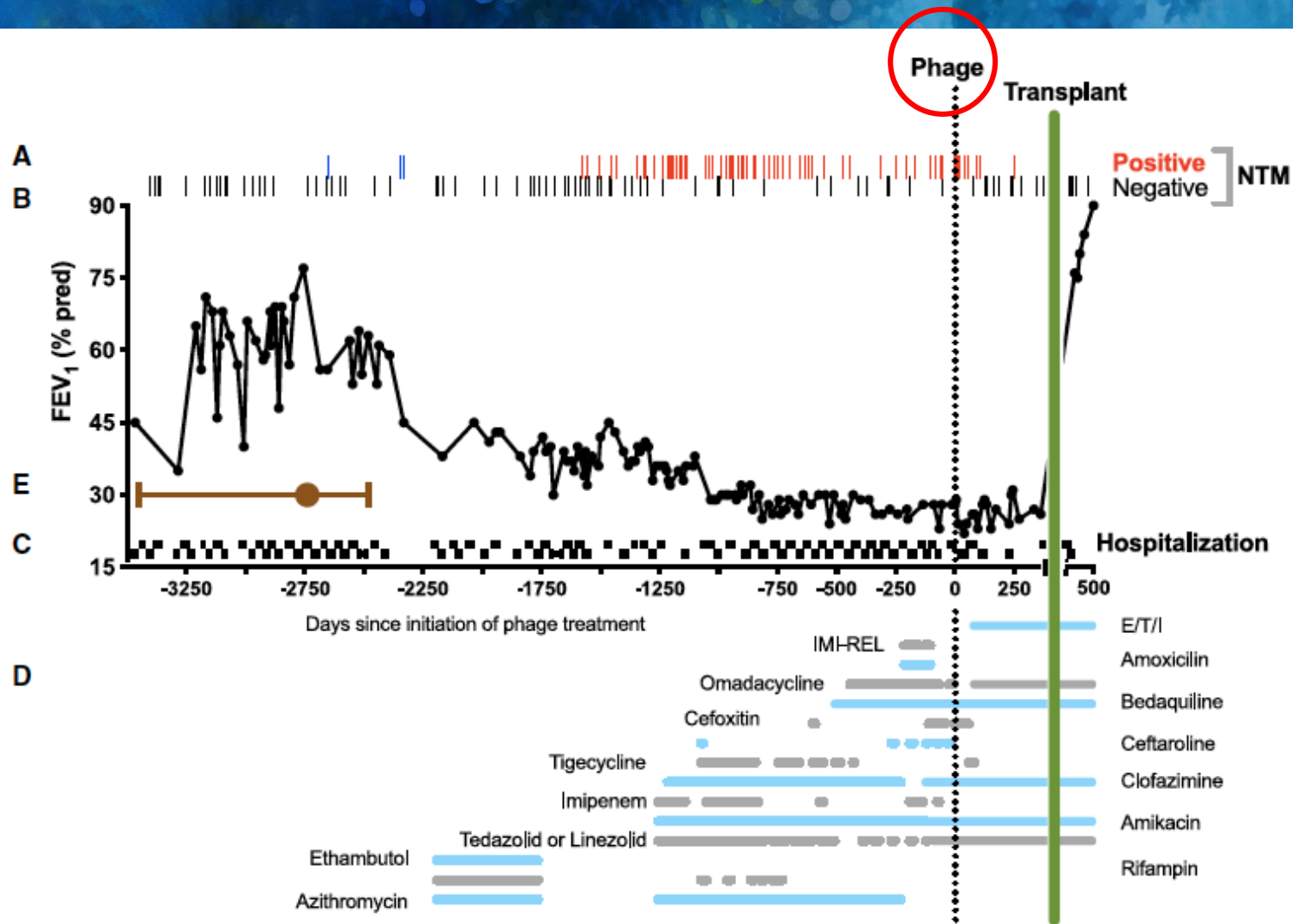
Whole-body (b) and cross-section (c) PET-CT scans 12 weeks before and 6 weeks post phage treatment

Mycobacteriophage Therapy for *M. abscessus*

- 26 year old man with cystic fibrosis
- Chronic MRSA and *Pseudomonas aeruginosa* infections
- Treated for MAC lung infection 5 years earlier
- *M. abscessus* subspecies *abscessus* isolated
- Treated with 4 to 5 drugs for over 4 years
- Remained culture positive with declining FEV1

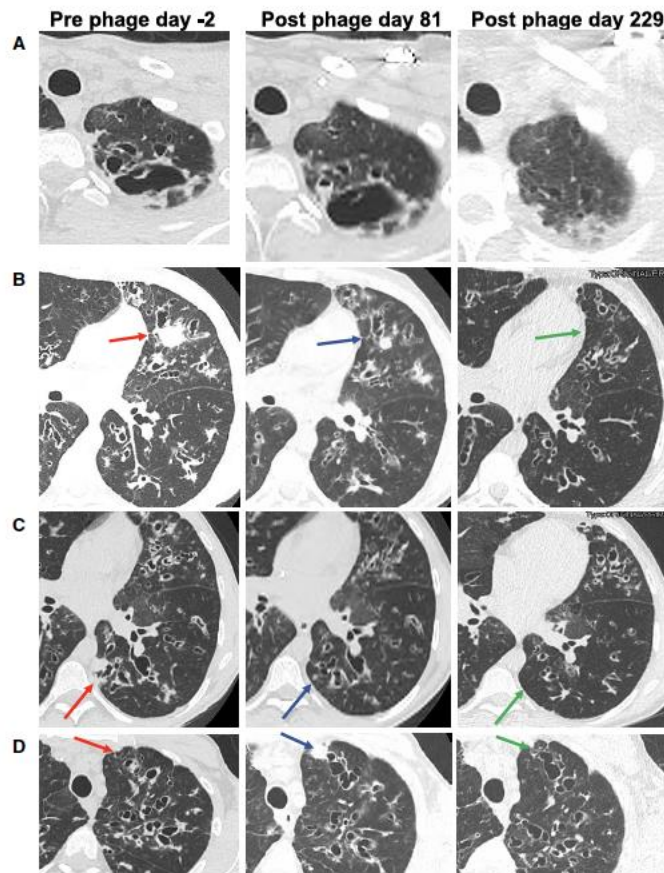


Phage Therapy for *M. abscessus*

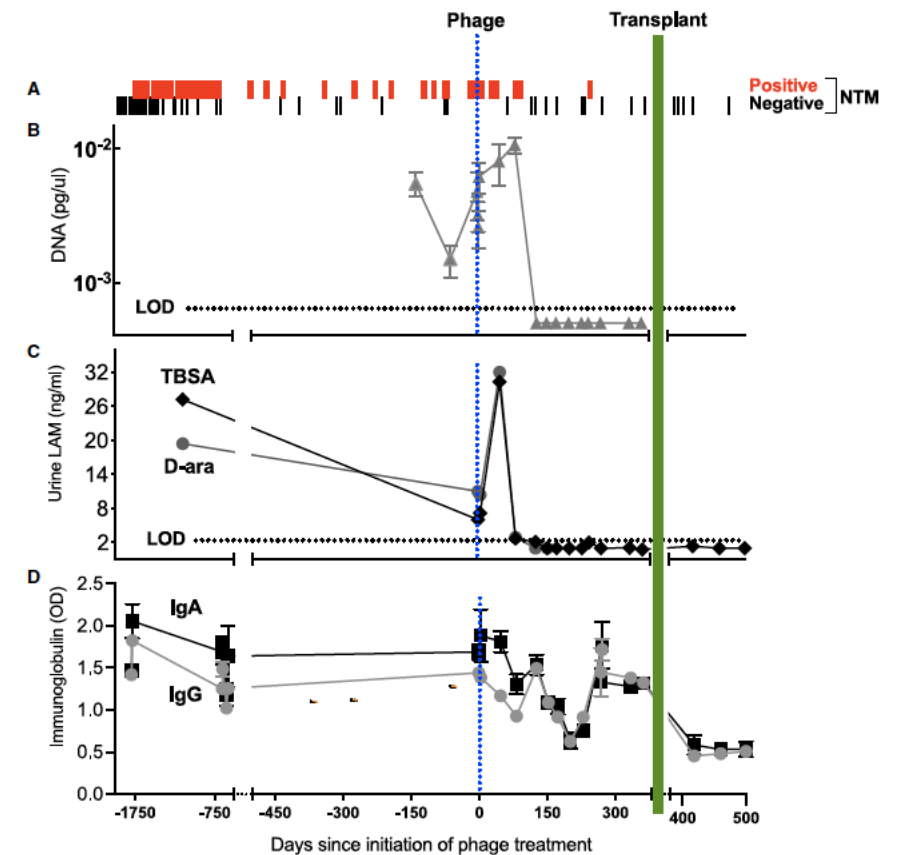


Treatment Outcomes with Phage

Radiographic Improvement



Biomarker Changes



Phage Therapy for Mycobacterial Infections in 20 Persons

- Isolates from 200 patients were screened for phage susceptibilities
 - One or more lytic phages were identified for 55 isolates
- Phage were administered intravenously, through inhalation or both in 20 patients with symptomatic mycobacterial infections
- Results:
 - No adverse reactions occurred
 - Favorable clinical or microbiologic responses were seen in 11 patients
 - Neutralizing antibody was identified in 8 patients possibly contributing to lack of treatment response
 - A single phage was administered in 11 patients and no phage resistance was identified

Phase 1 to 3 Clinical Trials in the US

Amikacin Liposome Inhalation Suspension - Study to Evaluate ALIS (Amikacin Liposome Inhalation Suspension) in Participants With Nontuberculous Mycobacterial Lung Infection Caused by *Mycobacterium avium* Complex (ENCORE) (Recruiting)

Epetraborole - A Phase 2/3, Randomized, Double-blind, Placebo-controlled, Multicenter, Prospective Study to Assess the Efficacy, Safety, and Pharmacokinetics of Orally Administered Epetraborole in Patients With Treatment-refractory *Mycobacterium avium* Complex Lung Disease (ON HOLD)

Omadacycline - A Ph. 2, Double-Blind, Randomized, Parallel-Group, Placebo-Controlled, Multi-Center Study to Evaluate the Efficacy, Safety, & Tolerability of Oral Omadacycline in Adults With NTM Pulmonary Disease Caused by *Mycobacterium abscessus* Complex (Recruiting)

SPR720 - A Randomized, Double-Blinded, Placebo-Controlled, Multicenter, Phase 2, Dose-Ranging Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of SPR720 as Compared With Placebo for the Treatment of Patients With Mycobacterium Avium Complex (MAC) Pulmonary Disease (Recruiting)

Gallium - A Phase 1b, Multi-center Study of Intravenous (IV) Gallium Nitrate in Patients With Cystic Fibrosis (CF) Who Are Colonized With **Nontuberculous Mycobacteria** (NTM) (The ABATE Study) (Recruiting)

ORC-13661 - Phase 2 Study of the Efficacy and Safety of ORC-13661 for the Prevention of Drug-Induced Hearing Loss in Patients Receiving Intravenous Amikacin for Treatment of **Non-Tuberculous Mycobacterium Disease** (Not yet recruiting)

2 vs 3 Drugs - Comparison of Two- Versus Three-antibiotic Therapy for Pulmonary *Mycobacterium avium* Complex Disease (Recruiting)

Clofazimine - Phase 2 Study of Clofazimine for the Treatment of Pulmonary *Mycobacterium avium* complex Disease (Recruiting)

World NTM Awareness Day!

