2018-2010 Projects

Development of novel metrics and frameworks for quantifying pan-microbial antimicrobial resistance selection pressures within environmental interfaces: aquaculture and the aquatic environment

Abstract

Antimicrobial resistance is a complex, microbial process driven by diverse pressures from humans, animals and the environment. Antimicrobial resistance is achieved when microbes acquire and express genes that allow them to survive even when exposed to antibiotics. Within environmental settings, antimicrobial resistance genes and bacteria can be transmitted through wind, air and water – making them difficult to trace. Subsequently, we have relatively little understanding of how various environmental pressures contribute to the development, persistence and spread of antimicrobial resistance.

Fortunately, recent technological advances now enable detection of all of the antimicrobial resistant genes within environmental samples (the "resistome"). With this new source of data, we can develop novel methods for identifying and measuring the amount of pressure on the resistome at different points within environmental systems. This, in turn, will give us improved understanding of how human activities might be causing microbial populations to increase the number, type and prevalence of antimicrobial resistance genes within different environments. We can then focus our efforts on modifying such human activities with the goal of decreasing antimicrobial resistance and protecting public health.

To develop these new methods, we propose to use the aquatic environment and fish farming as a representative system for understanding antimicrobial resistance and environmental pressures. Aquaculture is an important industry in Norway, and wild fish ecology is an important resource in Minnesota. Therefore, using aquaculture as a model system will benefit both localities while providing novel scientific discovery about antimicrobial resistance and its connection to human, animal and environmental health.

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Mechanism of action of novel NPR-A activators for treatment of cardiovascular diseases

Abstract:

Resistant hypertension (RHT) is a frequent disease and causes premature morbidity and death. RHT is defined as high blood pressure that remains above goal despite the use of three antihypertensive drugs of different classes. The prevalence of RHT continues to rise. Thus, the development of novel drugs that can control the elevated blood pressure in these patients is urgent and of high social and clinical impact for several millions of people worldwide. Natriuretic peptides play an important role in the regulation of blood pressure and it is shown that patients with RHT have an impaired natriuretic peptide system. In this project we are developing small molecular compounds to activate the natriuretic peptide receptor-A (NPR-A) for the treatment of patients with resistant hypertension. We have recently performed a high-throughput screening and identified three compounds showing activity at the NPR-A. The compounds were identified as allosteric enhancers. In this project we will further investigate the mechanism and site of action of these drugs. This will both provide new insight about the NPR-A, but also provide valuable information that can be used for further drug development with NPR-A as target. Our long-term goal is to offer better treatment for patients with uncontrolled high blood pressure.

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Energy conversion using phase change materials in the small temperature difference regime

Abstract:

The discovery of new methods of generating energy without adversely affecting the environment is a compelling scientific problem of our time. We propose to develop materials and devices for the direct conversion of heat to electricity using phase change materials having an abrupt change of polarization at the transformation. Here, "direct" means that electricity is generated by the material itself, without the need of a separate electrical generator. The method was described by V. Srivastava, Y. Song, K. Bhatti and R. D. James, The direct conversion of heat to electricity using multiferroic alloys, Advanced Energy Materials 1 (2011), 97-104. The research of the graduate students will focus on two key components of the ferroelectric case.

A path forward for this technology is enabled by two recent developments: 1) a systematic strategy for making highly reversible transforming materials (Nature 501 (2013), p. 88; Science 348 (2015), p. 968, 1004), and 2) methods of film growth of exceptional quality by hybrid molecular beam epitaxy giving leakage-free transforming ferroelectric films.

The rationale for the collaboration with Ole Martin Løvvik at UiO/SINTEF is that he is a leading authority on first principles methods for multiferroic phase change materials, including the prediction of phase diagrams, and this critical component is lacking at UMN. In addition, the UiO group brings outstanding expertise in transmission electron microscopy. The Norwegian side of this collaboration is supported by a new project, The Conversion between Magnetic, Electric and Thermal Energies (COMET), funded by the Research Council of Norway (FRIPRO program).

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Multi-omic informatics for characterizing microbiomes and their role in health, disease and environment

Abstract:

Communities of microorganisms (microbiomes) are increasingly known to play a critical role in health and disease in human hosts, and also as part of environmental ecosystems. Sequencing the genetic material (DNA) from these microbial communities catalogs the different organisms making up these complex systems, and how this composition may change under different conditions (e.g. health versus disease in humans, introduction of pollutants within an environmental ecosystem etc.). However, DNA sequencing provides an incomplete picture of the system. Consequently, researchers lack knowledge of how, at a detailed molecular level, microbiomes interact and respond to their surroundings. This knowledge could lead to new breakthroughs for engineering microbiomes to help fight disease, clean-up toxins in the environment, or even produce environmentally friendly biofuels. To gain such knowledge, measurement of additional molecules encoded by the microbial DNA (e.g. RNA, proteins) is necessary. Fortunately, large-scale data on the identify and abundance of RNA and protein can now be readily generated. Unfortunately, there is a lack of effective software that can analyze the data, in an integrated fashion, and help researchers make new discoveries. To address this current bottleneck, we will establish a new trans-Atlantic partnership between two highly complementary Minnesota and NMBU research teams. We will develop and optimize enabling software integrative analysis large-scale DNA, RNA and protein data. We will disseminate the software, putting it in the hands of researchers who will use it to advance knowledge of microbiomes and how these complex communities may be used to improve human and environmental health.

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Comparative studies of genetic variability and in vitro virulence comparison between the piscine toti-like viruses found in Norwegian Atlantic salmon and golden shiner from Minnesota

Abstract:

Cardiomyopathy syndrome (CMS) is a disease most often affecting the heart of large, slaughter-size salmon, which results in huge economic loss in Norwegian salmon industry. It has recently been considered as the most important disease problem in Norwegian salmon aquaculture in 2017, after sea lice infections. The disease is caused by the piscine myocarditis virus (PMCV), a unique virus found to have some genetic similarities to the viruses of the *Totiviridae* family, usually infecting simple single celled organisms.

Baitfish are economically and ecologically important throughout USA and recently a virus with similarities to the PMCV, was found in the Minnesota baitfish golden shiner (GS-PMCLV). The results of the project will address questions related to both viruses ability to cause disease and genetic signatures important for infection and degree of resulting disease.

The proposed project has a general strong relevance for understanding virus pathogenic mechanisms and will be of transformative nature for disease-limiting measures as therapy and vaccination against PMCV infection and CMS disease of Atlantic salmon. The research will also shed light on the GS- PMCLV detected in baitfish and increase the knowledge on its possibility to cause disease or not and also the risk of transmission throughout USA. Comparative studies on the two viruses will also be performed. This will increase the understanding of evolution of viruses of the *Totiviridae* and the increasing group of toti-like viruses and how these viruses adapt to infect in higher organisms than the original simple single-celled organisms that the registered toti-viruses infect.

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Characterization of the role of YthA in the development of resistance to antibiotics and antimicrobial peptides

Abstract:

Increasing antibiotic resistance is a huge threat to human health. It is thus of upmost importance both to develop new antibiotic treatments and to understand the development of antibiotic resistance. Bacteriocins are antimicrobial peptides (AMPs) produced by bacteria to compete against other species and to regulate their own population density. Many bacteriocins specifically target species closely related to the producers. The target organisms include species listed as in urgent need of new treatments by WHO, staphylococci, bacilli, streptococci and enterococci, and the pathogenic bacteria Listeria. In order to develop bacteriocins as drugs for therapeutic use, detailed knowledge of their mode of action, i.e., how a bacteriocin specifically recognizes its target cells and how resistance may develop is needed. In our recent work, a gene called ythA encoding a membrane-bound protein was found to be involved in the sensitivity of cells to bacteriocins. Interestingly, ythA mutants display resistance not only to bacteriocins but also to antibiotics. Very little is known about ythA although the gene and its homologues are widely distributed in bacteria. Due to its ubiquity, ythA might serve an important role in the development of antimicrobial resistance. In this project proposal, we will investigate the function of YthA, especially its role in resistance development. To reach this goal we will combine powerful genetic, biochemical and biophysical techniques to unravel its structure and molecular interactions/network behind resistance development, using the model organism *Lactococcus lactis,* as well as important pathogens (MRSA and VRE). This understanding can help develop new, design strategies to prevent antimicrobial resistance.

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A New Strategy for Designing Secreted Bioelectrical Components

Abstract:

The Norwegian Centennial Chair Program has named *solutions to environmental challenges* and *sustainable energy systems* as priority areas of research. A bottleneck in many sustainable energy and environmental remediation technologies is replacement of nonrenewable catalysts with biologically synthesized materials. In our study of bacteria able to act as electrical catalysts, we have discovered a unique cytochrome family that demonstrates many desirable properties. In its host, this conductive protein self-anchors between cells in biofilms, facilitating electrical flow to electrodes. This protein is secreted outside the cell and is highly stable, simplifying purification and production compared to most membrane-bound redox proteins. Other functional domains can be attached to this protein without affecting its secretion and redox function, producing new electron transfer abilities. We propose a new collaboration led by the Bond laboratory at the University of Minnesota and the Hersleth laboratory at the University of Oslo, to build heterologous expression platforms able to secrete the core protein as well as fusions that represent hybrid bioelectrical devices. Our ultimate goal is to produce the first known crystallographic information from this novel family of extracellular conductive proteins.

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