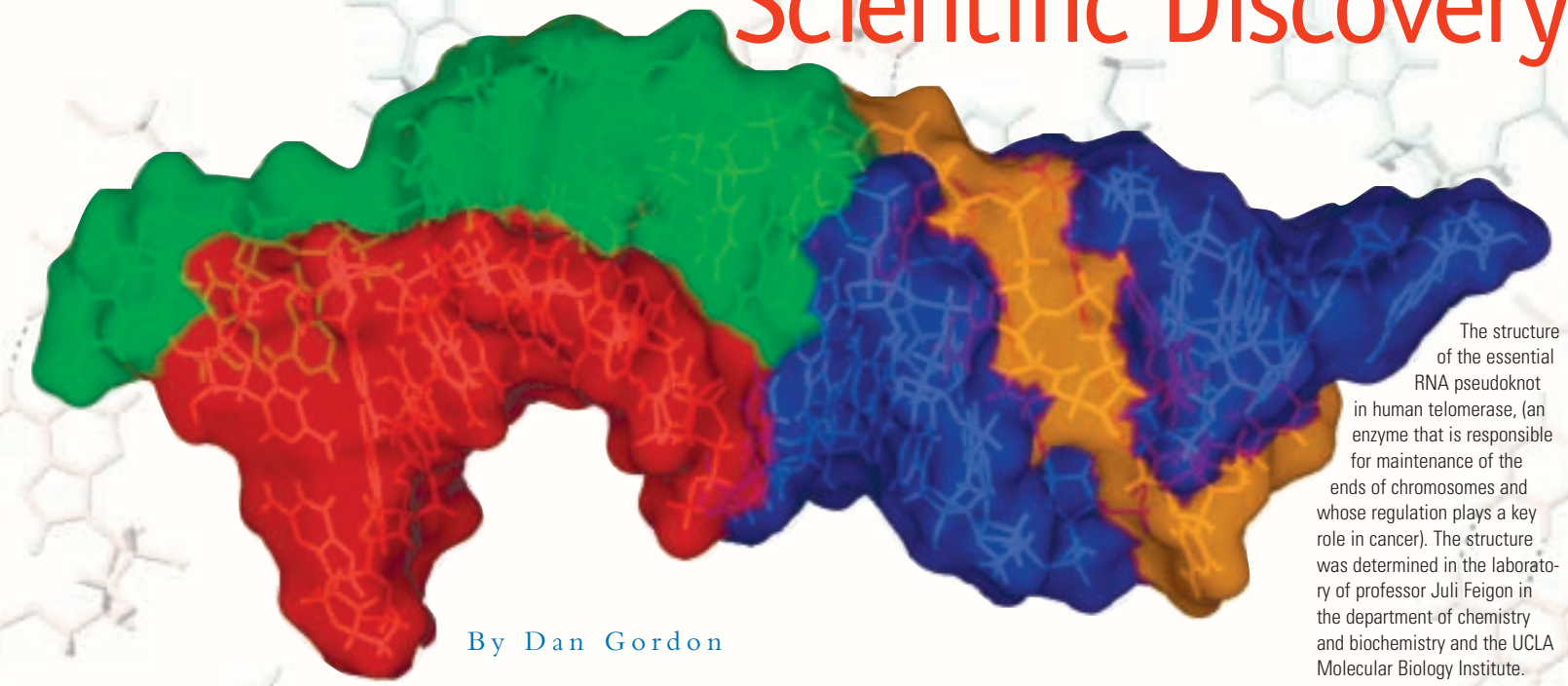
A Cauldron of Scientific Discovery



The structure of the essential RNA pseudoknot in human telomerase, (an enzyme that is responsible for maintenance of the ends of chromosomes and whose regulation plays a key role in cancer). The structure was determined in the laboratory of professor Juli Feigon in the department of chemistry and biochemistry and the UCLA Molecular Biology Institute.

By Dan Gordon

For more than 45 years, the Molecular Biology Institute has spawned unique interdisciplinary collaborations that are addressing the fundamental questions of life.

It started more than four decades ago when a small group of faculty from chemistry, biology and the medical school began to talk informally about the need to transcend traditional disciplinary boundaries. Against the backdrop of their discussions, a scientific revolution was underway—for the first time, life processes could be studied at the molecular level. In 1965, UCLA's Molecular Biology Institute (MBI) and a related interdepartmental graduate program were born with fewer than a dozen faculty members and three graduate students.

Like the science it supports, MBI has grown by leaps and bounds in the ensuing years. Today, there are approximately 165 faculty members and nearly half that number pursuing doctoral degrees in the interdepartmental program, many based in a building that has become a cauldron of scientific discovery—a building named after the Institute's founding director, who won a Nobel Prize for his own research efforts. The ever-more-potent tools of the molecular biology trade are fueling advances in much of the scientific world. And by bringing together researchers from disparate departments on campus, MBI continues to provide fertile ground for the interdisciplinary collaborations that have kept UCLA at the forefront of a science that now has the unprecedented ability to address fundamental questions of life.

In 1961, Richard Dickerson was a postdoctoral fellow in the Cambridge laboratory of John Kendrew, one of the scientists who had described the first two protein structures, myoglobin and hemoglobin. Kendrew was launching a new scientific publication that he was considering calling the *Journal of Molecular Biology*, but was hesitant.

"Kendrew asked, 'Is molecular biology a legitimate term?' " recalled Dickerson, who would later become MBI's second director, serving from 1983 to 1994. "People had been using the term since 1938, but it didn't really have meaning until molecular structures of proteins began to be worked out."

But as scientists began to solve the mysteries of proteins and DNA structure, the idea that life processes should be studied at the molecular level was taking hold. "Chemists were looking at what molecules did, and biologists were studying what organisms did," explained Steven Clarke, professor of chemistry and biochemistry and the current MBI director. "When people realized that biology could be explained in terms of the individual chemical molecules, everything changed."

Soon, the emerging field would include biophysics; through x-ray diffraction technology, scientists could, by tracking individual atoms, begin to describe how life works, as well as what goes wrong in cases where it *doesn't* work.

Paul Boyer was recruited from the University of Minnesota to join the UCLA faculty in 1963 and was soon asked to be the first director of the new institute. Boyer would quickly establish a culture of cross-disciplinary teamwork that continues to distinguish the institute to this day.

While guiding the MBI through its formative years, Boyer was also pioneering a new way of looking at a complex biological problem. In 1997, Boyer was awarded the Nobel Prize in Chemistry for his co-discovery of the process behind the synthesis of ATP, the energy molecule that drives biological reactions.

Boyer's work was the most celebrated of many important discoveries that have come out of the Institute. MBI researchers presented the first evidence that DNA could "bend" and found, in studying the process of drug binding, that small changes in the DNA helix could be read by proteins. MBI researchers laid the laboratory groundwork for the development of COX-2 inhibitors, an important advance in the area of anti-inflammatory pain medication. A new understanding of aging and molecular repair processes came out of work by MBI scientists, as did the concept of gene splicing.

The intellectual framework for these and other discoveries was established through MBI's educational mission and purposeful mixing of scientists. On Boyer Hall's six floors, MBI members from approximately 10 departments are situated strategically in ways designed to lead to the most productive daily interactions. At weekly seminars and annual retreats, informal discussions often spawn new ways of thinking and potentially fruitful collaborations.

"This institute has enabled us to formalize interactions that, at other universities, would be hit and miss," said Clarke. As molecular biology grows more complex, the interdisciplinary net is widening. MBI researchers are working more closely with neurobiologists at the UCLA Brain Research Institute toward a better understanding of the molecular mechanisms involved in learning and memory. While continuing to promote collaborations among biologists, chemists and faculty in the medical school, MBI is forging more ties with physicists, bioengineers and other researchers at the new California NanoSystems Institute on campus. Mass spectrometry and imaging technologies developed by engineers and physicists are opening new windows for looking at biology.

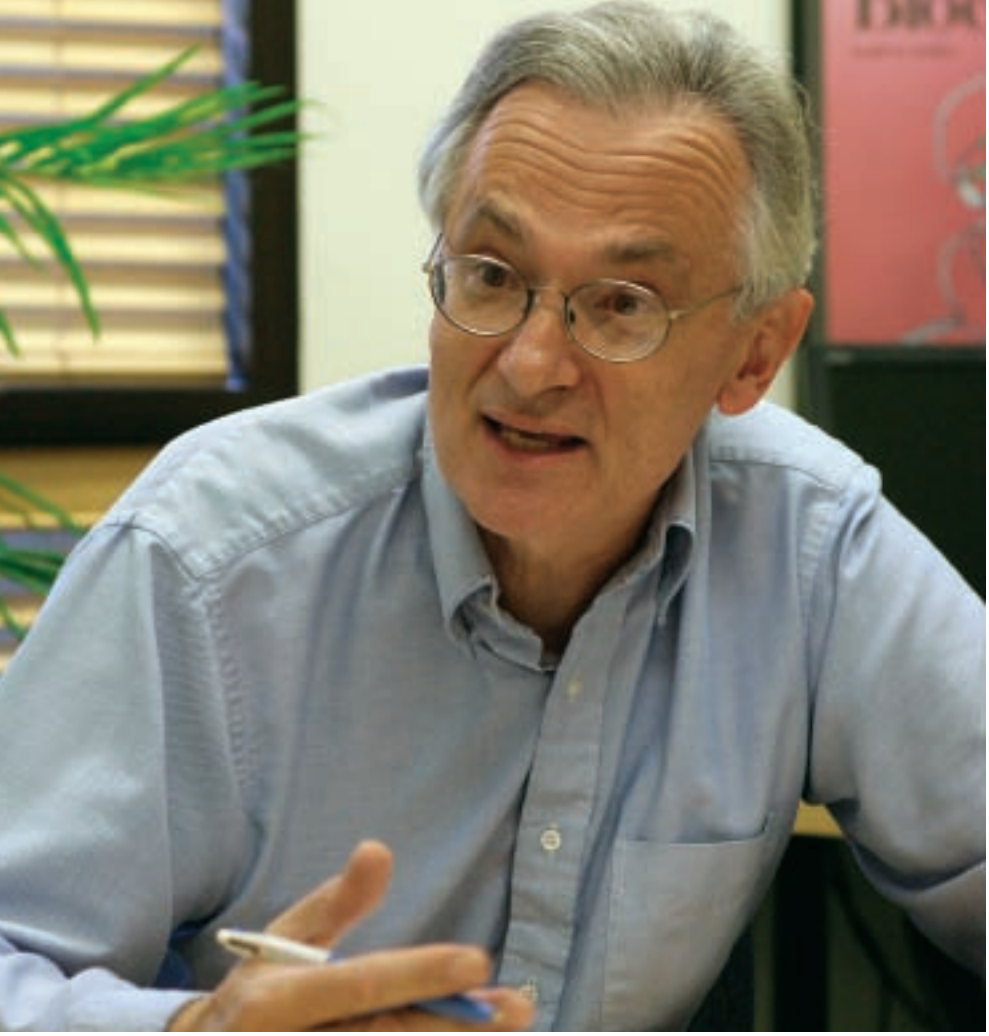
Clarke believes MBI's powerful mixing of expertise enables UCLA to stay at the cutting edge in the development of new scientific approaches. The last decade has seen the emergence of "omics" technologies. It started with genomics—studying genes in tandem rather than one at a time; more recently, scientists have begun to look at the full complement of proteins (proteomics), metabolites (metabolomics) and lipids (lipomics).

"These are new global ways of looking at molecules in the cell," said Clarke. "Rather than studying one problem, we're developing approaches to studying the interactions of all molecules and systems so that we can understand the function of the living organism."

Modern research tools are making it possible to address questions molecular biologists of previous generations couldn't have considered tackling.

Photo by Carol Petersen

The interdepartmental Ph.D. program in MBI, directed by biochemist Sabeeha Merchant, provides graduate students with unique opportunities to work with faculty from many UCLA departments—a much broader exposure to scientific fields than in traditional department-based programs. The program recently received a bequest from alumnus Philip Whitcome that, among other things, establishes an endowment for graduate student support.



Steven Clarke, director of the UCLA Molecular Biology Institute: "Chemists were looking at what molecules did, and biologists were studying what organisms did. When people realized that biology could be explained in terms of the individual chemical molecules, everything changed."

Recombinant DNA technology has dramatically accelerated the pace of the science. Now, researchers can easily examine a section of the human genome in pursuit of a gene affected in disease, see what protein that gene encodes and study the protein.

"The science is advancing so quickly that faculty can't be doing the same thing they were doing when they were hired," said Clarke. "We all have to wake up each morning and ask ourselves what new things we can learn that will help us be more efficient." To that end, MBI's continuing education—both formal and informal—is critical. Many individual donations through Campaign UCLA established the Sigman Lectureship, which brings internationally-renowned scientists to the campus to share their expertise.

Graduate students and new faculty help to ensure a steady infusion of new ideas. The interdepartmental Ph.D. program, originally established by Boyer and today under the leadership of Sabeeha Merchant, professor of biochemistry and MBI associate director, continues to provide graduate students with opportunities to work with faculty from multiple departments, exposing them to a much broader array of mentors from which to choose for their dissertation supervision than is available to students in traditional departmental Ph.D. programs.

The program will be reinvigorated thanks to a large bequest from alumnus Philip Whitcome that, among other things, establishes an endowment for graduate student support in MBI *(see page 30)*. Merchant said that the funding will enable the interdepartmental program to develop a track for specialized students who will be afforded greater independence and the ability to tailor the program to their goals.

When recruiting new faculty, Clarke said, MBI's leadership assesses where the science is moving and takes the opportunity to go after individuals whose area of expertise will best advance the research enterprise.

"These new faculty help to keep the older faculty sharp," Clarke said. "The older faculty can then apply their wisdom to these exciting new areas, as well as serving as mentors to the younger scientists."

That level of collegiality impressed the Institute's most recent faculty recruit, Feng Guo. After completing his postdoctoral training at the University of Colorado-Boulder, Guo, a structural biologist interested in the workings of a class of genes called microRNAs that are believed to regulate 10-30 percent of all protein gene expression, was pursued by top universities. UCLA was where he felt most at home.

"MBI has a strong structural biology community," Guo said. "But just as important, the researchers are so interactive and willing to help each other. The assistance I've been getting from other laboratories as I start mine has made a huge difference."

www.mbi.ucla.edu

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