Cold Spring Harbor Laboratory

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Cold Spring Harbor Laboratory is one of the oldest independent biological research centers in the United States, dating back to 1890 when the Brooklyn Institute of Arts and Sciences established a summer Biological Field Station for teachers and college students. In 1924, the Long Island Biological Association established a year-round research facility. In parallel, the Carnegie Institution of Washington in 1904 established the Station for Experimental Evolution on adjacent land. The two institutions coexisted for many years, often with a single director, and merged in 1963 to create the modern day Cold Spring Harbor Laboratory.

Located on 95 acres of wooded hills and harbor shoreline on the north shore of Long Island, the Laboratory (Fig. 1) consists of thirty buildings—many of which date back to the 19th century whaling era. Cold Spring Harbor Laboratory is a basic research facility focussing on cancer, neurobiology, and plant genetics. In addition to these research activities, the Laboratory each year hosts 15 international meetings on biomedical science and 24 advanced laboratory courses for scientists. The Laboratory also has activities at three nearby sites: the Banbury Center, a 45-acre conference facility; the Upland Farms Experimental Station, a 12-acre agricultural facility; and the DNA Leaning Center, an educational facility that serves to educate the public about the science of DNA.

There are currently 41 faculty, 7 visiting scientists, 130 postdoctoral fellows, and 54 graduate students working at Cold Spring Harbor. More than half of the science here is on the genetic basis of cancer. This vigorous research program evolved from the highly successful DNA tumor virus research established by James D. Watson when he was appointed director in 1968. From the identification of oncogenes—Michael Wigler of Cold Spring Harbor was among the first discoverers of the role of *ras* in human cancer—to the study of genetic signals that control cell division in normal and cancerous cells, the Laboratory is dedicated to the pursuit of a deeper understanding of cancer at its origin. This includes basic research on mechanisms of gene expression, DNA replication, cell division cycle controls, cell architecture, structural biology, and signal transduction. Recent discoveries in these areas include the identification in Carol Greider's laboratory of the RNA and protein components of the enzyme telomerase, an essential polymerase that maintains the integrity of the ends of chromosomes. Telomerase is not present in most normal human cells, but is activated in many tumor cells, providing a potential anti-tumor target.

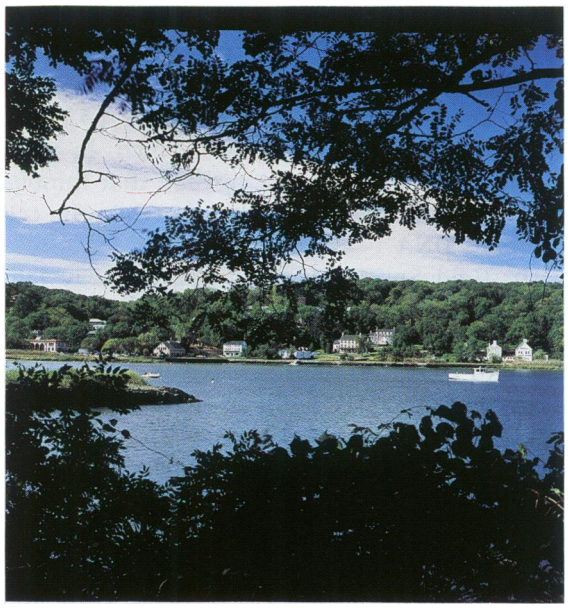

FIG. 1. Panoramic view of Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, U.S.A.

Photograph by Margo Bennett, Cold Spring Harbor Laboratory.

A recently expanded research area is apoptosis, an important aspect of the balance in developing tumors between cell proliferation and cell death. Three Cold Spring Harbor laboratories study the genetic basis of apoptosis and its relationship to normal development and tumor progression.

Cell division cycle controls have long been a major focus of research at the Laboratory. The

first members of a new family of cancer-related genes were identified by David Beach and his colleagues. These proteins inhibit cyclin-dependent protein kinases, which control progression through the cell division cycle. The first of these proteins were called p16 and p21. The gene encoding p16 is altered in a wide variety of human tumors, whereas p21 plays a dual role in cell cycle regulation, inhibiting DNA replication but allowing DNA repair. Damage to a cell's DNA by radiation or other mutagen induces p53, the well-known tumor suppressor, which, in turn, activates p21, beginning a cascade that inhibits progression through the cell cycle while the cell repairs its DNA.

In Cold Spring Harbor's neurobiology labs there have been great strides in understanding the molecular basis for learning and memory. Begun in 1991, our neuroscience effort grew out of the traditional strengths of the Laboratory in genetics and molecular biology and from the neuroscience courses held here each year. In the tradition of Cold Spring Harbor, we decided to focus the research of seven faculty members on a single problem, the molecular basis of cognition. In a short time, Drs. Tim Tully, Alcino Silva, and Jerry Yin have identified the cyclic-AMP-regulated transcription factor CREB as a key switch for the formation of long-term memory (LTM) in both *Drosophila* and mice. This team also established genetic differences between the formation of short-term memory and LTM. Tully and Yin recently reported that hyperactivation of CREB in *Drosophila* produced instant LTM, bypassing completely the usual requirements of repeated training required for the flies to learn to avoid an odor-associated shock.

In another team effort, Cold Spring Harbor continues to build on the Nobel Prize–winning work of Barbara McClintock done here in the 1940s and 1950s. McClintock's theory of transposable elements has provided the foundation for the current plant genetics group, which is made up by Venkatesan Sundaresan and Robert Martienssen, who are maize geneticists, and Hong Ma, who specializes in *Arabidopsis*. Together they have taken the transposons that McClintock found in maize, inserted them into *Arabidopsis*, a smaller plant with a much shorter generation time, and developed a powerful gene trap/enhancer trap system that enables rapid screening for gene mutations.

In addition to hands-on basic research, Cold Spring Harbor scientists work toward developing sophisticated research techniques. Michael Wigler and Nikolai Lisitsyn developed a powerful technique called representational difference analysis (RDA) in 1993. RDA enables comparisons between DNA present in diseased and healthy tissue in order to identify genetic defects that could be responsible for a particular disease. RDA has been used by some researchers to study the genetic basis of cancer and by others to identify foreign DNA present in Kaposi's Sarcoma, to identify new forms of hepatitis virus, and, most recently, to establish a possible association between human herpesvirus 6 (HHV-6) and multiple sclerosis.

An important aspect of life at Cold Spring Harbor is the advanced educational activities that make the environment unique. With nearly 6,000 visitors to the Laboratory each year, the meetings and courses on the Laboratory's main campus and the smaller conferences at the Banbury Center promote the exchange of information so vital to the progress of science. The Laboratory courses can have a significant impact. The phage course started by Max Delbrück 50 years ago this year, for instance, has had a profound influence on the development of molecular biology. Meeting subjects cover a broad range of topics in molecular and cellular biology, plant genetics, and neurobiology. They typically run for 4 days, morning through night, providing an intense brainstorming session for up to 450 scientists from around the world. The annual Cold Spring Harbor Symposium on Quantitative Biology, the Laboratory's flagship meeting, dates back to 1933 and has a global reputation as a prestigious and important annual meeting for biologists. It was here that in 1953 James Watson made the first public demonstration of the double helical structure of DNA.

Conferences at the Banbury Center operate on a smaller scale—they are limited to 40 participants each—in a more intimate setting for workshop-style meetings. Journalists, congressional staffers, and other nonscientists often participate in programs, sometimes in conjunction with the DNA Learning Center (DNALC), to learn more about issues such as science policy, funding, ethics, and research.

The DNALC is a hands-on public educational facility. Students of elementary and high schools and their teachers take part in interactive DNA experiments, as do college instructors, pharmaceutical executives, and some Banbury Center guests. The DNALC helps develop DNA curriculum for public and secondary schools, and collaborates in outreach programs for minorities at

schools in New York City and around the United States. Recently, the Learning Center helped establish genetics education programs in Moscow, Svalov, Sweden, and Sardinia, Italy.

The dissemination of information is another of Cold Spring Harbor's functions. CSHL Press was established in 1933, when it published the proceedings of the first Symposium on Quantitative Biology. Since that time, the Press has grown to become a highly respected publisher of textbooks, laboratory manuals, and scientific journals.

The Laboratory is a young place, in spirit as well as in the average ages of its scientists. Young scientists have long been attracted to Cold Spring Harbor thanks in part to its reputation for encouraging fresh, new talent to think and investigate freely. Interaction and collaboration are enthusiastically supported, both within the Laboratory and in arrangements with other institutions: Cold Spring Harbor Laboratory collaborates with Oncogene Science Inc. in research toward a therapy for Duchenne muscular dystrophy; for cancer research, we interact with clinicians at North Shore University Hospital and Sloan-Kettering Cancer Center; and we are involved in a consortium to map the genes that cause manic-depression in collaboration with investigators at Johns Hopkins University and Stanford University Schools of Medicine.

Cold Spring Harbor Laboratory has evolved into a multifaceted institution having an impact on many aspects of modern biomedical research. Our goal is to continue to change, while maintaining the vigorous research environment that has existed for over 100 years.

ACKNOWLEDGMENTS

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