BAARN 2020

SCHEDULE

Opening Remarks 9:00am-9:10am

Dr. Michael Gilmore, PhD

Session 1 – New Diagnostics 9:10am – 11:15am

9:10-9:30

Gowtham Thakku
Hung Lab, MGH/Broad/HMS

Multiplexed Bacterial Pathogen Identification and Resistance Testing using Cas13 in Droplet Microarrays

ABSTRACT
Rapid and accurate diagnosis of infections is fundamental to individual patient care as well as broader public health surveillance. Nucleic acid detection has emerged as a crucial method for pathogen identification, but may necessitate a diagnostic hypothesis (such as with amplification-based tests) or require complex infrastructure (as with next generation sequencing). Here, we present a high-throughput system that enables rapid identification of large panels of pathogens and resistance markers with significantly lower operating complexity than sequencing based methods. Our system utilizes two recently developed technologies: (1) Modular CRISPR-Cas13 based nucleic acid sensing that enhances sensitivity and specificity when combined with traditional amplification methods; and (2) A droplet microfluidics system that enables thousands of spatially multiplexed detection reactions at nanoliter volumes. We develop a method to identify unique pathogen genomic targets and demonstrate species-level detection of genomic DNA from nearly fifty clinically relevant bacterial species, all in a single assay. The system can easily be adapted for the detection of any large panel of nucleic acid targets and we also demonstrate the ability to detect multiple key bacterial resistance genes. The compatibility of CRISPR-Cas13 with freeze-drying opens up the possibility of a portable, highly multiplexed assay with broad developing world applications.

BIO
Gowtham is a fifth year PhD student in the Harvard-MIT Program in Health Sciences and Technology. He is advised by Deborah Hung and Paul Blainey at the Broad Institute. Gowtham's current research interests lie at the intersection of engineering, genomics and infectious disease, and he is excited by applications of novel diagnostic tools to clinical medicine and public health. Gowtham's interest in this field stems from a moral philosophy class he took as an undergraduate, and a subsequent summer program in bioethics.

9:30-9:50

Dr. Roby Bhattacharyya, MD PhD
MGH/Broad/HMS

Transcriptional Profiling for Rapid ID Diagnostics

ABSTRACT
Current growth-based antibiotic susceptibility testing (AST) is too slow to guide antibiotic selection in real time, leading to an overuse of empiric broad-spectrum antibiotics. We recently showed that antibiotic-induced transcriptional signatures distinguish susceptible from resistant bacteria and can be detected using a simple multiplexed hybridization assay, providing phenotypic AST within hours instead of days. This assay relies on the principle that susceptible cells become stressed upon brief antibiotic exposure, eliciting transcriptional changes within minutes that distinguish them from unharmed resistant cells. Here we report that, for three major antibiotic classes (beta-lactams, fluoroquinolones, and aminoglycosides), the same gene signatures we previously optimized for one member of each antibiotic class generalize to all members of that class. Furthermore, we show proof-of-concept that transcriptional profiling also predicts antifungal susceptibility in the eukaryotic pathogen Candida albicans. Together, these findings demonstrate the potential of

transcriptional assays as a possible pan-microbial approach to rapid phenotypic AST on a unified platform that can also detect genotypic resistance determinants.

BIO
Roby Bhattacharyya MD PhD is an Assistant Professor of Medicine in the Infectious Diseases Division at Massachusetts General Hospital and Harvard Medical School and an Associate Member at the Broad Institute in the Infectious Disease and Microbiome Program. He is a practicing infectious disease physician at MGH and leads a research laboratory at the Broad focusing on antimicrobial resistance, transcriptomics of pathogens and patients, and rapid diagnostics. Roby grew up in the Chicago area and received his MD and PhD in Biochemistry and Molecular Biology from the University of California at San Francisco.

9:50-10:10

Dr. Karel Brinda, PhD
Hanage/Baym Labs, HSPH/HMS
Rapid Inference of Antibiotic Resistance and Susceptibility by Genomic Neighbor Typing

ABSTRACT
Surveillance of drug-resistant bacteria is essential for healthcare providers to deliver effective empirical antibiotic therapy. However, traditional molecular epidemiology does not typically occur on a timescale that could affect patient treatment and outcomes. We present a method called 'genomic neighbor typing' for inferring the phenotype of a bacterial sample by identifying its closest relatives in a database of genomes with metadata. We show that this technique can infer antibiotic susceptibility and resistance for both Streptococcus pneumoniae and Neisseria gonorrhoeae. We implemented this with rapid k-mer matching, which, when used on Oxford Nanopore MinION data, can run in real time. This resulted in the determination of resistance within 10 min (91% sensitivity and 100% specificity for S. pneumoniae and 81% sensitivity and 100% specificity for N. gonorrhoeae from isolates with a representative database) of starting sequencing, and within 4 h of sample collection (75% sensitivity and 100% specificity for S. pneumoniae) for clinical metagenomic sputum samples. This flexible approach has wide application for pathogen surveillance and may be used to greatly accelerate appropriate empirical antibiotic treatment.

BIO

10:10-10:30

Dr. Ramy Arnaout, MD PhD
AstraDx/BIDMC/HMS
Rapid Multiplexed Phenotypic Antimicrobial Susceptibility Testing

ABSTRACT
Antimicrobial susceptibility testing (AST) is a critical component of caring for patients with bacterial infections but typically takes a day or more, with the delay contributing to significant morbidity and mortality. We have developed an optics-based platform that detects growth across a variety of bacterial species and strains in approximately 30 minutes, with determination of susceptibility vs resistance. Advantages include a phenotypic readout and the ability to test multiple antimicrobials in parallel, in full doubling-dilution series, with replicates for statistical rigor, using inexpensive, commercially-available disposables and at-will inkjet printing functionality for primary specimen analysis, if preferred.

BIO
Dr Arnaout is Associate Director of Clinical Microbiology at the Beth Israel Deaconess Medical Center and Assistant Professor of Pathology at Harvard Medical School.

10:30-11:15

Session 1 Panel Q&A - Gowtham Thakku, Drs. Roby Bhattacharyya, Karel Brinda, Ramy Arnaout

Stretch Break 11:15am – 11:30am

Session 2 – New Therapeutics 11:30am – 1:35pm

11:30-11:50

Dr. Cheleste Thorpe, MD
Tufts School of Medicine
Narrow Spectrum Therapy for C. difficile Preserves Host Microbiota and Secondary Bile Acids

ABSTRACT
Secondary bile acid production from a diverse commensal flora may be a critical factor in preventing recurrence of Clostridioides difficile infection (CDI), by inhibiting organism growth and limiting amounts of pro-germinant primary bile acids. Ridinilazole, a novel narrow spectrum drug for CDI, demonstrated superior sustained clinical response compared to vancomycin in a Phase 2 trial. Longitudinal stool sampling in this trial allowed us to assess microbiota and bile acids differentially present in subjects during/after treatment, and compare within treatment arms. Vancomycin treatment resulted in changes in a broad spectrum of phyla, with decreases in Bacteroidetes, Firmicutes and Actinobacteria and increases in Enterobacteriaceae. In contrast, ridinilazole's effect was confined to only several of the Firmicutes. Stool bile acid compositions were significantly different between ridinilazole-treated and vancomycin-treated subjects at end-of-treatment. In vancomycin-treated subjects, stool composition became dominated by conjugated primary bile acids, with decreased levels of secondary bile acids compared with baseline. In contrast, ridinilazole had minimal effects on bile acids at end-of-treatment; over time these subjects recovered a bile acid composition more similar to a healthy control group. Comparing subjects who recurred to those who did not, a statistically significant difference was observed in total secondary bile acids and in the ratio of total conjugated to secondary bile acids at end-of-treatment. In conclusion, microbiota-preserving CDI treatment also preserves bile acid composition, which may decrease the likelihood of recurrence.

BIO
Cheleste M. Thorpe MD is a practicing infectious disease physician at Tufts Medical Center. As an Associate Professor at Tufts Medical School, she researches gut immune activation and host-pathogen interactions, focusing on Shiga toxin-producing E. coli. Dr. Thorpe's research also includes translational work assessing the impact of antimicrobials on human gastrointestinal microbiota and metabolome, with a specific focus on treatment of C. difficile infection. She is interested in how microbial communities shift in response to disease and antibiotic treatments, and how those shifts may predispose to colonization with antibiotic resistant organisms. She is also interested in the epidemiology of C. difficile, especially with regard to circulating ribotypes and C. difficile antibiotic resistance patterns.

11:50-12:10

Dr. Bree Aldridge, PhD
Tufts School of Medicine
Engineering combination therapies for M. tuberculosis (and other badly behaving bacteria)

ABSTRACT
Mycobacterium tuberculosis infects billions of people worldwide and remains difficult to treat, requiring lengthy multidrug therapies to cure. Design of new multidrug therapies for TB is challenging because it has not been practical to systematically measure drug combination effects. We have recently developed a quantitative framework to efficiently measure, analyze, and predict pairwise and high-order drug interactions, allowing us to prioritize combinations for animal studies. We leverage the efficacy and ease-of-use of our assay to systematically measure drug combinations in multiple growth conditions. We aim to use this data compendium to more precisely map in vitro to in vivo efficacy data, account for the heterogeneity of tuberculosis infection, and formulate more effective drug regimens. The tools we develop for drug regimen design in tuberculosis are broadly application to other difficult to treat infections.

BIO
Bree Aldridge is an Associate Professor in the Department of Molecular Biology and Microbiology and Department of Biomedical Engineering at Tufts University. The Aldridge lab seeks to bring a quantitative framework to understand heterogeneity in tuberculosis and design multidrug therapies that target drug tolerant bacteria. She specializes in combining quantitative experiments and mathematical modeling to create intuitive descriptions of complex cell biology. Her lab website is: https://sites.tufts.edu/aldridgelab/

12:10-12:30

Dr. Johan Paulsson, PhD

Harvard Systems Biology
"Evolution of the enterococci parallels planetary events"

ABSTRACT
Populations of pathogenic bacteria can display great variability in their antibiotic tolerance, where a few cells can survive drugs and repopulate their hosts post-treatment. Many such behaviors have been hard to study because they are rare and transient. I will present platforms for directly observing persister dynamics and heteroresistance phenomena, as well as some clues about underlying mechanisms. I will also discuss recent technological advances in handling bacterial cells for both biophysical characterizations and drug screens.

BIO
Johan Paulsson is a Professor in Systems Biology at Harvard Medical School, where he has been a faculty member since 2005. Before that he was tenured faculty member of Applied Mathematics and Theoretical Physics at the University of Cambridge. Johan completed his undergraduate studies at Uppsala University, Sweden, in 1997, with degrees in mathematics and biology. He stayed on for a PhD using approaches from statistical physics to understand stochastic chemistry in cells. After moving to an experimental department, his research interests expanded to broadly consider single cell dynamics and microbial biophysics. In recent years, his group further focused on developing new assays and technologies for quantifying behaviors in cells, particularly with applications to persistence and resistance phenomena.

12:30-12:50
Dr. Ruben Tommasi, PhD
Entasis Therapeutics
An Adventure in Antibacterial Drug Discovery: Competing Methyl Effects on Biochemical Potency and Cell Accumulation

ABSTRACT
Antibacterial drug discovery is challenging and riddled with failures in our attempts to identify inhibitors with novel modes of actions. This has been discussed for many years and to date there has been no clear reason as to why so many programs on genetically validated targets have failed to render candidates to the clinic. One key reason why biochemical activity does not translate into microbiological activity is the challenge of cell permeation, in particular in the Gram-negative pathogens. While novel approaches to address this key need are being actively worked on, with sights on generating 'rules for permeation' for these challenging pathogens, we are still far from being able to routinely design molecules with permeation in mind. We present here our recent experience on optimizing covalent inhibitors of the well-validated targets of the β-lactam class of antibiotics, the Penicillin-Binding Proteins (PBPs). While seeking to enhance the efficacy of the diazabicyclooctane class of inhibitors towards broader spectrum PBP activity, we identified a dramatic methyl effect on the Pseudomonas aeruginosa PBP3 kinetic parameters. Unfortunately, this beneficial effect on biochemical potency came along with detrimental consequences for microbiology which were quite unexpected. Our efforts to overcome these challenges and learnings derived thereof will be shared in this presentation.

BIO
Dr. Tommasi obtained a doctorate degree in Organic Chemistry from the SUNY–Albany in 1992 with Prof Frank M. Hauser. Dr. Tommasi completed two Post-Doctoral assignments at UC Boulder with Prof. Gary Molander and Upjohn, where his work on the dihydropyrone class of HIV protease inhibitors lead to the discovery of Tipranavir. In 1994, Dr. Tommasi joined Ciba-Geigy (now Novartis) as a medicinal chemist, working in several therapeutic areas including arthritis, bone metabolism and infection. During his 17-year tenure at Novartis, Dr. Tommasi lead his teams to advance two candidates to Phase 2 clinical studies (HCV protease inhibitor – BZF961; EF-tu inhibitor for C. difficile – LFF571). In 2011, Dr. Tommasi joined AstraZeneca to lead the Infection Chemistry team. Currently, Dr. Tommasi is the Chief Scientific Officer of Entasis Therapeutics, the spinout of AstraZeneca's Infection franchise. These efforts have resulted in three Entasis clinical stage development candidates (2 Ph3 and 1 Ph1). One of Dr. Tommasi's main interests is to improve understanding of factors that affect drug permeation into Gram-negative organisms. Dr. Tommasi is the co-author of 37 papers and co-inventor of 14 patents.

12:50-1:35
Session 2 Panel Q&A **-** Drs. Cheleste Thorpe, Bree Aldridge, Johan Paulsson, & Ruben Tommasi

Stretch Break 1:35pm – 1:50pm

Session 3 – Alternative Therapeutics & Entering the Market 1:50pm – 3:55pm

1:50-2:10
Dr. Su Chiang, PhD
CARB-X
CARB-X: Supporting innovation to address drug-resistant bacteria

ABSTRACT
CARB-X is a global non-profit partnership dedicated to accelerating antibacterial research to tackle the global rising threat of drug-resistant bacteria. With up to US$480 million to invest in 2016-22, CARB-X funds the best science from around the world. The CARB-X portfolio is the world's largest early development pipeline of new antibiotics, vaccines, rapid diagnostics, and other products to prevent, diagnose, and treat life-threatening bacterial infections. CARB-X is led by Boston University and funded by the US Department of Health and Human Services Biomedical Advanced Research and Development Authority (BARDA), the Wellcome Trust, Germany's Federal Ministry of Education and Research (BMBF), the UK Government's Global Antimicrobial Resistance Innovation Fund (UK GAMRIF), the Bill & Melinda Gates Foundation, and receives in-kind support from the US National Institute of Allergy and Infectious Diseases (NIAID).

BIO
Su Chiang has been an Alliance Manager at CARB-X since 2018. Prior to that, she was Senior Associate Director at the Blavatnik Biomedical Accelerator at Harvard University, which supports the commercialization of Harvard faculty discoveries in applied life sciences. Earlier, she was Assistant Director of Small Molecule Screening at the New England Regional Center of Excellence in Biodefense and Emerging Infectious Diseases at Harvard, which fostered the development of vaccines and therapies against emerging and reemerging microbial pathogens. She has a Ph.D. in Medical Sciences (Microbiology and Molecular Genetics) from Harvard.

2:10-2:30
Dr. Silvia Caballero, PhD
Vedanta Biosciences
VE707, a live biotherapeutic product for MDRO decolonization as an infection prevention strategy

ABSTRACT
Current treatment options for infections with multidrug-resistant organisms (MDRO), such as carbapenem-resistant Enterobacteriaceae (CRE), rely on toxic, narrow-spectrum antibiotics with known resistance. MDRO gastrointestinal (GI) colonization often precedes infection in highly susceptible patient populations and is associated with a 5-10-fold infection risk, suggesting that MDRO intestinal decolonization could be a potential strategy to prevent infection with these organisms. Because microbiota disruption is a major risk factor for MDRO colonization, there has been increasing interest in fecal microbiota transplantation (FMT). Although clinical experience indicates that FMT is effective, MDRO decolonization rates range widely from 30-90%. This variability underscores the need for a uniform microbiome-based product that has robust efficacy and can be produced and administered in a standardized manner, circumventing FMT's associated safety concerns. Vedanta is addressing the critical need for novel therapeutics to prevent MDRO infection by developing VE707, a live biotherapeutic product (LBP) consisting of well-characterized, beneficial gut bacteria that can eliminate intestinal carriage of MDROs, restore a healthy microbiota and prevent infection and colonization recurrence.

BIO
Silvia Caballero is Associate Director of Infectious Diseases at Vedanta Biosciences working on developing a new class of microbiome-based therapies to combat the growing threat of antibiotic resistance. She leads the Multidrug Resistance program at Vedanta and is spearheading Vedanta's efforts to develop bacterial consortia designed to fight off superbugs in the intestine as a strategy to prevent infection. She earned her BA in Biological Sciences from Hunter College of the City University of New York and received her Ph.D. from Weill Cornell University where she investigated the role of the intestinal microbiota in preventing MDRO colonization. Her research led to the identification of bacterial species responsible for eliminating vancomycin-resistant Enterococcus from the gastrointestinal tract. This study was the first of its kind to demonstrate that a defined bacterial consortium could exert the same level of protection provided by an intact microbiota against a highly antibiotic-resistant pathogen. Silvia has received fellowships from the Gates Foundation and the Howard Hughes Medical Institute and was the recipient of the Innovator of the Year award in 2019 and 2018 by MIT's Technology Review Under 35 Global and Latin America editions.

2:30-2:50

Christina Larkin
Spero Therapeutics
Building a sustainable antibiotic commercial model

ABSTRACT
There are a lot of misconceptions about commercial sustainability in the antibiotic space. Because of some of the recent bankruptcies in the space it has caused the market to question the sustainability of antibiotic companies. The journey to building a sustainable model includes a hero product, frequently updated expert advice guidelines, value based pricing, reimbursement reform and multiple options for capital until breakeven. The talk will include an overview of high unmet need areas, learnings from the oncology market and solutions for reimbursement reform. A healthy ecosystem of biotech, payers, KOLs, investors, Pharma and government can help us bridge to sustainability and ultimately build a sustainable commercial model.

BIO
Cristina Larkin is the Chief Operating Officer at Spero Therapeutics in Cambridge, MA. A strategic, results-driven company builder passionate about solving complex business challenges and impacting the lives of patients. A key catalyst for fund raising efforts, and integral in building strong relationships with investors and clients. Adept at wearing a variety of leadership hats in areas such as overall corporate strategy, commercial, market access, medical affairs, people and culture, and finance. Proven experience building, launching, and leading teams in a wide diversity of therapy areas including Infectious Disease, Urology, Rheumatology, Women's Health, Analgesia, and CNS. Ms. Larkin has over 25+ years of experience developing strategic commercial insights for biopharmaceutical companies and their infectious disease products such as Avycaz, Dalvance, Teflaro, Levaquin and Floxin. Prior to joining Spero, she served as Assistant Vice President for Allergan, formerly Forest Laboratories. During that time, Ms. Larkin led the commercial hospital antibiotic franchise team and was responsible for the US launch and execution strategy for several antibiotics. Additionally, she was a member of the business assessments and business development team and played an integral role in the out-licensing of ceftaroline to AstraZeneca, the acquisition of Durata and more.

2:50-3:10

Dr. Minmin (Mimi) Yen, PhD MPH
PhagePro
Phage for the masses: Using phages as a global health intervention in low- and middle-income countries

ABSTRACT
In low- and middle-income countries (LMIC), the threat of antibiotic resistance is growing at an alarming rate. Widespread ease of access has increased antibiotic consumption rates and clinical misuse. These regions are also more likely to lack clean water and have issues with sanitation and hygiene, contributing to high numbers of diarrheal disease. LMIC are balancing the burdens of infectious and noncommunicable diseases, stretching their already low resources. Phages provide an affordable, convenient alternative to prevent and treat bacterial diseases, particularly in areas where logistical infrastructure is poor. PhagePro has developed a phage cocktail, ProphaLytic-Vc (PVC), that is targeted towards the causative agent of cholera Vibrio cholerae. Cholera is an acute diarrheal disease that causes rapid dehydration; death can occur as quickly as 12 hours. In addition to being endemic in 51 countries, cholera epidemics often occur in the aftermath of natural disasters or during humanitarian crises such as war. It is rapidly becoming extensively drug resistant, in part due to the use of antibiotic prophylaxis as a way to contain the outbreaks. PVC is intended as an antibiotic alternative to provide immediate protection for those most at-risk for cholera, including household contacts in endemic settings and refugee camps in epidemic settings. To be of most use, PhagePro is developing PVC as a solid formulation to be stable in hot and humid conditions, easing the burden of cold-chain logistics for mass distribution in emergency conditions. Phages have the potential to be transformative global health interventions, if the context for their use in LMIC is taken into account during product development. With a disproportionate number of antibiotic-resistant-related deaths predicted to occur in LMIC, phages are uniquely suited as a solution to this public health threat.

BIO
Mimi is passionate about bringing innovation to the world's most vulnerable communities to reduce global health inequities. As the CEO and co-founder of the early-stage biotech startup PhagePro, she has focused on reducing antimicrobial resistance in resource-limited settings.

Mimi graduated from MIT in 2011 and earned her PhD from Tufts. After her Ph.D., Mimi pursued a Master's in Public Health at Boston University. She has also served as the U.S. representative in the Young Leaders Circle for three years as a part of American Society of Microbiology's initiative to address the needs of international early-stage scientists. Currently, she serves as the U.S. One Young World Delegate to elevate the voices of healthcare workers around the world.

For her work with PhagePro, Mimi has been awarded multiple honors and fellowships including MIT Technology Review 35 Innovators Under 35, Massachusetts Next Generation Initiative, The Capital Network Female Founder Fellowship, and the Henri Termeer Legacy Program.

3:10-3:55
Session 3 Panel Q&A **–** Drs. Su Chiang and Silvia Caballero, Christina Larkin, Dr. Minmin Yen

Stuart Levy Keynote Address 4:00pm – 5:00pm

4:00-4:10
Dr. Michael Gilmore, PhD
Intro to Stuart Levy Keynote Address

4:10-5:00
Dr. Kim Lewis
Northeastern University
Discovering Antibiotics for Unmet Medical Needs

ABSTRACT
We are experiencing an Antimicrobial Resistance (AMR) crisis, brought on by the drying up of the antibiotic discovery pipeline, and the resulting unchecked spread of resistant pathogens. Antibiotic tolerance presents an independent unsolved problem. Bacterial populations form dormant persister cells that are not killed by commonly available antibiotics, and are responsible for recalcitrance of a wide range of infections, such as those associated with cystic fibrosis, biofilms of indwelling devices, and tuberculosis. We are developing platforms for antibiotic discovery that resulted in several developmental compounds. These include anti-persister compounds ADEP and lassomycin that act by corrupting the ClpP protease; teixobactin from uncultured bacteria that binds Lipid II and Lipid III, precursors of cell wall polymers, and for which there is no detectable resistance; and darobactins, a novel class of antibiotics from the nematode microbiome acting against Gram-negative pathogens that inhibit the outer membrane chaperone BamA.

BIO
Kim Lewis is a University Distinguished Professor and Director, Antimicrobial Discovery Center at Northeastern University in Boston, a Fellow of the American Society of Microbiology, and a Fellow of the American Association for the Advancement of Science. He obtained his Ph.D. in Biochemistry from Moscow University in 1980, and has been on the Faculty of MIT, University of Maryland, and Tufts University prior to coming to Northeastern. Dr. Lewis is a member of Faculty 1000, a recipient of the MIT C.E. Reed Faculty Initiative Award, and is a recipient of the NIH Director's Transformative Award.

Virtual Happy Hour 5:15pm – 6:15pm
Zoom info shared with registered participants