NTM Lecture Series for Providers

November 3-5, 2021
NATIONAL JEWISH HEALTH

Emerging Therapies in NTM-LD

Keira A. Cohen, MD
Johns Hopkins University School of Medicine

Disclosures

- Recipient of consulting fees from Insmed, HillRom and Microbion.

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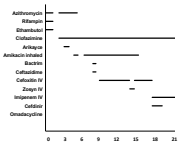
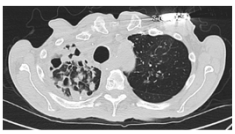
A Clinical Case

- 81 yo M with refractory macrolide-resistant *M. abscessus* and MAC lung disease in the setting of non-cystic fibrosis bronchiectasis
- Near continual multidrug treatment for NTM since 2015
- Drug resistance and drug intolerances, prior PEG tube, failure to thrive





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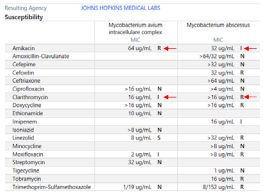
Case, continued

- Drug resistance and intolerances
  - Wasting syndrome - weight loss (>20lbs since 7/2018), fatigue, dyspnea, cough
  - Decline in FEV1
  - Hearing loss, disequilibrium, imbalance, nausea, anorexia, diarrhea, eosinophilia
  - Prolonged QTc



Resulting Agency: JOHNS HOPKINS MEDICAL LABS

Susceptibility

	Mycobacterium avium intracellulare complex MIC		Mycobacterium abscessus MIC	
Amikacin	64 ug/mL	R	32 ug/mL	I
Amoxicillin-Clavulanate			>64/32 ug/mL	N
Cefepime			>32 ug/mL	N
Cefoxitin			32 ug/mL	R
Ceftriaxone			>64 ug/mL	N
Ciprofloxacin	>16 ug/mL	N	>4 ug/mL	N
Clarithromycin	16 ug/mL	I	>16 ug/mL	R
Doxycycline	>16 ug/mL	N	>16 ug/mL	R
Ethionamide	10 ug/mL	N		
Imipenem			16 ug/mL	I
Isoniazid	>8 ug/mL	N		
Linezolid	8 ug/mL	S	>32 ug/mL	R
Minocycline			>8 ug/mL	N
Moxifloxacin	2 ug/mL	I	>8 ug/mL	R
Streptomycin	32 ug/mL	N		
Tigecycline			1 ug/mL	N
Tobramycin			16 ug/mL	R
Trimethoprim-Sulfamethoxazole	1/19 ug/mL	N	8/152 ug/mL	R

→ Referral to palliative care in 7/2019

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NTM Pipeline

- Omadacycline
- Recombinant IL-7 (CYT107)
- MAC 2v3
- Hypertonic saline
- (Inhaled GM-CSF)

Wu et al., Drug Disc Today, 2018

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Outline

- Antibiotics: new or repurposed
- Host directed therapies
- Novel antimicrobial strategies

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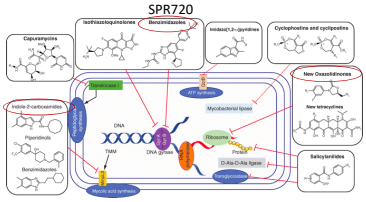
Abx in Preclinical Development

SPR720

MMPL-3 inhibitors



Omadacycline

Cantelli CR et al., Fut Med Chem, 2021

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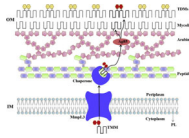
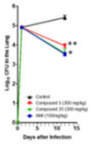
MmpL3 Transporter Inhibitors



- Mycobacterial membrane protein Large 3 (MmpL3) – inner membrane protein transports trehalose monomycolates (TMM)
- Essential to cell wall synthesis

SCID mouse *M. abscessus*



Inhibitor classes:

- Indole-2-carboxamide
- Piperidinol

Shao M et al., Eur J of Med Chem, 2020

Pandya AN, AAC, 2019

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Tetracyclines for NTM

- Tetracycline-modifying monooxygenase
  - MabTetX (MAB_1496c)[1] – induced by sublethal doses of tetracycline + doxycycline

  → Tigecycline not a substrate but lots of nausea/vomiting
- Omadacycline: LESS GI effects
- Multiple case series using omadacycline for *M. abscessus*[2,3]

[1]Rudra P, AAC, 2018

[2]Morrisette T et al., OFID, 2021

[3]Pearson JC et al., OFID, 2020

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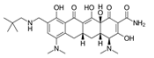
Omadacycline



Omadacycline

- Drug class: Tetracycline
- Approved indication: acute bacterial skin and skin structure infections and CAP
- Route: IV or PO
- Dosing: 300mg PO qday
- Adverse effects: GI side effects

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Omadacycline for *M. abscessus*

- Recently FDA granted omadacycline orphan drug designation for treatment against NTM
- Phase 2B clinical trial of safety and efficacy of omadacycline for *M. abscessus* lung disease
  - 75 adults with *M. abscessus*-LD
  - Randomized to omadacycline 300mg PO qday vs. placebo
  - Primary endpoints: improvements in symptoms, safety and tolerability at 12 weeks
- RCT status: recruiting

RCT: NCT04922554

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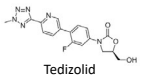
Tedizolid



Tedizolid

- Drug class: Oxazolidinone
- Approved indication: acute bacterial skin and skin structure infections
- Route: IV or PO
- Dosing: 200mg PO daily
- Adverse effects: Improved hematologic safety profile; peripheral and optic neuropathy
- In vitro evidence for use in NTM[1-4]

[1]Brown-Elliott BA et al., JCM, 2017
[2]Tang YW et al., Frontiers in Micro, 2018
[3]Ruth M et al., JAC, 2019
[4]Deshpande D, JAC, 2017

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Tedizolid vs. Linezolid for NTM

- Retrospective cohort of 24 solid organ transplant recipients with NTM disease[1]
  - 15 tedizolid; median 48 days (IQR 25-211)
  - 9 linezolid; median 24 days (IQR 19-79)
- Primary outcome: change in blood counts; not sig different
- Subgroup efficacy analysis
  - microbiologic or clinical cure: Tedizolid 7/12 vs. Linezolid 2/3.
- Dose reduction in all linezolid patients; only 1 tedizolid
- Other case reports of efficacious tedizolid use for NTM[2,3]

[1]Poon et al, OFID, 2021

[2]Yuste J et al, JAC, 2017
[3]Shaw TD, J Clin TB Other Mycobact Dis, 2021

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Dual β-lactam Therapy

- IV β-lactams imipenem and cefoxitin are part of GBT for *M. abscessus*
- Is one β-lactam enough? Are two redundant?
- More is more?

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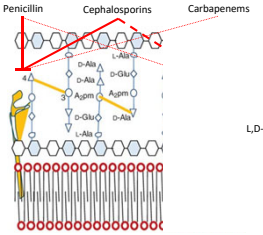
β-lactam Targets in Mycobacteria

Gyanu Lamichhane



D,D-transpeptidases (PBPs)

L,D-transpeptidases

β-lactam targets are NON-REDUDANT in mycobacteria

Gupta R, Nature Med, 2010
Kumar P, AAC, 2017

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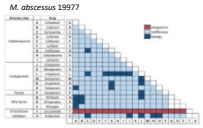
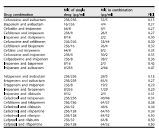
Dual β-lactams: in vitro synergy

M. abscessus 19977





Synergy[1]
- Imipenem + cefuroxime
- Imipenem + cefdinir
- Imipenem + cefpodoxime
- Imipenem + cefoxitin
- Imipenem + ertapenem

→ Synergistic combinations of β-lactams also reduced spontaneous mutation rate

Other in vitro synergy with dual β-lactams:
- Amoxicillin + Imipenem-Relebactam[2]
- Ceftaroline-Imipenem +/- Relebactam or Avibactam[3]

[2]Lopeman RC et al., Scientific Reports, 2020
[3]Dousa KM et al., AAC, 2020
[1]Story-Roller E et al., AAC, 2019

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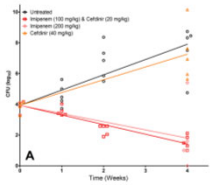
Dual β-lactams: in vivo



- Steroid-treated mouse model
- Aerosolized *M. abscessus* 19977
- Half-dosed β-lactams in vivo

Clinical efficacy of dual β-lactams in humans
→ Not published

Story-Roller E et al., AAC, 2019

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Amikacin Liposome Inhalation Solution (ALIS)

- ALIS FDA approved in 2018 for refractory MAC lung disease
- Phase 3 clinical trials ongoing to investigate efficacy and safety of ALIS non-refractory, non-cavitary MAC lung disease
  - ARISE (NCT04677543) – validation of PROs
  - ENCORE (NCT04677569) – efficacy and safety
- Status: recruiting

NCT04677543
NCT04677569

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MAC2v3

- Role of rifampin in standard MAC therapy has not been rigorously studied
  - Rifampin: common cause of adverse events
- Phase 2/3 RCT of 3x/week azithro + ethambutol (2 drugs) vs. azithro + ethambutol + rifampin (3 drugs) for non-cavitary MAC-LD
- Primary outcome: culture conversion by month 12; therapy completion by month 12
- Status: recruiting

NCT03672630 (PI: Winthrop)

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RHB-204: ClearR-MAC

- Clarithromycin (158.3mg)/rifabutin (40mg)/clofazimine (13.3mg) (RHB-204)
- Phase 3 double blind, placebo controlled RCT of novel regimen for MAC lung disease
- Primary outcome: sputum cx conversion at month 6.
- FDA – Fast Track designation
- Status: recruiting

NCT04616924

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Conclusions: novel/repurposed abx

- Preclinical development
  - New targets (MmpL3 inhibitors)
- Emerging antibacterial strategies
  - *M. abscessus*: dual β-lactams, omadacycline
  - MAC: oxazolidinones, extended indications for ALIS
- Ongoing clinical trials of new drugs/new regimens:
  - *M. absessus*: omadacycline
  - MAC: ALIS as first-line therapy, ClearR-MAC

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Host Directed Therapies

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MAC-HS: Hypertonic Saline

- Airway clearance: reduces bacterial burden in setting of structural lung disease
- Open-label, RCT of 7% HTS in MAC-LD patients.
- 1:1 randomization to standard MAC drugs vs. 7% HTS BID x 12 weeks.
- Primary outcome: culture conversion at 12 weeks
- RCT status: recruiting

NCT04921943 (OHSU)

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Inhaled GM-CSF

- Granuloycte-Macrophage colony stimulating factor (GM-CSF)
  - Glycoprotein secreted by macrophages, T-cells, mast cells, NK cells, endothelial cells and fibroblasts
  - Activates JAK-STAT, MAPK, PI3K
- In vivo efficacy demonstrated in mice[1]
- Clinical trials:
  - OPTMIMA: open-label multicentered pilot of rhGM-CSF for persistent pulmonary NTM in Australia[2]. Status: completed.
  - ENCORE: open-label multicentered pilot of rhGM-CSF in CF adults with chronic NTM[3]. Status: terminated early.

[1]Bermudez LE, et al., JID, 1994

[2]NCT03421743
[3]NCT03597347

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Recombinant IL-7 (IMPULSE-7)

- IL-7
  - Central to T-cell production, maturation and survival
  - Induces anti-MAC activity in human MDMs[1]
  - Phase 2a studies ongoing for sepsis, COVID-19
- Single center, phase II, single-blinded trial
- Adults with refractory MAC-LD, randomized to two doses of rIL-17 (CYT107) for two 4-week periods
- Immunotherapeutic response
- RCT status: recruiting

[1]Tantawichien T et al., JID, 1996
[2]NCT04154826

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Novel Antibacterial Strategies

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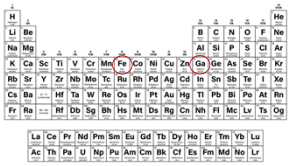
Gallium

- Disrupts iron-dependent processes
- Direct antibacterial effects for pseudomonas
- Prior phase 2 clinical trial of CF adults with pseudomonas IV gallium nitrate vs. placebo (IGNITE)



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IV Gallium: ABATE Study

- Phase 1b multicentered study of CF patients colonized with MAC and/or *M. abscessus*
- Gallium nitrate – continuous IV infusion of 200mg/m2/day Gallium nitrate x 5 days for two cycles
- Primary endpoints: safety and efficacy
- RCT status: recruiting

NCT04294043 (CFF, PI: Goss)

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Nitric Oxide

$$\text{L-arginine} + \text{NADPH} + O_2 \xrightarrow{\text{NO synthase}} \text{L-citrulline} + H_2O + \text{NO}$$

Nitric oxide:
- Free radical – short half-life
- Endogenous NO is a gaseous signaling molecule, can freely diffuse across membranes
- Modulates immune response → activates neutrophils, macrophages and epithelial cells
- Antimicrobial activity against a wide range of pathogens

Bodgan C, Nat Immunol, 2001
Fang FC, Nat Rev Microbiol, 2004

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iNO for NTM

- Multiple case reports[1,2] and a 9-person clinical trial[3] of iNO for refractory *M. abscessus* in CF
- Safety established
- Improvements in QOL, lung function and 6MWD
- Not powered for microbiologic efficacy

[1]Yaacoby-Bianu K et al., Ped Infect Dis J, 2017
[2]Bogdanovski K et al., Access microbiology, 2020
[3]Bentur L, J Cyst Fibros, 2020

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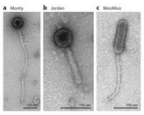
A Brief Primer on Phage

- Estimated ~10^{31} phage particles in the biosphere
- Phage: viruses that infect bacteria
  - Bacteria-specific, genus, species and strain-specificity
  - Many types – mostly dsDNA tailed phages
- Term "bacteriophage" coined in 1916
  - "bacteria" + "phagein" = bacteria eater



Dr. Felix d'Herelle
1873 - 1949

Hatfull GH, Ann Rev Virol, 2020

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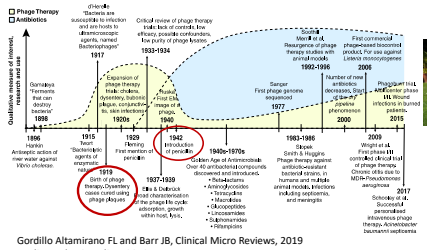
Timeline of Phage and Antibiotics



2019
Successful use of IV phage for *M. abscessus* by Hatfull and colleagues

Gordillo Altamirano FL and Barr JB, Clinical Micro Reviews, 2019
Devlin H, The Guardian, 2019

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First Use of Mycobacteriophage

- 15 y/o F with CF (F508del homozygous, FEV1 29% pred) c/b pancreatic insufficiency, IDDM, CFLD, s/p Nissen and gastrostomy.
- Chronic infection with pseudomonas and *M. abscessus massiliense* (rx x 8 yrs pre-transplant)
- On CFTR modulator (lumacaftor/ivacaftor) x 6 months
- Bilateral lung transplant – uncomplicated
- Post-transplant course – pulmonary consolidations, wound issues, adenopathy
  → *M. abscessus massiliense* isolated 1 mos post txp
  → Diagnosed with disseminated *M. abscessus*

Dedrick RM, Hatfull GH et al., Nature Med, 2019

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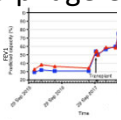
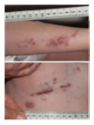
Pre-phage Clinical Assessments





Dedrick RM, Hatfull GH et al., Nature Med, 2019

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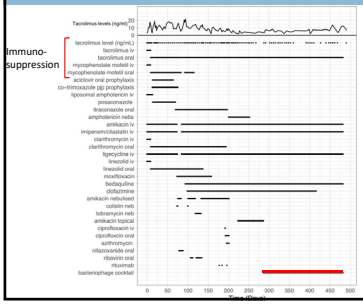

Therapeutic use of phage:

- Triple-phage cocktail
  - Muddy
  - BPsΔ*33*HTH_HRM10
  - ZoeJΔ*45*
- Topical test dose to sternal wound
- Phage IV 10^9 plaque forming units (PFU) q12 hrs

Dedrick RM, Hatfull GH et al., Nature Med, 2019

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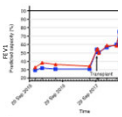
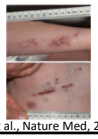
Pre- and Post-phage Clinical Assessment



12 weeks pre-Rx



12 weeks pre-Rx

Dedrick RM, Hatfull GH et al., Nature Med, 2019

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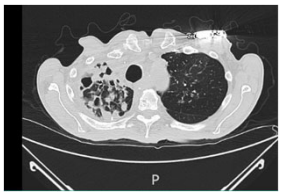
Back to the Initial Clinical Case

81 yo M with refractory *M. abscessus* and MAC lung disease in the setting of non-CF bronchiectasis, referred to palliative care.



Resulting Agency: JOHNS HOPKINS MEDICAL LABS

Susceptibility

	Mycobacterium avium intracellulare complex MIC		Mycobacterium abscessus MIC	
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Amoxicillin-Clavulanate			>64/32 ug/mL	N
Cefepime			>32 ug/mL	N
Cefoxitin			32 ug/mL	R
Ceftriaxone			>64 ug/mL	N
Ciprofloxacin	>16 ug/mL	N	>4 ug/mL	N
Clarithromycin	16 ug/mL	I	>16 ug/mL	R
Doxycycline	>16 ug/mL	N	>16 ug/mL	R
Ethionamide	10 ug/mL	N		
Imipenem			16 ug/mL	I
Isoniazid	>8 ug/mL	N		
Linezolid	8 ug/mL	S	>32 ug/mL	R
Minocycline			>8 ug/mL	N
Moxifloxacin	2 ug/mL	I	>8 ug/mL	R
Streptomycin	32 ug/mL	N		
Tigecycline			1 ug/mL	N
Tobramycin			16 ug/mL	R
Trimethoprim-Sulfamethoxazole	1/19 ug/mL	N	8/152 ug/mL	R

→ What about phage therapy in this patient?

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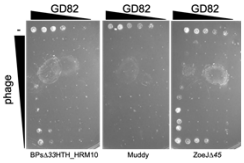
Phage Screening and Confirmation

→ Identified multiple phages with efficacy against our patient's *M. abscessus* (GD82)

→ Same three phages used in Dedrick et al.

→ No phage matches for MAC



→ FDA SPIND for the compassionate use of mycobacteriophage cocktail for refractory *M. abscessus* lung disease.

Dedrick, Hatfull & Cohen et al., Nat Med, 2021

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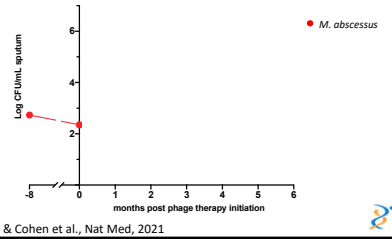
Mycobacterial Response



Dedrick, Hatfull & Cohen et al., Nat Med, 2021

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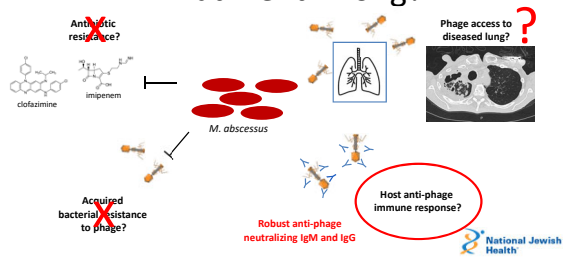
What went wrong?



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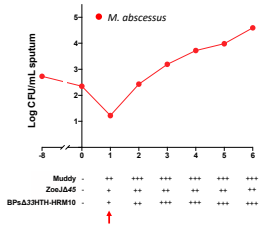
Phage Neutralization Correlates with Rx Failure



- Stark contrast to prior case
  - No serum anti-phage response seen
  - Identical phage cocktail, route and dose
- Immune status of the host:
  1st: post-lung transplant
  2nd: immunocompetent

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Conclusions: Phage Therapy for NTM

- Phage hold potential for clinical use against NTM
  - No serious adverse events
  - Transient mycobacterial efficacy
  - Treatment failure was associated with potent antibody-mediated phage neutralization
- Future lessons for phage therapy
  - Optimal host selection, dose, and route of administration still need to be determined
  - Divergent treatment strategies for immunocompetent vs immunosuppressed hosts?
  - Serial administration rather than "cocktail" approach may extend efficacy

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Conclusions

- Novel treatment paradigms and therapeutic options for NTM are greatly needed
- Modest pipeline of new/repurposed antibiotics and regimens
- Current clinical investigation includes:
  - *M. abscessus*: omadacycline
  - MAC: ALIS first-line therapy, MAC2v3, CleaR-MAC
  - Non-antibiotics: gallium, mycobacteriophage
  - Host-directed therapies: rIL7, hypertonic saline

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Thank you: it takes a village

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Andrew Wu
Aaron Ong

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Nikki Parrish, PhD

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