

A Nobel Incubator

How a single floor in a single building fostered extraordinary scientific talent

Richard Losick

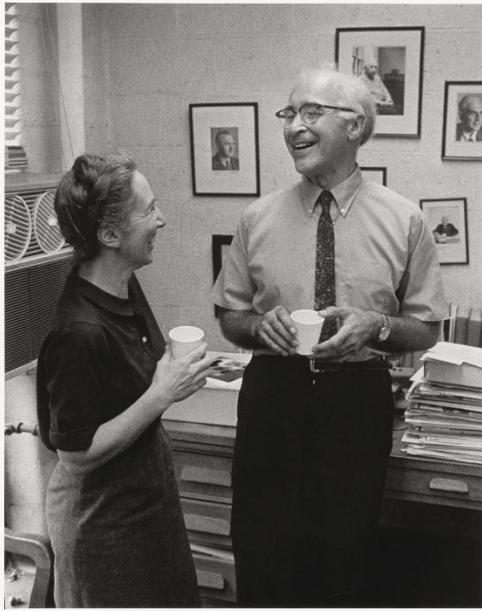
A striking phenomenon in the biomedical sciences is that great scientists sometimes arise in clusters at a particular time and place that fosters outstanding scientific achievement. Certain institutions, indeed certain places within institutions, succeed in creating a culture that attracts unusually creative young people and instills in them intensity and a thirst for solving big problems. Two well-known examples are the Medical Research Council Laboratory of Molecular Biology in Cambridge, England and the National Institutes of Health in Bethesda, Maryland. Not widely appreciated is the existence of a third such incubator here at Harvard College. This incubator was located on a single floor (the third) of the Biological Laboratories (the Bio Labs) on Divinity Avenue and was home to three Nobel Laureates and a training environment for six young investigators who would later win the Nobel Prize. Yet a tenth, future Laureate trained on the fourth floor.



A charismatic visionary

This remarkable story begins with George Wald who in the 1950s and 1960s elucidated the molecular basis for vision as a chemical switch in the visual pigment rhodopsin. Wald discovered that rhodopsin contains a light-absorbing molecule called retinal and that light causes retinal to undergo a simple structural change (from a “*cis*” to a “*trans*” configuration). This chemical switch, in turn, triggers a cascade of events, creating a signal that is relayed to the brain. Wald won the Nobel Prize in Physiology or Medicine in 1967 for his contributions to how photoreceptors work. Wald worked closely with Ruth Hubbard, who became his wife and who would later (1973) become the first woman to be promoted to the rank of tenured professor in Biology at Harvard.

*Entrance to the Biological Laboratories (1931)
(Harvard Library Photo Collections).*



Ruth and George Wald (Radcliffe Archives, circa 1967)

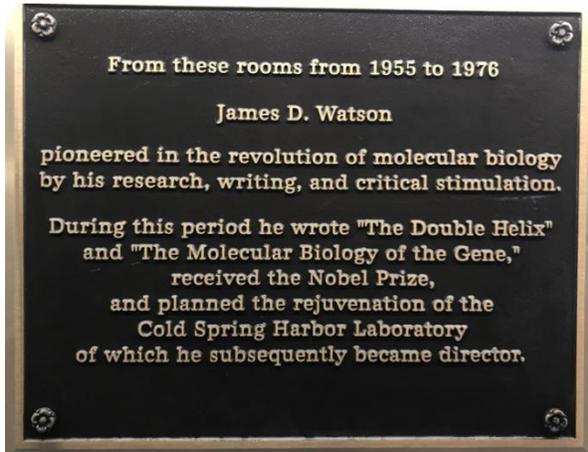
Wald was not only a brilliant scientist but also a charismatic and entertaining teacher. His introductory biology course, *The Nature of Living Things*, enthralled generations of undergraduates. One year when I was an undergraduate at Princeton my roommates and I made a pilgrimage to Cambridge with the twin goals of having a date with a “Cliffie” (Princeton was all male at the time) and attending Wald’s lecture on the *Origin of Death*. I still remember the lecture. Wald told the story of the Praying Mantis, a cannibalistic lover who eats her male partner after mating. Wald exclaimed that: “He who loves and runs away lives to love another day.” Little did I imagine that six years later this brilliant scientist and inspiring educator would be my neighbor on the third floor of the Bio Labs.

Upending science writing

Though our Nobel story begins with Wald, the catalyst for transforming the third floor into an incubator for the training of great young scientists was Jim Watson. Watson came to Harvard in 1955, having been recruited from Caltech by Chemistry professor Paul Doty. Watson had done his seminal work at the University of Cambridge in England where he had met Francis Crick and with whom he would share the Nobel Prize (1962) for the discovery of the structure of DNA, the genetic material. Their 1953 publication on the double-stranded nature of DNA and the pairing of bases between the strands was transformational. As Paul Doty said on the occasion of a birthday celebration for Jim, Watson (and Crick) will be one of the few names in science that will still be remembered 1,000 years from now.

Watson was an innovative writer as well as scientist. He wrote the textbook Molecular Biology of the Gene while in the Bio Labs in which he introduced the use of simple declarative statements (e.g. DNA is a double helix) as headings in place of the vague titles typically used in science writing (e.g. the structure of DNA). Molecular Biology of the Gene changed the writing of textbooks and journal articles. His shockingly frank (at the time, 1968) account of the discovery of the structure of DNA, The Double Helix (which famously begins with “I have never seen Francis Crick in a modest mood.”) elicited a protest from Crick. This led then Harvard President Nathan Pusey, with whom Watson had a testy relationship, to block its publication by the University Press. (Pusey once summoned Watson back to Harvard from the West Coast at a time when being out of town for more than a week during term required prior approval.) Watson also had a testy relationship with his then Biology Department

colleague E.O. Wilson, whose office was located just above Watson's in the Bio Labs and who Watson referred to as a stamp collector. At one point it appeared that Biology would promote Wilson before Watson but thanks to the intervention of then-Dean McGeorge Bundy both were promoted at the same time. Despite this history, they later became friends, after Wilson retired and Watson left Harvard for the Cold Spring



Harvard Laboratory in Long Island, New York (to which I will return). Once, after Watson had left Harvard, he appeared in my office out of the blue with his son and proceeded to escort me to the site of his former office where he queried me on the absence of commemorative plaques. As Chair of what was at the time Biochemistry and Molecular Biology, I commissioned Paul Doty to write the inscription on the plaque.

Plaque on the third floor of the Bio Labs.

But I digress. The heart of our story is the environment that Watson created that fostered an intense devotion to discovery. In a word, Watson successfully communicated to the community of students and young colleagues he created the importance of asking and pursuing big questions and choosing the simplest model systems in which to address these questions.

A physicist learns chemistry

This chapter begins with the poet Celia Gilbert who at the time was working as a technician in the Watson laboratory, leading her husband Wally Gilbert, a member of the Physics Department, to become interested in molecular biology. Wally Gilbert joined Watson on the third floor of the Bio Labs where they ran a single, integrated laboratory (which by 1967 had expanded to include a third professor Klaus Weber). Gilbert, who is now Chair of the Harvard Society of Fellows, made two great discoveries during this period. The first was the isolation of a protein (the lactose operon repressor) that regulates gene expression. This achievement was made in the late 1960s during a period of intense competition with Junior Fellow Mark Ptashne (who had been a graduate student with Matthew Meselson on the fourth floor). Ptashne isolated a protein that regulates the expression of genes of a bacterial virus (the lambda repressor). The work of Gilbert and Ptashne established that genes are (or can be) regulated by proteins and that these proteins work by binding to particular sites on DNA.

What was it that these regulatory proteins were recognizing in the DNA? This question led Gilbert to invent a chemical method to determine the sequence of bases (designated by the letters A, G, C, and T) in DNA. Gilbert, a theoretical physicist turned

molecular biologist, knew little chemistry. So how did he develop this chemical method? He picked the brain of his friend in Chemistry Jeremy Knowles, who would later become our beloved Dean of Arts & Sciences. Over lunches with Knowles in Harvard Square, Gilbert sought clues to possible chemical treatments that would break DNA molecules in a base-specific manner. Gilbert succeeded in establishing conditions that would do just this, making it possible to create a ladder of fragments for each of the four bases with each rung representing a particular base. Gilbert gave an inaugural lecture on his invention in the Bio Labs in which, armed only with a piece of chalk, he wrote out the entire sequence (several tens of As, Gs, Cs, and Ts in a seemingly random order) on the blackboard for the binding site for his repressor, and all without notes, duly impressing those in the audience! Gilbert's accomplishment (along with an alternative method developed in Cambridge, England by Fred Sanger) was recognized with a Nobel Prize in 1980 and ushered in the current era in which the sequence of bases in entire genomes of organisms from bacteria to humans can be determined with great rapidity.

Sink-or-swim

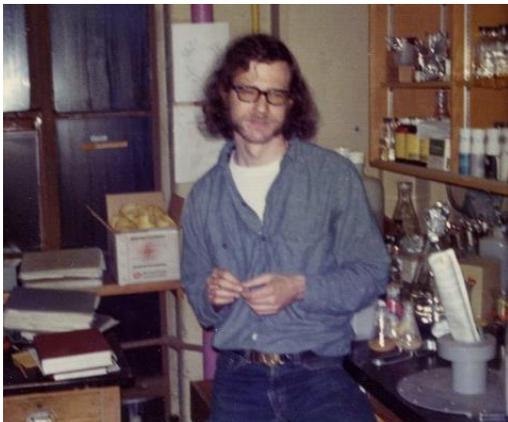
Also in the Watson-Gilbert lab was a young man by the name of Mario Capecchi, who received his Ph.D. with Watson in 1967. Capecchi's journey to a Nobel Prize is nothing less than extraordinary. Capecchi was born in Verona, Italy in 1937. His mother was a poet who joined a group known as the Bohemians who were outspoken against Fascism. When he was 3 ½, Capecchi's mother was arrested by German officers, resulting in his largely living on his own as a waif in the streets of northern Italy for almost five years and nearly starving to death before he was reunited with his mother. Mother and son moved to the United States to join relatives, and eventually Capecchi enrolled in Antioch College and worked for a semester at MIT where he learned about molecular biology. After Antioch, Capecchi interviewed with Watson who recruited him to Harvard. "Doing science in Jim's laboratory was exhilarating. Ninety-hour weeks were common.... They [Watson and Gilbert] were both very competitive. As students, we received the benefit of both, but also their scrutiny. They were merciless, but fair. You had to have a tough hide, but you learned rigor, both with respect to your science and your presentations. Once you made it through Jim's laboratory, the rest of the world seemed a piece of cake. It was excellent training. Despite the toughness, which at times was hard, Jim was extremely supportive. He also made sure that you, the student, received full credit for your work....if you did all of the work for a given paper, then you were the sole author on that paper. Among all of the laboratory heads in the world, I believe that Jim Watson was among very few in implementing this policy." While a graduate student, Capecchi made the important discovery of protein "factors" that are responsible for terminating the synthesis of individual proteins from their "messenger" RNA (RNA molecules that code for protein) after their synthesis is complete. Capecchi published multiple papers from the Watson-Gilbert lab and in no case did Watson include himself as an author. Capecchi received his Ph.D. in 1967 and then became a Junior Fellow of the Society of Fellows. Capecchi eventually became a professor at the



University of Utah where he maintained a low profile for almost 20 years before publishing his landmark discovery of a method for doing genetic engineering (creating “targeted” mutations) in mice for which he won a Nobel Prize in 2007.

Group photo with Mario Cappechi (MC), Jim Watson (JW) and Wally Gilbert (WG)(1962). Also in the photo Fred Goldberg, Alfred Tissieres and David Eisenberg (Cold Spring Harbor Laboratory Archives.)

Yet another future Laureate, Robert Horvitz, joined the Watson-Gilbert-Weber laboratory in 1969, receiving his Ph.D. with Gilbert in 1974. For his doctoral research Horvitz studied regulatory proteins that controlled the expression of genes in a bacterial virus called T4 by binding to the molecular machine (known as RNA polymerase) that copies the DNA into messenger RNAs. Horvitz published four papers based on his thesis research, all, as was the custom of the laboratory, without his mentor as a coauthor. Horvitz writes that “Life at Harvard was intense....Work started early in the morning and ended late at night. Students in the group were highly independent, relying more on other students and postdoctoral researchers than on faculty for input. “Sink-or-swim” seemed to be the prevailing attitude.We had three group meetings a week...These were serious times, as an audience of Jim Watson, Wally Gilbert, Klaus Weber and often Mark Ptashne ... left little uncritiqued. ...If you could survive a Harvard group meeting, you could survive anywhere.” From Harvard Horvitz moved to the Laboratory of Molecular Biology in Cambridge, England where he joined Sydney Brenner and John Sulston in studies of the nematode *C. elegans*, a centrally important



model organism for studies of development (of which we will have more to say). Horvitz then joined the Biology Department at MIT (where he had been an undergraduate). At MIT Horvitz continued his studies of *C. elegans*, discovering “death” genes that govern a phenomenon called programmed cell death (apoptosis). Horvitz shared the Nobel Prize with Brenner and Sulston in 2002. Horvitz is also a Graduate School of Arts & Sciences Centennial Medalist (2005).

Robert Horvitz on the third floor (circa 1970). (Kindly provided by R. Horvitz.)

A glowing achievement after failed research

By coincidence Horvitz had a high school friend and future Nobel Laureate named Marty Chalfie, who brings us to the next chapter of our story. Once when I was traveling with a group of scientists in India as part of a science mentoring program, Chalfie, a member of the group, told me to my surprise that as an undergraduate at Harvard he too had worked on the third floor of the Bio Labs, spending the summer after his junior year (1968) doing research with Klaus Weber. Unlike Capecchi and Horvitz, however, Chalfie's first shot at research was not a success: "It was so disheartening to completely fail that I decided I shouldn't be in biology." But he eventually changed his mind and did research with Brenner and Sulston at the Laboratory of Molecular Biology, overlapping for a few months with his high school friend Horvitz from whom he had learned about the worm research in Cambridge! From England Chalfie moved to Columbia University where he helped create a transformative tool for visualizing gene expression in living organisms (as first demonstrated with *C. elegans*) for which he won the Nobel Prize in 2008. This tool was a protein, the Green Fluorescent Protein, from a marine organism that naturally fluoresces green. Ironically, among the first scientists to identify the Green Fluorescent Protein was Woody Hastings, Professor and Master of North House, who worked on the fourth floor of the Bio Labs and with whom Chalfie had taken a course in his junior year. Chalfie has fond memories of Hastings from when he was an undergraduate.

A wandering spot leads to an amazing discovery

Not all of the future Nobel Laureates who trained on the third floor were members of the Watson-Gilbert-Weber laboratory. Next, we come to Rich Roberts, who joined the laboratory of Professor Jack Strominger as a postdoctoral fellow, moving to Harvard from the University of Sheffield in 1969. Roberts loved chess and squash; I too was drawn to squash but gave up any hope of being good at it after being trounced by Roberts. At Harvard, Roberts was faced with the challenge of determining the sequence of bases in a newly discovered and unusual RNA molecule involved in the formation of the wall that surrounds certain kinds of bacteria. Roberts heard that Sanger (with whom Gilbert would share the Nobel Prize for developing methods to sequence DNA) had improved on a method called the "wandering spot" to sequence RNA. So Roberts visited the Sanger lab to learn the wandering spot method and returned to Harvard where he determined the sequence of the unusual RNA. As a result of his visit to the Sanger lab, Roberts became the first scientist in the Boston area to be able to sequence RNA. Well, this caught the attention of Mark Ptashne and through Ptashne Jim Watson, who was just down the hall on the third floor. Watson was moving to the Cold Spring Harbor Laboratory to become director with the vision of using certain viruses as model systems to study gene expression in animal cells. Roberts's sequencing skills and accomplishments with Strominger made him an attractive candidate to join this effort, and Watson quickly made him an offer he couldn't refuse. At the Cold Spring Harbor Laboratory, adenovirus became the model system of choice and Roberts set out to map the start and stop points at which messenger RNAs are copied from the viral genome. This eventually led to a startling discovery; namely that

the coding sequence for proteins in the viral DNA (and as we now know in the genes of many higher organisms) is frequently interrupted by stretches (sometimes very long stretches) of non-coding sequence. Thus, when a gene is copied into RNA these interruptions (called introns) must be removed by a process known as splicing to create a contiguous protein-coding sequence in the messenger RNA. This discovery was so surprising that he and his co-workers felt justified in using the word “amazing” in the title of their seminal publication on this work, the only time to my knowledge that that word



has been used in a scientific research publication. Roberts shared the Nobel Prize for the discovery of introns with Phil Sharp at MIT in 1993. Ironically, another member of the third floor community, Watson’s graduate student Joan Steitz, would later identify the machinery that mediates splicing (and was recognized this year with a Lasker Award).

Rich Roberts (center) participating in the 2016 Ig Nobel Awards in Sanders Theater between Harvard Nobelists Eric Maskin and Dudley Herschbach.

Also in the Strominger laboratory, but only briefly, was Roger Kornberg. Kornberg had been an undergraduate at Harvard and had done his Ph.D. at Stanford (1972). After Stanford, he went to the Laboratory of Molecular Biology in Cambridge (as had Horvitz and Chalfie) to learn how to determine the atomic structure of proteins (by means of X-ray crystallography). Next, and following his stint in England, Kornberg came to Harvard as a Junior Fellow and was hosted in the Bio Labs by Jack Strominger who had known Kornberg’s father Arthur when both had been at the National Institutes of Health and Washington University School of Medicine. The elder Kornberg was one of the giants of molecular biology and biochemistry and was himself a Nobel Prize winner. Roger Kornberg only spent a year in Strominger’s lab, accepting an assistant professorship at the Harvard Medical School before moving permanently to Stanford. At Stanford the younger Kornberg used his X-ray crystallography skills to determine the structure of the molecular machine (RNA polymerase) that copies DNA into messenger RNA for which he, like his father before him, was awarded the Nobel Prize (in 2006).

It must be said that Strominger himself was and is a prime candidate for a Nobel Prize, indeed twice over. Once for his discovery of how the antibiotic penicillin works and then (with then Harvard colleagues Pam Bjorkman and Don Wiley) for isolating and determining the structure of a protein complex (the major histocompatibility complex)

that plays a central role in the ability of the immune system to recognize foreign proteins.

Elegant discoveries

The last chapter of our story unfolds in the late 1980s after Watson and Weber had left Harvard, Strominger had moved out of the Bio Labs (to the Sherman Fairchild Building), and Gilbert had become the CEO of the biotech company Biogen (only to return in 1985). This part of the story begins with Victor Ambros who came to the Bio Labs (yes, the third floor) as an assistant professor after having been a postdoctoral fellow at MIT with Horvitz. At Harvard Ambros made the surprising discovery that a regulatory gene in *C. elegans* called *lin-4*, which he had studied with Horvitz, did not encode a protein. Instead, the RNA product of the gene gives rise to a small “microRNA” that is itself a direct regulator of larval development. Yet another former inhabitant of the Bio Labs, Gary Ruvkun, discovered a second example of a microRNA in *C. elegans*. These proved to be discoveries of great significance as microRNAs are now known to be widespread regulators of gene expression in plants and animals.

This brings us to a young man named Craig Mello who started out as a graduate student at the University of Colorado. When Mello’s mentor left the University for a position in industry, Mello moved to Harvard with Dan Stinchcomb (then a postdoc in Colorado) who was returning to his alma mater as an assistant professor (having previously done senior thesis research on the third floor). Stinchcomb set up a joint *C. elegans* laboratory with Ambros, which at the time was located immediately adjacent to my own laboratory. Stinchcomb and Ambros both served as mentors to Mello. Mello was an excellent athlete and loved to play volley ball in the Bio Labs courtyard, hoping (but without success) to lead his lab mates to victory in the competition for the vaunted Rhino Cub!

Mello received his Ph.D. in 1990 for developing methods to introduce DNA into the worm, research that was unrelated to Ambros’s microRNA project. Yet not many years later after starting his own laboratory at the University of Massachusetts Medical School in 1994, Mello and his collaborator Andrew Fire made a discovery that proved to be intimately tied to the microRNAs that Ambros was studying. Mello and Fire discovered that double-stranded RNA molecules could be used to silence genes in the worm, a phenomenon they called RNA interference. RNA interference became an immensely useful tool in molecular biology and was the basis for a Nobel Prize to Mello and Fire in 2006. Additional research showed that microRNAs function to silence genes and do so by a mechanism that is closely related to that involved in RNA interference. In other words, Mello and Ambros had uncovered closely related phenomena. Arguably, Ambros merited recognition with a Nobel Prize as well!



Members of the laboratory of Victor Ambros (VA) with graduate student Craig Mello (CM) posing in front of the Bio Labs rhino. Also in the photo M. Ambros, S. Euling, R. Feinbaum, S. Kirsch, A. Lee, C. Lee, D. Levitan, Z. Liu, M. Mello, A. Rougvie, and A. Teffler. (circa 1988; kindly provided by C. Mello).

The fourth floor too

Mello brings our list to nine Nobel Laureates who worked or trained on the third floor. But I would be remiss if I did not mention Sid Altman, a postdoctoral researcher in the laboratory of Matt Meselson on the fourth floor of the Bio Labs (1967-1969). Altman, now a professor at Yale, is the co-discoverer (with Tom Cech) of ribozymes. Ribozymes are RNA molecules that act like enzymes to catalyze various chemical reactions. Prior to this discovery, it was believed that only proteins could be enzymes. The discovery of ribozymes provided fundamental new insights into the origin of life and the mechanism of protein synthesis.

The third and fourth floors of the Bio Labs were home to at least six additional individuals who arguably should have, won a Nobel Prize. These are, as mentioned, Victor Ambros (discovery of microRNAs), Mark Ptashne (isolation of the repressor), Joan Steitz (discovery of the machinery for RNA splicing), Jack Strominger (discovery of the mechanism of action of penicillin and isolation of the major histocompatibility complex), and Matt Meselson (for his proof with Frank Stahl that DNA replication is semi-conservative). The sixth is Robert Tjian (for his discovery of the first gene-specific transcription factor in mammalian cells). Tjian was a Junior Fellow at Harvard and then at the Cold Spring Harbor Laboratory, and later became president of the Howard Hughes Medical Institute.

What was it about the Bio Labs and the third floor in particular that attracted so many creative and dedicated scientists? Clearly, this high concentration of terrific scientists was more than just a coincidence. Probably there is no single answer but much of it surely has to do with the extraordinary environment at a particular time and place that fostered an intense devotion to discovery. This raises the question of whether future inhabitants of the Bio Labs can usher in another era of remarkable achievement but one that reflects the ways the culture and sociology of science has evolved over the intervening years.

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