

## **Development of Molecular Biology at the University of Wisconsin, Madison**

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### **Abstract**

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 in the late 1950's and early 1960's. This article is a chronology of how it happened. What are the factors that made this transition possible in Madison? What lessons have we learned from this experience?

*Keywords:* Molecular biology University Wisconsin Joshua Lederberg Laboratory of Molecular Biology and Biophysics

### **1. Interdisciplinary Biological Science**

Multidisciplinary programs began to impinge upon traditional academic departments in research Universities in the 1950's. 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 centers, people who work in cooperative teams might be at a career disadvantage (Service, 1999). Their home department insists on them to 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 university structure, based upon the experience at the University of Wisconsin.

### **2. University of Wisconsin: Building a Public Institution**

By 1890 the University of Wisconsin already had 4 colleges, 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 centers 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 Center and Institute for Molecular Virology. In 2007, there are 84 multidisciplinary Research Centers and Programs at the University, 20 of which are managed by the Graduate School.

Several factors encouraged research cooperation between departments. From the 1930's the close cooperation between faculty in the Department of Bacteriology and Biochemistry established the University of Wisconsin as a national center for fermentation technology and training. Early studies on determining the molecular weight of proteins occurred when the Chemistry Department and the Department of Biochemistry collaborated in using the first analytical ultracentrifuge in the U.S. 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. UW President Charles Van Hise 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 Wisconsin Alumni Research Foundation (WARF). This was founded in 1925 to manage the University's discovery that eventually eliminated the childhood disease rickets. The mission for WARF is to support scientific research at the university by patenting inventions arising from university research and transferring earnings back to the University to support research and graduate education.

### 3. Josh Lederberg era

Figure 1

Josh Lederberg was appointed Asst Professor in Genetics in 1947. He quickly expanded upon his initial studies on sexuality in *E. 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, as do somatic cells, reinforcing the notion that DNA was the genetic material, 3-4 years before the Hershey-Chase experiment

In the mid 1950's 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 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 (Lederberg, 1958), 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".

### 4. 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

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 eucaryotes. 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?

Figure 2

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 and Sol Spiegelman 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 charged 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 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 traveled 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 Ph.D. 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 program were Marjorie Tingle, Bill Salivar and Jordon Konisky.

William Sarles, Chair of Bacteriology, in responding to Dean Bowers (Sarles, 1960), 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." 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.

Added to the Biochemistry Department was Harrison ("Hatch") Echols, another physicist turned biologist. 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  $\lambda$ , for which he developed an international reputation. The Japanese-born Masayasu Nomura, after his post doctorate in Sol Spiegelman's laboratory studying bacteriophage messenger RNA in *E. coli*, joined the Genetics Department in 1963 and started his studies on the isolation and reconstruction of ribosomal proteins.

In the next five years additional faculty members in molecular biology were added to the campus. The Department of Bacteriology recruited William MacClain 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 the regulatory elements in the lac operon. Fredrick Blattner joined the Department of Genetics. His interest in  $\lambda$  bacteriophage 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 lambda prophage.

Already by 1965 the University of Wisconsin had a youthful and vibrant community of scientists utilizing molecular biology in a variety of diverse organisms. Conrad Elvehjem did not have the opportunity to see the final success of his efforts. He prematurely died on July 27, 1962.

## **5. The Tea Room**

In considering the nature of a common meeting place for members of the fledgling molecular biology program at UW, I was influenced by two approaches 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 Medical Research Council (MRC) Laboratory outside Cambridge, England 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 program. Bob Bock and I began to search for possible options.

### Figure 3

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 September 1, 1961 we submitted a request to NSF for \$1,957,500 to build Laboratory for Molecular Biology with H.O. Halvorson and R. M. Bock as PI's. 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 thought that the concept of such an interdisciplinary laboratory was a great idea and half thought it was very dangerous and threatened the existence of the present departments and should be killed immediately. After reviews by NIH, NSF and UW, it was decided to build one tall building, occupying a smaller foot-plan, to house both the Laboratories of Molecular Biology and Biophysics. Half the cost of construction would be covered by a grant from WARF.

On March 9, 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 hours to work with the architects to bring the cost of the building under the sum available. Of particular contention was 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.

### Figure 4

## 6. 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 received a Ph.D. in Biophysics in 1964, from Harvard University. His graduate work in the laboratory of Paul Doty included early studies on the physical-chemical properties of DNA, and the demonstration of the DNA nature of bacterial antibiotic resistance plasmids. Following postdoctoral training with Sydney Brenner in Cambridge, England, 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  $\beta$ -galactosidase in *E. coli* in Christian Anfinsen's lab of Chemical Biology at NIH, demonstrated that the operator locus does not specify any part of the  $\beta$ -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 Albery who had departed for MIT. Bock was still able to maintain a lab 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 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 Univ. of Chicago. After 3 years' postdoctoral study at the Laboratory of Molecular Biology in Cambridge, England, he joined the faculty of the University of Wisconsin in 1969. with an appointment in the Zoology Department. His key contributions included the discovery of tubulin, elucidating microtubule dynamics, introducing novel techniques to analyze 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 (Halvorson, 1969) 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."

The Molecular Biology and Molecular Virology Laboratory on Linden Drive was renamed in 1991 for Robert M. Bock, UW-Madison's longest-serving graduate school dean at 22 years.

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

## **7. The Longest Mile in the World**

Bascom Hill, the site of the Administration Building of the University of Wisconsin, is one mile from another hill where the State Capital resides. President Fred on his annual trips to secure the University budget described this distance as "The longest mile in the world." Fortunately this trip is reversible. Megan Jones *et al* 1996 points 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 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 centers 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 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 programs. The Dean of the Graduate School administers this program and serves as the de facto “vice chancellor for research.” Having WARF funds distributed through 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 programs providing the University of Wisconsin 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 recruited during the development of the molecular biology program.
  - From the mid 1940’s to the early 1960’s, when the molecular biology program 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 noted (2007): “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.”

## 8. Lessons Learned

I believe that there are several take-home lessons to be learned from the Wisconsin experience. While some of these may be site-specific, others provide guidance for developing new programs 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 cooperating with others, best conduct interdisciplinary science.

## 9. Acknowledgements

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

<b>Name</b>	<b>Relocation</b>	<b>Department</b>	<b>Recognition</b>
Julian Davies	Biogen (Geneva) Institute Pasteur Univ. BC Cubist Pharmaceuticals	President  Microbiol & Immunol President	Pres. ASM, RS (London and Canada)
Harrison {Hatch} Echols	Univ. California Berkeley	Biochemistry and Molecular Biology	NAS
Ernst Freese	NIH	Molecular Biol. NIADS	Chief of Laboratory
Harlyn Halvorson	Brandeis University Marine Biological Laboratory	Director Rosensteil Center President, Director	Pres. ASM, IOM, AAAS
Gobind Khorana	MIT	Biology and Chemistry	Nobel Prize, NAS, AAAS, APS, RS
Charles Kurland	Uppsala University	Molecular Biology	RAS, Chair EMBO committee Science and Society
Josuha Lederberg	Stanford University Rockefeller University	Genetics President	Nobel Prize, NAS, IOM, APS, RS
Masayasu Nomura	Univ. Cal. Irvine	Biological Chemistry	NAS, AAAS
Robert Rownd	Northwestern University Wayne State	Molecular Biology Ctr. Molecular Medicine and Genetics	Editor J. Bacteriology Director
Oliver Smithies	Univ. N. Carolina, Chapel Hill	Pathology	AAAS, NAS, RS
Robert Wells	U. Alabama Birmingham Texas A&M	Biochemistry  Biochem. Biophysics Biosciences & Technology	Pres, AMSBMB, Pres. FASEB, PAS

**Abbreviations:**

AAAS	American Academy of Arts and Sciences
APS	American Philosophical Society
IOM	Institutes of Medicine
NAS	National Academy of Science
RAS	Royal Academy of sciences
RS	Royal SocietyPAS                      Polish Academy of Sciences



**Figures**

**1. Josua Lederberg**

**National Academy Medicine Library Archives**



**2. President Elvehjem**

**Univerity Wisconsin Archives**



**3. Robert Bock**

**Lab. Molecular Biology Files**



**4. Laboratory of Molecular Biology and Biophysics**

**Lab. Molecular Biology Files**

