Focused Research Areas – short report 2017: Turning the Tide of Antimicrobial Resistance (TTA)

Oslo universitetssykehus

Project economy

Prosjekt	Klinikk	Prosjektleder	Kostnadssted	Prosjektnr.	Amount awarded 2017	Amount used 2017
Antibiotikaresistens – Turning the Tide of Antimicrobial resistance (TTA)	KLM	Fredrik Müller	840522	41873	2.000.000 kr	2.000.000 kr

Summary of important research activity 2017 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 in OUS divisions with complementary expertise teamed up with national and international collaborators. TTA is pursuing a general strategy to fight AMR.

Research activities, general for TTA:

27-28.4.17 TTA goes Nordic 2. The main goal for this meeting was to highlight news on AMR and promote Nordic interactions and collaboration on AMR-related topics. Prominent speakers from the Nordic countries as well as from France, Germany, India, Ireland, Israel, South Africa, Spain, Switzerland, and UK. The event was also partly funded by UiO: Life Science, NordForsk and NFR.

15.6.17 TTA general meeting. The various projects were presented by the WP leaders: Tone Tønjum, Dag Berild, Jørgen V. Bjørnholt and Pål Rongved from TTA, as well as Truls Leegaard (AHUS) and Dagfinn Skaare (SiV) from the HSØ Regional Network for AMR.

18.4-31.5.17 TTA contributed with several articles for OUS «Ekspertsykehusets blogg» in a series dedicated to antimicrobial resistance April and May 2017.

22-23.9.17 TTA participated at Forskningstorget, the research festival during the national Research days. This year's theme was "values" and TTA emphasized the importance of reducing the use of antibiotic and good hygiene to combat the development of antimicrobial resistance.

27.9.17 TTA members Tone Tønjum and Dag Berild presented at the Norwegian Cancer Society's seminar "Antibiotic resistance and cancer", Oslo Innovation Week.

10.10.17 TTA meeting: AMR and the microbiome. A joint OUS thematic meeting on research groups working on microbiota and antibiotic resistance.

23.11.17 Antimicrobial stewardship team/TTA workshop. Research and innovation opportunities in Antimicrobial stewardship programs aimed at specifying recommendations for improving antibiotic stewardship.

4.12.17 OUS open research seminar "The challenges of discovering new antibiotics".

7.12.17 National Consortium for Microbial Genomics on December 7 2017, an international seminar organized by TTA, Norwegian Institute of Public Health (NIPH), and the national NFR-funded research school Infection Biology and Antibiotics (IBA) to stimulate the development of whole genome sequencing (WGS) for AMR

and microbiology in a One Health and personalized medicine perspective in Norway. A new TTA-based IT-infrastructure is in the pipeline.

Research activities in the main work packages:

WP1: BASIC ASPECTS AND NOVEL DRUG TARGETS

WP1.1. Several novel antimicrobial candidate compounds have been tested: 1) The antibacterial technology based on the naturally occurring DinQ peptide was further developed, and resulted in a successful FORNY grant (268109) in collaboration with Inven2. 2a) The lead candidates of the ZinChel project ZN148 and ZN155 have been further documented. Testing shows a total lack of toxicity *in vitro* and *in vivo.* Significant *in vivo* efficacy in infection models as well as a lack of resistance frequency with clinical doses of meropenem were demonstrated. Metallo-betalactamases are irreversibly inhibited. The ZinChel lead candidate ZN148 is now investigated with the IMI EU project ENABLE. 2b) A new discovery is that 3 new classes of phenazine derivatives inhibit a number of both Gram+ and Gram- bacterial species synergistically with carbapenems. 2c) The two technologies were extensively disseminated in 2017. Patent protection: during 2017, ZinChel GB1613946.1 and Phenzines GB1621520.4 were transferred to PCT (to be published during spring 2018).

WP1.2. New discoveries on the role of mutation (1), transformation (2), recombination (3), replication (4, 5) and PTMs (6) on AMR development have been published. Two NFR-funded projects AMR-PART: Fighting antimicrobial resistance 4.5 mNOK to MIK OUS, AMR-CHROM 1 mNOK and AMR-Diag: A Novel Diagnostic Tool for Sequence Based Prediction of Antimicrobial Resistance with the Indian Council of Medical Research, 5.3 mNOK to Norwegian partners at Sykehuset Innlandet, Dept. of Microbiology OUS and the NIPH. An international meeting on genome dynamics and novel technologies fighting AMR is being planned for 2018.

WP2 CLINICAL RESEARCH APPROACHES TO FIGHT AMR

WP 2.1. The Norwegian VRE (Vancomycin-resistant enterococci) study, a collaboration between Helse-Nord, NIPH and OUS, has been partially financed by Helse-Nord. One PhD fellow will start February 2018. The study aims at describing the molecular epidemiology of VRE in Norway 2010-15 and by WGS unravel transmission patterns and possible targets for treatment and interventions. A WGS study of Staphylococcus aureus bacteremia has been initiated in collaboration with AHUS. The implementation of Whonet at OUS is delayed and, at the moment, partly hampers further progression on surveillance research.
In the project "Change in composition of fecal microbiota in patients receiving long term treatment with amoxicillin" the sampling of bacterial strains is completed. The data will be analyzed and published during 2018. Knut Eirik Eliassen defended his PhD thesis "Erythema migrans in Norwegian general practice - *incidence, treatment and follow-up*"05.12.2017. Funding: 8 mNOK from NFR: "Born in the twilight of antibiotic resistance: Implications of antibiotic use to the preterm infant respiratory microbiome and resistome development" in a collaboration between Norwegian researchers and two Indian hospitals.

WP2.2. New studies are planned on the impact of the microbiome on AMR, and TTA is open for additional collaborators in this field. The EURO-BESH study, addressing barriers and facilitators of screening for MDROs (Multi-drug resitant organisms) is not yet financed, but a small-scale pilot has been established as a collaboration between NIPH and OUS.

Selected publications (TTA scientists published 206 Pubmed-listed papers in 2017)

WP1: BASIC ASPECTS AND NOVEL DRUG TARGETS
WP1.2.

1. Castañeda-García A, Prieto AI, Rodríguez-Beltrán J, Alonso-Rodriguez N, Zegeye ED, Herranz M, Plocinski P, Tønjum T, Waddell S, Rojas A, Doherty A, Blázquez J. A non-canonical mismatch repair pathway in prokaryotes. Nature Comm 8:14246, 2017.
2. Beyene GT, Kalayou S, Riaz T, Tønjum T. Comparative proteomics of *N. meningitidis* wildtype and *dprA* null mutant strains links DNA processing to pilus biogenesis. BMC Microbiol 17(1):96, 2017

3. Hovland E, Beyene GT, Frye SA, Homberset H, Balasingham SV, Gómez-Muñoz M, Derrick JP, Tønjum T, Ambur OH. DprA from N. meningitidis: Properties and role in natural competence for transformation. *Microbiol* 163 (6) 2017.
4. Flåtten I, Helgesen E, Pedersen IB, Waldminghaus T, Rothe C, Taipale R, Johnsen L, Skarstad K. Phenotypes of dnaXE145A Mutant Cells Indicate that the Escherichia coli Clamp Loader Has a Role in the Restart of Stalled Replication Forks. J Bacteriol, 199 (24) 2017.
5. Pedersen IB, Helgesen E, Flåtten I, Fossum-Raunehaug S, Skarstad K. SeqA structures behind Escherichia coli replication forks affect replication elongation and restart mechanisms. Nucleic Acids Res, 45 (11), 6471-6485.
6. Birhanu AG, Yimer SA, Holm-Hansen C, Norheim G, Aseffa A, Abebe m, Tønjum T. Nε- and O-Acetylation in Mycobacterium tuberculosis Lineage 7 and Lineage 4 strains: Proteins Involved in Bioenergetics, Virulence and Antimicrobial Resistance are Acetylated. J Prot Res Oct 4 doi: 10.1021/acs.jproteome.7b00429, 2017.

WP2 CLINICAL RESEARCH APPROACHES TO FIGHT AMR

WP 2.1.

7. Di Ruscio, F; Bjørnholt, JV; Larssen, KW; Leegaard, TM; Moen, AE; Fossum & De Blasio, BF (2017). Epidemiology and spa-type diversity of meticillin-resistant Staphylococcus aureus in the community and healthcare settings in Norway. *Journal of Hospital Infection*.
8. Samuelsen, Ø; Overballe-Petersen, S; Bjørnholt, JV; Brisse, S; Doumith, M; Woodford, N Hopkins, KL; Aasnæs, B; Haldorsen, B, & Sundsfjord, A (2017). Molecular and epidemiological characterization of carbapenemase-producing Enterobacteriaceae in Norway, 2007 to 2014. *PLoS ONE*.
9. 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 and Tick-borne Diseases* 2017 ;Volum 8.(1) s. 1-8.
10. Fløystad, HK; Holm, AM; Sandvik, L; Vestreheim, DF; Brandsæter, BJ; Berild, D. Increased long-term mortality after survival of invasive pneumococcal disease: a population-based study. *Infectious diseases* 2017 ;Volum 49.(5) s. 365-372.

WP2.2.

11. Knudsen PK, Brandtzaeg P, Høiby EA, Bohlin J, Samuelsen Ø, Steinbakk M, Abrahamsen TG, Müller F, Gammelsrud KW. Impact of extensive antibiotic treatment on faecal carriage of antibiotic-resistant enterobacteria in children in a low resistance prevalence setting. PLoS One. 2017 Nov 7;12(11):e0187618.