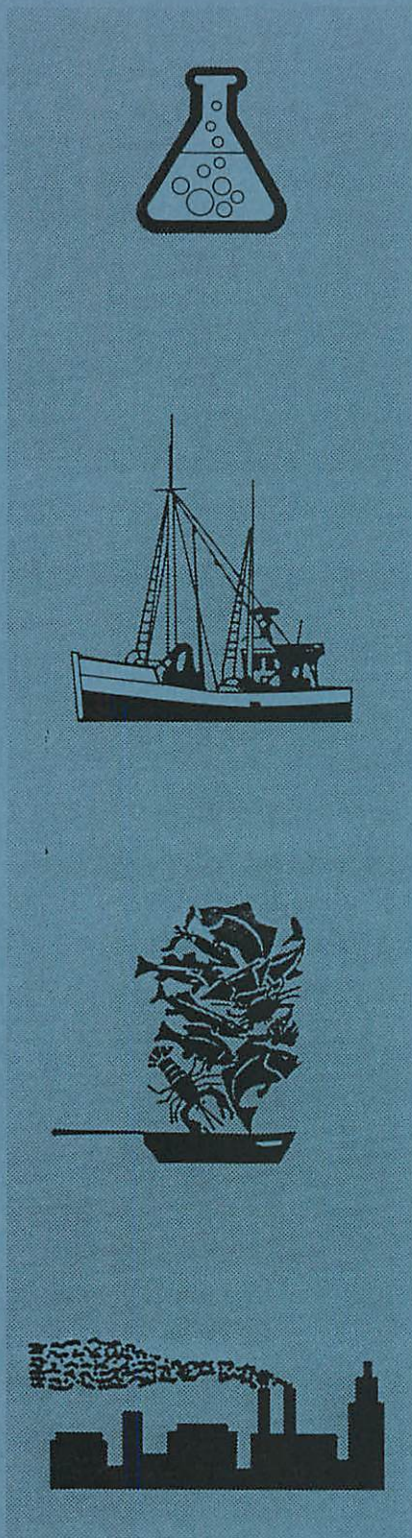

The National Sea Grant College Program Annual Report FY 89

Marine Biotechnology

by
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U.S. DEPARTMENT OF COMMERCE
National Oceanic and Atmospheric Administration

Annual Report on
Marine Biotechnology
Fiscal Year 1989

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Marine Biotechnology

Summary

Research in support of marine biotechnology continued to be an important component of the National Sea Grant College Program in fiscal year 1989. The research, which is largely fundamental in nature, is providing the scientific basis for using marine organisms or their components to provide goods and services. During the last year $2,325,000 in federal funds and $1,793,000 in matching funds supported 59 projects in four categories including biochemistry and pharmacology, molecular biology, biochemical engineering, microbiology and phycology. Notable advances were described in more than 90 recent papers. For example, procedures for genetic engineering of fish were demonstrated, recombinant vaccines for viral diseases of fish were successfully tested, a potent mammalian immunohormone was isolated for the first time from a plant, and a novel bioreactor for studying high pressure–high temperature relationships in bacterial growth and productivity was designed, constructed, and used to study biochemical processes of a methanogenic bacterium from a deep-sea vent.

The report describes major new initiatives of Japanese government, industry, and academe to develop marine biotechnology as a basis for economic growth in the twenty-first century. It discusses other issues and suggests opportunities and needs for future research.

Introduction

Marine biotechnology can be defined as the application of scientific and engineering principles to provide goods and services through mediation of marine biological agents. Biotechnology, including marine biotechnology, is not new. For centuries technologists, farmers, and home-makers have used it to produce food and alcoholic beverages. Exclusive of agriculture, use of biotechnology in sewage treatment and water purification now comprises the largest sector in volume. Biotechnical production of many other products such as organic acids and antibiotics also is important in commerce.

Rapid advancements in molecular biology and related sciences over the past few years have focused intense attention on biotechnology because of the techniques they are providing for rapidly changing and exploiting the metabolic and biosynthetic capabilities of plants, animals, and microorganisms. Most of the research and related industrial developments in biotechnology are based on the use of terrestrial organisms. Relatively little research has focused on marine organisms even though their much greater species and phylogenetic diversity and their use of a wide spectrum of environments suggest they should offer unique biological processes and components of potential usefulness.

Sea Grant's small program of research in marine biotechnology has been productive. It has advanced fundamental science, including advances needed for genetic engineering of marine species, showed many facets of unusual secondary metabolism and other biological processes, and provided the basis for new products and processes of commercial significance. For example, in the early 1970's Sea Grant paid for the pilot-scale production of chitosan, which can be derived from crustacean shells, and subsequently supported annually one or a few research projects dealing with the study of chitosan, its chemical and physical manipulation, its mechanisms of biological activity, and its use in a variety of ways. This research has been a significant factor in the development of new uses for chitin that one industrial newsletter, **Inside R&D** (October 4, 1989), says "are poised to propel chitin/chitosan sales to nearly $2 billion/year – and to change the competitive balance of companies in agriculture, cosmetics/toiletries, food/beverages, health care, immobilization and cell culture, product

TABLE 1
Funding for Sea Grant Projects in Marine Biotechnology in Fiscal Years 1988 and 1989 (in thousands of dollars)

Category	FY 88 No. of Projects	FY 88 Funding Fed	FY 88 Funding Match	FY 89 No. of Projects	FY 89 Funding Fed	FY 89 Funding Match
Biochemistry & Pharmacology	22	810	522	22	837	605
Genetic Engineering	15	730	513	14	710	528
Biochemical Engineering and Industrial Chemicals	8	237	287	10	361	299
Microbiology and Phycology	10	349	303	13	397	361
TOTALS	55	2,126	1,625	59	2,325	1,793

separation/recovery, waste/water treatment, and other industries."

Still extant are a broad spectrum of opportunities for academic research to advance fundamental knowledge of biological processes in marine systems and to provide the basis for further biotechnical development on a large scale. Some of these opportunities are discussed in a general way in the third section below which suggests the need for greater reliance on interdisciplinary research and educational programs.

Funding and Examples of Progress

In fiscal year 1989 fifty-nine projects were active. They were supported with $2,325,000 in federal funds and $1,793,000 in matching funds. The projects can be considered in the four broad categories shown in Table 1 which compares funding and number of projects over the last two fiscal years. Investigators in some projects, all of which are listed in Appendix B, may be surprised to find their research classified under biotechnology because a broad definition is used although traditional aquacultural research is excluded.

However, all projects included have produced or are expected to yield fundamental knowledge or practical information that will aid in providing goods and services through the use of marine organisms or their components. Table 2 shows the history of federal funding over the past ten years. Funding levels in Appendix B and the Tables do not include support for student research assistants in some of the projects.

The number of projects and level of funding in 1989 were up somewhat over 1988, but still below 1987's high. The biggest increase was in the category encompassing genetic engineering and other types of molecular biology. Research in this category recently has yielded significant achievements as the examples below show. The bibliographic references appear form in Appendix A.

The diagnosis and control of viral and bacterial diseases of fish, especially infectious pancreatic necrosis (IPNV), infectious hematopoietic necrosis (IHNV), and vibriosis, which are economically important in salmon culture, have been goals for several years. In one approach to these problems researchers at Oregon State University prepared subunit vaccines containing portions of genes encoding for the surface proteins of IPNV and IHNV. They cloned and expressed the genes in *Escherichia coli*. Crude extracts of *E. coli* expressing these proteins have proven to be effective vaccines in fish against lethal doses of the viruses (Gilmore et al., 1988). Thus, recombinant DNA technology can be used to meet industrial requirements for safe and effective, yet inexpensive vaccines for aquacultural species.

In related research in another laboratory at Oregon State University researchers developed a fluorescent antibody test (FAT) for the rapid detection of IHNV (LaPatra et al., 1989). All strains of IHNV tested, which included different electropherotypes, those isolated from selected salmonids at different life stages, and those from different geographic regions, reacted with the antisera. The FAT has been used for the detection of IHNV in blood smears and organ imprints from clinically infected juvenile fishes and in IHNV-infected cells in ovarian fluid from adult carriers. The test was equal in sensitivity to the plaque assay method and required less time to obtain a definitive diagnosis.

DNA technology also has been applied to production of transgenic fish which grow up to 50% faster than their parents. As part of their work Chen, Powers and associates (Agellon et al., 1988) showed that the rainbow trout has two genes for growth hormone (GH). They also showed (Chen et al., 1989) that biosynthetic preparations of these hormones in *E. coli* enhances growth of yearling trout through weekly intramuscular injection. Using carp and loach as test animals they have shown that introduction of additional copies of GH gene results in transgenic fish which produce elevated levels of growth hormone and grow faster than controls. A small, but significant, proportion of the first generation of fast-growing fish can pass this trait to their offspring. Thus, it appears that true-breeding fish strains of altered character can be produced.

In their efforts to develop techniques for genetically engineering fish, researchers at the University of Minnesota developed a fast and reliable procedure for generating subclones necessary for sequencing long stretches of DNA (Liu and Hackett, 1989). The procedure involves cloning a fragment of DNA into a single-stranded plasmid or phage vector containing a polycloning region; synthesizing variable lengths of double-stranded DNA using a "Universal Primer"; isolating the double-stranded DNA; and force cloning the double stranded DNA fragments into a complementary vector with the polycloning region in the reverse orientation. The resulting clones can be sequenced, using the same Universal Primer and T7 DNA polymerase, to provide overlapping DNA sequences. The researchers have used the new procedure to sequence thousands of bases without detecting any errors due to improper copying of the single-stranded template.

Research in the category of biochemistry and pharmacology also has been productive and previous reports in this series have provided examples of pharmaceutical developments resulting from this research. In 1989 the research continued to identify interesting and important natural products and to define their biological effects.

At Oregon State University where studies are continuing on seaweeds as sources of new products with potential biomedicinal application, researchers have identified another red alga, *Farlowea mollis*, as a rich source of structurally novel and physiologically active icosanoids whose

TABLE 2
Federal Funding for Sea Grant
Projects in Biotechnology in Fiscal Years 1980 - 1989
(in thousands of dollars)

FISCAL YEAR

Category	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989
Biochemistry and Pharmacology	440	402	525	440	671	820	865	916	810	837
Molecular Biology	--*	100*	266*	419*	487	537	624	778	730	710
Biochemical Engineering & Industrial Chemicals	349	285	454	515	540	581	384	393	237	361
Microbiology and Phycology	--*	50*	100*	284	248	206	342	593	349	397
TOTALS	789	837	1,345	1,658	1,946	2,144	2,215	2,680	2,126	2,325

*Estimate

complete structures they have solved (Solem et al., 1989). They also reported the first isolation from a plant of the potent mammalian immunohormone, 12-(S)-hydroxy-5,8,10,14-icosatetraenoic acid (Moghaddam et al., 1989).

Research in the same laboratory suggests that novel cytotoxic peptides from the tropical cyanobacterium, *Hormothamnion enteromorphoides*, may function to deter predation by herbivorous animals, including fish, zooplankton and mollusks. The major peptide, hormothamnin A, shows antimicrobial activity against two human pathogenic microorganisms and toxicity to cancer cells in vitro (Gerwick et al., 1989).

Collaborative work between researchers at the University of Oklahoma and the Bigelow Laboratory for Ocean Sciences also points to the ecological significance of marine secondary metabolites. This research on toxic cembranolides in sessile octacorals shows that the tissue fluids of the gorgonians examined are supersaturated with respect to these diterpenoids which are continuously produced and released into the water surrounding the animals (Ciereszko and Guillard, 1989). Thus, they could serve to prevent predation. The cembranolides immobilize marine flagellates. This property may serve the animals by immobilizing flagellates that serve as food and by converting certain dinoflagellates to their vegetative forms that occur as symbionts in many octacorals.

Researchers at the University of California at Santa Cruz have determined the novel structures of amino acids of five structural types that were isolated from sponges of the order Chorista. The researchers have been devoting attention to the nitrogen-containing heterocyclic compounds from this group of animals because these multifarious secondary metabolites are almost always accompanied by exciting biological activity, including powerful antibiosis. The researchers reported the complete amino acid chemistry of a Jaspidae sponge collected in the Fiji Islands and suggested biogenetic pathways for each of the most novel amino acid types (Adamczeski et al., 1989).

In further research to determine the mechanism by which stypoldione, a marine natural product, inhibits cell division researchers at the University of California at Santa Barbara have shown the stypoldione uncouples cytokinesis from mitosis at the lowest effective concentrations. Although it can disrupt microtubules at relatively higher concentrations, it inhibits cell division at the lowest effective concentrations by a selective action on cytokinesis through a mechanism that does not appear to involve disassembly of microtubules (O'Brien et al., 1989).

Researchers at the Scripps Institution of Oceanography and Cornell University have determined the structure of haliclonadiamine, an antimicrobial alkaloid from the sponge *Haliclona* sp. from Palau (Fahy et al., 1988). They selected the bright red sponge for study because it overgrows and kills corals and because initial screening of crude extracts of the sponge indicated significant antimicrobial activity, particularly against the fungus *Candida albicans*. They determined the structure of a crystalline diacetate derivative by single crystal X-ray diffraction.

Research at the University of California at Berkeley shows that certain seaweeds along the U.S. Pacific coast produce a unique plant hormone methyllanosol that stimulates growth in lettuce (Kubo, 1989). Methyllanosol is one of the first such plant growth regulators to be isolated from a marine organism. When it was used on lettuce plants, it boosted growth by 50 per cent. So far, the compound appears to be selective in its benefits by prompting growth in lettuce, but having no effect on some other plants such as rice.

Important results also were reported in the category of biochemical engineering recently. Thermophilic organisms offer many potential advantages for biotechnological processes, but realizing this potential requires appropriate experimental systems for studying organisms at high temperature and pressure. Thus, researchers at Cornell University developed a novel bioreactor for studying pressure-temperature relationships in bacterial growth and productivity at temperature up to 260°C and pressures up to 350 bar (Miller et al., 1988). The apparatus is versatile and corrosion resistant, and enables direct sampling of both liquids and gases from a transparent culture vessel without altering the reaction conditions. Gas recirculation through the culture can be controlled through the action of a magnetically driven pump.

Initial studies in this bioreactor of *Methanococcus jannaschii*, an extremely thermophilic methanogen isolated from a deep-sea hydrothermal vent, revealed that increasing the pressure from 7.8 to 100 bar accelerated the production of methane and cellular protein by this archaebacterium at 90°C, and raised the maximum temperature allowing growth from 90 to 92°C. Further increases in pressure had little effect on the growth rate at 90°C.

Discussion of Recent Developments, Issues, Opportunities and Needs for the Future

MARINE BIOTECHNOLOGY IN JAPAN

Japan is undertaking major initiatives in marine biotechnology as a basis for economic growth in the twenty-first century according to a report by a three-man team that under the auspices of the National Oceanic & Atmospheric Administration and the National Science Foundation visited Japan in September, 1989. The centerpiece of the Japanese initiatives will be the creation of three new institutes dedicated to marine biotechnology.

In a tripartite approach, Japanese government, industry and academe have joined forces to position themselves as world leaders in marine biotechnology. The dominant players at this time are the Japanese Ministry of International Trade and Industry (MITI) and 24 industrial partners who have committed 26.8 billion yen, or $189 million, to two of the three institutes for the next decade. Two other governmental agencies, the Ministry of Agriculture, Forestry and Fisheries (MAFF) and the Science and Technology Agency, are also moving aggressively to build new facilities and support research. MAFF will operate the third new institute for marine biotechnology.

In 1988, 24 private Japanese companies representing petroleum, steel, liquor, food, chemical, construction, and ship building came together in a consortium for establishing the Marine Biotechnology Institute Co., Ltd. (MBI). MITI has turned to the MBI to build and operate two new research institutes for the industrial utilization of marine organisms.

One institute is being built at Kamaishi to take advantage of organisms of the cold currents on Japan's east coast and the other at Shimizu where the currents are warm. Construction of each center is expected to cost three billion yen. The MBI will also operate a sophisticated research ship with space for a scientific crew of 32.

The research at the institutes is expected to be both long-term and fundamental in nature and will focus on new technologies to use marine organisms and to produce useful substances. A 20-person board of academic and governmental scientists advises the MBI, and some professors already are collaborating with the organization. The two institutes are expected to be sites of ongoing collaboration between university personnel and the permanent employees of the MBI who are sponsored by industry.

MAFF research has traditionally focused on edible species of algae, invertebrates and fishes, with some biotechnology work focused on selective breeding and gene recombination techniques. MAFF has now formulated a plan for the next generation of technology to a degree comparable to that of MITI.

MAFF's five-year strategy for marine biotechnology research, which had a budget of 1,500 million yen in fiscal year 1989, is concentrating on methods to use marine organisms in Japanese waters and on technology to use normally wasted parts of edible species. Being built at Kamaishi, the MAFF institute will be the same size as the separate MBI facility located there, will cost the same amount (three billion yen), and will employ 30 scientists and approximately 20 support staff. The agency will also expend six billion yen to build a new oceanic research vessel, the Kaiyomaru, equipped with advanced facilities.

The establishment of these three new institutes will certainly attract new investigators to marine biotechnology. While the younger field of molecular biology is being applied more often to marine biotechnology, the more traditional disciplines, such as natural products chemistry, chemical engineering, microbiology, and biochemistry, will also be heavily integrated into efforts at the new institutes. What will result, however, is that the experienced scientists and engineers from traditional areas will now pursue new lines of research.

On the academic front, university scientists and administrators as well as 30 commercial firms have formed the new Japanese Society for Marine Biotechnology. With leadership coming from the University of Tokyo and the Tokyo University for Agriculture and Technology, this society provides a forum to promote industrialization, international cooperation, and utilization of support technologies such as electronics and robotics. The society has already held the highly successful First International Marine Biotechnology Conference in Tokyo from September 4-6, 1989, and it is expected to help support the second conference in the United States in 1991.

Conducting this study of Japanese marine biotechnology with me were Professor Akira Mitsui of the University of Miami and Dr. Oskar Zaborsky of the National Research Council. As a result of our study, we suggest that federal agencies and industry in the United States should:

*Recognize the importance of marine biotechnology for its benefits and enhance support for R&D in this field,

*Keep informed about developments in Japan and exchange information more actively.

*Assess the opportunities and needs in marine biotechnology of benefit to both countries,

*Assist developing countries in marine biotechnology, especially in building an infrastructure,

*Participate in the 1991 international conference on marine biotechnology, and

*Develop new initiatives in marine biotechnology.

Copies of the report are available by writing: Division of International Programs, National Science Foundation, 1800 G. Street, N.W., Washington, D.C. 20550 or National Sea Grant College Program, NOAA, 6010 Executive Boulevard, Rockville, MD 20852.

GLOBAL CHANGE

In early December 1989, the National Research Council's Commission on Life Sciences sponsored two workshops to consider the feasibility of reducing [the putative] global warming by enhancing biological processes in the ocean. The primary participants in these workshops were distinguished scientists from governmental and academic institutions. The findings of those workshops appear below; some appear in paraphrased form.

Reducing Global Warming by Enhancing Carbon Dioxide Assimilation in Phytoplankton

> Marine deposition of carbon represents a long-term potential sink for atmospheric carbon dioxide. It is conceptually feasible to inhibit the increase of atmospheric carbon dioxide by enhancing primary production in the ocean. From existing models, the participants estimated that an additional two gigatons of carbon per year can be removed from the atmosphere at a cost of less than $10 billion per year if new primary production is enhanced and most unused nutrients are assimilated.

> One hypothesis suggests that primary producers in the southern oceans, equatorial oceans, and North Pacific Ocean do not use available nutrients because of limitations in metabolically available iron. Because they require iron only in nanomole concentrations, the participants projected the cost of adding sufficient iron over large oceanic areas to be low.

> Knowledge of the effects of variation in pCO_2 on the growth rate and elemental composition (cellular C:N:P) of natural marine phytoplankton communities is very limited. Developing better information of this kind will be required in order to predict reliably the capacity of the ocean to sequester excess atmospheric CO_2.

Reducing Global Warming by Enhancing Carbon Dioxide Assimilation in Macroalgae

> It is conceptually feasible to use marine plants to stabilize and reduce carbon dioxide in the atmosphere by –

* by enhancing transport of photosynthetic carbon to the deep ocean, and

* by using biomass as a replacement for fossil carbon in production of energy and materials.

> The participants recommend that steps be taken to develop and test a system to remove one billion tons of carbon dioxide per year from the atmosphere by production of marine biomass some of which can be processed into products of high value. They made the following (preliminary) recommendations:

"1. that we develop an on-going analysis of mitigation strategies (a systems approach) to determine research priorities.

2. That we study the potential of enhancing carbon dioxide fixation in a Sargasso Sea-type system.

3. That we study macroalgal carbon dioxide refossilization and use for food, fuel and chemicals.

4. We recommend that one or more test farms be in place and under evaluation by 1995, to meet established international goals to reduce carbon dioxide in the atmosphere."

The issue of increasing carbon dioxide in the atmosphere suggests other types of biotechnology for reducing dependence on fossil fuels and chemicals. Some research reported at the First International Marine Biotechnology Conference in Tokyo in September, 1989 bear on this topic. Among the most interesting are efforts to develop the scientific basis for using marine microalgae and photosynthetic bacteria for producing fuel and chemical products. The results of some of these efforts look promising and indicate that Sea Grant should be active in this field. For example, research by A. Mitsui at the

University of Miami on synchronous culture of marine unicellular aerobic nitrogen-fixing cyanobacteria indicates that the production of hydrogen, ammonia, carbohydrate-polymers, and various enzymes are cyclic events and that controls at the cellular and molecular levels can be used to enhance production of these substances.

E. Greenbaum of the Oak Ridge National Laboratory reported on the first measurements of the simultaneous photoproduction of hydrogen and oxygen in a marine green algae. Eight species in three genera were tested in CO_2-free seawater. Four of the five species of *Chlamydomonas* were able to produce hydrogen in the light after a period of three to four hours of dark anaerobic adaptation. One *Chlamydomonas* species had a steady-state rate of hydrogen and oxygen production during irradiation with a stoichiometric ratio near 2:1. This and other data presented suggest that this species makes seawater a potential substrate for solar production of hydrogen and oxygen.

In a recent paper on the R&D challenge presented by global warming, Fulkerson et al. (1989) make the following statements: "Although the R&D effort is broad, none of the nonfossil energy sources are ready to be substituted competitively for fossil fuels at the scale necessary to reduce CO_2 emissions. To correct this inadequacy, a three-pronged R&D strategy is required: improve the efficiency of energy conversion and use, improve nonfossil energy sources, and improve technologies tailored to meet the needs of developing nations." Items two and three of this strategy suggest activities appropriate for Sea Grant.

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Research and Educational Needs and Opportunities

The National Sea Grant College Program's research in support of marine biotechnological over the past ten years has demonstrated the potential for academic research to provide the basis for commercial activity at the level of tens or hundreds of millions of dollars annually. This research has advanced fundamental science by helping to define marine processes and it has trained students for productive careers. These advancements have been the result of only limited investment. They suggest that marine biotechnological research of broader scope and larger scale could play an important role in development of products and technology for the future. What are some of the relevant research opportunities?

For most marine natural products natural function in marine systems and behavior in a wide array of biological and pharmacological assays are unknown. These gaps in knowledge denote opportunities for research. By and large research on marine natural products has focused on lipid extracts of macroalgae and invertebrates. Few scientists have turned their attention to aqueous extracts, enzymes, other bioactive macromolecules, or to marine bacteria, fungi, yeasts, and microalgae as subjects of study. These neglected topics and classes of organism also represent areas of opportunity for research.

Trevan and Mak (1988) make the point that algae are a largely untapped source of potentially useful biotransformations. Their research in the United Kingdom focuses on the use of immobilized algae as biocatalysts performing biotransformations and **de novo** biosyntheses, in energy production, for bioaccumulation of wastes, and for inclusion into biosensors. More of this kind of research in American universities would benefit the United States.

Few marine invertebrates have been subjected to cell or tissue culture. Successful research to this end with organisms that produce useful metabolites could have several benefits. For example, it could help set the stage for using cells to produce pharmaceuticals, enzymes, growth regulators, pigments, and pesticides. It could provide techniques useful in studying the basic physiology and nutrition of organisms and for determining natural regulation of secondary metabolism. It could enhance the study of biochemical relationships between invertebrates and the symbiotic organisms associated with many of them. It could provide the science for using bioreactors, photobioreactors, and fermentors in exploiting the biosynthetic capabilities of marine organisms.

Application of DNA technology to the study of marine processes and development of DNA technology for genetic engineering of most classes of marine organisms offer opportunities for advancing science and enhancing the scientific basis for new biochemical products and services.

Marine organisms may play an increasing role in biotechnology and medicine as a result of unique functioning of their organelles and associated biochemical pathways. Biosensors promise to meet some important measurement needs for drugs, metabolites, and other biomolecules. Biosensors use an immobilized biological material, even a living material, in contact with a transducer to convert biochemical signals into quantifiable electrical signals. For example, the antennules of the blue crab have been used as a source of chemoreceptive nerve fibers for use in a biosensor (Belli and Rechnitz, 1988). Other chemoreceptors, which are biomolecular assemblies involved in numerous physiologic functions in marine organisms such as olfaction, are candidates for molecular recognition and application in biosensors.

Previously undiscovered marine organisms, even abundant representatives of little known groups such as the prochlorophytes, still come to light through field work in marine science (Chisholm and Olsen, 1988) and they should be investigated for unique bioprocesses and biosynthetic abilities.

These topics and others offer opportunities to study basic issues in biological systems and require or could benefit from interdisciplinary approaches to developing the fundamental science on which new technologies can be based. So far, however, most research in support of marine biotechnology is conducted within traditional disciplinary bounds. In his president's message to the American Chemical Society, Clayton Callis (1989) called for breaking down the artificial barriers that exist in the scientific and technical communities and those that exist between academe and industry. He said, "This is critical if we are to develop new technologies, for example, from discoveries in genetic engineering, new superconductors, new materials, new specialty products, in the most efficient ways possible."

The interdisciplinary requirements of research in support of marine biotechnology will make this field particularly fertile ground for illuminating scientific phenomena and advancing socially responsible technology.

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Appendix B
FISCAL YEAR 1989 PROJECTS

A. MARINE BIOTECHNOLOGY

TITLE/INVES./INST.		FEDERAL FUNDS	MATCH FUNDS
1. Biochemistry & Pharmacology			
Marine Pharmaceutical Discovery Program: Pharmacology R. Jacobs University of California Sea Grant College Program	12	76,306	89,260
Marine Pharmaceutical Discovery Program: Chemistry Comp B W. Fenical University of California Sea Grant College Program	12	45,921	18,725
Marine Pharmaceutical Discovery Program: Chemistry Comp A D. Faulkner University of California Sea Grant College Program	12	46,853	24,456
Marine Natural Products Develop New Chemotherapeutics P. Crews University of California Sea Grant College Program	12	23,331	34,513
Halogenation by Naturally Occuring Enzymes in Marine A. Butler University of California Sea Grant College Program	12	18,312	16,937
Potential Anti-Tumor Drug from Marine Waste By-Products K.P. Wong University of California Sea Grant College Program	12	39,608	31,756
Effects of Marine Micralgal Metabolites on Feeding Behavior and Growth of Bivalves N.M. Targett Delaware Sea Grant College Program	06	10,140	11,778
Marine Pharmaceuticals R. Moore University of Hawaii Sea Grant College Program	13	30,663	44,413
Marine Metabolites for Medicine P. Scheuer University of Hawaii Sea Grant College Program	13	30,000	22,000

Pharmacological Tropical Seaweeds V. Paul University of Hawaii Sea Grant College Program	13	28,131	20,852
Siscowet Trout as a Source of Antithrombotic, Hypocholesterolemic Fatty Acids for Human Medicine P.B. Addis Minnesota Sea Grant College Program	12	4,970	4,020
Isolation and Characterization of Phytotoxic Compounds from Lemna minor F.K. Gleason Minnesota Sea Grant College Program	13	24,490	4,860
Marine Organisms as Sources of Agrochemically Sgnificant Compounds J.H. Cardellina Montana State University	13	46,000	30,000
Modified Nucleosides of Marine Organisms G. Sharma New Jersey Marine Sciences Consortium Sea Grant Program	12	42,000	47,900
The n-3 Polyunsaturated Acids of Marine Lipids: Determination of Biochemical Effects, Optimum Dietary Intake and Oxidative St J.E. Kinsella New York Sea Grant Institute	12	22,275	63,576
Structural and Synthetic Studies on Marine Natural Products J.C. Clardy New York Sea Grant Institute	12	71,209	36,318
Bioactive Compounds from Marine Organisms F.J. Schmitz University of Oklahoma, Norman	12	70,200	35,574
Biomedicinals for Pacific Northwest Marine Algae W.H. Gerwick Oregon Sea Grant College Program	12	65,300	21,800
Absorption of Ethyl Ester and Triglycerides of Fish Oil Omega-3 Fatty Acids in Man W.E. Connor Oregon Sea Grant College Program	12	22,900	18,100

TITLE/INVES./INST.		FEDERAL FUNDS	MATCH FUNDS
Do Dietary Saturated Fatty Acids Reduce Effects of Fish Oils on Lipid Metabolism and hemostasis W.E. Connor Oregon Sea Grant College Program	12	35,100	28,200
New Compounds for Ice Suppression on Fish Antifreeze Proteins T. Caceci Virgina Graduate Marine Science Consortium Sea Grant Program	13	59,970	30,673
Crab Shell Chitosan, its Mode of Gene Activation L.A. Hadwiger Washington Sea Grant College Program	13	65,600	17,600
	SUBTOTAL:	$837,279	$605,411
	PASSTHROUGH:	0	

TITLE/INVES./INST.		FEDERAL FUNDS	MATCH FUNDS
2. Molecular Biology			
Development and Evaluation of Gene Probes for Use in the Diagnosis of Baculovirus Infections in Penaeid Shrimp (Thurman) Thurman University of Arizona, Tucson	13	34,900	21,600
Develop of DNA Probes - Pathogenic Marine Bac H. Shizura University of Southern California Sea Grant Program	45	39,574	37,113
Production of Transgenic Fish: Influence of Bovine Growth Hormone Gene. C.G. Kohler Illinios/Indiana Sea Grant Program	02	16,323	29,918
Genetic Enginerring of Fish and the Use of GH Hormone to Enhance Fish Growth D.A. Powers Maryland Sea Grant College Program	02	78,000	43,400
An Analysis of Normative & Conceptual Issues in the Regulation of Biotechnology in the Nation's Bays and Estuaries M. Sagoff Maryland Sea Grant College Program	20	24,800	11,700

Immunological Detection of the Brown Tide D.M. Anderson Woods Hole Oceanographic Institution Sea Grant Program	07	26,500	0
Development of Transcriptional Promoters for Gene Transfer into Fish P.B. Hackett Minnesota Sea Grant College Program	02	8,520	2,980
Vectors for Genetic Engineering in Marine Algae: the Ti Plasmid K.B. Taylor Mississippi/Alabama Sea Grant Consortium	05	54,793	43,078
Nucleic Acid Probes for the Oyster Parasite Haplosporidium Nelsoni S. Ford New Jersey Marine Sciences Consortium Sea Grant Program	08	30,500	38,400
Isolation and Characterization of the Interferon Genes of Rainbow Trout J.C. Leong Oregon Sea Grant College Program	08	82,500	22,600
Biotechnical Approaches To Improve Triploidy and Growth In Pacific Oysters K.K. Chew Washington Sea Grant College Program	03	79,900	69,900
Gene Analysis and Transformation in Marine Algae R.A. Cattolico Washington Sea Grant College Program	05	93,300	69,900
Control of Growth, Sex and Reproduction in Great Lakes Coolwater Fishes by Genetic and Endocrine Manipulation T.B. Kayes Wisconsin Sea Grant Institute	02	86,145	55,940
Anti-Idiotype Antibodies as Novel Immunogens and Diagnostic Reagents for Aquatic Birnaviruses B.L. Nicholson Maine/New Hampshire Joint Sea Grant College Program	08	54,160	81,764
	SUBTOTAL:	$709,915	$528,293
	PASSTHROUGH:	0	

TITLE/INVES./INST.		FEDERAL FUNDS	MATCH FUNDS
3. Biochemical Engineering			
Biopolymers from Marine Sources P.R. Austin Delaware Sea Grant College Program	13	14,040	35,100
Use of Chitosan for Plant Biotechnology Processes D.W. Knorr Delaware Sea Grant College Program	13	9,828	39,813
A Novel Technology for the Manipulation of Fish Reproductive Cycles: Controlled Release of Gonadotropin Releasing Hormones R.S. Langer Massachusetts Institute of Technology Sea Grant College Program	06	43,000	34,937
Biotechnological Applications of Marine Biopolymers M. Karel Massachusetts Institute of Technology Sea Grant College Program	06	57,000	29,164
Polypeptide Inhibitors of Corrosion from Marine Organisms S. Sikes Mississippi/Alabama Sea Grant Consortium	13	27,346	20,181
Development of Coastal Fish Oil Resources for Potential U.S. Health Industry J.G. Turcotte Rhode Island Sea Grant College Program	12	73,070	27,098
Advances in Anti-Scaling & Anti-Fouling Technology Based on the Properties of Natural Inhibitors of Mineralization A.P. Wheeler South Carolina Sea Grant Consortium	13	55,600	31,800
Chitosan Delivery Systems for Medicines G.G. Allan Washington Sea Grant College Program	13	42,600	21,600
A Biotechnological Application of biogenic Ice Nucleator for Energy Saving and Improved Quality in the Freezing of Seafood T.C. Lee New Jersey Marine Sciences Consortium Sea Grant Program	35	23,000	43,400

TITLE/INVES./INST.		FEDERAL FUNDS	MATCH FUNDS
Petroleum Seeps Program: Evaluation of Marine Microbial Chemoorganotropha/Chemolithoautotrophs for Contributions to Benthic H R.J. Portier 11 Louisiana Sea Grant College Program		15,001	14,769
	SUBTOTAL:	$360,485	$297,862
	PASSTHROUGH:	0	

TITLE/INVES./INST.	FEDERAL FUNDS	MATCH FUNDS
4. Microbiology & Phycology		
Genetics of Morphology and Growth in Laminaria from the North Atlantic Ocean C. Yarish 05 University of Connecticut Sea Grant Program	35,015	19,038
Role of Adsorbed Proteins in Bacterial Colonization and Growth on Surfaces D.L. Kirchman 01 Delaware Sea Grant College Program	16,536	34,542
Improving on Nature: Stress-Tolerant Plants from the Marine Estuarine Environments for Ecosystem Restoration and Agriculture J.L. Gallagher 05 Delaware Sea Grant College Program	21,060	47,996
Anticorrosive Properties of Adhesive Proteins Isolated from the Mussel Mytilus Edulis S.C. Dexter 13 Delaware Sea Grant College Program	16,380	18,689
Influence of Marine Bacterial Films on Cathodic Reaction and on Corrosion Prevention S.C. Dexter 38 Delaware Sea Grant College Program	9,360	17,609
Plant Tissue Culture Technology for Marine Angiosperms Used in Habitat Restoration K.T. Bird 05 Florida Sea Grant College Program	34,700	46,800

Technical Book on Tributylin: Editorial and Preproduction Services J.C. Cato Florida Sea Grant College Program	44	0	0
Microbiology and Chemistry of Vents D. Karl University of Hawaii Sea Grant College Program	32	22,000	21,652
Development of New Biofouling Inhibitor Delivery Systems D.C. Sundberg Maine/New Hampshire Joint Sea Grant College Program	45	40,999	24,648
The Role of Iron- and Manganese-Oxidizing Bacteria in marine Corrosion Processes R. Mitchell Harvard University	13	60,000	40,000
Studies of Hydrocarbon Seep Communities on the Texas/Louisiana Continental Slope J.M. Brooks Texas A&M University Sea Grant College Program	40	49,598	26,002
Influence of Complex Biofilms and Absorbed Pollutants on Oyster Set and Survival R. Weiner Maryland Sea Grant College Program	30	60,000	33,000
Metabolism of Antimicrobial Agents by Penaeid Shrimp K.D. McMurtrey Mississippi/Alabama Sea Grant Consortium	05	31,840	31,418
	SUBTOTAL:	$397,488	$361,394
	PASSTHROUGH:	20,000	
	GRAND TOTALS	$2,325,167	$1,792,960