***Editor's note: Exploring the life sciences has been a mission at Oak Ridge National Laboratory since the early 1950s, when researchers sought to understand the relationship of radiation to the human body. More than a half-century later, that early mission has embarked on a new course. The destination is a far bolder one: understanding life itself.***

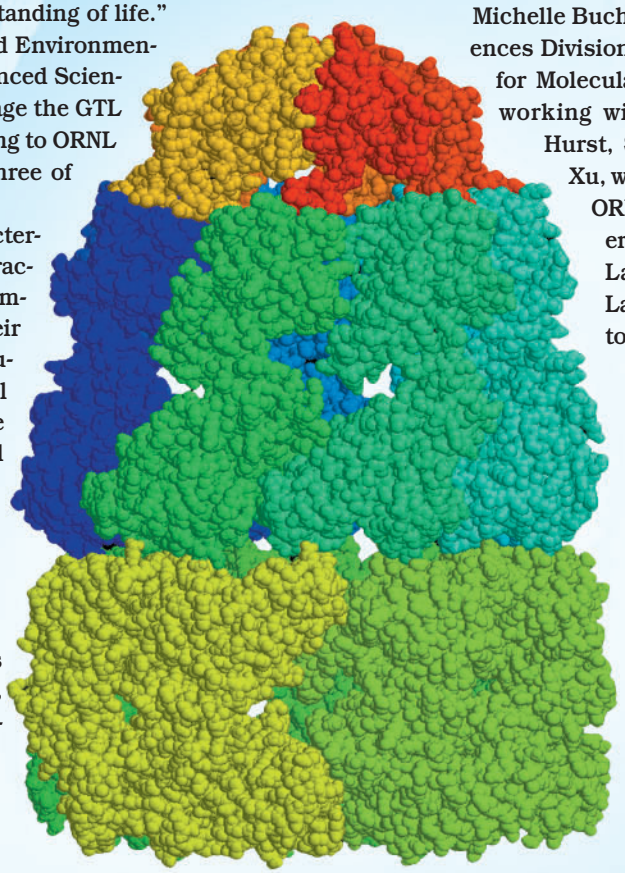
# Sailing Into Uncharted Waters

A researcher scooped up some "clean" water containing bacteria and transferred the "bugs" to water with a known contaminant. Now comes the difficult part: Predicting how large groups of bacterial proteins, the workhorses in and around each one-celled organism, will respond to chemical "signals" from the contaminant.

Identifying and characterizing the molecular machines of life—the multi-protein complexes that execute cellular functions and govern cell form—is one of four ambitious goals of a new program started in 2001 by the Department of Energy's Office of Science. The Genomes to Life (GTL) program seeks to "achieve the most far-reaching of all biological goals—a fundamental, comprehensive, and systematic understanding of life."

DOE's Office of Biological and Environmental Research and the Office of Advanced Scientific Computing Research will manage the GTL program jointly. Both provide funding to ORNL researchers, who are involved in three of five GTL projects.

Other GTL goals are to characterize gene regulatory networks, characterize the functional repertoire of complex microbial communities in their natural environments at the molecular level, and develop computational methods and capabilities to advance understanding of complex biological systems and predict their behavior.



## BIOLOGY IN THE POST-GENOME ERA

The GTL program follows DOE's Human Genome Program, which contributed to a revolutionary scientific achievement in 2000 with completion of the draft sequence of the human genome. Draft sequences of the genomes of several bacteria, the mouse, and other organisms also have been published. They show the order of chemical bases making up every gene in each organism.

Related to the Human Genome Program is the Microbial Genome Program, started in 1994. The program's purpose is to apply knowledge about microorganisms to help DOE achieve the agency's missions of developing clean energy sources and protecting the environment. These programs revolutionized biological research and provided what are now common tools used in forensics, pharmaceutical design, and disease diagnosis. Knowing the gene sequence, however, is only a first step in fully understanding how an organism works.

The long-term goal of the GTL program is to understand, at the molecular level, how genes, proteins, and other cellular molecules interact to carry out life's process within and between cells. Meeting this challenge will require teams of biological, chemical, physical, and computational scientists. Central to the program's success is the development of new analytical and computational tools.

Michelle Buchanan, director of ORNL's Chemical Sciences Division, is scientific director for GTL's Center for Molecular and Cellular Systems. Task leaders working with her include Mitch Doktycz, Greg Hurst, Steve Kennel, Mike Ramsey, and Ying Xu, who coordinate contributions from other ORNL staff. They collaborate with researchers from DOE's Pacific Northwest National Laboratory (PNNL), Argonne National Laboratory, and Sandia National Laboratories (SNL), as well as two universities.

"The program initially will identify and analyze protein complexes in two types of bacteria," Buchanan says. "Protein complexes enable cellular growth, metabolism, replication, repair, and responses to intracellular and extracellular signals, like molecules from pollutants. They are responsible for a cascade of molecular processes within and between cells. The complexes also dictate how a cell or organism interacts with its environment."

*Bob Hettich prepares to study bacterial proteins using a high-performance Fourier transform ion cyclotron resonance mass spectrometer.*

Buchanan's project will begin by focusing on the application of analytical tools to the identification and characterization of protein complexes to better understand the function of cells in two microbes. They are the *Shewanella oneidensis* (which can reduce oxidized metals in solid deposits in soils) and *Rhodopseudomonas palustris* (which can fix carbon monoxide or use organic molecules as a carbon source for basic metabolism).

"We plan to set up a high-throughput system to characterize the protein complexes in these microbes," Buchanan says. "We will use instruments such as mass spectrometers, the lab-on-a-chip device developed at ORNL, and imaging tools.

"Our data will help our computer scientists develop models so we can take shortcuts in identifying and describing protein complexes in different microbes. Our eventual goal is to do a bug a day."

Researchers working with the center will develop new capabilities to prepare and culture bacterial samples, do complex separations of components of protein complexes, identify proteins at the molecular level using mass spectrometry, characterize protein complexes in living cells by imaging, and apply bioinformatics and computational tools to collect and interpret data and form databases and tools for sharing by the biological community.

Ed Uberbacher, leader of the Computational Biology Group in ORNL's Life Sciences Division, says analytical tools and algorithms will be needed to determine how proteins interact, stimulate chemical reactions, and move materials inside and out of cells under different conditions.

"Proteins turn genes on and off, regulating their activities," he says. "When a bacterial cell is moved from clean to polluted water, proteins capture environmental signals and turn on genes that make proteins enabling the cell to adapt to its new environment. We want to characterize this cascade of changes."

For example, in a cell exposed to a pollutant, a phosphokinase enzyme may attach a phosphate to a protein to activate it. Mass spectrometry can confirm whether a protein is linked to a phosphate.

## NEW CENTER FOR ORNL?

ORNL is a potential site for one of four GTL research centers planned by the Office of Science. The center, called the Characterization and Imaging of Molecular Machines, would be anchored to the project led by ORNL.

Oak Ridge's chances of hosting one of the new GTL centers are improved by a robust array of supporting programs and facilities. ORNL's Center for Computational Sciences would provide one of the world's largest supercomputers capable of processing, for example, the vast amounts of data involved with protein folding. The program also would be supported by two new facilities, the Center for Functional Genomics, funded by the Office of Science, and the Joint Institute for Biological Sciences, funded by the state of Tennessee.

"If DOE awards Oak Ridge a GTL facility, it could be operating in the next four to six years," Buchanan says. "The complex would have offices for visiting scientists, students, and staff; biopreparation and culture labs; analytical instruments; robots; imaging instruments; clusters of computers; data visualization; and networked links to supercomputers."

*Synechococcus Sp* cyanobacteria take up carbon dioxide from the atmosphere and store it in the ocean. But what limits the ability of these bacteria to fix carbon in many areas of the ocean? To answer these and other questions, another GTL project will combine experimental and computational simulation tools for high-throughput characterization of protein complexes. The researchers also will try to identify proteins in regulatory pathways and determine how they interact using gene microarray data.

The leaders of the project, which involves collaborators from DOE national labs, universities, and research institutes, are Grant Heffelfinger of SNL and Al Geist of ORNL's Computer Science and Mathematics Division. Collaborating computer scientists from ORNL include Phil Locascio, Victor Olman, Nagiza Samatova, Manesh Shah, and Dong Xu.

How do gene regulatory networks behave in microbes in response to waste sites contaminated with metals and radionuclides? This question will be tackled by another GTL project involving ORNL. DOE's Lawrence Berkeley National Laboratory leads this project, which also has collaborators from three universities and a corporation. Jizhong Zhou of ORNL's Environmental Sciences Division is using microarrays to help provide data on changes in gene expression under differing environmental conditions for use in computer models. The goal is to rapidly predict gene and protein changes in microbes as they encounter various stresses.

Like the Portuguese explorers of the 16th century, ORNL researchers are sailing into uncharted waters, excited by the discoveries that surely lie ahead.