2016 EUROPE – NORDIC – U.S. SYMPOSIUM

"New Frontiers in Antibacterial Resistance Research"

Karolinska Institute

Stockholm

Introduction

NIAID and JPIAMR, along with the Swedish Research Council, held a Symposium entitled "New Frontiers in Antibacterial Resistance Research," 20 and 21 January 2016. The objectives of the symposium were:

- To discuss cutting-edge approaches to address antibacterial resistance.
- To foster communication and research collaborations among scientists in the EU and US
- To share information on funding opportunities to advance antibacterial resistance research.

Opening Session:

Moderator: Mats Ulfendahl, Karolinska Institutet and JPIAMR

The workshop began with welcoming remarks from Jonas Björck, Director from the Ministry for Higher Education and Research, Sweden and Robert Gilchrist, the Chargé d'Affaires, U.S. Embassy, Sweden. This was followed by two keynote presentations from Fernando Baquero and Henry F. Chambers. Dr. Baquero's presentation dissected the likelihood of different threats associated with antibiotic resistance. For example, we are unlikely to return to a truly "pre-antibiotic era" due to vast improvements in hygiene and supportive medical care since the introduction of antibiotics. However, numerous studies support the idea that antibiotic resistance increases the number of severe infections. Dr. Chambers's presentation focused on several critical components of the Anti-Resistance Tool Box: prevention; immunotherapies; and better use of existing antibiotics through the introduction and use of rapid diagnostics, stewardship, and better treatment strategies. He also discussed the promise of innovative clinical trial designs in the study and implementation of these tools.

Session 1: MOLECULAR EPIDEMIOLOGY AND EVOLUTION OF ANTIBACTERIAL RESISTANCE

Moderator: Henry F. Chambers, University of California San Francisco

There are both similarities and differences in the current patterns of resistant bacteria in the US and the EU. In session one, experts in the molecular epidemiology of resistant bacteria gave overviews of the current state of the problem on both sides of the Atlantic and also touched on the global dissemination of resistance genes. Jordi Vila Estape defined high risk bacterial clones as clones that (1) are associated with antimicrobial resistance of clinical importance, (2) have the ability to efficiently colonize the host, (3) are transmitted, and (4) produce infections. High risk clones have increased markedly since 2001 and are responsible for the majority of ESBL-producing *E. coli* (ST131, containing the CTX-M-15 ESBL gene), carbapenem-resistant *Klebsiella* in Europe (ST258, containing the KPC-2 gene and ST398 and ST101, containing the OXA-48 gene), and *Pseudomonas* (ST235, containing the VIM-2 gene). Barry Kreisworth introduced the idea of a "plasmid epidemic" in which plasmids containing resistance genes such as NDM, OXA and KPC-2 spread quickly throughout the world due to global travel and immigration. The KPC-2 gene, primarily associated with the ST258 clone, was first identified in the US and has since spread globally. Molecular epidemiology studies of carbapenem-resistant Enterobacteriaceae in China have revealed more heterogeneity in clonal distribution than in the US or EU. The recent discovery of the plasmid-encoded Mcr-1 gene, which confers resistance to the last-line drug colistin, is particularly worrisome and potentially linked to the use of colistin in agriculture. Lance Price discussed the contribution of antibiotic use in livestock production to antibiotic-resistant human infections. It is well-established that classical foodborne pathogens, such as *Salmonella*, can cause resistant infections in humans when food is not properly cooked. More recently, it has been established that livestock-associated pathogens, such as MRSA ST398, can cause infections in farmers and others who have direct contact with colonized animals. It is possible to use phylogentic analysis to determine transmission patterns between humans and animals. Recent studies suggest that a subset of urinary tract infections could be associated with certain foodborne *E. coli* strains. Overall, the speakers and discussion in this session stressed that active surveillance in humans, animals and the environment, screening of patients for multi-drug resistant bacteria upon hospital admission, and the development of rapid assays to detect high-risk clones should all be pursued. In the long-term, interventions that block the conjugation process could help prevent plasmid dissemination.

Session 2: APPROACHES TO COMBAT ANTIBACTERIAL RESISTANCE: ENABLING TECHNOLOGIES

Moderator: Otto Cars, ReAct and Uppsala University

Session two focused on technological innovations that hold promise for helping to address antimicrobial resistance. Roy Kishony's presentation explored combination therapy to slow down or even "reverse" resistance. Combination therapies need to be selected based on data to help limit

resistance. George Drusano discussed the use of pharmacological data and mathematical modeling to determine dosing regimens that suppress antibiotic resistance emergence, which often differ from the lowest doses that decrease the bacterial burden. Systematic analysis of the discussed approaches and clinical studies are needed for potential translation into clinical practice. Michael Mourez described the TRANSLOCATION project, a public-private collaboration within the IMI-funded New Drugs 4 Bad Bugs programme. The project aims to inform development of new antibiotics for Gram-negative bacteria by studying the bacterial permeability barrier and developing methods to examine uptake and efflux of antibiotics. A key component of the work is data sharing among all involved partners through an online tool, something increasingly called for within the field and which could serve as inspiration for other initiatives. Herman Goossens highlighted two areas where rapid diagnostics would be highly useful and could provide cost savings: to aid patient enrollment in clinical trials of narrow-spectrum drugs and for guiding treatment. The complexity and expense of developing new diagnostics is underappreciated, and there has been a long-term underfunding of diagnostic efforts. Furthermore, the needs and specifications for a diagnostic may differ dramatically depending on the application. Slava Epstein presented a new tool to facilitate drug discovery from microbial natural products. The "iChip" is a high throughput bacterial cultivation device allowing much improved recovery of microorganisms from environmental samples. The iChip promises to facilitate the identification of novel antibiotics from natural sources. Already, a number of new antibacterials have been isolated from bacteria using this tool, including the novel antibiotic teixobactin.

The talks and discussions of the session highlighted a number of key areas for action. First, the ability to share successes, failures and data could greatly facilitate R&D to address antibiotic resistance. This could be accomplished through the development of an open, web-based knowledge sharing center, such as those employed in the ND4BB programmes. Second, a roadmap for rapid diagnostics including needs, user requirement specifications, and business models for sustained investment and innovation could help inform future public and private efforts to spur diagnostics development. Third, consideration should be given to incorporating pharmacological modeling on preventing the emergence of resistance when new antibiotics are approved.

Session 3: NON-TRADITIONAL APPROACHES TO PREVENT AND TREAT ANTIBACTERIAL RESISTANT INFECTIONS

Moderator: Frank DeLeo, NIAID/NIH

There are many non-traditional approaches to prevent and treat antibacterial resistant infections that can be used as an alternatives to antibiotics or as adjunctive therapies to be used with antibiotics. Birgitta Agerberth discussed modulating the immune system with small molecules to combat bacterial infection. Her group has shown efficacy of phenylbutyrate (PBA) and vitamin D as adjunctive therapy in pulmonary tuberculosis patients in Dhaka. Olaf Schneewind discussed the challenges in developing vaccines to prevent *Staphylococcus aureus* infections but showed promising

data following vaccination with a strain of *S. aureus* with a mutation in the Staphylococcal protein A (SpA). This strain can provide protection in a mouse model. Steven Projan described the potential of monoclonal antibody preparations to prevent and treat bacterial infections. Monoclonal antibodies targeting *S. aureus, C. difficile*, and *P. aeruginosa* are currently in clinical trials. Fredrik Almqvist showed that chemically modifying virulence factors such as curli and amyloid proteins can increase efficacy, solubility, hydrophobicity and lipophilicity. These changes give promising results to prevent infection *in vitro*. Matthew Henn presented data showing that a synthetic microbiota in the form of ecobiotic drugs can address ecological dysbiosis that occurs as a result of antibiotic treatment. These drugs include consortia of commensal microbes that catalyze a change in the microbiome from a disease state to a state of health. Callum Cooper described the promise and limitations of phage therapy to treat bacterial infections. The advantages to phage therapy include their specificity and that they can increase in number in the presence of a suitable host and decay in the absence of a host. Phages are already part of the natural environment so the impact on the environment is limited. The disadvantages of phage therapy include resistance generation, which may be combatted by administering phage cocktails with different receptors; poor PK for systemic administration; and the predominance of uncharacterized phage genes. Finally, Ilana Kolodkin-Gal showed that bacterial biofilms can be imaged using X-rays (micro-CT-X-Ray). The X-rays reveals the mineral scaffolds, which are made up of calcium and carbon dioxide. These scaffolds are essential for the optimal development of phenotypically resistant bacterial communities, and therefore may have value as therapeutic targets.

Session 4: Clinical Research on Antibacterial Resistance

Moderator: *Niels Frimodt-Møller, Rigshospitalet*

Clinical trials to test new interventions and to provide information on how to better use existing ones are critically needed to combat antibiotic resistance. John Rex gave an overview of some of the issues with conducting trials for new antibiotic approval. Developing drugs specifically for MDR/XDR pathogen indications is very difficult due to issues with selecting sites with substantial numbers of these infections. Therefore, for initial drug approval, it is typically easier to conduct trials in one or more "core" indications for both susceptible and resistant pathogens. Ascertaining information about differences in activity against drug sensitive vs. resistant infections may be possible by conducting PK studies in these populations combined with MIC. Vance Fowler and Marc Bonten provided overviews of two clinical trials infrastructures that are currently in place: the US Antibacterial Resistance Leadership Group (ARLG) and the EU COMBACTE, part of the New Drugs 4 Bad Bugs Program of the Innovative Medicines Initiative. The ARLG is conducting a broad range of clinical studies and trials to address diagnostics development and utilization, stewardship programs, strategy trials to provide information on the optimal use of existing drugs, and trials to support the development of new drugs. COMBACTE is conducting several clinical trials focused on the development of new drugs and

prophylactic monoclonal antibodies. These clinical trials infrastructures can be leveraged and aligned to optimally address the many challenges in the conduct of clinical research to address antibacterial resistance. However, additional capacity may need to be built to provide a registration clinical trials network to facilitate drug development in core indications.