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The use of chemistry and other molecular tools to provide an understanding of biological processes has been the driving force for this department for over 100 years. Following this goal has resulted in many research advances including the discovery of the vitamins, the identification of many of these vitamins, the provision of anticoagulants, the synthesis of the first gene, and the elimination of many diseases such as rickets, blindness, goiter, infectious diseases, pellagra, anemia, and metabolic bone disorders. Most of the discoveries were made at the hands of students in the course of their graduate training in the Biochemistry Program. This program has been developed over the past 110 years to train outstanding scientists and teachers in the biochemical and related sciences. We rely on a strong faculty with broad research interests, excellent research space, strong financial support, and a tradition of research excellence to accomplish this. We are also strongly devoted to excellent teaching and training. This booklet outlines the salient features of our program and effort. I sincerely hope that we personally will have the opportunity to introduce you to the study of biochemistry.

Hector F. De Luca
Steenbock Research Professor and Chair
Department of Biochemistry
The University

The University of Wisconsin-Madison has earned its reputation as one of the great universities of this country; its academic programs are distinguished by high quality and great diversity. It includes 14 schools and colleges, more than 125 academic departments with over 150 undergraduate and 120 graduate degree programs, and more than 5,000 research projects. Few universities provide on a single campus the full range of sciences, liberal arts studies, and professional programs available at the UW-Madison.

Wisconsin has ranked among the top ten educational institutions in the country in every published study of faculty and administrative opinion since the early 1900s. A number of its individual departments, including Biochemistry, Chemistry, Bacteriology, Genetics, and Chemical Engineering, rank among the country's very best departments in their respective areas. UW-Madison has a long tradition of interdisciplinary cooperation, which, combined with the strength of individual departments, results in great strength across the whole spectrum of chemical and biochemical sciences.

The University attracts a diverse student body from all parts of the nation and the world. The diverse cultures represented at the UW-Madison add to the intellectual excitement expressed by its members.
Madison is a beautiful city situated on an isthmus between two spectacular lakes. The population of the city is approximately 200,000 and Madison boasts excellent public transportation, superior public schools, diverse cultural events, extremely low unemployment, and numerous opportunities for recreation. Madison is an exceptionally safe city which frequently earns recognition such as an "All American City" and "Best Place To Live in America" (Money Magazine, 1996). Because of its extensive bike trail system within the city and extending to surrounding areas, Madison is also ranked as one of the top ten bicycling cities in the U.S.

Students live in all parts of the city, although they are concentrated near the campus; more than one-half of the Biochemistry graduate students live within one mile of the department. Mad City, as it is called by many residents, is the state capital and the Capitol Square at the center of the isthmus is just one mile down State Street from the campus. The Capitol Square is the focal point for many events in the city including summertime Wednesday evening "Concerts on the Square," a weekly Saturday morning farmers' market of nationally recognized diversity, an annual "Art Fair On The Square," and a "Paddle and Portage" canoe race from Lake Mendota on the north side of the isthmus, across the Capitol Square to the shores of Lake Monona. State Street is a pedestrian mall that stretches from the capital square to the campus and contains numerous shops, restaurants, and bookstores. Many parks and beaches are found within the city including the UW-Madison arboretum, found-

Ph.D. parties) to Picnic Point at the western extreme of campus. Concert and performance series at the Memorial Union provide cultural outlets for university students and faculty, and the Elvehjem Art Museum, named for the renowned biochemist Conrad Elvehjem, is acclaimed for its permanent and visiting collections. Both indoor and outdoor recreational facilities allow students to pursue a wide range of sports and activities. The Hoofers Outing Club, housed next to Memorial Union on Lake Mendota, is a favorite venue for both novice and experienced sailors and sail boarders.

The UW-Madison Campus sits on the southern shore of Lake Mendota and is regarded as one of the most beautiful campuses in the world. The intellectual intensity and excitement of the University are complemented by the spectacular campus setting. An impressive array of architecturally diverse buildings gives way to a park-like atmosphere along the lakeshore, where a walking/ jogging trail hugs the shoreline from the Memorial Union Terrace (the site of many
The UW-Madison Department of Biochemistry celebrated its centennial in 1983. During the first half of this century a long series of significant contributions in fundamental and applied science came from this Department: The discovery and structural characterization of the B vitamins; the physiology and biochemistry of vitamins A, D, and K; the use of vitamin K analogs as anticoagulants and rodenticides, and the discovery of vitamin D synthesis by UV irradiation of sterols; clarification of the roles of selenium and vitamin E in metabolism. The use of microbial organisms in bioassays of required nutrients was pioneered here, and the development of large-scale microbial fermentations for production of antibiotics and other natural products was an important contribution of the Department.

In more recent years, the Department of Biochemistry has grown into a group of more than 30 professors with research interests across a broad spectrum. Mechanistic enzymology employs a variety of physical chemical techniques, chemical synthesis of substrate analogs, and kinetic studies to describe in detailed chemical terms the catalytic activity of enzymes. Protein engineering based on knowledge of enzyme activity and structure is an extension of these areas. Biophysical techniques including X-ray diffraction, nuclear magnetic and electron paramagnetic resonance spectroscopy, and mass spectroscopy provide information about the static and dynamic structures of natural products and proteins. Molecular genetics employs the powerful techniques of genetics and nucleic acid engineering to explore the structure of genes, their replication, expression, and recombination, the mechanisms that underlie these processes and are responsible for their regulation. Virology focuses on the structure and composition of viruses that infect plants, animals, and bacteria, on the genetic makeup of these viruses, and on the regulated expression of their genes during infection and replication. Molecular physiology aims to define in molecular terms a variety of physiological phenomena in plants, animals, and microorganisms: The requirement of vitamins A, D, and K in cellular differentiation and immunity, Ca homeostasis, and blood clotting, respectively; regulation of the cellular immune responses; modulation of ciliary and flagellar motility by external signals; regulation of gene expression by steroid hormones; signal transduction; proteins and membrane trafficking; cellular uptake of sterols; and cellular differentiation during development. Plant biochemistry focuses on biochemical processes such as the biosynthesis of the cell plate, regulation of flowering by light, and fixation of molecular nitrogen.
The graduate program in Biochemistry is designed to prepare students for careers in research, teaching, and areas related to the biochemical sciences. The Department offers a wide range of opportunities for students to develop their skills in research, teaching and the communication of science. Graduate research training in the Department stresses an attitude of inquiry and problem-solving. We hope to convey the adventure, as well as the methods, of research. The graduate thesis is performed with the mentoring of a Biochemistry faculty member and may involve collaborations with other students, other faculty, and scientists outside the Biochemistry Department. The graduate level course offerings are intended to provide a foundation of knowledge to prepare students to pursue careers in both basic and applied research and teaching. In addition to completing formal coursework and a substantial research project, students participate in the Department's teaching program for two semesters during their graduate studies. Participation in the teaching program is intended to acquaint students with teaching methods and to enable students to determine if they would like to include teaching as a component of their careers. Much of the learning by advanced students occurs in seminars and symposia presented on campus. Students themselves are given many opportunities to present their own research as well as literature topics in research group meetings and student seminar series; students thus practice the communication of scientific information. During their studies, students will be able to participate in Careers Day and exercises designed to provide first-hand information from scientists outside the University about different career paths. The goal of our graduate program is to produce broadly-trained, independent scientists with significant research accomplishments. This goal is evidenced in our mission which is: "Research Excellence Through Graduate Training."
History and Development

OF THE DEPARTMENT OF BIOCHEMISTRY AT UW-MADISON

The Department of Biochemistry builds on a long tradition of excellence in basic research that has led to important practical advances. A modern department, with emphases in cellular regulation, molecular genetics, protein structure, hormone action, virology, and developmental biology, has been built on this strong historical foundation.

Our department was founded in 1883. In the century since, its contributions have dramatically changed our understanding of the chemical basis of life and have illuminated how a molecular understanding of basic biological problems can improve the human condition. The Department's historical contributions are many and varied, and rank among the highlights in the emergence and rise to prominence of biochemistry and molecular biology. Among the important discoveries made at the Department of Biochemistry are the:

- discovery of Vitamin A and the Vitamin B complex
- discovery of the irradiation process for production of Vitamin D and elimination of rickets
- isolation of niacin and elimination of pellagra
- development of fermentation methods that led to the large-scale preparation of penicillin and other antibiotics
- development of methods for preservation of sperm, triggering the artificial insemination industry
- discovery of the anti-coagulants dicumarol and warfarin and their uses against heart disease and as rodenticides
- discovery of the key features of the incorporation of atmospheric nitrogen into amino acids
- first chemical synthesis of a gene
- development of methods for the kinetic analysis of enzyme reactions
- discovery and identification of the hormonal form of Vitamin D, and use of its analogs to treat disease
- elucidation of the structure of myosin, a key discovery in understanding muscle function

Among the faculty who contributed to this outstanding array of accomplishments have been a long line of colorful, opinionated and visionary scientists, among them Stephen Babcock, E.B. Hart, Conrad Elvehjem, E.V. McCollum, Harry Steenbock, Marvin Johnson, Robert Burris, Esmond Snell, Gobind Khorana, and Henry Lardy. Among the past and present members of the department are 17 members of the National Academy of Sciences.

The Department of Biochemistry has trained over 1,300 PhDs, many of whom now occupy important scientific and executive positions throughout the world. At present, the Department is comprised of 120 graduate students, 80 postdoctoral investigators, 60 technicians, 30 faculty, and 400 undergraduates. The current department strongly emphasizes outstanding research, while its highly effective teaching program has won campuswide recognition through awards for classroom instruction. Outstanding teachers include David Nelson and Michael Cox, the authors of a widely-used Biochemistry textbook.

On this proud foundation, driven by a desire to find the molecular explanation for basic biological phenomena, the Department's interests have widened and grown to embrace an ever-increasing diversity of areas and organisms. Central problems in developmental biology, protein structure and function, molecular genetics, nutrition, metabolism, enzymology, and more, dominate the intense research environment; the breadth of approaches is invigorating, and spans molecular biology, protein structure, molecular physiology and endocrinology, and synthetic and analytical chemistry. Interdisciplinary research is not only possible, but expected.

The desire to find molecular answers to fundamental problems in the biology and chemistry of life is the driving force of this department. We leave it to you to discover in this brochure the present research interests of the faculty. The Department relishes the challenges ahead, combining its modern methodologies and pioneering approaches with its established traditions, in an ambitious effort to understand the molecular basis of life.

(Front, L to R) Dr. and Mrs. Freudenberg (visiting), S. M. Babcock, E. B. Hart; (Back, L to R) W. H. Peterson, W. E. Torrington, C. A. Elvehjem, K. P. Link, H. Steenbock, C. L. Christiansen (Dean, College of Agriculture).
The major developmental change in the plant life cycle is the initiation of flowering. Many plant species have evolved the ability to regulate flowering in response to environmental variables such as changes in daylength or temperature. However, the biochemical mechanisms by which plants sense and respond to environmental cues are unknown. By genetic analysis, we have identified several genes that are involved in the environmental regulation of floral induction in Arabidopsis thaliana. We are continuing the genetic analysis of floral induction, and are cloning these "flowering genes." Our long-term goal is to elucidate the biochemical role of these genes in the flowering process.

We are also studying the process of leaf senescence, using Arabidopsis as a model experimental system. As leaves lose chlorophyll and turn yellow, a new developmental program is initiated that is designed to recycle leaf nutrients (particularly nitrogen). We have shown that this program involves major changes in leaf gene expression. We are studying the function and regulation of a number of genes that are uniquely expressed in senescing leaves. We have also begun to dissect this process genetically by identifying and characterizing mutations that alter the senescence program.

PUBLICATIONS


Photo, left to right: wild-type Arabidopsis thaliana, ld mutant. Both plants were grown under continuous light, which is an inductive daylength for Arabidopsis flowering. The ld (LUMINIDEPENDENS) mutation blocks the flowering response to inductive daylengths.
Insulin resistance is a syndrome in which a greater than normal amount of insulin is required to elicit a normal response. Insulin resistance afflicts about one-fifth of the population of the United States and is an important risk factor for heart disease, hypertension, and diabetes mellitus. Diet and genetics collaborate to produce insulin resistance. The major genes that mediate this syndrome are thought to be involved in hormone signal transduction.

We have screened mutagenized mice and various inbred mouse strains to identify variants with a highly exaggerated insulin resistance response to high-fat diets. Using the powerful tools of mouse genetics and molecular biology, we are mapping and identifying genes involved in this syndrome. Our goal is to identify the pathways in insulin’s target tissues by which nutrients alter hormone transduction mechanisms.

Lipoproteins are complexes of protein and lipid that circulate in the bloodstream. They are assembled at the endoplasmic reticulum through a process in which both the protein and lipid moieties must be translocated from the cytoplasm and coordinately assembled into particles that progress into the secretory pathway.

Lipoprotein assembly requires an endoplasmic reticulum heterodimeric protein, termed microsomal triglyceride transfer protein. One of the subunits is protein disulfide isomerase, an enzyme that catalyzes the formation or re-shuffling of intramolecular disulfide bonds. The other subunit catalyzes the transfer of triglyceride into the secretory pathway.

We have reconstituted the lipoprotein assembly process into insect tissue culture cells by infecting them with baculoviruses harboring the essential human genes for lipoprotein assembly. This is a highly versatile system that permits control of gene dosage and enables us to systematically mutagenize the participants in this protein and lipid trafficking process.
The mechanism of cytokinesis in higher plants is distinct from that of animal and yeast cells. In dividing plant cells, cytosol and organelles are partitioned between the two daughter cells by the formation of a new cross wall known as the cell plate. The focus of my lab is to understand the biochemical mechanisms that direct the formation of this new membrane compartment. Suspension-cultured tobacco and Arabidopsis cells are being used as model systems to study cell plate formation because of their amenability to transgenic, biochemical and morphological studies. Currently, we are using these cells to identify and to characterize the transport of several soluble and membrane secretory proteins to the plate.

Cell plate formation is initiated when Golgi-derived vesicles are guided by a specialized cytoskeletal structure called the phragmoplast toward the equatorial region of the dividing cell, where they fuse. The plate then extends out centrifugally as more vesicles fuse with it, until it joins with the original cell plasma membrane, separating the two daughter cells. Fusion of the transport vesicles may occur by homotypic (self) fusion, heterotypic fusion, or by a combination of these processes. Recent studies in yeast and animal cells suggest that these types of intracellular membrane fusion are mediated by two homologous but functionally distinct proteins, p97/Cdc48p and NSF. Homologs of these cytosolic fusogenic factors have also been identified in plants and one avenue of research in my lab is to examine their role in plate biogenesis. Additional biochemical studies are being conducted to identify candidates for other cytosolic and membrane components involved in the fusion process.

A complementary approach to the biochemical methodology is to exploit the genetic systems available in plants, particularly in Arabidopsis. Genetic studies will help to verify the in vivo role of proteins, identified through biochemical means in cell plate biogenesis. We have begun to identify and to characterize Arabidopsis plants containing insertion mutations in several genes of interest, including CDC48. Future studies will include genetic screens for mutants defective in cytokinesis in order to identify other proteins, such as those involved in regulation of cytokinesis, which may escape detection in a purely biochemical approach.

Right: Plant Cell Cytokinesis: The phragmoplast, a unique cytoskeletal structure composed of microtubules and microfilaments, appears late in mitosis. Golgi-derived vesicles coalesce within the equatorial region of this structure, to form a tubular-vesicular network filled with cell wall precursors. The cell plate expands outward as more vesicles fuse with it until it joins with the original cell plasma membrane, ultimately separating the daughter cells. (Figure adapted from Biology of Plants, P. H. Raven, R. F. Evert, S. E. Eichhorn, 1986 Worth Publishers, Inc.)

PUBLICATIONS


Research in this laboratory is directed at understanding how retinoids (natural or synthetic compounds related to vitamin A) function in embryogenesis, and more specifically, in neural development. The development of the nervous system is disrupted both in retinoid deficiency and in excess. Retinoids are used therapeutically in the fields of dermatology and oncology; however, embryotoxity as well as acute toxicity is encountered at pharmacological concentrations. Before the therapeutic potential of retinoids can be fully realized, it will be necessary to understand how vitamin A and its metabolites function normally at the cellular and molecular level, and how function is disrupted in toxicity.

Retinoids act by binding to two families of nuclear retinoid receptors (retinoic acid receptors, RARs; and retinoid-X receptors, RXRs). These receptors function as ligand-activated transcription factors which modulate gene transcription. RXRs also function as accessory proteins for RAR and other steroid hormone receptors. A major focus in the lab is to define how retinoid receptors interact with ligand, DNA and other proteins to regulate the transcription of retinoid-responsive genes.

A second major area of research involves the study of embryos derived from animals provided with either too little or too much retinoid during pregnancy. Our goal is to delineate the retinoid-responsive genes whose expression is altered in retinoid deficiency or excess, and to establish how these changes lead to an abnormal phenotype. Cultured human neuroblastoma cells and primary cultures of embryonic sympathetic neurons are also being used as model systems to elucidate the genes that are targets of retinoid action. These neuronal cell cultures represent good model systems because the vitamin A metabolite, retinoic acid, stimulates differentiation (neurite outgrowth) in both cell types, and supports the survival of embryonic chick sympathetic neurons at early developmental stages.

**PUBLICATIONS**


Photos: Embryonic (day 6.5) chick sympathetic neurons cultured for 7 days with nerve growth factor in the absence (left) or presence (right) of the vitamin A metabolite, all-trans retinoic acid. Only neurons receiving the vitamin A metabolite survive and extend neurites.
The fundamental thrust of research in this lab is to use kinetic studies to deduce enzyme mechanisms. By mechanism we mean: 1) the kinetic mechanism, which is a qualitative description of the order of substrate combination and product release from the enzyme, 2) determination of rate limiting steps from quantitative analysis of the kinetic mechanism, 3) the chemical mechanism, including the nature of any intermediates, the identification of any groups on the enzyme acting as acid-base catalysts, and the roles of any cofactors, 4) the nature of the transition state for the chemical reaction catalyzed by the enzyme.

A variety of kinetic experiments is used to deduce this information. The algebraic form of the rate equation as a function of substrate concentrations limits the kinetic mechanism, while inhibition patterns for products or dead end inhibitors vs. the various substrates pin it down, and often help to determine the rate limiting steps. Isotope exchange and partitioning studies complete the analysis of kinetic mechanism. The chemical mechanism is deduced by studying the pH variation of the kinetic parameters (this identifies the acid-base catalysts, and necessary protonation states of the substrate for binding and catalysis), and by certain isotope effect studies. When both a deuterium and a $^{13}$C isotope effect can be measured on the same reaction, the size of the $^{13}$C isotope effect with a deuterated and unlabeled substrate tells whether the reaction is stepwise (deuteration decreases the observed $^{13}$C isotope effect) or concerted (deuteration raises it). In the former case, quantitative analysis tells whether the deuterium- or $^{13}$C-sensitive step comes first.

The transition state structures are deduced from isotope effects in the same fashion as the physical organic chemist does. But in order to determine the intrinsic isotope effects on the chemical steps it is necessary to measure several isotope effects and solve the equations for them simultaneously. These can be deuterium and tritium isotope effects on the same step, or $^{13}$C or other heavy atom isotope effects with a deuterated and unlabeled substrate when both isotope effects are on the same step. These methods give narrow limits on isotope effects, and in favorable cases an $\alpha$-secondary deuterium isotope effect and its effect on a $^{13}$C isotope effect supply two more equations with only one more unknown and provide an exact solution for the system.

Current projects being studied involve the chemistry of several enzymes, and the mechanisms of phosphoryl and acyl transfer. These studies employ $^{15}$N, $^{13}$C and $^{18}$O isotope effects.
Genetic recombination is perhaps the least understood of all the processes that contribute to DNA metabolism. Many classes of DNA rearrangements occur in all cells and play important roles in gene regulation, development, carcinogenesis, and evolution. The goal of this laboratory is to understand how these genetic rearrangements come about. The approach is to study in detail the isolated enzymes that play central roles in different classes of genetic recombination events. Currently, two systems are under investigation: recombinational DNA repair in E. coli and a programmed DNA deletion event that occurs during macronuclear development in Tetrahymena thermophila.

The RecA protein is the key component required for recombinational DNA repair in bacteria. This protein is capable of pairing two homologous molecules of DNA, exchanging strands of DNA between them. The reaction occurs in several phases that are easily distinguished experimentally. Our efforts are directed at: 1) a study of the structure of a putative 3-stranded DNA pairing intermediate, and 2) a determination of the mechanism by which complexes of RecA protein bound to DNA promote a unidirectional DNA strand exchange reaction coupled to ATP hydrolysis. The system offers a variety of unique problems on protein-nucleic acid interactions, unusual DNA structures, and biochemical energetics.

In addition to RecA, we are studying several other E. coli proteins involved in recombinational DNA repair. These include the RecF, RecO, and RecR proteins, which function early in recombinational processes, and the RuvA and RuvB proteins which function late. The RecF, O, and R proteins appear to act together to regulate the formation and disassembly of RecA protein complexes on DNA. The RuvA and B proteins form a complex that plays a key role in processing branched DNA recombination intermediates. All of these proteins currently present a variety of challenging mechanistic questions.

Our newest enterprise is an effort to examine a novel DNA deletion event in the ciliate, T. thermophila. Ciliates are single-celled eukaryotes with two nuclei. The micronucleus is analogous to a germline nucleus and is normally silent. The macronucleus is the vegetative nucleus, producing mRNA to support cell functions. During mating, the existing macronuclei are destroyed and replaced with new ones derived from the micronucleus. An impressive array of genomic rearrangements occur during macronuclear development including over 6,000 site-specific DNA deletion events which are observed 10-14 hours after mating begins. We are currently working on two of these deletion events, addressing mechanistic issues in vivo and in vitro.

PUBLICATIONS


Below: RecA filament
Professor H. F. DeLuca's laboratory has been devoted to the understanding of metabolism and mechanism of action of vitamins A and D. Initially, work in this group centered around describing which forms of vitamin D and vitamin A are active in correcting deficiency disease. In particular, in the 1960's by means of isolation, chemical identification and chemical synthesis, this laboratory demonstrated that vitamin D itself is biologically inactive and must be modified by sequential action by the liver and kidney to prepare the hormone derived from vitamin D, namely 1,25-dihydroxyvitamin \( \text{D}_3 \). Not only the hormonal form but many of its analogs were chemically synthesized in this research group and developed for the treatment of a variety of diseases including osteoporosis, vitamin D dependency rickets, and bone disease of kidney failure. More recently, this laboratory has devoted its efforts to understanding how 1,25-dihydroxyvitamin \( \text{D}_3 \) functions in the target tissues. A receptor which recognizes this hormone has been identified in target tissue nuclei. It has been cloned and its entire amino acid and nucleotide coding sequence has been determined. We have successfully expressed it in large quantities in baculovirus and bacteria and are in the process of crystallizing the protein for threedimensional structural work. Response elements or specific DNA sequences to which the receptor binds in order to initiate transcription of the genes have also been identified. Other molecular biology techniques are being applied to isolate genes and identify the proteins that are made in response to 1,25-dihydroxyvitamin \( \text{D}_3 \). By locating the receptor in tissues not previously recognized as targets of vitamin D action, new functions for vitamin D have been identified. It is now clear that 1,25-(OH)\( _2 \)D\( _3 \) serves as a developmental hormone as well as a hormone responsible for regulating calcium and phosphorus. It has also been found to be necessary for reproductive function in females, for the immune system, and for the development of giant osteoclasts responsible for remodeling bone. Our laboratory uses a combination of molecular biology techniques, organic chemical techniques, physiological techniques, and cell biology techniques to learn the molecular mechanism of action of these fat-soluble substances. There is considerable effort dedicated to collaboration with the medical world for the application of the newly synthesized analogs of the vitamin D compounds and of vitamin A compounds for the treatment of disease. The most recent disease coming under treatment is psoriasis, a skin disorder which is very nicely controlled by specific analogs of 1,25-dihydroxyvitamin \( \text{D}_3 \).

**PUBLICATIONS**


Biochemical, catalytic and spectroscopic studies of iron-containing enzymes; protein engineering.

We have recently established that catalytically essential diiron centers are found in the plant stearoyl-acyl carrier protein Δ9 desaturase (Δ9D) and the bacterial toluene-4-monoxygenase (T4MO). These soluble, multicomponent enzymes utilize O2 and NADPH to catalyze the oxidation of hydrocarbons. Δ9D is ultimately responsible for the biosynthesis of oleic acid, the most abundant unsaturated fatty acid, while T4MO catalyzes the para-hydroxylation of toluene. These enzyme complexes are of interest because they can oxidize stable C-H bonds. We are interested in determining the molecular details of these oxidation reactions.

Broadly stated, our research goals are to define the structure and the reactivity of the active site diiron center, to probe the catalytic contributions of the active site protein residues, and to determine the consequences of protein-protein and protein-substrate interactions on the outcomes of enzymatic catalysis. Our research group makes extensive use of biochemical, catalytic and spectroscopic techniques as metalloenzyme active site probes. Through application of these techniques, resting states as well as highly reactive intermediates of the diiron enzyme catalytic cycle are being characterized. In addition to providing fundamental mechanistic and structural information, these characterizations form the basis for ongoing site-directed mutagenic manipulations of the protein- and substrate-components of the enzyme complex. Since we obtain both of Δ9D and T4MO from recombinant overexpression systems, we also remain interested in innovative ways to use advanced fermentation technologies to further improve the productivity and yield of our enzymes from these vectors.

It is reasonable to assume that the catalytic diversity of the enzymes containing diiron centers is related to the many possibilities for variation in the ligand types and coordination numbers, in the geometry of ligand binding, and in the polarity of the environment surrounding the diiron center. Highly specific protein-protein interactions must also contribute to the rates and yield of catalytic turnover. Through the detailed characterization of the attributes of these versatile catalysts, we would ultimately like to assemble bioengineered diiron enzymes capable of the oxidative biotransformation of a wide variety of hydrocarbons.

PUBLICATIONS


Mechanisms of enzyme and coenzyme action; stereochemistry and mechanisms of phospho- and nucleotidyl transferase action; structure and function of multienzyme complexes.

The central thrust of my research is the elucidation of the mechanisms of enzymatic reactions. Two aspects of the field of mechanistic enzymology are particularly interesting to me, and are the basis for ninety percent of my research: a) The question of how enzymes utilize binding interactions directed to nonreacting parts of substrate molecules to catalyze the chemical transformations of the reacting parts of substrates is one principal focus of my research. These interactions provide the energy for the structural transition of enzymes into active conformations. Statements that are commonly advanced to explain enzymatic catalysis by the active conformation of an enzyme include those in which the enzyme is postulated to stabilize transition states or to destabilize ground states in E•S complexes, or both. These are very general statements that do not explicitly account for the actions of particular enzymes. A specific description of catalysis, in both structural and dynamic terms, is needed for a few enzymes. Serine proteases, isomerases, and the enzymes of galactose metabolism are subjects of my research in this field, and b) The second focus of my research is the elucidation of the mechanisms of enzymatic reactions that are so obscure in chemical terms that no obvious chemical precedent is available. These enzymes depend upon cofactors about which little is known. Lysine 2,3-aminomutase is one example of such an enzyme, and it is one subject of my current research in this field. Lysine 2,3-aminomutase catalyzes the 1,2-amino group migration in the interconversion of L-lysine and L-β-lysine. The required cofactors include pyridoxal-5'-phosphate (PLP), S-adenosylmethionine, an iron-sulfur cluster, and Co(II). PLP normally functions to stabilize carbamions in enzymatic reactions; however, in the lysine 2,3-aminomutase reaction it appears to facilitate the rearrangement of a substrate radical. S-Adenosylmethionine is normally a biological alkylating agent; however, in the lysine 2,3-aminomutase reaction it functions as a hydrogen transfer agent. Analogous vitamin B_{12}-dependent aminomutases are also under investigation. The chemical interactions of these cofactors and the mechanisms by which they function in catalysis are under investigation. The detailed structure of the enzyme and the chemistry by which it interacts with cofactors are also under intensive investigation by use of physical, chemical and biological methods.


Research in our laboratory involves the molecular biology and replication of eukaryotic DNA viruses. We are particularly interested in the baculoviruses, a group of large DNA viruses that are pathogenic to invertebrates. These unique viruses are known for their prolific multiplication in insect (moth) cells and are the most popular eukaryotic vectors for high level expression of foreign gene products (proteins). Moreover, these DNA viruses exhibit a highly controlled but complex program of transcription during replication which makes them useful and attractive models for studies on eukaryotic gene regulation. Our goal is to investigate the molecular mechanisms that govern baculovirus replication to better understand fundamental problems in regulation of eukaryotic gene expression and the interaction of viruses with their host cell.

We study the early and late replication stages of the prototype baculovirus, Autographa californica nuclear polyhedrosis virus (AcMNPV) in cultured cells. AcMNPV uses a complex regulatory scheme to ensure the proper timing and level of expression of essential genes. Early genes encode transcriptional regulatory factors, whereas late genes encode virus structural proteins. We are examining the mechanisms that control the proper turn on and turn off of viral genes during infection by focusing on the molecular interactions between cis-acting DNA regulatory sequences and virus/host transcription factors. We have characterized the promoters and enhancers required for proper transcription of early AcMNPV genes and continue to investigate the trans-acting factors involved.

AcMNPV also causes programmed cell death. PCD or apoptosis is a built-in, signal-induced process by which a cell self-destructs. Whereas regulated apoptosis is critical for normal development, aberrant apoptosis is associated with tumorigenesis, neurodegenerative diseases, immunodeficiency, and viral pathogenesis. The baculoviruses encode novel PCD suppressors (including p35 and iap) that function to block apoptosis in diverse organisms, including humans. Thus, baculovirus infection provides a powerful and convenient system for molecular analysis of the induction and suppression of apoptosis. Such studies are yielding important insight into the regulation of PCD and should facilitate the long term design of novel therapeutic strategies for treatment of apoptosis-linked diseases in humans.

Techniques used in the laboratory include gene cloning and sequencing, site-directed mutagenesis, in vitro transcription and RNA mapping, construction of recombinant baculoviruses, protein purification, and immunoblot analysis, and others pertinent to molecular virology such as cell culture and virus propagation.

**PUBLICATIONS**


The focus of the Gorski research program is on the molecular mechanisms of estrogen action. In order to function, estrogenic hormones require that a cell contain both a viable estrogen receptor and a transduction system in which the estrogen-receptor interaction brings about changes resulting in certain arrays of genes being expressed and others inhibited. The models of steroid hormone action that have been proposed to date do not adequately explain the observed complex responses to estrogen hormones.

The specific aspects of estrogen action we are investigating include the following four elements: 1) the physical structure of the receptor following estrogen binding; 2) estrogen regulation of estrogen receptor interaction with DNA and chromatin proteins; 3) regulation of receptors during pre- and postnatal development; and 4) estrogen regulation of cell replication and DNA synthesis in normal and hyperplastic tissues.

Changes in the physical structure of the receptor induced by estrogen binding represent the primary action of the hormone. The difference in receptor structure induced by estrogenic versus antiestrogenic ligands must delineate a critical structural change that we would like to define. The role of the steroid binding domain of the receptor in these structural changes and in interactions with transcription factors is one of our major interests.

Estrogen-stimulated DNA synthesis and cell replication are being studied because of their obvious role in growth and development. Genetic differences in DNA synthesis in the pituitary in response to estrogen are seen in certain rat strains and will be the object of further study. Estrogen not only stimulates DNA synthesis but also appears to turn off DNA synthesis in some tissues. The role of the cyclins and other cell cycle regulatory factors are being studied in these estrogen-dependent systems. We are also interested in finding the specific genes that may account for the difference in DNA synthesis in certain strains of rats.

There is evidence that estrogenic effects on DNA synthesis require the presence of estrogen over several hours of time. This suggests that DNA synthesis is not just a final step in a cascade of events initiated by the early action of estrogen.

Thus, the study of estrogen receptors, chromatin structure, estrogen-induced gene expression, and DNA synthesis allow a broadly integrated approach to understanding the molecular aspects of estrogen regulation of cell function and growth.

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**PUBLICATIONS**


Molecular mechanisms that regulate immune responses.

We investigate molecular mechanisms that regulate lymphocyte development and function. One research area emphasizes how the hormones 1,25-dihydroxyvitamin D3 (calcitriol) and retinoic acid inhibit chronic autoimmune diseases like multiple sclerosis and arthritis through their actions on T lymphocytes. A second research area emphasizes how new B lymphocytes are directed to develop into long-lived memory B cell precursors.

Experimental autoimmune encephalomyelitis (EAE) is an autoimmune disease believed to be a model for the human disease, multiple sclerosis. EAE is induced by immunizing B10.PL mice with myelin basic protein, a constituent of the central nervous system. In collaboration with Hector DeLuca, our lab discovered that administering calcitriol before inducing EAE completely prevented the progressive paralytic disease. More importantly, when calcitriol was provided after severe paralysis had occurred, the hormone reversed the disability symptoms. Withdrawal of calcitriol resulted in a resumption of progressive paralysis. Finally, a deficiency of vitamin D resulted in an increased susceptibility to EAE. Thus, calcitriol or its analogs are potentially important for treatment of multiple sclerosis. Retinoic acid has a similar effect on EAE.

Our current research goal is to elucidate how the hormones calcitriol and retinoic acid block progressive autoimmune disease. We hypothesize that these hormones are potent transcriptional inhibitors of several inflammatory cytokines, in particular interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α) and interleukin-12 (IL-12). We have shown that retinoic acid inhibits IFN-γ transcription. Current experiments aim to map the retinoic acid responsive element in the IFN-γ promoter and to characterize the retinoic acid-responsive proteins that bind to this element and transduce the retinoic acid signal into a process that limits IFN-γ transcription. We plan similar studies for calcitriol. We will first identify the target cells for calcitriol action, and then investigate how calcitriol controls the cell's functions. Our preliminary data suggest that calcitriol stimulates synthesis of the anti-inflammatory cytokine transforming growth factor-beta.

Our second research area is B lymphocyte development. Our lab discovered a B cell intrinsic locus, Bcmd (B cell maturation defect), that causes most B lymphocytes to die prematurely before they become memory B cell precursors. Consequently, Bcmd mice have a profound peripheral B cell deficiency and they display no immunological memory. We are approaching the problem of identifying the Bcmd gene product and its function using biochemical and genetic methods. We are mapping Bcmd to facilitate positional gene cloning strategies. We are also studying growth factor receptor signal transduction and the synthesis of proteins like BCL-2 that block apoptosis in Bcmd B cells with the goal of learning where the mutant Bcmd gene product functions.

PUBLICATIONS


Three-dimensional structures of proteins by x-ray crystallographic analysis.

Our laboratory is involved in determining the three-dimensional structures of a variety of enzymes by single crystal x-ray diffraction techniques. Knowledge of the molecular structure of an enzyme is critically important in understanding its function, and x-ray crystallography is, to date, one of the two most powerful techniques available for obtaining such information. The laboratory is presently focusing on five enzymatic systems as described below.

The first area of research involves the structural investigation of kanamycin nucleotidyldtransferase (KNTase). This enzyme is plasmid-coded and confers bacterial resistance to kanamycin and other aminoglycoside antibiotics. The enzyme catalyzes transfer of the nucleoside monophosphate group from a nucleotide to the 4′-hydroxyl group of the antibiotic, thereby rendering the drug inactive. We have solved the structure of the enzyme, complexed with AMPcPP and kanamycin, to 2.5 Å resolution.

Another area of research interest focuses on the enzyme, acetyl-CoA carboxylase. This enzyme is found in all animals, plants, and bacteria and catalyzes the first committed step in fatty acid synthesis. It is a multi-component enzyme containing a biotin carboxylase, a biotin carboxyl carrier protein, and a carboxyl transferase. In E. coli, these components can be isolated separately yet still display their distinct functional properties. To date we have determined and refined to 2.0 Å resolution the structure of the biotin carboxylase component of acetyl-CoA carboxylase.

The third enzyme under investigation in the laboratory is UDP-galactose 4-epimerase from E. coli. This enzyme catalyzes the NAD+ dependent interconversion of UDP-galactose and UDP-glucose and is essential for galactose metabolism. Recently we determined the structure of the enzyme complexed with NADH and UDP-glucose to 1.8 Å resolution. This x-ray crystallographic investigation defined the active site geometry of the enzyme and suggested that Ser 124 is an essential amino acid for catalysis.

The last two enzymes presently being studied in our group are phosphotriesterase isolated from the soil microbe, Pseudomonas diminuta and 4-chlorobenzyol-CoA dehalogenase found in Pseudomonas sp. strain CBS3. Phosphotriesterase hydrolytically degrades various phosphate-based pesticides as well as several highly toxic nerve agents including sarin and soman. The 4-chlorobenzyol-CoA dehalogenase is a component of the metabolic pathway that converts 4-chlorobenzoate to 4-hydroxybenzoate. Halogenated hydrocarbons are often employed in various production and manufacturing processes and pose potential environmental and human health risks. The structures for both enzymes have now been determined to high resolution and experiments are presently being conducted to more fully characterize their three-dimensional architectures, active site geometries, catalytic mechanisms, and substrate specificities.

PUBLICATIONS


Replication and structure of DNA.

Our current research centers around the replication of DNA. We wish to learn why organisms have evolved a variety of strategies for the replication of their genes. In many bacteriophages, DNA replication initiates from a well-defined origin, but in some instances the genes are replicated unidirectionally, whereas in others a bidirectional mechanism is employed. Some genomes replicate as circular structures while others are linear. In higher organisms replication initiates from a large number of positions along the genome. What advantages are conferred by these various replication strategies?

Another related area of interest concerns the control of DNA replication. How does an organism achieve balanced replication so that its genes are neither under- or over-replicated and how is this coupled with the actual physical division of the cell? We have recently discovered how to interfere with the control process that is concerned with the primary initiation of DNA replication in bacteriophage λ, and in this way hope to gain insights into the control process itself. Phage λ DNA initiates bidirectional replication from a unique position on its genome, and once replication has started, two daughter origin sequences are formed. Normally these daughter origins are inactive while a round of replication is in progress. Apparently a control process prevents daughter origins from initiating a new wave of replication until the current round terminates.

Under a number of abnormal conditions we can disturb this control process. For instance, if replication takes place in the presence of caffeine or the antitumor drug cis-Pt, daughter origins can reinitiate while a round of replication is in progress, leading to multiple waves of replication and complex replicative structures. We are presently investigating these aberrant replicators in order to determine how the control process operates.

During the first round of replication the bidirectional λ replicator has a θ configuration; the parental section is negatively supercoiled while the two daughter segments are relaxed. The control process, just discussed, may simply arise from supercoiling. A supercoiled origin sequence might be active, whereas if it is relaxed (as in the daughter section of the replicative intermediate) it might be inert. To more fully explore this possibility we have developed a novel electron microscopic method that allows us to unambiguously determine the supercoiled state of DNA in complex replicative structures. The method is based on the fact that the efficiency of intercalation of the drug psoralen is much higher for negatively supercoiled than for relaxed DNA.

Our research relies heavily on physical and electron microscopic methods.
We want to understand how cells are regulated to grow and differentiate during the development of a multicellular organism. To this end, we use a combination of genetics and molecular biology to analyze controls of cell fate and pattern formation in the nematode Caenorhabditis elegans.

One project is aimed at understanding how cells interact with each other to control cell fate. We have focused on a signal transduction pathway that controls the decision between mitosis and meiosis in the germline and controls embryonic induction in the early embryo. The GLP-1 membrane receptor of this pathway has been investigated both genetically and molecularly. In addition, the lag-1 gene appears to encode a DNA binding protein and potential transcriptional activator that may act downstream of the receptor, and lag-2 appears to encode the signaling ligand for the receptor. We are exploring the function and regulation of lag-1, lag-2, and glp-1 by both genetic and molecular means.

A second project focuses on how maternal mRNAs are regulated during development. We have analyzed translational regulatory elements in the 3' untranslated regions (3' UTRs) of two genes that control sexual fate during development. In addition, we have identified a regulatory element in the glp-1 3' UTR that is required for spatial regulation of GLP-1 in the early embryo. This element appears to regulate the translation of glp-1 mRNA in two of the four blastomeres at the four-cell stage and promises to provide an experimental entry into the problem of embryonic pattern formation in nematodes.

A third project explores the control of organ formation during development. We are taking a genetic approach to the identification of genes that regulate formation of the pharynx during embryogenesis and formation of the gonad during postembryonic development.

**PUBLICATIONS**


Figure: Our working model for signal transduction by GLP-1, LAG-1 and LAG-2 proteins. LAG-2 is the putative ligand and is expressed as a membrane protein in the signaling cell; GLP-1 is the receptor; LAG-1 is the downstream effector. The ligand/receptor interaction is thought to activate LAG-1, a DNA binding protein, for entry into the nucleus and subsequent control of cell fates.
The themes of the laboratory are the biosynthesis, structure, function, and regulation of complex metalloenzymes. The systems that we employ for our studies are the nitrogenase enzyme system that reduces N₂ to ammonium and the carbon monoxide oxidation system that allows some bacteria to grow with CO as a carbon and energy source.

At the N₂-reducing site of nitrogenase is the iron-molybdenum cofactor (FeMo-co) which consists of MoFe₇S₉ and the organic acid homocitrate. We have devised an in vitro FeMo-co synthesis system and used this to identify and isolate factors involved in the synthesis. The nifB,N,E,V,H,X and Q gene products are involved in the biosynthesis of FeMo-co and we are investigating the roles of these gene products in the synthesis of FeMo-co.

The nifH gene product is a particularly intriguing protein as it is also involved in N₂ reduction as the unique electron donor to the FeMo-co-containing dinitrogenase protein. NiFh is also required for the correct insertion of FeMo-co into the dinitrogenase protein and NiFh is the site of regulation of nitrogenase activity in vivo by reversible ADP-ribosylation.

Nitrogen fixation is an energetically demanding process and when cells are presented with a good source of nitrogen, the synthesis of nitrogenase ceases. In addition, some bacteria such as *Rhodospirillum rubrum* employ a system of covalent modification of the NifH protein to turn off nitrogenase. The signal is transduced through an enzyme called DRAT which performs the ADP-ribosylation of the NifH protein, thus preventing electron flow to nitrogenase. The process is reversed by an enzyme called DRAG.

*Rhodospirillum rubrum* is able to use carbon monoxide as a carbon and energy source. The enzyme carbon monoxide dehydrogenase (CODH) is the key enzyme in this process and it contains a unique NiFe₄S₄ cluster. The structure of this enzyme and its metal clusters occupies the interests of a significant portion of the lab members. The products of the cooCTJ genes are involved in processing Ni for the active site of the enzyme. We are developing assays for enzymes involved in Ni processing and the construction of the NiFeS cluster at the active site of CODH. CooA is a CO-responsive transcriptional activator for the coo system and we are investigating the mechanisms of CO-response by this protein.

**Publications**


NMR spectroscopy and its biological applications; structure function relationships in proteins; stable-isotope-assisted multinuclear NMR spectroscopy; processing and analysis of multi-dimensional NMR data.

The central theme of our research is the application of nuclear magnetic resonance (NMR) spectroscopy to the solution of biochemical problems. The unique power of NMR lies in its ability to provide detailed chemical and structural information at an atomic level about molecules in solution—even when they are present in living cells or organisms. The general strategy is to use multidimensional (2D, 3D, and 4D), multinuclear magnetic resonance techniques to detect and assign resonances from atoms of biological interest (e.g., $^1$H, $^{13}$C, $^{15}$N, and $^{31}$P). With these assignments in hand, we can then interpret the wealth of spectral information present in coupling constants, relaxation rates, cross-relaxation rates, and chemical shifts. Proton-proton cross-relaxation rates and a variety of measured coupling constants are used to derive three-dimensional structures of these macromolecules. Relaxation rates, line-shapes, and nuclear Overhauser effect measurements provide information about molecular motions and conformational changes. The kinds of information gained from such investigations can be critical for learning how these molecules work and how they can be redesigned to have desired properties.

Our work focuses on protein systems: Enzymes, electron transport proteins, proteinase inhibitors, and nucleic acid binding proteins. We exploit recombinant DNA technology as a means for producing the large amounts of protein needed for NMR investigations and for introducing stable isotopes of interest (most commonly $^2$H, $^{13}$C, and $^{15}$N). Mutagenesis studies allow us to test hypotheses about the roles of individual amino acid residues in determining properties such as local structure, conformations and mobilities of side chains, hydrogen exchange kinetics, rates of protein folding or unfolding, $pK_a$ values, oxidation-reduction potentials, and ligand binding.

Graduate students and postdoctoral fellows in the laboratory usually focus on a particular biochemical system and use NMR as one of the tools for its analysis. They are expected to become experienced in preparing samples and in carrying out functional studies. Alternatively, they may focus on developing instrumentation or novel ways of collecting or analyzing NMR data.

PUBLICATIONS


Mechanisms of hormone action; signal transduction and second messengers; regulation of hormone and neurotransmitter secretion; inositol phospholipid biochemistry.

Neural and endocrine cells serve as key physiological integrators that both receive and emit signals in the form of hormones and neurotransmitters. The secretion of peptide hormones and neurotransmitters from endocrine and neural cells occurs via the exocytotic fusion of secretory granules/vesicles with the plasma membrane. An elevation of cytoplasmic calcium, caused by activation of signal transduction pathways, is the principal trigger for granule/vesicle fusion; however, the mechanism of calcium triggering remains to be elucidated. The operation of the regulated secretory pathway also requires ATP; however, the reactions that consume ATP remain to be identified. Our current research is focused on identifying the calcium-activated and ATP-dependent biochemical reactions that are responsible for regulated fusion.

We developed methods for cell permeabilization that enable preservation of secretory mechanisms in semi-intact cells. A key result from early studies was that soluble cytosolic proteins were required for the process. A two-stage assay was developed in which it was demonstrated that ATP acted at a step prior to calcium, and each step was shown to require distinct cytosolic proteins. Two of three proteins required for ATP-dependent priming (PEP proteins) were identified as phosphatidylinositol transfer protein, phosphatidylinositol 4-monophosphate 5-kinase, leading to the novel concept that the requirement for ATP in the regulated secretory pathway is for the phosphorylation of phospholipids. A single protein was required to reconstitute the calcium-regulated step. Termed CAPS (for Calcium-dependent Activator Protein in Secretion), this protein is a novel calcium-dependent protein that interacts with phosphorylated lipids and with membranes.

Research in progress is focused on the biochemical and molecular biological characterization of the CAPS and PEP proteins. Other studies are directed at discovering new proteins that are required for regulated secretion and determining the role of additional known membrane proteins.

The mechanisms for regulated neurotransmitter and peptide hormone secretion share common features. Research in this area hopes to uncover universal mechanisms that underlie processes as apparently diverse as learning, inflammatory responses and insulin secretion.

PUBLICATIONS


Membrane biogenesis; biosynthesis of glycosyl-phosphatidylinositol anchored membrane proteins; transbilayer movement of phospholipids; intracellular cholesterol transport.

Biological membranes contain a diverse spectrum of lipids that are asymmetrically distributed between the two leaflets of the bilayer. We are interested in aspects of membrane biogenesis concerned with lipid synthesis and transport. We are studying the biosynthesis of glycosylphosphatidylinositol (GPIs), a family of complex eukaryotic glycolipids used to anchor a variety of proteins to cell membranes. We are also interested in the transbilayer movement (flip-flop) of lipids that is essential for the assembly of the lipid bilayer of biological membranes, and the transport of newly synthesized cholesterol from the endoplasmic reticulum (ER) to the plasma membrane. A summary of research projects is given below.

GPI biosynthesis. Our research efforts are directed towards (1) isolating components of the microsomal machinery involved in attaching GPls to newly translated and translocated proteins, (2) determining the subcellular distribution and modes of intracellular transport of non-protein-linked GPls, (3) photoaffinity labeling to identify the glycosyltransferase involved in initiating GPI assembly, and (4) studying the assembly of the unique galactose sidechain found in the GPls of African trypanosomes.

Phospholipid flipases. Glycerophospholipids are synthesized on the cytoplasmic face of biogenic membranes and initially located in the cytoplasmic leaflet of the membrane bilayer. The lipids must flip across the bilayer to populate the exoplasmic (luminal) leaflet for membrane assembly. Current models suggest that flip-flop is catalyzed by specific proteins termed flipases. Our research in this area is currently aimed at (1) purification of a phosphatidylcholine flipase from mammalian ER and (2) isolation of flipase-defective bacillus mutants.

Cholesterol transport. Cholesterol is synthesized in the ER and delivered to the plasma membrane via a vesicular transport pathway. Recent work suggests that the cholesterol carrying vesicles are not the same as those that carry secretory proteins out of the ER. We are currently attempting to isolate these putative cholesterol-carrying vesicles.

Publications


Figure: Flipase assay using fluorescent phospholipids.
Biochemistry of behavior in Paramecium: Role of Ca²⁺, cyclic nucleotides, and protein kinases.

We study signal transductions in the protozoan Paramecium, using biochemical, genetic, molecular genetic, cell biological, and electrophysiological tools. Paramecium propels itself through the surrounding medium by the coordinated beating of the cilia that cover its surface. In response to chemical, mechanical, and thermal stimuli the cell changes direction or speed by changing the orientation or frequency of its ciliary beat. Stimuli initially register as a change in membrane potential, and then Ca²⁺, cyclic AMP, and cyclic GMP serve as second messengers that regulate the ciliary beat. We have purified the protein kinases of Paramecium that are regulated by these second messengers, and have cloned the genes that encode them, and are now using them to study the mechanism by which ciliary motion is controlled. We are characterizing ciliary proteins that are phosphorylated by these kinases, and exploring their role in the ciliary beat.

One of the extracellular compounds to which Paramecium responds is GTP, apparently through a plasma membrane receptor that may be related to the purinoceptors found in many animal cells that respond to extracellular ATP. Extracellular GTP elicits slow oscillations in the membrane potential of Paramecium, which correspond to alternating periods of forward and backward swimming. Mutants specifically defective in their behavioral response to GTP also lack this membrane response to GTP. The mechanism by which the extracellular signal (GTP) is transduced into a change in swimming behavior are central interests of the laboratory. The mechanisms of intracellular sequestration of Ca²⁺ are also under investigation by genetic and biochemical approaches. As an experimental organism, Paramecium offers the advantages of large size (easy electrophysiology and microinjection), good classical genetics, and easily quantifiable behavior in a unicellular organism that can be cultured in the laboratory. The long-term goal of this research is to describe a behavioral response in molecular terms, from reception of stimulus to change in ciliary beat.

PUBLICATIONS


Our interests concern structure-function relationships in virus particles, particularly relating to RNA synthesis and interactions with cell membranes. For most studies we use reoviruses, which infect mammalian hosts, have a genome comprising 10 segments of dsRNA, and form nonenveloped icosahedral virions with two concentric protein capsids.

One focus of our work concerns the enzymes for RNA synthesis, processing, and transport within the reovirus inner capsid. These enzymes include the RNA polymerase, RNA triphosphatase, RNA guanylyltransferase, two RNA methyltransferases, and a putative RNA helicase. They function to synthesize and export 5'-capped mRNAs using the genomic dsRNAs as templates. We are currently focused on viral proteins λ3, λ2, and λ1, which possess polymerase, guanylyltransferase, and NTPase activities, respectively. Using expressed proteins, we are localizing their sequences for binding RNA and small substrates, catalysis, and interactions with each other and other proteins. Our goal is to develop an atomic-scale model for the transcriptionally latent and active forms of the inner capsid.

A second focus concerns three other viral proteins – μNS, σNS, and σ3 – that bind to either ss- or dsRNA and play roles in particle assembly. In early assembly, the 10 viral mRNAs are condensed within a nascent particle before acting as substrates for minus-strand synthesis and creation of dsRNA. This process is poorly characterized but must involve mechanisms for each mRNA to be recognized and properly placed within the nucleoprotein complex. To learn more about these steps, we are using expressed μNS, σNS, and σ3 proteins to define their structures, interactions with each other and other viral proteins, and interactions with RNA.

A third project concerns the mechanism by which the reovirus particle, which lacks a lipid envelope, crosses the cell membrane to enter the cytoplasm where transcription and assembly occur. The myristoylated outer-capsid protein μ1 appears to mediate penetration by interacting directly with the lipid bilayer after changing its conformation from that in infectious particles. We are using assays to monitor both protein-membrane interactions and conformational changes in μ1 in efforts to define the molecular basis of membrane penetration by this nonenveloped virus.

Our research relies on a variety of techniques as dictated by current findings, with an emphasis on methods in genetics, molecular biology, protein biochemistry, and structural biology.


Data for image of reovirus particle provided by Prof. T. S. Baker, Purdue University.
During the development of a multicellular organism, an assortment of morphologically and functionally distinct cell types emerge in an orderly sequence from a single cell. It is the objective of our laboratory to define the molecular events that trigger the transformation of a specific mammalian progenitor cell into a permanently differentiated cell type. To address the problem, we are studying a cell line of mouse fibroblasts (preadipocytes) that undergo differentiation to adipocytes in cell culture.

In addition to understanding general cellular differentiation, this has become an area of intense research because of the far-reaching implications of adipocyte differentiation and regulation on human diseases such as obesity, diabetes, cancer, and heart disease. It has been shown that the area and size of fat storage influences one's tendency toward diseases such as non-insulin-dependent diabetes mellitus. Fat deposition in obese individuals is aberrant in comparison to nonobese individuals. This distinction is probably genetic, and may involve malfunctions of key enzymes or transcription factors. The ties between adiposity and disease provide motivation to elucidate the mechanisms involved in the control of this process. With the characterization and understanding of the key regulatory genes involved in maintaining the preadipocyte state, manipulation of fat deposition and control of many metabolic disorders may be possible.

During the differentiation process the levels of expression of a large number of adipocyte-specific genes increase in a coordinate fashion. One of these genes encodes stearoyl-CoA desaturase, an enzyme involved in the biosynthesis of unsaturated fatty acids as well as the regulation of this process. We are using molecular biology approaches to characterize the mechanisms that regulate the expression of the stearoyl-CoA desaturase gene, the objective being to determine the molecular events which define the differentiation process.

During our investigation of the regulation of adipocyte-specific genes during preadipocyte differentiation, we discovered that the expression of these same genes is under dietary and hormonal control in liver tissue. Recently, we have initiated studies aimed at defining the role of fatty acids, carbohydrates, peroxisome proliferators and insulin in the regulation of the stearoyl-CoA desaturase gene in liver and adipocytes.

We recently cloned the human homologue of stearoyl-CoA desaturase gene. The availability of this gene will enable us to study issues that affect human health.

**PUBLICATIONS**


The amino acid sequence of a protein encodes its three-dimensional structure, and this structure manifests itself in biological function. Spanning the chemistry–biology interface, we are illuminating in atomic detail both the chemical basis and the biological purpose for protein structure and protein function.

Nuclease can reveal insights into both enzymatic catalysis and protein–nucleic acid interactions. RNase A (C\(_{57}\)H\(_{89}\)N\(_{18}\)O\(_{18}\)S\(_{12}\)) is a venerable enzyme that catalyzes the nonspecific cleavage of RNA. In contrast, I-Ppol endonuclease catalyzes DNA cleavage only within a specific 15-base pair sequence. By manipulating the sequences of these nucleases and their substrates, we are delineating the precise contribution of amino acid residues to nucleic acid recognition and turnover. In addition, we are elucidating the molecular basis for the remarkable cytotoxic and angiogenic activities of some unusual homologs of RNase A.

Foldases catalyze the folding of other proteins. For example, protein disulfide isomerase (PDI) expedites protein folding by shuffling disulfide bonds. We have complemented an inviable PDI-deficient yeast strain with various mutant pdi genes and with mutant (but not wild-type!) genes that code for thioredoxin, a small PDI homolog. This genetic system is enabling us to illuminate the chemical properties of foldases (e.g., disulfide E\(^{\text{v}}\) and thiol pK\(_{\text{a}}\)) that are required for catalysis of disulfide bond isomerization in vivo.

Collagen is the most abundant protein in vertebrates. A longstanding paradigm is that the impressive stability of this fibrous protein arises from interstrand hydrogen bonds mediated by networks of bridging water molecules. We are testing this hypothesis by using synthetic collagen mimics with varying abilities to form such hydrogen bonds.

Finally, we are using genetic selections and screens to identify molecules that inhibit the dimerization of HIV-1 protease and other enzymes of therapeutic interest.

Our efforts are leading to insights into the relationship between amino acid sequence and protein function (or dysfunction), as well as to the creation of novel proteins with desirable properties.

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**PUBLICATIONS**


The three-dimensional structure of a protein plays a central role in determining its function. One of the best tools for studying structure is X-ray crystallography. We are using this technique to investigate the relationship between structure and function for large proteins and macromolecular assemblies. One of our major projects at this time is directed toward understanding the structure and function of myosin: a molecule that serves as a molecular motor in all eukaryotic cells.

Myosin is the major protein component of muscle, in which it plays both an enzymatic and structural role. It is made up of six polypeptide chains organized so as to produce two globular pear-shaped heads attached to a long rod. The rod-like portion of the molecular aggregate forms the backbone of the muscle thick filaments; whereas the myosin heads are responsible for generation of force during muscle contraction through interaction with the actin thin filaments and hydrolysis of ATP. A number of years ago we succeeded in obtaining the structure of this molecule. This has proved to be a highly challenging crystallographic project on account of the large size of the molecule and its inherent flexibility.

These efforts have now produced our first view of a molecular motor and have immediately solved several long standing questions about how this molecule transduces chemical energy into directed movement. In particular it has shown the position of the active site and putative actin binding sites. It has also revealed the location of the light chains and has suggested the role that these segments of the macromolecular assembly might play in muscle contraction. Recent studies have focused on the catalytic mechanism for ATP hydrolysis and characterization of the nucleotide binding site. There are still many unanswered questions. For example, it is known that there must be a conformational change in the myosin head during contraction. Our structure suggests how this might be accomplished; however, these hypotheses need to be tested by further structural and biochemical studies.

In addition to the work on the myosin head, this laboratory has participated in the determination of the structure of a wide range of macromolecules which include both glycolytic enzymes and proteins involved in bioluminescence. Many of these projects were started as collaborations with members of the Department of Biochemistry and provide an opportunity to experience a wider range of crystallographic techniques and expand our understanding of the role of structure in biochemical processes.

**PUBLICATIONS**


Specificity, stability and mechanisms of formation of protein-nucleic acid complexes; biophysical studies of the *E. coli* cytoplasm; NMR and computational studies of polyelectrolyte properties of nucleic acids and their complexes.

The focus of our research is on the thermodynamics (origins of stability and specificity) and the kinetic mechanisms of formation of key protein-DNA complexes in the control of gene expression, including Lac repressor-lac operator and RNA polymerase-promoter complexes. An important part of these projects is in *vitro* *in vivo* comparisons, which involve characterizing the inherent differences between these two environments.

In *E. coli*, the extent of repression of the lac operon is determined by the equilibrium extent of binding of Lac repressor protein to its specific operator site. We are investigating the thermodynamic consequences of selected substitutions and deletions of key binding-site functional groups as well as flanking regions of the protein and DNA recognition surfaces in order to dissect contributions to stability and to the extreme specificity of the repressor-operator complexes. For RNA polymerase-promoter interactions, where the specificity may be kinetically determined in *vitro* at the level of the overall association rate constant, we use filter binding, fluorescence, footprinting and other methods to characterize the initial specific binding step and the subsequent conformational changes in the polymerase and the promoter that occur on the pathway (sketched below) to formation of an initiated open complex.

We have shown that reductions in DNA polyelectrolyte charge density and removal of nonpolar surface from water in the binding site and in local or global coupled protein folding transitions are important determinants of specificity and stability of protein-DNA complexes. Each of these has its own characteristic thermodynamic signature, in strong effects of salt concentration on the binding constant, and in the heat capacity and entropy changes accompanying binding, which can be used to dissect and quantify their contributions. In addition to applying this analysis of thermodynamic signatures to characterize our systems, we are extending it to other classes of conformational changes coupled to binding of proteins to DNA.

Graduate students from Biochemistry, Chemistry and Biophysics are conducting this research. The broad range of backgrounds and interests of these students has been a key factor in our research successes and contributes to a stimulating research environment. Many of my students have gone on to academic positions in biochemistry and chemistry departments; others are engaged in research in the biotechnology and chemical industries.

**PUBLICATIONS**

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Activation of enzymic reactions by metal ions; biophysical applications of spectroscopy.

The research activities in our laboratory are concentrated in the area of mechanistic enzymology. Within this area there is an emphasis on understanding the various means by which inorganic cations serve as obligatory activators of enzyme catalyzed reactions. Enzymes exploit the electronic charge and coordination properties of metal ions to promote reactions of substrate molecules. Insight into the roles of metal ions in the chemical activation of substrates comes from an elucidation of the structures of enzymic complexes with natural substrates, substrate analogues, specific inhibitors, and modified forms of the enzyme. We are using various forms of spectroscopy as well as X-ray crystallography to solve structures of enzyme substrate complexes. We are also interested in detecting and characterizing free radical intermediates in enzymic reactions.

PUBLICATIONS


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Protein-DNA recognition reactions are a critical component in biological processes which control gene expression, govern gene replication and change genome organization. My laboratory is interested in studying various processes which use protein-DNA recognition reactions so that we can elucidate the molecular mechanisms of these reactions.

A specific protein-DNA recognition reaction which we are studying is the transcription initiation process; what does RNA polymerase "see" when it interacts with a promoter DNA sequence, what steps are involved in initiating mRNA synthesis, and how is this process regulated? Our studies have concentrated on the E. coli lactose operon promoter.

A second process in which protein-DNA recognition reactions play a role is transposition. Transposition is the genetic translocation process caused by transposable elements such as Tn5. My laboratory is studying the reactions which regulate Tn5 transposition such as host control of the synthesis of the Tn5 protein which is required for transposition, definition of the end Tn5 DNA sequences required for transposition, and analysis of protein binding to the end sequences and other reactions which occur during transposition.

Our approaches to analyzing these processes make use of any technique which we believe will provide us with answers. In general we use microbial genetics, molecular biology approaches and modern cloning and site specific mutagenesis techniques. Students are encouraged to develop their own projects, follow their own leads and develop new experimental approaches.

PUBLICATIONS


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Bioorganic chemistry of natural products. Mass spectrometry and applications to structural and biochemical problems.

In broad terms, our work is concerned with the chemistry and biochemistry of biologically active natural products. For example, the characterization and synthesis of vitamin D metabolites, the design and preparation of structural analogs, and the isolation and identification of dinoflagellate neurotoxins and other physiologically active metabolites produced by microorganisms and plants have been major activities in the laboratory. Current efforts are directed principally to vitamin D chemistry and are designed to address questions relating to the mechanism of action of the vitamin and the structural basis for its action in different systems. This work comprises studies on the interaction between vitamin D metabolites and their protein receptors (plasma carrier protein, intracellular receptor protein), the structural requirements for ligand/protein binding, the characterization of the vitamin binding site on the proteins (e.g., via preparation and covalent attachment of affinity ligands, and the mapping of attachment sites), and conformational changes attendant upon ligand/protein association. In addition, other on-going or planned synthetic/biological work concerns the structural basis for expression of vitamin D activity in different organs in vivo (e.g., intestine, bone), the structural specificity of enzymes of vitamin D metabolism and the design of mechanism-based inhibitors for some of these enzymes, and the structural requirements for the expression of the more recently observed cell-differentiation activity of vitamin D compounds. Experimentally, the above efforts involve synthetic organic and biochemical work, and all rely heavily also on spectroscopic tools, especially NMR and mass spectrometry.

PUBLICATIONS


Metabolism and metabolic role of vitamin K: prothrombin biosynthesis.

Research in this group is directed toward problems that have their background in a physiological response. At the present time most of the lab's efforts are directed toward an understanding of the metabolism and function of vitamin K.

Vitamin K (2-Me-3-phytyl-1,4-naphthoquinone) is a cofactor for the microsomal enzyme that catalyzes the post-translational modification of specific glutamyl residues in precursor proteins to form γ-carboxylglutamyl (Gla) residues in completed proteins. The plasma coagulation factors Prothrombin, Factor VII, Factor IX, Factor X, Protein C, and Protein S are vitamin K-dependent proteins, and some of the research in this laboratory is directed toward an understanding of the role of Gla residues in the function of these proteins. One aspect of research in the laboratory involves attempts to determine the mechanism of action of the vitamin K-dependent carboxylase. It is known that the vitamin K-dependent step involves abstraction of the hydrogen at the γ-position of the substrate Glu residue with the concomitant formation of vitamin K epoxide. The precursor proteins that are substrates for this enzyme contain an amino terminal propeptide extension that both recognizes the enzyme and modulates its activity, and the mechanism of this control is under investigation.

Microsomes also contain a vitamin K epoxide reductase activity that recycles the epoxide to the stable form of the vitamin, the quinone, and eventually to the active coenzyme form, the hydroquinone. This is the enzymatic step which is inhibited by the clinically useful oral anticoagulants, and studies of the structure and mechanism of action of this enzyme are an important part of the research effort of the laboratory.

Techniques with increased sensitivity for assessing a vitamin K deficiency in laboratory animals and humans have been developed in recent years, as have sensitive methods for the analysis of vitamin K in plasma. The laboratory is now involved in studies directed toward a determination of the human requirement for vitamin K and the possible role of vitamin K in promoting skeletal health.

The cell biology of clotting factor biosynthesis in cultured cells is also being studied. In some species the secretion of prothrombin is halted when vitamin K action is blocked, and in other species under γ-carboxylated forms of prothrombin are secreted. This response is related to the degree to which undercarboxylated forms of prothrombin are degraded in the E.R. during protein processing, and the factors regulating this pathway are under investigation.

PUBLICATIONS


The work in my laboratory lies at the interface between biochemistry, developmental biology and cell biology. Ultimately, we want to understand the mechanisms by which mRNAs are controlled—how nuclear transcripts mature into functional mRNAs, and how mature mRNAs are regulated in the cytoplasm. We want to understand the mechanism and regulation of mRNA translation, stability and cellular localization. These interests have drawn us into several different but intertwined areas of investigation.

A primary focus concerns the mechanisms by which mRNAs are controlled in the egg and early embryo. The ultimate aim of our work in this area is to understand the molecular mechanisms that control mRNAs during the first few hours of an animal’s life. In this crucial, earliest period, transcription typically has not yet begun: RNA, not DNA, is pivotal. Proper regulation of mRNAs that were in the egg before fertilization is essential for many key developmental events, including pattern formation, sex determination and control of the embryonic cell cycle. We want to understand, in detailed molecular terms, how such mRNAs are controlled. For these studies, we use the frog, Xenopus laevis, because of its assets in biochemistry, cell biology and micromanipulation. We inject mutant or wild type mRNAs and proteins into living frog eggs, and identify and purify the factors responsible for control using egg cell-free systems.

Although embryos have special adaptations, they exploit mechanisms common to all cells. The yeast, S. cerevisiae, mirrors many of the same issues we confront in the embryo, and offers special opportunities for molecular genetics. We study related problems in yeast and in frog embryos, hoping to reveal common features and exploit the power of both systems. Recent work has focused on how the poly(A) tail, and the proteins attached to it, influence the life and death of the mRNA.

The region of the mRNA between the termination codon and poly(A) tail—the 3′ untranslated region—was long thought to be a barren desert and of little interest. Recent work in many labs, including my own, demonstrates that this is not the case; instead, 3′UTRs are key repositories of regulatory information. We want to understand how 3′UTRs function and evolve. To do so, we focus on the function of specific elements that regulate translation and stability, using molecular genetics and biochemistry.

Finally, we are interested in RNA, and how RNAs and proteins interact. Each RNA has a unique and complex shape. As a result, RNAs can catalyze reactions and bind specifically to a wide variety of ligands. Our work on RNA-protein interactions impinges on each of these areas. Using the yeast S. cerevisiae, we have developed a novel assay by which a wide variety of RNA-protein interactions can be readily detected, and dissected genetically. The system is unconstrained by the biological functions of the RNAs and proteins involved, so that a wide variety of interactions are amenable to analysis. We intend to apply this approach to dissect interactions that are vital in the control of mature mRNAs, and that underlay infection by certain RNA viruses, such as those causing human disease.

PUBLICATIONS


Jennifer Bork
B.S., Biology, B.S., Chemistry, Alma College

Phenotypic and molecular characterization of spf-1, a gene required for C. elegans gonadogenesis

I am interested in understanding how several developmental processes are coordinated to form a complicated organ with distinct morphology and function(s), from a small group of precursor cells. To address this problem, I am studying the formation of the somatic gonad in the nematode, Caenorhabditis elegans. The C. elegans somatic gonad provides an excellent model for studying organogenesis. My research is focused on the genetic, phenotypic, and molecular characterization of a gene, spf-1. spf-1 is essential for an initial stage in gonadogenesis and appears to influence early cell-fate decisions.

Graduate school is an intense learning environment in that you are constantly surrounded by new information and people who are both interested and interactive! And, of course, there is The Terrace...

Kris Dickson
B.S., Biochemistry, Indiana University

Interactions between polyadenylation factors and their effect on the polyadenylation state of mRNA molecules

I am currently interested in researching the interaction between two factors thought to be involved in cytoplasmic polyadenylation, CPSF and CPEB. Immunoprecipitation and RNA microinjection experiments are underway to elucidate how these two factors function to determine the timing and extent of polyadenylation of a wide variety of mRNAs in the cytoplasm. In turn, these changes in poly(A) length influence translation and mRNA stability in the developing embryo.

So why am I at Madison? Simple. I really like the people here. Good research is probably going on at all the schools you applied to. But, science is both research and discussion. To really have a successful graduate experience, you have to enjoy interacting with the researchers around you. For me, that meant choosing Madison. I think you'll feel the same when you visit. After all, the department is that much better now... I'm here!

Rod Echols
B.S., Chemistry, University of Houston

Cloning and characterization of a novel RAC kinase gene from Paramecium tetraurelia

The main focus of my research is to clone a Paramecium RAC (related to A and C kinase) gene. This gene is important because it has been reported that the enzyme which it codes has a SH2-like (Src homology 2) domain in its 5' region.

One of the good things about the Biochemistry Department here at the University of Wisconsin-Madison is that the students are always encouraged to tackle tough problems and push the envelope of knowledge.

The large diversity of students with expertise in various fields is also an advantage of the Department. I have benefited immensely from collaborations with students in many different fields of specialization which enables me to extend my research goals from neuroscience and behavior to oncology.

Jeff Haas
B.S., Biochemistry, University of California at Davis

Protein engineering of the substrate for the enzyme stearoyl-ACP Δ9 desaturase

We are interested in how the interaction of spinach type I acyl-carrier protein (ACP) with the plant enzyme stearoyl-ACP Δ9 desaturase affects the structure and reactivity of the diiron-oxo cofactor in the desaturase. The goal of the current project is to obtain sufficient quantities of ACP for spectroscopic studies with the desaturase. Using recombinant DNA techniques, we have engineered a number of novel plasmids from which holo-ACP can be produced in Escherichia coli. We are now working on generating and purifying stearoyl-ACP in vitro.

I have really enjoyed working in the Enzyme Institute and living in Madison. The enthusiasm of the students and diversity of faculty and student research makes this department an exciting place to work. Where else can you get orange custard chocolate chip ice cream?
Angiogenesis is defined as the formation of new capillaries from an existing capillary network. Many protein factors that promote angiogenesis have been identified, including angiogenin, a ribonuclease A homologue. Ribonuclease inhibitor negatively regulates the in vivo activity of angiogenin. The goal of my project is to engineer several angiogenin derivatives that are insensitive to the effects of ribonuclease inhibitor. These mutants will, in turn, be used to investigate the molecular mechanisms of angiogenesis.

Biochemistry at UW-Madison is an outstanding program—the Department and surrounding community consistently provide students with all resources necessary to meet the challenges of graduate school.

When the process of bone resorption is interrupted, the phenotype osteopetrosis develops. We are investigating this irregular vitamin D endocrinology using the op/op mouse model. The op/op mouse represents one example of an inborn metabolic error yielding osteopetrosis. op/op mice do not produce functional macrophage-colony stimulating factor (M-CSF), a protein involved in osteoclast cell differentiation. Osteopetrosis is characterized by dense bones and a lack of tooth eruption due to the inability to resorb bone.

Having a supportive, intelligent advisor, like Dr. Hector DeLuca, who criticizes constructively and rewards accordingly, has made my graduate career a positive experience.

As an undergraduate I became interested in applying the concepts and approaches of inorganic chemistry in a biological context, and found the Department of Biochemistry at UW-Madison ideally suited for this pursuit. The focus of my graduate research is the characterization of a novel nickel- and iron-containing metal center in the enzyme Carbon Monoxide Dehydrogenase. I have greatly enjoyed the enthusiastic and collaborative atmosphere within Biochemistry and between other departments as well. Furthermore, the campus location is an added bonus; Madison offers an endless supply of extracurricular diversions!

Stearoyl-CoA desaturase (SCD) is an enzyme that catalyzes the Delta9-desaturation of fatty acids before they are packaged and secreted as VLDL from the liver. I have characterized the induction of the SCD gene 1 by insulin and carbohydrates and its repression by thyroid hormone and dietary fat in mouse liver and localized the genetic response elements for these agents in cultured liver cells.

Working on multiple projects at one time, I have learned a variety of molecular biology techniques which helped me find a great postdoc for the future.
Many prospective students ask what type of jobs and careers our graduates take. Below is a partial listing of the current positions of students who received their Ph.D.s from the Department of Biochemistry at the University of Wisconsin-Madison. The list ranges from the distant past to some new graduates as of 1996. It is of interest that many of our graduates have pursued research careers on projects quite distant from the projects on which they trained. This confirms our belief that the graduate training provided at the University of Wisconsin-Madison prepares students to tackle any intellectually challenging research problem. Some of our graduates have used their scientific training to pursue careers in teaching, technical writing, administration, and even law.

Larry D. Satter, Ph.D. 1965, J. Suttie
Director, Dairy Forage Research Center and Professor, Department of Dairy Science, University of Wisconsin-Madison

James R. Carlson, Ph.D. 1966, J. Suttie
Associate Dean and Associate Director, Agricultural Research Center, College of Agriculture and Home Economics, Washington State University, Pullman

Robert V. Klucas, Ph.D. 1967, R. Burris
Professor and Chair, Department of Biochemistry, University of Nebraska-Lincoln

Lee Baxter-Lowe, Ph.D. 1976, H. DeLuca
Professor of Medicine and Director, Molecular Genetics Program, Center for Cancer Treatment and Research, University of South Carolina-Columbia

Jeffrey L. Browning, Ph.D. 1976, D. Nelson
Senior Scientist, Department of Immunology, Biogen, Cambridge, MA

Jerry B. Dodson, Ph.D. 1976, R. Wells
Professor and Chair, Department of Microbiology, Michigan State University

Frank M. Rauschel, Ph.D. 1976, W. Cleland
Professor, Department of Chemistry, Texas A&M University

Susan M. Hutson, Ph.D. 1976, H. Lardy
Professor of Biochemistry, Bowman Gray School of Medicine of Wake Forest University

James A. Sadowski, Ph.D. 1976, J. Suttie
Associate Professor, Jean Mayer USDA Human Nutrition Research Center, School of Nutrition Science and Policy at Tufts University

David W. Emerich, Ph.D. 1977, R. Burris
Professor, Department of Biochemistry, University of Missouri-Columbia

Jeffrey A. Engler, Ph.D. 1977, R. Inman
Professor, Department of Biochemistry and Molecular Genetics, University of Alabama-Birmingham

Richard A. Jorgensen, Ph.D. 1978, W. Reznikoff
Research Geneticist, Department of Environmental Horticulture, University of California-Davis

James M. Hogle, Ph.D. 1978, M. Sundaralingam
Edward S. Harkness Professor of Biological Chemistry and Molecular Pharmacology, Harvard Medical School

Kathleen Postle, Ph.D. 1978, W. Reznikoff
Professor, Department of Microbiology and Department of Biochemistry/Biophysics, Washington State University, Pullman

James E. Rife, Ph.D. 1978, W. Cleland
Associate Professor, Department of Chemistry and Geology, Manlato State University

John S. Blanchard, Ph.D. 1979, W. Cleland
Professor of Biochemistry, Department of Biochemistry, Albert Einstein College of Medicine

Charles E. Grimshaw, Ph.D. 1979, W. Cleland
Consultant, Assay Design and Development, AMGEN, Thousand Oaks, CA

Stephen C. Hardies, Ph.D. 1979, R. Wells
Associate Professor, Department of Biochemistry, University of Texas Health Sciences Center

Lynne E. Maquat, Ph.D. 1979, W. Reznikoff
Cancer Research Scientist in Human Genetics, Professor, Departments of Cellular and Molecular Biology and Biochemistry, Roswell Park Memorial Institute

Gregory D. Reinhardt, Ph.D. 1979, H. Lardy
Professor, Department of Biochemistry and Biophysics, Texas A&M University

Joseph A. Toce, Ph.D. 1979, R. Boek
Vice President, Reliable Biopharmaceutical, St. Louis

Daniel J. Arp, Ph.D. 1980, R. Burris
Professor, Department of Botany and Plant Pathology and Director, Molecular and Cellular Biology Program, Oregon State University

William S. Brusilow, Ph.D. 1980, D. Nelson
Associate Professor, Department of Biochemistry, Wayne State University

Theresa A. Salerno, Ph.D. 1980, P. Kaesberg
Assistant Professor, Department of Chemistry, Manlato State University

Jeffrey D. Edzo, Ph.D. 1980, C. Raetz
Professor, Department of Medicine, Division of Cellular and Molecular Medicine, University of California-San Diego

Roger A. Sunde, Ph.D. 1980, W. Hoekstra
Nutritional Sciences Leader, Professor of Nutritional Sciences and Biochemistry, Department of Nutritional Sciences, University of Missouri-Columbia

Vernon E. Anderson, Ph.D. 1981, W. Cleland
Associate Professor, Department of Biochemistry, Case Western Reserve University

Joseph H. Guth, Ph.D. 1983, R. Burris
Division Patent Counsel, Chiron Corporation, Emeryville, CA

Jeffrey D. Hermes, Ph.D. 1983, W. Cleland
Director, Molecular Design and Diversity, Merck Research Laboratories

Sabera Merchant, Ph.D. 1983, B. Selman
Professor, Department of Chemistry and Biochemistry, University of California-Los Angeles

Associate Director, Winton Hill Technical Center, Procter & Gamble Company

Laura S. Privalle, Ph.D. 1983, R. Burris
Senior Regulatory Scientist, Ciba Seeds, Agricultural Biotechnology Research Unit, Research Triangle Park, NC

Christine E. Bulawa, Ph.D. 1984, C. Raetz
Professor, Department of Chemistry and Biochemistry, University of California-Los Angeles

Karen K. Klyczek, Ph.D. 1984, C. Hayes
Assistant Professor, Department of Biology, University of Wisconsin-River Falls

Theresa E. Dowling Paul, Ph.D. 1985, P. Ludden
Senior Associate Scientific Information Analyst, Department of Biochemistry, Chemical Abstracts Service, Columbus, OH
Anne E. Griep, Ph.D. 1985, H. DeLuca
Assistant Professor, Department of Anatomy,
University of Wisconsin-Madison Medical School

Paul F. Lambert, Ph.D. 1985, W. Reznikoff
Associate Professor, Department of Oncology, McArdle Laboratory for Cancer Research, University of Wisconsin-Madison Medical School

Roy H. Kanemoto, Ph.D. 1986, P. Ludden
Project Leader, Applications Development,
Hewlett Packard Co., Bioscience Products,
Palo Alto

Mark R. Pope, Ph.D. 1986, P. Ludden
Project Manager-Diabetes Diagnostics,
Venture, Abbott Laboratories, Chicago

Bernard H. Selling, Ph.D. 1986, R. Ruedcker
Associate Director of Core Biotechnology,
Wyeth Ayerst Laboratories, Radnor, PA

Gary M. Wood, Ph.D. 1986, J. Sutie
Associate Professor, Department of Chemistry, University of Wisconsin-Parkside

Dring N. Crowell, Ph.D. 1987, W. Reznikoff
Assistant Professor, Department of Biology, Indiana University-Purdue University at Indianapolis

Mark P. Krebs, Ph.D. 1987, W. Reznikoff
Assistant Professor, Department of Biomolecular Chemistry, University of Wisconsin-Madison Medical School

Leslie A. Miglietta, Ph.D. 1987, D. Nelson
Senior Editor, Clarity Editing, Bethel, CT

Susan M. Smith, Ph.D. 1987, C. Hayes
Assistant Professor, Department of Nutritional Sciences, University of Wisconsin-Madison

Sheila A. Anderson, M.S. 1988, A. Harper
4th Year Veterinary Medicine Student,
School of Veterinary Medicine, University of Wisconsin-Madison

Timothy R. Hoover, Ph.D. 1988, P. Ludden
Assistant Professor, Department of Microbiology, University of Georgia

Robert G. Lowery, Ph.D. 1988, P. Ludden
Director of Product Development, PanVera Corporation, Madison

Andrew D. Robertson, Ph.D. 1988, J. Markley
Associate Professor, Department of Biochemistry, College of Medicine, University of Iowa

Janet E. Lindsley, Ph.D. 1989, M. Cox
Assistant Professor, Department of Biochemistry, School of Medicine, University of Utah

Jan A. Cheatham, Ph.D. 1989, H. Lardy
Assistant Faculty Associate, Department of Zoology, University of Wisconsin-Madison

Laura J. Conway, Ph.D. 1989, M. Wickens
Training for Genetic Counseling, Bryn Mawr College

Haian Fu, Ph.D. 1989, R. Burris
Assistant Professor, Department of Pharmacology, Emory University School of Medicine

Martin Hochstrasser, Ph.D. 1989, D. Nelson
Department of International Regulatory Affairs, The R.W. Johnson Research Institute, Switzerland

Julie A. Carman, Ph.D. 1990, C. Hayes
Research Investigator, Department of Cardiovascular Molecular and Cellular Biology, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton

Peter G. Obrenov, Ph.D. 1990, J. Kimble
Assistant Professor, Laboratory for Molecular Biology, Department of Biological Sciences, University of Illinois at Chicago

Julie A. Ahringer, Ph.D. 1991, J. Kimble
Group Leader, Department of Genetics, University of Cambridge, England

Scott A. Ensign, Ph.D. 1991, P. Ludden
Assistant Professor, Department of Chemistry and Biochemistry, Utah State University

Catherine A. Fox, Ph.D. 1992, M. Wickens
Assistant Professor, Department of Biomolecular Chemistry, University of Wisconsin-Madison

J. David Furlow, Ph.D. 1992, J. Gorski
Postdoctoral Fellow, Department of Embryology, Carnegie Institution of Washington

Russell J. Wiese, Ph.D. 1992, H. DeLuca
Postdoctoral Fellow, Department of Cell Biology, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Co.

Annette Schnemann, Ph.D. 1992, R. Ruedcker
Assistant Member, Department of Molecular Biology, The Scripps Research Institute

Diana L. Wroe, Ph.D. 1992, P. Ludden
Scientist II, Process Science Department, Connective Therapeutics, Inc., Palo Alto

Randall E. Bolger, Ph.D. 1993, J. Sutie
Development Scientist, PanVera Corporation, Madison

Andrew P. Hinck, Ph.D. 1993, J. Markley
Staff Fellow, Molecular Structural Biology Unit, National Institute of Dental Research, Bethesda

Gary M. Nielsen, Ph.D. 1993, P. Ludden
Science and Math Teacher at Cheverus High School, Augusta, ME

Margaret E. Benton, Ph.D. 1994, J. Sutie
Postdoctoral Fellow, Department of Human Oncology, University of Wisconsin-Madison

Ruth A. Ettringer, Ph.D. 1994, H. DeLuca
Postdoctoral Research Associate, Virginia Mason Research Center, Seattle

Assistant Professor, St. Olaf College

Ronald M. Allen, Ph.D. 1995, P. Ludden
Research Scientist, E. I. DuPont, Wilmington

Daniel G. Gretch, Ph.D. 1995, A. Atie
Assistant Professor, Department of Biology, Wuerzburg College

Charles G. Hooogastra, Ph.D. 1995, J. Markley
Helen Hay Whitney Postdoctoral Fellow, Department of Chemistry and Biochemistry, University of Colorado at Boulder

Steven M. Rodems, Ph.D. 1995, P. Friesen
Research Associate, Department of Biology, University of California-San Diego

Joseph E. Wedekind, Ph.D. 1995, J. Raymond
Burroughs Wellcome Fund Fellow of the Life Sciences Research Foundation, Department of Structural Biology, Stanford University School of Medicine

Deneen M. Wollk, Ph.D. 1995, H. DeLuca
Postdoctoral Fellow, Eccles Institute of Human Genetics, University of Utah

Ivan P. Moskowitz, Ph.D. 1996, J. Rothman
3rd Year Medical Student, University of Wisconsin-Madison Medical School

Steven S. Pullen, Ph.D. 1996, P. Friesen
Postdoctoral Associate, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT

Leslie L. Waite, Ph.D. 1996, M. Cox
Postdoctoral Fellow, Division of Infectious Diseases, University of California-San Francisco

* Note: this list is accurate as of 10/96.
Faculty Collaborations

When you lock the lab doors, you lock a lot more out than you lock in" Robert H. Burris, Emeritus Professor and former Chair of Biochemistry is fond of quoting Charles Kettering. A spirit of cooperation and collaboration was instilled by the founders of the Department of Biochemistry and continues today. Effective, multidisciplinary collaboration is an essential feature of current biochemical research. There are many collaborations among students, faculty, and staff of the Biochemistry Department and many more collaborations with other groups on campus. Shown here are examples of a few of the interactions of Biochemistry students and faculty with members of related departments on campus. These collaborations enhance not only the research efforts, but also the training of Biochemistry graduate students.

Biochemistry student Thomas Thompson (left), Professor Ivan Rayment (center left), Associate Professor Jorge Escalante (Bacteriology; center right), and Bacteriology student Michael Thomas (right) collaborate on determining the structure and function of enzymes in the biosynthetic pathway of Cobalamin (vitamin B12) in Salmonella typhimurium.

Associate Professor Ron Raines (left) and Professor Bob Auerbach (Zoology; right) collaborate on revealing the molecular basis of angiogenesis.


Associate Professor Tony Buecker (Botany; left) Professor Rick Amasino (center) and Biochemistry student Susheng Gan (right) collaborate to identify genes that regulate flowering as well as leaf senescence.

Assistant Professor Rick Eisenstein (Nutritional Sciences; left) and Professor Marvin Wickens (right) collaborate on using yeast to study iron metabolism.
Professor Paul Ludden (left), Professor Gary Roberts (Bacteriology; center) and Biochemistry student Sandra Grunwald (right) collaborate on the biosynthesis and regulation of metalloenzymes such as nitrogenase.


Professor John Suttie (left), Biochemistry student Sherri Millis (center), and Professor Frank Greer (Pediatrics; right) collaborate on studies of vitamin K nutrition in infants.


Associate Professor Ron Raines (left) and Assistant Professor Laura Kiessling (Chemistry; right) study the chemistry and enzymology of RNA cleavage.

Professor John White (Director of IMR; left), Biochemistry student Anne Lynn Gillian, Assistant Professor Max Nibert and Dr. Victoria Frohlich (Deputy Director of IMR; right) collaborate on using different methods of electron and light microscopy to investigate the structure of reovirus particles and the cell biology of reovirus infections.

CHOICE OF Thesis Advisor

In order to assist new students in choosing a laboratory for their Ph.D. thesis project, the New Student Orientation Committee arranges rotations and faculty research presentations. In the fall semester of the first year the new students attend a comprehensive series of seminars, given by the faculty on their research programs. This provides an opportunity to become aware of current research efforts in the Department. Following this, the students are encouraged to talk in depth with those faculty members whose research is in the area of their interest. The students rotate through several laboratories, where they may undertake short-term projects. Students are also invited to laboratory meetings of research groups. Toward the end of the fall semester, the students are asked to submit a short list, indicating an order of preference for a major professor. The students are then assigned to a laboratory of their choice by mutual faculty/student consent.

The Biochemistry Faculty encourages all students to make a relatively early decision on a thesis advisor, since this allows many students to begin productive thesis research in the first year of graduate school. The option to change advisors exists, although a change can delay the completion of the Ph.D. During the beginning of the research work the major professor may collaborate closely with the student, introducing new techniques and concepts. As the work progresses, the student is expected to develop as an independent investigator and play the major role in applying new techniques and theories related to his or her work.

When a student has completed his or her original research, and has compiled the results into a thesis, the work is presented orally before an examining committee of five faculty members. The final presentation usually takes place 2-3 years following the preliminary exam.

Examinations

The preliminary examination, which is required of all students majoring in biochemistry who seek admission to candidacy for the Ph.D. degree, is a combined written and oral examination. It must be taken by students who have just completed three semesters of residence in graduate work.

The written part of the exam is a critical evaluation of a research proposal submitted by the students to their examining committees. The proposals are in the areas that the students intend to pursue for their dissertation. The written exam is designed both to test the students and to prepare the students for writing and submitting research proposals later in their careers. The oral part of the exam, the defense of the proposal, is scheduled after successful completion of the written part. In this part of the exam, students are evaluated on their ability to communicate their ideas and justify their experiments.

Equal Opportunity

True learning requires free and open debate, civil discourse and tolerance of many different individuals and ideas. We are preparing students to live and work in a world that speaks with many voices and from many cultures. Tolerance is not only essential to learning, it is an essential to be learned. The University of Wisconsin-Madison is built upon these values and will act vigorously to defend them. We will maintain an environment conducive to teaching and learning that is free from intimidation for all.

In its resolve to create this positive environment, the UW-Madison will ensure compliance with federal and state laws protecting against discrimination. In addition, the UW-Madison has adopted policies that both emphasize these existing protections and supplement them with protections against discrimination that are not available under either federal or state law.

Federal and state laws provide separate prohibitions against discrimination that is based on race, color, creed, religion, sex, national origin or ancestry, age, or disability. State law additionally prohibits discrimination that is based on sexual orientation, arrest or conviction record, marital status, pregnancy, parental status, military status, or veteran status. The application of specific state prohibitions on discrimination may be influenced by an individual's status as an employee or student.

University policies create additional protections that prohibit harassment on the basis of cultural background and ethnicity. Inquiries concerning this policy may be directed to the appropriate campus admitting or employing unit or to the Equity and Diversity Resource Center, 179A Bascom Hall, University of Wisconsin-Madison, Madison, WI 53706 (608) 263-2378, TDD (608) 263-2473.
Modern biochemical research depends heavily on instrumentation and other supporting facilities. Individual laboratories in the Department are well equipped with instrumentation necessary to achieve the goals of the lab. In addition, there are many pieces of shared equipment in the Department. The Department and the campus have a commitment to maintaining the most modern equipment for biochemical research, and both departmental and campus funds along with federal grant funds are used to maintain and upgrade the instruments available for research.

**National Magnetic Resonance Facility at Madison (NMRFAM).** NMRFAM is an NIH-funded, shared instrumentation laboratory located in the Biochemistry Department and directed by Professor John Markley. NMRFAM contains five modern multi-nuclear NMR spectrometers with field strengths between 400 MHz and 750 MHz equipped for the most demanding multidimensional, multinuclear spectroscopic applications. NMRFAM staff members carry out core research projects and make available to service and collaborative users the techniques and technology developed through these projects. Projects focus on structural determinations and development of methods. The facility also supports in vivo and ex vivo experiments, such as physiological and micro-imaging experiments.

**Biophysics Instrumentation Facility.** The instruments in the facility include an isothermal titration calorimeter, differential scanning calorimeter, analytical ultracentrifuge, circular dichroism spectrometer, Fourier transform infrared spectrometer, and surface plasmon resonance detector. This ensemble of instruments enables thorough characterization of conformation, structure, and complexation. These interrelated properties are the basis for biological function. The facility is directed by Professor Ron Raines and supervised by an Instrumentation Specialist who helps students perform their experiments.

Also found in laboratories of the Department are state-of-the-art equipment for mass spectrometry, electron paramagnetic resonance, X-ray diffraction, fluorescence spectroscopy and anisotropy, fluorescence activated cell sorting, phosphorimaging, microcalorimetry, electron microscopy and chromatography.

**Computing Facilities.** Members of the Department are linked by an advanced computer network and significant facilities for computing, sequence analysis and molecular graphics are available. Through the campus computer network students have access to e-mail, the Internet and database services such as Biosis and Medline. Madison is home to both the Genetics Computer Group and DNA*, private companies that specialize in development of software for sequence analysis and through their proximity, researchers at UW-Madison become aware of the latest advances in sequence and database analysis.

**Support Facilities.** Housed within the Department are an electronic workshop, a machine shop, a pilot plant for growth and processing of large quantities of microorganisms, modern animal care facilities, plant growth chambers and an excellent stockroom that maintains supplies for many of the day-to-day needs for biochemical and molecular biology experiments. In the new Biotechnology Center Building adjacent to Biochemistry are found service labs to perform automated DNA sequencing, protein and peptide sequencing and oligonucleotide synthesis. The Biotechnology Center also houses a transgenic animal lab and the nearby Biotron provides controlled environments for experiments with recombinant DNA that require containment. An outstanding media lab that assists researchers in the preparation of illustrations, photographs, and slides for the presentation of their results is equipped with the latest in computers and digital presentation equipment.

**Libraries.** The Biochemistry Department maintains a specialized biochemical library that is available 24 hours a day and both the Steenbock Memorial Library and the Health Science Library are nearby.

**Biotechnology in Madison.** The facilities of the Biochemistry Department are enhanced by the facilities of the many other laboratories of biological and chemical departments on campus. Madison is also a major center of the biotechnology industry and the presence of Promega, Novagen, PanVera, Agencourt and other biotech companies adds to the expertise available in the Madison scientific community. The spirit of cooperation that exists among the groups on campus and between the private companies and the campus scientists adds to the research environment.

**New Building.** In the spring of 1998, the members of the Biochemistry Department will move into new facilities designed for the most modern biochemical experiments. A drawing of this 197,600 square foot building is found inside the back cover of this brochure.
Course Offerings

The size and breadth of interest of the faculty permits the Department to offer a wide variety of courses geared to meet individual needs and interests. Students are provided flexibility in their choice of courses. In order to broaden their training, graduate students are required to take a minor of their choice, in addition to their major. Students in general take 18 semester credits towards the Ph.D. degree. Descriptions of the specific courses are given in the Graduate School Bulletin. Credit for graduate level biochemistry courses taken at other institutions may be requested through the departmental Examinations-Certification Committee.

The first graduate year emphasizes formal course work within the Department. Graduate students are encouraged to commence research in the laboratory of their supervising professor during the first year, and to devote an increasing portion of their time to independent work as their career progresses. During the fourth semester a written and an oral examination are given to all students seeking a Ph.D. degree. Award of the doctorate requires satisfactory performance in course work and examinations, and presentation of a thesis based upon original research. A little more than five years beyond the bachelor's degree is the normal period for completion of all requirements for the Ph.D. degree.

As part of their general training, all students are required to assist on a part-time basis in the departmental teaching program for two semesters, normally during the second or third year of the student's program.

A large number of seminars on a wide range of subjects are also part of the formal training program. Journal clubs within research areas are commonplace and are an important and required part of graduate training. Each year there is a seminar series focused on a specific area. These are augmented by seminar presentations on topics of current interest. Recent series include:

- Signal Transduction and Molecular Neurobiology
- Current Topics in Metabolic Regulation
- Development and Control of Gene Expression
- New Directions in Structural Biochemistry
- The Cell Cycle and Its Regulation
- Protein Folding and Assembly
- Receptor-Ligand Interactions
- Transcription and Development
- Intracellular Protein and Lipid Traffic
- Protein-Nucleic Acid Interactions

A major event in the Department each year is the organization and presentation of an international symposium on an area of current importance. Students have the opportunity to participate in these symposia at which leading researchers from around the world present the latest results on important topics. These symposia are supported by the Steenbock endowment to the Department and following the first Steenbock Symposium on Fat-Soluble Vitamins many topics have been covered. Recent symposia have focused on:

- RNA Polymerase and the Regulation of Transcription
- Current Advances in Vitamin K Research
- Hormone, Thermogenesis and Obesity
- Osteoporosis: Basis, Assessment and Treatment
- Molecular Biology of Atherosclerosis
- Cellular Communication in Plants
- Protein-Nucleic Interactions
- High Pressure Effects in Molecular Biophysics and Enzymology
- Behavior and Signaling in Microorganisms
- Biosynthesis of Metal Clusters for Enzymes.
ADMISSION

For admission to graduate study in the Department of Biochemistry, the student must complete a B.S. or B.A. degree in a recognized college or university. The basic background for biochemistry would ordinarily be provided by an undergraduate degree in biochemistry, chemistry, physics, or in one of the biological, medical, or agricultural sciences with a strong complement of chemistry courses.

The applicant should have a grade average of B or better in order to be considered. The Department has the following background chemistry requirements:

1. Quantitative analytical chemistry, lecture and laboratory.
2. Two semesters of organic chemistry and one of organic laboratory.
3. A calculus-based course in physical chemistry.
4. One semester of biochemistry.

There are no specific requirements in other supporting fields, but students are encouraged to acquire an adequate mathematics, physics, biology, and genetics background. Ideally, these should be taken during the undergraduate years. However, arrangements can be made to take some of them after the student is admitted to graduate work. The Biochemistry Department does not have a formal language requirement for advanced degrees.

All students are required to take the Graduate Record Examinations, and an undergraduate research experience is also strongly recommended.

APPLICATION

Most of the students admitted in a given academic year are selected between January and March. Applications can be considered at any time, but we strongly recommend that a completed application be submitted by January 1. Applicants are expected to take the Graduate Record Examination, including the advanced exam in Biochemistry (preferred), Chemistry or Biology, and should do so at the October or December sitting so that the scores will be available by February.

Application forms and further information may be obtained by writing to:

Chair, Graduate Admissions Committee
Department of Biochemistry
University of Wisconsin-Madison
420 Henry Mall
Madison, WI 53706-1569, USA
E-mail: clarkel@biochem.wisc.edu
Web site: http://www.biochem.wisc.edu

FINANCIAL AID

The Department offers stipends in the form of traineeships or research assistantships to all its Ph.D. candidates, and assists those with outstanding records in competing for University and national fellowship awards. In addition, if a student is particularly suited and interested in a certain professor’s work, that professor may make a personal offer of support from his/her research funds. Low-cost, comprehensive insurance plans are available. For the current stipend levels, see enclosed insert.

HOUSING

More than 1,000 modern apartments in an attractive location on campus near Lake Mendota are operated by the University for married graduate students. Rental rates (1996-97) are $356.00-$441.00 per month for a one-bedroom apartment, $425.00-$528.00 for a two-bedroom apartment and $508.00-$631.00 for a three-bedroom apartment (unfinished); there is a waiting list for these units. For further information on these apartments contact:

Assignment Office
Division of University Housing
Sligher Hall
University of Wisconsin-Madison
625 Babcock Drive
Madison, WI 53706
Phone: (608) 262-2522

Most Biochemistry graduate students live off-campus and a variety of rooms and apartments can be found in the area surrounding the campus and elsewhere in Madison. Private rooms cost $200.00-$320.00 per month, depending on quality and location, and rent for apartments (2-4 bedrooms) averages $350.00 per bedroom. Costs for furnished and unfurnished apartments are about the same. Further information on this type of housing may be obtained from:

Campus Assistance Center
University of Wisconsin-Madison
420 North Lake Street
Madison, WI 53706
Phone: (608) 263-2400
The Department of Biochemistry is proud of its emeritus faculty, many of whom remain active in research and other areas. The emeritus faculty provide a link to previous eras of biochemistry and a significant source of wisdom and advice as we chart future eras. Shown here are: (Standing, left to right) Roland R. Rueckert, Robert H. Burris, Henry A. Lardy, Julius Adler, Helmut Beinert, (Seated, left to right) Paul J. Kuesberg, Laurens Anderson and William G. Hoekstra. Among this distinguished group are five members of the National Academy of Sciences, a recipient of the National Medal of Science, two recipients of the Wolff Award and many other honors and awards. Members of this group have also served as chairs of Biochemistry and the Molecular Virology Institute.