Focused Research Areas – short report 2016

Project economy

Prosjekt	Klinikk	Prosjektleder	Kostnadssted	Prosjektnr.	Amount awarded 2016	Amount used 2016
Antibiotikaresistens – Turning the Tide of Antimicrobial resistance (TTA)	KLM	Fredrik Müller	840522	41873	1.000.000 kr	846 000

Summary of important research activity 2016 and additional funding obtained (brief description)

Antimicrobial resistance (AMR) is emerging as a local and global threat to health care practice. TTA is working towards a unified approach for innovative preventive and therapeutic measures, along with development of novel diagnostics and drugs to combat AMR. The TTA consortium is formed by strong research groups with complementary expertise in OUS divisions, teamed up with national and international collaborators.

Research activities, general for TTA:

13.9.16 National kick-off meeting at OUS/Ullevål with CEO Bjørn Erikstein on the opening address and Anders Nilsson, Stockholm university, Sweden as the key-note speaker on novel bacteriophage therapy, with prominent researchers from Haukeland hospital/UiB, NVH, Stavanger university hospital, St Olavs hospital/NTNU, UNN/UiTø, FHI and OUS/UiO.
23-24.9.16 Stand at Forskningstorget, the research festival during the National Research days, presentations on TTA-AMR on TV God morgen Norge and P3 etc etc.
20-21.10.2016 Lysebu, TTA consortium meeting where the steering group was established.
28.11.2016 DNVA, TTA Goes Nordic. Position meeting to network with relevant partners in the Nordic countries, as well as important international collaborators. The event was partly funded by NordForsk (NOK 500 000).

Research activities in the main work packages:

WP1: BASIC ASPECTS AND NOVEL DRUG TARGETS

WP1.1. Several antimicrobial candidate compounds have been tested. 1) A novel antibacterial peptide based on the naturally occurring peptide (DinQ) was further characterized (1). Due to their novel mechanism of action, these drug compounds are expected to be less prone to suffer from bacterial resistance than current drugs. 2) The lead candidates of the ZinChel project were tested against gram-negative (GN) MBL-based resistant strains in the K-Res lab at UNN (Ørjan Samuelsen). The lead candidate adjuvants ZN148 and ZN155 (patents 10-11) were found to effectively eliminate resistance of carbapenems in general in multidrug-resistant clinical GN isolates. The lead candidates were tested *in vivo* in mice for tolerability, and shows virtually no toxicity after large repeated doses. In addition, a new class of phenazine derivatives, derived from the natural compound myxin, showed strong bacteriocidic activity against MRSA and promising activity against *E. faecium* vanA bacteria in the same lab.

WP1.2. The mechanisms of horizontal gene transfer (HGT) driving antibiotic resistance have been characterized in GN with *Neisseria gonorrhoeae* as *a model organism* for generating potential anti-HGT intervention (2). Characterization of the evolution of chromosomally mediated drug resistance under sub-inhibitory amounts of drugs and other forms of stress has been performed (3,4).Drug resistance arising in rheumatic heart disease was also monitored (5). These studies have the potential to generate new drug targets.

WP2 CLINICAL RESEARCH APPROACHES TO FIGHT AMR

WP 2.1. Surveillance and clinical trials: Implementation of a new surveillance program for AMR and antibiotics use in OUS has commenced and studies of the impact of antibiotic use on AMR is undergoing. Active surveillance in all OUS patients will contribute to a more efficient detection of patients with MRSA, ESBL and

VRE to provide an improved estimate on the problem of influx of AMR into the hospital ().
WP2.2. **Novel infection control interventions.** Novel interventions and tools exploiting the AMR organisms as part of the human microbiota to define personalized approaches are currently being implemented ().

Selected publications

1. Kristiansen KI, Weel-Sneve R, Booth JA, Bjørås M. Mutually exclusive RNA secondary structures regulate translation initiation of DinQ in *Escherichia coli*. RNA. 2016 Nov;22(11):1739-1749.
2. Beyene GT, Balasingham SV, Frye SA, Namouchi A, Homberset H, Kalayou S, Riaz T, Tønjum T. Characterization of the Neisseria meningitidis Helicase RecG. *PLoS One* 11(10):e01645882016.
3. Yimer SA, Namouchi A, Zegeye ED, Holm-Hansen C, Norheim G, Abebe M, Aseffa A, Tønjum T. Deciphering the recent phylogenetic expansion of the originally deeply rooted *Mycobacterium tuberculosis* lineage 7. BMC Evolutionary Biology 16:241, 2016
4. Namouchi A, Gómez-Muñoz M, Frye SA, Moen LV, Rognes T, Tønjum T, Balasingham SV. The *Mycobacterium tuberculosis* transcriptional landscape under genotoxic stress. *BMC Genomics* 17(10):791
5. Zegeye N, Asrat D, Woldeamanuel Y, Habte A, Gedlu E, Tønjum T, Aseffa A. Throat carriage rate and antibiotic susceptibility pattern of *beta*-hemolytic streptococci in children on prophylaxis for rheumatic heart disease. *BMC Inf Dis* 16(1):510, 2016.
6. Floeystad HK, Holm A, Sandvik L, Vestrheim DF, Brandsaeter B, Berild D. Increased long-term mortality after survival of invasive pneumococcal disease: a population-based study. Infect Dis (Lond). 2017 Jan 17:1-11.
7. Eliassen KE, Berild D, Reiso H, Grude N, Christophersen KS, Finckenhagen C, Lindbæk M. Incidence and antibiotic treatment of erythema migrans in Norway 2005-2009. Ticks Tick Borne Dis. 2017 Jan;8(1):1-8.
8. Grøntvedt CA, Elstrøm P, Stegger M, Skov RL, Skytt Andersen P, Larssen KW, Urdahl AM, Angen Ø, Larsen J, Åmdal S, Løtvedt SM, Sunde M, Bjørnholt JV. Methicillin-Resistant Staphylococcus aureus CC398 in Humans and Pigs in Norway: A "One Health" Perspective on Introduction and Transmission. Clin Infect Dis. 2016 Dec 1;63(11):1431-1438.
9. Mandal S, Godfrey KM, McDonald D, Treuren WV, Bjørnholt JV, Midtvedt T, Moen B, Rudi K, Knight R, Brantsæter AL, Peddada SD, Eggesbø M. Fat and vitamin intakes during pregnancy have stronger relations with a pro-inflammatory maternal microbiota than does carbohydrate intake. Microbiome. 2016 Oct 19;4(1):55.

WP 1 Patent applications:
10. ZinChel: GB1613946.1 and WO2015049546A1 (Rongved)
11. Phenaziner: GB1621520.4 and WO2015063516A2 (Rongved)
12. Anti-dormancy cocktail for bacteria: 803US1PRO (Tønjum)

Additional funding obtained

1. NordForsk NOK 500 000 2016-17, 2. Research Council of Norway INTPART mNOK 4.5 2017-19, 3. Helse Sør-Øst network mNOK 6H-SØ 2017-19; a number of additional applications for funding in Norway and abroad are in the pipeline.

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