NEWS

A Hothouse of Molecular Biology

Green thumbs at a British lab helped cultivate the achievements of the much-feted Watson and Crick and a slew of other luminaries. Can its success be duplicated, or even sustained?

Shortly after Sydney Brenner learned that he and two former labmates had won the 2002 Nobel Prize, he received this e-mail from a Chinese researcher: "I wish also to win a Nobel Prize. Please tell me how to do it." The answer, Brenner announced at the award ceremony last December, is simple. "First you must choose the right place … with generous sponsors to support you." In addition, he urged, "choose excellent colleagues." For Brenner and a dozen other Nobel laureates, the right place was Cambridge, U.K., and the right people were their peers at one of the world's first laboratories devoted to molecular biology.

What started about 55 years ago as a pilot program in biophysics at the University of Cambridge eventually became the Laboratory of Molecular Biology (LMB), now home to about 300 researchers and alma mater to hundreds of molecular biology's most influential. Among the dozen Nobelists the lab has spawned are James Watson and Francis Crick, who co-discovered the structure of DNA there 50 years ago. Watson has called LMB "the most productive center for biology in the history of science."

The lab's recipe for success dates back to its early days, when leaders such as Max Perutz had the luck and insight to pick the best and the brightest (among them some quite unorthodox choices) and secure them almost unlimited support, both financial and collegial. In the budding field of molecular biology, "his operation became known as the place to be," says John Sulston, who shared last year's Nobel Prize in physiology or medicine with Brenner and H. Robert Horvitz.

The lab welcomed researchers who wandered across disciplines and then encouraged them to interact closely. Even today, when interdisciplinary work has become de rigueur, LMB stands out for its cross-fertilization and community spirit. Lab groups there remain small and flexible, sharing equipment and often budgets. The fiefdoms that plague university departments are absent. "All these elements add up to a strong formula for doing good science," says LMB molecular biologist Matthew Freeman.

Although Watson and Crick are perhaps the most famous, the list of 750 or so alumni reads like a Fortune 500 of biology. Scientists there essentially created the field of structural biology. Over the past 5 decades, they invented key technologies such as DNA sequencing. And they have helped to elucidate some of the most fundamental questions in biology: how genes carry the instructions for proteins, for instance, and how a single cell develops into an animal.

Prized moment. Francis Crick, Maurice Wilkins, John Steinbeck (Nobel laureate in literature), James Watson, Max Perutz, and John Kendrew (left to right) all left Stockholm with Nobel Prizes in hand.

One great mind begat another, as the lineage of Nobel laureates makes clear (see graphic). Prize winner William Lawrence Bragg, director of the physics lab where LMB was conceived, brought in Max Perutz, who in turn recruited John Kendrew and Crick. Crick attracted Watson and Brenner. Brenner's protégés included Sulston and Horvitz.

When then-director Perutz moved the lab to its own building in 1962, Frederick Sanger and Aaron Klug came on board. Sanger brought in César Milstein and John Walker. Perutz, Kendrew, Crick, and Watson won their prizes in 1962. Sanger claimed one in 1958 and a second in 1980; Klug garnered the prize in 1982; Milstein and his student, Georges Köhler, in 1984; and Walker in 1997. The most recent winners are Brenner, Sulston, and Horvitz.

Can such stellar results continue? Big labs that churn out lots of data already threaten the lab's preeminence. And the lab's own exponential growth threatens to dilute the intense interactions that have characterized the place. But LMB's current director, structural biologist Richard Henderson, feels confident it will still provide fertile soil. As Perutz once wrote, "Well-run laboratories can foster [creativity in science]. But discoveries cannot be planned; they pop up, like Puck, in unexpected corners."

Roots in physics

LMB had it origins in the illustrious 19th century Cavendish Laboratory, part of the University of Cambridge. Cavendish scientists excelled in physics. J. J. Thomson discovered the electron there, and Ernest Rutherford smashed the atom.

In 1915, Bragg, working with his father at the Cavendish, became the youngest person to win a Nobel Prize. The father-son team's success set the stage for a new direction for the lab: biophysics. They had figured out how to use x-ray crystallography to probe the inner nature of crystals. In so doing, they created a window into the molecular structure of biological materials as well.

After World War II, Bragg was finally able to sneak biology through the lab's back door. Knowing that the Medical Research Council (MRC)—even then the United Kingdom's biggest research supporter—was keen on melding physics and biology, he convinced it to create the MRC Unit for Research on the Molecular Structure of Biological Systems in 1947. Its two members were Perutz, a chemist who wanted to try x-ray crystallography on proteins, and his student, physical chemist Kendrew. For the next 10 years, Perutz and Kendrew raced to identify the molecular makeup of two key blood proteins, myoglobin and hemoglobin. They devised better ways of doing x-ray crystallogra-

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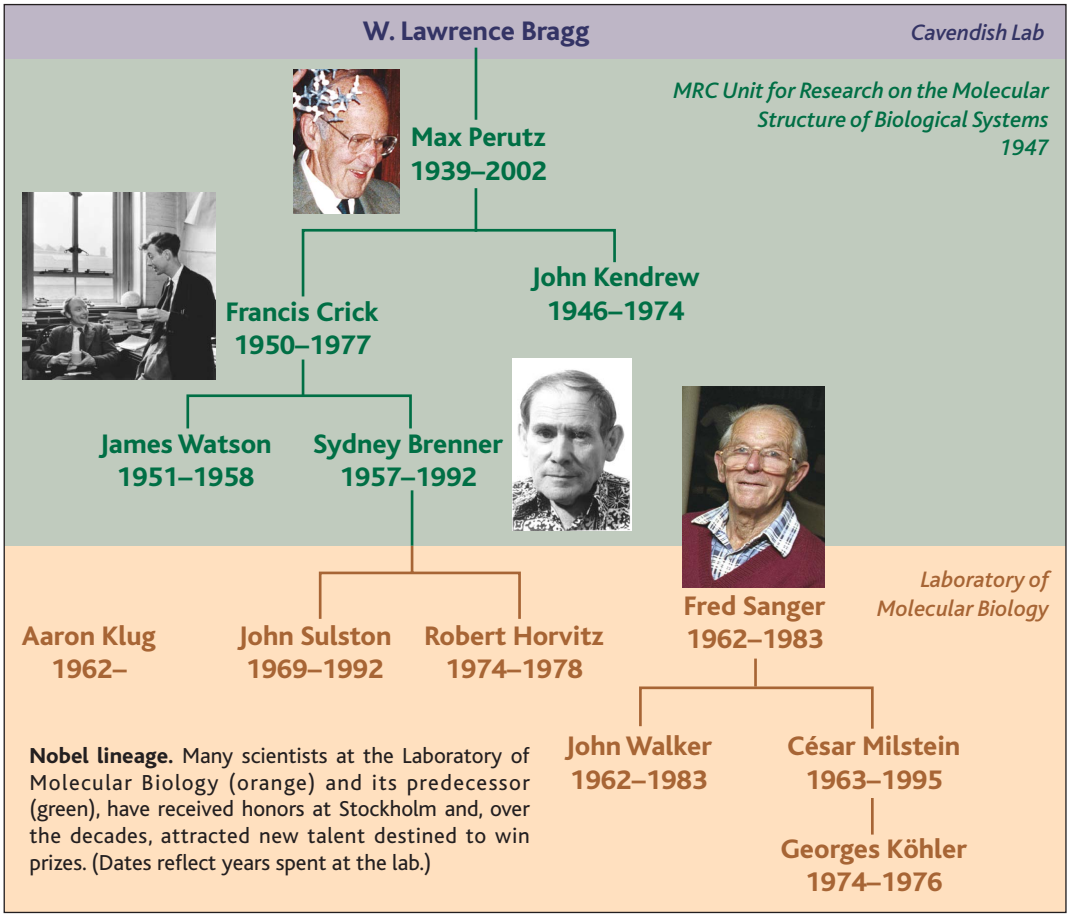

Nobel lineage. Many scientists at the Laboratory of Molecular Biology (orange) and its predecessor (green), have received honors at Stockholm and, over the decades, attracted new talent destined to win prizes. (Dates reflect years spent at the lab.)

phy and faster ways of analyzing the reams of data generated—harnessing the mathematics department's primitive electronic digital computer for their calculations.

Perutz recruited allies from diverse backgrounds: Crick was a physicist, Watson a zoologist, and Brenner a physician. Space was tight. Crick and Watson—and, later, Crick and Brenner—sat back to back in one office. "By 1956," Perutz wrote, "the Unit had grown so large, I spent my time scrounging for a little bench space in a butterfly museum here or the abandoned cyclotron room there." Together—closely—they began to turn biology on its ear.

Life's secret

Watson and Crick shared a common passion: to figure out what genes were made of. Crick, like many of his contemporaries, thought genes were proteins; Watson believed they consisted of DNA.

Soon after Watson arrived in Cambridge in 1951, the brash young American—he was 23 at the time—convinced Crick that DNA was the stuff of genes, and they became obsessed with determining DNA's structure. They assumed that the structure would reveal how genetic information was passed from one generation to the next. Their first attempts were a flop, however, and Perutz instructed the pair to leave DNA to Rosalind Franklin and Maurice Wilkins, who were using x-ray crystallography to study this molecule at King's College in London. Ostensibly working on other projects, Watson and Crick continued debating possible structures during almost daily lunches, walks, teas, dinners, and even outings on the Cam River.

Crowded spaces. When Max Perutz and his budding molecular biologists outgrew their space in the Cavendish lab (*right*), they moved into a hut behind this famous physics center (*above*).

Only after Linus Pauling of the California Institute of Technology in Pasadena, seen as the lab's fiercest rival, came up with an incorrect view of DNA did they get the go-ahead to continue their work. With the help of one of Franklin's prize x-ray diffraction images, they finally figured out how the components of DNA fit together.

On 28 February 1953, they began to build a paper-metal model demonstrating the pairing of the bases in this double helix. As the story goes, at lunch that day in the Eagle Pub, Crick couldn't contain his excitement, announcing, "We've found the secret of life."

But beyond the Eagle, their colleagues and the world didn't take much notice. At the time, "there was much more excitement about the Slinky wire-frame spring walking down the stairs," recalls Michael Fuller, then a lab assistant and now the lab's special projects coordinator. Unraveling the mathematics of how this new toy worked "seemed to excite [lab scientists] a lot more than the DNA model itself."

It took another decade for Crick and others to work out some of the basic principles underlying gene function, information that gradually helped confirm his boast. Watson left the lab for Harvard in 1958, where he sought out the secrets of a different nucleic acid, RNA. Brenner became Crick's closest collaborator, working with bacterial viruses, or phages, to verify Crick's ideas. Together they helped crack the triplet nature of the DNA code and track the path of information from gene to protein. Molecular biol-

CREDITS: (BOTTOM, LEFT TO RIGHT) MRC LABORATORY OF MOLECULAR BIOLOGY; COMPUTER LABORATORY, UNIVERSITY OF CAMBRIDGE

ogy was gathering steam, and Perutz's crew was stoking its engines.

A very good year

1962 was a vintage year for LMB. By then, Kendrew and Perutz had gotten their first real look at the structures of myoglobin and hemoglobin. Kendrew's student Hugh Huxley of University College London had begun his groundbreaking work demonstrating that sliding filaments powered muscle contraction. And Watson and Crick's model had inspired a slew of work on the gene-to-protein transition and the replication of DNA.

That was also the year that Perutz's crew left the Cavendish and set up their own shop: the official Laboratory of Molecular Biology. They moved into a new six-story building on the outskirts of town. Gone were the buttoned-up lab coats, required attire at the Cavendish. "Things became much freer, lighter," says Fuller. Per Perutz's order, there were no doors, no locked cabinets—no secrets among scientists.

Breaking through. John Kendrew stands over a model of the structure of myoglobin, the first protein structure to be solved and the beginning of a new era in protein science.

Sanger, whose work at the University of Cambridge on insulin had earned him a Nobel in 1958, helped open the doors on the new lab. Klug came, too, attracted to LMB's shiny new space and colleagues interested in the structure and function of proteins.

Champagne corks flew that fall when telegrams arrived telling not just Watson and Crick but also Perutz and Kendrew that they had won Nobel Prizes, the latter pair for chemistry. The reputation of the lab soared. By the late 1960s, American postdocs "were the engines that powered the lab," says John White, one of those postdocs, who is now at the University of Wisconsin, Madison. White calls the group "Jim Watson wannabees." They were a stark contrast to their British colleagues, who liked to solve problems at tea instead of at the lab bench. The synergy worked well.

One transatlantic transplant from the Salk Institute for Biological Studies in California was actually a Brit: Sulston. He was one of the first dozens of young scientists who would eventually come to work with Brenner on his fondly named "worm project." In 1974, Horvitz made the trip from Harvard for the same reason. What lured them was Brenner's goal of using the nematode to help figure out how genes affect development. "Most people thought it was rather a joke," Sulston recalls.

True to the lab's tradition, Sulston wasn't given much space, not even a desk. As far as Brenner was concerned, "desks encouraged time-wasting," says Sulston. Perched at a lab bench, Sulston began the painstaking task of watching the cells of the nematode embryo multiply under a microscope and then drawing what he saw. "When [Horvitz] came and found me looking through the microscope, he didn't think it was very scientific," Sulston recalls. Before long, "he started doing it with me."

Dynamic duo. César Milstein (left) and his student Georges Köhler developed a method for making monoclonal antibodies, now used all over the world.

Together, they tracked how individual cells divide and specialize to make the adult worm. They noticed that cells that had fulfilled their functions sometimes died, a phenomenon they dubbed programmed cell death. By working out the genetics of this process, Sulston and Horvitz opened up a new field in cell biology, earning the 2002 Nobel.

One floor away, Klug was chasing after the structure of viruses. The new imaging method he and his colleagues developed, which used electron micrographs to work out three-dimensional structures, earned Klug a Nobel in 1982. But he, too, was drawn to the unfinished business of RNA and DNA. Klug and his colleagues eventually worked out the structures of transfer RNA, which shuttles amino acids to where they can be added to the nascent protein. In addition, Klug determined the structure of RNAs that act as enzymes to cut up yet other RNA; he also helped show how DNA is packaged as a chromosome (see p. 282).

Multitalented. While working on virus structures (modeled in photo), Aaron Klug developed new crystallographic methods.

Quiet tenacity

Sanger and some of his protégés were as quiet and unassuming as Watson, Brenner, and Crick were outspoken. Sanger "was not known to be spouting ideas at a 100 miles per hour like Francis Crick or Sidney Brenner," says Alan Coulson, a nematode biologist who began his career as a technician for Sanger in the 1960s. Like Perutz and Kendrew before him, however, Sanger had tenacity. He spent day after day for years trying to devise a way to sequence DNA. Sanger eventually figured out a relatively efficient way to label the different bases and decipher their order, winning his second Nobel in 1980.

For several soon-to-be laureates, including Walker and Milstein, Sanger was just the "right" person. At first, to check the accuracy of the sequencing, Walker determined the amino acid sequence of those proteins encoded by the genes that Sanger was deciphering. They began with the DNA of bacterial viruses but later moved on to the mitochondria, where Walker found the enzyme that became the focus of his career, ATP synthase.

In keeping with the bare-bones bureauc-

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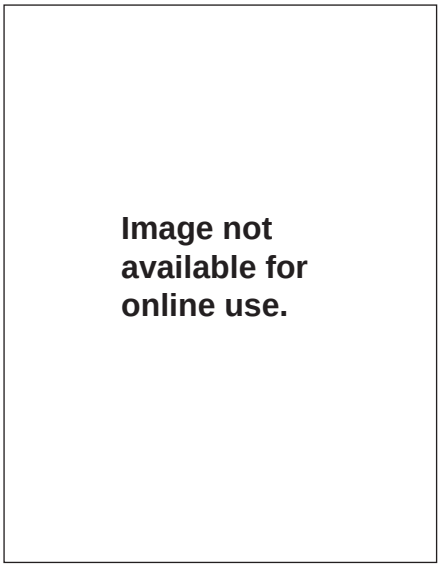
racy of the place, Walker never needed to write a proposal about this new research direction. At the time, MRC relied on the lab chiefs to decide how to spend the money it allotted to the lab; they, in turn, trusted their colleagues to come up with good projects. Thus, Sanger merely asked a few questions before saying, " 'Why don't you get on with it?' " Walker recalls.

At the outset, the project did not garner much support. "Quite a number said I was a fool and that I was going to wreck my career," says Walker. Instead, he shared the 1997 Nobel for determining the structure of ATP synthase. He then went on to figure out how this key membrane protein works.



Well covered. Nematode biology became so popular that LMB researchers were each assigned to study just a small part of the organism.

Milstein also sought out Sanger's leadership, collaborating with him while a Cambridge Ph.D. student. Later, when political unrest forced him to leave his native Argentina, he joined Sanger at LMB. Even more unassuming than his mentor, he didn't strike his colleagues as Nobel material. LMB researcher K. J. Patel likens Milstein to the seemingly bumbling—yet effective—TV detective Columbo. Sometimes Milstein could be seen out in a nearby field pacing, tape recorder in hand. He'd walk through the halls distracted and oblivious. "But he was really quite a deep thinker," says Klug.

When Milstein joined LMB, Sanger suggested that he focus on antibodies instead of enzymes. It turned out to be sage advice. With Köhler, Milstein eventually developed a way to make unlimited amounts of monoclonal antibodies, a uniform set of proteins that all home in on the same target, paving the way for a Nobel Prize in physiology or medicine in 1984.

CREDITS: (TOP TO BOTTOM) MRC LABORATORY OF MOLECULAR BIOLOGY; *RADICAL SCIENCE JOURNAL* **4**, 20 (1976); MRC LABORATORY OF MOLECULAR BIOLOGY

Right place, right people

A British newspaper once described LMB as a Nobel factory. But Klug takes issue with that characterization: "It's more like a plantation, where you plant the seed." The fertilizer came in many forms—money, equipment, collegiality, to name a few.

For about a decade following World War II, MRC's science budget grew about 17% annually. "Anything could be done. There were no limits," says Hugh Pelham, an LMB cell biologist. And to get those funds, all the researchers had to do was ask. After 30 years with MRC, Walker boasts, "To this day, I have only ever written one grant." The support has been consistent, although modest at times; there was no money for wood-paneled offices or elegant oak desks, for example.

New generation. Laboratory of Molecular Biology director Richard Henderson (center) hopes his young researchers will follow in their forerunners' footsteps.

Money flowed even without clear "results." Perutz, for instance, spent decades before his hemoglobin work panned out. Similarly, the worm researchers were far from prolific during the project's first 10 years. Even in today's "publish or perish" climate, that attitude still prevails: "It's not whether you have published a lot of papers, it's more whether you have done some fundamental work," says LMB bioinformaticist Sarah Teichmann.

When LMB researchers needed a new instrument, Perutz made sure technicians and engineers were there to build it, a model he learned at the Cavendish. "We were interested in topics that stretched the techniques," says Walker, explaining how the lab developed technologies such as x-ray crystallography, DNA sequencing, and confocal microscopes.

That left researchers free to concentrate on their work. "Your time was almost entirely devoted to research," says Thomas Pollard, a cell biologist at Yale University and LMB alum. Even senior scientists worked at the bench—a tradition that continues today and goes far to explain the lab's vitality, says Gerald Rubin of the Howard Hughes Medical Institute in Chevy Chase, Maryland, who did his graduate work at LMB. Perutz spent 90% of his working time at the bench until his death last year, focusing most recently on neurodegenerative disease. Klug still maintains a lab, although he's officially retired.

The tight space only intensified the camaraderie. Rubin recalls being assigned the lab bench between the pH meter and the balance—about a meter wide. Individual offices, even for the top scientists, were out of the question until more space was recently added. "I think [crowding] was a good thing," says Brenner. Similarly, the lack of alternative dining options—then and now—meant that everyone ate together, and conversations and critiques were free-flowing.

Ultimately, it was the people who made the place. "The LMB was able to concentrate in one place very exceptional scientists," says Pollard. Today, some of that talent would probably not make the first cut for a university position, given the apparent discrepancy between the scientist's experience and the job description. Sulston, for instance, was a chemist working on the origins of life when he came to study the worm. "Max [Perutz] had this uncanny ability to see something special, not necessarily

Creative energy. Milstein, Klug, Walker, and Sanger each pushed molecular biology in a new direction with their achievements.

academic ability, and to home in on that," says Fuller. "There's a history of people with no qualifications who are now senior."

Past as prologue

At the end of April, hundreds of former LMB researchers will converge on Cambridge to celebrate the 50th anniversary of Watson and Crick's DNA paper. They include numerous Nobel laureates whose prizewinning research came after their time at LMB, as well as prominent department heads, institute directors, and journal editors. There is no doubt in their minds that LMB is unique. "I don't think if you had put the same people in a U.S. institution that they would have done as well," says Rubin.

But can it continue to be so special? Thirty years ago, "the field was much smaller. It was *the* place for U.S. postdocs to go, and the best went," Rubin explains. "Now there are many good places." Although funds still flow relatively freely, paperwork, regulations, and other constraints have crept in, Henderson notes. And while he and his colleagues pride themselves on their small labs, which range in size from 1 to 10 people, they worry that they will fall behind. "There's so much more you can do with more manpower," says Pelham.

Biological incubator. Hundreds of budding molecular biologists got their start at the Laboratory of Molecular Biology, opened in 1962.

To keep pace with the burgeoning scientists and staff—about 400, more than twice the number 30 years ago—the building has doubled in size every decade since 1962. A new building is in the works. Says Klug, "I am worried that we will get too big and lose the ethos on which the lab has been built."

LMB now relies on a glossy annual report rather than word of mouth to publicize its accomplishments. Commercial considerations are also gaining prominence. For instance, 25 years ago MRC didn't bother to patent Milstein's technique for making monoclonal antibodies, now a fundamental tool in many industries. The same was true of Sanger's sequencing technology. Today, patenting is encouraged, says Henderson, and several companies, such as Celltech, are associated with the lab.

Klug and Henderson suspect that the place is good for at least a couple of more Nobels. Even today, with universities, medical foundations, and other organizations working to create hotbeds of scientific creativity, LMB still earns strong kudos. Says Yale's Joan Steitz: "There have been very good research institutions that have tried to capture the flavor and spirit, but they haven't got it."

–ELIZABETH PENNISI

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NEWS

DNA's Cast of Thousands

Watson and Crick's discovery revealed much, suggested more, but left many details unanswered. Ever since, researchers have been discovering the proteins that unlock DNA and the genetic code

When James Watson and Francis Crick elucidated the structure of DNA, they discovered an elegantly simple molecule. With cardboard cutouts, metal, and wire, they showed how DNA's two chains wound around each other, with the paired bases inside, one full rotation every 10 bases. Their model immediately suggested how DNA copied itself and enabled genetic information to flow from one generation to the next. They boasted that they had found the "secret of life"—essentially, biology's master molecule that controlled the fate of the cell and, consequently, of the organism.

Fifty years of research since then has shown that, despite its precision design, this molecule can't dance without a team of choreographers. Like a puppet, DNA comes alive only when numerous proteins pull its "strings." At the time of their discovery, Watson and Crick had only the haziest of ideas about how this double helix interacted with proteins. But rebuilt today, Watson and Crick's bare-bones model would be draped with proteins that kink and curl, repair, and otherwise animate DNA.

DNA ascendant

The age of DNA began well before Crick and Watson were born. In the 1860s, Friedrich Miescher, a Swiss working in Tübingen, Germany, isolated a strange, phosphorus-rich material from the cell nucleus. Within decades, it was clear that this peculiar substance—later identified as nucleic acids—was fundamental to the cell's chemistry. Somehow.

Throughout the early part of the 20th century, biochemists argued about DNA's role. Some postulated that it was the stuff of genes; others insisted that proteins carried

Naked DNA. Watson and Crick's first model of DNA didn't begin to reveal the complex set of proteins the molecule needs to do its job.

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