

PLENARY PRESENTATIONS

MODERN TRENDS IN NATURAL ANTIBIOTIC DISCOVERY

M.Y. Zhitlov, L. T. D Nguyen., S.S. Terekhov, V.A. Korshun, V.A. Alferova

*Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Miklukho-Maklaya 16/10,
117997 Moscow, Russia*

Natural compounds remain a major source of novel drug candidates with intriguing biological activities. Recently, we isolated a new family of peptide antibiotics, named gausemycins, which display striking structural novelty and an original membrane-associated mechanism of antibacterial activity [1,2]. Modern natural product discovery is increasingly focused on rare microbial taxa, silent biosynthetic gene clusters, and condition-specific secondary metabolites [3]. However, conventional antibiotic discovery workflows remain labor-intensive, require relatively large culture volumes, and often explore only a limited number of cultivation conditions. This restricts access to the “microbial dark antiome”: antimicrobial metabolites produced only by rare strains or under specific cultivation regimes. In this context, miniaturization represents one of the most promising strategies for expanding antibiotic discovery pipelines [4].

To address these limitations, we developed μ AIDEN—Microculture Activity-Informed Detection and Elucidation of Natural Products—a miniaturized, activity-guided workflow for natural antibiotic discovery and dereplication. μ AIDEN combines selective isolation of environmental microorganisms, emulsion-based enrichment of rare active strains, microculture cultivation, GFP-guided activity screening, HPLC microfractionation, and software-assisted alignment of chromatographic and bioactivity data. The workflow enables activity-guided dereplication with very low sample consumption and allows analytical efforts to be focused on biologically active cultivation conditions and fractions.

The workflow was applied to more than 50 isolates representing diverse microbial taxa and environmental sources, demonstrating its applicability to a broad range of antibiotic-producing microorganisms and structurally diverse antibiotic families. As a proof of concept, strain Fr5 showed a strongly condition-dependent activity profile and produced a previously uncharacterized antimicrobial peptide only under a specific cultivation condition. The work was supported by the Russian Science Foundation (project no. 25-14-00281).

Referens:

1. Tyurin, A.P.; Alferova, V.A.; Paramonov, A.S. et al. *Angew. Chem. Int. Ed.* 2021, 60, 18694–18703, doi:10.1002/anie.202104528.
2. Kravchenko, T.V.; Paramonov, A.S.; Kudzhaev, A.M. et al. *J. Nat. Prod.* 2024, 87, 664–674, doi:10.1021/acs.jnatprod.3c00612.
3. Baranova, A.A.; Alferova, V.A.; Korshun, V.A.; Tyurin, A.P. *Life* 2023, 13, 1073, doi:10.3390/life13051073.
4. Zhitlov, M.Y.; Korshun, V.A.; Alferova, V.A. *Antibiotics* 2025, 14, 1232, doi:10.3390/antibiotics14121232.