

University of Prince Edward Island

Faculty of Veterinary Medicine
Summary of Dissertation

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DEGREE OF DOCTOR OF PHILOSOPHY

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Temperature-dependent regulation of natural product biosynthesis in Arctic actinomycetes

The discovery of new bacterial natural products often requires screening many strains, frequently leading to the rediscovery of known compounds. A major limitation in natural product discovery is that many biosynthetic gene clusters (BGCs) remain silent or are expressed at very low levels under standard laboratory conditions. Although actinomycetes produce nearly two-thirds of known microbial antibiotics, much of their biosynthetic potential remains unexplored. To activate silent BGCs and fully unlock their metabolic potential, an investigation into the molecular mechanisms regulating natural product biosynthesis is required.

The present study investigated four marine *Streptomyces* strains that exhibit temperature-dependent metabolite production at 15 °C compared with conventional growth temperatures (20-30 °C). *S. luridiscabei* RKAG285 produced a metabolite putatively identified as deboroaplastomycin C, *S. laculatispora* RKAG290 showed increased landomycin production, and *S. fildesensis* RKAG293 and RKAG337 produced actinomycin D exclusively. The temperature ranges supporting metabolite production were defined, demonstrating that low temperature is an environmental trigger that can activate silent biosynthetic pathways.

Whole-genome sequencing and antiSMASH analysis identified the landomycin BGC in *S. laculatispora* RKAG290 and the actinomycin D BGC in *S. fildesensis* RKAG293. These BGCs were further characterized. In contrast, the actinomycin D BGC was not detected in *S. fildesensis* RKAG337 despite confirmed metabolite production, suggesting possible plasmid localization of the biosynthetic genes.

Because landomycin biosynthesis has not previously been linked to temperature regulation, transcriptomic analysis of *S. laculatispora* RKAG290 was performed. This analysis identified potential low-temperature regulators, including the pathway-specific regulator *lanK*. Genetic tool development was initiated, including establishing a conjugation protocol and beginning both *lanK* expression and knockout strategies, to provide a foundation for future functional studies.

Overall, this thesis advances understanding of temperature-dependent natural product biosynthesis in Arctic streptomycetes and provides a framework for elucidating temperature-dependent regulatory mechanisms and activating silent biosynthetic pathways in actinomycetes.

Publications

Kuznetsova A.I., Haltli B.A, Kerr R.G. (2022) Draft Genome Sequences of Three Streptomyces Isolated from Frobisher Bay Marine Sediments. *Microbiology Resource Announcements*. Vol. 11, No. 10. <https://doi.org/10.1128/mra.00604-22>

Grunwald A., Haltli B., Kuznetsova A.I., Duncan N, Correa H., Lanteigne M., Kerr R. (2026) Temperature-dependent metabolite production by Arctic marine actinomycetes. *Marine Drugs*. In Preparation.

Kuznetsova A.I., Haltli B.A, Kerr R.G. (2026) Cold-Induced activation of a landomycin biosynthetic gene cluster in *Streptomyces laculatispora* RKAG290. *Frontiers in Microbiology*. In Preparation.

Presentations

Kuznetsova A.I. Temperature as a factor for activation of silent biosynthetic gene clusters in streptomyces isolated from marine sediments. UPEI Graduate Studies and Research Conference; Charlottetown, PEI; October 13–14, 2022 (Oral presentation).

Kuznetsova A.I. The effect of temperature on bacterial natural product biosynthesis. Maritimes Natural Products Conference; Saint John, NB; August 14–16, 2019 (Oral presentation).

Kuznetsova A.I. The effect of temperature on bacterial fermentation to enhance the drug discovery process. UPEI Graduate Studies and Research Conference; Charlottetown, PEI; May 15–17, 2019 (Oral presentation).

Kuznetsova, A. Temperature-dependent regulation of natural product biosynthesis in Arctic actinomycetes. Maritimes Natural Products Conference; Halifax, NS; August 22–24, 2018 (Oral presentation).

Biographical Data

Born in Moscow, Russia

Awards

2017 Dr. J. Regis Duffy Graduate Scholarship in Science

2018 Dr. J. Regis Duffy Graduate Scholarship in Science

2018 Award for outstanding presentation, in recognition and appreciation of research contributions to the Maritimes Natural Products Conference.