The 2013 BAARN symposium is dedicated to the memory of the late, great John Quinn, MD, a close friend and colleague to many BAARN members who lost his battle with cancer just a few weeks ago on October 26. He was 62.

John was a native of Chicago. He graduated from the University of Illinois and Rush Medical College. He did his internship and residency in Internal Medicine at Loyola University and his ID fellowship at the University of Chicago. He spent 25 years there in various academic ID posts including Michael Reese Hospital, the University of Illinois, Northwestern, and most recently Rush and Cook County Hospital. He ran a research lab devoted to understanding molecular epidemiology and mechanisms of antibiotic resistance, primarily in gram negative bacilli, and published more than 130 papers on these topics. As Dave Shlaes recently posted in his blog, “John realized that to make an even greater impact on the lives and health of patients, a turn to the dark side – the pharmaceutical industry – was going to be the best way to bring new and needed therapies forward.” So in 2008 he moved to industry, taking a position at Pfizer R & D in Groton, CT. He split his time there between clinical development and research. When that group was shut down in 2011, he joined AstraZeneca Infection in Waltham, MA until about a year ago, when he decided to make the most of the time he had left with family and friends. John is survived by his beautiful wife Maria Virginia Villegas, an academic ID physician who runs a research institute in Cali, Colombia and four children, whom he described as “a store manager, an IT guy, a medical student, and a school teacher in the Bronx”.

John was hugely supportive of the creation of the BAARN and made many valuable suggestions on how to make it happen and whom to include. Although we would have much preferred to have him join us today in person, we take great comfort in knowing he is right here with all of us in spirit.
2013 BAARN SYMPOSIUM AGENDA
“Antibiotics as a hotspot for R&D: What’s new? What’s changing? What does it take to succeed?”

Tuesday, November 19, 2013
AstraZeneca, 35 Gatehouse Drive, Waltham MA 02451

8:00 am Shuttle service departs from Kendall Square station (free parking also available at AZ)

8:00-9:00 am Registration - AZ lobby
• Participants will receive BAARN directory
• Coffee and light breakfast will be available in atrium before event

9:00 – 9:10 Welcome & Introduction – Mike Gilmore and Manos Perros, 2013 Symposium Chairs

Morning Session: Our Changing Landscape

I. The face of Infectious Disease in Boston: Evolution of Clinical Practice and Case studies
9:10 - 9:30 David Snydman, MD, Chief of Infectious Diseases, Tufts Medical Center
9:30 - 9:50 David Hooper, MD, Chief of Infection Control Unit, Mass General Hospital
9:50 - 10:10 Richard Ellison, MD, Professor of Medicine, UMass Medical School; Epidemiologist, UMass Memorial Medical Center

II. Emerging regulatory landscape and pathogen-directed therapies
10:20 - 10:40 John Rex, AZ, “How Changes in the Regulatory Landscape will impact future anti-infective therapy”
10:40 - 11:00 Steven Brecher, Chief, Dept of Micro, VA Boston Healthcare System, “Rapid bacterial diagnostics – are we there yet?”

11 – 11:15 Coffee/bio break

III. Emerging Resources
11:15 -11:35 Joyce Sutcliffe, Tetraphase, “New funding paradigms for antibiotic R&D”
11:35 - 11:50 Michael Pollastri, Northeastern University, “Open Access Drug Discovery”

IV. Panel discussion: what does it take to succeed in antibiotic R&D?
11:50 -12:30 Nicole Mahoney, Senior Officer for Pew Charitable Trusts’ Antibiotics & Innovation Project, moderator
Panelists: Manos Perros (AZ), David Shlaes (blogger/consultant), Steve Gilman (Cubist), Mike Gilmore (Harvard), Helen Boucher (Tufts), Paul Dunman (Rochester), Louis Rice (Brown University)

12:30-1:45 Boxed Lunch/Poster Session/Networking (Atrium, Cafeteria, M0.008)

Afternoon Session: Game Changing Research is in the BAARN

I. Novel Compounds and Targets
1:45 - 2:00 Victoria Knight-Connoni, Cubist, “Digging for Gold in the BAARN: The future of Natural Products in Drug Discovery”
2:00 - 2:15 Tom Bernhardt, Harvard, “A high-throughput genetic screen for new factors involved in Gram-negative envelope biogenesis”
2:15 - 2:30 Len Duncan, Vertex, “Essentiality is not enough: Lessons learned from bacterial DNA Ligase”
2:30 - 2:45 Jinjun Shi, MIT, “Polymeric Nanoparticles for Targeted Delivery of Antibiotics”
2:45 - 3:00 Jim Collins, Boston University, “Network biological approaches to bacterial infections”

3:00 - 3:15 Coffee/bio break

II. Novel Approaches
3:15 - 3:30 Andrew Tomaras, Pfizer, “Keeping it Real: in vivo relevant screening for new antibacterial agents”
3:30 - 3:45 Don Moir, Microbiotix, "A Stereoselective Inhibitor Identifies a New T3SS Target"
3:45 - 4:00 Deb Hung, Broad Institute, “Beyond the Bug”

III. Open Discussion: Antibiotics without MICs - feasible or fantasy?
4:00 - 4:30 pm, Eleftherios Mylonakis, Brown University, moderator
With pros & cons presented by Deb Hung (Broad) and David Hooper (MGH)

4:30 pm Wrap Up by symposium chairs

4:30 - 6 pm Cocktails /Posters/Networking, con’t. (Cafeteria)

6:00 pm shuttle service departs from AstraZeneca to Kendall Square station
Eric Sello, PhD  
Professor of Chemistry  
Brown University, 47 George St, Providence, RI 02912  
jason_sello@brown.edu  

Research Interests: Our lab works in synthetic biology and systems biology, with a particular focus on using network biology approaches to study antibiotic action, bacterial defense mechanisms, and the emergence of resistance.  

Title of Poster: Antibacterial Activity of and Resistance to Small Molecule Inhibitors of the ClpP Peptidase

Eleftherios Mylonakis, MD, PhD  
Professor of Medicine and Chief of Infectious Diseases, Rhode Island and Miriam Hospitals  
Warren Alpert Medical School of Brown University, Providence, RI 02912  
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Dr. Mylonakis is recognized for his research on the study of microbial pathogenesis and host responses. His studies have included clinical and laboratory studies and the use of mammalian and invertebrate model hosts. His investigations have identified novel virulence factors, cross kingdom pathogen-pathogen interactions, novel agents and evolutionarily conserved traits that are involved in host virulence and immune responses during fungal infection.  

Title of Session: Antibacterials without MICs: Feasible or Fantasy?

Louis B Rice, MD  
Chair, Department of Medicine, Physician-in-Chief, Rhode Island and Miriam Hospitals  
Warren Alpert Medical School of Brown University, Providence, RI 02912  
LRICE@lifespan.org  

Research interests include understanding the mechanisms of antibiotic resistance in bacteria; preventing hospital infections; and developing antibiotic usage strategies that will minimize the emergence and spread of antibiotic resistance.
Ashlee Earl  
Research Scientist/Group Leader, Bacterial Genomics  
The Broad Institute  
7 Cambridge Center, Room 4112, Cambridge, MA 02142  
aearl@broadinstitute.org  
Research Interests: antibiotic resistance, bacterial comparative genomics, metagenomics

Michael Feldgarden  
Research Scientist  
The Broad Institute  
7 Cambridge Center, Room 301B-5031, Cambridge, MA 02142  
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Research Interests: genomics, metagenomics

Mark Fitzgerald  
Research Chemist  
The Broad Institute  
7 Cambridge Center, Room 4112, Cambridge, MA 02142  
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Research Interests: antibacterial drug discovery

Deborah Hung, MD, PhD  
Assistant Professor  
The Broad Institute, Harvard Medical School, Mass General Hospital  
7 Cambridge Center, Cambridge, MA 02142  
dhung@broadinstitute.org  
Research Interests: The Hung lab is interested in developing new paradigms for intervening on infection using a combination of chemical biology and genomics to understand mechanisms by which one can disrupt the pathogen-host interaction.  
Title of Talk: Beyond the Bug

Christina Scherer, PhD  
Director, Anti-infective Discovery  
The Broad Institute  
7 Cambridge Center, Room 3031D, Cambridge, MA 02142  
cscherer@broadinstitute.org  
Research Interests: infectious diseases drug discovery and development, including bacterial, parasitic, and viral diseases.  
Title of Poster: Diversity Oriented Synthesis-derived compounds with selective activity against C. difficile

MIT (Massachusetts Institute of Technology)

Barbara Imperiale, PhD  
Professor of Biology and Chemistry  
MIT Dept. of Biology  
77 Mass. Ave., 68-380, Cambridge, MA 02139  
imper@mit.edu  
Research Interests: protein glycosylation in pathogenic bacteria; prokaryote-specific saccharide biosynthesis; bacterial glycoconjugate virulence factors

Jinjun Shi, PhD  
Assistant Professor  
Brigham and Women’s Hospital  
20 Shattuck Street, MBR607A  
Boston, MA 02115  
jinjun.shi@zeus.bwh.harvard.edu  
Research Interests: nanotechnology, drug delivery, gene therapy, immunotherapy, cancer,  
Title of Talk: Polymeric Nanoparticles for Targeted Delivery of Antibiotics
Research Interests: The laboratory’s primary interest is in identifying and characterizing the molecular aspects of the process of signal transduction in prokaryotes and in hosts that interact with prokaryotes, from the discovery of virulence factors in bacteria and fungus to host defense responses in plants and worms. The laboratory is using whole genome approaches to investigate these aspects of microbial pathogenesis and host defense responses. We are particularly interested in elucidating those aspects of pathogenesis that are similar irrespective of the pathogen and the host.

Title of Talk: A high-throughput genetic screen for new factors involved in Gram-negative envelope biogenesis

Research Interests: I am interested in using bacterial genetics to uncover new vulnerabilities in the process of bacterial envelope biogenesis to target with antibiotics. I am also excited by the potential of employing traditional molecular genetic logic in the development of cell-based small molecule screens with enhanced pathway specificity.

Research Interests: I am interested in the interactions and evolution of infectious organisms, with particular focus on virus infections of the eye.

Research Interests: We use everything from genomics to pathogenesis studies to understand multidrug resistant hospital pathogens, including enterococci, staphylococci and streptococci. We developed the collaborative, interdisciplinary Harvard-wide Antibiotic Resistant Program to develop new ways to prevent and treat these infections, and to understand how current practices are contributing to the resistance problem.

Research Interests: Currently transitioning from Bausch + Lomb, where I was in charge of non-clinical trials for their new ocular fluoroquinolone besifloxacin, to the Mass. Eye and Ear Infirmary, were I will continue to work on bacterial infections of the eye.

Title of Poster: Emergence of epidemic multi-drug resistant Enterococcus faecium from animal and commensal strains
Michael Valentino, PhD
Postdoctoral Fellow
Massachusetts Eye and Ear Infirmary, Harvard Medical School
243 Charles St. C703, Boston, MA 02114
michael_valentino@meei.harvard.edu

Research Interests: Infectious disease, Antibiotic resistance, Translational medicine, Comparative genomics, Molecular genomics, Streptococcus, Enterococcus, Staphylococcus

Title of Poster: Genomics of the Conjunctival Pathogen Streptococcus pneumoniae

Daria Van Tyne, PhD
Postdoctoral Fellow
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Hera Vlamakis, PhD
Instructor
Harvard Medical School, Microbiology and Immunobiology – Kolter Lab
Building HIM Room 1042A, 77 Louis Pasteur Ave
Boston, MA 02115
hera_vlamakis@hms.harvard.edu

Research Interests: I am interested in biofilm formation in bacteria and how molecules that inhibit biofilm formation might synergize with antibiotics.

Christopher Walsh, PhD
Professor
Harvard Medical School
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christopher_walsh@hms.harvard.edu

Research Interests: Molecular basis of biological catalysis with a focus on the structure and function of enzymes. Much of the current focus of interest is on the mechanism of action of antibiotics and bacterial siderophores.

Anastasiya Yakhnina, PhD
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4 Blackfan Circle, Boston, MA 02115
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Research Interests: Antibiotic development, bacterial cell division, outer membrane permeability of gram-negatives, high-throughput screens

Title of Poster: Blocking cell separation in Pseudomonas aeruginosa leads to defects in the outer membrane permeability barrier

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Research Interests: wastewater, marine microbiology, antibiotic resistance, environmental health

Tânia Ribeiro, PhD  
Cell2b - Advanced Therapeutics  
Senior Scientist (Harvard grad)  
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John Santa Maria  
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Research interests: drug discovery, antibiotics, microbiology, genetics, chemical biology, teichoic acids, cell wall, Staphylococcus aureus, transposon mutagenesis, synthetic lethality, conditional essentiality, high-throughput screening  
Title of Poster: Mapping the S. aureus Cell Wall Interactome

Samantha Wellington  
Graduate Student  
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Research interests: Small molecule inhibitors of M tuberculosis and mechanisms of latency and drug resistance
Brian Conlon, PhD  
Postdoctoral Fellow  
Northeastern University  
134 Mugar Life Sciences, 360 Huntington Ave., Boston, MA 02115  
brian.patrick.conlon@gmail.com  
**Research Interests:** Antibiotic discovery, Microbiology, Molecular Biology, Persister cells, Antibiotic Resistance, Antibiotic Tolerance  
**Title of Poster:** Eradication of bacterial populations by activation of the ClpP protease

Vincent Isabella, PhD  
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Northeastern University  
134 Mugar Life Sciences, 360 Huntington Ave., Boston, MA 02115  
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**Research Interests:** Microbiology, Molecular Biology, Next generation sequencing, Transcriptomics, Transposomics, Infectious disease, Antibiotic discovery, Drug development, Cell-based screening  
**Title of Poster:** Eradication of bacterial populations by activation of the ClpP protease

Mike Pollastri, PhD  
Associate Professor  
Northeastern University  
Department of Chemistry, Hurtig 102  
360 Huntington Avenue, Boston, MA 02115  
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**Research Interests:** medicinal chemistry for parasitic diseases (African sleeping sickness, Chagas, leishmaniasis, and malaria)  
**Title of Talk:** A new "open" data sharing model for infectious diseases

Jane Kramer, JD  
Director  
Tufts University Alliance for the Prudent Use of Antibiotics  
200 Harrison Ave., Posner 3 Business  
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**Research Interests:** Innovation in antibiotics

Barbara Lapinskas  
Administrative Director  
Tufts University Alliance for the Prudent Use of Antibiotics  
200 Harrison Ave., Posner 3 Business  
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**Title of Poster:** Alliance for the Prudent Use of Antibiotics

Kathleen Young  
Program Consultant/former CEO  
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**Research Interests:** Public Policy ; Consumer and Provider ; Antibiotic resistance
Arietis Corp. is a Boston-based biotechnology company focused on the discovery and development of novel antimicrobial agents. Our drug discovery pipeline includes a drug discovery platform focused on sterilizing antifungal treatments, capable of taking the standard “static” antifungals beyond “cidal,” both killing actively growing pathogens and eliminating persister populations that are responsible for treatment failure and recurrence. We also have programs for the identification of narrow spectrum antibiotics specifically targeting H. pylori, the cause of gastric and duodenal ulcers. Founded in 2006, the Arietis approach and technology are totally novel and will bridge an important gap in antimicrobial therapeutics. Arietis has forged productive alliances and partnerships within the biotechnology community that advance our capacity to develop effective drug products. We are committed to providing innovative solutions to the problem of persistent infections, thereby decreasing the burden on health systems worldwide. The company was created based on technology invented by its founder, Professor Kim Lewis, Director of the Antimicrobial Center at Northeastern University.

Microbiotix is a privately-held, clinical stage biopharmaceutical company engaged in the discovery and development of novel small molecule anti-infective drugs. The Company’s clinical programs are focused on hepatitis C virus (HCV) and human cytomegalovirus (HCMV).

Title of Talk: A Stereoselective Inhibitor Identifies a New T3SS Target
We are a pharmaceutical company focused on the discovery, development, and commercialization of innovative medicines that are designed to save lives and alleviate suffering. Our lead product candidate, omadacycline, is a new tetracycline-derived, broad-spectrum antibiotic being developed for use as a first-line monotherapy for serious community-acquired bacterial infections where antibiotic resistance is of concern for treating physicians.

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Tetraphase is a clinical-stage biopharmaceutical company using its proprietary chemistry technology to create novel antibiotics for serious and life-threatening multi-drug resistant (MDR) infections. Since the company’s inception in 2006, Tetraphase has developed an antibiotics platform that offers the potential to dramatically improve the treatment of both broad spectrum and MDR bacterial infections.

Trudy Grossman, PhD
Senior Director, Biology
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Research Interests: Antibiotic drug discovery, microbiology, mechanism of action

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Research Interests: Antibiotic development

Joyce Sutcliffe, PhD
Senior VP, Biology
Tetraphase Pharmaceuticals, Inc.
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Research Interests: antibacterials, antibacterial resistance, development strategy
Title of Talk: New funding paradigms for antibiotic R&D
Jim Coull, PhD
CTO
AdVanDx
400 Trade Center, Suite 6990
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Research Interests: Rapid diagnosis of infectious disease, molecular technologies, mechanisms of drug resistance

Tucker Kelly, JD
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AdVanDx
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AdvanDx is a leading provider of rapid and accurate molecular diagnostic tests for identification of pathogens causing critical infections in hospitalized patients. Our mission is to help healthcare providers optimize antibiotic therapy earlier in order to improve patient outcomes while limiting unnecessary antibiotic use and reducing hospital costs.

BioMérieux’s mission is to contribute to the improvement of public health worldwide through in vitro diagnostics.

Dana Marshall
President
Bacterioscan
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title of Poster: Rapid AST Determination Using Forward Laser Scatter

Rhonda Soest, RN
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ECI Biotech is a premier developer and manufacturer of innovative, patented ExpressDetect® sensors for rapid infection determination at the point-of-care (PoC) for professional use, as well as consumer OTC markets.

Mitch Sanders, PhD
CEO and Founder
ECI Biotech, 88 Ball Street, Northborough MA 01532
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Our research interests are in the early detection of active infections thereby being best suited for companion diagnostic opportunities. This technology is commercialization stage and we are looking for new partner opportunities.

Title of Poster: Development of Rapid PoC Companion diagnostics to Measure Active Infections

John Beeler
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T2 Biosystems is disrupting the landscape of clinical diagnostics with T2MR director detection which enables healthcare professionals to save lives and reduce costs by providing sensitive, accurate and rapid assay results. T2 Bio’s products detect molecular, hemostasis or immunodiagnostic targets directly from unpurified clinical samples in hospitals, labs and physicians’ offices.

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John Rex, MD SYMPOSIUM CHAIR  
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Title of Talk: The Changing Regulatory Landscape and Implications for Antibiotic R&D

Dean Brown, PhD  
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Title of Poster: Charge and Molecular Weight (MW) Descriptors Correlate to Efflux Susceptibility in *Pseudomonas aeruginosa* and *Escherichia coli*

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Michael Huband  
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Title of Poster: In Vitro Activity of AZD0914: A New Benzisoxazole DNA Gyrase Inhibitor against *Neisseria gonorrhoeae*

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Ruben Tommasi, PhD
Senior Director, Chemistry
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Title of Poster: Improving our understanding of porin permeability in Gram-negative bacteria

Greg Basarab, PhD
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Greg Bisacchi, PhD
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Veronica Kos, PhD
Postdoctoral Fellow, BioScience
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Title of Poster: Genetic characterization of antibacterial resistance in P. aeruginosa

other AZ colleagues attending:
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Research Interests: Antibiotic Drug Discovery, Natural Products, Microbiology, Mechanism of Action  
Title of Talk: Searching for Gold in the BAARN: The Future of Natural Products in Drug Discovery

Aileen Rubio, PhD  
Director, Infectious Diseases  
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Research Interests: New antibacterial project creation with proof of concept data to enable early decision making.

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Jared Silverman, PhD  
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Research Interests: Antibiotic discovery and development, mechanism of action, mechanisms of resistance
Andrew Tomaras, PhD
Senior Principal Scientist
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Title of Talk - Keeping it Real: in vivo relevant screening for new antibacterial agents

Leonard Duncan, PhD
Senior Research Scientist
Vertex Pharmaceuticals, Inc.
Bioventures Center
2500 Crosspark Rd., Coralville, IA 52241
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Title of Talk: Essentiality is not enough: Lessons learned from bacterial DNA Ligase

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Research Interests: My laboratory has an NIH-funded program of International Collaborations in Infectious Disease Research, in collaboration with the International Centre for Diarrhoeal Disease Research in Dhaka, Bangladesh, to analyze human mucosal immune responses following natural V. cholerae infection, to analyze gene expression in V. cholerae directly in human samples, to use human immune responses following cholera to identify bacterial genes uniquely expressed during human infection, and to use this information to develop an improved cholera vaccine.

David Hooper, MD
Professor of Medicine. Harvard Medical School
Chief, Infection Control Unit
Associate Chief, Division of Infectious Diseases
Massachusetts General Hospital
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Research Interests: New antibacterial project creation with proof of concept data to enable early decision making.

Title of Talk: Current clinical problems of antimicrobial resistance

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TUFTS MEDICAL CENTER

Helen Boucher, MD, FIDSA, FACP
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Title of Talk: Rapid bacterial diagnosis: are we there yet?
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Title of Poster: Intrinsic antibiotic resistance of enteric bacteria: Translational research is needed

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Pew Charitable Trusts’ Antibiotics and Innovation Project develops and supports policies that will spur innovation of new antibiotics to fight infections today and to ensure a healthy nation in the future.
Title of Session: Tackling the Challenges of Antibiotic R&D

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Micromyx is a CRO dedicated to serve the pharmaceutical and biotechnology industry in their efforts to develop anti-infectives. At our company we perform all the non-clinical microbiological testing necessary to support an IND and NDA (e.g. profiling, resistance development, test method development, mechanism of action, etc), and we also serve as consultants.

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Open Access Drug Discovery
Michael Pollastri, Northeastern University
Neglected tropical diseases (NTDs) are infectious diseases affecting the poorest people in the world. There has been little done to find new drugs for NTDs within the pharmaceutical industry, owing to the cost pressures inherent in the risky and expensive drug discovery process. As a result, this work is primarily carried out in a wide range of academic and non-profit institutions, coupled with private companies and public-private partnerships. The Global Health Initiative at Northeastern University has, at its core, a drug discovery effort that is focused on identifying new therapeutics for African sleeping sickness, Chagas disease, leishmaniasis, and malaria. Successfully executing such projects relies on a panoply of research capabilities that cut across multiple disciplines and involve faculty with vastly different expertise. Few institutions possess all of these. Thus, capabilities in parasitology, screening, drug metabolism, computational chemistry, cheminformatics/bioinformatics, and in vivo infection models, matched with our medicinal chemistry expertise, comprise a distributed model of discovery, driven from within Northeastern. This model could easily be expanded for other infectious diseases. As a means to illustrate this model, the structure and infrastructure of our ongoing collaborator network will be described, and the challenges and advantages of working on NTD drug discovery in this manner will be discussed, highlighted with case studies of medicinal chemistry projects that have been effectively advanced for these diseases.

Digging for Gold in the BAARN: The future of Natural Products in Drug Discovery
Victoria Knight-Connoni, Cubist
Natural products have been optimized by nature for their biological activity and have historically been a productive source of novel bioactive compounds. Approximately 75% of antibacterial and antitumor drugs are natural products or inspired by natural products. Traditional approaches to microbial natural product discovery involve culturing strains, preparing extracts, and using bioactivity-guided fractionation to isolate active compounds. This approach limits identification to the compounds expressed under a given set of culture conditions and often requires screening a large numbers of strains. Identification of low abundance compounds requires modifications to the traditional methods to increase the titer of secondary metabolites.

A high-throughput genetic screen for new factors involved in Gram-negative envelope biogenesis
Tom Bernhardt, Harvard
The envelope of Gram-negative bacteria is a formidable barrier that is difficult for antibiotics to penetrate. Thus, the list of treatments effective against these organisms is small and with the rise of new resistance mechanisms is shrinking rapidly. New therapies to treat Gram-negative infections are therefore sorely needed. This goal will be greatly aided by a detailed mechanistic understanding of envelope assembly. Although excellent progress in the identification of envelope biogenesis systems has been made in recent years, many aspects of the process remain to be elucidated. We therefore developed a simple, quantitative, and high-throughput assay for mutants with envelope defects and used it to screen an ordered deletion library of Escherichia coli. The screen was robust and correctly identified numerous mutants known to be involved in envelope assembly. Importantly, the screen also implicated 102 genes of unknown function as encoding factors that likely impact envelope biogenesis. As a proof of principle, one of these factors, ElyC (YcbC), was characterized further and shown to play a critical role in the metabolism of the essential lipid carrier used for the biogenesis of cell wall and other bacterial surface polysaccharides. Further analysis of the function of ElyC and other hits identified in our screen is likely to uncover a wealth of new information about Gram-negative envelope biogenesis and the vulnerabilities in the system suitable for drug targeting. Moreover, the screening assay described here should be readily adaptable to other organisms to study the biogenesis of different envelope architectures.

Essentiality is not enough: Lessons learned from bacterial DNA Ligase
Len Duncan, Vertex
The urgent need for new Gram-negative antimicrobials has led to the exploration of numerous novel bacterial targets. Demonstrating that a proposed target gene is essential for bacterial growth often plays a critical role in early evaluation efforts. However, it has become clear that such a finding, by itself, may not be sufficient to begin a drug discovery campaign and that additional data are required to rationally rank potential alternative targets. An example of this principle is NAD*-dependent DNA ligase, which has been the target of several recent discovery campaigns. Although LigA function is indeed essential for growth, we found that two aspects of LigA physiology are likely to hinder the discovery of efficacious inhibitors. First, data from protein depletion experiments and System Dynamics Modeling confirmed that LigA activity is present in large excess relative to minimal growth requirements: it is necessary to decrease the normal level of LigA in E. coli by ~98% before growth is severely affected. Second, high-level resistance (with little or no impact on fitness) readily develops against several different chemical scaffolds that target the AMP-binding site in LigA. Importantly, many of these mutations map to amino acid residues within the OB, Zn and HhH DNA-binding domains. This suggests that the effects of known LigA inhibitors can be negated by alterations in regions of LigA that are distant from the compound-binding site. These findings, coupled with the well-known intrinsic resistance of Gram-negative bacteria, make the successful development of LigA inhibitors appear to be particularly challenging.
Polymeric Nanoparticles for Targeted Delivery of Antibiotics
Jinjun Shi, MIT

The application of polymeric nanotechnologies on drug delivery has demonstrated tremendous success in treatment of various diseases. We have recently successfully developed targeted, controlled-release polymer nanoparticles for the delivery of different types of therapeutics including small molecules and vaccines. These technologies have laid the foundation for the development and clinical translation of BIND-014 nanoparticles for solid tumors (Phase II) and SEL-068 vaccine nanoparticles for smoking cessation and relapse prevention (Phase I). Recent studies have also shown the great potential of polymeric nanotechnologies for infection treatment by selective targeting of bacterial membranes for lysis, improved drug delivery, enhanced drug function, among others. This talk will overview some of these efforts and our recent work of developing surface charge-switching polymeric nanoparticles for bacterial cell wall-targeted delivery of antibiotics. Furthermore, the application of nanoparticle-mediated RNA interference on antimicrobial therapy will be discussed.

Network biological approaches to bacterial infections
Jim Collins, Boston University

In this talk, we will highlight recent work in synthetic biology and systems biology aimed at elucidating the mechanisms of action of antibacterials and bacterial responses to antibiotic treatment. We discuss how the insights arising from these studies can be harnessed to create more effective antibotics and innovative antibacterial therapies to treat resistant and persistent infections.

Keeping it Real: in vivo relevant screening for new antibacterial agents
Andrew Tomaras, Pfizer

The discovery of new antibacterial agents is becoming increasingly challenging. For those who remain committed to this disease area, the path is littered with hurdles that include the identification of new sources of chemical matter, the avoidance of pre-existing or rapid resistance generation, as well as the establishment of predictive pre-clinical models that effectively forecast compound efficacy. The use of classical in vitro methods, justified by historical successes, has also been proven unsuccessful at predicting in vivo efficacy in several instances recently. Additionally, by conducting new screens for novel antibacterial agents using standard conditions as opposed to those that are more physiologically-relevant in vivo, our ability to identify bacterial targets and pathways that are crucial for virulence and/or in vivo survival has been significantly hindered. This talk will describe new screening paradigms for antibacterial drug discovery in the future.

A Stereoselective Inhibitor Identifies a New T3SS Target
Don Moir, Microbiotix

The type III secretion system (T3SS) is a clinically important virulence mechanism in Pseudomonas aeruginosa that translocates protein effector toxins into human phagocytic cells, crippling the host rapid immune response. Multiple animal infection model and human association studies indicate that T3SS is strongly associated with disease severity and poor clinical outcomes. The P. aeruginosa needle tip protein PcrV has been the only known target of a T3SS inhibitor, the monoclonal antibody KB001, which is in clinical studies for ventilator-associated pneumonia and cystic fibrosis. We previously identified a small molecule phenoxyacetamide inhibitor of P. aeruginosa T3SS with highly responsive SAR including pronounced stereoselectivity, which indicated interaction with a specific protein target (Aiello et al., 2010). To identify the target, mutations conferring resistance to the inhibitors were selected, and the mutant locus was mapped by deep sequencing. Selection for resistance to an inhibitor of this non-essential target was accomplished by engineering a selection strain to exhibit gentamicin resistance (GmR) and to secrete a T3SS effector-β-lactamase fusion protein (ExoS-BLA), both under T3SS regulation. Selection for GmR in the presence of T3SS inhibitor MBX 2359, followed by screening for loss of inhibition of secretion of ExoS-BLA, yielded several mutants. All mutant strains harbored mutations in the same T3SS structural gene, pscF, encoding the T3SS needle protein. Mutant alleles complemented a pscF deletion strain and were sufficient to provide inhibitor resistance to a variety of phenoxyacetamide T3SS inhibitor analogs but not to previously published inhibitors with hydrazone, phenylmaleimide, or thiazoloinodole scaffolds.

Beyond the Bug
Deb Hung, Broad Institute

In this era of increasing antibiotic resistance, there is great need for new antibiotics with novel mechanisms. However, in addition to the discovery of new molecules that selectively kill bacteria, our growing understanding of the complex host-pathogen interaction suggests novel ways to intervene to decrease morbidity and mortality. One such strategy is to target the host, which potentially in conjunction with classical antibiotics, could provide a novel therapeutic model that is no longer pathogen-centric and that could lead to increased survival.
Targeting the Gram-Negative Outer Membrane
D. G. Brown, M. Gagnon, AstraZeneca Pharmaceuticals, Waltham, MA

Background: A significant barrier preventing many compounds from intrinsic antibacterial activity is their susceptibility to efflux. We hypothesized that both charge and MW may be important for the ability of *P. aeruginosa* and *E. coli* to recognize and efflux potential antibacterial compounds. Methods: A diverse set of putative antibacterial compounds were screened for antibacterial activity using two pairs of isogenic strains of *P. aeruginosa* and *E. coli* (parents, and a MexAB-OprM or TolC, respectively). An efflux ratio was defined as the MIC of the parent divided by the MIC of the efflux pump mutant. Two categories were assigned as either low efflux (ratio <8), or high efflux (>20). The low efflux set contained 128 compounds for *P. aeruginosa* and 78 for *E. coli*. The high efflux set contained 962 compounds for *P. aeruginosa* and 3503 for *E. coli*. Charge and MW descriptors were calculated for each set. Results: Molecules with MW ranges of 400-600 were 5-fold more likely to be in the high efflux (vs. low efflux) category for *P. aeruginosa* and 2-fold for *E. coli*. In *E. coli*, 52% of these were positively charged molecules, whereas in *P. aeruginosa* only 12% fell in this category. Conclusions: In contrast to the previously reported analysis on *H. influenzae* (Manchester et al. J. Med. Chem 2012, 55, 2532-37) where a proportional increase of efflux with molecular weight was observed, this new analysis on *P. aeruginosa* and *E. coli* demonstrated a U-shaped dependence of molecular weight on efflux. This analysis points to both unique size and electrostatic permeability requirements between Gram-negative species. This analysis will help enable the design of novel Gram-negative antibacterial screening libraries by incorporation of these features.

**Eradication of bacterial populations by activation of the ClpP protease**
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Antibiotic tolerance is a property of persister cells, phenotypic variants of regular bacteria. Conventional antibiotics kill by corrupting their targets, but these are inactive in dormant persisters, leading to tolerance. Persisters cells have been implicated in recalcitrance of chronic disease and various biofilm infections such as endocarditis, cystic fibrosis, osteomyelitis and infections of implanted devices. We reasoned that a compound capable of activating and dysregulating a target in dormant cells would kill persisters. The acyldepsipeptide antibiotic (ADEP4) has been shown to activate the proteolytic core of the Clp protease (ClpP) in an ATP independent manner. Stationary phase populations of bacteria have a high proportion of persister cells. We found that ADEP4 had impressive bactericidal activity against stationary phase S. aureus, and resulted in the degradation of over 400 intracellular targets, with ribosomal proteins displaying the highest level of degradation. clpP mutants are resistant to ADEP4 and occur at high frequency, however, we find that they display increased susceptibility to killing by a range of conventional antibiotics. Combining ADEP4 with rifampicin leads to eradication of persisters and stationary phase populations of S. aureus. We found that this eradication of populations was not limited to S. aureus, and similar efficacy was seen against a variety of bacteria. The ADEP4/rifampicin combination similarly eradicated S. aureus biofilm and a deep-seated murine infection. ATP-independent protease activation provides an approach to killing persisters and eradicating chronic infections.

**Intrinsic antibiotic resistance of enteric bacteria: Translational research is needed**
Alice Erwin, Erwin Consulting, Somerville, MA

Hypothesis: Study of intrinsic resistance mechanisms has yielded knowledge useful in discovery of new gram-negative antibiotics. Background: Medicinal chemists ask, "What kinds of compounds get into bacteria?" Microbiologists respond, "We don't know." Recent research has given us a much better understanding of the structure and function of efflux pumps, the passage of antibiotics through porins, and the mechanisms of outer membrane biogenesis and modulation. Approach: We searched the literature on each aspect of intrinsic resistance from the 1970's through the present, seeking studies that compared chemical compounds in susceptibility to a resistance mechanism or in an assay reflecting that mechanism. Results: The vast majority of such studies determined antibacterial activity of a set of diverse compounds toward mutants with altered resistance. While these studies demonstrate that chemical structures differ greatly in susceptibility to intrinsic resistance, there are very few studies in which the magnitude of MIC shift was determined for a series of closely related compounds. Direct study of the interaction of wild-type or mutated porins or efflux pumps with a handful of diverse compounds has allowed identification of likely substrate binding sites and defined the route of substrates. However, it is not yet possible to determine what aspects of a compound affects its function as a substrate for a pump or porin. Conclusion: Existing data do not provide a basis for rational design of compounds predicted to have greater permeation or reduced efflux.
Background: Neisseria gonorrhoeae (NG) is a significant cause of sexually transmitted infections. Historically, penicillin (PEN) was effective in the treatment of gonorrhea however plasmid-mediated penicillinase-producing NG has spread worldwide limiting empiric use of PEN. Additionally, resistance development has occurred for several of the alternative antimicrobial class agents used for empiric therapy of NG infections, including fluoroquinolones (ciprofloxacin, CIP), macrolides (azithromycin, AZM) and tetracycline (TET). Most recently, NG isolates with resistance to ceftriaxone (CRO) and cefixime (CFX) have been reported. AZD0914 is a new inhibitor of bacterial DNA gyrase with activity against fluoroquinolone-resistant Gram-positive and fastidious Gram-negative species including NG. In this study, AZD0914 was tested against a collection of 100 clinical and reference isolates of NG, including isolates intermediate or resistant to AZM, CIP, PEN, and/or TET. Methods: Agar dilution MIC testing of AZD0914 and comparators was conducted according to CLSI guidelines (M07-A9 and M100-S23). Results: AZD0914 was highly active against all NG isolates tested exhibiting a MIC range of ≤0.004-0.25 µg/mL and a MIC\textsubscript{50/90} of 0.06/0.125 µg/mL, respectively. 99% of the isolates were inhibited at MICs ≤0.125 µg/mL. The MIC\textsubscript{50/90} values for AZM were 0.25/0.5 µg/mL; for CFX, 0.03/0.06 µg/mL; for CRO, 0.015/0.06 µg/mL; for CIP, 0.25/2 µg/mL; for PEN, 2/≥2 µg/mL, and for TET, 1/2 µg/mL. Against CIP-intermediate and -resistant isolates, AZD0914 MIC\textsubscript{50/90} values were also 0.06/0.125 µg/mL. Conclusions: AZD0914 was highly active against NG including isolates resistant to CIP, AZM, PEN, and/or TET. AZD0914 exhibited similar in vitro antibacterial activity against both susceptible and resistant NG, indicating a general lack of cross resistance to other drug classes. The high level of in vitro activity and lack of cross resistance to fluoroquinolone-resistant isolates supports further investigations with AZD0914.

Genetic characterization of antibacterial resistance in Pseudomonas aeruginosa
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Objective: Pseudomonas aeruginosa is associated with a number of nosocomial infections and is the major cause of morbidity among individuals afflicted with cystic fibrosis. Many clinical isolates are resistant to a wide variety of antibiotics, making P. aeruginosa infections arduous to eradicate. Antibiotic resistance is challenging to predict as a combination of alleles including classic resistance markers, changes in the presence or activity of pumps, porins, and membrane permeability may be involved. Antibiogram results for an isolate typically take 48 h to generate, time that is critical for treatment. We set out to characterize the key genetic determinants of resistance in clinical isolates of P. aeruginosa. Methods: A total of 415 isolates were selected based upon antibiogram data concerning β-lactams, from several different hospitals and infection sites. Genome sequences were generated for all isolates and an initial analysis was completed for 55 P. aeruginosa to establish methods. Genomes were assembled using CLC Genomic Workbench. OrthoMCL was used to generate clusters of orthologs, and RAxML and FastTree for phylogenetic analysis. Results: A compounds in susceptibility to a resistance mechanism or in an assay reflecting that mechanism. Results: The vast majority of such studies determined antibacterial activity of a set of diverse compounds toward mutants with altered resistance. While these studies demonstrate that chemical structures differ greatly in susceptibility to phylogenetic tree was generated based upon the core genome to provide a snapshot of the overall population structure of P. aeruginosa. The phylogenetic analysis suggested that isolates were diverse and did not segregate based upon country of origin, nor site of isolation. Analysis of genes contributing to the resistome, indicated that a number of different mutations that lead to the inactivation of porins, particularly OprD were present in the β-lactam resistant population. Variations were also identified in a number of other key genes associated with resistance to β-lactams and other drug classes. Conclusions: We have provided an initial snapshot of the genetic diversity of P. aeruginosa and identified gene candidates that can be used to predict the resistance phenotype of a bacterium

Alliance for the Prudent Use of Antibiotics
Barbara Lapinskas and Jane Kramer
Alliance for the Prudent Use of Antibiotics, Tufts University, 200 Harrison Avenue, Posner 3 (Business), Boston, MA

Antibiotics are humanity’s key defense against disease-causing microbes. The growing prevalence of antibiotic resistance threatens a future where these drugs can no longer cure infections and killer epidemics run rampant. The Alliance for the Prudent Use of Antibiotics (APUA) has been the leading global non-governmental organization fighting to preserve the effectiveness of antimicrobial drugs since 1981. With affiliated chapters in over 66 developed and developing countries, we conduct research, education and advocacy programs to control antimicrobial resistance and ensure access to effective antibiotics for current and future generations.
Emergence of epidemic multi-drug resistant Enterococcus faecium from animal and commensal strains

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Enterococcus faecium, natively a gut commensal organism, emerged as a leading cause of multidrug-resistant hospital-acquired infection in the 1980s. As the living record of its adaptation to changes in habitat, we sequenced the genomes of 51 strains, isolated from various ecological environments, to understand how E. faecium emerged as a leading hospital pathogen. Because of the scale and diversity of the sampled strains, we were able to resolve the lineage responsible for epidemic, multidrug-resistant human infection from other strains and to measure the evolutionary distances between groups. We found that the epidemic hospital-adapted lineage is rapidly evolving and emerged approximately 75 years ago, concomitant with the introduction of antibiotics, from a population that included the majority of animal strains, and not from human commensal lines. We further found that the lineage that included most strains of animal origin diverged from the main human commensal line approximately 3,000 years ago, a time that corresponds to increasing urbanization of humans, development of hygienic practices, and domestication of animals, which we speculate contributed to their ecological separation. Each bifurcation was accompanied by the acquisition of new metabolic capabilities and colonization traits on mobile elements and the loss of function and genome remodeling associated with mobile element insertion and movement. As a result, diversity within the species, in terms of sequence divergence as well as gene content, spans a range usually associated with speciation.

Antibiotic Susceptibility Testing Using Forward Laser Scattering
Stephen M. Brecher, Ph.D1, Theodore S. McMinn 2, Dana A. Marshall2
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Background: The need to respond to unknown or antibiotic-resistant bacterial infections supports the requirement for improved methods to quantify bacterial concentration and growth. Optical Density (OD) measurements are a well-established method for estimation but have limited sensitivity, and improved precision at lower bacterial concentrations would enable earlier and faster detection and determination of antibiotic minimum inhibitive concentration (MIC). Methods: A novel light scatter measurement was used to measure concentrations and growth rates for nonpathogenic E. coli in real-time while incubating in Luria Broth (LB) media from a starting concentration of 1x 10^5 CFU/mL. Samples were exposed to eleven different concentrations of Cipro (Alfa Aesar Ward Hill,MA) and bacterial concentration changes were measured. Results were calibrated and confirmed using traditional blood agar cultures. Results: The scatter instrument detected measurable growth within 20 minutes, and differential growth rates between the lower antibiotic concentrations could be unambiguously measured, and MIC estimated within 120 minutes. Conclusion: Forward laser scattering can be a rapid method for determining antibiotic MIC with initial bacterial concentrations below the sensitivity limits of current OD methods. The implications are reduced time to determine antibiotic effectiveness at minimum therapeutic concentrations and at bacterial concentrations as low as 10^5 CFU/mL in LB and possibly other fluids, including native body fluids such as urine.

Development of Rapid PoC Companion diagnostics to Measure Active Infections
Mitch Sanders, CEO ECI Biotech, 88 Ball Street, Northborough MA 01532

ECI Biotech has 24 patents related to measure virulence factors that are biomarkers for active infections. ECI provides a new paradigm for the development of companion diagnostics to measure active infections. This includes but is not limited to wound care, orthopedics, critical care and infusion therapy. ECI’s rapid tests are in general less specific than antibody based tests but have a much higher analytical sensitivity. The tests measure active infection and can be used to assist with clinical trial enrollment or a measure of therapeutic efficacy after treatment.
Innovative strategies are needed to combat methicillin resistant Staphylococcus aureus (MRSA) infections and compound combinations are increasingly viewed as a promising option. We describe a rapid method to identify synthetic lethal target combinations given a transposon library and a small molecule with a known target. We report that two cell envelope modifications previously implicated in S. aureus pathogenesis are synthetically lethal, suggesting a new approach to combination therapy.

Diversity Oriented Synthesis-derived compounds with selective activity against C. difficile.

Jeremy R. Duvall, Maurice D. Lee, IV, Giovanni Muncipinto, Joshua Bittker, Michelle A. Palmer, Michael Foley, and Christina A. Scherer. The Broad Institute, 7 Cambridge Center, Cambridge, MA 02142, USA

The Broad Institute’s Diversity Oriented Synthesis library is composed of 100,000 unique small molecules that combine the accessibility of more traditional pharmaceutical libraries with the structural complexity of natural products. This collection holds great promise for the identification of novel antimicrobial agents. We screened the collection against a clinical isolate of the opportunistic pathogen, Clostridium difficile (strain BAA-1382). The overall hit rate was 0.5%, with approximately 300 compounds selected for MIC determination against C. difficile. One compound series exhibited promising stereoselective structure activity relationships (SSAR) and SAR, and was chosen for further profiling. The hit compounds were potent (MICs ≤ 8 μg/mL) and selective for C. difficile, with little to no activity against other bacterial species. Hit compounds were well tolerated in mice, and exhibited efficacy in a mouse model of acute C. difficile infection.

Antibacterial Activity of and Resistance to Small Molecule Inhibitors of the ClpP Peptidase

Corey L. Compton, Karl R. Schmitz, Robert T. Sauer and Jason Sello, Department of Biology, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02138

There is rapidly mounting evidence that intracellular proteases in bacteria are compelling targets for antibacterial drugs. Multiple reports suggest that the human pathogen Mycobacterium tuberculosis and other actinobacteria may be particularly sensitive to small molecules that perturb the activities of self-compartmentalized peptidases, which catalyze intracellular protein turnover as components of ATP-dependent proteolytic machines. Here, we report chemical syntheses and evaluations of structurally diverse β-lactones, which have a privileged structure for selective, suicide inhibition of the self-compartmentalized ClpP peptidase. β-lactones with certain substituents on the α- and β-carbons were found to be toxic to M. tuberculosis. Using an affinity-labeled analog of a bioactive β-lactone in a series of chemical proteomic experiments, we selectively captured the ClpP1P2 peptidase from live cultures of two different actinobacteria that are related to M. tuberculosis. Importantly, we found that the growth inhibitory β-lactones also inactivate the M. tuberculosis ClpP1P2 peptidase in vitro via formation of a covalent adduct at the ClpP2 catalytic serine. Given the potent antibacterial activity of these compounds and their medicinal potential, we sought to identify innate mechanisms of resistance. Using a genome mining strategy, we identified a genetic determinant of β-lactone resistance in Streptomyces coelicolor, a non-pathogenic relative of M. tuberculosis. Collectively, these findings validate the potential of ClpP inhibition as a strategy in antibacterial drug development and define a mechanism by which bacteria could resist the toxic effects of ClpP inhibitors.

Improving our understanding of porin permeability in Gram-negative bacteria


The need for novel antibacterial therapies continues to increase as resistance to established therapies increases. While there are well established genetic tools to identify and validate essential biochemical targets for antibacterials, translation of these into viable drug discovery targets is still hampered by our inability to identify suitable small molecule inhibitors that exhibit meaningful minimum inhibitory concentrations (MIC), especially versus Gram-negative pathogens. This stems from the fact that despite decades of effort and multiple generations of antibacterials, we still understand very little about what drives compound permeation through bacterial membranes. In this report, we describe efforts we have underway to shed light on cell permeation. We describe how we are using molecular dynamics simulations and modeling of the recognition pocket of OprD to assist in the understanding of structural elements that impact cell permeation through this porin. Ultimately, our goal is to establish structure permeation relationships that could be used to proactively design molecules with superior permeation into Gram-negative pathogens.
Genomics of the Conjunctival Pathogen *Streptococcus pneumoniae*

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*Streptococcus pneumoniae* is a prevalent cause of bacterial conjunctivitis, especially in children. One bacterial lineage in particular, ST448, has caused multiple outbreaks of conjunctivitis and was recently shown by our group to be a major contributor to non-outbreak related ocular infections throughout the US. These findings suggest that some lineages of *S. pneumoniae* possess a unique ocular tropism and are capable of spawning epidemics. In the present study we set out to sequence 21 representative conjunctivitis strains to begin to identify candidate functions these outbreak strains possess that potentially contribute to the ability to cause epidemics, and account for their unusual tropism.

Comparative analysis shows that strains of epidemic conjunctivitis *S. pneumoniae* form a distinct clade that is highly divergent from nasopharyngeal strains. Approximately 20% of the epidemic conjunctivitis genome encodes genes that are only found within this clade. Among the unique genes are several molecules that likely contribute to the ocular tropism, including agglutinin receptors acquired from distantly related Streptococci, a metalloprotease that cleaves mucins decorating the ocular surface, and a variation of typically highly conserved virulence factor that has implications on altered host evasion. Absent from ocular genomes are genes for capsular biosynthesis and surrounding genetic elements, as well as several loci encoding metabolic genes.

The genome landscape content of epidemic conjunctivitis strains are substantially different from even the nearest strain, and possesses a number of genes with the potential to contribute to its prevalence in outbreak and non-outbreak infections and tropism for the ocular surface.

Blocking cell separation in *Pseudomonas aeruginosa* leads to defects in the outer membrane permeability barrier

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*Pseudomonas aeruginosa* is an opportunistic gram-negative pathogen that is one of the leading causes of hospital-acquired infections. *Pseudomonas* infections are notoriously difficult to treat due to the intrinsic resistance of the bacterium to a wide spectrum of antibiotics. The primary antibiotic resistance determinant of *Pseudomonas* is the low permeability of its outer membrane to antimicrobial compounds. Defects in the cell separation systems of *Escherichia coli* and *Salmonella typhimurium* lead to increased antibiotic susceptibility. The cell separation system is comprised of the peptidoglycan amidases, which cleave the septal peptidoglycan to allow for separation of the incipient daughter cells during division, and on the LytM factors, which activate the amidases. *Pseudomonas* encodes two amidases (AmiA and AmiB) and three LytM factors (EnvC, LytM2, and NlpD). We sought to examine the role of these proteins in the *Pseudomonas* cell separation and to test whether their disruption would increase outer membrane permeability to antibiotics. We found that *Pseudomonas* AmiB is essential for viability, and its loss leads to cell chaining and filamentation. Moreover, cells depleted for AmiB show hypersensitivity to a variety of antibiotics belonging to different classes, including vancomycin, as well as to the detergent SDS. Additionally, double disruption mutants lacking other cell separation factors also caused to cell chaining and antibiotic hypersensitivity phenotypes. Our results identify AmiB and the LytM factors of *Pseudomonas* as promising targets of antimicrobial therapy.