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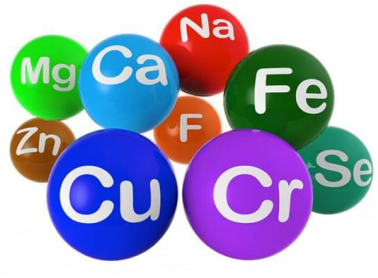

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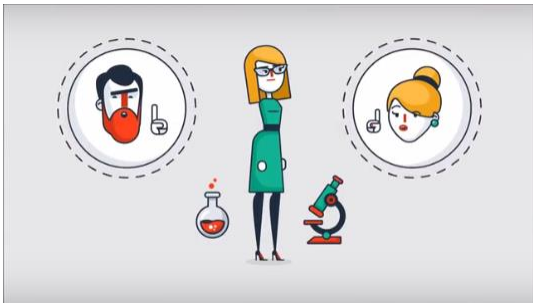
An individual development planning tool for you!



- Know your career options
- Develop strategies to strengthen your skills
- Map a plan to achieve your career goals

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Lauren Celano, Co-founder and CEO of Propel Careers
Chris McCarthy, Senior Communications Officer, American Chemical Society

Thursday, July 13, 2017

Ice Cream Chemistry: *The Science of Flavor*

Maya Warren, University of Wisconsin-Madison
Bill Courtney, Washington University

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AAPS/DDDI 2nd Regional Meeting

Evolving Strategies for Drug Candidates Optimization in a Changing Pharmaceutical Landscape

Friday August 4, 2017 (8:00 a.m. – 5:00 p.m.)
University of Maryland School of Pharmacy, Baltimore, MD

The DDDI regional meeting is a focused forum for drug discovery and preclinical scientists in the pharmaceutical field to discuss the most relevant topics in drug design and discovery and an excellent networking opportunity for attendees.

Covered Topics:
- Formulation Support in Drug Discovery
- Early Phase Drug Development and Population PK
- Transforming skillsets in early development to meet the changing NCE/NBE landscape in discovery space
- Academic collaboration and preparing for the discovery support role in industry

Who Should Attend?
Pharmaceutical professionals with expertise and interest in different areas of drug discovery, particularly:
- Medicinal Chemistry
- Discovery Biology
- Pharmacology
- Pharmacokinetics
- Pharmacodynamics and Drug Metabolism
- Pharmaceutical Sciences
- Toxicology

Keynote Speakers:
- **Mike Hageman, PhD** (Former Exec. Director, Bristol-Myers Squibb)
- **Capt. Edward D. Bashaw, PharmD** (Director, U.S. Food and Drug Administration)
- **Justin Pennington, PhD** (Director, Merck & Co.)

Featured Speakers:
- **Vladimir Papov, PhD** (Boehringer Ingelheim)
- **Jonathan Philips, PhD** (Toxicology Fellow, Vertex Pharmaceuticals)
- **David Rodrigues, PhD** (Research Fellow, Pfizer Inc.)
- **Joseph Fortunak, PhD** (Associate Professor, Howard University)
- **Steven Fletcher, PhD** (Associate Professor, University of Maryland School of Pharmacy)

Contact: Sunny Bhardwaj
Email: sunny.bhardwaj2@merck.com
Website: http://www.aaps.org/DDDIRM17/

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Catch up on Last Year's Design and Delivery Symposium

January 28	The Importance of Drug-Target Kinetics in Drug Design	Robert Copeland - Epizyme, Inc Dan Erlanson - Carmot Therapeutics
February 25	Long-Acting Injectable Medications: Strategies and Mechanistic Considerations	Jules Remenar - Alkermes Annette Bak - Merck
March 31	Modified Release Formulations for Solubility Starved Compounds	Mengwei Hu - Merck John Morrison - BMS
April 28	*The Medicinal Chemist of Tomorrow (Special Topic)*	Joel Barrish - Achillion Ravi Nargund - Merck Molly Schmid - Tech Coast Angels
May 19	Design of Deliverable Macrocycles	Scott Lokey - UC Santa Cruz Nicholas Meanwell - BMS
June 23	Dreaming Big and Thinking Small: Applying Medicinal Chemistry Strategy to Antibody-Drug-Conjugates	L. Nathan Tumey - Pfizer Peter Senter - Seattle Genetics
July 28	Nucleic Acids Therapeutics: Making Sense of Antisense Oligonucleotides	Punit Seth - Ionis Richard Olson - BMS
August 18	Crystallography as a Drug Design and Delivery Tool (Special Topic)	Robert Wenslow - Crystal Pharmatech Vincent Stoll - Abbvie Andrew Brunskill - Merck
September 29	Dealing with Reactive Drug Metabolites in Drug Discovery: Can We Predict Toxicities of Drug Candidates that form Reactive Metabolites?	Deepak Dalvie - Pfizer Frederick Peter Guengerich - Vanderbilt University
October 27	Rational Design of Small Molecules Targeting RNA	Matt Disney - Scripps Rl Florida Amanda Garner - University of Michigan
November 10	Cell Penetrating Peptides to Improve Cellular Drug Uptake	Dehua Pei - The Ohio State University Scott Hart - Bristol-Myers Squibb

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2017 Drug Design and Delivery Symposium

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"Viral Hepatitis: The Search for a Cure"
Michael Sofia of Arbutus Biopharma

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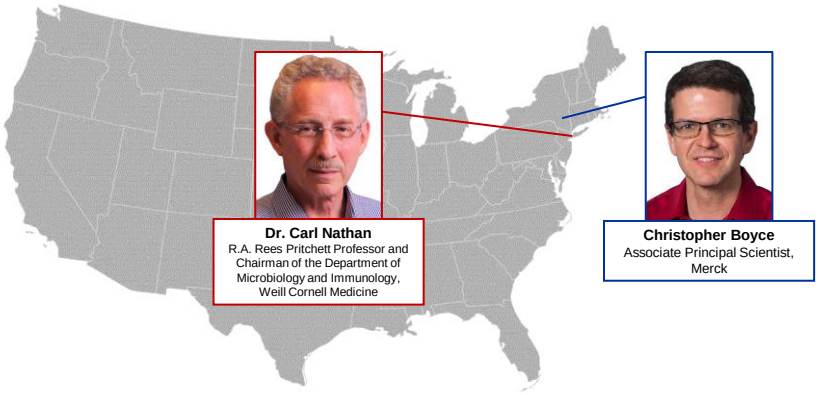
2017 Drug Design and Delivery Symposium

"Tuberculosis: An Introduction for Medicinal Chemists"



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Weill Cornell Medicine

Tuberculosis: An Introduction for Medicinal Chemists

Carl Nathan, MD
Weill Cornell Medicine
June 29, 2017

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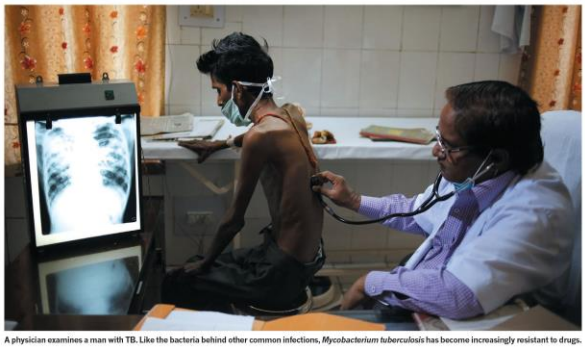


Nature 545: 23, 2017

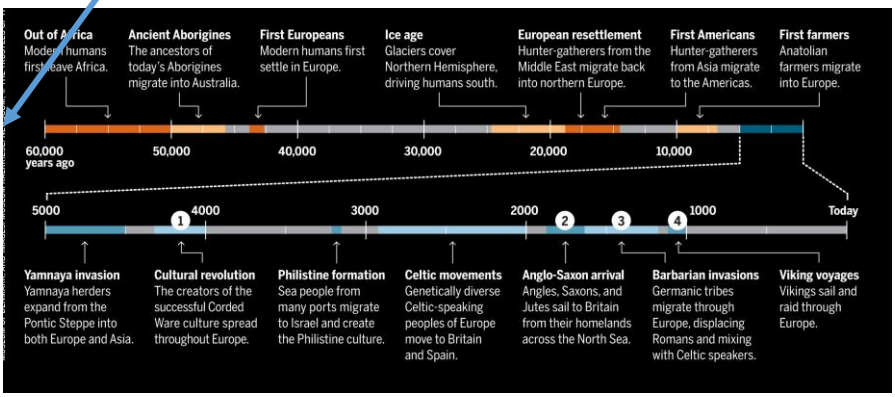
A physician examines a man with TB. Like the bacteria behind other common infections, *Mycobacterium tuberculosis* has become increasingly resistant to drugs.

Topics

- TB biology: framing the problem
- The TB pharmacopoeia: an innovation gap
- TB drug discovery: an innovation engine
- TB drug development: special challenges
- Looking ahead: new drugs, new targets, new hope

Co-evolution of *Mycobacterium tuberculosis* with humans, its only naturally-transmitting host

~70,000 years ago: parasitism of humans with M. tuberculosis



Adapted from Gibbons, A. Science 356: 678, 2017

Det Syke Barn, Edvard Munch, 1885
Nasjonalmuseet for kunst, Oslo

Nathan, Cell Host and Microbe 5: 220, 2009

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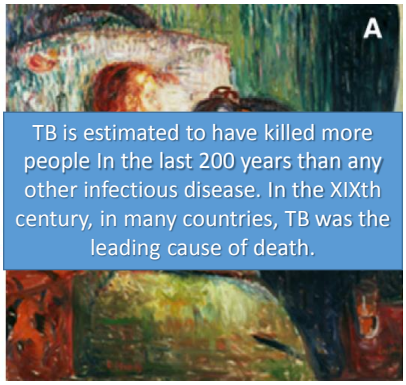

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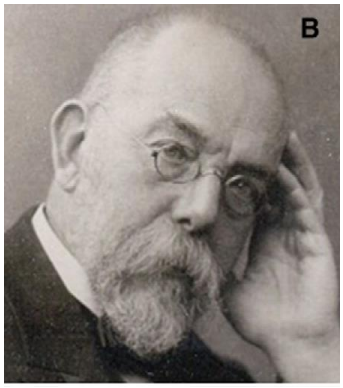

Robert Koch announced the cause of tuberculosis in 1882; Nobel prize, 1905

Nathan, Cell Host and Microbe 5: 220, 2009

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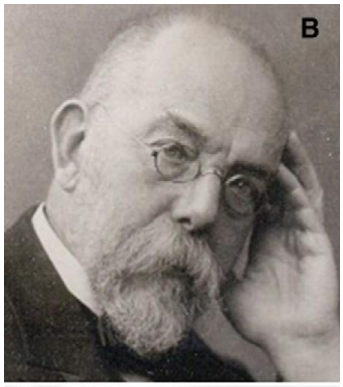

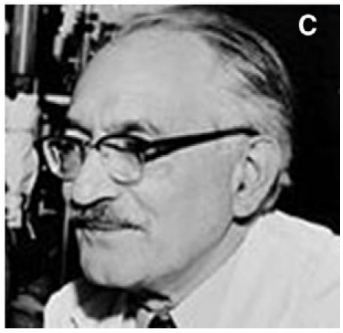

Selman Waksman co-discovered streptomycin, the first effective anti-TB drug; Nobel prize, 1952; announced “the complete eradication of this disease is in sight”, 1964

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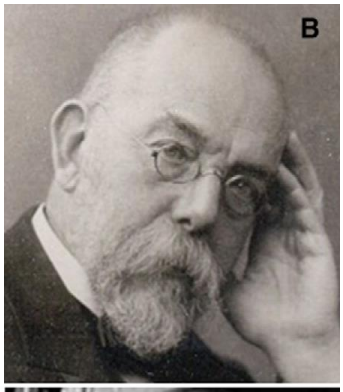

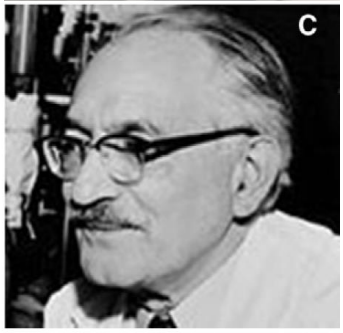

- **1946:** First randomized, controlled clinical trial in the practice of medicine: failure of monotherapy
- **1950:** Introduction of combination chemotherapy to the practice of medicine

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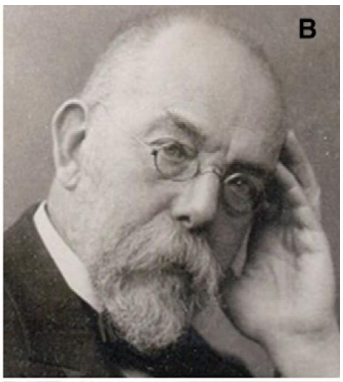
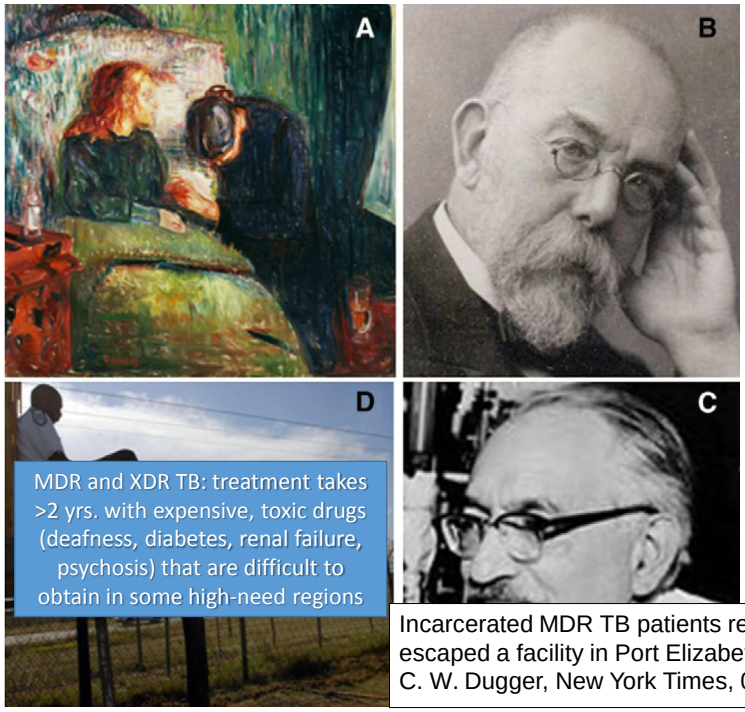


Incarcerated MDR TB patients repeatedly escaped a facility in Port Elizabeth, SA.
C. W. Dugger, New York Times, 03-25-08



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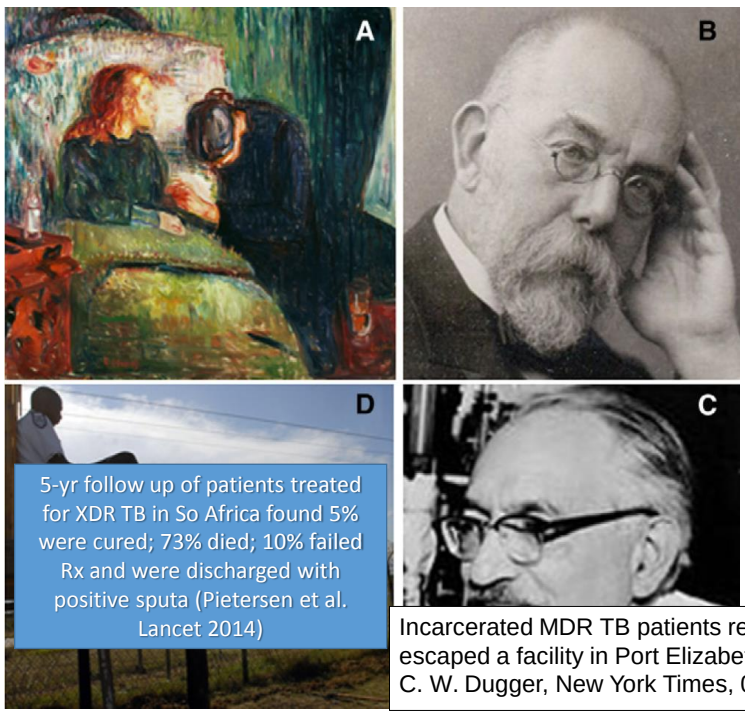

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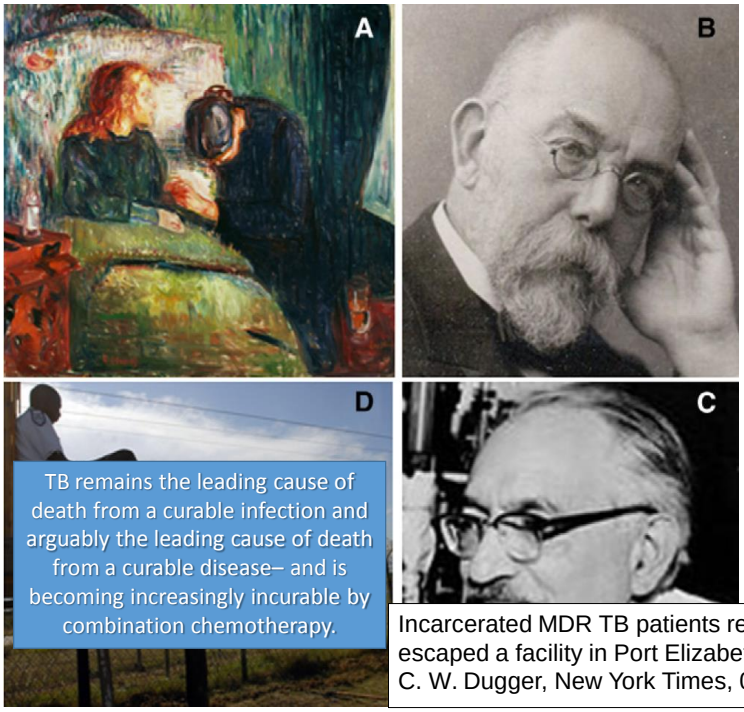
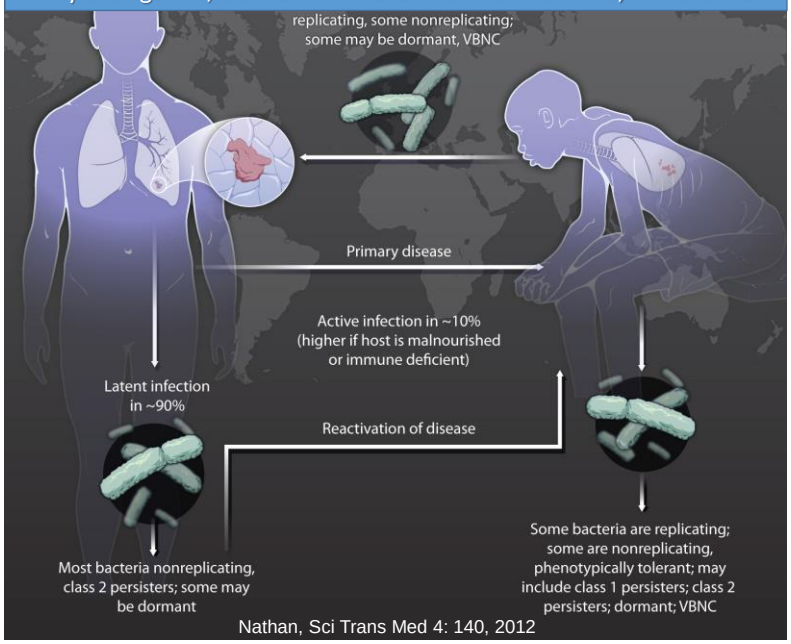


Incarcerated MDR TB patients repeatedly escaped a facility in Port Elizabeth, SA.
C. W. Dugger, New York Times, 03-25-08

Life cycle of *Mycobacterium tuberculosis*: Of 100 people infected, only 5-10 get TB, but each of these infects 10-20 more, and 3-5 die.



Nathan, Sci Trans Med 4: 140, 2012

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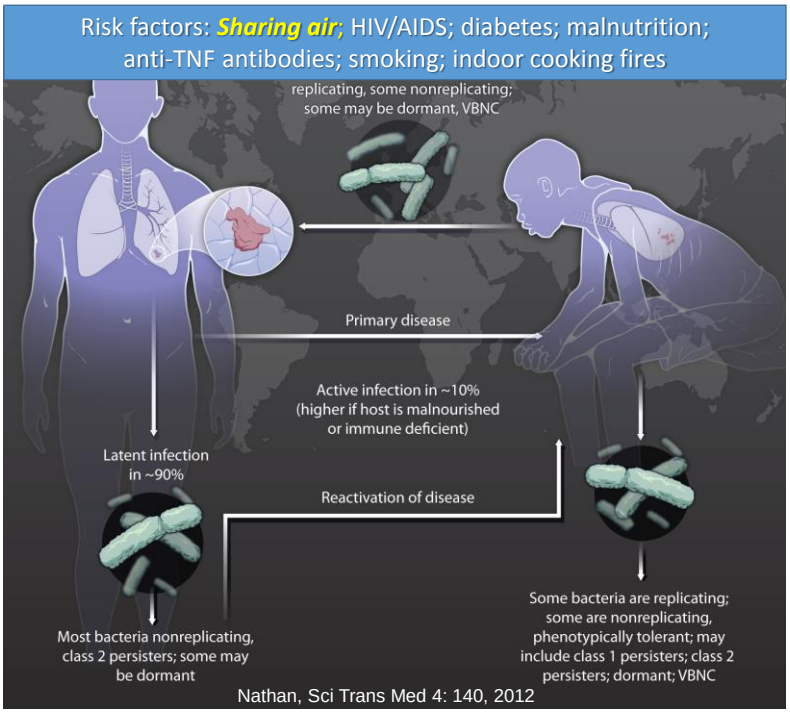

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Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

If you sequence the genomes of >1000 clinical isolates of M. tuberculosis (Mtb), what sequences do you think will be found to be most conserved?

- Virulence factors
- Active site residues in essential enzymes
- Epitopes (the minimal portion of antigens) recognized by T lymphocytes of the human immune system
- All of the above
- None of the above

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Mtb's interaction with human immunity: implications for medicinal chemistry

- The very immune response that Mtb must induce for its transmittal threatens Mtb's own survival. Mtb needs to withstand the antibacterial effects of human immunity well enough to remain infectious.
- This implies that Mtb encodes enzymes that can counter human antibacterial chemistry.
- Drugs that inhibit such enzymes might allow for elimination of latent TB and aid the treatment of active TB.

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Antimicrobial Resistance

Bacterial pathogens some of whose clinical isolates are now resistant to most antibiotics:

Neisseria gonorrhoeae
Enterococcus faecium
Staphylococcus aureus
Klebsiella pneumoniae
Acinetobacter baumanni
Pseudomonas aeruginosa
Enterobacter species
Some salmonella
Some shigella
Mycobacterium tuberculosis

Heritable

- Mutation of target that reduces binding but preserves function
- Post-translational modification of target
- Increased expression of target
- Expression of a compensatory pathway
- Modification or increased catabolism of drug
- Decreased activation of prodrug
- Decreased drug uptake or increased export

*Tuomanen, *Rev Infect Dis,* 1986

32

Antimicrobial Resistance

Bacterial pathogens some of whose clinical isolates are now resistant to most antibiotics:

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Enterococcus faecium
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Acinetobacter baumanni
Pseudomonas aeruginosa
Enterobacter species
Some salmonella
Some shigella
Mycobacterium tuberculosis

Heritable

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- Post-translational modification of target
- Increased expression of target
- Expression of a compensatory pathway
- Modification or increased catabolism of drug
- Decreased activation of prodrug
- Decreased drug uptake or increased export

Non-heritable: "phenotypic tolerance"

- Conditional resistance not attributable to changes in genome sequence
- "Persistence": survival of bacteria during treatment of a host with a drug to which the pathogen is sensitive under standard laboratory conditions at concentrations achieved in the host

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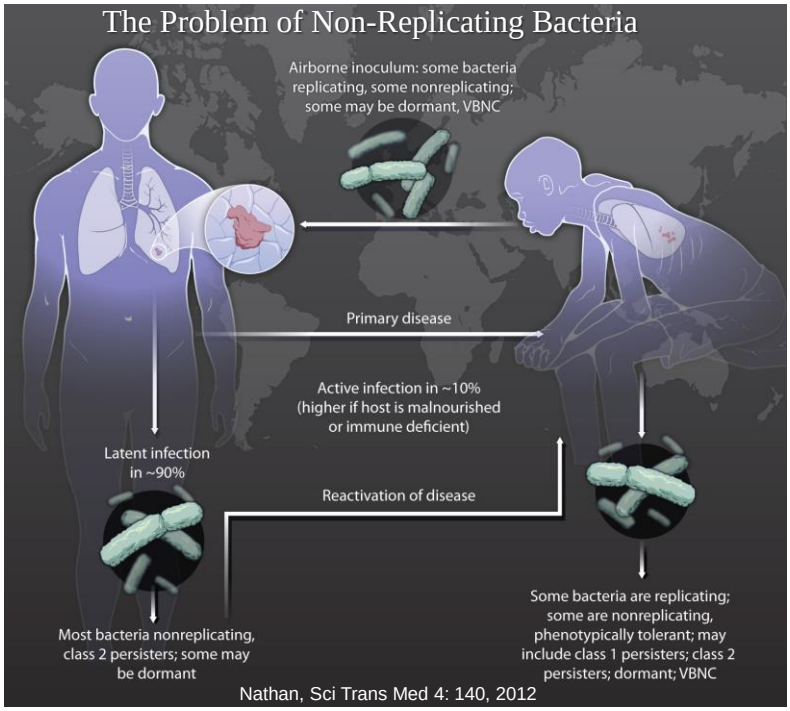

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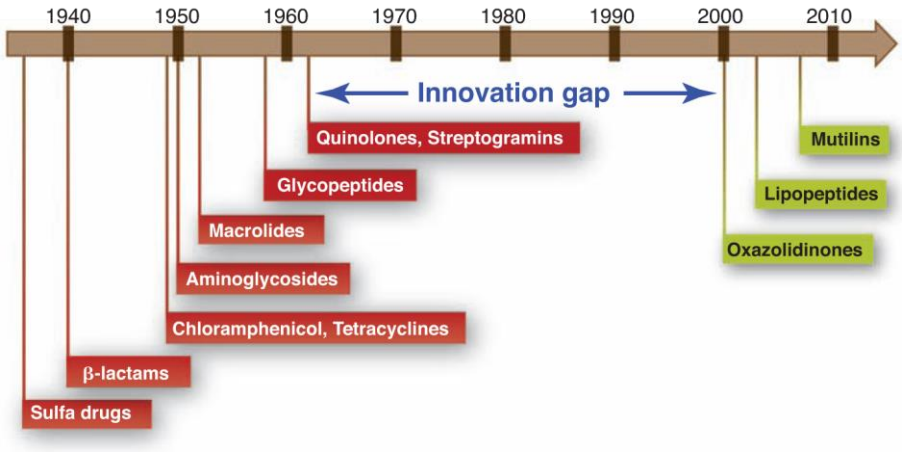
The Innovation Gap in Antibiotic Discovery



Fischbach MA and Walsh CB. Antibiotics for emerging pathogens. Science 325: 1089, 2009

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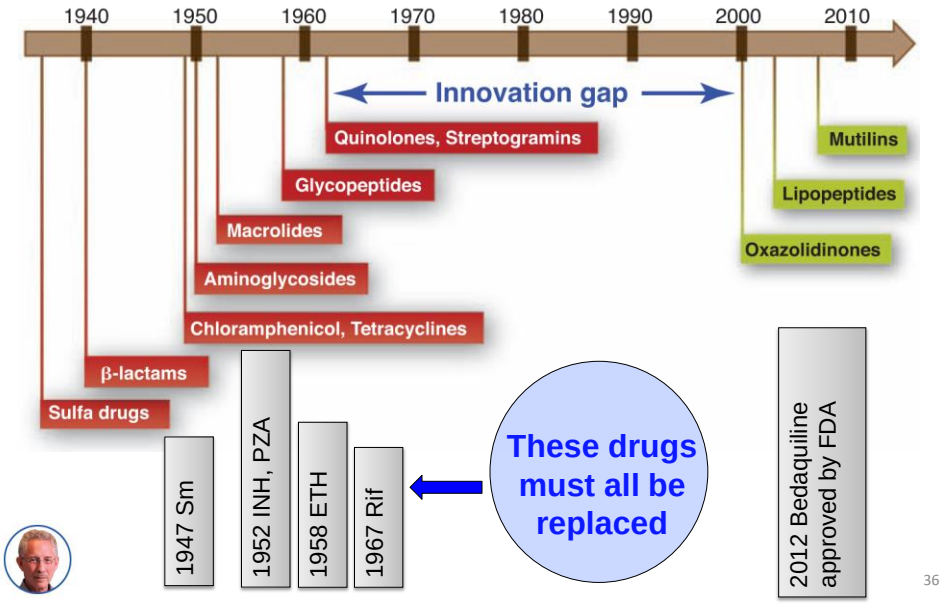
The Innovation Gap in TB Drug Discovery



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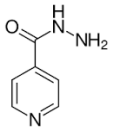
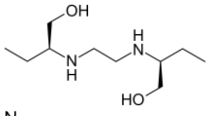
Standard TB chemotherapy: from tiny to huge, without regard to the Rule of Five

- Isoniazid



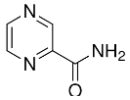
- Inhibits outer membrane mycolic acid synthesis; only kills replicating Mtb

- Ethambutol



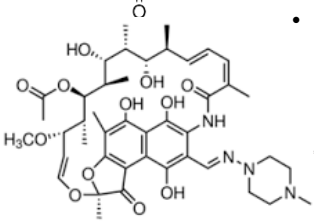
- Inhibits outer membrane arabinogalactan synthesis: only kills replicating Mtb

- Pyrazinamide



- Inhibits multiple targets*; barely kills Mtb in vitro, and only under mild acidity

- Rifampin



- Inhibits RNA polymerase; kills replicating Mtb very well and non-replicating Mtb to a limited extent at higher concentrations

*Resistance to PZA has been conferred by mutations in enzymes involved in ribosomal trans-translation, ppGpp metabolism, aspartate decarboxylase, protein degradation, and DNA /RNA (de)polymerization

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Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

What's the best way to cope with TB drug resistance?
(multiple correct answers may be possible)

- **A)** Most Isoniazid resistance is due to loss of KatG, an enzyme that activates isoniazid (a prodrug) to a product that inhibits the mycolate synthase InhA. **Make a new InhA inhibitor that doesn't require activation by KatG.**
- **B)** Ethambutol inhibits an arabinosyl transferase in arabinogalactan synthesis. **Target another enzyme in the same pathway.**
- **C)** Rifampin resistance is due to point mutations in RNA polymerase (RNAP). **Find an RNAP inhibitor that binds to a different site on the enzyme.**
- **D) Try something else.**

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Challenges in TB Drug Development

- We need **multiple new drugs to use together**, avoiding DDI with each other and with medications for prevalent co-morbidities, such as HIV/AIDS and diabetes.
- These agents must have a **very low COG**.
- We can't efficiently select drugs that will cure TB quickly unless we better **understand the biology**.
- **No physicochemical rules predict what drugs will cross Mtb's multilayer cell wall**, which includes a layer of wax that is expected to be solid at body temperature.
- Mtb transforms the **majority of xenobiotics** that penetrate it.
- **Drug levels vary across lesion types**. Bacterial susceptibility to a given drug at a given level varies across lesions types as well.
- **We have no PD assay that reports total body burden of Mtb**. PD measurements rely on sputum, which arises chiefly from one type of lesion. Current assays grossly under-report temporarily non-replicating forms of Mtb.

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Audience Survey Question

ANSWER THE QUESTION ON BLUE SCREEN IN ONE MOMENT

What's the best way to shorten TB therapy?

(multiple correct answers may be possible)

- **Find new targets.** Combine new drugs active against replicating Mtb with new drugs active against non-replicating Mtb.
- **Add another dimension to SAR**: intrabacterial PK-PD.
- **Add another dimension to host PK-PD**: lesional heterogeneity of drug levels and of pathogen susceptibility.
- None of the above.

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Why Have Infectious Bacterial Diseases Become "Neglected"?

"Antibiotic discovery is not very fashionable these days, and yet resistance has evolved to every antibiotic…. Despite various bacterial threats to public health (multiply drug-resistant strains, emerging pathogens and biothreat organisms), most large pharmaceutical companies and many biotechnology companies have left the area. Many factors contributed… but the fact remains that a better return on investment can be made in other disease areas… **What might be less well appreciated is just how difficult it is technically…** GlaxoSmithKline (GSK) spent 7 years (1995–2001) evaluating more than 300 genes for their potential as targets for novel antibacterials and showing genetically that more than 160 of them are essential…. From the 70 HTS campaigns run between 1995–2001… only 5 leads were delivered, … [a] **success rate [that] was four- to five-fold lower than for targets from other therapeutic areas at this time… this was … financially unsustainable"**

nature REVIEWS DRUG DISCOVERY

Payne DJ, Gwynn MN, Holmes DJ & Pompliano DL. Drugs for bad bugs: confronting the challenges of antibacterial discovery. Nature Reviews Drug Discovery 6, 29, 2007

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Present Targets of Antibacterials

Synthesis of nucleic acids, proteins, cell walls or folate*

*Walsh, Nature Reviews Microbiology 1: 65, 2003

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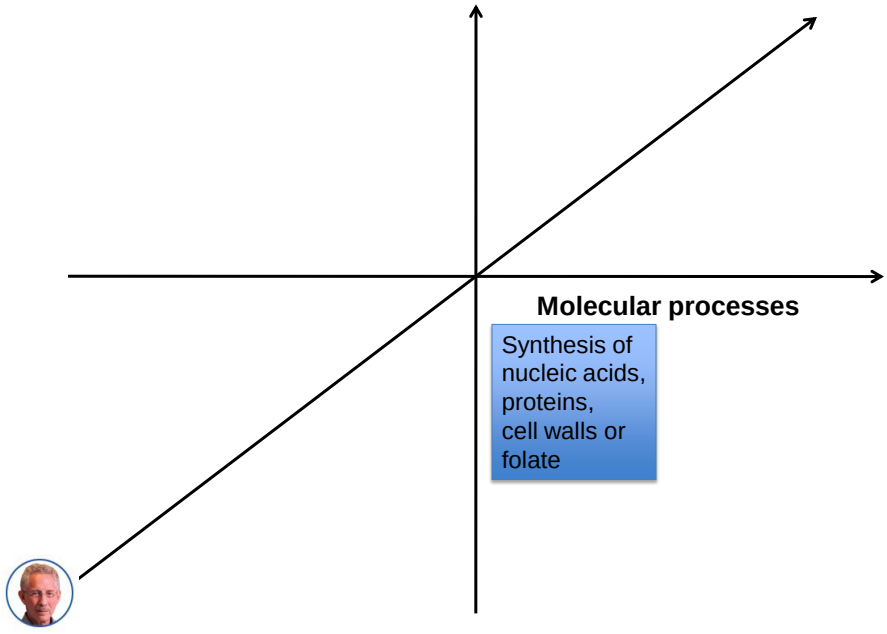
Coordinates of Anti-Infective Target Space



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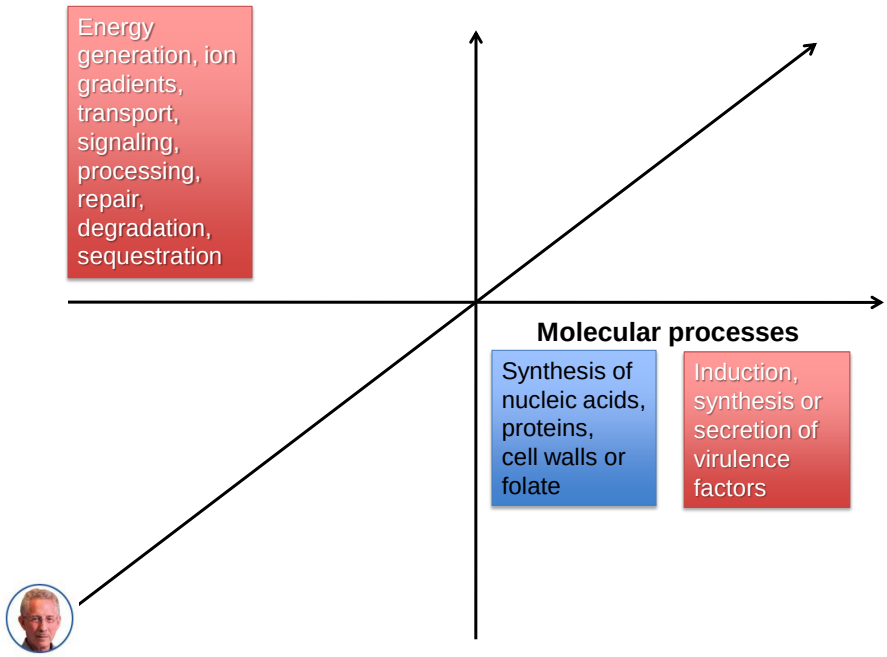

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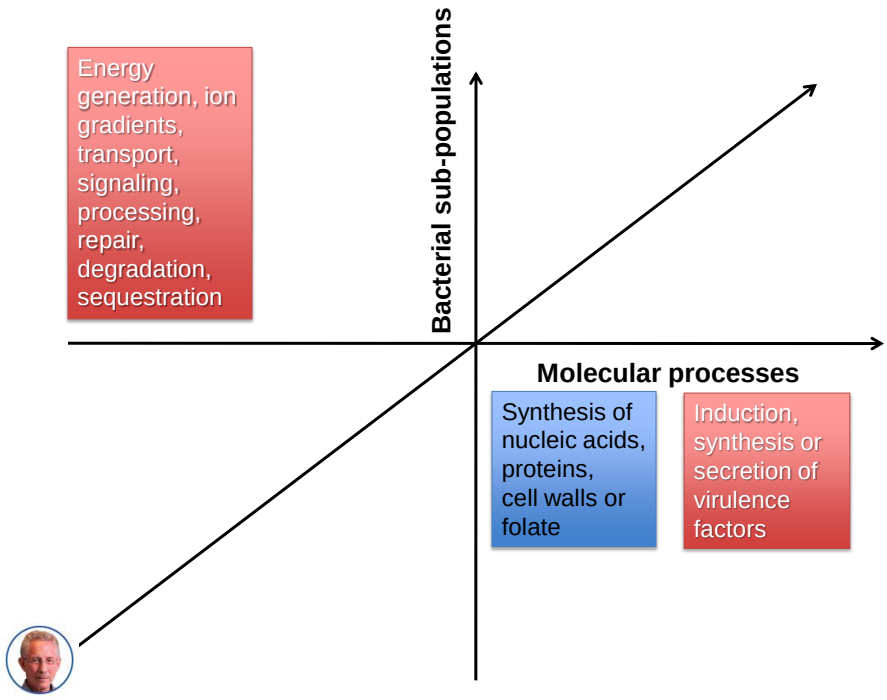
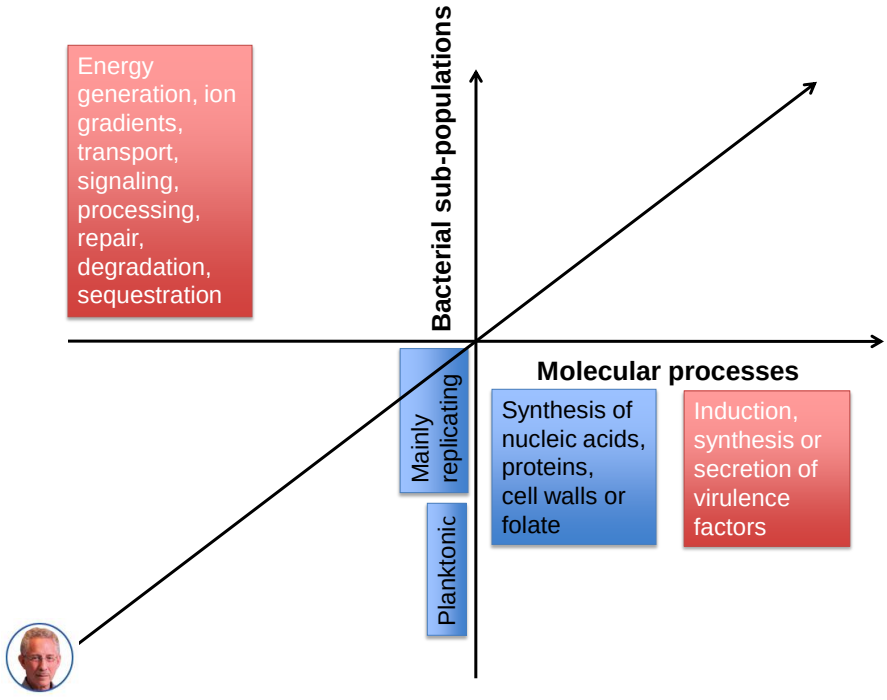

Energy generation, ion gradients, transport, signaling, processing, repair, degradation, sequestration
Bacterial sub-populations
Molecular processes
Synthesis of nucleic acids, proteins, cell walls or folate
Induction, synthesis or secretion of virulence factors

45


Energy generation, ion gradients, transport, signaling, processing, repair, degradation, sequestration
Bacterial sub-populations
Molecular processes
Mainly replicating
Planktonic
Synthesis of nucleic acids, proteins, cell walls or folate
Induction, synthesis or secretion of virulence factors

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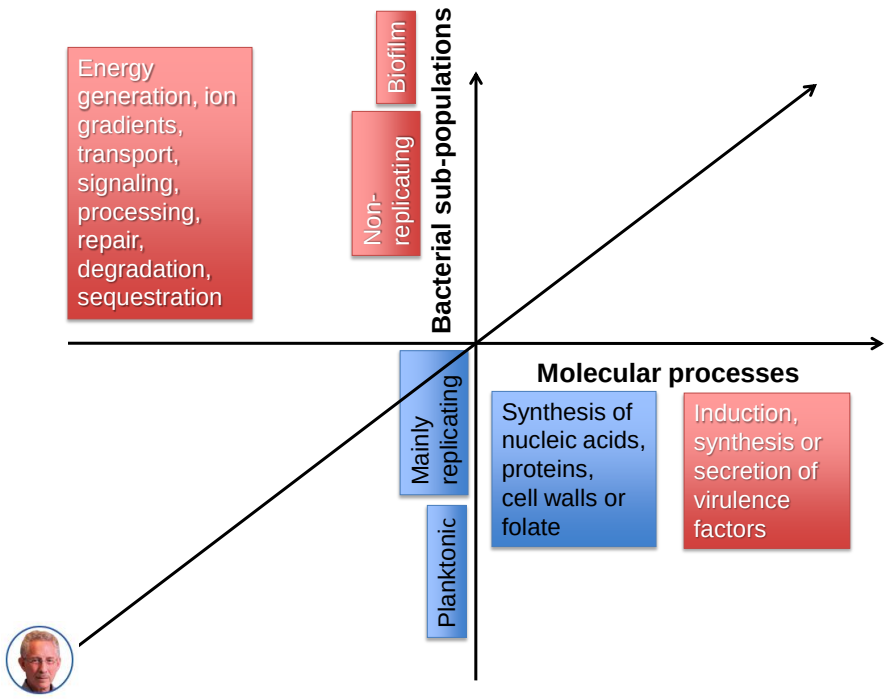
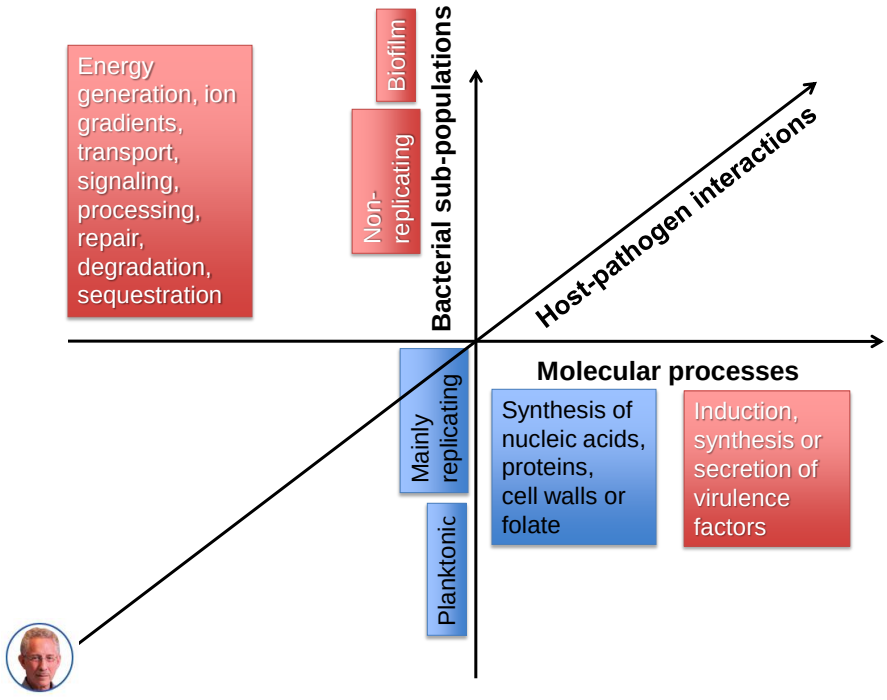
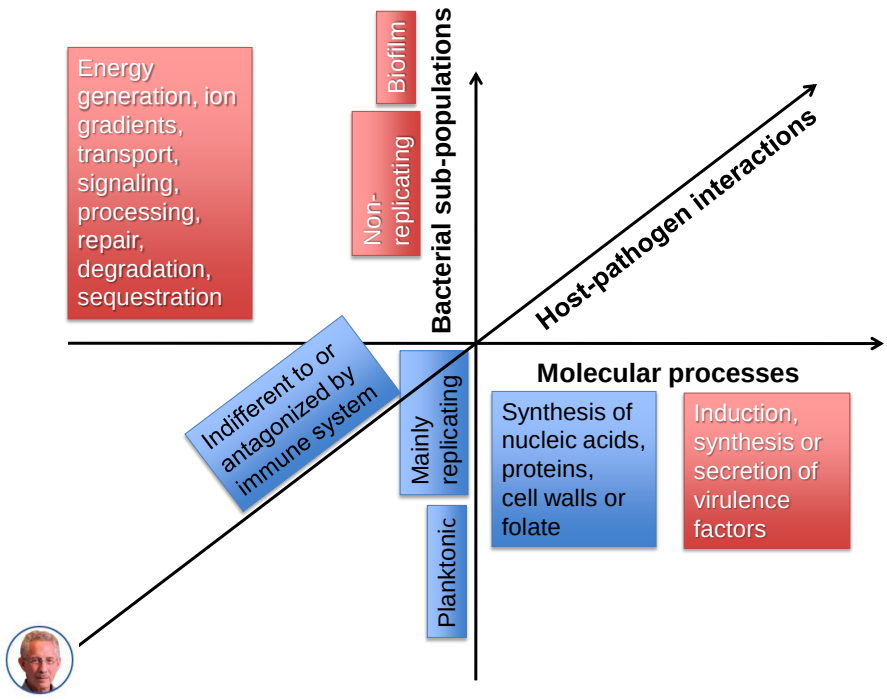

Energy generation, ion gradients, transport, signaling, processing, repair, degradation, sequestration
Biofilm
Non-replicating
Bacterial sub-populations
Molecular processes
Mainly replicating
Planktonic
Synthesis of nucleic acids, proteins, cell walls or folate
Induction, synthesis or secretion of virulence factors

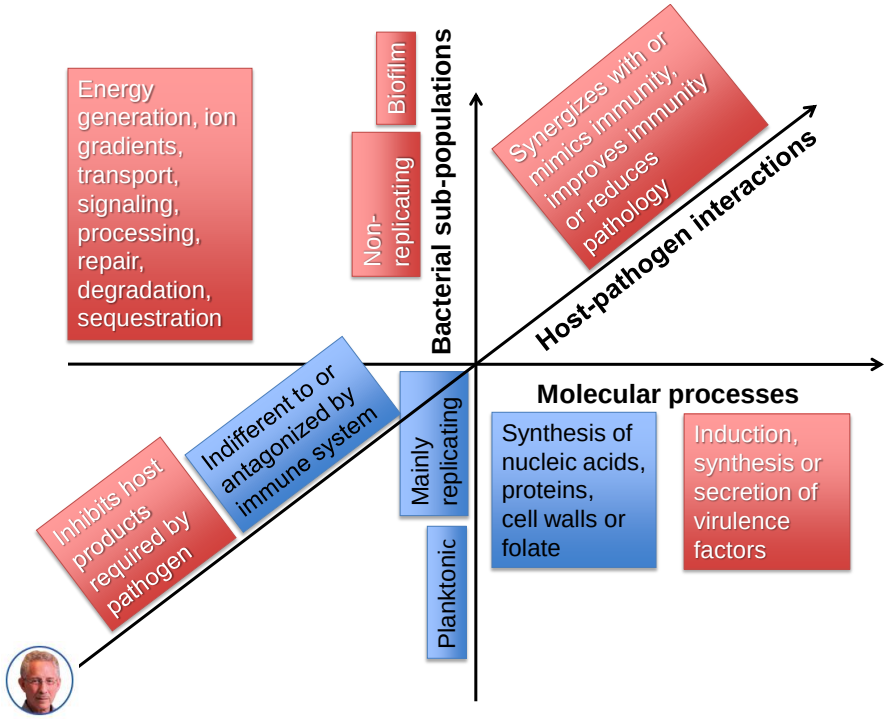
47


Energy generation, ion gradients, transport, signaling, processing, repair, degradation, sequestration
Biofilm
Non-replicating
Bacterial sub-populations
Host-pathogen interactions
Molecular processes
Mainly replicating
Planktonic
Synthesis of nucleic acids, proteins, cell walls or folate
Induction, synthesis or secretion of virulence factors

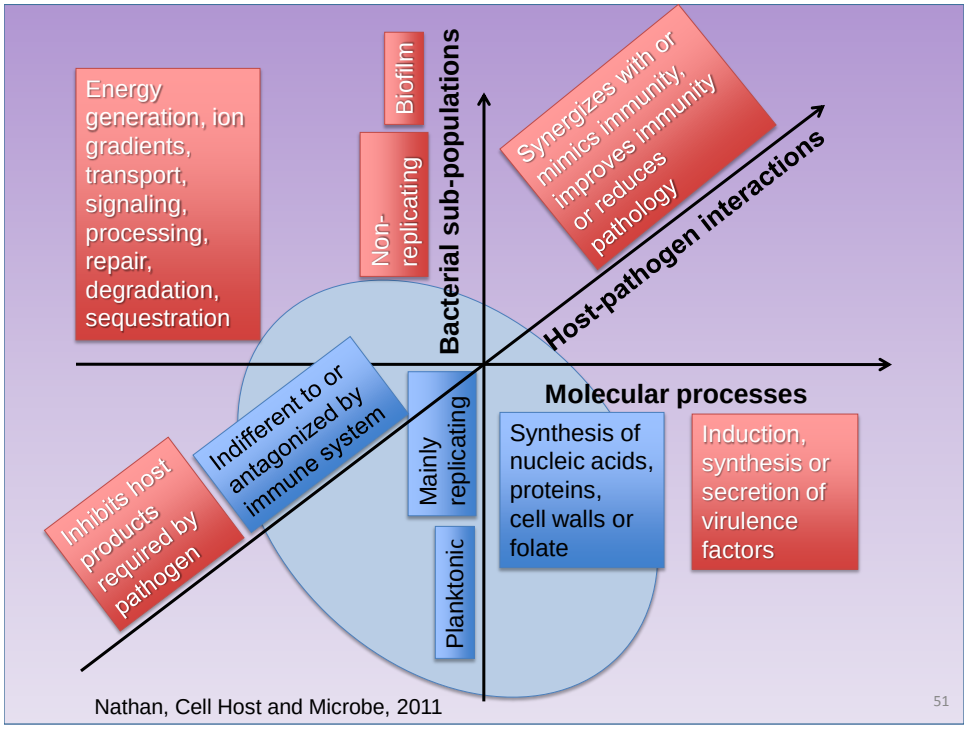
48

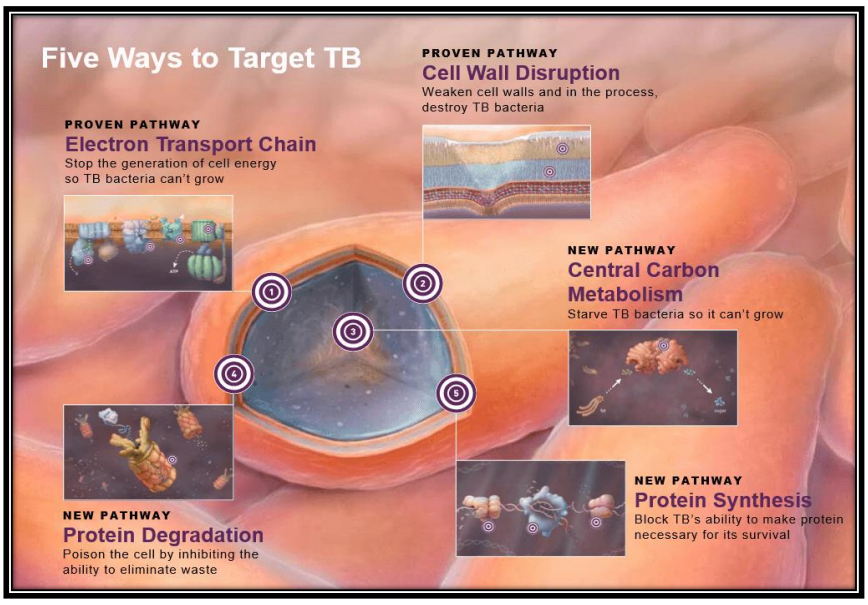

Energy generation, ion gradients, transport, signaling, processing, repair, degradation, sequestration
Biofilm
Non-replicating
Bacterial sub-populations
Host-pathogen interactions
Molecular processes
Indifferent to or antagonized by immune system
Mainly replicating
Planktonic
Synthesis of nucleic acids, proteins, cell walls or folate
Induction, synthesis or secretion of virulence factors

49


Energy generation, ion gradients, transport, signaling, processing, repair, degradation, sequestration
Biofilm
Non-replicating
Bacterial sub-populations
Synergizes with or mimics immunity, improves immunity or reduces pathology
Host-pathogen interactions
Molecular processes
Inhibits host products required by pathogen
Indifferent to or antagonized by immune system
Mainly replicating
Planktonic
Synthesis of nucleic acids, proteins, cell walls or folate
Induction, synthesis or secretion of virulence factors

50





Slide kindly provided by Dr. Nader Fotouhi, CSO of Global Alliance for TB Drug Development

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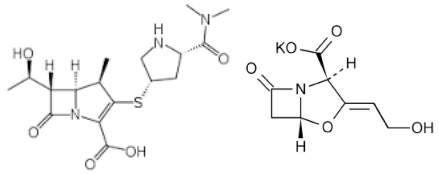
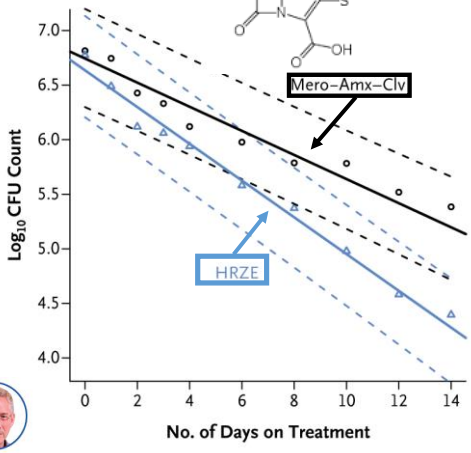
The NEW ENGLAND JOURNAL of MEDICINE

Potential resurrection of β-lactams for treatment of TB

β-Lactams against Tuberculosis — New Trick for an Old Dog?





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Madrid, Spain

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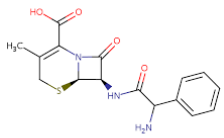
β-lactams with selective activity against non-replicating (NR), phenotypically tolerant Mtb

Cephalosporins bactericidal to NR Mtb:

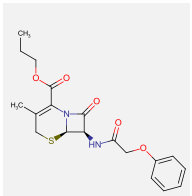
- Activity is clavulanate-independent, time-dependent
- Sterilize to limit of detection at 1-3 μg/mL
- Kil Mtb in primary macrophages (1.5-2 $\log_{10}$)



Cephalexin: inactive

Selective action on NR Mtb:

- No activity against replicating Mtb, with or without clavulanate
- No activity against replicating *E. coli*, *S. pneumoniae, P. aeruginosa* or *S. aureus*, or NR *C. albicans*
- LD50's ≥ 100 μg/mL against HepG2 cells and macrophages



KUC102765N

*B Gold et al. J. Med. Chem. 2016 (**with J. Aubé's team at UNC**)

54

β-lactams with selective activity against non-replicating (NR), phenotypically tolerant Mtb

Cephalosporins bactericidal to NR Mtb:

- Activity is clavulanate-independent, time-de
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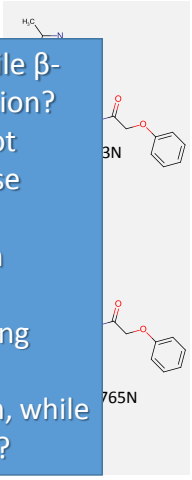

- Why is the C2 carboxylic acid ineffective, while β-lactams in clinical use require an acidic function?
- Why do these compounds kill NR Mtb but not replicating Mtb, while β-lactams in clinical use almost exclusively kill replicating bacteria?
- How is selectivity for NR Mtb consistent with inhibition of transpeptidases and carboxypeptidases, the peptidoglycan-building targets of β-lactams in clinical use?
- Why are these compounds narrow-spectrum, while β-lactams in clinical use are broad-spectrum?

*B Gold et al. J. Med. Chem. 2016 (**with J. Aubé's team at UNC**)

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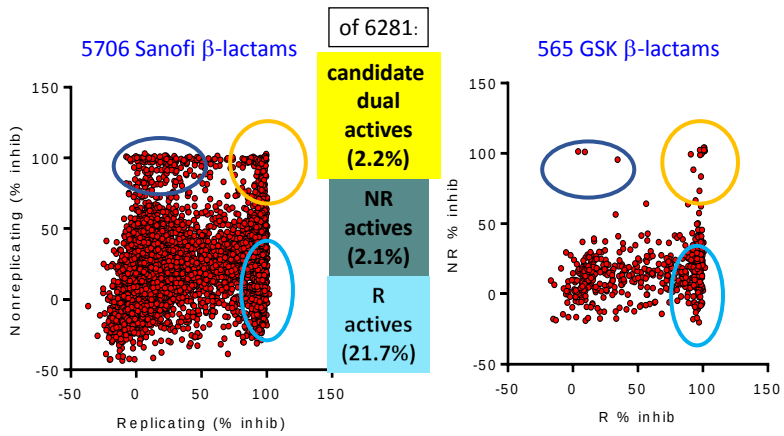
Collaboration with pharma partners to find β-lactams that kill *both* replicating and non-replicating Mtb



C Roubert, L Goullieux, E Bacqué, S Lagrange, L Fraisse

R Bates, D Barros, A Mendoza-Losana

Ben Gold, Landys Lopez-Quezada, Yan Ling, Julia Roberts, Madeleine Wood, , David Zhang

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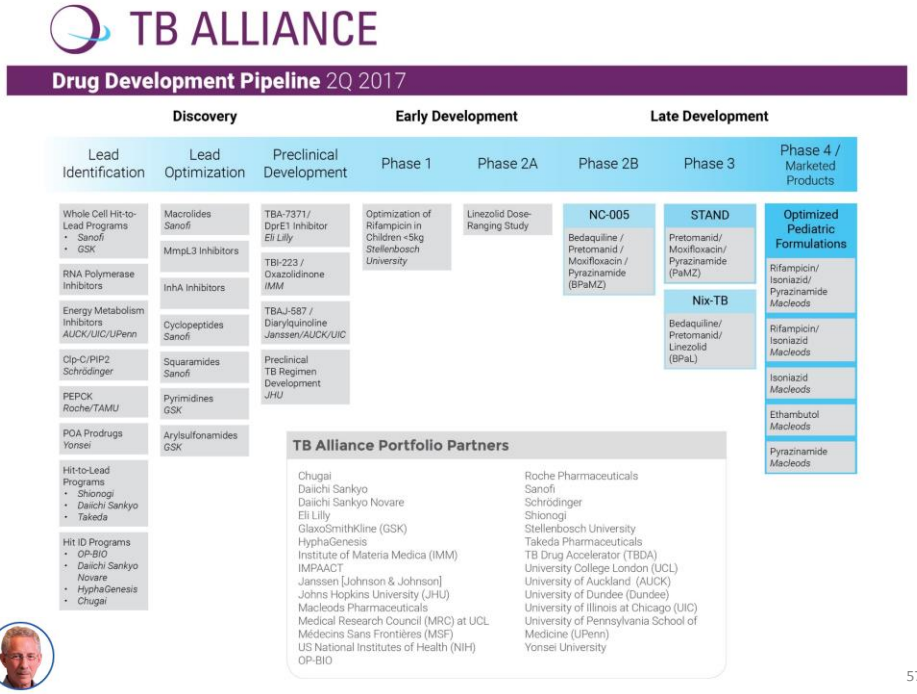

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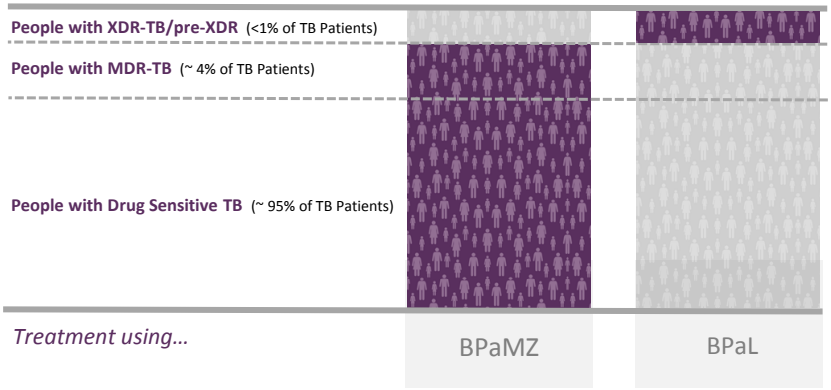
Treatment for All Patients with TB



B: Bedaquiline. Pa: Pretomanid. M: moxifloxacin. Z: Pyrazinamide. L: Linezolid.

Adapted from slide kindly provided by Dr. Carl Mendel, CEO of Global Alliance for TB Drug Development

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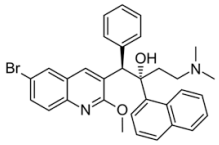
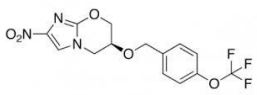
Tomorrow's Potential TB Chemotherapy: New Structures and New Mechanisms

- Bedaquiline



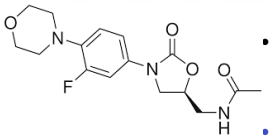
- Inhibits ATPase; kills both replicating and possibly non-replicating Mtb

- Pretomanid



- Imitates human immunity, generating NO-like species; interferes with both mycolic acid and ATP synthesis; kills both replicating and non-replicating Mtb

- Linezolid



- Inhibits bacterial (and mitochondrial) ribosomes

- What's coming?
- Safer diarylquinolines; oxazolidinones that spare mitochondrial ribosomes; TB-active β-lactams

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Innovations in antimicrobial drug development arising in TB research

- New target classes: E.g., protein degradation rather than synthesis.
- Intrabacterial PK-PD: Near-instantaneous separation of bacteria from the incubation medium followed by LC-MS to quantify bacterial uptake, identify intrabacterial transformation of drug candidates and observe impact on the metabolome
- Lesional PK: Positional mass spectrometry and laser capture mass spectrometry on frozen sections to identify lesion-specific drug levels
- New academic-academic relationships: NIH-funded, multi-institutional consortia (TB Research Unit Network: TBRU-N)
- New academic-industrial/industrial-industrial relationships: Extension of public-private partnerships that began in WWII with the Penicillin and Malaria Projects* and evolved in MMV, DNDi, the TB Drug Accelerator, the Global Alliance for TB Drug Development and the Tres Cantos Open Lab Foundation

*Nathan, C. Cooperative development of antimicrobials: looking back to look ahead. Nature Rev. Microbiol. 13:651-657, 2015

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Take Home Message

- Tuberculosis is the world's leading cause of death from an infectious disease, and a leading example of the growing problem of antimicrobial drug resistance.
- In a globalized world, anyone can be at risk from TB.
- Ideally we'd prevent TB with a vaccine, but immunologists are struggling to come up with a good one.
- ***Chemists***: ***the ball is in your court!***

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- Nathan, C. Bacterial pathogenesis: Fresh approaches to anti-infective therapies. *Science Translational Medicine* 4: 1-13, 2012
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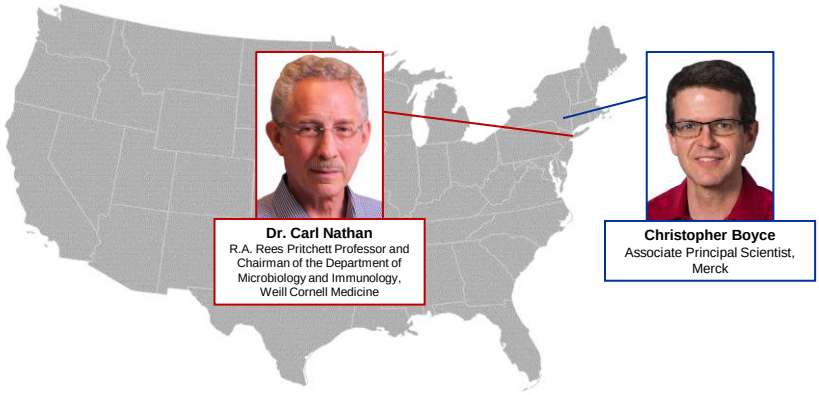

Dr. Carl Nathan
R.A. Rees Pritchett Professor and Chairman of the Department of Microbiology and Immunology, Weill Cornell Medicine

Christopher Boyce
Associate Principal Scientist, Merck

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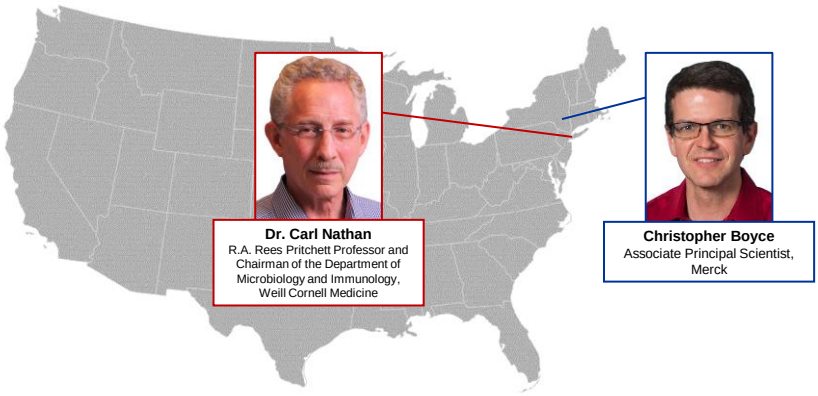

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Evolving Strategies for Drug Candidates Optimization in a Changing Pharmaceutical Landscape

Friday August 4, 2017 (8:00 a.m. – 5:00 p.m.)
University of Maryland School of Pharmacy, Baltimore, MD

The DDDI regional meeting is a focused forum for drug discovery and preclinical scientists in the pharmaceutical field to discuss the most relevant topics in drug design and discovery and an excellent networking opportunity for attendees.

Covered Topics:
- Formulation Support in Drug Discovery
- Early Phase Drug Development and Population PK
- Transforming skillsets in early development to meet the changing NCE/NBE landscape in discovery space
- Academic collaboration and preparing for the discovery support role in industry

Who Should Attend?
Pharmaceutical professionals with expertise and interest in different areas of drug discovery, particularly:
- Medicinal Chemistry
- Discovery Biology
- Pharmacology
- Pharmacokinetics
- Pharmacodynamics and Drug Metabolism
- Pharmaceutical Sciences
- Toxicology

Keynote Speakers:
- **Mike Hageman, PhD** (Former Exec. Director, Bristol-Myers Squibb)
- **Capt. Edward D. Bashaw, PharmD** (Director, U.S. Food and Drug Administration)
- **Justin Pennington, PhD** (Director, Merck & Co.)

Featured Speakers:
- **Vladimir Papov, PhD** (Boehringer Ingelheim)
- **Jonathan Philips, PhD** (Toxicology Fellow, Vertex Pharmaceuticals)
- **David Rodrigues, PhD** (Research Fellow, Pfizer Inc.)
- **Joseph Fortunak, PhD** (Associate Professor, Howard University)
- **Steven Fletcher, PhD** (Associate Professor, University of Maryland School of Pharmacy)

Contact: Sunny Bhardwaj
Email: sunny.bhardwaj2@merck.com
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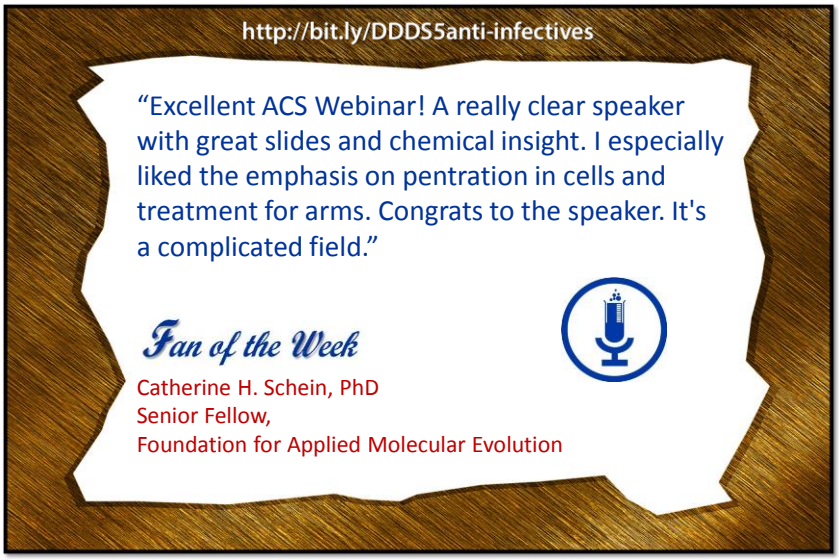

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