EARLY DISCOVERY OF NEW ANTIBIOTICS WORKSHOP REPORT 12-13 January 2017

Auditorium Bio Park, 11 rue Watt, 75013 Paris, France

The workshop on Antibiotic Discovery was hosted by France (ANR), UK (MRC) and JPIAMR and brought together over 20 projects on new targets and compounds funded by the two calls of JPIAMR and a Network call as well as by EC and IMI. The 14 funded JPIAMR project presentations is part of the JPIAMR monitoring policy of funded projects.

The aim of the workshop was to share ideas on antibiotic development by bringing together the PIs in projects areas of AB early discovery and those in clinical development in order to identify potential candidates and increase awareness of entry requirements, exchange experiences, approaches and lessons learnt so far.

This report gives a short description of the presented projects, the challenges and lessons learnt.

Executive Summary:

Session 1 - Target oriented Antibiotic discovery *chaired by Antoine Andremont*

After an introductory talk on the challenges to bring a new antibiotic to the market, the presentations of the first session were focused on target oriented antibiotic discovery.

Considering the growing evidence on the influence of the microbiome on the human health, alternative approaches like reducing virulence or targeting biofilms by inhibiting quorum sensing are valuable and promising.

In order to tackle the technical problems which, occur during the identification of suitable compounds, it was recommended to use mutant bacterial strains for the first assays. E.g., mutant strains for efflux pumps could be a tool to be shared among researchers who face similar problems.

Other challenges and difficulties in finding compound candidates are toxicity and specificity as well as efficiency after metabolism. Solubility of compounds is also mentioned as a challenge. Taken these together, the characterization of the compounds is crucial. This is a process that takes time and this partly due that efficient predictive suitable assays and tools to do medicinal chemistry is lacking.

The overall impression of the presentations suggested that multidisciplinary teams are needed wherever possible. Even clinical partners are necessary from the beginning of the project. It could be one of JPIAMR´s future tasks to provide a contact platform or a market place for research teams offering different technologies or infrastructures.

Session 2 - Discovery of new antibiotics, *chaired by Jonathan Pearce*

Session two focused on projects with different strategies to identify new antibiotics but also to design new combinations antibiotics and/or non-antibiotic combinations. Strategies that were presented were antimicrobial peptides (AMP) with potential as new sustainable therapeutics as they are less prone to induce high-level resistance, clinical trials with aim to assess the effectiveness of old antibiotics in a modern drug evaluation concept and efforts to discover and characterize new molecules of botanical origin that selectively inhibit β-lactamases.

Three JPIAMR networks/working groups within the area of drug discovery also presented their work and explained their plan and ideas and the outcome will finally be presented at the end of 2017. As the JPIAMR research projects, the JPIAMR networks represented different approaches for the discovery of new antibiotics, histidine kinase inhibitors as novel anti infectives, exploration of old drugs for inhibitory discovery and re-implementation of phage therapy based on the use of bacteriophages that are natural viral predators that specifically parasite bacteria to replicate.

The BEAM network represents 50 SMEs from 12 countries and their objective is to produce a new position paper regarding the establishment of economic incentives in order to better sustain the innovation efforts of SMEs.

Overall, many initiatives are ongoing in the search for new antibiotics with different approaches. One question is how to continue from the new understanding and new knowledge generated by the ongoing projects. One key is how to involve SMEs in the process and the BEAM network is a good initiative in that direction but this probably needs further discussion how to do that in the best way.

One issue that was brought up is the lack of incentives to share negative results in order to avoid the same mistakes.

General considerations session 3: Way forward and closing remarks, *chaired by Laura Piddock*

The focus if the discussion was discovery on new compounds. The chair of the session started with a discussion around in vivo studies. L. Piddock asked the speakers and the audience if we should change the discovery paradigm and rather start with animal studies than with cell-free systems? After the presentations there seems to be that cell free system does not work. Reflections that came up was that animal models may indeed be used at an early stage in the process but may not be a general solution. It would be interesting to find ways to share animal models in Europe and invent what is done in this area. Another option is also to modify in vitro systems, for example to look at C. Elegans model and how that can be utilized. A suggestion was made to do a workshop around in vivo models in a broad aspect, including ethical issues.

The JPIAMR roadmap was discussed in the sense of what where are the gaps and should there be more focus on some areas. The conclusion was that there are areas and that it is important to analyse that when the roadmap is updated. For example, was it suggested to bring stakeholders together at an early stage in the process to discuss this.

The next topic that was discussed was the funding landscape and how to synergize the activities and realigning tasks. There are several players at the arena and the role of JPIAMR is more on the discovery side than for example implementation. It is important to have continuous dialogue on how to collaborate with the players, which JPIAMR already do, for example IMI. The audience was also informed that JPIAMR will take part in a new initiative, a joint action named EU-JAMRI, with 45 other partners in Europe. The application is now under negotiation with DG-Santé. The initiative aim to propose concrete steps enabling European countries to strengthen the implementation of efficient and evidence-based measures to tackle AMR and HCAI, building on existing initiatives.

A more concrete question in those line for a project how to include for example new members in a consortia or substitute member that for any reason leave the consortia. Guidance for this was asked for.

As a final remark was on how to make the awareness of the work done JPIAMR can increase.

All speakers were thanked for sharing their experiences of their work and the audience for listening and giving valuable input to the discussions regarding early discovery of new antibiotics.

Short summary of the presentations

IMI-ENABLE: A European Antibacterial Drug Discovery Platform

(Eric Bacqué, France)

Dr. Bacqué highlighted the challenges to bring new AB to the market and the main reasons for the empty pipeline of novel-class antibiotics: the low return of investment for the pharma industry, the restriction of use of new antibiotics, limited populations infected by resistant strains and regulation issues. ENABLE, the European Gram-Negative Antibacterial Engine (the Topic 3 of the joint IMI-EFPIA New Drugs For Bad Bugs (ND4BB) Initiative) aims at facilitating to discover and develop new anti-Gram(-) antibiotics, from hit to Phase I. The ENABLE project consists of private and public partners, with a budget of 85 million €. Within the ENABLE platform, multiple programs are run in parallel in order to enhance the chances for success. Like in industry research, there are rigorous progression criteria. Advantages for the groups are regular meetings and reporting, legal support, storage of compounds, and a large set of assays. Electronic lab notebooks help with quality management. The program is attractive to investors, since there is no IP dilution, but a true collaborative spirit. ENABLE has to face of course the usual problems with new compounds: the substances are often toxic, and resistance emerges. The program could further benefit from clinical experience and partners.

http://nd4bb-enable.eu/

New AntiBacterials with Inhibitory activity on Aminoacyl-tRNA Synthetases

(Aigars Jirgensons, Latvia)

The project has focused on the development of new anti-bacterials which target the catalytic site of aminoacyl-tRNA synthetases. These enzymes are promising targets, since they are conserved between bacteria and different from the respective eukaryontic enzymes. Therefore they offer a chance for broad spectrum antibiotics. One prominent example is Mupirocin which is active against the Ile-tRNA synthetase of S. aureus.

The consortium of this EU FP7 funded project consists of companies and public partners with complementary expertise. A virtual screening delivered 600 hits which were filtered to 5 hits. The strengths of this project are focused synthetic libraries, simplified analogues of natural products, fragment based lead discovery, and a rational design of inhibitors. The IC50 lies within a nano- to micromolar range. The project had also to cope with several difficulties: some compounds only have weak antibiotic activity or are active against human enzymes, some modelled fragments are not active at all. Other problems the researchers are often faced with are penetration difficulties and/or efflux out of the bacterial cell. As possible solutions, medical chemistry for the modification of compounds were discussed, as well as the use of mutant strains for efflux pumps for first assays.

Non-conventional approaches for peptidoglycan cross-linking inhibition

(Michel Arthur, France)

Penicillin was the first antibiotic and members of this drug family, the β-lactams, and remain the most broadly prescribed first-line treatment. Since the targets of rs-lactams, the peptidoglycan

transpeptidases, have been validated by more than 70 years of successful use, the consortium aims at developing antibiotics structurally unrelated to fl-lactams and acting on the same targets but with different modes of action and on new interaction sites. P-lactams inactivate the transpeptidases by acting as structure analogues of the acyl donor of the transpeptidation reaction. The consortium focuses on the interaction of the transpeptidases with the second substrate, the acyl acceptor, to design inhibitors that will not be affected by existing resistance mechanisms and may act in synergy with fl-lactams. The project offers several advantages: the carbapenems have multiple paralogues, are highly conserved, their penetration is not needed, and a fluorescence-based transpeptidase assay exists. Via “click chemistry” very versatile modifications can easily be introduced. The consortium is built of teams with mixed expertises like chemistry, biochemistry, structural biology, and microscopy. The challenges of this project are the low affinity of candidate compounds to penicillin binding proteins and the lower membrane permeability of big structures.

New intervention strategy for tuberculosis: Blocking multiple essential targets

(Magnus Steigedal, Norway)

Mycobacterium tuberculosis is the causative agent of tuberculosis (TB), a disease responsible for almost 1.5 million deaths per year. In recent years, different classes of drug resistant strains have emerged, making the discovery of novel tuberculostatic drugs a major priority. A major disadvantage of most existing and new TB compounds is that they target a single molecule, which significantly increases the chance of resistance development. The project focuses on type VII secretion (T7S) systems as promising new drug targets. The secretion systems are similar but not interchangeable, with 3 systems always necessary and expressed. There is a good chance that by blocking multiple T7S systems the development of drug resistance can be reduced. Two complementary approaches are used: (1) the identification of secretion blockers based on secretion activity assays and (2) identification of compounds that bind/target specific essential components of T7S systems. In addition, synergistically working compounds form a library of known and approved drugs are identified. In the project several assays for the activity and safety of the components are used, e.g. a fibroblast survival assay and, due to the differences between cell culture and situation in the host, a validation and combination with known drugs in zebrafish. These tests are necessary, since the bacteria often “hide” in granulomas in the host and the tolerance phase of disease (dormancy) is difficult to test. A problem which might occur is that ATPase inhibitors might be found which are not specific for secretion systems. In this case, the specificity for secretion systems should be increased by using mutant strains.

Investigating the Mechanism of Eradication of Multi Drug Resistant Bacteria by Inorganic (mixed metal oxides), Organic (antibiotic), and Protein-based Nanoparticles: Results obtained in the NPERDMDR project

(Aharon Gedanken, Israel)

The partners of the project have applied different approaches to eliminate resistant bacteria, not by discovering new compounds, but by physico-chemical manipulations of existing antibiotics. The first approach was based on previous work demonstrating the ability of metal oxides such as ZnO, CuO, and Zn0.11Cu0.890 to eradicate resistant bacteria. Following this attempt aqueous colloidal solutions of these oxides were prepared and examined for killing of resistant bacteria, but negative results were obtained. More promising are nanoparticles (NPs) of antibiotic produced by sonochemistry. At the high temperature under the ultrasound wave the chemistry can go on. NPs of tetracycline were prepared and deposited on graphene oxide. These NPs demonstrated efficient killing of tetracycline resistant S. aureus. Positive results were also obtained for the composite of Lignin-Ag, and Lignin ZnO. Mixed particles have highest activity, the right ratio is decisive. Nanoparticles can pass membranes. The major advantage of this technique is that every material can be coated (textiles, etc.) with every antibiotic. By the capping agents like silver, lignins etc. even biofilms are targeted. Spheres encapsulating commercial antibiotic compounds showed also promising results. The nano spheres have a higher activity than the compounds alone. The eradication mechanism is under study.

Sensitizing Pseudomonas aeruginosa biofilms to antibiotic and attenuating virulence through quorum sensing inhibition

(Miguel Camara, UK)

An alternate approach to treat bacterial infections is based on targeting virulence rather than bacterial viability. The SENBIOTAR (Sensitizing Pseudomonas aeruginosa biofilms to antibiotics and reducing virulence through novel target inhibition) project is using this approach in the opportunistic human pathogen Pseudomonas aeruginosa through the optimization of strategies aimed at inhibiting quorum sensing (QS)-mediated virulence gene expression driven by the Pseudomonas Quinolone (PQS) system. P. aeruginosa is characterized by expressing several virulence factors which makes this approach highly valuable. The PQS system has immunomodulatory effects in the host and on gene expression in bacteria, regulates expression of virulence factors and biofilm formation. The consortium is currently performing extensive hit-to-lead optimization of compounds and antisense peptide nucleic acids (PNAs) which can inhibit this QS system and identified hits which, not only attenuate virulence in P. aeruginosa , but also increase the effectiveness of antibiotics against this organism both in biofilms and a rat chronic lung infection model. Currently formulations for these inhibitors are developed and their pharmacokinetic properties are determined.

Strengths of the project are assays on several levels: a cytotoxicity assay, biosensor development, and in vivo validation with PQS knock-out strains forming reduced biofilms. But there are also drawbacks which lie either in the compounds, the bacteria, or in the patients: some compounds have no effect on growth, and the PNAs are often toxic. The IC50 of antagonists and PNAs is within the

nanomolar range and has to be reduced. The effect varies with different clinical isolates. Then the compounds are metabolized which reduces efficiency: compounds with lower toxicity and higher stability have to be found and different time points must be tested. Another influencing factor which has to be considered is the cytokine production of the host.

DesInMBL. Design of inhibitors of Metallo-beta-lactamases

(Thierry Naas, France)

The pandemic NDM-1 and other plasmid-borne metallo-fi-lactamases (MBLs) disseminating worldwide in Gram-negative organisms threatens to take medicine back into the pre-antibiotic era since the mortality associated with infections caused by these "superbugs" is very high and the choices of treatment are very limited. In Southern Europe 1/3 – 2/3 of clinical isolates are resistant to all carbapenems. Using combined complementary approaches (microbiology, biochemistry, structural biology, molecular modelling and chemical synthesis) the project created vital insights into structure-function relationship of MBLs, allowing to better understand substrate specificities, to determine key residues involved in carbapenem recognition and hydrolysis, and to foresee the impact of mutations on the hydrolysis profile, with the ultimate goal to finally develop an MBL pan inhibitor using a consensus pharmacophore common to all clinically-relevant MBLs. The project builds upon unique strain collections and a β-lactamase data base. The approaches used (virtual screening, structure-based drug design, rational optimization) are suitable for the search for a paninhibitor by sequence comparison and mutagenesis. There is already a series of promising candidates, with the minimal inhibitory concentration in the micromolar range. Additionally, the consortium is performing an in silico analysis of metagenomics data for novel variants. Challenges which have still to be resolved result from solubility problems of the compounds or of immuno toxicology.

Report (session 2): Discovery of new Antibiotics

Introduction to ND4BB Presentation Translocation

(Mathias WINTERHALTER)

This 5-year project strives to bring new understanding to the molecular mechanisms by which drugs enter and exit Gram-negative bacteria. This knowledge will be gained through using novel assays to measure penetration and efflux processes, coupled with high resolution structural data on porins, siderophore receptors and efflux-pumps and combined with all-atom molecular simulations by which the molecular path of small molecules can be examined in detail. TRANSLOCATION will also help streamlining the design and development of new drugs by creating a cross Topic database, the `ND4BB Information Centre' for pre-existing and on-going antibacterial research data. *The project has*

identified several challanges: lack for whole cell uptake assays, size detection challange bacteria are small and rapidly dividing, non-specific binding.

The speaker also brought up the issue regarding the lack of incentives to share negative results.

FORMAMP (nanotech/antimicrobial peptides)

(Helena BYSELL)

Antimicrobial peptides (AMPs) have great potential as new, sustainable therapeutics against infectious diseases as they are less prone to induce high-level resistance due to their fast and nonspecific mechanism of action. FP7 project, FORMAMP evaluates different nanoformulation strategies for AMPs in order to increase stability and effect and enable local administration to treat skin and lung infections. Results show maintained or enhanced antibacterial effect when AMPs are associated to different nanocarriers compared to the free AMPs. These results display great potential in future drug delivery applications. H. Bysell presented the formulation strategies used within FORMAMP to obtain increased stability as well as the latest results from in vitro and ex vivo effect studies of the developed formulations. The project have identified 5 AMD candidates so far. *Next steps fort he project is to understand the mechanisms-synergistic effect, formulation strategies for biofilms, further evaluation of effect and toxicity on refined models and stability studies.*

AIDA (combination therapy)

(Johan MOUTON)

In an era of increasing emergence of drug resistance and lack of new antibiotics, old off-patent antibiotics are increasingly being prescribed to patients, alone or in combination. Many of these were developed in an age before the advent of a structured process for drug assessment and approval, and the establishment of clinical efficacy and effectiveness in randomized controlled trials in particular. The AIDA project aim to assess the effectiveness of 5 old antibiotics in three randomized controlled trials using modern drug evaluation concepts. In two of these trials, combination therapy was compared with monotherapy. Microbiological and PK/PD studies are applied to determine clinically-relevant outcomes for the individual patient, including efficacy, toxicity and emergence of drug resistance. aExperience gained in reviving old antibiotics and their clinical assessment are that combintions will be required but the reasons are multiple. *Prospective studies are nearing the end of inclusion and experiences are that clinical trials face many challenges; competition in recruting patients to trials, patients are often severly ill with comorbidity and what is beneficial for the population is not always beneficial for the individual patient. Rational dosing of single drugs and combinations require team efforts.*

REBeL Repotentiating Beta Lactam antibiotics

(Mariel Pikkemaat)

The most common form of resistance to 13-lactam antibiotics is the expression of f3-lactamase enzymes. These bacterial enzymes are capable of inactivating 13-lactam drugs by hydrolyzing their 13-lactam ring, rendering them ineffective. Co-administration of a Klactam antibiotic with a 13-lactamase inhibitor is a recognized strategy to circumvent this type of bacterial resistance. The REBEL project aims to discover and characterize new molecules of botanical origin that selectively inhibit fl-lactamases. New Klactamase inhibitors will be obtained by systematically screening the PECKISH library, a collection containing more than 4600 unique aqueous, ethanolic and other extracts from more than 860 different plant species. The screening strategy involves miniaturized growth inhibition assays based on a range of modified E. coli bacteria expressing different (types of) P-lactamases. Extracts showing specific P-lactamase inhibitory activity are subjected to further isolation, identification and structural confirmation of the bioactive compound. Full characterization of the newly identified inhibitors, including the design and synthesis of analogues, using biochemical and crystallographic studies will be carried out. Ultimately this project should yield the identification of new lead compounds for the development of clinical 13- lactamase inhibitors.

Questions regarding how to improve the deliver oft he compound were discussed and the project can see that with nano-particles, but further studies are needed. Another question was that growth phase is important in laboratory but is it important in patients?

EVOBIOTIC Capturing the natural antibiotic'ome: Developing Nature's EVOlved AntiBIOTIC Collective (Jean-Luc Pernodet)

Natural products (NPS), also called secondary metabolites constitute an important part of our pharmacopeia. Microorganisms are prolific NP producers and many of their products find applications as antibiotics. Micro-organisms possess the ability to produce a much wider spectrum of NPs than previously suspected (greater than 10 times as inferred from genomics). The project aim at developing innovative genomemining strategies to explore as thoroughly as possible the natural diversity of NP biosynthetic gene dusters. This should help to uncover the secondary metabolomes of antibiotic producers and to define antibiotic interactions and synergy. We also plan to use synthetic biology approaches (e.g. combinatorial biosynthesis and mutasynthesis) to increase the chemical diversity of NPs produced by bacteria belonging to the genus Streptomyces.

ABIMMUNE Repurposing disused antibiotics with immune modulators as antimicrobial strategy for respiratory tract infections (Jean-Claude SIRARD)

The project ABIMMUNE aims to enhance the therapeutic arsenal against respiratory infections. The idea is to combine Neglected and Disused AntiBiotics (NDAB) with registered immune modulators that impact host innate immunity. There are several advantages to this approach: first, antibacterial activity of innate immunity is independent of antibiotic-resistance. Second, it is difficult for the

pathogen to develop resistance to innate immunity. Third, targeting host innate immunity may reinstate some immune defense in vulnerable patients. Fourth, innate immunity and ND-AB may synergize to kill bacteria. Fifth, using ND-AB may globally dampen the proportion of bacteria resistant to first-line antibiotics, allowing their maintenance in clinics.

CO-ACTION Developing combinations of CO-ACTIVE antimicrobials and non-antimicrobials (Johan MOUTON)

In the search of alternatives for effective antimicrobial therapy for the lack of new agents, the CO-ACTION project — a collaboration between 6 international partners - was set up to develop and provide a framework for evaluating and validating the effectiveness of antibiotic (AB)- and non-antibiotic (NA) combinations in the preclinical setting based on a pharmacokinetic/pharmacodynamic (PKPD) approach. Significant interaction is sought by screening for synergy between (ND-)AB and NA using a variety of existing techniques; in addition new methods in search of synergy are developed. The provide the basis for selecting potential synergistic combinations and subsequent validation using PKPD experiments in vitro and in vivo, as well as modelling synergistic interactions and finally testing COMs in animal models. During the first year of the project 30 NA were evaluated for synergy of which two potential candidates are being further evaluated initially*. Challenges identified in animal studies were animal welfare regulations, combinations showing synergism in vitro and modelling for optimal dosing.*

COMBINATORIALS Novel drugs and drug combinations against bacterial growth, survival and persistence from high-throughput screening to mechanism of action (Athanasios TYPAS)

Drug combinations and drug re-purposing can act as a first line of defense against the alarming rise of multi-drug resistant bacterial infections, yet their current use in clinics is limited. To better understand the potential of drug combinations, we are combining high-throughput screening, with pharmacokinetic/pharmacodynamic modelling and downstream mechanistic analysis in three clinically relevant pathogens: uropathogenic Escherichia coli, Staphylococcus aureus, and Streptococcus pneumoniae. The general principles derived from recently screening in the project — 3,000 pairwise combinations of different antibiotics, selected human targeted drugs and food additives in 3 prominent gram-negative pathogens, and the potential clinical utility of the discovered drug synergies. *Drug interactions are conserved between species but the conservation is higher in one drug compared to cimbinations of drug. A question that came up was why are drug interactions so conserved?*

A conclusion was that polypharmacy may be a strong driver for AMR.

Four JPIAMR WGs/Networks

Histidine Kinase Inhibitors as Novel Anti-infective (Jerry Wells)

We have previously identified a panel of inhibitors targeting bacterial histidine kinases in bacteria that block expression of activities required to cause disease and cope with environmental stresses. Inhibiting the processes in disease-causing bacteria offers some clear advantages, as the drugs would disarm the pathogen, enabling the host innate immune system to eradicate them from the body. As only infectious bacteria will be affected the community of beneficial bacteria which compete with pathogens in the intestine, upper respiratory tract and urogenital tract and should be relatively unaffected. This Transnational Network will meet to aligning research activities and devise a strategy to develop new anti-infective drugs targeted to histidine kinases in multi-drug resistant pathogens.

Exploiting an old drug as basis for inhibitory discovery (Klaas Martinus Pos)

Our JPI AMR working group includes academic and industry researchers with skills in medical microbiology, pharmacokinetics, structural biology, biochemistry, drug design, mathematics, and drug discovery/development. We organized a conference/network meeting and invited key experts in the treatment of UTIs and impact of AMR (including in the elderly), properties of the drug nitrofurantoin (clinical practice, medicinal chemistry, pharmacokinetics and pharmacology) and nitrofurantoin resistance, to cover experience from 'bench to bedside'. The delivery of the proposed network will be a consortium in the framework of H2020 or Marie Curie ITN that can provide both a new paradigm and a scientific basis of inhibitor discovery based on an old drug and that can be translated to drug development.

PhageForward: towards the re-implementation of phage therapy (Laurent Debarbieux)

The rapid rise of antibiotic resistance has surged an increasing interest to develop phage therapy, a century-old approach based on the use of bacteriophages that are natural viral predators that specifically parasite bacteria to replicate. Currently phage therapy is only accepted and practiced in parts of Eastern Europe such as Russia, Georgia and Poland. Progress has yet to be made in the rest of the world on a functional and practical legal frame-work that is flexible enough to exploit and further explore the specificity of bacteriophages. PhageForward will contribute to opinion formation on relevant stakeholders on three main topics, regulation, production and intellectual property, to build an infrastructure that paves the way for the re-implementation of phage therapy.

BEAM Alliance

The BEAM Alliance represents 50 European biopharmaceutical companies (small and medium size) from 12 European countries involved in developing innovative products to combat antimicrobial resistance in humans and beyond. The Working Group objective is to produce a new position paper regarding establishment of economic incentives in order to better sustain the innovation efforts of small and medium biopharmaceutical companies. The Working Group will collaborate with the existing community of stakeholders dedicated to implementing tangible strategies, including the EC DG SANTE, the UK AMR Review, WHO and the DRIVE-AB consortium. The BEAM Alliance Working

Group should thus allow for expression of a unique and unprecedented opinion from the European SMEs perspective.

Workshop Agenda

DAY ONE: 12 January 2017

14h INTRODUCTION AND WELCOME

14:00 – 14:10 Welcoming words from the organizing committee
By Carlos Segovia, JPIAMR Chair
By Antoine Andremont, University Paris-Diderot Medical School, France

14:10 SESSION 1: Target oriented Antibiotic discovery
Moderator: *Antoine Andremont, University Paris-Diderot Medical School, France*
Rapporteur: *Barbara Junker, DLR, Germany*

Introduction: challenges to bring a new antibiotic to the market

14:15 – 14:45 IMI-ENABLE: A European Antibacterial Drug Discovery Platform
By Eric Bacqué, Sanofi

14:45 – 15:05 NABARSI (drug development)
By Aigars Jirgensons, Latvian Institute for Organic Synthesis

15:05 – 15:25 NAPCLI Non-conventional approaches for peptidoglycan cross-linking inhibition
By Michel Arthur, INSERM, University Pierre et Marie Curie; University Paris Descartes, Paris, France.

15:25 – 15:45 NoTBsec New intervention strategy for tuberculosis: blocking multiple essential targets
By Magnus Steigedal, Norwegian University of Science and Technology

15:45 – 16:10 Questions

16h10 – 16h30 Break

16:30 – 16:50 NPERDMDR Investigating the Mechanism of Eradication of Multi Drug Resistant Bacteria by Inorganic (mixed metal oxides), Organic (antibiotic), and Protein-based Nanoparticles
By Aharon Gedanken, Bar-Ilan University, Israel

16:50 – 17:10 SenBioTAR Sensiting Preudomonas aeruginosa biofilms to antibiotic and reducing virulence through novel target inhibition.
By Miguel Camara, University of Nottingham, United Kingdom

17:10 – 17:30 DesInMBL: Structure-guided design of pan inhibitors of metallo-β-lactamases.
By Thierry Naas, University of Paris Sud, Paris, France

17:30- 18:00 Questions

DAY TWO: 13 January 2017

SESSION 2: Discovery of new Antibiotics

Moderator: *Jonathan Pearce, MRC, UK*

Rapporteur: *Antoine Andremont, University Paris-Diderot Medical School, France*

9:00 – 9:30 Introduction to ND4BB Presentation Translocation
By Mathias WINTERHALTER, Department of Life Sciences & Chemistry Jacobs University Bremen, Germany

9:30 – 9:50 FORMAMP (nanotech/antimicrobial peptides)
By Helena BYSELL, SP Technical Research Institute of Sweden

9:50 – 10:10 AIDA (combination therapy)
By Johan MOUTON, Erasmus University Medical Center / Dept. of Medical Microbiology and Infectious Diseases [EMC], Netherlands.

10:10 – 10:30 REBeL Repotentiating Beta Lactam antibiotics
By Mariel Pikkemaat, RIKILT, Institute of Food Safety Wageningen, University and Research Centre, Netherlands.

10:30 – 10: 50 Questions

10:50 – 11:00 Break

11:00 – 11:20 EVOBIOTIC Capturing the natural antibiotic'ome: Developing Nature's EVOlved AntiBIOTIC Collective
By Jean-Luc Pernodet, University Paris Sud

11:20 – 11:40 ABIMMUNE Repurposing disused antibiotics with immune modulators as antimicrobial strategy for respiratory tract infections
By Jean-Claude SIRARD, Institut Pasteur de Lille, Centre d'Infection et d'Immunité, Lille, France

11:40 – 12:00 CO-ACTION Developing combinations of CO-ACTIVE antimicrobials and non-antimicrobials
By Johan MOUTON, Erasmus University Medical Center / Dept. of Medical Microbiology and Infectious Diseases [EMC], Netherlands

12:00 – 12:30 Questions

12:30 – 13:30 Lunch

13:30 – 13:50 COMBINATORIALS Novel drugs and drug combinations against bacterial growth, survival and persistence from high-throughput screening to mechanism of action
By Athanasios TYPAS, European Molecular Biology Laboratory, Genome Biology Unit, Germany.

13:50 – 14:20
JPIAMR WGs/Networks (´05 min each):

- *Jerry Wells - Wageningen University – Histidine Kinase Inhibitors as Novel Anti-infective*
- *Klaas Pos - Goethe University Frankfurt* – Exploiting an old drug for inhibitory discovery
- *Laurent Debarbieux* - Institut Pasteur – PhageForward project
- *Pierre-Alain Bandinelli - Da Volterra – BEAM Alliance*

14:20 – 14:40 Questions

14:40 – 15:30
SESSION 3: WAY FORWARD AND CLOSING REMARKS
Moderator: *Laura Piddock, Birmingham University, UK*

- Round table: Analysis of the current European level portfolio: how to synergize the approaches, how to progress for new strategies / optimize funding around discovery
- Alignment of programmes
- Closing remarks

15:30 Meeting Ends