

Cold Spring Harbor Laboratory (1890-)

Cold Spring Harbor Laboratory (CSHL) is a non-profit research institution that specializes in cancer, neuroscience, plant biology, quantitative biology, and genomics. The organization is located on the shores of Cold Spring Harbor in Laurel Hollow, New York. The Brooklyn Institute of Arts and Sciences established the CSHL in 1890, to provide scientists with facilities to research Charles Darwin's evolutionary theory. The first mission of CSHL was biological science education. Since 1998, CSHL has housed the Watson School of Biological Sciences, a PhD program dedicated to scientific research. Nobel Laureates who conducted experiments at the CSHL include Barbara McClintock, Alfred Hershey, James Watson, Francis Crick, and Sydney Brenner. Throughout its history, researchers at CSHL have studied embryology, reproductive medicine, and genetics.

In 1889, John D. Jones donated eight acres of land and buildings he owned on the south shore of Cold Spring Harbor, formerly a part of the Cold Spring Harbor Whaling Company, to the Brooklyn Institute of Arts and Sciences to build CSHL. Jones was the son of John H. Jones, managing agent of the Cold Spring Harbor Whaling Company. The CSHL's proximal location to the seashore provided its researchers a wealth of plants and animals to study. The CSHL offered its first course on biology on 7 July 1890 as an extension of the Brooklyn Institute of Arts and Sciences. In 1898, Charles Davenport, professor of evolutionary biology at Harvard University, in Cambridge, Massachusetts, became the first director of CSHL.

In 1902, philanthropist Andrew Carnegie founded the Carnegie Institute in Washington, D.C., as an organization to fund and support exceptional scientific discovery. Davenport requested the Carnegie Institute of Washington to start a genetics research program within CSHL. Davenport's request was granted in June 1904 with the establishment of the Station for Experimental Evolution in Washington, D.C., later renamed the Carnegie Institution Department of Genetics in 1921. Hugo de Vries, who proposed the concept of gene, presented a commemorative speech at the Station's opening.

In 1910, Davenport founded the Eugenics Record Office (ERO) at CSHL, which encouraged eugenics research. Eugenics is a theory that holds that controlled reproduction can change a population's genetics, and that human reproduction should be controlled to some extent. Davenport approached Harry H. Laughlin, a fellow eugenicist, to be superintendent in 1910. From 1910 to 1921, Laughlin served alongside Davenport as superintendent, and from 1921 to 1939, as Davenport's assistant director. The two established the Eugenics Research Association at CSHL in 1913. Davenport and Laughlin described the Eugenics Research Association as an organization dedicated to promoting a eugenic agenda based on scientific research. For example, in 1927, the Eugenics Research Association began to study the ancestry of United States senators. Laughlin was secretary-treasurer of the Eugenics Research Association after 1917. *Eugenical News*, a journal dedicated to the public promotion of eugenics through anti-immigration and racist propaganda, was the first publication of the Eugenics Research Office in 1916.

Every summer until its closing in 1939, researchers met at the Eugenics Research Office at CSHL to learn how to conduct eugenics research, such as doing interviews, compiling medical histories, and forming human pedigrees. The ERO's Record of Family Traits and Family Tree Folder organized the genealogies of families with medical conditions based mostly on voluntary surveys. Davenport's work with an albino family led to the first genetics-based study of albinism, a disorder that causes the complete or partial spotting of skin, eyes, or hair color due to a defect in melanin, which is usually responsible for pigmentation in organisms. Results of Davenport's study were published in the 1916 article "Heredity of Albinism."

In June 1920, Laughlin cited eugenics research conducted at the ERO when he served as an expert agent for the Committee on Immigration and Naturalization in the US House of Representatives. Laughlin's testimony culminated in the passage of the Immigration Restriction Act of 1924, an act that reduced United States immigration to one-fifth of what was previously allowed.

In 1924, Davenport appointed his son-in-law, Reginald Harris, to be director of the Biological Laboratory at CSHL, which expanded CSHL's research focuses from eugenics to broader biological issues. Harris had previously studied at CSHL in 1916 as an undergraduate, and he then worked the Cornell Entomological Expedition to South America with James C. Bradley from 1919 to 1920, during which he studied insects in South America. In 1933, Harris changed the focus of the Biological Laboratory to research quantitative biology with an emphasis on physiology and biophysics, and he created the Cold Spring Harbor Symposium on Quantitative Biology.

The declining support for the US eugenics movement around World War II caused the ERO to close in 1939. Geneticist Milislav Demerec became director of the CSHL in 1941. Demerec researched bacteria and the viruses that infect bacteria called bacteriophages. Through his research of bacterial genetics at CSHL, Demerec increased the yield of the antibiotic penicillin during World War II by isolating mutants of the fungus *Penicillium chrysogenum*.

In 1945, Max Delbrück, who had inspired Demerec to research bacterial genetics, taught the first advanced course at the CSHL, called the Phage Course. Because Delbrück was a biophysicist, he focused on quantitative biology and biological research that intersected with engineering, biochemistry, and physics. The Phage Course influenced molecular genetics because it taught students to ascertain the physical properties of the gene. Delbrück taught the Phage Course until 1970. During that time, he introduced students to basic bacteriophage research methods and procedures. Graduates of the Phage Course include molecular biologists Seymour Benzer, Franklin Stahl, and John Cairns. For his students' graduations from the Phage Course, Delbrück organized parties, which included games inspired by genetic principles. For example, a game inspired by recombination, the process by which DNA is broken and synthesized, included two people going into a closet and exchanging articles of clothing. The new outfits that were created represented the new phenotypes, or outward expressions of the genetic makeup of an organism (genotype) that resulted from recombination.

Some students of the Phage Course became members of the Phage Group, a society headed by Delbrück and focused on bacteriophage research. Members of the Phage Group included microbiologist Salvador Luria and molecular geneticist Alfred Hershey. Luria collaborated with Delbrück in teaching the Phage Course and in the Phage Group leadership. Luria and Delbrück conducted experiments together, one of which which became called the Luria-Delbrück experiment in 1943. The Luria-Delbrück experiment showed that genetic mutations in bacteria could occur at random. In 1969, Delbrück and Luria, along with Hershey, received the Nobel Prize in Physiology or Medicine for their work on the viral genetic structure and replication mechanisms of bacteria.

In 1941, Demerec invited Barbara McClintock, who studied chromosome behavior and structure, to CSHL. In 1942, McClintock became a full-time researcher, and she later said that she enjoyed the freedom that CSHL gave her because she did not have to teach or consistently apply for external funding. CSHL provided McClintock land to grow maize for her experiments. Evelyn Fox Keller, a biographer of McClintock, said that at the CSHL, McClintock was not subject to as much discrimination as women scientists elsewhere because of her full-time position. In 1944 at CSHL, McClintock began working on the research that led her to discover transposable elements or transposons, DNA sequences capable of moving locations within an organism's chromosomes. The National Academy of Sciences, a society in the US that advises the federal government in science, medicine, and engineering, elected McClintock to the organization in 1944. McClintock worked at CSHL until her retirement in 1967, but she stayed involved as a scientist emerita. In 1983, she received the Nobel Prize in Physiology or Medicine for her lifetime research on transposons.

Alfred Hershey joined the Genetics Research Unit at CSHL in 1950, and he worked in the Animal House, later renamed the McClintock Laboratory. In 1952, Hershey and his laboratory assistant Martha Chase conducted the Waring Blender experiment. The Waring Blender experiment used bacteriophage proteins and the bacteria *Escherichia coli* to show that genes are composed of DNA,

not of proteins. Hershey directed the Genetics Research Unit at CSHL from 1962 until retiring in 1974. Chase left CSHL in 1953, but returned each summer during the 1950s to attend the Phage Group meetings.

James Watson, who described the double-helix structure of DNA alongside with Francis Crick in 1953, participated at CSHL throughout his career. Watson first publicly described the double helix structure of DNA at the 1953 Cold Spring Harbor Symposium titled "Viruses," and he stayed active in CSHL for the rest of his career. In 1948, Watson was a graduate student in Luria's laboratory at Indiana University in Bloomington, Indiana, where he met Delbrück.

In November 1953, biologist and geneticist Sydney Brenner asked then-director Demerec to work at the CSHL. Demerec approved, and in July 1954, after working in South Africa, Brenner arrived in the United States and spent his first two and a half months at the CSHL. During that time, Brenner took bacteriophage and bacterial genetics courses while researching the amino acid tryptophan. While at CSHL, Brenner networked with molecular geneticists like Delbrück, Luria, and behavioral geneticist Seymour Benzer. Brenner helped establish *C. elegans* as a model organism for research in developmental biology, because researchers could conveniently reproduce these organisms in large quantities for many generations. Additionally, Brenner helped to show that amino acid sequences in the genetic code must be read in order (non-overlapping), which led Crick to posit the existence of an RNA molecule, later called transfer RNA (tRNA), that links DNA and messenger RNA to amino acids. In 2002, Brenner received the Nobel Prize in Physiology or Medicine with Howard Robert Horvitz and John Sulston for their discoveries on genetic regulation.

By 1962, the Carnegie Institute of Washington no longer supported the Department of Genetics, so the Department of Genetics joined with the Biological Laboratory to create the Cold Spring Harbor Laboratory of Quantitative Biology. In 1970, the name was shortened to Cold Spring Harbor Laboratory because research projects were beginning to encompass more than just quantitative biology. Due to the lack of funding from the Carnegie Institute of Washington, CSHL struggled with funds, but director John Cairns handled the CSHL's finances. Cairns served as director from 1963 until he resigned to return to research at CSHL in 1968.

While a professor at Harvard, Watson became director of the CSHL in 1968. Watson focused on cancer research, hiring virologist Joe Sambrook in 1969 to establish the Tumor Virus Group at CSHL. The Tumor Virus Group defined and mapped major genes of viruses that commonly use humans as hosts (adenoviruses) and the major genes of a DNA virus that sometimes causes tumors (SV40).

In 1973, philanthropist and investment banker Charles S. Robertson endowed CSHL with eight million dollars in the form of the Robertson Research Fund, bringing monetary support to CSHL. Robertson also donated his Banbury Estate in Lloyd Harbor, part of Long Island, New York. In 1977 the estate became the Banbury Conference Center.

As a privately funded research institution, CSHL chooses its research projects relating to cancer, neuroscience, plant biology, quantitative biology, bioinformatics, and genomics. CSHL is one of about sixty institutions endorsed by the Cancer Centers Program of the National Cancer Institute in Rockville, Maryland. The Arnold and Mabel Beckman Laboratory, established in 1990, pursues neuroscience research. Plant biology research at CSHL focuses on developmental plant genetics that affect crop productivity, climate change, and biodiversity. Biological plant research expanded during the 1980s with the building of the Page Laboratory. The Simons Center for Quantitative Biology applies mathematics, engineering, computer science, and theoretical physics to CSHL's genomic analysis and image processing.

From maize to mice, scientists researched cancer at CSHL. The 1916 discovery of the susceptibility of Japanese waltzing mice (*Mus musculus molossinus*) to transplanted connective tissue cancers (sarcomas) by Clarence Little at CSHL led E. Carleton MacDowell to develop mice with heightened vulnerability or resistance to cancer. 1980s cancer research focused on genes that stimulate the cell cycle (oncogenes), yeast genetics, and the control of the cell cycle and growth. In 1987, the US National Cancer Institute (NCI), headquartered in Bethesda, Maryland, awarded the CSHL with a grant, which shifted its focus on DNA tumor viruses.

In 1988, one of the first CSHL fellows, Carol Greider, conducted research on telomeres, the end sequences of DNA that protects chromosomes during cell division. Greider received the 2009 Nobel Prize in Physiology or Medicine with Elizabeth Blackburn and Jack Szostak for showing how the enzyme telomerase works in conjunction with telomeres to protect chromosomes within a cell.

Educational programs expanded under Watson's term as director. The DNA Learning Center became an early organization dedicated to providing accessible information to the public about genetics. Bruce Stillman had worked at the CSHL in the 1970s and 1980s, researching DNA replication. CSHL instituted postgraduate courses, including the Yeast Genetics course, in addition to the DNA Learning Center in 1988. Watson became president of CSHL when Stillman became director in 1994. In 1998, CSHL became a PhD-awarding establishment with the launch of the Watson School of Biological Sciences. Stillman became president of CSHL in 2003 when Watson became chancellor. In 2007, Watson retired from his position. CSHL's largest expansion came in the form of the Hillside Laboratories, established in 2009. The Hillside Laboratories increased research space by forty percent, allowing two hundred research personnel to work throughout the six buildings.

Genomics research for the CSHL is based at the Woodbury Genome Center in Woodbury, New York, a few miles away from CSHL. In November 2013, CSHL began construction on a fifteen million dollar drug testing facility. Researchers there work on drugs to treat pancreatic, lung, liver, prostate, and breast cancer, along with leukemia and melanoma.

Aside from its research agenda, CSHL focuses on communication. Annual meetings are held at the Long Island location as well as the Cold Spring Harbor Asia Conference in Suzhou, China. The Banbury Center holds meetings for scientists and global specialists to discuss policy surrounding molecular genetics and biology, neuroscience, human genetics, and scientific innovations. The CSHL Press publishes papers and journals such as *Genome Research* and *Genes and Development*.

As of 2014, Bruce Stillman is the chief executive officer and president of the CSHL.

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