The first JPIAMR transnational call InnovaResistance: Innovative approaches to address antibacterial resistance- 2014

Antibacterial resistance is a multifaceted problem needing vast and versatile solutions. No individual sector or nation has the capacity to independently handle this major societal challenge. Therefore, to collectively address antibacterial resistance at a national level and to increase the current impact of public research through more effective, efficient, and aligned investment, the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) was established in 2011.

This initiative brings together 19 JPIAMR member countries, consisting of 18 European countries (Belgium, Czech Republic, Denmark, Estonia Finland, France, Germany, Greece, Italy, the Netherlands, Norway, Poland, Romania, Spain, Sweden, Switzerland, Turkey, the UK), and Canada, Israel, Argentina, and Japan.

Seven projects were funded under the first transnational call of JPIAMR. The successful proposals included partners from 11 different countries with a total of over 8 million Euros committed.

The MRC provided funding for the UK partners of successful proposals (x3)

Links:
http://www.jpiamr.eu/
http://www.jpiamr.eu/fundedprojects/

JPIAMR 1st Joint Call: InnovaResistance		
Project Coordinator	**Institution**	**Title of Award**
Michel Arthur	INSERM, France	Non-conventional approaches for peptidoglycan cross-linking inhibition
Project Partners	**Summary**	
Waldemar Vollmer, Newcastle University, United Kingdom Tanneke den Blaauwen, University of Amsterdam, Netherlands Jean-Pierre Simorre, CNRS, France John Mc Kinney, Swiss Federal Institute of Technology Lausanne (EFPL), Switzerland Natalie Strynadka, University of British Columbia, Canada	Peptidoglycan (PG) is an attractive and validated target for antibacterial drug development for two main reasons. First, it is an essential and unique bacterial cell wall polymer with no counterpart in human cells, minimizing the risk of drug toxicity. Second, the essential PG synthases are exposed at the outer surface of the cytoplasmic membrane, making them highly accessible for antibiotic inhibition. Formation of the PG network requires glycosyltransferases for glycan chain elongation and transpeptidases for peptide cross-linking. Transpeptidation involves two stem peptides that act as acyl donor and acceptor substrates, respectively. The acyl donor site is targeted by the ß-lactams, which form covalent adducts, and this interaction is well characterized. In contrast, nothing is known on the interaction of the transpeptidases with the acceptor substrate. To combat the erosion of the activity of ß-lactams, we propose to identify additional drugable sites in the transpeptidases, including the acceptor binding site, and develop lead antibacterial agents acting on these sites. Our first objective is to characterize the mode of recognition of the acyl acceptor by transpeptidases and identify compounds blocking the binding of this substrate. We will use NMR spectroscopy to map the acceptor site and develop specific inhibitors based on modelling and virtual screening. Our second objective is to identify the partners of transpeptidases that regulate the coordinated elongation of glycan chains and cross-linking of stem peptides. This will allow us to select additional drugable sites in transpeptidases and associated proteins within the PG polymerization complexes. We will map key interactions by FRET analyses in live bacteria producing fluorescent proteins and by in vitro transpeptidase/glycosyltransferase assays in complexes obtained by tandem-affinity purification. Microfluidic cultures and time-lapse microscopy will assess the impact of inhibitors on cell division and viability. The interaction of lead compounds with their targets will be characterized by X-ray crystallography. These complementary approaches will enable the consortium to develop novel strategies for transpeptidase inhibition and obtain leads active against ß-lactam-resistant bacteria.	

JPIAMR 1st Joint Call: InnovaResistance		
Project Coordinator	**Institution**	**Title of Award**
Miguel Camara	**University of Nottingham, United Kingdom**	SENBIOTAR- Sensiting *Pseudomonas aeruginosa* biofilms to antibiotic and reducing virulence through novel target inhibition
Project Partners	**Summary**	
Peter Nielsen, University of Copenhagen, Denmark Roger Levesque, University of Laval, Canada Christel Bergström, Uppsala University, Sweden	The traditional approach to combating bacterial infections has been based on the use of antibiotics which kill bacteria or inhibit their growth. There has also been a strong emphasis on the identification of essential gene targets for drug intervention. A major problem with therapeutic approaches targeting viability is that they induce strong selective pressures resulting in the rapid emergence of antimicrobial resistance. An alternate approach is to inhibit virulence rather than bacterial viability and this will be explored in the SENBIOTAR project. In the opportunistic human pathogen *Pseudomonas aeruginosa*, virulence is co-ordinately controlled at the bacterial population level through quorum sensing (QS), a global cell-to-cell communication system employing diffusible signal molecules. *P. aeruginosa* strains with mutations in the Pseudomonas Quinolone Signal (PQS) QS pathway are avirulent in experimental animal infections. The partners of this consortium will exploit this information by optimising hit compounds and peptide nucleic acids (PNAs) they identified previously which target PQS biosynthesis and/or PQS signal transduction. These hits have been shown to not only render *P. aeruginosa* avirulent but also to sensitize biofilms to the action of antibiotics. One of the limitations of using inhibitors of virulence is the fact that immunocompromised patients may not be able to clear the targeted pathogen efficiently. However, if the pathogen can, at the same time, be sensitised to antibiotics then there is great scope for dual therapy with PQS inhibitors and antibiotics. SENBIOTAR will bring together world experts in QS, medicinal chemistry, PNAs, drug delivery and preclinical studies to optimise the activity of the hit compounds and PNAs (hit-to-lead optimization) with the intention of identifying lead compounds which strongly inhibit QS, attenuate virulence and sensitise biofilms to conventional antibiotics at sub-micromolar concentrations. This will be achieved by improving (a) their physicochemical properties without the emergence of cytotoxicity, and (b) delivery to the site of infection. These studies will be performed using a combination of in vitro virulence and biofilm bioassays alongside experimental animal lung infection models. The lead compounds developed by SENBIOTAR will also have significant potential for the treatment of wound, bloodstream and medical-device associated infections caused by *P. aeruginosa*.	

JPIAMR 1st Joint Call: InnovaResistance		
Project Coordinator	**Institution**	**Title of Award**
Nathan Magarvey	McMaster University, Canada	EVOBIOTIC- Capturing the natural antibiotic'ome: Developing Nature's EVOIved AntiBIOTIC Collective
Project Partners	**Summary**	
Julian Davies, University of British Columbia, Canada Eliora Ron, Tel Aviv University, Israel Raymond Andersen, University of British Columbia, Canada Jean-Luc Pernodet, Paris-Sud University, France **Gregory Challis, University of Warwick, United Kingdom**	Naturally evolved antibiotics are our primary mode of treating drug-resistant pathogens. Although individual antibiotics do succumb to resistance via pressures they place on organisms, the producers of these agents innovate through modular antibiotic drug (bio) synthesis programs to naturally thwart drug resistance mechanisms. Moreover these same antibiotic drug biosynthesis programs, are now revealed to construct other agents that perturb microbial physiology apart from killing (i.e. blocking resistance). The evolutionary constraints that have produced these evolved genetically encoded natural drugs are difficult to envision but their specificities, dynamic actions, multi-pronged functions have clearly rendered them as privileged molecules. Much research has defined the codes embedded within these natural small molecule biosynthesis programs and surprisingly these codes and rules are largely followed across all known organisms that generate polyketide and nonribosomal peptide molecules. In addition to the cracking of the nonribosomal and polyketide codes, further facilitating their genomic-based identification is the clustering of genes associated with the synthesis of a particular molecule-type (natural product/antibiotic) and a collinear pattern used in their synthesis. Collectively, these natural principles and rules have now created an exceptional opportunity to drive the detection and discovery of these molecules using a genomic start point. New transformative approaches to antibiotic discovery are needed, and the research in this proposal will lead to disruptive innovation, and a major departure in how historically antibiotics have been found and investigated. With our unique approaches we will enrich in agents with new modes of action, and those with a high likelihood of synergizing with clinically used antibacterials. The following aims are designed to provide this forward-looking view of how to treat antibiotic resistant bacteria: AIM 1) Uncover the secondary metabolomes of antibiotic producers and define antibiotic chemical-chemical interactions and synergy. AIM 2) Interrogate the bioproduction of antibiotics from genomically identified unexplored microbes using metabolomics AIM 3) Test naturally evolved drugs against secretion systems and serum resistance systems of gram negative/drug-resistant organisms	