RESEARCH REPORT
Plant Genomics
Environmental Microbiology, Biofuels Research, Evolutionary, Ecological and Environmental Systems Biology, Regulatory Targets of MicroRNAs, Integrative Systems Biology, Genomics-Enabled Microbial Observatory, Immune Systems, Alkaloid Biosynthetic Pathways, Bacterial Populations in the Wild, Treatment of Stomach Ulcers, Ocean Microbes..
# Plant Genomics

This report by MIT’s Industrial Liaison Program identifies selected MIT research and faculty with expertise in the area of plant genomics and related work, including bacteria, microbes, fungi, yeasts.

For more information, please contact MIT’s Industrial Liaison Program at +1-617-253-2691.

## PLANT GENOMICS

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DEPARTMENT OF CIVIL & ENVIRONMENTAL ENGINEERING: ENVIRONMENTAL MICROBIOLOGY

The CEE Environmental Microbiology research group investigates environmental microbiology and microbial ecology using modern molecular, genomic and computational approaches. Aquatic systems are a particular focus of the group, but studies are wide-ranging and include marine plankton, sediments, animal-microbial systems and deep-subsurface microbial habitats.

Microbial organisms and activities mediate many key biogeochemical and environmental processes. Yet methods for identifying, quantifying and modeling microbes and microbial activities in the environment are poorly developed. Members of the CEE Environmental Microbiology research group are therefore actively engaged in devising new approaches for studying microbes at the level of single cells, individual species, populations, entire microbial communities and ecosystems. Activities include the development of new technologies based on microfluidics, genomics, flow cytometry and other technological advances that will allow us to describe and quantify microbes and microbial processes in the environment more precisely.

Members of the Environmental Microbiology research group have specific expertise in general microbiology, ecology, genetics, genomics, bioinformatics, oceanography, microfluidics and environmental microbiology. Their research includes investigation of both laboratory-based model systems (for example, Prochlorococcus and Vibrio species), as well as studies focused on complex microbial assemblages in the environment.

Members of the group are also actively engaged in large collaborative efforts (for example, the Darwin Project and the Center for Microbial Oceanography: Research and Education) that combine the efforts of physical scientists, biologists, ecologists, oceanographers and mathematical modelers. These efforts seek to develop and apply new integrative approaches to study microbial evolution, ecology and biogeochemistry as well as to better describe, model and predict the complex microbial communities and processes that underpin ecosystem properties, behavior and services. http://cee.mit.edu/research/environmentalmicrobiology

Researchers:

Eric Alm, Assistant Professor (Joint with the Department of Biological Engineering)
Sallie W. Chisholm, Professor (Joint with the Department of Biology)
Edward DeLong, Professor (Joint with the Department of Biological Engineering)
Martin Polz, Associate Professor
Roman Stocker, Assistant Professor
Janelle Thompson, Assistant Professor

Center for Microbial Oceanography (C-MORE)

The Center for Microbial Oceanography: Research and Education (C-MORE) was established in August 2006 as a National Science Foundation (NSF) sponsored Science and Technology Center. The center is designed to facilitate a more comprehensive understanding of the biological and ecological diversity of marine micro-organisms.
Life has its origins in the sea: the first living things were microbes. Marine microbes are the most abundant life forms on Earth, and everything about them is extraordinarily diverse: their structures, their genomes, their physiologies, and their ecological interactions with each other and with the rest of life on the planet.

As a global research information center working across disciplines, C-MORE brings together teams of experts—scientists, educators, and community members—who usually have little opportunity to interact, facilitating the creation and dissemination of a new understanding of the critically important role of marine microbes in global habitability.

The center’s mission and unifying vision is expressed in the motto: Linking Genomes to Biomes.

The Center’s activities are shared among five partner institutions (coordinated at the University of Hawaii at Manoa. http://cmore.soest.hawaii.edu/):

- MIT
- Woods Hole Oceanographic Institution
- Monterey Bay Aquarium Research Institute
- University of California, Santa Cruz
- Oregon State University

Research objectives of the integrated center
Edward DeLong (Research Coordinator), MIT

The broad spectrum of planned research activities will be coordinated by Ed DeLong, MIT. Four separate research themes have been identified, each with a Theme Leader to help track progress and facilitate exchange. See: http://cmore.soest.hawaii.edu/research.htm

C-MORE research will be organized around four interconnected themes: (I) Marine microbial biodiversity: From genomes and cultivation to ecology, (II) Microbial metabolism and the mechanisms of C, N, P and energy flow, (III) Remote and continuous sensing of microbial processes and links to climate variability, and (IV) Ecosystem modeling, computer simulation and prediction. The knowledge gained in our research will be incorporated into complementary field research and physical-biogeochemical modeling efforts that are already funded by independent teams of investigators. The proposed science themes parallel contemporary research foci in marine sciences. They will steer our technology development requirements, and will serve as the basis for the development of new education and outreach programs. Much of this proposed research will build upon ongoing field and laboratory studies and will benefit from the logistical support infrastructures that are already in place in support of the Hawaii Ocean Time-series (HOT) program and as part of the Monterey Bay Microbial Observatory and Monterey Ocean Observing System (MOOS) program in collaboration with F. Chavez (MBARI) and others.
PROF. VLADIMIR BULOVIC
VanBuren N Hansford (1937) Associate Professor of Communications and Technology; Director, Laboratory of Organic Optics and Electronics (LOOE)
http://www.rle.mit.edu/rleonline/People/VladimirBulovic_cv.html

Bulovic's research interests include studies of physical properties of organic and organic/inorganic nanocrystal composite thin films and structures, and development of novel optoelectronic organic and hybrid nano-scale devices. His papers and patents cover the areas of organic and nanostructured light emitting diodes, lasers, photovoltaics, photodetectors, chemical sensors, and programmable memories, majority of which have been licensed and utilized by both start-up and multinational companies.

The Darwin Project
The Darwin Project is an initiative to advance the development and application of novel models of marine microbes and microbial communities, identifying the relationships of individuals and communities to their environment, connecting cellular-scale processes to global microbial community structure. http://esi.mit.edu/content/blogcategory/40/71/

MIT ENERGY INITIATIVE: BIOFUELS RESEARCH AREA
Principal Investigator: Prof. Gerald R Fink
Other Investigators: Prof. Paul I Barton, Prof. Sallie W Chisholm, Prof. Charles L Cooney, Prof. John M Deutch, Prof. William H Green, Jr, Prof. John B Heywood, Prof. Gregory J McRae, Prof. Kristala L Jones Prather, Prof. Anthony J Sinskey, Dr. Gregory N Stephanopoulos, Prof. Jefferson W Tester
http://web.mit.edu/mitei/research/transformations/biofuels.html

Liquid fuels derived from oil supply 96 percent of the nation's transportation sector. This reliance — together with growing global demand for oil, the concentration of oil reserves in the Middle East and greenhouse gas emissions from oil production and consumption — raise significant geopolitical and environmental concerns about oil dependence.

Conversion of renewable sources of energy to liquid fuels provides an avenue to address these concerns. However, today's technology for converting biomass to liquid fuels is not scalable to amounts sufficient to displace a large fraction of oil consumption. Currently, ethanol made from corn is a renewable resource used to produce liquid fuels in the United States, but this new market and the associated increases in demand for corn have already significantly affected food prices and agricultural practices.

Producing alternatives to gasoline from other types of biomass — alternative crops, switchgrass and agricultural waste, for example — would eliminate "food vs. fuel" concerns. However, economic, scalable and sustainable production of ethanol from cellulose is difficult and expensive. It requires focused, multidisciplinary research involving biochemistry, genetics, enzymes and catalysts to identify the best plant candidates, enhance plant growth, improve biomass fermentation and optimize biofuels processing. As with other renewables, the dynamics of the natural resource base — including the effects of droughts, floods, and infestations — must be taken into account to ensure that biofuels represent robust, sustainable, affordable and
environmentally benign supplies of energy. Land use, water use and biodiversity are examples of important issues for biofuels production at a scale that materially reduces petroleum use and carbon dioxide emissions.

**PROF. ERIC J ALM**

Henry L Doherty Assistant Professor of Ocean Utilization; Assistant Professor of Biological Engineering

http://cee.mit.edu/alm
http://almlab.mit.edu/ALM/ALM.html
http://cee.mit.edu/node/2222
http://csbi.mit.edu/people/alm.html

Eric Alm has been at MIT since 2005, and is the Doherty Assistant Professor of Ocean Utilization. Research in Professor Alm's group includes both computational/theoretical and experimental approaches to understanding the evolution of microorganisms, emphasizing a 'systems-level' perspective. Some areas of special interest include:

(*) Tools for detecting natural selection in microbes
(*) The evolutionary origin of gene families
(*) Mining metagenomic sequence data
(*) Experimental evolution of microbes
(*) Modeling bacterial ecology
(*) Gene regulatory networks in bacteria
(*) Protein structure and design

**Alm Laboratory for Microbiology: Evolutionary, Ecological, and Environmental Systems Biology**

The Alm lab develops complementary computational and experimental methods for studying microbial evolution. Ongoing projects include the detection of selection in ancestral bacteria, the experimental evolution of marine Vibrio, and the refinement of the Tree of Life. http://almlab.mit.edu/ALM/ALM.html

**Natural Diversity of Environmental Stress Tolerance in Marine Bacteria**

Using marine Vibrio strains as a model system, we investigate to what extent observed sequence diversity corresponds to measurable differences in salinity and temperature tolerance phenotypes, two ecologically important factors for this group of organisms. We have designed two-dimensional gradients in 23 cm square dishes containing solid growth medium to monitor temperature and salinity tolerances over a broad range of both factors. Growth patterns indicate the strain-specific minimum and maximum tolerances and interactions between the factors (salinity and temperature). We compared the specific boundaries of growth for multiple strains of Vibrio splendidus and V. alginolyticus.

While the obtained profiles differ in their shape and limits, some consistent features appear. Tolerance to increasing salinities correlated positively with temperature tolerance. However, higher salinity constrained the limits of temperature tolerance, so that the maximum salinity tolerance occurred at intermediate temperatures.
Similarly, growth at higher temperatures led to a tradeoff, limiting the range of salinity tolerance. Interestingly, at high salinities, low temperatures tended to suspend growth, leaving viable cells that could be regenerated when the temperature gradient was removed, while higher temperatures led to killing.

Via combining this integrated ecological and experimental approach with genome re-sequencing we are trying to draw connections between genetic diversity and ecologically relevant phenotypes and tradeoffs.


**AdaptML: Modeling the Evolution and Ecology of Gene Families**

To date, modeling the behavior of cellular networks under laboratory conditions has received more attention than modeling how ecological factors affect diversity in natural environments. As we move toward the ultimate goal of integrating laboratory model organism studies with field data, a key challenge will be identifying the geochemical/ecological factors that underlie community diversity, and the phylogenetic boundaries of natural ecological populations. Thus, computational frameworks for automatically learning models of sequence evolution in the context of metadata (e.g., site geochemistry/ecology) will need to be developed.

We have developed one such framework: AdaptML, a maximum-likelihood-based tool for studying both the sequence evolution and ecological history of a set of gene sequences. To perform this latter task, AdaptML employs a hidden-Markov-model-like strategy of assigning gene sequences to unseen states we term "habitats." These habitats are inferred automatically and designed to recapitulate sequence partitioning observed in the wild. AdaptML was initially developed and tested in collaboration with Martin Polz's lab, using data from 1027 strains of marine Vibrio hsp60 gene sequences harvested off the coast of Maine. We showed that AdaptML can be used to analyze this dataset and to help build models of Vibrio resource partitioning.

http://almlab.mit.edu/ALM/Research/Entries/2008/5/10_Adaptation_in_Metagenomes.html

**Induced and Targeted Mutagenesis of Plastid Encoded Genes**

Diatoms belong to the most abundant microalgae in our oceans. Due to their vast abundance and ecological success their contribution (20%) to the global annual biomass production equals the productivity of the rain forests.

Focusing on the marine Diatom Phaeodactylum tricornutum we are studying a unique mechanism that allows us to induce random mutagenesis within in a plastid encoded target gene. So far mutagenesis was induced in psbA (encoding for the D1 protein of photosystem II) and the 16S rRNA gene. Currently we examine how precisely we are able to restrict mutagenesis to an area of interest. Besides understanding the underlying molecular mechanism, we are also interested in providing a useful tool for bioengineering purposes. So far, possible target genes only include genes that - after experiencing point mutations - can induce a selectable phenotype. To overcome this restriction we use fluorescence-activated cell sorting to establish the selection of mutants with deviating photosynthetic phenotypes.

**Genetic Transformation of Chloroplasts in Red Algae**

This project is trying to develop a method for inducing directed mutations in the chloroplast genome of red algae, or diatoms, permitting more rapid development of mutant libraries of these organisms. If this project is successful, the next step will be to extend the methods to green algae, whose chloroplasts are genetically closer to those in plants. Success in this effort could lead ultimately to entirely new, faster methods for mutation and trait selection in crops, flowers, and weeds.

**PROF. DAVID BARTEL**
Professor of Biology; Howard Hughes Medical Institute (HHMI) Investigator; Member, Whitehead Institute

http://mit.edu/biology/www/facultyareas/facresearch/bartel.html
http://www.whitehead.mit.edu/research/faculty/bartel.html
http://web.wi.mit.edu/bartel/pub/
http://csbi.mit.edu/people/bartel.html

Whitehead Member David Bartel has made major contributions to recent advances in understanding the roles that ribonucleic acid (RNA) plays in contemporary biology and may have played in early evolution. Bartel joined Whitehead Institute in 1994 as a Whitehead Fellow, following the completion of his PhD at Harvard University. In 1996 he was appointed an Associate Member of Whitehead and assistant professor of biology at MIT. Bartel is now a Howard Hughes Medical Institute Investigator, a Member at Whitehead and professor at MIT.

**Bartel Laboratory**
We study small RNAs that regulate gene expression. Our main focus is on microRNAs (miRNAs), which are ~22-nt RNAs that specify gene repression by base-pairing to messages of protein-coding genes in plant and animal cells. Our lab is uncovering a widespread influence of miRNAs on metazoan gene expression and interesting roles that miRNAs play during growth and development of plants and animals. For example, our work indicates that more than a third of human protein-coding genes are conserved regulatory targets of miRNAs, and that the miRNA regulation of one of these genes is important for preventing human cancers.

**Regulatory Targets of MicroRNAs**
Principal Investigator: Prof. David Bartel
Other Investigator: Prof. Christopher B Burge
Depts/Labs/Centers: Department of Biology, Whitehead Institute for Biomedical Research

The discovery of hundreds of miRNA genes immediately raised the question of what all these tiny RNAs are doing. To address this question, we have developed methods of predicting miRNA targets without bringing in too many false-positive predictions. In plants, the miRNAs have extensive pairing to their targets, and the evolutionarily conserved targets are mostly genes that play important roles during development. In animals, the miRNAs usually recognize shorter sites (typically 7 or 8 nt in length), which match a short region of the miRNA containing the ‘seed’ sequence. Our mammalian predictions, obtained in collaboration with Christopher Burge, can be viewed at TargetScan.org.
Animal miRNAs have a great abundance and diversity of targets, with more than one-third of human genes under selective pressure to maintain pairing to miRNAs. When considering nonconserved targeting, the fraction of human genes regulated by miRNAs grows even higher. Experiments using reporter assays and mRNA expression arrays provide additional evidence that miRNAs have a widespread influence on both the expression and evolution of mammalian protein-coding genes. For example, mRNAs preferentially expressed in the same tissue as a highly expressed miRNA are strongly depleted in 7mer matches to that miRNA, presumably because these messages have important roles in that tissue, and during the course of evolution they have avoided acquiring sites to co-expressed miRNAs that would compromise their function. This selective avoidance of 7mer matches to miRNAs provides compelling evidence that 7mer sites are often sufficient for repression in animals.

Although a 7mer site matching a miRNA is often sufficient for mediating some repression, it is not always sufficient, indicating that other characteristics help specify targeting. Using both computational and experimental approaches, we uncovered five general features of site context that boost site efficacy. Combining these determinants, we constructed a model of target recognition that successfully predicts site performance, thereby providing an important resource for choosing which of the many miRNA-target relationships are most promising for experimental follow-up. Because our approach accurately distinguishes effective from ineffective sites without recourse to evolutionary conservation, it also identifies effective nonconserved sites and siRNA off-targets.

**PROF. SALLIE W CHISHOLM**
Professor of Civil and Environmental Engineering and Biology; Lee and Geraldine Martin Professor of Environmental Studies; Director, MIT Earth System Initiative
http://chisholmlab.mit.edu/
http://cee.mit.edu/chisholm
http://csbi.mit.edu/people/chisholm.html

The research goal of the Chisholm lab is to understand the ecology of phytoplankton in the oceans and the biogeochemical cycles that they mediate. Currently, we are focused on the cyanobacterium Prochlorococcus as a model system. It is the most abundant photosynthetic microbe in the sea and can account for up to half of the photosynthetic biomass over vast oceanic regions. Prochlorococcus is a minimal phototroph, which means that it converts CO2, solar energy and inorganic nutrients into a living cell with approximately 1,700 genes. It is a useful model for understanding the autotrophic mode of life, for studies of comparative genomics and metabolic reconstruction, and for investigating the role of microdiversity in shaping the structure and evolution of microbial communities.

The global abundance of Prochlorococcus arises in part from the existence of physiologically and genetically distinct ecotypes that require different light intensities for growth and have adapted to life under different conditions in the oceans. The genomes of eleven Prochlorococcus strains have been sequenced, allowing us to compare differences in genomic architecture within and between ecotypes, the core genes shared by all, and the genes that are unique in each strain. Some of these unique genes have obvious roles in determining relative fitness in different
environments; others have unknown functions, and likely hold clues to unknown agents of natural selection in the oceans.

Other aspects of our research include:

- Studies of different strains of lytic phage that infect Prochlorococcus, including phage/host specificity, infection dynamics, genome comparisons, whole genome expression analyses, and phage-host genetic exchange.
- Whole genome expression profiles of two model Prochlorococcus ecotypes, helping us understand their adaptations to particular conditions that they experience in the oceans.
- Comparisons of the distribution and abundance of Prochlorococcus ecotypes in the global oceans, to provide a framework for interpreting the evolution of their metabolic differences.
- Sequencing the genomes of native Prochlorococcus cells, to help us understand co-existing genomic diversity among native populations.

Ultimately, we wish to understand how genomic and metabolic differences among Prochlorococcus ecotypes determine their global distributions in the oceans. The challenge will be to link our understanding of their biology at fundamentally different scales, and to work toward a unified understanding of this one small representative of the diversity of life on earth.

**Chisholm Lab**

The Chisholm lab is a group of graduate students, post-doctoral associates, research scientists, research assistants and MIT undergraduates, focused on understanding the role of marine phytoplankton in the ocean's "metabolism". Using the cyanobacterium Prochlorococcus as a model system, we are studying its ecology at all levels of organization - from the genome level to the whole ocean. Our approach to this problem includes laboratory and field studies, as well as modeling. We use the tools of genomics and systems biology in this pursuit, and our studies also include the study of the abundant viruses (cyanophages) that infect Prochlorococcus.

The focus of the research in my laboratory is the marine microorganism, Prochlorococcus. This organism is the dominant primary producer in the oceans, the smallest known phototroph, and the most abundant photosynthetic cell on the planet. Over the past ten years we have set as our goal to develop Prochlorococcus as a model system for cross-scale systems biology. We seek to understand the biology of this single organism from the genome level to the global scale. To this end I have built a sizable group of students and post-docs spanning the fields of biochemistry, genomics, virology, microbial ecology, and oceanography, all united around this tiny cell, Prochlorococcus. It is our conviction that we must break down the barriers between disciplines to fully understand Life, in all of its dimensions. [http://chisholmlab.mit.edu/](http://chisholmlab.mit.edu/)

Our work is shaped in large part by the following set of questions:

**The origins and nature of genomic diversity in closely related Prochlorococcus strains:** How different are the genome sequences of closely related Prochlorococcus strains? What are the patterns of gene loss and gain among the strains and what do they tell us about the evolutionary drivers? Does the core genome - those genes shared by all strains - supply all of the metabolic functions necessary for life? Can we interpret the strain to strain differences in gene content in the context of the distributions of 'ecotypes' along environmental gradients in the field? What are the features of Prochlorococcus genomic diversity in the growing meta-genomic data
base in the oceans, and what can it tell us about the forces that shape the assembly of these communities?

**Phage/Host interactions:** What is the diversity of phage that infect Prochlorococcus in the oceans, and what are the characteristics of their lytic cycle? What are the host ranges of different phage, and how do these relate to the properties of host and phage? What role do phage play in horizontal gene transfer in this system? in overall mortality? What is the gene flow between host and phage over evolutionary time, and how has this shaped the ecology of both?

**Ecotype dynamics in the oceans:** How does the abundance of Prochlorococcus ecotypes change with time and space in the oceans, and what selective and neutral forces shape these patterns? How well can we predict these patterns using realistic coupled physical/chemical/biological models?

**Role of Prochlorococcus in ocean food webs and biogeochemistry:** What types of carbon compounds are produced and excreted by Prochlorococcus in the ocean habitat? What types of microbes assimilate these metabolites, and is this a mutualistic relationship? What organisms eat Prochlorococcus? What 'sensing' mechanisms have evolved between mutualistic partners and predator and prey?

We have developed a battery of tools and capabilities to help us address these questions, including:

- An extensive culture collection of 40 Prochlorococcus strains isolated from the world’s oceans
- A culture collection of hundreds of phage strains that infect them
- The complete genome sequences of 11 Prochlorococcus strains and of 3 phage that infect them
- A computational infrastructure for genome analysis
- Affymetrix micro-arrays for two hosts and phage enable functional genomic analyses
- High speed cell sorting, proteomic capabilities
- Access to regular sampling at time series stations in the Atlantic and Pacific Oceans where Prochlorococcus is numerically dominant
- Q-PCR techniques for measuring ecotype abundances in the field

**Integrative Systems Biology**

The marine cyanobacterium Prochlorococcus is the smallest and most abundant photosynthetic cell on the planet. The goal of the lab is to understand this single microbe from the genome to the global scale, thereby developing the field of integrative systems biology. Work centers on the following topics:

(*) The origins, nature and ecological impacts of genomic diversity among Prochlorococcus
(*) The metabolic machinery of Prochlorococcus as a model for solar energy conversion
(*) The role of viruses in Prochlorococcus ecology
(*) The role of ecotypic variation in the dynamics and stability of the global Prochlorococcus population
(*) The role of Prochlorococcus in ocean food webs and biogeochemistry

We use the tools of genomics, metagenomics, transcriptomics and proteomics, and we have a vast culture collection of Prochlorococcus and phage as well as the complete genome sequences of 12
Prochlorococcus strains. Regular sampling programs take place off Bermuda and Hawaii, and we participate in research cruises throughout the global oceans.

PROF. EDWARD F. DELONG
Professor of Civil and Environmental Engineering
http://cee.mit.edu/delong
http://web.mit.edu/be/people/delong.htm
http://openwetware.org/wiki/DeLong_Lab
http://csbi.mit.edu/people/delong.html

Teaching Interests: Environmental genomics; Microbial diversity; Photobiology; Integrating microbial systems biology with systems ecology

Microbial life has been integral to the history and function of life on Earth for over 3.5 billion years. As such, microbes have evolved to be the fundamental engines that drive the cycles of energy and matter on Earth, past and present. Additionally, microbes represent the single largest source of evolutionary and biochemical diversity on the planet. Despite their significance, our understanding of the evolution and ecology, and the structure and function of natural microbial communities is limited both conceptually and technologically. Yet the potential of this vast reservoir of genetic and biochemical diversity is enormous, from the perspective of both basic knowledge creation, as well as that of synthetic applications. For these reasons, a major focus of our lab centers on devising and applying new approaches to describe, quantify and model the complexity of natural microbial assemblages, in particular bacteria and archaea, and understand its natural significance and applied potential.

The lab is currently engaged in applying contemporary genomic technologies to dissect complex microbial assemblages. While biotic processes that occur within natural microbial communities are diverse and complex, much of this complexity is encoded in the nature, identity, structure, and dynamics of interacting genomes in situ. This genomic information can now be rapidly and generically extracted from the genomes of co-occurring microbes in natural habitats, using standard genomic technologies. We are now exploring and applying these and related technologies, to better describe and exploit the genetic, biochemical, and metabolic potential that is contained in the natural microbial world. The central focus is on marine systems, due to the fundamental environmental significance of the oceans, as well their suitability for enabling development of new technologies, methods, and theory.

A Genomics-enabled Microbial Observatory in the Monterey Bay National Marine Sanctuary

Previous efforts by the DeLong Lab in Monterey Bay have generated large-insert genomic “libraries” from genomic fragments of Monterey Bay microbes (each “book” in the library containing a large fragment of the DNA from a single marine microbe from the Bay). These libraries have been characterized extensively, both phylogenetically (who’s there?) through surveys of rDNA genes and functionally (what might they be doing?) through surveys of genes known to be involved in, for example, pulling carbon dioxide out of the atmosphere and turning it into cellular building blocks, or capturing sunlight and transforming it into energy. In this current Monterey Bay Microbial Observatory project funded by NSF, the genomic information in the libraries is now being used to develop microarrays targeting specific microbes within the Bay, to allow a high-throughput means for studying their ecology in the Bay across space and time.
(Current technologies allow the tracking of one or a few microbial groups but generally not representatives across the whole community.)

Monterey Bay is a long-term ecological research site, with the efforts of several major research institutions focused on understanding the Bay's oceanography. DNA samples have been collected by the DeLong Lab at monthly intervals since 1998, in tandem with the Monterey Bay Aquarium Research Institute's (MBARI) Biological Oceanography Group's (BOG) research cruises. DNA samples from several sites and depths in Monterey Bay are collected and archived monthly by the DeLong Lab group, in conjunction with the MBARI Biological Oceanography Group's regular CTD cruises. The microarrays will be used to query these archived time-series DNA samples, in order to track the targeted organisms across depth, space and over time.

Among the specific questions we hope to address in this project are: What are the seasonal microbial population changes in Monterey Bay? How do these changes differ between the photic and subphotic communities? How do discrete oceanographic events like transient upwelling plumes influence the microbial community? What about larger-scale oceanographic events, such as El Ninos? In what ways, if any, does the community change along the coastal to offshore transect? The prototype array has been made and is currently being tested, and the next generation array will allow us to begin answering these questions. The central motivator underlying all these specific questions is our shocking ignorance about marine microbes, these fundamentally important microscopic drivers of our planet’s biogeochemistry. As our countries and citizens grapple with the complex issue of global change, we must provide the best information we can about how marine microbes respond to and control atmospheric composition, and to do that we must begin by figuring out who is there and how the communities respond to “normal“ environmental perturbations.

Results: Using a microarray design approach developed by the DeRisi Lab at UCSF for identifying and tracking viruses involved in human illness, we designed microarrays specific to the fragments of microbial DNA captured in the DeLong Lab genomic libraries. When tested against their perfect match target DNA, these microarrays show hybridization under standard conditions, and also can discriminate between closely related microbes. This specificity occurs not only with laboratory DNA samples but also with cells spiked into a coastal seawater - i.e., in a background of complex community DNA. We are testing the array further in the lab with increasingly complex mixtures of DNA, and diminishingly small amounts, to test where the limit of detection is for this array, and also to develop the optimal DNA amplification protocol to allow us to work with environmental DNA samples without skewing the community composition captured in the DNA. http://openwetware.org/wiki/DeLong:MBMO

“Proteorhodospin photosystem gene expression enables photophosphorylation in a heterologous host.”
Martinez, A., A. Bradley, J. Waldbauer, R. Summons and E. F. DeLong. 2007. PNAS
http://openwetware.org/images/a/a0/Martinez_etal_pnas07.pdf
Dr. Gerald R. Fink is the American Cancer Society Professor of Genetics at the Massachusetts Institute of Technology. Previously, he was Professor of Genetics from 1976 to 1979 and Professor of Biochemistry from 1979 to 1982 at Cornell University. Dr. Fink's major research interest is in the field of Infectious Disease Research; specifically, he is searching for agents that can prevent fungal infections.

He is a member of the Board of Trustees of Cold Spring Harbor Laboratory, a Non-Resident Fellow of the Salk Institute, a member of the Scientific Advisory Boards of the Biozentrum in Basel and the Howard Hughes Medical Institute, and a member of the NIH Child Health and Human Development Board of Scientific Counselors. He served as the President of the Genetics Society of America from 1988 to 1989.

Dr. Fink was elected to membership in the National Academy of Sciences in 1981 and the Institute of Medicine in 1996. Other honors he has received include the Wilbur Lucius Cross Medal from the Yale Graduate School Association, the Emil Christian Hansen Foundation Award for Microbiological Research, the Yale Science and Engineering Award, the Genetics Society of America Medal, Honorary Doctor of Science from Amherst University, the National Academy of Sciences-U.S. Steel Prize in Molecular Biology and a Guggenheim Fellowship.

**Fink Research Overview**

Fungi are increasingly the cause of death as there are few effective fungal antibiotics. Fungi gain entry to the body by adhering to indwelling devices such as catheters. The adhesion is intimately linked to the β-glucan and the mannoproteins (adhesins) molecules that encase the fungal cell. The analysis of adhesion and filamentation in the model system, Saccharomyces cerevisiae guides our studies in the less tractable pathogen, Candida albicans. The genomes of both fungi encode many mannoproteins that confer unique adherence properties. These adhesins are required for interactions of fungal cells with each other (flocculation and filamentation), with inert surfaces (agar and plastic) and with mammalian cells. These cell surface molecules are the antigens recognized by the phagocytic cells of the immune system. Fungi are able to vary these cell surface molecules. Recent work has shown that antisense RNA plays a key role in the expression of these cell surface molecules. We use genetics, biochemistry and genomics to address questions such as: What mechanisms generate the diversity of cell surface molecules? What cell surface molecules are recognized by the cells of the immune system? How do macrophages and neutrophils distinguish between a pathogen, Candida albicans, and a non-pathogen, Saccharomyces cerevisiae.

**Variation to Elude the Immune System**

The cell surface molecules of fungi vary by both genetic and epigenetic mechanisms that confuses the immune system. The β-glucan and the mannoproteins on the surface of fungi are the signature molecules recognized by the phagocytic cells of the immune system in their attempt to destroy pathogens. But, fungi have genetic, epigenetic and regulatory mechanisms that change the ensemble of surface molecules to avoid or alter recognition. The surface mannoproteins
(adhesins) of Saccharomyces cerevisiae, Candida albicans and Candida glabrata form a superfamily united by a common structure consisting of three domains (A, B, C). The amino terminal domain (A) provides much of the affinity for surfaces. This domain is followed by a segment of variable length (B) that is extremely rich in serines and threonines and contains many tandem repeats. The carboxyterminal region (C), links the mannoprotein to the \(-\)glucan.

http://www.whitehead.mit.edu/research/summaries/fink.html

**PROF. SARAH E. O’CONNOR**

Latham Family Career Development Associate Professor of Chemistry

http://web.mit.edu/chemistry/www/faculty/oconnor.htm

http://csbi.mit.edu/people/o%27connor.html

http://web.mit.edu/oconnor/www/Home.html

Sarah E. O’Connor is an associate professor of Chemistry at MIT. Her research efforts focus on understanding how nature enzymatically constructs complex natural products, and how these metabolic pathways can be used to produce novel compounds. She received her BS degree in Chemistry from the University of Chicago and her PhD from Prof. Barbara Imperiali working at both Caltech and MIT. She was an Irving S. Sigal post-doctoral fellow with Chris Walsh at Harvard Medical School. She joined the faculty at MIT in 2003.

**Natural Product Biosynthesis**

Many antibiotics, anti-tumor drugs and other pharmaceuticals are produced by bacteria, fungi or plants. These molecules are often harvested from the environment for clinical purposes. Unfortunately, isolation of compounds from the environment can also be an expensive and low yielding process. Furthermore, isolation procedures provide limited opportunities to modify the chemical and biological properties of the natural product.

Understanding the enzymes that catalyze natural product synthesis may enable production in more tractable host organisms and may also facilitate reprogramming of biosynthetic pathways to produce "unnatural" natural products with improved pharmacological activities.

The O’Connor group explores the enzyme-based biosynthetic pathways that generate structurally complex and clinically useful natural products. Our goals are to use the pathways to produce novel products, understand the mechanisms of the individual enzymes, to modulate the substrate specificity of the enzymes and to discover new enzymes involved in natural product biosynthesis. A strong emphasis is placed on plant derived compounds. Although plants produce many pharmaceutically important, structurally complex products, relatively little is known about plant metabolic pathways.

We take a multi-disciplinary approach to address these questions: protein expression, plant cell culture, molecular biology, enzymology, assay design, natural product isolation and chemical synthesis are key components of our research.

http://web.mit.edu/oconnor/www/Research.html

**Alkaloid Biosynthetic Pathways**

Alkaloids—nitrogen containing natural products—comprise some of the most structurally interesting and medicinally useful molecules found in nature. However, alkaloid biosynthesis is
not well understood compared to other classes of natural products. We are focusing on the terpene indole alkaloid biosynthetic pathway from periwinkle (Catharanthus roseus). This pathway is responsible for the biosynthesis of thousands of structurally complex and clinically used compounds, such as vinblastine, ajmaline and quinine.


"Chemists engineer plants to produce new compounds: Periwinkle plant cells could synthesize potential drugs"

Anne Trafton, MIT News Office, January 18, 2009

In work that could expand the frontiers of genetic engineering, MIT chemists have, for the first time, genetically altered a plant to produce entirely new compounds, some of which could be used as drugs against cancer and other diseases.

The researchers, led by Sarah O'Connor of the Department of Chemistry, produced the new compounds by manipulating the complex biosynthetic pathways of the periwinkle plant. This sort of manipulation, which O'Connor and her graduate student, Weerawat Runguphan, report in the Jan. 18 issue of Nature Chemical Biology, offers a new way to tweak potential drugs to make them less toxic (and/or more effective).

Genetic engineering is not new: Scientists have known for years how to get plants to resist pests and herbicides or to produce substances such as insecticides by inserting genes from other plants or animals. What is new, however, is the ability to induce plants to create new products by tinkering with the plants' own synthetic pathways.

O'Connor's laboratory has studied periwinkle for several years because it produces a variety of alkaloid compounds of pharmacological interest, including vinblastine, a drug commonly used to treat cancers such as Hodgkin's lymphoma.

Periwinkle also produces serpentesines, which have shown promise as anti-cancer agents, and ajmalicine, which is used to treat hypertension. Other plant-produced compounds have shown pharmacological activity but are too toxic for use in humans.

The current work builds on research O'Connor and grad student Elizabeth McCoy reported two years ago. They found that periwinkle cell cultures could produce novel compounds if fed starting materials slightly different from their normal substrates.

"That inspired us to think about metabolic engineering in a much more sophisticated way," said O'Connor, the Latham Family Career Development Associate Professor of Chemistry. "We can virtually re-engineer the pathway."

O'Connor and Runguphan focused on an enzyme involved in an early step of the alkaloid synthesis pathway. The enzyme normally accepts a terpenoid called secologanin and tryptamine, an alkaloid, as substrates.

Another graduate student, Peter Bernhardt, engineered a mutant form of the enzyme that can accept tryptamine with a halogen (such as chlorine or bromine) attached. Runguphan grew
genetically engineered plant cell cultures that produce the mutant enzyme and got them to synthesize several compounds that periwinkle plants would normally never produce.

The halogens could serve as points of attachment to add other novel chemical groups to the compounds, modifying their effectiveness and/or toxicity as drugs, said O'Connor.

So far all of the genetic engineering has been done in plant cell cultures, but Runguphan has started growing a tiny whole periwinkle plant with the mutant enzyme.

In the future, the researchers plan to use the same approach to produce additional compounds, in hopes of creating new and more effective drug candidates.

The research was funded by the National Science Foundation, the National Institutes of Health and the American Cancer Society.

PROF. MARTIN F POLZ
Associate Professor of Civil and Environmental Engineering; MIT/Woods Hole Oceanographic Institution (WHOI) Joint Program
http://cee.mit.edu/polz
http://web.mit.edu/polz/

Professor Polz studies environmental microbiology, looking at the dynamics that govern microbes’ interactions and evolution to learn the role of individual populations within the community, the range of genomic similarity that defines a functional unit, and what mechanisms govern diversification of microbial populations in the environment. His research group addresses these questions using a combination of quantitative molecular approaches, genomics, physiology and modeling. The group is also exploring environmental and evolutionary mechanisms that trigger the emergence of pathogenic variants among microbes.

Polz Lab
The main focus of research in the Polz lab is the exploration of structure-function relationships in microbial communities.

Environmental microbiology is at an important crossroads. Over the last twenty years we have learned that microbes are the most ubiquitous organisms on Earth, yet the dynamics that govern their interactions and evolution remain poorly understood. What is the role of individual populations within the community? What is the range of genomic similarity that defines a population as a functional unit? What mechanisms govern diversification of microbial populations in the environment?

We address these questions using a combination of quantitative molecular approaches, genomics, physiology, and modeling. Our primary model system is the coastal ocean where we study patterns of diversity among co-occurring bacterioplankton from the level of the entire community to the individual genome. For the latter, we focus on bacteria of the genus Vibrio, which are longstanding models of heterotrophic, marine bacteria and also contain many pathogenic variants (e.g., V. cholerae, V. vulnificus). As part of the Woods Hole Center for Oceans and Human Health (COHH), we are also exploring environmental and evolutionary mechanisms that trigger the
emergence of pathogenic variants within the vibrios. We are also part of the Earth Systems Initiative and the Microbial Systems Group at MIT. http://web.mit.edu/polz/

**Enumerating the organisms in the ocean**

We are using molecular genomics methods to estimate the microbial diversity in a natural ecosystem. One ml of seawater contains about one million bacterial cells. Yet, more than 99% of marine microbes are difficult or impossible to culture and cannot be studied in the laboratory, including most of the dominant species. To estimate their diversity and relationships to one another, we study a subset of genes that are common to all microbial species, such as 16S rRNA. These model genes turn out to exhibit enormous genetic diversity even within a single sample of seawater, suggesting that a great number of genomes co-exist in the ocean. Our observation that many species have closely related sequences suggests that these communities undergo continuous creation of diversity by sequence mutation, but lack a strong mechanism to remove that diversity. http://csbi.mit.edu/people/polz.html

**Genomic structures of closely related organisms**

We have isolated a large strain collection of oceanic bacterioplankton for studies of genomic diversity. This collection, like other native species, exhibits a range of relationships -- from closely related to more distantly related. Analysis of genome structure shows that the closely related strains undergo extremely high levels of exchange of genetic material leading to co-existence of polymorphism within populations. Because such exchange of genetic material does not happen with equal frequency between more distantly related strains, we currently hypothesize that these mechanisms may delineate closely related strains as an "ecological/evolutionary unit." This unit may function in the marine bacterioplankton ecosystem in an analogous way that species function among eukaryotes. http://csbi.mit.edu/people/polz.html

**The Ecology and Evolution of Bacterial Populations in the Wild**

The principal model system is bacteria of the genus Vibrio co-occurring in the coastal ocean. These afford the opportunity to study a wide range of environmental adaptations since their lifestyles range from free-living to symbiotic and pathogenic. Current research addresses:

(*) The genomic diversity within and between ecologically differentiated populations
(*) The temporal and spatial dynamics of populations
(*) The diversity and role of extrachromosomal elements (plasmids, viruses) in horizontal gene transfer
(*) The selection for pathogenicity (genes) in the environment
(*) The diversity and range of antagonistic interactions

Researchers use a combination of ecological, genomic and molecular genetic tools. For example, we are in the process of sequencing ~100 genomes and many more plasmids and viruses in collaboration with Professor Eric Alm’s lab and the Broad Institute.

**PhysioMapper**

PHYSIOMAPPER is an online resource for comparing multiple properties of bacterial strains, presenting the information as an exportable table or mapped onto a 16S rRNA phylogenetic tree.
The tool provides sequence and physiological/metabolic information about sets of organisms that match user-provided physiological/metabolic search patterns. At present, over seventy bacterial strains are represented, chosen primarily from Delta-Proteobacteria. Users are encouraged to contribute new strains to the database. PhysioMapper is a work in progress. http://www.bugaco.com/physiomapper/

**PROF. ANTHONY J SINSKEY**
Faculty Director, Center for Biomedical Innovation (CBI); Co-Director, Malaysia-MIT Biotechnology Partnership Programme (MMBPP)
http://mit.edu/biology/www/facultyareas/facresearch/sinskey.html
http://web.mit.edu/biology/sinskey/www/home.html
http://csbi.mit.edu/people/sinskey.html

Anthony J. Sinskey, Sc.D. is a Professor of Biology and Health Sciences and Technology at MIT. He conducts interdisciplinary research in metabolic engineering focusing on the fundamental physiology, biochemistry and molecular genetics of important organisms. His wide-ranging research interests involve helping lead the MIT-Malaysia Biotechnology Partnership Program and his MIT laboratory has collaborative projects with colleagues in the chemical and electrical engineering departments on the design, fabrication and instrumentation of microreactors.

As an authority on biotechnology and business, Professor Sinskey has been actively involved in the start-up of new companies and in consulting new and established firms. Prof. Sinskey has published numerous technical reports and papers in microbiology, biotechnology, biopolymer engineering and metabolic engineering, holds key research patents licensed from MIT, serves on the editorial boards of several renowned journals, and is a member of the board of directors of several biotechnology/pharmaceutical companies.

Professor Sinskey has participated in the founding and development of successful biotechnology companies including Metabolix, Genzyme, Natural Pharmaceuticals, Merrimack Pharmaceuticals, Tepha and ABEC. He is recognized as a leading expert in the formation of new biotechnology enterprises and a renowned academic entrepreneur.

“**Bacterial 'battle for survival' leads to new antibiotic: Holds promise for treating stomach ulcers**”

Anne Trafton, MIT News Office, February 26, 2008,

War may actually be healthy for you (war between two microscopic bugs, that is).

MIT biologists have provoked soil-dwelling bacteria into producing a new type of antibiotic by pitting them against another strain of bacteria in a battle for survival.

The antibiotic holds promise for treatment of Helicobacter pylori, which causes stomach ulcers in humans. Also, figuring out the still-murky explanation for how the new antibiotic was produced could help scientists develop strategies for finding other new antibiotics.

The work is reported in the February issue of the Journal of the American Chemical Society.
A combination of luck, patience and good detective work contributed to the discovery of the new antibiotic, according to Philip Lessard, research scientist in Professor Anthony Sinskey's laboratory at MIT.

Sinskey's lab has been studying Rhodococcus, a type of soil-dwelling bacteria, for many years. While sequencing the genome of one Rhodococcus species, the researchers noticed that a large number of genes seemed to code for secondary metabolic products, which are compounds such as antibiotics, toxins and pigments.

However, Rhodococcus does not normally produce antibiotics. Many bacteria have genes for antibiotics that are only activated when the bacteria are threatened in some way, so the researchers suspected that might be true of Rhodococcus.

Kazuhiko Kurosawa, a postdoctoral associate in the Department of Biology, decided to try to provoke the bacteria into synthesizing antibiotics by placing them in stressful environments. He tried turning the temperature up and down, then altered the bacteria's growth medium, but nothing worked.

Kurosawa then decided to stress the Rhodococcus bacteria by forcing them to grow in the presence of competing bacteria, a strain of Streptomyces. Streptomyces produces an antibiotic that normally kills other bacteria, but in one of the experimental test tubes, Rhodococcus started producing its own antibiotic, which wiped out the Streptomyces.

The researchers isolated the antibiotic, dubbed it rhodostreptomycin and started testing it to see what else it would kill. It proved effective against many other strains of bacteria, most notably Helicobacter pylori. Rhodostreptomycin is a promising candidate to treat H. pylori because it can survive in very acidic environments such as the stomach.

The antibiotic turned out to be a type of molecule called an aminoglycoside, composed of peculiar sugars, one of which has a ring structure that has not been seen before. The ring structure could offer chemists a new target for modification, allowing them to synthesize antibiotics that are more effective and/or stable.

"Even if [rhodostreptomycin] is not the best antibiotic, it provides new structures to make chemical derivatives of," said Lessard. "This may be a starting point for new antibiotics."

One mystery still to be solved is why Rhodococcus started producing this antibiotic. One theory is that the presence of the competing strain of bacteria caused Rhodococcus to "raise the alarm" and turn on new genes.

The version of Rhodococcus that produces the antibiotic has a "megaplasmid," or large segment of extra DNA, that it received from Streptomyces. A logical conclusion is that the plasmid carries the gene for rhodostreptomycin, but the researchers have sequenced more than half of the plasmid and found no genes that correlate to the antibiotic.

Another theory is that the plasmid itself served as the "insult" that provoked Rhodococcus into producing the antibiotic. Alternatively, it is possible that some kind of interaction of the two bacterial genomes produced the new antibiotic.
"Somehow the genes in the megaplasmid combined with the genes in Rhodococcus and together they produced something that neither parent could make alone," said Lessard.

If scientists could figure out how that happens, they could start to manipulate bacterial genomes in a more methodical fashion to design new antibiotics.

Other authors of the paper are T.G. Sambandan, research scientist in MIT's Department of Biology, MIT professors Anthony Sinskey of biology and ChoKyung Rha of the Biomaterials Science and Engineering Laboratory, and Ion Ghiviriga and Joanna Barbara of the University of Florida.

The research was funded by the Cambridge-MIT Institute and the Malaysia-MIT Biotechnology Partnership Program.

Malaysia-MIT Biotechnology Partnership Programme (MMBPP)

Anthony Sinskey, ChoKyung Rha
http://minihelix.mit.edu/malaysia/index.htm

The Malaysia MIT Biotechnology Partnership Programme (MMBPP) is a research and development partnership. The main objective of the MMBPP is to develop advanced technologies that command the future of biotechnology. The MMBPP pulls together the expertise and resources of Malaysia with the ability of MIT to advance the science and technology. Thus, the MMBPP synergistically drives technical progress and scientific discovery to create a unique resource based biotechnology. The programme aims at biotechnology to explore, capitalize, and further develop Malaysian natural resources. Furthermore, the MMBPP creates and adds value to the natural and human resources of Malaysia.

The MMBPP was launched with a five-year plan with two research sub-programmes:

- Natural Product Discovery from the Malaysian indigenous medicinal plants - first with Eurycoma longifolia (Tongkat Ali) and Centella asiatica (Pegaga), and
- Oil Palm Technology - production of high value substances using oil palm as a new generation "manufacturing plant."

Tongkat Ali, the most well-known traditional Southeast Asian herbal medicine, is believed to cure thousands of diseases. Although Tongkat Ali is still widely available in the market, its supply is rapidly diminishing. The research on Eurycoma longifolia focuses on: 1) in vitro propagation via somatic embryogenesis, 2) quantitative measurement of the chemical or bioactive constituents, and 3) development of standardized commercial formulations. Similarly for Centella asiatica, studies including identification and characterization of accessions, genetic fingerprinting, bioassays, bioreactor feasibility, etc. are aimed at the enhancement of bioactive metabolites production.

The oil from Oil Palm is a major cash crop in Malaysia. The research on oil palm focuses on two major areas. First, developing and improving methods for the cultivation of oil palm in tissue and suspended culture. Second, Oil Palm engineering produces biodegradable plastics, furthering the value of the crop.
The MMBPP, approved as a national biotechnology programme by the National Research Council, Mesyuarat Majlis Penyelidikan Dan Kemajuan Sains Negara (MPKSN), is sponsored by the Ministry of Science Technology and the Environment of Malaysia, with the National Biotechnology Directorate as the designated authority. The MMBPP is formulated with the consensus of the biotechnology community of Malaysia and participating MIT research personnel, and is guided by the framework set forth by the National Science Advisor of Malaysia. The MMBPP has had strong support and sanction of the Prime Minister of Malaysia, the Right Honorable Y.A.B. Dato Seri Dr. Mahathir Bin Mohamad from its inception.

Exchange of Malaysian and MIT research personnel to facilitate the interaction, progress, and training of researchers in critical areas such as genomics, bioinformatics, and bioprocess, are an integral part of the MMBPP. The engagement of Malaysian scientists on MMBPP research at MIT, in collaboration with the MIT researchers in areas currently important in biotechnology including genomics, bioinformatics, proteomics, bioassay etc., is aimed at training the professionals who will lead the biotechnology development and be responsible for the new biotechnology industry in Malaysia.

A total of eighteen academic, industrial and government research institutions including six Biotechnology Cooperative Centers along with MIT collaborate in the MMBPP. They are the Forest Research Institute Malaysia (FRIM), Palm Oil Research Institute Malaysia (PORIM), Applied Agricultural Research (AAR), FELDA Agricultural Services Sdn Bhd, Golden Hope Plantations, Guthrie Biotech Laboratory Sdn Bhd, Institute for Medical Research (IMR), IOI Plantations Bhd, Malaysian Agricultural Research and Development Institute (MARDI), Sime Darby Plantations, Standards and Industrial Research Institute of Malaysia (SIRIM), Technology Park Malaysia (TPM), TropBio Sdn Bhd, United Plantations Bhd, Universiti Kebangsaan Malaysia (UKM), Universiti Malaysia (UM), Universiti Putra Malaysia (UPM), and Universiti Science Malaysia (USM). The MMBPP has approximately 200 research personnel in Malaysian institutions and 27 research personnel, including Malaysian scientists, working at MIT.

**PROF. CHOKYUN RHA**

Professor of Biomaterials Science and Engineering  
[http://csbi.mit.edu/people/rha.html](http://csbi.mit.edu/people/rha.html)

Professor Rha is Director of the Biomaterials Science and Engineering Laboratory. In the MIT BioMicro Center, ChoKyun Rha's research is investigating the gene expression profiles of human cells in response to compounds isolated from Centella asiatica and Eurycoma longifolia, two Malaysian plants of pharmaceutical interest. In addition, the laboratory focuses on the Eukaryotic response to cellular stress and aging by studying Saccharomyces cerevisiae.

The interest of the Rha lab is to determine the structure, function and properties of complex biological molecules. A wide variety of techniques, including transcriptional profiling, genomic sequencing and analysis, LC and GC mass spectroscopy, molecular imaging and micro-rheology, are employed to examine the bioactivities of living systems at the genomic and molecular level to provide the basis for identifying and engineering plants to produce natural products for medicinal and industrial use.
Biomaterials Science and Engineering Laboratory

The lab research focuses on two sub-programmes in a collaboration with Malaysia: Natural Product Discovery and Oil Palm Technology. [http://web.mit.edu/biomicro/research/rha.html](http://web.mit.edu/biomicro/research/rha.html)

**Natural Product Discovery**

The studies on Eurycoma longifolia (Tongkat Ali) include studies on micropropagation and chemical fingerprinting. As part of this project, methods and tools are under development for the preparation and standardization (relative to the bioactive components) of extracts from Tongkat Ali. These methods should increase the market value of Tongkat Ali preparations by establishing recognizable standards for quality and potency. In addition, the lab works on the quantitative measurement of the chemical or bioactive constituents of Eurycoma longifolia (Tongkat Ali) and development of standardized commercial Tongkat Ali formulations. The lab works towards the enhancement of bioactive metabolite production in Centella Asiatica (Pegaga) by chemical standardization and biological characterization.

**Oil Palm Technology**

Using tissue culture methods, studies are underway that examine methods of improving oil palm productivity. This study encompasses such methods and tools as bioinformatics, robotics, and genetics. As needed, other methods will be incorporated to help achieve the goal of reliable micropropagation of oil palm. The project also focuses on metabolic engineering in transgenic oil palm.

**Determining genetic diversity through single nucleotide polymorphisms**

Analysis of single nucleotide polymorphisms (SNP) single base changes in DNA sequence that distinguish one individual tree from another enabled us to identify Tongkat Ali trees that came from different geographical regions. In coordination with their component profiles, we can identify the particular trees which produce the most important biologically-active agents. This information then permits the selection of highly productive trees for propagation and genetic engineering of the species with the highest potential productivity and benefit.

“ALIENS AT SEA: ANTHROPOLOGIST HELMREICH STUDIES RESEARCHERS STUDYING OCEAN MICROBES”

Stephanie Schorow, MIT News Office, February 5, 2009

When MIT Professor of Anthropology Stefan Helmreich set out to examine the world of marine microbiologists for a new book, his research took an unexpected twist.

Helmreich, who has been recognized for his innovative cultural anthropology work, had decided to study scientists who chase some of the world's smallest creatures in some of the world's most forbidding places. So he spent long hours interviewing microbial biologists such as Penny Chisholm, the Lee and Geraldine Martin Professor of Environmental Studies at MIT, and Edward DeLong, professor in MIT's Department of Biological Engineering and the Department of Civil and Environmental Engineering and an associate member at the Broad Institute.

He wanted to understand not only how they went about their research, but also what sentiments and belief systems guided them as they scrutinized microbes like Prochlorococcus, a sea-dwelling microbe of global importance that Chisholm co-discovered in 1986.
But during the years of Helmreich's research, the entire field shifted gears. By the time he finished his book, “Alien Ocean: Anthropological Voyages in Microbial Seas,” published in early 2009 by University of California Press, marine microbiologists were calling their discipline "microbial oceanography" -- a reflection that they were not just studying individual single-celled creatures in the ocean, but the ocean itself.

Microbiologists now saw the sea as a microbial soup, a relic of what was on the Earth billions of years ago, filled with life forms both alien and familiar to humans; such perceptions changed the way scientists approached research, he says.

As Helmreich puts it: "Microbes are not only in the sea, they ARE the sea."

'Something of massive consequence'

With frequent references to classical literature and pop culture, "Alien Ocean" explores how microbiologists are re-imagining the sea through the language and techniques of genomics, bioinformatics, biotechnology, biodiversity mapping and systems modeling. The book "is not just about microbiologists sitting around on boats getting seasick looking at very tiny things," he says. "We're looking at something of massive consequence here."

Helmreich has long been interested in exploring other worlds; his 1998 book, "Silicon Second Nature: Culturing Artificial Life in a Digital World," examined virtual life. He became intrigued with marine microbiology in 1998 while attending a conference in Monterey; his interest began to jell into a book project about 2003. Rather than write a kind of "Our Oceans, Ourselves" manifesto, he deliberately employed the figure of the "alien" in the title and throughout the text to describe the unexpected world of these weird little creatures, many of which were new to science.

Chisholm welcomed Helmreich's focus. "Most people don't even know the oceans are microbial-dominated. And they certainly have no idea that there is so much microbial diversity out there, nor do they know about ocean genomics," she says. "We now think of the oceans as a 'Sea of Genes.' I call it 'dissolved information.' I remember being pleased that he was drawn to this concept. It was validating, as I was never quite sure that it was a compelling image."

To get inside the microbiologists' minds, Helmreich traveled to the Sargasso Sea, where he helped graduate students collect water samples for Chisholm's lab. He rode boats with DeLong's postdoctoral associates in Monterey Bay to dredge the sea floor and find "the message in the mud." He examined invasive algae in Waikiki, Hawaii, and explored the sea floor around hydrothermal vents in the Juan de Fuca Ridge in the Pacific. He spent hours querying researchers about their perceptions of microbes, as "extremophiles," "little living machines" or "tape recorders of their environment."

"I'm trained in anthropology so I'm interested in what people do, why they think they do it, and what it might mean in broader social frameworks -- politically, economically, socially, morally, ethically, spiritually," Helmreich says. "The question I wanted to answer was this: How is it that people working in the field of microbial ocean biology come to see their work as meaningful both to them and to the rest of us?"
He learned, for example, that Chisholm saw ocean phytoplankton as a kind of forest that could, in time-lapse photography, be seen to breathe. "I believe the earth is a living entity," she told him. He saw DeLong as claiming that, "the entwined orders of nature and society cannot exist without microbes" and that "microbes are mostly allies to be understood rather than enemies to be defeated."

DeLong said his post-doc students, whom Helmreich pressed to explain their work, benefited by being questioned about their underlying beliefs about science. "Sometimes we're so swept up in the details, that we don't see the forest for the trees," DeLong says. "Often times we take a lot for granted. We consider many points of view and facts as being given, but they aren't -- they're built on presumptions."

Science, Helmreich concludes, cannot be divorced from culture. Medieval Christians saw the ocean as frightening chaos; 19th Century Romantics saw it as a symbol of the sublime, both beautiful and terrifying. In the 20th Century, filmmakers like Jacques-Yves Cousteau made the underwater world seem downright friendly. Today, we speak of saving the ocean from overfishing, pollution, and global warming. And, he says, we do not know whether the future sea will be friend or foe; much depends on what we humans do.

"The very fact of caring about the ocean changes the kinds of questions we ask and the kind of things that we take to be facts worth finding out," Helmreich says.