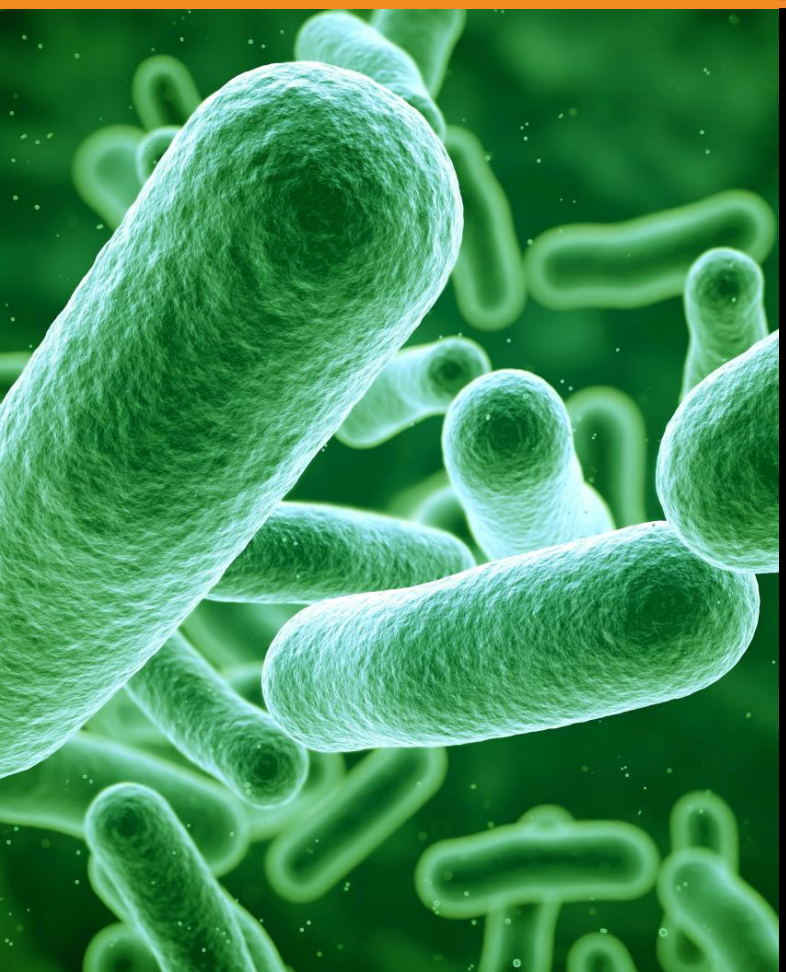
Turning the Tide of Antimicrobial resistance

TTA

GOES NORDIC 2

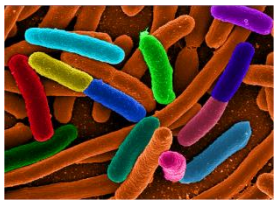


April 27-28 2017

Rotunda and Mezzanine
The University of Oslo
Gaustad, Norway

TTA

TURNING THE TIDE
OF ANTIMICROBIAL
RESISTANCE



TTA GOES NORDIC

2nd Turning the Tide of Antimicrobial resistance – TTA goes Nordic 2
April 27-28 2017
The Rotunda and Mezzanine at the University of Oslo at Gaustad

Organized by
Dag Berild
Fredrik Müller
Tone Tønjum
Jessica Lönn-Stensrud
Meryl S. Lillenes
Mari Støen

Sponsored by

TTA
TURNING THE TIDE OF ANTIMICROBIAL RESISTANCE

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SCOPE

We are delighted to welcome you to TTA goes Nordic 2 – the 2nd Turning the Tide of Antimicrobial resistance conference. This international conference is hosted by the University of Oslo and Oslo University Hospital. It will focus on current concepts and challenges in antimicrobial resistance (AMR).

AMR is an urgent public health threat. AMR is emerging as a local and global peril to health care practice, and the new multidrug-resistant and extensively drug-resistant superbugs represent a diagnostic and therapeutic challenge worldwide. The World Health Organization recently reported that 'a post-antibiotic era - in which common infections and minor injuries can kill - far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century'. Due to this impending crisis, an urgent situation faces society and health care.

Our ambition is to offer a unique opportunity for scientists at all levels to discuss the latest topics in the rapidly developing field of AMR, to promote scientific interactions and networking between the Nordic countries and beyond.

AMR is a prime example of a research field in swift development, not the least because of integrated approaches and multidisciplinary interactions between different segments of the life sciences, general practice and public health. The TTA goes Nordic speakers are leaders in their fields and, together, they offer a broad and exciting program that addresses key topics in AMR. The TTA goes Nordic 2 meeting will thus promote a convergent approach to be considered as a blueprint for research and innovation for the future. In the long run, the goals are to understand the mechanisms of AMR development and to delay or even prevent their onset. In turn, the desired outcomes will be reduced antibiotics use and novel AMR diagnostics prevention and therapeutics.

TTA goes Nordic 2 is organized by TTA - Turning the Tide of Antimicrobial resistance network and the Genome Dynamics group. It is supported by UiO:Life Science, Nordforsk, the Research Council of Norway, Helse SørØst and Oslo University Hospital.

We thank you for attending the TTA goes Nordic 2 conference and contributing to its success!

Welcome to Oslo!

Dag Berild
Professor, MD
UiO, OUH
dagber@ous-hf.no

Fredrik Müller
Professor, MD
Head of microbiology dep.
UiO, OUH
fredrik.muller@rr-research.no

Tone Tønjum
Professor, MD
UiO, OUH
tone.tonjum@medisin.uio.no

Jessica Lönn-Stensrud
PhD, TTA coordinator
Jessica.lonn-stensrud@rr-research.no

Meryl S. Lillenes
PhD, TTA coordinator
m.s.lillenes@medisin.uio.no

PROGRAM

Thursday 27th of April 2017

09:00	Registration
09:30	**Tone Tønjum**: Welcome to TTA goes Nordic 2
09:35	**Finn-Eirik Johansen**, Director UiO:Life Science, University of Oslo, Norway – TTA2 sponsor: Opening remarks
09:40	**Bjørn Erikstein**, CEO, Oslo University Hospital, Norway – TTA2 sponsor
	The current challenge of AMR — **Chair: Tone Tønjum**
09:50	**Jasper Littman**, Robert Koch Institute: Antibiotic resistance: An ethical challenge
10:20	**Niels Frimodt-Møller**, Rigshospitalet, Copenhagen, Denmark: The fight against AMR: The menace of vancomycin resistant enterococci (VRE) outbreaks
10:40	**Nina Langeland**, University of Bergen, Norway: Infection with resistant Gram-negative bacteria in children in Tanzania: mortality and risk factors
11:00	**Stephen Gordon**, University College Dublin, Ireland: One Health insights into Tuberculosis
11:20	Coffee
	The evolution of AMR — **Chair: Jørgen V. Bjørnholt**
11:50	**Jesús Blázquez**, National Centre for Biotechnology, Madrid, Spain: Low level antibiotic resistance: steps to clinical resistance and more
12:10	**Digby Warner**, Cape Town University, South Africa: A moving target: evolution of drug resistance in *Mycobacterium tuberculosis*
12:30	**Tim Tolker-Nielsen**, University of Copenhagen, Denmark: Multifaceted aminoglycoside antibiotic tolerance in biofilms
12:50	**Eliora Ron**, Tel Aviv University, Israel: Can we cope with antibiotic resistant septicemic *Eschericia coli*?
13:10	**Lene Juel-Rasmussen**, University of Copenhagen, Denmark: Host-microbe interaction driven by mismatch repair
13:30	Lunch

Thursday 27th of April 2017

14:30	**Patrice Normann**, University of Fribourgh, Switzerland: Resistance to polymyxins: the fall of the last soldier
14:50	**Ørjan Samuelsen**, The Arctic University of Norway, Tromsø, Norway: Genomic epidemiology of carbapenemase-producing *Enterobacteriaceae* in Norway
15:10	**Avinash Sonawane**, KIIT University, Bhubaneswar, Orissa, India: Mechanisms of host immune evasion and antimicrobial resistance by *Mycobacterium tuberculosis*
15:30	**Fredrik Almqvist**, Umeå University, Sweden: Discovery and development of Mycobacterial Tolerance Inhibitors; Disarming of isoniazid resistance in *Mycobacterium tuberculosis*
15:50	Coffee

AMR detection **Chair: Fredrik Müller**

16:20	**Dan Andersson**, Uppsala University, Sweden: Rapid determination of antibiotic resistance
16:40	**Patrice Normann**, University of Fribourgh, Switzerland: Rapid diagnostic of emerging antibiotic resistance
17:00	Closing remarks and practical information
19:00	Dinner (Restaurant Palmen at Grand Hotel)

Friday 28th of April 2017

09:00	Welcome to Day 2 by TTA	
	Novel drugs against AMR bugs	**Chair: Pål Rongved**
09:05	**Diarmaid Hughes**, Uppsala University, Sweden: The evolutionary trajectory to fluoroquinolone resistance	
09:25	**Jeremy P. Derrick**, Manchester University, UK: Antibiotic drug discovery- pitfalls and opportunities	
9.45	**Pål Rongved**, University of Oslo, Norway: New technology to fight the ticking time-bomb of antimicrobial resistance	
10:05	**Sven Bergström**, Umeå University, Sweden: Using 2-pyridone amide to treat and understand Chlamydia biology and pathogenesis	
10:25	Coffee	
	New principles in the treatment of AMR	**Chair: Karianne W. Gammelsrud**
10.55	**Mona Johannessen**, The Arctic University of Norway: Know your enemy- then disarm them	
11.15	**Birgitta Agerberth**, Karolinska Institutet, Sweden: Host-directed TB therapy involving the induction of antimicrobial peptides	
11.35	**Magnus Steigedal**, NTNU, Trondheim Norway: New intervention strategy for tuberculosis: blocking multiple essential targets	
11.55	**Brigitte Gicquel**, Institute Pasteur, Paris, France: The Continuous Chemotherapeutic Fight Against Tuberculosis	
12:15	Lunch	
13.15	**Reeta Satokari**, University of Helsinki, Finland: Fecal microbiota transplantation and eradication of antibiotic resistant bacteria	
13.35	**Magnus Lundgren**, Uppsala University, Sweden: Using gene technology against antibiotic resistant pathogens: prospects and concerns	
13.55	**Hanna Tiainen**, University of Oslo, Norway: Polyphenolic nanocoatings for improved peri-implant healing	
14:15	Coffee	

Friday 28th of April 2017

Current perspectives on handling AMR — **Chair: Dag Berild**

14.35 **Jens Lundgren**, Rigshospitalet, Copenhagen, Denmark:
We suggest "Personalised medicine in AMR treatment"

Panel discussion on current AMR challenges — **Chair: Jessica Lönn-Stensrud**

15.15 Panel members: **Stener Kvinnsland, Eliora Ron**, **Lene Juel-Rasmussen** and **Jasper Littman**

How can we reduce the over-use of antibiotics?
How can we reduce the environmental spill-over of antibiotics?
What are the current black holes in AMR science?
How can international collaboration be strengthened?

16:00 Closing remarks by Fredrik Müller

INTRODUCTORY SPEAKERS

Finn-Eirik Johansen
Director
UiO:Life Science, University of Oslo, Norway

Bjørn Erikstein
CEO
Oslo University Hospital (OUS), Norway

SPEAKERS

Jasper Littmann
Strategic advisor to the President
Office of the President
Robert Koch Institute,
Berlin,,
Germany

Antibiotic resistance: An ethical challenge

Antibiotic Resistance has been widely described as one of the major health threats of the 21st century - a fact that is now increasingly recognised at the policy level. However, little attention has so far been paid to the ethical questions that antibiotic resistance raises for health care workers, patients and policy makers. This presentation will provide an overview of the main normative challenges posed by antibiotic resistance, chief among which is the question, what we are willing to do as a society to preserve the effectiveness of antibiotics for future patients.

Selected papers:

Viens, A, Littmann J The Ethical Significance of Antimicrobial Resistance, Public Health Ethics (2015) 8 (3): 209-224

Littmann J, Buyx A, Cars O, "Antibiotic resistance: An ethical challenge", International Journal of Antimicrobial Chemotherapy (2015) Vol 46 (4), 359–361

Niels Frimodt-Møller
Professor, MD, DMSc
Head of department
Dept. of Clinical Microbiology,
Rigshospitalet,
Copenhagen,
Denmark

The fight against AMR: The menace of vancomycin resistant enterococci (VRE) outbreaks

VRE outbreaks have increased since 2012 in the Copenhagen Regional hospitals. E. faecium is promiscuous in easily exchanging DNA e.g. also the transposon (Tn1546), which carries the vanA gene. Since a patient can have several different clones of E. faecium in the gut flora, transmission of one clone can via DNA-transfer result in another clone appearing a new patient, thus obscuring the incident as two separate VRE-occurrences. During the last 4 years isolates of VRE have been typed by whole-genome-sequencing (WGS). This has shown, that during 2012-15 multiple clones appeared, while in 2016 a shift occurred to a dominant clone ST218, which has spread in this region. The members of this clone are virtually impossible to discern by WGS. So in spite of these new methods, we have returned to classify an outbreak solely on finding VRE in two or more patients in the same department at the same time.

Selected papers:

Sørensen TL, Blom M, Monnet DL, Frimodt-Møller N (corresponding author), Poulsen RL, Espersen F. Transient intestinal carriage after ingestion of antibiotic-resistant Enterococcus faecium from chicken and pork. N Engl J Med 2001, 345: 1161-6

Lester CH, Frimodt-Møller N, Sørensen TL, Monnet DL, Hammerum AM.In vivo transfer of the vanA resistance gene from an Enterococcus faecium isolate of animal origin to an E. faecium isolate of human origin in the intestines of human volunteers. Antimicrob Ag. Chemother 2006; 50: 596-9

Nielsen KL, Stegger M, Godfrey PA, Feldgarden M, Andersen PS, Frimodt-Møller N. Adaptation of Escherichia coli traversing from the faecal environment to the urinary tract. Int J Med Microbiol. 2016; 306: 595-603

Nina Langeland
Professor
Department of Clinical Science
University of Bergen, Norway

Infection with resistant Gram-negative bacteria in children in Tanzania: mortality and risk factors.

Under-five mortality is, even in 2017, very high in low-Income countries. Identified causes include malaria, diarrheal disease and HIV. Bacterial infections are gradually recognised as major contributors of child mortality. Our data show that even more than 15 years ago antimicrobial resistance to recommended antimicrobial agents were responsible for a majority of fatalities in hospitalized children in Dar es Salaam. With more than 70% mortality in bloodstream infections caused by ESBL-producing bacteria, compared with overall mortality of 35% in bacteremia in general, this called for interventions. Ten years later, in 2010-2011 faecal carriage of ESBL-producing gram-negatives was investigated among healthy and hospitalized children in Dar es Salaam, and prior antibiotic consumption, HIV positivity and young age were significant risk factors for ESBL carriage.

Selected papers:

1. Blomberg B, Jureen R, Manji KP, Tamim BS, Mwakagile DSM, Urassa WK, Fataki M, Msangi V, Gjerde M, Maselle S & Langeland N (2005) High case-fatality rate from bacteremia caused by Gram-negative bacteria with extended-spectrum beta-lacatamases (ESBL) in Tanzanian children. J Clin Microbiol 43, 2, 745-749.

2. Moyo S, Haldorsen B, Aboud S, Blomberg B, Maselle SY, Sundsfjord A, Langeland N and Samuelsen Ø (2014) The first identified VIM-2-producing Pseudomonas aeruginosa from Tanzania is associated with sequence types 244 and 640 and the location of blaVIM-2 in an tniC integron. Antimicrob Agents Chemother. 2014 Oct 20. pii: AAC.01436-13

3.Tellevik MG, Blomberg B, Kommedal Ø, Maselle SY, Langeland N & Moyo SJ (2016) High prevalence offaecal carriage og ESBL-producing Enterobacteriaceae among children in Dar es Salaam, Tanzania. PLoS One Dec 9;11(12):e0168024

Stephen Gordon
Professor
School of Veterinary Medicine
University College Dublin
Ireland

One Health insights into Tuberculosis

One Health is the term given to the collaborative efforts of multiple disciplines - working locally, nationally, and globally - to achieve optimal health for people, animals, and our environment. Tuberculosis (TB) in humans and animals is a paradigm of such One Health concepts, but these ideas are not new. The potential for comparative analyses of human and animal TB to catalyse the development of new approaches to TB control was recognized by Theobald Smith who first differentiated human and bovine tubercle bacilli in 1896. Smith contended that comparative studies would "lead eventually to more light on the whole subject of tuberculosis from the preventive as well as the therapeutic side". In this presentation I will discuss our work on comparative analyses of M. tuberculosis and M. bovis as the exemplar human- and animal-adapted TB pathogens, and look to what these studies can teach us about the virulence, evolution and host adaptation of the tubercle bacilli.

Selected papers:

Healy C, Golby P, MacHugh DE, Gordon SV. The MarR family transcription factor Rv1404 coordinates adaptation of Mycobacterium tuberculosis to acid stress via controlled expression of Rv1405c, a virulence-associated methyltransferase. Tuberculosis (Edinb). 2016 Mar;97:154-62..

Behr MA, Gordon SV. Why doesn't Mycobacterium tuberculosis spread in animals? Trends Microbiol. 2015 Jan;23(1):1-2. doi: 10.1016/j.tim.2014.11.001. PubMed PMID: 25435136.

Avanzi C, Del-Pozo J, Benjak A, Stevenson K, Simpson VR, Busso P, McLuckie J, Loiseau C, Lawton C, Schoening J, Shaw DJ, Piton J, Vera-Cabrera L, Velarde-Felix JS, McDermott F, Gordon SV, Cole ST, Meredith AL. Red squirrels in the British Isles are infected with leprosy bacilli. Science. 2016 Nov 11;354(6313):744-747. PubMed PMID: 27846605.

Jesus Blazquez
Professor
Department of Microbial Biotechnology
National Centre for Biotechnology - National Research Council, Madrid
Spain

Low level antibiotic resistance: steps to clinical resistance and more

Martín-Gutiérrez G, Rodríguez-Martínez JM, Pascual Á, Rodríguez-Beltrán J, Blázquez J. Plasmidic qnr genes confer clinical resistance to ciprofloxacin under urinary tract physiological conditions. Antimicrob. Agents Chemother. In press. DOI: 10.1128/AAC.02615-16. 2017.

Martín-Gutiérrez G, Rodríguez-Beltrán J, Rodríguez-Martínez JM, Costas C, Aznar J, Pascual Á, Blázquez J. Urinary tract physiological conditions promote ciprofloxacin resistance in low-level-quinolone-resistant Escherichia coli. Antimicrob Agents Chemother. 60: 4252-8. PMID:27139482. 2016.

Digby Warner
Associate professor
Department of Pathology and Institute of Infectious Disease & Molecular Medicine
University of Cape Town,
South Africa

A moving target: evolution of drug resistance in Mycobacterium tuberculosis
The Continuous Chemotherapeutic Fight Against Tuberculosis

An SOS-inducible DNA repair system - the "mycobacterial mutasome" comprising the specialist DNA polymerase, DnaE2, and accessory factors, ImuA′ and ImuB - has been implicated in drug resistance in Mycobacterium tuberculosis. We have developed fluorescent reporters to investigate subcellular localization of mutasome components in bacilli exposed to genotoxic stress. ImuB co-localizes with the β clamp in discrete foci during mutagenic DNA repair; in contrast, ImuA′ and DnaE2 do not exhibit specific intrabacillary localization. A mutant strain deficient in the ImuB β clamp-binding site (ImuBAAAAG) fails to co-localize with the β clamp, reinforcing the inferred essentiality of the ImuB-β clamp protein-protein interaction for mutasome recruitment and induced mutagenesis. Moreover, exposure to the novel β clamp-targeting antimycobacterial agent, griselimycin, prevents β clamp localization. Notably, griselimycin also disrupts ImuB recruitment despite inducing the SOS response. Our results therefore suggest the capacity of griselimycin to block induced mutagenesis by disrupting mutasome assembly and function.

Selectedpapers:

1. Ditse Z, Lamers MH, Warner DF. (2017) DNA replication in Mycobacterium tuberculosis. Microbiol Spectr. doi:10.1128/microbiolspec.TBTB2-0027-2016

2. Warner DF, Koch A, Mizrahi V. (2014) Diversity and disease pathogenesis in Mycobacterium tuberculosis. Trends Microbiol. doi:10.1016/j.tim.2014.10.005

3. Warner DF, Ndwandwe DE, Abrahams GL, Kana BD, Machowski EE, Venclovas Č, Mizrahi V. (2010) Essential roles for imuA'- and imuB-encoded accessory factors in DnaE2-dependent mutagenesis in Mycobacterium tuberculosis. Proc Natl Acad Sci USA 107:13093-13098.

Tim Tolker-Nielsen
Professor
Department of Immunology and Microbiology
University of Copenhagen
Denmark

Multifaceted aminoglycoside antibiotic tolerance in biofilms

Microbial biofilms are tolerant of host immune responses and antibiotic treatment, and therefore cause a range of problematic infections. Knowledge about biofilm-associated antibiotic tolerance mechanisms is warranted in order to develop effective treatments against biofilm infections. Using Pseudomonas aeruginosa biofilms as a model for Gram-negative biofilms and Streptococcus mutans biofilms as a model for Gram-positive biofilms, we have uncovered mechanisms involved in biofilm-associated aminoglycoside antibiotic tolerance. These mechanisms include: 1) shielding against antibiotics by biofilm matrix components such as exopolysaccharide and extracellular DNA, 2) modification of cell surface charge by addition of amino-arabinose to lipopolysaccharide in case of P. aeruginosa, and by addition of adenylate to teichoic acids in case of S. mutans, and 3) systems that counteract oxidative stress. Our findings emphasize that biofilm-associated antibiotic tolerance is caused by multiple mechanisms.

Selected papers:

Goltermann L and Tolker-Nielsen T. (2017) Importance of the exopolysaccharide matrix in antimicrobial tolerance of Pseudomonas aeruginosa aggregates. Antimicrob Agents Chemother In press.

Nilsson M, Rybtke M, Givskov M, Høiby N, Twetman S and Tolker-Nielsen T (2016) The dlt genes play a role in antimicrobial tolerance of Streptococcus mutans biofilms. Int J Antimicrob Agents 48:298-304

.

Nilsson M, Givskov M, Twetman S and Tolker-Nielsen T (2017) The oxidative stress response regulator SpxA1 plays a role in antimicrobial tolerance of Streptococcus mutans biofilms. Submitted for publication.

Eliora Ron
Department of Molecular Microbiology and Biotechnology
Professor
Tel Aviv University
Israel

Can we cope with antibiotic resistant septicemic Eschericia coli?

Septicemic E. coli have become a major human pathogen, especially due to their high antibiotic resistance. The infections are severe in terms of morbidity and mortality as well as the heavy cost burden on the community. Because there is a very large number of serotypes, developing a simple vaccine is not practical. Therefore, it is essential to use functional genomics approaches to identify novel targets and develop new drugs.

Selected papers:

Huja, S., Oren, Y., Trost, E., Brzuszkiewicz, E., Biran, D., Blom, J., Goesmann, A., Gottschalk, G., Hacker, J., Ron, E. Z. & Dobrindt, U. (2015). Genomic avenue to avian colisepticemia. Mbio 6. 01681-14

Oren, Y., Smith, M. B., Johns, N. I., Kaplan Zeevi, M., Biran, D., Ron, E. Z., Corander, J., Wang, H. H., Alm, E. J. & Pupko, T. (2014). Transfer of noncoding DNA drives regulatory rewiring in bacteria. Proc Natl Acad Sci U S A. 111:16112-7

Huja, S., Y. Oren, D. Biran., S. Meyer., U. Dobrindt, J. Bernhard., D. Becher, M. Hecker, R. Sorek and E. Z. Ron (2014) Fur is the Master Regulator in ExPEC (Extraintestinal Pathogenic Escherichia coli) Response to Serum. mBio 5: e01460-14

Lene Juel-Rasmussen
Professor
Managing Director
Center for Healthy Aging,
University of Copenhagen,
Denmark

Host-microbe interaction driven by mismatch repair

In order to regulate or maintain the integrity of the genome, a sophisticated interwoven system of DNA repair pathways remove the vast majority of the plethora of deleterious lesions. However, DNA repair may sometimes fail or become limited due to excess of DNA damage resulting in DNA damage accumulation. When the DNA is replicated there is a risk that errors occur as a result of mistakes made by the DNA polymerases. Bases mispairs arising during DNA replication are substrates for repair by the conserved DNA mismatch repair (MMR) pathway. If repair fails the resulting persistent mutations can lead to changes of the genetic makeup of organisms, which can either increase or decrease fitness of cells, tissue or organisms.

The microbiota of the intestinal tract play critical roles in energy metabolism and human health, and disruptions of the dynamic interaction between host and bacteria are significant factors of a variety of diseases including cancer as well as aging.

It is well known that environmental factors such as chemicals and radiation cause DNA damage. In contrast, the consequences of bacterial infection on the integrity of host DNA are poorly understood. To investigate if bacterial infections might accelerate genomic damage in the host, we have examined how two well-known bacterial pathogens, Helicobacter pylori and Enterococcus faecalis that are associated with the development of colorectal and gastric cancer, might promote genomic instability in human cells post-infection. We show that both pathogens are implicated in the induction of genomic instability in DNA of gastric epithelial cells. Instability in nuclear DNA is coupled to down-regulation of central DNA repair activities that includes MMR. By down-regulating MMR pathways, bacterial infections have the potential to inflict direct changes in the DNA of the host, such as oxidative damage, methylation, chromosomal instability, microsatellite instability, and mutations.

Based on our results, we propose that bacterial infections promote genomic instability by (1) a combination of increased endogenous DNA damage and decreased repair activities and (2) the generation of a transient mutator phenotype that induces mutations in the nuclear genome.

Selected papers:

1. Machado AMD, Figueiredo C, Touati E, Máximo V, Sousa S, Michel V, Carneiro F, Nielsen FC, Seruca R, Rasmussen LJ. 2009. Helicobacter pylori infection induces genetic instability of nuclear and mitochondrial DNA in gastric cells. Clin. Cancer Res. 15: 2995-3002.

2. Strickertsson JAB, Desler C, Bertelsen TM, Machado AMD, Wadstrøm T, Winther O, Rasmussen LJ, Hansen LF. 2013. Enterococcus faecalis causes inflammation, intracellular ROS production, and DNA damage in human gastric cancer cells. PLoS One. 8(4) e63147.

3. Machado AM, Desler C, Bøggild S, Strickertsson JA, Hansen LF, Figueiredo C, Seruca R, Rasmussen LJ. 2013. Helicobacter pylori infection affects mitochondrial function and DNA repair, thus, mediating genetic instability in gastric cells. Mech. Aging Dev. 134:460-466.

Patrice Nordman
Professor
Head of department
Molecular
Microbiology Unit,
University of Fribourg,
Switzerland

Rapid diagnostics of emerging antibiotic resistance

Clinically-significant multidrug-resistant bacteria are increasingly reported within enterobacterial species (e.g., Escherichia coli, Klebsiella pneumoniae, Enterobacter spp) and Pseudomonas aeruginosa and Acinetobacter baumannii. The antibiotic resistance traits that are currently widespread in these Gram-negatives are mostly extended-spectrum ß-lactamases (ESBL) and carbapanemases producers. The ESBLs confer resistance to all -lactams, with the exception of cephamycins and carbapenems, while carbapenemases confer resistance to virtually all -lactams including carbapenems.. Among the latest emerging antibiotic resistance traits, polymyxin resistance and pandrug resistance to aminoglycosides are also of concern. The rapid diagnostic techniques available have a turn around time ranging from 30 min to a few hours whereas the "old-fashioned" antibiotic susceptibility tests take usually 18 h. They are are based not only on molecular biology but also on biochemistry, physics, immunology and rapid culture techniques. Those techniques now may contribute to an optimal therapeutic choice as well as controlling their spread in nosocomial settings.

Selected papers:

Nordmann P., Jayol A, Dobias J., Poirel L. (2017). Rapid Aminoglycoside NP test for rapid detection of multiple aminoglycoside resistance in Enterobacteriaceae. J. Clin Microbiol., pii: JCM.02107-16. doi: 10.1128/JCM.02107-16

Nordmann P., Jayol A., Poirel L. (2016). Rapid detection of polymyxin resistance in Enterobacteriaceae. Emerg Infect Dis. 22:1031-1036.

Nordmann P., Poirel L., Dortet L. (2012). Rapid detection of carbapenemase-producing Enterobacteriaceae. Emerg Infect Dis. 18:1503-1507.

Resistance of polymyxins; the fall of the last soldier?

Polymyxins are well-established antibiotics that have recently regained significant interest as a consequence of the increasing incidence of infections due to multidrug-resistant Gram-negative bacteria. Colistin and polymyxin B are being seriously reconsidered as last-resort antibiotics in many areas where multidrug resistance is observed in clinical medicine. In parallel, the heavy use of polymyxins in veterinary medicine is currently being reconsidered due to increased reports of polymyxin-resistant bacteria. Susceptibility testing is challenging with polymyxins. Whereas chromosomally-mediated polymyxin resistance has been reported in Enterobacteriaceae, Pseudomonas aeruginosa and Acinetobacter baumannii since a few years, more precise mechanisms of polymyxins resistance are extensively described. Plasmid-mediated resistance to polymyxins (MCR-1 and related) are now reported in Enterobacteriaceae since November 2015. Their main location is Escherichia coli of veterinary origin. This novel resistance trait may represent one of the very few example of transfer of resistance genes from animals to humans. Their reservoir are Moraxella-like species.

Selected papers:

Nordmann P., Jayol A, Dobias J., Poirel L. (2017). Rapid Aminoglycoside NP test for rapid detection of multiple aminoglycoside resistance in Enterobacteriaceae. J. Clin Microbiol., pii: JCM.02107-16. doi: 10.1128/JCM.02107-16

Nordmann P., Jayol A., Poirel L. (2016). Rapid detection of polymyxin resistance in Enterobacteriaceae. Emerg Infect Dis. 22:1031-1036.

Nordmann P., Poirel L., Dortet L. (2012). Rapid detection of carbapenemase-producing Enterobacteriaceae. Emerg Infect Dis. 18:1503-1507.

Ørjan Samuelsen
Professor
Norwegian National Advisory Unit on Detection of Antimicrobial Resistance and Dept. of Pharmacy
University Hospital of North Norway and UiT - The Arctic University of Norway
Norway

Genomic epidemiology of carbapenemase-producing Enterobacteriaceae in Norway

The prevalence of carbapenemase-producing Enterobacteriaceae (CPE) is increasing worldwide. Infections caused by CPE are difficult to treat due to multidrug-resistance and require a heightened degree of surveillance, infection prevention and control. In Norway, reporting of CPE cases is mandatory to the Norwegian Surveillance System for Communicable diseases after confirmation at the Norwegian National Advisory Unit on Detection of Antimicrobial Resistance. Confirmed CPE isolates are characterized phenotypically and genotypically, including by whole-genome sequencing. Here we review the genomic epidemiology of CPE cases identified in Norway from 2007-2016 showing that the majority of cases are directly associated with travel or hospitalization abroad, but both intra-hospital and one inter-hospital outbreak have occurred. Genomic characterization show that the CPE isolates in Norway exhibits a broad diversity of genetic backgrounds and carbapenemase variants that mirror the global epidemiology.

Selected papers:

Grundmann H, Glasner C, Albiger B, Aanensen DM, Tomlinson CT, Andrasević AT, Cantón R, Carmeli Y, Friedrich AW, Giske CG, Glupczynski Y, Gniadkowski M, Livermore DM, Nordmann P, Poirel L, Rossolini GM, Seifert H, Vatopoulos A, Walsh T, Woodford N, Monnet DL; European Survey of Carbapenemase-Producing Enterobacteriaceae (EuSCAPE) Working Group. Occurrence of carbapenemase-producing Klebsiella pneumoniae and Escherichia coli in the European survey of carbapenemase-producing Enterobacteriaceae (EuSCAPE): a prospective, multinational study. Lancet Infect. Dis: 2017;17(2):153-163

Albiger B, Glasner C, Struelens MJ, Grundmann H, Monnet DL; European Survey of Carbapenemase-Producing Enterobacteriaceae (EuSCAPE) working group. Carbapenemase-producing Enterobacteriaceae in Europe: assessment by national experts from 38 countries, May 2015. Eurosurveill. 2015;20(45)

Tofteland S, Naseer U, Lislevand JH, Sundsfjord A, Samuelsen O. A long-term low-frequency hospital outbreak of KPC-producing Klebsiella pneumoniae involving Intergenus plasmid diffusion and a persisting environmental reservoir.PLoS ONE 2013;8(3):e59015

Avinash Sonawane
Professor and Dean
School of
Biotechnology, KIIT
University,
Bhubaneswar, Odisha,
India
Dept. of Clinical
Microbiology
KIIT University,
Bhubaneswar
India

Mechanisms of host immune evasion and antimicrobial resistance by Mycobacterium tuberculosis

Mycobacterium tuberculosis (Mtb), causative agent of tuberculosis, employs various strategies against antibacterial molecules to facilitate its persistence in macrophages. These include modulation of host derived antimicrobial peptides, biofilm formation and synthesis of glycoconjugates that remodel the bacterial cell surface. Recently, we have shown that Mtb peptidoglycan amidase is responsible for resistance against two prominent anti-tuberculosis drugs isoniazid and pyrazinamide. We further report that Mtb peptidoglycan amidase induced biofilm formation and also increased cell wall hydrophobicity resulting in cell aggregation and drug resistance. Several reports have shown that macrophages are able to kill Mtb through the action of antimicrobial peptide cathelicidin. We found that Mtb lipoprotein LprE helps bacteria to survive by down-regulating the expression of cathelicidin (CAMP) in infected human macrophages. We showed that down-regulation of CAMP expression by LprE was due to inhibition of p38 MAPK, 25-hydroxyvitamin D-1α-hydroxylase (Cyp27B1) and vitamin-D receptor (VDR) via TLR-2 signaling pathway. Mtb LprE was also found to inhibit phago-lysosome fusion by down-regulating the expression of several endosomal markers and cytokines. Recent study has shown that Mtb persist not only in macrophages but also in bone marrow mesenchymal stem cells (BM-MSCs) even after successful antibiotic treatment. We observed that Mtb infection down-regulates the expression of cathelicidin not only in macrophages but also in BM-MSCs to facilitate its survival in bone marrow. In contrast, avirulent mycobacteria such as M. bovis-BCG and M. smegmatis were readily killed by inducing the expression of cathelicidin in BM-macrophages and MSCs. We demonstrated that Mtb infection modulated the expression of cathelicidin in BM-MSCs by p38 MAPK pathway via TLR-4, myeloid differentiation primary response 88 (MyD88) and interleukin-1 receptor-associated kinase-4 (IRAK-4) and NF-kB. Altogether, we have shown that Mtb glycoproteins play an important role in drug resistance and also manipulate innate immunity to facilitate its persistence

Selected papers:

1. Srabasti Sengupta, Saba Naz, Ishani Das, Abdul Ahad, Avinash Padhi, Sumanta Naik, Geetanjali Ganguli, Kaliprasad Patnaik, Sunil Raghav, Vinay Nandicoori and Avinash Sonawane (2016). Mycobacterium tuberculosis EsxL inhibit MHC-II expression by promoting hypermethylation in class-II transactivator via induction of nitric oxide synthetase and p38- MAPK in macrophages. J. Biol. Chem. (Accepted).

2. 7. Soumitra Mohanty, Michael Dal Molin, Geetanjali Ganguli, Avinash Padhi, Prajna Jena1, Petra Selchow, Srabasti Sengupta1, Michael Meuli, Peter Sander and Avinash Sonawane (2016). Mycobacterium tuberculosis EsxO (Rv2346c) promotes bacillary survival by inducing oxidative stress mediated genomic instability in macrophages. Tuberculosis (Edinburg) 96:44-57

3. 12. Mohanty, S., Jagannathan, L., Ganguli G., Padhi, A., Alaridah, A., Saha, P., Godaly, G., Banerjee, S., Sonawane, A. (2015): Mycobacterium tuberculosis phosphoribosyltransferase modulates antibacterial effector functions leading to evasion of innate immunity in macrophages and Zebra fish. J. Biol. Chem. 290(21):13321-43

Fredrik Almqvist
Professor
Department of Chemistry
Umeå University
Sweden

Discovery and development of Mycobacterial Tolerance Inhibitors; Disarming of isoniazid resistance in Mycobacterium tuberculosis

During Mycobacterium tuberculosis (Mtb) infection, host-derived stresses induce physiological changes in the bacteria that lead to the formation of antibiotic-tolerant persisters. The recalcitrance of persister Mtb to therapy precludes eradication of the infection and contributes to the formation of antibiotic resistant bacteria by requiring long durations of treatment. Using a chemical approach to dissect hypoxia-induced persister formation, we identified small molecules that inhibit the development of isoniazid (INH) tolerant Mtb. INH is a key component of anti-tuberculosis therapy and the rise in INH-resistance is crippling efforts to control the tuberculosis epidemic. Mechanistic studies revealed that these small molecule mycobacteria tolerance inhibitors (MTIs) dysregulate redox homeostasis, electron transport, and environmentally cued changes in lipid metabolism, thus implicating these processes in drug and stress tolerance. In addition, MTIs prevent the selection for INH-resistant mutants and restore INH-sensitivity in a katG mutant that is otherwise resistant to INH.

Selected papers:

Pinkner, J. S.; Remaut, H.; Buelens, F.; Miller, E.; Åberg, V.; Pemberton, N.; Hedenström, M.; Larsson, A.; Seed, P.; Waksman, G.*; Hultgren, S. J.* and Almqvist, F.*, Rationally designed small compounds inhibit pilus biogenesis in uropathogenic bacteria. Proc. Natl. Acad. Sci. USA. 2006, 103, no. 47, 17897-17902.

Cegelski, L.; Pinkner, J. S.; Hammer, N. D.; Hung, C. S.; Cusumano, C. K.; Chorell, E.; Åberg, V.; Garofalo, C. K.; Walker, J. N.; Seed, P. C.; Almqvist, F.*; Chapman, M. R.* Hultgren, S. J.*, Small molecule inhibitors target E. coli amyloid biogenesis and biofilm formation, Nature Chemical Biology, 2009, 5, No 12, 913- 919

Good, J. A. D.; Andersson, C.; Wall, J.; Hansen, S.; Krishnan. K. S.; Grundström, C.; S. Niemiec, M. S.; Vaitkevicius, K.; Chorell, E.; Sauer, U. H.; Wittung-Stafshede, P.; Sauer–Eriksson, E. *; Almqvist, F.*; Johansson, J.*, Inactivating the Listeria monocytogenes virulence regulator PrfA with ring-fused 2-pyridones. Cell Chemical Biology, 2016, 23, 404-414.

Dan Andersson,
Professor
Medical Biochemistry and Microbiology,
Uppsala University,
Sweden

New phenotypic methods for rapid antibiotic susceptibility testing

Identification of bacteria and their antibiotic susceptibility pattern at the hospital laboratory usually takes 2 days and by that time the patient has often already been prescribed antibiotics, which might potentially be useless. This pattern of use leads to many cases of inappropriate treatment and contributes to the emergence and spread of antibiotic resistance. Thus, there is an urgent need for fast and cheap diagnostic methods that can give more accurate information regarding resistance profiles to avoid inappropriate treatment.

We have developed two new rapid (30 min and 4h, respectively) diagnostic methods that allow determination of which pathogen causes the infection and its susceptibility to antimicrobials. The methods are based on phenotypes and are generalizable to any pathogen and antibiotic. The methods have been tested and validated for urinary tract infections. These methods will be described and their advantages and disadvantages discussed.

Selected papers:

Mezger A, Gullberg E, Göransson J, Zorzet A, Herthnek D, Tano E, Nilsson M and Andersson DI (2015). A general method for rapid determination of antibiotic susceptibility and species in bacterial infections. J Clin Microbiol. 53:425-432.

Diarmaid Hughes
Professor
Medical Biochemistry and Microbiology
Uppsala University
Sweden

The evolutionary trajectory to fluoroquinolone resistance

The evolution of resistance to ciprofloxacin in E. coli always requires multiple genetic changes, usually including mutations affecting two different drug target genes, gyrA and parC. Among resistant clinical isolates the genotype, gyrA S83L D87N, parC S80I is significantly overrepresented suggesting that it has a selective advantage. By combining experimental data and mathematical modelling, we addressed the reasons for the predominance of this specific genotype. The experimental data were used to model trajectories of mutational resistance evolution under different conditions of drug exposure and population bottlenecks. We identified the order in which specific mutations are selected in the clinical genotype, showed that the high frequency genotype could be selected over a range of drug selective pressures, and was strongly influenced by the relative fitness of alternative mutations and factors affecting mutation supply.

Selected papers:

Huseby, D.L., Pietsch, F., Brandis, G., Garoff, L., Tegehall, A. and Hughes, D. (2017) Mutation supply and relative fitness shape the genotypes of ciprofloxacin-resistant Escherichia coli. Mol Biol Evol doi: 10.1093/molbev/msx052.

Jeremy Derrick
Professor
School of Biological Sciences
The University of Manchester
UK

Antibiotic drug discovery- pitfalls and opportunities

Biosynthesis pathways have long been advocated as attractive targets for antibiotics, the classic example being the folic acid biosynthetic pathway. The pathway is validated by the sulphonamides, which target dihydropteroate synthase, and inhibitors of dihydrofolate reductase. Here I will outline the history of our work on the enzymes of the folate pathway to illustrate how, even when armed with a great deal of information about the structure and mechanism of the constituent enzymes, the design of novel inhibitors can still be challenging. I will also present more recent data on a new inhibitor, epidermicin, which shows promising activity against MRSA in a cotton rat nasal colonization model.

Selected papers:

Bermingham & Derrick Bioessays. (2002) 24:637-48. The folic acid biosynthesis pathway in bacteria: evaluation of potential for antibacterial drug discovery.

Halliwell et al. J Antimicrob Chemother (2017) 72: 778-781. A single dose of epidermicin NI01 is sufficient to eradicate MRSA from the nares of cotton rats.

Pål Rongved
Professor
School of Pharmacy
The University of Oslo
Norway

New technology to fight the ticking time-bomb of antimicrobial resistance.

The magnitude of the challenge posed by antimicrobial resistance (AMR) to modern healthcare is now widely accepted. Today, about 700,000 people die from infectious diseases worldwide. Left unchecked, it is estimated (O'Neill, May 2016) that by 2050 there will be 10 million AMR-related deaths a year, at a cost of about 100 trillion USD. Multidrug-resistant (MDR) strains of Gram-negative (GN) bacteria (ESBL) are the most threatening, but Gram-positive (GP) organisms like MRSA (methicillin-resistant Staphylococcus aureus), VRE (vancomycin-resistant enterococci) and mycobacteria causing multi-resistant tuberculosis (TB) are a growing concern (Hoppe et al, 2016) increasingly are threatening. In example, totally drug resistant tuberculosis (TDT TB) is now threatening lives in India and other parts of Asia. The list of ESKAPE pathogens (Rice et al, 2009; IDSA 2009) are all targets for the potential diagnostic and therapeutic technology discussed in the talk.

Selected papers:

1. Inhibitors of metallo-β-lactamase comprising a zinc chelating moiety. WO2015049546A1. Rongved, Paal; Aastrand, Ove Alexander Hoegmoen; Bayer, Annette; Leiros, Hanna-Kirsti Schroeder; Samuelsen, Oerjan; Edvardsen, Kine Susann Waade.

2. Synthesis and initial in vitro biological evaluation of two new zinc-chelating compounds: comparison with TPEN and PAC-1. Åstrand Ove Alexander Høgmoen; Aziz Gulzeb; Ali Sidra F; Paulsen Ragnhild Elisabeth; Hansen Trond Vidar; Rongved Pål, Bioorganic and medicinal chemistry (2013), 21, 5175-5181.

3. (Acetonitrile){2-[bis(pyridin-2-ylmethyl-κ2N)amino- κN]-N-(2,6-dimethylphenyl)-acetamide- κO}-(perchlorato- κO)zinc(acetonitrile){2-[bis(pyridin-2-ylmethyl-κ2N)amino-κN]-N-(2,6-dimethylphenyl).

Sven Bergstrom
Professor
Department of Molecular biology
Umea University
Sweden

Using 2-pyridone amide to treat and understand Chlamydia biology and pathogenesis

Chlamydia trachomatis is a successful intracellular pathogen which causes the majority of bacterial sexually transmitted diseases. Bacterial replication and the generation of infectious progeny are the hallmarks of efficient pathogenesis for Chlamydia. We herein describe a novel mechanism for Chlamydial attenuation, through the inhibition of a host cell signalling pathway. We show that inhibition of ERK signalling by small molecule inhibitors result in production of non-infectious Chlamydia progeny. The 2-pyridone amides were shown to inhibit ERK signalling and were an effective treatment of vaginal chlamydia infections in a murine model. The 2-pyridone amide ERK-inhibitors were non-toxic to host cells and present a novel treatment approach for intracellular infections.

Selected papers:

Engström P, Krishnan KS, Ngyuen BD, Chorell E, Normark J, Silver J, Bastidas RJ, Welch MD, Hultgren SJ, Wolf-Watz H, Valdivia RH, Almqvist F, Bergström S. A 2-Pyridone-Amide Inhibitor Targets the Glucose Metabolism Pathway of Chlamydia trachomatis. MBio. 2014 Dec 30;6(1). pii: e02304-14. doi: 10.1128/mBio.02304-14.

Engström P, Bergström M, Alfaro AC, Krishnan KS, Bahnan W, Almqvist F and Bergström S. Expansion of the Chlamydia trachomatis inclusion does not require bacterial replication

International Journal of Medical Microbiology. Int J Med Microbiol. 2015. 305(3) 378-382 doi: 10.1016/j.ijmm.2015.02.007.

Good JAD, Silver J, Núñez-Otero C, Bahnan , Krishnan K, Salin O, Engström P, Svensson R, Artursson P, Gylfe Å, Bergström S*, Almqvist F*. Thiazolino 2-pyridone amide inhibitors of Chlamydia trachomatis infectivity. 2016. J Med Chem, DOI 10.1021/acs.jmedchem.5b01759. *Shared senior authors

Mona Johannessen
Professor
Department of Medical biology, Research Group of Host-microbe interaction
UiT- The Arctic University of Norway
Norway

Know your enemy- then disarm them

Virulence factors include adhesins that mediate attachment to host tissue, proteins with immune evasive properties and toxins interfering with host cells. They are cell wall-anchored, secreted or released by bacterial membrane vesicles, and often influence the severity of infection. To meet the challenge from multi-drug resistant pathogens a successful disarmament of the bacteria could reduce infection severity and aid the body's natural defenses to eliminate the infection. Staphylococcus aureus colonize the human skin. We identified desmoglein1 in keratinocytes as host ligand for the bacterial adhesin SdrD, and found furthermore that SdrD has immune evasive properties. We also showed that S. aureus TIR-domain containing protein, TirS, interferes with host intracellular signaling providing immune evasive properties to the bacterium. Recently, we found that bacterial membrane vesicles from S. aureus both improve bacterial survival in blood and have immunogenic properties. Further molecular studies of these virulence determinants will identify targets for intervention.

Selected papers:

1) Askarian F, van Sorge NM, Sangvik M, Beasley FC, Henriksen JR, Sollid JUE, van Strijp JAG, Nizet V and Johannessen M (2014). A Staphylococcus aureus TIR Domain Protein Virulence Factor Blocks TLR2-Mediated NF-κB Signaling. Journal of Innate Immunity 6; 485-498

2) Askarian F, Ajayi C, Hanssen AM, van Sorge NM, Pettersen I, Diep DB, Sollid JUE, Johannessen M (2016). The interaction between Staphylococcus aureus SdrD and desmoglein 1 is important for adhesion to host cells. Sci Rep 6: 22134

3) Askarian F, Uchiyama S, Valderrama JA, Ajayi C, Sollid JU, van Sorge NM, Nizet V, van Strijp JA, Johannessen M. Serine-Aspartate Repeat Protein D Increases Staphylococcus aureus Virulence and Survival in Blood (2016). Infect Immun 85(1). pii: e00559-16. doi: 10.1128/IAI.00559-16.

Birgitta Agerberth
Professor
Department of Laboratory Medicine (LabMed), Division of Clinical Microbiology
Karolinska Institutet
Sweden

Host-directed TB therapy involving the induction of antimicrobial peptides

Innate immunity constitutes the front line of our defense system against pathogens and relies partly on antimicrobial peptides (AMPs). The induction of the human antimicrobial peptide LL-37 has been shown to contribute to the elimination of *Mycobacterium tuberculosis* (Mtb), where LL-37 also activates autophagy in macrophages. We have shown that Phenylbutyrate (PBA) exhibits a potent synergy with Vitamin D in mycobacterial killing by inducing the expression of LL-37 and thus also activation of autophagy.
We have conducted a phase two clinical trial on newly diagnosed TB patients in Dhaka, Bangladesh. The clinical trial was a 4-arm double-blinded randomized placebo control trial on 288 TB patients. The outcome of this study will be presented.
We have continued to analyze the expression of cytokines, chemokines and autophagy markers in samples generated in the clinical trial. Furthermore, studies are ongoing to investigate how vitamin D and PBA affect anti-TB drugs in macrophages that have been infected with different Mtb strains, including multi-resistant strains.

Selected papers:

Mily A, Rekha RS, Kamal SMM, Akhtar E, Sarker P, Rahim Z, Gudmundsson GH, **Agerberth B,** Raqib R (2013) "Oral intake of phenylbutyrate with or without vitamin D_3 upregulates the cathelicidin LL-37 in human macrophages: A dose finding study for treatment of tuberculosis" *BMC Pulm Med* **13**:23.

Mily A, Rekha RS, Kamal SM, Arifuzzaman AS, Rahim Z, Khan L, Haq MA, Zaman K, Bergman P, Brighenti S, Gudmundsson GH, **Agerberth B**, Raqib R (2015) "Significant Effects of Oral Phenylbutyrate and Vitamin D3 Adjunctive Therapy in Pulmonary Tuberculosis: A Randomized Controlled Trial" *PLoS One* **10**(9):e0138340.

Nylen F, Miraglia E, Cederlund A, Ottosson H, Strömberg R, Gudmundsson GH and **Agerberth B** (2014) "Boosting innate immunity: development and validation of a cell-based screening assay to identify LL-37 inducers" *Innate immunity* **20**(4):364-76.

Rekha RS, Muvva SSVJ, Wan M, Raqib R, Bergman P, Brighenti S, Gudmundsson GH, **Agerberth B** (2015) "Phenylbutyrate induces LL-37-dependent autophagy and intracellular killing of *Mycobacterium tuberculosis* in human macrophages" *Autophagy* **11**(9):1688-99.

Yuk JM, Shin DM, Lee HM, Yang CS, Jin HS, Kim KK, Lee ZW, Lee SH, Kim JM, Jo EK (2009) "Vitamin D3 induces autophagy in human monocytes/macrophages via cathelicidin" *Cell host & microbe* **6**:231-243.

Magnus Steigedal
CEMIR
Researcher
NTNU
Norway

New intervention strategy for tuberculosis: blocking multiple essential targets

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 process, which significantly increases the chance of resistance development. We focus on type VII secretion (T7S) systems as promising new drug targets. We predict that, by blocking multiple T7S systems, we will considerably reduce the development of drug resistance. We use two complementary approaches: (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. We also identify synergistically working compounds form a library of known and approved drugs.

Brigitte Gicquel
Professor
Head of the Mycobacterial Genetics Unit, Institut Pasteur Paris
France
Head of the Emerging Bacterial Pathogens Unit, Institut Pasteur Shanghai
China

The Continuous Chemotherapeutic Fight Against Tuberculosis

After the implementation of the first chemotherapeutic treatments against tuberculosis (TB), antibiotic resistances started to appear. Similarly, after the implementation of rifampicin within the short-term poly-chemotherapeutic treatment, multidrug resistant (MDR) TB emerged. Despite the dramatic decrease of TB incidence thanks to the standardized short-term poly-chemotherapeutic treatment, a high number of MDR TB cases became a growing concern. An analysis of the mutations in the non-essential pncA gene responsible for pyrazinamide resistance in several countries showed its occurrence essentially in MDR TB clinical isolates and even more pronounced in MDR strains also resistant to fluoroquinolones (FQ). The fact that RMP and FQ induce mutator phenotypes in many bacterial species may be considered to play a role for accelerating the acquisition of new antibiotic resistant mutations during the long term TB treatment with regards to other bacterial diseases as well.

Selected papers:

Alame-Emane AK, Xu P, Pierre-Audigier C, Cadet-Daniel V, Shen X, Sraouia M, Siawaya JF, Takiff H, Gao Q, Gicquel B. Pyrazinamide resistance in Mycobacterium tuberculosis arises after rifampicin and fluoroquinolone resistance. Int J Tuberc Lung Dis. (2015) 19:679-84.

Pierre-Audigier C, Surcouf C, Cadet-Daniel V, Namouchi A, Heng S, Murray A, Guillard B, Gicquel B. Fluoroquinolone and pyrazinamide resistance in multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. (2012) 16:221-3,

Minime-Lingoupou F, Pierre-Audigier C, Kassa-Kélémbho E, Barilone N, Zandanga G, Rauzier J, Cadet-Daniel V, Le Faou A, Gicquel B. Rapid identification of multidrug-resistant tuberculosis isolates in treatment failure or relapse patients in Bangui, Central African Republic. Int J Tuberc Lung Dis. (2010) 14:782-5

Reetta Satokari
Adjunct Professor
Immunobiology Research Program, Faculty of Medicine
University of Helsinki
Finland

Fecal microbiota transplantation and eradication of antibiotic resistant bacteria

Faecal microbiota transplantation (FMT) is an effective treatment for recurrent Clostridium difficile infection (rCDI) refractory to antibiotic tratments. FMT restores the disrupted intestinal microbiota and subsequently suppresses C. difficile. We addressed the long-term recovery of fecal and mucosal microbiota and changes in gut resistome in rCDI patients treated with FMT. Post-FMT, the patients´ fecal microbiota profiles were more similar to their own donors than what is generally observed for unrelated subjects and this striking similarity retained throughout the 1-year follow-up. In the mucosa, particularly Bacteroidetes increased in abundance. FMT reduced antibiotic resistance genes (resistome) in microbiota of rCDI patients. Furthermore, we were able to identify bacteria commonly established in all CDI patients and to reveal a therapeutic core microbiota, which can aid in the development of bacteriotherapy. Currently, FMT is considered for other indications than CDI too, including the eradication of antibiotic-resistant bacteria.

Selected papers:

Jalanka J, Mattila E, Jouhten H, Hartman J, de Vos WM, Arkkila P, Satokari R. 2016. Long-term effects on luminal and mucosal microbiota and commonly acquired taxa in faecal microbiota transplantation for recurrent Clostridium difficile infection. BMC Medicine, 14(1):155.

Jouhten H, Mattila E, Arkkila P, Satokari R. 2016. Reduction of antibiotic resistance genes in intestinal microbiota of recurrent Clostridium difficile patients after fecal microbiota transplantation. Clin Inf Dis 63(5):710.

Cammarota G, Ianiro G, Tilg H, Rajilić-Stojanović M, Kump P, Satokari R, Sokol H, Arkkila P, Pintus C, Hart A, Segal J, Aloi M, Masucci L, Molinaro A, Scaldaferri F, Gasbarrini G, Lopez-Sanroman A, Link A, de Groot P, de Vos W, Högenauer C, Malfertheiner P, Mattila E, Milosavljević T, Nieuwdorp M, Sanguinetti M, Simren M, Gasbarrini A, The European FMT Working Group. European Consensus Conference on Faecal Microbiota Transplantation in Clinical Practice. 2016, Gut, in press, online Jan 13

Magnus Lundgren
Department of Cell and Molecular Biology
Uppsala University
Sweden

Using gene technology against antibiotic resistant pathogens: prospects and concerns

Modern gene technology provides unprecedented opportunities to alter genetic material in living cells. In this presentation I will give an overview of possible applications of gene editing in the struggle against pathogenic microorganisms and their antibiotic resistance. Gene editing can function as a specific antimicrobial by inducing damaging mutations in the pathogen. Alternatively, gene editing can be used to inactivate or delete known antibiotic resistance genes, facilitating conventional treatment. The method for delivering the gene editing system to the pathogen is a main hurdle, as it should be both efficient and specific. Delivery by bacteriophage is being explored but face similar benefits and limitations as phage therapy, where phages are used for treatment of infections. Phages co-evolve with host cells, providing an essentially limitless source of variants for targeting the cell, but they are sensitive biological entities with narrow host spectrum and short patient retention time.

Hanna Tiainen
Postdocotral Fellow
Department of Biomaterials Assistant Professor
University of Oslo
Norway

Polyphenolic nanocoatings for improved peri-implant healing

In the quest for finding new strategies to enhance tissue integration and to reduce the risk of bacterial colonisation around bone-anchored implants, titanium surfaces were functionalised with polyphenolic coatings. The functionalised surfaces were screened for their biological performance using cultures of primary human osteoblasts and bioluminescent Staphylococcus epidermidis Xen43. No toxic effect of the coatings on osteoblasts was detected. While tannic acid coatings seemed to induce a delay in osteoblast maturation, they revealed anti-inflammatory potential. Similar effects were observed for pyrogallol coatings deposited for 24 h. The effects on osteoblast were found to be related to the release of phenolic compounds from the surfaces. While the phenolic coatings could not inhibit biofilm formation of S. epidermidis on the titanium surfaces, released phenolic compounds also had a significant effect on planktonic bacteria.In conclusion, the assessed coating systems represent a versatile functionalisation method which exhibit promising effects for bone-anchored implant applications.

Selected papers:

S Geißler, A Barrantes, P Tengvall, PB Messersmith, H Tiainen. Deposition kinetics of bioinspired phenolic coatings on titanium surfaces. Langmuir 2016, 32, 8050-8060.

Jens Lundgren
Department of Infectious Diseases, CHIP - Centre of Excellence for Helth, Immunity and Infections
Professor
Rigshospitalet, University of Copenhagen
Denmark

Personalised medicine in AMR treatment

Selected papers:

Rath D, Amlinger L, Hoekzema M, Devulapally PR, Lundgren M (2015). Efficient programmable gene silencing by Cascade. Nucleic Acids Research 43(1):237-246.

Rath D, Amlinger L, Rath A, Lundgren M (2015). The CRISPR-Cas immune system: biology, mechanisms and applications. Biochimie 117:119-128.

Brouns SJJ, Jore MM, Lundgren M, Westra ER, Slijkhuis RJ, Snijders AP, Dickman MJ, Makarova KS, Koonin EV, Van der Oost J (2008). Small CRISPR RNAs guide antiviral defense in prokaryotes. Science, 321:960-964.

NOTES

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TURNING THE TIDE OF ANTIMICROBIAL RESISTANCE

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TTA - Turning the Tide of Antimicrobial resistance:
http://ous-research.no/amr/

CONTACT

Tone Tønjum; mobile : +47 90152936, email: tone.tonjum@medisin.uio.no
Jessica Lönn-Stensrud; mobile: +47 90850391, email: jessica.lonn-stensrud@rr-research.no