California Sea Grant Sea Grant
Final Project Progress Report

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Biomedical Development of New Marine Microbial Resources

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Project Hypotheses
Unique marine actinomycetes reside in ocean sediments and represent a resource for drug discovery.
Genome sequences can be mined for new biosynthetic genes and their products.

Project Goals and Objectives
Perform detailed studies on the diversity of actinomycetes in marine sediments with the aim of identifying new marine taxa. Assess the biosynthetic potential of these strains at both the genetic and chemical level with the aim of discovering new antibiotics and biochemical tools. Use the complete genome sequences of two marine actinomycetes to resolve their genetic potential to produce unique secondary metabolites and as a guide to mine these strains for the production of new compounds.

Briefly describe project methodology
Marine sediments are collected using a variety of devices including an autonomous corer that can reach depths <2 km. These samples are processed using methods that are selective for actinomycete cultivation. Actinomycete diversity is assessed using sequence-based approaches and strains are tested for the production of antibacterial compounds. Active molecules are isolated and structurally characterized and, in select cases, the genes responsible for their production are cloned, sequenced, and experimentally characterized.

Describe progress and accomplishments toward meeting goals and objectives
Significant progress has been made towards meeting the goals of this program. Our studies led to the publication of six manuscripts including one by Sea Grant trainee Kevin Penn (Penn et al., 2009) describing the comparative genomics of two marine actinomycetes. A paper by past Sea Grant trainee Erin Gontang was just accepted and this manuscript describes some of the new sequence-based approaches we are applying to natural product discovery. Two additional papers from Sea Grant Trainees Jackie Winter and Andrew Schultz were published describing the biosynthesis of secondary metabolites with a focus on prenyl-transferases. Additionally, the principal investigators have been active in writing reviews and others papers related to the topic of this grant. We also

completed field studies at the Wrigley Marine Station on Catalina Island. Approximately 250 samples were collected during this trip and hundreds of new actinomycetes have been cultured and will be incorporated into our diversity and natural product research.

Project modifications
No project modifications have been made.

Project outcomes
The data acquired from this project are being widely disseminated in the form of publications and oral presentations at international meetings. All sequence data, including that from the biodiversity and biosynthesis studies, as well as the two genome sequences, have been deposited in public databases and are being broadly accessed by the scientific community. Strains described in our publications are regularly sent to other scientists at their request.

Impacts of project
This project has led to the cultivation of a large number of marine actinomycetes that are now being studied as a source of new medicines. Any new medicines or drug leads that are discovered have the potential to provide major societal benefits outside of tthe academic advances to which they are associated. It has also aided in the interpretation of two unusual bacterial genome sequences, which has provided broad new insight into bacterial evolution and adaptation.

Benefits, commercialization and application of project results
N/A

Economic benefits generated by discovery
This research has provided new insight into the diversity of actinomycetes in marine sediments off Southern California and led to a large collection of strains that will continue to be explored as a resource for drug discovery. Diversity studies of this type provide a tangible framework within which to assess biodiversity and its value for marine biotechnology. Although microorganisms are often overlooked in discussions of biodiversity, it is clear that the genetic resources in the marine environment off the state of California have tremendous potential economic benefit and can be effectively accessed for biotechnological purposes.

Issue-based forecast capabilities
N/A

Tools, technologies and information services developed
N/A

Publications
Conference papers, proceedings, symposia
Title: Exploiting the Genetics of Natural Product Biosynthesis for small molecule discovery.
Authors: Jensen PR
Date: June 2008
Conference Title: Engineering Conference International, Natural Products Discovery and Production II
Location: Whisler, BC

Title: Exploiting the Genetics of Natural Product Biosynthesis for small molecule discovery.
Authors: Jensen PR
Date: June 2008
Conference Title: Annual Meeting of the Society for Industrial Microbiology
Location: San Diego, CA

Title: Diversity, species concepts, and the evolutionary significance of secondary metabolite production in a model group of marine Actinobacteria.
Authors: Jensen PR
Date: August 2008
Conference Title: Annual Meeting of the International Society for Microbial Ecology
Location: Cairns, Australia

Title: What's in a name? Linking species concepts to natural product discovery in the post-genomic era.
Authors: Jensen PR
Date: July 2009
Conference Title: Annual Meeting of the Society for Industrial Microbiology
Location: Toronto, Canada

Title: Diversity, species concepts, and the evolutionary significance of secondary metabolite production in a model group of marine Actinobacteria.
Authors: Jensen PR
Date: August 2009
Conference Title: International Symposium on the Biology of the Actinomycetes
Location: Shanghai, China

Title: Natural products from the sea: quest to uncover novel therapeutics.
Authors: Jensen PR
Date: November 2009
Conference Title: Pediatric Translational Research Symposium
Location: San Diego, CA

Title: Exploring and exploiting the biosynthesis of nonproteinogenic amino acids in marine microbial metabolites.
Authors: Moore BS
Date: August 2008
Conference Title: 3rd CMDD International Symposium on Marine Natural Products and Drug Discovery
Location: Seoul, Korea

Title: Genomic exploration and exploitation of marine bacteria for natural product discovery.
Authors: Moore BS
Date: March 2009
Conference Title: Zing Conference on Natural Products
Location: Antigua

Title: Genomic exploration and exploitation of marine bacteria for natural product discovery.
Authors: Moore BS
Date: March 2009
Conference Title: 3rd Tokyo University of Science International Collaboration Workshop
Location: Tokyo, Japan

Title: The ever-evolving face of natural product biosynthesis.
Authors: Moore BS
Date: July 2009
Conference Title: The 50th Annual Meeting of the American Society of Pharmacognosy
Location: Honolulu, HI

Title: Biosynthesis in marine actinomycete bacteria.
Authors: Moore BS
Date: August 2009
Conference Title: International Symposium on Chemical Biology
Location: Xiamen, China

Title: Adventures in marine actinomycete natural product biosynthesis.
Authors: Moore BS
Date: September 2009
Conference Title: 4th CMDD International Symposium on Marine Natural Products and Drug Discovery
Location: Seoul, Korea

Title: Genomics-inspired discovery and engineering of natural anticancer agents.
Authors: Moore BS
Date: December 2009
Conference Title: International Symposium on Herbal Medicines and Vaccines for Cancer Therapy
Location: Taipei, Taiwan

Peer-reviewed journal articles or book chapters
Title: Genomic islands link secondary metabolism to functional adaptation in marine Actinobacteria.
Authors: Penn K, Jenkins C, Nett M, Udwary DW, Gontang EA, McGlinchey RP, Foster B, Lapidus A, Podell S, Allen EE, Moore BS, Jensen PR.
Date: 2009.
Journal: The ISME Journal. 3:1193-1203.

Title: Linking species concepts to natural product discovery in the post-genomic era
Authors: Jensen P.R.
Date: 2009.
Journal: J. Ind. Microbiol. Biotechnol. Doi 10.1007/s10295-009-0683-z.

Title: Sequence-based analysis of secondary metabolite biosynthesis in marine actinobacteria.
Authors: Gontang EA, Gaudêncio SP, Fenical W, Jensen PR.
Date: 2010
Journal: Appl. Environ. Microbiol. Accepted.

Title: Formation of the pyridazine natural product azamerone by biosynthetic rearrangement of an aryl diazoketone.
Authors: Winter JM, Jansma A, Handel TM, Moore BS.
Date: 2009.
Journal: Angew. Chem. Int. Ed. Engl. 48:767-770.

Title: The structural characterization of cyclic non-ribosomal peptides by tandem mass spectrometry.
Authors: Liu WT, Ng J, Meluzzi D, Bandeira N, Gutierrez M, Simmons TL, Schultz AW, Linington R, Moore BS, Gerwick W, Pevzner D, Dorrestein P C.
Date: 2009.
Journal: Anal. Chem. 81:4200-4209.

Title: Functional characterization of the cyclomarin/cyclomarazine CymD prenyltransferase directs the biosynthesis of unnatural cyclic peptides.
Authors: Schultz AS, Lewis CA, Luzung MR, Baran PS, Moore BS.
Date: 2010.
Journal: J. Nat. Prod. DOI: 10.1021/np9006876.

Students
Andrew W. Schultz
UCSD/SIO
Department of Marine Chemistry
Theses/dissertation title: Biosynthesis and bioengineering of marine cyclic peptides
Supported by Sea Grant funds? [] yes [x] no

Jackie M. Winter
UCSD/SIO
Department of Marine Chemistry
Theses/dissertation title: Discovery and application of marine bacterial halogenating enzymes
Supported by Sea Grant funds? [] yes [x] no
Start date: 02/01/2009
End date: 1/31/2010

Kevin Penn
UCSD/SIO
Department of Marine Biology
Theses/dissertation title: TBD
Supported by Sea Grant funds? [x] yes [] no
Start date: 02/01/2009
End date: 01/31/2010

How many students/volunteers were involved in the project? 1

International implications
None

Keywords
marine actinomycetes, marine natural products, drug discovery, genomics, biosynthesis