

History of Biology and the Cell

Development of Molecular Biology at the University of Wisconsin, Madison

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Dramatic changes in the foundation of academic departments in our universities are uncommon. With the demonstration that DNA was the cellular source of genetic information, and that this information could be regulated, the field of molecular biology was born. Later, when scientists found that they could tinker with this information, the field matured. In an unusually rapid manner, molecular biology was integrated into the University of Wisconsin, Madison, in the late 1950s and early 1960s. This present article is a chronology of how it happened. What are the factors that made this transition possible in the University of Wisconsin? What lessons have we learned from this experience?

Interdisciplinary biological science

Multidisciplinary programmes began to impinge upon traditional academic departments in research universities in the 1950s. Integrating these institutes into the academic community was not without its own problems. Academic departments are traditionally conservative and vigorously defend their territorial borders. Invariably concern arises over the creation of first- and second-class citizenship when faculty members are appointed without having all the normal academic responsibilities. In new multidisciplinary research centres, people who work in co-operative teams might be at a career disadvantage (Service, 1999). Their home department insists that members remember: ‘who evaluates you for tenure and the quality of your work?’ This division impairs not only the evolution of research interests of universities, but also the timely incorporation of new understandings of the science into the academic curriculum. What follows is a case study on incorporating multidisciplinary biological science into the uni-

versity structure, based upon the experience at the University of Wisconsin, Madison.

University of Wisconsin: building a public institution

By 1890 the University of Wisconsin already had four colleges and one school: Letters and Sciences, Mechanics and Engineering, Agriculture, Law and a School of Pharmacy. A Medical School was added in 1904. In the College of Agriculture, the Biochemistry Department was founded in 1883, the Department of Bacteriology in 1886, the Department of Plant Pathology in 1907 and the Department of Experimental Breeding (later Genetics) in 1909.

Multidisciplinary centres appeared early on the campus. The McArdle Laboratory for Cancer Research was established in 1940, and the Enzyme Institute in 1948. Also added in the post-war period were the Primate Centre and Institute for Molecular Virology. In 2007, there are 84 multidisciplinary research centres and programmes at the University, 20 of which are managed by the Graduate School.

Several factors encouraged research co-operation between departments. From the 1930s, the close co-operation between faculty in the Department of Bacteriology and Biochemistry established the University of Wisconsin as a national centre for fermentation

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Abbreviations used: MIT, Massachusetts Institute of Technology; MRC, Medical Research Council; NIH, National Institutes of Health; NSF, National Science Foundation; WARF, Wisconsin Alumni Research Foundation.

Joshua Lederberg

Courtesy of the National Library of Medicine.



technology and training. Early studies on determining the molecular mass of proteins occurred when the Chemistry Department and the Department of Biochemistry collaborated in using the first analytical ultracentrifuge in the U.S.A. The second factor was positioning of a land grant college in a state governed by the Progressive Political Party. The borders of the University are the borders of the state. Charles Van Hise, the President of the University of Wisconsin in 1904, declared that he would “never be content until the beneficent influence of the university [is] available to every home in the state.” Thirdly, a great deal of credit for developing science on the Madison campus is due to the WARF (Wisconsin Alumni Research Foundation). This was founded in 1925 to manage the University’s discovery that eventually eliminated the childhood disease rickets. The mission of WARF is to support scientific research at the university by patenting inventions arising from university research and transferring earnings back into the University to support research and graduate education.

The Josh Lederberg era

Josh Lederberg was appointed Assistant Professor in Genetics in 1947. He quickly expanded upon his initial studies on sexuality in *Escherichia coli* and set up a school for training bacterial geneticists. Lederberg soon displayed interests beyond genetics. Other faculty members in Madison interested in genetic subjects quickly joined him. The next year James Crow, a *Drosophila* population geneticist from

Dartmouth College, joined the Department. A few years later, Jim Crow, among others, was responsible for convincing Sewell Wright, the father of population genetics at the University of Chicago, to relocate to the University of Wisconsin upon his retirement.

The Swiss-born electron microscopist, Hans Ris, joined the Zoology Department in 1949. He had demonstrated that sperm and egg cells contain half of the DNA compared with somatic cells, reinforcing the notion that DNA was the genetic material 3–4 years before the Hershey–Chase experiment.

In the mid-1950s Waclaw Szybalski, a Polish microbial biochemist, joined the Oncology Department at Wisconsin. Szybalski, under the advice of Øjvind Winge, the Danish father of yeast genetics, emigrated in 1949 to the Biology Laboratory at Cold Spring Harbor on Long Island to join Milislav Demerec, where he developed an enduring interest in microbial genetics.

Lederberg was largely responsible for my being recruited in 1956 to the Department of Bacteriology while I was on sabbatical in the Laboratory of Jacques Monod at the Pasteur Institute in Paris.

In 1957 Lederberg was made Chairman of a new Department of Medical Genetics and started an active interest in human genetics. He brought a Genoese Italian population geneticist, Luigi Luca Cavalli-Sforza, to Madison who was interested in whether the genes of modern populations might contain an historical record.

In 1958 Lederberg received the Nobel Prize for studies on bacterial genetics. He left for Stanford University on April 1, 1959. In his resignation letter to President Elvehjem, he wrote “Genetics and biochemistry are rapidly converging on the fine structure and biosynthesis of nucleic acid, but there are very few individual workers or balanced research teams that can most effectively bridge the gap between the sciences” (Lederberg, 1958).

Meeting the challenge

When the news of Josh Lederberg’s resignation reached the campus, there was great concern, since his departure would leave a large void on the Wisconsin campus in an emerging area combining genetics with the chemistry of DNA. There seemed to be a consensus that this new area, being called molecular biology, was not confined to one department, but was shared with many departments.

President Elvehjem

Courtesy of University Wisconsin-Madison Archives.



On a late Friday afternoon, I called President Conrad Elvehjem's office and asked for an appointment. It was granted immediately. I proposed to the President that we replace Josh not with one person, but a group that could cover his interests. I further urged President Elvehjem that, with the newly emerging field of microbial genetics, there were many Departments at the University that had a new interest in molecular biology. Soon molecular biology would move beyond *E. coli* and also deal with eukaryotes. Since there were no empty buildings on the Madison campus, why not devote all new appointments in various biology departments in the next few years to this new field?

President Elvehjem was enthusiastic about the concept and formed a committee who met the next morning. As I recall, the committee included John Bowers, Dean of the Medical School, Jim Crow, Bob Burris, P.P. Cohen, Hans Ris, Hank Lardy and myself. The President authorized us to make 12 appointments. These candidates would be brought to campus under the aegis of the graduate school, and then decisions would be made as to which department they would join. The committee invited outside consultants to assist the University. Two of these consultants were Salvador Luria, recently relocated to MIT (Massachusetts Institute of Technology), and Sol Spiegel-

man from the recently modernized Department of Microbiology at the University of Illinois in Urbana. Luria suggested that molecular biology was likely to become the core of modern biology and the University should create a Center of Molecular Biology with the responsibility for promoting research and training in the area.

The University of Wisconsin was quick to respond. The next several years were occupied with recruiting this new community of scientists. Robert H. Burris, Chair of the Committee for Molecular Biology, oversaw this effort.

The recruitment program started in 1959 and continued actively over the next few years. The newly formed Department of Medical Genetics recruited Robert De Mars from the NIH (National Institutes of Health) and initiated interviews with Oliver Smithies (immunogenetics) in 1959, who joined the faculty the next year. Ernst Freese, a physicist turned geneticist from Harvard, was hired to fill Josh Lederberg's position in the Department of Genetics. Hank Lardy travelled to Vancouver, Canada, in 1960 to interest Ghobin Khorana, a nucleic acid chemist, in relocating to Madison. In 1960 Gobin Khorana joined the Enzyme Institute with an appointment in the Chemistry Department. That same year Howard Temin, an animal virologist from Renato Dulbecco's Laboratory at Caltech, joined the Oncology Department. Both Khorana and Temin went on to earn Nobel Prizes. By July 1960, Julius Adler joined the Departments of Biochemistry and Genetics. After receiving his PhD in Biochemistry at Wisconsin, he held postdoctoral positions with Arthur Kornberg at Washington University School of Medicine and Dale Kaiser at Stanford University. His use of *E. coli* to study responses to chemical stimulation attracted immediate attention.

Hans Ris, chair of a subcommittee (Hans Ris, Harlyn Halvorson, Ernst Freese and Walter Plaut) of the ad hoc Genetics Advisory Committee requested that the Graduate Division establish an interdisciplinary course of studies leading to the PhD in Molecular Biology (Ris, 1960). A committee of interested professors from various departments would handle certification and examinations. Among the first class of graduate students in the Molecular Biology programme were Marjorie Tingle, Bill Salivar and Jordon Konisky.

William Sarles, Chair of Bacteriology, in responding to Dean Bowers replied "Since July 1, 1959, we

have been in an awkward position because we do not have a 'position' in our budget for a microbial geneticist We are now preparing an application for a training grant program which we hope will provide the funds necessary to establish a position" (Sarles, 1960). David Pratt, trained in bacterial virology, was ultimately recruited to fill that position.

Millard Susman, who received his training in bacteriophage T4 microbial genetics, joined the Department of Genetics in 1962. Charles Kurland, after postdoctoral work at the Microbiology Institute of the University of Copenhagen, joined the Department of Zoology and Genetics, where he carried out a seminal study of the *E. coli* ribosome.

Harrison ("Hatch") Echols, another physicist turned biologist, was also added to the Biochemistry Department. After receiving his PhD in physics from the University of Wisconsin, he studied the genetic control of repression of alkaline phosphatase in *E. coli* at MIT in the laboratory of Cy Levinthal. In Madison he studied the 'glucose effect' in inducer transport in *E. coli*. Soon, he turned his attention to a study of the bacteriophage λ , for which he developed an international reputation. The Japanese-born Masayasu Nomura, after his post doctorate in Sol Spiegelman's laboratory studying bacteriophage mRNA in *E. coli*, joined the Genetics Department in 1963 and started his studies on the isolation and reconstruction of ribosomal proteins.

In the next 5 years additional faculty members in molecular biology were added to the campus. The Department of Bacteriology recruited William McClain, who was interested in tRNA precursors. The Biochemistry Department recruited Julian Davies studying ribosomal function and mechanisms of resistance to antibiotics in bacterial pathogens, Robert D. Wells interested in DNA structure, James Dahlberg interested in viral biochemistry and William Reznikoff interested in the regulatory elements in the lac operon. Fredrick Blattner joined the Department of Genetics. His interest in bacteriophage λ led to its sequencing and ultimately the sequence of the entire genome of *E. coli*. The Department of Physiological Chemistry recruited James Dahlberg a viral biochemist. The Oncology Department added William Dove who worked on integrated λ prophage.

Already by 1965, the University of Wisconsin had a youthful and vibrant community of scientists utilizing molecular biology in a variety of diverse organ-

isms. Conrad Elvehjem did not have the opportunity to see the final success of his efforts. He prematurely died on 27 July 1962.

The tea room

In considering the nature of a common meeting place for members of the fledgling molecular biology program at the University of Wisconsin, I was influenced by two approaches that were continents apart. The first was the Salk Institute for Biological Studies, north of San Diego, where the experimental laboratory designed by Earl Wall to encourage scientific exchange by designing flexible space while maintaining eye contact fascinated me.

The second influence came from the MRC (Medical Research Council) Laboratory outside Cambridge, U.K., and the Pasteur Institute in Paris. The MRC was a small institution that had a prominent 'tea room' where every afternoon the staff would assemble for tea and to share their research interests with the Crick–Brenner team. Since the staff came from different scientific disciplines, these afternoon teas played a critical role in cross-disciplinary exchange of ideas. The second site was the working library of the Microbial Physiology Unit of the Pasteur Institute. At lunch the staff would assemble with Jacques Monod, Andre Lwoff and Francois Jacob to discuss their research and topical issues in biology. As this laboratory was a focal point for American scientists and visiting scientists, it became an intellectual meeting ground for the new biology.

By 1961, it became clear that to sustain the molecular biology thrust at the University of Wisconsin, we needed a campus focus point for the programme. Bob Bock and I began to search for possible options.

With the encouragement of Robert H. Burris, Chairman of the Committee for Molecular Biology, the committee itself, and the Dean of the School of Agriculture, land was provided on a parking lot next to the Biochemistry Building for two low buildings, one for Molecular Biology and another for Biophysics. Based upon the laboratory concepts being proposed by Earl Wall, to use wide-open contiguous space for laboratories, Bob Bock and I laid out plans for a small, low building with maximal floor space on each floor to encourage scientific interactions. On 1 September 1961, we submitted a request to NSF (National Science Foundation) for \$1 957 500 to build the Laboratory for Molecular Biology with H.O. Halvorson

Robert Bock

Courtesy of John White, Laboratory of Molecular Biology, University of Wisconsin.



and R. M. Bock as principle investigators. Bill Beeman and Paul Kaesberg pursued a parallel request to NIH to fund an adjacent Biophysics Building.

The NSF site visit team for our building request were sharply divided. Half of the team thought that the concept of such an interdisciplinary laboratory was a great idea, and the other half thought it was very dangerous and threatened the existence of the present departments and should be killed immediately. After reviews by the NIH, NSF and the University of Wisconsin, it was decided to build one tall building, occupying a smaller area, to house both the Laboratories of Molecular Biology and Biophysics. Half the cost of construction would be covered by a grant from WARF.

On 9 March 1965, the bids for the Laboratories of Molecular Biology and Biophysics were opened and the total exceeded available funds for construction. This occurred shortly after two Engineering Departments of the State administration were publicly criticized for exceeding budgets on state construction. The decision was to hold the line on the cost of the Laboratories of Molecular Biology and Biophysics. Bob and I were told that we had 24 h to work with the architects to bring the cost of the building under the sum available. Of particular contention was

Laboratory of Molecular Biology and Biophysics Lab

Courtesy of John White, Laboratory of Molecular Biology, University of Wisconsin.



the top floor of the building, which contained the 'tea room' for lunches, conferences, etc. This room had an excellent view of Lake Mendota and the campus, and would be our focal point for informal scientific exchange. Bob and I met with the architects and were able to make a few modifications to reduce the cost. However, it turned out that redesigning the building to remove the top floor would actually increase the cost of the building. The next day, Bob and I went to the Governor's office to argue that retaining the 'tea room' actually cost negative dollars. The Governor agreed and after deducting bid alternatives and negotiating further reductions, the budget cost was reduced to \$2 382 341. Construction was initiated in June 1965, and the facility was occupied in November 1966.

Strengthening the base

Upon returning to Madison, from a sabbatical in France, I was offered the Chairmanship of the newly constructed Laboratory of Molecular Biology, which I was pleased to accept in 1966.

With the Governor's approval in June 1965, recruitment for five molecular biologists began. The first one to be recruited was Robert Rownd. Bob had received a PhD in Biophysics in 1964 from Harvard University. His graduate work in the laboratory of Paul Doty included early studies on the physico-chemical properties of DNA, and the demonstration of the DNA nature of bacterial antibiotic resistance plasmids. Following postdoctoral training with Sydney Brenner in Cambridge, U.K., he accepted a postdoctoral fellowship with Jacques Monod at the Pasteur Institute in Paris, before moving to Madison in 1966.

Gary Craven was the next scientist to join the Laboratory and the genetics department that same year. His studies on the chemical, physical and immunological properties of β -galactosidase in *E. coli* in Christian Anfinsen's laboratory of Chemical Biology at NIH demonstrated that the operator locus does not specify any part of the β -galactosidase molecule. On relocating to Madison, Gary directed his interests to the structure and function of ribosomes and the mechanism of complementation in *E. coli*.

In 1969 Bob Bock was appointed Dean of Graduate School, replacing Robert Alberty who had departed for MIT. Bock was still able to maintain a laboratory on the fourth floor of the Laboratory. That year Kenneth Munkries was recruited with a joint appointment in the Genetics Department. His research area in molecular genetics focused on the structure, assembly and function of enzymes and membranes in *Neurospora*.

In the next year and a half, the remaining two laboratories in the laboratory were occupied. The next appointment was Deric Bownds who earned his PhD degree on the site of attachment of retinal in rhodopsin from the laboratory of George Wald at Harvard in 1967. He then spent a postdoctoral period in the Department of Neurobiology, Harvard Medical School, in the laboratory of Ed Kravitz studying the analysis of enzymes and substrates of GABA (γ -aminobutyric acid) metabolism in single axons, before joining the Laboratory of Molecular Biology and the Department of Zoology.

The final appointment was Gary Borisy. He was trained originally under Ed Taylor at the University of Chicago. After 3 years' postdoctoral study at the MRC Laboratory of Molecular Biology in Cambridge, U.K., he joined the faculty of the University of Wis-

consin in 1969, with an appointment in the Zoology Department. His key contributions included the discovery of tubulin, elucidating microtubule dynamics, introducing novel techniques to analyse cytoskeletal function in living cells, dissecting the mechanism of chromosome movement and understanding the supramolecular basis of the actin machinery in cell motility.

Robert Rownd and Gary Craven organized a graduate course in molecular biology in 1967. In 1969 Rownd assumed the leadership of the campus-training grant in molecular biology.

I was able to report to Dr Estelia K. Engel that "As of July 1, 1969 the staffing of the Laboratory of Molecular Biology has been completed. . . . We feel that the initial intent of a diversified staff representing various disciplines from the physically oriented aspects of molecular biology to the more biological problems has been achieved" (Halvorson, 1969).

The Molecular Biology and Molecular Virology Laboratory on Linden Drive was renamed in 1991 in honour of Robert M. Bock, longest-serving Graduate School Dean of the University of Wisconsin at 22 years.

In February of 1971 President Schottland of Brandeis University provided me with the opportunity to build a Basic Sciences Research Centre, funded by a gift from the industrialist Louis Rosenstiel. It was an exciting challenge and on 1 June 1971, with several trucks loaded with our furniture and equipment, and those of my laboratory group, we all departed for Massachusetts.

The longest mile in the world

Bascom Hill, the site of the Administration Building of the University of Wisconsin, is 1 mile from another hill where the State Capital resides. President Edwin B. Fred (President of the University of Wisconsin, 1945–1958) on his annual trips to secure the University budget described this distance as "The longest mile in the world." Fortunately, this trip is reversible. Jones et al. (1996) pointed out that Wisconsin was the first state to develop a joint legislative research office. In 1901 under the leadership of Progressive Governor Robert LaFollette, Wisconsin established the Legislative Research Bureau drawing in part on the expertise of the University to provide legislators with needed science and technology policy

Table 1 | Transitional Molecular Biology Faculty at the University of Wisconsin

AAAS, American Academy of Arts and Sciences; APS, American Philosophical Society; ASBMB, American Society for Biochemistry and Molecular Biology; IOM, Institutes of Medicine; NAS, National Academy of Science; NIADID, National Institute of Allergy and Infectious Diseases; PAS, Polish Academy of Sciences; RAS, Royal Academy of Sciences; RS, (Fellow of the) Royal Society.

Name	Relocation	Department/position	Recognition
Julian Davies	Biogen (Geneva)	President	President of ASM
	Institut Pasteur		RS (London and Canada)
	University of British Columbia	Microbiology and Immunology	
	Cubist Pharmaceuticals	President	
Harrison ('Hatch') Echols	University of California, Berkeley	Biochemistry and Molecular Biology	NAS
Ernst Freese	NIH	Molecular Biology NIADID	Chief of Laboratory
Harlyn Halvorson	Brandeis University	Director, Rosensteil Center	President of ASM, IOM and AAAS
	Marine Biological Laboratory		President, Director
Gobind Khorana	MIT	Biology and Chemistry	Nobel Prize, NAS, AAAS, APS and RS
Charles Kurland	Uppsala University	Molecular Biology	RAS, Chair of EMBO Committee for Science and Society
Josuha Lederberg	Stanford University	Genetics	Nobel Prize, NAS, IOM, APS and RS
	Rockefeller University	President	
Masayasu Nomura	University of California, Irvine	Biological Chemistry	NAS, AAAS
Robert Rownd	Northwestern University	Molecular Biology	Editor for Journal of Bacteriology
	Wayne State	Center for Molecular Medicine and Genetics	Director
Oliver Smithies	University of North Carolina, Chapel Hill	Pathology	AAAS, NAS and RS
Robert Wells	University of Alabama, Birmingham	Biochemistry	President of ASBMB and FASEB, member of PAS
	Texas A&M	Biochemistry and Biophysics Biosciences and Technology	

support. The Wisconsin commitment of the land-grant university to solve public sector problems provided, I believe, the foundation for its success a half century later in introducing interdisciplinary science into the university.

A number of other factors contributed to the University of Wisconsin success story.

- The University has a long history of collaboration of scientists on campus on research projects. The isolation of Madison from other research centres may have initially contributed to this collaboration.
- Wisconsin had the College of Agriculture, College of Arts and Sciences, College of Engineering and a

Medical School on the same campus. The mutual reinforcement was a great advantage.

- The genius of Harry Steenbock that 'science should support science' led in 1925 to the formation of WARF. His vision was for technology transfer combined with financial spin-offs for faculty across the Madison campus. Faculty and staff at the university own all inventions and intellectual property developed without federal funding. The annual WARF gift has been used to support research start-up commitments, enhancing career development, graduate training and funding new programmes. The Dean of the Graduate School administers this programme and serves as the de facto 'vice chancellor for research'. The distribution of WARF funds

throughout the graduate school meant that faculty members had a second chance for research funds, one that was separate from departmental lines. WARF has provided seed money for investment in quality people and programmes, providing the University of Wisconsin with a great competitive advantage.

- The Wisconsin Academic Farm System. The University has had a long-term strategy of recruiting scientists in their early creative years, supporting them with resources and students, and rapidly promoting them. Not infrequently these 'transitional faculty' move on to other prestigious universities and research institutions. Table 1 traces this population from the University of Wisconsin that was recruited during the development of the molecular biology programme.
- From the mid 1940s to the early 1960s, when the molecular biology programme was initiated and developed, the University of Wisconsin was fortunate to have decisive and bold scientific leadership at the level of the President, Deans and scientific department chairs. Departments were willing to stay outside the box of their narrow disciplines to get good people. As William Reznikoff (2007) noted: "I don't think that Gary Craven or Fred Blattner considered themselves true geneticists when they joined the Genetics Department. Likewise, I considered myself more of a geneticist than a biochemist."

Lessons learned

I believe that there are several take-home lessons to be learned from the Wisconsin experience. Although some of these may be site-specific, others provide guidance for developing new programmes on other campuses.

- Since evolution is conservative and all biological mechanisms are dependent upon common mechanisms, academic biological departments share common roots and interests.
- Changing the culture of academic departments requires an extensive integrated effort.
- Teaching and research are both faculty responsibilities. Care should be taken to avoid first- and second-class academic citizenships.
- Scientists trained in a discipline and co-operating with others conduct interdisciplinary science best.

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