4. Evidence (case studies)

4.1. Case Studies

In this section, we present five case studies that highlight examples of the science in the IBL's research themes and Science Communication and Society Research Group. Besides, representing scientific highlights, these case studies also illustrate the collaborative nature and the societal relevance of our research.

Development and Disease

From stress to success: how bacteria exploit life without a cell wall

Societal relevance: prevention of antimicrobial resistance development, SDG3.
Stakeholders: Leiden University
Principal Investigator: prof. dr. Dennis Claessen
Funding sources: NWO-Vici

The cell wall is a fundamental structure that envelops almost all bacteria and provides protection against external stressors. It is also a crucial recognition point for the immune system. However, recent studies have shown that many bacteria can transiently shed their cell wall, resulting in reduced recognition by our immune cells and insensitivity to antibiotics. IBL researchers led by Dennis Claessen are interested in investigating the physiological consequences of this wall-deficient lifestyle. Principal investigators in all other research themes work together within our institute to understand the interaction of these cells with eukaryotic hosts, such as plants and animals, and with bacteriophages. We investigate the role of wall-deficient cells in the development of antimicrobial resistance and its consequences for the evolution of bacteria.

The shedding of the cell wall by bacteria can have significant consequences for the host. By losing many of the epitopes that serve as recognition points for our immune system, these cells are less easily recognized, allowing bacteria to shelter inside the host. Furthermore, without a cell wall, these cells become insensitive to most of the antibiotics that target the process of cell wall synthesis, complicating treatment strategies for pathogenic bacteria that exploit this strategy. We are therefore developing novel approaches to combat bacterial infections and improving current treatment strategies for pathogens that exploit this fascinating adaptation strategy.

Our research team discovered a new mechanism for extracellular material uptake in wall-deficient cells, which resembles endocytosis in eukaryotes. This newly identified mechanism not only allows for the uptake of DNA but also polysaccharides and even 150-nm lipid nanoparticles. This discovery sheds light on how primordial cells may have acquired food and genetic material before the invention of the bacterial cell wall. As most bacteria can transiently shed their cell wall, this ancient mechanism may have been retained and come in handy in conditions where bacteria are challenged to maintain their cell wall, such as under the influence of antibiotic regimes. Furthermore, given that cell wall-deficient bacteria are considered a model for early life forms, our work provides an essential contribution to the understanding of the evolution and adaptation of microorganisms.

References

Kapteijn R, et al. (2022). Endocytosis-like DNA uptake by cell wall-deficient bacteria. Nat Commun. 13: 5524.

Evolution and Biodiversity

Effects on fishes from the energy and nature transition in the North Sea

Societal relevance*:* SDG14
Embedding: Evolution & Biodiversity
Principal Investigator: Hans Slabbekoorn
Funding Sources: Joint Industry Program (PCAD4Cod); Rijkswaterstaat; NWO-NWA (APELAFICO)

The ecosystem of the North Sea is under pressure from the energy transition, requiring space for offshore windfarms (Slabbekoorn et al., 2019). Construction of offshore windmill clusters causes huge noise impact on the local and surrounding ecosystem, not only due to the activities themselves, but also due to the increase and change in shipping activity and spatial impact on activities such as dredging and fishing.

IBL-researchers led by Hans Slabbekoorn investigated the effect of windfarm construction on benthic fish, i.e. species associated with the sea bottom such as flatfish and Atlantic cod. The PCAD4Cod project revealed that cod remain in the area during seismic survey and pile-driving (van der Knaap et al., 2021). However, the fish became less active, and individual fish left the foraging area sooner than expected. These effects may accumulate to population level impact through consequences for growth, maturation, and reproduction in the years to come (Soudijn et al. 2020). Currently, we investigate the effect of pile-driving sounds on pelagic fish, i.e. species that occur across the water column, such as herring or mackerel. Pelagic fish communities play a key role in the food chain and are of large commercial value. Fishes may become deaf, injured, or even get killed, when getting close to a seismic sound source or pile driving. Sounds further away still cause deterrence or disturbance. APELAFICO is a collaborative project with many industrial and societal partners, including Rijkswaterstaat, collecting data on pelagic fish in and around offshore windfarms (Kok et al., 2021). The project assesses how many fish are present and explores how we may deter (and thereby save) fish using sound prior to a potentially fatal exposure.

The scale of the energy transition within and around the Dutch national waters means the largest ecological change to the North Sea in human history. We expect that the IBL will continue to play an important role in future explorations of ecological impact and to take responsibility in advisory tasks in the context of marine management, legislation, and regulation.

References

Kok, A.C.M., et al., 2021. An echosounder view on the potential effects of impulsive noise pollution on pelagic fish around windfarms in the North Sea. Env pollution 290: 118063; Slabbekoorn, H., et al., 2019. Population-level consequences of seismic surveys on fishes: An interdisciplinary challenge. Fish & Fisheries 20: 653–685; Soudijn, F.H., et al., 2020. Population-level effects of acoustic disturbance in Atlantic cod: a size-structured analysis based on energy budgets. Proc Royal Soc B 287: 20200490; Van der Knaap, I., et al. 2021. Effects of a seismic survey on movement of free-ranging Atlantic cod. Curr Biol 31: 1555-1562.

Host-Microbe Interactions

Harnessing microbes for sustainable crop protection against biotic and abiotic stress

Societal relevance: Sustainable crop protection; SDG2, SDG15
Embedding: Host-Microbe Interactions; Development & Disease
Principal Investigators: Balazadeh, van Wezel, Raaijmakers, Carrion (IBL, NIOO-KNAW, University of Málaga)
Funding sources: NWO Open Technology Programme, NWO-MicroGRICE

A major challenge for mankind is to feed the increasing human population in a sustainable manner. Improvement of sustainable crop production is a critical element of achieving these ambitious goals. Currently, more than one third of the crop yield is lost due to abiotic and biotic stress factors such as drought, salinity, pests and diseases. Microorganisms living in association with plants have a largely unexplored functional potential to expand the genomic capabilities of their hosts, providing nutrient acquisition, specialised metabolites as bioprotectants against fungi and bacteria, enhanced immunity against pests and enhanced tolerance to abiotic stresses (drought, salt).
Over the past 10 years, plant-microbe interactions have become one of the major research themes at the IBL, and the HMI research theme had a highly positive effect on cross-cluster communication and collaboration. Carrion, van Wezel and Raaijmakers (Microbial Sciences) identified microorganisms capable of protecting plants against plant pathogens (Mendez et al., 2011; Carrion et al., 2019); this could then be harnessed to enhance growth of Arabidopsis and tomato (Patent application WO2018073454). Collaborative research between Carrion and Balazadeh (Plant Sciences), an expert in heat and drought stress resilience in plants, then revealed that several disease-suppressive bacteria conferred drought-stress resilience to Arabidopsis and to tomato plants. Using a combination of state-of-the-art omics, computational, and genetic engineering methods, the team is now identifying the genes and metabolites that are involved in bacteria-mediated plant drought tolerance. In cooperation with industrial partners, this allows the team to develop novel bio-based strategies to reduce the impact of (a) biotic stresses on crop productivity, and in a sustainable way.

Figure 5. Wheat plants which show drought tolerance after Flavobacterium inoculation (Rahimi et al., in prep)

References

Carrion, V. J. et al., 2019. Pathogen-induced activation of disease-suppressive functions in the endophytic root microbiome. Science 366, 606-612 (2019); Mendes, R. et al., 2011. Deciphering the rhizosphere microbiome for disease-suppressive bacteria. Science 332, 1097-1100).

Bioactive Molecules

Novel semisynthetic glycopeptides with best-in-class antimicrobial potential

Societal relevance: novel antibiotics to fight antimicrobial resistance; SDG3.
Embedding: Bioactive Molecules; LED3 collaboration Faculty of Science
Principal Investigator: Prof. dr. Nathaniel Martin
Funding Source: NWO-TTW NACTAR

Methicillin-resistant Staphylococcus aureus (MRSA) is a major cause of community and hospital-acquired infections resulting in significant morbidity and mortality. For many years the glycopeptide antibiotic vancomycin has been used to effectively treat MRSA infections. However, it is currently estimated that 30% of all healthcare-associated enterococcal infections are resistant to vancomycin. Infections due to vancomycin-resistance total nearly 400,000 per year and account for half of all AMR-associated deaths in the United States and in Europe. The development of next generation glycopeptides remains an import goal for antibiotic development.

The Martin group recently discovered and patented a new class of semisynthetic “guanidino” lipoglycopeptides that exhibit potent activity against a range of Gram-positive pathogens including vancomycin-resistant strains (Figure 6). Minimum inhibitory concentration (MIC) studies demonstrate a significant enhancement in the antibacterial activity compared to vancomycin and other clinically used glycopeptides, in some case of >1000-fold. The molecules have superior in vivo activity over vancomyin and lower cytotoxicity than telavancin and oritavancin. Mechanistic studies reveal a strong binding interaction for the guanidino lipoglycopeptides with both wild-type lipid II (D-Ala-D-Ala) and the resistant form bearing the D-Ala-D-Lac modification found in vancomycin resistant strains. In addition, the guanidino lipoglycopeptides were found to have low propensity to induce resistance.

The Leiden University Holding is in the process of setting up a spin-out company to fund further preclinical studies to fully assess the best-in-class potential of these promising new glycopeptide antibiotics and to further chart their path towards first-in-human trials.

Figure 5. Structure of novel guanidino lipoglycopeptide discovered by Martin group. This antibiotic shows potent activity against vancomcyin resistant enterococci (VRE) cells.

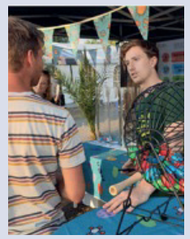
Science Communication and Society

IMPACTLAB

Societal Relevance: open access measurement instruments and support for evaluating the impact of science communication; SDG4.
Embedding: Science Communication and Society
Principal Investigator: Dr. Anne Land
Funding Source: NWO-NWA

Science communication is getting increasingly more attention within academia and society, but often it is not entirely clear what the impact is of all these science communication activities. In 2020, Anne Land-Zandstra (SCS) together with Madelijn Strick of Utrecht University was commissioned by the National Science Agenda (NWA) of NWO to develop and study a way to measure the impact of science communication. In 2021, they started the project Impactlab. Together with a postdoc who worked in both universities they developed a toolbox, a decisions tree and a question bank that enables organizers of science communication to measure the impact of their projects. Using this toolbox, they performed research to examine the factors that play a role in effective science communication.

The instruments were developed based on existing literature and previous studies about the impact of science communication. Several theoretical frameworks were implemented such as emotional memory (used as a proxy for impact) and science capital (i.e. the prior knowledge, experience, capacity of visitors related to science). At the same time, the Impactlab established numerous connections with the field of science communication to make sure the developed materials were useful for the practical field of science communication, which revealed a great need for the Impactlab. Requests for workshops to learn how to measure impact of science communication and how to use the materials were coming in on a regular basis, making the Impactlab adjust its approach to offer this kind of support for the field next to the focus on “producing” research. The outreach resulted in many people using and testing the materials, within and outside the Netherlands. Although the initial phase of the project finished in 2023, the Impactlab toolbox and platform and the need for effective evaluation of science communication remains.



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Peeters, W., et al. (2022). Een nieuw aanpak voor meten van impact in de wetenschapscommunicatie: Theoretisch kader en praktische uitwerking. Tijdschrift voor Communicatiewetenschap, 50(3), 231-250.
Land-Zandstra, A., et al. (2023). Het meten van impact van wetenschapscommunicatie: Eindrapport IMPACTLAB.

4.2 Spin-out

Cantoni Therapeutics – an IBL spinout company

Founded in early 2023, Cantoni Therapeutics is a biopharmaceutical spinout company from Martin group in the IBL. Co-founded by former Martin group postdoc dr. Matthijs van Haren and Prof. Nathaniel Martin, Cantoni aims to develop innovative small molecule inhibitors targeted towards the enzyme nicotinamide N-methyltransferase (NNMT). NNMT is an unexploited target with therapeutic potential in the treatment of metabolic disease and numerous cancers.